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Original Article

Practical model to identify liver transplant recipients at low risk of postoperative haemorrhage, bile leakage and ascites

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Abstract

Background: This study aimed to identify a subgroup of recipients at low risk of haemorrhage, bile leakage and ascites following liver transplantation (LT).

Methods: Factors associated with significant postoperative ascites (more than 10 ml/kg on postoperative day 5), bile leakage and haemorrhage after LT were identified using three separate multivariable analyses in patients who had LT in 2010–2019. A model predicting the absence of all three outcomes was created and validated internally using bootstrap procedure.

Results: Overall, 944 recipients underwent LT. Rates of ascites, bile leakage and haemorrhage were 34.9, 7.7 and 6.0 per cent respectively. The 90-day mortality rate was 7.0 per cent. Partial liver graft (relative risk (RR) 1.31; $P = 0.021$), intraoperative ascites (more than 10 ml/kg suctioned after laparotomy) (RR 2.05; $P = 0.001$), malnutrition (RR 1.27; $P = 0.006$), portal vein thrombosis (RR 1.56; $P = 0.024$) and intraoperative blood loss greater than 1000 ml (RR 1.39; $P = 0.003$) were independently associated with postoperative ascites and/or bile leak and/or haemorrhage, and were introduced in the model. The model was well calibrated and predicted the absence of all three outcomes with an area under the curve of 0.76 ($P = 0.001$). Of the 944 patients, 218 (23.1 per cent) fulfilled the five criteria of the model, and 9.6 per cent experienced postoperative ascites (RR 0.22; $P = 0.001$), 1.8 per cent haemorrhage (RR 0.21; $P = 0.033$), 4.1 per cent bile leak (RR 0.54; $P = 0.048$), 40.4 per cent severe complications (RR 0.70; $P = 0.001$) and 1.4 per cent 90-day mortality (RR 0.13; $P = 0.004$).

Conclusion: A practical model has been provided to identify patients at low risk of ascites, bile leakage and haemorrhage after LT; these patients could potentially qualify for inclusion in non-abdominal drainage protocols.

Introduction

Despite significant improvements in surgical technique and perioperative management, liver transplantation (LT) remains a complex procedure associated with high postoperative complication rates, reaching up to 90 per cent in recent large series[1,2]. Of these, bile leakage and haemorrhage alone account for as much as 6–17 and 4–12 per cent respectively of the overall morbidity, and greatly impair the postoperative course of patients[1,3,4]. One of the main goals of prophylactic abdominal drainage placement at the end of the procedure is to shorten the time to diagnosis of haemorrhage and bile leakage, and also to prevent parietal complications related to non-drained ascites effusion[5]. In this setting, abdominal drain placement is generally considered a harmless preventive measure and is still performed routinely in the vast majority of transplant centres.

In patients undergoing planned liver resection, various randomized studies and meta-analyses have emphasized that routine abdominal drainage does not lead to improvement in the overall postoperative course of patients[6,7]. On the contrary, it has been suggested that routine abdominal drainage could favour the occurrence of various complications such as ascending infections, prolong the duration of fluid effusions including ascites and bile leakage, and thus lead to an overall increase in complication rates and hospital stay[8,9]. Hence, abdominal drainage is no longer undertaken routinely in daily practice, even in patients with cirrhosis undergoing liver resection[10] or those having a major hepatectomy[11].

In an era where practices such as early oral intake, extubation, mobilization and short hospital stay are gaining increasing acceptance, identification of those patients who might safely qualify for a non-drainage policy would allow the implementation of early rehabilitation in the setting of liver transplantation and improve the postoperative outcomes of these patients[6,12,13]. In this context, the present study aimed to develop a prediction

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model for postoperative ascites, bile leakage and haemorrhage following LT. This would allow the identification of a subset of patients at low postoperative risk who could potentially qualify for inclusion in non-abdominal drainage protocols.

Methods

Details of all recipients who underwent deceased-donor orthotopic liver transplantation (LT) between January 2010 and December 2019 were retrieved from a prospective database and included in this retrospective single-centre (Beaujon Hospital, Clichy, France) observational study. Recipients who had LT with caval replacement, without abdominal wall closure or combined pulmonary and/or cardiac transplantation, were excluded. Data collection included recipient and donor demographic data, intraoperative details and postoperative outcomes after LT.

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local ethics committee, which waived the need for written informed consent (Institutional Review Board number IRB00006477, Hôpitaux Universitaires Paris Nord Val de Seine).

Preoperative evaluation

The decision to perform LT was based on the recommendation of a multidisciplinary team involving hepatologists, hepatopancreatobiliary (HPB) surgeons, anaesthetists, radiologists and pathologists. Preoperative evaluation included complete blood and liver function tests (as recorded before LT), hepatic venous pressure gradient measurement and systematic liver biopsy, as well as routine anaesthetic and cardiorespiratory evaluation. Preoperative liver function was evaluated using the model for end-stage liver disease (MELD)[1]. Nutritional status was evaluated using anthropometric measures. Malnutrition was defined as a BMI of 18.5 kg/m^2 or less and/or loss of weight of 5 or 10 per cent during the past month or the past 6 months respectively[14]. BMI was estimated using the dry weight of patients. Cross-sectional imaging (CT or MRI) was performed within 1 month before LT to assess technical insights of the LT procedure, with specific emphasis on the presence of portal vein thrombosis, portosystemic shunts and quality of recipient arteries. The definition of portal vein thrombosis included all Yerdel grades[15]; therefore even patients with partial thrombosis were considered to have portal vein thrombosis.

Surgical management

Total hepatectomy was performed using the left to right approach with caval flow preservation, as described previously[16]. Portocaval shunt was performed routinely in patients with a non-cirrhotic liver and on a case by case basis in patients with cirrhosis, depending on tolerance to portal clamping. Caval anastomosis was performed using the piggyback technique, with implantation on the common trunk or the right hepatic vein according to the size of the graft[17]. Direct and short arterial reconstructions were considered preferentially[18]. Postreperfusion syndrome was defined as a decrease in mean arterial pressure of more than 30 per cent below the baseline value, for at least 1 min, occurring during the first 5 min after reperfusion of the liver graft (unclamping of the hepatic hilum)[19]. A prophylactic abdominal drain was inserted routinely and maintained up to postoperative day (POD) 5. The nature of the drain (passive or closed-suction) was left to the discretion of the operating surgeon. The drain was removed in the absence of significant ascites, bile leakage or haemorrhage.

Donor-related data and intraoperative details, such as donor age and BMI, history of cardiac arrest, duration of warm and cold ischaemia, intraoperative presence of ascites (10 ml/kg suctioned after laparotomy), presence of portal vein thrombosis, whole or partial liver graft, duration of transplantation, blood loss and presence of reperfusion syndrome, were collected.

Postoperative outcomes

After LT, patients were admitted to the ICU and subsequently transferred to the Department of Hepatology. Patients were seen daily by a physician until hospital discharge. Doppler ultrasound assessments of inflow and outflow were performed routinely at the end of surgery and daily on POD 1–5. Contrast-enhanced abdominal CT was performed routinely before discharge, or earlier in patients with suspected abdominal or pulmonary complications. Significant postoperative ascites was defined as abdominal drainage output of more than 10 ml/kg/day after POD 5[20]. Bile leakage was defined as a bilirubin concentration in the drainage fluid (surgical or radiological drainage) more than three times the concentration of the plasma bilirubin level and/or any clinicoradiological suspicion of biloma on radiological imaging[21]. Postoperative haemorrhage was defined as a reduction in the haemoglobin level of more than 3 g/dl after surgery compared with the immediate postoperative baseline level and/or the need for postoperative transfusion of packed red blood cells for a reduced haemoglobin level and/or the need for radiological intervention (such as embolization) and/or relaparotomy to stop bleeding[22]. Early graft dysfunction was defined according as the presence of one or more of the following validated criteria[23]: bilirubin concentration of 10 mg/dl or above on POD 7, international normalized ratio of 1.6 or more on POD 7, and alanine or aspartate aminotransferase level above 2000 units/l within the first 7 days after surgery. Primary non-function was defined as a consequence of early graft dysfunction leading to retransplantion or death. Postoperative complications were stratified according to the Dindo–Clavien classification[24], which defines severe complications as grade IIIa and above. Complications were considered as those occurring within 90 days of surgery, or at any time during the hospital stay. Mortality was considered as occurring within both 90 days and 1 year.

Statistical analysis

All statistical tests were two-sided, and $P < 0.050$ was considered statistically significant for all analyses. Variables are presented as median (i.q.r.) values or as numbers with percentages, as appropriate. Continuous variables were compared using the Kruskal–Wallis or Mann–Whitney test, as appropriate. Categorical variables were compared with χ^2 or Fisher's exact test, as appropriate.

Preoperative and intraoperative factors associated with postoperative ascites, bile leakage and haemorrhage were identified using three separate backward stepwise logistic regression, including non-collinear, clinically relevant, preoperative variables. All regression analyses were repeated using the bootstrap procedure (2000 times) to validate the variable selection. The categorical variable of interest for the predictive model used in this study was 'absence of ascites, bile leak and haemorrhage', defined as the absence of all three outcomes during the postoperative course. To avoid clinical misinterpretation and overestimation related to odds ratios, the effect sizes of exposure were represented using relative risk (RR) values, which were calculated using robust Poisson regressions[25,26].

To improve the generalization of the model by avoiding overfitting and increasing model interpretability and applicability, a dimensionality reduction in the number of factors associated with the variables of interest was performed using forward stepwise logistic regression, including all variables from the three previous multivariable analyses with $P < 0.100$. Thereafter, selected variables were forced into a logistic regression to create the model, which was repeated using the bootstrap procedure (2000 times). Performance of the model was assessed using Cox and Snell's R^2. Model discrimination and its threshold were assessed using the receiver operating characteristic (ROC), with area under the curve (AUC), positive likelihood ratio and diagnostic RR based on the confusion matrix. Model calibration was assessed using the Hosmer–Lemeshow test and a calibration plot[27]. Internal validation of the model's performance (correction for optimism) was performed using both 5-fold cross-validation and the bootstrap procedure (2000 times)[28]. All statistical analyses were performed with SPSS® Statistics v.24 software (IBM, Armonk, NY, USA) and R statistical software version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 944 recipients underwent deceased-donor LT. Demographic data, aetiologies of the underlying liver disease, perioperative evaluation, type of LT, and donor and graft related data are summarized in *Table 1*.

Median duration of LT and intraoperative blood loss were 320 (280–365) min and 1000 (600–1800) ml respectively. A portocaval shunt was performed in 239 recipients (25.3 per cent) and 445 (47.1 per cent) developed reperfusion syndrome.

Postoperative outcomes after liver transplantation

Complications and severe complications occurred in 584 (61.9 per cent) and 506 (53.6 per cent) patients respectively. Sixty-six patients (7.0 per cent) died within 90 days of LT. Early graft dysfunction and primary non-function occurred in 206 (21.8 per cent) and 8 (0.8 per cent) patients respectively. At 1 year of follow-up, the mortality rate was 9.6 per cent.

Overall, significant postoperative ascites, bile leak and haemorrhage were experienced by 329 (34.9 per cent), 73 (7.7 per cent) and 57 (6.0 per cent) patients respectively. A total of 534 patients (56.6 per cent) did not have any of these three outcomes. Multivariable analysis of the preoperative, intraoperative and donor-related factors predicting the occurrence of all three outcomes is shown in *Table 2*.

Among the 329 patients experiencing significant ascites, 42 (12.8 per cent) had an associated bile leak (28 patients) and/or haemorrhage (22 patients). Of the 73 patients who had bile leakage, 43 (58.9 per cent) had associated significant ascites (35 patients) and/or haemorrhage (18 patients). Among the 57 patients experiencing haemorrhage, 31 (54.4 per cent) had significant associated ascites (25 patients) and/or bile leakage (16 patients). Details of the occurrence of significant ascites, bile leak and haemorrhage in the whole cohort are given in *Table S1*.

Model predicting absence of ascites, bile leak and haemorrhage after liver transplantation

Variables independently associated with the absence of postoperative significant ascites, bile leak and haemorrhage were reduced to five after forward logistic regression (*Table 3*). Of these, intraoperative blood loss was the sole continuous variable that predicted the absence of all three outcomes (AUROC 0.65, 95 per cent c.i. 0.62 to 0.69; $P = 0.001$). The Youden index cut-off was 1000 ml or less (sensitivity 72 per cent, specificity 64 per cent), which corresponded to the median blood loss of the whole population.

These five categorical variables were then introduced into a logistic regression, establishing a predictive model with five criteria, which was then validated using a bootstrap procedure (2000 times) (*Table 3*). This model provided a probability of absence of all three outcomes (ascites, bile leak and haemorrhage) with an apparent AUC of 0.77 (95 per cent c.i. 0.73 to 0.81; $P = 0.001$), and was well calibrated. After correction for optimism, the adjusted AUC decreased to 0.76. The ROC curve, calibration plot, and 5-fold cross-validated and bootstrap optimism-adjusted AUCs are displayed in *Figs S1–S3*.

Selection of low-risk recipients following liver transplantation

According to the model, fulfilling the five criteria predicted the absence of significant ascites, bile leak and haemorrhage with a

Table 1 Characteristics of the study population

	No. of patients* ($n = 944$)
Recipient demographic data	
Age (years)†	55 (47–61)
BMI (kg/m^2)†	25 (23–28)
Male sex	634 (67.2)
Underlying liver disease	
Cirrhosis	681 (72.1)
Alcohol	354 (37.5)
Non-alcoholic steatohepatitis	144 (15.3)
Hepatitis C virus infection	179 (19.0)
Hepatitis B virus infection	91 (9.6)
Biliary	51 (5.4)
Other	44 (4.7)
Hepatocellular carcinoma	262 (27.8)
Polycystic liver disease	58 (6.1)
Fulminant hepatitis	109 (11.5)
LT procedure	
Combined liver–kidney transplantation	77 (8.2)
Retransplantation	79 (8.4)
Emergency LT	163 (17.3)
Whole liver graft	838 (88.8)
Partial graft	106 (11.2)
Split liver graft	77 (8.2)
Reduced graft	20 (2.1)
Auxiliary LT	9 (1.0)
Preoperative and intraoperative evaluation	
MELD score†	15 (9–24)
Malnutrition	348 (36.9)
Pre-LT dialysis	127 (13.5)
Intraoperative ascites	425 (45.0)
Portal vein thrombosis	81 (8.6)
Donor and graft characteristics	
Age (years)†	59 (42–75)
BMI (kg/m^2)†	24 (22–27)
Male sex	481 (51.0)
Cardiac arrest	227 (24.0)
Donation after cardiac death	32 (3.4)
Graft weight (g)†	1300 (1100–1500)
Donor : recipient weight ratio (%)†	2 (1–2)
Duration of cold ischaemia (min)†	411 (347–494)
Duration of warm ischaemia (min)†	45 (37–50)

*With percentages in parentheses unless indicate otherwise; † values are median (i.q.r.). LT, liver transplantation; MELD, Model for End-stage Liver Disease.

Table 2 Multivariable analysis of preoperative, donor-related and intraoperative factors associated with ascites, biliary leak and haemorrhage after liver transplantation

	Coefficient*	P*	Adjusted RR†	P†
Ascites				
MELD score (every increase of 5 points)	0.21 (0.08, 0.34)	0.001	1.12 (1.05, 1.20)	0.001
No malnutrition	−0.57 (−0.99, −0.21)	0.006	0.74 (0.69, 0.91)	0.004
Whole graft	−0.46 (−0.99, 0.091)	0.092	0.77 (0.58, 1.01)	0.056
No intraoperative ascites (>10 ml/kg)	−1.53 (−1.91, −1.21)	0.001	0.38 (0.29, 0.50)	0.001
No portal vein thrombosis	−0.85 (−1.51, −0.20)	0.009	0.67 (0.52, 0.87)	0.003
No reperfusion syndrome	−0.36 (−0.75, 0.03)	0.067	0.83 (0.68, 1.01)	0.070
Blood loss (every increase of 500 ml)	0.13 (0.03, 0.23)	0.008	1.05 (1.02, 1.09)	0.005
Bile leakage				
No malnutrition	−0.63 (−1.23, −0.62)	0.045	0.58 (0.34, 1.01)	0.056
Whole graft	−1.39 (−2.06, −0.66)	0.001	0.31 (0.18, 0.54)	0.001
Blood loss (every increase of 500 ml)	0.13 (0.09, 0.24)	0.033	1.11 (1.01, 1.23)	0.033
Donor BMI (every increase of 5 kg/m^2)	−0.60 (−1.20, −0.21)	0.005	0.58 (0.38, 0.89)	0.013
Haemorrhage				
Portal vein thrombosis	−0.84 (−1.77, 0.35)	0.087	0.48 (0.21, 1.10)	0.085
Emergency LT	0.61 (−0.47, 1.43)	0.143	1.69 (0.82, 3.52)	0.157
Blood loss (every increase of 500 ml)	0.19 (0.06, 0.30)	0.001	1.18 (1.08, 1.30)	0.001

Values in parentheses are 95 per cent confidence intervals. Variables introduced in the first step of the three backward stepwise logistic regression analyses were: recipient age (years), recipient BMI (kg/m^2), partial graft, repeat liver transplantation (LT), combined liver–kidney transplantation, donation after cardiac death, malnutrition, Model for End-stage Liver Disease (MELD) score, emergency LT, donor age, donor BMI (kg/m^2), donor cardiac arrest, portal vein thrombosis, intraoperative ascites, duration of cold ischaemia (min), duration of warm ischaemia (min), portocaval shunt, blood loss (ml), duration of surgery (min) and reperfusion syndrome. RR, relative risk. *Bootstrapped (2000 times) logistic regression. †Robust Poisson regression including all variables retained after stepwise backward logistic regression.

Table 3 Modelling prediction of absence of ascites, bile leakage and haemorrhage after liver transplantation

	Coefficient‡	P‡	Adjusted RR§	P§
Independently associated variables*				
Whole liver graft	0.80 (0.17, 1.40)	0.006	1.32 (1.04, 1.66)	0.020
No intraoperative ascites	1.64 (1.20, 2.03)	0.001	2.01 (1.65, 2.44)	0.001
No malnutrition	0.56 (0.11, 0.96)	0.007	1.26 (1.06, 1.49)	0.009
No portal vein thrombosis	0.91 (0.22, 1.62	0.007	1.54 (1.05, 2.24)	0.026
Intraoperative blood loss (every increase of 500 ml)	−0.18 (−0.28, −0.08)	0.001	0.92 (0.88, 0.97)	0.001
Predictive model†				
Whole liver graft	0.77 (0.12, 1.41)	0.007	1.31 (1.04, 1.64)	0.021
No intraoperative ascites	1.65 (1.25, 2.12)	0.001	2.05 (1.68, 2.50)	0.001
No malnutrition	0.60 (0.17, 1.02)	0.002	1.27 (1.07, 1.51)	0.006
No vein thrombosis	0.90 (0.23, 1.04)	0.007	1.56 (1.06, 2.29)	0.024
Intraoperative blood loss ≤1000 ml	0.64 (0.22, 1.04)	0.001	1.39 (1.09, 1.48)	0.003
Constant	−2.87 (−3.81, −2.13)	0.001	–	–

Values in parentheses are 95 per cent confidence intervals. *Variables independently associated with absence of ascites, biliary leak and haemorrhage after liver transplantation (LT); variables introduced in the first step of the stepwise forward logistic regression were: donor BMI, Model for End-stage Liver Disease score, postreperfusion syndrome, whole-graft LT, no intraoperative ascites, no malnutrition, no portal vein thrombosis and intraoperative blood loss. †Predictive of absence of ascites, biliary leak and haemorrhage after LT with five criteria (Cox and Snell R^2 =0.356; P=0.795, Hosmer–Lemeshow test). RR, relative risk. ‡ Bootstrapped (2000 times) logistic regression. § Robust Poisson regression including all variables retained after stepwise forward logistic regression.

specificity of 92 per cent, a positive likelihood ratio of 4.3 and an RR of 1.74 (95 per cent c.i. 1.53 to 1.98; $P = 0.001$).

Among the 944 recipients, 218 (23.1 per cent) fulfilled all five predictive criteria and defined the group of low-risk recipients. These low-risk recipients had a lower MELD score than the remaining 726 patients (median 10 (i.q.r. 7–17) *versus* 15 (10–24) respectively; $P = 0.001$) and less cirrhosis (48.2 *versus* 79.3 per cent; $P = 0.001$), but more frequently had hepatocellular carcinoma (HCC) 61.9 *versus* 17.5 per cent; $P = 0.001$) and polycystic liver disease (9.6 *versus* 5.1 per cent; $P = 0.014$).

In addition to the lower risk of significant ascites (RR 0.22, 95 per cent c.i. 0.13 to 0.35; $P = 0.001$), haemorrhage (RR 0.21, 0.06 to 0.88; $P = 0.033$) and bile leak (RR 0.54, 0.23 to 0.98; $P = 0.048$), these low-risk patients had a decreased risk of severe complications (RR 0.70, 0.59 to 0.85; $P = 0.001$), 90-day mortality (RR 0.13, 0.03 to 0.53; $P = 0.004$) and 1-year mortality (RR 0.15, 0.05 to 0.46;

Table 4 Comparison of outcomes of low- and high-risk recipients following liver transplantation

	High-risk recipients ($n = 726$)	Low-risk recipients ($n = 218$)	P^*
No ascites, bile leak or haemorrhage	350 (48.2)	184 (84.4)	0.001
Ascites	308 (42.4)	21 (9.6)	0.001
Bile leak	64 (8.8)	9 (4.1)	0.021†
Haemorrhage	53 (7.3)	4 (1.8)	0.002
Reoperation	175 (24.1)	35 (16.1)	0.012
Surgical-site infection	72 (9.9)	11 (5.0)	0.026
Early graft dysfunction	160 (22.0)	46 (21.0)	0.769
Primary non-function	6 (0.8)	2 (0.9)	0.999†
Complication	473 (65.2)	111 (50.9)	0.001
Severe complication	418 (57.6)	88 (40.4)	0.001
90-day mortality	63 (8.7)	3 (1.4)	0.001
1-year mortality	87 (12.0)	4 (1.8)	0.001

Values in parentheses are percentages. *χ^2 test, except. †Fisher's exact test.

Table 5 Comparison of misclassified and well classified low-risk patients

	Misclassified recipients ($n = 34$)	Well classified recipients ($n = 184$)	$P^\dagger$
Demographic data			
Age (years)*	52 (42–57)	55 (48–61)	0.309‡
BMI (kg/m^2)*	25 (24–30)	25 (23–28)	0.534‡
Male sex	30 (88.2)	106 (57.6)	0.001
MELD score*	11 (8–22)	11 (8–18)	0.828‡
Donor-related data			
Age (years)*	50 (41–70)	58 (44–78)	0.242‡
BMI (kg/m^2)*	23 (21–27)	25 (22–28)	0.476‡
Steatosis on imaging	6 (17.6)	10 (5.4)	0.023§
Diabetes	6 (17.6)	18 (9.8)	0.228§
Cardiac arrest	14 (41.2)	38 (20.7)	0.009
Donation after cardiac death	4 (11.8)	4 (2.2)	0.022§
Duration of cold ischaemia (min)*	395 (353–443)	400 (350–457)	0.634‡
Duration of warm ischaemia (min)*	44 (36–52)	45 (40–56)	0.302‡
Outcomes			
Vascular-related complication	0 (0.0)	4 (2.2)	0.999
Reoperation	10 (29.4)	25 (13.6)	0.021
Early graft dysfunction	17 (50.0)	29 (15.8)	0.001
Infectious complication	16 (47.1)	44 (23.9)	0.006
Bacteraemia	8 (23.5)	10 (5.4)	0.002
Urinary tract infection	10 (29.4)	26 (14.1)	0.027
Pulmonary infection	6 (17.6)	14 (7.6)	0.097
Complication	26 (76.5)	85 (46.2)	0.001
Severe complication	23 (67.6)	65 (35.3)	0.001
90-day mortality	1 (2.9)	2 (1.1)	0.400§

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). MELD, Model for End-stage Liver Disease. † χ^2 test, except. ‡ Mann–Whitney *U* test and § Fisher's exact test.

$P = 0.001$) than the other 726 patients. Comparison of the outcomes for low- and high-risk recipients is detailed in *Table 4*.

Misclassified and well classified low-risk recipients

Of the 218 recipients classified as low risk according to the model, 34 (15.6 per cent) actually had ascites and/or bile leakage and/or haemorrhage while fulfilling the five criteria of the model, and were considered as 'misclassified' low-risk patients. The comparison of misclassified and well classified low-risk patients is provided in *Table 5*.

Among the misclassified low-risk recipients, 21 experienced significant ascites, nine had bile leaks and four had a postoperative haemorrhage; none experienced more than one of the three outcomes. On POD 7, the median ascites volume was 300 (250–1200) ml. Two bile leaks were diagnosed within the first 7 days after surgery. One was related to anastomotic leakage and the other arose from the site of protocol biopsy, and both required reoperation. Four bile leaks occurred after reoperation for complications related to other causes (1 evisceration, 1 exploratory laparotomy for sepsis, 2 bowel perforations). The three remaining bile leaks occurred after POD 15 and at least 1 week after removal of the abdominal drain; endoscopic drainage was required in two cases and percutaneous drainage in one.

Discussion

This study has provided an accurate and clinically relevant model, including five easy to assess criteria, to anticipate recipients at low risk of postoperative haemorrhage, bile leakage and significant ascites. Clinically relevant modelling of outcome prediction after LT should aim to provide a practical tool, based on

simple criteria, that could easily be used routinely, rather than an overfitted explanatory model involving countless and/or difficult to assess parameters. In this setting, the model provided in the present study included only five simple criteria predictive of significant of ascites, bile leakage or haemorrhage after LT.

Beyond its pure statistical performance, the relevance of this model lies in the fact that all five criteria are acknowledged to explain the occurrence of ascites, bile leak and haemorrhage. First, malnutrition, intraoperative ascites and portal thrombosis allow the severity of both underlying liver disease and portal hypertension, which are well known to be associated with increased risk of postoperative ascites and haemorrhage, to be captured. Assessment of these three variables is more practical and stronger than the MELD score, which was not retained after forward regression. In addition, malnutrition plays a pivotal role in the healing process and was found to be independently associated with the risk of bile leakage[29]. Second, partial grafts are known to be associated with a higher risk of haemorrhage and bile leak, given the presence of a large cut surface. Finally, intraoperative blood loss represents a reliable surrogate of intraoperative difficulties, such as technical complexity, but also impaired haemostasis related to the underlying liver disease and high haemorrhagic risk as a consequence of significant portal hypertension[30]. Moreover, substantial intraoperative blood loss may lead to impaired outcomes through haemodynamic instability and subsequent increased parenchymal or biliary ischaemic injury, but also enhanced reperfusion syndrome.

In this study, the proposed five criteria can be assessed easily at the end of LT, before parietal closure. Their assessment does not require any calculation or measurement, and is not time-consuming. In addition to postoperative ascites, bile leakage and haemorrhage, recipients who fulfilled all five criteria were also at low risk of overall and severe complications, and postoperative mortality. In this population of low-risk recipients, the model classified more than 80 per cent of the patients accurately, but 15.6 per cent nevertheless experienced ascites, bile leak or haemorrhage. Even though a predictive model can never achieve an accuracy of 100 per cent, various hypotheses could provide an explanation for this rate of misclassified patients. On one hand, the model does not anticipate the consequences of severe complications, such as severe sepsis, on the postoperative course. Misclassified patients experienced more complications, especially severe complications and bacteraemia, which have been reported repeatedly to participate in or promote liver failure, haemodynamic instability and coagulopathy, favouring all three of the outcomes of interest[31,32]. On the other hand, this model was not designed to predict early graft failure. Misclassified low-risk recipients received grafts of lower quality and experienced early graft failure more frequently than well classified patients. Indeed, these lower-quality grafts recovered slowly from ischaemia leading to decreased liver function, which could partly explain the higher rate of ascites or coagulopathy after LT[33,34]. Hence, the rate of misclassified recipients would likely be lower after exclusion of patients who received a marginal graft[35,36]. Nonetheless, despite the occurrence of ascites or bile leakage, these misclassified patients did not seem to have benefited from prophylactic abdominal drainage. In these patients, the clinical impact of ascites was low, with a median of 300 ml in the drainage fluid on POD 7 and nine patients experienced a bile leak, for which abdominal drainage did not provide any diagnostic benefit.

The non-drainage policy in liver resection was introduced more two decades ago. It has gained progressive acceptance[37] and is now recommended in various settings[38,39]. Considering the lack of evidence supporting routine abdominal drainage in LT recipients, the model provided here may allow the safe selection of ideal candidates for prospective evaluation of a non-drainage policy in the setting of LT. Although its reproducibility was not assessed by external validation, the model was derived and internally validated from a large and unselected population including all causes of LT (27.8 per cent had HCC) with a wide range of severity of the underlying liver diseases, as highlighted by the intermediate median MELD score. In this setting, the existence of a subset of low-risk recipients was plausible. Above all, the five criteria of the model are clinically relevant and their association with outcomes has been emphasized repeatedly. In this context, the originality of the present findings is not related to the inherent novelty of the criteria, but in their combination for safe selection of low-risk recipients for a non-drainage protocol. This combination identified low-risk recipients who had LT in favourable clinical settings, as is likely to occur in the French liver transplant cohort, illustrated by their lower MELD score and higher rate of LT for HCC. Likewise, this combination of five criteria is unlikely to occur in other liver transplant cohorts worldwide where recipients have an increased perioperative risk, thereby allowing objective exclusion of these high-risk patients from such protocols.

Early rehabilitation is now a widely accepted concept in the field of HPB surgery, and has been reported to be feasible, safe and cost-effective, and to shorten hospital stay in patients undergoing liver resection[40]. These early rehabilitation protocols involving surgeons, anaesthetists and physiotherapists were recently successfully applied to LT recipients in preliminary studies[41], supporting that LT recipients could benefit from such management[13,42]. In this context, the results of the present study could help in selecting patients qualifying for early rehabilitation to promote its safe diffusion.

The present study has various limitations related to its retrospective nature. First, the study assumed that the benefit of prophylactic abdominal drainage was limited to the improvement of diagnosis and management of ascites, bile leakage and haemorrhage, whereas other objective or subjective purposes may lead surgeons to place an abdominal drainage. As an example, this study did not take into account several technical aspects, such as the disparity of calibre between the donor and recipient common bile ducts, which could potentially influence the risk of bile leakage[4] and prompt prophylactic drain placement. Second, the definitions of outcomes were derived from consensual or widely employed definitions. However, the cut-off used for ascites (10 ml/kg in the drainage fluid, POD 5) could be discussed in the view of anaesthetic management and fluid requirement during the postoperative course of LT recipients. Morevover, this definition of ascites did not allow the occurrence of significant ascites and ascites infection to be distinguished. In addition, although low BMI is a well established factor associated with malnutrition in patients with cirrhosis, its performance as a screening tool is limited owing to fluctuations related to fluid retention, whereas its easy use facilitates the applicability of the model. Although the association between estimated dry BMI and the criterion 'no intraoperative ascites' reduces the risk of misinterpretation related to fluid retention, assessment of food intake (and possible barriers) and mid-arm circumference would improve the performance of the malnutrition criteria[29]. Otherwise, sarcopenia is a promising surrogate of malnutrition in patients with cirrhosis. However, modalities to measure muscle quantity and quality lack validation and diffusion; thus, clinical evaluation currently

remains the first-line screening tool[43]. Finally, because abdominal drain placement was performed routinely in this series, the study could not assess the results of a non-drainage policy, especially regarding the risk and management of ascites, bile leak and haemorrhage in low-risk recipients without abdominal drainage. At this point, this study is hypothesis-generating only. Nevertheless, the development of innovating protocols, such as a non-drainage policy following LT, needs to be validated by preliminary retrospective studies. Therefore, the reported model may represent a practical tool for screening a relevant subgroup of patients to be included in a prospective trial investigating a non-drainage policy in LT.

Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

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