3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome

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Summary

Background **Mortality after liver transplantation depends on heterogeneous recipient and donor factors. Our aim was to assess risk of death and to develop models to help predict mortality after liver transplantation.**

Methods **We analysed data from 34 664 first adult liver transplants from the European Liver Transplant Registry to identify factors associated with mortality at 3-months (n=21 605 in training dataset) and 12-months (n=18 852 in training dataset) after transplantation. We used multivariable logistic regression models to generate mortality scores for each individual, and assessed model discrimination and calibration on an independent validation dataset (n=9489 for 3-month model and n=8313 for 12-month model).**

Findings **2540 of 21 605 (12%) individuals in the 3-month training sample had died by 3 months. Compared with those transplanted in 2000–03, those transplanted earlier had a higher risk of death. Increased mortality at 3-months post-transplantation was associated with acute liver failure (adjusted odds ratio 1·61), donor age older than 60 years (1·16), compatible (1·22) or incompatible (2·07) donor–recipient blood group, older recipient age (1·12 per 5 years), split or reduced graft (1·96), total ischaemia time of longer than 13 h (1·38), and low United Network for Organ Sharing score (score 1: 2·43; score 2: 1·67). However, cirrhosis with hepatocellular carcinoma, alcohol cirrhosis, hepatitis C or primary biliary cirrhosis, donor age 40 years or younger, or less, hepatitis B, and larger size of transplant centre (⩾70 transplants per year) were associated with improved early outcomes. The 3-month mortality score discriminated well between those who did and did not die in the validation sample (C statistic=0·688). We noted similar findings for 12-month mortality, although deaths were generally underestimated at this timepoint.**

Interpretation **The 3-month and 12-month mortality models can be effectively used to assess outcomes both within and between centres. Furthermore, the models provide a means of assessing the risk of post-transplantation mortality, giving clinicians important data on which to base strategic decisions about transplant policy in particular individuals or groups.**

Introduction

The measurement of surgical outcomes, especially in cardiac surgery, has been extensively researched.[1] In liver transplantation, several models have been used to identify factors associated with outcomes.[2–6] However, most models are based on data from a single centre; thus their results cannot confidently be extrapolated to other populations of individuals receiving transplants.[7] Furthermore, the models are restricted to an assessment of survival at 12 months after transplantation. Although mortality at 12 months reflects surgical mortality, it also captures mortality associated with recurrent disease, chronic rejection, and retransplantation. Mortality rates at timepoints earlier than 12 months predominantly include surgical mortality, however, and could be associated with different factors to those linked to mortality at 1 year.

Data from the European Liver Transplant Registry (ELTR) have been used to establish the intrinsic mortality risk associated with liver transplantation without identified risk factors;[8] the results of the study by Adam and colleagues suggest that every centre could assess its own performance by combining this risk with the quoted relative risk ratios of known risk factors. However, the approach used to estimate the risk ratios (proportional hazards regression) does not provide absolute expected mortality rates, thereby limiting the practical application of these results. Furthermore, the results were based on transplants undertaken up to December, 1997. As survival continues to improve after liver transplantation, these models need to be updated.

Our aim, therefore, was to assess 3-month and 12-month mortality after first liver transplantation in a cohort of adult recipients from the ELTR who had transplants up to 2003.

Methods

Population

The ELTR database contains information about all liver transplants done in 23 European countries since 1968.[9] The methods used to obtain the data and details of the data collected have been described previously,[8] and

Panel: Calculation of 3-month and 12-month mortality scores

Consider, for example, a male recipient of a liver transplant done in 2000 with the following characteristics: acute liver failure, donor age 27 years, donor-recipient blood group compatible, recipient HBV negative, recipient aged 52 years, received a full graft, UNOS status 1, total ischaemia time 6·4 h, transplanted in a centre that did 91 transplants in the same year. The 3-month mortality score would be calculated as:

−3·38
+0·48 (acute liver failure)
−0·21 (donor aged ⩽40 years)
+0·20 (donor-recipient blood group compatible)
+(0·113[52−40]/5) (recipient aged 52 years)
+0·89 (UNOS status 1)
−0·23 (centre did ⩾70 transplants in year)
giving a 3-month mortality score of −1·986.

The exponential (e) of −1·98=0·137. Thus, the estimated probability that this individual will die within 3-months is calculated as:

0·137/(1+0·137)=0·12 (12%)

results of an audit[10] published in 2003 confirm the validity of the data. Data are submitted anonymously by either national transplant registries (UK, Spain) or by individual centres. Here, we present analyses based on data from transplants done in adults between Jan 1, 1988, and June 30, 2003.

The ELTR does not obtain individual consent from patients for inclusion of their data, since the French National ethics committee (Commission Nationale de L'Informatique et des Libertés)—which was consulted because the ELTR is based in Paris—considered it unnecessary. All data are anonymised.

Procedures and statistical analysis

We identified factors independently associated with 3-month and 12-month mortality with multivariable logistic regression models. Each dataset was randomly split into a training set (about 70% of transplants) used to generate the model, and a validation set (about 30% of transplants) for assessing the model's adequacy of fit. We used the training set to identify factors independently associated with mortality, using a backwards selection procedure.

Factors considered were: year of transplantation, disease cause (acute liver failure, hepatocellular carcinoma, alcoholic cirrhosis, hepatitis C virus [HCV] cirrhosis, primary biliary cirrhosis, other), recipient sex and age, donor sex and age, United Network of Organ Sharing (UNOS) status of recipient (1=intensive care unit bound, 2=continuous hospitalisation, 3=continuous medical care, 4=at home with normal function), recipient's HCV antibody status (note that these patients might have had other primary causes for their cirrhosis), and hepatitis B virus (HBV) surface antigen (HbsAG) status, donor and recipient ABO blood groups and matching status (identical, compatible, incompatible, not known), bypass type (extracorporal, lateral clamping, none, not known), graft type (full, split or reduced, unknown), total ischaemia time, and size of the transplant centre. We initially divided donor and recipient age into 10-year age groups. However, after identifying factors associated with mortality, we examined the adjusted odds ratios associated with each age group to assess if combining categories was appropriate to simplify the model. As a result, donor age was recategorised into three groups (⩽40, 41–60, and >60 years) for both final models. The odds ratios associated with each recipient age group increased progressively with increasing age. As such, we used recipient age as a continuous variable in the final model. Total ischaemia time was initially divided into eight groups based on percentiles. After fitting the final models, only a total ischaemia time greater than 13 h conferred a significant increase in the odds of mortality. Centre size was based on the number of transplants done in every transplant year, changing over time as centres did more or less transplants in a year. We also stratified centre size into eight groups based on percentiles; we assessed adjusted odds ratios to test the appropriateness of combining any groups. As a result, we reclassified centres as doing less than 37 (small), 37–69 (medium), or 70 or more (large) transplants yearly. We did not adjust models by country in accord with agreed ELTR policy; predicted rates therefore indicate average mortality rates expected over Europe.

We used the parameter estimates from the final models (the logarithms of the adjusted odds ratios) to derive scores for every individual for use in estimating the probability of death over the 3-months or 12-months post-transplantation. The score is calculated by multiplying the appropriate parameter estimates shown in table 2 by the corresponding covariate values for each individual (see panel for example). This mortality score can then be used to give an estimate of the probability of that individual dying within 3 months of transplantation, using the following equation:

$$\text{Probability} = \frac{E^{\text{score}}}{(1+E^{\text{score}})}$$

where e^{score} represents the exponential of the score. A risk calculator for the calculation of predicted mortality probabilities (95% CI) is available from authors.

We tested the adequacy of the models in three ways. First, we compared the scores of those who had or had not died with unpaired *t* tests. Second, we calculated the discriminative ability of the model with Harrell's C index.[11] Third, to assess the calibration of the models,

we stratified patients according to the deciles of the distribution of their mortality scores, and compared observed and expected numbers of deaths in each group with the Hosmer-Lemeshow statistic.[12] Because the fit of any model is always better on the dataset used to generate the model than on the general population, we also calculated these statistics for the validation set to give unbiased estimates of model adequacy. We did all analyses with SAS, version 8.02.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows patients' characteristics. 52 386 transplants were done between Jan 1, 1988, and June 30, 2003. Of these, we excluded the data for the following: 6977 retransplants; 5146 transplants done in children younger than age 15 years; 848 combined organ transplants; and 55 transplants with no follow-up information. A further 4696 transplants had missing information on the key data items: recipient sex (n=13), donor sex (n=4119), and donor age (n=3984). The missing data were associated primarily with earlier transplants (missing data: 27% [1988–1991], 21% [1992–1995], 5% [1996–1999], and 5% [2000–2003]) and were primarily due to the progressive addition of new data items to the ELTR questionnaire.[10] We therefore assessed data for 34 664 first liver transplants in adults. Our assessment of 3-month mortality is based on 31 094 transplants, since we excluded 552 individuals transplanted after April 1, 2003 (who did not have the potential for 3 months of follow-up) and 3018 individuals who were not known to have died but whose follow-up was less than 3 months. The assessment of 12-month mortality is based on 27 165 transplants, excluding 2858 individuals transplanted after June 30, 2002 (who did not have the potential for 12 months of follow-up) and 4641 individuals whose follow-up was less than 12 months.

For the 3-month model, we included 21 605 of 31 094 individuals (69%) in the training sample, of whom 2540 (12%) had died by 3 months post-transplantation (table 1). Table 2 shows results from the multivariable model for outcomes at 3 months. Compared with the most recently transplanted cohort of 2000–03, those who received transplants in earlier periods were at a higher risk of death ($p<0·0001$). After adjustment for the period of transplant, an increased risk of mortality at 3-months post-transplantation was associated with acute liver failure, donor age older than 60 years, compatible or mismatched donor–recipient blood groups, older recipient age, poor clinical status (lower UNOS scores), the receipt of a split or reduced graft, and total ischaemia time of longer than 13 h. By

	3-month mortality		12-month mortality	
	Number (%)	Number (%) dead in 3 months	Number (%)	Number (%) dead in 12 months
Transplant information				
Patients in training sample	21 605 (100%)	2540 (12%)	18 852 (100%)	3391 (18%)
Year of transplant				
1988–1991	2526 (12%)	444 (18%)	2446 (13%)	607 (25%)
1992–1995	4859 (22%)	604 (12%)	4678 (25%)	884 (19%)
1996–1999	7735 (36%)	829 (11%)	7478 (40%)	1195 (16%)
2000–2003	6485 (30%)	663 (10%)	4250 (23%)	705 (17%)
Number of transplants done by centre in year of transplant				
≤20	2795 (13%)	436 (16%)	2492 (13%)	577 (23%)
21–28	2536 (12%)	339 (13%)	2293 (12%)	426 (19%)
29–36	2573 (12%)	338 (13%)	2214 (12%)	458 (21%)
37–45	3004 (14%)	340 (11%)	2661 (14%)	453 (17%)
46–54	2736 (13%)	284 (10%)	2398 (13%)	408 (17%)
55–69	2555 (12%)	235 (9%)	2161 (11%)	337 (16%)
70–100	2727 (13%)	284 (10%)	2237 (12%)	391 (17%)
>100	2679 (12%)	264 (10%)	2396 (13%)	341 (14%)
Recipient information				
Cause of liver failure				
Acute liver failure	1917 (9%)	529 (28%)	1672 (9%)	548 (33%)
Hepatocellular carcinoma	2248 (10%)	209 (9%)	1946 (10%)	398 (20%)
Alcoholic cirrhosis	4652 (22%)	453 (10%)	4102 (22%)	586 (14%)
HCV cirrhosis	3668 (17%)	371 (10%)	3240 (17%)	562 (17%)
Primary biliary cirrhosis	1833 (8%)	171 (9%)	1602 (8%)	227 (14%)
Other	7287 (34%)	807 (11%)	6290 (33%)	1070 (17%)
Sex				
Male	13510 (63%)	1494 (11%)	11745 (62%)	2037 (17%)
Female	8095 (37%)	1046 (13%)	7107 (38%)	1354 (19%)
Age (years)				
≤20	598 (3%)	73 (12%)	517 (3%)	78 (15%)
21–30	1330 (6%)	165 (12%)	1118 (6%)	186 (17%)
31–40	2794 (13%)	294 (11%)	2476 (13%)	355 (14%)
41–50	5802 (27%)	657 (11%)	5120 (27%)	857 (17%)
51–60	7784 (36%)	937 (12%)	6747 (36%)	1288 (19%)
61–70	3245 (15%)	407 (13%)	2835 (15%)	619 (22%)
>70	52 (<1%)	7 (13%)	39 (<1%)	8 (21%)
UNOS status				
1	2570 (12%)	684 (27%)	2246 (12%)	745 (33%)
2	1636 (8%)	248 (15%)	1350 (7%)	300 (22%)
3	6830 (32%)	667 (10%)	5842 (31%)	951 (16%)
4	4998 (23%)	326 (7%)	4259 (23%)	502 (12%)
Unknown	5571 (26%)	615 (11%)	5155 (27%)	893 (17%)
Anti-HCV positive	5298 (28%)*	514 (10%)	4672 (28%)*	809 (17%)
HBsAg positive	2722 (13%)*	281 (10%)	2370 (13%)*	394 (17%)
Donor information				
Sex				
Male	13357 (62%)	1554 (12%)	11656 (62%)	2068 (18%)
Female	8248 (38%)	986 (12%)	7196 (38%)	1323 (18%)
Age (years)				
≤10	172 (1%)	21 (12%)	158 (1%)	32 (20%)
11–20	3261 (15%)	361 (11%)	2965 (16%)	475 (16%)
21–30	4067 (19%)	443 (11%)	3659 (19%)	592 (16%)
31–40	3741 (17%)	438 (12%)	3297 (17%)	568 (17%)
41–50	4300 (20%)	529 (12%)	3939 (21%)	713 (18%)
51–60	3573 (17%)	446 (12%)	3003 (16%)	594 (20%)
61–70	1888 (9%)	232 (12%)	1543 (8%)	311 (20%)
>70	603 (3%)	70 (12%)	490 (3%)	106 (22%)
Donor–recipient ABO group				
Identical	19877 (92%)	2189 (11%)	17 338 (92%)	2980 (17%)
Compatible	1450 (7%)	279 (19%)	1275 (7%)	319 (25%)
Incompatible	182 (1%)	56 (31%)	157 (1%)	68 (43%)
Not known	96 (<1%)	16 (17%)	82 (<1%)	24 (29%)

(continues)

(continued)				
Transplant information				
Bypass type				
Extracorporeal	5948 (28%)	792 (13%)	5437 (29%)	1059 (19%)
Lateral clamping	4919 (23%)	514 (10%)	4157 (22%)	712 (17%)
None	8738 (40%)	944 (11%)	7599 (40%)	1290 (17%)
Unknown	2000 (9%)	290 (15%)	1659 (9%)	330 (20%)
Graft type				
Full	20 116 (93%)	2273 (11%)	17 597 (93%)	3100 (18%)
Split or reduced	997 (5%)	174 (17%)	764 (4%)	171 (22%)
Unknown	492 (2%)	93 (19%)	491 (3%)	120 (24%)
Total ischaemia time (h)				
≤5·0	2814 (13%)	281 (10%)	2461 (13%)	404 (16%)
>5·0–6·2	2287 (11%)	232 (10%)	1980 (11%)	324 (16%)
>6·2–7·5	2791 (13%)	288 (10%)	2364 (13%)	405 (17%)
>7·5–8·6	2226 (10%)	251 (11%)	1936 (10%)	306 (16%)
>8·6–9·9	2407 (11%)	268 (11%)	2089 (11%)	344 (16%)
>9·9–11·3	2753 (13%)	314 (11%)	2337 (12%)	426 (18%)
>11·3–13·0	2489 (12%)	278 (11%)	2197 (12%)	389 (18%)
>13·0	2454 (11%)	345 (14%)	2204 (12%)	452 (21%)
Unknown	1384 (6%)	283 (20%)	1284 (7%)	341 (27%)

*Anti-HCV status available for 19 216 patients at 3 months and 16 670 patients at 12 months. HBsAg status available for 20 250 patients at 3 months and 17 664 patients at 12 months. Proportions of deaths in age groups refer to total per group.

Table 1: **Patients' characteristics**

contrast, cirrhosis with a hepatocellular carcinoma, high alcoholic cirrhosis, HCV or primary biliary cirrhosis, donor age of younger than 40 years, HBsAg positivity, and larger size of centre were all associated with a better 3-month outcome in multivariable analyses.

We used the estimates from the multivariable logistic regression model to generate a 3-month predictive score for every individual in the training sample (mean [SD] score –2·19 [0·67]). In those who had died within 3 months, the mean (SD) score was –1·75 (0·76) compared with –2·24 (0·63) in those who remained alive at 3 months (p=0·0001, unpaired *t* test). The C statistic from this model was 0·691, indicating a reasonable ability of the score to discriminate between those who died and those who remained alive at 3-months post-transplantation. We stratified patients according to the deciles of the distribution of scores; table 3 shows the expected and observed number of deaths within each stratum. The Hosmer-Lemeshow statistic was 8·94 (p=0·35), suggesting no evidence of lack of fit. When the same predictive score was calculated for the 9489 patients in the validation sample (mean –2·20 [0·66]), we noted similar results. In particular, the C statistic was 0·688 and the Hosmer-Lemeshow test was not significant, indicating a similar level of performance to that seen with the training sample.

With respect to the 12-month model, we included 18 852 of 27 165 individuals (69%) in the training sample, of whom 3391 (18%) had died by 12 months (table 1). Results from the multivariable model for 12-month outcomes (table 2) were very similar to those for 3-month outcomes. The mean [SD] predicted mortality score in the training sample was –1·63 (0·61) (–1·32 [0·65] in those who had died and –1·70 [0·58] in those still alive at 12 months post-transplantation). The model C statistic was 0·667 and the Hosmer-Lemeshow test statistic was 2·70 (p=0·95). However, by contrast with the 3-month results, when we calculated the score for the 8313 individuals in the validation sample, the Hosmer-Lemeshow test gave a significant result (p=0·002), suggesting that the 12-month score lacked calibration. Examination of the observed and expected number of deaths in each stratum suggested that the 12-month predictive score generally underestimated the risk of mortality in this sample, although its discriminative ability remained good.

Table 4 shows the causes of death in those dying at 3-months and at 12-months after transplantation. Although the number of deaths was higher at 12 months, the relative proportions of individuals dying from each cause were broadly similar with the exceptions of non-tumoural liver disease recurrence and tumours, which both arose with a higher frequency over the first year than over the first 3 months.

Discussion

We used a large European dataset to identify the main risk factors for 3-month and 12-month mortality in adults undergoing a first liver transplantation. The large size of the ELTR database as well as its representativeness mean that it is a powerful tool for developing and assessing predictive models for outcome after liver transplantation. The models we have generated can be used to assess the likelihood of early mortality in a patient about to undergo transplantation by considering recipient characteristics and potential donor and transplant-related characteristics. The models can also be used by centres to assess their past performance and compare it with the performance of other European centres over a similar period.

We included transplants done from 1988 onwards. We chose this date because it corresponds to the standardisation of liver transplantation across Europe and the by then widespread use of cyclosporin-based immunosuppression, which resulted in improved surgical outcomes.[7] However, even after excluding any transplants done before this date, 3-month and 12-month mortality rates have continued to improve over time.[9,13]

Acute liver failure was associated with an increased risk of mortality at both timepoints, consistent with the results of previous analyses of this dataset[8] and other studies.[14,15] Compared with other causes, individuals who needed a transplant because of cirrhosis with hepatocellular carcinoma, alcoholic cirrhosis, HCV cirrhosis, or primary biliary cirrhosis generally had a reduced risk of mortality, especially at 3-months post-transplantation. As before, non-identical blood groups

and a longer total ischaemia time were significantly associated with a poorer prognosis.[8] In general, non-matched donors are likely to be used when the need for transplant is urgent. However, the effects of a non-identical blood group remained significant after adjustment for other factors in the model, including acute liver failure and UNOS status, suggesting that these findings are not fully explained by a poorer clinical status at the time of transplantation. We also noted that total ischaemia time in excess of 13 h was a risk factor for mortality (previous analyses identified a cutoff of 12 h[8]). Although the precise threshold for ischaemia time is unclear, attempts to reduce total ischaemia times below 12 h are likely to improve outcomes.

One of the advantages of the models presented is that they could be used to estimate an individual's risk of mortality under different transplant conditions. Thus, the risk of mortality after a transplant with a non-matched donor can be weighed against the risk of mortality if the transplant is delayed until a matched donor can be found. Similarly, the benefits of introducing methods to reduce total ischaemia time—eg, by operating throughout the night—can be balanced against the possible risks of this clinical scenario.[16,17]

As in the previous report[18] that presented results from an analysis of the data from the ELTR, split or reduced liver transplants were associated with a poor outcome. The split or reduced liver transplant category included transplants from living donors; unfortunately, because of the small number of such transplants (only 2% of all transplants) we could not separate the relative contributions of each factor to survival. However, since transplants from living donors are increasing in frequency, further analysis of this cohort will soon be possible.

The accuracy of a predictive model will always seem to be unduly high if it is assessed on the same dataset used to generate the model; thus models should be validated on data from an external source.[19] Although we have not validated this model on data from a different source, the large size of the ELTR dataset allowed subdivision into training and validation samples. Both models generated had good discriminative ability, indicating that those with higher scores were more likely to die over both the short-term and the longterm. Whereas the 3-month model was also well calibrated, the 12-month model showed a tendency to underestimate mortality rates by around 10%. This finding is not surprising—while preoperative factors are likely to be the strongest predictors of death in the first few months after transplant, post-operative factors could start to play a more important part over the longer-term. For example, changes in renal function over follow-up, and severity and frequency of cellular rejection could all contribute to mortality over the longer-term. Our analyses, which are based on preoperative factors only, will not capture these factors. Furthermore, over time patients increasingly become at risk of other, non-transplant-related causes of death. Thus, although the model will be especially useful for stratifying patients according to their risk of death over 12 months, absolute estimates of risk should be interpreted with caution.

Several limitations of the database should be acknowledged. First, only the details obtained as part of the ELTR registry could be studied. Neither recipient renal function, nor recipient ventilation before liver transplantation are recorded in the database, and markers of liver status—eg, Pugh's score or MELD (model for endstage liver disease)—are not available. Although these factors might contribute to the increased mortality risk, their overall importance is likely to be subsumed by other factors, such as UNOS

	3-month mortality*		12-month mortality*	
	Estimate	Odds ratio (95% CI)	Estimate	Odds ratio (95% CI)
Intercept†	..	−3·38	..	−2·94
Year of transplant				
1988–1991	0·62	1·86 (1·60–2·16)	0·61	1·84 (1·60–2·11)
1992–1995	0·22	1·25 (1·10–1·41)	0·23	1·26 (1·12–1·42)
1996–1999	0·08	1·08 (0·97–1·21)	0·00	1·00 (0·90–1·12)
2000–2003	Reference			
Cause of liver failure				
Acute liver failure	0·48	1·61 (1·34–1·93)	0·27	1·30 (1·09–1·56)
Hepatocellular carcinoma	−0·29	0·75 (0·63–0·88)	0·09	1·09 (0·95–1·25)
Alcoholic cirrhosis	−0·26	0·77 (0·68–0·88)	−0·33	0·72 (0·64–0·81)
HCV cirrhosis	−0·20	0·82 (0·71–0·94)	−0·09	0·91 (0·81–1·03)
Primary biliary cirrhosis	−0·52	0·59 (0·49–0·71)	−0·57	0·56 (0·48–0·67)
Other	Reference			
Age of donor (years)				
⩽40	−0·21	0·81 (0·74–0·89)	−0·27	0·76 (0·70–0·83)
41–60	Reference			
>60	0·15	1·16 (0·99–1·36)	0·19	1·21 (1·06–1·37)
Donor–recipient ABO groups				
Identical	Reference			
Compatible	0·20	1·22 (1·05–1·42)	0·14	1·15 (1·00–1·33)
Incompatible	0·73	2·07 (1·47–2·91)	0·91	2·47 (1·76–3·48)
HBsAg positive	−0·38	0·68 (0·59–0·79)	−0·28	0·76 (0·67–0·86)
Recipient age (per 5 years older)†	0·11	1·12 (1·10–1·14)	0·13	1·14 (1·12–1·16)
Split or reduced graft	0·67	1·96 (1·61–2·35)	0·45	1·57 (1·30–1·89)
UNOS status				
1	0·89	2·43 (2·07–2·85)	0·85	2·33 (2·00–2·71)
2	0·51	1·67 (1·43–1·94)	0·43	1·54 (1·34–1·78)
3	Reference			
4	−0·43	0·65 (0·57–0·74)	−0·35	0·71 (0·63–0·79)
Total ischaemia time (h)				
⩽13	Reference			
>13	0·32	1·38 (1·21–1·57)	0·24	1·27 (1·13–1·43)
Unknown	0·67	1·95 (1·68–2·27)	0·52	1·67 (1·46–1·92)
Size of centre (transplants per year)				
⩽36	0·30	1·36 (1·23–1·50)	0·19	1·22 (1·10–1·34)
37–69	Reference			
⩾70	−0·23	0·80 (0·71–0·90)	−0·21	0·81 (0·73–0·90)

*All variables significant at 0·0001 level. †Results of model scaled so that intercept relates to a transplant recipient aged 40 years and odds ratios indicate effect of a 5-year increase in age. When estimating mortality score for an individual, subtract 40 years from score and divide by 5 before entering covariate in model.

Table 2: **Results from multivariable logistic regression model of factors associated with mortality at 3-months and at 12-months post-transplantation**

	Training sample			Validation sample		
	Number of patients	Number of deaths expected	Number of deaths observed	Number of patients	Number of deaths expected	Number of deaths observed
3 months						
1	2161	88·4	78	949	38·6	41
2	2161	120·0	104	948	52·3	60
3	2159	143·1	137	950	62·3	65
4	2165	165·2	184	948	71·2	78
5	2157	187·8	201	949	82·2	91
6	2160	215·5	217	949	94·1	89
7	2161	251·8	265	949	109·4	122
8	2160	303·6	289	949	131·7	138
9	2161	396·4	402	949	170·0	169
10	2160	669·2	663	949	293·2	285
Total	21 605	2541	2540	9489	1105·1	1138
Hosmer-Lemeshow statistic*	..	..	8·94 (p=0·35)	..	..	5·87 (p=0·83)
C statistic	..	..	0·691	..	..	0·688
12 months						
1	1884	132·6	123	831	57·9	57
2	1886	181·4	181	831	79·1	102
3	1886	215·6	217	832	93·7	105
4	1887	247·4	241	831	107·6	126
5	1881	278·7	295	831	122·3	138
6	1888	316·8	312	832	138·9	145
7	1885	360·0	370	831	157·8	187
8	1885	415·6	412	832	183·4	197
9	1885	503·2	490	831	220·6	234
10	1885	739·8	750	831	323·5	349
Total	18 852	3391·1	3391	8313	1484·8	1640
Hosmer-Lemeshow statistic*	..	..	2·70 (p=0·95)	..	..	27·54 (p=0·002)
C statistic	..	..	0·667	..	..	0·662

*Follows a χ^2 distribution with 8 degrees of freedom for training sample and 10 degrees of freedom for validation sample.

Table 3: **Expected and observed number of deaths at 3-months and at 12-months post-transplantation stratified by regression score (1=lowest; 10=highest score) in training and validation samples**

status. Furthermore, the MELD score is primarily used for the assessment of allocation and eligibility for transplantation, and, since it does not take into account operative or donor factors, it is a poor predictor of post-transplantation survival.[20,21] Second, we excluded patients with missing data on key data items, such as recipient sex and donor age and sex, as well as those with insufficient follow-up to assess outcomes at 3-months and 12-months post-transplantation. The former group of patients was largely restricted to transplants done in earlier time periods, and their exclusion should not, therefore, adversely effect the results from the more recently done transplants. By contrast, however, those with insufficient follow-up tended to be individuals who were transplanted, as expected, in 2002–03. Finally, some variability in the characteristics of patients undergoing transplantation in the different European countries included in this registry is likely. According to ELTR policy, we have not adjusted for country; our results thus indicate the average effect of each factor on mortality across Europe.

	3-months post-transplantation	12-months post-transplantation*
Intraoperative death	264 (7%)	252 (5%)
Infection	1002 (27%)	1295 (26%)
Liver complications or rejection	97 (3%)	191 (4%)
Technical complications	279 (8%)	327 (6%)
Primary non-function or dysfunction	229 (6%)	219 (4%)
Non-tumoral recurrence	20 (1%)	178 (4%)
Other liver complication	75 (2%)	97 (2%)
Gastrointestinal causes	108 (3%)	131 (3%)
Cardiovascular causes	291 (8%)	344 (7%)
Cerebrovascular causes	260 (7%)	310 (6%)
Other organ failure (renal, pulmonary, bone marrow, multiple organ)	401 (11%)	503 (10%)
Tumours	33 (1%)	407 (8%)
Other causes	408 (11%)	492 (10%)
Unknown	211 (6%)	285 (6%)
Total	3678 (100%)	5031 (100%)

Data are number (%). *Deaths at 12 months exclude any deaths occurring in individuals transplanted after June 30, 2002, in line with the analytical method; thus not all deaths at 3-months post-transplantation are included in the 12-month column.

Table 4: **Causes of death at 3-months and at 12-months post-transplantation**

The 3-month and 12-month mortality prognostic indices we have investigated can be used to assess outcomes both within and between centres, using the most recently transplanted patients in the ELTR (2000–03) as the reference cohort. Furthermore, the models provide a means of assessing the risk of post-transplant mortality, according to potential donor characteristics,[22] thus giving clinicians important data on which to base strategic decisions about transplant policy in particular individuals or groups.[12]

Contributors

A K Burroughs was the main investigator and conceived the study together with K Rolles. C A Sabin did the statistical analyses. R Adam, V Delvart, and V Karam contributed to the report with their knowledge of the ELTR database and experience of a previous ELTR publication on part of the same dataset. A K Burroughs and C Sabin drafted the report and all authors then contributed to subsequent drafts. All other authors listed contributed patients to the database, and commented on and approved the final version of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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