A simple approach to risk stratification in adult heart transplantation

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Received 17 December 1998; received in revised form 9 June 1999; accepted 29 June 1999

Abstract

Objective: While there are numerous reports in the literature of risk factors for graft failure after heart transplantation, simple models for risk stratification are lacking. This study describes a simple method for risk stratification in adult heart transplantation that can be applied when the size of a dataset is insufficient for formal regression modelling. Methods: Multi-centre prospective cohort study. Fourteen risk factors documented in the literature as increasing post transplant graft failure were used to formulate a model. Risk factors included in the model were recipient age >50 years, pre-operative ventilatory support, pre-operative circulatory support, >1 previous sternotomy, pulmonary vascular resistance >2.5 wood units, male with body surface area >2.5 m², retransplant, ischaemic time >3.5 h, donor age >45 years, donor inotropic support >10 μg/kg per min dopamine, female donor, ratio donor/recipient body surface area <0.7, donor with diabetes and history of donor drug abuse. Four risk groups were defined depending on the number of risk factors present: Low, none; moderate, 1; high, 2 or 3; very high, 4 or more. Graft survival to 30 days was chosen as the primary outcome. The model was tested on 373 adult transplants performed in the UK between April 1995 and December 1996. Results: Twenty eight transplants were low risk, 82 moderate, 201 high and 62 very high. The 30-day survival (70% CI) for the risk groups was low, 97% (93±100), moderate 95% (92±98), high 87% (84±89) and very high 80% (75±83) (P < 0.02). Conclusions: This preliminary model enables some stratification of heart transplant procedures according to donor and recipient risk profile. Further work will be directed at refining and validating the model. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Heart transplantation; Predictive modelling; Risk factors

1. Introduction

While there are many reports on risk factors for mortality after cardiac transplantation, simple prognostic models are lacking. Systems of stratifying heart transplants are needed for four principal reasons: assisting individual patient decisions and allowing more informed consent; enabling stratified comparison of results; assisting in resource allocation; and in defining populations and adjusting for case-mix in research, registries and epidemiological studies. There are distinct obstacles to predictive modelling in cardiac transplantation. It is difficult to obtain a sufficient sample size for mathematical modelling, as transplant activity is low. Recruiting large numbers over several years will not necessarily provide a good modelling sample, as populations recruited over a long period exhibit heterogeneity due to advances in medical practices and changing donor and recipient pools. Large multi-centre studies can, to some extent, overcome the problem of sample size while allowing recruitment over a short period. This work is part of the UK cardiothoracic transplant audit – a national cohort study accruing data on intrathoracic transplantation since April 1995. As this audit is yet to achieve sufficient numbers for formal modelling, we have used a subjective approach to derive a risk-stratification model and report our preliminary results. This model is the first stage to multivariate modelling and will be validated as further data accrue. Our study objective was to develop a simple preliminary model of risk-stratification that would enable classification of heart transplants into broad risk categories.

2. Materials and methods

2.1. UK cardiothoracic transplant audit

The UK cardiothoracic transplant audit is a national prospective study of intrathoracic transplantation. The audit was established in 1995 by all the thoracic transplant centres in the United Kingdom (UK). Data are collected on
all patients registered on the national waiting list for heart transplantation in the UK; further data are requested at transplant and at designated follow-up points. Data collected include demographic, clinical, donor, and outcome variables. Extensive data validation routines are an integral feature of the data processing systems – these include regular visits to transplant centres to verify the accuracy of a random sample of data and rigorous computer-based checks that query incomplete, invalid and suspect data. Full details of the audit methodology will be reported elsewhere. There is a legal obligation to report all organ transplants in the United Kingdom to the UK transplant support service authority (UKTSSA); the number of transplants and patients due for follow-up, and hence the data completeness, can therefore be ascertained at any time. The audit can also accurately ascertain completeness of recruitment of patients placed on the national waiting list. Patients put on the local waiting list, but not added to the national waiting list are not picked up. There is no legal obligation to register patients on the national list and some patients may die (or be removed from the local list) without ever joining the national waiting list. The extent of loss of data from this source is unknown.

2.2. Outcome variable and patient population

Thirty-day graft survival was chosen as the model end-point (event: death or retransplantation). The 30-day end point was used because much of the previous work done by others (which formed the basis of this work) used a similar outcome. In addition, the primary goal of the model was to predict early graft failure. All adult patients in the cohort (registrations on the national waiting list since April 1995) who had undergone transplantation by December 1996 form the population for this analysis. Paediatric transplants (recipients aged 15 or less) were excluded because of differing risk profiles [1]. There were no other exclusions.

2.3. Selection of predictor variables

A subjective approach [2] was used to select risk factors for inclusion in the model. In a subjective approach variables are typically selected by a panel as opposed to objective methods that involve mathematical reduction of numerous data items collected on a large number of patients. To incorporate some objectivity, predictor variables were chosen from the published literature. Using MEDLINE, papers documenting risk factors for early failure after heart transplantation between 1986 and 1996 were identified. Risk factors were accepted into the model if they met the following criteria – relative risk for graft failure should equal or exceed 1.2, risk factor can be categorised into two groups, risk factor was preferably obtained through multivariate analysis, association should be biologically plausible, source of data and methods used should be adequately described and appropriate, and the risk factor should be easily and routinely collected in the UK. These criteria were not absolute – a subjective element remained in the variable section. For example, although size is widely believed to be an important factor in matching donors to recipients, statistical data to support this are lacking. Young et al. [3] have demonstrated an interaction between sex and size with small female donors posing the greatest risk. We extrapolated from these data, combined with widely accepted matching criteria that size mismatch (small donor – large recipient) is an adverse factor, and therefore included it in the model. Drug abuse was included because of epidemiological and experimental studies suggesting myocardial toxicity of cocaine [4] although there were no supporting clinical studies. Numerical data were collapsed into categorical groups as defined in the literature. Variables included in the model are listed in Table 1.

2.4. Definition of risk groups

From Table 1, it follows that a transplant could have a number of risk factors ranging from 0 to 14. Where data on a given risk factor were unavailable, the factor was assumed to be absent. The number of risk factors was computed for each transplant (risk factors were given equal weighting). Following examination of the risk profile (Fig. 1), transplants were arbitrarily grouped into four risk categories: low risk if no risk factors were identified; moderate risk for one risk factor; high risk for two or three risk factors; and very high risk for four risk factors or more. As an alternative to giving each factor equal weight, we could have used weights proportional to the risk estimates published in the literature. This would not have been entirely straightforward; for example, our model used categorical scaling for numerical variables while relative risks in the literature were often derived on a continuous scale. Additionally, not all factors had risk estimates explicitly stated in the literature. For this reason, and as our objective was to develop a preliminary model, equal weights were applied.

Table 1

<table>
<thead>
<tr>
<th>Factors included in the model</th>
<th>Donor factors</th>
<th>Recipient factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemia time greater than 3.5 h</td>
<td>Age greater than 50 years</td>
<td>On ventilator</td>
</tr>
<tr>
<td>Age greater than 45 years</td>
<td>Circulatory support</td>
<td>(inotropic or mechanical)</td>
</tr>
<tr>
<td>Inotropic support greater than 10 µg/kg per min dopamine or equivalent</td>
<td>More than one previous sternotomy</td>
<td></td>
</tr>
<tr>
<td>Female donors</td>
<td>Pulmonary vascular resistance greater than 2.5</td>
<td></td>
</tr>
<tr>
<td>Size mismatch (donor-recipient body surface area ratio less than 0.7)</td>
<td>wood units</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Large male patients (body surface area &gt;2.5 m²)</td>
<td></td>
</tr>
<tr>
<td>Drug abuse</td>
<td>Retransplantation</td>
<td></td>
</tr>
</tbody>
</table>
2.5. Data analysis

Survival probabilities were estimated using the Kaplan-Meier method, while categorical data were compared with the chi squared test. Cox proportional hazards modelling was used to estimate relative risks. Data were analysed using the LIFETEST, FREQ and PHREG procedures in SAS statistical software version 6.12 (SAS Institute, Cary, NC).

3. Results

3.1. Population characteristics

A total of 377 patients from the waiting list cohort had been transplanted by the end of December 1996. Data had not been returned for four patients, leaving 373 transplants for analysis. The number of patients contributed by each of the eight adult transplant units varied from 23 to 75, the largest contributing 20% of the population and the smallest 6%. The mean recipient age was 49 (SD 10) and 83% were male. The indication for transplant was coronary artery disease in 45%, cardiomyopathy in 39%, congenital in 5%, valvular disease in 3%, retransplant in less than 1% and other pathology in 8%. The mean donor age was 33 (SD 12). The majority of transplants (97%) were orthotopic. The 30-day survival was 88% (70% CI 86–90).

3.2. Risk distribution and survival

At least one risk factor was reported in 262 (70%) donors and 290 (78%) recipients. The commonest risk factors were recipient age >50 years (58%), female donor (39%), high pulmonary vascular resistance (PVR) (31%), ischaemic time more than 3.5 h (24%), donor age >45 years (22%), and circulatory support (14%). The median number of factors per transplant was 2 (interquartile range 1–3) (Fig. 1).

The distribution of transplants across the risk groups and the corresponding 30-day graft survival is shown in Table 2.

There is separation of risk groups, although with some overlap of 70% confidence margins. The use of post-operative organ support was used as a surrogate marker for internal validity; this increased significantly as risk increased (Table 3).

3.3. Relative risk estimates

Using Cox proportional hazards regression, the relative risk estimates for 30-day graft failure for the moderate, high and very high categories were 1.6 (70% CI 1.0–2.4), 4.8 (70% CI 3.3–7.1) and 6.8 (70% CI 4.6–10.2), respectively compared to baseline low risk transplants (Relative risk = 1).

4. Discussion

This model was derived from assessment of 373 transplants done within a 21-month period in the UK. The sample was a complete non-selected adult cohort representing our national experience. The study therefore minimises bias associated with small numbers, non-representativeness of single centre studies, and combination of heterogeneous time periods. The sample is similar in demographics to records held by the United Kingdom transplant support service authority [5] and can therefore be regarded as an accurate representation of transplantation in the UK.

4.1. Choice of model

A subjective approach to variable selection was chosen because the number of transplants was inadequate for meaningful formal analysis. For reliable modelling, it has been suggested that no more than \( n/10 \) predictors should be examined to fit a multiple regression model where \( n \) is the number of events [6]. This cohort had 44 events and using these criteria would allow for only four predictors. Relaxing the criteria to allow one predictor per every three events would allow for 14 predictors but would likely compromise reliability of the model. We therefore decided a priori to model the data into four risk groups as an objective approach to variable selection was not appropriate. The subjective technique has the advantage of being able to force variables into the model, especially uncommon variables thought to be relevant, but which on their own would not achieve statistical significance. The variable selection

<table>
<thead>
<tr>
<th>Risk group</th>
<th>( n )</th>
<th>%</th>
<th>30 day survival (%)</th>
<th>(70% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>28</td>
<td>7</td>
<td>97</td>
<td>93–100</td>
</tr>
<tr>
<td>Moderate</td>
<td>82</td>
<td>22</td>
<td>95</td>
<td>92–98</td>
</tr>
<tr>
<td>High</td>
<td>201</td>
<td>54</td>
<td>87</td>
<td>84–89</td>
</tr>
<tr>
<td>Very high</td>
<td>62</td>
<td>17</td>
<td>80</td>
<td>75–86</td>
</tr>
</tbody>
</table>

* Log-rank test \( \chi^2 = 10.02; P = 0.02. *
was based on published literature thus maintaining some objectivity.

The model successfully stratifies survival by the four risk groups. While we believe that the confidence intervals would be narrower with a larger sample size, it would be unrealistic to assume that four risk groups will explain all variation in mortality. The major disadvantage of the model is reduced discrimination (the ability of a model to separate patients with different responses [6]), especially among the high risk group which includes half of our transplants. A model with better discrimination would fragment high risk transplants into smaller sub-groups. Some more complex models we tested had better discrimination but at the price of reduced predictive ability. Complex models would also defeat the objective of this work, which was to derive a simple model. Loss of discrimination is a price to pay for model simplicity. For the purpose of transplantation outcomes and daily clinical practice, discrimination into four groups is probably adequate. More sophisticated models are required where increased discrimination is necessary.

There are few published data available on risk stratification in heart transplantation. Most of the work in this area has been from the cardiac transplant research database (CTRD) [7–9], a collaboration of over 40 transplant centres in United States and Canada. Risk profiles have been constructed for major post-transplant events [10]. The clinical application of their models is not straightforward hence the development of software to assist specific patient prediction [10]. There are however limitations to the direct extension of the CTRD model to a British or European population. The CTRD cohort is a selected sample of the larger transplant units in the North America; the results may therefore not be representative of global or North American practice. For example, centres not approved by Medicare did not contribute to the initial report [7], resulting in a systematic exclusion of the majority of heart transplant centres in the United States, many of which are low volume centres (as Medicare approval is partly dependent on centre volume [11]). Centres not in the CTRD study had an average of 13 transplants per year compared to 24 in the CTRD group. Low centre volume is associated with poorer outcomes [11] and risk profiles in excluded centres could differ. The CTRD therefore represents practice in the high volume US centres and generalisation may be inappropriate.

Another factor limiting generalisation of North American data to European centres is that data from the UK [12] and France [13] have shown that the practice and outcome of heart transplantation differs from that reported in the United States. Several factors have been suggested as contributing to the superior survival reported in North America [12,14], but regardless of the underlying reasons, such discrepancy threatens reliable and valid extension of prognostic models derived on US patients to their UK counterparts. Although risk factors are likely to be similar in a European cohort (several of the factors included in this model were based on American data), the predicted outcome will not be the same (unless the differential outcomes are purely due to case-mix). A need therefore exists to define risk profiles for British and European populations.

4.2. Strengths and limitations of model

The major strength of this model lies in its representativeness and simplicity. The study does not exclude any transplant centres or transplanted patients in the UK. It therefore characterises the entire national cardiac transplant experience within the study period; no sources of variation, known or unknown, are excluded and all centres (and hence patients) are included regardless of their output or outcomes. The model is simple and can easily be applied in clinical and non-clinical situations.

There are limitations of this study. The sample size, although a relatively large sample from the transplant perspective, is small for modelling purposes. We believe that with a larger sample, it will be possible to derive a more sensitive discriminatory risk classification (through multivariate modelling) and that the estimates will be more precise. The sample size was however beyond the investigators’ control. The 30-day outcome as a surgical outcome generally underestimates peri-procedural risk [15], an effect more pronounced in transplantation, as the hazard continues well beyond 30 days [7]. Finally, being a multi-centre study with no control on clinical practice, heterogeneity in practice and outcome is inevitable. Inclusion of all patients and centres was however necessary to permit generalisation of the results.

Several assumptions are inherent in the model – only factors included in the model can contribute to risk, risk factors are additive with no interactions, factors have equal weighting, and for numerical data, risk increases only when categorical boundaries are crossed. All these assumptions are violated to some degree and the ability of the model to still discriminate implies some degree of robustness. The assumption of equal weighting imposes the strongest restriction on the data and further work will be directed towards weighting of variables.

It is expected that with further refinement this model will be sufficiently robust to assist in decision making and enable risk stratified outcome evaluation, but at present the model remains exploratory. There are several potential applications of simple models for risk stratification. Simple strati-
fication of individual recipients enables doctors and patients to have realistic ideas of the likely risk [16] thereby forming the basis for truly informed consent [10]. For example, our data suggest that a recipient with 3 risk factors will expect, on average, a 53–82% probability of survival to 1 year depending on the quality of the donor heart. Stratification can aid the clinical decision making process of recipient and donor selection and the matching donors to recipients [10]. Some donor-recipient risk profiles may imply the risk of transplantation exceeds the risk on the waiting list (such as the allocation of a marginal donor heart to a patient at low risk of death on the waiting list) and in some very high risk patients, the risk of transplantation may be considered too excessive for acceptance on the waiting list. Stratification also enables results from different centres to be more accurately compared thus enabling doctors to effectively audit their practice. Finally, health purchasers and decision makers need reliably stratified outcome data to guide decision making [16]. Risk stratification has obvious advantages and uses, but models can only be reliably applied to populations similar to that from which they were derived. We have described our attempts to derive such a model from national data. Although there are several limitations to our approach, the model does have some discriminatory ability; and we suggest similar approaches may be used when modelling small samples in other areas of cardiac surgery. This model is preliminary – further work will be directed towards validation and refinement of the model through formal mathematical modelling.

Acknowledgements

This work was carried out for the UK Cardiothoracic Transplant Audit Steering Group, members of which are listed in Appendix A. The work was funded by the Department of Health. The views expressed are those of the authors and not necessarily of the Department of Health. We thank the centre data co-ordinators, Sharon Beer, Yvonne Davenport, Jane Harte, Andrea Husain, Ian Martin, Lindsay Reynolds, Sheilagh Vidler, Bruce Whitehead and Neil Wrightson for providing us with data. Data collection and processing was done in conjunction with the United Kingdom Transplant Service Support Authority.

Appendix A

A.1. Members of steering group and participating centres

Mr Robert S. Bonser (Queen Elizabeth Hospital, Birmingham), Mr John Dark (Freeman Hospital, Newcastle), Mr Abdul K. Deiraniya (Wythenshawe Hospital, Manchester), Mr H. Brendan Devlin/Dr Barnaby Reeves (The Royal College of Surgeons of England), Dr Peter Doyle (Department of Health representative), Mr Marc R. de Leval (Great Ormond Street Hospital for Sick Children, London), Mr Timothy J. Locke (Northern General Hospital, Sheffield), Mr Andrew J. Murday (St George’s Hospital, London), Mr John Wallwork (Papworth Hospital, Cambridge), Professor David J. Wheatley (Glasgow Royal Infirmary, Glasgow), Professor Sir Magdi Yacoub (Harefield Hospital, Middlesex).

References