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Preoperative risk factors for massive transfusion, prolonged ventilation requirements, and mortality in patients undergoing liver transplantation

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Background: Despite improvements in techniques and management of liver transplant patients, numerous perioperative complications that contribute to perioperative mortality remain. Models to predict intraoperative massive blood transfusion, prolonged mechanical ventilation, or in-hospital mortality in liver transplant recipients have not been identified. In this study we aim to identify preoperative factors associated with the above mentioned complications.

Methods: A retrospective observational analysis was conducted on data collected from 124 orthotopic liver transplants performed at a single institution between 2014 and 2017. A multivariable logistic regression using backwards elimination was performed for three defined outcomes (massive transfusion ≥ 10 units packed red blood cells (PRBC), prolonged mechanical ventilation > 24 h, and in-hospital mortality) to identify associations with preoperative characteristics.

Results: Statistically significant ($P < 0.05$) associations with massive transfusion ≥ 10 units PRBC were hepatocellular carcinoma and preoperative transfusion of PRBC. Significant associations with prolonged mechanical ventilation > 24 h were hepatitis C, alcoholic hepatitis, elevated preoperative alanine aminotransferase, and hepatorenal syndrome. Male gender was protective for requiring prolonged mechanical ventilation. End-stage renal disease and hepatitis B were significantly associated with increased in-hospital mortality.

Conclusions: This study identified risk factors associated with common perioperative complications of liver transplantation. These factors may assist practitioners in risk stratification and may form the basis for further investigations of potential interventions to mitigate these risks.

Keywords: Artificial respiration; Blood transfusion; Hepatitis C; Hepatocellular carcinoma; Liver cirrhosis; Liver transplantation.

Introduction

Liver transplantation has become an effective life-saving procedure for patients with acute liver failure, end-stage liver disease, and hepatic malignancy. Despite this, there are many perioperative complications that arise during liver transplantation that contribute to perioperative mortality [1]. The Model for End-Stage Liver Disease (MELD) score has been useful in predicting mortality in patients awaiting liver transplantation [2,3]. However, the MELD score has been shown to have non- or low-predictive value for many complications, including intraoperative massive blood transfusion [4,5] and prolonged mechan-

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ical ventilation [6]. Models similar to the MELD score to predict intraoperative massive blood transfusion, prolonged mechanical ventilation, or in-hospital mortality in liver transplant recipients have not been identified [7–10]. We aimed to identify preoperative factors associated with massive transfusion ≥ 10 units packed red blood cells (PRBC), prolonged mechanical ventilation > 24 h, and in-hospital mortality in liver transplant recipients by conducting a retrospective review of comorbidities, preoperative abnormalities, and laboratory values. We hypothesized that specific pre-operative patient characteristics would be associated with the above mentioned complications.

Materials and Methods

Study sample

Data were collected retrospectively from the data warehouse of the University of California, San Diego (UCSD) Healthcare Systems. All data from surgical patients undergoing orthotopic liver transplantation from April 2014 to August 2017 were extracted. The resulting dataset remained de-identified and did not contain sensitive patient-health information as defined by the UCSD Human Research Protections Program, and therefore, was exempt from the informed consent requirement and approved by our Institutional Review Board (IRB), IRB number 171557. During the study period there was no change in surgery or anesthesia leadership of the liver transplant program.

Data and outcomes

The outcomes studied were intraoperative massive transfusion ≥ 10 units PRBC, prolonged mechanical ventilation > 24 h, and in-hospital mortality. Through literature review and expert discussion, we pre-determined factors potentially associated with these outcomes. Characteristics collected for analysis included patient age, sex, body mass index, MELD score, etiology of liver failure (hepatitis C, hepatitis B, alcohol use, hepatocellular carcinoma [HCC], primary biliary cirrhosis, non-alcoholic steatohepatitis [NASH], cryptogenic, and 'other'), comorbidities (hepatorenal syndrome, hepatopulmonary disease, atrial fibrillation, congestive heart failure, portopulmonary hypertension, coronary artery disease, end-stage renal disease, diabetes mellitus, coagulopathy, cardiac valve abnormality, pulmonary hypertension, and diastolic dysfunction), preoperative laboratory values, and need for preoperative transfusion of PRBC, fresh frozen plasma, cryoprecipitate, and platelets.

Statistical analysis

Statistical analysis was performed using R, a software environment for statistical computing (R Core Team [2013]. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available from <http://www.R-project.org/>). A multivariable logistic regression using backwards elimination was performed for each of the three outcomes (transfusion ≥ 10 units PRBC, prolonged mechanical ventilation > 24 h, and in-hospital mortality) to identify associations. All variables were included in the initial model building process of the multivariate analysis. In a step-by-step fashion, we removed one variable at a time from the model that had the highest P value greater than 0.05. This was performed until all variables in the model had $P < 0.05$ in its association with the outcome. None of the variables that were not statistically significant in its association with the outcome were included in the final model. The odds ratio (OR) and corresponding 95% CI were then reported. Multicollinearity was assessed with variance inflation factor (VIF). We determined that if $VIF < 5$, correlation between predictor variables were not high. In the multivariable logistic regression analysis, all predictors demonstrated a $VIF < 5$. When summarizing demographic data, categorical variables were summarized as count and percentages, while continuous variables were reported as mean and standard deviation (SD).

Results

The patient demographics of the 124 patients included in the study are shown in Table 1. The mean age was 55.3 years old (SD 10.7 years). Of the patients, 59.7% were males. Etiologies of liver failure are presented in Tables 1 and 2. Common co-morbidities include diabetes type II, hepatorenal syndrome, congestive heart failure, end-stage renal disease, and coronary artery disease. All liver transplants during the study period were performed by a single primary surgeon. Postoperative outcomes are shown in Table 3: 55.6% of patients required intraoperative massive transfusion ≥ 10 units of PRBC, 53.2% of patients required prolonged ventilation $>$ than 24 h, and 10.5% of patients died during the hospitalization. The mean number of days for postoperative ventilation was 7.8 days (SD 15.5 days). The mean number of days for ICU and hospital length of stay were 8.9 days (SD 13.8 days) and 25.7 days (SD 23.4 days), respectively.

The results of the final multivariable logistic regression model are listed in Table 4 with OR, 95% CI, and P value. Significant risk factors for massive transfusion were HCC and preoperative transfusion of PRBC. Increased preoperative hematocrit, increased pre-

Table 1. Preoperative Characteristics of Cases

Characteristics	N	%
Total liver transplants	124	-
Age (yr)	55.3 (10.7)	
Sex (Male)	74	59.7
BMI (kg/m ²)	25.7 (5.2)	
MELD score	29.4 (11.7)	
Etiology of liver disease		
Hepatitis C	42	33.9
Hepatitis B	4	3.2
Alcohol	32	25.8
Hepatocellular carcinoma	16	12.9
Primary biliary cirrhosis	10	8.1
Non-alcoholic steatohepatitis	13	10.5
Cryptogenic	8	6.5
Other	12	9.7
Comorbidities		
Hepatorenal syndrome	48	38.7
Hepatopulmonary disease	5	4.0
Atrial fibrillation	6	4.8
Congestive heart failure	5	4.0
Portopulmonary hypertension	7	5.6
Coronary artery disease	10	8.1
End-stage renal disease	45	36.3
Diabetes mellitus	34	27.4
Coagulopathy	4	3.2
Cardiac valve abnormality	30	24.2
Pulmonary hypertension (PAP ≥ 25 mmHg)	51	41.1
Diastolic dysfunction	19	15.3
Preoperative transfusion		
Packed red blood cells	41	33.1
Fresh frozen plasma	35	28.2
Cryoprecipitate	27	21.8
Platelets	28	22.6

Values are presented as mean (SD) or number of patients (N) and percentage. BMI: body mass index, MELD: model for end-stage liver disease, PAP: pulmonary artery pressure.

operative fibrinogen, and increased alanine aminotransferase (ALT) were protective for preventing massive postoperative transfusion. Risk factors for postoperative ventilation greater than 24 h included hepatitis C, alcoholic hepatitis, elevated preoperative ALT, and hepatorenal syndrome. Male sex was protective for postoperative ventilation greater than 24 h. End-stage renal disease and hepatitis B were associated with increased in-hospital mortality.

Discussion

Despite orthotopic liver transplantation being the most effective

Table 2. Preoperative Laboratory Values

Hematocrit (%)	29.4 (7.3)
Platelets (10 ⁹ /L)	90.0 (99.8)
INR	2.1 (1.1)
PTT (s)	45.6 (16.5)
Fibrinogen (g/L)	1.847 (0.833)
WBC (10 ⁹ /L)	7.8 (5.5)
BUN (mmol/L)	8.32 (7.11)
Creatinine (mmol/L)	0.12 (0.10)
AST (μkat/L)	2.44 (3.96)
ALT (μkat/L)	2.29 (7.00)
Alkaline phosphatase (μkat/L)	2.65 (1.86)
Albumin (mmol/L)	0.049 (0.09)

Values are presented as mean (SD). INR: international normalized ratio, PTT: partial thromboplastin time, WBC: white blood cells, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Table 3. Intraoperative and Postoperative Outcomes

	N	%
Intraoperative transfusion requirements		
Packed red blood cells (units)	16.3 (17.4)	
Fresh frozen plasma (units)	12.2 (13.1)	
Platelets (units)	3.5 (3.6)	
Cryoprecipitate (units)	5.9 (10.8)	
Total (units)	37.8 (37.9)	
Massive transfusion (≥ 10 units PRBC)	69	55.6
Mortality		
Intraoperative	5	4.0
Postoperative (inpatient)	8	6.5
Total perioperative mortality	13	10.5
Postoperative ventilation greater than 24 h	66	53.2
Postoperative ventilator requirement (days)	7.8 (15.5)	
Intensive care unit length of stay (days)	8.9 (13.8)	
Hospital length of stay (days)	25.7 (23.4)	

Values are presented as mean (SD) or number of patients (N) and percentage.

method for survival of liver failure, it carries significant risks of morbidity and mortality. The main findings of our study are: the presence of HCC and preoperative transfusion correlated with intraoperative massive transfusion of ≥ 10 units of PRBC. Hepatitis C, alcoholic hepatitis, and hepatorenal syndrome correlated with an increased risk of postoperative mechanical ventilation greater than 24 h. Male sex correlated with a reduced risk of prolonged mechanical ventilation greater than 24 h. Hepatitis B and end-stage renal disease correlated with an increase in in-hospital mortality.

Massive transfusion during liver transplantation has been asso-

Table 4. Multivariable Logistic Regression Modeling Various Outcomes

	OR (95% CI)	P value
Massive transfusion \geq 10 units PRBC		
Hepatocellular carcinoma	5.01 (1.20–21.09)	0.032
Hematocrit (per 1% increase)	0.93 (0.87–0.99)	0.043
Incremental fibrinogen (per 0.01 g/L increase)	0.99 (0.99–0.99)	< 0.001
Incremental ALT (per 0.017 μ kat/L increase)	0.99 (0.99–0.99)	0.013
Preoperative PRBC transfusion	6.63 (1.82–24.2)	0.004
Postoperative mechanical ventilation > 24 h		
Male sex	0.43 (0.19–0.98)	0.044
Hepatitis C	2.84 (1.16–6.94)	0.027
Alcoholic hepatitis	3.36 (1.27–8.92)	0.015
Preoperative ALT	1.004 (1.0003–1.008)	0.031
Hepatorenal syndrome	2.53 (1.09–5.86)	0.034
In-hospital mortality		
End-stage renal disease	10.42 (2.16–50.21)	0.003
Hepatitis B	24.24 (2.03–289.73)	0.016

Values are presented as odds ratio (95% CI). ALT: alanine aminotransferase, PRBC: packed red blood cells, OR: odds ratio.

ciated with higher mortality, prolonged length of stay, and increased rate of infectious complications [11]. Improvement in intraoperative management has significantly decreased transfusion needs and improved overall mortality and morbidity [12]. Current research has primarily concentrated on intraoperative management. In contrast, we have concentrated on preoperative factors influencing morbidity and mortality of liver transplant recipients. Our statistical analysis demonstrates that patients with HCC and preoperative transfusion have an increased risk for massive transfusion.

The increased risk of bleeding in HCC patients is likely due to the rich blood supply of the tumor. The high pressure of arterial vascularization of the tumor is associated with increased rate of hemorrhage and difficulty obtaining hemostasis [13]. While this is not a modifiable risk factor, the presence of HCC should alert the transplant team for potential higher transfusion needs.

A recent study by Massicotte et al. [14] revealed that preoperative anemia was associated with a higher risk of transfusion during liver transplant and suggests that optimizing hemoglobin before surgery could be potentially valuable. This is consistent with our finding preoperative anemia and preoperative transfusion to be significantly correlated with high transfusion requirement. This could be that transfusion increases central venous pressure, which has been found to be associated with increased bleeding [14].

We report herein that hepatitis, C alcoholic hepatitis, and hepatorenal syndrome are correlated with mechanical ventilation greater than 24 h. Male sex was found to have reduced the risk of mechanical ventilation greater than 24 h. In a previous analysis of

a nationwide database prolonged mechanical ventilation has been associated with increased mortality and graft failure [7]. In this study female gender was also associated with increased need for prolonged mechanical ventilation and the authors attributed this to the fact that female liver transplant patients seem to be older, more frail, and potentially have more advanced liver failure [7].

Numerous studies have examined the association of post-transplant mortality with postoperative decline in kidney function [15–17] and preoperative hepatorenal syndrome [18]. However, these studies did not note the association of hepatorenal syndrome and prolonged ventilation, which we found to be statistically significant. The etiology of this association deserves closer investigation, but one hypothesis may be that the relative hypervolemia and increased capillary permeability of patients with hepatorenal syndrome may lead to increased work of breathing and poor gas exchange post-operatively. This may suggest that increased attention to fluid status intraoperatively may be beneficial.

Prior study of the association of hepatitis C and alcoholic cirrhosis with prolonged ventilation was not found in any of the literature reviewed for this study. Despite the unclear etiology of this association, the presence of hepatitis C or alcoholic cirrhosis may assist with risk stratification and patient planning.

Finally, our data analysis found hepatitis B and end-stage renal disease to have significant association with post-transplant in-hospital mortality. Impaired kidney function and post-transplant mortality has been frequently reported, though most studies found a postoperative decline in kidney function to have a higher association with long-term mortality than measurements of pre-

operative function [15–18]. Our finding of an association between end-stage renal disease and in-hospital mortality is not unexpected, given the common postoperative complications seen in patients with end-stage renal disease. A large study of dialysis patients undergoing general surgery utilizing the American College of Surgeons NSQIP database found significantly increased rates of death, thromboembolism, stroke, myocardial infarction, pneumonia, and urinary tract infections [19].

Prior studies of liver transplant outcomes have not found increased mortality rates in patients with hepatitis B as compared to hepatitis C, alcoholic cirrhosis, autoimmune hepatitis, and malignancy [20]. The etiology of our finding of significant association between hepatitis B and in-hospital mortality is unclear. One hypothesis may be that fulminant hepatic failure represents an increased proportion of the hepatitis B patients.

Our results have to be seen within the context of its limitations. This is a retrospective single center study. Though all results may not be generalizable, the study period was chosen due to the stable surgical, anesthesiology, and medicine transplant teams, which allowed us to focus on the variables in question without having to account for significant differences in patient care. The study population size of 124 is relatively small, which may have left the study underpowered to identify perioperative associations of smaller effect.

In summary we hope that this study prompts further attempts to improve methodologies for predicting perioperative complications in orthotopic liver transplant patients. Though some conclusions were consistent with the known pathophysiology of comorbidities, such as an association between end stage renal disease and in-hospital mortality, other etiologies remain elusive, such as an association between hepatitis C and prolonged mechanical ventilation. These associations prompt many questions deserving of closer investigation. Further investigations should include a more in-depth analysis, including removal of confounding variables, inclusion and exclusion criteria, and further analysis of postoperative events leading to mortality and prolonged mechanical ventilation. Our goal in this and in future studies is to define and refine specific predictive values, allowing practitioners to have a preliminary system of predicting which patients may have an increased risk of massive transfusion, prolonged mechanical ventilation, and in-hospital mortality.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Dennis Danforth (Formal analysis; Writing – original draft; Writing – review & editing)

Rodney A. Gabriel (Formal analysis; Investigation; Methodology; Software)

Anthony I. Clark (Data curation; Formal analysis; Investigation; Writing – original draft)

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