# Pre-operative predictors of red blood cell transfusion in liver transplantation

Diogo Sobreira Fernandes, Cátia C. Pereira Real, Paula A. Sá Couto Romão, Filinto B. Marcos Correia de Barros, Isabel M. Marques Aragão, Luis F. Guimarães Fonseca, José M. Gonçalves Aguiar, Teresa M. Costa Branco, Zélia M. Fernandes Moreira, Simão M. Barros Esteves

*Department of Anaesthesiology, Intensive Care and Emergency Medicine, Centro Hospitalar do Porto, Oporto, Portugal*

## Introduction

Orthotopic liver transplantation (OLT) is a complex procedure that can be associated with massive intra-operative haemorrhage and high requirements of blood products[1]. Intra-operative transfusion of red blood cells (RBC) is a major predictor of post-operative mortality[2]. It is still not clear whether RBC transfusion indicates a poor clinical condition and the need for more complex surgery, or whether it has a negative effect on immunomodulation[3,4]. In recent years, there has been a trend to reduce the use of blood products due to improved surgical techniques, anaesthetic management, coagulation monitoring, and decreased haemoglobin value triggers for RBC transfusion[5,6]. The ability to predict blood product use for the individual patient before surgery would optimise pre-operative patient management and improve co-ordination of resources[7]. However, the variables associated to increased blood product usage vary between centres[8]. Therefore, it is essential that each centre identifies its own risk factors and high-risk patients for perioperative transfusion before a definitive standardised model can be developed[9,10]. Our centre has been running a liver transplantation programme since 1995 and around 1,100 liver transplants have been performed. The aim of this study was to identify which patient pre-operative variables best predict blood transfusion requirements during liver transplantation.

## Materials and methods

The study was approved by the investigation review board (003-DEFI-NA-CES). We retrospectively reviewed the anaesthetics records of 543 consecutive patients who had undergone OLT in our centre from June 2006 to June 2014. Re-transplantation (n=86) and liver transplantation for familial amyloid polyneuropathy (n=116) were excluded from the analysis as these were considered to be different entities; this left a final study cohort of 341 patients. Besides intra-operative RBC, platelets and fresh frozen plasma (FFP) consumption, the following pre-operative variables were collected for each patient: age, gender, Model for End-Stage Liver Disease score (MELD), primary diagnosis, international normalised ratio (INR), serum albumin and haemoglobin value. The transplanted liver was obtained from brain death or domino donors (livers structurally normal from patients with familial amyloid polyneuropathy). The MELD score was calculated using the standard formula with no adjustments for special conditions[11]. The liver transplantation team (6 hepato-biliary surgeons and 7 anaesthesiologists) and the surgical and anaesthetic protocols used were the same throughout the study period. The Piggyback hepatectomy technique was used in all performed liver transplants; no intra-operative cell salvage is used in our centre. Decision to transfuse RBC was based on the Patient Blood Management principles[12]: the stage of transplant surgery, patient co-morbidities and physiological triggers. The number of RBC units was dichotomised according to our sample median (≤2 and >2 RBC units). Statistical associations between pre-operative variables and intra-operative RBC requirements were first examined by univariate logistic regression. Subsequently, those pre-operative variables found to be significant were analysed through multivariate logistic regression to assess their independent contribution to intra-operative RBC transfusion. Goodness of fit for the multivariate model was analysed using the Hosmer and Lemeshow test. Linearity assumption in the logit scale for the continuous variables was also checked. $p<0.05$ was considered significant. Five patients were excluded from the multivariate analysis because of missing values. Statistical analysis was performed using Stata/SE11.2 for Windows (StataCorp LP, College Station, TX, USA)[13].

## Results

Patients' characteristics are listed in Table I. The results obtained from the univariate logistic regression are shown on Table II. The pre-operative variables found at this stage to be significantly associated with intra-operative RBC consumption were: MELD score, haemoglobin value, serum albumin, INR and primary diagnosis. Multivariate logistic regression of these variables revealed that only pre-operative MELD score, haemoglobin value and cholestatic liver disease were independently associated with intra-operative RBC transfusion (Table III). According to this multivariate analysis, for each point increase in MELD score,

*Blood Transfus 2017;* **15**: *53-6* DOI 10.2450/2016.0203-15

**Table I** - Population characteristics (n=341).

| Variable | Numbers (percentages) or mean (median; interquartile range) |
|---|---|
| *Age (years)* | 51.0 (53; 46-59) |
| *Gender* | |
| Male | 231 (67.7%) |
| Female | 110 (32.3%) |
| *Primary diagnosis* | |
| Alcoholic cirrhosis | 155 (45.5%) |
| Fulminant hepatic failure | 32 (9.4%) |
| Hepatocarcinoma | 51 (14.9%) |
| Hepatitis B and C virus-related cirrhosis | 42 (12.3%) |
| Cholestatic liver disease | 26 (7.6%) |
| Miscellaneous | 35 (10.3%) |
| *MELD score* | 14.9 (13.5; 10.0-18.0) |
| *RBC units (U)* | 3.6 (2.0; 0-5) |
| *Intraoperative massive blood transfusion* | 55 (16.1) |
| *Patients who received platelet transfusion* | 52 (15.2) |
| *Patients who received fresh frozen plasma transfusion* | 99 (29.29) |
| *Preoperative haemoglobin (mg dL$^{-1}$)* | 11.8 (12.0; 9.95-13.5) |
| *Preoperative INR* | 1.51 (1.3; 1.1-1.6) |
| *Preoperative serum albumin (mg dL$^{-1}$)* | 3.3 (3.3; 2.9-3.8) |

Intraoperative massive blood transfusion (MBT) was defined as transfusion of >6 units of red blood cells (RBC). MELD: Model for End-Stage Liver Disease score; INR: international normalised ratio.

**Table II** - Univariate logistic regression of preoperative variables and >2 intraoperative RBC units transfusion (n=341).

| Variables | Odds ratio (95% CI) | p |
|---|---|---|
| *Age (years)* | 1.01 (0.99-1.04) | 0.14 |
| *Gender* | 1.41 (0.89-2.23) | 0.14 |
| *MELD Score* | 1.09 (1.05-1.13)* | 0.001 |
| *Diagnosis* | | |
| Fulminant hepatic failure | 2.01 (0.89-4.52) | 0.09 |
| Hepatocellular carcinoma | 0.35 (0.17-0.69)* | 0.003 |
| Cholestatic liver disease | 0.41 (0.17-0.99)* | 0.047 |
| Hepatitis B and C virus-related cirrhosis | 1.11 (0.56-2.19) | 0.77 |
| Miscellaneous | 0.69 (0.33-1.44) | 0.32 |
| *Preoperative serum albumin (mg/dL$^{-1}$)* | 0.56 (0.40-0.79)* | 0.001 |
| *Preoperative haemoglobin (mg/dL$^{-1}$)* | 0.71 (0.64-0.79)* | 0.001 |
| *Preoperative INR* | 1.59 (1.14-2.21)* | 0.006 |

*p<0.05. RBC: red blood cell; CI: confidence interval; MELD: Model for End-Stage Liver Disease score; INR: international normalised ratio.

the odds of transfusing more than two units of RBC increases by 7% (95% CI: 2-13%). For each g/dL$^{-1}$ increase in pre-operative haemoglobin, the odds of transfusing more than two units of RBC decreases by 25% (95% CI: 14-34%). Among cholestatic liver disease patients, the odds of transfusing more than two units of RBC decreases by 64% compared to alcoholic hepatic cirrhosis patients (95% CI: 6-86%).

## Discussion

Despite the decreasing need observed over the years for blood products during OLT, intra-operative haemorrhage remains a problem, and blood products are a precious and costly resource. Therefore, the ability to predict blood product use before surgery would improve co-ordination of resources by the transfusion department for each case and identify

**Table III** - Multivariate logistic regression of preoperative variables and >2 intraoperative RBC units transfusion (n=336).

| Variables | Odds ratio (95% CI) | p |
|---|---|---|
| *MELD Score* | 1.07 (1.02-1.13)* | **0.01** |
| *Preoperative hemoglobin (mg dL$^{-1}$)* | 0.75 (0.66-0.86)* | **0.001** |
| *Preoperative serum albumin (mg dL$^{-1}$)* | 1.09 (0.71-1.67) | 0.69 |
| *Preoperative INR* | 0.89 (0.58-1.38) | 0.60 |
| *Diagnosis* | | |
| Fulminant hepatic failure | 0.68 (0.20-2.29) | 0.53 |
| Hepatocellular carcinoma | 0.74 (0.34-1.59) | 0.44 |
| Cholestatic liver disease | 0.36 (0.14-0.94)* | **0.04** |
| Hepatitis B and C related cirrhosis | 1.13 (0.54-2.38) | 0.75 |
| Miscellaneous | 0.65 (0.28-1.48) | 0.30 |

*p<0.05 (significant values in bold). RBC: red blood cells; CI: confidence interval; MELD: Model for End-Stage Liver Disease score; INR: international normalised ratio.

those patients most likely to benefit from blood-saving strategies[7].

Familial amyloid polyneuropathy is an autosomal hereditary systemic disease characterised by hepatic production of an abnormal protein that causes systemic amyloidosis. These patients were excluded from the analysis since hepatic function and structure is preserved and is, therefore, associated with less complex surgery and less intra-operative blood loss; RBC transfusion median at our centre is zero.

In this study, the median/mean of RBC units transfused intra-operatively was 2/3.6 and 104 patients (30.5%) did not receive any RBC. These results are in agreement with the decreasing use of blood products found in the literature[14,15]. In our study, median intra-operative haemorrhage was 3,000 mL (interquartile range: 1,700-5,300 mL). Since a single team of 7 anaesthesiologists carried out the transplantation procedure throughout the study period, the variability of transfusion practices at our centre for OLT was minimal.

In accordance with other authors[14,15], we chose our sample median to categorise intra-operative RBC consumption in order to increase the power of the study. This cut-off (two RBC units) was lower than those used in other studies[8,14]. The analysis did not focus on the patients submitted to massive blood transfusion (MBT), since only 55 patients (16.1%) were submitted to MBT. The predictors of platelets and FFP transfusion were not studied, since in this sample requirement for such blood products was low.

Several studies have also identified the MELD score and pre-operative haemoglobin value as being independently associated with intra-operative RBC transfusion[1,8,15].

Cholestatic liver disease was associated with less transfusional need when compared to alcoholic hepatic cirrhosis (our reference category, because it is the most prevalent primary diagnosis for OLT in our centre). The aetiologies of liver disease are diverse, and there are differences in the haemostatic profiles according to each one. Other studies have also found that in patients with cholestatic liver disease the haemostatic balance is generally better preserved than in patients with non-cholestatic disease[16,17]. Our results are consistent with those studies.

In this study, intra-operative variables (intra-operative bleeding, patient and organ survival, re-transplantation, surgical time and cold ischemia) were not analysed. The aim of this study was to analyse pre-operative variables and predict the intra-operative consumption of RBC in order to improve the management of blood component resources in our transfusion department. Blood is a costly resource. In the future, the authors hope to build and validate a logistic regression model that predicts individual RBC transfusion requirements for liver transplantation.

## Conclusions

In our centre, pre-operative factors that were independently associated with intra-operative RBC consumption were: haemoglobin value, cholestatic liver disease, MELD score. Haemoglobin value was inversely related to RBC consumption, while MELD score was directly associated with the intra-operative administration of more than two RBC units. Cholestatic liver disease (relative to alcoholic hepatic cirrhosis) was associated with a lower requirement for intra-operative RBC transfusion.

## Authorship contributions

DSF wrote the paper, CCPR performed the research, PASCR and FBMCDF designed the research study. All the Authors, including those that were mentioned, participated in the acquisition of data, revised the paper

critically, contributed to the interpretation of data and approval of the submitted and final versions.

**Keywords:** erythrocyte transfusion, end-stage liver disease, blood loss, risk factors, adults.

*The Authors declare no conflicts of interest.*

## References

1) Steib A, Freys G, Lehmann C, et al. Intraoperative blood losses and transfusion requirements during adult liver transplantation remain difficult to predict. Can J Anaesth 2001; **48**: 1075-9.
2) Rana A, Petrowsky H, Hong JC, et al. Blood transfusion requirement during liver transplantation is an important risk factor for mortality. J Am Coll Surg 2013; **216**: 902-7.
3) Benson AB, Burton JR, Austin GL, et al. Differential effects of plasma and red blood cell transfusions on acute lung injury and infection risk following liver transplantation. Liver Transpl 2011; **17**: 149-58.
4) Azevedo LD, Stucchi RS, Ataíde EC, Boin IF. Assessment of causes of early death after twenty years of liver transplantation. Transplant Proc 2013; **45**: 1116-8.
5) Massicotte L, Lenis S, Thibeault L, et al. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantations. Liver 2006; **12**: 117-23.
6) Coakley M, Reddy K, Mackie I, et al. Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. J Cardiothorac Vasc Anesth 2006; **20**: 548-53.
7) Spahn DR, Theusinger OM, Hofmann A. Patient blood management is a win-win: a wake-up call. Br J Anaesth 2012; **108**: 889-92.
8) Cywinski JB, Alster JM, Miller C, et al. Prediction of Intraoperative Transfusion Requirements During Orthotopic Liver Transplantation and the Influence on Postoperative Patient Survival. Anesth Analg 2014; **118**: 428-37.
9) Escoresca Ortega AM, Mogollon Jiménez MV, Hinojosa Pérez R, et al. Application of the McCluskey Index to Predict Blood Product Requirements During Liver Transplantation. Transplant Proc 2008; **40**: 2981-2.
10) Findlay JY, Rettke SR. Poor prediction of blood transfusion requirements in adult liver transplantations from preoperative variables. J Clin Anesth 2000; **12**: 319-23.
11) Freeman RB Jr, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Transpl 2002; **8**: 851-8.
12) Shander A, Van Aken H, Colomina MJ, et al. Patient blood Management in Europe. Br J Anaesth 2012; **109**: 55-68.
13) Hosmer DW Jr, Lemeshow S, Sturdivant RX, et al. *Applied Logistic Regression.* 3rd ed. Hoboken: Wiley; 2013.
14) Massicotte L, Sassine MP, Lenis S, et al. Transfusion predictors in liver transplant. Anesth Analg 2004; **98**: 1245-51.
15) Mangus RS, Kinsella SB, Nobari MM, et al. Predictors of blood product use in orthotopic liver transplantation using the piggyback hepatectomy technique. Transplant Proc 2007; **39**: 3207-13.
16) Pihusch R, Rank A, Gohring P, et al. Platelet function rather than plasmatic coagulation explains hypercoagulable state in cholestatic liver disease. J Hepatol 2002; **37**: 548-55.
17) Ben-Ari Z, Panagou M, Patch D, et al. Hypercoagulability in patients with primary biliary cirrhosis and primary sclerosing cholangitis evaluated by thrombelastography. J Hepatol 1997; **26**: 554-9.

Arrived: 10 August 2015 - Revision accepted: 28 October 2015
**Correspondence:** Diogo Sobreira Fernandes
Centro Hospitalar do Porto
Largo Prof. Abel Salazar
4099-001 Porto, Portugal
e-mail: sobreirafernandes@gmail.com