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Original Article

The association of pre-operative anaemia with survival after orthotopic liver transplantation

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Summary

Anaemia is common in patients with end-stage liver disease. Pre-operative anaemia is associated with greater mortality after major surgery. We analysed the association of pre-operative anaemia (World Health Organization classification) with survival and complications after orthotopic liver transplantation using Cox and logistic regression models. We included patients undergoing their first orthotopic liver transplantation between 2004 and 2016. Out of 599 included patients, 455 (76%) were anaemic before transplantation. Pre-operative anaemia was not associated with the survival of 485/599 (81%) patients to 1 year after liver transplantation, OR (95%CI) 1.04 (0.64–1.68), $p = 0.88$. Pre-operative anaemia was associated with higher rates of intra-operative blood transfusions and acute postoperative kidney injury on multivariable analysis, OR (95%CI) 1.70 (0.82–2.59) and 1.72 (1.11–2.67), respectively, $p < 0.001$ for both. Postoperative renal replacement therapy was associated with pre-operative anaemia on univariate analysis, OR (95%CI) 1.87 (1.11–3.15), $p = 0.018$.

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Introduction

Orthotopic liver transplantation can cure patients suffering from acute or chronic liver failure, the outcome of which is associated with several patient variables, such as age, diabetes mellitus, postoperative acute kidney injury and peritonitis [1–5]. Survival to one postoperative year is about 80% [6].

Pre-operative anaemia is present in about one-third of patients who undergo major surgery and it is associated with subsequent morbidity and mortality [7, 8]. The incidence of anaemia before orthotopic liver transplantation is as high as 75%, but it is uncertain whether it is associated with outcome [6, 9, 10].

Packed red blood cells are often transfused to correct anaemia, yet transfusion is associated with adverse outcomes and may cause increased morbidity and mortality after cardiac, orthopaedic and abdominal surgery [11–16]. Transfusion is also associated with adverse outcomes after liver transplantation [2, 17].

Our primary aim was to evaluate the association of anaemia before orthotopic liver transplantation with survival to 1 year and secondarily survival to the end of follow-up. We were also interested in the associations of peri-operative variables, including blood transfusion, with these outcomes and their interactions with pre-operative anaemia.

Methods

The ethics committee of the Medical University of Vienna approved this study. We studied patients admitted to our hospital for orthotopic liver transplantation between January 2004 and December 2016. We did not include

children (< 18 years), patients having concurrent lung or kidney transplantation, and patients with missing haemoglobin values within 24 pre-operative hours.

Orthotopic liver transplantation was performed under general anaesthesia, with caval replacement without the routine of veno-venous bypass. Blood group and physiological body-to-weight ratio were matched between donor grafts and transplant recipients. All patients were admitted to an intensive care unit (ICU) postoperatively. Immunosuppressive therapy was started with intravenous dexamethasone 40 mg before graft reperfusion. For the first five postoperative days patients received a reduced dexamethasone dose every 24 h, followed by a daily dose of 4 mg for 3 months (and longer for patients with autoimmune disease). Anti-thymocyte globulin 2.5 $mg.kg^{-1}$ was started on arrival in the ICU and continued for 3 days, after which immunosuppressive therapy was continued with low-dose tacrolimus or cyclosporin A at target concentrations of 6–8 $ng.ml^{-1}$ and 130–150 $ng.ml^{-1}$, respectively.

We determined the association of WHO-defined pre-operative anaemia (< 13 $g.dl^{-1}$ for men and < 12 $g.dl^{-1}$ for women) with 1-year survival. We performed secondary analyses of the association of the severity of anaemia in men and women with survival, categorised as mild (11–13 $g.dl^{-1}$ and 10–12 $g.dl^{-1}$, respectively), moderate (8–11 $g.dl^{-1}$ and 8–10 $g.dl^{-1}$, respectively) or severe (< 8 $g.dl^{-1}$) [18]. The secondary outcome was survival to the end of 2017.

We assessed the associations of pre-operative variables other than anaemia with outcomes such as age; sex; body mass index; model for end-stage liver disease (MELD) score; coronary artery disease; chronic obstructive pulmonary disease; diabetes mellitus; and pre-operative hospitalisation. We defined coronary artery disease as the presence of coronary atherosclerosis (> 50% stenosis of a coronary artery), or previous percutaneous coronary intervention. We defined pre-operative hospitalisation as inpatient treatment for at least 3 days before liver transplantation, or repeated

Table 1 Characteristics of 599 patients who had orthotopic liver transplantation, categorised by pre-operative anaemia. Values are mean (SD), median (IQR [range]) or number (proportion).

Characteristic	All patients (n = 599)	Anaemic		p value
		No (n = 144)	Yes (n = 455)	
Pre-operative				
Age; years	53 (10)	55 (8)	53 (11)	0.001
Sex; male	434 (72%)	101 (70%)	333 (73%)	0.54
Body mass index; $kg\ m^{-2}$	26.1 (4.4)	26.4 (4.2)	26 (4.5)	0.42
MELD score	16 (7)	13 (6)	17 (7)	< 0.001
Coronary artery disease	20 (3%)	6 (4%)	14 (3%)	0.52
COPD	38 (6%)	10 (7%)	28 (6%)	0.89
Diabetes mellitus	135 (23%)	42 (29%)	93 (20%)	0.038
Hospitalisation	60 (10%)	6 (4%)	54 (12%)	0.011
Intra-operative				
Cold ischaemia time; min	471 (139)	482 (147)	468 (136)	0.32
Warm ischaemia time; min	79 (19)	77 (18)	79 (20)	0.24
Transfusion				
Packed red blood cells	2 (0–5 [0–40])	0 (0–2 [0–19])	3 (1–6 [0–40])	< 0.001
Fresh frozen plasma	7 (4–12 [0–62])	5 (0–9 [0–30])	8 (4–12 [0–62])	< 0.001
Platelets	0 (0–1 [0–9])	0 (0–0 [0–3])	0 (0–1 [0–9])	0.020
Postoperative				
Surgical complications	113 (19%)	21 (15%)	92 (20%)	0.18
Early allograft dysfunction	138 (23%)	27 (19%)	111 (24%)	0.20
Acute kidney injury	412 (69%)	82 (57%)	330 (73%)	< 0.001
Renal replacement therapy	126 (21%)	20 (14%)	106 (23%)	0.023
Length of ICU stay; days	6 (4–11 [0–98])	5 (4–9 [1–90])	7 (4–12 [0–98])	< 0.001
Length of hospital stay; days	19 (14–28 [6–196])	15 (13–25 [6–118])	20 (14–30 [9–196])	0.002

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; MELD, model for end-stage liver disease.

hospital admissions within 1 month before liver transplantation. We also analysed intra-operative and postoperative variables: cold ischaemia time; warm ischaemia time; and transfused blood products – packed red blood cells, fresh frozen plasma and platelets; surgical revision; early allograft dysfunction; acute kidney injury; and renal replacement therapy. We defined surgical revision as surgery for bleeding, vascular or biliary duct stenosis, biliary duct leak or intra-abdominal haematoma and peritonitis within one postoperative month. We defined early allograft dysfunction as at least one of serum bilirubin concentration ≥ 10 mg.dl^{-1} or international normalised ratio ≥ 1.6 7 days after surgery; or serum aminotransferase concentration > 2000 IU.ml^{-1} within one postoperative week [19]. We defined acute kidney injury with standard criteria [20]. We categorised patients by whether they had renal replacement therapy within one postoperative week.

We did not calculate sample size for this retrospective study. We used two-sample t-test or Wilcoxon rank-sum test for continuous variables and Chi-square test or Fisher's exact test for categorical variables to compare patients with and without anaemia. We analysed 1-year survival using univariable and multivariable logistic regression and overall survival using univariable and multivariable Cox proportional hazard regression models. We used Schoenfeld residuals to test for violation of proportional hazards. We used accelerated failure time models for sensitivity analysis. We used cubic splines to test for non-linear associations of continuous variables with outcome. We tested for interactions between variables. We used a stepwise selection and retention method for multivariable model selection, adding and removing variables at $p < 0.05$, so that the final model only included variables with $p < 0.05$. We used univariable and multivariable logistic regression models for the association of anaemia with postoperative acute kidney injury, renal replacement therapy, early allograft dysfunction and surgical complications and linear regression models for the association of anaemia and packed red blood cell transfusion. We used R, release 3.3.3 [21] and SAS 9.4 for the statistical analyses. We considered $p < 0.05$ to be statistically significant.

Results

We studied 599/659 patients, most of whom were anaemic before orthotopic liver transplantation (Table 1 and Table S1). The mean (SD) pre-operative haemoglobin concentration was 13.8 (1.1) g.dl^{-1} for 144 patients who were not anaemic and 10.2 (1.5) g.dl^{-1} for 455 anaemic patients. Anaemic patients were younger but with worse liver disease, for which they were more

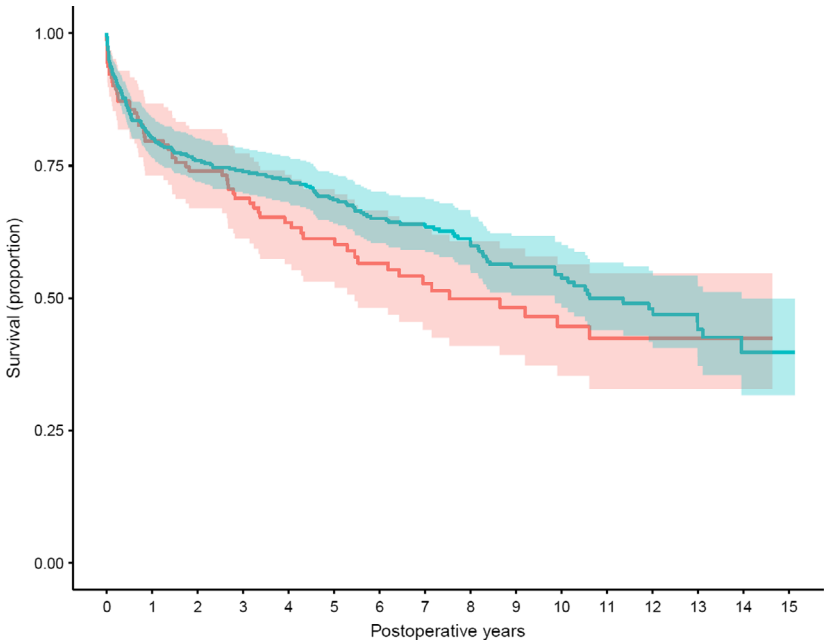

Figure 1 Survival after orthotopic liver transplantation of 599 patients, categorised by pre-operative haemoglobin concentration as not anaemic in 144 patients (green line); or anaemic in 455 patients (red line). Corresponding 95%CIs are shown as green or red areas, respectively. There were no statistically significant differences during the first year or for overall survival, $p = 0.88$ and $p = 0.20$, respectively.

often hospitalised, and they were more likely to have diabetes (Table 1).

There were 114/599 (19%) deaths in the first postoperative year from infection in 36 (32%); bleeding in 15 (13%); graft failure in 11 (10%); multi-organ failure in 9 (8%); cardiovascular events in 6 (5%); cancer in 5 (4%); surgical complications in 5 (4%); disease recurrence in 3 (3%); respiratory failure in 3 (3%); and unknown in 19 (17%). The median (IQR [range]) follow-up was 4 (1–9 [0–15]) years, and the median survival (95%CI) was 11 (8–13) years. There were 235 deaths during follow-up from infection in 51 (22%); bleeding in 20 (9%); graft failure in 18 (8%); multi-organ failure in 15 (6%); cardiovascular events in 12 (5%); cancer in 11 (5%); surgical complications in 5 (2%); disease recurrence in 13 (6%); respiratory failure in 5 (2%); and unknown in 84 (36%).

Survival to one postoperative year and to the end of follow-up was not associated with anaemia (Fig. 1), but was associated with a number of variables (Tables 2 and 3). Pre-operative anaemia was associated with increased peri-operative events, OR (95%CI): 1.70 (0.82–2.59) for intra-operative red blood cell transfusion, $p < 0.001$; and OR (95%CI) 1.72 (1.11–2.67) for acute post-operative kidney injury, $p < 0.001$. Pre-operative anaemia showed association with renal replacement therapy; OR (95%CI) 1.87 (1.11–3.15), $p = 0.018$ in univariate analysis; however, when correcting for confounding factors, for instance the MELD score, this association did not remain significant. Anaemia was not associated with early allograft dysfunction and surgical complications, OR (95% CI) 1.40 (0.87–2.24) and 1.47 (0.88–2.47), $p = 0.16$ and $p = 0.14$, respectively.

Table 2 The association of variables with survival to 1 year after orthotopic liver transplantation for 599 patients.

	Univariable model			Multivariable model		
Variables	**OR**	**95%CI**	**p value**	**OR**	**95%CI**	**p value**
Pre-operative						
Anaemia grade						
Any	1.04	0.64–1.68	0.88			
Mild	1.09	0.62–1.94	0.76			
Moderate	1.00	0.59–1.70	0.99			
Severe	1.00	0.39–2.54	> 0.99			
Haemoglobin	0.99	0.90–1.10	0.87			
Age; years	0.98	0.96–1.00	0.087			
Sex; male	0.97	0.61–1.54	0.90			
Body mass index; $kg^{-1}.m^2$	0.99	0.94–1.04	0.61			
MELD score	0.95	0.93–0.98	0.001			
Coronary artery disease	1.50	0.43–5.24	0.52			
COPD	1.62	0.61–4.26	0.33			
Diabetes mellitus	0.89	0.54–1.45	0.63			
Hospitalisation	0.52	0.28–0.98	0.043			
Intra-operative						
Cold ischaemia time; min^{-1}	1.00	1.00–1.00	0.43			
Warm ischaemia time; min^{-1}	1.00	0.98–1.01	0.38			
Transfusion						
Packed red blood cells	0.91	0.87–0.95	< 0.001	0.95	0.91–0.99	0.027
Fresh frozen plasma	0.96	0.94–0.99	0.002			
Platelets	0.72	0.58–0.88	0.001			
Postoperative						
Surgical complications	0.26	0.16–0.41	< 0.001	0.42	0.25–0.70	0.001
Early allograft dysfunction	0.48	0.30–0.75	0.001			
Acute kidney injury	0.63	0.39–1.01	0.055			
Renal replacement therapy	0.22	0.14–0.34	< 0.001	0.35	0.21–0.58	< 0.001
Year liver transplantation	0.96	0.91–1.02	0.16			

COPD, chronic obstructive pulmonary disease; MELD, model for end-stage liver disease; OR, odds ratio; CI, confidence interval.

Table 3 The association of variables with survival to the end of follow-up after orthotopic liver transplantation for 599 patients.

	Univariable model			Multivariable model		
Variables	**HR**	**95%CI**	**p value**	**HR**	**95%CI**	**p value**
Pre-operative						
Anaemia grade						
Any	1.21	0.91–1.62	0.20			
Mild	1.15	0.81–1.62	0.43			
Moderate	1.30	0.94–1.80	0.11			
Severe	0.96	0.54–1.68	0.88			
Haemoglobin	0.96	0.90–1.02	0.22			
Age; years	0.97	0.96–0.99	< 0.001	0.98	0.96–0.99	0.001
Sex; male	0.78	0.58–1.05	0.10			
Body mass index; $kg^{-1}.m^2$	0.99	0.96–1.02	0.56			
MELD score	0.98	0.97–1.00	0.071			
Coronary artery disease	0.79	0.43–1.45	0.52			
COPD	0.81	0.49–1.32	0.40			
Diabetes mellitus	0.70	0.53–0.94	0.017	0.71	0.53–0.96	0.025
Hospitalisation	0.91	0.59–1.42	0.69			
Intra-operative						
Cold ischaemia time; min^{-1}	1.00	1.00–1.00	0.17			
Warm ischaemia time; min^{-1}	1.00	0.99–1.01	0.48			
Transfusion						
Packed red blood cells	0.95	0.92–0.97	< 0.001			
Fresh frozen plasma	0.98	0.96–0.99	0.003			
Platelets	0.84	0.76–0.93	0.001			
Postoperative						
Surgical complications	0.49	0.37–0.66	< 0.001	0.62	0.45–0.86	0.004
Early allograft dysfunction	0.72	0.54–0.96	0.025			
Acute kidney injury	0.84	0.64–1.12	0.23			
Renal replacement therapy	0.44	0.33–0.58	< 0.001	0.50	0.37–0.68	< 0.001
Year liver transplantation	0.98	0.94–1.01	0.23			

COPD, chronic obstructive pulmonary disease; MELD, model for end-stage liver disease; HR, hazard ratio; CI, Confidence interval.

Discussion

We found that pre-operative anaemia was not associated with survival after liver transplantation. Pre-operative anaemia was associated with peri-operative blood transfusion and postoperative acute kidney injury.

Pre-operative anaemia is associated with worse outcome after major cardiac and non-cardiac surgery [7, 14, 22]. Some previous studies have reported an association of pre-operative anaemia with survival after liver transplantation [10], while others have not [6]. Pre-operative anaemia may be indirectly associated with survival after liver transplantation, as survival is worse after blood transfusion [16, 17, 23]. The decision to transfuse blood is affected by variables such as the MELD score or cold ischaemia time, which are associated with impaired coagulation, as well as haemoglobin concentration. Thus, the univariate association of the MELD score with survival to one postoperative year in our cohort is consistent with its association with coagulation.

Pre-operative anaemia was associated with acute post-operative kidney injury in our cohort. We assume that pre-operative anaemia was also associated with renal replacement therapy, with which anaemia was associated in isolation from other variables. Other studies have reported contradictory evidence for association of anaemia with renal replacement therapy after liver transplantation, which in turn is associated with worse survival [2, 6, 24].

Acute and chronic gastro-intestinal haemorrhage, malnutrition, iron deficiency, folate or vitamin B12 deficiency and suppression of bone marrow are mainly responsible for anaemia in end-stage liver disease patients [9, 25–28]. Increasing pre-operative haemoglobin

concentrations reduces peri-operative blood transfusion after gynaecological, obstetric, oncologic, orthopaedic and abdominal surgery [29–32]. We think that patients awaiting liver transplantation might benefit from pre-operative iron supplementation, which needs to be investigated in prospective randomised studies.

Unfortunately, due to insufficient diagnostic data, the cause of anaemia remains unknown in most of our patients. Iron status was only available for approximately half the study population. Further limitations of our study are the retrospective and monocentric design, which might limit the generalisability of our results. We analysed survival after operations that spanned 12 years, during which medical interventions have changed – such as the use of hydroxyethyl starch – as has general population survival, but date of surgery was not associated with observed survival in our cohort [33, 34].

In conclusion, pre-operative anaemia was not associated with survival after liver transplantation. However, anaemia was associated with blood transfusion, postoperative acute kidney injury and renal replacement therapy.

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Supporting Information

Additional supporting information may be found online via the journal website.

Table S1. Prevalence of anaemia according to the aetiology of liver disease.