Text around TRAC (kidney)

1. OVERVIEW

What is TRAC?

The Transplant Risk/benefit Assessment and Communication (TRAC) tool is an online personalised calculator that can help doctors and nurses communicate risk and benefit about transplantation to patients, and can help patients more easily understand the numbers and statistics presented to them in clinic.

It helps visualise possible outcomes for patients from the point of listing or point of transplant for deceased donor lung transplantation.

What does TRAC do?

TRAC is a communication tool designed to aid discussions between patients and clinicians. It will help clinicians and patients to visualise outcomes based on data for patients with similar characteristics in the past.

The calculator asks for some details about the patient and presents results in the form of graphs and tables and charts based on those details.

Who is TRAC for?

TRAC tool has been designed to be used by clinicians with patients and their families. It is a communication tool and should not be used by itself to make decisions.

Patients should use TRAC in consultation with a medical professional.

Data from adult (aged ≥18 years) patients only have been used to develop these tools, and they are not suitable for paediatric patients.

The data used to develop this site has been developed patients registered for deceased donor kidney transplants in the UK, or who have received a deceased donor kidney-only transplant in the UK so will not be suitable for patients from other countries. Patients registered on another organ transplant list (e.g. pancreas list) either before, during or after their kidney registration were also not included. The results from the TRAC tool will therefore not be suitable for those patients who fall outside these inclusion criteria.

Who built TRAC?

Development of the statistical models was undertaken by the NHS Blood and Transplant Statistics and Clinical Studies team.

The website has been built using a user centre design approach by the Winton Centre for Risk & Evidence Communication at the University of Cambridge who are funded by a generous donation from the David and Claudia Harding Foundation and the Winton Charitable Foundation.

2. TECHNICAL

2.1 Model development

The models behind the TRAC tool were developed using UK Transplant Registry (UKTR) data which is held by NHS Blood and Transplant (NHSBT). The UKTR database contains information on all patients who are listed for transplantation in the UK, and all patients who are transplanted with a solid organ transplant in the UK with follow-up data.

NHSBT Statisticians work closely with transplant clinicians to compile a large list of potential variables (e.g. age, primary renal disease) from the UK Transplant Registry to test in their models. Each of these variables are statistically tested and kept in the model if found to have an important relationship with the outcome of interest (e.g. post-transplant survival). These variables are referred to as 'risk factors'. Some of the models used by the TRAC tool are also used regularly by NHSBT in their organ specific annual reports (https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/) and in other analyses.

At the end of the modelling process values were obtained called 'parameter estimates' which quantify the estimated impact of each risk factor upon the outcome of interest. Please refer to the Mathematical Section (Section 3) to see exactly how a change in parameter estimates affects the outcome of interest. There will also be an estimated baseline risk curve plotted over time that represents an 'average' patient in the study cohort. The most common/mean value from the model development dataset for each risk factor is indicated as the baseline value as this value is represented by the baseline curve. The parameter estimates are then used by the TRAC tool to essentially shift this baseline curve when the values of the risk factors are changed from the 'average' values. This way, the patient can plot a curve for values of the risk factors that are relevant to their own circumstances. For all models, transplant centre was treated as a stratifying factor, i.e. a separate baseline curve was produced for each centre.

Although the TRAC tool is based on reputable models, it cannot say what the outcomes for a particular patient will be. It can only provide a summary of survival and waiting list outcomes for people in the past with similar characteristics.

This tool has been developed using retrospective registry data. Therefore, changes to the Kidney Offering Scheme in 2019 are NOT reflected in these models.

All statistical analyses for this website were generated using SAS Enterprise Guide software, Version 7.1. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

2.2 What might happen to me from time of listing?

The dataset used for this model comprised of all adult (aged ≥18 years) first kidney-only registrations (i.e. people joining the transplant waiting list) between 1 January 2010 and 31 December 2015.

From the point of joining the waiting list, receiving a transplant is one of three competing events (transplant, death on the list, removal from the list) that a patient is 'at risk' of.

We considered outcome data up to 5 years from listing for all patients in the modelling cohort. A model for 'time to transplant', a model for 'time to death on the list' and a model for 'time to removal from the list' was then developed using Cox Regression (Section 3.1).

Each patient in the cohort was assigned to 1 of 4 categories:

1) Patients who were transplanted with either a living or deceased donor transplant

2) Patients who died on the list whilst awaiting transplantation

3) Patients who were removed from the list prior to transplantation. This could occur for a number of reasons including patient choice or a deterioration in health such that a transplant was no longer suitable.

4) Patients who were still waiting on the list. Patients who were suspended were classed as still waiting on the list.

The covariates used in the model were those which have previously been shown to have an impact on outcome and those which were thought to be clinically significant.

Following development of the Cox Proportional hazards models, a numerical approximation algorithm was applied which combined the model results from the time to transplant model with the time to death on the list/removal from the list model (Section 3.2). This algorithm enabled the estimated chances of each of the listed outcomes at any particular time up to three years post-listing to be presented side-by-side and the sum of the probabilities of each of these happening at a particular time t to equal 100%.

2.3 Patient and graft survival after a deceased donor kidney transplant

The patient cohort for these models comprised all adult (aged ≥18 years) first kidney-only transplants that occurred in the UK between 1 January 2010 and 31 December 2017.

Cox proportional hazards models were built where the following 22 factors were tested for inclusion in the models:

Donor age, type, cause of death, sex, cmv status, hypertension, BMI, height, weight retrieval creatinine, recipient age, ethnicity, sex diabetic nephropathy as a cause of renal failure, waiting time, matchability, blood group, cold ischaemia time and HLA mismatch.

Factors tested were those collected by NHSBT and available on the database and thought to potentially be clinically relevant. The model was built using a forward-step approach. Transplant centre was added to the model as a strata.

The post-transplant survival proportional hazards model operates such that each risk factor multiplies the baseline cumulative hazard by a fixed amount known as the hazard ratio or relative risk - essentially the proportional change in mortality risk. This means the cumulative hazard is the product of two components: the baseline hazard (chances of death or graft failure for a patient with a baseline set of characteristics at time of transplant) and the hazard ratios for the risk factors (the increased/decreased risk of death due to changes in these risk factors compared to the baseline characteristics). The cumulative hazard is then translated in to a survival function as described in the mathematical description.

Five-year deceased donor post-transplant patient survival

Post-transplant patient survival was defined as the time from transplant until the time of death. These data were censored at the last known follow-up date post-transplant if this was within 5 years of transplantation.

The following factors were found to be significant and included in the model; recipient age, recipient ethnicity, waiting time, recipient primary renal disease, donor age, donor hypertension, HLA MM level.

The baseline characteristics and effect of each risk factor is shown in the table below:

Risk Factor	Factor level	Parameter estimate
Recipient Age (years)	18 - 29	-0.56443
	30 – 39	-0.0144
	40 – 49	Baseline
	50-59	0.60208
	60 – 69	1.18271
	70 +	1.62701

Recipient ethnicity	White	Baseline
	Non-white	-0.18166
Recipient waiting time (years)	<=1	-0.18491
	1 to <=3	Baseline
	3 to <=5	0.04909
	5 to <=7	0.32106
	>= 7	0.69479
Recipient primary renal disease - Diabetes	No	Baseline
	Yes	0.68609
Donor Age (years)	0 - 29	-0.50465
	30 – 39	0.15711
	40 – 49	-0.12827
	50-59	Baseline
	60 – 69	-0.01357
	70 +	0.09648
HLA MM level	1 (000)	Baseline
	2 (100, 010, 110, 200, 210, 001,101, 201)	0.29717
	3 (020, 120, 220, 011, 111, 211)	0.39373
	4 ((021, 121, 221, 002, 102, 202, 012, 112, 212, 022, 122, 222)	0.26281
Donor Hypertension	No	Baseline
	Yes	0.28452

This model was tested for goodness of fit using a concordance statistic (c-statistic) which was found to be 0.71.

Five-year deceased donor post-transplant graft survival

'Graft survival' refers to death-censored graft survival and was defined as the time from transplantation to return to long-term kidney replacement therapy or re-transplantation, whichever occurred first. Data were censored at the time of death or at last known follow-up.

The following factors were found to be significant and included in the model; recipient age, waiting time, graft number, recipient primary renal disease, donor age, donor BMI, donor hypertension, HLA MM level.

The baseline characteristics and effect of each risk factor is shown in the table below:

Risk Factor	**Factor level**	**Parameter estimate**
Recipient age (years)	18 - 29	0.84483
	30 – 39	0.29385
	40 – 49	Baseline
	50-59	-0.07373
	60 – 69	-0.14067
	70 +	-0.10022
Recipient waiting time (years)	<=1	Baseline
	1 to <=3	0.21323
	3 to <=5	0.31039
	5 to <=7	0.45953
	>= 7	0.83033
Recipient graft number	First kidney transplant	Baseline
	Re-graft	0.22099
Recipient primary renal disease - Diabetes	No	-0.3411
	Yes	Baseline
Donor Age (years)	0 - 29	-0.52485
	30 – 39	-0.31482
	40 – 49	-0.17204
	50-59	Baseline
	60 – 69	0.42198
	70 +	0.5792
Donor BMI	<25	-0.04701
	25 to <=30	Baseline
	> 30	0.0478
Donor Hypertension	No	-0.2105
	Yes	Baseline
HLA mismatch level	1 (000)	Baseline
	2 (100, 010, 110, 200, 210, 001,101, 201)	-0.00426

	3 (020, 120, 220, 011, 111, 211)	0.17315
	4 ((021, 121, 221, 002, 102, 202, 012, 112, 212, 022, 122, 222)	0.25438

This model was tested for goodness of fit using a concordance statistic (c-statistic) which was found to be 0.63.

2.4 Patient and graft survival after a living donor kidney transplant

The patient cohort for these models comprised all adult (aged ≥18 years) first kidney-only transplants that occurred in the UK between 1 January 2010 and 31 December 2015.

Cox proportional hazards models were built where the following 17 factors were tested for inclusion in the models -

Donor factors: age, sex, relationship to recipient, BMI, ethnicity, status, hypertension, BMI, height, weight retrieval creatinine

Recipient factors: age, sex, ethnicity, diabetic nephropathy as a cause of renal failure, waiting time, dialysis status, matchability, blood group, cold ischaemia time, HLA mismatch and graft number.

Factors tested were those collected by NHSBT and available on the database and thought to potentially be clinically relevant. The model was built using a forward-step approach. Due to fewer numbers, the transplant centre was not included as a strata and national results have been demonstrated.

Five-year living donor post-transplant patient survival

Post-transplant patient survival was defined as the time from transplant until the time of death. These data were censored at the last known follow-up date post-transplant if this was within 5 years of transplantation.

The following factors were found to be significant and included in the model; recipient age, waiting time and HLA MM level.

The baseline characteristics and effect of each risk factor is shown in the table below:

Risk Factor	Factor level	Parameter estimate
Recipient age (years)	18 - 29	-0.9248
	30 – 39	-0.74681
	40 – 49	Baseline
	50-59	0.25157

	60 +	1.11962
Recipient waiting time (months)	<=6	Baseline
	6 to <=12	0.19494
	12 to <=24	0.35923
	>= 24	0.72515
Recipient primary renal disease - Diabetes	No	Baseline
	Yes	0.63358
HLA mismatch level	1 (000)	0.20284
	2 (100, 010, 110, 200, 210, 001,101, 201)	0.07945
	3 (020, 120, 220, 011, 111, 211)	Baseline
	4 ((021, 121, 221, 002, 102, 202, 012, 112, 212, 022, 122, 222)	-0.31232

Five-year living donor post-transplant graft survival

'Graft survival' refers to death-censored graft survival and was defined as the time from transplantation to return to long-term kidney replacement therapy or re-transplantation, whichever occurred first. Data were censored at the time of death or at last known follow-up.

The following factors were found to be significant and included in the model; recipient age, waiting time, matchability, donor age, HLA MM level.

The baseline characteristics and effect of each risk factor is shown in the table below:

Risk Factor	**Factor level**	**Parameter estimate**
Recipient age (years)	18 - 29	0.59926
	30 – 39	0.05547
	40 – 49	Baseline
	50-59	-0.22508
	60 +	-0.593
Recipient waiting time (months)	<=6	Baseline
	6 to <=12	-0.27936
	12 to <=24	-0.56228
	>= 24	0.12898
Matchability	Easy	-0.12951

	Moderate	-0.30066
	Difficult	Baseline
Donor age (years)	0 - 29	-0.20838
	30 - 39	-0.34797
	40 - 49	Baseline
	50 - 59	-0.16584
	60 +	0.26716
HLA mismatch level	1 (000)	-0.48192
	2 (100, 010, 110, 200, 210, 001,101, 201)	-0.38607
	3 (020, 120, 220, 011, 111, 211)	Baseline
	4 ((021, 121, 221, 002, 102, 202, 012, 112, 212, 022, 122, 222)	-0.18314

2.5 Input covariates

Explanation of donor and recipient input covariates:

Recipient age (years) - Age at point of being actively listed onto the National Kidney Transplant List**.** This has been divided into categories by decade.

Sex - Male or female. Note this refers to sex, not gender**.**

Recipient ethnicity – White or non-white.

Recipient waiting time (years) – Time waiting on deceased donor kidney waiting list until time of transplant (active and suspended). This can serve as a proxy for 'time on dialysis' as most patients are either already on dialysis or due to commence dialysis within 6 months at the time of listing for transplantation.

Graft number - If the patient has had any previous kidney transplants.

Primary renal disease - diabetes - Whether diabetes is the cause of renal disease of not. This does NOT mean 'is the patient diabetic?'

Highly sensitised (cRF >85%) - any antibodies in the blood – e.g. as a result of pregnancy or a previous organ transplant.

Blood group – Patient's blood group: O, A, B, AB

Dialysis at registration – Refers to any form of dialysis (peritoneal or haemodialysis) at the time of listing for transplantation.

Matchability - Whether due to a range of factors, such as blood group, it will be 'easy', 'moderate', or 'difficult' to find a matching organ. The ODT provides further details on how

this is calculated and a tool for calculating matchability for individual patients: https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/calculators/

Donor age – The age at which the donor donated their organs.

Donor BMI – Donor BMI as recorded at the donating hospital site. Calculated as weight (kilograms) divided by height (m^2)

Donor Hypertension – Whether the donor suffered from high blood pressure as recorded by NHSBT on data collection forms at the time of listing.

HLA MM level – Human Leukocyte Antigen (HLA) matching level. HLA are proteins located on the surface of white blood cells and other tissues. When people share the same HLA's, they are said to be a 'match'. There are may different types of HLA, and the matching can occur to different degrees, hence the different levels of matching.

Centre - This refers to which of the 23 UK adult kidney transplant centres the patient will be receiving their transplant. (This is not always the dialysis centre at which they are followed up).

3. MATHEMATICAL SECTION

3.1 Cox proportional hazards model

The Cox proportional hazards model operates such that each risk factor multiplies the baseline cumulative hazard by a fixed amount known as the hazard ratio or relative risk - essentially the proportional change in the risk of the event occurring.

Using the example of post-transplant survival, this means that the cumulative hazard of post-transplant death is the product of two components: the baseline hazard (chances of dying for a patient with a baseline set of characteristics at time of transplant) and the hazard ratios for the risk factors (the increased/decreased risk of death due to changes in these risk factors compared to the baseline characteristics).

In the case of post-transplant survival, the cumulative hazard is then translated into a survival function which is what the TRAC tool presents. This is described in mathematical form below. In the case of the 'What might happen to me from time of listing?' models, the cumulative hazard is further manipulated.

The estimated cumulative hazard for the ith individual for the event of interest (e.g. death post-transplant), after t days has the form:

$$H_i(t) = \exp(\beta' x_i) H_0(t)$$

where:

- $H_0(t)$ is estimated using the Breslow (1972) estimate
- β is estimated by constructing a partial likelihood function, independent of $H_0(t)$, which is maximised with respect to the parameters in β.

- x_i represents the set of characteristics for the i[th] individual.

This can be translated into a survival function through the following equation:

$$S_i(t) = \exp(-H_i(t))$$

The phreg function in SAS V.7.1 (SAS Institute, Cary, North Carolina, USA) was used to compute these estimates.

3.2 Numerical Approximation Algorithm for Cause-Specific Cox Proportional Hazards Models

When using Cause-Specific Cox proportional hazards models for competing risks (time to transplant, time to death on the list/removal from the list), the following algorithm was applied to the resulting model output in order to adjust for the associated informative censoring bias.

The estimated cumulative hazard for the i[th] individual for competing risk j (e.g. transplant), after *t* days has the form:

$$H_{ji}(t) = \exp(\beta_j' x_i) H_{j0}(t)$$

$h_{ji}(t)$ is then the instantaneous hazard at time t, i.e. the risk of leaving the list with cause j, given the patient is still on the list at time t.

Assuming independent causes of leaving the list, the probability of still being on the list at time t is

$$S_i(t) = exp\left[-\sum_j H_{ji}(t)\right]$$

The TRAC tool displays this probability that an individual i will still be on the list at time t, $S_i(t)$, as well as the probability that an individual will leave the list by time t due to each cause j, $F_{ji}(t)$. These latter probabilities are represented by the following equation:

$$F_{ji}(t) = \int h_{ji}(t) S_i(t) dt$$

However, as this is not available in closed form, the following numerical approximation algorithm is used by the TRAC tool to estimate and present each $F_{ji}(t)$:

- Set $S_i(1) = 0$ and each $F_{ji}(1) = 0$. Where j=1 (transplant), j=2 (removal from the list), j=3 (death on the list).
- Run through the following steps for time t=1,2,…
    - Assuming a patient is still on the list at the start of day t, estimate the probability of a loss of type j as $h_{ji}(t) = H_{ji}(t+1) - H_{ji}(t)$
    - Calculate $p_{ji}(t) = h_{ji}(t) S_i(t)$ as the probability of leaving the list with cause j at time t.

- Then the cumulative probability of leaving the list by time t+1 due to cause j will be $F_{ji}(t+1) = F_{ji}(t) + p_{ji}(t)$
- Set $S_i(t+1) = S_i(t) - \sum_j p_{ji}(t)$

- For any time point t, the sum of $S_i(t)$, $F_{1i}(t)$ and $F_{2i}(t)$ will equal 1.

4. MODEL VALIDATION

The models once developed will undergo statistical validation tests. The post transplant outcome models have been developed on 70% of the dataset and tested on the remaining 30% using a risk sore method. In addition, factors have been checked for proportionality, and residuals have been assessed. The 'predictive ability' of the models will also be ascertained using various statistical methods.

5. FUTURE VERSIONS

The parameter estimates will be updated annually as we re-run the models on a more recent time period. The risk factors included in the model will be updated every 3-5 years as we re-test potential risk factors in the models.

6. LEGAL DISCLAIMER

TRAC uses statistical model based on information from many thousands of patients on the UK transplant registry. However, it can only provide a 'best guess' of likely outcomes based on past data, and it can never provide an accurate prediction for an individual. Patients should always consult their own specialist, who will be able to discuss the results in a more personalised context.

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References