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# Improving Decision Support for Organ Transplant

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***Abstract*—**We find in our data that an alarming number of viable deceased donor kidneys are discarded every year in the US, while waitlisted candidates are dying every day. We observe as many as 85% of transplanted organs are refused at least once for a patient that scored higher on the match list. There are hundreds of clinical variables involved in making a clinical transplant decision and there is rarely an ideal match. Decision makers exhibit an optimism bias where they may refuse an organ offer assuming a better match is imminent. We propose a semi-parametric Cox proportional hazard model, augmented by an accelerated failure time model based on patient-specific suitable organ supply and demand to estimate a time-to-next-offer. Performance is assessed with Cox-Snell residuals and decision curve analysis, demonstrating improved decision support for up to a 5-year outlook. Providing clinical decision-makers with quantitative evidence of likely patient outcomes (e.g., time to next offer and the mortality associated with waiting) may improve decisions and reduce optimism bias, thus reducing discarded organs and matching more patients on the waitlist.

***Keywords*—**Decision science, KDPI, optimism bias, organ transplant.

## I. Introduction

KIDNEY transplantation remains the best treatment choice for patients with end stage kidney disease (ESKD) as well as the most cost-effective therapy option for candidates [1]. However, the transplant decision maker must assess whether the candidate will receive a better offer in the near future [2]. Despite performing roughly 24,700 kidney transplants in 2020, less than one percent of all kidney offers were accepted. This often results in organs being accepted at other centers for patients with lower priority on the donation match run. Approximately 20-25% of viable kidneys are discarded without being accepted due to excessive cold ischemia that develops when a match cannot be identified in time [9]. Meanwhile, more than five thousand waitlisted patients die each year without receiving a transplant [9].

Matched organs are rarely perfect and clinical decisions involve hundreds of variables for both donor and recipient. This creates a large cognitive load and inconsistency in clinical decisions. Different metrics are used to assist transplant centers with evidence-based medicine. Perhaps the most widely used measure of kidney quality is the kidney donor profile index (KDPI), which is a weighted model of ten different factors including both clinical and demographic parameters. Lower KDPI scores are associated with longer estimated function. For example, a KDPI of 25 means that the kidney is in the top 25$^{th}$ percentile of all kidneys recovered each year [9]. In other words, the kidney is in the top 25% of kidneys one would expect to see. The organ procurement and transplantation network (OPTN) attempts to match kidneys with the highest longevity with patients that have the highest estimated post-transplant survival (EPTS) score, which is a transplant candidate specific score based on how long a candidate will need the organ compared to other candidates. An EPTS score of 80 means that the candidate will require the organ longer than 80% of other candidates on the waitlist [9]. These are only two measures used in the transplant decision process, which is complex and governed by a number of policy, regulatory, and clinical factors established by law (42 CFR § 121.8 - Allocation of organs). The final decision to transplant, however, is made by healthcare professionals.

The transplant decision making process poses both a unique and illustrative case study for artificial intelligence (AI). The problem is not easily solved with improved match algorithms when decision makers ignore the current solution [9]. Ultimately, these algorithms reflect policy and policy is a reflection of a culture's values. These policies must balance the values of optimal medical outcomes, deceased donor organ utilization, and equity. For example, the discard rate in the UK is one third smaller than that of the US [3]. The UK's "fast track" scheme for marginal kidneys at risk of discard prioritizes organ utilization over equity and outcome to a greater degree than in the US resulting in higher organ utilization. The UK is not using a better algorithm, they are implementing medical data in a different way. The "match score" is less of a clinical "match" and more of a "sequence" dictating whose turn it is to receive an organ [3]. In the US, the sequence is biased towards equity [3]. Surgeons and transplant centers, within this context, must decide on what is the best decision for their patient and may have legitimate doubts regarding a proposed organ offer. While predictive survival analysis can be used to model mortality under different conditions, combining this score with a forecast of a patient specific future supply of deceased donor organs is more challenging and combining that with policies biased towards equity is even more difficult to assess.

Decision making in this high-pressure environment is very heterogeneous [4] and influenced by factors beyond organ quality [5]-[8]. Centers that decline organs typically do so because they expect a better offer for their patient that often does not appear. This optimism bias in clinical decision making is well supported in the literature [9]-[11]. Husain et al [11]

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suggest a risk-aversion bias stemming from the Hippocratic oath of "do no harm" in fact leads to refusal decisions that negatively affect patient survival and outcomes. The data suggest that this phenomenon is steadily increasing over time [3], [5], [12]-[16].

The United Network for Organ Sharing (UNOS) has conducted several behavioral studies that demonstrate changes in the presentation of clinical data can significantly affect organ acceptance decisions [4], [9], [13]. For example, McCulloh et al. [9] demonstrate that providing an empirically based "Time to Better Offer (TTBO)" in months along with a mortality estimate of "probability of death before better offer" can increase consistency in clinical decisions, improve decision confidence, and may eliminate optimism bias. Their study used anonymized data, systematically altered to measure the effects on clinical decision making. The actual calculation of TTBO and associated mortality is more challenging.

Predicting TTBO and the associated mortality risk of waiting until a better organ is offered is composed of two sub-problems, namely TTBO and the mortality risk of remaining on the waitlist. The dependent variables, Time to a Better Offer and waitlist mortality, for these mathematical models are a time-to-event data point containing right-censored observations. A right-censored observation occurs when a subject leaves the study before an event occurs, which could be due to death or removal from the waitlist for a number of other personal or clinical reasons. Right censored survival analysis is typically modeled with a product limit estimator [17], [18] given as,

$$\hat{S}(t) = \prod_{i:t_i<t}\left(1-\frac{d_i}{n_i}\right) \quad (1)$$

where $S(t)$ is the survival function, $d_i$ is the number of deaths and $n_i$ is the number of individuals to survive up to time $t_i$. The product limit estimator, however, does not consider other clinical determinants of health to model patient-specific outcomes.

A proportional hazards model improves on the survival function allowing the effects of covariates to improve survival estimation [19]. The proportional hazards model is given as,

$$\hat{S}(t) = \prod_{i:t_i<t}\left(1-\frac{\Theta_i}{\sum_j \theta_j}\right) \quad (2)$$

where $\Theta$ is a model of covariates that change the hazard function over time.

An alternative to the proportional hazards model is the accelerated failure time model [20]. While the proportional hazard model is semi-parametric and treats covariates as a relative hazard weight or multiplier, the accelerated failure time model accelerates the hazard using a fully parametric model such as a probability distribution. Kay and Kinnersley [20] argue that this model is more explainable in terms of a treatment (e.g. transplant offer) affecting life expectancy. The performance of the accelerated failure time model is dependent upon the choice and fit of the underlying parametric probability distribution.

Measuring the performance of time-to-event hazard models in a clinical setting can also be problematic. The Akaike information criterion (AIC), concordance index, and Brier score do not provide any information for assessing whether the model is useful in practice. A common approach for model goodness-of-fit is visual inspection of residuals. For hazard models, however, Cox-Snell residuals provide a more generalized approach for non-linear and autoregressive time-series models [21]. A problem with Cox-Snell residuals, however, is that the evidence of fit is not necessarily close for small sample size, such as the more extreme data points with long time until next offer. For evaluation of donor offer survival models, however, the Cox-Snell is more appropriate than other goodness-of-fit approaches.

This paper does not directly investigate medical decision-making surrounding kidney transplant offer acceptance. The literature is clear that there exists bias, uncertainty, and lack of consensus on proper organ offer acceptance decisions. The literature further demonstrates that decision making can be uniformly improved by providing clinical decision makers with reliable estimation of the time it will take to receive an equivalent or better offer and an estimate of patient survival likelihood without transplant [9]. To address this problem, this paper proposes a machine-learning model to provide needed estimates and enhance evidence-based medical decisions. Specifically, we propose a "Time-To-Next-Offer" (TTNO) model using Organ Procurement Transplantation Network (OPTN) data that feed into model for estimating patient survival without transplant using OPTN data. Finally, we propose a goodness-of-fit approach bounded by a realistic clinical decision outlook.

## II. Methods

There were several challenges in providing TTNO estimation. In addition to operationalizing "TTBO", providing an estimate of estimated transplant survival until better offer requires an estimate of TTBO. The recent UNOS study demonstrating the utility in providing estimates of future offers in conjunction with mortality risk to decision makers used a "time-to-better-offer" (TTBO) in notional offers [9]. The term "better" was not fully defined for the study. This introduces complexity in the measure itself. A "better" offer could mean an increase of 1 point in KDPI, an increase in 20 points, or some percentage increase. There may be additional clinical factors affecting transplant decisions.

For this paper, we modify TTBO to TTNO, where we model the estimated time until a kidney with some quality score, $k$, or better is achieved. Our empirical runs use KDPI for $k$ with KDPI $\leq$ 30 and KDPI $\leq$ 50. We define estimated transplant survival as median time to "TTBO". Hence, we define $M$ as median estimated TTNO, where the survival function of TTNO is $S(M) = 0.5$, which then will be used in the survival function assessing estimated survival without transplant at the specified time $t$ (depicted in Fig. 1). This effectively decomposes a complex problem into two tractable sub-problems.

We evaluated several models for TTNO estimation. As stated earlier, the semi-parametric proportional hazard model, while allowing for patient-specific clinical variables, does not have a

good way of modeling arrival times for organs with a particular quality score, in this case KDPI ≤ 30 and KDPI ≤ 50. Thus, all TTNO models use an accelerated failure time model. These models require parametric probability distributions fit to the data. We investigate the Exponential, Weibull, Lognormal, and Loglogistic distributions under best-fit conditions for estimating both the KDPI ≤ 30 and KDPI ≤ 50 conditions.

Patient mortality while on the waitlist is modeled with a proportional hazards model based on prior literature [22]. The existent parameters needed to be re-evaluated because the model was over a decade old. Given clinical improvements in dialysis survival [23] and transplant [24], we suspected there was potential for clinical concept data drift [25].

Data for model estimation were obtained from the OPTN database and are available upon request. Specifically, we use the kidney-pancreas (KidPan), KidPan Waitlist History (WLH), and Potential Transplant Recipient (PTR) data. The source data are patient-centric and not specifically collected for this study. It was therefore converted to a model-ready dataset with separate cohorts for TTNO and mortality.

The TTNO data cohort are constructed from the KidPan WLH, PTR, and inactive times files. The KidPan WLH contains records of all changes to a patient's waitlisting status. Status changes can include offer, death, or removal for some other reason such as illness, injury, or personal reasons. For reasonable scope, candidates with a status change between January 1, 2016 and January 1, 2020 were included in the data cohort. The PTR data contain offer histories of all kidney transplant candidates, including geographic and biological predictors of time to offer such as: Blood Type, Calculated Panel-Reactive Antibody (CPRA), Number of Human Leukocyte Antigen (HLA) Mismatches, Dialysis Time, Sequence Number, Organ Procurement Organization (OPO) and Transplant Center. Reference variables are defined as the values of the predictor variables at the time of the last offer of interest. Wait time is defined as the time between events of interest (i.e. offers). Observations are uncensored if the candidate received an offer meeting the KDPI threshold of interest, k. They are censored if the candidate died, accepted an offer that was not less than the KDPI threshold, or if the study ended before a qualifying offer was received.

The waitlist mortality model was constructed from the KidPan and KidPan WLH sources. For the waitlist mortality model, candidates with a status change between January 1, 2010 and January 1, 2020 were included. The Kidpan File contains case histories of all kidney transplant candidates, including biological predictors of candidate mortality such as: Age, Body Mass Index (BMI), CPRA, Prior transplant history, Diabetes status, Polycystic Status, Albumin levels. Observations with dialysis dates before January 1, 1980 were excluded. Age values were between 18 and 70 years. BMI values were restricted to those between 7.5 and 50. Data were randomly split into testing and training data sets for model fit and evaluation. Wait time is defined as the time from waitlisting to the candidate's death date, transplant date, or the end of the study, whichever is earliest. Observations are uncensored if the candidate died awaiting a transplant; they are censored if the candidate received a transplant, or if they were alive at the end of the study.

Model goodness-of-fit was assessed with a visual inspection of the Cox-Snell (CS) residual plot. Cox-Snell Residuals are a transformation of the survival probability of each observation given as,

$$r = -\ln\left(S_i(t)\right) \tag{3}$$

In a well-fitting model, the CS residuals should fall along a 45-degree diagonal on the cumulative hazard vs. time plot. Residual plots are inspected for the cumulative hazard against different predictive factors to identify potential leverage and bias in addition to goodness of fit. We considered martingale and deviance residuals, which have consistent findings for these data, however, the CS residual plots are more intuitive for right-censored survival data.

The relative performance of TTNO models using different probability distributions and k-values is compared using a concordance index. The concordance index is used in a similar manner as the coefficient of determination R2, used in linear regression, however, the concordance index accounts for the right-censored data in survival analysis. Brentnall and Cuzick [26] review concordance indices for right-censored data and proportional hazards models. The concordance index measures how well a biomarker, or in our case k predicts the time to an event, deceased donor organ offer.

Another important consideration is ensuring equity in model performance, where they perform well for all people. Top-line accuracy metrics are validated for many subgroups across blood type, level of immune sensitization (CPRA), and level of donor-candidate genetic compatibility (HLA mismatch), among other factors.

Although performance metrics (e.g., concordance index) are important to selecting the optimal model, these metrics do not answer the question: Is this model potentially useful in practice? This requires assessing how a model informed strategy compares to current practice. Known as a net benefit analysis [27], we compare the ability of the proposed model to an approximation of current practice (rejecting all organ offers in hopes of obtaining a better one) and hypothetical strategy of always accepting the current organ offer. While the accepting all offers is illustrative, we argue rejecting all organ offers is an acceptable comparator because, in practice, less than one percent of all organ offers are accepted.

## III. Results

The best fit TTNO accelerated failure time model used a loglogistic distribution and model variables shown in Table I. The loglogistic distribution achieved a concordance index as high as 0.710. The next best fitting distribution was the Weibull with a concordance index as high as 0.660. The exponential distribution is a special case of the Weibull, yet had a concordance index well below 0.600, as did the lognormal. The TTNO model is given as,

$$\mathrm{O} = f(\mathrm{N}, \mathrm{H}, \Delta, \mathrm{B}, \mathrm{X}, \mathrm{E}, \mathrm{T}, \Gamma) \tag{4}$$

TABLE I
TTNO MODEL FACTORS

| Variable Name | Variable Description | Data Type |
|---|---|---|
| N | Sequence number, converted to bins | Factor (11 levels) |
| H | Number of HLA mismatches | Factor (6 levels) |
| Δ | Whole number of dialysis years at last offer | Integer |
| B | Simplified Blood Type | Factor (4 levels) |
| X | Candidate CPRA at match run, converted to bins | Factor (17 levels) |
| E | Candidate Expected Post-Transplant Survival | Float (0-1) |
| T | Candidate transplant center at match run | Factor (248 level) |
| Γ | Boolean flag indicating if data represents KAS250 allocation policy era | 0 (old era) or 1 (KAS250 era) |

TABLE II
WAITLIST MORTALITY MODEL FACTORS

| Variable Name | Variable Description | Data Type |
|---|---|---|
| $\alpha$ | Candidate Age in decades | Integer |
| $\kappa$ | Kidney-only transplant type | Integer |
| $\psi$ | Kidney-pancreas transplant type | Integer |
| $\delta$ | Whether candidate is diabetic | Integer |
| $\omega$ | Whether candidate was on dialysis at waitlisting | Float |
| $\rho$ | End stage renal disease | Float |
| $\beta$ | Candidate BMI | Float |
| $\mu$ | 1 if candidate BMI is missing; 0 otherwise | Integer |
| $\phi$ | 1 if candidate is polycystic; 0 otherwise | Integer |
| $\tau$ | 1 if candidate has had a previous transplant; 0 otherwise | Integer |
| $\lambda$ | Year candidate was placed on the waiting list | Integer |
| $\chi$ | Candidate Albumin level at waitlisting | Float |
| $\theta$ | Albumin slope change | Float |
| $\pi$ | Log of the number of years candidate had been on dialysis at waitlisting | Float |
| $\xi$ | CPRA at waitlisting, divided into bins | Factor (3 levels) |

CS residuals plot cumulative hazard over time for all predictive factors. For expository purpose, Figs. 1-4 show different blood types A, B, O, AB, respectively. These plots are consistent with other predictive factors. The gray points indicate observed CS residuals. The blue line indicates the average cumulative hazard under the TTNO model with light blue shading depicting a 95% confidence interval. The red line indicates the average CS residual.

Ideal CS residuals should follow a diagonal 45-degree line. The TTNO model CS residuals follow this ideal pattern, demonstrating good fit, for the first 150-200 days, but exhibit a diminishing hazard for longer TTNO time estimates which is consistent across all plots. This observed bias and increased variance is likely due to leverage due to fewer data points at extreme TTNO estimates. A good example of this is the contrast between the rarest blood type, AB, in Fig. 4 with more common blood types A, B, and O.

This introduces an interesting question of practicality. Fig. 5 displays the waitlist mortality probability along the y-axis and the TTNO estimate along the x-axis, where the heat map indicates the volume of patients. The vast majority of patients have relatively high survival likelihood until next offer and TTNO under 250 days, where model fit is good. It is also possible that decision makers will be more discouraged by higher TTNO estimates and more likely accept the offer for any time greater than ~150 days and accuracy beyond this estimate is of little practical use.

The best fit waitlist mortality model follows a proportional hazards model with factors listed in Table II and given as,

$$\Psi = \alpha + \kappa\delta + \psi\delta + \omega + \rho\kappa\delta + \rho\psi\delta + \beta + \mu + \phi + \tau + \lambda + \chi + \theta + \pi + \alpha\kappa\delta + \alpha\psi\delta + \chi\psi\delta + \beta\kappa\delta + \xi\psi\delta \quad (5)$$

## IV. DISCUSSION

Decisions surrounding kidney transplant are complex and high pressure. Transplant decision makers must make the best decision for their patients. It is important to recognize, however, the optimism bias that exists in humans and the demonstrated ability of evidence-based medicine to improve outcomes. Providing decision makers reliable TTNO and mortality estimates have been shown to reduce, if not eliminate optimism bias, resulting in better decisions for the patient. The paper offers a viable TTNO model to deliver improved evidence-based decision for kidney transplantation. It is also important to recognize and respect organs from deceased donors, which are being discarded at alarming rates. Improving the speed and quality of decisions not only affects kidney patients but makes better utilization of the donated organs.

The proposed TTNO and mortality model provides a well-supported estimate to inform transplant decision makers. The model performs best for the first ~150 days, when refusals are most likely. This solution offers a responsible, human-in-the-loop, approach, where people are still make the life-and-death decisions, but informed by a mathematical model that can better aggregate at-scale supply-demand data and reduce the cognitive load and uncertainty in the present-day situation.

There are two scenarios for caution. One is that the model may predict very short TTNO for very sick patients. The other is that the model may predict patients survive too long. These scenarios, while they occur with very low likelihood, may discourage a decision maker from accepting an organ, when that may be in the best global interests. Ultimately, most offers occur within two years and very few offers are likely to fall within the danger zone.

There is also a potential for data drift due to allocation changes, improvements in dialysis, advances that increase patient survivability, and cultural shifts as more decision-makers adopt evidence-based practices. Potential revisions to regulations governing organ match lists and donation priorities will also affect underlying model data. It will be important that any implementation tune machine learning models periodically. For this reason, we have intentionally omitted model coefficients from the paper.

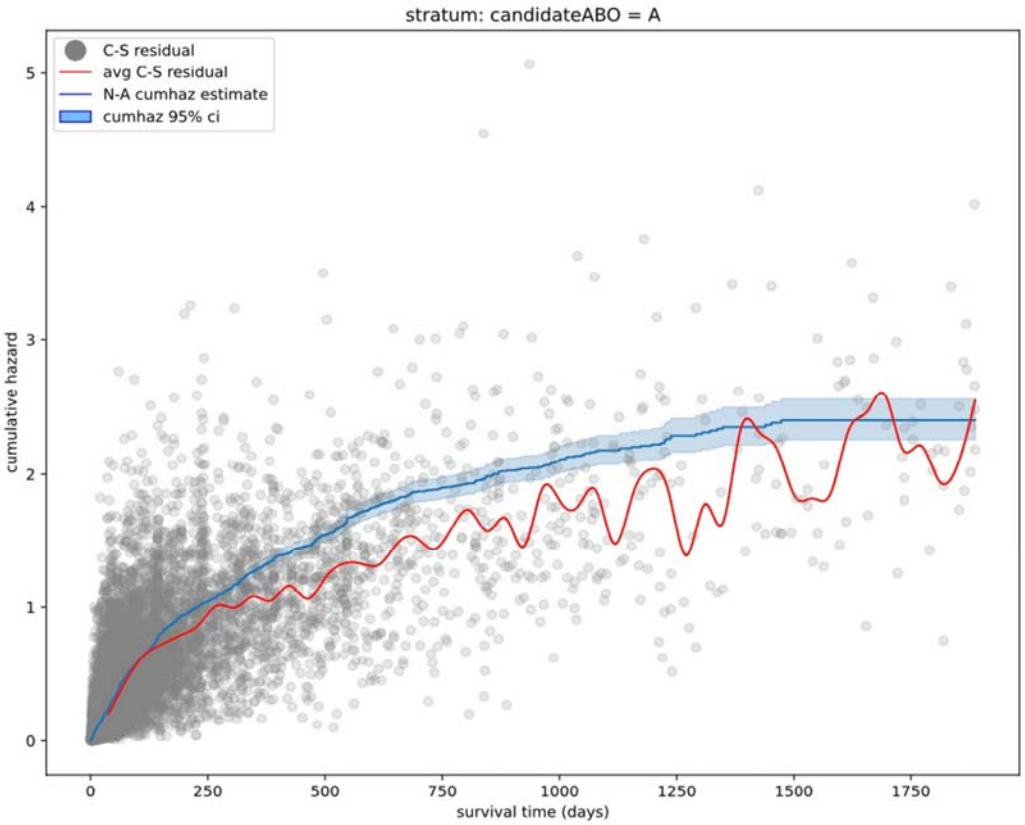


Fig. 1 TTNO CS Residual for A Blood Type

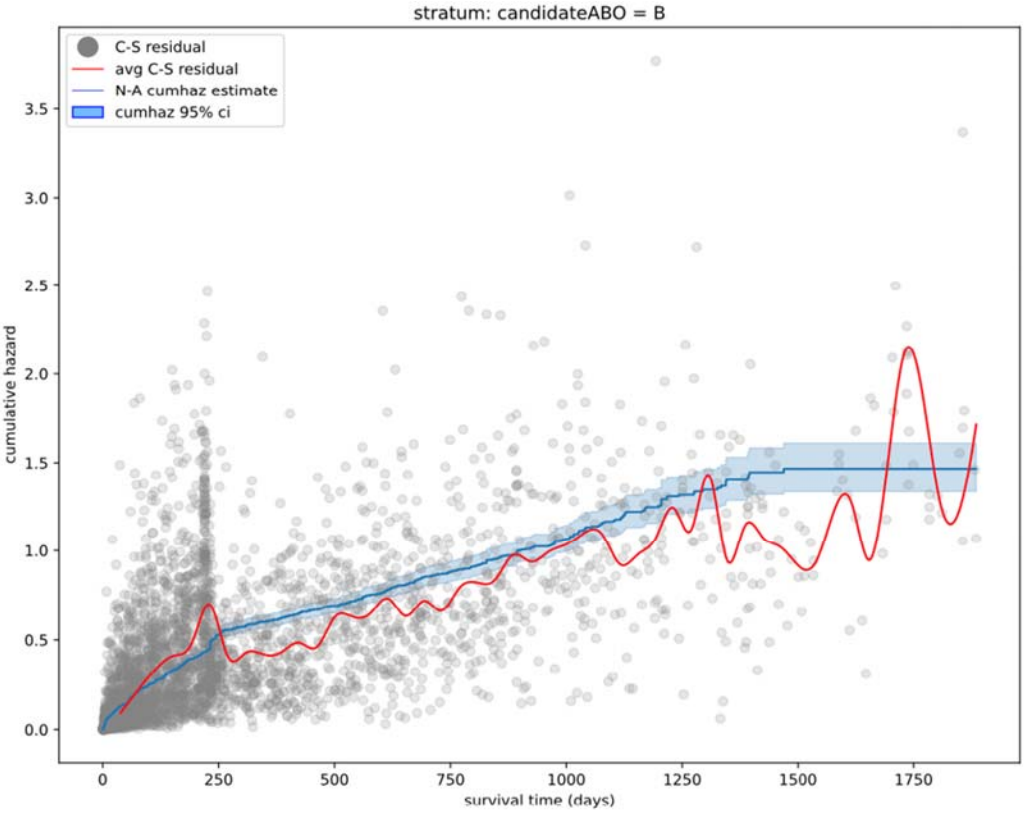


Fig. 2 TTNO CS Residual for B Blood Type

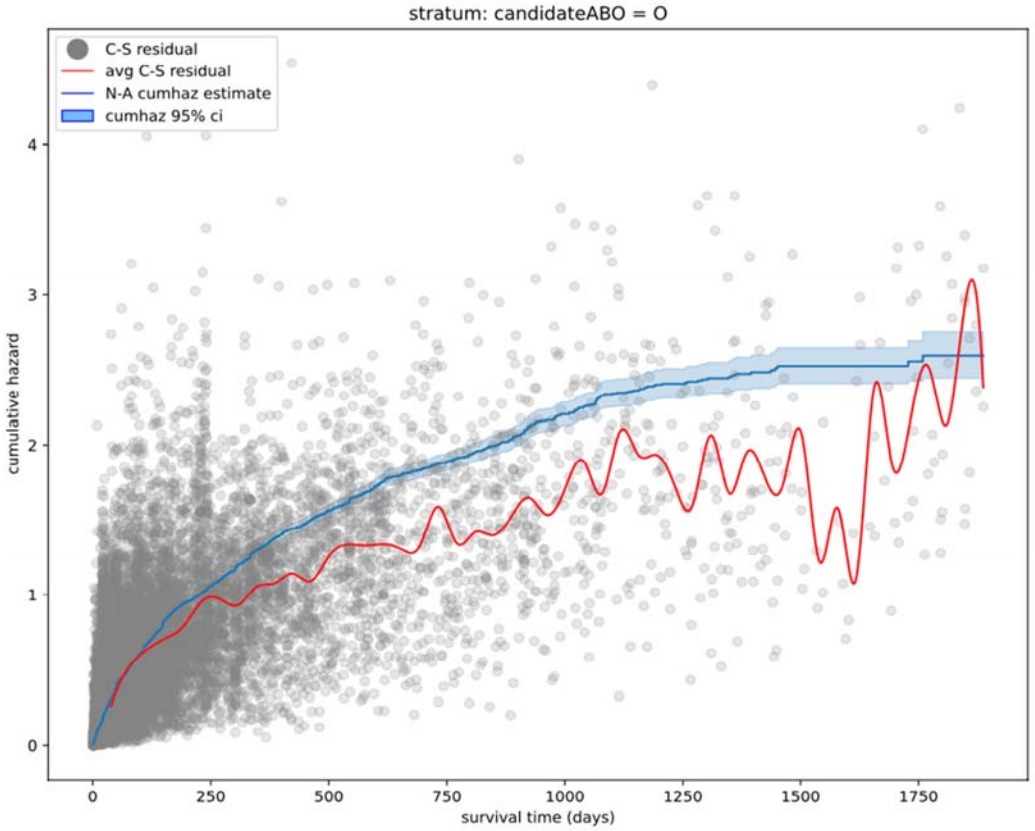


Fig. 3 TTNO CS Residual for O Blood Type

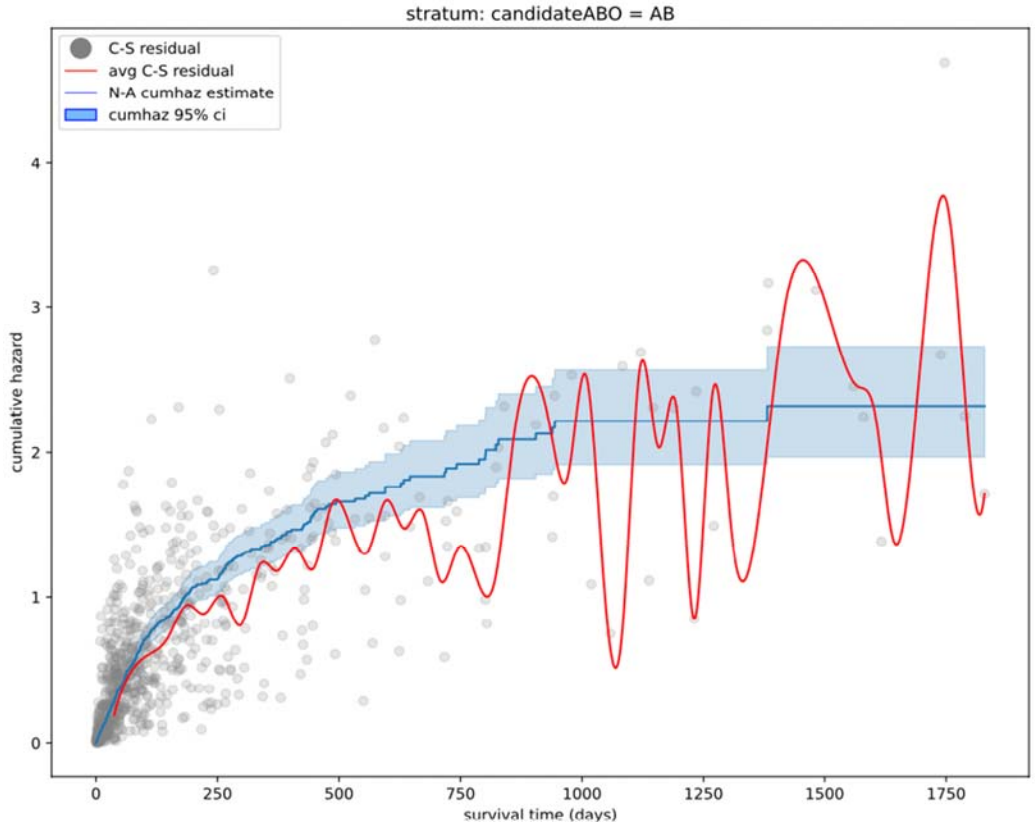


Fig. 4 TTNO CS Residual for AB Blood Type

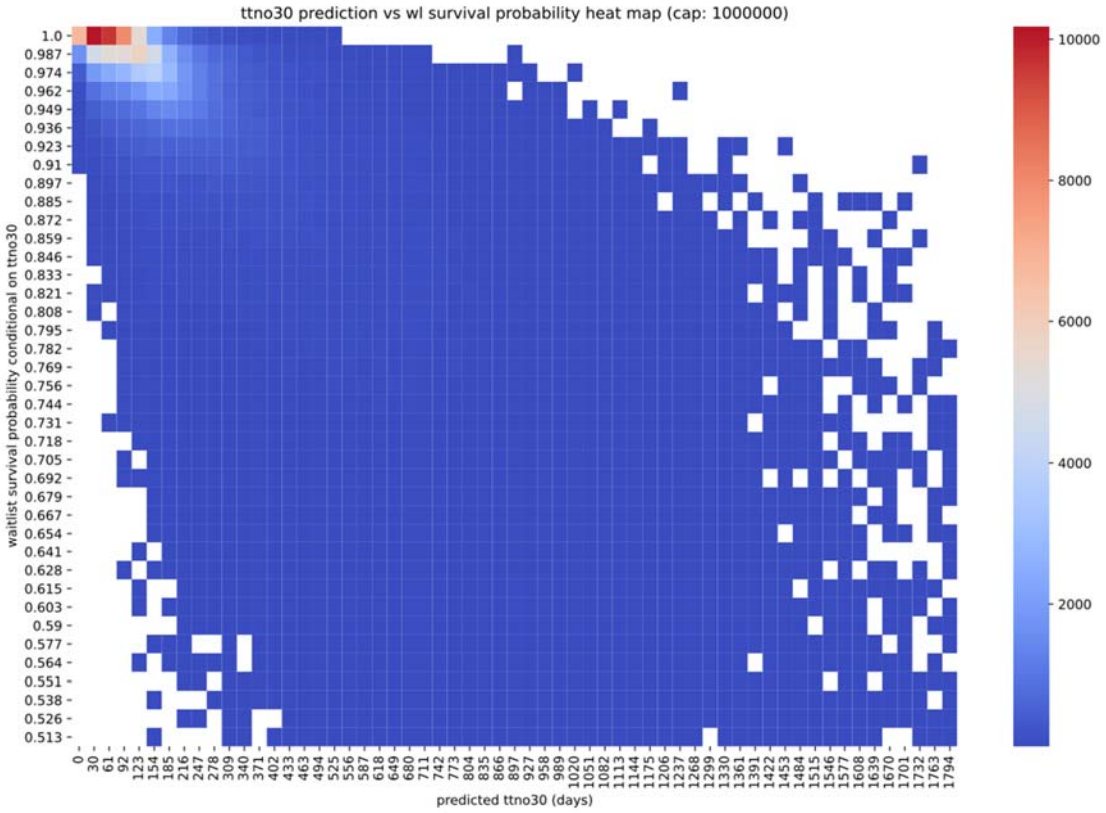


Fig. 5 TTNO Estimate vs Waitlist Survival Likelihood

Doctors make better decisions when equipped with estimates of waiting list mortality and TTNO. A pilot study implemented at six transplant centers across the OPTN demonstrated increased offer acceptance consistent with the behavioral study conducted by McCulloh et al. [9]. OPTN will implement the TTNO measure nation-wide in December 2022 which is likely to result in an additional 5,000 successful transplantations with the adoption of the proposed TTNO [28]. The proposed models indicate that they can improve upon current clinical practice.

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