Text around TRAC (lung)

1. OVERVIEW

1.1 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.

1.2 What does TRAC do?

This 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.

Currently the results presented for lung patients are: waiting time (from the point of listing) and chance of getting a transplant whilst acknowledging the risk of death on the list or removal from the list, also survival of the individual after receiving a transplant.

To create the results presented, data about patients in the past were used to build statistical models. When you enter details into TRAC, the calculator looks at these models and extracts results based on what happened to people “like this”.

1.3 Who is TRAC for?

The 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.

Only adult (aged ≥16 years) patients have been used to the develop the tool; it is not suitable for paediatric patients due to the small number of patients involved which would not generate robust models. Patients who were not eligible for National Health Service (NHS) treatment and adult patients registered (for clinical reasons) on a paediatric waiting list were not included. Patients registered on another organ transplant list (eg, kidney list) either before, during or after their lung registration were also not included. The results from the TRAC tool will therefore not be suitable for patients from outside the UK or for those patients who fall outside these inclusion criteria.

This tool has been developed using retrospective registry data (Section 2.2). Changes to the UK Lung Offering Scheme in May 2017 are not reflected in these models and hence results presented will not be meaningful for patients registered on the Urgent or Super-Urgent Lung Offering Scheme.

1.4 Who built TRAC?

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

The website has been built 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.

1.5 Contact

statistical.enquiries@nhsbt.nhs.uk

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 worked closely with transplant clinicians to compile a large list of potential variables (e.g. age, disease group) from the UKTR to test in the 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. survival after transplant). These variables are referred to as 'risk factors'.

At the end of the modelling process, values are 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 curve which represents an 'average' patient in the study cohort. This curve when plotted over time represents the estimated chances of survival (for the example of survival after transplant) for a patient in the model development dataset with the mean/most common value of all the risk factors in the model. The parameter estimates are then used by the TRAC tool to shift this baseline curve when the values of the risk factors are changed from the mean/most common values. This way,

TRAC users can select values of each risk factor that best represent their own characteristics and view model results for patients 'like me'. For all models, transplant centre was treated as a stratifying factor, i.e. a separate baseline curve was produced for each centre, in order to represent different practice at each centre. Details of the modelling development can be found in Kourliouros et al (2019).

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.

Patient primary disease is recorded on the UKTR and the following groupings were used for the analysis: COPD (encompassing alpha-1-antitrypsin deficiency and emphysema), cystic fibrosis (CF, also encompassing patients with bronchitectasis) and pulmonary fibrosis (PF, encompassing all fibrotic lung diseases). All other lung diseases were grouped under the category 'other'.

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2.2 Datasets used

All data used to develop the lung models behind the TRAC tool were obtained from the UKTR held by NHSBT as of 14 May 2016. The patient cohort comprised all adult (aged ≥16 years) first lung-only registrations (i.e. people joining the transplant waiting list) between 1 January 2004 and 31 March 2014. Patients who met any of the following exclusion criteria were not studied: patients registered for a heart-lung block or other multiorgan transplant; patients registered on another organ transplant list (eg, kidney list) either before, during or after their lung registration; patients registered outside the UK or not entitled to 'National Health Service (NHS) treatment and adult patients registered (for clinical reasons) on paediatric lists.

This dataset was used to build the 'what might happen to me from point of transplant' models. In order to build the 'survival after transplant' model, we used the subset of patients from this dataset who had been transplanted as at time of data extraction (14 May 2016).

2.3 What might happen to me from time of listing?

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'. 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). Because the event of transplant would prevent the event of death on the list/removal from the list from happening, and vice-versa, these Cox Regression models were cause-specific Cox proportional hazard models. When modelling time to transplant, for example, a patient who died on the list at time t would be 'censored' at time t and still considered in the time to transplant modelling cohort

but whose time of transplant was 'unknown'. When modelling time to death on the list/removal from the list, the same patient data would be used but there would be no censoring and instead the patient would experience the event of interest at time t.

For the purposes of the TRAC tool, the death on the list data has been combined with removal from the list as 1) there were few removals and 2) for lung patients, removal from the list is often sadly due to a deterioration in the patient's condition. We also made further changes to these models by 1) capping outcome data up to 3 years from listing for all patients in the modelling cohort and 2) removing any risk factors that were no longer statistically significant in both the time to transplant model and the time to death on the list/removal from the list model ($p>0.05$) and 3) turning all continuous variables into categorical variables. This resulted in two models, one for time to transplant and one for time to death on the list/removal from the list.

However, to adjust for the fact that the cause-specific Cox proportional hazards model patient-specific estimates would be biased (because once a patient experienced one of the competing events at time t, they would no longer be eligible for any other event), 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 following 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%:

1) Transplant
2) Death on the list or removal from the list
3) Alive and still waiting on the list

The parameter estimates for each of the risk factors in the time to transplant model and the time to death on the list/removal from the list model are shown below. The most common 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. Although the two models were developed separately, any risk factor that was found to be significantly influential for one model was retained in the other model in order to keep the same risk factors in all models (although parameter estimates would be different). Transplant centre was treated as a stratifying factor, i.e. a separate baseline curve was produced for each centre.

		Time to Transplant	**Time to Death on list/Removal**
Risk Factor	**Level**	**Parameter estimate**	**Parameter estimate**
Sex	Male	Baseline	Baseline
	Female	-0.38678	-0.53792
Disease group	CF	-0.27915	0.74608
	Other	-0.49067	0.45214
	PF	-0.40466	1.00088
	COPD	Baseline	Baseline

Daily dose of prednisolone at registration	0	Baseline	Baseline
	1-14	-0.12438	0.22476
	>=15	-0.06195	0.44636
In hospital at registration	No	Baseline	Baseline
	Yes	0.22507	0.85886
NYHA class at registration	I	0.23597	0.06752
	II	0.23597	0.06752
	III	Baseline	Baseline
	IV	-0.17597	0.72899
Age at registration	16-29	-0.09551	-0.43455
	30-39	-0.03777	-0.3855
	40-49	-0.01883	-0.4963
	50-59	Baseline	Baseline
	60+	0.13814	-0.12119
BMI at registration	<20	0.07151	0.17363
	20-24.9	Baseline	Baseline
	25+	0.02804	-0.20066
FVC at registration	<1.2	-0.42216	0.71482
	1.2-1.9	-0.22505	0.39432
	2-3.9	Baseline	Baseline
	4+	-0.11767	0.10000
Previous thoracotomy	No	Baseline	Baseline
	Yes	-0.51580	-0.03420
Blood group	O	Baseline	Baseline
	A	0.62671	0.09077
	B	0.08311	0.09386
	AB	0.84437	-0.02572

2.4 Patient survival after transplant

Post-transplant 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 or if the patient died after 5 years of transplantation. The model used was taken from the NHSBT Annual Report on Cardiothoracic Organ Transplantation (https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/). For a more detailed description of the model when applied to the cohort used

in the TRAC tool see Kourliouros et al (2019). However, for the purposes of the TRAC tool we decided to turn all continuous variables into categorical variables.

The parameter estimates for each of the risk factors in the post-transplant survival model are shown below. The most common 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. Transplant centre was treated as a stratifying factor, i.e. a separate baseline curve was produced for each centre.

Factor	Level	Parameter estimate
Donor CMV	Negative	Baseline
	Positive	0.29226
Donor history of smoking	No	Baseline
	Yes	0.24582
Recipient daily dose of prednisolone at registration	0	Baseline
	<15	0.27341
	>=15	0.48876
Transplant type	Single lung	0.04977
	Bilateral lung	Baseline
Disease Group	CF	-0.40421
	Other	0.20102
	PF	0.04841
	COPD	Baseline
Recipient age at transplant	16-29	0.24259
	30-39	-0.05644
	40-49	-0.05089
	50-59	Baseline
	60+	0.22292
Donor:recipient calculated TLC mismatch	<-1	-0.15398
	-1-0.99	Baseline
	1+	-0.00718
Recipient FVC at registration	<1.2	0.10249
	1.2-1.9	-0.01281
	2-3.9	Baseline
	4+	-0.26149
Recipient bilirubin at registration	<5	0.10959
	5-9.9	Baseline

	10-19.9	0.09579
	20+	0.20564
Recipient cholesterol at registration	<4	0.1342
	4-6.1	Baseline
	6.2-7.4	0.13093
	7.5+	-0.5613

3. MATHEMATICAL SECTION

3.1 Cox proportional hazards model

The Cox proportional hazard 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). 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 (Section 3.2).

The estimated cumulative hazard for the i^{th} 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 9.4 (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 (death on the list/removal from 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 used by the TRAC tool did not undergo statistical validation but are based on existing published models (Kourliouros et al 2019, Annual Report on Cardiothoracic Transplantation 2019/2020.).

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 models developed using patient data recorded 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.

7. Privacy

8. Cookie policy

9. References

Annual Report on Cardiothoracic Transplantation 2019/2020. NHS Blood and Transplant. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/19874/nhsbt-annual-report-on-cardiothoracic-organ-transplantation-201920.pdf. Published 2020. Accessed 01/03/2021

Kourliouros A, Hogg R, Mehew J, et al. Patient outcomes from time of listing for lung transplantation in the UK: are there disease-specific differences? Thorax 2019;74:60-68.

Breslow, N. E. (1972), “Discussion of Professor Cox’s Paper,” J. Royal Stat. Soc. B, 34, 216–217.

10. Explanation of data items required for input by TRAC user:

10.1 Patient factors at time of registration

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

Blood group - O, A, B or AB

Lung primary disease group

Cystic Fibrosis (CF): Patients registered on to the lung waiting list with Primary Disease recorded as either 'Cystic Fibrosis' or 'Bronchitectasis'

Pulmonary fibrosis (PF): Patients registered on to the lung waiting list with Primary Disease recorded as 'Fibrosing Lung Disease'

Chronic obstructive pulmonary disease (COPD): Patients registered on to the lung waiting list with Primary Disease recorded as either 'alpha-1-antitrypsin deficiency' or 'emphysema'

Other: Patients registered on to the lung waiting list with Primary Disease not listed under any of the above categories.

Previous thoracotomy - Has the patient (at time of registration) undergone any previous thoracotomy procedures (yes/no)?

In hospital at registration - Is the patient in hospital at the time of registration (yes/no)?

Age at registration - Age at time of registration onto the lung transplant waiting list in complete years (e.g. 51 years and 9 months recorded as 51 years)

BMI at registration - Patient Body Mass Index at time of registration calculated as (weight (kg))/〖height(m)〗^2

NYHA Class at registration

New York Heart Association Classification (NYHA) Class defined as:

Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.

Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.

Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Daily dose of prednisolone at registration

Recorded in mg and categorised as follows:

0 (no dosage administered)

<15: dose administered but less than 15mg

≥15mg: dose administered greater or equal to 15mg

Forced vital capacity (FVC) at registration - Lung function as Forced Vital Capacity recorded in litres

Recipient bilirubin at registration - Measured in µmol/l

Recipient cholesterol at registration - Measured in mmol/l

Centre - This refers to which of the 5 UK adult lung transplant centres the patient will be receiving their transplant.

10.2 Factors at time of transplant

Patient age at transplant - Age in complete years (e.g. 51 years and 9 months recorded as 51 years)

Transplant type - Single or bilateral lung transplant received

Donor to recipient (patient) calculated Total Lung Capacity (TLC) mismatch

Mismatch = recipient calculated TLC – donor calculated TLC

Where calculated TLC is:

If male, TLC = 7.99*(height(cm)/100) - 7.08

If female, TLC = 6.6*(height(cm)/100) -5.79

Donor CMV status - Is donor Cytomegalovirus positive or negative

Donor smoking status - Is the donor a current or past cigarette smoker (yes/no)?