Intraoperative risk factors of acute kidney injury after liver transplantation

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Abstract
Acute kidney injury (AKI) is one of the most common complications of liver transplantation (LT). We examined the impact of intraoperative management on risk for AKI following LT. In this retrospective observational study, we linked data from the electronic health record with standardized transplant outcomes. Our primary outcome was stage 2 or 3 AKI as defined by Kidney Disease Improving Global Outcomes guidelines within the first 7 days of LT. We used logistic regression models to test the hypothesis that the addition of intraoperative variables, including inotropic/vasopressor administration, transfusion requirements, and hemodynamic markers improves our ability to predict AKI following LT. We also examined the impact of postoperative AKI on mortality. Of the 598 adult primary LT recipients included in our study, 43% (n = 255) were diagnosed with AKI within the first 7 postoperative days. Several preoperative and intraoperative variables including (1) electrolyte/acid-base balance disorder (International Classification of Diseases, Ninth Revision codes 253.6 or 276.x and International Classification of Diseases, Tenth Revision codes E22.2 or E87.x, where x is any digit; adjusted odds ratio [aOR], 1.917, 95% confidence interval [CI], 1.280–2.869; p = 0.002); (2) preoperative

Abbreviations: aHR, adjusted hazard ratio; AKI, acute kidney injury; aOR, adjusted odds ratio; BMI, body mass index; BUN, blood urea nitrogen; CDC, Center for Disease Control and Prevention; CI, confidence interval; CMV, cytomegalovirus; c-statistic, concordance statistic; DBD, donation after brain death; DCD, donation after circulatory death; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; INR, international normalized ratio; KDIGO, Kidney Disease Improving Global Outcomes; LT, liver transplantation; MAP, mean arterial pressure; MDRD-4, Modification of Diet in Renal Disease, 4 variable; MELD, Model for End-Stage Liver Disease; MPOG, Multicenter Perioperative Outcomes Group; OTIS, Organ Transplant Information System; pRBC, packed red blood cells; RRT, renal replacement therapy; SD, standard deviation.

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INTRODUCTION

Acute kidney injury (AKI) is one of the most common complications following liver transplantation (LT), with more than half of all LT recipients demonstrating at least acute renal failure.[1,2] Posttransplant AKI is associated with longer stays in the intensive care unit,[3] increased graft rejection,[4] higher hospital costs,[3] and higher mortality[5,6] independent of pretransplant renal function.[7]

Previous studies have shown that donor factors and recipient preoperative factors increase the risk of AKI[8,9] and chronic kidney disease[10,11] following LT. A variety of preoperative and postoperative factors (e.g., exposure to calcineurin inhibitors) have been linked to post-LT AKI.[7] The long-term impact of intraoperative events, such as acidosis, low hematocrit values, or duration of each transplant stage, and anesthesia factors, such as norepinephrine and blood transfusion (including red blood cells, plasma, and cryoprecipitate) on posttransplant AKI is not well studied.

Real-time data capture within electronic medical records allows the opportunity to link intraoperative data[12] with postoperative outcomes, thus refining our understanding of the impact of the perioperative period. Given the time-sensitive nature of the development of AKI, the identification of perioperative predictors of posttransplant renal dysfunction could allow the development of renal protection strategies directed at high-risk patients, and the identification of intraoperative predictors may enable modification of intraoperative care to reduce the risk of renal injury in at-risk patients.

The objective of this study is to identify modifiable risk factors associated with AKI following LT. Our hypothesis was that the addition of intraoperative variables, including inotrope/vasopressor administration, transfusion requirements, and hemodynamic markers, improves our ability to predict AKI following LT. In addition, intraoperative variables specifically curated at key stages of the transplant, such as reperfusion, might further improve our ability to predict AKI and provide insight into the mechanism of renal injury.

PATIENTS AND METHODS

Study design

For this retrospective observational study performed at our academic quaternary care center, we obtained institutional review board (HUM00153452) approval. This article was prepared in accordance with the standards set forth by the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[13] Study methods including data collection, outcomes, and statistical analyses were established prospectively and presented at an institutional peer review committee on October 10, 2018, prior to data access.[14] No organs from executed prisoners were used.

Data collection

Our primary data sources were collected via combined queries of (1) the local University of Michigan Multicenter Perioperative Outcomes Group (MPOG) data set and (2) Michigan Medicine’s Organ Transplant Information System (OTIS). The local MPOG data set collects information from the electronic perioperative anesthesia database (Centricity, General Electric Healthcare, Waukesha, WI) and electronic health record (Epic, Verona, WI). OTIS is an internal clinical database that tracks patients from waitlist enrollment through death and contains demographic, clinical, and donor variables. In addition, OTIS contains the information reported to the Scientific Registry of Transplant Recipients and tracks standardized outcomes, including (1) AKI, (2) postoperative dialysis, (3) mortality, (4) graft failure, and (5) retransplantation.

Inclusion and exclusion criteria

All primary, adult liver recipients who received transplants at Michigan Medicine between 2008 and 2018 were included in our study. Patients were excluded if they had preoperative stage 5 end-stage renal
Primary outcome

Our primary outcome was stage 2 or 3 AKI as defined by Kidney Disease Improving Global Outcomes (KDIGO) guidelines, using the maximum measured serum creatinine within the first 7 days following transplantation compared with preoperative serum creatinine closest to the time of transplant. These guidelines specify stage 2 as 2.0 to 2.9 times baseline and stage 3 as 3.0 times baseline or ≥4.0 mg/dL or the initiation of renal replacement therapy (RRT).[16] RRT receipt within the 7 days was considered stage 3 regardless of the creatinine change. We did not consider urine output rate in our classification, as this information was not uniformly available within our database. Only considering KDIGO stage 2 or 3 AKI allowed us to model the most severe and drastic changes in kidney function.

Secondary outcome

The secondary outcome was survival, censored at the length of follow-up in our database.

Covariates

In the MPOG database, data are stored, validated, and extracted for quality improvement and research purposes.[16,17] From the combined data set, we curated 107 covariates that were grouped as (1) demographic, (2) procedural, (3) etiology of liver failure, (4) donor/graft-variables that were grouped as (1) demographic, standardized entry in the history and physical evaluation were curated from a combination of diagnostic codes, performed preoperatively by the anesthesia provider, and free-text search for relevant terminology. Diagnostic codes were grouped according to a previously validated approach.[18] Examples include (1) preoperative anemia (defined as iron deficiency or folate and B12 deficiencies) and (2) preoperative electrolyte/acid-base balance disorders (defined as syndrome of inappropriate antidiuretic hormone secretion or various electrolyte and acid/base disorders).[19] Electrolyte/acid-base balance disorders are based on the Elixhauser Comorbidity Index, which is positive if the patient has International Classification of Diseases, Ninth Revision [ICD-9]/International Classification of Diseases, Tenth Revision [ICD-10] diagnosis codes for syndrome of inappropriate antidiuretic hormone secretion [ICD-9 253.6x and ICD-10 E22.2x] or various electrolyte and acid/base disorders [ICD-9 276 and 276.x and ICD-10 E86.x, E87.x, E88.x], where x is any digit.) In addition, we calculated time-weighted averages of physiologic measures taken throughout the LT process. Finally, we adjusted for preoperative (baseline) estimated glomerular filtration rate (eGFR) calculated using the MDRD-4.[21]

Statistical analysis

Exploratory data analysis techniques, such as histograms, QQ-Plots, box-plots, scatterplots and basic descriptive (means, medians, interquartile ranges) were used to assess the distribution of dependent measures. This allowed us to identify the distribution of outcomes which in turn facilitated appropriate modeling strategies. In addition, these techniques also were used to explore the most informative transformations of the covariates, confounders, and relevant predictors considered in the analysis. Extreme values were identified and their removal from the analysis was determined. Missing patterns and rates were assessed. Descriptive statistics were compiled on LT patients developing and not developing postoperative AKI.

Patients who had not received pretransplant dialysis were analyzed for development of AKI and subsequent mortality. Mortality was determined from the LT database. First, patients who developed AKI were compared with patients without AKI using Fisher's exact and chi-square tests for categorical variables and an independent t test for continuous variables. Heavily skewed variables, such as transfusion quantities and norepinephrine doses, were log transformed for inclusion in the regressions. Missing data were imputed via the method of multiple imputation using fully conditional specification and predictive mean matching. To determine the independent associations with AKI, we used logistic regressions with forward selection using the likelihood ratio.

Mortality was analyzed using Cox proportional hazards models. First, the proportionality assumption was confirmed with Schoenfeld residuals. Then all variables
were entered using forward selection. For both the logistic regression and Cox proportional hazards models, the multiple imputation models were combined with Rubin’s rules. Variables with $p < 0.05$ and 95% confidence intervals (CIs) that excluded 1 were deemed statistically significant. No adjustment was made for multiple models. Discriminations of the logistic regression models were assessed with the concordance statistic (c-statistic), which was calculated separately for each model, and the pooled results and standard errors were calculated after logistic transform using the method of DeBray. Pooled results were then back transformed for presentation.\(^{22}\)

**Power**

Power analysis and sample size determination were done for 2 correlated proportions with a range between 10% and 20% dropout. Parameters used for this analysis were determined based on previous knowledge. We assumed the incidence of AKI to be 40% and that mild hypotension was associated with an increased adjusted odds ratio (aOR) of AKI of 1.34 (95% CI, 1.16–1.56). In addition, we assumed a 2-sided test with $\alpha = 0.05$ and an intracluster correlation of 0.5. Results from this analysis indicated that a sample ranging between 185 and 600 would provide 85% power to test our research questions. Power analysis was performed with PASS 2021 software (NCSS Statistical Software, Kaysville, UT, USA). In addition, simulation studies show that for different intraclass correlations structures a sample size ranging between 150 to 500 will provide power ranging between 80% and 90% to test the significance of parameters.\(^{23}\) Although the study was powered to detect the significance of individual parameters, the study may be underpowered to find a difference in discrimination between the preoperative (models 1 and 2) and preoperative and intraoperative (models 3 and 4) models.

**Models**

**Preoperative recipient-specific model (Model 1)**

We first created a model that assessed association between our primary outcome, AKI, and a variety of patient-specific variables that would be known preoperatively (model 1). Variables included in each model can be found in Table S1.

**Preoperative and donor-specific model (Model 2)**

The next model incorporated donor-specific variables, including donor age, donor sex, donor cause of death, and graft ischemic time.

**Phase-specific model: Reperfusion (Model 3)**

To test our hypothesis that variables specific to each phase of transplantation may have a previously undetected association that could further improve AKI prediction, we created a model using intraoperative data censored to the period following reperfusion. Additional variables in this model included transfusions and norepinephrine administration given during reperfusion and laboratory values, including lactate, potassium, and ionized calcium measured during reperfusion.

**Model with data at case completion (Model 4)**

Model 4 was composed of full data known at case completion, including case duration, total transfusion requirements, and cumulative dosage of norepinephrine.

**Mortality (Models 5 and 6)**

Model 5 comprised data known by the end of the operation plus AKI and receipt or not of dialysis. We also performed a nonpredetermined analysis to assess the relationship between the subset of patients with stage 3 AKI needing dialysis within 7 days following transplantation and mortality (model 6). All statistical analyses were performed in SPSS 27.0 (IBM, Armonk, NY).

**Comparison of model discrimination**

Model discrimination was quantified using the area under the receiver operator characteristic curve (c-statistic). Comparison between the discrimination of preoperative models (models 1 and 2) and preoperative and intraoperative models (models 3 and 4) was done using the Hanley and McNeil method to calculate the $z$ score for each of the values. We then combined the $z$ scores with Rubin’s rules and calculated the 2-tailed $p$ value.\(^{24}\)

**RESULTS**

**Cohort characteristics and univariate associations**

Of the 598 adult primary LT recipients included in our study, 43% (n = 255) were diagnosed with AKI within the first 7 postoperative days, and 149 (25%) had KDIGO stage 2 and 106 (18%) stage 4. Of the patients, 66.1% (n = 395) were men, and the median age at the time of transplant was 54 years (standard deviation [SD], 11 years). A total of 80.6% of the patients (n = 482) identified as White, and 7.5% (n = 45) identified as Black. Median body mass index (BMI)
was 29.2 kg/m² (SD, 6.1 kg/m²). Patients had a median baseline eGFR of 78.7 mL/min/1.73 m² (SD, 41) and Model for End-Stage Liver Disease (MELD) of 19 (SD, 8). In addition, 11% (n = 63) had preoperative anemia, 61% (n = 365) had a preoperative electrolyte/acid-base balance disorder, and 35% (n = 208) had preexisting cardiac arrhythmia.

Patients subsequently developing AKI were more likely to have a higher BMI (30.3 kg/m² [SD, 6.6 kg/m²]) compared with 28.4 kg/m² [SD, 5.5 kg/m²]; p < 0.001), preexisting anemia (14.9% vs. 7.3%; p = 0.003), cardiac arrhythmia (41.2% vs. 30.0%; p = 0.006), and fluid/electrolyte disorder (70.2% vs. 54.2%; p < 0.001). Somewhat surprisingly, patients developing AKI following LT also had a higher baseline eGFR (87.3 mL/min/1.73 m² [SD, 42.9 mL/min/1.73 m²] compared with 72.4 mL/min/1.73 m² [SD, 37.7 mL/min/1.73 m²]; p < 0.001) and lower MELD scores (18 [SD, 7] compared with 20 [SD, 9]; p < 0.001). Intraoperatively, patients developing AKI required larger volume transfusion with red cells (10.7 units [SD, 17.1 units] vs. 8.2 units [SD, 14.5 units]; p < 0.001) and plasma (13.7 units [SD, 17.6 units] vs. 11.0 units [SD, 13.6 units]; p < 0.001). Characteristics for our full cohort, as well as the univariate descriptive differences between the AKI and non-AKI cohorts are presented in Tables 1–3.

We found that 3.8% (n = 23) patients died within 30 days of transplant, 9.0% (n = 54) died within 1 year, and 13.0% (n = 78) died within 3 years. Additional details can be found in Table 4.

**Model composed of recipient-specific, preoperative variables (Model 1)**

In an adjusted multivariate logistic model, several preoperative variables, including (1) BMI (aOR, 1.077; 95% CI, 1.044–1.112; p < 0.001), (2) electrolyte/acid-base balance disorder (aOR, 2.040; 95% CI, 1.374–3.030; p < 0.001), (3) preoperative anemia (aOR, 2.985; 95% CI, 1.623–5.489; p < 0.001), and (4) cardiac arrhythmia (aOR, 1.818; 95% CI, 1.240–2.666; p = 0.002) were associated with post-LT AKI. (Cardiac arrhythmias are based on the Elixhauser Comorbidity Index, which is positive if the patient has ICD-9/ICD-10 diagnosis codes for mechanical complication of pacemaker/defibrillator [ICD-9 996.01, 996.04; ICD-10 T82.1x], atrioventricular block and various dysrhythmias [ICD-9 426.0x, 426.7x, 426.9x, 426.1, 426.0, 426.2, 426.3, 427.x except 427.5; ICD-10: I441.x, I442.x, I443.x, I45.6x, I45.9x, I47, I48, I49, I47.x, I48.x, I49.x], tachycardia, bradycardia unspecified [ICD-9 785.0x; ICD-10: R00.0x, R00.1x, R00.8x]; or defibrillator, pacemaker, cardiac device [ICD-9 V45.0x, V53.3x; ICD-10: Z45.0x, Z95.0x], where x is any digit.)

In addition, the preoperative laboratory data, including (1) lower serum albumin (aOR, 0.611; 95% CI, 0.431–0.865; p = 0.01), (2) lower blood urea nitrogen (BUN; aOR, 0.963; 95% CI, 0.944–0.982; p < 0.001), (3) lower international normalized ratio (INR; aOR, 0.606; 95% CI, 0.420–0.875; p = 0.01), and (4) higher eGFR (aOR, 1.007; 95% CI, 1.001–1.013; p = 0.03), were also associated with AKI. Full results of the multivariate logistic regression are provided in Table 5. Model 1 had good discrimination (c-statistic, 0.741 ± 0.026). (The following is the interpretation of the c-statistic: 0.5 or less for a poor model, more than 0.7 for a good model, more than 0.8 for a strong model, and 1.0 for a perfect model.)

**Phase-specific modeling—Reperfusion phase (Model 3)**

Next we created a model that examined the contribution from individual phases of LT. Based on univariate analysis (Table 4), we selected reperfusion phase as the phase of transplantation that provided the most informative, phase-specific data. Model 3 includes laboratory studies, MAP, and norepinephrine administration from the reperfusion phase. Notably, reperfusion potassium (aOR, 1.513; 95% CI, 1.103–2.077; p = 0.01) and reperfusion lactate (aOR, 1.081; 95% CI, 1.003–1.166; p = 0.04) were the only reperfusion phase-specific variables included in model 3. In addition, lower age (aOR, 0.979; 95% CI, 0.962–0.995; p = 0.01) and unexpected preoperative weight loss (aOR, 1.596; 95% CI, 1.006–2.532; p = 0.05) now became significant. Model discrimination increased to 0.759 ± 0.032. A calibration plot for model 3 showing the proportion of patients with AKI for each quintile of risk is shown in Figure S1A.

**Full data, case completion model (Model 4)**

Model 4 included the full available data at case completion. This included data from all 3 phases of LIVER TRANSPLANTATION
### TABLE 1 Characteristics of LT patients developing stage 2 or 3 AKI: recipient and donor factors

| Variable               | Level | All data (n = 598) | No KDIGO Stage 2 or 3 (n = 343) | KDIGO Stage 2 or 3 (n = 255) | p value |
|------------------------|-------|-------------------|---------------------------------|------------------------------|---------|
|                        | Mean, n | SD, Percentage | Mean, n | SD, Percentage | Mean, n | SD, Percentage | Chi-square test, t test |
| Age, years             | 54    | 11.0            | 54    | 11              | 52    | 11              | 0.06 |
| BMI, kg/m²             | 29.2  | 6.1             | 28.4  | 5.5             | 30.3  | 6.6             | <0.001 |
| Sex                    | Female | 203 33.9         | 117 34.1         | 86 33.7         | 0.92   |
|                        | Male   | 395 66.1         | 226 65.9         | 169 66.3         |         |
| Race                   | White/Caucasian (3) | 482 80.6 | 278 81.0 | 204 80.0 | 0.65 |
|                        | Black (reference) | 45 7.5       | 25 7.3          | 20 7.8          |         |
|                        | Other (Not White/Caucasian or Black) (1) | 19 3.2 | 13 3.8 | 6 2.4 |         |
|                        | Unknown (2) | 52 8.7 | 27 7.9 | 25 9.8 |         |
| Liver failure etiology | Hepatitis B virus | 18 3.0 | 9 2.6 | 9 3.5 | 0.52 |
|                        | Hepatitis C virus | 183 30.6 | 99 28.9 | 84 32.9 | 0.29 |
|                        | Hepatocellular carcinoma | 170 28.4 | 96 28.0 | 74 29.0 | 0.78 |
|                        | Nonalcoholic steatohepatitis | 84 14.0 | 43 12.5 | 41 16.1 | 0.22 |
|                        | Cryptogenic cirrhosis | 52 8.7 | 29 8.5 | 23 9.0 | 0.81 |
|                        | Primary sclerosing cholangitis | 62 10.4 | 36 10.5 | 26 10.2 | 0.91 |
|                        | Alpha-1-antitrypsin deficiency | 19 3.2 | 12 3.5 | 7 2.7 | 0.60 |
|                        | Fulminant liver failure | 25 4.2 | 19 5.5 | 6 2.4 | 0.05 |
|                        | Alcohol-related cirrhosis | 127 21.2 | 74 21.6 | 53 20.8 | 0.82 |
|                        | Biliary Etiology | 33 5.5 | 22 6.4 | 11 4.3 | 0.27 |
|                        | Autoimmune hepatitis | 24 4.0 | 16 4.7 | 8 3.1 | 0.35 |
| Donor factors          | Age, years | 40 16.0 | 40 16 | 40 15 | 0.67 |
| Donor sex              | Female | 226 37.8         | 132 38.5         | 94 36.9         | 0.53   |
|                        | Male   | 367 61.4         | 207 60.3         | 160 62.7         |         |
|                        | CDC high-risk donor | 91 15.2 | 47 13.7 | 44 17.3 | 0.23 |
|                        | DBD    | 536 89.6         | 315 91.8         | 221 86.7         | 0.11   |
|                        | DCD    | 40 6.7           | 19 5.5           | 21 8.2           |         |
| Graft ischemic times   | Warm ischemia, minutes  | 31 9.0 | 31 9 | 32 9 | 0.24 |
|                        | Cold ischemia, minutes | 364 170.0 | 371 180 | 355 156 | 0.26 |
|                        | Total ischemia, minutes | 391 153.0 | 394 149 | 387 157 | 0.60 |
| Variable                  | Level       | All data (n = 598) | No KDIGO Stage 2 or 3 (n = 343) | KDIGO Stage 2 or 3 (n = 255) | p value |
|---------------------------|-------------|--------------------|--------------------------------|-----------------------------|---------|
|                          |             | Mean, n SD, Percentage | Mean, n SD, Percentage | Mean, n SD, Percentage | Chi-square test, t test |
| Donor CMV status         | Positive    | 345 57.7           | 195 56.9                    | 150 58.8                    | 0.35    |
|                          | Negative    | 249 41.6           | 147 42.9                    | 102 40.0                    |         |
|                          | Unknown     | 4 0.7              | 1 0.3                       | 3 1.2                       |         |
| Donor EBV status         | Positive    | 401 67.1           | 228 66.5                    | 173 67.8                    | 0.54    |
|                          | Negative    | 33 5.5             | 22 6.4                      | 11 4.3                      |         |
|                          | Unknown     | 164 27.4           | 93 27.1                     | 71 27.8                     |         |
| Donor cause of death     | Anoxia      | 124 20.7           | 71 20.7                     | 53 20.8                     | 0.20    |
|                          | Asphyxiation| 19 3.2             | 12 3.5                      | 7 2.7                       |         |
|                          | Blunt injury| 2 0.3              | 1 0.3                       | 1 0.4                       |         |
|                          | Cardiovascular| 23 3.8     | 15 4.4                      | 8 3.1                       |         |
|                          | Cerebrovascular| 174 29.1   | 108 31.5                    | 66 25.9                     |         |
|                          | Central nervous system tumor | 1 0.2 | 1 0.3 | 0 0.0 |             |
|                          | Drowning    | 3 0.5             | 0 0.0                       | 3 1.2                       |         |
|                          | Drug intoxication| 25 4.2 | 12 3.5 | 13 5.1 |         |
|                          | Electrical  | 1 0.2             | 0 0.0                       | 1 0.4                       |         |
|                          | Gunshot/stab| 47 7.9            | 29 8.5                      | 18 7.1                      |         |
|                          | Intracranial hemorrhage/stroke | 34 5.7 | 16 4.7 | 18 7.1 |         |
|                          | Motor vehicle accident| 30 5.0 | 16 4.7 | 14 5.5 |         |
|                          | Other (Not White/Caucasian or Black) | 9 1.5 | 5 1.5 | 4 1.6 |         |
|                          | Seizure     | 1 0.2             | 0 0.0                       | 1 0.4                       |         |
| Donor cause of death     | Trauma      | 164 27.4           | 97 28.3                     | 67 26.3                     | 0.80    |
|                          | Anoxia/asphyxiation| 143 23.9 | 83 24.2 | 60 23.5 | 0.94    |
|                          | Stroke      | 208 34.8           | 124 36.2                    | 84 32.9                     | 0.63    |
|                          | Drug intoxication| 25 4.2 | 12 3.5 | 13 5.1 | 0.29    |
|                          | Cardiovascular| 23 3.8 | 15 4.4 | 8 3.1 | 0.49    |
|                          | Anemia (iron deficiency) | 63 10.5 | 25 7.3 | 38 14.9 | 0.00    |
|                          | Cardiac arrhythmia | 208 34.8 | 103 30.0 | 105 41.2 | 0.01    |
| Variable                        | Level                      | All data (n = 598) | No KDIGO Stage 2 or 3 (n = 343) | KDIGO Stage 2 or 3 (n = 255) | p value |
|--------------------------------|----------------------------|--------------------|--------------------------------|------------------------------|---------|
|                                | Mean, n, SD, Percentage    | Mean, n, SD, Percentage | Mean, n, SD, Percentage | Mean, n, SD, Percentage | Chi-square test, t test |
| Valvular diseases of the heart  |                            |                    |                                |                              |         |
|                                | 46, 7.7                    | 24, 7.0            | 22, 8.6                        |                              | 0.48    |
| Chronic obstructive pulmonary disease | 93, 15.6                  | 58, 16.9           | 35, 13.7                       |                              | 0.27    |
| Fluid and electrolyte disorders | 365, 61.0                  | 186, 54.2          | 179, 70.2                      |                              | <0.001  |
| Diabetes mellitus (recipient)  | None                       | 379, 63.4          | 215, 62.7                      | 164, 64.3                    | 0.96    |
|                                | Uncomplicated              | 175, 29.3          | 101, 29.4                      | 74, 29.0                     |         |
|                                | Complicated                | 29, 4.8            | 17, 5.0                        | 12, 4.7                      |         |
|                                | Missing/unknown            | 15, 2.5            | 10, 2.9                        | 5, 2.0                       |         |
| Hypertension (recipient)       | None                       | 304, 50.8          | 179, 52.2                      | 125, 49.0                    | 0.63    |
|                                | Uncomplicated              | 195, 32.6          | 109, 31.8                      | 86, 33.7                     |         |
|                                | Complicated                | 84, 14.0           | 45, 13.1                       | 39, 15.3                     |         |
|                                | Missing/unknown            | 15, 2.5            | 10, 2.9                        | 5, 2.0                       |         |
|                                | Hypothyroidism             | 87, 14.5           | 50, 14.6                       | 37, 14.5                     |         |
|                                | Neurologic disorders       | 73, 12.2           | 38, 11.1                       | 35, 13.7                     | 0.35    |
|                                | Peripheral vascular disorders | 37, 6.2         | 16, 4.7                        | 21, 8.2                      | 0.08    |
|                                | Pulmonary circulation disorders | 39, 6.5       | 18, 5.2                        | 21, 8.2                      | 0.15    |
|                                | Unexpected or unanticipated weight loss | 132, 22.1 | 63, 18.4                       | 69, 27.1                     | 0.01    |
| Other comorbidities            | Cerebrovascular disease    | 6, 1.0             | 3, 0.9                         | 3, 1.2                       | 0.71    |
|                                | Ischemic heart disease     | 19, 3.2            | 13, 3.8                        | 6, 2.4                       | 0.32    |
|                                | Snoring                    | 184, 30.8          | 97, 28.3                       | 87, 34.1                     | 0.10    |
| Recipient CMV status           | Positive                   | 332, 55.5          | 200, 58.3                      | 132, 51.8                    | 0.12    |
|                                | Negative                   | 259, 43.3          | 137, 39.9                      | 122, 47.8                    |         |
|                                | Equivocal                  | 5, 0.8             | 4, 1.2                         | 1, 0.4                       |         |
| Recipient EBV status           | Positive                   | 556, 93.0          | 317, 92.4                      | 239, 93.7                    | 0.15    |
|                                | Negative                   | 26, 4.3            | 15, 4.4                        | 11, 4.3                      |         |
transplantation as well as cumulative case totals (eg, norepinephrine dose during dissection, norepinephrine dose during anhepatic phase, norepinephrine dose during reperfusion, and total norepinephrine administered intraoperatively). For laboratory studies, time-weighted averages (using preoperative values from case initiation until the first intraoperative value was obtained) were calculated for each phase of transplantation and again for the total case duration. Notably, the addition of full case data did not alter the model selected or improve discrimination when compared with the model comprised entirely of preoperative and reperfusion phase data (Table 5).

Comparison of model discrimination

There was no difference in discrimination between the 2 preoperative models (model 1, recipient-specific; and model 2, recipient and donor characteristics; c-statistic, 0.741 ± 0.026). Furthermore, there was no statistically significant difference in discrimination between the 2 preoperative and intraoperative models (model 3, reperfusion phase; and model 4, full data, case completion; c-statistic, 0.759 ± 0.032). The addition of intraoperative details also did not significantly improve model discrimination (comparing the c-statistic of models 2 and 3 using the method of Hanley and McNeil [24]; p = 0.10).

Association with mortality

Next, we determined the independent associations between factors and mortality using Cox proportional hazards models. The first mortality model (model 5) included our primary outcome (KDIGO stage 2 or 3 AKI) as a covariate in addition to other factors specified previously. In this model, we found patients with hepatocellular carcinoma (adjusted hazard ratio [aHR], 1.611; 95% CI, 1.075–2.414; p = 0.02), longer warm ischemia time in minutes (aHR, 1.025; 95% CI, 1.006–1.045; p = 0.01), logarithm of total fresh frozen plasma (FFP) administered (aHR, 3.412; 95% CI, 1.959–5.942; p < 0.001), lower reperfusion ionized calcium (aHR, 0.835; 95% CI, 0.707–0.987; p = 0.04), and more acidic reperfusion pH (per 0.10 point change; aHR, 0.469; 95% CI, 0.367–0.601; p < 0.001) had a greater hazard for mortality. Notably, posttransplant AKI was not associated with mortality (Table 6).

In model 6, receipt of dialysis was a strong independent predictor of mortality (aOR, 3.324; 95% CI, 1.603–6.894; p = 0.001; Table 6). A Kaplan-Meier curve showing survival in the population requiring dialysis compared with not requiring dialysis is shown in Figure 1.
DISCUSSION

Using robust, validated observational databases, we report an overall AKI incidence of 43% within the first 7 days following LT. We identify several demographics and comorbidities including BMI, preexisting electrolyte/acid-base balance disorder, anemia, and cardiac arrhythmias that are associated with the primary outcome. In addition, preoperative studies including serum albumin, BUN, and INR informed the risk of AKI.

Our study builds on prior studies to integrate data from the electronic health record and intraoperative record with standard, reportable transplantation outcomes. We leveraged this capability to study associations through the intraoperative course. Our results show that increased potassium and lactate following graft reperfusion improve the prediction of patients susceptible to postoperative AKI. Furthermore, the addition of full case data does not improve model discrimination.

Concordance with previous studies

Our observed incidence of 43% is consistent with previous studies when accounting for differences in defining AKI (≥KDIGO stage 1 vs. ≥stage 2) and more stringent exclusion of patients with baseline renal dysfunction. We found no relationship between female sex and AKI, which agrees with some studies but contrasts with another study placing female patients at increased risk. The influence of preoperative risk factors such as anemia and electrolyte/acid-base balance disorders have been found in previous studies.

Our finding that preoperative hypoalbuminemia is associated with postoperative AKI agrees with previous findings in the LT population as well as other surgical populations. Other preoperative variables, including hyponatremia and etiology of liver failure, have been shown to influence postoperative AKI; however, these were not found to be significant in our study. This could be secondary to differences in patient population or, potentially, results from a redundancy in preoperative variables, leading to the selection of some variables and nonselection of others by our methodology. Specifically, our methodology selected preoperative diagnosis of electrolyte/acid-base balance disorders as a significant risk factor, which also includes the ICD-10 code for hyponatremia (E87.1), suggesting that it is electrolyte disorders in general not just 1 type (hyponatremia) that is associated with AKI.

Although MELD score has been previously shown to predict AKI after LT, other studies have failed to replicate this association. Our study did not find any association between MELD score and AKI. An additional surprising finding was that patients with a higher baseline eGFR have a higher susceptibility for post-transplant AKI. This conflicts with prior studies showing higher serum creatinine (lower eGFR) to be associated with previous studies. We found no relationship between female sex and AKI, which agrees with some studies but contrasts with another study placing female patients at increased risk. The influence of preoperative risk factors such as anemia and electrolyte/acid-base balance disorders have been found in previous studies.

| Variable | Level | All data (n = 598) | No KDIGO Stage 2 or 3 (n = 343) | KDIGO Stage 2 or 3 (n = 255) | p value |
|----------|-------|-------------------|-----------------------------|-----------------------------|--------|
|          |       | Mean | SD  | Mean | SD  | Mean | SD  | t test |
| Serum creatinine (mg/dL) | 1.2 | 0.7 | 1.3 | 0.7 | 1.0 | 0.6 | <0.001 |
| eGFR, mL/minute/1.37 m² | 78.7 | 40.6 | 72.4 | 37.7 | 87.3 | 42.9 | <0.001 |
| Bilirubin (mg/dL) | 8.1 | 9.1 | 8.6 | 9.5 | 7.3 | 8.3 | 0.09 |
| BUN (mg/dL) | 22.0 | 15.0 | 24.7 | 17.6 | 18.4 | 11.1 | <0.001 |
| White blood cell count (K/uL) | 6.1 | 3.3 | 6.2 | 3.5 | 5.9 | 3.0 | 0.33 |
| Hematocrit (%) | 31.4 | 6.2 | 31.3 | 6.3 | 31.6 | 6.1 | 0.64 |
| Platelets (%) | 97.8 | 71.2 | 102 | 75 | 92 | 65 | 0.07 |
| Sodium | 136 | 5.0 | 136 | 5 | 135 | 5 | 0.10 |
| Albumin (g/dL) | 3 | 0.6 | 3.1 | 0.6 | 2.9 | 0.6 | <0.001 |
| Fibrinogen (mg/dL) | 222 | 131 | 224 | 130 | 220 | 132 | 0.73 |
| INR | 1.6 | 0 | 1.7 | 0.7 | 1.6 | 0.5 | 0.05 |
| MELD score | 19 | 8 | 20 | 9 | 18 | 7 | 0.01 |
| MELD (laboratory) | 19 | 8 | 20 | 9 | 18 | 7 | 0.01 |
| MELD (with exception points added) | 23 | 6 | 24 | 6 | 22 | 6 | <0.001 |
| MAP (prior to reperfusion), mm Hg | 73 | 11 | 72 | 11 | 73 | 11 | 0.44 |
| Variable                      | Level                                           | All data (n = 598) | No KDIGO Stage 2 or 3 (n = 343) | KDIGO Stage 2 or 3 (n = 255) | p value |
|------------------------------|------------------------------------------------|-------------------|-------------------------------|-------------------------------|---------|
|                              | Level                                           | Mean     | SD   | Mean     | SD   | Mean     | SD   | t test |
| Intraoperative data          | Transfusion pRBC, units                         | 2        | 3    | 2        | 3    | 2        | 3    | 1.00   |
| Dissection phase             | Transfusion FFP, units                          | 3        | 4    | 3        | 4    | 3        | 5    | 0.80   |
|                              | Transfusion cryoprecipitate (5-packs)           | 0        | 2    | 0        | 2    | 0        | 1    | 0.86   |
|                              | Hematocrit (%)                                 | 28.9     | 5.7  | 28.9     | 5.9  | 28.8     | 5.4  | 0.84   |
|                              | Glucose (mg/dL)                                | 119      | 34   | 119      | 30   | 120      | 39   | 0.80   |
|                              | Lactate (mmol/L)                               | 2.1      | 1.2  | 2.1      | 1.2  | 2.1      | 1.2  | 0.85   |
|                              | pH                                             | 7.4      | 0.1  | 7.4      | 0.1  | 7.4      | 0.1  | 0.61   |
|                              | Ionized calcium (mmol/L)                       | 1.16     | 0.80 | 1.22     | 1.03 | 1.06     | 0.12 | 0.04   |
|                              | Sodium (mmol/L)                                | 136      | 5    | 136      | 5    | 136      | 5    | 0.27   |
|                              | Potassium (mmol/L)                             | 3.9      | 0.5  | 3.9      | 0.5  | 3.9      | 0.5  | 0.83   |
|                              | Norepinephrine, μg                             | 141      | 386  | 135      | 394  | 148      | 376  | 0.70   |
| Anhepatic                    | Transfusion pRBC, units                         | 2        | 5    | 2        | 5    | 2        | 4    | 0.93   |
|                              | Transfusion FFP, units                          | 3        | 4    | 2        | 5    | 3        | 4    | 0.75   |
|                              | Transfusion cryoprecipitate (5-packs)           | 0        | 1    | 0        | 1    | 0        | 0    | 0.49   |
|                              | Hematocrit                                    | 26.4     | 5.0  | 26.4     | 5.5  | 26.3     | 4.7  | 0.69   |
|                              | Glucose                                       | 145      | 46   | 146      | 45   | 144      | 47   | 0.50   |
|                              | Lactate                                       | 4.1      | 1.9  | 4.1      | 1.9  | 4.2      | 1.9  | 0.54   |
|                              | pH                                            | 7.35     | 0.10 | 7.35     | 0.12 | 7.36     | 0.06 | 0.45   |
|                              | Ionized calcium (mmol/L)                       | 1.08     | 0.19 | 1.08     | 0.19 | 1.09     | 0.20 | 0.55   |
|                              | Sodium                                        | 137      | 6    | 137      | 5    | 136      | 7    | 0.17   |
|                              | Potassium                                     | 4.0      | 0.6  | 4.0      | 0.7  | 3.9      | 0.6  | 0.21   |
|                              | Norepinephrine, μg                             | 104      | 241  | 99       | 241  | 110      | 241  | 0.57   |
| Immediate reperfusion        | Norepinephrine, μg                             | 6        | 14   | 6        | 14   | 6        | 14   | 0.74   |
|                              | MAP, mm Hg                                     | 55       | 14   | 55       | 14   | 56       | 14   | 0.45   |
| Reperfusion                  | Transfusion pRBC, units                         | 5        | 10   | 4        | 9    | 6        | 12   | 0.02   |
|                              | Transfusion FFP, units                          | 6        | 10   | 5        | 8    | 7        | 12   | 0.01   |
|                              | Transfusion cryoprecipitate (5-packs)           | 2        | 5    | 2        | 4    | 3        | 5    | 0.05   |
|                              | Hematocrit                                    | 23.4     | 4.9  | 23.8     | 5.7  | 23.0     | 3.6  | 0.05   |
|                              | Glucose                                       | 204      | 54   | 201      | 54   | 208      | 53   | 0.13   |
|                              | Lactate                                       | 5.1      | 2.5  | 4.9      | 2.4  | 5.4      | 2.5  | 0.01   |
|                              | pH                                            | 7.34     | 0.06 | 7.34     | 0.07 | 7.34     | 0.06 | 0.91   |
|                              | Ionized calcium (mmol/L)                       | 1.88     | 2.41 | 1.87     | 2.27 | 1.89     | 2.59 | 0.94   |
|                              | Sodium                                        | 138      | 5    | 138      | 5    | 138      | 5    | 0.95   |
|                              | Potassium                                     | 3.8      | 0.6  | 3.8      | 0.6  | 3.9      | 0.6  | 0.02   |
|                              | Norepinephrine, μg                             | 623      | 1227 | 514      | 1157 | 770      | 1303 | 0.01   |
| Total intraoperative results | Transfusion pRBC, units                         | 9        | 16   | 8        | 14   | 10       | 17   | <0.001 |
|                              | Transfusion FFP, units                          | 12       | 16   | 11       | 14   | 14       | 18   | <0.001 |
|                              | Hematocrit                                    | 26.5     | 4.3  | 26.6     | 4.5  | 26.3     | 4.0  | 0.33   |
|                              | Glucose                                       | 156      | 38   | 154      | 37   | 158      | 40   | 0.13   |
|                              | Lactate                                       | 3.5      | 1.7  | 3.4      | 1.7  | 3.6      | 1.7  | 0.04   |

(Continues)
with posttransplant AKI\(^2,42-44\). This interesting result could result from (1) covariates that were unable to be quantified in our data (such as graft mismatch), (2) inefficiencies associated with eGFR equation accuracy in patients with cirrhosis, (3) unaccounted operative factors such as procedural or technical complexity (eg, with vascular clamping for anastomosis), or (3) physiologic etiology (BUN is also lower in the AKI, perhaps secondary to dilutional effect from ascites).\(^{45}\) Finally, Black patients were not more likely to develop AKI following LT, which builds on an earlier study showing no difference in early hemodialysis based on race, but lower discontinuation of dialysis in Black transplant patients.\(^{46}\)

A variety of donor factors have been shown to be associated with posttransplant AKI, including donation after cardiac death,\(^{47}\) ischemia time,\(^{48,49}\) high-risk grafts,\(^{32}\) and older donor age.\(^{32}\) Our study failed to show any association between donor-specific variables and posttransplant AKI. This may be the result of improved institutional effort in matching high-risk donors with recipients at lower risk for complications such as AKI and lower risk donors with higher risk recipients.

Our study builds on prior work incorporating intraoperative variables into the prediction model. Prior studies have characterized the effect of major classes of intraoperative variables, including blood transfusion,\(^{25,49}\) hemodynamic variables (most notably, intraoperative hypotension),\(^{25,50-52}\) vasopressor/inotropic support,\(^{25,51,52}\) surgical technique,\(^{25}\) laboratory values,\(^{12,25,52}\) and hypovolemia.\(^{26,30}\) Our study failed to show an association between intraoperative MAP or intraoperative transfusion (packed red blood cells [pRBC], FFP, or cryoprecipitate) with the primary outcome. We did, however, find an association between higher lactate and potassium levels, but not norepinephrine doses and AKI. Further study is needed to determine if potassium and lactate levels may act as intermediate variables, mediating the effects of blood transfusions and blood pressure. Further study is also needed to determine if factors such as hypotension, which seems to fluctuate earlier, may be an earlier marker than potassium and lactate, which would be lagging indicators. The kidney excretes potassium and metabolizes lactate. Rises in potassium and lactate may be an early marker of renal dysfunction and ischemia. This might allow for an early intervention that reverses renal ischemia and prevents dysfunction from progressing to AKI. Further study is needed to better understand the possible protective association of INR with AKI. One potential explanation is that correction of INR leads to resuscitation with a high volume of FFP, which may lead to a better volume reserve that protects

| Variable   | Level     | Mean (SD) | p value |
|------------|-----------|-----------|---------|
| pH         |           | 7.36 (0.06) | 0.90    |
| Ionized calcium |   | 1.79 (2.43) | 0.95    |
| Sodium     |           | 137 (5)    | 0.92    |
| Potassium  |           | 3.9 (0.5)  | 0.41    |

| Table 4 | Patient outcomes after LT (n = 598) |
|---------|------------------------------------|
| Stage   | n       | Percentage | Stage | Total | Percentage |
| (A) Outcome: KDIGO |
| 0       | 227     | 38.0       | 0 or 1 | 343   | 57.4       |
| 1       | 116     | 19.4       |        |       |            |
| 2       | 149     | 24.9       | 2 or 3 | 255   | 42.6       |
| 3       | 106     | 17.7       |        |       |            |

| (B) Outcome: mortality |
|------------------------|
| Total | Percentage | Yes (n = 255) | Percentage | No (n = 343) | Percentage | p value (chi-square test) |
| 30 days | 23 | 3.8 | 9 | 3.5 | 14 | 4.1 | 0.12 |
| 90 days | 31 | 5.2 | 15 | 5.9 | 16 | 4.7 | 0.44 |
| 1 year | 54 | 9.0 | 24 | 9.4 | 30 | 8.7 | 0.08 |
| 3 years | 78 | 13.0 | 43 | 16.9 | 35 | 10.2 | 0.02 |
### TABLE 5  Multivariate logistic regression results in Models 1 to 4

| Model 1 |  |  |  |
|---------|-----------------|-----------------|-----------------|
| Patient demographics | BMI | 1.077 | 1.044–1.112 | <0.001 |
| Comorbidities | Fluid or electrolyte disorders | 2.040 | 1.374–3.030 | <0.001 |
|  | Iron-deficiency anemia | 2.985 | 1.623–5.489 | <0.001 |
|  | Cardiac arrhythmia | 1.818 | 1.240–2.666 | 0.00 |
| Preoperative laboratory values | Albumin | 0.611 | 0.431–0.865 | 0.01 |
|  | Sodium | 0.965 | 0.928–1.003 | 0.07 |
|  | BUN | 0.963 | 0.944–0.982 | <0.001 |
|  | INR | 0.606 | 0.420–0.875 | 0.01 |
|  | eGFR, MDRD-4 | 1.007 | 1.001–1.013 | 0.03 |

| Model 2 |  |  |  |
|---------|-----------------|-----------------|-----------------|
| Patient demographics | BMI | 1.077 | 1.044–1.112 | <0.001 |
| Comorbidities | Fluid or electrolyte disorders | 2.040 | 1.374–3.030 | <0.001 |
|  | Iron-deficiency anemia | 2.985 | 1.623–5.489 | <0.001 |
|  | Cardiac arrhythmia | 1.818 | 1.240–2.666 | 0.00 |
| Preoperative laboratory values | Albumin | 0.611 | 0.431–0.865 | 0.01 |
|  | Sodium | 0.965 | 0.928–1.003 | 0.07 |
|  | BUN | 0.963 | 0.944–0.982 | <0.001 |
|  | INR | 0.606 | 0.420–0.875 | 0.01 |
|  | eGFR, MDRD-4 | 1.007 | 1.001–1.013 | 0.03 |

| Model 3 |  |  |  |
|---------|-----------------|-----------------|-----------------|
| Patient demographics | Age | 0.979 | 0.962–0.995 | 0.01 |
|  | BMI | 1.079 | 1.044–1.114 | <0.001 |
| Comorbidities | Fluid or electrolyte disorders | 1.917 | 1.280–2.869 | 0.00 |
|  | Iron-deficiency anemia | 2.612 | 1.405–4.854 | 0.00 |
|  | Cardiac arrhythmia | 1.629 | 1.101–2.410 | 0.02 |
|  | Unexpected weight loss | 1.596 | 1.006–2.532 | 0.05 |
| Preoperative laboratory values | Albumin | 0.576 | 0.410–0.808 | 0.00 |
|  | BUN | 0.952 | 0.935–0.996 | <0.001 |
|  | INR | 0.469 | 0.321–0.685 | <0.001 |
|  | eGFR, MDRD-4 | 1.007 | 1.001–1.013 | 0.03 |
| Reperfusion variables | Reperfusion potassium | 1.513 | 1.103–2.077 | 0.01 |
|  | Reperfusion lactate | 1.081 | 1.003–1.166 | 0.04 |

| Model 4 |  |  |  |
|---------|-----------------|-----------------|-----------------|
| Patient demographics | Age | 0.979 | 0.962–0.995 | 0.01 |
|  | BMI | 1.079 | 1.044–1.114 | <0.001 |
| Comorbidities | Fluid or electrolyte disorders | 1.917 | 1.280–2.869 | 0.00 |
|  | Iron-deficiency anemia | 2.612 | 1.405–4.854 | 0.00 |
|  | Cardiac arrhythmia | 1.629 | 1.101–2.410 | 0.15 |
|  | Unexpected weight loss | 1.596 | 1.006–2.532 | 0.05 |
| Preoperative laboratory values | Albumin | 0.576 | 0.410–0.808 | 0.00 |
|  | BUN | 0.952 | 0.935–0.996 | <0.001 |
|  | INR | 0.469 | 0.321–0.685 | <0.001 |

(Continues)
### TABLE 5 (Continued)

| Reperfusion variables                      | aOR   | 95% CI          | p value |
|--------------------------------------------|-------|-----------------|---------|
| eGFR, MDRD-4                               | 1.007 | 1.001–1.013     | 0.03    |
| Reperfusion potassium, mmol/L              | 1.513 | 1.103–2.077     | 0.01    |
| Reperfusion lactate, mmol/L                | 1.081 | 1.003–1.166     | 0.04    |

Note: Model 1, preoperative variables: AKI after LT (c-statistic = 0.741 ± 0.026); model 2, preoperative variables plus donor factors (c-statistic = 0.741 ± 0.026); model 3, preoperative variables, donor factors, and intraoperative variables: reperfusion (c-statistic = 0.759 ± 0.032); model 4, complete end of case data (c-statistic = 0.759 ± 0.032).

### TABLE 6 Cox proportional hazards ratio models associated with mortality in Models 5 and 6

| Model 5                                                                 | aHR  | 95% CI          | p value |
|-------------------------------------------------------------------------|------|-----------------|---------|
| **Patient demographics**                                                |      |                 |         |
| Black/African American (Reference)                                      |      |                 |         |
| Race                                                                    |      |                 |         |
| White                                                                   | 1.010| 0.498–2.045     | 0.98    |
| Unknown                                                                 | 3.058| 1.314–7.117     | 0.01    |
| Other                                                                   | 3.388| 1.159–9.902     | 0.03    |
| Comorbidities                                                           |      |                 |         |
| Pulmonary/circulation disorders                                         | 1.731| 0.863–3.472     | 0.12    |
| **Preoperative laboratory values**                                      |      |                 |         |
| Hepatocellular carcinoma                                               | 1.611| 1.075–2.414     | 0.02    |
| Platelets                                                               | 1.005| 1.003–1.007     | <0.001  |
| eGFR, MDRD-4                                                            | 1.008| 1.003–1.013     | 0.00    |
| Platelets                                                               | 1.431| 0.964–2.124     | 0.08    |
| EBV positive                                                            | 0.702| 0.352–1.399     | 0.29    |
| Warm ischemia time, minutes                                            | 1.025| 1.006–1.045     | 0.01    |
| **Intraoperative details**                                              |      |                 |         |
| log(cryoprecipitate total)                                             | 2.345| 0.865–6.359     | 0.09    |
| log(FFP total)                                                          | 3.412| 1.959–5.942     | <0.001  |
| Reperfusion ionized calcium                                            | 0.835| 0.707–0.987     | 0.04    |
| **Outcomes**                                                            |      |                 |         |
| Reperfusion pH (scale 10)                                              | 0.469| 0.367–0.601     | <0.001  |
| KDIGO stage 2 or 3                                                     | 1.202| 0.818–1.767     | 0.35    |
| **Model 6**                                                             |      |                 |         |
| **Patient demographics**                                                |      |                 |         |
| Black/African American (Reference)                                      |      |                 |         |
| Race                                                                    |      |                 |         |
| White                                                                   | 0.926| 0.455–1.884     | 0.83    |
| Unknown                                                                 | 2.962| 1.286–6.822     | 0.01    |
| Other                                                                   | 3.138| 1.066–9.232     | 0.04    |
| Comorbidities                                                           |      |                 |         |
| Pulmonary/circulation disorders                                         | 1.453| 0.714–2.957     | 0.30    |
| **Preoperative laboratory values**                                      |      |                 |         |
| Hepatocellular carcinoma                                               | 1.72 | 1.138–2.599     | 0.01    |
| Platelets                                                               | 1.005| 1.003–1.007     | <0.001  |
| eGFR, MDRD-4                                                            | 1.009| 1.004–1.014     | <0.001  |
| CMV positive                                                            | 1.523| 1.021–2.271     | 0.04    |
| EBV positive                                                            | 0.758| 0.399–1.44      | 0.38    |
| **Intraoperative details**                                              |      |                 |         |
| Warm ischemia time, minutes                                            | 1.025| 1.005–1.045     | 0.02    |
| **log(cryoprecipitate total)**                                          | 2.115| 0.742–6.024     | 0.16    |
| log(FFP total)                                                          | 3.152| 1.801–5.517     | <0.001  |
| Reperfusion ionized calcium                                            | 0.830| 0.696–0.991     | 0.04    |
| **Outcomes**                                                            |      |                 |         |
| Reperfusion pH (scale 10)                                              | 0.499| 0.385–0.647     | <0.001  |
| Dialysis by day 7                                                      | 3.324| 1.603–6.894     | 0.001   |

Note: In model 5, the primary outcome KDIGO 2 or 3 is included. In model 6, RRT is included.
against the decreased organ perfusion associated with large hemorrhages.

Posttransplant AKI was not an independent risk for mortality. This contrasts with prior studies showing a strong association.[27,48] This could be because the study was powered to detect the secondary outcome of mortality, which occurred with much lower frequency than the primary outcome. However, as we found that receipt of dialysis within 7 days after transplant was associated with late mortality, it may be that AKI with recovery of renal function has little effect on mortality, whereas AKI that persists is associated with mortality. This is similar to a study in cardiac surgery patients where AKI, defined by KDIGO, was not associated with late mortality when discharge renal function was included in the model[53] or, as the subanalysis in patients requiring dialysis within 7 days suggests, that the effect may be driven by a smaller subset of all posttransplant patients with AKI.

Strengths and weaknesses

The limitations of our study include the retrospective design from a single center that limits the causality. In addition, this cross-sectional study only allows us to look at associations at isolated time points, limiting how much we can truly infer from the results. However, given the extreme strength of associations, stage-specific prediction models based on these findings would elucidate specific intraoperative changes needed to prevent AKIs. This risk-prediction model could be trained with multicenter data, allowing it to be widely applicable and implemented into current anesthesia management best practices. Although we had accurate and complete urine output during the intraoperative period, we did not have urine output consistently documented for 7 postoperative days. Therefore, our primary outcome did not include urine output in the diagnostic criteria despite inclusion in the KDIGO definition. Another limitation is that surgical technique (classical bicaval anastomosis vs. piggyback) was not collected as part of our standardized reporting metrics. Future studies will control for this covariate through the language processing of operative reports. A final limitation is that our objective was to stratify the risk for postoperative AKI at the time of transplantation completion. Model discrimination might be improved by incorporating postoperative data, specifically administration of nephrotoxic immunosuppressants,[54] subsequent development of sepsis,[41] and early allograft dysfunction,[55]; however, this was beyond the scope of our objective.

Conclusions

In this retrospective observational study performed at an academic quaternary care center, we found a 43% incidence of AKI within the first
7 days following LT and receipt of dialysis within 7 days of LT was associated with increased mortality. Our study demonstrated that most AKI discrimination (0.741 ± 0.026 compared with 0.759 ± 0.032 for full model) can be obtained with preoperative factors. The addition of intraoperative data did not improve overall model discrimination, although the study may have been underpowered to detect this change. Even if adequately powered, the overall improvement in discrimination by adding intraoperative data is minimal. This may suggest that by the time the intraoperative data are collected, renal injury has already mostly occurred. These high-risk patients would be ideal for prospective studies to prevent AKI. In addition, intraoperative intermediate outcomes of potassium and lactate levels, potentially indicative of early renal ischemia or dysfunction, contribute a small component of overall AKI risk. Future studies on intraoperative and postoperative management may assess whether early intervention can mitigate this risk.

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CONFLICT OF INTEREST
Nothing to report.

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