Organ allocation models in Eurotransplant

The work in this thesis is supported by Eurotransplant International Foundation and the Dutch Research Council through Gravitation grant NETWORKS 024.002.003.

A catalogue record is available from the Eindhoven University of Technology Library.
ISBN: 978-90-386-6419-4

Cover design by H.C. de Ferrante. The geographic map featured on the cover of this thesis shows the member countries of Eurotransplant. The map's color scheme illustrates the local availability of organ donors relative to population density. Dots indicate the locations of the 66 centers with active kidney transplant programs (blue), and the 38 centers with active liver transplant programs (red). In total, more than 11,000 candidates currently await a transplant within these programs.

This thesis was typeset using (R) Markdown, LaTeX and the `bookdown` R-package, using the amsterdown template.

Printing: Gildeprint B.V.

Organ allocation models in Eurotransplant

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Technische
Universiteit Eindhoven, op gezag van de rector magnificus prof.dr. S.K. Lenaerts,
voor een commissie aangewezen door het College voor Promoties,
in het openbaar te verdedigen op donderdag 3 juli 2025 om 13.30 uur

door

Hans Christiaan de Ferrante

geboren te ’s-Gravenhage

Dit proefschrift is goedgekeurd door de promotoren en de samenstelling van de promotiecommissie is als volgt:

Voorzitter:	prof.dr. M.T. de Berg	
Promotor:	prof.dr. F.C.R. Spieksma	
Copromotor:	dr. B.M.L. Smeulders	
Leden:	prof.dr. E.R. van den Heuvel	
	prof.dr. M.J. Coenraad	(Leids Universitair Medisch Centrum)
	prof.dr.med. K. Budde	(Charité – Universitätsmedizin Berlin)
	prof.dr. J.J. van de Klundert	(Universidad Adolfo Ibáñez)
	dr. E. Spierings	(Universitair Medisch Centrum Utrecht)

Het onderzoek dat in dit proefschrift wordt beschreven is uitgevoerd in overeenstemming met de TU/e Gedragscode Wetenschapsbeoefening.

Contents

Dankwoord

Chapter 1

Introduction

1.1 Eurotransplant

In the 1960s, it was observed that kidney transplantation outcomes were improved when the donor and recipient were siblings with matching leukocyte antigens. Anticipating that leukocyte-antigen compatibility would also improve the outcomes of deceased-donor kidney transplantation, the Dutch immunologist Jon van Rood proposed an international collaboration he named *Eurotransplant*, in which kidneys from deceased-organ donors would be allocated to kidney transplant candidates on the basis of leukocyte-antigen matching [1]. In 1967, the first kidney was transported internationally, by army helicopter from Leuven, Belgium, to Leiden, the Netherlands, which represents the symbolic start of Eurotransplant [2]. Over the decades that followed, the scope of Eurotransplant broadened beyond the exchange of kidneys, starting with the allocation of livers in the 1970s, followed by pancreases and hearts in the 1980s, lungs in 1988, and intestines in 1999 [3].

In 2025, eight European countries participate in Eurotransplant: Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia. In the 58-year history of Eurotransplant, more than 190,000 donors have been reported to the organization [4]. With the deceased-donor organs that become available, some 6,000 transplantations are performed per year [5]. However, persistent donor shortages also mean that not all patients can be helped in time. In fact, more than a thousand patients die each year while waiting for a transplant [6].

When a donor is reported, Eurotransplant is responsible for the allocation of the available organs. This means that Eurotransplant has to find suitable recipients from the 13,500 candidates who wait for a transplant in the 76 transplantation programs that are active in the region [4]. Ideally, Eurotransplant completes the allocation procedure prior to the explantation of the available organs, which can mean that Eurotransplant has to

find suitable recipients within six hours of the reporting of the donor. Completing the allocation within this time window can be challenging, as most donors have multiple organs available for transplantation, donors can be reported at any time of the day, and the transplant centers frequently decline the organs that are offered to their patients.

The central problem in organ allocation is to determine to which candidates the available organs ought to be offered. In this thesis, we study this allocation question for the allocation of the liver and the kidneys in Eurotransplant. Eurotransplant's daily operations currently depend on allocation systems that are the product of almost sixty years of scientific, legal, and ethical discussions on allocation. In this first chapter, we describe the background of these systems, and discuss how they have been shaped by objective medical criteria and fairness considerations.

1.2 Objective medical criteria for organ allocation

In the 1990s, the Netherlands, Belgium and Germany introduced legal frameworks that govern the prioritization of candidates for transplantation. To meet the new legal requirements, Eurotransplant updated its allocation systems in the 1990s [7]. The legal frameworks required that the ranking of candidates for transplantation is (i) transparent and (ii) based on objective medical criteria [7, 8]. In the transplantation literature, a distinction is often made between three objective medical criteria: medical urgency, medical utility, and transplant benefit [9]. Which medical criterion is used to prioritize candidates affects which candidates have access to transplantation, as we illustrate in Figure 1.1 for three hypothetical candidates: candidate A, B, and C. For medical and historical reasons, the specific criterion that is used for allocation differs by organ.

The first principle, medical urgency (or medical need), gives priority to the candidate who would be expected to die first without an organ transplantation. In our hypothetical example, an allocation based on medical urgency would prioritize candidate A, because they are expected to die first without a transplant. Eurotransplant uses such "sickest-first" allocation for the liver, with candidates ranked using Model for End-Stage Liver Disease (MELD) scores. These MELD scores quantify a candidate's expected 90-day mortality risk based on biomarkers measurable from the candidate's blood. A potential concern about sickest-first allocation is that organs could be allocated to candidates whose life expectancy would remain short, even with a transplant. For example, allocation of the organ to candidate B may seem preferable to allocation to candidate A, because candidate B would survive much longer with the transplant.

The second principle, which is referred to as "medical utility" in the transplant literature, quantifies which candidates would be expected to live the longest with the transplant. Under this utilitarian principle, candidate C would be prioritized over candidates A and B (see Figure 1.1). An example of utility-based allocation in Eurotransplant is leukocyte-antigen matching in kidney transplantation, a practice that has positive effects on the survival of the kidney graft and transplant recipient. A general concern about the ranking of candidates based on medical utility is that it can lead to the transplantation of relatively healthy patients who have little need for a transplant. In our hypothetical example, it could be argued that candidate B should be prioritized over candidate C, since candidate B has a much greater need for transplantation.

The third principle, transplant benefit, quantifies which candidate is expected to benefit most from receiving the organ. Such benefit is typically defined as the contrast between medical utility and medical urgency. For Figure 1.1, we defined transplant benefit as the number of life years gained by transplantation. With this definition of benefit, a benefit-based allocation would prioritize candidate B who gains the most life years through transplantation. A theoretical advantage to this allocation is that it may prevent the transplantation of candidates who have a short life expectancy after transplantation (candidate A), while also preventing the transplantation of candidates who have little need for a transplant (candidate C). Within Eurotransplant, prioritization of candidates for lung transplantation is based on the principle of transplant benefit.

Although an allocation that is based on medical utility, medical urgency, or transplant benefit is conceptually straightforward, applying these principles for organ allocation is complex. One issue is that neither Eurotransplant nor the transplant centers know the lifetime a candidate would have, either with or without the transplant. Allocation in Eurotransplant therefore relies on statistical models that quantify the expected survival of candidates.

1.3 Fairness in organ allocation

With candidates ranked based on their expected survival, the basis of organ allocation in Eurotransplant is formed by objective medical criteria. However, prioritizing candidates solely based on these criteria leads to unfair or unjust waiting list outcomes. To address this, Eurotransplant's allocation systems also include mechanisms aimed at making allocation fair.

One type of fairness mechanisms are the balancing mechanisms that regulate the international exchange of organs among Eurotransplant's member countries. These balancing mechanisms were introduced after it was observed that the kidney procurement and kidney transplant rates were *"totally out of balance"* between Eurotransplant's member countries, which was deemed unfair to countries with high organ donation rates

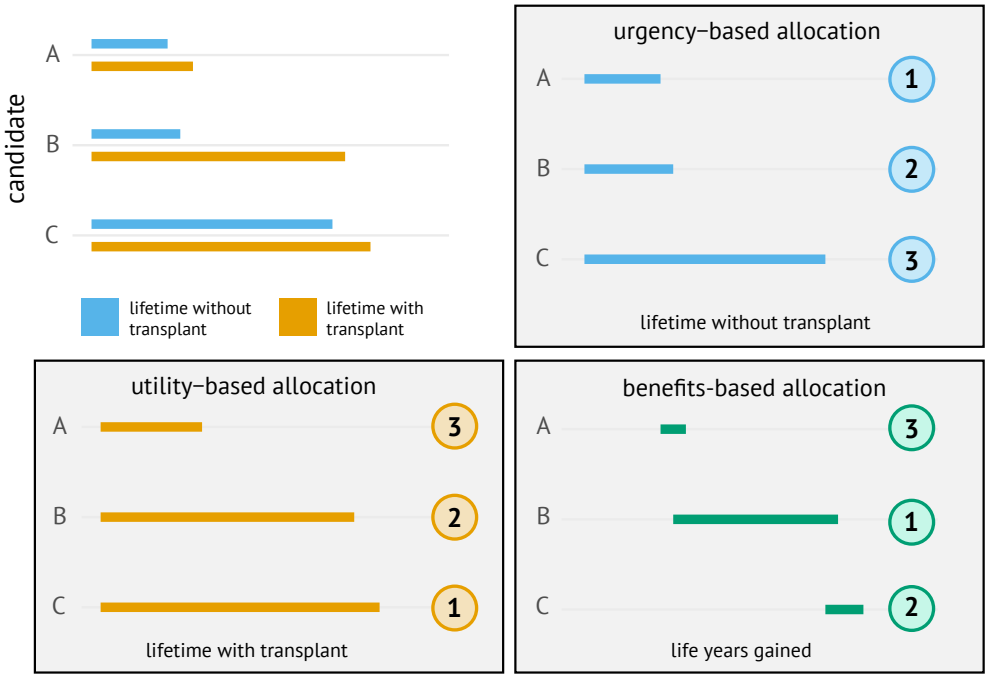


Figure 1.1: Hypothetical scenario in which a choice has to be made between three transplant candidates: candidates A, B, or C. The numbers in circles are the ranks for the hypothetical candidates under urgency-based, utility-based, and benefits-based allocation.

[10]. Their continued importance is underscored by the fact that donor procurement rates still vary widely between the member countries. For example, Belgium reported approximately 30 deceased-organ donors per million people per year over the last decade, while Germany reported only 10 [11]. It is deemed just that Belgian patients benefit from the high Belgian donation rate, and Eurotransplant is even legally required under the Belgian transplantation law to guarantee a "reasonable balance" in the number of organs imported to and exported from Belgium [12]. The balancing mechanisms ensure such a balance.

Other fairness mechanisms are aimed at giving patients an equal chance of finding a transplant [13]. For example, Eurotransplant's liver allocation system includes ABO blood group rules which give patients access to roughly the same number of potential donors, regardless of their ABO blood group. This ensures that no patients are disadvantaged by their own blood group [14]. Mechanisms are also in place to facilitate access to transplantation for candidates for whom a suitable donor is difficult to find. For example, in kidney allocation, candidates with difficult-to-match leukocyte-antigen typings receive additional points [15].

A separate issue is that some patient groups may be underserved by how medical urgency, medical utility, or transplant benefit have been defined in Eurotransplant's allocation systems. For example, several groups of liver transplant candidates are not at risk of an imminent waiting list death, which is what is scored by MELD. These candidates may nonetheless require access to transplantation, for example because of quality of life concerns, or risk of disease irreversibility. To help such candidates access transplantation, the liver allocation system awards exception points to these patient groups. In kidney allocation, prioritization is based on medical utility because patients with end-stage renal disease can survive for prolonged periods of time on dialysis. However, some candidates may lose access to dialysis, and Eurotransplant has implemented rules that facilitate access to transplantation for such candidates.

There are also patients who may deserve access to transplantation based on ethical grounds. In Eurotransplant, children have been given special attention. Another group consists of patients who lose their graft shortly after an initial transplantation procedure. Special rules facilitate access to a repeat transplant for these patients.

Considerations of fairness are thus integral to Eurotransplant's current allocation systems. The importance of fairness was also underscored by the 2007 Joint Declaration that was signed by the Ministers of Health of Eurotransplant's member countries, which states that maximizing equality of opportunity for patients is the *"most important factor for allocation"* [16]. Nevertheless, achieving fairness in organ allocation is not a simple task; in describing Eurotransplant's kidney allocation system, former medical director Guido Persijn wrote that an allocation system in which transplantation is equally accessible for all patients is *"very difficult to implement in practice"*, with the implemented allocation systems merely an *"attempt"* towards this goal [8].

It is thus not surprising that Eurotransplant regularly identifies flaws in its allocation systems, and revises the systems based on the available evidence. A recent example of such a flaw was the "blood group O problem" in kidney allocation [17], which arose because Eurotransplant allowed the transplantation of blood group O kidneys into non-O candidates in case of a perfect leukocyte-antigen match. Because of this rule, blood group O candidates – who cannot accept non-O kidneys because of blood group incompatibility – accumulated on the waiting list. As a result, blood group O candidates faced higher mortality rates than non-O candidates (13% vs 8%) and waited two years longer for a transplant [17]. This problem was addressed in 2010 by also requiring blood group identity for perfectly matched donors. Since then, the gap in waiting times between the blood groups has shrunk, although blood group O candidates continue to experience longer waiting times than blood groups A and AB [18].

The central role of fairness in allocation motivated the first goal of this thesis, which is to study questions related to equality of opportunity in Eurotransplant's kidney and liver allocation systems. Specifically, in Chapter 4 we study why females are more likely than males to have an adverse waiting list outcome in liver transplantation, and in Chapter 7 we study how immunization affects access to kidney transplantation. These chapters confirm that these patient groups are disadvantaged in the current allocation systems.

1.4 Challenges in improving organ allocation systems

The previous sections discussed that Eurotransplant's allocation systems have room for improvement. The primary forums to discuss potential improvements to the allocation systems are Eurotransplant's organ-specific advisory committees, whose members are medical specialists who are affiliated with active transplantation programs in Eurotransplant. These committees can submit recommendations to the Board of Eurotransplant and national competent authorities on how allocation may be improved. Before such recommendations are implemented, approval from these bodies is required.

Changing the allocation systems is a slow process, despite regular meetings of the advisory committees. One challenge is the complexity of the allocation procedure in Eurotransplant. When a donor becomes available, Eurotransplant runs computer algorithms against a central database to generate organ-specific *match lists*. The transplant centers register their candidates in this database, while donor procurement organizations register donors in this database. The candidates who are eligible for the organ offer appear on the match lists, and the order in which they appear determines the sequence in which Eurotransplant offers the organs to candidates. Improving the allocation system may therefore seem as simple as refining the match list order.

However, discussions on the match list order are not straightforward as match lists behave very differently from regular queuing systems. For example, being highly ranked on the current match list does not guarantee that a candidate will attain a similar rank on the next match list. The top-ranked candidate is also often not transplanted, as the transplant centers regularly decline organ offers because of concerns about the quality of the donor, logistical reasons, or temporary non-transplantability of their patient.

Additional challenges arise from the fact that Eurotransplant's member countries have different priorities and needs in allocation, in large part because of the international variation in organ donation rates. For example, Belgium has more than twice as many organ donors per million people as Germany. With these varying donation rates, it is often difficult to reach consensus on which patient groups deserve additional attention. Even when the interests of the member countries are aligned, it is often not clear how much additional support a patient group would need to realize equality of opportunity.

Due to these challenges, Eurotransplant's allocation systems evolve only slowly in response to developments in the field. In fact, the core components of Eurotransplant's liver and kidney allocation systems have changed little over the past two decades. For example, kidney allocation in Eurotransplant is still based on a point system that was introduced in 1996 despite substantial changes in the waiting list and donor pool. Liver allocation in Eurotransplant has been based on MELD since 2006, while other regions have switched to different allocation mechanisms for the liver (e.g., [19, 20]).

To advance, Eurotransplant requires tools which can give insight into the adequacy and unintended consequences of proposed policy changes. This motivated the second goal of this thesis, which is to develop discrete-event simulation software for this purpose. These simulators replicate the kidney and liver allocation procedures in Eurotransplant, and were developed in close collaboration with relevant stakeholders. In Chapters 5 and 8, we describe and validate simulators for the liver and kidney, respectively, and we demonstrate their usefulness through clinically motivated case studies.

1.5 Outline of this thesis

The thesis is divided into two parts. In Part I, we focus on the allocation of the liver. In Chapter 2, we describe the history of Eurotransplant's liver allocation system and identify potential areas for improvement. In Chapter 3, we propose a method that can be used to revise MELD more efficiently. In Chapter 4, we describe sex disparity in liver waiting list outcomes in Eurotransplant and study the mechanisms through which this disparity arises. In Chapter 5, we describe and validate the ELAS simulator, a discrete-event simulator tailored to Eurotransplant.

In Part II, we turn to allocation of the kidneys. Chapter 6 outlines the kidney allocation programs used by Eurotransplant, describes their historical development, and discusses contemporary challenges in kidney allocation. In Chapter 7, we examine how having a pre-existing sensitization against HLA antigens affects a candidate's relative transplant rate. In Chapter 8, we present the ETKidney simulator, a discrete-event simulator for kidney allocation in Eurotransplant.

We reflect on the findings and contributions of this thesis in Chapter 9.

Part I

Allocation of the liver

Chapter 2

Liver allocation in Eurotransplant

Liver transplantation is the only curative therapy for patients with acute liver failure or end-stage liver disease (ESLD), and is the preferred treatment option for several other liver conditions. The majority of candidates who wait for a liver transplant have cirrhosis, a chronic liver condition in which inflammation leads to scarring of the liver. Cirrhosis can be caused by hepatitis B, hepatitis C, alcohol abuse, metabolic disorders, or a combination thereof [21]. By itself, cirrhosis is not an indication for a liver transplantation. However, cirrhosis may progress to a stage where the patient develops clinical symptoms, such as ascites, encephalopathy, or variceal bleeding [21]. With such "decompensating" symptoms, liver transplantation can be indicated. Eventually, decompensated cirrhosis may progress into multiple organ failure – a syndrome now recognized as acute-on-chronic liver failure (ACLF), which is associated with a high short-term mortality risk [22].

Cirrhosis is also a risk factor for developing hepatocellular carcinoma (HCC), the most common form of liver cancer. While most patients with HCC have cirrhosis, they typically have a well-preserved liver function [21]. Despite not having progressed to ESLD, these candidates may require a liver transplantation to prevent tumor progression and to reduce the risk of tumor recurrence after transplantation. For patients with HCC who meet the internationally accepted Milan criteria, liver transplantation is internationally recognized as the most effective surgical therapy [23].

Besides cirrhosis, there are many other conditions that can be an indication for liver transplantation. One group of patients who urgently require access to transplantation consists of patients with acute liver failure (ALF). Acute liver failure is characterized by an unexpected and abrupt loss of liver function, which can be triggered by among others acute viral hepatitis, mushroom poisoning, or paracetamol intoxication. Without transplantation, patients with ALF are expected to die within days [24]. Examples

of chronic, non-cirrhotic indications are polycystic liver disease and cholestatic liver disease. Polycystic liver disease is a genetic disorder that causes cysts to grow in the liver and predominantly affects females. Although polycystic liver disease is not life-threatening, the condition can cause debilitating symptoms that may justify liver transplantation. One type of cholestatic liver disease is primary sclerosing cholangitis (PSC), which has a higher incidence in males. PSC is characterized by inflammation of the bile ducts which leads to scarring. If PSC is recurrent, liver transplantation may be indicated because it is a pre-stage for cholangiocarcinoma and associated with a reduced quality of life [21].

This far-from-exhaustive overview of indications for liver transplantation shows that the liver waiting list consists of heterogeneous groups of patients, who require access to liver transplantation for different reasons. Designing a liver allocation system that adequately serves these heterogeneous patient groups is a difficult task. In this chapter, we describe how Eurotransplant has tried to balance the interests of these patient groups.

2.1 Liver allocation prior to MELD

In the 1990s, Eurotransplant had limited involvement in the allocation of livers. In fact, the exchange of livers was mandatory only for candidates who had a High Urgency (HU) status [7]. Candidates with acute liver failure or other *de novo* life-threatening conditions were eligible for this status. If no such candidates were available for transplantation, the transplantation center responsible for procurement of the liver could freely select a candidate from their own waiting list for transplantation (subject to blood group rules) [14]. If the procurement center did not have suitable candidates available, Eurotransplant used a rotation system to offer the liver to other centers. Contacted centers could again freely select a candidate from their waiting list for transplantation [25, 26]. How candidates were prioritized was thus mostly left to the discretion of the transplant centers.

In July 2000, Eurotransplant introduced a patient-oriented allocation system for the liver [27], as was required under the Dutch and German transplantation laws that were introduced in the 1990s [7]. In this system, candidates for liver transplantation were categorized into four medical urgency groups: high urgency (T1), chronic disease with acute decompensation (T2), chronic disease with complications (T3), or chronic disease without complications (T4). Candidates with a T1 status received international priority, while elective candidates (T2-T4) were prioritized using a point system that awarded points for the candidate's medical urgency (T2-T4), their waiting time, and their location relative to the donor [28]. Candidates were categorized into a T2, T3, or T4 status based on their Child-Pugh score, which can be used to assess the prognosis of candidates with cirrhosis [27, 29].

The most important disadvantage of this patient-oriented system was that waiting time had a dominant role [27, 29], which incentivized the transplant centers to refer their candidates early for transplantation. In Eurotransplant, this contributed to a tenfold increase in the number of candidates who waited for liver transplantation between 1991 and 2006 [29]. As a result, waiting times in Germany exceeded 200 days even for candidates with a T2 status, who by definition have acute decompensation [27]. With these waiting times, it was observed that the candidates with the shortest waiting times faced an increased risk of dying [28]. This indicated that the allocation system failed to adequately rank candidates on medical urgency.

Classifying medical urgency based on the Child-Pugh score was also contentious because these scores are partially based on a subjective assessment of the candidate's encephalopathy grade and ascites grade [29, 30]. Concerns were voiced in the Eurotransplant Liver and Intestine Committee (ELIAC) that centers abused these subjective criteria, and *"tried to push their candidates into a T2 status"* [31]. Moreover, ascites and encephalopathy are also specifically linked to cirrhosis, such that candidates with other liver conditions were typically assigned a T4 status [27]. Consensus in ELIAC was that this was unfair to candidates with hepatocellular carcinoma or metabolic disorders [32].

2.2 MELD-based liver allocation in the United States

In the United States, a similar liver allocation system had been in use since 1998. This system also prioritized candidates using four medical urgency categories that were based on the Child-Pugh score. Freeman et al. (2004) reported that under this system there was *"virtually no relation between waiting time and mortality for each medical urgency status"*. This finding – reported on behalf of UNOS, the organ allocation organization of the United States – motivated a search for an alternative disease severity score that could be used to prioritize candidates for liver transplantation. This disease severity score would become the Model for End-stage Liver Disease (MELD) score, which was implemented in 2002.

Notably, this MELD score was not originally developed to predict survival on the liver transplantation waiting list. Instead, MELD was developed by Malinchoc et al. (2000) to predict 90-day survival after an elective transjugular intrahepatic porto-systemic shunt (TIPS) procedure [33]. These procedures are indicated in cirrhotic patients with acute decompensation to prevent variceal rebleeding, or to treat refractory ascites. Malinchoc et al. demonstrated that this model outperformed the Child-Pugh score in predicting 90-day survival after TIPS.

Whether this scoring system could also be used to rank candidates for liver transplantation was first studied by Kamath et al., who showed that MELD could also predict the 90-day mortality of three other cirrhotic patient groups: hospitalized cirrhotic patients who did not undergo a TIPS procedure, ambulatory patients with cirrhosis, and patients with biliary cirrhosis [34]. Furthermore, Kamath et al. showed that including clinical symptoms or disease etiology only minimally improved the model's predictive performance, which meant that survival could be adequately predicted based on blood-based biomarkers alone. Candidates for liver transplantation could thereby be prioritized solely based on objective medical criteria, which was considered advantageous. Subsequent external validations have demonstrated that MELD is indeed superior to the Child-Pugh score for predicting 90-day survival on the liver waiting list [30].

Based on these findings, a policy to prioritize patients using MELD was approved in the United States in November 2001. Under this system, which was implemented in February 2002, MELD scores are calculated based on measurements of serum bilirubin (mg/dl), serum creatinine (mg/dl) and the International Normalized Ratio (INR) of prothrombin time, using the following formula:

$$6.43 \; + 3.78 \ln(\text{bilirubin}) + 9.57 \ln(\text{creatinine}) + 11.20 \ln(\text{INR}) \, .$$

In calculating MELD scores, the laboratory measurements for biomarkers are set to a minimum of 1 to prevent negative scores. UNOS also proposed to cap serum creatinine at 4.0 mg/dl, to limit MELD scores to a maximum of 40, and to rank candidates by their rounded MELD scores. Because of these choices, MELD scores range from 6 to 40.

It was anticipated that a purely MELD-based allocation would underserve candidates with metabolic disease, cholestatic liver disease, or hepatocellular carcinoma [34, 30]. To help such candidates access transplantation, policymakers in the United States also introduced an elaborate exception point system that awards exception points for various non-cirrhotic indications.

2.3 MELD-based liver allocation in Eurotransplant

In 2003, the ELIAC recommended assessing whether MELD could replace the Child-Pugh score for liver allocation in Eurotransplant [29]. Following this recommendation, delegates from Eurotransplant visited UNOS in 2003 and 2004 to study how a MELD-based allocation system could be adapted for Eurotransplant. These visits ultimately led to the introduction of MELD-based liver allocation in Eurotransplant in December 2006.

Because of these visits, the core of Eurotransplant's MELD-based liver allocation system closely mirrors UNOS' implementation. For example, both systems give priority to candidates with acute liver failure and prioritize "elective" (i.e., non-HU) candidates using MELD scores. In both systems, prioritization is based on the *"match-MELD"* score, which is the maximum of the *"lab-MELD"* score (calculated from biomarkers) and exception points. Eurotransplant also uses the exact same formulas as UNOS to calculate the lab-MELD and exception scores.

Within MELD-based liver allocation in Eurotransplant, international sharing is mandatory only for candidates with a High Urgency (HU) status and those awaiting a combined transplantation. Otherwise, candidates located in the same country as the donor have priority in Eurotransplant. A distinctive feature of Eurotransplant's liver allocation system is that an obligation system was introduced, which ensures that livers exported with international priority are paid back by the importing country [35]. Another difference lies in the prioritization of pediatric candidates: within Eurotransplant, children are prioritized with exception points, while UNOS uses PELD, a disease severity score developed specifically for children [36].

MELD-based liver allocation in Eurotransplant has to abide by the national regulations of its member countries, which introduces considerable complexity into the allocation system. For example, only in Germany and the Netherlands is the ranking of candidates completely based on the match-MELD. In Austria, Croatia, Hungary and Slovenia, procurement centers are still allowed to select a candidate from their own waiting list, as was the case under the center-based allocation system of the 1990s. In Belgium, a mixture of center- and patient-based allocation is used, with centers free to select a candidate for Donation after Cardiac Death (DCD) donors, but not for Donation after Brain Death (DBD) donors [35]. National competent authorities have varying opinions regarding which indications deserve to be prioritized with exception points. To accommodate these different views, Eurotransplant's member countries have completely separate exception point systems, with exception points valid only for national allocation.

2.4 Areas for improvement in MELD-based allocation systems

Since Eurotransplant switched allocation by MELD in December 2006, several potential areas for improvement for MELD-based liver allocation have been identified. One known limitation of MELD is that it underestimates the waiting list mortality risks for certain cirrhotic patient groups. These include candidates with low serum sodium levels (hyponatremia) [37]. This has motivated UNOS to switch in 2016 to liver allocation based on the MELD-Na score, which adds serum sodium to the MELD formula. A second patient group consists of female transplantation candidates, who are more likely to have an adverse waiting list outcome than males in the United States [38]. To address this

disparity, UNOS liver allocation has become based on MELD 3.0 in 2023, which adds serum albumin to the formula and adds 1.33 to the MELD score of female transplant candidates [20]. In Chapter 4, we examine whether females are also more likely to face an adverse waiting list outcome in Eurotransplant, and assess why that would be the case.

A second area of improvement concerns the formula that is used to calculate MELD scores. The coefficients in this formula were based on a Cox proportional hazards model that was developed for the prediction of survival after a TIPS procedure, not survival on the liver waiting list. A rich literature exists which seeks to re-estimate these coefficients on candidates for liver transplantation [39–41]. A related area of criticism concerns the choices that UNOS has made in introducing MELD, such as capping creatinine at 4.0 mg/dl and calculating MELD with minimum values of 1 for all biomarkers. Studies have argued that these choices lacked empirical support and have revised these upper and lower limits [41]. For Eurotransplant specifically, Goudsmit et al. proposed ReMELD and ReMELD-Na, which were scores obtained by revising MELD and MELD-Na with retrospective data from Eurotransplant [42]. In a case study in Chapter 5, we assess how implementation of the ReMELD-Na score would affect waiting list outcomes in Eurotransplant.

The studies that revise MELD based on liver transplant candidate data typically associate a candidate's 90-day waiting list survival with their MELD biomarkers reported at listing. This approach inefficiently uses the data that is available at Eurotransplant, because most candidates have multiple sets of MELD biomarkers available as centers are required to regularly recertify the MELD scores of their candidates. In Chapter 3, we assess how this information can be used to revise MELD more efficiently.

A third potential area of improvement is that the prioritization of candidates based on a sickest-first principle may result in transplanting candidates who have a short life expectancy after transplantation. In Eurotransplant, mixed results exist as to whether allocation based on MELD leads to worse post-transplant outcomes [43, 44]. At least in theory, an allocation based on transplant benefit could help prevent such futile transplantations. Such a benefits-based allocation system was first proposed in the United States by Schaubel et al. [9], but it was never implemented. In the United Kingdom, allocation of livers has become based on the *Transplant Benefit Score* (TBS) since 2018 [19]. TBS has been contentious because it underserved candidates with HCC [45] and it is thought to have reduced access to transplantation for young liver transplant candidates [46].

A fourth area of improvement is the exception point system that is used to prioritize non-cirrhotic candidates for transplantation. In the United States, studies have reported that candidates eligible for exception points were overprioritized [47, 48], which has led to a substantial deprioritization of candidates with exception points in OPTN, which is the national system that manages organ allocation in the United States. For example, UNOS first lowered the number of points awarded to candidates with HCC in 2003, which was

followed by removal of exception points for those with stage I HCC. In 2005, the priority for candidates with stage II HCC was again lowered, which was followed by a "Delay and Cap" policy for HCC in 2015 [49]. With this policy, candidates with HCC would not be eligible for exception points until they had waited six months for a liver transplant (the "delay"), and would receive a maximum exception score of 34 points on the MELD scale (the "cap"). In 2019, UNOS completely removed the 90-day upgrades for all exception points, a decision motivated by findings that these 90-day upgrades were linked to an increase in the median MELD score at transplantation of 22 in 2005 to 27 in 2012 [50]. To counter such "MELD inflation", candidates with exceptions are now awarded a fixed number of points in the United States, which is specified relative to the median MELD at transplantation (MMAT) [51]. For HCC, this number is set to the MMAT minus three points.

In Eurotransplant, in contrast, changes to the exception point system have been adopted only sporadically. For example, only in the Netherlands was a six-month waiting period adopted for HCC, analogous to UNOS's 2015 "Delay and Cap" policy. This lack of policy reform is surprising because several articles have suggested that candidates with exception points are also overprioritized in Eurotransplant [52, 53]. Notable in this regard is a study by Umgelter et al. [54], who concluded on behalf of ELIAC that patients with exception points appear to be advantaged compared to candidates without exception points. In Chapter 5, we examine how changes to the exception point system would affect waiting list outcomes in Belgium, the country in which most exceptions are awarded within Eurotransplant.

As this chapter sets out, the literature is rich with ideas on how MELD-based liver allocation can be improved. A major barrier to implementing these ideas is that Eurotransplant has lacked the tools to quantitatively assess how a change in allocation rules would impact the liver waiting list outcomes. To fill this gap, we developed a discrete-event simulator that mimics the liver allocation system in Eurotransplant. We describe this simulator in detail in Chapter 5.

Chapter 3

Revising MELD from calendar-time cross-sections with correction for selection bias

---

An article based on this chapter has appeared in *BMC Medical Research Methodology*, de Ferrante, H.C., De Rosner-van Rosmalen M., Smeulders, B.M.L., Vogelaar, S., Spieksma, F.C.R., 2024, 10.1186/s12874-024-02176-8, [55]

Abstract

Eurotransplant allocates livers using the MELD score as originally proposed by UNOS. Several studies have revised this UNOS-MELD score using retrospective data on liver transplant candidates. The standard approach taken in such studies is to model 90-day waiting list mortality from the time of listing, based on biomarkers reported at listing, while censoring candidates at delisting or transplantation. This approach ignores a candidate's biomarkers that were reported after registration, and ignores informative censoring by transplantation and delisting.

We study how MELD revision is affected by using calendar-time cross-sections and by correcting for informative censoring with inverse probability censoring weighting (IPCW). To this end, we revised UNOS-MELD on patients with cirrhosis who were on the Eurotransplant waiting list between 2007 and 2019 (n=13,274) with Cox models with as endpoints 90-day survival (a) from registration and (b) from weekly drawn calendar-time cross-sections. We refer to the score revised from cross-section with IPCW as *DynReMELD*. We compare DynReMELD to UNOS-MELD and ReMELD, a prior revision of UNOS-MELD for Eurotransplant, in a geographical validation.

Our results show that revising MELD from calendar-time cross-sections leads to significantly different MELD coefficients. IPCW increases estimates of absolute 90-day waiting list mortality risks by approximately 10 percentage points. DynReMELD shows improved discrimination compared to UNOS-MELD (delta c-index: 0.0040, $p<0.001$) and ReMELD (delta c-index: 0.0015, $p<0.01$), with differences comparable in magnitude to the addition of an extra biomarker to MELD (delta c-index: ±0.0030).

Correction for selection bias by transplantation or delisting with inverse probability censoring weighting does not improve the discrimination of revised MELD scores, but does substantially increase estimates of absolute 90-day mortality risks. Revision from cross-section uses waiting list data more efficiently, and improves discrimination compared to revision of MELD exclusively based on the information available at listing.

3.1 Introduction

Eurotransplant calculates MELD scores with a formula originally introduced by UNOS in 2002. We refer to this score as UNOS-MELD. Various limitations of UNOS-MELD have been described, including that

1. it was not developed to predict mortality on the liver waiting list [33],
2. it overemphasizes renal dysfunction [40],
3. it uses biomarker caps that are not evidence-based [41],
4. it is poorly calibrated for specific subgroups, such as patients with hyponatremia [37].

These limitations have motivated several studies to revise MELD, either by re-estimating the equation's coefficients using registry data on liver transplant candidates (e.g., [40, 41]), or by expanding the scoring system with new biomarkers (e.g., MELD-Na [37] or MELD 3.0 [20]). In 2020, the equation's coefficients and caps of MELD were revised by Goudsmit et al. using retrospective data from Eurotransplant. The resulting score is referred to as the "ReMELD" score [42].

MELD revision typically proceeds by modeling waiting list mortality up to 90 days after waiting list registration based on biomarkers reported at registration (e.g., [41, 37, 20, 42]). This *"from registration"* approach poorly aligns with the clinical use of MELD: in allocation, candidates are prioritized on their last reported MELD score, and not on the MELD score that was reported at listing. Moreover, revising MELD *"from registration"* ignores waiting list deaths that occur more than 90 days after listing, which are two-thirds of all liver waiting list deaths within Eurotransplant.

Previously, such waste of statistical information was avoided by adjusting for MELD biomarkers as time-varying covariates ([40, 39]). However, MELD biomarkers also increase as part of the death process [56], such that use of MELD biomarkers as time-varying covariates leads to issues of reverse causality. This reverse causality problem is exacerbated by the fact that MELD scores can be updated voluntarily at any time and by the fact that sicker patients are required to update their MELD scores more frequently.

To prevent these issues, we propose revising MELD *"from cross-section"* using methodology developed by Gong and Schaubel [57]. With this approach MELD is revised by modeling the remaining time-until-death from pre-specified calendar-time cross-sections rather than from registration. Biomarkers measured after listing and deaths recorded more than 90 days after listing thereby inform MELD revision. To prevent issues of reverse causality, adjustment at each cross-section is for historical

biomarker information only. The evolution of biomarkers after the cross-section date affects survival, transplantation and delisting rates, which makes transplantation and delisting informative censoring mechanisms. Prior revisions of MELD censor patients at transplantation or delisting, which introduces bias. We study how MELD revision is affected by correcting for dependent censoring with inverse probability censoring weighting, which was first proposed by Gong and Schaubel [57].

3.2 Materials and methods

3.2.1 Study population and data

Adult patients with any active waiting list status on the Eurotransplant waiting list between December 16, 2006, and December 31, 2019, were extracted from the Eurotransplant database. Only patients with cirrhosis were included in the study, which is the patient group on which UNOS-MELD was originally validated. Patients with other diagnoses, those prioritized through exception points, and those awaiting a repeat transplantation or combined transplantation were excluded (except combined liver-kidney transplantation candidates). Patients with impossible values for MELD biomarkers (e.g., all zeroes for bilirubin, creatinine, and the INR) were excluded.

To activate a candidate on the liver waiting list, centers have to report MELD biomarkers to Eurotransplant. Reported MELD scores are valid for a maximum of one year, and expire in a shorter time window for sicker patients (within seven days for MELD scores greater than 25 [58]). Failure to update the MELD score results in the lowest possible MELD score of 6 being used for allocation. Consequently, MELD updates are available for most transplant candidates in the Eurotransplant database. Centers can set candidates to non-transplantable (NT) if they are temporarily not available for transplantation, which ensures that the transplant center is not contacted with offers for these patients.

3.2.2 MELD scores, UNOS-MELD and ReMELD

We define a MELD scoring system as a system that calculates a score based on serum bilirubin, serum creatinine and the INR, using the following formula:

$$\text{intercept} \ + \text{coef}_{\text{bili}} \ln\left(\text{bili}\right) + \ \text{coef}_{\text{crea}} \ln\left(\text{crea}\right) + \text{coef}_{\text{INR}} \ln\left(\text{INR}\right),$$

with serum bilirubin and serum creatinine measured in mg/dl. A specific MELD score proposes values for the intercept and coefficients, and bounds for the values of MELD biomarkers. A MELD score also has to propose how to calculate MELD scores for

candidates who received dialysis twice in the week before measurement of MELD biomarkers (henceforth "patients on biweekly dialysis"), since dialysis reduces measured creatinine levels. Eurotransplant currently uses UNOS-MELD for allocation, i.e.

$$6.43 + 3.78 \ln(\text{bilirubin}) + 9.57 \ln(\text{creatinine}) + 11.20 \ln(\text{INR}),$$

in which creatinine is capped at 4.0 mg/dl, a lower limit of 1.0 is imposed on all biomarkers, and creatinine is set to 4.0 mg/dl for patients on biweekly dialysis.

Various revisions of MELD have been proposed (e.g., see [41, 42, 56]). One alternative – that was developed specifically for Eurotransplant – is ReMELD [42], which calculates the score as

$$8.422 + 7.728 \ln(\text{bili}) + 3.446 \ln(\text{crea}) + 10.597 \ln(\text{INR}).$$

In calculating ReMELD scores, bilirubin is bounded between 0.3 and 27 mg/dl, the INR is bounded between 0.1 and 2.6, and creatinine is bounded between 0.7 and 2.5 mg/dl. Creatinine is also set to the upper cap of 2.5 mg/dl for patients on biweekly dialysis.

3.2.3 Revision *"from registration" vs. "revision from cross-section"*

In revising MELD, authors typically re-estimate MELD coefficients *"from registration"*. By this, we mean that authors use Cox proportional hazards models to model 90-day waiting list mortality after registration with adjustment for MELD biomarkers that were reported at listing. Coefficients for the MELD scoring system are then commonly derived by rescaling the estimated regression coefficients ($\widehat{\beta}$) to the UNOS-MELD scale. This rescaling is typically achieved by matching quantiles of the linear predictor to corresponding quantiles of UNOS-MELD scores (e.g., [41, 42]). This *"from registration"* approach ignores any MELD measurements recorded after registration, as well as patient deaths recorded more than 90 days after registration. We propose to avoid such waste of statistical information by revising MELD with a *"from cross-section"* approach. The key differences between these approaches are illustrated in Figure 3.1.

The *"from cross-section"* approach uses methodology developed by Gong and Schaubel [57], and models the remaining time-until-death from pre-specified calendar-time cross-sections (see right panel, Figure 3.1). This approach uses cross-section calendar times as the time origin, and the time elapsed since the cross-section date as the timescale. The coefficients are estimated with a Cox proportional hazards model that is stratified by the cross-section. At each cross-section only patients with an active registration (i.e., without non-transplantable status) are included in the analysis, and Cox models adjust only for biomarker information reported *before* the cross-section.

We point out that patients waiting at multiple calendar-time cross-sections contribute multiple observations to the Cox model fit (right panel, Figure 3.1). Thereby, revision of MELD is also affected by (i) waiting list deaths that occur more than 90 days after listing, and (ii) biomarker measurements taken after listing.

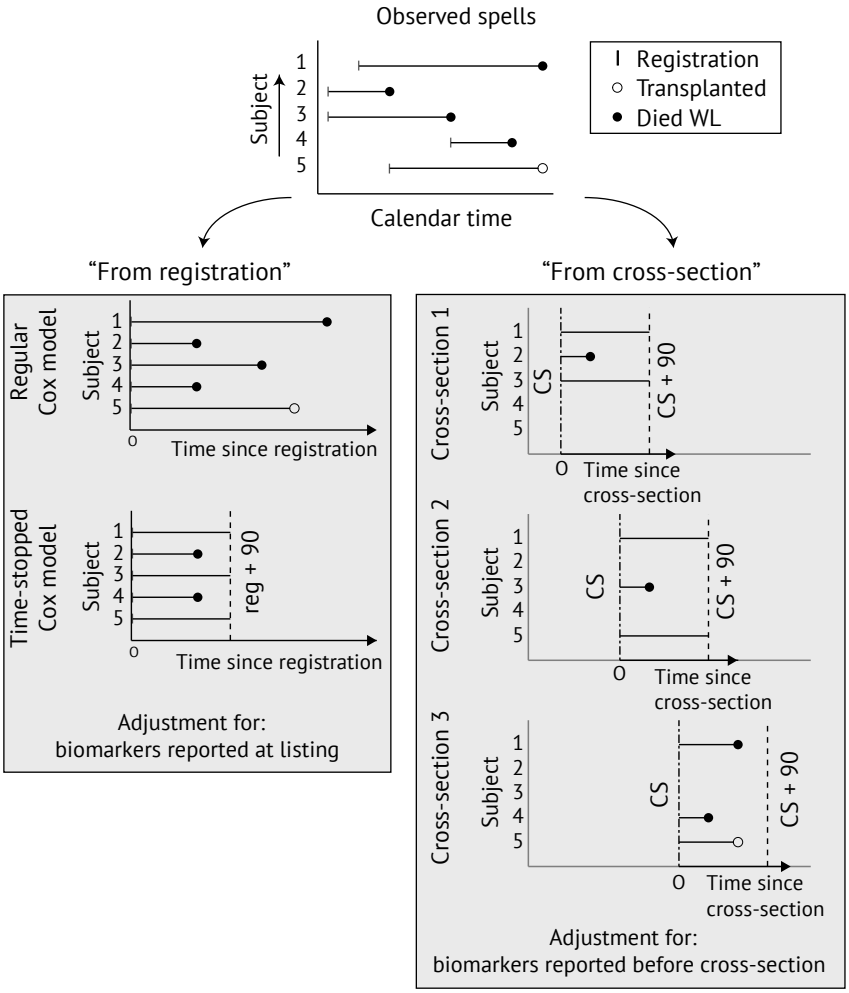


Figure 3.1: Illustration of from "registration" and "from cross-section" approaches to modeling waiting list mortality. For revision of MELD, typically 90-day time-stopped Cox models are used. The "from registration" approach (left) uses time since registration as the timescale and adjusts for biomarkers reported at registration. The "from cross-section" approach (right) models time-until-death from cross-section dates, pre-specified in calendar time, and adjusts for MELD biomarkers reported before the cross-section date. WL, waiting list.

In this chapter, we compare revision of MELD *"from registration"* to revision *"from cross-section"*. In revising MELD *"from registration"*, we stratify models by country of listing. For the *"from cross-section"* approach, we use weekly cross-sections from December 22, 2006 to December 31, 2019 and stratify Cox models by the candidate's country of listing and by cross-section. The candidate survival status 90 days after the cross-section date is used as an endpoint, and adjustment at each cross-section is for the last reported MELD biomarker values before the cross-section date.

3.2.4 Outcome definition

Time-until-death is modeled with 90-day time-stopped Cox PH models. Delisted patients who die within 90 days of deregistration are treated as if they had died on waiting list exit (as in [42]). Patients who were transplanted or delisted within 90 days are censored. Inverse probability censoring weighting (IPCW) is used to correct for selection bias due to transplantation and delisting.

3.2.5 Inverse probability censoring weighting to correct for dependent censoring

Consistent estimation of parameters β with a standard Cox PH model requires that the censoring process is independent of survival, conditional on covariates. This independent censoring assumption is violated for both the *"from registration"* and *"from cross-section"* approaches, because only MELD biomarkers reported at listing (or before the cross-section date) are included as covariates, while MELD biomarkers reported after listing (or cross-section) affect patient survival and transplantation/delisting rates. Gong and Schaubel proposed a procedure that can correct for the bias introduced by dependent censoring due to transplantation. This procedure weighs candidates by their inverse probability of having been transplanted between the cross-section and exit date (IPCW-T weights, T for transplantation). Such probabilities can be estimated using an extended Cox proportional hazards model, which uses the candidate's transplantation status as the outcome.

We expand in this chapter on Gong and Schaubel's approach by also constructing inverse probability censoring weights for delisting (IPCW delisting (IPCW-D) weights). Under the assumption that delisting and transplantation are conditionally independent, a joint inverse probability censoring weight can then be obtained by multiplying IPCW-T and IPCW-D weights (see also [59]). Details on how weights were constructed are included in Appendix A. In this chapter, we assess how IPCW affects revised MELD coefficients both *"from registration"* and *"from cross-section"*.

3.2.6 Adjustment variables, caps, and functional forms

Cox PH models adjust for variables present in MELD, i.e., serum bilirubin, serum creatinine, and the INR. Spline terms are used to assess whether the relation between log-transformed biomarkers and the mortality rate is approximately linear. Final models use logarithmic transformations for the biomarkers, with lower and upper limits for biomarkers optimized over regions where violation of log-linearity was visually apparent (as in Leise et al. [41] and Goudsmit et al. [42]).

On the Eurotransplant liver waiting list, more than 10% of patients receive biweekly dialysis, and measured creatinine is not used to calculate lab-MELD scores for these patients. To also ignore measured creatinine in revising MELD for these patients, we set creatinine to 1.0 mg/dl for patients on dialysis (leading to $\ln(1.0) = 0$ MELD points). Instead, we use whether the patient receives biweekly dialysis as an adjustment variable.

3.2.7 Development and validation cohorts

To enable revision and geographical validation for all Eurotransplant countries, we aimed to use a 70%/30% center-based split per country. Such a split was feasible for Germany (70%/30%), Belgium (70.1%/29.9%) Austria (62.6%/37.4%), and the Netherlands (74.3%/25.7%), but not for Hungary (1 center), Slovenia (1 center), and Croatia (1 large center, 2 very small centers). Therefore, Hungarian, Slovenian and Croatian patients (11% of the total cohort) were randomly split into 70%/30% development/validation cohorts.

All models – including those used to estimate inverse probability weights – were fitted on the development cohort only. The validation cohort was used to compare the newly developed score – which we name *DynReMELD* – to ReMELD and UNOS-MELD.

3.2.8 Comparison to UNOS-MELD and ReMELD

We revised MELD *"from registration"* and *"from cross-section"* both with and without IPCW. Without IPCW, MELD was also revised with ReMELD's linear predictor used as an offset. This enables assessment of whether revision of MELD on all cirrhotic patients yields a significantly different equation from ReMELD. We define *DynReMELD* as the equation obtained by quantile matching the linear predictor revised *"from cross-section"* with IPCW to quantiles of UNOS-MELD.

We compare the discrimination of MELD, ReMELD and DynReMELD using the c-index in the validation cohort. This c-index quantifies the degree to which patients with a higher score die earlier on the Eurotransplant waiting list. In the literature, the c-index is most commonly estimated with Harrell's c-index, which is a consistent estimator of the c-index in case of independent censoring. Because this assumption is implausible in liver transplantation, we use Gerd's c-index [60]. This c-index is a consistent estimator for the c-index provided that a consistent estimator of the conditional probability of remaining uncensored is available [60, 61]. We estimate Gerd's c-indices for two separate prediction tasks, namely (i) prediction of time-until-death from listing based on biomarkers reported at listing, and (ii) prediction of remaining time-until-death from calendar-time cross-sections based on the last reported MELD biomarkers.

Assessment of calibration for *DynReMELD* is complicated by the fact that models developed with IPCW are counterfactual prediction models, and it is not clear how to assess calibration for such models [62]. Instead of assessing calibration, we report estimates of absolute 90-day survival risks for *DynReMELD* estimated with and without IPCW. These 90-day survival estimates are of interest to Eurotransplant, as Eurotransplant uses them to convert awarded exception scores to the MELD scale.

3.3 Results

This study included 13,343 liver waiting list registrations for 13,274 patients[1] with cirrhosis waiting for a first liver transplant. We note that candidates with exception points (for example, HCC) were not included in our study cohort. We excluded 107 patients (<1%) because they reported impossible MELD biomarker values (e.g., zeroes for all biomarkers). Baseline characteristics of development and validation cohorts are included in Table 3.1.

[1] A small group of patients is removed from the waiting list without transplant, but later re-registered.

Table 3.1: Baseline characteristics and observed waiting list outcomes for the development and validation cohorts.

variable	level	development (n=9,288)	validation (n=4,055)	p-value
UNOS-MELD at listing	mean (Q1-Q3)	21.0 (13.0-28.0)	20.3 (12.0-28.0)	<0.001
bilirubin (mg/dl) at listing	mean (Q1-Q3)	7.53 (1.63-8.54)	7.06 (1.43-8.00)	0.009
creatinine (mg/dl) at listing	mean (Q1-Q3)	1.54 (0.810-1.75)	1.46 (0.803-1.60)	0.001
INR	mean (Q1-Q3)	1.79 (1.29-2.00)	1.75 (1.21-1.91)	0.024
biweekly dialysis	yes	1096 (11.8%)	504 (12.4%)	0.318
	no	8192 (88.2%)	3551 (87.6%)	
patient sex	male	6226 (67.0%)	2761 (68.1%)	0.239
	female	3062 (33.0%)	1294 (31.9%)	
age at listing	mean (Q1-Q3)	53.8 (49.0-61.0)	54.4 (49.0-61.0)	<0.001
cirrhosis aetiology	alcoholic	4949 (53.3%)	2292 (56.5%)	<0.001
	autoimmune/cryptogenic	1596 (17.2%)	619 (15.3%)	
	hepatitic	1712 (18.4%)	528 (13.0%)	
	metabolic/other	669 (7.2%)	484 (11.9%)	
	NAFLD	362 (3.9%)	132 (3.3%)	
outcome by December 31, 2019	waiting list death	2265 (24.4%)	980 (24.2%)	<0.001
	transplanted	5068 (54.6%)	2105 (51.9%)	
	removed (other)	700 (7.5%)	278 (6.9%)	
	recovered	610 (6.6%)	327 (8.1%)	
	waiting	645 (6.9%)	365 (9.0%)	

NAFLD; non-alcoholic fatty liver disease.

3.3.1 Number of MELD scores informing the revision of MELD

With cross-sections, 8,779 out of 9,288 (95%) patients in the development cohort are active at a cross-section date, and inform revision of MELD. The remaining 509 patients were transplanted, delisted, or marked non-transplantable before a cross-section date was reached (which means they exited the waiting list within at most 7 days of listing). We note that these 509 candidates do not inform revision of MELD from cross-section.

Biomarker measurements taken after listing are ignored by the *"from registration"* approach, while these measurements inform revision of MELD with a *"from cross-section"* approach. Table 3.2 shows that the number of unique MELD scores informing MELD revision increases about sevenfold with a *"from cross-section"* approach, from 9,264 to 67,433. The number of observed waiting list deaths and event rates also increase substantially with the *"from cross-section"* approach. For example, *"from cross-section"* the number of included MELD scores between 36 and 40 triples from 456 to 1,248, with 47% of these patients dying 90 days after cross-section, compared to only 31% *"from registration"*.

Table 3.2: Number of UNOS-MELD scores used for the model fit in the "from registration" approach, and "from cross-section" approach.

			event within 90 days	
		# usable MELD scores	death or removed unfit	transplanted
	from registration	9264	846 (9.1%)	2598 (28.0%)
	from cross-section	67433	5906 (8.8%)	11071 (16.4%)
By MELD				
6-14	from registration	3291	67 (2.0%)	389 (11.8%)
	from cross-section	28192	454 (1.6%)	1565 (5.6%)
15-24	from registration	4355	382 (8.8%)	1199 (27.5%)
	from cross-section	30806	2938 (9.5%)	5766 (18.7%)
25-35	from registration	1160	253 (21.8%)	711 (61.3%)
	from cross-section	7187	1922 (26.7%)	3144 (43.7%)
36-40	from registration	458	144 (31.4%)	299 (65.3%)
	from cross-section	1248	592 (47.4%)	596 (47.8%)

3.3.2 Revising the MELD formula using Cox models

Evidence-based caps were derived using the procedure proposed by Leise et al. [41]. This procedure involves estimating Cox proportional hazard models with different caps applied and choosing the caps that result in the maximal log-likelihood. The procedure is applied separately for each biomarker, with the biomarker under consideration modeled linearly and the other biomarkers modeled non-linearly using spline terms. Figure 3.2 summarizes the results of this procedure. The optimal caps were found to be 0.6–55 mg/dl for bilirubin, 0.8–2.5 mg/dl for serum creatinine, and 1.0–3.0 for the INR.

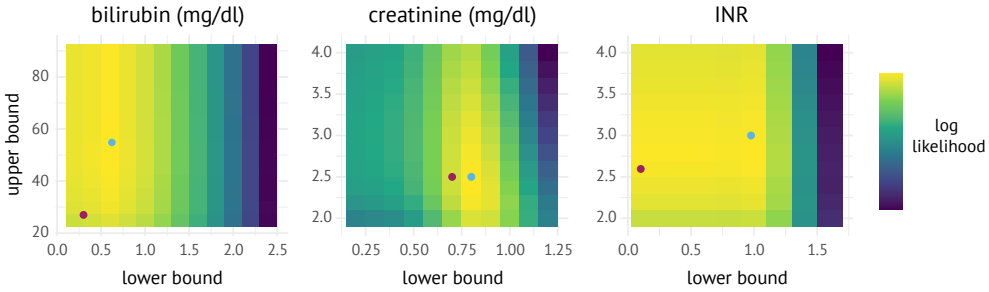


Figure 3.2: Heatmaps of the log-likelihood values for combinations of lower and upper bounds for serum bilirubin (mg/dl), serum creatinine (mg/dl), and the INR. Blue dots represent the optimal caps in the development data; purple dots represent the caps derived for ReMELD.

3.3.2.1 Coefficients revised from registration

Panel A of Table 3.3 shows MELD coefficients revised *"from registration"*. The first column shows that parameter estimates are jointly not significantly different from 0 (χ^2_3 = 4.1,p = 0.25) when using ReMELD's prognostic index as an offset. The insignificance of these estimates confirms that ReMELD adequately predicts 90-day mortality *"from registration"* for all cirrhotic patients. IPCW changes the biomarker coefficients only slightly (by less than a standard error).

3.3.2.2 Coefficients revised from cross-section

Panel B of Table 3.3 shows MELD coefficients revised *"from cross-section"*. The first column shows that coefficients are jointly significantly different from 0 with ReMELD used as an offset (χ^2_3 = 801,p < 0.001). Hence, ReMELD does not adequately predict 90-day mortality from cross-section. Estimated coefficients suggest ReMELD underestimates the effect of creatinine (z= 5.2, p < 0.001) and bilirubin (z = 6.1, p < 0.001), but not the INR ($z = 0.3, p = 0.76$). IPCW appears to increase MELD biomarker coefficients slightly (by less than a standard deviation).

Table 3.4 shows the relative weights put on the MELD components by the equation revised from cross-section with IPCW. These weights, originally defined by Sharma et al. [40], quantify the increase in MELD score resulting from a one-standard deviation increase in a given biomarker, relative to a one-standard deviation increase in all biomarkers. These weights also show that the refitted equation puts more weight on bilirubin (41%) than UNOS-MELD (36%) and ReMELD (37%), and puts less weight on the INR (28% vs. 32% for UNOS-MELD and 34% for ReMELD).

3.3.3 Definition of the DynReMELD score

Quantile matching of UNOS-MELD to the linear predictor revised *"from cross-section"* with IPCW (Table 3.3, panel B) yielded the following equation for *DynReMELD:*

$$4.14 \ln(\text{bilirubin}) + 9.12 \ln(\text{creatinine}) + 9.42 \ln(\text{INR}) + 8.50$$

with creatinine bounded between 0.8 and 2.5 mg/dl, bilirubin between 0.6 and 55 mg/dl, and the INR between 1.0 and 3.0. We calculate DynReMELD scores by setting creatinine to the upper cap (2.5 mg/dl) for patients on dialysis. This choice was made to keep DynReMELD in line with existing clinical implementations of MELD, and is relatively harmless because the creatinine level required to attain the same priority as biweekly dialysis is $\exp\left(\frac{1.86}{2.15}\right) \approx 2.4$ mg/dl (Table 3.3, Panel B, third column).

Table 3.3: Comparison of MELD coefficients for different model fits from registration (panel A) and "from cross-section" (panel B), for (1) revision with ReMELD's prognostic index as an offset, (2) revision without the offset, and (3) revision with IPCW.

panel A - from registration

	(1) ReMELD offset	(2) refitted, no IPCW	(3) refitted, IPCW
ln(bilirubin (mg/dL))	0.03 (0.05)	0.69 (0.05)	0.73 (0.06)
ln(creatinine[1] (mg/dL))	0.10 (0.09)	1.62 (0.01)	1.61 (0.12)
ln(INR)	0.12 (0.17)	2.02 (0.17)	2.19 (0.21)
biweekly dialysis		1.85 (0.12)	1.73 (0.13)
LR Test	4.1 (df = 3)	1482 (df = 4)	1883 (df = 4)

panel B - from cross-section

	(1) ReMELD offset	(2) refitted, no IPCW	(3) refitted, IPCW
ln(bilirubin (mg/dl))	0.22 (0.04)	0.92 (0.04)	0.97 (0.04)
ln(creatinine[1] (mg/dl))	0.40 (0.08)	2.07 (0.08)	2.15 (0.08)
ln(INR)	0.04 (0.13)	2.06 (0.13)	2.22 (0.15)
biweekly dialysis		1.87 (0.12)	1.86 (0.12)
LR Test	801 (df = 3)	22 197 (df = 4)	26 933 (df = 4)

[1] set to 1.0 mg/dl in case of biweekly dialysis

Table 3.4: Relative weights put on bilirubin, creatinine and INR by UNOS-MELD, ReMELD and DynReMELD. Relative weights were calculated $w_i = \frac{\beta_i \mathrm{SD}_i}{\sum_j \beta_j \mathrm{SD}_j}$, where β_i is the coefficient on biomarker i and SD_i its standard deviation in the development cohort.

biomarker	standard deviation	UNOS-MELD	ReMELD	DynReMELD
bilirubin (mg/dl)	0.85	0.36	0.37	0.41
creatinine (mg/dl)	0.29	0.32	0.29	0.31
INR	0.26	0.32	0.34	0.28

3.3.4 Predictive performance

Table 3.5 shows estimates of Gerd's c-index for UNOS-MELD, ReMELD and DynReMELD, for (a) predicting 90-day waiting list survival from listing based on biomarkers reported at listing, and (b) predicting 90-day waiting list survival from calendar-time cross-sections based on the biomarkers that were last reported for the candidate. The first panel shows c-indices evaluated for predicting 90-day waiting list survival from listing based on biomarkers reported at listing for UNOS-MELD, ReMELD and DynReMELD. Point estimates appear to slightly favor DynReMELD, but bootstrapped pairwise differences are not statistically significant. The second panel shows that DynReMELD outperforms UNOS-MELD and ReMELD when predicting 90-day waiting list survival based on

candidates' last reported biomarkers, with DynReMELD attaining higher c-indices ($p < 0.001$) in both development and validation cohorts. In the validation cohort, the c-index of DynReMELD (0.7895) is approximately 0.0040 higher than UNOS-MELD (0.7855), and 0.0015 higher than ReMELD (0.7879).

Table 3.5: C-indices at 90 days after listing with bootstrapped standard errors shown in brackets.

score	development	validation
time-until-death from listing, based on biomarkers at listing		
UNOS-MELD	0.8494 (0.008)	0.8637 (0.011)
ReMELD	0.8503 (0.008)	0.8623 (0.011)
DynReMELD	$0.8523^{\dagger}$ (0.008)	0.8641 (0.011)
remaining time-until-death from cross-sections, based on last reported biomarkers		
UNOS-MELD	0.8099 (0.002)	0.7855 (0.004)
ReMELD	0.8203^{***} (0.002)	0.7879 (0.004)
DynReMELD	$0.8217^{***\dagger\dagger\dagger}$ (0.002)	$0.7895^{***\dagger\dagger}$ (0.004)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, compared to UNOS-MELD
† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$, compared to ReMELD

3.3.5 Estimated absolute survival risk per MELD Score

This section reports absolute 90-day mortality risks for UNOS-MELD and DynReMELD estimated *"from cross-section"*. The estimation of mortality risks *"from cross-section"* is complicated by the fact that most individuals contribute multiple, correlated observations to the Cox model. In principle, this dependence can be broken by reporting cross-section-specific estimates of 90-day waiting list survival, but such estimates are imprecise. To partially break the dependence, we chose to estimate 90-day survival on a data set that included, for each reported set of biomarkers, only the first cross-section where the patient had an active waiting list status. Table 3.6 shows 90-day mortality risks estimated in this way.

The table shows that inverse probability censoring weighting increases estimates of absolute 90-day mortality risks by almost 10 percentage points. Failing to correct for informative censoring therefore results in mortality equivalents that understate the counterfactual mortality risk. This is of interest to Eurotransplant, as these mortality equivalents are used by Eurotransplant to assign exception points.

Candidates with multiple sets of biomarkers still contribute multiple observations to estimating 90-day mortality risks *from cross-section*. Dependence between such observations can bias estimates of the 90-day mortality risks. It is reassuring that point estimates of 90-day mortality risks *from registration* (see Table 3.7) are close to estimates *from cross-section* (generally less than 5 percentage point differences are observed).

Table 3.6: The 90-day mortality equivalents that are used by Eurotransplant, as well as estimates of the 90-day mortality risk per score. These were estimated with Cox models fitted "from cross-section", with adjustment for the MELD point score.

	UNOS-MELD		DynReMELD	
score	no IPCW	IPCW	no IPCW	IPCW
20	0.103 [0.098-0.108]	0.122 [0.117-0.127]	0.097 [0.092-0.101]	0.113 [0.108-0.118]
22	0.149 [0.142-0.155]	0.179 [0.171-0.186]	0.145 [0.139-0.151]	0.173 [0.166-0.180]
24	0.212 [0.202-0.221]	0.258 [0.247-0.270]	0.214 [0.205-0.224]	0.260 [0.249-0.271]
25	0.251 [0.239-0.263]	0.308 [0.294-0.322]	0.259 [0.247-0.271]	0.315 [0.301-0.329]
26	0.297 [0.282-0.311]	0.365 [0.348-0.382]	0.310 [0.295-0.325]	0.379 [0.361-0.396]
28	0.407 [0.385-0.428]	0.498 [0.473-0.522]	0.435 [0.413-0.457]	0.529 [0.503-0.553]
29	0.470 [0.444-0.495]	0.572 [0.544-0.599]	0.508 [0.482-0.533]	0.612 [0.583-0.639]
30	0.538 [0.508-0.566]	0.649 [0.617-0.678]	0.585 [0.555-0.613]	0.696 [0.664-0.725]
31	0.609 [0.576-0.640]	0.725 [0.691-0.755]	0.664 [0.632-0.694]	0.777 [0.744-0.805]
32	0.681 [0.645-0.714]	0.796 [0.762-0.825]	0.742 [0.708-0.772]	0.848 [0.817-0.874]
33	0.751 [0.714-0.784]	0.859 [0.827-0.885]	0.814 [0.780-0.842]	0.907 [0.880-0.927]
34	0.816 [0.780-0.846]	0.910 [0.883-0.931]	0.875 [0.845-0.900]	0.949 [0.929-0.964]
35	0.872 [0.839-0.899]	0.949 [0.927-0.964]	0.925 [0.899-0.943]	0.977 [0.963-0.985]
36	0.918 [0.890-0.940]	0.974 [0.960-0.984]	0.959 [0.941-0.972]	0.991 [0.984-0.995]
37	0.953 [0.930-0.968]	0.989 [0.980-0.994]	0.981 [0.969-0.989]	0.997 [0.994-0.999]
39	0.989 [0.979-0.994]	0.999 [0.997-1.000]	0.998 [0.995-0.999]	1.000 [1.000-1.000]
40	0.996 [0.991-0.998]	1.000 [0.999-1.000]	0.999 [0.998-1.000]	1.000 [1.000-1.000]

Table 3.7: Estimates of absolute 90-day mortality risks "from registration" and "from cross-section". Reported risks were estimated without IPCW.

	UNOS-MELD		DynReMELD	
score	from cross-section	from registration	from cross-section	from registration
20	0.103 [0.098-0.108]	0.136 [0.127-0.144]	0.097 [0.092-0.101]	0.125 [0.116-0.132]
22	0.149 [0.142-0.155]	0.187 [0.176-0.197]	0.145 [0.139-0.151]	0.176 [0.166-0.186]
24	0.212 [0.202-0.221]	0.254 [0.240-0.267]	0.214 [0.205-0.224]	0.247 [0.233-0.260]
26	0.297 [0.282-0.311]	0.339 [0.321-0.356]	0.310 [0.295-0.325]	0.339 [0.321-0.356]
28	0.407 [0.385-0.428]	0.443 [0.420-0.466]	0.435 [0.413-0.457]	0.453 [0.429-0.476]
30	0.538 [0.508-0.566]	0.564 [0.535-0.591]	0.585 [0.555-0.613]	0.586 [0.556-0.613]
32	0.681 [0.645-0.714]	0.691 [0.657-0.721]	0.742 [0.708-0.772]	0.724 [0.690-0.753]
34	0.816 [0.780-0.846]	0.810 [0.776-0.839]	0.875 [0.845-0.900]	0.847 [0.815-0.873]
36	0.918 [0.890-0.940]	0.905 [0.877-0.927]	0.959 [0.941-0.972]	0.935 [0.912-0.953]
40	0.996 [0.991-0.998]	0.991 [0.983-0.995]	0.999 [0.998-1.000]	0.997 [0.993-0.999]

3.4 Discussion

Prior literature revised the MELD score with liver waiting list candidate data *"from registration"* (e.g., [37, 20, 42]), which ignores any MELD biomarker measurements that are reported after registration and any waiting list death that occurs more than 90 days after registration. We used methodology proposed by Gong and Schaubel [57] to model waiting list mortality from calendar-time cross-sections, which can avoid such waste of statistical information in revising MELD. Moreover, we assessed how revision of MELD was affected by correction for selection bias by transplantation or delisting with inverse probability censoring weighting.

We showed that the *"from cross-section"* approach uses waiting list registry data substantially more efficiently, with the number of waiting list deaths and MELD scores informing revision of MELD increasing sevenfold compared to revision *"from registration"*. DynReMELD, the score obtained by quantile matching UNOS-MELD to the risk equation that was developed *"from cross-section"* with IPCW, attains significantly higher c-indices than ReMELD and UNOS-MELD in a geographical validation cohort for predicting remaining time-until-death based on last reported MELD biomarkers ($p < 0.001$). This is important for Eurotransplant, as Eurotransplant liver allocation prioritizes candidates based on their last reported MELD scores and not MELD at listing. In magnitude, the improvements in c-indices (0.0015 compared to ReMELD, and 0.0040 compared to UNOS-MELD) are comparable to the addition of serum sodium to ReMELD (approx. delta c-index of 0.0030) [42] and the addition of serum albumin to MELD 3.0 (delta c-index of 0.0028) [20]. MELD revision from cross-section with IPCW can thus improve urgency-based risk stratification. Our results suggest that the improvement is due to modeling time-remaining-until-death from cross-sections and not IPCW, as IPCW changed estimated coefficients only slightly.

We believe the main reason why DynReMELD outperforms ReMELD in geographical validation is that revision *"from cross-section"* uses Eurotransplant registry data substantially more efficiently than revision *"from registration"*, as the latter method only uses the MELD biomarkers that were reported at listing and the first 90 days of waiting list survival. This raises the question whether revision *"from registration"* cannot also be improved upon by using available registry data more efficiently. One way of doing this would be to include MELD biomarkers as time-varying covariates. However, because MELD biomarkers also increase inherently as part of the death process, use of biomarkers as time-varying covariates leads to issues of reverse causality. Follow-up data could, in principle, also be used more efficiently by not restricting revision *"from registration"* to the first 90 days after listing. However, we found that this leads to violations of the proportional hazards assumption for MELD biomarkers.

We also assessed how estimates of the 90-day mortality risks are affected by (a) revision *"from cross-section"* and (b) correcting for dependent censoring with IPCW. Revision *"from cross-section"* does not meaningfully change estimated 90-day mortality risks, with risks estimated *"from cross-section"* differing by less than 5 percent points from risks estimated *"from registration"*. This means that we do not find that there are meaningful differences in 90-day mortality risks between a candidate who reported a particular MELD score at listing and another one who reported that same score as part of a MELD recertification. Mitigation of selection bias with IPCW did increase estimated 90-day waiting list mortality risks for both UNOS-MELD and DynReMELD by 10 percentage points. Failure to account for informative censoring by transplantation/delisting thus leads to an underestimation of 90-day mortality equivalents, which can be problematic as Eurotransplant uses these estimates to assign MELD scores for candidates who receive exception points.

Eurotransplant currently consists of 38 liver transplant centers located in seven European countries. These centers differ structurally in terms of patient populations, liver transplantation volumes, and willingness to accept donors of marginal quality. A strength of our study is that we assigned candidates to either the development or validation cohort based on their center of listing, which means that the predictive performance of DynReMELD was evaluated in a cohort independent from the centers on which the score was developed.

A limitation of our work is that revision of MELD *"from cross-section"* only uses the last MELD biomarkers reported before the cross-section date. Eurotransplant uses these same biomarker measurements for allocation, but they may be outdated representations of a patient's health status. Alternatively, one could model the evolution of MELD biomarkers over time with linear mixed models, and use a best linear unbiased predictions (BLUP) of biomarkers at every cross-section time. This BLUP approach was first proposed by Maziarz et al. [63] for landmarking, a statistical technique which bears similarities to Gong and Schaubel's approach. We did not use a BLUP approach to revise MELD, since irregular spacing of MELD measurements complicates modeling the biomarker process. Deployment of BLUP models would also be practically challenging for Eurotransplant. Moreover, MELD scores for patients with significant 90-day mortality risks are rarely outdated as Eurotransplant requires frequent re-certification of MELD scores for sicker patients. For example, MELD scores are on average 12 days old at cross-section for candidates with MELD scores ranging between 20 and 25 (corresponding to a 90-day mortality risk of 10 to 25%), and 3 days old for MELD scores greater than 25 (which corresponds to a mortality risk of 25% or greater).

A final limitation of our work is that DynReMELD was based only on bilirubin, creatinine and the INR, while updated versions of MELD exist that use additional biomarkers. Future work could focus on revising these UNOS-MELD alternatives *"from cross-section"*. This was not pursued in this chapter, because serum sodium and albumin are unavailable in Eurotransplant registry data for most patients on the liver waiting list.

Chapter 4

Sex disparity in liver allocation within Eurotransplant

An article based on this chapter has appeared in *American Journal of Transplantation*, de Ferrante, H.C., De Rosner-van Rosmalen M., Smeulders, B.M.L., Vogelaar, S., Spieksma, F.C.R., 2025, 10.1016/j.ajt.2024.06.018 [64]

Abstract

On Eurotransplant's liver waiting list, females are relatively more likely to die than males, and they are relatively less likely to be transplanted. With adult candidates listed for liver transplantation between 2007 and 2019 (n=21,170), we study whether such sex disparity is inherent to the Model for End-Stage Liver Disease (MELD) scoring system, or the indirect result of a small candidate body size limiting access to transplantation. We use Cox proportional hazards models to quantify (i) the direct effect of sex on waiting list mortality, independent of sex's effect through MELD scores, and (ii) the direct effect of sex on the transplant rate, independent of the effect of sex through MELD and candidate body size. We find that adjusted waiting list mortality hazard ratios for female sex are insignificant (HR = 1.03, 95% CI: 0.88–1.20), which means that we lack indications that MELD systematically underestimates the waiting list mortality rates for females. transplant rates are estimated to be 25% lower for females than for males in unadjusted analyses (HR = 0.74, 95% CI: 0.71–0.77), but hazard ratios become insignificant after adjustment for mediators, most importantly candidate height and weight (HR = 0.98, 95% CI: 0.93–1.04). Sex disparity in Eurotransplant thus appears to be largely a consequence of the lower transplant rates for females, which are explained by differences in body size between males and females.

4.1 Introduction

Prior research has shown that females are disadvantaged under MELD-based liver allocation compared to males [38, 65–67]. There are two leading explanations for such sex disparity in MELD-based liver allocation [68], which we refer to as the *"GFR hypothesis"* and the *"size mismatch hypothesis"*.

The GFR hypothesis proposes that MELD is biased against female candidates because MELD is based on serum creatinine instead of glomerular filtration rates (GFR). With the same serum creatinine level, the GFRs of females are lower than the GFRs of males [69]. MELD would therefore systematically underestimate the 90-day mortality risks for females. The GFR hypothesis has frequently been invoked to propose alternatives to MELD which replace serum creatinine with sex-specific estimates of the glomerular filtration rate [70–72]. These alternatives award one to three extra points on the MELD scale to female liver transplant candidates [68, 73–75].

The second hypothesis relates to donor-recipient size matching in liver transplantation. Such size matching is crucial in liver transplantation because (i) the liver must anatomically fit within the recipient's abdominal cavity, and (ii) the liver has to meet the candidate's metabolic demands. The size-mismatch hypothesis suggests that transplant candidates with a smaller stature – who are predominantly female – are disadvantaged in MELD-based liver allocation because donor-recipient size mismatch would require them to turn down liver offers more frequently. This size mismatch hypothesis has received less attention in the literature than the GFR hypothesis. Empirical evidence for it comes from Lai et al. (2010), who showed that the lower transplant rates for females in the United States are largely explained by differences in candidate height [66]. Further evidence comes from Allen et al. (2018), who showed with competing risk analyses that height indirectly explains most of the increased waiting list deaths observed in female candidates [75]. A 2023 study by Sneiders et al. on retrospective data from Eurotransplant has also linked a low body weight to adverse liver waiting list outcomes [76].

In this chapter, we use causal mediation analysis to study the GFR hypothesis and the size mismatch hypothesis. A first goal is to study whether there is evidence of a direct effect of sex on the waiting list mortality rate, independently from MELD, as is implied by the GFR hypothesis. A second goal is to quantify sex disparities in transplantation rates, and to assess whether such disparities are mediated by candidate body size – as is implied by the size mismatch hypothesis. To address these research questions, we use retrospective data from Eurotransplant.

4.2 Materials and methods

4.2.1 Study population

Candidates who were activated on the liver waiting list between January 1, 2007 and December 31, 2019, were considered for inclusion. We study sex disparity in two subpopulations. The first subpopulation consists of candidates with common chronic indications for liver transplantation. This population was obtained by excluding pediatric candidates (<16 years), candidates with rare metabolic diseases or rare exceptions (awarded <15 times per year), those with acute liver failure, and those waiting for a living donor transplantation, a repeat liver transplantation, or a multi-organ transplantation. The second subpopulation consists of candidates with cirrhosis who did not have HCC, which is the patient group for which MELD was originally developed and validated [34]. This population was obtained by additionally excluding patients with exception points, cholestatic liver disease, polycystic liver disease, and hepatocellular carcinoma. We refer to this second population as "non-HCC candidates with cirrhosis".

4.2.2 MELD scores

Liver allocation in Eurotransplant is based on match-MELD scores, i.e., the maximum of a candidate's lab-MELD score (UNOS-MELD) and their exception scores. Exception scores can be obtained for candidates with specific indications who meet predefined eligibility criteria (standardized exceptions, SEs), or through case-by-case review from national audit groups (non-standardized exceptions, NSEs). Granted exceptions award an initial 90-day mortality equivalent. The awarded mortality equivalents increase with every 90 days of waiting time for most exceptions. For this study, candidates with five types of exceptions were included: hepatocellular carcinoma (HCC), polycystic liver disease, biliary sepsis, primary sclerosing cholangitis, and NSEs. Other exceptions were excluded and are awarded, on average, less than 15 times per year. The amount of points awarded for these exceptions varies by country, and they can be found in the Eurotransplant liver manual [58].

Several alternatives to UNOS-MELD have been proposed, which include MELD-Na, ReMELD-Na and MELD 3.0. MELD 3.0 adds serum sodium, and was used for liver allocation by UNOS from January 2016 to July 2023. ReMELD-Na is a revision of MELD-Na on Eurotransplant registry data [42]. MELD 3.0 adds serum sodium, serum albumin and female sex to the MELD formula, and was adopted for liver allocation by UNOS in July 2023. There are indications that MELD-Na has exacerbated sex disparity [75], while MELD 3.0 aims to rectify sex disparity by explicitly awarding points for female sex [20]. This motivated us to also quantify sex disparity in mortality rates for these three alternative scores.

Serum sodium and serum albumin are required to calculate these three MELD alternatives. A problem is that values for these biomarkers are missing for most candidates, as they were voluntarily reportable in Eurotransplant in the study period. In this chapter, main analyses for MELD-Na, ReMELD-Na and MELD 3.0 are done on subgroups for whom the required biomarkers were available at listing (i.e., complete case analysis). We compare this with multiple imputation (MI) as a sensitivity check.

4.2.3 Statistical analyses

Mediation analysis is used to (i) quantify the total and the controlled direct effect of sex on transplant rates (Section 4.2.3.1), and (ii) to quantify the controlled direct effect of candidate sex on the waiting list mortality rate, independent of MELD (Section 4.2.3.2). For both analyses, directed acyclic graphs (DAGs) were constructed to guide our modeling strategy and communicate visually our causal assumptions [77].

4.2.3.1 Mediation analysis for the transplant rate

The left-hand side of Figure 4.1 shows the DAG for transplantation analyses. In this model, sex is the exposure and transplantation (TXP) is the outcome. The candidate's MELD score and body size (height or weight) both represent mediators of the relation between sex and transplantation. MELD acts as a mediator because sex affects MELD through differences in serum creatinine (as proposed by the GFR hypothesis), and MELD is used to prioritize candidates for liver transplantation. Body size acts as a mediator, because sex influences height and weight, and because having a smaller stature limits a candidate's access to transplantation due to size mismatch (the size mismatch hypothesis).

To identify the controlled direct effect of sex on transplantation, all back-door paths from sex to transplantation must be blocked. Adjusting for MELD and body size is not sufficient for this, because doing so can open back-door paths via common causes of the mediators (MELD / body size) and the outcome (transplantation). U1-type variables (see Figure 4.1) represent common causes of MELD and the transplant rate. These include whether the candidate receives biweekly dialysis, their exception score, their age, and their disease group, which affect both a candidate's MELD score and their center's willingness to accept and transplant a liver offer. U2-type variables represent common causes of a candidate's body size and their transplant rate. Two important U2-type variables are frailty (which is associated with a lower weight, and a possible contraindication for liver transplant) and diabetes (which is associated with a higher weight, and a possible contraindication).

In principle, adjusting for MELD, body size, U1-type variables, and U2-type variables would be sufficient to close all back-door paths. Unfortunately, frailty and diabetes

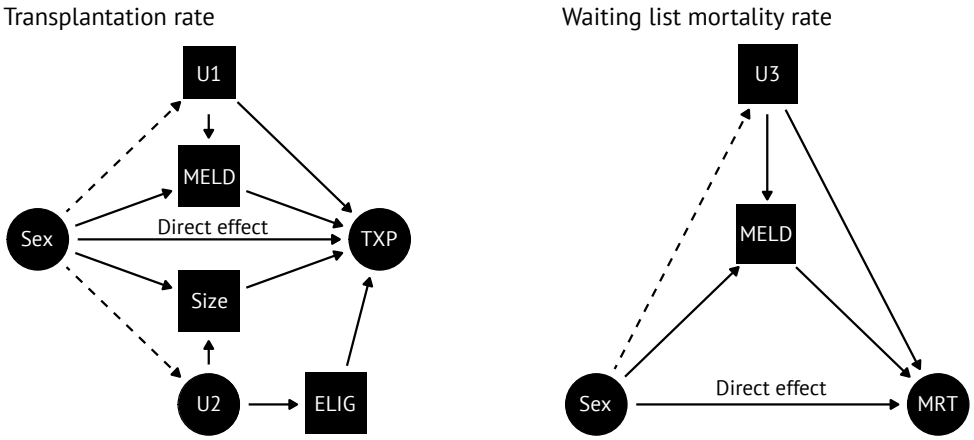


Figure 4.1: Directed acyclic graphs (DAGs) for mediation analyses of the effect of sex on transplantation (TXP, left) and the effect of sex on pre-transplant mortality rates (MRT, right). Squares indicate the minimal sufficient adjustment set required to identify the controlled direct effect of sex on the outcome. U1, U2, and U3 represent common causes of the mediator-outcome relations. Dotted arrows indicate that sex is allowed to affect U1, U2, and U3; their presence or absence does not impact the identification of the controlled direct effect under our identification strategy.

(U2-type variables) are not reported to Eurotransplant, which makes this adjustment strategy infeasible. We instead assume that U2-type variables only affect the transplantation rate through candidate eligibility (ELIG) for transplantation. Under this assumption, we can alternatively identify the controlled direct effect of sex on transplantation by adjusting for U1, MELD, size, and ELIG (time-varying variable).

We consider this assumption plausible for two reasons. Firstly, our patient cohort is restricted to candidates who were actually activated on the liver waiting list. Such waiting list activation represents a strong signal that the candidate is deemed fit enough for transplantation by their center, as frail or overweight candidates would be required to improve their health status before waiting list activation (for example in consultation with a dietitian). Secondly, in our experience, centers tend to report candidates who are temporarily unavailable for transplantation because of a poor health status as non-transplantable to Eurotransplant. Temporary non-transplantability (ELIG) is thus a strong proxy for U2-type variables that is observed by Eurotransplant, and can be adjusted for in our analysis.

To estimate the effects of sex on transplant rates, we use Cox proportional hazards models which use time since waiting list activation as the timescale. For quantification of the direct effect of sex on the transplant rate, we adjust match-MELD, body size (height, weight, or both), and U1-type variables (dialysis, type exception received, candidate age, and disease group / cirrhosis etiology through stratification). Transplantation eligibility is explicitly controlled for by adjusting for whether a candidate is temporarily non-transplantable (NT), and implicitly controlled for by only including actively waiting listed candidates in the analysis (which signals that the candidate is deemed eligible for liver transplantation by the transplant center). In our analyses, we further adjust for pure predictors of the transplantation rate (country of listing through stratification, blood group, time spent non-transplantable). The following variables are time-varying: primary disease group, non-transplantable (NT) status, time spent NT (separately for too good / too bad / other), the match MELD, type of exception, and receival of dialysis twice within a week before the last reported lab-MELD score. Continuous variables are adjusted for with natural cubic spline transformations with 4 degrees of freedom.

Three sensitivity checks are done. The first is to examine whether there are sex-height and sex-weight interactions. This sensitivity check is motivated by findings by Allen et al., who reported that the relation between candidate height and the relative transplant rate differs significantly by candidate sex in the United States [75]. The other sensitivity checks are related to Eurotransplant-specific allocation mechanisms that give physicians freedom to choose candidates for transplantation. Two such mechanisms are allocation through extended allocation (15% of placements) and competitive rescue allocation (10% of placements), which Eurotransplant jointly refers to as *non-standard* allocation mechanisms. To rule out that sex disparities are the result of physician preferences in non-standard allocation, we repeat analyses with transplantation through standard allocation as the outcome (our second sensitivity check). Another mechanism that allows centers to freely choose a living waiting list candidate for transplantation are center offers. As the third sensitivity check, we repeat the analysis on candidates listed in countries without center offers (Germany and the Netherlands).

4.2.3.2 Mediation analyses for the waiting list mortality rate

The right-hand side of Figure 4.1 shows the DAG for mortality analyses. Sex is the exposure, and waiting list mortality is the outcome. We are interested in the controlled direct effect of sex on the mortality rate, not mediated by lab-MELD. This requires control for sex, lab-MELD, and confounders of the relation between lab-MELD and mortality (U3-type variables). We estimate this direct effect of sex on mortality rates with Cox proportional hazards models, with adjustment for lab-MELD at listing (UNOS-MELD, MELD-Na, ReMELD-Na, or MELD 3.0) and U3-type variables (disease group through stratification, biweekly dialysis, candidate age, and type exception). Models are

additionally stratified by the candidate's country of listing. Waiting list death is used as the outcome. Candidates who died within 90 days of delisting are treated as a waiting list death. Candidates still waiting 90 days after waiting list activation are censored, as are candidates who were transplanted or delisted within 90 days of listing.

Several sensitivity checks are conducted. Firstly, we repeat the analyses in datasets where serum sodium and albumin at listing were imputed with multiple imputation (MI). Secondly, we compare to using death / removed unfit as a combined outcome. Thirdly, Lai et al. reported that sex disparity increased with renal dysfunction [66], motivating us to repeat the analyses in candidates with high MELD scores (MELD ⩾18, 31% of candidates) and elevated creatinine (⩾1.0 mg/dl, 39% of candidates). Finally, to exclude that impending waiting list deaths are prevented with center offers, we repeat the analysis in Dutch and German candidates only.

4.2.3.3 Correction for dependent censoring in mortality analyses

The standard Cox PH model assumes that censoring is non-informative, which means that conditional on covariates, censored candidates have similar expected survival as non-censored candidates. In mortality analyses, candidates are censored at transplantation while adjustment is for the MELD score reported at listing. The non-informative censoring assumption then entails that transplanted candidates and not (yet) transplanted candidates with the same MELD score at listing would face similar mortality risks if they had remained on the waiting list.

This assumption is implausible for the Eurotransplant liver waiting list, as Eurotransplant ranks candidates by their last reported MELD score and not MELD at listing. Of the two candidates with the same MELD score at listing, the candidate with a higher last reported MELD score would thus face a higher mortality and higher transplant rate. In expectation, transplanted candidates therefore have lower without-transplant survival than non-transplanted candidates, which violates the non-informative censoring assumption.

One can correct for this bias with inverse probability censoring weighting (IPCW), as was previously applied in studying sex disparity by Wood et al. [78]. In this chapter, we use statistical methodology developed by Gong and Schaubel to account for selection bias by transplantation [79]. Details on this procedure are included in Appendix A. A sensitivity check is included to assess how IPCW affects estimates of the direct effects of sex.

4.2.3.4 Multiple imputation

Multiple imputation is used as a sensitivity check in quantifying the direct effect of sex on the waiting list mortality rate. For this, we used multiple imputation with chained equations (MICE) to impute serum sodium and serum albumin values at listing using predictive mean matching, constructing M=10 completed datasets. After imputing serum sodium and albumin, MELD-Na, MELD 3.0, and ReMELD-Na were calculated using the imputed values. We included the event indicator and estimated baseline cumulative hazard in the imputation procedure, as recommended by White et al. [80]. MICE yields unbiased estimation of regression coefficients under a missing at random (MAR) assumption. This assumption would be violated if a candidate's actual serum sodium or albumin value influenced whether that value was available at Eurotransplant. Such a violation is implausible in our setting, as missingness arises almost entirely from center-level policies: some centers always report serum sodium and albumin to Eurotransplant, while other centers never report these biomarkers. The availability of these laboratory values is not determined by the candidate's true biomarker level, but exclusively by their center's reporting policy for serum sodium and albumin.

4.3 Results

This study considered 31,756 candidate listings for inclusion (see Figure 4.2). From these registrations, we excluded pediatric candidates (n=1,652), listings for repeat liver transplantation (n=3,865) or multi-organ transplantation (n=1,523), candidates with acute liver failure or a High Urgency (HU) status (n=1,753), and candidates with rare metabolic diseases or rare exceptions (n=755). The main cohort consisted of 21,188 listings belonging to 21,170 candidates.

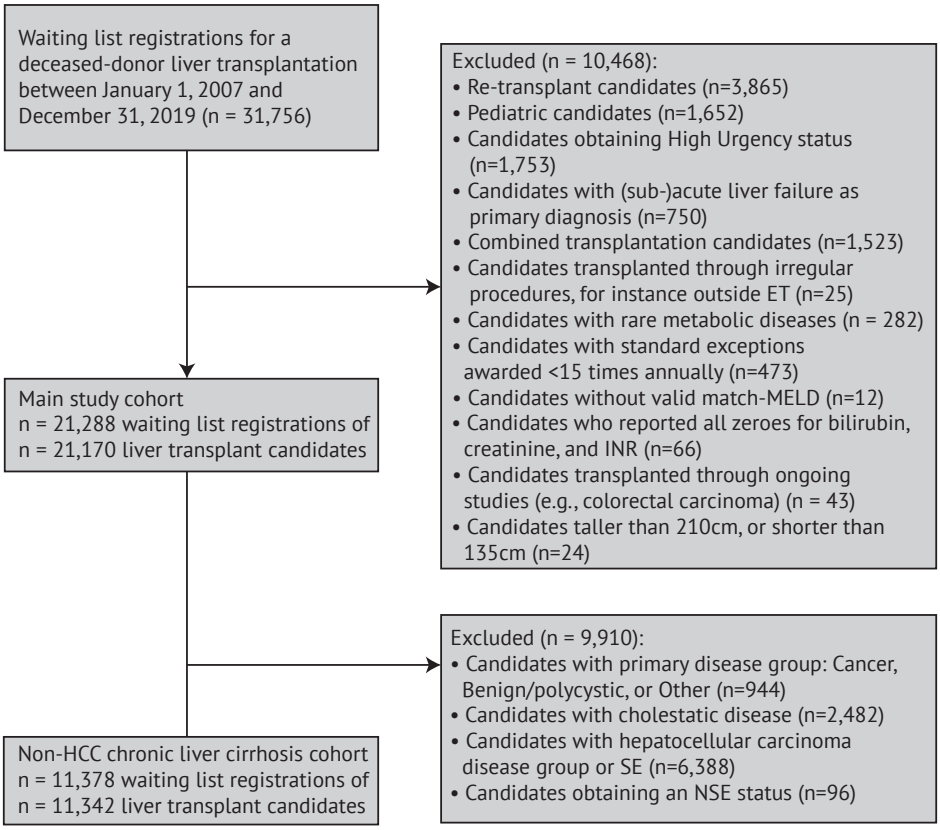


Figure 4.2: Flow diagram for how the main study cohort and the subpopulation of non-HCC candidates with cirrhosis were selected from all candidates listed between January 1, 2007 and December 31, 2019.

Table 4.1 describes the baseline characteristics of candidates included in the main cohort, of which 6,597 (31%) are female and 14,573 (69%) are male. We use standardized mean differences (SMD) to compare the distributions of baseline variables across sexes, with SMD greater than 0.10 interpreted as meaningful imbalance. On average, females are 2 years younger (SMD: 0.19), 12 cm shorter (SMD: 1.8) and 15 kg lighter (SMD: 1.0) than males. Females also have on average 0.13 mg/dl lower serum creatinine at listing (SMD: 0.20) and 0.6 mg/dl higher bilirubin (SMD: 0.08). Despite these differences, the calculated UNOS-MELD scores are similar between the sexes (SMD: 0.00). There is sex imbalance in etiologies of end-stage liver disease (SMD: 0.49), with notably fewer females listed with HCC (11.8% of females compared to 21% of males). Relatively fewer females receive exception points (SMD: 0.32).

Table 4.1: Baseline characteristics of primary liver transplant candidates included in this study. For candidates with multiple listings only the first listing was used (n=118).

variable	level	females (n=6,597)	males (n=14,573)	SMD
disease group	cirrhosis	3,771 (57.2%)	7,976 (54.7%)	0.487
	benign tumor or PLD	306 (4.6%)	62 (0.4%)	
	cancer	129 (2.0%)	172 (1.2%)	
	cholestatic	1,092 (16.6%)	1,350 (9.3%)	
	HCC	1,096 (16.6%)	4,654 (31.9%)	
	metabolic	72 (1.1%)	233 (1.6%)	
	other	131 (2.0%)	126 (0.9%)	
exception at listing	cholestatic	163 (2.5%)	324 (2.2%)	0.318
	HCC	780 (11.8%)	3,180 (21.8%)	
	NSE	115 (1.7%)	168 (1.2%)	
	PLD	127 (1.9%)	24 (0.2%)	
	none	5,412 (82.0%)	10,877 (74.6%)	
match-MELD	mean [Q1-Q3]	16 [10-20]	16 [10-20]	0.002
lab-MELD	mean [Q1-Q3]	15.8 [9.7-19.6]	15.7 [10.2-18.8]	0.025
MELD-Na	mean [Q1-Q3]	17.4 [11.0-22.4]	17.4 [11.0-22.0]	0.007
ReMELD-Na	mean [Q1-Q3]	14.9 [9.3-19.4]	15.3 [10.3-19.3]	0.058
bilirubin (mg/dl)	mean [Q1-Q3]	5.51 [1.10-6.08]	4.87 [1.17-4.66]	0.083
creatinine (mg/dl)	mean [Q1-Q3]	1.00 [0.67-1.10]	1.13 [0.78-1.22]	0.200
INR	mean [Q1-Q3]	1.49 [1.13-1.60]	1.47 [1.17-1.60]	0.038
serum sodium (mmol/l)	mean [Q1-Q3]	137 [134-140]	136 [134-140]	0.044
	missing	4,238 (64.2%)	9,118 (62.6%)	
serum albumin (g/dl)	mean [Q1-Q3]	3.3 [2.9-3.8]	3.3 [2.8-3.7]	0.073
	missing	5,219 (79.1%)	11,502 (78.9%)	
dialysis twice in the last week		171 (2.6%)	332 (2.3%)	0.020
candidate height (cm)	mean [Q1-Q3]	165 [160-169]	177 [172-182]	1761
candidate weight (kg)	mean [Q1-Q3]	69 [59-77]	84 [74-94]	1020
age at registration (years)	mean [Q1-Q3]	53 [47-61]	55 [50-62]	0.185
exit reason (90 days)	transplanted	1,458 (22.1%)	4,266 (29.3%)	
	died	514 (7.8%)	979 (6.7%)	
	waiting	4,464 (67.7%)	8,927 (61.3%)	
	censored	82 (1.2%)	159 (1.1%)	
	removed	79 (1.2%)	242 (1.7%)	
exit reason (1 year)	transplanted	2,764 (41.9%)	7,844 (53.8%)	
	died	904 (13.7%)	1,755 (12.0%)	
	waiting	2,381 (36.1%)	3,765 (25.8%)	
	censored	272 (4.1%)	419 (2.9%)	
	removed	276 (4.2%)	790 (5.4%)	

Abbreviations: PLD, polycystic liver disease; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease sodium; NSE, non-standard exception; ReMELD-Na, refitted MELD-Na for Eurotransplant; SMD, standardized mean difference.

In terms of outcomes, Table 4.1 shows that relatively fewer females than males are transplanted 90 days after listing (22% vs. 29%), and relatively more females die within 90 days of listing (7.8% vs. 6.7%). This sex disparity has increased one year after listing, with only 41.9% of females transplanted compared to 53.8% of males, and 13.7% of female candidates having died on the waiting list compared to 12.0% of males.

The cohort of non-HCC candidates with cirrhosis (n=11,342) was obtained by excluding candidates with HCC (n=6,388), non-cirrhotic indications for liver transplantation (n=3,426) or NSEs (n=96) (see Figure 4.2). Baseline characteristics of this subpopulation are reported in Table 4.2. Also among this group, relatively fewer females are transplanted (26% vs. 32% of males) and relatively more females die (10.5% vs. 9.8%) within 90 days of listing.

Figure 4.3 shows the distributions of the time spent by candidates on the waiting list until waiting list exit (death, delisting, or transplantation), separately for exception and non-exception patients. Whether or not they receive exception points, females spend approximately 75 more days on the waiting list than males.

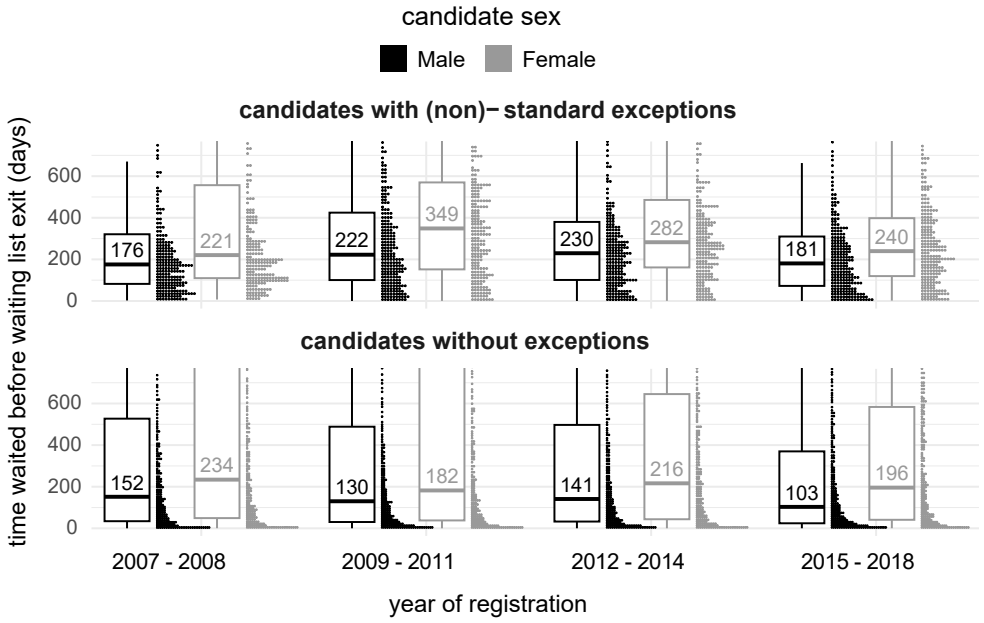


Figure 4.3: Distributions of the time spent on the waiting list until waiting list exit (transplantation, death, or delisting), by sex and year of waiting list inclusion. The top panel shows waiting times for candidates with (non-)standard exceptions, the bottom panel for candidates without exceptions. Distributions were visualized with quantile dotplots, using 250 quantiles. The numbers displayed in the boxplots are the median number of days spent on the waiting list per group.

Table 4.2: Baseline characteristics for the subcohort of non-HCC candidates with cirrhosis.

variable	level	females (n=3,667)	males (n=7,675)	SMD
cirrhosis aetiology	alcoholic	1,686 (46.0%)	4,547 (59.2%)	0.37
	autoimmune/cryptogenic	933 (25.4%)	961 (12.5%)	
	NAFLD[a]	189 (5.2%)	264 (3.4%)	
	hepatitis B	166 (4.5%)	435 (5.7%)	
	hepatitis C	438 (11.9%)	870 (11.3%)	
	metabolic/other/unknown	255 (7.0%)	598 (7.8%)	
lab-MELD	mean [Q1-Q3]	18.5 [12.4-22.3]	18.5 [13.0-21.9]	0.005
MELD-Na	mean [Q1-Q3]	19.8 [13.9-24.7]	20.2 [14.8-24.5]	0.043
ReMELD-Na	mean [Q1-Q3]	17.2 [12.1-21.6]	17.9 [13.4-21.7]	0.100
bilirubin (mg/dl)	mean [Q1-Q3]	6.64 [1.64-7.56]	6.17 [1.70-6.20]	0.055
creatinine (mg/dl)	mean [Q1-Q3]	1.12 [0.71-1.26]	1.26 [0.81-1.40]	0.182
INR	mean [Q1-Q3]	1.66 [1.28-1.80]	1.63 [1.30-1.79]	0.037
serum sodium (mmol/l)	mean [Q1-Q3]	136 [133-139]	135 [132-139]	0.102
	missing	2,180 (59.4%)	4,398 (57.3%)	
serum albumin (g/dl)	mean [Q1-Q3]	3.2 [2.8-3.6]	3.2 [2.7-3.6]	0.099
	missing	2,697 (73.5%)	5,512 (71.8%)	
dialysis twice in last week		137 (3.7%)	262 (3.4%)	0.017
candidate height (cm)	mean [Q1-Q3]	165 [160-169]	177 [172-182]	1809
candidate weight (kg)	mean [Q1-Q3]	69 [59-77]	85 [74-95]	0.99
age at registration (years)	mean [Q1-Q3]	54 [48-61]	55 [49-61]	0.102
exit reason (90 days)	transplanted	947 (25.8%)	2,458 (32.0%)	
	died	380 (10.4%)	756 (9.9%)	
	waiting	2,272 (62.0%)	4,319 (56.3%)	
	censored	39 (1.1%)	75 (1.0%)	
	removed	29 (0.8%)	67 (0.9%)	
exit reason (1 year)	transplanted	1,424 (38.8%)	3,851 (50.2%)	
	died	643 (17.5%)	1,290 (16.8%)	
	waiting	1,365 (37.2%)	2,149 (28.0%)	
	censored	126 (3.4%)	179 (2.3%)	
	removed	109 (3.0%)	206 (2.7%)	

[a] Many candidates with NAFLD have likely been registered under the autoimmune/cryptogenic disease code, as NAFLD could only be reported via free text during the study period.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease sodium; ReMELD-Na, refitted MELD-Na for Eurotransplant; SMD, standardized mean difference.

4.3.1 Transplantation analyses

Figure 4.4 shows the estimated transplantation hazard ratios (HRs) for female sex. The unadjusted effect of sex in the full cohort (top panel) suggest that the transplant rates are approximately 25% lower for females (HR = 0.74, 95% CI: 0.71–0.76). When adjusting for candidate body size (weight + height) plus confounders of the mediator-outcome relations, no sex difference in transplant rates is found (HR = 0.98, 95% CI: 0.93–1.04). Similar results are found in non-HCC candidates with cirrhosis (bottom panel), with 22% lower transplant rates for females in total (HR = 0.78, 95% CI: 0.74–0.82) but no sex difference in transplant rates when adjusting for body size, MELD, and confounders of both mediator-outcome relations (HR = 1.00, 95% CI: 0.93–1.07).

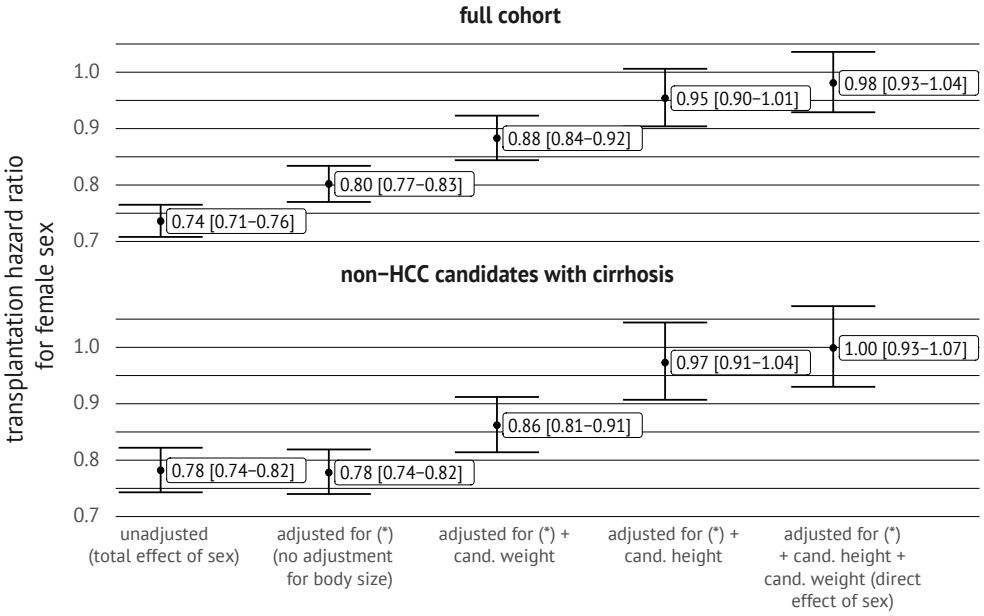


Figure 4.4: Estimates for the transplantation hazard ratios for female sex with 95% confidence intervals, in the full cohort (top panel) and the subpopulation of non-HCC candidates with cirrhosis (bottom panel).

Table 4.3 shows the results of sensitivity checks for this analysis. The results are qualitatively similar when using transplantation through standard allocation as the outcome (first row), and when estimating transplantation hazard ratios in the countries without center offers (second row); in both cases, the estimated hazard ratios are non-significant after adjustment for mediators and confounders of the mediator-outcome relation. Figure 4.5 shows estimated spline terms for the relation between the relative transplantation rate and height or weight, separately for males and females. For both sexes, a lower height or weight is associated with a reduced transplant rate. Height-sex (p=0.48) and weight-sex (p=0.11) interactions are insignificant in ANOVA tests.

Table 4.3: Sensitivity checks for the transplantation hazard ratio of female sex. Numbers in square brackets are 95% confidence intervals.

sensitivity check	unadjusted effect of sex (total effect)	adjusted [a] + height and weight (direct effect of sex)
full cohort, non-rescue transplantation as the outcome	0.783 [0.749-0.819]	0.991 [0.930-1.055]
full cohort restricted to Germany and the Netherlands (no center offers)	0.735 [0.700-0.772]	0.962 [0.994-1.066]

[a] Variables adjusted for are the following: match-MELD, disease group, biweekly dialysis, type of (non) standardized exception received, candidate blood group, candidate age, and time spent non-transplantable.

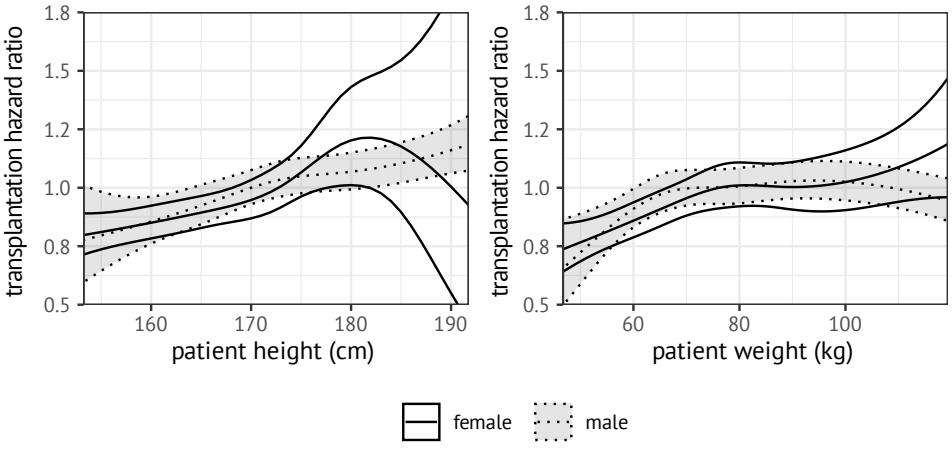


Figure 4.5: Estimated relations between candidate height and the relative transplant rate, and candidate weight and the relative transplant rate, separately for males and females. These relations were estimated with cubic spline terms with 4 degrees of freedom.

4.3.2 Waiting list mortality analyses

Figure 4.6 shows estimates of the mortality hazard ratios for female sex, adjusting for the lab-MELD score and confounders of the relation between lab-MELD and the waiting list mortality rate. The waiting list mortality hazard ratios include unity when adjusting for UNOS-MELD, both in the entire cohort (HR = 1.03, 95% CI: 0.88–1.20) and in non-HCC candidates with cirrhosis (HR 0.94, 95% CI: 0.80–1.11). Point estimates appear slightly increased for MELD-Na and ReMELD-Na and decreased for MELD 3.0 (but confidence intervals include the null).

Table 4.4 reports sensitivity checks for these results. With multiple imputation (MI), point estimates for MELD-Na, ReMELD-Na and MELD 3.0 are closer to the null. For MELD 3.0, the estimated hazard ratios become statistically significant, both in the full cohort (HR = 0.83, 95% CI: 0.71–0.97) and in non-HCC candidates with cirrhosis (HR = 0.77, 95% CI: 0.66–0.91). Results are similar when using waiting list death / removed unfit as a joint outcome (third row). Point estimates are slightly increased in candidates with high UNOS-MELD scores or elevated creatinine, but remain statistically insignificant (except for ReMELD-Na in high-MELD candidates, 95% CI: 1.02–1.59, fourth row). Results change little when estimated in Germany and the Netherlands, the Eurotransplant member countries without center offers (sixth row). Not correcting for dependent censoring with IPCW also appears to slightly increase point estimates.

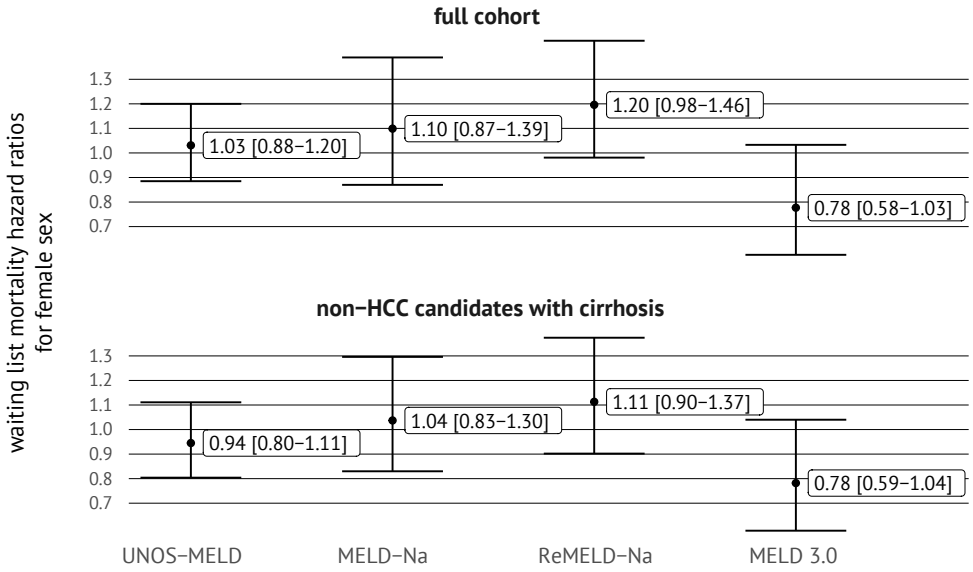


Figure 4.6: Estimates for waiting list mortality hazard ratios for female sex with 95% confidence intervals, with adjustment for a lab-MELD score (UNOS-MELD, MELD-Na, ReMELD-Na or MELD 3.0) and confounders of the relation between lab-MELD and waiting list mortality.

Table 4.4: Sensitivity checks for the waiting list mortality analyses. Shown are the hazard ratios and 95% confidence intervals, estimated using IPCW with adjustment for MELD, and confounders of the relation between the MELD score and the transplant rate (candidate age, disease group, type exception and biweekly dialysis).

sensitivity check	UNOS-MELD	MELD-Na	ReMELD-Na	MELD 3.0
full cohort, with MI	1.031 [0.885-1.200]	1.038 [0.895-1.204]	1.110 [0.958-1.285]	0.831 [0.715-0.966]
non-HCC candidates with cirrhosis, with MI	0.945 [0.804-1.111]	0.956 [0.817-1.120]	1.021 [0.872-1.196]	0.773 [0.658-0.907]
waitlist death or removed unfit as outcome	1.002 [0.864-1.162]	1.097 [0.874-1.376]	1.190 [0.981-1.443]	0.778 [0.589-1.028]
full cohort, MELD 18+	1.068 [0.908-1.257]	1.180 [0.920-1.513]	1.273 [1.022-1.587]	0.866 [0.632-1.187]
full cohort, creatinine $\geq$ 1.0 mg/dl	1.118 [0.921-1.357]	1.199 [0.889-1.615]	1.249 [0.965-1.617]	0.745 [0.509-1.089]
recipient-driven countries	1.018 [0.847-1.224]	1.131 [0.832-1.539]	1.225 [0.948-1.583]	0.645 [0.427-0.974]
full cohort, no IPCW	1.097 [0.981-1.226]	1.182 [0.994-1.404]	1.226 [1.034-1.455]	0.898 [0.700-1.151]
non-HCC candidates with cirrhosis, no IPCW	1.034 [0.909-1.176]	1.098 [0.908-1.328]	1.135 [0.939-1.372]	0.837 [0.639-1.096]

Abbreviations: HCC, hepatocellular carcinoma; IPCW, inverse probability censoring weighting; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease sodium; MI, multiple imputation; ReMELD-Na, refitted MELD-Na for Eurotransplant; UNOS, United Network for Organ Sharing.

4.3.3 Liver offer acceptance behavior

To explore potential explanations for the reduced transplant rates among candidates with a small stature, match lists generated between December 31, 2006 and December 31, 2019, were exported from the Eurotransplant database. Figure 4.7 shows the distributions of weights and heights for these match lists, separately for candidates and donors. The plot shows that candidates and donors have broadly similar height and weight distributions, with considerable overlap. Figure 4.8 shows univariate associations between graft offer acceptance and donor-candidate body size differences. The figure suggests that size mismatch is indeed associated with declining an organ offer. These associations are stronger if the candidate weighs substantially lighter than the donor, or if the candidate is substantially shorter.

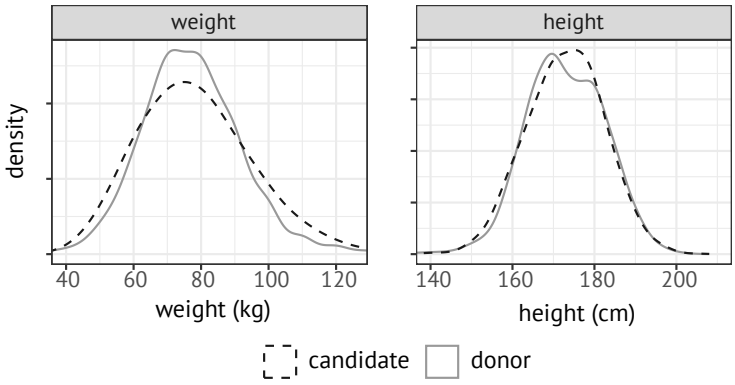


Figure 4.7: Distributions of weights and heights for candidates and donors who appeared on Eurotransplant match lists between December 31, 2006 and December 31, 2019.

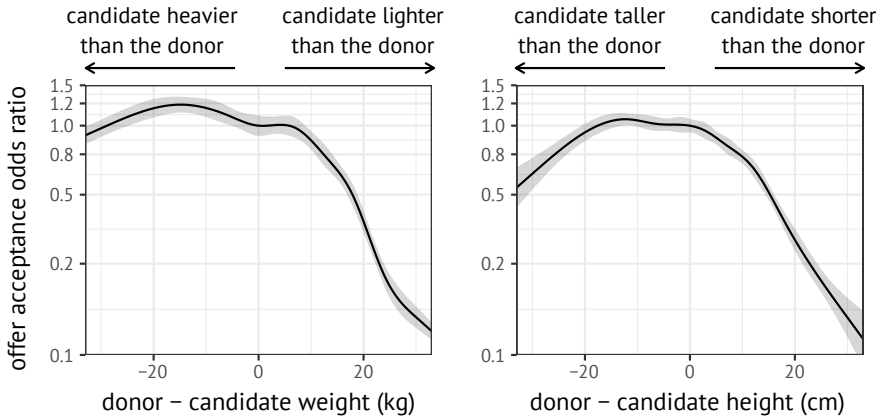


Figure 4.8: Univariate relations between the offer acceptance rate and the difference in donor and candidate body size, quantified through height or weight. These univariate relations were estimated with logistic models, using spline terms with 8 degrees of freedom.

4.4 Discussion

This chapter reports on sex disparity in liver waiting list outcomes in Eurotransplant. Despite being listed at similar UNOS-MELD scores as males, relatively fewer females are transplanted, and relatively more females die within 90 days of listing. Similar results have been described in other geographic regions [38, 65–67].

We find that the transplant rates of females are approximately 25% lower than those of males in Eurotransplant, both in the full cohort and among non-HCC candidates with cirrhosis. This disparity disappears when adjusting for candidate height and weight, with the estimated 95% confidence intervals for the transplantation hazard ratio of 0.93–1.04 in the full cohort, and 0.93–1.07 in non-HCC candidates with cirrhosis. Interactions of body size with candidate sex are also insignificant, which suggests that small body sizes are equally disadvantageous to males and females. We interpret these findings as evidence for the size mismatch hypothesis: the smaller stature of female candidates limits their chances of finding a suitable liver transplant, which results in sex disparity in liver waiting list outcomes.

A potential explanation for the size mismatch hypothesis comes from the analysis of the offer acceptance behavior of transplant centers: while weights and heights are similarly distributed in the donor and patient populations, univariate analyses of offer acceptance rates suggest that offers are more likely to be accepted for transplantation when the donor has a similar or smaller body size than the patient. As a result, there is high demand for small organs, which disadvantages the small-statured patients who depend on such offers for transplantation. Because these small-statured patients are predominantly female, this also results in sex disparity.

Existing analyses from the United States have reported that females remain disadvantaged after adjustment for age, height and weight, while our analyses suggest that height and weight fully mediate the effect of sex on the transplantation rate. This discrepancy could be explained by the fact that these existing studies have adjusted for continuous variables either linearly [65, 67] or with quantiles [66, 81], instead of with non-linear spline transformations. We find that such adjustment strategies bias hazard ratios downwards (results not shown).

Regarding waiting list mortality rates, we find that the hazard ratios for female sex include the null when adjusting for UNOS-MELD and relevant confounders, both in the full cohort and in non-HCC candidates with cirrhosis. We thus find no evidence that females face higher waiting list mortality rates than males when at the same UNOS-MELD score. In other words, we find no evidence for the GFR hypothesis in our main analyses.

Studies from the United States have reported higher waiting list mortality rates for females when adjusting for MELD or its biomarkers. For example, Moylan et al. (2008) report a statistically significant hazard ratio of 1.09 for female sex when adjusting for UNOS-MELD [38], Wood et al. (2021) report that without-transplant survival is 0 to 5 percentage lower for females with MELD-Na [78], and Kim et al. (2021) find a hazard ratio of 1.23 in developing MELD 3.0 [20]. Compared to these estimates, the point estimates we obtained in the main analyses with adjustment for UNOS-MELD are low (1.03 in the full cohort, and 0.94 in non-HCC candidates with cirrhosis).

Our sensitivity checks lead to several potential explanations for this discrepancy. Firstly, candidates in the United States are sicker than candidates in Eurotransplant, with median MELD-Na scores at transplantation of 27 in OPTN [82] compared to 21 in Eurotransplant. We find that re-estimation of the mortality hazard ratios in subgroups with higher MELD scores increases the estimated hazard ratio for female sex slightly. Secondly, 61% of our cohort has low creatinine (<1.0 mg/dl). For these candidates, a systematically lower creatinine for females would not translate into lower MELD scores, because MELD scores are calculated with a lower limit of 1.0 mg/dl for creatinine. When we re-estimate waiting list mortality hazard ratios in the 39% of candidates with elevated creatinine (⩾1.0 mg/dl), the point estimate increases to 1.12, which is more in line with existing literature (although it remains statistically insignificant). We also find that not correcting for dependent censoring by transplantation increases the point estimates slightly.

A final difference is that our main results pertain to UNOS-MELD, whereas recent studies adjust for scores which prioritize additionally on serum sodium (MELD-Na) or serum sodium and serum albumin (MELD 3.0). With adjustment for MELD-Na or ReMELD-Na instead of UNOS-MELD, our point estimates of the waiting list mortality hazard ratio also increase to ±1.10 for MELD-Na and ±1.20 for ReMELD-Na. They even become statistically significant in some sensitivity checks for ReMELD-Na. These point estimates suggest that the mortality rate of females is underestimated by 0.5 to 1 points on the MELD scale. When adjusting for MELD 3.0 instead of UNOS-MELD, the point estimates for the mortality hazard ratio are below 1. This suggests that the 1.33 extra points awarded to females in MELD 3.0 may overestimate the mortality rates for females in Eurotransplant.

A clinical implication of our findings is that transplant centers should be aware of the disadvantaged position of small-statured candidates when deciding whether to accept a liver offer. Eurotransplant should also strive to rectify the sex disparity that results from its current liver allocation algorithm. In the literature, the GFR hypothesis is frequently invoked to motivate awarding points for female sex, either explicitly [20] or indirectly by replacing creatinine in MELD by sex-specific estimates of the GFR [70–72]. By awarding points to females, such scores reduce sex disparity. However, they do not target a smaller stature, which represents the root cause of sex disparity according to our analysis.

A more efficient way of addressing sex disparity could involve giving extra priority to small-statured candidates, regardless of their sex. We point out that such an allocation score cannot be developed solely based on a Cox proportional hazards model which uses waiting list death as the outcome and which adjusts for MELD biomarkers and candidate height. The reason for this is that body size only indirectly results in waiting list deaths by limiting the transplant rate of small-statured candidates. This indirect mechanism is not captured when modeling the waiting list mortality with Cox PH models; rectifying sex disparity due to the size mismatch hypothesis will require a different approach.

One such approach could be to develop allocation scores with simulation, as is done by Wood et al. [78]. A relevant proposal in this regard is a study by Bernards et al., who assessed the effects of explicitly awarding points to short candidates with Liver Simulation Allocation Model (LSAM) simulations [83]. They report that awarding 1 extra MELD point to the 8% shortest waiting list candidates (<156cm) is sufficient to result in equalized outcomes across height groups in the United States. A similar simulation study should be conducted for Eurotransplant, to assess how sex disparity on the liver waiting list can be rectified.

Our study also has several limitations. Firstly, validity of the mediation analyses depends on two unverifiable assumptions: no unmeasured confounding of mediator-outcome relations, and the assumption that confounders of the body size-transplantation rate act through candidate eligibility. Secondly, we rely on accuracy of information in the Eurotransplant database. Thirdly, our quantifications of the direct effect of sex on mortality are potentially underpowered when adjusting for sodium-based MELD scores, as serum sodium is missing for most candidates in Eurotransplant registry data. Fourthly, serum urea is not available in the Eurotransplant database such that comparison to allocation scores which replace creatinine with estimated GFRs was not possible.

In conclusion, this chapter has described sex disparities in liver waiting list outcomes in Eurotransplant. In contrast to the existing literature, we lack evidence that UNOS-MELD systematically underestimates pre-transplant mortality rates in females. Our analysis instead suggests that transplantation rates are lower in females because of their smaller stature. In addition to externally validating MELD 3.0 and GEMA-Na, Eurotransplant should consider prioritizing small-statured candidates to rectify sex disparity.

Chapter 5

The ELAS simulator

An article based on this chapter has appeared in *Operations Research, Data Analytics and Logistics*, de Ferrante, H.C., de Rosner-van Rosmalen M., Smeulders, B.M.L., Spieksma, F.C.R, Vogelaar, S., 2025, 10.1016/j.ordal.2025.200476 [84]

Abstract

In this chapter, we present the ELAS simulator. This discrete-event simulator was built for the Eurotransplant Liver Allocation System (ELAS), which is used by Eurotransplant to allocate the livers of deceased organ donors. The simulator closely mimics ELAS and has been made publicly available to (i) provide transparency regarding the models Eurotransplant uses to evaluate liver allocation policies, and (ii) facilitate collaborations with policymakers, scientists, and other stakeholders in evaluating policy changes to ELAS. In this chapter, we describe the design and the modules of the ELAS simulator. One of the included modules is the obligation module, which is instrumental in ensuring that international cooperation in liver allocation benefits all member countries of Eurotransplant.

By default, the ELAS simulator simulates liver allocation according to the actual Eurotransplant allocation rules. Stochastic processes, such as graft offer acceptance behavior and listing for a repeat transplantation, are approximated with statistical models that were calibrated on data retrieved from the Eurotransplant database. We validate the ELAS simulator by comparing simulated waiting list outcomes to historically observed waiting list outcomes between January 1, 2016, and December 31, 2019.

The ELAS simulator has a modular design, which gives end users maximal control over the rules and assumptions under which Eurotransplant liver allocation is simulated. This makes the simulator useful for policy evaluation, as we illustrate with two clinically motivated case studies. For these case studies, we collaborated with hepatologists and transplantation surgeons from two liver advisory committees affiliated with Eurotransplant.

5.1 Introduction

The Eurotransplant Liver and Intestine Advisory Committee (ELIAC) plays a key role in developing liver allocation policies in Eurotransplant; ELIAC monitors the Eurotransplant liver allocation system (ELAS) and makes proposals to the Eurotransplant Board on how to improve liver allocation rules according to the latest medical insights. Since the introduction of MELD-based liver allocation in December 2006, ELIAC has brought forward several issues with ELAS; for example, it has been reported that ELAS overprioritizes candidates who receive exception points [54], and that MELD disadvantages candidates with small body sizes [76]. Despite the identification of such issues, the current liver allocation system has changed little since the initiation of MELD-based liver allocation in Eurotransplant.

An important reason for the lack of policy change in ELAS is that Eurotransplant has lacked tools that can help map the impact of allocation policy changes on liver waiting list outcomes. There is a long history of using operations research and discrete-event simulation for this purpose, with early work including the development of the UNOS Liver Allocation Model (ULAM) for U.S. liver allocation [85].

In the United States, this work has culminated in the Simulation Allocation Models (SAMs) [86], which is a family of discrete-event simulators maintained by the Scientific Registry of Transplant Recipients (SRTR). LSAM – SRTR's tool for liver allocation [86] – is used routinely by the scientific community and policymakers to study alternative liver allocation rules. For example, LSAM has been used to study the impact of expanding MELD with extra biomarkers [37, 20], the impact of alternative geographic sharing rules [36, 87–90], and the impact of policy changes that improve access to transplantation for specific patient groups such as pediatric and female patients [91, 92, 83]. Other organ allocation organizations also routinely note the use of simulators for evaluation of new liver allocation policies, for example in France [93] and the United Kingdom [19].

Simulation can thus play a key role in moving Eurotransplant's liver allocation system forward. This was recognized by Eurotransplant in the late 1990s, when computer simulations motivated a switch from ABO blood group-identical liver allocation to the restricted ABO-compatible matching policies that are still in use today [14]. However, a simulation model developed specifically for Eurotransplant has not been available.

Existing simulation models are also not applicable to Eurotransplant. Such models typically simulate allocation for a single patient population, while Eurotransplant needs to balance the interests of the populations from its eight member countries. Moreover, existing models typically implement allocation rules that are specific to the country for which the simulator was designed. For example, allocation rules in LSAM emphasize the physical distance between the donor and transplantation candidate, as geographical sharing in the United States is primarily constrained by these physical distances.

Conversely, in Eurotransplant, geographical sharing is mostly impeded by country borders. ELAS therefore gives priority to candidates who are located in the same country as the donor, and implements a mechanism that ensures that livers transplanted with priority across country borders are repaid to the exporting country. These mechanisms have not been implemented for existing simulation models, making these models a poor fit for Eurotransplant.

This has motivated us to develop a discrete-event simulator that is tailored to ELAS. We refer to this simulator as the *ELAS simulator*. Code for the ELAS simulator is implemented in Python and made publicly available together with synthetic data.[1] By default, the ELAS simulator simulates liver allocation according to Eurotransplant allocation rules. The modular design of the simulator enables end users to use the simulator for policy evaluation.

It is clear that the development of the ELAS simulation could not be done, and was not done, in isolation. Multiple stakeholders were involved in various phases of the project. In particular, members of the Eurotransplant Liver and Intestine Advisory Committee (ELIAC), who are hepatologists and transplant surgeons who represent Eurotransplant's member countries, have given feedback on numerous occasions on the conceptual design of the simulator; also, at Eurotransplant Annual Meetings, physicians and transplantation coordinators have commented on various aspects of the simulator.

This chapter is structured as follows. In Section 5.2, we give a description of Eurotransplant's liver allocation system (ELAS). In Section 5.3 we discuss the design of the ELAS simulator, and give an overview of the general flow of the simulations. In Section 5.4, we describe important modules of the ELAS simulator, each of which emulates a key aspect of the liver allocation process. In Section 5.5, we discuss verification and validation of the ELAS simulator. In Section 5.6, we illustrate with two clinically motivated case studies that the ELAS simulator is useful for policy evaluation. We conclude and discuss in Section 5.7.

5.2 The Eurotransplant Liver Allocation System (ELAS)

We provide a simplified description of ELAS below. Comprehensive descriptions of ELAS are available elsewhere (see [35, 58]). Fundamental to ELAS is the laboratory MELD (lab-MELD) score, which quantifies a candidate's 90-day waiting list mortality risk based on serum bilirubin, serum creatinine, and the INR [34]. However, candidate prioritization is not solely based on lab-MELD scores, because certain patient groups would be underserved by such an allocation.

[1] http://github.com/hansdeferrante/Eurotransplant_ELAS_simulator

Specifically, ELAS also prioritizes candidates with:

- the High Urgency (HU) status,
- the Approved Combined Organ (ACO) status that is given to candidates who require a combined transplantation of a liver with a heart, lung, pancreas, or intestine,
- pediatric MELD (PED-MELD) scores that are assigned automatically to candidates of pediatric age,[2] and
- Standard and Non-Standard exception (SE / NSE) MELD scores that can be awarded to patients who require access to liver transplantation for other reasons than a high short-term mortality risk.

When a liver becomes available for allocation, Eurotransplant runs the liver *match algorithm* against a central database in which candidates for liver transplantation are registered. This computer algorithm implements the prioritization mechanisms of ELAS. Based on all the waiting candidates, this algorithm returns a list of candidates eligible to receive the liver graft. This match list is ordered based on donor and candidate characteristics, and the order determines the sequence in which candidates are offered the liver graft by Eurotransplant. An actual Eurotransplant liver match list for an adult blood group A donor reported from the Netherlands is shown in Table 5.1.

At the highest level, the Eurotransplant match list order is based on *match tiers*. Candidates in higher tiers have priority over candidates in lower tiers. The first ELAS tier consists of candidates with the High Urgency (HU) status. The second tier consists of candidates with the Approved Combined Organ (ACO) status. Candidates with HU or ACO status are given international priority in Eurotransplant. A payback mechanism is used for grafts accepted internationally in HU and ACO tiers. Specifically, international HU / ACO transplantations create an *obligation* for the receiving country to offer the next available liver within the same blood group to the donor country until the obligation is settled (see Section 5.4.2 for more information). Candidates without an HU or ACO status are referred to as *elective* candidates in Eurotransplant. These elective candidates are ranked in the remaining tiers.

Whether candidates appear on the match list and the rank at which they appear is jointly determined by patient *eligibility* criteria (blood groups), *ranking* criteria (MELD, pediatric status, donor/recipient blood group combination), and *filtering* criteria (patients can indicate that they do not want to be considered for certain donors with allocation profiles). These patient eligibility criteria, ranking criteria, and filtering criteria are multi-factorial and differ between the member countries of Eurotransplant.

[2] younger than 18 in all countries since March 2025.

Table 5.1: Example of a match list for an adult liver graft donated by a blood group A donor in the Netherlands. Under the restricted ABO blood group rules, candidates with blood group A and AB are eligible for this liver. At the moment of allocation, the Netherlands has an obligation to return a blood group A liver graft to Croatia, resulting in Croatian candidates being ranked higher than all Dutch candidates in the elective tiers. This specific liver graft was declined by all Croatian and Dutch candidates and finally transplanted into a Belgian recipient.

tier	offered to	candidate country	rank	match-MELD	lab-MELD	PED-MELD	(N)SE-MELD	cand. blood group	offer accepted?
HU	patient	Austria	1		25	22		AB	No
elective	center (29 patients)	Croatia	2						No
	patient	Netherlands	3	28	16		28	A	No
			4	22	22			A	No
			5	20	8		20	A	No
			6	20	20			A	No
			7	17	17			A	No
			8	17	17			A	No
			9	16	16			A	No
			10	15	15			A	No
			11	14	14			A	No
			12	14	14			AB	No
			13	14	14			A	No
			14	13	13			A	No
			15	13	13			A	No
			16	9	9			A	No
			17	9	9			A	No
			18	9	9			A	No
			19	8	8			A	No
			20	8	8			A	No
			21	6	6			A	No
		Belgium	22	35	35			A	Yes

A rule common to all countries is that elective candidates listed in the same country as the donor have priority over elective candidates listed in other countries. Other factors that affect the ranking of candidates include the combination of the donor and candidate blood groups, whether the donor and/or candidate are pediatric, whether the adult is low-weight (<55 kg), as well as where the candidate is located geographically relative to the donor (same center, same region, same country, or different countries). The order of the match list in elective tiers is also affected by the existence of obligations. For example, when the match list shown in Table 5.1 was created, the Netherlands had an obligation to offer a blood group A liver to Croatia. Consequently, in the elective tier all Croatian candidates were ranked above the Dutch candidates. The most important factor for ranking candidates in elective tiers is the *match*-MELD score (see Table 5.1). This match-MELD score is the maximum of a candidate's lab-MELD score and any received exception points (PED-MELD, SE-MELD, or NSE-MELD). We point out that exceptional scores (SE-MELDs or NSE-MELDs) are valid only for national allocation or when an offer is based on an obligation to pay back a liver.

Most offers in ELAS are *recipient-driven*, which means that Eurotransplant offers the liver graft to a named candidate [35]. Under specific circumstances, Eurotransplant makes a *center offer* to candidates, which means that centers are allowed to select any blood group compatible candidate from their waiting list for transplantation. Offers to Croatia based on an obligation are an example of center offers, which explains why a single offer to 29 Croatian patients appears on the match list in Table 5.1. The position of center offers on the match list is determined by the highest rank that is achieved by any candidate listed in the center in elective tiers. We note that national regulations differ on when offers are center-driven. These rules are described in the Eurotransplant liver manual (see [58]).

The order of the match list determines the sequence in which Eurotransplant contacts centers in *standard allocation*. In cases where the loss of a transplantable graft is anticipated, Eurotransplant can deviate from this allocation order (see [35, 58]). For example, Eurotransplant is allowed to start an *extended allocation* procedure 2 hours before the planned explantation procedure (1 hour in Germany). Centers in the vicinity of the donor center are then contacted, and are given 30 minutes to propose up to two candidates for transplantation. The proposed candidate with the highest rank on the match list is then selected for transplantation. If extended allocation is unsuccessful, Eurotransplant can also offer the graft to centers located further away from the donor center on a first-come, first-served basis with *competitive rescue allocation*. In total, 20% to 25% of liver grafts are transplanted through *non-standard* allocation mechanisms [35]. Extended allocation accounts for the majority of these placements.

5.3 The design of the ELAS simulator

The ELAS simulator was designed to enable end users to assess the impact of changes to the liver allocation rules on waiting list mortality rates and access to transplantation. We follow existing literature by using discrete-event simulation (DES) for this purpose [94, 85, 95, 86]. With DES, complex processes are analyzed by determining how system states are affected by a sequence of discrete events. Within the ELAS simulator, the system states are (i) the statuses of transplant candidates (whether they remain alive, their last known MELD score, their accrued waiting time, and other information used in allocation), and (ii) obligations to return a graft. The discrete events which affect these system states are (i) patient events, which directly modify the candidate's state (e.g. updates to the MELD score), and (ii) liver donation events, which generally lead to the transplantation of a candidate, and which may result in the creation or redemption of an obligation to pay back a liver graft.

Which candidate is transplanted when a donor becomes available is affected by several stochastic processes. One such process is the graft offer acceptance behavior of the transplant centers. Such behavior plays a key role in liver allocation because the transplant centers frequently decline liver grafts they deem unsuitable for their candidates.[3] Another stochastic process is that recipients of a liver transplant can experience a early graft failure, and may be listed for a repeat transplantation. To accurately simulate outcomes of the Eurotransplant liver allocation process, the ELAS simulator also has to mimic these stochastic processes.

For discussion of the design of the ELAS simulator, we find it helpful to distinguish between

1. the *organ allocation environment*, with which we refer to the overall setting in which allocation policies operate. This environment is deterministically defined by the simulation settings and input streams. Of key importance are the simulation input streams, which are the datasets that define the donors which become available for transplantation, the candidates who appear on the liver waiting list, and the donor and patient events that drive ELAS simulations. These input streams also specify the nested structure of agents in the ELAS simulations: donors and patients are nested in hospitals and transplant centers, which are in turn nested in the Eurotransplant member countries. The organ allocation environment has to be specified in advance of any simulation. We discuss the requirements for input streams in Section 5.3.1. How simulations are initialized based on input streams is discussed in Section 5.3.2. How simulations proceed is illustrated in Section 5.3.3, and

[3] In fact, only 20% of transplanted livers are accepted by the top-ranked candidate in Eurotransplant.

2. *simulation modules*, which are implemented in Python code. These modules emulate key aspects of the liver allocation procedure. These processes include the generation of liver match lists according to ELAS' liver allocation rules, the simulation of graft offer acceptance behavior, ELAS' obligation system, and ELAS' exception point system. We discuss the implemented modules in Section 5.4.

With this overall design, the ELAS simulator is similar to LSAM, the simulator that has been used extensively to study organ allocation in the United States. We also point out several differences. Most importantly, the ELAS simulator is developed specifically for Eurotransplant, and takes into account the multi-national setting; we include international sharing rules and allow for allocation rules to differ per country. Other major differences include that (i) centers can decline liver offers for all their candidates in ELAS simulations, (ii) the ELAS simulator can approximate outcomes of non-standard allocation while LSAM always places livers through standard allocation, (iii) organ offer acceptance models specific to pediatric candidates are included, (iv) the splitting of liver grafts is simulated, and (v) simulation of re-listing for repeat transplantation is based on historical re-listing data.

5.3.1 The organ allocation environment

To simulate liver allocation with the ELAS simulator, users must provide input streams. These input streams consist of donor and patient information, which is used by the ELAS simulator to construct the discrete events that drive the simulator. Users of the ELAS simulator are free to base these input streams on actual registry data, reordered registry data, synthetic data, or combinations thereof. Ideally, the choice on which input stream is used is based on the end user's research question of interest. For example, end users interested in evaluating the impact of small changes to allocation rules may use historical data from the Eurotransplant registry for simulation, while end users interested in evaluating the effect of an expansion to the donor pool may need to extend the historical donor pool with synthetic donor data.

The input stream for donors must specify all the administrative and medical information that is required for liver allocation, for predicting the acceptance of liver offers, or for predicting post-transplant survival. Such information includes the donor reporting date, the donor hospital and donor reporting center, the donor weight and height, the donor blood group, and the donor death cause. In the ELAS simulator, this information is static and represents the state of the donor on the day they were reported to Eurotransplant.

Basic administrative and medical information necessary for allocation is also required for the input streams for transplant candidates. Such information includes the candidate's center of listing, the candidate's disease group, the candidate's age and weight, and the candidate's blood group. To identify candidates listing for a repeat transplantation, a candidate identifier must be specified. Next to this static candidate information, dynamic information is required on the evolution of candidate's medical condition while they await liver transplantation. For this, the ELAS simulator requires an input stream of candidate status updates. These status updates specify when and how a candidate's state changes while they wait on the Eurotransplant waiting list. Examples of such status updates are new biomarker measurements, the reception of exception scores or upgrades thereof (NSE / SE / PED-MELD), changes to the candidate's waiting list status (HU / ACO / NT status), and an exit status for each candidate (waiting list removals or waiting list deaths). Because candidates regularly modify their *allocation profiles*, profiles were also implemented as status updates. With these allocation profiles, centers can indicate that a candidate does not want to receive offers from certain liver donors. For example, many candidates specify that they do not want to be offered grafts from donors above a certain age threshold.

Discrete-event simulators for organ allocation require complete knowledge on what would happen to a candidate if they would remain on the waiting list until waiting list death or waiting list removal. For candidates transplanted in reality, such information is necessarily partly counterfactual; after all, transplantation prevents us from observing what would have happened to the transplanted candidate if they had remained on the waiting list. For other simulators, this *counterfactual status problem* was tackled by complementing the real statuses of a transplanted candidate with statuses copied over from a similar but not-yet-transplanted candidate [94, 86]. We propose a procedure that completes the status updates of transplanted candidates in this way, and describe this procedure in detail in Appendix B.

To summarize it briefly, the procedure first constructs a *risk set* for each transplanted candidate. This is a set of candidates who (i) remain on the waiting list, (ii) are similar to the candidate on a set of pre-specified characteristics, and (iii) face similar 90-day mortality risks in the absence of transplantation. A complete status update trajectory can then be constructed by (i) randomly sampling a candidate from the risk set, and (ii) copying over the future status updates from the sampled candidate. By running this procedure repeatedly, we construct for each candidate multiple potential status update trajectories. This allows us to also quantify the uncertainty in this status update completion procedure in simulations.

5.3.2 Initialization of the ELAS simulator's system state

End users of the ELAS simulator must specify a simulation start and end date, which jointly define the simulation time window. When the simulation starts, the system state is initialized by loading from the input streams all the donors who were reported during the simulation window, and all the candidates who had an active waiting list status during the simulation window. For the loaded candidates, all status updates are pre-processed until the simulation start date. This ensures that the states of candidates at simulation start coincide with their actual status on the simulation start date, as specified in candidate input streams.

A potential problem is formed by candidates who (i) have in reality received a transplantation after the simulation start date and (ii) were listed for repeat liver transplantation before the simulation end date, as these candidates could simultaneously await a primary and repeat transplantation in simulation runs. To prevent this, the ELAS simulator by default ignores re-listings of such candidates from the candidate input stream. Instead, patient re-listing is simulated by the post-transplant module. This module simulates the post-transplant survival, and the potential re-listing of transplant recipients based on candidate and donor characteristics (see Section 5.5.2.1).

The initialization of the discrete-event simulation is finalized by scheduling for each donor and transplant candidate a single event in the Future Event Set (FES). For donors, events are scheduled at the donor reporting date that is specified in the donor input stream. For each candidate, a single patient event is scheduled at the time of the candidate's first available status update after the simulation start date. Subsequent updates are scheduled in the FES only after the existing patient event has been handled.[4]

5.3.3 Overview of the simulation

Figure 5.1 shows how patient and donor events from the FES are processed in the ELAS simulator. In case of a patient event, the corresponding candidate's status is updated according to their earliest scheduled status update. In case a donor event is processed, a match list is created. To appear on this match list, candidates must have an active waiting list status (T, HU, or ACO) and they must be compatible with the donor according to ELAS blood group rules. The entities that appear on these match lists are offers to patients and center offers (if applicable). These offers are ordered deterministically based on the allocation rules specified in the organ allocation environment. By default, the actual ELAS allocation rules are followed, which are summarized in Section 5.4.1.

[4] This is necessitated by the fact that processing of a status update may result in automatic scheduling of a new update, see Section 5.4.3.

The ordered match list serves as an input to the graft offering module (see Section 5.4.4). This module mimics the graft offering process in Eurotransplant and returns the candidate who accepts the liver offer, if any. We point out that it is not clear based on the match list alone which candidate is transplanted with the liver. One reason for this is that offers are regularly declined by the transplant centers: in fact, over half of the transplanted liver grafts in Eurotransplant were declined by 10 or more candidates before being accepted for transplantation. A second reason is that Eurotransplant can deviate from the standard allocation procedure to prevent the loss of transplantable organs (see Section 5.2). In simulating whether a candidate accepts the offer, the module can simulate both standard and non-standard allocation.

The ELAS simulator assumes that the candidate who accepts the liver graft is transplanted, and removes any scheduled events for this transplanted candidate from the Future Event Set. If a liver was allocated across country borders in HU or ACO tiers, the obligation system module creates an obligation for the importing country to return a liver graft in the future (or settles an obligation for the exporting country, in case an existing obligation exists). For livers exported based on an obligation, obligations are also settled. The post-transplant module simulates a time-until-liver-failure for each transplantation (see Section 5.5.2.1). In case the transplant recipient is simulated to be listed for a repeat liver transplantation before the candidate's simulated death date, the post-transplant module schedules a "synthetic" re-listing for the candidate (see Section 5.4.5.3).

The processing of patient and donor events continues until the simulation end date is reached. At the end of the simulation, information on transplantations is written to an output file. A list of discarded grafts is also written to output files, as are the final states of all candidates present in the simulation. These final states include candidate exit statuses (waiting, waiting list death, transplanted, or waiting list removal), as well as their last reported MELD scores. Such information may be summarized to calculate the statistics relevant for a specific research question. We chose to write raw information to files rather than predefined summaries of information to give end users maximum flexibility in reporting more complicated statistics.

5.4 Modules of the ELAS simulator

This section describes the key modules of the ELAS simulator: the match list module (Section 5.4.1), the obligation system module (Section 5.4.2), the exception module (Section 5.4.3), the graft offering module (Section 5.4.4), and the post-transplant module (Section 5.4.5).

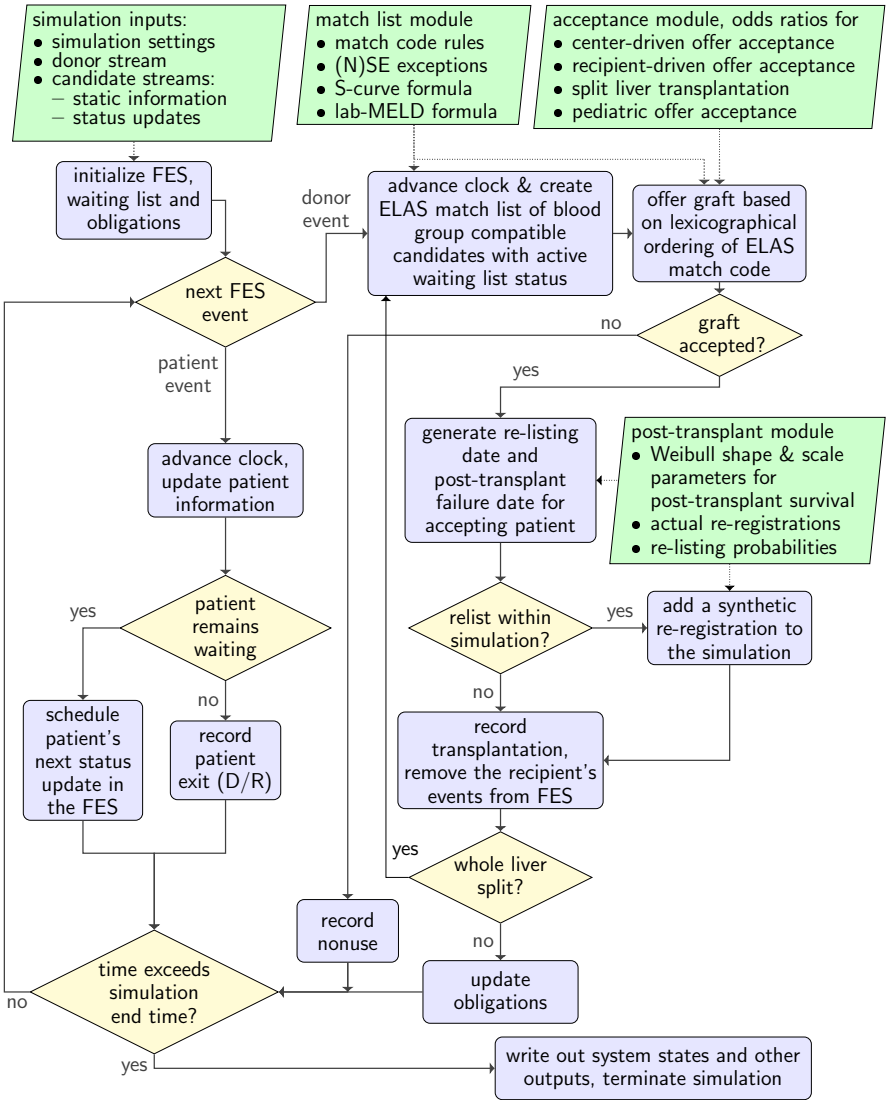


Figure 5.1: Event handling flowchart for the ELAS simulator. Inputs and parameters are represented using parallelograms. D, deceased on the waiting list; ELAS, Eurotransplant Liver Allocation System; FES, Future Event Set; MELD, Model for End-Stage Liver Disease; R, waiting list removal.

5.4.1 The match list module

When a liver graft is to be allocated, the match list module creates an ordered list of candidates who sequentially receive offers until a candidate accepts the liver graft. To appear on these match lists, candidates must (i) have an active waiting list status (transplantable, HU, or ACO), and (ii) have a blood group compatible with that of the donor, according to ELAS allocation rules. By default, the match list module collapses offers to candidates who are eligible for center offers into a single center offer object. The rank of this center offer is set equal to the rank of the top-ranked candidate eligible for that center offer. The match lists returned by the match list module are thereby ordered lists of center-driven and patient-driven offers, coinciding with the structure of match lists Eurotransplant actually uses for allocation (see the example match list in Table 5.1).

The precise ordering returned by the match list module is based on the liver allocation rules that must be pre-specified as part of organ allocation environment. The rules made available with the ELAS simulator are the ELAS allocation rules used between 2016 and 2024. end users of the ELAS simulator can modify these allocation rules to study waiting list outcomes under alternative allocation policies. Technically, the ranking of ELAS match objects (patient- or center offers) is based on *match codes*. These match codes consist of several components. The values of these components are determined by Eurotransplant allocation rules, donor and patient characteristics, and the existence of obligations. Currently, these match codes consist of:

1. **match tiers**, which are used to give international priority to patients with HU status or ACO status,
2. **match layers**, which differ per country and are used to give priority to certain patient groups (for example, to pediatric candidates, to blood group-identical candidates, to local candidates, or to candidates located in other countries based on obligations),
3. **match obligation ranks**, which are used as a tiebreaker in case the donor country has obligations to return livers to multiple countries,
4. **match-MELDs**, which are used to rank candidates in the elective tiers,
5. **match locality**, which is used to prioritize patients regionally in Germany in elective tiers,
6. **waiting time**, which is the number of days with a HU or ACO status in the HU and ACO tiers. In elective tiers, waiting time is defined as the number of days a candidate has had a match-MELD score at least as high as the current match-MELD score,
7. **the patient listing date**, which is used as a tiebreaker.

The order of the match list is based on the lexicographical ordering of these components.

5.4.2 The obligation system module

An important feature of Eurotransplant's obligation system is that obligations within the same blood group are automatically *linked*. For example, if Croatia has an obligation to return a blood group A liver to Belgium, and an obligation is created for Belgium to return a blood group A liver to Germany, the two existing obligations are replaced by a *linked* obligation for Croatia to return a blood group A liver to Germany.

The obligation module implemented for the ELAS simulator creates obligations for grafts that are procured internationally in HU or ACO tiers, and automatically replaces linkable obligations by a linked obligation. The module can also return for a given blood group the outstanding obligations per country, as well as the number of days these obligations have existed. This information is required by the ELAS simulator's match list module to determine match obligation ranks.

5.4.3 The exception score module

Patient groups who are considered to be underserved by a purely lab-MELD-based allocation can apply for standard (SE) or non-standard (NSE) exceptions in ELAS. Candidates who receive such (N)SE and PED-MELD scores are awarded predefined 90-day mortality equivalents, which are specified in percentages. The exceptions, their eligibility criteria, and their 90-day mortality equivalents vary by member country. For example, in the Netherlands candidates with hepatocellular carcinoma are awarded a 10% mortality equivalent, while a 15% mortality equivalent is awarded in Belgium. Pediatric patients in Eurotransplant automatically receive PED-MELD scores based on their age, which are also based on 90-day mortality equivalents.

For allocation, these mortality equivalents are translated to the MELD scale. For example, a 10% and 15% mortality equivalent correspond to MELD scores of 20 and 22, respectively [58]. The awarded 90-day mortality equivalent increases every 90 days[5] for most (N)SEs and PED-MELDs, according to exception- and country-specific increments. Some exceptions are implemented as "bonus SEs". These bonus SEs add a fixed percentage mortality equivalent to the lab-MELD's 90-day mortality equivalent.[6]

The exception score module implements this system, and is initialized based on an external file. This file has to specify which exceptions exist, and relevant exception

[5] (N)SEs that require manual re-certification increase immediately after re-certification, which can occur 14 days before expiry (i.e., every 76–90 days). Simulations assume that these (N)SEs upgrade every 80 days in case no re-certification is known for the candidate. (N)SEs and PED-MELD with automatic re-certification increase every 90 days.

[6] For example, a candidate with biliary sepsis in Germany with a MELD score of 21 would receive a 30 percent point bonus amount. Their lab-MELD score of 21 corresponds to a 90-day mortality equivalent of 26%, giving them in total a 26% + 30% = 56% mortality equivalent, which corresponds to a MELD score of 30.

attributes (the initial mortality equivalent awarded, the 90-day increment, the maximal equivalent awarded, the maximum age after which the exception no longer increases, and whether the SE is a regular SE or a bonus SE). For the default organ allocation environment, all (N)SEs and PED-MELDs existing in 2023 were implemented. end users may modify the attributes of these exceptions to simulate Eurotransplant liver allocation under alternative (N)SE / PED-MELD rules. Simulation settings also have to include parameters for the formula used to translate 90-day mortality equivalents to the MELD scale.[7]

By default, the ELAS simulator assumes that the candidate status input stream also specifies when exceptions are upgraded or expire. In case no future exception status is present in the candidate status queue for an NSE / SE / PED-MELD, the ELAS simulator assumes that the candidate would continue to re-certify their exception according to the exception-specific re-certification schedule. This choice is motivated by the fact that almost all candidates with exceptions re-certify them.

5.4.4 The graft offering module

For a match list, the graft offering module returns the candidate who accepts the graft offer (if any), or indicates that all eligible candidates have rejected the offer. If the graft has been turned down for all eligible candidates, the simulator can either (a) force placement of the graft in the candidate who was most likely to accept the graft offer, or (b) record a discard.

The graft offering process is mimicked by (i) offering liver grafts to patients/centers in order of their ranking on the match list, and (ii) modeling organ offer acceptance as a Bernoulli process, with acceptance probabilities predicted based on logistic models that using donor and patient characteristics (as in the SAM software, see [96]). The graft offering module also includes a logistic model to predict whether a liver graft is split by the transplant center after acceptance. Such split procedures allow centers to transplant two candidates with one liver, and are typically performed to transplant one pediatric and one adult patient.

There are several reasons why a candidate may not be offered a liver in ELAS allocation despite being ranked high enough for an offer. These reasons include that:

[7] This transformation is based on a Cox proportional hazards model which uses MELD as the only predictor, and which uses a MELD score of 10 as the reference group. The curve used by Eurotransplant is given by:

$$S_{90} = 0.98037^{\exp\left(0.17557(\texttt{UNOS-MELD}-10)\right)},$$

where 0.98037 is the 90-day mortality equivalent for a MELD score of 10, and 0.17557 is the slope on MELD.

1. Centers frequently decline the graft for all candidates who appear on the match list, even when making patient-driven offers (for example because of poor donor quality or capacity constraints). If centers decline for the entire center, the center will not be contacted again with an offer for the transplantation of a specific patient.
2. Offers are not made to candidates whose allocation profiles exclude them from being offered the liver graft (for example because the donor is too old).
3. Center offers are not directly offered by Eurotransplant to individual candidates. Instead, the transplant center chooses a candidate for transplantation.
4. Eurotransplant can deviate from the standard allocation procedure in case allocation time is limited. Offers to candidates not located in the vicinity of the graft are then bypassed.

These reasons motivated us to

1. Implement a two-stage patient-driven offer acceptance procedure. In the first stage, a center-level logistic model is used to predict based on donor characteristics alone whether the center is willing to accept the graft. Provided that the center is willing to accept the graft, a patient-level logistic model is used to predict graft offer acceptance based on patient and donor characteristics.
2. Skip offers to elective candidates whose allocation profiles indicate that they do not want to receive the liver graft.
3. Estimate logistic regressions separately for center- and patient-driven offers.
4. Approximate deviation from standard allocation (see 5.4.4.1).

In the ELAS simulator, separate logistic models are used for four candidate groups: (i) pediatric candidates with HU / ACO statuses, (ii) elective pediatric patients, (iii) adult candidates with HU / ACO statuses, and (iv) elective adult candidates. This stratification is motivated by findings in the existing literature that a single acceptance model poorly captures offer acceptance behavior for specific patient groups. For example, Wood et al. [97] note poor prediction for pediatric patients in LSAM.

To enable end users to change how graft offer acceptance decisions are made, the odds ratios necessary for calculating the graft offer acceptance probabilities are kept in csv files external to the program. Default odds ratios supplied with the ELAS simulator were estimated based on offers of whole liver grafts procured between January 1, 2012 and December 31, 2019. When estimating these odds ratios, we ignored offers that were incompatible with the allocation profiles of candidates and offers that were accepted in non-standard allocation. To account for correlations in organ acceptance behavior,

odds ratios were estimated with mixed effect models. In these models, we included random effects for donor heterogeneity (as in [98]), patient heterogeneity, and center heterogeneity.

5.4.4.1 Simulation of non-standard allocation

Approximately 25% of livers are placed through non-standard allocation in Eurotransplant. Without approximating such deviation from non-standard allocation, the ELAS simulator would place too many grafts nationally in Belgium and Germany, as both countries have implemented rules to prioritize local offers in non-standard allocation. This motivated us to approximate deviation from standard allocation in the graft offering module.

To address this, we approximate the initiation of non-standard allocation by

1. simulating the maximum number of offers until non-standard allocation is initiated with a Cox proportional hazards model. This Cox model models the probability that non-standard allocation is triggered based on donor characteristics (malignancy, death cause, drug abuse, marginal donor criteria, virology), using the number of offers made as the timescale. The Cox model was stratified by donor country and blood group. The baseline hazards for this Cox proportional hazards model are shown in Figure 5.2.
2. offering the graft in the order of the match list, while maintaining a count of the number of offers made,
3. if the maximum number of offers is reached
    - stop offering the graft to candidates whose allocation profiles exclude rescue donors,
    - give priority to regional candidates in Germany and to local candidates in Belgium.

In counting the number of offers made, a center-level rejection is counted as a single offer, and a candidate-level rejection is counted only if (a) the graft was compatible with the candidates allocation profile and (b) the graft was previously rejected by fewer than five candidate from the same center.

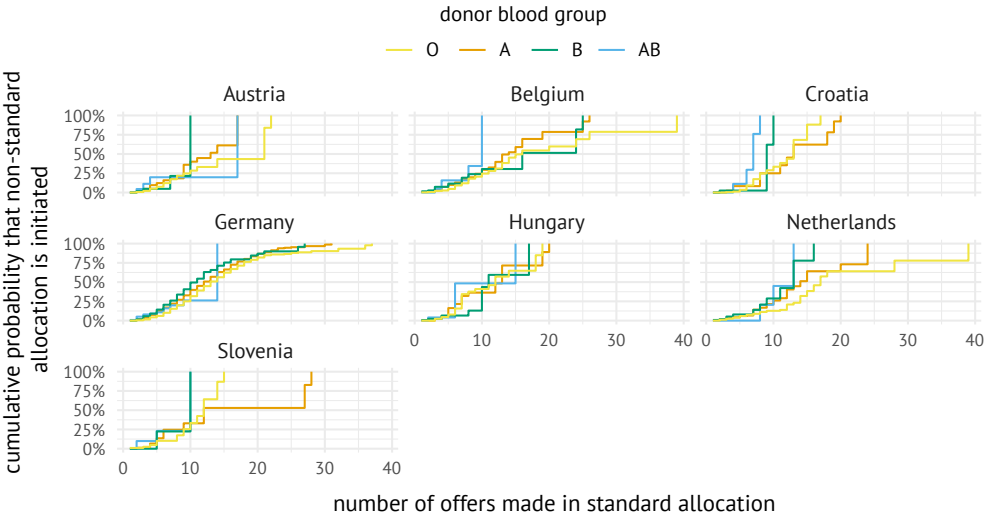


Figure 5.2: The relation between the number of offers made in standard allocation and the probability that non-standard allocation is initiated. The country- and blood group-specific survival curves were generated by predicting the number of offers for an average patient.

We note that this implementation is a heavily simplified representation of non-standard allocation in Eurotransplant. Because candidates are still prioritized based on the match list order, this implementation is closer to extended allocation than to rescue allocation (which operates on a first-come, first-served basis). Implementing competitive rescue allocation was not pursued because (i) it is not clear from donor information alone when competitive rescue allocation is initiated, (ii) there are three types of competitive rescue allocation in Eurotransplant, and (iii) not all centers are willing to accept grafts via competitive rescue allocation [58].

5.4.5 The post-transplant module

Over 10% of liver waiting list registrations in Eurotransplant concern candidates who are listed for a repeat liver transplantation. To accurately simulate such re-listings, a post-transplant module was implemented for the ELAS simulator. Upon transplantation, this module simulates a time-to-failure t, defined as the time at which the candidate would die in absence of re-transplantation. T is modeled using a Weibull distribution, with parameters for recipient and donor characteristics. The module also simulates a time-to-relisting r, at which the candidate enlists for a repeat transplantation. Finally, if a candidate is simulated to list for a repeat transplantation, the post-transplant module adds a listing for the repeat transplantation of that candidate to the waiting list.

The parameters needed to simulate the post-transplant survival of liver transplantation recipients were estimated on Eurotransplant liver transplantations between January 1, 2012 and December 31, 2019. Since we expected post-transplant survival and re-listing to be different for elective candidates and those with the HU or ACO status, we estimated the parameters separately for these groups.

5.4.5.1 Simulating time-to-failure for transplant recipients

A Weibull model is used to simulate a time-to-event until patient death or liver transplantation, separately for HU/ACO and elective candidates. The used Weibull distribution is parametrized with a shape parameter k and scale parameter $\lambda = \beta^\intercal x$ where x are relevant patient and donor characteristics. The survival function for the Weibull distribution is given by:

$$S(t|x) = \exp\left(- \left(\frac{t}{\beta^\intercal x}\right)^k \right).$$

After obtaining estimates for β and k based on historical data using Weibull regression, a time-to-event t_i for a patient-donor pair i can be simulated by inverse transform sampling from this distribution. Specifically, we can draw a random number $u \sim \texttt{unif}(0, 1)$ and simulate a patient's time-to-event as

$$t_i = \hat{\beta}^\intercal \mathbf{x_i} \Big(- \ln(u)^{\frac{1}{k}} \Big).$$

By default, post-transplant survival of elective candidates is simulated based on a broad set of patient attributes (MELD biomarkers, patient age, country, sex, exception scores, BMI), donor attributes (year reported, donor age, split, DCD or DBD, death cause, malignancy, tumor history), and match attributes (candidate-donor weight difference, travel time, blood group compatibility, match geography). Paucity of data on HU and ACO transplantations motivated us to adjust for fewer variables in the non-elective model (weight difference, donor death cause, donor age, patient age, lab-MELD score, match geography, and an indicator for transplant history). Country-specific shape parameters are used to simulate t for elective candidates, while a single shape parameter is used to simulate it for candidates with the HU or ACO status.

5.4.5.2 Simulating a time-to-relisting r for transplant recipients

The simulation of a candidate's time-to-relisting is complicated by the fact that a patient's time-to-relisting r_i necessarily has to occur before their time-to-failure t_i. To simulate re-listing times in the ELAS simulator, we estimated the probability of re-listing using the Kaplan-Meier estimator, with the time elapsed relative to the event time t_i as the timescale. A re-listing time can then be simulated by inverse transform sampling from the Kaplan-Meier curve, i.e., (i) sample a random $u \sim \text{unif}(0, 1)$, (ii) choose the first s such that $\mathbb{P}[R/T > s] \geq u$, and (iii) calculate the time-to-relisting as $s \cdot t$.

In case no such t exists, the patient will die without being listed for repeat transplantation. The estimated empirical distribution of R relative to T is shown in Figure 5.3, stratified by discretized T. The figure shows that the fraction of patients who have died without having listed for repeat transplantation depends strongly on their time-to-failure T. For example, almost 70% of candidates who experience an event within one week after transplantation are listed for a repeat liver transplantation, while only 20% of candidates who experience an event more than five years after initial transplantation are listed for repeat transplantation.

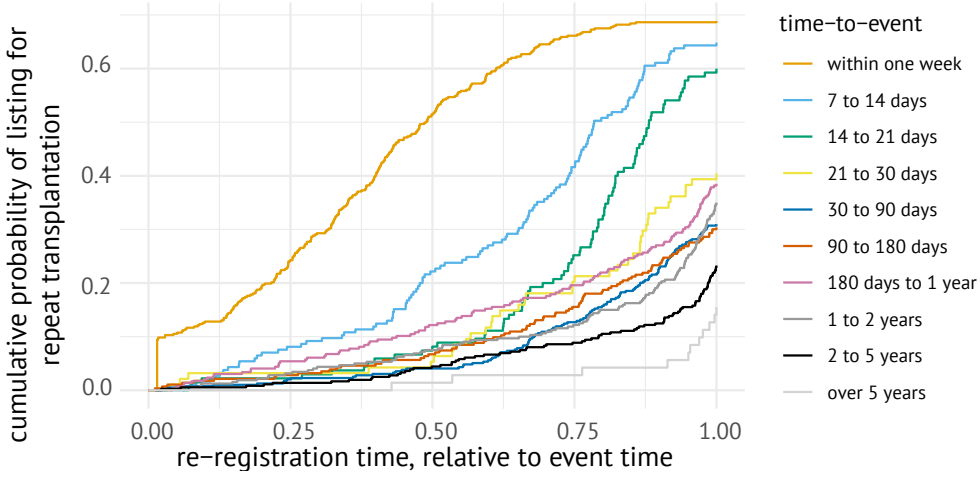


Figure 5.3: Cumulative incidence curves showing the probability of listing for repeat transplantation, stratified by time-to-event categories. These curves were estimated with the Kaplan-Meier estimator based on candidates transplanted between January 1, 2012 and December 31, 2019.

5.4.5.3 Construction of synthetic re-registrations

If a candidate is re-activated on the waiting list before the simulation end date, i.e., $r < t$, the post-transplant module adds a *synthetic* repeat listing to the waiting list. This synthetic listing is generated by combining the fixed patient characteristics of the transplant recipient with the dynamic status updates of a candidate who was actually re-listed for transplantation. This re-listing is chosen such that the candidates (a) have similar time-to-failure t and similar time-to-relisting r, and (b) match on a pre-specified set of characteristics.

By default, the post-transplant module finds a matching re-registration k by:

1. Considering re-listings where candidates match in terms of whether they were re-listed within 14 days[8] after transplantation, were listed in the same country, are similarly aged (<20 years difference), and have a similar time-to-relisting and time-to-event (both <1 year difference),
2. Selecting from these potential re-listings the m=5 listings for repeat transplantation with the closest Mahalanobis distance between (r_i, t_i) and (r_k, t_k), and
3. Sampling one re-listing at random from these m re-listings.

A synthetic re-listing is then constructed by combining the patient attributes from transplant recipient i with status updates from patient k. The post-transplant module does not copy profile status updates from k to i, as these allocation profiles are considered patient-specific. Exception scores from k are copied only if both patients were listed in the same country, since certain (N)SEs are associated with listing for repeat transplantation (e.g., hepatic artery thrombosis).

5.5 Verification and validation

The previous section described the design of the ELAS simulator and its modules. In this section, we describe our efforts to ensure that the ELAS simulator adequately represents ELAS. For this, we distinguish between model *verification*, which refers to efforts taken to identify coding errors in the software, and model *validation*, which refers to efforts taken to assess whether simulated outcomes closely approximate actual outcomes of Eurotransplant liver allocation. For a general discussion of model verification and model validation, we refer to Carson [99].

[8] Patients that are re-listed for liver transplantation within 14 days of transplantation can be eligible for an HU status under the current allocation rules [58].

5.5.1 Verification

To implement liver allocation rules in the ELAS simulator, we have used the 2016 functional specifications for ELAS. To verify the correctness of our implementation of ELAS allocation rules, we exported ELAS match lists for 500 randomly selected donors who were reported between January 1, 2016 and December 31, 2019. We constructed unit tests to verify that the ELAS simulator correctly generated the match codes for these lists based on the reported donor and candidate information. We also constructed unit tests to ascertain that the simulator returned candidates in exactly the same order as the exported match lists.

To ensure the correctness of the exception module, we exported (N)SE exception score definitions directly from the Eurotransplant database. For the obligation system module, we used the functional specifications of the ELAS obligation system to guide our implementation. These functional specifications contain examples of how obligations have to be linked, including how to date the obligations that arise from multiple linkable obligations. We implemented these examples as unit tests for the ELAS simulator.

5.5.2 Validation

Discrete-event simulators for organ allocation are typically validated by comparing simulated statistics over a set time window to the actual statistics from the same time period [86, 94]. Properties commonly validated are the number of transplantations and waiting list deaths, typically also stratified by patient groups. We follow this practice to validate the ELAS simulator.

We do not use traditional hypothesis testing (or confidence intervals) to compare simulated and actual statistics, as *"traditional hypothesis testing is not appropriate for measuring model validity because the null hypothesis that the true system and model are identical is almost always false"* [94]. In fact, any difference between actually observed outcomes and simulations can be made statistically significant by increasing the number of simulation runs. Instead, we give insight into the variability of ELAS simulator outputs by reporting 95% interquantile ranges (95% IQRs) for simulation runs. These interquantile ranges are obtained by simulating liver allocation 200 times, and reporting the 2.5th and 97.5th percentiles for simulated outcomes of interest. When the real summary statistic for an outcome of interest falls within the 95% interquantile range, we say that the ELAS simulator is *"well-calibrated"* for this outcome.

For input-output validation, we simulate Eurotransplant liver allocation 200 times between January 1, 2016, and December 31, 2019. The donor input stream consists of all 6,417 donors that were reported in this simulation window whose livers were transplanted after allocation through ELAS. Characteristics of these donors are shown

in Table 5.2. The candidate input stream consists of all patients who had an active waiting list status in the simulation period. In total, these are n=7,137 patients who were activated on the waiting list between January 1, 2016, and December 31, 2019 (see Table 5.3), and n=1,831 patients waiting on January 1, 2016 (see Table 5.4).

Table 5.2: Characteristics of the donors used for simulation.

variable	level	Austria (n=610)	Belgium (n=1160)	Croatia (n=514)	Germany (n=2927)	Hungary (n=406)	Netherlands (n=672)	Slovenia (n=128)
sex	female	292 (47.9%)	496 (42.8%)	241 (46.9%)	1375 (47.0%)	180 (44.3%)	327 (48.7%)	53 (41.4%)
	male	318 (52.1%)	664 (57.2%)	273 (53.1%)	1552 (53.0%)	226 (55.7%)	345 (51.3%)	75 (58.6%)
age (years)	mean [Q1-Q3]	51 [41-63]	52 [40-65]	58 [49-71]	52 [41-66]	46 [36-59]	50 [42-61]	55 [44-70]
type	HB	604 (99.0%)	854 (73.6%)	514 (100%)	2927 (100%)	406 (100%)	425 (63.2%)	128 (100%)
	NHB	6 (1.0%)	306 (26.4%)	–	–	–	247 (36.8%)	–
death cause	anoxia	69 (11.3%)	312 (26.9%)	22 (4.3%)	482 (16.5%)	32 (7.9%)	126 (18.8%)	9 (7.0%)
	CVA	398 (65.2%)	515 (44.4%)	401 (78.0%)	1772 (60.5%)	291 (71.7%)	372 (55.4%)	60 (46.9%)
	trauma	130 (21.3%)	272 (23.4%)	84 (16.3%)	533 (18.2%)	76 (18.7%)	146 (21.7%)	54 (42.2%)
	other	13 (2.1%)	61 (5.3%)	7 (1.4%)	140 (4.8%)	7 (1.7%)	28 (4.2%)	5 (3.9%)
marginal	no	553 (90.7%)	1062 (91.6%)	436 (84.8%)	2566 (87.7%)	379 (93.3%)	628 (93.5%)	108 (84.4%)
	yes	57 (9.3%)	98 (8.4%)	78 (15.2%)	361 (12.3%)	27 (6.7%)	44 (6.5%)	20 (15.6%)
ET-DRI	mean [Q1-Q3]	1.44 [1.2-1.7]	1.61 [1.2-1.9]	1.56 [1.3-1.8]	1.46 [1.2-1.7]	1.41 [1.1-1.6]	1.62 [1.4-1.9]	1.46 [1.2-1.7]

Based on donors reported in the simulation period whose livers were allocated and transplanted via ELAS. CVA, cerebrovascular accident; HB, heartbeating; NHB, nonheartbeating; ET-DRI, ET donor risk index.

Table 5.3: Characteristics of newly registered patients who were used for simulations

variable	level	Austria (n=663)	Belgium (n=1128)	Croatia (n=558)	Germany (n=3682)	Hungary (n=315)	Netherlands (n=685)	Slovenia (n=106)
status at listing	active	622 (93.8%)	1053 (93.4%)	509 (91.2%)	3028 (82.2%)	299 (94.9%)	576 (84.1%)	105 (99.1%)
	inactive	41 (6.2%)	75 (6.6%)	49 (8.8%)	654 (17.8%)	16 (5.1%)	109 (15.9%)	1 (0.9%)
sex	female	163 (24.6%)	354 (31.4%)	152 (27.2%)	1320 (35.9%)	135 (42.9%)	257 (37.5%)	40 (37.7%)
	male	500 (75.4%)	774 (68.6%)	406 (72.8%)	2362 (64.2%)	180 (57.1%)	428 (62.5%)	66 (62.3%)
listing age (years)	mean [Q1-Q3]	55 [51-64]	55 [49-65]	57 [53-65]	50 [45-62]	48 [36-61]	51 [44-63]	54 [51-63]
disease group	(S)ALF	47 (7.1%)	96 (8.5%)	33 (5.9%)	511 (13.9%)	13 (4.1%)	97 (14.2%)	7 (6.6%)
	cholestatic	62 (9.4%)	105 (9.3%)	70 (12.5%)	560 (15.2%)	78 (24.8%)	156 (22.8%)	20 (18.9%)
	cirrhosis	301 (45.4%)	432 (38.3%)	236 (42.3%)	1432 (38.9%)	147 (46.7%)	165 (24.1%)	57 (53.8%)
	HCC	193 (29.1%)	342 (30.3%)	148 (26.5%)	719 (19.5%)	29 (9.2%)	180 (26.3%)	15 (14.2%)
	other	60 (9.0%)	153 (13.6%)	71 (12.7%)	460 (12.5%)	48 (15.2%)	87 (12.7%)	7 (6.6%)
HU status	yes	76 (11.5%)	131 (11.6%)	42 (7.5%)	654 (17.8%)	26 (8.3%)	110 (16.1%)	13 (12.3%)
	no	587 (88.5%)	997 (88.4%)	516 (92.5%)	3028 (82.2%)	289 (91.7%)	575 (83.9%)	93 (87.7%)
lab-MELD at listing	mean [Q1-Q3]	17 [11-22]	18 [10-23]	17 [11-21]	20 [12-28]	15 [10-17]	18 [10-23]	18 [12-23]
(N)SE at listing	yes	69 (10.4%)	439 (38.9%)	186 (33.3%)	866 (23.5%)	–	66 (9.6%)	–
	no	594 (89.6%)	689 (61.1%)	372 (66.7%)	2816 (76.5%)	315 (100%)	619 (90.4%)	106 (100%)

Based on patients activated on the waiting list in the simulation period. (S)ALF, (Sub-)Acute Liver Failure; HCC, hepatocellular carcinoma; (N)SE, (non-)standard exception.

Table 5.4: Characteristics of patients already present on the waiting list on January 1, 2016.

variable	level	Austria (n=64)	Belgium (n=172)	Croatia (n=57)	Germany (n=1276)	Hungary (n=121)	Netherlands (n=124)	Slovenia (n=17)
status (Jan 1, 2016)	active	47 (73.4%)	143 (83.1%)	32 (56.1%)	790 (61.9%)	101 (83.5%)	86 (69.4%)	14 (82.4%)
	inactive	17 (26.6%)	29 (16.9%)	25 (43.9%)	486 (38.1%)	20 (16.5%)	38 (30.6%)	3 (17.6%)
sex	female	20 (31.3%)	62 (36.0%)	21 (36.8%)	447 (35.0%)	68 (56.2%)	40 (32.3%)	5 (29.4%)
	male	44 (68.8%)	110 (64.0%)	36 (63.2%)	829 (65.0%)	53 (43.8%)	84 (67.7%)	12 (70.6%)
listing age (years)	mean [Q1-Q3]	53 [50-63]	54 [46-65]	52 [45-61]	49 [43-59]	49 [40-60]	48 [38-61]	52 [45-63]
disease group	(S)ALF	2 (3.1%)	2 (1.2%)	0 (0%)	25 (2.0%)	0 (0%)	1 (0.8%)	0 (0%)
	cholestatic	7 (10.9%)	28 (16.3%)	6 (10.5%)	219 (17.2%)	37 (30.6%)	32 (25.8%)	5 (29.4%)
	cirrhosis	37 (57.8%)	61 (35.5%)	46 (80.7%)	712 (55.8%)	60 (49.6%)	34 (27.4%)	8 (47.1%)
	HCC	12 (18.8%)	46 (26.7%)	1 (1.8%)	174 (13.6%)	15 (12.4%)	35 (28.2%)	2 (11.8%)
	other	6 (9.4%)	35 (20.3%)	4 (7.0%)	146 (11.4%)	9 (7.4%)	22 (17.7%)	2 (11.8%)
HU status	yes	0 (0%)	2 (1.2%)	0 (0%)	12 (0.9%)	0 (0%)	0 (0%)	0 (0%)
	no	64 (100%)	170 (98.8%)	57 (100%)	1264 (99.1%)	121 (100%)	124 (100%)	17 (100%)
lab-MELD (Jan 1, 2016)	mean [Q1-Q3]	15 [11-18]	14 [9-18]	12 [9-14]	13 [9-16]	13 [9-15]	12 [8-14]	13 [11-14]
(N)SE (Jan 1, 2016)	no	64 (100%)	84 (48.8%)	56 (98.2%)	1066 (83.5%)	121 (100%)	102 (82.3%)	17 (100%)
	yes	-	88 (51.2%)	1 (1.8%)	210 (16.5%)	-	22 (17.7%)	-

Based solely on patients with an active waiting list status between January 1, 2016 and December 31, 2019. (S)ALF, (Sub-)Acute Liver Failure; HCC, hepatocellular carcinoma; (N)SE, (non-)standard exception

These counts do not include candidates who were transplanted with a living donor as ELAS is only used to allocate deceased-donor livers. We also excluded candidates whose country of listing changed (29 listings in total). For simulation, we use actual donor arrival times and actual candidate status histories, which were completed with the status completion procedure described in Appendix B. For each of the 200 simulation runs, a different file of completed candidate status updates is used. These files differ in the completed status update trajectories per candidate.

Table 5.5 shows the validation results for waiting list outcomes. This table shows that the ELAS simulator is well-calibrated for the number of split liver transplantations, the number of total listings and those for a repeat transplantation, the number of waiting list removals, and the number of waiting list deaths. A statistic for which the simulator is not well-calibrated is the active waiting list size at simulation termination, which is 4.5% larger in simulations than in reality. The ELAS simulator is well-calibrated for the number of waiting list deaths per country, except for in Germany where the number of waiting list deaths is underestimated by 52 deaths (-8.1%), on average, over the 200 simulations. Inspecting waiting list deaths by groupings of the lab-MELD score shows that the ELAS simulator underestimates the number of waiting list deaths in candidates with the highest MELD scores (-8.1% for MELD 31–40) and HU / ACO candidates (-27.2%), while the simulator overestimates the number of waiting list deaths in candidates with low MELD scores (+11.8% for MELD 6–10).

Table 5.5: Validation of waiting list outcomes between January 1, 2016 and December 31, 2019. For simulations, the numbers shown are the averages and 95% interquantile ranges of outcomes over 200 simulations. The averages and ranges are displayed in bold if the simulator is not well-calibrated, i.e. the observed statistic does not fall within the 95% IQR.

category	simulated results (average and 95% IQR)	actual data (2016-2019)
deceased-donor livers		
total transplantations	6,415 [6,398-6,432]	6,418
number of livers split	173 [156-192]	181
split transplantations	346 [311-383]	354
waiting list		
patient listings	12,086 [12,034-12,141]	12,110
relisting (synthetic)	650 [598-705]	652
final active waiting list	**1,528 [1,485-1,571]**	1,462
removals (excl. recoveries)	860 [831-1,888]	857
deaths	1,636 [1,582-1,690]	1,686
waiting list mortality by country		
Austria	85 [72-100]	82
Belgium	169 [148-190]	165
Croatia	109 [97-121]	98
Germany	**1,096 [1,051-1,140]**	1,148
Hungary	62 [52-72]	72
Netherlands	93 [79-107]	101
Slovenia	22 [17-29]	20
waiting list mortality by lab-MELD		
lab-MELD 6-10 deaths	**123 [113-134]**	110
lab-MELD 11-20 deaths	498 [473-524]	482
lab-MELD 21-30 deaths	387 [361-413]	379
lab-MELD 31-40 deaths	**505 [467-542]**	546
HU / ACO deaths	**123 [103-142]**	169

Table 5.6 shows validation results relating to transplantations, separately for standard and non-standard allocation. The ELAS simulator is well-calibrated for most summary statistics, including the number of placements through each allocation mechanism, as well as the number of transplantations stratified by pediatric status and candidate sex. The simulator is not well-calibrated for the number of transplantations within all Eurotransplant countries. In total, 55 too many transplantations ($+4.2\%$) are performed in the simulations in Belgium, while on average 35 (-5.6%) and 15 (-3.0%) too few transplantations are simulated in Austria and Croatia, respectively. Restricting attention to standard allocation, we find that too few grafts are accepted in Austria (-6.8%), Croatia (-6.0%) and Hungary (-7.4%). Generally, too few grafts are accepted locally or regionally in simulations (-15%).

Table 5.6: Validation of transplantations between January 1, 2016 and December 31, 2019. For simulations, the numbers shown are the averages and 95% interquantile ranges over 200 simulations. Ranges are displayed in bold if the observed statistic does not fall within the 95% IQR.

	total transplantations		standard allocation only	
category	simulated results (average and 95% IQR)	actual	simulated results (average and 95% IQR)	actual
transplantations by allocation mechanism				
HU or ACO	942 [905-977]	931	935 [899-968]	927
obligation	**325 [302-354]**	290	**325 [302-354]**	290
MELD-based	3850 [3636-4052]	4005	3850 [3636-4052]	4005
extended or rescue	1298 [1099-1503]	1192	—	—
transplant recipients				
female	2142 [2107-2186]	2140	1764 [1690-1829]	1825
male	4273 [4227-4310]	4278	3346 [3196-3484]	3397
pediatric recipient	418 [396-439]	424	397 [372-417]	405
match geography				
local or regional	2506 [2398-2600]	2523	**1577 [1496-1668]**	1850
national	2664 [2543-2779]	2647	2430 [2267-2581]	2298
international	1245 [1183-1300]	1248	1104 [1049-1155]	1074
Austria	**585 [561-605]**	620	**534 [508-563]**	573
Belgium	**1122 [1098-1142]**	1067	997 [937-1040]	983
Croatia	**481 [466-493]**	496	**456 [437-470]**	485
Germany	3178 [3148-3208]	3166	2161 [1993-2323]	2165
Hungary	298 [284-312]	312	**287 [270-301]**	310
Netherlands	656 [626-681]	656	583 [527-618]	607
Slovenia	96 [88-103]	101	92 [83-100]	99
transplantations by patient type (adult non-HU/ACO only)				
lab-MELD only	3250 [3195-3299]	3289	2453 [2327-2567]	2482
HCC	**1190 [1158-1221]**	1150	903 [848-962]	917
NSE	**259 [239-275]**	286	**205 [179-224]**	248
other SE	558 [533-579]	547	421 [388-453]	453
transplantations by match-MELD (adult non-HU/ACO only)				
match-MELD 6–10	**434 [400-476]**	493	337 [304-368]	360
match-MELD 11–20	1388 [1294-1487]	1466	970 [913-1021]	982
match-MELD 21–30	**2482 [2386-2574]**	2285	1792 [1633-1933]	1769
match-MELD 31–40	**952 [899-1000]**	1025	**884 [826-935]**	989
unknown	–	3		
transplantations by lab-MELD (adult non-HU/ACO only)				
lab-MELD 6–10	**1292 [1254-1337]**	1373	**974 [910-1028]**	1066
lab-MELD 11–20	2143 [2058-2226]	2181	1535 [1458-1605]	1553
lab-MELD 21–30	**1044 [993-1093]**	942	752 [675-816]	739
lab-MELD 31–40	778 [731-828]	769	721 [669-780]	738
unknown	–	7	0	4

Regarding transplantations categorized by type of exception, we find that the ELAS simulator is well-calibrated for the number of transplantations in non-exception candidates and in candidates with SE other than HCC. The total number of transplantations with HCC is overestimated by 40 on average (+3.5%), but is well-calibrated if attention is restricted to standard allocation. The simulator underestimates the number of transplantations in candidates with NSEs, both in standard allocation (-17.5%) and in total (-9.5%).

In terms of the number of transplantations per MELD score via standard allocation, the ELAS simulator appears to be mostly well-calibrated, with only the number of transplantations in candidates with lab-MELD scores between 6 and 10 underestimated (-8.6%) and those in candidates with match-MELD between 31 and 40 overestimated (+11.8%). Additional differences emerge when we also include transplantations which followed non-standard allocation: the ELAS simulator then generally underestimates the number of transplantations in candidates with low MELD scores (MELD: 6–10) and overestimates the number of transplantations in those with high MELD scores (MELD: 21–30 and 31–40).

5.5.2.1 Validation of post-transplant outcomes

Figure 5.4 compares the simulated post-transplant event rates with the actual post-transplant event rates, estimated per country at several time horizons. These t-day post-transplant survival probabilities were estimated with the Kaplan-Meier estimator. The simulated event rates are close to the actual event rates in all Eurotransplant regions. Only in Croatia and Slovenia, the simulated post-transplant event rates appear to be slightly biased downwards. Figure 5.5 shows that the estimated re-listing probabilities are also comparable to the observed re-listing probabilities.

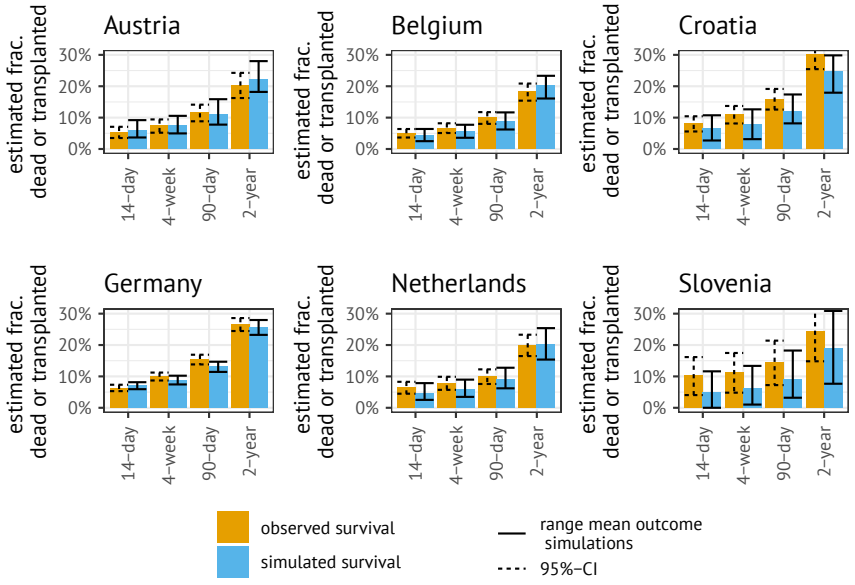


Figure 5.4: The estimated event probabilities for transplant recipients, per country for different time horizons. An event was defined as re-transplantation or waiting list death, whichever occurred first.

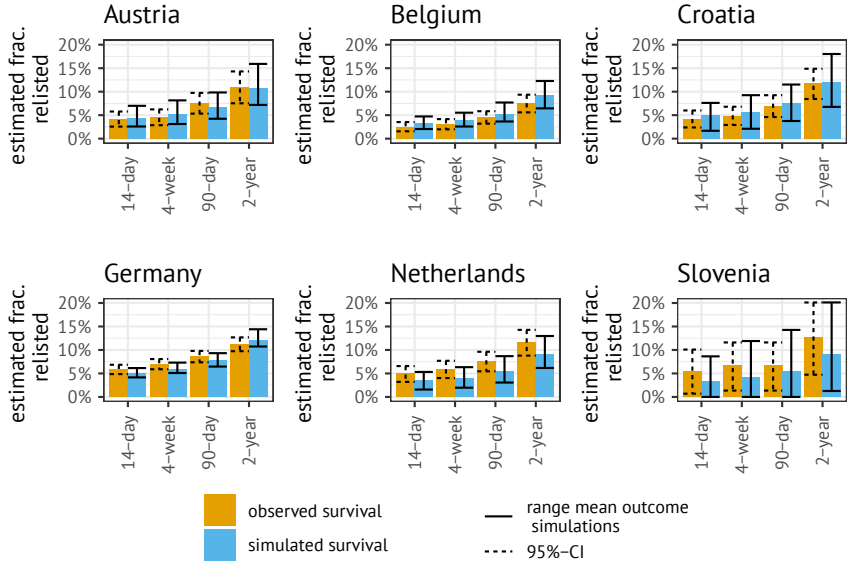


Figure 5.5: Estimated re-listing rates for transplant recipients, per country for different time horizons.

5.5.2.2 Discussion of validation results

The ELAS simulator appears to be well-calibrated for most waiting list and transplantation patterns within Eurotransplant. An important exception is the total number of transplantations and waiting list exits by lab- and match-MELD score. For example, the simulator overestimates the total number of transplantations among candidates with high urgency (MELD 31–40 or HU/ACO status), and underestimates the number of waiting list deaths in this group (see Tables 5.5 and 5.6). Table 5.6 shows that such miscalibration is present to a much lesser degree in standard allocation, with the number of transplantations only slightly overestimated for candidates with the highest match-MELD scores (31-40) and the lowest lab-MELD scores (6-10).

A potential explanation for this miscalibration is that the simulator assumes that candidates who accept a liver graft offer are always transplanted. In practice, however, transplant centers can cancel transplantation procedures after an initial acceptance, for example because of logistical issues, unfavorable histopathology findings, or instability of the transplant candidate. In such cases, Eurotransplant can re-offer the graft to candidates who are located in the vicinity of the graft via extended or rescue allocation. This generally results in the placement of livers in candidates with lower urgency, particularly in the case of rescue allocation, which operates on a first-come, first-serve basis. We note that such rescue allocation was not implemented for the ELAS simulator.

To assess whether competitive rescue allocation could partially explain the observed miscalibration, we inspected the placements of the 241 liver grafts procured from donors in the simulation period that were initially accepted by one candidate, declined before transplantation, and then re-offered to other candidates via competitive rescue allocation. For these 241 livers, Table 5.7 shows the MELD scores of the initially accepting candidate and final transplant recipient. In general, re-offering via rescue allocation indeed leads to lower MELD scores at transplantation, providing a partial explanation for the miscalibration in low-MELD groups in Table 5.5 and 5.6.

A second outcome on which the simulator is not well-calibrated is the number of transplantations per country. For example, in Belgium there are on average 55 (+4%) more transplantations in simulations than in reality. This may also be explained by the lack of competitive rescue allocation, through which approximately 10–15 grafts are transferred per year from Belgium to Germany. The fact that too many grafts are transplanted in Belgium may also explain why the number of transplantations in candidates with HCC is overestimated (see Table 5.6), as Belgium has the highest proportion of candidates that are listed with HCC. This seems supported by the fact that no miscalibration is observed for the number of transplants within candidates with HCC when restricting to livers allocated via standard allocation only (see Table 5.6).

Table 5.7: Priority of candidates in cases where a liver was initially accepted but later declined, and then re-allocated to a different recipient through competitive rescue liver allocation between January 1, 2016, and December 31, 2019. The table shows the number of candidates in each priority score category. For MELD scores, separate counts are included for the match-MELD score and lab-MELD score.

score	initially accepting candidate		final liver recipient	
urgency category				
HU/ACO	23		0	
MELD	match-MELD	lab-MELD	match-MELD	lab-MELD
31–40	60	38	1	0
21–30	107	56	53	31
11–20	45	85	140	157
6–10	6	39	47	53

We thus have two potential explanations for miscalibration of the ELAS simulator, which are (i) the simulator does not allow planned transplantation procedures to be cancelled after an initial acceptance, and (ii) the simulator does not implement competitive rescue allocation. We have chosen not to implement these two mechanisms in the ELAS simulator because (i) the focus of policy discussions in ELIAC is standard allocation, not competitive rescue allocation, (ii) cancellations after an initial acceptance are relatively rare (about 4% of transplantations), and (iii) the decision to proceed with rescue allocation is made on a case-by-case basis, which is difficult to model correctly because of the limited availability of structured data on rescue allocation. In our view, the simulated outcomes are sufficiently close to observed outcomes to make the ELAS simulator useful for policy evaluation. We illustrate this in Section 5.6 with two case studies.

5.6 Case studies: the impact of modifying ELAS rules

With two case studies, we illustrate that the ELAS simulator can be used for quantifying the impact of liver allocation policy changes. For the first case study (Section 5.6.1), we collaborated with representatives from the Belgian Liver and Intestine Advisory committee (BeLIAC) to study the impact of changes to the Belgian exception score system. In the second case study (Section 5.6.2), we study the impact of basing Eurotransplant liver allocation on ReMELD-Na scores instead of UNOS-MELD scores, which was a topic on the agenda of ELIAC in 2023.

To evaluate these ELAS policy changes, we simulate Eurotransplant liver allocation 50 times between January 1, 2016, and December 31, 2019, and compare the outcomes simulated under the modified ELAS rules to the outcomes simulated under the current

ELAS rules. We test whether modified policies lead to significantly different outcomes with traditional hypothesis testing. To increase the power of these tests, we use common random number generators [100] to eliminate any variance that is attributable to factors which we assume to be independent from the allocation policy. Specifically, we use common random numbers to synchronize the splitting of liver grafts, the graft offer acceptance behavior of candidates, and the triggering of rescue allocation across policies for each of the 50 replications. By synchronizing these processes across policies, pairwise t-tests can be used to establish the statistical significance of the impact of policy changes.

5.6.1 Case study 1: the exception score system in Belgium

Nearly half of the liver transplant candidates that are listed in Belgium receive exception points, which makes Belgium the country with relatively most awarded (N)SEs in Eurotransplant. Most of these (N)SEs increase with every 90 days of waiting time, which increases the match-MELD score that elective candidates require in Belgium to be offered a liver graft. This has led to concerns that candidates without exception points are crowded out of transplantation.

To address this, the BeLIAC has considered imposing a cap on (N)SE-MELDs of 30, which corresponds to maximizing the awardable 90-day mortality equivalent with a 50% mortality equivalent. In joint discussions, the BeLIAC also expressed an interest in capping (N)SE-MELDs at 25, as well as alternative policy options. These alternatives were slowing down (N)SE-MELDs by reducing the 90-day increments (referred to as "*slower*" policies), and lowering the initial mortality equivalents awarded for (N)SEs (referred to as "*lowered*" policies). Table 5.8 provides an overview of the policy options discussed within BeLIAC.

At the request of BeLIAC, these policy alternatives were evaluated with the ELAS simulator. Figure 5.6 and Table 5.9 summarize the results, which both focus on livers from DBD donors (DCD donors are center offers in Belgium). Figure 5.6 visualizes the distributions of the simulated (N)SE-MELD scores at DBD transplantation for exception candidates (left), and laboratory MELD scores at DBD transplantation for non-exception candidates (right). The figure shows that capping (N)SE-MELDs at 30 barely affects their distribution at transplantation, while the other policy alternatives reduce the median (N)SE-MELD at transplantation by up to 4 points on the MELD scale (left side). It also shows that lab-MELD scores at DBD transplantation for non-exception candidates become lower when (N)SEs are capped (right side). In fact, the median lab-MELD at DBD transplantation becomes up to 3 MELD points lower with *slower* and *lowered* policies, than the median observed under the current allocation rules. These alternative policies thus increase access to transplantation for candidates with lab-MELD scores between 20 and 23, which may be desired as they face a 90-day mortality risk between 10 to 15%.

Table 5.8: Policy options for the Belgian (N)SE system. Modifications are applied only to all Belgian SEs and the NSE, and not to the PED-MELD score as PED-MELD scores are valid internationally. A dash (-) indicates that the policy did not change an (N)SE attribute.

policy option	initial equivalent	90-day increment	maximum mortality equivalent
current	10% (MELD 20) for most (N)SEs, 15% (MELD 22) for HCC	10% (2-4 MELD points)	100%
capped (25)	-	-	25%[a] (MELD 25)
capped (30)	-	-	50%[a] (MELD 30)
slower	-	5% (1-2 MELD points)	-
slowest	-	2.5% (1 MELD point)	-
lowered	lowered to 8% (MELD 18) for existing (N)SEs with initial equivalents <20%	-	-

[a] Set to the initial equivalent if the initial equivalent exceeds the proposed cap. For example, candidates with biliary atresia maintain a 60% mortality equivalent.

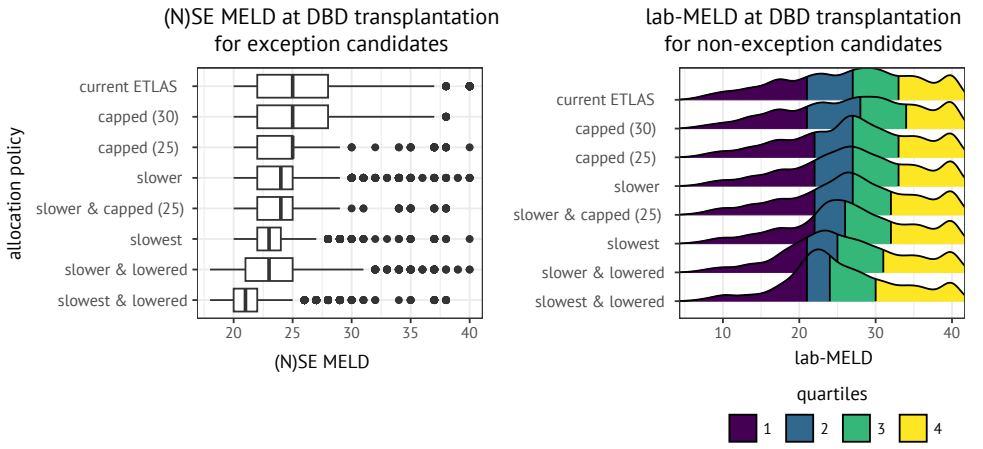


Figure 5.6: Distribution of (N)SE MELD scores at transplantation for exception candidates (left) and laboratory MELD scores at transplantation for non-exception candidates (right) in ELAS simulations. Only transplantations that were the result of patient-driven allocation are shown. Boxplots and distributions were calculated over 50 simulations.

Table 5.9 shows summary statistics for the simulated waiting list outcomes, separately for exception and non-exception candidates. Comparing the third column (actual 2016-2019 statistics) to the fourth column (averages and 95% IQRs over the 50 simulations) shows that the ELAS simulator is well-calibrated for the number of transplantations, waiting list deaths, and waiting list exits. This reassures us that the ELAS simulator reasonably describes these allocation patterns. Of policy interest are the remaining columns of Table 5.9, which show for every (N)SE policy alternative the average number of events over the 50 simulations. Comparing these outcomes to the outcomes simulated under current (N)SE rules shows that almost all policies significantly change the number of transplantations, the number of waiting list deaths, and the number of waiting list removals.

The greatest effects are sorted by combining the *slowest* and *lowered* policies (final column), with which on average 20 (+5%) extra candidates without exception points are transplanted. According to the simulation results, this policy could have avoided 12 waiting list deaths in non-exception candidates in Belgium (-10%), which corresponds to 3 waiting list deaths per year. The cost of this policy change is that we see a slight increase in the number of waiting list removals for exception patients, with on average 1–2 extra exception patients per year removed because they became unfit for transplantation, or because they had HCC or another form of cancer.

Table 5.9: Waiting list exits for elective candidates in Belgium between January 1, 2016, and January 1, 2020. The numbers displayed are the average number of exits over 50 simulations. Scenarios modifying the allocation rules were compared to simulations under the current ELAS rules with pairwise t-tests.

exit reason	patient type	current (real)	current (sim)	capped (30)	capped (25)	slower	slower & capped (25)	slowest	slower & lowered	slowest & lowered
transplanted	(N)SE	438	450 [428 – 470]	445	448	443***	445*	440***	438***	433***
	None	387	405 [379 – 423]	406*	408**	412***	409***	413***	420***	425***
waiting list death	(N)SE	27	27 [19 – 40]	28	27	28	29	29*	29	29*
	None	119	126 [108 – 141]	126	122**	122*	122**	117***	116***	114***
unfit	(N)SE	20	14 [8 – 17]	14	14*	14**	14*	15***	16***	17***
	None	23	21 [16 – 29]	21	20	21	20	20	20	20*
removed HCC or Cancer	(N)SE	8	8 [5 – 16]	9	10**	10**	11***	11***	11***	13***
	None	6	6 [2 – 14]	6	6	6	6	6	6	6

* p < 0.05, ** p < 0.01, *** p < 0.001

5.6.2 Case study 2: basing Eurotransplant liver allocation on ReMELD-Na

Candidates with hyponatremia, i.e. low serum sodium levels, face systematically higher waiting list mortality rates than suggested by their MELD score [37]. To adequately prioritize these patients, MELD-Na was introduced in 2016 for liver allocation in the United States. In 2020, Goudsmit et aFl. revised this MELD-Na score with retrospective data from Eurotransplant, leading to the *ReMELD-Na* score.

In May 2023, the ELIAC recommended basing Eurotransplant liver allocation on ReMELD-Na instead of UNOS-MELD. A matter of concern for ELIAC was that ReMELD-Na scores range from 1 to 36, while UNOS-MELD scores range from 6 to 40. Basing laboratory MELD scores on ReMELD-Na without updating the MELD-curve could therefore mean that non-exception candidates – who depend on lab-MELD for access to transplantation – could only receive match-MELD scores up to 36, while candidates with (N)SE or PED-MELD scores could still receive match-MELD scores up to 40. A switch to ReMELD-Na could thereby inadvertently give extra priority to candidates with exception points, who already appear to have an advantage in ELAS [54].

To support this discussion, we simulated two scenarios for liver allocation using ReMELD-Na. For both scenarios, lab-MELD scores were based on ReMELD-Na, calculated using:

$$\begin{aligned}\text{ReMELD-Na} = 7.85 + 9.03\ln(\text{crea}) + 2.97\ln(\text{bili}) + 9.52\ln(\text{INR}) + \\ 0.392(138.6 - \text{Na}) - 0.351(138.6 - \text{Na})\ln(\text{crea}).\end{aligned}$$

In the first scenario, the exception score system remained unchanged, which means that PED-MELD and (N)SE-MELD scores are calculated based on the UNOS-MELD survival curve. This curve is given by the following formula:

$$S_{90}^{\texttt{UNOS-MELD}} = 0.98037^{0.17557(\texttt{UNOS-MELD}-10)}.$$

In the second scenario, PED-MELD and (N)SE-MELD scores are instead calculated based on a survival curve developed specifically for ReMELD-Na. This curve was obtained by estimating a Cox proportional hazards model on Eurotransplant registry data using ReMELD-Na as the only covariate. The obtained ReMELD-Na curve is given by the following formula:

$$S_{90}^{\text{ReMELD-Na}} = 0.9745^{0.2216(\text{ReMELD-Na}-10)}.$$

Table 5.10 shows simulated waiting list outcomes under these ReMELD-Na policies, summarized over 50 simulations. The third column shows that introducing ReMELD-Na without updating the S-curve results in approximately 70 extra waiting list deaths in total ($p < 0.001$), which corresponds to 15–20 extra waiting list deaths per year. This finding is likely explained by ELIAC's concern that a switch to ReMELD-Na inadvertently deprioritizes candidates who depend on lab-MELD scores for access to transplantation. The fourth column shows that switching to ReMELD-Na with the updated S-curve could have averted 25 waiting list deaths in total ($p < 0.001$).

Table 5.10: Average number of simulated waiting list exits for candidates under UNOS-MELD and ReMELD-Na, with and without updating the S-curve. The numbers in brackets are 95% interquantile ranges, observed over 50 simulations of ELAS between January 1, 2016, and January 1. Paired t-tests were used to test whether either scenario significantly affected the simulated waiting list outcomes.

exit status	UNOS-MELD (current)	ReMELD-Na (old S-curve)	ReMELD-Na (updated S-curve)
waiting list deaths	1633.4 [1581.2-1685.6]	1703.3*** [1643.2-1763.3]	1608.3*** [1546.9-1669.7]
transplantations	6414.5 [6400.1-6428.9]	6417.7* [6401.6-6433.7]	6410.3*** [6396.7-6423.8]
removed	859.9 [834.8-885]	837.9*** [812.9-862.8]	870.4*** [842.7-898.1]

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

An important limitation of this analysis is that serum sodium measurements are not available for most candidates in Eurotransplant registry data. When serum sodium was missing in simulations, we calculated ReMELD-Na scores with a serum sodium level of 138.6 mmol/l, which results in 0 points being awarded for hyponatremia. Because this means that hyponatremia could not be prioritized in all candidates, the reduction of 25 waiting list deaths is a conservative projection.

Whether serum sodium is reported to Eurotransplant depends primarily on the candidate's listing center, because the transplant centers either never or almost always report serum sodium to Eurotransplant. This motivated us to also assess the number of waiting list deaths stratified by the listing center's track record of reporting serum sodium. For this, we categorize centers into centers with high, medium and low serum sodium completeness. Table 5.11 shows the total number of waiting list deaths per type of center. It can be seen that the reduction in waiting list deaths is indeed concentrated in centers with high serum sodium completeness, with 28 fewer waiting list deaths observed in such centers. Under the (optimistic) assumption that this reduction in waiting list deaths is representative for all centers in Eurotransplant, using ReMELD-Na as the basis for liver allocation could have prevented up to 80 waiting list deaths over the simulation period.

Table 5.11: Simulated number of waiting list deaths for candidates between January 1, 2016, and January 1, 2020, under UNOS-MELD (current) and ReMELD-Na with an updated S-curve.

serum sodium completeness	center count	patient count	waiting list deaths under UNOS-MELD	waiting list deaths under ReMELD-Na
high	14	3995	589.3 [554.8-623.9]	561*** [518.6-603.4]
medium	13	3098	446.9 [404-489.7]	446.9 [402.1-491.7]
low	10	4775	590.3 [551.3-629.3]	593.8 [555.3-632.4]

high: serum sodium known for >75% of candidates; medium: serum sodium known for >50% of candidates; low: otherwise.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

In discussions with ELIAC and national competent authorities on ReMELD-Na, concerns were raised about the impact of ReMELD-Na on pediatric, adolescent, and female transplant candidates. Table 5.12 shows the simulated impact of ReMELD-Na on these vulnerable patient groups. The switch to ReMELD-Na has little impact on outcomes for these patients, suggesting that the reduction in waiting list deaths is concentrated in males aged 30 years or older.

The table also shows the impact of ReMELD-Na on candidates with renal dysfunction: fewer candidates on biweekly dialysis are transplanted under ReMELD-Na, as are candidates who require a combined liver and kidney transplantation. Such a change could potentially be welcomed, as there are indications in the literature that UNOS-MELD overprioritized candidates with renal dysfunction [40].

Table 5.12: Averages of the simulated number of waiting list exits per vulnerable patient group based on simulation of ELAS between January 1, 2016 and December 31, 2019.

		UNOS-MELD	ReMELD-Na	diff.	per year
pediatric cand. (<18 yrs)	transplanted	220 [205-235]	209 [196-220]	-11	-2.8
	deceased	24 [20-28]	25 [20-31]	1	0.2
adolescents (18-29 yrs)	transplanted	232 [216-247]	219 [206-232]	-13	-3.3
	deceased	25 [21-29]	27 [21-33]	2	0.5
females	transplanted	1599 [1562-1637]	1586 [1557-1614]	-13	-3.3
	deceased	524 [497-551]	522 [500-544]	-2	-0.5
liver + kidney candidates	transplanted	236 [225-246]	204 [192-217]	-32	-8.0
	deceased	57 [50-64]	68 [59-77]	11	2.8
candidates on dialysis	transplanted	442 [414-470]	376 [352-401]	-66	-16.5
	deceased	257 [237-276]	275 [253-297]	18	4.5

5.7 Conclusions and discussion

To help align the interests and perspectives of its member countries, Eurotransplant requires a tool that can quantify the impact of proposed policy changes to its liver allocation system. Discrete-event simulation is an excellent tool for this purpose, and is already routinely used in other geographic regions to revise organ allocation policies. This chapter reports on the development of the ELAS simulator, which is the first simulator tailored to the unique challenges of Eurotransplant as a multi-national organ exchange organization.

To build trust in the ELAS simulator as a policy evaluation tool, we have validated the ELAS simulator by comparing simulated outcomes to observed outcomes between January 1, 2016, and December 31, 2019. We found that the simulator is able to closely replicate most patterns in Eurotransplant liver allocation. In our own view, and in ELIAC's, the remaining differences are sufficiently small for the ELAS simulator to contribute to liver allocation policy evaluation within Eurotransplant. We have illustrated this with two case studies. The case study on the Belgian exception point system has been discussed within BeLIAC, and has led to a recommendation to cap (N)SE scores in Belgium at 28. The case study on ReMELD-Na has led to a recommendation to switch to allocation based on ReMELD-Na, which was implemented on March 25, 2025.

Although this demonstrates that the ELAS simulator is useful for policy evaluation, the software also has limitations. A first limitation is that our simulations are driven by Eurotransplant registry data, which does not capture all information relevant for liver allocation development. For example, in the second case study we have seen that serum sodium is not available in Eurotransplant registry data for many candidates, which complicated the assessment of the impact of allocation based on ReMELD-Na. This limitation could be addressed by prospective data collection of factors relevant to allocation. Secondly, the statistical models for graft offer acceptance behavior and post-transplant survival were calibrated to historical data. Developments in liver transplantation threaten the external validity of these models. An example of such a development is machine perfusion, which is enhancing the outcomes after liver transplantation [101] and which is altering the graft offer acceptance behavior of transplant centers. This limitation can potentially be addressed by re-calibrating the statistical models with contemporary data.

From a policy perspective, several areas remain in which Eurotransplant's liver allocation system may be improved. These areas include taking post-transplant outcomes into account when allocating livers [19], broader geographic sharing of livers for candidates with very high MELD scores [102, 103], and rectifying sex disparity in liver waiting list outcomes [64]. We anticipate that the ELAS simulator can play a role in informing ELIAC of the impact of policy changes related to these topics.

Part II

Allocation of the kidney

Chapter 6

Kidney allocation in Eurotransplant

Up to 100 million Europeans have Chronic Kidney Disease (CKD) [104]. CKD is characterized by the progressive loss of kidney function, and its causes include diabetes, hypertension, and glomerulonephritis. Patients with CKD can eventually progress to End-Stage Renal Disease (ESRD), which means that they become dependent on renal replacement therapies (RRTs) such as dialysis or kidney transplantation. Whereas other forms of end-stage organ failure cannot be managed with therapy, end-stage kidney failure can be managed for extended periods with dialysis [7]. However, kidney transplantation is the preferred treatment option for most patients with ESRD because it is associated with a reduction in patient mortality and improves the patient's quality of life [105].

Kidney transplantation became the preferred treatment option for patients with ESRD in the 1980s, when substantial improvements were observed in post-transplant outcomes [7]. As a result, the kidney waiting list in Eurotransplant expanded from less than 2,000 patients in 1980 to approximately 10,500 patients in 1994 [106]. Since then, the number of patients awaiting kidney transplantation has remained stable in Eurotransplant with approximately 10,000 patients currently waiting for a kidney transplant.

Eurotransplant allocates kidneys from deceased-organ donors to these waiting patients. When Eurotransplant was initiated, candidates were prioritized solely based on Human Leucocyte Antigen (HLA) matching. Currently, Eurotransplant uses an allocation system which tries to balance HLA matching with fairness considerations. In this chapter, we describe the history of this system and some contemporary challenges in the allocation of deceased-donor kidneys. We also briefly describe the work included in this thesis that can inform discussions on addressing these challenges.

6.1 HLA matching versus fairness

In the late 1960s, immunologists observed that the best outcomes after kidney transplantation were observed in pairs of siblings who had compatible ABO blood groups and matching leukocyte antigen groups [107]. Anticipating that such a matching effect also existed when transplanting kidneys from deceased donors, Jon van Rood proposed Eurotransplant, a program in which a central office would use a computer to locate the best-matching candidate for the kidneys that became available from deceased donors [1]. Shortly after Eurotransplant was initiated in 1967, similar organizations were established in other geographic regions, motivated by the idea that outcomes after deceased-donor transplantation could only be improved through collaboration [108].

Already in 1970, this idea became controversial with a strong debate emerging between immunologists and clinicians on the actual importance of leukocyte-antigen matching in deceased-donor kidney transplantation [109, 110]. The commitment of immunologists to HLA matching was strengthened in the 1970s and 1980s, as they unraveled many complexities of what became known as the Human Leucocyte Antigen (HLA) system. The discovery of HLA-DR antigens in 1977 was particularly important, as these antigens were shown to have a stronger effect on prognosis after kidney transplantation than the earlier discovered HLA-A and HLA-B antigens [111, 112, 108].

At the same time, it was recognized that HLA matching was far from a magic bullet; many patients with poorly matched kidneys had good outcomes after transplantation [113, 110]. Based on such observations, clinicians questioned whether HLA matching was worth the effort, especially because the practice resulted in disparities in access to transplantation [114]. For example, in the United States, it was observed that black patients were waiting three times longer than white patients for a kidney transplant. Thomas Starzl, who is known as "the father of modern transplantation", criticized the blind focus on HLA matching in kidney allocation, referring to it as *"the institutional organization of racial bias"* [107, 159]. To reduce such disparities, Starzl's transplant center instead used a point system to prioritize candidates for transplantation, in which tissue matching played a role that was *"significant but far from overriding"* [115].

This criticism of HLA matching intensified in the 1980s with the advent of cyclosporine A. This immunosuppressant strongly reduced the incidence of acute rejection of kidney transplants, and was responsible for the major improvements in kidney transplant outcomes that were observed in the 1980s. Shortly after the introduction of cyclosporine A, several single-center studies suggested that this immunosuppressant had made HLA matching in kidney transplantation redundant [116, 117]. These early findings have since been contradicted by multi-center and registry-based studies, which showed that HLA matching continues to be strongly associated with graft and patient survival [118, 119].

Based on these later studies, consensus has arisen that the best outcomes are observed in patients who receive transplants with zero mismatches on the HLA-A, HLA-B, and HLA-DR loci [118, 120]. However, the extensive polymorphism of the HLA system means that perfectly matched kidneys are not available for most candidates. In fact, it was already known in the 1980s that only about one in five patients can receive a perfectly matched kidney with a waiting list of 10,000 patients [121]. Most patients thus have to settle for a kidney with HLA mismatches. In that case, consensus is that HLA-DR matching is more important than HLA-B matching, which in turn is more important than HLA-A matching [122–124].

Because of the role of HLA matching was contended, kidney allocation first became more decentralized in the 1980s [108]. For example, in 1988 Eurotransplant introduced a kidney allocation system that mandated exchange of kidneys between centers only for (a) patients who had zero HLA mismatches with the kidney and (b) the so-called "*hyper-immunized patients*" (see Section 6.2.2) [7]. Otherwise, the center responsible for procurement of the kidneys could choose patients from their own waiting list for transplantation, subject to blood group compatibility rules and minimum HLA match criteria (defined as 2 DR matches, or 1 B + 1 DR match) [7]. Procurement centers also had the option to voluntarily offer the kidneys to the Eurotransplant pool. Candidates would then be prioritized by compatibility at the HLA-DR locus, followed by compatibility at the HLA-B locus, and finally compatibility at the HLA-A locus [7].

When Eurotransplant evaluated this system in the 1990s, concerns were raised over the fact that (i) 10 percent of patients consistently waited more than five years for kidney transplantation, (ii) transplant rates were low for candidates with rare HLA types or homozygosity at any of the HLA loci, and (iii) procurement and transplant rates were imbalanced between the centers and countries [125]. These fairness concerns eventually led to the adoption of the Eurotransplant Kidney Allocation System (ETKAS) in 1996, which was based on a point system that had been proposed by Wujciak and Opelz in the years before. Besides this program, Eurotransplant has used two other programs to allocate deceased-donor kidneys since the 1990s: the Acceptable Mismatch (AM) program for the allocation of kidneys to hyper-immunized candidates (Section 6.2.2), and the Eurotransplant Senior Program (ESP) for the allocation of kidneys from donors aged 65 years or older (Section 6.2.3).

6.2 Kidney allocation programs in Eurotransplant

6.2.1 The Eurotransplant Kidney Allocation System (ETKAS)

Wujciak and Opelz tried to address the dilemma between HLA matching and fairness by using computer simulations to develop a point system for kidney allocation [126, 127]. This system awarded points for the absence of HLA mismatches, but also points for a candidate's waiting time to ensure that no candidate would be left behind. Additionally, to avoid extreme waiting times for difficult-to-match patients, the system awarded points for the *"mismatch probability"*, a quantification of how common favorably matched kidneys are for the patient.

Eurotransplant implemented a modified version of this point system for kidney allocation in 1996, and the resulting program has become known as the Eurotransplant Kidney Allocation System (ETKAS) program. The modifications made included that ETKAS awards extra priority to pediatric candidates, and implements a mechanism to balance the international transfer of kidneys [127].

One year after the introduction of ETKAS, in 1997, it was concluded that ETKAS successfully achieved its primary goals; the system had increased the number of transplantations among pediatric and long-waiting candidates and it had corrected imbalances in the international exchange of kidneys [15, 8]. Despite this apparent success, it was also pointed out by Wujciak and Opelz that ETKAS *"could not be considered a final and unalterable product"*, which instead would require *"continued fine-tuning depending on new developments"* [127].

In light of these comments, it is not surprising that several refinements have been made to ETKAS since 1996. One refinement concerns the definition of waiting time. When ETKAS was initiated, waiting time was defined as the number of days a candidate had spent on the waiting list, which conferred an advantage to patients who were referred early to the kidney waiting list. To address this, Eurotransplant redefined waiting time to the number of days a candidate had received dialysis in January 2000 [128]. A second issue was that ABO blood group O kidneys could be transplanted in non-O candidates in case of a zero mismatch, which led to an increased waiting list mortality and longer waiting times for blood group O patients [17]. In June 2010, this issue was addressed by always requiring candidates and donors to have identical ABO blood groups in ETKAS.

Shortcomings of ETKAS have also been identified for which an adequate solution has remained elusive. A notable example is that the ETKAS point system places equal emphasis on the HLA-A, HLA-B and HLA-DR loci, which has been described to lead to additional mismatches on the HLA-DR locus [15, 129]. Several proposals have been made to instead emphasize HLA-DR matching in ETKAS (e.g., Doxiadis et al. [130]) which have been rejected by national competent authorities (e.g., Heemskerk et al. [131]). As a

result, ETKAS still places equal emphasis on HLA matching at the A locus as on matching at the DR locus.

Another example of such a shortcoming are the mismatch probability points (MMPPs), which are used to facilitate access to transplantation for difficult-to-match candidates. One issue is that MMPPs are calculated using a formula that disregards HLA haplotype linkage disequilibrium [132]. A second issue is that at most 100 MMPPs are awarded in ETKAS, which may be insufficient to provide immunized patients with equality of opportunity [133–135].

6.2.2 Immunized candidates & the Acceptable Mismatch (AM) program

Many kidney transplant candidates have developed antibodies against donor HLA antigens before they are listed for a kidney transplant, for instance because of a prior blood transfusion, a pregnancy, or a previous transplantation. If a donor carries the HLA antigens against which the candidate has developed such donor-specific antibodies (DSAs), transplantation can be contraindicated because it is likely to result in antibody-mediated rejection of the kidney.

In Eurotransplant, transplant centers have historically been required to conduct a complement-dependent cytotoxicity (CDC) crossmatch before transplantation, in which the serum of the patient is mixed with lymphocytes isolated from the donor. If such a crossmatch leads to the cell death of the lymphocytes, transplantation is strongly contraindicated [136], and even prohibited in Germany. In the past, transplantation centers were also required to regularly test the sera of their patients against a representative panel of donors to determine their candidates' panel-reactive antibody (PRA) levels. Such tests are known as the CDC-PRA tests and the obtained PRA levels quantify the percentage of the donor pool against which the candidate has a positive crossmatch. CDC testing could also be used to derive against which antigens a candidate had developed DSAs, albeit at limited resolution. Since the 1980s, centers have been able to report such antigens to Eurotransplant as *unacceptable antigens*, which ensures that there candidates would not be offered kidneys that carry those antigens.

Having a pre-existing immunization can thus prevent a candidate from receiving a kidney transplant, in particular for candidates with high PRA levels. This can lead to an accumulation of immunized patients on the waiting list, which was indeed observed in the late 1980s. In 1988, Frans Claas and Jon van Rood proposed to strategically select donors for the *"hyper-immunized"* candidates based on *"acceptable antigens"* [137], which formed the basis of the Acceptable Mismatch (AM) program that was initiated in 1989. These acceptable antigens were defined as antigens against which an immunized patient had not developed DSAs, and could be identified by crossmatching the candidate's serum against panels of HLA-typed blood donors that carried exactly one antigen mismatch with

the patient [137, 138]. In the AM program, highly immunized candidates (PRA >85%) are given priority to donors who carried HLA antigens that were either matching with or acceptable to the candidate. Since its initiation, the AM program has continually been updated by the Eurotransplant Reference Laboratory (ETRL). For example, acceptable antigens were initially only defined for HLA-A and HLA-B, while currently five HLA loci are used for AM allocation [139].

CDC-PRA assays, in which a candidate's sera is tested against a panel of donor lymphocytes, has thus had an important role in determining a candidate's degree of immunization. In recent years this technology has largely been replaced by solid-phase assays, in which the patient's serum is directly tested against isolated HLA antigens [140]. Centers regularly screen the sera of their candidates with these solid-phase assays and report the donor-specific antibodies that are identified using solid-phase assays as unacceptable to Eurotransplant. Notable is that these solid-phase assays are more sensitive than CDC-PRA assays, which means that DSAs can be identified that lack CDC-reactivity. Transplantation in the presence of such DSAs is also associated with inferior outcomes [141], but not an absolute contraindication [142]. Instead, European guidelines recommend that the decision to transplant in the presence of such a DSA should be based on an individualized risk assessment. This risk assessment should critically evaluate the DSA in light of potential sensitization events and should assess the impact of designating it as unacceptable on the likelihood of finding an HLA-compatible kidney [140].

Since 2016, Eurotransplant calculates a *virtual* PRA (vPRA) for each candidate based on their reported unacceptable antigens. This vPRA is defined as the percentage of donors that carry the unacceptable antigens in a database of 10,000 donors that is maintained by the ETRL. Advantages of the vPRA compared to the PRA are (i) that measurement variability associated with the PRA can be avoided, and (ii) that the vPRA is directly based on unacceptable antigens, which makes it a better measure of the relative restriction in the donor pool faced by immunized candidates. In 2020, the vPRA completely replaced the PRA in kidney allocation in Eurotransplant. For example, mismatch probability points have been awarded since 2020 based on the vPRA instead of the PRA, and candidates with a PRA below 85% but a vPRA exceeding 85% can enter the AM program under specific conditions [138].[1]

[1] For the AM program, unacceptable antigens either require CDC reactivity, or documentation that links the DSA to a sensitizing event.

6.2.3 The Eurotransplant Senior Program

In 1999, Eurotransplant initiated the Eurotransplant Senior Program (ESP), which is used to offer kidneys from donors 65 years or older with priority to candidates 65 years or older. The aim of ESP was (i) to promote the usage of kidneys from older donors and (ii) to reduce waiting times for candidates 65 years or older [143]. These aims were achieved by prioritizing candidates solely based on their accrued dialysis time and by offering kidneys only to candidates located in the vicinity of the donor [144]. HLA typing of ESP donors was not performed in order to maximally reduce cold ischemia times. This meant that transplantations within ESP were done without consideration of HLA match quality. Because the donor's HLA typing was unknown at the time of allocation, immunized candidates were not allowed to participate in ESP.

Currently, all countries require the HLA typing of ESP donors to be available before allocation, which has enabled immunized candidates to participate in ESP. A Eurotransplant paired kidney donation study has demonstrated that outcomes for patients 65 years or older also improve with HLA-DR matching [145]. Based on these findings, proposals to prioritize HLA-DR matching in ESP have been made which are scheduled for implementation in 2025.

6.3 Contemporary challenges in kidney allocation

Since the introduction of ETKAS and ESP in the 1990s, the landscape of kidney transplantation has changed substantially. For example, Eurotransplant's donor and patient populations have aged due to demographic developments, and the immunological evaluation of transplant candidates has changed with the introduction of solid-phase assays. Despite this changing landscape, the core principles of Eurotransplant's kidney allocation systems have remained largely unchanged. This raises the question of whether these systems adequately address contemporary challenges in kidney transplantation.

One such challenge concerns the immunized candidates who depend on ETKAS for access to transplantation. Transplant professionals from Eurotransplant's kidney transplantation centers have regularly expressed concerns that this patient group is disadvantaged in ETKAS. Empirical evidence for such a disadvantage comes from Germany where retrospective analyses have shown that patients with vPRAs exceeding 85% are disadvantaged [134, 135]. In Chapter 7, we examine the relation between the vPRA and the transplant rate using retrospective data from all Eurotransplant member countries. We indeed find that immunized candidates face reduced access to transplantation in ETKAS. European guidelines already recommend that this disparity should be addressed by directly awarding points for the vPRA using a sliding scale [140]. In Chapter 8, we design such a sliding scale for ETKAS.

A second challenge comes from the changing patient and donor demographics. Since the Eurotransplant Senior Program (ESP) was introduced in 1999, the percentage of patients aged 65 years or older at listing has increased from 6% in 1999 to 22% in 2024, and the percentage of donors aged 65 years or older has increased from 11% to 24%. With this changing demographic, concerns have been voiced over the fairness of ESP. For example, in Germany, the median dialysis time at transplantation currently differs by more than four years between candidates aged over 65 and those under 65 [146]. This means that a German candidate who starts dialysis at age 60 is unlikely to receive a kidney transplant until their 65th birthday, and is expected to be transplanted shortly thereafter.

Eurotransplant also has not implemented any form of candidate-donor age matching within ETKAS, with the exception of pediatric candidates, who have priority to kidneys procured from pediatric donors. Organ allocation organizations in France, the U.K. and the U.S. have all implemented mechanisms which direct kidneys from young donors to young patients [147–149]. Calls have been made in the recent literature to also introduce such continuous candidate-donor age matching in Eurotransplant [150]. In Chapter 8, we evaluate a form of continuous-donor age matching for ETKAS.

A third challenge is that ETKAS has continued to place equal emphasis on HLA-A, HLA-B, and HLA-DR matching, while virtually all other organ exchange organizations emphasize matching at the HLA-DR locus, or matching at both the HLA-B and HLA-DR loci [151]. In Chapter 8, we examine how waiting list outcomes are affected if more priority is given to matching at the HLA-B and HLA-DR loci.

This thesis explores several directions in which kidney allocation in Eurotransplant could be improved. Instrumental to studying the impact of these policy changes is the ETKidney simulator, a discrete-event simulator that mimics ETKAS and ESP allocation based on data from the Eurotransplant database. We describe and validate this simulator in Chapter 8.

Chapter 7

Access to transplantation for immunized candidates

An article based on this chapter has appeared in *Transplantation*, de Ferrante, H.C., Smeulders, B.M.L., Tieken, I., Heidt, S., Haasnoot, G., Claas, F.H.J., Vogelaar, S., Spieksma, F.C.R., 2023. 10.1016/j.ajt.2024.06.018 [152]

Abstract

The presence of donor-specific antibodies (DSAs) before transplantation is associated with graft rejection and poor transplantation outcomes. Kidney transplant centers can assign HLA antigens as unacceptable, to prevent kidney offers against which their candidates have developed clinically relevant antibodies. In this chapter, we assess to what degree having unacceptable antigens affects access to transplantation in ETKAS.

For this, candidates for kidney-only transplantation listed between January 1, 2016, and January 1, 2020 were included (n=19,240). Cox regression was used to quantify the relation between the relative transplant rate and the vPRA. Models used accrued dialysis time as the timescale, were stratified by patient country and blood group, and adjusted for non-transplantable status, patient age, sex, history of kidney transplantation, and the prevalence of 0 HLA-DR mismatched donors in Eurotransplant's donor pool.

Transplant rates were 23% lower for vPRA >0–50%, 51% lower for vPRA 75–85%, and decreased rapidly for vPRA >85% ($p < 0.001$). The inverse relation between transplant rate and vPRA is independent of Eurotransplant country, listing time, and the availability of donors with 0 HLA-DR mismatches. Results were similar when quantifying the relation between vPRA and the attainment of a sufficiently high rank for ETKAS offer, which suggests that the lower transplant rates for immunized patients are due to ETKAS allocation, and not the offer acceptance behavior of kidney transplant centers. We conclude that the current ETKAS allocation mechanism inadequately compensates immunized patients for reduced access to transplantation.

7.1 Introduction

The presence of pre-formed HLA antibodies restricts a candidate's potential donor pool, which could imply that immunized candidates face prolonged waiting times. In Eurotransplant, highly immunized candidates (vPRA >85%) may access the AM program, in which more than half of the patients are transplanted within a year of entry [153]. However, fewer than 10% of the immunized candidates meet the AM entry criteria, and the remaining 90% of immunized candidates depend on ETKAS for access to transplantation.

In ETKAS, immunized candidates are indirectly prioritized via the mismatch probability, which is the probability that among the next 1,000 reported donors, there is no blood group-identical donor, who has no HLA antigens unacceptable to the candidate and who has at most 1 HLA mismatch with the candidate. However, it has been questioned whether enough points are given to the mismatch probability to avoid prolonged waiting times for immunized candidates [133]. An additional problem is that an increased vPRA may only marginally increase the mismatch probability for some patient groups, such as candidates with a difficult-to-match HLA typing or those with blood group AB [134]. These criticisms suggest that the priority currently awarded to immunized patients in ETKAS is insufficient.

In Eurotransplant, two prior studies have examined the relation between the relative transplant rate and immunization, both using cohorts from Germany. These studies used the vPRA to quantify immunization status. Firstly, a six-center study by Ziemann et al. studied the impact of vPRA on time-to-transplantation with a 2012 cohort, using Cox proportional hazard (PH) models with time elapsed since 2012 as the timescale [134]. Adjusting for blood group, accrued dialysis time, and the vPRA, Ziemann et al. reported that a 1% increase in vPRA is associated with an approximate 1% decrease in transplant rate. A limitation of the Ziemann et al. study is that the 2012 cohort precedes the actual implementation of the vPRA in Eurotransplant, such that those vPRA values may not be a reliable proxy for a candidate's degree of immunization.

Zecher et al. [135] studied the relation between vPRA and the transplant rate with a 2019 German population-wide cohort. Instead of the time a candidate had spent on the waiting list, Zecher et al. used time-on-dialysis as the timescale. Adjusting for recipient age, sex, blood group, percentage time being transplantable, allocation region, and enrolment in the AM program, Zecher et al. described that only highly immunized patients (vPRA >85%) have significantly lower transplant rates in Germany (42% lower). Whether this finding is generalizable to other Eurotransplant member countries is an open question, because dialysis time is a bottleneck in Germany but not in Eurotransplant's other member countries.

In this chapter, we examine the relation between the vPRA and the relative transplant rate, using a 2016 to 2020 cohort of all kidney-only transplant candidates on the ETKAS waiting list. Unlike the aforementioned studies, we were able to use vPRA as a time-varying variable, and can adjust for a candidate's non-transplantable status.

7.2 Materials and methods

7.2.1 Study population and data

Kidney-only transplant candidates on the ETKAS waiting list between January 1, 2016, and January 1, 2020 were included. The start date of January 1, 2016 was chosen because the median vPRA reported for immunized candidates stabilized in 2016. The end date was chosen because Covid-19 substantially reduced transplant activity in 2020 [154]. Candidates waiting for a living donor transplantation and transplant candidates with additional priority in allocation were excluded. The latter group included patients who require a combined transplantation, pediatric patients, and patients with a High Urgency (HU) status. Our analyses use accrued dialysis time as the timescale. This means that the transplantation rate could not be modeled for preemptively listed patients, i.e. patients who did not start dialysis before being activated on the Eurotransplant kidney waiting list. Patients listed preemptively thus entered our analysis only on the date they started dialysis, and patients that were transplanted preemptively were excluded. transplant candidates were censored at age 65 because candidates above this age become eligible for allocation through the Eurotransplant Senior Program (ESP). We also censored candidates at entry into the AM program.

7.2.2 Outcome variables

Time-to-transplantation was used as the primary outcome. Patients waiting for a transplant on January 1, 2020 were censored, as were patients that were delisted for other reasons than transplantation (waiting list death or removal). An unmeasured confounder of the relation between vPRA and the transplant rate may be local (center) policies with respect to accepting kidney offers. For example, risk averse centers or doctors may use a liberal definition of unacceptability (increasing the vPRA) and have strict requirements for donor-recipient match quality (turning down more kidney offers). This risk-averseness could thereby increase the candidate's vPRA and prolong their waiting time, which could induce an association between the vPRA and the transplant rate that is not due to ETKAS allocation itself.

This motivated us to also assess the relation between vPRA and the kidney offer rate. Pivotal for this is careful definition of what constitutes an offer. The relation between vPRA and time to actual offer can also be confounded by kidney offer acceptance policies, as allocation profiles can be used to specify that a candidate wishes to be excluded from potential kidney offers (for example, based on donor age, extended criteria donors, and HLA match quality). To avoid confounding bias in a time-to-offer analysis, we define time-to-offer as the first time a patient was ranked high enough on a kidney match list to have received an actual offer (ignoring offer turndowns due to allocation profiles). This information is retrievable from unfiltered match lists from the Eurotransplant database. We refer to this outcome as "time-to-any-offer".

This time-to-any-offer may be of limited clinical relevance. For instance, it could be that the offered kidney had a poor HLA match quality with the candidate, or that the kidney was first declined by many other candidates for quality reasons. We therefore also assess the relation between vPRA and a "high-quality" offer, where "high quality" is defined as an offer with no HLA-DR mismatches that was declined for quality reasons by fewer than five higher-ranked candidates.

7.2.3 Adjustment variables, transformations, and stratification

Multivariable Cox proportional hazards (PH) models were used to study the relation between the vPRA and the transplant rate. The vPRAs used were calculated against ETRL donor panel (v3.0), which includes HLA data on the serological split level for HLA-A, -B, -C, -DR and -DQ. We note that centers and local HLA laboratories may have differing policies in labeling antigens as unacceptable [134]. For over half of immunized patients the set of unacceptable antigens changed while on the ETKAS waiting list. This motivated use of vPRA as a time-varying variable.

Cox models used time-on-dialysis as the timescale, since ETKAS allocation is driven by accrued dialysis time and not waiting time. A potential issue with using time-on-dialysis as the time scale is that patients may have started with dialysis before they were listed for kidney transplantation in ETKAS. Such previously accrued dialysis time could bias the analysis, as a standard Cox model would consider patients with previously accrued dialysis time to have been at risk of transplantation before they were actually listed on the kidney waiting list of Eurotransplant. To avoid such bias, we estimate the relation between vPRA and waiting list outcomes using the extended Cox model, which allows for delayed entry.

One prior study did not use a non-linear transformation for vPRA [134], which implicitly makes the assumption that an increase from vPRA 0% to 1% has the same effect as an increase from 99% to 100%. This assumption is implausible, because a candidate with a vPRA of 1% can still access 99% of donors, while a candidate with vPRA 100% cannot receive any offers. Another study allowed for a non-linear effect of vPRA by discretizing the vPRA (0%, 0.1–50%, 50.1–85%, 85.1–95%, and >95%). One disadvantage to discretizing the vPRA is that it assumes that candidates in the same group (e.g., vPRA 0.1% and 50%) all have the same reduction in relative transplant rate. A second disadvantage is that it wastes statistical information [155]. We therefore use in our preferred specification a spline transformation for the vPRA (with 8 degrees of freedom). We compare this strategy to using a fine-grained discretization of the vPRA (0%, >0–25%, 25–50%, 50–75%, 75–85%, 85–95%, 95–99%, 99–100%).

Confounders adjusted for in the analysis are the patient age at listing, patient sex, and the number of previously received kidney transplants (none, 1 or 2+). For each patient, we also counted the number of 0 HLA-DR mismatched kidneys among the last 10,000 donors reported to Eurotransplant (ignoring blood group identity), and adjusted for this number in our analyses. We adjusted for the HLA-DR locus because this locus most strongly affects outcomes after kidney transplantation. We did not adjust for the mismatch probability because the mismatch probability is indirectly based on the vPRA, which leads to issues of multicollinearity. Finally, we adjusted for whether the patient was non-transplantable (time-varying variable). All these confounders have to be reported to Eurotransplant to activate a candidate on the kidney waiting list, such that there was no missing data. We adjusted for penalized spline terms of continuous confounders with 4 degrees of freedom (candidate age and the number of 0 HLA-DR mismatched kidneys).

How much dialysis time a candidate needs in order to receive an offer through ETKAS strongly depends on their country of listing and blood group. Such heterogeneity makes a proportional hazards assumption for blood group and recipient country implausible and motivated us to stratify Cox proportional hazards models by recipient country and blood group. Within Germany, we stratified based on the seven organ procurement regions because donor availability differs by region.

7.3 Results

This study included 19,420 patients on the ETKAS waiting list between January 1, 2016, and January 1, 2020 (see Table 7.1). In total, 1,316 patients were excluded because they were transplanted preemptively. Unacceptable antigens were reported for 21% of the candidates that met inclusion criteria, either at registration or before study start (January 1, 2016). For almost 21% of patients this first set of unacceptable antigens reported was updated after their registration, or after study start. In total, unacceptable antigens were reported for almost 30% of patients during the study period. Immunization (defined as vPRA >0%) was associated with being female, having had a previous transplantation, having accrued more time on dialysis, and having spent more time on the waiting list ($p < 0.001$, see Table 7.1). Figure 7.2 plots per Eurotransplant center the distribution in vPRA for immunized patients. Although there is center-to-center variation in reported vPRAs, most variation in vPRA is at the patient level.

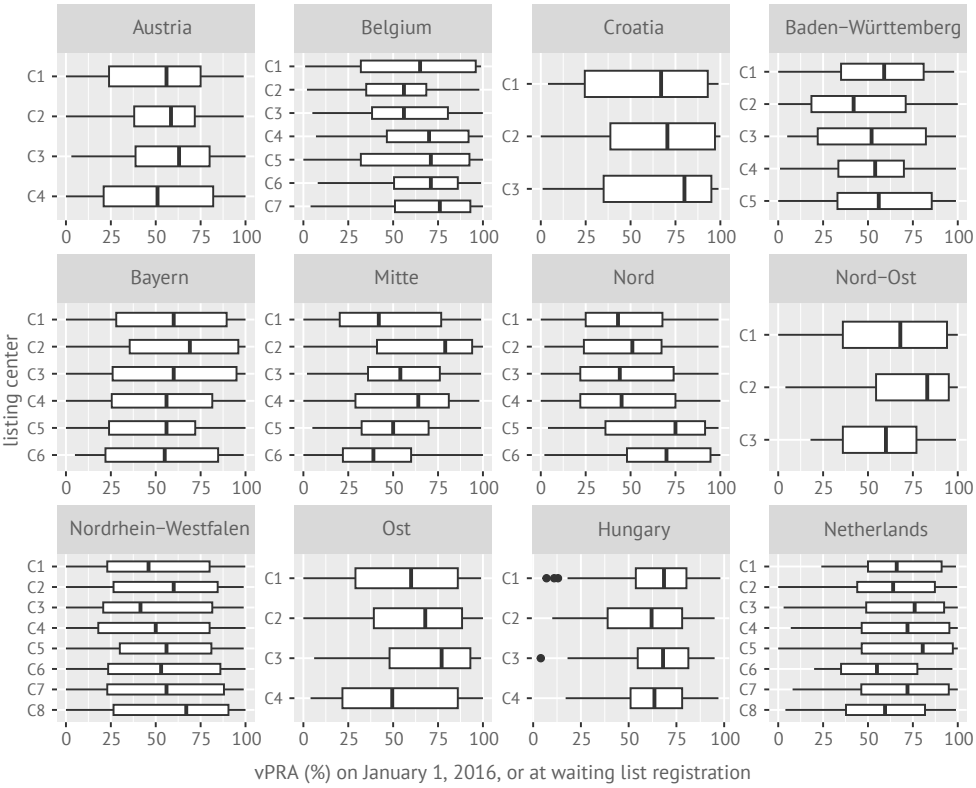


Figure 7.1: Distributions of the vPRA (%) per center for immunized patients who were active on the kidney transplant waiting list between January 1, 2016, and January 1, 2020.

Table 7.1: The baseline characteristics of our patient cohort, stratified by level of the vPRA. The Kruskal-Wallis test was used for group comparisons of continuous variables. Fisher's exact test was used for group comparisons of categorical variables.

	by vPRA				total
level	0	0.1-49.9%	50-84.9%	85-100%	
	(n=15319)	(n=1442)	(n=1534)	(n=1110)	(n=19405)
patient sex					
female	5,097 (33.3%)	741 (51.5%)	828 (53.9%)	600 (53.1%)	7,266 (37.4%)
male	10,219 (66.7%)	699 (48.5%)	707 (46.1%)	529 (46.9%)	12,154 (62.6%)
age at registration					
median [Q1-Q3]	50 [41-57]	49 [40-56]	48 [40-55]	47 [39-54]	50 [41-56]
patient blood group					
O	6558 (42.8%)	651 (45.1%)	624 (40.7%)	438 (39.5%)	8271 (42.6%)
A	5856 (38.2%)	528 (36.6%)	602 (39.2%)	445 (40.1%)	7431 (38.3%)
B	2215 (14.5%)	208 (14.4%)	228 (14.9%)	160 (14.4%)	2811 (14.5%)
AB	690 (4.5%)	55 (3.8%)	80 (5.2%)	67 (6.0%)	892 (4.6%)
accrued dialysis time at registration or by January 1, 2016 (years)					
median [Q1-Q3]	2.0 [0.82-4.5]	3.0 [1.2-5.6]	3.1 [1.3-5.8]	3.7 [1.8-6.6]	2.2 [0.91-4.8]
previous kidney transplantations					
0	14,366 (93.8%)	925 (64.1%)	658 (42.9%)	361 (32.5%)	16310 (84.1%)
1	895 (5.8%)	462 (32.0%)	714 (46.5%)	567 (51.1%)	2638 (13.6%)
2+	58 (0.4%)	55 (3.8%)	162 (10.6%)	182 (16.4%)	457 (2.4%)
final vPRA (before waitlist exit, or AM/ESP entry)					
0%	13,522 (88.3%)	68 (4.7%)	26 (1.7%)	5 (0.5%)	13621 (70.2%)
0.01-49.9%	868 (5.7%)	1049 (72.7%)	40 (2.6%)	2 (0.2%)	1959 (10.1%)
50-84.9%	565 (3.7%)	199 (13.8%)	1068 (69.6%)	63 (5.7%)	1895 (9.8%)
85-100%	364 (2.4%)	126 (8.7%)	400 (26.1%)	1040 (93.7%)	1930 (9.9%)
changed vPRA during the study period (between January 1, 2016 and December 31, 2019)					
yes	1797 (11.7%)	611 (42.4%)	841 (54.8%)	775 (69.8%)	4024 (20.7%)
no	13522 (88.3%)	831 (57.6%)	693 (45.2%)	335 (30.2%)	15381 (79.3%)
status on January 1, 2020					
ETKAS transplant	5,982 (39.1%)	535 (37.2%)	547 (35.6%)	242 (21.4%)	7,306 (37.6%)
death or delisted unfit	719 (4.7%)	79 (5.5%)	97 (6.3%)	68 (6.0%)	963 (5.0%)
delisted other	155 (1.0%)	12 (0.8%)	16 (1.0%)	11 (1.0%)	194 (1.0%)
AM entry	89 (0.6%)	39 (2.7%)	118 (7.7%)	265 (23.5%)	511 (2.6%)
ESP entry	1,009 (6.6%)	108 (7.5%)	102 (6.6%)	63 (5.6%)	1,282 (6.6%)
waiting	7,362 (48.1%)	667 (46.3%)	655 (42.7%)	480 (42.5%)	9,164 (47.2%)
time transplantable (years, between January 1, 2016 and December 31, 2019)					
median [Q1-Q3]	1.1 [0.42-2.2]	1.4 [0.51-2.7]	1.3 [0.51-2.6]	1.3 [0.47-2.6]	1.1 [0.42-2.3]
proportion time transplantable (between January 1, 2016 and December 31, 2019)					
median [Q1-Q3]	91% [59%-100%]	95% [65%-100%]	95% [67%-100%]	96% [66%-100%]	92% [60%-100%]

7.3.1 The association of the vPRA with ETKAS transplant rates

The curve in Figure 7.2 shows the estimated relation between the relative transplant rate and the vPRA. The relative transplant rate decreases with a higher vPRA. Adjusting for vPRA categories rather than with a spline term yields similar results (horizontal dotted lines, Figure 7.2). The relative transplant rate for patients with vPRA 0.1-50% is estimated to be 23% lower than non-immunized patients, and 51% lower for patients with vPRA 75–85%. For vPRAs exceeding 85%, the relative transplant rate decreases rapidly: it is 65% lower for candidates with vPRA ranging between 85% and 95% than for non-immunized candidates, and 94% lower for candidates with vPRAs ranging between 99 and 100%.

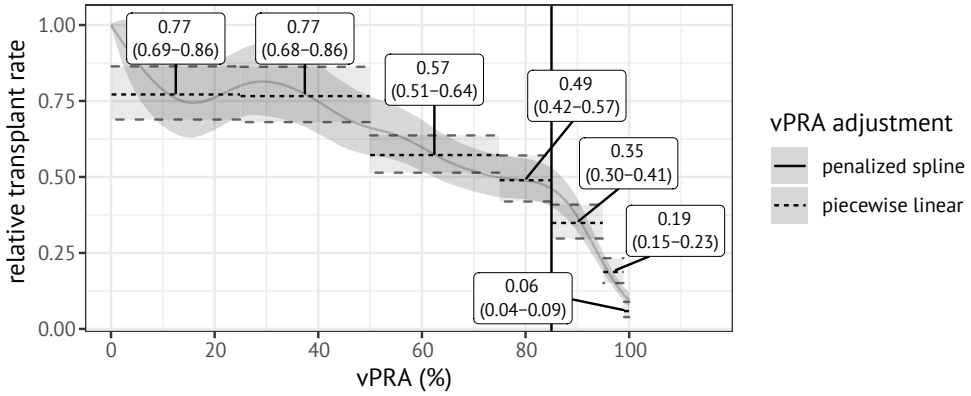


Figure 7.2: Relation between the relative ETKAS transplant rate and vPRA. This relation was estimated with a Cox proportional hazards model using vPRA as a time-varying variable and adjustment for other variables. The solid grey line was estimated using penalized spline terms with 8 degrees of freedom; the dotted lines were obtained by adjusting for discretized vPRA. Labels indicate point estimates of the hazard ratios for vPRA categories with 95% confidence intervals.

7.3.2 Predicted transplant probabilities for a synthetic patient across Eurotransplant regions and blood groups

Figure 7.3 shows predicted transplant probabilities for a hypothetical patient based on a Cox proportional hazards model fitted with delayed entry. This hypothetical patient was defined as a patient who is a 49-year-old, male primary transplant candidate, who had accrued 2 years of dialysis time at listing and who remained transplantable and non-immunized (vPRA 0%) during their waiting list registration. The predicted probability of transplantation is almost 100% within the first 4 years of registration in all Eurotransplant countries except for Germany where the predicted probability of

transplantation is just over 25% (except for blood group AB). Comparing transplant probabilities across blood groups shows that blood group AB patients have the highest transplant rates in Austria, Hungary, and Germany, but not in the Netherlands and Belgium. This suggests that a proportional hazards assumption is implausible for blood group and highlights the need for stratifying Cox models by both blood group and recipient location.

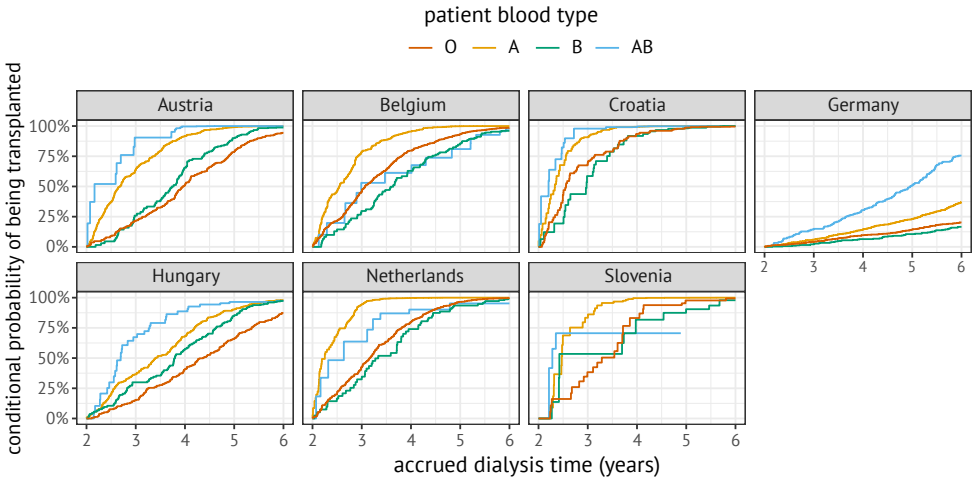


Figure 7.3: Predicted conditional probabilities of being transplanted within four years upon entering the waiting list with two years of dialysis time, stratified by blood group and listing country. Predictions were made for a 49-year-old, male candidate who was listed for their first kidney transplantation. For Germany, distributions are displayed per DSO region.

7.3.3 Sensitivity checks for the main result

Our main result is that a candidate's relative transplant rate decreases substantially with an increasing vPRA, and that this decrease accelerates for a vPRA exceeding 85%. Figure 7.4 shows sensitivity checks for this result. For panel A models were re-estimated separately for German and non-German patients. The inverse relation between the vPRA and relative transplant rate is reproduced in both regions. An apparent difference between Germany and the other Eurotransplant member countries is that the relative transplant rates only appears to decrease for vPRAs greater than 50% for German candidates, while a decrease is visible over the whole domain for Eurotransplant's other member countries. In panel B, we re-estimated models separately in patients registered before and after January 1, 2016, the study start state. This sensitivity check was motivated by the fact that candidates already on the waiting list on January 1, 2016 are a non-representative selection of the kidney transplant candidate population.

The estimated spline curves are again very similar. In panel C, we assessed the impact of not using vPRA as a time-varying variable. The obtained curves differ minimally, although it appears that using time-fixed versions of the vPRA modestly increases effect sizes. Finally, in panel D we assessed sensitivity of our result to the availability of 0 DR-mismatched donors in Eurotransplant's donor pool. Also here, no meaningful differences are found.

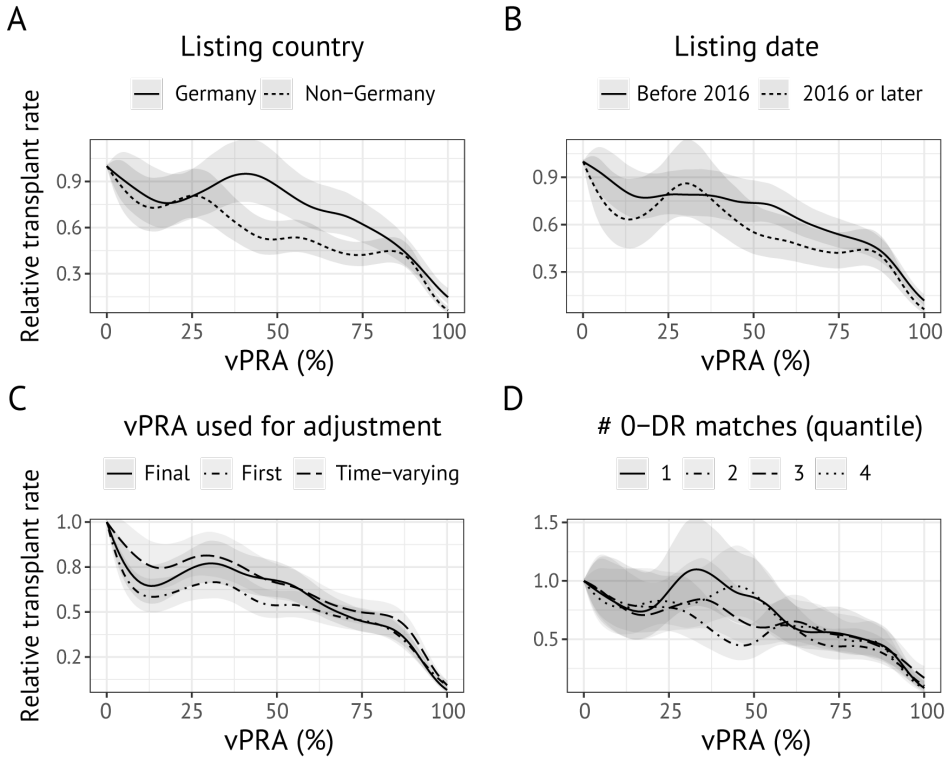


Figure 7.4: Sensitivity checks for the relation between the vPRA and relative transplant rate. Panel (a) shows penalized spline terms estimated separately for German allocation regions and Eurotransplant countries. Panel (b) shows penalized spline terms estimated separately for patients already on the waiting list on January 1, 2016, versus those registered afterwards. Panel (c) assesses whether the spline term is affected by whether a time-varying vPRA is used. Panel (d) shows how the relation between the relative transplant rate and vPRA varies by quantiles of the number of 0 DR-matchable donors. Panels (a), (b), and (d) use vPRA as a time-varying variable.

7.3.4 The association of the vPRA with ETKAS offer rates

The hazard ratios estimated for time-to-any-offer and time-to-high-quality-offer are shown in Table 7.2. The hazard ratios obtained for the time-to-any-offer analysis (first row, Table 7.2) differed minimally from the hazard ratios obtained for the relative transplant rate, at 28% lower for vPRAs 50-75%, 61% lower for vPRA 75–85%, and a strong decrease for vPRA >85%. When using a high-quality offer as an outcome the inverse relation also reproduces (second row), although estimated hazard ratios are attenuated. For example, patients with a vPRA between 75 and 85% have an approximate 33% lower high-quality offer rate than their non-immunized peers, while they have a 51% lower transplant rate and a 61% lower any-offer rate.

Table 7.2: Hazard ratios estimated in the time-to-offer analyses. The hazard ratios were estimated with a Cox proportional hazards model that uses vPRA as a time-varying variable and adjusts for other variables.

	by vPRA						
offer	0.01-24.9%	25-49.9%	50-74.9%	75-84.9%	85-94.9%	95-98.9%	99-100%
any offer	0.93 (0.85-1.01)	0.72 (0.66-0.79)	0.56 (0.51-0.6)	0.39 (0.35-0.44)	0.27 (0.24-0.31)	0.16 (0.14-0.19)	0.06 (0.05-0.08)
high-quality offer	0.88 (0.77-1.02)	0.90 (0.78-1.03)	0.72 (0.63-0.81)	0.67 (0.56-0.8)	0.51 (0.43-0.62)	0.46 (0.37-0.57)	0.20 (0.15-0.29)

7.3.5 Mismatch probability points awarded for the vPRA

Immunized patients are indirectly awarded points in ETKAS through points awarded for the mismatch probability (MMP), which is a quantification of the frequency of favorably matched donors. Candidates with rare blood groups or difficult-to-match HLAs may receive very few extra points for being sensitized, as the MMP is by definition higher for candidates with rare blood groups or those with difficult-to-match HLA phenotypes. To highlight this, we calculated for all immunized patients the difference between mismatch probability points calculated based on their actual vPRA, and mismatch probability points with a vPRA of 0%. This difference is the number of mismatch probability points that the candidate received on the basis of their vPRA.

Figure 7.5 shows the distributions of MMP points that the immunized patients in our cohort received based on the vPRA. Immunization indeed results only in a marginal increase in the number of points received for candidates with rare blood groups: the median sensitized candidate with blood group AB receives fewer than 20 additional MMP points, regardless of their vPRA. Moreover, a quarter of patients with the highest vPRAs (>85%) receive less than 50 mismatch probability points based on their vPRA. The number of additional MMP points awarded based on the vPRA thus appears meagre compared to the median number of ETKAS points needed for transplant through ETKAS, which exceeded 900 points between January 1, 2016, and January 1tab1, 2020.

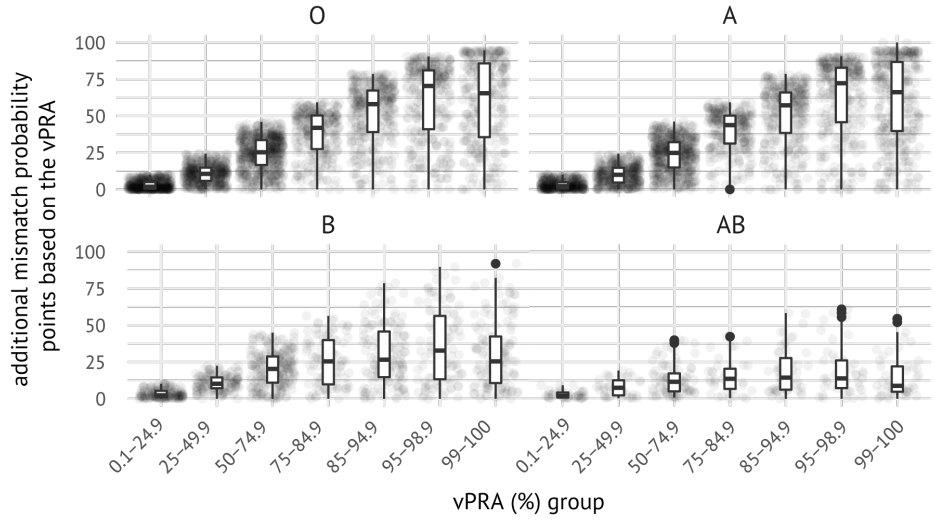


Figure 7.5: Mismatch probability points awarded to immunized patients based on their vPRA. Each dot represents an immunized patient in the cohort. Statistics were obtained by calculating the difference in MMP calculated with the actual vPRA versus the MMP calculated with a vPRA of 0%.

7.4 Discussion

More than 90% of immunized kidney transplant candidates in Eurotransplant rely on ETKAS for access to kidney transplantation. Concerns exist that these candidates are inadequately served by the mismatch probability points, and that they face extended waiting times [133–135]. This motivated us to study the relation between the vPRA and relative transplant rate in ETKAS. Our study is the first to quantify this relation Eurotransplant-wide, and complements two previous studies that used German cohorts [134, 135],

We studied the relation with Cox regression stratified by blood group and recipient country, using accrued dialysis time as the timescale. In this analysis, we allowed for delayed entry and included the vPRA as a time-varying variable. This study design avoids some methodological issues of the previous studies. Dialysis time is a more appropriate timescale than Ziemann et al.'s time-since-listing, as ETKAS allocation prioritizes based on accrued dialysis time and not waiting time. Zecher et al. used total accrued dialysis time as the outcome, and associated this with the vPRA recorded on January 1, 2019, which was their study start date. This appears problematic as over half of the immunized patients change the set of unacceptable antigens during registration, which means that the vPRA recorded on January 1, 2019 is not pre-determined to their accrued dialysis time. Our analyses avoided this issue by allowing for delayed entry of transplant candidates (not modeling transplant rates before January 1, 2016) and using the vPRA as a time-varying variable.

Our results show that a higher vPRA is associated with significantly reduced relative transplant rates in ETKAS. Unlike prior studies, reductions in transplant rates are already highly significant for vPRAs below 85%, with transplant rates 23% lower for vPRAs from 0–50% ($p < 0.001$) and 51% lower for vPRAs 75–85% ($p < 0.001$). Transplant rates are even lower for candidates with vPRA exceeding 85%; for example, candidates with vPRAs greater than 99% face 94% lower transplant rates. We note that candidates with vPRAs exceeding 85% may still depend on access to transplantation through ETKAS, for example because their center does not participate in the AM program or because the candidate does not meet AM criteria (unacceptable antigens require CDC reactivity or documentation of a sensitizing event [153]). One possible reason why even candidates with very low vPRAs (0-10%) face reduced access to transplantation is that immunized candidates could not be selected in non-standard allocation in the study period, which accounts for approximately 10% of kidney transplantations in Eurotransplant.

A strength of our study is the inclusion of several sensitivity checks, which show that the inverse relation between vPRA and the transplant rate generalizes beyond Germany, is independent of whether the patient was listed before or after 2016, and is independent of the type of vPRA used (time-varying, first vPRA, or final vPRA). The difficulty of finding a high-quality match (defined as the number of donors with 0 HLA-DR matches) also does not affect the relation.

A limitation to our study is that attention was restricted to patients eligible for ETKAS only, with patients censored if they enrolled into the AM program or became eligible for ESP. Zecher et al. instead adjusted in their analyses for enrolment in the AM program. We did not pursue this, as AM allocation is not based on accrued dialysis time which makes the proportional hazards assumption implausible. Ziemann et al. and Zecher et al. both also studied time-to-transplant for ESP patients. We did not pursue this, as candidates can choose to continue their participation in ETKAS after their 65th birthday, and it is

not clear how to correct for the resulting selection bias. Moreover, elderly patients listed in other Eurotransplant member countries can simultaneously participate in ETKAS and ESP, and it is unclear how to appropriately account for the simultaneous participation of candidates in these in our analysis. Another limitation to our study is that sensitization against HLA-DQA, -DPA and -DPB may further limit transplant rates due to positive physical cross-matches. These antibody specificities were not captured by the vPRA used in this analysis.

Our secondary analyses showed that the vPRA is also inversely related to ETKAS kidney offer rates, both when considering any offer as an outcome and when considering only high-quality offers as an outcome. This suggests that the reduced transplant rate for immunized patients is a result of ETKAS allocation, and not the kidney offer acceptance behavior of the transplant centers. We showed that many immunized patients receive only a marginal amount of additional MMP points based on their vPRA, in particular those with a difficult-to-match HLA or rare blood group. A potential policy implication of our work is thus that it seems worthwhile to revise the number of points that is awarded for the MMP, which has remained capped at 100 points since the introduction of ETKAS in 1996.

Finally, our work can help inform decision-making on whether to assign non-CDC reactive antigens as unacceptable. For ETKAS such decisions are made based on personalized risk assessments by doctors and local HLA laboratories, not on criteria prescribed by Eurotransplant. Our finding that increases in the vPRA beyond 85% strongly decreases the transplant rate may, for example, motivate local transplant professionals to be cautious in assigning antigens without CDC-reactivity as unacceptable for patients with already high vPRA (>85%). In this way, our work could help avoid situations where caution of local transplant teams unintentionally prolongs a candidate's waiting time.

Chapter 8

The ETKidney simulator

An article based on this chapter has been submitted for publication: de Ferrante, H.C., Laguna-Goya, R., Smeulders, B.M.L., Spieksma, F.C.R., Tieken, I.

Abstract

A barrier to modernizing ETKAS and ESP kidney allocation rules is that Eurotransplant lacks tools to quantitatively assess the impact of kidney allocation policy changes. We present the ETKidney simulator, which was developed for this purpose. This tool simulates kidney allocation according to the actual ETKAS and ESP allocation rules. The ETKidney simulator was developed in close collaboration with medical doctors from Eurotransplant, and was presented to the Eurotransplant Kidney Advisory Committee as well as other major stakeholders. To enhance trust in the tool, the ETKidney simulator has been made publicly available together with synthetic data.

In this chapter, we describe the ETKidney simulator in detail and validate the simulator by comparing simulated outcomes to actual ETKAS and ESP outcomes between April 1, 2021, and December 31, 2024. We illustrate how the simulator can contribute to the evaluation of alternative kidney allocation policies with three clinically motivated case studies. We anticipate that the ETKidney simulator will be pivotal in modernizing ETKAS and ESP allocation rules by enabling informed decision-making on kidney allocation rules in collaboration with national competent authorities.

8.1 Introduction

Potential improvements to ETKAS and ESP are regularly proposed, and are often based on medical insights or ethical considerations. For instance, proposals have been made to emphasize DR matching in ETKAS [156, 130], motivated by findings that mismatches at the HLA-DR locus are most deleterious to graft survival [157, 158]. Other proposals include making candidates under the age of 65 eligible for ESP [159], introducing HLA-DR matching in ESP [145], introducing candidate-donor age matching [150], basing HLA matching on epitope matching [160], and giving extra priority to the candidates who are immunized but do not qualify for the Acceptable Mismatch (AM) program [134, 135].

Within Eurotransplant, such areas for improvement are regularly discussed by the Eurotransplant Kidney Advisory Committee (ETKAC), whose members are nephrologists who represent the Eurotransplant member countries, an abdominal surgeon, and an immunologist. Despite regular ETKAC discussions on the aforementioned topics, ETKAS and ESP have not changed much since their initiations in 1996 and 1999, respectively. To support discussions within ETKAC and discussions with national competent authorities, Eurotransplant requires a tool that can quantify the impact of policy changes in ETKAS and ESP. Computer simulations can be used for this purpose.

The use of computer simulations to design kidney allocation systems is not new. In fact, ETKAS itself was based on computer simulations that were published in in 1993 [161, 126]. Other organ allocation organizations also routinely note the usage of computer simulations. For example, in the United States, the Kidney-Pancreas Simulated Allocation Model (KPSAM) was used to revise allocation rules in 2014 [149], and this tool continues to be used for the proposal of further changes to allocation [162, 163]. The kidney allocation policies in France and the United Kingdom were also updated on the basis of bespoke computer simulations in 2015 and 2019, respectively [164, 147, 165]. A bespoke model for Eurotransplant has not been available.

This motivated us to develop a simulation toolbox that enables Eurotransplant and other stakeholders to quantify the impact of changes to ETKAS and ESP allocation rules. This tool, which we refer to as the ETKidney simulator, uses discrete-event simulation (DES) to mimic kidney allocation within Eurotransplant. The simulator was developed in close collaboration with medical doctors from Eurotransplant and was presented on several occasions to ETKAC, which has welcomed the ETKidney simulator as a tool to inform policy discussions on kidney allocation. The Python code of the simulator is made publicly available together with synthetic data to enable collaborations with policymakers and scientists in evaluating alternative ETKAS and ESP allocation rules.[1]

[1] https://github.com/hansdeferrante/Eurotransplant_ETKidney_simulator

In this chapter, we describe how kidneys are allocated within Eurotransplant (Section 8.2) and how this process is approximated by the simulator (Sections 8.3 and 8.4). We also give insight into how closely the simulator approximates outcomes of ETKAS and ESP with input-output validation (Section 8.5), and demonstrate how the ETKidney simulator can contribute to policy evaluation with three clinically relevant case studies (Section 8.6).

8.2 The kidney allocation programs of Eurotransplant

Figure 8.1 shows how Eurotransplant allocates the deceased-donor kidneys that become available for kidney-only transplantation.[2] Three standard allocation programs are used to place these kidneys: the AM program, ETKAS and ESP (see Figure 8.1). The program through which Eurotransplant offers the kidney(s) is determined by the age of the donor. Kidneys from donors under the age of 65 are first offered for transplantation through the AM program, which accounted for 3% of kidney-only transplantations between 2014 and 2023, and then through ETKAS, which accounted for 69% of kidney-only transplantations. The ESP is used to allocate kidneys from donors aged 65 or older, and accounted for 16% of kidney-only transplantations [167].

The remaining 11% of kidney-only transplantations between 2014 and 2023 resulted from *non-standard allocation*, which Eurotransplant can initiate if the loss of a transplantable graft is anticipated. In non-standard allocation, Eurotransplant offers the grafts to centers in the vicinity of the kidney(s), either through extended or rescue allocation. In extended kidney allocation, centers have 60 minutes to propose candidates. In rescue allocation, offers are competitive, which means that the first center to respond receives the kidney. Not all kidneys offered by Eurotransplant are eventually transplanted. In fact, approximately 24% of the kidneys that were offered by Eurotransplant for transplantation between 2014 and 2023 were discarded [168].

Match lists determine which candidate receives an offer at what moment. The composition and ordering of candidates on match lists are determined by program-specific *eligibility*, *filtering*, and *ranking criteria*. The eligibility criteria determine whether a candidate is allowed to appear on the match list under Eurotransplant kidney allocation rules. Examples of eligibility criteria are that the candidate must have the same blood group as the donor, and that the donor's HLA must not include an HLA antigen that the center has reported as unacceptable for the candidate.

[2] In case a multi-organ donor is reported to Eurotransplant, the donor's kidneys may first be accepted by candidates waiting for a combined transplantation of a kidney with another organ (heart, lung, pancreas, liver, or intestine). These combined transplantations account for 7% of all deceased-donor kidney transplants in Eurotransplant [166].

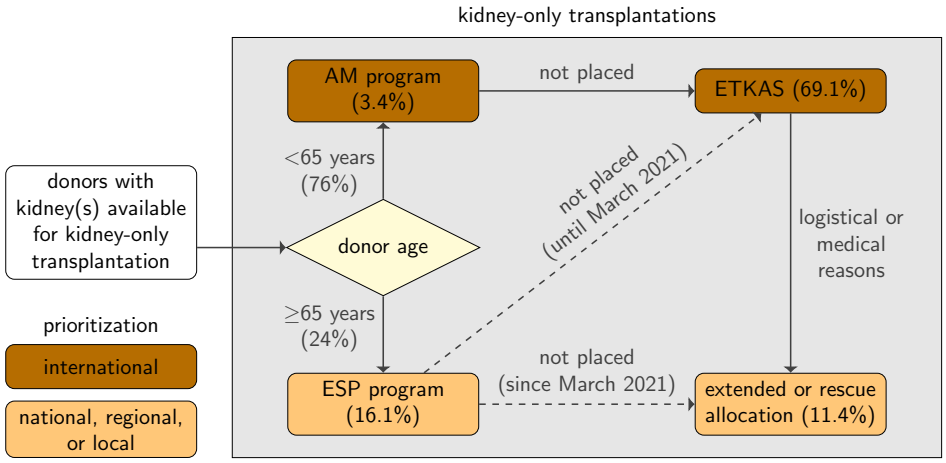


Figure 8.1: Flow chart illustrating how Eurotransplant offers kidneys for kidney-only transplantation. The percentages shown represent the proportion of kidney-only transplantations performed through each mechanism between 2014 and 2023. Kidneys declined by all candidates in ESP were re-allocated via ETKAS until March 2021. Since March 2021, such kidneys are instead offered via extended ESP allocation, in which non-local candidates and those aged below 65 can participate since March 2021.

The filtering criteria also determine whether Eurotransplant contacts the center to make an offer for a specific candidate. While eligibility criteria are rules imposed by Eurotransplant, filtering criteria represent the preferences that transplant centers have on kidney offers. The filtering criteria can be distinguished into:

1. *allocation profiles*, with which centers can indicate that their patient does not want to receive offers from donors with certain characteristics (e.g. donors above a certain age, donors with a specific virology, or other donor-related characteristics), and
2. *HLA mismatch criteria*, with which centers can specify their minimum requirements for the HLA match quality between the donor and candidate on the HLA-A, -B, and -DR loci.

Finally, the ranking criteria determine the position of a candidate on the match list. An overview of the ETKAS- and ESP-specific ranking criteria is included in Section 8.4.3.

In standard allocation, Eurotransplant only offers kidneys to candidates who appear on the *filtered match list*, which means that candidates must meet the program's eligibility and filtering criteria. In extended allocation, centers are allowed to select candidates from the *unfiltered match list*, which means that candidates only have to meet the program's eligibility criteria. In rescue allocation, centers can also propose other candidates for

transplantation, including those with non-identical ABO blood groups.

8.3 Purpose and design of the ETKidney Simulator

We use discrete-event simulation (DES) to simulate kidney allocation according to the actual ETKAS and ESP allocation rules implemented in March 2021. Simulation of the AM program is beyond the scope of the ETKidney simulator, because the definition of acceptable antigens is based on an individualized risk-benefit analysis which requires specialized immunological knowledge. We note that the simulator has not been designed for the analysis of kidney discard rates.

Relevant states for the simulation are (i) the statuses of candidates on the ETKAS or ESP waiting lists, (ii) the export balances of Eurotransplant member countries, which affect a candidate's rank on ETKAS match lists because of Eurotransplant's balance point system (see Section 8.4.2). In DES, we study how these system states evolve in response to a series of discrete events. For the ETKidney simulator, we distinguish between three types of events, which are:

1. *candidate status updates*; these include changes to a candidate's waiting list status (transplantable, non-transplantable, HU, removed, transplanted, or deceased), their allocation profiles, their unacceptable antigens, their HLA mismatch criteria, the reporting of an antibody screening, or a choice between ETKAS or ESP in Germany (where these programs are mutually exclusive),

2. *donor arrivals*; these are donors reported to Eurotransplant for whom one or two kidneys become available for kidney-only transplantation through ETKAS or ESP, which generally results in a transplantation, and

3. *balance update events*; these are transplantations across country borders through allocation programs other than ETKAS and ESP. These transplantations also count towards the export balances of Eurotransplant's member countries, based on which balance points are awarded.

8.3.1 Input data for the ETKidney simulator

Users of the ETKidney simulator have to specify the input streams that define the candidate status updates and donor arrival events. Furthermore, an input stream of international transplantations can be specified, which is used to initialize ETKAS balances and to define balance update events. For candidates and donors, the data in the input streams must include all administrative and medical information required by

the eligibility, filtering, and ranking criteria. Additional information may be required by the graft offer acceptance module to simulate the decision-making of kidney transplant centers in accepting kidney offers, and by the post-transplant module to simulate post-transplant survival.

For candidates, the input streams must include complete information on what would happen to each candidate until they exit the waiting list, either because of a waiting list removal or a waiting list death. This requirement implies that candidate input streams cannot be solely based on historical registry data: after all, waiting list removals or waiting list deaths have not been observed for candidates who were transplanted via ETKAS or ESP.

For simulations done in this chapter, we use input streams based on historical data. The actual status update trajectories of candidates are complemented with statuses copied over from comparable candidates who remained registered on the waiting list. For this, we use a procedure to complete a candidate's status updates that was originally developed for the ELAS simulator (see Chapter 5 and Appendix B).

8.3.2 Initialization of the ETKidney simulator's system state

The balance system is initialized using data from the input stream for international transplantations: all international transplantations that were performed prior to the simulation start date are processed, which ensures that the balances are correctly initialized. Additionally, the simulator schedules a balance update event for every cross-border transplantation that occurs within the simulation window via combined transplantations or via the AM program. This is necessary to accurately simulate the evolution of balances, because such transplantations also count towards a member country's export balance.

From candidate input streams, the simulator loads all candidates who have an active status on the waiting list within the simulation window. The listings of candidates listed for repeat kidney transplantation whose initial transplantation takes place within the simulation window are excluded, which is necessary to ensure that a candidate cannot simultaneously wait for a primary and repeat transplantation in ETKidney simulation runs. For each candidate, a single patient event is scheduled in the Future Event Set (FES) timed at the candidate's first available status update. The scheduling of subsequent status updates is postponed until the status update has been processed.

From donor input streams, all donors reported during the simulation window are loaded. For each donor, a donor event is scheduled in the FES on the donor reporting date.

8.3.3 Overview of the simulation

Figure 8.2 illustrates how events are processed in the simulation. The balance update events are handled by simply updating the export balances of the countries that were involved in the international transplantation. The patient events are handled by updating the status of the corresponding patient. Handling of donor events is more complex, because the allocation of the kidney(s) through ETKAS or ESP has to be approximated by the simulator.

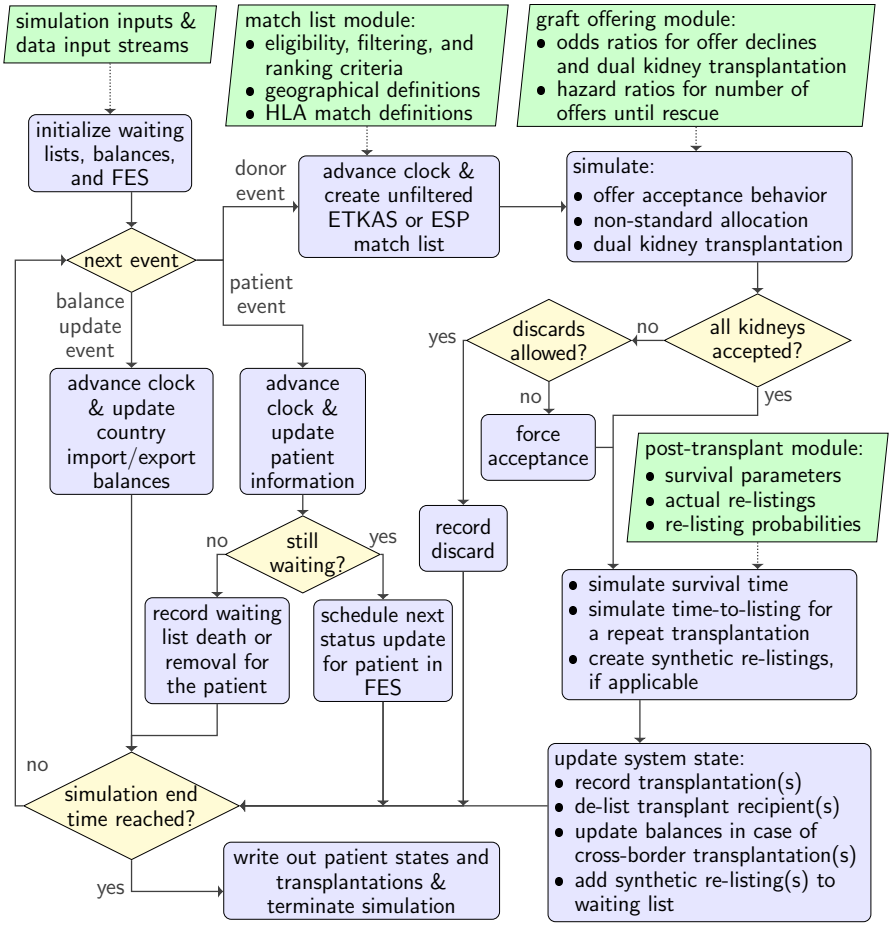


Figure 8.2: Event handling flowchart for the ETKidney simulator. Inputs and parameters are represented using parallelograms. If a kidney is declined by all candidates, simulation settings determine whether a discard is recorded or a candidate is forced to accept the kidney for transplantation. FES, Future Event Set.

To approximate such kidney-only allocation, the ETKidney simulator's *match list module* was developed (see Section 8.4.3). This module first creates, depending on the age of the donor, an unfiltered ETKAS or ESP match list that contains for each candidate who meets the corresponding program's eligibility criteria a *match record*. These match records are automatically ordered based on the respective program's ranking criteria, with the number of points awarded to each match record determined by the *point score module* (see Section 8.4.3).

Using the ordered match list as the input, the *graft offering* module simulates which candidates accept the kidneys (see Section 8.4.4). In rare cases, all candidates on the match list are simulated to decline the kidney offer. If this happens for an ESP match list, the graft offering module will try to place the kidneys through non-standard ESP allocation, which is how Eurotransplant allocates kidneys from donors aged 65 or older since March 2021. In the rare event that kidneys remain unplaced, the graft offering module can either (i) record a discard for the kidney(s), or (ii) force transplantation of the candidate who was predicted to be most likely to accept the graft. For the simulations in this chapter, option (ii) is used because the donor input stream used for simulation consists only of donors whose kidneys were actually transplanted through ETKAS and ESP.

After a graft has been accepted, transplantations are recorded with the kidney balances updated in case of a cross-border transplantation. The *post-transplant module* simulates post-transplant outcomes for transplant recipients. In case a candidate is simulated to enlist for repeat transplantation, this module also schedules a *synthetic re-listing* (see Section 8.4.5.2).

8.4 Modules of the ETKidney simulator

This section describes key modules of the ETKidney simulator: the HLA system module (Section 8.4.1), the balance system module (Section 8.4.2), the match list and point system module (Section 8.4.3), the graft offering module (Section 8.4.4), and the post-transplant module (Section 8.4.5).

8.4.1 The HLA system module

The HLA system module implements all mechanisms through which Eurotransplant prioritizes HLA matching. These procedures are (i) determining how many mismatches there are at the HLA loci of interest, (ii) calculating the vPRA on the basis of unacceptable antigens, and (iii) calculating the mismatch probability.

8.4.1.1 Calculation of HLA mismatches

The HLA system module can determine, for a given patient HLA and given donor HLA, how many antigen mismatches there are per locus (0, 1, or 2). The simulation settings file specifies at which HLA loci mismatches are to be determined. By default, the module only counts mismatches at the HLA-A, -B, and -DR loci, because the current ETKAS point system only awards points for these mismatches. HLA-A and HLA-B mismatches are determined at the level of broad antigens, while HLA-DR mismatches are determined at the level of split antigens (as is done for allocation in ETKAS, see [169]).

8.4.1.2 Quantification of virtual Panel-Reactive Antibodies (vPRA)

A candidate's vPRA affects a candidate's position on the match list because the vPRA is used to calculate the mismatch probability. In simulations included in this chapter the vPRA is quantified by counting the fraction of donors that carry unacceptable antigens in the ETRL donor panel (V4.0). This database includes the HLA phenotypes of 10,000 donors that were recently reported to Eurotransplant. The HLA system module can also quantify the vPRA against a user-specified input database of 10,000 donor HLAs.

8.4.1.3 Calculation of the Eurotransplant mismatch probability (MMP)

ETKAS awards points for the mismatch probability, which is the chance that there is *no* favorably matched donor for a candidate among the next 1,000 donors reported to Eurotransplant. Eurotransplant calculates this mismatch probability analytically as:

$$\texttt{MMP} = \Big(1 - f_{BG} \cdot (1 - \texttt{vPRA}) \cdot p_{\leq 1mm}\Big)^{1000},$$

where f_{BG} is the candidate's blood group frequency and $p_{\leq 1mm}$ is a quantification of the probability that a donor has at most 1 HLA-ABDR mismatch with the candidate.

By default, $p_{\leq 1mm}$ is calculated with analytic formulas for the probability of receiving exactly 0 mismatches and exactly 1 mismatch, which are also used for ETKAS allocation. A disadvantage of this approach is that both these formulas assume that HLA antigens are independently distributed according to their population frequencies, which ignores HLA linkage disequilibrium. To resolve this, the HLA system module can also quantify the availability of favorably matched donors by counting the number of 0- or 1-ABDR mismatched donors among the pool of 10,000 donors used to calculate the vPRA, which we denote by $f_{\leq 1mm}$. Using this quantity, we define the *"1-ABDR HLA mismatch frequency"* as

$$\Big(1 - f_{\leq 1mm}\Big)^{1000}.$$

We note that this quantity does not take into account the candidate's blood group, nor the candidate's vPRA. We use this quantity in the second case study (see Section 8.6.2).

8.4.2 The balance system module

To balance the international exchange of kidneys, Eurotransplant keeps track of the *net kidney export balances* of its member countries, and awards points in ETKAS based on these balances.[3] Within Austria, an additional regional balance system exists to ensure that the Austrian regions benefit equally from cross-border transplantations [169]. The balance system module implements both these national and regional balance systems for the ETKidney simulator. Initialization of the net export balances is possible, and can be based on historical data. By default, separate balances are maintained for each donor age group (0-17 years, 18-49 years, 50-64 years, or 65 years or older), which is consistent with how balances have been maintained since April 1, 2019 [169].

8.4.3 The match list module & point system module

The match list module is used to create ETKAS or ESP match lists, which serve as input for the graft offering module. Only candidates who meet the corresponding program's eligibility criteria appear on match lists, with each candidate ranked based on *tiers* and *points*. Candidates ranked in higher tiers receive priority over candidates in lower tiers. Within each tier, candidates are ranked by points. In ETKAS, tiers are in order of descending priority:

1. candidates with zero HLA-ABDR mismatches with the donor,
2. pediatric candidates, in case the donor is also pediatric,
3. all other candidates.

The ETKAS point system awards:

1. 33.33 points per year of accrued dialysis time,
2. 400 minus 66.66 points per HLA-ABDR mismatch. These points are doubled if the candidate is pediatric,
3. 100 points if the candidate is pediatric,

[3] The number of balance points awarded is calculated by subtracting from each member country's export balance the export balance of the country which is the largest importer (a negative number), and multiplying the outcome by the balance weight. This balance weight is currently 30.

4. 500 points if the candidate has the High Urgency (HU) status,
5. up to 100 mismatch probability points,
6. balance points, the amount of which is determined based on the net export balances of Eurotransplant's member countries,
7. up to 300 distance points if the candidate is located in the same country as the donor. The specific amount awarded depends on the country, see the kidney manual for an overview [169].

Since March 2021, ESP allocation has been based on nine tiers, which are defined based on the location of the candidate relative to the donor and whether the candidate is 65 years or older. Within ESP tiers points are awarded based on the dialysis time that a candidate has accrued [169].

8.4.4 The graft offering module

The graft offering module mimics how Eurotransplant offers kidneys to centers for transplantation, and returns, based on a match list, the candidates who accept the kidney for transplantation (if any). How kidney offers are simulated in the ETKidney simulator is illustrated in Figure 8.3. The module first simulates, based on the donor, the maximum number of offers made in standard allocation. We denote this number by k. The module then makes kidney offers to candidates in order of their ranking on the *filtered* match list, either until k offers have been made or until all available kidneys have been accepted for transplantation.

If not all kidneys have been accepted after k offers in standard allocation, the match lists are re-ordered with priority for candidates located in the vicinity of the donor to approximate non-standard allocation. At this point, the module also makes offers to candidates who appear only on the *unfiltered* match list, as centers can select such candidates in extended and rescue allocation. Offers in non-standard allocation are made either until all kidneys have been accepted or until the match list is exhausted. The module then returns the candidates who have accepted the kidneys.

8.4.4.1 Simulating the switch to non-standard allocation

The graft offering module switches to non-standard allocation following k declines. We modeled K with a Cox proportional hazards model with adjustment for donor characteristics (donor age, virology, death cause, last creatinine, diabetes, smoking, proteinuria, blood group, and extended donor criteria). Cox models were stratified by the program (ETKAS / ESP), and within ETKAS additionally by the donor country. The

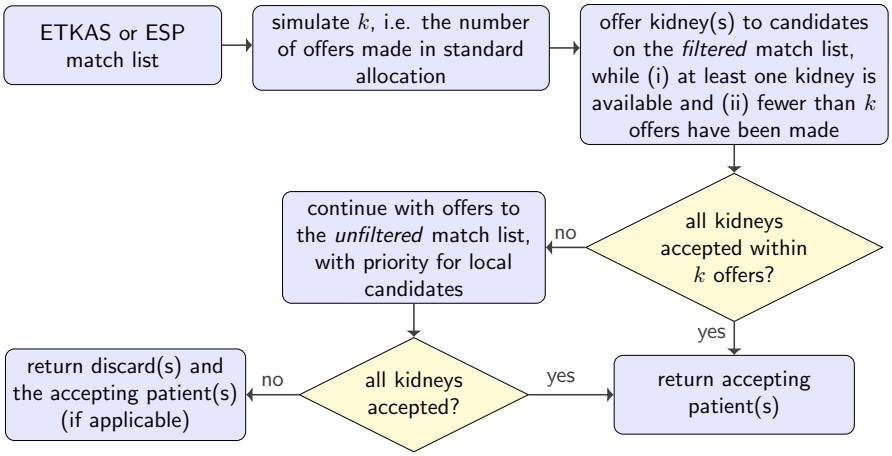


Figure 8.3: Flow chart summarizing how the ETKidney simulator approximates the graft offering process.

baseline hazards and parameters needed to simulate from this model are made available with the ETKidney simulator. These were estimated on match lists generated between January 1, 2014, and January 1, 2024. ESP match lists from before March 2021 were excluded for estimation of these parameters, because non-standard allocation was rarely used in ESP before March 2021.[4]

8.4.4.2 Simulating kidney offer acceptance behavior with a two-staged approach

To simulate the center offer acceptance behavior of transplant centers, a two-stage acceptance procedure was implemented that

1. simulates *center-level* decisions based on donor characteristics (donor death cause, age, last creatinine, blood group, DBD / DCD donation, and extended donor criteria) and center characteristics (country, distance to the donor). These models simulate whether a center is willing to accept the kidney(s) for any candidate in the center, and

2. simulates *patient-level* decisions to determine whether the center accepts a kidney offer for a specific candidate. These decisions are simulated only if the center is willing to accept the donor, and are simulated based on donor characteristics (see above), candidate characteristics (age, pediatric status, HU status, vPRA,

[4]Before March 2021, kidneys which could not be successfully allocated via ESP were offered via ETKAS. After March 2021, such kidneys are allocated via non-standard ESP allocation.

dialysis time, prior kidney transplantation), and match characteristics (HLA match, geographic distance, candidate-donor age difference).

Logistic models are used to simulate both center- and patient-level decisions. We anticipated that kidney offer acceptance behavior would differ between ETKAS and ESP, because HLA match quality has historically been ignored in ESP and because the programs have different donor and patient populations. Therefore, the ETKidney simulator uses separate models to simulate the offer acceptance behavior of transplant centers in ETKAS and ESP.

The odds ratios required for simulations are made publicly available with the ETKidney simulator, and were estimated on match lists with mixed effect logistic regressions. Random effects were included to account for within-donor, within-candidate and within-center correlations in organ offer acceptance decisions. For ETKAS, odds ratios were estimated on historical data between January 1, 2012, and January 1, 2021. For ESP, odds ratios were estimated between January 1, 2018, and January 1, 2024. We included data from after 2021 to estimate the ESP odds ratios, because ESP offers to candidates younger than 65 and international candidates have only been allowed since March 2021.

8.4.4.3 Simulation of dual kidney transplantations

Annually, approximately 20 to 30 candidates receive a dual kidney transplantation, a procedure that is permitted when loss of both grafts is anticipated or for specific anatomical reasons. The graft offering module simulates whether such a dual kidney transplantation is performed based on donor and patient characteristics (candidate age, donor age, country of listing, and rescue allocation). For this, a logistic model is used. The odds ratios provided with the ETKidney simulator were estimated on match lists from January 1, 2018, to January 1, 2024, using only offers where both grafts remained available for transplantation.

8.4.5 The post-transplant module

In total, 13% of the candidates on the kidney waiting list have received a prior kidney transplant, which makes it important to simulate post-transplant survival in the ETKidney simulator. This simulation is important even for short-term simulations, as nearly 3% of kidney transplant recipients enlist for a repeat kidney transplantation within one year of transplantation [170]. The post-transplant module was implemented to simulate survival after kidney transplantation and to simulate listing for repeat transplantation.

8.4.5.1 Simulation of post-transplant failure time and a potential re-listing date

For each kidney transplantation, the post-transplant module simulates a patient failure time t based on donor characteristics (age, DBD/DCD donor, last creatinine, death cause, hypertension, malignancy, diabetes), patient characteristics (age, dialysis time, repeat kidney transplantation, country of listing), and match characteristics (HLA match, standard or non-standard allocation, year of transplantation, international transplantation). This failure time is defined as a post-transplant death or a repeat kidney transplantation, whichever occurs first. We modeled T with a Weibull model based on recipient, donor, and transplantation characteristics (as done for the ELAS simulator, see Section 5.4.5.1). The scale and shape parameters supplied with the ETKidney simulator were estimated based on ETKAS and ESP transplantations that were performed between January 1, 2011, and January 1, 2021.

Most transplant recipients enlist for a repeat kidney transplantation before a patient failure materializes. Because a potential re-registration must logically occur before a patient death or re-transplantation, we simulate the time-to-relisting r based on the empirical distribution of R relative to T (explained in Section 5.4.5.2 for the ELAS simulator). For the ETKidney simulator, we stratified these distributions based on candidate age groups and time-until-failure t, which both strongly affect whether a candidate is listed for repeat kidney transplantation (see Figure 8.4).

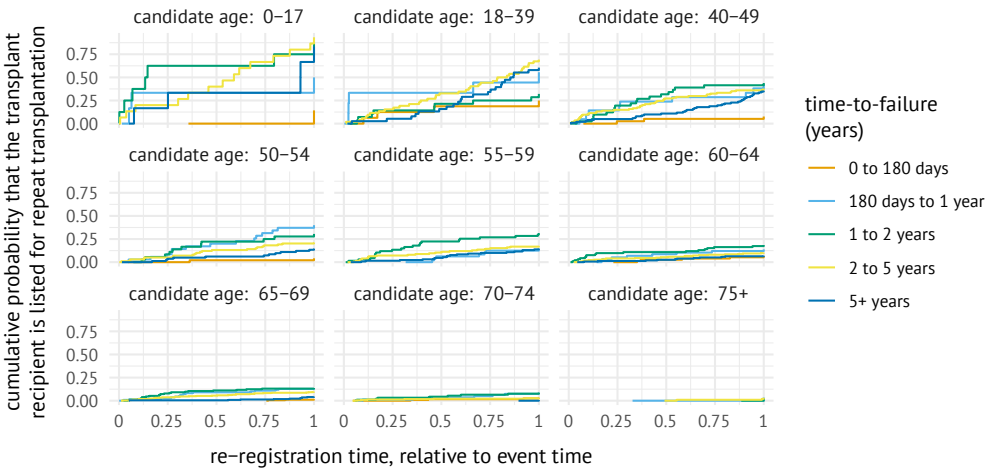


Figure 8.4: Cumulative incidence curves showing the probability of listing for repeat transplantation, stratified by time-to-event categories. These curves were estimated with the Kaplan-Meier estimator based on candidates transplanted between January 1, 2011, and January 1, 2024.

8.4.5.2 Constructing synthetic re-registrations

In case transplant recipients are simulated to enlist for a repeat transplantation before the simulation end date, the post-transplant module creates a *synthetic re-listing* for this candidate. This synthetic re-listing is created by combining the static information from the transplant recipient with the dynamic candidate status updates from an actually re-listed candidate. The actually re-listed candidate is chosen such that they are similar to transplant recipient in terms of background characteristics as well as in time-to-failure t and time-to-relisting r.

By default, the post-transplant module finds a matching re-registration k by:

1. Considering re-listings where candidates match on country of listing and on whether they were re-listed within 1 year after transplantation[5], are of similar age (<20 years difference), have similar time to re-listing and time-to-failure, and have a similar number of years on dialysis.
2. Selecting the m=5 listings for repeat transplantation with the closest Mahalanobis distance between (r_i, t_i) and (r_k, t_k).
3. Sampling a random re-registration from the m re-registrations.

A synthetic re-registration is then constructed by combining patient attributes from patient i with the urgency code updates and PRA re-certifications from patient k. These status updates affect whether a candidate is eligible for a match list offer, as candidates with a non-transplantable status or outdated PRA screenings are not eligible for offers in ETKAS and ESP. Other status updates (vPRA, allocation profiles, diagnosis groups, HLA, reported dialysis initiation dates) are not copied over because they are considered patient-specific. We note that the PRA screenings are only used to determine the eligibility of the candidate, and not to predict graft offer acceptance behavior or post-transplant survival.

A specific challenge for simulating listing for repeat transplantation is that kidney transplantation is a strongly immunizing event [171]. Many repeat transplant candidates will therefore have developed *de novo* Donor-Specific Antibodies (dnDSAs) that centers can report as unacceptable. Candidates who are listed for repeat transplantation therefore tend to have higher vPRAs and face reduced access to kidney transplantation.

[5]Transplant recipients who require dialysis within one year of their initial kidney transplant may receive a portion of their previous waiting time back, see the Eurotransplant kidney manual [169].

It is not clear how to simulate such *de novo* immunization, because:

- HLA antigens are cross-reactive, which means that patients typically also develop DSAs against HLA antigens that were not present in the donor [172],
- the immunogenicity of donor HLAs also depends on the patient's own HLA [172], and
- HLA laboratories and transplant centers have different attitudes in labeling the HLA antigens of the initial donor as unacceptable [173, 174].

Accurate simulation of *de novo* immunization falls outside of the scope of the ETKidney simulator. Instead, a very simple procedure was implemented that assumes that candidates have a fixed probability of becoming immunized against any mismatched donor antigen. By default, this probability is set to 20%. This probability was chosen because having one additional mismatch per locus increases the probability of reporting unacceptable antigens against that specific locus with 10 to 25% on average (depending on the locus) [175].

8.5 Verification and validation

This section describes verification and validation efforts undertaken to ensure that the ETKidney simulator closely mimics ETKAS and ESP.

8.5.1 Verification of the ETKidney simulator

We built unit tests to ensure that the behavior of the modules aligns with their intended functionality. For example, unit tests were constructed to verify whether HLA match qualities returned by the HLA system module were equal to HLA match qualities recorded on actual ETKAS match lists. Unit tests were also used to ascertain that the HLA system module returned the correct mismatch probabilities and vPRAs.

The simulation of the graft offering process and of post-transplant survival is based on statistical models whose parameters were estimated in the statistical programming language *R*. Unit tests were constructed to ensure that the probabilities predicted in the ETKidney simulator based on these parameters matched the probabilities predicted in R, for both offer acceptance decisions as well as post-transplant survival.

8.5.2 Validation of the ETKidney simulator

To ensure face validity of the model, medical doctors from Eurotransplant were actively involved in the development and conceptual design of the simulator. We also had meetings with ETKAC and the ETRL on various occasions in which the ETKidney simulator was discussed. Moreover, the model was presented at the 2024 Eurotransplant Annual Meeting to collect feedback from additional major stakeholders, such as medical doctors and transplantation coordinators affiliated with the transplant centers.

We assess the operational validity of the model using input-output validation. For this, we simulate ETKAS and ESP kidney allocation between April 1, 2021, and January 1, 2024 under the actual allocation rules used within this simulation window. The simulation start date of April 1, 2021 was chosen because the allocation of ESP donors changed in March 2021. For the donor input stream, we used all 4,326 donors reported in the simulation window whose kidneys were transplanted after allocation through ETKAS or ESP (see Table 8.1 for their characteristics). For the candidate input stream, we used all n=9,393 candidates activated on the ETKAS or ESP waiting list during the simulation period (Table 8.2), and the n=14,647 candidates already registered candidates on April 1, 2021 (Table 8.3).

Table 8.1: Characteristics of the donors used for simulation.

variable	level	Austria (n=372)	Belgium (n=627)	Croatia (n=189)	Germany (n=2,072)	Hungary (n=265)	Netherlands (n=704)	Slovenia (n=97)
kidneys available	2	260 (69.9%)	471 (75.1%)	127 (67.2%)	1,625 (78.4%)	208 (78.5%)	532 (75.6%)	71 (73.2%)
	1	112 (30.1%)	156 (24.9%)	62 (32.8%)	447 (21.6%)	57 (21.5%)	172 (24.4%)	26 (26.8%)
type	HB	350 (94.1%)	345 (55.0%)	189 (100%)	2,072 (100%)	265 (100%)	260 (36.9%)	97 (100%)
	NHB	22 (5.9%)	282 (45.0%)	–	–	–	444 (63.1%)	–
sex	female	166 (44.6%)	256 (40.8%)	75 (39.7%)	965 (46.6%)	113 (42.6%)	314 (44.6%)	28 (28.9%)
	male	206 (55.4%)	371 (59.2%)	114 (60.3%)	1,107 (53.4%)	152 (57.4%)	390 (55.4%)	69 (71.1%)
age	0-17 years	22 (5.9%)	16 (2.6%)	15 (7.9%)	85 (4.1%)	12 (4.5%)	12 (1.7%)	9 (9.3%)
	18-49 years	118 (31.7%)	235 (37.5%)	69 (36.5%)	650 (31.4%)	136 (51.3%)	191 (27.1%)	34 (35.1%)
	50-64 years	166 (44.6%)	264 (42.1%)	70 (37.0%)	786 (37.9%)	100 (37.7%)	291 (41.3%)	37 (38.1%)
	65+ years	66 (17.7%)	112 (17.9%)	35 (18.5%)	551 (26.6%)	17 (6.4%)	210 (29.8%)	17 (17.5%)
ABO blood group	O	136 (36.6%)	260 (41.5%)	60 (31.7%)	784 (37.8%)	67 (25.3%)	329 (46.7%)	35 (36.1%)
	A	168 (45.2%)	285 (45.5%)	91 (48.1%)	914 (44.1%)	121 (45.7%)	279 (39.6%)	43 (44.3%)
	B	45 (12.1%)	69 (11.0%)	28 (14.8%)	270 (13.0%)	51 (19.2%)	74 (10.5%)	14 (14.4%)
	AB	23 (6.2%)	13 (2.1%)	10 (5.3%)	104 (5.0%)	26 (9.8%)	22 (3.1%)	5 (5.2%)
death cause	anoxia	63 (16.9%)	227 (36.2%)	14 (7.4%)	452 (21.8%)	39 (14.7%)	190 (27.0%)	13 (13.4%)
	CVA	232 (62.4%)	262 (41.8%)	129 (68.3%)	1,180 (56.9%)	175 (66.0%)	362 (51.4%)	47 (48.5%)
	trauma	75 (20.2%)	121 (19.3%)	39 (20.6%)	375 (18.1%)	48 (18.1%)	136 (19.3%)	34 (35.1%)
	other	2 (0.5%)	17 (2.7%)	7 (3.7%)	65 (3.1%)	3 (1.1%)	16 (2.3%)	3 (3.1%)

Based on donors reported between April 1, 2021, and December 31, 2024, who had their kidneys allocated and transplanted via ETKAS or ESP. Abbreviations: HB, heartbeating; NHB, nonheartbeating

Table 8.2: Characteristics of newly registered patients who were used for simulations.

variable	level	Austria (n=859)	Belgium (n=1,461)	Croatia (n=352)	Germany (n=4,547)	Hungary (n=665)	Netherlands (n=1,406)	Slovenia (n=103)
type transplant	primary	721 (83.9%)	1,278 (87.5%)	328 (93.2%)	3,978 (87.5%)	609 (91.6%)	1,173 (83.4%)	88 (85.4%)
	repeat	138 (16.1%)	183 (12.5%)	24 (6.8%)	569 (12.5%)	56 (8.4%)	233 (16.6%)	15 (14.6%)
age	0-17 years	22 (2.6%)	35 (2.4%)	7 (2.0%)	252 (5.5%)	28 (4.2%)	15 (1.1%)	3 (2.9%)
	18-49 years	279 (32.5%)	467 (32.0%)	124 (35.2%)	1,617 (35.6%)	283 (42.6%)	351 (25.0%)	44 (42.7%)
	50-64 years	376 (43.8%)	616 (42.2%)	155 (44.0%)	1,898 (41.7%)	270 (40.6%)	562 (40.0%)	35 (34.0%)
	65+ years	182 (21.2%)	343 (23.5%)	66 (18.8%)	780 (17.2%)	84 (12.6%)	478 (34.0%)	21 (20.4%)
ABO blood group	O	332 (38.6%)	656 (44.9%)	132 (37.5%)	1,730 (38.0%)	182 (27.4%)	617 (43.9%)	42 (40.8%)
	A	365 (42.5%)	583 (39.9%)	130 (36.9%)	1,962 (43.1%)	303 (45.6%)	522 (37.1%)	44 (42.7%)
	B	108 (12.6%)	159 (10.9%)	72 (20.5%)	618 (13.6%)	121 (18.2%)	210 (14.9%)	14 (13.6%)
	AB	54 (6.3%)	63 (4.3%)	18 (5.1%)	237 (5.2%)	59 (8.9%)	57 (4.1%)	3 (2.9%)
vPRA at listing	0%	675 (78.6%)	1,059 (72.5%)	221 (62.8%)	3,249 (71.5%)	510 (76.7%)	1,016 (72.3%)	72 (69.9%)
	>0-84.9%	134 (15.6%)	298 (20.4%)	101 (28.7%)	970 (21.3%)	94 (14.1%)	282 (20.1%)	20 (19.4%)
	85+%	50 (5.8%)	104 (7.1%)	30 (8.5%)	328 (7.2%)	61 (9.2%)	108 (7.7%)	11 (10.7%)
dialysis status	on dialysis	803 (93.5%)	1,247 (85.4%)	327 (92.9%)	4,479 (98.5%)	586 (88.1%)	1,057 (75.2%)	96 (93.2%)
	preemptive	56 (6.5%)	214 (14.6%)	25 (7.1%)	68 (1.5%)	79 (11.9%)	349 (24.8%)	7 (6.8%)
dial. time at listing	mean [Q1-Q3]	1.7 [0.5-2.3]	1.3 [0.0-1.7]	1.6 [0.4-2.4]	2.4 [0.8-3.0]	1.2 [0.1-1.5]	1.0 [0.0-1.1]	2.4 [0.7-2.9]

Based on patients listed in ETKAS or ESP between Apr 1, 2021 and December 31, 2024, with at least one active status in this period.

Table 8.3: Characteristics of patients already present on the waiting list on April 1, 2021.

variable	level	Austria (n=807)	Belgium (n=1,223)	Croatia (n=374)	Germany (n=9,513)	Hungary (n=1,006)	Netherlands (n=1,631)	Slovenia (n=93)
status	active	563 (69.8%)	907 (74.2%)	135 (36.1%)	6,480 (68.1%)	770 (76.5%)	712 (43.7%)	46 (49.5%)
	inactive	244 (30.2%)	316 (25.8%)	239 (63.9%)	3,033 (31.9%)	236 (23.5%)	919 (56.3%)	47 (50.5%)
type transplant	primary	581 (72.0%)	972 (79.5%)	304 (81.3%)	7,813 (82.1%)	941 (93.5%)	1,321 (81.0%)	74 (79.6%)
	repeat	226 (28.0%)	251 (20.5%)	70 (18.7%)	1,700 (17.9%)	65 (6.5%)	310 (19.0%)	19 (20.4%)
age	0-17 years	5 (0.6%)	16 (1.3%)	5 (1.3%)	159 (1.7%)	14 (1.4%)	9 (0.6%)	0 (0%)
	18-49 years	264 (32.7%)	433 (35.4%)	144 (38.5%)	3,334 (35.0%)	404 (40.2%)	392 (24.0%)	36 (38.7%)
	50-64 years	401 (49.7%)	532 (43.5%)	149 (39.8%)	4,639 (48.8%)	402 (40.0%)	691 (42.4%)	40 (43.0%)
	65+ years	137 (17.0%)	242 (19.8%)	76 (20.3%)	1,381 (14.5%)	186 (18.5%)	539 (33.0%)	17 (18.3%)
ABO blood group	O	408 (50.6%)	654 (53.5%)	145 (38.8%)	4,216 (44.3%)	368 (36.6%)	826 (50.6%)	38 (40.9%)
	A	239 (29.6%)	332 (27.1%)	133 (35.6%)	3,468 (36.5%)	372 (37.0%)	478 (29.3%)	24 (25.8%)
	B	131 (16.2%)	200 (16.4%)	75 (20.1%)	1,383 (14.5%)	206 (20.5%)	278 (17.0%)	22 (23.7%)
	AB	29 (3.6%)	37 (3.0%)	21 (5.6%)	446 (4.7%)	60 (6.0%)	49 (3.0%)	9 (9.7%)
vPRA group	0%	479 (59.4%)	694 (56.7%)	189 (50.5%)	5,573 (58.6%)	717 (71.3%)	1,085 (66.5%)	50 (53.8%)
	>0-84.9%	209 (25.9%)	299 (24.4%)	100 (26.7%)	2,650 (27.9%)	173 (17.2%)	337 (20.7%)	19 (20.4%)
	85+%	119 (14.7%)	230 (18.8%)	85 (22.7%)	1,290 (13.6%)	116 (11.5%)	209 (12.8%)	24 (25.8%)
dialysis status	on dialysis	789 (97.8%)	1,164 (95.2%)	358 (95.7%)	9,497 (99.8%)	924 (91.8%)	1,455 (89.2%)	90 (96.8%)
	preemptive	18 (2.2%)	59 (4.8%)	16 (4.3%)	16 (0.2%)	82 (8.2%)	176 (10.8%)	3 (3.2%)
dial. years dial.	mean [Q1-Q3]	3.2 [1.5-4.2]	3.1 [1.1-4.1]	3.4 [1.6-4.2]	5.7 [3.1-7.7]	3.0 [1.2-4.3]	1.9 [0.0-2.8]	4.0 [1.8-5.5]

Based on patients listed in ETKAS or ESP before Apr 1, 2024, with at least one active status in this period.

To enable accurate simulation of the ETKAS balance system, we also exported from the Eurotransplant database all cross-border transplantations that followed allocation via the AM program or were a combined transplantation. These transplantations were used to define the input stream of international transplantations. In simulations, we schedule donor arrivals, candidate status updates, and balance update events on the dates this information was actually reported to Eurotransplant. Our input-output validation exercise thus keeps the inputs as close as possible to reality, and assesses whether the outputs of the ETKidney simulator are comparable to the actual outputs of ETKAS and ESP.

Importantly, the outputs of the simulator depend on several stochastic processes: the offer acceptance behavior of the transplant centers, listing for a repeat transplantation after an initial kidney transplantation, and the switching to non-standard allocation by Eurotransplant. To give insight into variability of simulator outputs, we simulate ETKAS and ESP allocation 200 times over the simulation window and report 95% interquantile ranges for relevant summary statistics. These 95% IQRs are obtained by simulating allocation 200 times and reporting the 2.5th and 97.5th percentiles of simulation outputs. For each of these 200 simulation runs, we use a different set of completed status trajectories (see Section 8.3.1). We say that the ETKidney simulator is *"well-calibrated"* for a quantity of interest if the observed summary statistic falls within the 95% IQR of the 200 simulations.

Results of input-output validation

Table 8.4 reports results of this input-output validation for kidney waiting list outcomes. The ETKidney simulator is well-calibrated for almost all summary statistics: the total number of transplantations, the number of dual kidney transplantations, the number of ETKAS or ESP transplantations, the number of re-listings, and the number of waiting list deaths per country in all countries. We only observe miscalibration for the number of waiting list deaths in Hungary (-11%) and the active waiting list size at simulation termination (2% too many candidates have an active waiting list status).

Table 8.5 reports input-output validation results for ETKAS and ESP transplantations. For ETKAS, the simulator is well-calibrated for the number of transplantations placed by allocation mechanism (standard or non-standard), transplantations by candidate age group, and transplantations in repeat transplant candidates. The simulator is also well-calibrated for the number of transplantations by HLA match quality, with only the number of zero-mismatched transplantations overestimated (+5%). The number of transplantations in candidates with vPRAs exceeding 95% is underestimated (-17%). This miscalibration appears to have been the result of the introduction of the virtual crossmatch in January 2023, potentially because the number of positive crossmatches in the recipient center decreased after the introduction of the virtual crossmatch in Eurotransplant [176] (see Table 8.6 for miscalibration after January 2023). The simulator is well-calibrated for the number of transplantations per country, with only a slight overestimation observed in Croatia (+3%) and a slight underestimation observed in Hungary (-2%). The degree of geographical sharing is underestimated in ETKAS: there are too many local or regional transplantations in simulations (+5%), and too few inter-regional (-11%) or international (-9%) transplantations.

Table 8.5 also shows that the ETKidney simulator is well-calibrated for most relevant outcomes in ESP: the number of transplantations in primary and repeat kidney transplant candidates, and the number of transplantations by HLA match quality and immunization status. The simulator overestimates the number of kidneys transplanted after non-standard allocation in ESP (+23%). An apparent consequence of this is that the number of kidneys allocated to candidates under the age of 65 is overestimated (+28%), particularly in Belgium, the Netherlands, and Slovenia where centers appear to be reluctant to transplant a candidate under the age of 65 with an ESP donor (see Table 8.7). Finally, the simulator is well-calibrated for the number of transplantations by recipient country and match geography, with the only exception Germany where 2% too many ESP kidneys are transplanted.

Overall, the ETKidney simulator appears to be well-calibrated for most outcomes of ETKAS and ESP allocation. The results of this input-output validation exercise were discussed with medical doctors from Eurotransplant and ETKAC, who deemed differences small enough to make the simulator useful for determining the impact of alternative kidney allocation policies. We illustrate this with case studies in the next section.

Table 8.4: Input-output validation of waiting list outcomes between April 1, 2021 and January 1, 2024. For simulations, the numbers shown are the averages and 95% interquantile ranges (IQR) of outcomes over 200 simulations. Ranges are displayed in bold if the simulator is not well-calibrated, i.e. the actual statistic does not fall within the 95% IQR.

category	simulated results (average and 95% IQR)	actual data (2021-2024)
transplantations through ETKAS or ESP		
number of unique donors	4326	4326
number of transplantations	7546 [7530-7560]	7549
number of transplantations by type		
single kidney	7471 [7440-7500]	7484
dual kidney	74 [60-90]	65
number of transplantations by allocation mechanism		
ESP	1740 [1727-1752]	1745
ETKAS	5805 [5797-5814]	5804
waiting list		
initial active waiting list	9589	9589
number of listings	24028 [24010-24046]	24038
re-listings in simulated period	106 [88-124]	116
final active waiting list size	**10142 [+2%, 10095-10194]**	9958
waiting list removals (count)	1449 [1427-1473]	1469
waiting list deaths (count)	1146 [1122-1165]	1140
number of waiting list deaths by country		
Austria	73 [67-80]	73
Belgium	82 [73-90]	73
Croatia	40 [36-46]	40
Germany	723 [705-740]	713
Hungary	**128 [-11%, 121-135]**	144
Netherlands	92 [84-99]	90
Slovenia	7 [5-10]	7

Table 8.5: Validation of the number of transplantations between April 1, 2021, and January 1, 2024. For simulations, the numbers shown are averages and 95% IQRs over 200 simulations. Statistics are displayed in bold if the actual value does not fall within the 95% IQR.

	ETKAS		ESP	
category	simulated results (average and 95% IQR)	actual	simulated results (average and 95% IQR)	actual
allocation mechanism				
standard	5044 [4881-5169]	5000	**1117 [-10%, 1049-1188]**	1237
non-standard	761 [632-915]	804	**623 [+23%, 551-690]**	508
recipient characteristics				
pediatric recipient	339 [321-358]	325	0	0
aged 65 or over	734 [700-769]	725	**1512 [-4%, 1475-1548]**	1567
aged below 65	5071 [5034-5105]	5079	**228 [+28%, 192-261]**	178
primary transplant	5038 [5001-5068]	5039	1661 [1644-1677]	1665
repeat transplant	768 [734-795]	765	80 [67-92]	80
HLA-ABDR mismatches				
0 ABDR	**650 [+5%, 624-675]**	617	3 [1-6]	4
0 or 1 BDR	1136 [1083-1179]	1153	62 [50-77]	55
1B+1DR or 2 B+0 DR	2468 [2406-2534]	2492	316 [285-348]	336
2DR or 3+ BDR	1551 [1490-1609]	1542	1360 [1328-1388]	1350
sensitization status (vPRA)				
0%	**4211 [+2%, 4173-4255]**	4142	1477 [1455-1502]	1468
0.01-84.9%	1320 [1279-1356]	1355	256 [233-278]	264
85-94.9%	173 [155-191]	186	6 [2-10]	9
95+%	**101 [-17%, 87-114]**	121	**2 [-50%, 1-3]**	4
recipient country				
Austria	532 [525-538]	530	106 [87-128]	118
Belgium	912 [905-918]	914	107 [83-132]	120
Croatia	**277 [+3%, 272-283]**	270	38 [26-51]	26
Germany	2648 [2635-2659]	2651	**1081 [+3%, 1049-1118]**	1048
Hungary	**464 [-2%, 457-470]**	472	19 [11-28]	24
Netherlands	854 [847-860]	849	380 [349-406]	398
Slovenia	119 [113-124]	118	9 [4-15]	11
match geography				
local or regional	**4087 [+5%, 3993-4164]**	3902	1374 [1324-1424]	1408
interregional	**637 [-11%, 590-680]**	715	174 [138-206]	178
international	**1081 [-9%, 1012-1164]**	1187	192 [153-225]	159

Table 8.6: Input-output validation of the number of transplantations by vPRA, before and after the introduction of the virtual crossmatch on January 24, 2023.

vPRA (%)	before virtual crossmatch		after virtual crossmatch	
	simulated (mean and 95% IQR)	actual	simulated (mean and 95% IQR)	actual
0%	2751 [2711-2792]	2755	**1460 [1428-1489]**	1387
0.01-84.9%	875 [842-909]	861	**446 [417-474]**	494
85-94.9%	114 [99-128]	117	59 [48-69]	69
95+%	67 [56-78]	75	**34 [25-44]**	46

Table 8.7: Input-output validation of the number of transplantations with ESP donors in candidates under the age of 65, by recipient country of listing.

country of listing	number of ESP transplantations in candidates aged below 65	
	simulated (mean and 95% IQR)	actual
Austria	19 [12-28]	20
Belgium	**14 [6-23]**	3
Croatia	13 [7-21]	8
Germany	156 [131-184]	139
Hungary	3 [1-6]	6
Netherlands	**18 [8-30]**	1
Slovenia	**5 [2-10]**	1

8.6 Case studies

Together with ETKAC, three topics for case studies were selected in which the ETKidney simulator could help quantify the impact of alternative kidney allocation rules. The selected topics all concern the ETKAS program, and are (i) emphasizing matching at the HLA-B and HLA-DR locus, (ii) the introduction of a sliding scale based on the vPRA, and (iii) candidate-donor age matching. To limit the effects of transient effects, we extend the simulation period for these case studies from January 1, 2016 to January 1, 2024. We simulate all policy alternatives 20 times, and use traditional hypothesis testing to assess whether alternative policies significantly change the outcomes compared to the current policy. To increase the power of these tests, we use common random numbers [100] as a variance reduction technique. Consequently, the outcomes that are simulated under the alternative allocation rules can be compared to the outcomes simulated under the current rules with pairwise t-tests.

8.6.1 Case study 1: emphasizing matching at HLA-B and HLA-DR loci

Since its initiation in 1996, the ETKAS point system has placed equal emphasis on matching at the HLA-A, HLA-B, and HLA-DR loci, despite broad consensus that HLA-DR mismatches are more deleterious to graft survival than HLA-A and HLA-B mismatches [129, 157]. Internal analyses on registry data from Eurotransplant suggest that mismatches on the HLA-B and HLA-DR locus are indeed more strongly associated with graft loss than mismatches on the HLA-A locus. This motivated us to simulate policies that emphasize matching at the HLA-B and HLA-DR loci relative to the HLA-A locus.

The current ETKAS point system awards 400 points for HLA matching and penalizes HLA mismatches on the A, B, and DR loci with 66.7 points per mismatch. We assess the impact of three alternative HLA matching policies. These policies all continue to award up to 400 points for candidate-donor HLA match quality, but shift weight from the HLA-A locus to the HLA-B and HLA-DR loci (see Table 8.8). The first policy is referred to as the $\mathrm{B} + 2\mathrm{DR}$ policy, because it gives no weight to the HLA-A locus, maintains the same weight for the HLA-B locus (-66.7 points), and doubles the weight on the HLA-DR locus (-133.3 points). The second policy, referred to as the $0.5\mathrm{A} + \mathrm{B} + 1.5\mathrm{DR}$ policy, shifts only half of the weight placed on the HLA-A locus to the HLA-DR locus. The final policy, referred to as $1.5\mathrm{B} + 1.5\mathrm{DR}$, penalizes mismatches at the HLA-B and HLA-DR loci both with 100 points per mismatch.

Table 8.8: Overview of the points awarded per locus for the alternative HLA-matching policies.

policy	HLA-A	HLA-B	HLA-DR
current	-66.7	-66.7	-66.7
B + 2DR	0	-66.7	-133.3
0.5A + B + 1.5DR	-33.3	-66.7	-100
1.5B + 1.5DR	0	-100	-100

Simulation results for these three alternative policies are summarized in Table 8.9. These results show that the policy alternatives reduce the number of transplantations with 2 DR or 3 or more B+DR mismatches by 25 to 39%, and increase the number of transplantations with 1 B or 1 DR mismatch by 26 to 49%. Thus, the policies indeed succeed in improving match quality on the HLA-B and HLA-DR locus.

Table 8.9: The simulated change in the number of transplantations under alternative HLA-ABDR matching policies. The numbers displayed are the averages of the differences observed over 20 simulations. mm: mismatches.

		change in number of transplantations compared to current policy					
	average number of transplantations observed under the current policy	B + 2DR		0.5A + B + 1.5DR		1.5B + 1.5DR	
By HLA-ABDR mismatch count							
0	1925	-9	(-0%)	-1	(-0%)	-6	(-0%)
1	952	-181†††	(-19%)	-55†††	(-6%)	-99†††	(-10%)
2	3855	-634†††	(-16%)	-252†††	(-7%)	-509†††	(-13%)
3	6037	-358†††	(-6%)	-76†††	(-1%)	-224†††	(-4%)
4	3235	+837†††	(+26%)	+282†††	(+9%)	+642†††	(+20%)
5	730	+340†††	(+47%)	+104†††	(+14%)	+191†††	(+26%)
6	78	+2	(+3%)	0	(0%)	+7†	(+9%)
By HLA-ABDR match quality							
000	1925	-9	(-0%)	-1	(-0%)	-6	(-0%)
*00, *10, *01	3264	+1364†††	(+42%)	+850†††	(+26%)	+1585†††	(+49%)
*20, *11	7234	+209†††	(+3%)	+240†††	(+3%)	+131†††	(+2%)
**2, *21	4388	-1567†††	(-36%)	-1087†††	(-25%)	-1708†††	(-39%)
By homozygosity of the candidate the HLA-B and HLA-DR locus							
B and DR	473	-39†††	(-8%)	-17†††	(-4%)	-30†††	(-6%)
DR	1662	-207†††	(-12%)	-104†††	(-6%)	-94†††	(-6%)
B	1052	+31†††	(+3%)	+14††	(+1%)	-19†††	(-2%)
none	13625	+212†††	(+2%)	+110†††	(+1%)	+144†††	(+1%)

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$

However, results also show that there are unintended consequences of this policy: the total number of ABDR mismatches at transplantation increases with all alternative policies and there are 5 to 12% fewer transplantations in candidates who have homozygosity at the HLA-B or HLA-DR loci, who are already disadvantaged in the current ETKAS system. Results such as those presented in Table 8.9 can facilitate discussions by ETKAC on whether the improved match quality at HLA-B and HLA-DR loci is worth the increase in total mismatches and the reduced access to kidney transplants for homozygotes.

8.6.2 Case study 2: a sliding scale for the vPRA

Prior studies have suggested that immunized candidates have reduced access to transplantation in ETKAS (see [134, 135] and Chapter 7). In this case study, we assess whether this disparity can be alleviated by awarding points directly for the vPRA. For this, we modify the ETKAS point system in two ways. The first modification is that we directly award points for the vPRA using a *sliding scale*. Such a sliding scale for the vPRA has been a part of kidney allocation in the United States since 2014 [177]. The number of points awarded based on this sliding scale is calculated as

$$\texttt{weight} \cdot \frac{\texttt{base}^{\texttt{vPRA}}}{\texttt{base} - 1}.$$

The maximum number of points awarded by the sliding scale depends on its *weight*, and its steepness depends on the *base*. The second modification is that we no longer directly award points for the vPRA via the mismatch probability. Instead, we replace mismatch probability points by the 1-ABDR HLA mismatch frequency (see Section 8.4.1.3). This quantity awards points to candidates based on how difficult-to-match their HLA phenotype is, and not their blood group or their vPRA.

Representatives of ETKAC reached consensus that the aim of the sliding scale should be that a candidate's chance of being transplanted through ETKAS should not decline up to a vPRA of 85%. Above this vPRA, candidates could have access to the AM program, or should consider removing unacceptable antigens in case they do not meet AM criteria. We used the ETKidney simulator to simulate ETKAS for different combinations of weights and bases, and quantify the association between vPRA and the relative transplant rate using Cox proportional hazards model on the outcomes simulated by the ETKidney simulator. For this, the same model specification is used as in Chapter 7. In Figure 8.5 the estimated relation between vPRA and the transplant rate is shown for several sliding scales. From this figure, the sliding scale with a base of 5 and weight of 133 appears to be the most acceptable option: with this sliding scale, the relative transplant rate of sensitized candidates no longer decays until a vPRA of 85%, as was desired by ETKAC.

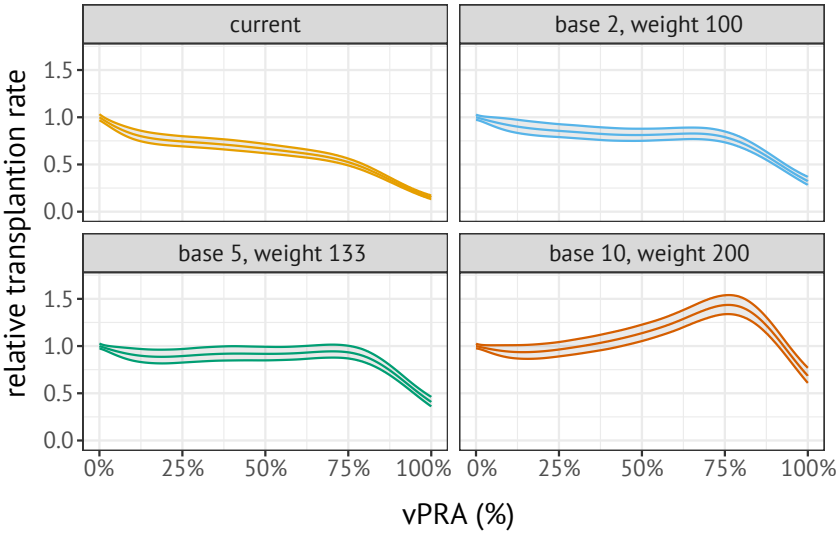


Figure 8.5: Relations between the relative transplant rate and the vPRA in ETKAS, estimated on ETKidney simulator outcomes. These relations were estimated with a Cox proportional hazards model, using a spline transformation for the vPRA.

8.6.3 Case study 3: candidate-donor age matching

Consensus in the transplantation literature is that kidneys procured from young donors should preferentially be transplanted in young candidates [178–182]. While allocation systems in France and the United Kingdom have implemented mechanisms that explicitly award points for continuous candidate-donor age matching [147, 148], the ETKAS point system does not award points based on candidate or donor age (except for bonus points that are given to pediatric patients). In this case study, we (i) use retrospective data from Eurotransplant to quantify the associations of candidate and donor age with patient and graft survival with cause-specific hazard models, and (ii) simulate and evaluate two age matching policies for ETKAS.

To quantify the relation between donor or candidate age and post-transplant survival, we consider all patients transplanted with a kidney through ETKAS or ESP between 2004 and 2019. We exclude candidates with the HU status and candidates without any follow-up information (n = 7,458), leaving n = 36,576 transplantations. We fit cause-specific Cox proportional hazards models on these transplantations for (i) graft loss and (ii) death with a functioning graft. We censored both time-to-event variables ten years after transplantation, because completeness of follow-up data beyond this time horizon is poor (available for less than 30% of patients). Besides donor and candidate age, we adjust for donor characteristics (DCD/DCD donation, hypertension, last creatinine,

death cause, diabetes, malignancy), candidate characteristics (dialysis time), and match characteristics (a zero-mismatch indicator, the number of mismatches per locus for the HLA-A, -B, and -DR loci, and match geography). To allow for non-linear relations between continuous variables and the hazard rate, we adjust for spline transformations of the continuous variables. The estimated relations between donor or candidate age and patient and graft survival are shown in Figure 8.6. These results are qualitatively similar to results obtained by Coemans et al. [181], who report that the hazard rate of graft loss decays linearly with recipient age while it increases quadratically with donor age, and that the mortality hazard rate increases quadratically with candidate age (note that the y-axis for the second panel is shown on the logarithmic scale).

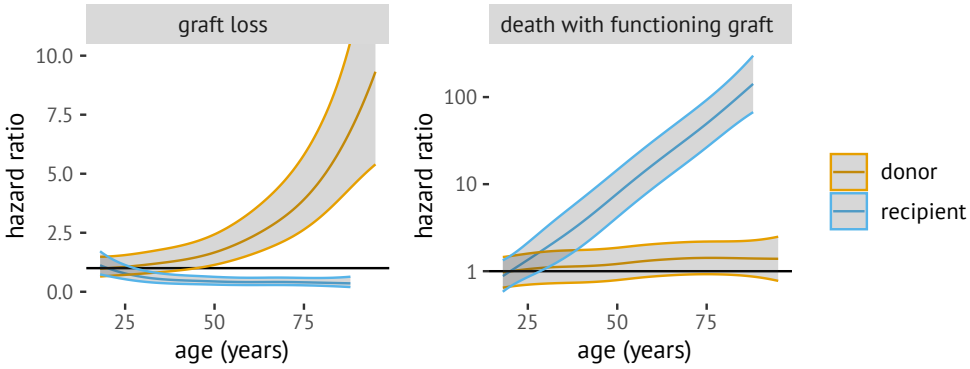


Figure 8.6: Estimated relations between graft loss and death with a functioning graft. Note that the hazard ratio for death with a functioning graft is shown on the logarithmic scale.

We simulate two candidate-donor age matching policies, both inspired by the French kidney allocation policy that was introduced in 2015 [147]. Like ETKAS, the French policy awards points for candidate waiting time, HLA matching between the donor and candidate, the candidate's likelihood of being favorably matched with a kidney, and the geographic distance between the donor and candidate. However, in France an "age filter" is applied to the total number of points awarded, with candidates ranked based on the filtered number of points. For example, the French age filter is 0% for a candidate who is over 20 years older than the donor, which means that such candidates receive 0% of their total points for ranking. The French age filter is asymmetrical with allocation of kidneys from a young donor to an older patient discouraged more strongly than the allocation of a kidney from an older donor to a young candidate.

Inspired by this French age filter, we evaluate two asymmetrical age filters for ETKAS (see Figure 8.7). Both filters give a candidate 100% of their ETKAS points in case the age difference between the candidate and donor is 5 years or less. The "strict" filter (blue) is similar to the French age filter in that it gives almost no points in case the candidate is

much older than the donor. The "muted" filter (orange) gives a larger fraction of the total number of ETKAS points, which we anticipated to be more acceptable for Eurotransplant because it maintains a better balance in the international exchange of kidneys.

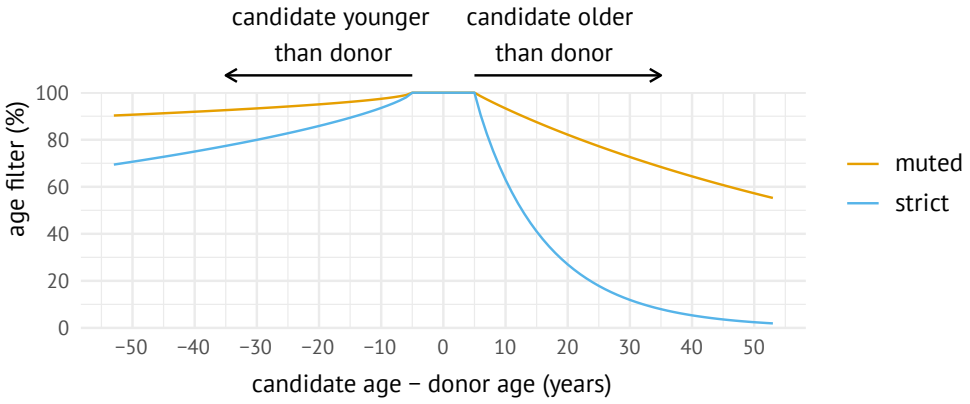


Figure 8.7: Evaluated age filters for ETKAS.

Simulated outcomes for the muted and strict age matching policies are compared to the current policy in Table 8.10. The table shows that the muted and strict policies increase the number of age-matched transplantations (defined as transplantations with a candidate-donor age difference of at most five years) by 60% and 138%, respectively. An unintended consequence is that the muted and strict age filters lead to reduced HLA match quality at transplantation, with a 12% and 33% increase in the number of level 4 mismatched kidney transplantations (2 DR, or 3 or 4 B+DR mismatches), respectively. Table also 8.10 shows that the muted policy only modestly increases international sharing (+5%) and inter-regional sharing (+7%), while the strict policy leads to a 37% increase in international transplantations. The strict age filter increases the number of extended or rescue transplantations (+7%), potentially because international offers are relatively more likely to be declined.

To evaluate whether the benefits of candidate-donor age matching outweigh its unintended consequences, we use the earlier mentioned cause-specific hazard models to predict the probability of death with a functioning graft ten years after transplantation for all simulated transplantations. For this, we predict the cumulative incidence of death with functioning graft using a cause-specific hazards approach [183]. By summing up these 10-year event probabilities for all candidates, we obtain the expected number of events ten years after transplantation, which is visualized in Figure 8.8 for the current policy (green), the muted age filter (orange), and the strict age filter (blue). These results suggest that the muted and strict age filter could reduce the numbers of deaths with a functioning graft 10 years after transplantation by 11% and 18%, respectively.

Table 8.10: The simulated change in the number of transplantations in ETKAS under continuous candidate-donor age matching policies. The numbers displayed are the average differences over 20 simulations. mm: mismatches.

		change in number of transplantations compared to current policy			
	average number of transplantations observed under the current policy	muted age filter		strict age filter	
age difference					
candidate 35+ years older	708	-497***	(-70%)	-557***	(-79%)
candidate 15-34 years older	3166	-1742***	(-55%)	-2549***	(-81%)
candidate 6-14 years older	3256	+434***	(+13%)	-1756***	(-54%)
max 5 year difference	4810	+2919***	(+61%)	+6640***	(+138%)
candidate 6-14 years younger	2624	-151***	(-6%)	-230***	(-9%)
candidate 15-34 years younger	2064	-873***	(-42%)	-1386***	(-67%)
candidate 35+ years younger	184	-86***	(-47%)	-155***	(-84%)
HLA match quality					
level 1 (0 ABDR mm)	1922	-8	(-0%)	-40***	(-2%)
level 2 (at most 1 BDR mm)	3250	-380***	(-12%)	-902***	(-28%)
level 3 (2B or 1DR+1B mm)	7224	-156***	(-2%)	-496***	(-7%)
level 4 (2DR or 3+ BDR mm)	4417	+547***	(+12%)	+1446***	(+33%)
match geography					
local or regional	11744	-297***	(-3%)	-1514***	(-13%)
national	1796	+121***	(+7%)	+306***	(+17%)
international	3272	+179***	(+5%)	+1215***	(+37%)
type of allocation					
standard allocation	14487	+50	(+0%)	-160*	(-1%)
non-standard	2325	-47	(-2%)	+167*	(+7%)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

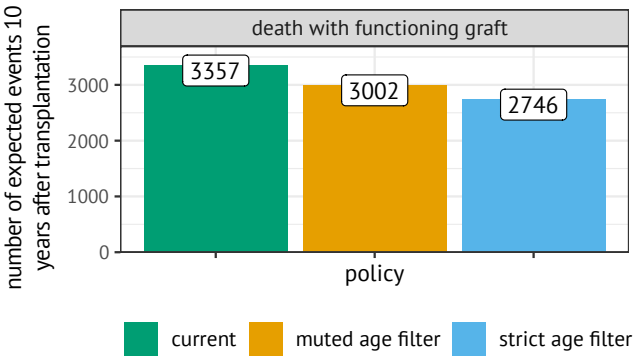


Figure 8.8: Expected number of post-transplant events ten years after transplantation, predicted based on candidate, donor, and transplantation characteristics with competing risk models.

8.7 Discussion and conclusion

Eurotransplant has long recognized the important role computer simulations could have for allocation development. For example, in the one-year evaluation of ETKAS that was published in 1998, the organization stressed that *"introduction of a change must be preceded by a computer simulation study"* [15]. However, Eurotransplant has only recently started the development of tools required for such simulation studies, with initiatives including the development of the ELAS simulator (see Chapter 5) and the passing a recommendation by the Thoracic Committee to develop a simulation tool for heart and lung allocation in 2024. Within this line of research, we present the ETKidney simulator.

Discrete-event simulators are already routinely used to update allocation rules in other geographic regions [85, 165, 164]. The most prominent simulator for kidney allocation is the Kidney-Pancreas Simulated Allocation Model (KPSAM), which was developed to simulate kidney allocation in the United States and which is made publicly available for research by the SRTR. KPSAM differs from the ETKidney simulator in several aspects. Firstly, KPSAM users have to manually specify in simulation inputs when a candidate would list for a repeat transplantation, as well as how their statuses would evolve after their return to the waiting list; in the ETKidney simulator, simulation of re-listings is instead based on historical data. Secondly, in KPSAM the graft offer acceptance behavior is simulated according to a single, patient-level logistic regression, while the ETKidney simulator additionally includes logistic regressions at the center level to capture that centers regularly decline kidneys for all their candidates. Thirdly, in KPSAM the kidneys that become available for allocation are discarded after a fixed number of offers, while the ETKidney simulator has functionality to simulate based on donor characteristics after how many offers Eurotransplant would stop offering the kidney in standard allocation. Thereafter, the ETKidney simulator switches to non-standard allocation. Such out-of-sequence offering is not simulated in KPSAM.

More important than these technical differences is that the ETKidney simulator is a bespoke model for Eurotransplant, which implements Eurotransplant-specific allocation mechanisms such as the points for the mismatch probability and the balance system that Eurotransplant uses to balance the international transfer of kidneys. Eurotransplant needs such a bespoke model in its communication with national competent authorities, who are interested not only in the overall effects of policies but also in the specific impacts that the policy changes have on their national waiting list populations.

To build trust in the simulator, we have used input-output validation to show that the simulator can closely approximate contemporary transplantation patterns of ETKAS and ESP. Results of this validation exercise were discussed with medical doctors from Eurotransplant, and presented at the Eurotransplant Annual Meeting to additional major stakeholders, including representatives from national competent authorities as well as medical professionals from the kidney transplant centers. In the view of many of these stakeholders, the simulator has become a useful tool for kidney allocation policy development as we have also demonstrated in this chapter through three clinically motivated case studies.

From discussions with ETKAC, ETRL and other stakeholders, it became clear that the policies proposed in these case studies have to be refined further. The first case study focused on HLA matching at the A, B, and DR loci. This focus was motivated by the fact that HLA-B and HLA-DR are most strongly associated with graft loss in Eurotransplant. However, HLA matching in kidney transplantation also aims to prevent *de novo* sensitization. Recent literature has shown that HLA-DQ mismatches are most strongly associated with antibody formation [184, 175]. Further simulations should explore how HLA-DQ matching can be included in ETKAS.

The aim of the second case study was to develop a sliding scale that provides candidates with vPRAs below 85% with equality of opportunity in ETKAS. This aim was based on the fact that candidates with a vPRA >85% may have access to the AM program. However, it has been observed that certain patient groups in the AM program are transplanted within months of entering the program [138], which suggests that these candidates may not require priority that is given by the AM program. Based on these findings, ETRL and Eurotransplant's advisory committees have recommended changing the AM entry criterion to a donor frequency of 2%, which corresponds to a vPRA of approximately 95%. The sliding scale proposed in this case study should be revised to ensure that candidates with vPRAs between 85% and 95% are not disadvantaged in ETKAS.

The final case study suggested that continuous candidate-donor age matching is a promising avenue to improve kidney allocation in Eurotransplant, because it substantially reduces the number of post-transplant deaths with a functioning graft. However, these reductions are partly due to a decrease in transplantations among candidates aged 55 and older. A question that should be explored further is whether these candidates should be given access to donors aged 65 and over, as was already unanimously recommended in a 2018 European Consensus Meeting [159]. Such access could be achieved by allowing candidates between 55 and 65 to participate in ESP, or by allocating donors aged over 65 via ETKAS. The preferred route should be discussed together with the advisory committees and national competent authorities.

We acknowledge that the ETKidney simulator also has limitations. Firstly, the graft offer acceptance models and post-transplant survival models are calibrated to historical data. These models may lack external validity for future post-transplant survival and future offer acceptance behavior. An example of this, encountered during input-output validation, is that the simulator appears to underestimate the number of transplantations in immunized candidates after the introduction of the virtual crossmatch in Eurotransplant in January 2023. This limitation could be addressed by refitting the organ acceptance models in the future on more contemporary data. A second limitation is that validation was only based on historical input-output validation. Ideally, we would have been able to observe ETKAS and ESP outcomes under alternative allocation rules, and study whether the simulator would be able to capture simulated outcomes under these alternative rules [185]. Unfortunately, this was not feasible, since ETKAS and ESP allocation rules have undergone only minimal changes since their introductions in 1996 and 1999, respectively. A final limitation is that Eurotransplant is not allowed to publicly release information that could potentially identify its donors and candidates, which prevents exact reproduction of our simulations by external parties. We have tried to address this limitation by making synthetic data available on which kidney allocation can be simulated.

In conclusion, we are confident that the ETKidney simulator is a valuable tool for quantifying the impact of kidney allocation policy changes in Eurotransplant, as we demonstrated with three clinical case studies. We anticipate that the simulator can play a pivotal role in modernizing ETKAS and ESP allocation rules, in collaboration with subject-matter experts from ETKAC, the ETRL, and national competent authorities.

Chapter 9

The way forward

In Chapters 1, 2, and 6, we have placed the liver and kidney allocation systems in their historical context. A common thread throughout these chapters is that fairness mechanisms have become a central component of Eurotransplant's allocation systems. In fact, Eurotransplant's member countries have identified equality of opportunity as *"the most important factor for allocation"* [16].

This motivated the first goal of this thesis: the investigation of research questions relating to equality of opportunity. In Chapter 4, we assess whether, and why, female candidates for liver transplantation are more likely than male candidates to have an adverse waiting list outcome in Eurotransplant. In Chapter 7, we examine whether immunized candidates are adequately prioritized in ETKAS. The findings of these chapters highlight that both the liver and kidney allocation systems have room for improvement.

An important barrier to implementing such improvements has been that Eurotransplant did not have tools available to quantify the impact of allocation policy changes. To overcome this barrier, a second goal of this thesis was to develop tools that provide insight into the adequacy and the unintended consequences of allocation policy changes. In Chapters 5 and 8, we have provided detailed descriptions of the ELAS and ETKidney simulators. These simulators mimic the liver and kidney allocation processes in Eurotransplant, based on Eurotransplant allocation rules and Eurotransplant registry data. To build trust in these tools, we have developed these simulators in close collaboration with subject-matter experts. They have been validated through input-output validation and are publicly available online. The simulators have already become valuable tools for allocation policy development, as we illustrated through clinically motivated case studies in Chapters 5 and 8.

In this chapter, we reflect on the findings of this thesis, and what is needed to advance Eurotransplant's liver and kidney allocation systems.

9.1 This thesis is a sharp look at familiar problems

The problems studied in this thesis were brought to our attention by clinicians affiliated with Eurotransplant's advisory committees and the ETRL, who experience these issues in their daily work. The studied problems are therefore not new. In fact, sex disparity in liver transplantation has been a prominent topic for over a decade [38, 65, 66], and disadvantages for immunized candidates have previously been reported in both Germany [134, 135] and the United States [177].

This lack of novelty does not mean that these problems are not worth revisiting. One reason to re-examine these problems in this thesis is that consensus between Eurotransplant's member countries is often required to change allocation policies. Investigating disparities using Eurotransplant-wide cohorts can help build such consensus. In some cases, Eurotransplant-wide cohorts are also needed to achieve sufficient statistical power. For example, the disadvantages faced by female candidates on the liver waiting list (Chapter 4) are likely too subtle to be detectable in single-center studies or even those conducted at the national level.

Eurotransplant's expertise on the allocation systems can also be essential to contextualize any observed disparities. For instance, disparities may vary between countries due to heterogeneity in national allocation policies, or they may evolve over time as the allocation rules change. An important realization is also that disparities in waiting list outcomes need not be the result of allocation. For example, they can also arise through the offer acceptance behavior of transplant centers. Eurotransplant's expertise on the allocation systems was critical in designing informative sensitivity checks relating to its allocation mechanisms (standard vs. non-standard allocation; center-driven vs. patient-driven offers), time periods, and countries (see Chapters 4 and 7).

A final motivation to revisit these existing problems is that the existing literature relies too heavily on the standard assumptions of the Cox proportional hazards model, which are implausible in the context of the transplantation waiting list. For example, in liver transplantation, dependent censoring due to transplantation is typically ignored, which introduces bias when modeling waiting list mortality (see Chapters 3 and 4). In kidney allocation, the modeling of access to transplantation is complicated by the relevance of two timescales: time since waiting list registration and time on dialysis. In our analyses, we have preferred to use dialysis as the timescale, as candidates are prioritized by dialysis time and not waiting time. However, care must then be taken to ensure that the adjustment variables are predetermined to the outcome (see Chapter 7).

9.2 We need to look beyond survival models for allocation

In transplantation research, efforts to improve allocation models often narrowly focus on the improvement of the statistical models that predict medical urgency, medical utility, or transplant benefit. In the literature on liver transplantation, for example, a plethora of refinements to MELD have been proposed, which include delta-MELD [39], integrated MELD [186], Updated MELD [40], ReFit MELD [41], MELD excluding INR [187], UKELD [188], MELD-Na [37], MELD-Plus [189], MELD lactate [190], ReMELD and ReMELD-Na [191], MELD 3.0 [20], and GEMA-Na [70].

Few of these models have been implemented for organ allocation, and those that were implemented have had a limited impact on the number of waiting list deaths. For example, in the United States, only MELD-Na and MELD 3.0 have been adopted for liver allocation. MELD-Na was introduced because LSAM simulations suggested that the score could prevent 40 to 60 waiting list deaths annually. MELD 3.0 was primarily introduced to rectify sex disparity, but was also projected to reduce waiting list mortality by up to 20 deaths per year [20]. These projections meant that MELD-Na could avert 2 to 3% of liver waiting list deaths in the United States, whereas MELD 3.0 was projected to reduce mortality by less than 1%. Although this is an improvement, it also shows that revising MELD is not a magic bullet in preventing liver waiting list deaths.

In Chapter 5, we quantified the impacts of introducing ReMELD-Na on liver waiting list outcomes in Eurotransplant. We find that ReMELD-Na could avert between 5 and 20 waiting list deaths per year, which corresponds to 1 to 4 percent of the waiting list deaths in Eurotransplant. Partially based on these findings, liver allocation in Eurotransplant has become based on ReMELD-Na since March 25, 2025. Eurotransplant is currently examining whether allocation can be improved further with MELD 3.0 or GEMA-Na. Although these efforts are worthwhile, it should be realized that further refinements to MELD may have diminishing returns, and could also reduce the number of waiting list deaths by less than one percent.

Other approaches are thus necessary to meaningfully reduce mortality on the liver waiting list. These approaches should look beyond the refinement of survival models for waiting list mortality. One approach – which is under-explored for liver allocation in Eurotransplant – is to reconsider the priority for candidates with exception points. In a second case study in Chapter 5, we show that modifying the exception point system in Belgium could reduce the number of Belgian waiting list deaths by up to 10%. Based on this information, BeLIAC asked Eurotransplant in February 2025 to cap all exception points in Belgium by 28 points. Similar revisions of the exception point systems should be explored with other national competent authorities. A different approach to reducing the number of waiting list deaths – which was not explored in this thesis – is to increase geographical sharing for candidates with extreme MELD scores, as is done in the United

States for MELD scores exceeding 35 [102] and in Italy for MELD scores exceeding 30 [103]. A simulation study could be conducted that examines the effects of broader geographic sharing in Eurotransplant.

Liver allocation can also be improved by making it fairer. In Chapter 4 we describe that the smaller stature of females limits their access to transplantation, which indirectly increases the number of waiting list deaths in females. This finding suggests that waiting list outcomes between males and females cannot be equalized by only revising MELD using a Cox proportional hazards model with waiting list death as the outcome; such models cannot compensate for the disparities in waiting list outcomes that are indirectly due to access to transplantation. Instead, we suggest in Chapter 4 that a simulation study should be conducted to assess how many extra points small-statured candidates would need to rectify sex disparity.

While the inclusion of factors that are not directly related to survival may appear arbitrary, it is important to note that the current allocation system already includes such factors. For example, pediatric patients are already prioritized based on exception points, and blood group O candidates are protected by the restricted ABO blood group rules. Ultimately, we believe that there is no compelling reason for basing liver allocation *solely* on MELD. We note that this idea already appears to have been accepted by policymakers in the United States, where a policy-making process is underway to award points for factors other than pre-transplant mortality (quantified by MELD) [20]. Explicitly included among these factors is candidate height.

9.3 We should look beyond aggregate outcomes

ELIAC and national competent authorities have been hesitant to introduce MELD-Na for liver allocation because the literature indicates that this score has exacerbated sex disparity in liver allocation (e.g., [75]). Our results in Chapter 4 are compatible with this finding and suggest that females indeed have a slightly higher waiting list mortality rate than males when at the same MELD-Na score. This disadvantage corresponds to a 0.5 to 1 point difference on the MELD scale. The ReMELD-Na case study in Chapter 5 also shows that introducing ReMELD-Na would primarily prevent waiting list deaths among male candidates. Although this confirms concerns that ReMELD-Na would increase sex disparity, it should not be interpreted as an argument against ReMELD-Na per se; our analysis shows that ReMELD-Na would reduce the number of waiting list deaths for both sexes (albeit insignificantly for females).

This illustrates that new allocation policies should not be introduced or rejected based on a single summary statistic. Instead, simulation studies should be conducted that quantify the impact of allocation policy changes on several subgroups, as we do in Chapter 5 for several vulnerable patient groups. Policymakers can then make rational decisions about whether the improvements for some patient groups can justify the unintended consequences these policy changes inevitably have on others. Not doing such a simulation can also harm certain patient groups. A cautionary example appears to have been the 2018 introduction of the Transplant Benefit Score (TBS) in the United Kingdom. While this scheme improved overall survival benefit [19], the policy has been controversial because it inadvertently reduced access to transplantation for young liver transplant candidates, as well as for those with hepatocellular carcinoma (HCC) [45, 46].

Policymakers should also be aware that using statistical models in allocation results in statistical discrimination. In a retrospective cohort of liver transplantation recipients from Eurotransplant (*unpublished*), we find that the sickest 3% of candidates for liver transplantation still have a graft survival probability two years after transplantation that exceeds 60%. These patients were on average 50 years old, had MELD scores exceeding 30 at listing, were admitted to the ICU before transplantation, and presented with grade 3 acute-on-chronic liver failure (ACLF), which alone is associated with a 28-day mortality exceeding 80% [22]. A benefits-based allocation could deny these patients access to liver transplantation. This would mean that the six out of ten patients who would survive more than two years with a functioning graft could be denied a liver transplantation, because four others would not survive. Whether such an allocation is ethically acceptable is a normative question that cannot be answered based on aggregate statistics.

9.4 Scientific evidence is rarely the bottleneck

The recommendations that are prepared by Eurotransplant's advisory committees require approval from the Eurotransplant Board and the national competent authorities before they are implemented. A frequently mentioned barrier to obtaining approval from the national competent authorities is that any change to allocation has to be based on scientific evidence.

In our view, the availability of scientific evidence is rarely the bottleneck – at least not for the case studies included in this thesis. For example, there is broad consensus that kidneys from young donors should be preferentially allocated to young candidates [178–182], there is consensus that HLA-DR matching is more important than HLA-A or HLA-B matching in kidney allocation [129, 157], and ample evidence exists that hyponatremia is associated with an increased mortality on the liver waiting list [37, 191].

We think that the primary bottleneck lies in translating these findings into allocation policies that are acceptable to all stakeholders. Significant progress could be made if national competent authorities are willing to accept the results of the ELAS and ETKidney simulators as scientific evidence. In the United States, discrete-event simulation already plays such a role; tools such as LSAM and KPSAM have been instrumental in shaping the liver and kidney allocation policies in OPTN, the organ-sharing network of the United States.

Another issue has been that proposals to improve the allocation systems are sometimes too radical. The fact that ETKAS still gives equal priority to HLA matching at the A, B, and DR loci is not because emphasizing matching at the HLA-DR locus has not been explored. In fact, several policies have been proposed that emphasize matching on the HLA-DR locus. However, these proposals introduced new tiers for DR-matching (e.g., [130]), which represents a radical overhaul of the current points-based system. National competent authorities could not agree to this overhaul, for example because it strongly increased the number of international transplantations [131]. A more fruitful approach to improving the allocation system is to consider incremental changes that are supported by solid evidence and backed by a broad set of stakeholders. We see giving relatively more points to matching on the HLA-DR locus than the HLA-A locus – a policy explored in Chapter 8 – as an example of such an incremental approach.

9.5 The "chicken-and-egg" problem in allocation development

A persistent "chicken-and-egg" problem in Eurotransplant is that the transplant centers are reluctant to report information to Eurotransplant that is not required for allocation, while policymakers are reluctant to introduce new allocation policies that have not been validated in Eurotransplant. We encountered such a problem in the ReMELD-Na case study in Chapter 5; serum sodium is absent in the Eurotransplant database for most candidates, which complicates studying the impact of ReMELD-Na for liver allocation.

It is important to note that serum sodium is virtually always measured alongside the other MELD biomarkers, which makes missingness of serum sodium a reporting issue, not a data availability issue. The same issue exists for serum albumin, which is required for MELD 3.0, and serum urea, which is required for GEMA-Na. This severely limits the utility of the Eurotransplant database for developing and validating liver allocation scores, especially when the SRTR makes data from the United States available for research, where the reporting of these biomarkers has been mandatory for years. For example, centers in the United States have been required to report serum sodium with every MELD update since 2004, twelve years before MELD-Na was introduced for allocation [192]. To develop liver allocation scores specifically for Eurotransplant, more prospective data collection is needed in Eurotransplant.

In kidney allocation, a similar "chicken-and-egg" problem complicates the study the impact of epitope matching. Such epitope matching has been described as a promising alternative to HLA matching at the serological level because (i) epitopes provide a more precise assessment of immunological compatibility that could improve post-transplant outcomes [160], and (ii) epitope matching can be more equitable than HLA matching [193]. However, studying whether epitope matching would improve outcomes after kidney transplantation requires high-resolution HLA typings, and such typings are not yet routinely reported to Eurotransplant [194].

Transplant centers express valid concerns over the increase in workload associated with prospective data collection. A task for Eurotransplant is to minimize this workload by limiting any prospective data collection to information that is deemed necessary for allocation development. For liver transplantation, the burden can be reduced by mandating the collection of specific biomarkers only at listing, which would enable external validation of new liver allocation scores using a "from registration" approach (see Chapter 3). An ELIAC recommendation in this direction is currently awaiting approval from the national competent authorities.

The workload for the transplant centers can also be reduced through automated data reporting. A success story in this regard is the introduction of the virtual crossmatch in January 2023, after which donor procurement organizations no longer need to manually enter the HLA typings of their donors. As a result, HLA typings of donors are now routinely available at Eurotransplant at an intermediate resolution. Implementing a similar automated reporting system for candidate HLA data has been requested by HLA typing laboratories, and should be a priority for Eurotransplant.

Special attention should also be given to the collection of follow-up information. The simulation of listing for repeat transplantation in the ETKidney and ELAS simulators depends on this information. Such information is also required to quantify the impact of allocation policy changes on post-transplant outcomes, a matter that is regularly inquired about by the advisory committees. A growing concern is that several centers within Eurotransplant have stopped reporting follow-up information to the Eurotransplant registry. Long-term follow-up information is therefore not available for many transplant recipients.

9.6 We need more constructive dialogue

The core principles of Eurotransplant's current liver and kidney allocation systems have changed little since their respective introductions in 2007 and the 1990s. This stagnation stands in contrast to other regions and is surprising given the demographic shifts of our patient and donor populations, and clinical advancements in the field. The

work presented in this thesis has described several areas for improvement in kidney and liver allocation. The primary challenge lies in translating these findings into allocation policies acceptable to Eurotransplant, national competent authorities, transplant centers, and ultimately, the patients who wait for a transplant.

Over the past two decades, allocation development has become a slow and tedious process. This has, at times, strained the relationships of Eurotransplant with its stakeholders. Some member countries even question whether there is a role for Eurotransplant in allocation development. These stakeholders should recognize – as is highlighted by this thesis – that Eurotransplant allocation systems are highly complex and must balance multiple, competing objectives. Improving these systems is not as straightforward as proposing a new statistical or machine learning model to score medical urgency, medical utility, or transplant benefit, and solely focusing on such solutions can harm vulnerable patient groups. In my view, Eurotransplant's expert knowledge on these allocation systems makes it deserving of a seat at the table when new allocation policies are discussed.

At the same time, it is important that Eurotransplant listens to the clinical experts who on a daily basis experience the limitations of the current allocation systems. The topics studied in this thesis were motivated by conversations with these experts; for example, the size mismatch hypothesis in Chapter 4 was raised (off-topic) by a BeLIAC representative, and several nephrologists have expressed frustrations about the fact that the immunized candidates who are ineligible for the AM program are falling through the cracks in ETKAS (which we confirm in Chapter 7). It is true that Eurotransplant's allocation systems feature mechanisms to help address these disparities. For example, livers from donors weighing less than 46 kg are offered with priority to candidates weighing less than 55 kg, and immunized candidates receive some extra priority through mismatch probability points. It can simultaneously be true that these mechanisms fall short of realizing equality of opportunity, and Eurotransplant should be more open to recognizing this.

Historically, the main forums to develop new allocation policies in Eurotransplant have been the organ advisory committees. With the introduction of legal frameworks in the 1990s, national competent authorities now also have a strong say. A source of frustration appears to be that Eurotransplant submits finalized recommendations to national competent authorities, sometimes without prior consultation. To avoid this, Eurotransplant should engage these and other stakeholders earlier in policy discussions. An obstacle to playing such a role is that Eurotransplant has limited capacity for allocation development, employing only two full-time biostatisticians and seven medical doctors who have to spend most of their time on operational duties.

This stands in stark contrast to other regions where dedicated research departments or organizations have been established that focus exclusively on allocation development. Notable is the SRTR in the United States, which was established in 1984 to support statistical analyses relating to solid organ donation and which has developed the SAM family of simulators. SRTR operates on an annual budget of 7 million USD. Because of this investment gap, it not surprising that the heart, lung, and liver allocation systems used in Eurotransplant were developed in the United States. If we want to develop allocation systems tailored to our European patients, Eurotransplant's member countries should be open to providing long-term funding for allocation research and development.

In the end, meaningful progress on the organ allocation policies can only be achieved through more constructive dialogue among Eurotransplant, the national competent authorities, and subject-matter experts affiliated with the transplantation centers. Together, these stakeholders should carefully consider how to weigh the ethical trade-offs involved in the allocation of deceased-donor organs. The simulators presented in this thesis can contribute to these discussions by making the associated trade-offs explicit.

Appendix A

Inverse Probability Censoring Weights

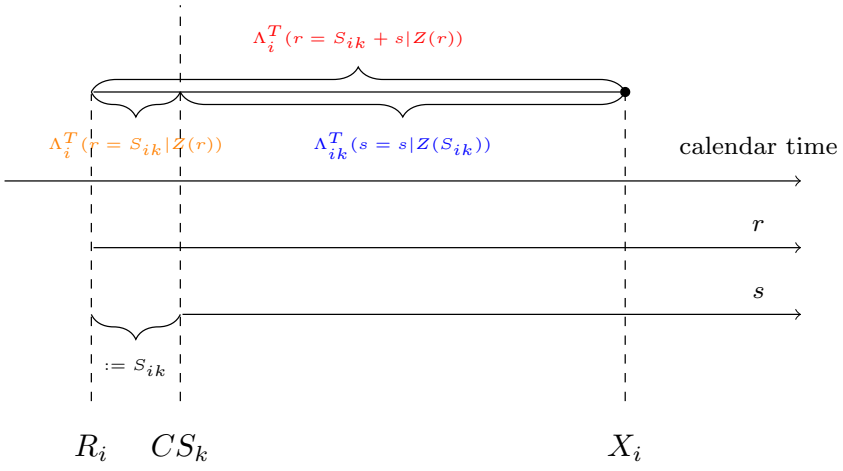
In the transplantation literature, survival on the liver waiting list is regularly modeled with Cox proportional hazards models adjusting for biomarkers reported at listing. Such a model can consistently estimate the parameters of the Cox proportional hazards model under the assumption of conditionally independent censoring. However, this independent censoring assumption is implausible for liver waiting list survival, because expected waiting list survival is continuously monitored using MELD scores. Throughout part I of the thesis, we use inverse probability censoring weighting (IPCW) to correct for such dependent censoring, based on an approach originally proposed by Gong and Schaubel (2013) [57]. In this technical supplement, we explain how these IPCW weights are defined in the context of the calendar-time cross-sections, defined in Chapter 3. They may be readily adapted to a "*from registration*" approach.

Definition of IPCW weights

A graphical summary of how the inverse probability censoring weights are defined is shown in Figure A.1.

Let R_i denote the registration date in calendar time for patient i, and r denote the time elapsed since patient i's registration time R_i. Each patient has a waiting list death time (D_i), removal or censoring time (C_i), and transplantation time T_i, all defined relative to the time origin R_i. In general, only one of these events is observable to us per patient, i.e., we observe $X_i = \min(D_i, C_i, T_i)$.

Note that candidates for transplantation may become (temporarily) non-transplantable.



$$W^A(s) := Y_{ik}(s)\exp(\Lambda_i^T(r = S_{ik} + s|Z(r)) - \Lambda_i^T(r = S_{ik}|Z(r)))$$

$$W^B(s) := Y_{ik}(s)\frac{\exp(\Lambda_i^T(r=S_{ik}+s|Z(r))-\Lambda_i^T(r=S_{ik}|Z(r)))}{\exp(\Lambda_{ik}^T(s=s|Z(S_{ik})))}$$

Figure A.1: Figure demonstrating how inverse probability censoring weights (IPCW) are calculated for a subject i. Subject i is registered at R_i, is active at cross-section date CS_k, and experiences an event at time X_i. Since subject i has an active registration at CS_k, this subject contributes an observation to the data set. To correct for dependent censoring, the spell is weighted by the inverse probability that patient i is transplanted between CS_k and X_i, controlling for time-varying $Z(r)$ (type A weight). To this end, cumulative hazards treatment hazards are estimated from registration R_i to CS_k, and R_i to X_i. The type A weight is the inverse probability of being transplanted before X_i, conditional on not being transplanted up to CS_k. It is thus strictly greater than 1, thereby unstabilized. Gong and Schaubel propose to normalize the type A weight by the conditional probability of comparable subjects in cross-section k experiencing an event between CS_k and X_i, conditional on the time-frozen covariate information $Z(S_{ik})$.

To account for this, let $A_i(r)$ denote whether patient i has an active registration r time units after registration, i.e., $A_i(r) = 1$ only if patient i is eligible for transplantation at calendar time $R_i + r$. In addition, updated covariate information (for instance, MELD scores) may be reported for patient i. Denote with $Z_i(r)$ all covariate history reported up to r time units after registration for patient i. Note that this covariate history can consist of observed covariates and other summaries of treatment eligibility history ($A_i(r)$).

The key idea in Gong and Schaubel (2013) is to introduce a series of cross-section dates ($CS_1, \ldots CS_K$), and model the mortality hazard from each cross-section onwards for patients who have an active registration at cross-section date CS_k. These mortality

hazard models are partly conditional, which means they adjust only for covariate history observed prior to CS_k. The timescale the models use is the time elapsed since the cross-section date CS_k, which we denote by s. For notational convenience, it is helpful to define the time registered for patient i until cross-section k by S_{ik}, i.e. $S_{ik} = CS_k - R_i$. Gong and Schaubel's approach can then be represented with the following hazard model

$$\lambda_{ik}^{D}(s) = A_i(S_{ik})\lambda_{0k}^{D}(s)\exp\left\{\beta_{\mathbf{0}}^{'}\mathbf{Z_i}(S_{ik})\right\}, \quad s > 0$$

where $A_i(S_{ik})$ indicates patients are active at the cross-section, $\lambda_{0k}^{D}(s)$ is a baseline hazard stratified by cross-section, and $Z_i(S_{ik})$ is patient i's covariate history observed before cross-section date CS_k.

Direct estimation of Equation A1 through Cox regression results in biased $\widehat{\beta_0}$, since covariate information (e.g., MELD) reported after cross-section date CS_K may still affect the probability of transplantation and waiting list mortality after CS_k. To correct for this, Gong and Schaubel propose weighing spells observed from cross section CS_k to time r by the inverse conditional probability of remaining on the waiting list up to time r, i.e.

$$W_{\text{ik}}(r) = \left[P\left(T_i > r | T_i > S_{\text{ik}}, Z_i(t), t \leq r\right)\right]^{-1} = \left[\frac{P\left(T_i > r | Z_i(t), t \leq r\right)}{P\left(T_i > S_{\text{ik}} | Z_i(t), t \leq S_{\text{ik}}\right)}\right]^{-1}.$$

Gong and Schaubel refer to this weight as the "type A" weight. Note that this weight is only defined as if the conditional probability of being transplanted between the cross-section and r is strictly larger than 0. This assumption is known as positivity.

If we additionally assume that there is no unmeasured confounding of the relation between transplantation and survival, IPCW can be used to construct a "pseudo-population", which would have been observed if transplantation had not existed. This means that under these assumptions, we can consistently estimate β_0 through Cox regression on the weighted population.

To construct this pseudo-population, we have to estimate these IPCW weights. For this, Gong and Schaubel propose the following treatment hazard model:

$$\lambda_i^T(r | Z_i(r)) = A_i(r)\,\lambda_0^T(r)\exp\left\{\theta_{\mathbf{0}}^{'}\mathbf{Z_i}(r)\right\}.$$

This treatment hazard model use time since registration (r) as the timescale, and adjusts for time-varying covariate information $(Z_i(r))$. Using the definition of the hazard rate, one can show that the type A weight reduces to

$$
\begin{aligned}
W_{ik}(r) &= \left[\frac{P(T_i > r \mid Z_i(t), t \leq r)}{P(T_i > S_{ik} \mid Z_i(t), t \leq S_{ik})} \right]^{-1} \\
&= \exp\Big[\int_{S_{ik}}^{r} A_i(u)\, \lambda_0^T(u)\, \exp\{\theta_0' Z_i(u)\}\, du \Big], \\
&= \exp[\Lambda_i^T(r) \; - \; \Lambda_i^T(S_{ik})].
\end{aligned}
$$

where $\Lambda_i^T(r) = \int_0^r \lambda_i^T(u|Z(u))$ du is the cumulative hazard of transplantation.

The type A weight allows for unbiased estimation of β_0 under no unmeasured confounding and positivity. However, since $W_{ik}(r)$ is an inverse probability weight, it is greater than or equal to 1 for all individuals and cross-sections. This can result in instabilities when conditional probabilities become small. To avoid this, Gong and Schaubel also propose to stabilize the type A weight by a partial conditional estimate of the conditional probability of being transplanted, i.e., stabilize $W_{ik}(r)$ with

$$
P\left(T_i > r | Z_i\left(S_{\text{ik}}\right), t \leq r\right).
$$

Gong and Schaubel attain an estimate of this probability using the following partly conditional treatment hazard model,

$$
\lambda_{ik}^T(s) = A_{ik}(s)\lambda_{0k}^T(s) \exp\left\{\theta_0' Z_i(S_{ik})\right\}.
$$

Note that this model is partly conditional and uses time since cross-section (s) as the timescale. Gong and Schaubel confirm with simulations that empirically the type B weight results in smaller standard errors than the type A weight. Also note that IPCW weights can be calculated both for the chance of obtaining a transplantation, as well as for the chance of being removed from the waiting list. Under the assumption that waiting list removal and transplantation are conditionally independent, a joint weight can be obtained which is the product of IPCW weights for transplantation and IPCW weights for delisting. Throughout part I of the thesis, we use these joint type B weights to correct for dependent censoring by transplantation and delisting.

For the treatment and delisting hazard models, we adjust for a broad set of confounders since IPCW relies on a no-unmeasured confounding assumption. Patient factors adjusted for are sex, blood group, weight, listing country, and age at listing. Clinical variables adjusted for are whether the patient has a downgraded MELD, is simultaneously listed for a kidney, and the percentage of time a patient has been non-transplantable (too good/too bad/other). We directly adjust for MELD rather than MELD components, since Eurotransplant allocates based on MELD. Since allocation is a national affair, we also interact MELD with the patient country.

Appendix B

Completing the status updates streams for transplant recipients

The ELAS and ETKidney simulators require complete streams of status updates to be available for all patient registrations, which means that every registration must end with a waiting list removal (R) or death (D). However, most kidney or liver candidates are transplanted, making these endpoints – and any status that would have occurred between transplantation and candidate death or removal – unobserved. This is a general problem faced for the development of discrete-event simulators for organ allocation. The SAM simulators address it by matching transplant recipients to not-yet-transplanted patients based on their predicted remaining lifetime, with remaining life time predicted using a standard Cox model [96]. However, this approach does address for repeated measures, does not match on other relevant characteristics that might affect a candidate's health status trajectory (such as disease group), and also does not correct for informative censoring from transplantation, which can bias mortality estimates.

To address these limitations, we modify an existing statistical procedure from Tayob and Murray [195] to complete the status update streams for patient registrations in the ELAS and ETKidney simulators. This procedure constructs for every transplant recipient i a risk set of R_i of not-yet-transplanted patients, who (a) have similar covariate profiles as patient i and (b) have similar predicted remaining survival, where remaining survival is predicted using methodology that accounts for repeated measures and corrects for informative censoring. Algorithm B.1 summarizes this procedure. Steps 1 to 2 construct pseudo-observations for the expected log remaining survival time, and Step 3 fits a model for log survival as a function of covariates. These steps are performed once on the full cohort to estimate model coefficients (β^{PO}). Step 4 is iteratively applied for each transplant recipient, until their registration ends with a waiting list death (D) or waiting list removal (R).

Algorithm B.1: status completion procedure

1. **Estimate the counterfactual survival function $S_T^{\mathbf{IPCW}}(t)$:**
   (a) fit an extended Cox model for transplantation,
   (b) predict probability of transplant in order to construct IPCW weights,
   (c) estimate the survival function with Kaplan-Meier, using IPCW weights.

2. **Construct pseudo-observations:**
   For every status update, reported by patient i at time t, construct pseudo-observations PO_{it} for the log restricted remaining survival time, i.e. for
   $$\log(T_{it}^*) = \log(\min(T_{it}, \tau)),$$
   where T_{it} is defined as the remaining survival time of candidate i at time t. The pseudo-observations PO_{it} can be computed solely based on $\hat{S}_T^{\text{IPCW}}(t)$, using formula (2) that appears in Tayob and Murray (2017).

3. **Estimate a model for the log remaining survival time:**
   With pseudo-observations PO_{it} as the outcome, fit the model
   $$\mathbb{E}[\log(T_{it}^*)|Z_i(t)] = \beta^\intercal Z_i(t),$$
   where each status update is paired with the covariate vector $Z_i(t)$, i.e. the covariates of patient i at time t. To account for within-patient correlations, β is estimated with Quasi-Least Squares using a Markov correlation matrix. This yields estimates $\hat{\beta}^{\text{PO}}$.

4. **For every transplant recipient i's last status update:**
   4.1. construct a risk set R_i of comparable patients, who
      (a) who have a later censoring time than patient i,[a]
      (b) have similar predicted expected log survival as patient i, i.e.
      $$|\hat{\beta}^{\text{PO}\ \intercal} Z_k(C_i) - \hat{\beta}^{\text{PO}\ \intercal} Z_i(C_i)| < \epsilon$$
      for some ϵ, where $Z_k(C_i)$ are covariates of patient k at i's censoring time C_i,
      (c) match with candidate i on a set of pre-determined characteristics.
   4.2. Within candidate's i risk set R_i, estimate a risk-set-specific conditional counterfactual survival curve $S^{\texttt{IPCW}}(t|R_i)$. Use inverse transform sampling from this function to match candidate i to a specific candidate $k \in R_i$.
   4.3. Copy over the future statuses of matched patient k to candidate i.
   4.4. Repeat steps 4.1 to 4.3 until candidate's i spell ends with a waiting list removal or waiting list death.

[a] This requirement is relaxed when very few such candidates exist

Summary of Tayob and Murray (2017)

Algorithm B.1 uses statistical methodology developed by Tayob and Murray [195]. Tayob and Murray aim to model the 12-month restricted survival time $T^* = \min(T, \tau)$ of lung transplant candidates from pre-determined, regularly spaced landmark times $j = 1, ..., J$. To this end, they define T^*_{ij} as the τ-restricted remaining survival time of subject i from landmark time j, and use $\tau = 12$ months in their application. The central goal of their paper is to estimate the expected log-survival time conditional on covariates, i.e. to model

$$\mathbb{E}[\log(T^*)|Z] = \beta^\intercal Z.$$

They face three statistical challenges in the estimation of this model:

1. T^*_{ij} is unobserved for most candidates due to censoring,
2. transplantation represents an informative censoring mechanism,
3. the T^*_{ij}s exhibit within-patient correlations across the landmark times j.

To address these challenges, Tayob and Murray proceed as follows:

1. Tayob and Murray construct for each censored T^*_{ij} a risk set R_i of individuals who are (a) uncensored, (b) have similar expected survival as candidate i, and (c) have similar covariates as patient i. They construct these risk sets by following steps 1 through 4.1 of Algorithm B.1. In constructing these risk sets, Tayob and Murray require candidates to have similar covariate profiles to ensure that patients in the risk set are comparable despite the substantial heterogeneity of patients on the waiting list for lung transplantation. After step 4.1 of Algorithm B.1, Tayob and Murray derive $M = 10$ imputes of T^*_{ij} by inverse transform sampling from the risk-set specific survival function $S^{\text{IPCW}}(t|R_i)$. They then use these imputes to fit the model $\mathbb{E}[\log(T^*)|Z] = \beta^\intercal Z$, with coefficients pooled using Rubin's rules.
2. they use inverse probability censoring weighting (IPCW) to correct for informative censoring by transplantation in estimating the survival function in step 1 and step 4.2.
3. In estimating $\mathbb{E}[\log(T^*)|Z] = \beta^\intercal Z$ in step 3 (and in their final step), Tayob and Murray address the within-patient correlations by fitting the model with Generalized Estimating Equations (GEE) with an unstructured working correlation matrix. This approach yields consistent estimates of β if the model is correctly specified (the correlation structure is allowed to be misspecified).

Tayob and Murray conduct extensive statistical simulations to show that their procedure can indeed estimate $\mathbb{E}[\log(T^*)|Z] = \beta^\intercal Z$ with minimal bias, and with similar efficiency to estimates obtained if censoring had never occurred.

Modifications to Tayob and Murray's procedure for Algorithm B.1.

Tayob and Murray thus construct for every transplant recipient i a risk set R_i of comparable patients, and use this risk set to sample imputes for T^*_{ij}. Our goal is to construct such a risk set R_i, and use this risk set to match candidate i to a specific candidate $k \in R_i$, who has similar remaining life time and covariates. To achieve this, Algorithm B.1 has the following deviations from Tayob and Murray:

- Tayob and Murray only match censored candidates to non-censored candidates at specific landmark times $j = 1, ..., J$. To enable discrete-event simulations, we must match transplant recipients to not-yet-transplanted candidates at the actual time of each transplant recipient's last known status update, which we denote by t. The set of t is fully determined by the observed data, as the timings at which a candidate reports status update are not set by Eurotransplant. We define T^*_{it} as the restricted remaining survival time measured from t onwards, and construct pseudo-observations PO_{it} for the log restricted remaining survival time at time t. This is done by steps 1 and 2 of Algorithm B.1.
- The time points t correspond to any moment at which a candidate has reported a status update, and are therefore irregularly spaced and patient-specific. Because this makes the number of time points large, estimation of β^{PO} in step 3 using GEE with an unstructured working correlation matrix is infeasible. Instead, we estimate β^{PO} with Quasi-Least Squares (QLS) with a Markov correlation structure [196]. This structure assumes that the within-patient correlations between the pseudo-observations PO_{it} decay with their spacing in t.
- After step 4.2, Tayob and Murray use inverse-transform sampling from the risk-set-specific survival function $S^{\text{IPCW}}(t|R_i)$ to sample imputes for T^*_{ij}. We instead use inverse-transform sampling from $S^{\text{IPCW}}(t|R_i)$ to match candidate i to a specific candidate $k \in R_i$. We then copy over the status updates from patient k to patient i, and repeat this step until all candidates have status updates that end with a waiting list removal (R) or (D) (see Step 4.4 of Algorithm B.1).

In the remainder of this appendix, we describe the steps of Algorithm B.1 in more detail.

For the ELAS simulator, Algorithm B.1 was run separately for HU and elective candidates, with the time origin of t defined for both candidate groups as the date a candidate was listed for transplantation. For the HU model, we used τ=14 days as the time horizon. For the elective candidates, we used τ=90 days.

For the ETKidney simulator, Algorithm B.1 was run on all kidney transplant candidates, with the time origin defined as the dialysis initiation date. A time horizon of 365 days was used ($\tau = 365$ days).

B.1 Step 1 and 2: Construction of the pseudo-observations

Step 1: Consistent estimation of the survival function

Algorithm B.1 requires us to consistently estimate the survival function in Step 1 and Step 4.2. A statistical challenge for this is that we have to deal with informative censoring by transplantation. To correct for such informative censoring, we use a Cox model to predict the probability that a patient is transplanted over time, and estimate the survival function weighing observations by their inverse probability of being transplanted.

For the ELAS simulator, this censoring model adjusted for recipient sex, recipient blood group, spline terms of recipient weight and age, recipient disease group, percentage of time NT (total/too bad/too good), the national match MELD, whether the patient is on dialysis, whether the patient has a downmarked MELD score, and whether the patient has an exception (Y/N).

For the ETKidney simulator, this censoring model adjusted for are candidate sex, candidate blood group, spline terms of candidate age, the disease group (congenital, polycystic, neoplasms, diabetes, glomerular disease, renovascular / vascular disease, tubular and interstitial disease, or other), the HLA-ABDR mismatch frequency (defined in Section 8.4.1.3)

Figure B.1 shows estimated survival functions without (orange) and with (blue) correction for dependent censoring for elective liver transplantation patients, stratified by their laboratory MELD score at listing. The estimates of the 90-day survival probabilities decrease due to inverse probability weighting, with 90-day waiting list survival estimated with IPCW up to 7.4% lower for MELD 25–29 than 90-day waiting list survival estimated without IPCW. This is expected, as candidates who are deteriorate on the waiting list have a higher probability of being transplanted on the waiting list.

With these censoring models, we can construct IPCW weights for each patient, based on the predicted probability of being transplanted at each time point. Using these IPCW weights, we then estimate the counterfactual survival function with the Kaplan–Meier estimator. This approach allows us to consistently estimate the survival function under dependent censoring, as required for step 1 of Algorithm B.1.

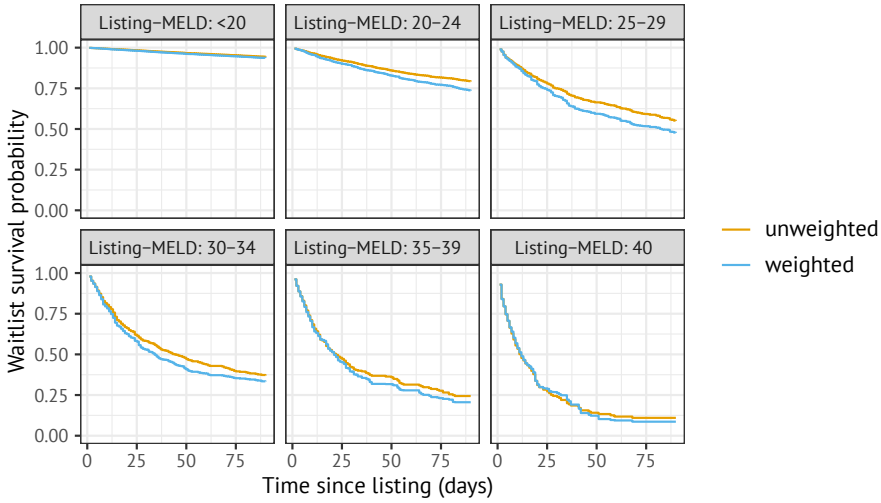


Figure B.1: Estimated survival probabilities estimated in the cohort, with (blue) and without (orange) Inverse Probability Censoring Weighting to correct for informative censoring by transplantation.

Step 2: Construction of pseudo-observations

To predict the expected remaining lifetime for candidates on the waiting list, we directly model candidate's expected residual remaining survival time T^* using:

$$\mathbb{E}[\log(T^*)|Z] = \beta^\intercal Z.$$

For this, we would ideally know the remaining time-to-event T^*_{it} for all patients i and status update times t. However, censoring and transplantation within τ time units of t prevent us from observing T^*_{it}. Formula (2) of Tayob and Murray [195] describes how pseudo-observations for $\log(T_{ij}*)$ can be constructed using only the survival function $\hat{S}^{\text{IPCW}}(t)$ that was estimated in Step 1 of Algorithm B.1. We used this formula to calculate pseudo-observations PO_{it} for $\log(T^*_{it})$. Armed with pairs (PO_{it}, Z_i), we can estimate β^{PO} in step 3 of Algorithm B.1.

B.2 Step 3: Fitting a model for the mean restricted survival time

With pairs (PO_{it}, Z_i) we can model the expected log remaining survival time as

$$\mathbb{E}[\log(T^*) \mid Z] = \beta^\intercal Z \tag{B.1}$$

A statistical challenge to estimating β is that we have to deal with the within-patient correlations in PO_{it} across status update times t. Tayob and Murray faced a similar issue, with correlations between T^*_{ij} over the landmark times j. They addressed this issue by estimating β with Generalized Estimating Equations (GEE) with an unstructured correlation matrix correlation over the landmark times j (which requires $j(j+1)/2$ parameters). This allows for consistent estimation of β, even if the correlation structure is misspecified.

Unfortunately, this specific estimation strategy is not feasible in our setting: in our case, the pseudo-observations PO_{it} are indexed by t, i.e., all the timings at which candidates reported status updates to Eurotransplant, which would blow up the dimensions for an unstructured working correlation matrix. To estimate the model, we instead estimate the model with Quasi-Least Squares with a Markov correlation structure [197]. This Markov correlation structure assumes that the correlation between measurements PO_{is} and PO_{it} decays with their separation in time:

$$\texttt{Corr}(PO_{is}, PO_{it}) = \alpha^{|s-t|}.$$

Parameters α and β of this model can be estimated with the `qlspack` R package [196]. With this approach, β can also be consistently estimated even if the correlation structure is misspecified.

For the ELAS simulator, we use different model specifications for HU and elective patients for equation B1. For HU patients, the covariates include recipient age at registration, the laboratory MELD score, whether the patient is on biweekly dialysis, recipient sex, and disease group. For elective patients, we adjust for age at registration, recipient weight, MELD components (serum creatinine, bilirubin, INR, biweekly dialysis), recipient sex, disease group, cirrhosis etiology, type of exception score, whether it is a repeat transplant candidate, and whether the patient has failed to re-certify their MELD score. Continuous variables are transformed with spline terms.

For the ETKidney simulator, we use covariates for candidate age, candidate sex, whether the candidate has previously received a kidney transplantation, as well as the time the candidate has waited on the kidney waiting list.

B.3 Step 4: Constructing future statuses

To complete the set of status updates for transplant recipient i, we first construct a risk set R_i of not-yet-transplanted candidates who are comparable to the transplant recipient (step 4.1). As in Tayob and Murray, a minimum requirement to match transplanted candidates to not-yet-transplanted candidates is:

$$|\hat{\beta}^{\text{PO}\ \intercal} Z_k(C_i) - \hat{\beta}^{\text{PO}\ \intercal} Z_i(C_i)| < 0.50,$$

i.e., candidates have similar expected log restricted survival.

We additionally require candidates to match on other covariates, as is done by Tayob and Murray. A motivation for requiring candidates to also match on covariate profiles is that organ waiting lists are highly heterogeneous, and we want to ascertain that the candidate's risk set only consists of patients that are actually comparable to the patient. For example, by matching on disease groups for liver transplantation candidates, we can prevent that a candidate with chronic liver cirrhosis is matched to a candidate with hepatocellular carcinoma, even if these patients have similar predicted remaining survival time.

For the ELAS simulator, we require candidates to always match on pediatric status. For other discrete and continuous variables, we use an adaptive matching procedure, in which we strive towards $|R_i|$ = 35 candidates in the risk set for HU patients, and $|R_i| = 50$ candidates for non-HU patients. Specifically, the discrete variables used for matching are

1. whether the patient is a repeat transplant candidate
2. current urgency code (non-transplantable)
3. (N)SE group
4. disease group
5. urgency reason (NT too good / NT other / NT too bad)
6. biweekly dialysis (twice in week preceding MELD measurement)
7. recipient country.

Continuous match variables used are the laboratory MELD score, age at registration, (N)SE MELD score (for elective patients only), where we restrict absolute differences in continuous variables to pre-determined caliper widths (lab-MELD: 5, age: 15 years, (N)SE-MELD: 5). In case matching according to all criteria fails to result in a risk set of sufficient size, we drop a discrete match criterion (from 7 to 1 in the list above). In case dropping all discrete match criteria does not result in adequately sized risk set, we increase caliper widths for continuous variables. In total, about 50% of transplant recipients can be matched to a risk set on all characteristics, and 80% of transplant recipients can be matched on the first 4 discrete variables (with the most restrictive caliper widths).

For the ETKidney simulator, we always match candidates on whether they have had a previous kidney transplantation, as well as whether they have an active waiting list status. The procedure also tried to match candidates based on disease group, reason why they were non-transplantable, and candidate country of listing. These constraints were relaxed in case fewer than 50 candidates could be included in the risk set. Finally, the procedure also imposed constraints on the differences in accrued dialysis time and age at listing using pre-determined caliper widths.

Example of a constructed risk set for the ELAS simulator

In Table B.1 we show an example of a constructed risk set for a patient who was transplanted, and for whom we had to complete their status update trajectory. The first row of Table B.1 shows that this transplant recipient was listed in 2014 in Germany at an age of 64 for cirrhosis. The patient reported a lab-MELD score equal to 33 points 36 days after registration, and was transplanted 6 days later. Based on our model (equation B1), the expected log residual survival time for this patient is approximately 3.51, which corresponds roughly to 34 days of remaining lifetime.

The other rows of Table B.1 show 10 of the candidates who were present in patient i's risk set R_i. These patients remain at risk 36 days after waiting list registration ($\min(C_k, T_k) > C_i$) and are similar in terms of predicted expected log survival. Turning to other characteristics, we see that the matching procedure did not match on listing country and receival of biweekly dialysis. The risk set is comparable in terms of continuous variables (lab-MELDs ranging from 28 to 38, ages from 53 to 69).

Table B.1: Example of the risk set R_i for a selected liver transplant recipient.

year	status time t	C_k	T_k	$\exp(\log(\hat{T}^*))$	lab-MELD	age	ped.	reTX	urg	(N)SE	diag.	dial.	country
transplant recipient													
2014	36.0	41.9	-	33.7	33	64	0	0	T	none	Cirrh.	1	DE
risk set													
2012	40.1	46	-	32.8	34	65	0	0	T	none	Cirrh.	0	DE
2015	41.1	55.8	-	34.9	30	63	0	0	T	none	Cirrh.	1	DE
2013	40.1	47.9	-	32.4	38	56	0	0	T	none	Cirrh.	1	DE
2012	36.4	42.1	-	35.3	35	68	0	0	T	none	Cirrh.	1	BE
2010	40.2	58.9	-	35.5	28	68	0	0	T	none	Cirrh.	0	DE
2016	37.7	86.3	-	35.6	34	53	0	0	T	none	Cirrh.	1	DE
2009	41.8	-	84.8	36.3	33	53	0	0	T	none	Cirrh.	0	DE
2008	35.1	42.1	-	29.9	30	69	0	0	T	none	Cirrh.	0	DE
2012	37.3	44.9	-	38.4	37	64	0	0	T	none	Cirrh.	0	BE
2010	7.4	-	946.9	29.4	29	63	0	0	T	none	Cirrh.	0	AU

Within risk set R_i, we can obtain a personalized estimate of the conditional probability of the candidate i's survival t time units after their censoring time (i.e. $\hat{S}_T^{\text{IPCW}}(t|R_i, T > C_i)$). For the 64-year-old, German transplant candidate discussed in Table B.1, the survival function estimated using Kaplan-Meier with IPCW in their risk

set R_i is shown by Figure B.2. This suggests that the 64-year old candidate with a MELD score of 33 would have a waiting list death probability of approximately 60% in the 90 days following their censoring time.

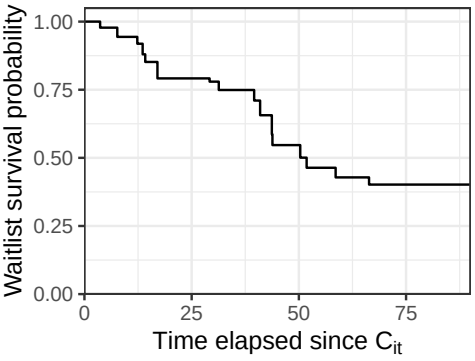


Figure B.2: Conditional survival function, estimated with inverse probability censoring weighting for the risk set R_i, where i is the 64-year-old German candidate appearing in Table B.1.

Example of a constructed risk set for the ETKidney simulator

Table B.2 shows an example of a constructed risk set for a female candidate who was transplanted after waiting for 4.5 years for a kidney transplantation with 6 years of accrued dialysis time in total. The first row of Table B.2 shows that this transplant recipient was listed in 2014 in Germany for polycystic kidney disease. The remaining rows of Table B.2 show 10 (out of 50) waiting list candidates in patient i's risk set R_i. These patients remain at risk having waited 2162 days on dialysis for transplantation. They are also similar to the patient in terms of other covariates: all matched candidates are patients with polycystic kidney disease waiting in Germany, and around age 60.

Table B.2: Example of the risk set R_i for a selected kidney transplant recipient. Note that matching in the ETKidney simulator is based on dialysis vintage, not waiting time.

year	waiting time	C_i	T_i	dialysis vintage	age	repeat transplant	urg.	diag	country
Transplant recipient									
2014	1602	1618	-	2162	64	0	T	Polycystic	DE
Risk set									
2017	1506	2229	-	1965	62	0	T	Polycystic	DE
2010	1595	-	2346	2410	62	0	T	Polycystic	DE
2012	1635	-	2837	2495	61	0	T	Polycystic	DE
2014	1961	-	2619	1905	62	0	T	Polycystic	DE
2016	1467	-	1747	2009	59	0	T	Polycystic	DE
2015	1775	2255	-	2245	59	0	T	Polycystic	DE
2016	1464	-	-	1869	58	0	T	Polycystic	DE
2019	1567	-	-	2499	58	0	T	Polycystic	DE
2010	1459	2333	-	1991	58	0	T	Polycystic	DE
2011	1686	3531	-	1898	61	0	T	Polycystic	DE

B.4 Step 4.2: matching the patient to a particular patient in the risk set

The aim of step 4.2 in Algorithm B.1 is to match censored patient i to a single candidate k from their risk set ($k \in R_i$). We do this by inverse transform sampling from the risk-set-specific survival function $\hat{S}_T^{\text{IPCW}}(t \mid R_i,\, T > C_i)$. Specifically, we (i) draw a random number u from the uniform distribution, and (ii) find the smallest time t such that $\hat{S}_T^{\text{IPCW}}(t \mid R_i,\, T > C_i) \leq u$.

If such a t exists, it corresponds to the observed event (removal or death) time of some patient $k \in R_i$. We therefore complete the status update trajectory for patient i by copying over the future status updates of this patient k.

If no such t exists within the truncation time horizon τ, this means patient i would be alive and remain waitlisted τ days after their censoring time. In this case, we select a candidate from those with censored restricted survival times, i.e., from the set $\{k \in R_i : T_k > C_i + \tau\}$. Among these, a single patient is randomly chosen with sampling probabilities proportional to their IPCW weights at time τ.

We note that this procedure can also match a transplant recipient to another patient who receives a transplant. In that case, we still copy over all subsequent status updates from the matched candidate, excluding the transplant event itself. In those cases, Step 4 of Algorithm B.1 is iteratively applied, until the candidate's registration ends with a removal (R) or death (D) status.

Summary

Every year, more than 6,000 organ transplantations are performed in the eight European countries that participate in Eurotransplant. Despite this, the persistent shortage of donor organs means that about 1,000 patients die annually while waiting for an organ transplantation.

Eurotransplant is responsible for offering the deceased-donor organs to the candidates who await a transplantation. To which patient Eurotransplant makes an offer is determined by allocation rules, which have been shaped by almost six decades of scientific, legal, and ethical discussions between Eurotransplant and the national competent authorities of the eight member countries. Eurotransplant has implemented these rules in allocation algorithms, which determine which candidates are eligible to receive an organ offer, and in what order they ought to be contacted.

A central goal of Eurotransplant's allocation systems is that patients should have an equal opportunity of receiving a transplant. A first goal of this thesis is to study research questions relating to such equality of opportunity. Our results show there is room for improvement. For example, female patients on the liver waiting list are more likely to experience an adverse outcome than male patients. We link this disparity to the smaller body size of female transplantation candidates – and not sex itself, as is suggested by the existing literature. Similarly, kidney transplant candidates who are immunized face reduced access to transplantation under the current rules. This latter disadvantage persist even though Eurotransplant has implemented special mechanisms to support these groups.

One reason why such disadvantages persist is that Eurotransplant lacks the tools to quantify the impact of policy changes. This complicates discussions within Eurotransplant's advisory committees on how the allocation can be improved. To overcome this barrier, the second goal of this thesis is to develop discrete-event simulators for liver and kidney allocation. These tools allow Eurotransplant to assess the impact of alternative allocation policies on waiting list outcomes, and can facilitate collaborations with clinicians, policymakers, and other stakeholders on how allocation can be improved. We validated these simulation tools on historic data, and the simulators

already support discussions within Eurotransplant on how policies can be improved. For example, the liver simulator has been used to support discussions on switching to a new score for liver allocation.

Although these tools do not eliminate the difficult ethical trade-offs involved in organ allocation, they help Eurotransplant by making these trade-offs explicit. Thereby, the simulators can pave the way for a more informed and constructive dialogue among clinicians, policymakers, and other stakeholders on how the allocation of deceased-donor organs can be improved.

Course of Life

Hans de Ferrante was born on March 20, 1995 in 's-Gravenhage, the Netherlands. He completed his secondary education at St. Odulphus-Lyceum in Tilburg.

In 2013, Hans began his academic journey at Eindhoven University of Technology, where he pursued a Bachelor of Science in Biomedical Engineering. For this degree, he focused on molecular biology, organic chemistry, and computational biology. In 2014, Hans started a second Bachelor of Science in Econometrics and Operations Research at Tilburg University. He graduated cum laude for these degrees in 2017 and 2018, respectively. During his undergraduate studies, Hans took part in the iGEM competition in Boston, spent a semester abroad at the University of Hong Kong, and participated in the Netherlands-Asia Honours Summer School (NAHSS) in Chengdu, China.

Hans continued his studies with a Master of Science in Systems Biology and Bioinformatics at the Vrije Universiteit and Universiteit van Amsterdam. For this degree, he wrote a master's thesis on protein-protein interface prediction from amino acid sequence, and he served as a teaching assistant for several bioinformatics courses. Parallel to this, Hans pursued a Master of Science in Econometrics and Mathematical Economics at Tilburg University. Hans wrote his master's thesis for Econometrics and Mathematical Economics while working as a data science intern at Pacmed in Amsterdam. The topic of this thesis was causal inference for the treatment of breast cancer, using national registry data maintained by Integraal Kankercentrum Nederland (IKNL). He graduated cum laude for both degrees in 2020. From 2018 to 2020, Hans also worked as a part-time research assistant in data science at CentERdata in Tilburg.

Hans started his PhD project at Eindhoven University of Technology under the supervision of dr. Bart Smeulders and prof.dr. Frits Spieksma in September 2020. His research focuses on liver and kidney allocation in Eurotransplant. This thesis presents results of this research.

Hans will defend his thesis at Eindhoven University of Technology on July 3rd, 2025.

List of publications

Journal articles

- Hans de Ferrante, Marieke de Rosner-van Rosmalen, Bart M.L. Smeulders, Frits C.R. Spieksma, and Serge Vogelaar (2025). *A discrete event simulator for policy evaluation in deceased-donor liver allocation in Eurotransplant*. In: *Operations Research, Data Analytics and Logistics*.
- Hans de Ferrante, Marieke de Rosner-van Rosmalen, Bart M.L. Smeulders, Serge Vogelaar, and Frits C.R. Spieksma (2025).
  Sex disparity in liver allocation within Eurotransplant. In: *American Journal of Transplantation*.
- Hans de Ferrante, Bart Smeulders, Ineke Tieken, Sebastiaan Heidt, Geert W. Haasnoot, Frans H.J. Claas, Serge Vogelaar, and Frits Spieksma (2023). *Immunized Patients Face Reduced Access to Transplantation in the Eurotransplant Kidney Allocation System*. In: *Transplantation*.
- Hans de Ferrante, Marieke de Rosner-van Rosmalen, Bart M.L. Smeulders, Serge Vogelaar, Frits C.R. Spieksma (2024). *Revising model for end-stage liver disease from calendar-time cross-sections with correction for selection bias*. In: *BMC Medical Research Methodology*.

Pre-prints

- Hans de Ferrante, Rocio Laguna Goya, Bart M.L. Smeulders, Frits C.R. Spieksma, and Ineke Tieken (2025). *The ETKidney simulator: a discrete event simulator to assess the impact of alternative kidney allocation rules in Eurotransplant*. *arXiv:2502.15001*.

Bibliography

[1] J. J. van Rood, “A proposal for international cooperation in organ transplantation: Eurotransplant,” in *Histocompatibility Testing 1967: Report of a Conference and Workshop, Torino and Saint-Vincent, Italy, 14–24 June 1967*, R. Curtoni, P. Mattiuz, and R. Tosi, Eds., Copenhagen, Denmark, 1967, pp. 451–452.

[2] Eurotransplant International Foundation, “Introduction,” in *Together on a Life-Saving Mission: The World of Eurotransplant*. Leiden, the Netherlands: Eurotransplant International Foundation, 2017, ch. 1, p. 7.

[3] R. M. Langer, B. Cohen, and A. Rahmel, “History of Eurotransplant,” *Transplantation Proceedings*, vol. 44, no. 7, pp. 2130–2131, 2012.

[4] Eurotransplant, “Eurotransplant Statistics Library. Report 3002p: active waiting list (at year-end) in all ET, by year, by organ combination,” Online, 2024. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=11162-33135-33157&format=html&download=0

[5] ——, “Eurotransplant Statistics Library. Report 2082p: organs transplanted in all ET, by year, by donor type, by organ,” Online, 2024. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=10941-33135&format=html&download=0

[6] ——, “Eurotransplant Statistics Library. Report 4512p: waiting list mortality in all ET, by year, by organ,” Online, 2025. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=11151-33135-33195&format=html&download=1

[7] B. J. J. M. Haase-Kromwijk, J. de Meester, and G. G. Persijn, “Eurotransplant Foundation: the original framework of organ exchange,” *Best Practice & Research Clinical Anaesthesiology*, vol. 13, no. 2, pp. 169–178, 1999.

[8] G. G. Persijn, “Allocation of organs, particularly kidneys, within Eurotransplant,” *Human Immunology*, vol. 67, no. 6, pp. 419–423, 2006.

[9] D. E. Schaubel, M. K. Guidinger, S. W. Biggins, J. D. Kalbfleisch, E. A. Pomfret, P. Sharma *et al.*, "Survival benefit-based deceased-donor liver allocation," *American Journal of Transplantation*, vol. 9, no. 4, pp. 970–981, 2009.

[10] G. G. Persijn, J. M. Smits, and U. Frei, "Eurotransplant kidney allocation," *The Lancet*, vol. 355, no. 9197, p. 71, 2000.

[11] Eurotransplant, "Eurotransplant Statistics Library. Report 1031p: deceased donors used, per million population, by year, by donor country," Online, 2024. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=10867-33157&format=html&download=0

[12] Federale Overheidsdienst Binnenlandse Zaken, "Wet van 13/06/1986 betreffende het wegnemen en transplanteren van organen," https://etaamb.openjustice.be/nl/wet-van-13-juni-1986_n2009000473.html, 1986. [Online]. Available: https://etaamb.openjustice.be/nl/wet-van-13-juni-1986_n2009000473.html

[13] J. de Meester, G. G. Persijn, J. M. Smits, and Y. Vanrenterghem, "The new Eurotransplant kidney allocation system: a justified balance between equity and utility?" *Transplant International*, vol. 12, no. 4, pp. 299–300, 1999.

[14] J. de Meester, M. Bogers, H. de Winter, J. M. Smits, L. Meester, M. Dekking *et al.*, "Which ABO-matching rule should be the decisive factor in the choice between a highly urgent and an elective patient?" *Transplant International*, vol. 15, no. 8, pp. 431–435, 2002.

[15] J. de Meester, G. G. Persijn, T. Wujciak, G. Opelz, and Y. Vanrenterghem, "The new Eurotransplant kidney allocation system: report one year after implementation." *Transplantation*, vol. 66, no. 9, pp. 1154–1159, 1998.

[16] Eurotransplant, "Eurotransplant Manual. Chapter 1: Introduction." [Online]. Available: https://www.eurotransplant.org/allocation/eurotransplant-manual/

[17] P. Glander, K. Budde, D. Schmidt, T. F. Fuller, M. Giessing, H.-H. Neumayer *et al.*, "The 'blood group O problem' in kidney transplantation — time to change?" *Nephrology Dialysis Transplantation*, vol. 25, no. 6, pp. 1998–2004, 2010.

[18] Eurotransplant, "Eurotransplant Statistics Library. Report 2194p. kidney transplant (deceased donor) recipients in all et, median time to transplant, by year, by blood group," Online, 2025. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=10649-33135-33195&format=html&download=0&action=login

[19] E. Allen, R. Taylor, A. Gimson, and D. Thorburn, "Transplant benefit-based offering of deceased donor livers in the United Kingdom," *Journal of Hepatology*, vol. 81, no. 3, pp. 471–478, 2024.

[20] W. R. Kim, A. Mannalithara, J. K. Heimbach, P. S. Kamath, S. K. Asrani, S. W. Biggins *et al.*, "MELD 3.0: the Model for End-Stage Liver Disease updated for the modern era," *Gastroenterology*, vol. 161, no. 6, pp. 1887–1895.e4, 2021.

[21] J. G. O'Leary, R. Lepe, and G. L. Davis, "Indications for liver transplantation," *Gastroenterology*, vol. 134, no. 6, pp. 1764–1776, 2008.

[22] V. Arroyo, R. Moreau, and R. Jalan, "Acute-on-chronic liver failure," *New England Journal of Medicine*, vol. 382, no. 22, pp. 2137–2145, 2020.

[23] P. R. Galle, A. Forner, J. M. Llovet, V. Mazzaferro, F. Piscaglia, J.-L. Raoul *et al.*, "EASL clinical practice guidelines: management of hepatocellular carcinoma," *Journal of Hepatology*, vol. 69, no. 1, pp. 182–236, 2018.

[24] R. T. Stravitz and W. M. Lee, "Acute liver failure," *The Lancet*, vol. 394, no. 10201, pp. 869–881, 2019.

[25] U. Jost and B. Ringe, "Principles of Liver Allocation in Eurotransplant," in *Procurement, Preservation and Allocation of Vascularized Organs*. Springer Netherlands, 1997, ch. 23, pp. 201–207. [Online]. Available: http://dx.doi.org/10.1007/978-94-011-5422-2_23

[26] J. de Meester, B. J. J. M. Haase-Kromwijk, G. G. Persijn, and B. Cohen, "Organization and Logistics in Organ Exchange," in *Organ and Tissue Donation for Transplantation*. London: Hodder Headline Group, 1997, ch. 12, pp. 226–238.

[27] C. P. Strassburg, T. Becker, J. Klempnauer, and M. P. Manns, "Lebertransplantation zwischen Indikation und Spenderallokation," *Der Internist*, vol. 45, no. 11, pp. 1233–1245, 2004.

[28] Eurotransplant, "Minutes of the March 2002 ELIAC Meeting," 2002, archive of Eurotransplant.

[29] G. E. Jung, J. Encke, J. Schmidt, and A. Rahmel, "Model for End-Stage Liver Disease: neue Grundlage der Allokation für die Lebertransplantation," *Der Chirurg*, vol. 79, no. 2, pp. 157–163, 2008.

[30] R. Wiesner, E. Edwards, R. Freeman, A. Harper, R. Kim, P. Kamath *et al.*, "Model for End-Stage Liver Disease (MELD) and allocation of donor livers," *Gastroenterology*, vol. 124, no. 1, pp. 91–96, 2003.

[31] Eurotransplant, "Minutes of the January 2006 ELIAC Meeting," 2006, archive of Eurotransplant.

[32] ——, "Minutes of the September 2001 ELIAC Meeting," 2001, archive of Eurotransplant.

[33] M. Malinchoc, P. S. Kamath, F. D. Gordon, C. J. Peine, J. Rank, and P. C. J. ter Borg, "A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts," *Hepatology*, vol. 31, no. 4, pp. 864–871, 2000.

[34] P. S. Kamath, R. H. Wiesner, M. Malinchoc, W. Kremers, T. M. Therneau, C. L. Kosberg *et al.*, "A model to predict survival in patients with end-stage liver disease," *Hepatology*, vol. 33, no. 2, pp. 464–470, 2001.

[35] I. Jochmans, M. van Rosmalen, J. Pirenne, and U. Samuel, "Adult liver allocation in Eurotransplant," *Transplantation*, vol. 101, no. 7, pp. 1542–1550, 2017.

[36] R. B. Freeman, R. H. Wiesner, J. P. Roberts, S. McDiarmid, D. M. Dykstra, and R. M. Merion, "Improving liver allocation: MELD and PELD," *American Journal of Transplantation*, vol. 4, pp. 114–131, 2004.

[37] W. R. Kim, S. W. Biggins, W. K. Kremers, R. H. Wiesner, P. S. Kamath, J. T. Benson *et al.*, "Hyponatremia and mortality among patients on the liver-transplant waiting list," *The New England Journal of Medicine*, vol. 359, no. 10, pp. 1018–1026, 2008.

[38] C. A. Moylan, C. W. Brady, J. L. Johnson, A. D. Smith, J. E. Tuttle-Newhall, and A. J. Muir, "Disparities in liver transplantation before and after introduction of the MELD score," *JAMA*, vol. 300, no. 20, pp. 2371–2378, 2008.

[39] R. Merion, "Longitudinal assessment of mortality risk among candidates for liver transplantation," *Liver Transplantation*, vol. 9, no. 1, pp. 12–18, 2003.

[40] P. Sharma, D. E. Schaubel, C. S. Sima, R. M. Merion, and A. S. F. Lok, "Re-weighting the Model for End-Stage Liver Disease score components," *Gastroenterology*, vol. 135, no. 5, pp. 1575–1581, 2008.

[41] M. D. Leise, W. R. Kim, W. K. Kremers, J. J. Larson, J. T. Benson, and T. M. Therneau, "A revised Model for End-Stage Liver Disease optimizes prediction of mortality among patients awaiting liver transplantation," *Gastroenterology*, vol. 140, no. 7, pp. 1952–1960, 2011.

[42] B. F. J. Goudsmit, H. Putter, M. E. Tushuizen, S. Vogelaar, J. Pirenne, I. P. J. Alwayn *et al.*, "Refitting the Model for End-Stage Liver Disease for the Eurotransplant region," *Hepatology*, 2020.

[43] E. Nagler, H. Van Vlierberghe, I. Colle, R. Troisi, and B. de Hemptinne, "Impact of MELD on short-term and long-term outcome following liver transplantation: a European perspective," *European Journal of Gastroenterology & Hepatology*, vol. 17, no. 8, pp. 849–856, 2005.

[44] T. J. Weismüller, A. Negm, T. Becker, H. Barg-Hock, J. Klempnauer, M. P. Manns *et al.*, "The introduction of MELD-based organ allocation impacts 3-month survival after liver transplantation by influencing pretransplant patient characteristics," *Transplant International*, vol. 22, no. 10, pp. 970–978, 2009.

[45] A. Attia, I. A. Rowe, E. M. Harrison, T. Gordon-Walker, and B. M. Stutchfield, "Implausible algorithm output in UK liver transplantation allocation scheme: importance of transparency," *The Lancet*, vol. 401, no. 10380, pp. 911–912, 2023.

[46] A. Attia, J. Webb, K. Connor, C. J. C. Johnston, M. Williams, T. Gordon-Walker *et al.*, "Effect of recipient age on prioritisation for liver transplantation in the UK: a population-based modelling study," *The Lancet Healthy Longevity*, vol. 5, no. 5, pp. e346–e355, 2024.

[47] A. B. Massie, B. Caffo, S. E. Gentry, E. C. Hall, D. A. Axelrod, K. L. Lentine *et al.*, "MELD exceptions and rates of waiting list outcomes," *American Journal of Transplantation*, vol. 11, no. 11, pp. 2362–2371, 2011.

[48] D. S. Goldberg, K. Krok, S. Batra, J. F. Trotter, S. M. Kawut, and M. B. Fallon, "Impact of the hepatopulmonary syndrome MELD exception policy on outcomes of patients after liver transplantation: an analysis of the UNOS database," *Gastroenterology*, vol. 146, no. 5, pp. 1256–1265.e1, 2014.

[49] A. Pillai, T. Couri, and M. Charlton, "Liver allocation policies in the USA: past, present, and the future," *Digestive Diseases and Sciences*, vol. 64, no. 4, pp. 985–992, 2019.

[50] P. G. Northup, N. M. Intagliata, N. L. Shah, S. J. Pelletier, C. L. Berg, and C. K. Argo, "Excess mortality on the liver transplant waiting list: unintended policy consequences and Model for End-Stage Liver Disease (MELD) inflation," *Hepatology*, vol. 61, no. 1, pp. 285–291, 2015.

[51] K. Bonner, R. Hirose, and J. K. Heimbach, "The evolution of the national liver review board," *Current Transplantation Reports*, vol. 5, no. 1, pp. 7–13, 2018.

[52] J. C. Goet, B. E. Hansen, M. Tieleman, B. van Hoek, A. P. van den Berg, W. G. Polak *et al.*, "Current policy for allocation of donor livers in the Netherlands advantages primary sclerosing cholangitis patients on the liver transplantation waiting list – a retrospective study," *Transplant International*, vol. 31, no. 6, pp. 590–599, 2017.

[53] H. J. Metselaar, A. P. van den Berg, and M. J. Coenraad, "Why we need fairer allocation rules for patients with hepatocellular carcinoma awaiting a liver transplant?" *Transplant International*, vol. 30, no. 11, pp. 1092–1094, 2017.

[54] A. Umgelter, A. Hapfelmeier, W. Kopp, M. van Rosmalen, X. Rogiers, M. Guba *et al.*, "Disparities in Eurotransplant liver transplantation wait-list outcome between patients with and without Model for End-Stage Liver Disease exceptions," *Liver Transplantation*, vol. 23, no. 10, pp. 1256–1265, 2017.

[55] H. C. de Ferrante, M. van Rosmalen, B. M. L. Smeulders, S. Vogelaar, and F. C. R. Spieksma, "Revising Model for End-Stage Liver Disease from calendar-time cross-sections with correction for selection bias," *BMC Medical Research Methodology*, vol. 24, no. 1, 2024.

[56] K. Bambha, W. R. Kim, W. K. Kremers, T. M. Therneau, P. S. Kamath, R. Wiesner *et al.*, "Predicting survival among patients listed for liver transplantation: an assessment of serial MELD measurements," *American Journal of Transplantation*, vol. 4, no. 11, pp. 1798–1804, 2004.

[57] Q. Gong and D. E. Schaubel, "Partly conditional estimation of the effect of a time-dependent factor in the presence of dependent censoring," *Biometrics*, vol. 69, no. 2, pp. 338–347, 2013.

[58] Eurotransplant, "Eurotransplant Manual manual. chapter 4: ET Liver Allocation System (ELAS)." [Online]. Available: https://www.eurotransplant.org/allocation/eurotransplant-manual/

[59] E. M. Schnellinger, E. Cantu, M. O. Harhay, D. E. Schaubel, S. E. Kimmel, and A. J. Stephens-Shields, "Mitigating selection bias in organ allocation models," *BMC Medical Research Methodology*, vol. 21, no. 1, 2021.

[60] T. A. Gerds, M. W. Kattan, M. Schumacher, and C. Yu, "Estimating a time-dependent concordance index for survival prediction models with covariate dependent censoring," *Statistics in Medicine*, vol. 32, no. 13, pp. 2173–2184, 2012.

[61] N. Hartman, "Concordance indices for risk scores with policy evaluations," *Health Services Research*, 2025.

[62] L. Lin, M. Sperrin, D. A. Jenkins, G. P. Martin, and N. Peek, "A scoping review of causal methods enabling predictions under hypothetical interventions," *Diagnostic and Prognostic Research*, vol. 5, no. 1, 2021.

[63] M. Maziarz, P. Heagerty, T. Cai, and Y. Zheng, "On longitudinal prediction with time-to-event outcome: comparison of modeling options," *Biometrics*, vol. 73, no. 1, pp. 83–93, 2017.

[64] H. C. de Ferrante, M. de Rosner-van Rosmalen, B. M. L. Smeulders, S. Vogelaar, and F. C. R. Spieksma, "Sex disparity in liver allocation within Eurotransplant," *American Journal of Transplantation*, vol. 25, no. 1, pp. 139–149, 2025.

[65] A. K. Mathur, D. E. Schaubel, Q. Gong, M. K. Guidinger, and R. M. Merion, "Sex-based disparities in liver transplant rates in the United States," *American Journal of Transplantation*, vol. 11, no. 7, pp. 1435–1443, 2011.

[66] J. C. Lai, N. A. Terrault, E. Vittinghoff, and S. W. Biggins, "Height contributes to the gender difference in wait-list mortality under the MELD-based liver allocation system," *American Journal of Transplantation*, vol. 10, no. 12, pp. 2658–2664, 2010.

[67] J. E. Locke, B. A. Shelton, K. M. Olthoff, E. A. Pomfret, K. A. Forde, D. Sawinski *et al.*, "Quantifying sex-based disparities in liver allocation," *JAMA Surgery*, vol. 155, no. 7, p. e201129, 2020.

[68] E. C. Verna and J. C. Lai, "Time for action to address the persistent sex-based disparity in liver transplant access," *JAMA Surgery*, vol. 155, no. 7, p. 545, 2020.

[69] E. Cholongitas, L. Marelli, A. Kerry, D. W. Goodier, D. Nair, M. Thomas *et al.*, "Female liver transplant recipients with the same GFR as male recipients have lower MELD scores – a systematic bias," *American Journal of Transplantation*, vol. 7, no. 3, pp. 685–692, 2007.

[70] M. L. Rodríguez-Perálvarez, A. M. Gómez-Orellana, A. Majumdar, M. Bailey, G. W. McCaughan, P. Gow *et al.*, "Development and validation of the gender-equity model for liver allocation (GEMA) to prioritise candidates for liver transplantation: a cohort study," *The Lancet. Gastroenterology & Hepatology*, vol. 8, no. 3, pp. 242–252, 2023.

[71] R. P. Myers, A. A. M. Shaheen, A. I. Aspinall, R. R. Quinn, and K. W. Burak, "Gender, renal function, and outcomes on the liver transplant waiting list: assessment of revised MELD including estimated glomerular filtration rate," *Journal of Hepatology*, vol. 54, no. 3, pp. 462–470, 2011.

[72] S. K. Asrani, L. W. Jennings, W. Kim, P. S. Kamath, J. Levitsky, M. K. Nadim *et al.*, "MELD-GRAIL-Na: glomerular filtration rate and mortality on liver-transplant waiting list," *Hepatology*, vol. 71, no. 5, pp. 1766–1774, 2020.

[73] M. B. W. Costa, C. Gärtner, M. Schmidt, T. Berg, D. Seehofer, and T. Kaiser, "Revising the MELD score to address sex-bias in liver transplant prioritization for a German cohort," *Journal of Personalized Medicine*, vol. 13, no. 6, p. 963, 2023.

[74] E. Cholongitas, M. Thomas, M. Senzolo, and A. K. Burroughs, "Gender disparity and MELD in liver transplantation," *Journal of Hepatology*, vol. 55, no. 2, pp. 500–501, 2011.

[75] A. M. Allen, J. K. Heimbach, J. J. Larson, K. C. Mara, W. R. Kim, P. S. Kamath *et al.*, "Reduced access to liver transplantation in women: role of height, MELD exception scores, and renal function underestimation," *Transplantation*, vol. 102, no. 10, pp. 1710–1716, 2018.

[76] D. Sneiders, A.-B. R. M. van Dijk, S. Darwish-Murad, M. van Rosmalen, N. S. Erler, J. N. M. IJzermans *et al.*, "Quantifying the disadvantage of small recipient size on the liver transplantation waitlist, a longitudinal analysis within the Eurotransplant region," *Transplantation*, 2023.

[77] A. M. Lipsky and S. Greenland, "Causal directed acyclic graphs," *JAMA*, vol. 327, no. 11, pp. 1083–1084, 2022.

[78] N. L. Wood, D. VanDerwerken, D. L. Segev, and S. E. Gentry, "Correcting the sex disparity in MELD-Na," *American Journal of Transplantation*, vol. 21, no. 10, pp. 3296–3304, 2021.

[79] Q. Gong and D. E. Schaubel, "Estimating the average treatment effect on survival based on observational data and using partly conditional modeling," *Biometrics*, vol. 73, no. 1, pp. 134–144, 2017.

[80] I. R. White, P. Royston, and A. M. Wood, "Multiple imputation using chained equations: issues and guidance for practice," *Statistics in Medicine*, vol. 30, no. 4, pp. 377–399, 2011.

[81] L. D. Nephew, D. S. Goldberg, J. D. Lewis, P. Abt, M. Bryan, and K. A. Forde, "Exception points and body size contribute to gender disparity in liver transplantation," *Clinical Gastroenterology and Hepatology*, vol. 15, no. 8, pp. 1286–1293.e2, 2017.

[82] A. J. Kwong, N. H. Ebel, W. R. Kim, J. R. Lake, J. M. Smith, D. P. Schladt *et al.*, "OPTN/SRTR 2020 Annual Data Report: Liver," *American Journal of Transplantation*, vol. 22, no. S2, pp. 204–309, 2022.

[83] S. Bernards, E. Lee, N. Leung, M. Akan, K. Gan, H. Zhao *et al.*, "Awarding additional MELD points to the shortest waitlist candidates improves sex disparity in access to liver transplant in the United States," *American Journal of Transplantation*, vol. 22, no. 12, pp. 2912–2920, 2022.

[84] H. de Ferrante, M. de Rosner-Van Rosmalen, B. Smeulders, F. Spieksma, and S. Vogelaar, "A discrete event simulator for policy evaluation in deceased-donor liver allocation in eurotransplant," *Operations Research, Data Analytics and Logistics*, vol. 45, p. 200476, Dec. 2025. [Online]. Available: http://dx.doi.org/10.1016/j.ordal.2025.200476

[85] A. A. B. Pritsker, M. E. Kuhl, J. P. Roberts, M. D. Allen, J. F. Burdick, D. L. Martin *et al.*, "Organ transplantation policy evaluation," in *Proceedings of the 27th Conference on Winter simulation - WSC '95*, ser. WSC '95, C. Alexopoulos, K. Kang, W. R. Lilegdon, and D. Goldsman, Eds. INFORMS, 1995, pp. 1314–1323.

[86] D. Thompson, L. Waisanen, R. Wolfe, R. M. Merion, K. McCullough, and A. Rodgers, "Simulating the allocation of organs for transplantation," *Health Care Management Science*, vol. 7, no. 4, pp. 331–338, 2004.

[87] D. A. Axelrod, A. Gheorghian, M. A. Schnitzler, N. Dzebisashvili, P. R. Salvalaggio, J. Tuttle-Newhall *et al.*, "The economic implications of broader sharing of liver allografts," *American Journal of Transplantation*, vol. 11, no. 4, pp. 798–807, 2011.

[88] S. E. Gentry, A. B. Massie, S. W. Cheek, K. L. Lentine, E. H. Chow, C. E. Wickliffe *et al.*, "Addressing geographic disparities in liver transplantation through redistricting," *American Journal of Transplantation*, vol. 13, no. 8, pp. 2052–2058, 2013.

[89] A. Goel, W. R. Kim, J. Pyke, D. P. Schladt, B. L. Kasiske, J. J. Snyder *et al.*, "Liver Simulated Allocation Modeling: were the predictions accurate for Share 35?" *Transplantation*, vol. 102, no. 5, pp. 769–774, 2018.

[90] S. Akshat, S. E. Gentry, and S. Raghavan, "Heterogeneous donor circles for fair liver transplant allocation," *Health Care Management Science*, vol. 27, no. 1, pp. 20–45, 2024.

[91] E. R. Perito, D. B. Mogul, D. VanDerwerken, G. Mazariegos, J. Bucuvalas, L. Book *et al.*, "The impact of increased allocation priority for children awaiting liver transplant: a liver simulated allocation model (LSAM) analysis," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 68, no. 4, pp. 472–479, 2019.

[92] J. K. Heimbach, R. Hirose, P. G. Stock, D. P. Schladt, H. Xiong, J. Liu *et al.*, "Delayed hepatocellular carcinoma Model for End-Stage Liver Disease exception score improves disparity in access to liver transplant in the United States," *Hepatology*, vol. 61, no. 5, pp. 1643–1650, 2015.

[93] F. Bayer, B. Audry, C. Antoine, C. Jasseron, C. Legeai, O. Bastien *et al.*, "Removing administrative boundaries using a gravity model for a national liver allocation system," *American Journal of Transplantation*, vol. 21, no. 3, pp. 1080–1091, 2021.

[94] S. M. Shechter, C. L. Bryce, O. Alagoz, J. E. Kreke, J. E. Stahl, A. J. Schaefer *et al.*, "A clinically based discrete-event simulation of end-stage liver disease and the organ allocation process," *Medical Decision Making*, vol. 25, no. 2, pp. 199–209, 2005.

[95] J. Ratcliffe, T. Young, M. Buxton, T. Eldabi, R. Paul, A. Burroughs *et al.*, "A simulation modelling approach to evaluating alternative policies for the management of the waiting list for liver transplantation," *Health Care Management Science*, vol. 4, no. 2, pp. 117–124, 2001.

[96] Scientific Registry of Transplant Recipients, "Liver Simulation Allocation Model - user's guide," 2019. [Online]. Available: https://www.srtr.org/media/1361/lsam-2019-User-Guide.pdf

[97] N. L. Wood, D. B. Mogul, E. R. Perito, D. VanDerwerken, G. V. Mazariegos, E. K. Hsu *et al.*, "Liver Simulated Allocation Model does not effectively predict organ offer decisions for pediatric liver transplant candidates," *American Journal of Transplantation*, vol. 21, no. 9, pp. 3157–3162, 2021.

[98] N. Agarwal, I. Ashlagi, M. A. Rees, P. Somaini, and D. Waldinger, "Equilibrium allocations under alternative waitlist designs: evidence from deceased donor kidneys," *Econometrica*, vol. 89, no. 1, pp. 37–76, 2021.

[99] J. S. Carson, "Verification and validation: a consultant's perspective," in *Proceedings of the 21st Conference on Winter simulation*, ser. WSC '89, New York, NY, USA, 1989, pp. 552–558.

[100] A. M. Law, "Variance-reduction techniques," in *Simulation Modeling and Analysis*, fifth edition ed., ser. McGraw-Hill series in industrial engineering and management science. Dubuque: McGraw-Hill Education, 2015, ch. 11, pp. 588–596.

[101] N. A. Terrault, C. Francoz, M. Berenguer, M. Charlton, and J. Heimbach, "Liver transplantation 2023: status report, current and future challenges," *Clinical Gastroenterology and Hepatology*, vol. 21, no. 8, pp. 2150–2166, 2023.

[102] A. B. Massie, E. K. H. Chow, C. E. Wickliffe, X. Luo, S. E. Gentry, D. C. Mulligan *et al.*, "Early changes in liver distribution following implementation of Share 35," *American Journal of Transplantation*, vol. 15, no. 3, pp. 659–667, 2015.

[103] M. Ravaioli, Q. Lai, M. Sessa, D. Ghinolfi, G. Fallani, D. Patrono *et al.*, "Impact of MELD 30-allocation policy on liver transplant outcomes in Italy," *Journal of Hepatology*, vol. 76, no. 3, pp. 619–627, 2022.

[104] R. Vanholder, L. Annemans, A. K. Bello, B. Bikbov, D. Gallego, R. T. Gansevoort *et al.*, "Fighting the unbearable lightness of neglecting kidney health: the decade of the kidney," *Clinical Kidney Journal*, vol. 14, no. 7, pp. 1719–1730, 2021.

[105] M. Tonelli, N. Wiebe, G. Knoll, A. Bello, S. Browne, D. Jadhav *et al.*, "Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes," *American Journal of Transplantation*, vol. 11, no. 10, pp. 2093–2109, 2011.

[106] E. I. Foundation, "Annual Report 2005," 2005. [Online]. Available: https://www.eurotransplant.org/wp-content/uploads/2019/12/ar_2005.pdf

[107] M. H. van Dorp, "HLA & transplantatie: de ontwikkeling van een matchingspraktijk," Ph.D. dissertation, University of Maastricht, 2001. [Online]. Available: http://dx.doi.org/10.26481/dis.20011116md

[108] S. Bak-Jensen, "To share or not to share? institutional exchange of cadaver kidneys in Denmark," *Medical History*, vol. 52, no. 1, pp. 23–46, 2008.

[109] J. Dausset and F. T. Rapaport, "The HLA Story," in *Immunology*, R. B. Gallagher, J. Gilder, G. J. V. Nossal, and G. Salvatore, Eds. London: Academic Press, 1995, ch. 10, pp. 111–120. [Online]. Available: https://www.sciencedirect.com/science/article/pii/B9780122740206500118

[110] J. J. van Rood, "Weighing optimal graft survival through HLA matching against the equitable distribution of kidney allografts," *New England Journal of Medicine*, vol. 350, no. 6, pp. 535–536, 2004.

[111] G. G. Persijn, B. W. Gabb, A. van Leeuwen, A. Nagtegaal, J. Hoogeboom, and J. J. van Rood, "Matching for HLA of A, B, and DR loci in renal transplantation by Eurotransplant," *The Lancet*, vol. 311, no. 8077, pp. 1278–1281, 1978.

[112] G. G. Persijn, A. van Leeuwen, J. Parlevliet, B. Cohen, Q. Lansbergen, J. D'Amaro *et al.*, "Improved kidney graft survival in Eurotransplant by HLA-DR matching and prospectively given blood transfusions," *The Ulster Medical Journal*, vol. 50, no. Suppl 1, pp. 54–61, 1981.

[113] P. I. Terasaki, J. Dausset, R. Payne, van Rood, J.J., van Leeuwen *et al.*, "History of HLA: A personalized view," in *History of HLA: Ten Recollections*. UCLA Tissue Typing Laboratory, 1990, ch. 10, pp. 232–233. [Online]. Available: http://www.piterasaki.org/HistoryOfHLA.pdf

[114] C. M. Kjellstrand, "Age, sex, and race inequality in renal transplantation," *Archives of Internal Medicine*, vol. 148, no. 6, p. 1305, 1988.

[115] T. E. Starzl, T. R. Hakala, A. Tzakis, R. Gordon, A. Stieber, L. Makowka *et al.*, "A multifactorial system for equitable selection of cadaver kidney recipients," *JAMA*, vol. 257, no. 22, pp. 3073–3075, 1987.

[116] S. M. Greenstein, R. S. Schechner, P. Louis, D. Senitzer, A. Matas, F. J. Veith *et al.*, "Evidence that zero antigen-matched cyclosporine-treated renal transplant recipients have graft survival equal to that of matched recipients. reevaluation of points," *Transplantation*, vol. 49, no. 2, pp. 332–336, 1990.

[117] P. Harfmann, R. Dittmer, R. Busch, R. Arndt, H. Krämer-Hansen, and H. Huland, "Renal transplantation using cyclosporine with and without regard to HLA matching: a randomized prospective unicenter study," *The Journal of Urology*, vol. 142, no. 3, pp. 691–693, 1989.

[118] G. Opelz, "Correlation of HLA matching with kidney graft survival in patients with or without cyclosporine treatment: for the Collaborative Transplant Study," *Transplantation*, vol. 40, no. 3, p. 240, 1985.

[119] G. Opelz and B. Döhler, "Effect of human leukocyte antigen compatibility on kidney graft survival: comparative analysis of two decades," *Transplantation*, vol. 84, no. 2, pp. 137–143, 2007.

[120] P. J. Morris, R. J. Johnson, S. V. Fuggle, M. A. Belger, and J. D. Briggs, "Analysis of factors that affect outcome of primary cadaveric renal transplantation in the UK. HLA task force of the kidney advisory group of the United Kingdom transplant support service authority (UKTSSA)," *The Lancet*, vol. 354, no. 9185, pp. 1147–1152, 1999.

[121] J. Cicciarelli, P. I. Terasaki, and M. R. Mickey, "The effect of zero HLA class I and II mismatching in cyclosporine-treated kidney transplant patients," *Transplantation*, vol. 43, no. 5, pp. 636–640, 1987.

[122] A. Ting and P. J. Morris, "The role of HLA matching in renal transplantation," *Tissue Antigens*, vol. 25, no. 5, pp. 225–234, 1985.

[123] V. C. Joysey, "Tissue typing policy," in *Transplantation*, G. R. D. Catto, Ed., Dordrecht, 1989, pp. 59–93.

[124] J. Thorogood, G. G. Persijn, G. M. T. Schreuder, J. D'Amaro, F. A. Zantvoort, J. C. van Houwelingen *et al.*, "The effect of HLA matching on kidney graft survival in separate posttransplantation intervals," *Transplantation*, vol. 50, no. 1, p. 146, 1990.

[125] J. de Meester and G. G. Persijn, "Allocation of cadaver organs to transplant recipients in Eurotransplant: principles and policies, anno 1998," in *Organ Allocation: Proceedings of the 30th Conference on Transplantation and Clinical Immunology, 2–4 June, 1998*, J. L. Touraine, J. Traeger, H. Bétuel, J. M. Dubernard, J. P. Revillard, and C. Dupuy, Eds., Dordrecht, 1998, pp. 61–66. [Online]. Available: https://doi.org/10.1007/978-94-011-4984-6_8

[126] T. Wujciak and G. Opelz, "A proposal for improved cadaver kidney allocation," *Transplantation*, vol. 56, no. 6, pp. 1513–1517, 1993.

[127] G. Opelz and T. Wujciak, "What to expect from a good kidney allocation system," in *Organ allocation: Proceedings of the 30th conference on transplantation and clinical immunology, 2–4 june, 1998*, J. L. Touraine, J. Traeger, H. Bétuel, J. M. Dubernard, J. P. Revillard, and C. Dupuy, Eds., Dordrecht, 1998, pp. 57–60. [Online]. Available: https://doi.org/10.1007/978-94-011-4984-6_7

[128] J. de Meester, G. G. Persijn, F. H. J. Claas, and U. Frei, "In the queue for a cadaver donor kidney transplant: new rules and concepts in the Eurotransplant," *Nephrology Dialysis Transplantation*, vol. 15, no. 3, pp. 333–338, 2000.

[129] P. Vereerstraeten, D. Abramowicz, L. De Pauw, and P. Kinnaert, "Experience with the Wujciak-Opelz allocation system in a single center: an increase in HLA-DR mismatching and in early occurring acute rejection episodes," *Transplant International*, vol. 11, no. 5, pp. 378–381, 1998.

[130] I. I. N. Doxiadis, J. W. de Fijter, M. J. K. Mallat, G. W. Haasnoot, J. Ringers, G. G. Persijn *et al.*, "Simpler and equitable allocation of kidneys from postmortem donors primarily based on full HLA-DR compatibility," *Transplantation*, vol. 83, no. 9, p. 1207, 2007.

[131] M. B. A. Heemskerk, B. J. J. M. Haase-Kromwijk, F. H. J. Claas, I. I. N. Doxiadis, G. W. Haasnoot, J. J. H. van der Heide *et al.*, "Regional kidney allocation based only on full HLA-DR compatibility is not feasible," *Transplantation*, vol. 88, no. 4, p. 600, 2009.

[132] T. Wujciak and G. Opelz, "Matchability as an important factor for kidney allocation according to the HLA match," *Transplantation Proceedings*, vol. 29, no. 1–2, pp. 1403–1405, 1997.

[133] C. Süsal and C. Morath, "Virtual PRA replaces traditional pra: small change but significantly more justice for sensitized patients," *Transplant International*, vol. 28, no. 6, pp. 708–709, 2015.

[134] M. Ziemann, N. Heßler, I. R. König, N. Lachmann, A. Dick, V. Ditt *et al.*, "Unacceptable human leukocyte antigens for organ offers in the era of organ shortage: influence on waiting time before kidney transplantation," *Nephrology Dialysis Transplantation*, vol. 32, no. 5, pp. 880–889, 2017.

[135] D. Zecher, F. Zeman, T. Drasch, I. Tieken, S. Heidt, G. W. Haasnoot *et al.*, "Impact of sensitization on waiting time prior to kidney transplantation in Germany," *Transplantation*, vol. 106, no. 12, p. 2448, 2022.

[136] R. Patel and P. I. Terasaki, "Significance of the positive crossmatch test in kidney transplantation," *The New England Journal of Medicine*, vol. 280, no. 14, pp. 735–739, 1969.

[137] F. H. J. Claas and J. J. van Rood, "The hyperimmunized patient: from sensitization toward transplantation," *Transplant International*, vol. 1, no. 2, pp. 53–57, 1988.

[138] S. Heidt, M. D. Witvliet, G. W. Haasnoot, and F. H. J. Claas, "The 25th anniversary of the Eurotransplant Acceptable Mismatch program for highly sensitized patients," *Transplant Immunology*, vol. 33, no. 2, pp. 51–57, 2015.

[139] Eurotransplant, "Eurotransplant Manual. Chapter 10: Histocompatibility Testing." [Online]. Available: https://www.eurotransplant.org/allocation/eurotransplant-manual/

[140] N. Mamode, O. Bestard, F. Claas, L. Furian, S. Griffin, C. Legendre *et al.*, "European guideline for the management of kidney transplant patients with HLA antibodies: by the European society for organ transplantation working group," *Transplant International*, vol. 35, 2022.

[141] P. Amico, G. Hönger, M. Mayr, J. Steiger, H. Hopfer, and S. Schaub, "Clinical relevance of pretransplant donor-specific HLA antibodies detected by single-antigen flow-beads," *Transplantation*, vol. 87, no. 11, pp. 1681–1688, 2009.

[142] W. R. Mulley and J. Kanelles, "Understanding crossmatch testing in organ transplantation: a case-based guide for the general nephrologist," *Nephrology*, vol. 16, no. 2, pp. 125–133, 2011.

[143] J. M. A. Smits, G. G. Persijn, J. C. van Houwelingen, F. H. J. Claas, and U. Frei, "Evaluation of the Eurotransplant Senior Program. the results of the first year," *American Journal of Transplantation*, vol. 2, no. 7, pp. 664–670, 2002.

[144] U. Frei, J. Noeldeke, V. Machold-Fabrizii, H. Arbogast, R. Margreiter, L. Fricke *et al.*, "Prospective age-matching in elderly kidney transplant recipients - a 5-year analysis of the Eurotransplant Senior Program," *American Journal of Transplantation*, vol. 8, no. 1, pp. 50–57, 2008.

[145] J. de Fijter, G. Dreyer, M. Mallat, K. Budde, J. Pratschke, J. Klempnauer *et al.*, "A paired-kidney allocation study found superior survival with HLA-DR compatible kidney transplants in the Eurotransplant Senior Program," *Kidney International*, vol. 104, no. 3, pp. 552–561, 2023.

[146] B. Kolbrink, N. Kakavand, J. C. Voran, H. U. Zacharias, A. Rahmel, S. Vogelaar *et al.*, "Allocation rules and age-dependent waiting times for kidney transplantation," *Deutsches Ärzteblatt international*, 2024.

[147] B. Audry, E. Savoye, M. Pastural, F. Bayer, C. Legeai, M.-A. Macher *et al.*, "The new French kidney allocation system for donations after brain death: rationale, implementation, and evaluation," *American Journal of Transplantation*, vol. 22, no. 12, pp. 2855–2868, 2022.

[148] C. J. E. Watson, R. J. Johnson, and L. Mumford, "Overview of the evolution of the UK kidney allocation schemes," *Current Transplantation Reports*, vol. 7, no. 2, pp. 140–144, 2020.

[149] A. K. Israni, N. Salkowski, S. Gustafson, J. J. Snyder, J. J. Friedewald, R. N. Formica *et al.*, "New national allocation policy for deceased donor kidneys in the United States and possible effect on patient outcomes," *Journal of the American Society of Nephrology*, vol. 25, no. 8, pp. 1842–1848, 2014.

[150] F. A. von Samson-Himmelstjerna, B. Kolbrink, K. Budde, R. Schmitt, and K. Schulte, "Continuous donor-recipient age matching: a chance for kidney allocation in the Eurotransplant region," *American Journal of Transplantation*, 2024.

[151] D. A. Wu, C. J. Watson, J. A. Bradley, R. J. Johnson, J. L. Forsythe, and G. C. Oniscu, "Global trends and challenges in deceased donor kidney allocation," *Kidney International*, vol. 91, no. 6, pp. 1287–1299, 2017.

[152] H. C. de Ferrante, B. M. L. Smeulders, I. Tieken, S. Heidt, G. W. Haasnoot, F. H. J. Claas *et al.*, "Immunized patients face reduced access to transplantation in the Eurotransplant Kidney Allocation System," *Transplantation*, vol. 107, no. 10, pp. 2247–2254, 2023.

[153] S. Heidt, G. W. Haasnoot, M. J. H. van der Linden-van Oevelen, and F. H. J. Claas, "Highly sensitized patients are well served by receiving a compatible organ offer based on acceptable mismatches," *Frontiers in Immunology*, vol. 12, 2021.

[154] G. Putzer, L. Gasteiger, S. Mathis, A. van Enckevort, T. Hell, T. Resch *et al.*, "Solid organ donation and transplantation activity in the Eurotransplant area during the first year of COVID-19," *Transplantation*, vol. 106, no. 7, pp. 1450–1454, 2022.

[155] D. G. Altman and P. Royston, "The cost of dichotomising continuous variables," *British Medical Journal*, vol. 332, no. 7549, p. 1080, 2006.

[156] P. Vereerstraeten, D. Abramowicz, M. Andrien, E. Dupont, L. De Pauw, and P. Kinnaert, "Allocation of cadaver kidneys according to HLA-DR matching

alone would result in optimal graft outcome in most recipients," *Transplantation Proceedings*, vol. 31, no. 1-2, pp. 739–741, 1999.

[157] J. P. Roberts, R. A. Wolfe, J. L. Bragg-Gresham, S. H. Rush, J. J. Wynn, D. A. Distant *et al.*, "Effect of changing the priority for HLA matching on the rates and outcomes of kidney transplantation in minority groups," *New England Journal of Medicine*, vol. 350, no. 6, pp. 545–551, 2004.

[158] R. J. Johnson, S. V. Fuggle, J. O'Neill, S. Start, J. A. Bradley, J. L. R. Forsythe *et al.*, "Factors influencing outcome after deceased heart beating donor kidney transplantation in the United Kingdom: an evidence base for a new national kidney allocation policy," *Transplantation*, vol. 89, no. 4, pp. 379–386, 2010.

[159] C. Süsal, G. Kumru, B. Döhler, C. Morath, M. Baas, J. Lutz *et al.*, "Should kidney allografts from old donors be allocated only to old recipients?" *Transplant International*, vol. 33, no. 8, pp. 849–857, 2020.

[160] M. Niemann, N. Lachmann, K. Geneugelijk, and E. Spierings, "Computational Eurotransplant kidney allocation simulations demonstrate the feasibility and benefit of T-cell epitope matching," *PLOS Computational Biology*, vol. 17, no. 7, p. e1009248, 2021.

[161] T. Wujciak and G. Opelz, "Computer analysis of cadaver kidney allocation procedures," *Transplantation*, vol. 55, no. 3, p. 516, 1993.

[162] A. Israni, A. Wey, B. Thompson, J. Miller, V. Casingal, M. Pavlakis *et al.*, "New kidney and pancreas allocation policy: moving to a circle as the first unit of allocation," *Journal of the American Society of Nephrology*, vol. 32, no. 7, pp. 1546–1550, 2021.

[163] M. A. Mankowski, M. Kosztowski, S. Raghavan, J. M. Garonzik-Wang, D. Axelrod, D. L. Segev *et al.*, "Accelerating kidney allocation: simultaneously expiring offers," *American Journal of Transplantation*, vol. 19, no. 11, pp. 3071–3078, 2019.

[164] C. Jacquelinet, B. Audry, C. Golbreich, C. Antoine, J.-M. Rebibou, J. Claquin3 *et al.*, "Changing kidney allocation policy in France: the value of simulation," *AMIA Annual Symposium Proceedings*, vol. 2006, pp. 374–378, 2006.

[165] L. Mumford and C. J. Watson, "Working towards a new deceased donor kidney offering scheme in the UK," *Transplantation*, p. S153, 2018.

[166] Eurotransplant, "Eurotransplant Statistics Library. Report 2152p: kidney transplants, deceased donors in all ET, by year, by organ combination," Online, 2024. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=11246-33135-33153&format=html&download=0

[167] ——, "Eurotransplant Statistics Library. Report 2072p: kidney-only transplants (deceased donor) in all ET," Online, 2024. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=11151-33135-33195&format=html&download=1

[168] ——, "Eurotransplant Statistics Library. Report 1132p: kidney donation, deceased donors in all ET, by year, by allocation phase," Online, Leiden, 2024. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=11196-33135-33195&format=html&download=0

[169] ——, "Eurotransplant manual. chapter 4: kidney (etkas and esp)," Online, 2024. [Online]. Available: https://www.eurotransplant.org/allocation/eurotransplant-manual/

[170] ——, "Eurotransplant Statistics Library. Report 4002p: waiting list registrations in all ET, by year, by organ," Online, 2024. [Online]. Available: https://statistics.eurotransplant.org/reportloader.php?report=10597-33135&format=html&download=0

[171] D. Lopes, T. Barra, J. Malheiro, S. Tafulo, L. Martins, M. Almeida *et al.*, "Effect of different sensitization events on HLA alloimmunization in kidney transplant candidates," *Transplantation Proceedings*, vol. 47, no. 4, pp. 894–897, 2015.

[172] D. P. Lucas, M. S. Leffell, and A. A. Zachary, "Differences in immunogenicity of HLA antigens and the impact of cross-reactivity on the humoral response," *Transplantation*, vol. 99, no. 1, pp. 77–85, 2015.

[173] C. Süsal, D. L. Roelen, G. Fischer, E. F. Campos, M. Gerbase-DeLima, G. Hönger *et al.*, "Algorithms for the determination of unacceptable HLA antigen mismatches in kidney transplant recipients," *Tissue Antigens*, vol. 82, no. 2, pp. 83–92, 2013.

[174] M. Ziemann, B. Suwelack, B. Banas, K. Budde, G. Einecke, I. Hauser *et al.*, "Determination of unacceptable HLA antigen mismatches in kidney transplant recipients," *HLA*, vol. 100, no. 1, pp. 3–17, 2022.

[175] D. Isaacson, J. D. Schold, M. W. Gmeiner, H. C. Copley, V. Kosmoliaptsis, and A. R. Tambur, "HLA-DQ mismatches lead to more unacceptable antigens, greater sensitization, and increased disparities in repeat transplant candidates," *Journal of the American Society of Nephrology*, vol. 33, no. 12, pp. 2293–2305, 2022.

[176] S. Heidt, C. S. M. Kramer, G. W. Haasnoot, A. H. Schmidt, Y. M. Zoet, F. H. J. Claas *et al.*, "Introduction of the donor center virtual crossmatch in Eurotransplant," *HLA*, vol. 104, no. 2, 2024.

[177] D. E. Stewart, A. Y. Kucheryavaya, N. L. Reinsmoen, and J. J. Friedewald, "Smoothing it out: creating a sliding scale for assigning CPRA-based allocation points," *American Journal of Transplantation*, vol. 12, no. s3, p. 128, 2012.

[178] J. Waiser, M. Schreiber, K. Budde, L. Fritsche, T. Böhler, I. Hauser *et al.*, "Age-matching in renal transplantation," *Nephrology Dialysis Transplantation*, vol. 15, no. 5, pp. 696–700, 2000.

[179] M. Pippias, K. J. Jager, A. Åsberg, S. P. Berger, P. Finne, J. G. Heaf *et al.*, "Young deceased donor kidneys show a survival benefit over older donor kidneys in transplant recipients aged 20–50 years: a study by the ERA–EDTA registry," *Nephrology Dialysis Transplantation*, vol. 35, no. 3, pp. 534–543, 2020.

[180] F. J. van Ittersum, A. C. Hemke, F. W. Dekker, L. B. Hilbrands, M. H. L. Christiaans, J. I. Roodnat *et al.*, "Increased risk of graft failure and mortality in Dutch recipients receiving an expanded criteria donor kidney transplant," *Transplant International*, vol. 30, no. 1, pp. 14–28, 2017.

[181] M. Coemans, T. H. Tran, B. Döhler, A. B. Massie, G. Verbeke, D. L. Segev *et al.*, "A competing risks model to estimate the risk of graft failure and patient death after kidney transplantation using continuous donor-recipient age combinations," *American Journal of Transplantation*, vol. 0, no. 0, 2024.

[182] D. S. Keith, A. Demattos, M. Golconda, J. Prather, and D. Norman, "Effect of donor recipient age match on survival after first deceased donor renal transplantation," *Journal of the American Society of Nephrology*, vol. 15, no. 4, p. 1086, 2004.

[183] L. C. de Wreede, M. Fiocco, and H. Putter, "Mstate: an R package for the analysis of competing risks and multi-state models," *Journal of Statistical Software*, vol. 38, pp. 1–30, 2011.

[184] A. R. Tambur, V. Kosmoliaptsis, F. H. J. Claas, R. B. Mannon, P. Nickerson, and M. Naesens, "Significance of HLA-DQ in kidney transplantation: time to reevaluate human leukocyte antigen–matching priorities to improve transplant outcomes? an expert review and recommendations," *Kidney International*, vol. 100, no. 5, pp. 1012–1022, 2021.

[185] R. G. Sargent, "Verification and validation of simulation models: an advanced tutorial," in *2020 Winter Simulation Conference (WSC)*. Orlando, FL, USA: INFORMS, 2020, pp. 16–29.

[186] A. Luca, B. Angermayr, G. Bertolini, F. Koenig, G. Vizzini, M. Ploner *et al.*, "An integrated MELD model including serum sodium and age improves the prediction of early mortality in patients with cirrhosis," *Liver Transplantation*, vol. 13, no. 8, pp. 1174–1180, 2007.

[187] D. M. Heuman, A. A. Mihas, A. Habib, H. S. Gilles, R. T. Stravitz, A. J. Sanyal *et al.*, "MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy," *Liver Transplantation*, vol. 13, no. 1, pp. 30–37, 2006.

[188] J. Neuberger, A. Gimson, M. Davies, M. Akyol, J. O'Grady, A. Burroughs *et al.*, "Selection of patients for liver transplantation and allocation of donated livers in the UK," *Gut*, vol. 57, no. 2, pp. 252–257, 2007.

[189] U. Kartoun, K. E. Corey, T. G. Simon, H. Zheng, R. Aggarwal, K. Ng *et al.*, "The MELD-Plus: a generalizable prediction risk score in cirrhosis," *PLOS ONE*, vol. 12, no. 10, p. e0186301, 2017.

[190] N. Sarmast, G. O. Ogola, M. Kouznetsova, M. D. Leise, R. Bahirwani, R. Maiwall *et al.*, "Model for End-Stage Liver Disease-lactate and prediction of inpatient mortality in patients with chronic liver disease," *Hepatology*, vol. 72, no. 5, pp. 1747–1757, 2020.

[191] B. F. J. Goudsmit, H. Putter, M. E. Tushuizen, J. Boer, S. Vogelaar, I. P. J. Alwayn *et al.*, "Validation of the Model for End-Stage Liver Disease sodium (MELD-Na) score in the Eurotransplant region," *American Journal of Transplantation*, vol. 21, no. 1, pp. 229–240, 2020.

[192] O. Liver and I. O. T. Committee, "Report to the Board of Directors, June 23-24, 2014, Richmond, Virginia," 2014. [Online]. Available: https://optn.transplant.hrsa.gov/media/1834/liver_boardreport_20140702.pdf

[193] M. A. Mankowski, L. Gragert, B. Keating, B. E. Lonze, D. L. Segev, R. Montgomery *et al.*, "Balancing equity and human leukocyte antigen matching in deceased-donor kidney allocation with eplet mismatch," *American Journal of Transplantation*, 2024.

[194] G. E. Karahan, G. W. Haasnoot, and S. Heidt, "Equitable allocation through human leukocyte antigen eplet matching: a promising strategy with several challenges," *American Journal of Transplantation*, 2025.

[195] N. Tayob and S. Murray, "Statistical consequences of a successful lung allocation system - recovering information and reducing bias in models for urgency," *Statistics in Medicine*, vol. 36, no. 15, pp. 2435–2451, 2017.

[196] J. Xie, J. Shults, J. Peet, D. Stambolian, and M. F. Cotch, "Quasi-least squares with mixed linear correlation structures," *Statistics and its interface*, vol. 3, no. 2, pp. 223–234, 2010.

[197] J. Shults and J. M. Hilbe, *Quasi-Least Squares Regression*, ser. Monographs on Statistics & Applied Probability. Philadelphia, PA: Chapman & Hall/CRC, 2014.