**About the TRAC tool**

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**How it works**

The estimates that the TRAC tool produces are derived from models developed by NHS Blood and Transplant (NHSBT) statisticians. Statisticians work closely with transplant clinicians to compile a large list of potential variables from the UK Transplant Registry to test in their models. Each of these variables are 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 we obtain values which we call ‘parameter estimates’ which quantify the estimated impact of each risk factor upon the outcome of interest. There will be an estimated baseline risk curve plotted over time that represents an ‘average’ patient in the study cohort. 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.

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.

The technical section has more detail on how the TRAC tool was developed.

**The technical section**

The TRAC tool is an online tool designed to help clinicians and patients make informed decisions surrounding listing for transplantation and to visualise how outcomes for patients with similar characteristics in the past have looked.

The tool is easy to use: simply enter data for an individual patient on the following risk factors:

* Sex
* Ethnic group
* Blood group
* Lung primary disease group
* Previous thoracotomy
* In hospital at registration
* Age at registration
* BMI at registration
* Height at registration
* Transplant centre
* New York Heart Association (NYHA) Classification at registration
* Height at registration
* Daily dose of prednisolone at registration
* Forced vital capacity (FVC) at registration

Estimates for 1) survival from time of listing (irrespective of whether a transplant was received), 2) chance of transplant, 3) chance of death on the list and 4) chance of removal from the list are then presented from the time of listing, over time, in visual and text formats.

In order to obtain estimates for post-transplant survival, simply enter additional information on the following risk factors (please note that these include donor and transplant related risk factors):

* Donor CMV (Cytomegalovirus) status
* Donor smoking status
* Transplant type (single versus bilateral lung)
* Recipient age at transplant
* Donor to recipient calculated TLC (Total Lung Capacity) mismatch
* Recipient bilirubin at registration
* Recipient cholesterol at registration

Click here to find out more about the algorithms.

**The algorithms**

All models used by the TRAC tool were developed using data obtained from the UK Transplant Registry held by NHS Blood and Transplant (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. TRAC tool estimates will therefore not be applicable to patients who fall outside of these cohort criteria.

Primary disease is recorded on the NHSBT lung recipient registration form 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), pulmonary fibrosis (PF, encompassing all fibrotic lung diseases). All other lung diseases were grouped under the category ‘other’.

For all models, transplant centre was treated as a stratifying factor (i.e. a separate baseline risk curve was produced for each centre).

1. **Five year survival from listing**

Survival from registration was defined as the time from joining the transplant list until death, regardless of whether the patient received a transplant or not. These data were censored at one of the following time points: date of removal from the list if this occurred within 5 years of registration, the last known follow-up date post-transplant if this was within 5 years of registration or 5 years after registration if the patient was still waiting at this time (either on the active or suspended list). The model used was based on the model that is regularly used by NHSBT in their annual cardiothoracic report (<https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/>). Specifically, this was a Cox proportional hazards model, which included the following recipient risk factors: age, sex, ethnicity, blood group, body mass index (BMI), previous thoracotomy and in hospital at registration (yes/no).Unlike the annual cardiothoracic report model, era was not included as a factor (due to the requirement of the model to generalise estimates for any period of time) and transplant centre was treated as a stratifying factor (i.e. a separate baseline survival curve was produced for each centre) as opposed to a fixed or random effect. A centre and primary disease group interaction was also included.

Details of the mathematical form of this model are given in the [mathematical description](https://www.predict.nhs.uk/predict-mathematics.pdf).

The survival from listing 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 dying for a patient with a baseline set of characteristics at time of listing) 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](https://www.predict.nhs.uk/predict-mathematics.pdf). The baseline characteristics and effect of each risk factor is shown in the table below.

Parameter estimates for five-year survival from listing:

|  |  |  |
| --- | --- | --- |
| **Risk Factor** | **Factor level** | **Parameter estimate** |
| **Sex** | Male | 0.02381 |
|  | Female | 0 (baseline) |
|  |  |  |
| **Ethnic group** | White | -0.14127 |
|  | Non-white | 0 (baseline) |
|  |  |  |
| **Blood group** | O | -0.06262 |
|  | A | -0.09483 |
|  | B | -0.0026 |
|  | AB | 0 (baseline) |
|  |  |  |
| **Disease group** | CF | 0.44096 |
|  | Other | 0.51052 |
|  | PF | 0.6237 |
|  | COPD | 0 (baseline) |
|  |  |  |
| **Previous thoracotomy** | No | 0.08859 |
|  | Yes | 0 (baseline) |
|  |  |  |
| **In hospital at registration** | No | -0.71756 |
|  | Yes | 0 (baseline) |
|  |  |  |
| **Age at registration** | Per unit increase | 0.00282 |
|  |  |  |
| **BMI at registration** | Per unit increase | -0.01452 |
|  |  |  |
| **Interaction between centre and disease group** | CF and Papworth | -0.10414 |
| CF and Harefield | 0.00217 |
|  | CF and Birmingham | 0.01827 |
|  | CF and Manchester | -0.08704 |
|  | Other and Papworth | 0.07221 |
|  | Other and Harefield | -0.29172 |
|  | Other and Birmingham | -0.36563 |
|  | Other and Manchester | 0.07678 |
|  | PF and Papworth | 0.47684 |
|  | PF and Harefield | 0.38515 |
|  | PF and Birmingham | -0.2256 |
|  | PF and Manchester | 0.5759 |
|  | COPD and Papworth | 0 |
|  | COPD and Harefield | 0 |
|  | COPD and Birmingham | 0 |
|  | COPD and Manchester | 0 |

1. **Five-year post-transplant survival**

Post-transplant survival was defined as the time from transplant until the time of death. These data were censored at time of last follow-up where no death was reported. The model used was taken from the NHSBT annual cardiothoracic report ((<https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/>).  This was a Cox proportional hazards model, which included the following risk factors: donor cytomegalovirus status; donor history of smoking; recipient daily dose of prednisolone at registration; donor/recipient predicted Total lung capacity (TLC) mismatch between donor and recipient; recipient Forced Vital Capacity (FVC at registration; recipient bilirubin at registration; recipient cholesterol at registration; recipient age at transplant; ischaemia time (hours); transplant type (single vs bilateral transplant); primary disease group (CF, COPD, PF, other) and an interaction term between primary disease group and transplant type.

Recipient age was incorporated as a non-linear variable through the inclusion of natural cubic spline terms with ‘knots’ at the 5th, 35th, 65th and 95th percentile values of the observed range of recipient age.

Details of the mathematical form of this model are given in the [mathematical description](https://www.predict.nhs.uk/predict-mathematics.pdf).

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 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 in to a survival function as described in the[mathematical description](https://www.predict.nhs.uk/predict-mathematics.pdf). The baseline characteristics and effect of each risk factor is shown in the table below.

Parameter estimates for five-year post-transplant survival:

|  |  |  |
| --- | --- | --- |
| **Factor** | **Level** | **Parameter estimate** |
| **Donor CMV** | Negative | -0.27408 |
|  | Positive | 0 (baseline) |
|  |  |  |
| **Donor history of smoking** | No | -0.29989 |
|  | Yes | 0 (baseline) |
|  |  |  |
| **Recipient daily dose of prednisolone at registration** | 0 | -0.51788 |
| <15 | -0.31793 |
|  | >=15 | 0 (baseline) |
|  |  |  |
| **Transplant type** | Single lung | -0.04581 |
|  | Bilateral lung | 0 (baseline) |
|  |  |  |
| **Disease Group** | CF | -0.49712 |
|  | Other | 0.21874 |
|  | PF | -0.13768 |
|  | COPD | 0 (baseline) |
|  |  |  |
| **Recipient age at transplant (spline with knots at 22, 46, 56, 63)** | β1 | -0.04681 |
| β2 | 0.00152 |
| β3 | -0.00342 |
|  |  |  |
| **Donor:recipient calculated TLC mismatch** | unit increase | 0.12000 |
|  |  |  |
| **Recipient FVC at registration** | unit increase | -0.01838 |
|  |  |  |
| **Recipient bilirubin at registration** | unit increase | -0.0005104 |
|  |  |  |
| **Recipient cholesterol at registration** | unit increase | -0.33890 |
|  |  |  |
| **Interaction between transplant type and disease group** | Single lung and Other | -0.27878 |
| Single lung and PF | 0.34847 |
|  | Single lung and CF | 0 |
|  | Single lung and COPD | 0 |
|  | Bilateral lung and Other | 0 |
|  | Bilateral lung and PF | 0 |
|  | Bilateral lung and CF | 0 |
|  | Bilateral lung and COPD | 0 |

1. **Chance of transplant, death on the list and removal from the 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’ upon entering the lung transplant list. Therefore, a model for each of these outcomes was developed using Fine and Gray methodology (Fine and Gray, 1999). Details of the mathematical form of these models are given in the [mathematical description](https://www.predict.nhs.uk/predict-mathematics.pdf).

Each patient in the cohort was assigned to 1 of 4 categories: 1) transplanted, 2) died on the list, 3) removed from the list, 4) still waiting on the list, as at 14 May 2016. Patients who were suspended were classed as still waiting on the list. Three Fine and Gray regression models were developed which each produced a Cumulative Incidence Function (CIF), one for each of the three competing risks of interest.

The CIF is the product of two components: the baseline subdistribution hazard (representing the chances of risk event *k* occuring for an ‘average’ patient at time of listing) and the additional effects of risk factors (the increased/decreased risk of risk event *k* due to changes in these risk factors compared to the ’average’ patient).

The baseline characteristics and effect of each risk factor are shown in the table below. Note that if a parameter estimate is indicated as ‘NA’, the associated risk factor is not included in the model (as it was not found to be statistically significant).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Chance of transplant model** | **Chance of death on the list model** | **Chance of removal from the list model** |
| **Factor** | **Level** | **Parameter estimate** | **Parameter estimate** | **Parameter estimate** |
| Sex | Male | 0.09037 | 0.29382 | -0.23781 |
|  | Female (baseline) | 0 | 0 | 0 |
|  |  |  |  |  |
| Disease group | CF | -0.6157 | 1.2652 | NA |
|  | Other | -0.39355 | 1.06977 | NA |
|  | PF | -0.46493 | 1.53982 | NA |
|  | COPD (baseline) | 0 | 0 | NA |
|  |  |  |  |  |
| Daily dose of prednisolone at registration | 0 | NA | -0.4657 | NA |
|  | 1-14 | NA | -0.15045 | NA |
|  | >=15 (baseline) | NA | 0 | NA |
|  |  |  |  |  |
| In hospital at registration | No | NA | -0.68634 | NA |
|  | Yes (baseline) | NA | 0 | NA |
|  |  |  |  |  |
| NYHA class at registration | I | 0.49371 | -0.14598 | NA |
|  | II | 0.61964 | -0.60249 | NA |
|  | III | 0.38872 | -0.49059 | NA |
|  | IV (baseline) | 0 | 0 | NA |
|  |  |  |  |  |
| Ethnic group | White | NA | 0.30468 | NA |
|  | Non-white (baseline) | NA | 0 | NA |
|  |  |  |  |  |
| FVC at registration (spline with knots at 0.94, 1.63, 2.22, 3.55) | β1 | NA | -0.52418 | NA |
|  | β2 | NA | -0.49369 | NA |
|  | β3 | NA | 1.43224 | NA |
|  |  |  |  |  |
| Age at registration | unit increase | NA | NA | 0.02096 |
|  |  |  |  |  |
| Age at registration (spline with knots at 21, 44, 56, 63) | β1 | NA | -0.23800 | NA |
|  | β2 | NA | 0.00167 | NA |
|  | β3 | NA | -0.00612 | NA |
|  |  |  |  |  |
| BMI at registration | unit increase | NA | -0.04171 | NA |
|  |  |  |  |  |
| Height at registration | unit increase | 0.02549 | NA | NA |
|  |  |  |  |  |
| Bilirubin at registration | unit increase | NA | NA | -0.04270 |
|  |  |  |  |  |
| Previous thoracotomy | No | 0.47662 | NA | NA |
|  | Yes (baseline) | 0 | NA | NA |
|  |  |  |  |  |
| Blood group | O | -0.75435 | NA | NA |
|  | A | -0.24449 | NA | NA |
|  | B | -0.73069 | NA | NA |
|  | AB (baseline) | 0 | NA | NA |
|  |  |  |  |  |
| Interaction between centre and disease group | CF and Papworth | -0.13220 | NA | NA |
|  | CF and Harefield | 0.24719 | NA | NA |
|  | CF and Birmingham | -0.19162 | NA | NA |
|  | CF and Manchester | 0.35085 | NA | NA |
|  | CF and Newcastle | 0 | NA | NA |
|  | Other and Papworth | -0.30320 | NA | NA |
|  | Other and Harefield | -0.34429 | NA | NA |
|  | Other and Birmingham | -0.25284 | NA | NA |
|  | Other and Manchester | -0.26010 | NA | NA |
|  | Other and Newcastle | 0 | NA | NA |
|  | PF and Papworth | -0.45062 | NA | NA |
|  | PF and Harefield | -1.41890 | NA | NA |
|  | PF and Birmingham | -0.13796 | NA | NA |
|  | PF and Manchester | -0.08801 | NA | NA |
|  | PF and Newcastle | 0 | NA | NA |
|  | COPD and Papworth | 0 | NA | NA |
|  | COPD and Harefield | 0 | NA | NA |
|  | COPD and Birmingham | 0 | NA | NA |
|  | COPD and Manchester | 0 | NA | NA |
|  | COPD and Newcastle | 0 | NA | NA |

**Mathematical description**

1. **Cox proportional hazards models**

**(used for modelling a) survival from listing, b) post-transplant survival)**

The estimated cumulative hazard for the ith individual for mortality after being placed on the lung registration list, *t* days post-listing has the form:

where:

* is estimated using the Breslow (1972) estimate
* is estimated by constructing a partial likelihood function, independent of , which is maximised with respect to the parameters in .
* represents the set of characteristics for the ith individual.

This is translated into the survival functions presented in the TRAC tool through the following equation:

The phreg function in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) was used to compute these estimates. The same methodology applies to post-transplant survival.

1. **Fine-Gray competing risks models**

**(used for modelling c) chance of transplant, d) chance of death on the list, e) chance of removal from the list)**

The TRAC tool plots the Cumulative Incidence Function (CIF) for each of the three competing risks from time of listing. The CIF for ‘risk’ *k* (e.g. transplant) is written as *Ck(t)* and is linked to the subdistribution hazard in the following way:

David, is this equivalent to:

where *t* is the number of days post listing.

The Fine and Gray regression model (Fine and Gray, 1999) directly models the subdistribution hazard such that:

where:

* is estimated using the Breslow (1972) estimate
* is estimated using the Newton-Raphson algorithm to maximise the partial likelihood function for the parameters in .
* represents the set of characteristics for the ith individual.

The subdistribution hazard, , is the instantaneous risk of event *k* ocurring given that the patient has not yet experienced risk event k. Therefore importantly, patients that experience a risk event other than risk k (i.e. a competing risk event), are retained in the risk set for the calculation of , and hence , after this event. Weights are incorporated into the partial likelihood function such that patients who experience no event before time t are given a weight of 1, whereas patients who experience competing events before *t* are given a weight that reduces with time.

The phreg function in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) was used to compute these estimates.

**Description of risk factors – for the “ i’s”**

* Sex

Male or female

* Ethnic group

White or Non-White

* 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 in complete years (e.g. 51 years and 5 months recorded as 51 years)

* BMI at registration

Patient Body Mass Index at time of registration calculated as

* Height at registration

Height in cm

* Transplant centre
* NYHA Class

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

* Donor CMV status

Is donor Cytomegalovirus positive or negative

* Donor smoking status

Is the donor a current or past cigarette smoker (yes/no)?

* Transplant type

Single or bilateral lung transplant received

* Recipient age at transplant

Age in complete years (e.g. 51 years and 5 months recorded as 51 years)

* Donor to recipient calculated 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

* Recipient bilirubin at registration

Measured in µmol/l

## Recipient cholesterol at registration

Measured in mmol/l

**References**

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

Fine, J. P. and Gray, R. J. (1999), “A Proportional Hazards Model for the Subdistribution of a Competing Risk,” *Journal of the American Statistical Association*, 94, 496–509.

# Addendum

## Limits of parameters

**From:** Hogg Rachel   
**Sent:** 15 November 2018 11:52  
**To:** Mehew Jennifer  
**Subject:** RE: Winton centre work

Hi Jenny,

I’ve put the ranges for the continuous variables, along with the median and IQR (to give a feel of what is more likely values) in the table below for the variables in each model:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Variable** | **Range** | **Median** | **IQR** |
| Survival from listing | Age at registration | 16 - 69 | 51 | 35 - 58 |
|  | BMI at registration | 14.0 - 35.7 | 23.0 | 20.0 - 26.9 |
|  |  |  |  |  |
| Post-transplant survival | TLC mismatch | -2.2 - 4.5 | -0.1 | -0.4 - 0.4 |
|  | FVC at registration | 0.35 - 6.8 | 2.06 | 1.56 - 2.60 |
|  | Bilirubin at registration | 1 - 77 | 9 | 6 - 13 |
|  | Cholesterol at registration | 1.3 - 9.0 | 4.9 | 3.9 - 4.9 |

Rachel