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Incidence and Risk Factors for Progression of Acute Kidney Injury to Chronic Kidney Disease After Liver Transplantation: A Retrospective Cohort Study

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Keywords: acute kidney injury | chronic kidney disease | incidence | independent risk factor | liver transplantation | surgery

ABSTRACT

Acute kidney injury (AKI) following liver transplantation has the potential to progress to chronic kidney disease (CKD), which can result in extended hospital stays, elevated healthcare costs, and increased mortality rates. This retrospective cohort study seeks to examine the prognosis of AKI progression to CKD post-liver transplantation and to identify its independent risk factors. A cohort of 443 patients who developed AKI post-liver transplantation was analyzed, with participants categorized into a CKD group and a non-CKD group. The progression of AKI to CKD was observed in 29.3% (130 out of 443) of cases. Patients who developed CKD exhibited a significantly higher 1-year mortality rate of 4.6% ($p = 0.004$). Multivariate logistic regression analysis identified several independent risk factors for the progression from AKI to CKD, including preoperative diabetes (odds ratio [OR] 2.62; 95% confidence interval [CI] 1.32, 5.21), hepatic malignancy (OR 1.95; 95% CI 1.06, 3.57), elevated preoperative serum creatinine (SCr) levels (OR 1.02; 95% CI 1.01, 1.03), transition from postoperative AKI to acute kidney disease (AKD) (OR 3.99; 95% CI 1.94, 8.23), AKD stages 2 and 3 (OR 2.48; 95% CI 1.33, 4.61), and an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 within 30 days (OR 3.03; 95% CI 1.70, 5.40). Conversely, higher preoperative hematocrit (HCT) levels (OR 0.00; 95% CI 0.00, 0.26) and recovery from AKD (OR 0.49; 95% CI 0.27, 0.86) were associated with a reduced risk of progression from postoperative AKI to CKD. The progression of AKI to CKD following liver transplantation is independently associated with preoperative diabetes, hepatic malignancy, elevated preoperative SCr levels, postoperative transition from AKI to AKD, AKD stages 2 and 3, and an eGFR of less than 60 mL/min/1.73 m^2 within 30 days.

Liping Li, Jinxuan Dai and Yiqian Liu contributed equally to this work.

1 | Introduction

Liver transplantation is widely recognized as the most effective treatment for end-stage liver disease, providing hope to numerous patients. Nonetheless, it is crucial to consider the challenges associated with this procedure. Acute kidney injury (AKI) is among the most prevalent complications observed in patients following liver transplantation. Depending on the diagnostic criteria employed, the incidence of AKI post-transplantation is reported to range from 17% to 95%, with an average incidence of approximately 40.7% [1–3]. The presence of AKI not only increases patient mortality rates but also poses a risk of progression to chronic kidney disease (CKD), thereby prolonging hospitalization and increasing healthcare costs [4]. Research indicates that CKD can develop irrespective of the underlying cause of AKI [5]. Furthermore, a significant number of patients with AKI may progress to end-stage renal disease (ESRD) despite initial recovery of renal function during the early postoperative period, a trend observed even in those without a preoperative history of CKD [6, 7]. Additionally, AKI not only contributes to the onset of new CKD but also accelerates the progression to ESRD in patients with pre-existing CKD prior to surgery. The long-term risk of ESRD, coupled with its associated high mortality rate, imposes a substantial burden on patients and their families [6–8].

CKD represents a prevalent and significant complication following liver transplantation. Studies have shown that the prevalence of CKD ranges from 4.0% to 27.5% within the first year, 15% to 60% after 5 years, and 25% to 50% after 10 years post-transplantation [9, 10]. CKD is a major contributor to adverse outcomes following liver transplantation, including allograft dysfunction and cardiovascular events, and it may also increase the risk of patient mortality. The etiology of CKD post-liver transplantation is complex and multifactorial [11]. Preoperative factors such as advanced age, female gender, a history of diabetes mellitus or hypertension, hyperlipidemia, and hepatitis C, as well as postoperative factors including calcineurin inhibitor toxicity, prolonged ischemia, and hemodynamic instability, may serve as independent risk factors for the development of CKD following liver transplantation [10, 12].

The inability to achieve early recovery of renal function following the onset of AKI in post-liver transplantation patients may lead to persistent renal impairment through a series of complex pathophysiological mechanisms, potentially progressing to CKD [13]. AKI markedly increases the risk of CKD development after liver transplantation unless renal function is restored within the first 90 days postoperatively [14]. While pre-transplant renal dysfunction has been extensively studied, there remains a gap in understanding regarding perioperative predictors of CKD progression in liver transplant recipients who experience AKI. Identifying risk factors could inform early interventions to prevent this transition. This study represents the first retrospective analysis of patients with AKI following liver transplantation, aiming to identify perioperative high-risk factors that contribute to the progression from AKI to CKD [15–17]. The findings of this analysis are intended to enhance the identification of high-risk patients and support the implementation of targeted perioperative management strategies.

2 | Methods

2.1 | Study Design and Population

This study received approval from the Institutional Review Board of The Third Affiliated Hospital of Sun Yat-sen University on May 14, 2023 (approval no. [2024]02-609-02). We identified patients who underwent liver transplantation and subsequently developed AKI postoperatively at our institution between January 2015 and February 2023. The inclusion criteria were as follows: (1) age ≥ 18 years; (2) patients who underwent liver transplantation and experienced postoperative AKI; (3) a minimum postoperative follow-up period of 1 year; and (4) availability of comprehensive clinical data. The exclusion criteria were defined as follows: (1) patients who underwent simultaneous liver and kidney transplantation; (2) patients with pre-existing CKD or those reliant on dialysis as well as individuals with CKD stage 5 who did not receive consistent dialysis therapy during the postoperative follow-up period (as defined below); (3) patients who did not experience postoperative AKI; (4) patients who succumbed within 90 days post-surgery; (5) patients requiring unplanned secondary surgical intervention due to procedure-related complications within the 3-month postoperative timeframe; (6) patients diagnosed with other renal disorders, either pre-existing or newly developed post-surgery; (7) patients with incomplete or unavailable data; and (8) patients who developed new-onset CKD stage 5 postoperatively without regular dialysis treatment.

2.1.1 | Hospitalization Details

The details of hospitalization encompass a range of critical factors, including demographic characteristics such as sex, age, and body mass index (BMI) as well as comorbidities like hypertension, diabetes mellitus, coronary artery disease, myocardial infarction, and AKI. The preoperative status is assessed using the model for end-stage liver disease (MELD) score, which incorporates includes considerations of portal hypertension, ascites, hepatic encephalopathy, preoperative intensive care unit (ICU) admission, and the duration of hospitalization prior to surgery. The etiology of liver transplantation is classified into conditions such as hepatitis A, B, and C, mixed hepatitis, autoimmune hepatitis, cirrhosis, hepatic malignancy, and drug-induced liver injury. Preoperative laboratory data are also collected, including hematocrit (Hct), platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), direct bilirubin (DBil), indirect bilirubin (IBil), albumin (Alb), serum creatinine (Cr), blood urea nitrogen (BUN), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fib), international normalized ratio (INR), serum potassium, serum sodium, serum calcium, bicarbonate, and estimated glomerular filtration rate (eGFR). Additionally, donor characteristics such as hepatic steatosis and ABO-incompatible status are considered. The study encompasses a comprehensive analysis of surgical and anesthesia data, including operation time (min), anesthesia duration (min), recipient warm ischemia time (min), recipient cold ischemia time (min), and intraoperative fluid balance. The study also investigates the administration of intraoperative medications, including recombinant factor VIIa, terlipressin, norepinephrine, epinephrine, metaraminol, prothrombin complex concentrate, and fibrinogen. Postoperative outcomes are also meticulously assessed, including

the occurrence of AKI and its staging, recovery from AKI, recurrent AKI, the requirement for dialysis within 7 days post-surgery, and early allograft dysfunction within the same timeframe. Furthermore, the study assesses acute kidney disease (AKD) and its staging, recovery from AKD, recurrent AKD, CKD and its staging, mortality within 12 months, and various complications such as hepatic artery thrombosis within 6 months, portal vein thrombosis, hepatic artery stenosis, non-anastomotic and anastomotic biliary strictures, post-transplant lymphoproliferative disorder, portal vein stenosis, recurrent hepatocellular carcinoma, hepatic vein stenosis, and hospital or ICU readmission within 6 months.

Based on preliminary research findings and clinical practice insights, we systematically collected comprehensive baseline data, preoperative conditions, perioperative laboratory tests, perioperative medications, and postoperative complications for the enrolled patients from both the electronic medical record system and our institution's advanced data analytics platform. Research cohorts were delineated and established within perioperative specialty databases according to predefined inclusion and exclusion criteria. Relevant data points for the specified perioperative period were carefully selected and extracted. Indicators not yet integrated into the databases were manually queried and supplemented to construct detailed case report form (CRF) tables. In this study, the incidence of missing data was relatively low, with an overall missing rate of less than 5% and a reasonably uniform distribution pattern. Based on these characteristics, we employed single imputation methods to manage the missing data. For continuous variables, those following normal or approximately normal distributions were imputed using mean values. This approach, based on central tendency, is particularly appropriate for normally distributed data as it effectively maintains the overall characteristics of the dataset. For variables with skewed distributions, we applied median imputation, a robust method that minimizes the influence of outliers on the imputation results. For categorical variables, we utilized mode imputation, replacing missing values with the most frequently occurring category. This method effectively captures the predominant characteristics of categorical data. Patients with more than 30% missing data were classified as dropouts and subsequently excluded from the analysis. All participants in this study were postoperative patients. Routine laboratory tests conducted post-surgery served as the definitive diagnostic criteria.

2.2 | Outcomes

The primary objective of this study is to assess the incidence of progression from AKI to CKD in patients following liver transplantation. Secondary objectives include evaluating the impact on patients who develop new-onset CKD (defined below) after experiencing AKI post-liver transplantation, with a particular focus on hospital readmissions and mortality within a 12-month timeframe. CKD is diagnosed when the estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73 m^2 for more than 3 months; thus, new-onset CKD was defined based on the eGFR measured 3 months following the diagnosis of AKI. Previous studies has demonstrated that one year afterliver transplantation, patients with comorbid CKD have a mortality risk that is 4.48 times greater than that of patients without CKD [18, 19]. To evaluate the effect of new-onset CKD on postoperative complications, a 12-month follow-up period post-surgery was implemented. Participants were stratified into two groups based on the development of CKD: the CKD group and the non-CKD group.

2.3 | Definition

According to the kidney disease improving global outcomes (KDIGO) guidelines, AKI is characterized by an increase in serum creatinine (SCr) exceeding 0.3 mg/dL within 48 h followingsurgery, or an increase to 1.5 times the baseline SCr within a 7-day period [20]. The Acute Disease Quality Initiative (ADQI) defines AKD as acute or subacute kidney damage and/or loss of kidney function occurring within 7–90 days following an AKI event [3]. AKD is further stratified into stages based on SCr levels: stage 1 is defined by SCr levels 1.5–1.9 times the baseline, stage 2 by SCr levels 2.0–2.9 times the baseline, and stage 3 by SCr levels three times the baseline or an elevated blood creatinine level of $\geq$ 353.6 μmol/L ($\geq$ 4.0 mg/dL) or the necessity for renal replacement therapy. New-onset CKD is defined as the development of AKI post-surgery in patients without pre-existing CKD, accompanied by an estimated glomerular filtration rate (eGFR) of $<$ 60 mL/min/1.73 m^2 persisting for more than 3 months [21]. The eGFR is calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [22]. CKD is classified into as follows: stage 3a with 45 $<$ eGFR $<$ 60 mL/min/1.73 m^2, stage 3b with 30 $<$ eGFR $<$ 45 mL/min/1.73 m^2, stage 4 with 15 $<$ eGFR $<$ 30 mL/min/1.73 m^2, and stage 5 with eGFR $<$ 15 mL/min/1.73 m^2.

Recovery from AKI was defined as the return of serum creatinine (SCr) to a level within the baseline SCr value plus 0.3 mg/dL within 7 days following the onset of AKI. Recurrent AKI was characterized by the patient fulfilling the KDIGO diagnostic criteria for AKI within 48 h after recovery from the initial AKI episode. Recovery from AKD was defined as a reduction in SCr to a level within the baseline SCr value plus 0.3 mg/dL occurring between 8 and 90 days after the onset of AKI. Recurrent AKD was identified when the patient met the diagnostic criteria for AKD within 48 h following recovery from the initial AKD episode.

2.4 | Statistical Analysis

A statistical analysis was performed using IBM SPSS statistical software version 29.0 to compare the clinical and laboratory characteristics of patients according to their CKD status (non-CKD vs. CKD). For continuous variables exhibiting normal distributions, data were presented as mean ± SD, while those with non-normal distributions were presented as median (interquartilerange). Categorical variables were described using frequencies and proportions. Pearson's chi-squared test was employed for the comparison of categorical variables, Student's *t*-test was used for continuous variables with normal distributions, and the Wilcoxon rank-sum test was applied for non-normally distributed continuous variables. To identify risk factors associated with the progression from AKI to CKD following liver transplantation, both univariate and multivariate logistic regression analyses were conducted. A collinearity diagnosis was conducted on variables

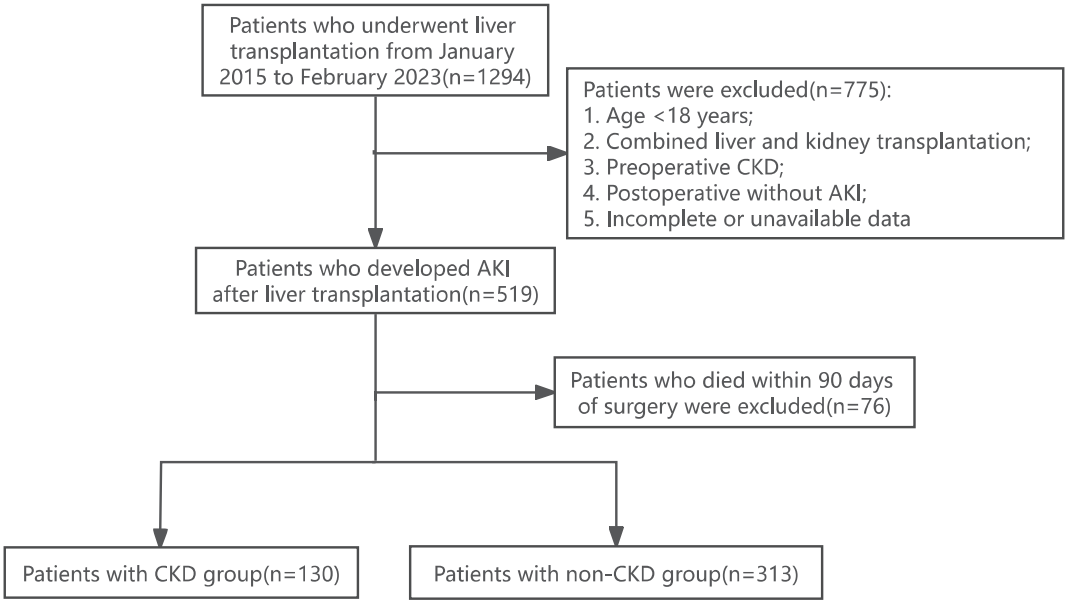

FIGURE 1 | Enrollment flow chart for the present study.

significantly correlated with the outcome in the univariate logistic regression analysis. Factors exhibiting collinearity were excluded from the univariate logistic regression, and significant factors were subsequently included in the multivariate logistic regression analysis. Factors exhibiting collinearity in the univariate analysis were excluded prior to their inclusion in the multivariate logistic regression analysis. The analyses were executed using Python version 3.7.9.

3 | Results

3.1 | Baseline Participant Characteristics

A total of 519 patients developed AKI following liver transplantation at the Third Affiliated Hospital of Sun Yat-sen University between January 2015 and February 2023. After excluding 76 patients who succumbed within 90 days post-surgery, 443 patients were ultimately included in this study (Figure 1). Of these, 130 patients (29.3%) were categorized into the CKD group, comprising 84 individuals (19.0%) with CKD stage 3a, 22 (5.0%) with CKD stage 3b, 14 (3.2%) with CKD stage 4, and 10 (2.3%) with CKD stage 5. The baseline demographic and clinical characteristics of both groups are presented in Table 1. The analysis indicated that patients aged 65 years or older (5.75% vs. 11.54%, $p = 0.035$), those with preoperative diabetes (13.59% vs. 25.40%, $p = 0.003$), and individuals with liver cirrhosis (79.92% vs. 89.11%, $p = 0.039$) or liver cancer (28.43% vs. 41.54%, $p = 0.007$) exhibited a higher likelihood of developing CKD stages 3–5 following liver transplantation. When compared to the non-CKD stages 3–5 group, the CKD stages 3–5 group demonstrated a lower hematocrit (HCT) level (0.29 ± 0.07 vs. 0.28 ± 0.06, $p = 0.0024$), higher serum creatinine (SCr) (64.00 [55.00, 75.00] μmol/L vs. 76.00 [64.25, 93.00] μmol/L, $p < 0.001$), decreased estimated glomerular filtration rate (eGFR) (113.01 [99.08, 124.11] mL/min/1.73 m^2 vs. 97.60 [73.78, 111.35] mL/min/1.73 m^2, $p < 0.001$), and increased blood urea nitrogen (BUN) levels (4.17 [3.08, 6.10] mmol/L vs. 5.67 [4.21, 7.99] mmol/L, $p < 0.001$).

3.2 | Intraoperative Variables

The CKD cohort exhibited a tendency towards prolonged durations of both surgery and anesthesia, necessitated greater volumes of blood transfusions, required higher doses of sodium bicarbonate, and demonstrated lower average urine output (all $p < 0.05$, Table 2).

3.3 | Postoperative Variables

Patients in the CKD cohort exhibited a reduced rate of recovery from AKI, an increased incidence of AKD and its more severe stages (stages 2 and 3), and a diminished probability of recovery from AKD. Additionally, our analysis revealed that individuals in the CKD cohort demonstrated a heightened risk of developing new hepatic dysfunction and required modifications to their calcineurin inhibitor (CNI) regimen within 7 days postoperatively. Furthermore, this group showed elevated serum creatinine (SCr) levels and an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 within 30 days (Table 3).

3.4 | Univariate and Multivariate Regression Analysis

Univariate regression analysis identified 21 perioperative indicators significantly associated with the progression from postoperative AKI to CKD. These indicators underwent collinearity diagnostics, revealing that the duration of surgery and anesthesia were excluded due to high collinearity (variance inflation factor > 10) (Table 4). Following covariate adjustment, multiple logistic regression analyses revealed that preoperative

TABLE 1 | Baseline participant characteristics.

Characteristics	Non-CKD group ($n=313$)	CKD group ($n=130$)	p
Gender (male)	272 (86.90%)	104 (80.00)	0.065
Age (≥ 65 years)	18 (5.75%)	15 (11.54%)	0.035
BMI (overweight)	75 (23.96%)	29 (22.31%)	0.370
Classification of liver transplantation			
Hepatitis B	201 (72.83%)	71 (67.62%)	0.315
Hepatitis C	5 (1.81%)	5 (4.72%)	0.215
Mixed hepatitis	3 (1.15%)	3 (2.97%)	0.448
Hepatic malignancy	89 (28.43%)	54 (41.54%)	0.007
Drug-induced liver injury	5 (1.92%)	1 (0.99%)	0.873
Alcoholic liver disease	16 (5.78%)	11 (10.38%)	0.116
Autoimmune hepatitis	5 (1.93%)	3 (2.97%)	0.839
Hepatolenticular degeneration	3 (1.15%)	0 (0.00%)	0.563
Cirrhosis	207 (79.92%)	90 (89.11%)	0.039
Alcoholic cirrhosis	13 (4.69%)	10 (9.43%)	0.081
Primary biliary cirrhosis	3 (1.08%)	4 (3.77%)	0.183
Hypertension	24 (7.77%)	15 (11.90%)	0.171
Preoperative diabetes	42 (13.59%)	32 (25.40%)	0.003
Coronary heart disease	7 (2.27%)	3 (2.38%)	1.000
Preoperative length of stay (days)	8.00 (2.00, 23.25)	12.00 (3.00, 24.50)	0.083
Preoperative length of stay in ICU	155 (56.16%)	48 (45.71%)	0.068
Preoperative hepatic encephalopathy	88 (28.12%)	32 (24.62%)	0.450
Preoperative portal hypertension	200 (64.72%)	81 (64.29%)	0.931
Preoperative ascites	157 (50.97%)	71 (56.35%)	0.309
Preoperative laboratory data			
HCT	0.29 ± 0.07	0.28 ± 0.06	0.024
PLT (10/L)	61.00 (40.00, 97.00)	63.00 (41.25, 97.25)	0.682
IBIL (mol/L)	100.30 (18.50, 208.50)	54.90 (12.53, 187.60)	0.054
ALB (g/L)	35.00 (32.00, 38.30)	34.15 (31.60, 37.88)	0.135
Hypoalbuminemia	156 (49.84%)	77 (59.23%)	0.071
WBC (10^9/L)	4.86 (3.24, 7.88)	5.09 (3.15, 7.95)	0.930
ALT (U/L)	44.00 (26.00, 91.00)	39.00 (25.00, 73.75)	0.280
AST (U/L)	67.00 (40.00, 121.00)	67.00 (42.00, 111.50)	0.909
TBIL (mol/L)	253.80 (41.61, 518.30)	145.16 (33.21, 459.58)	0.197
BUN (mmol/L)	4.17 (3.08, 6.10)	5.67 (4.21, 7.99)	<0.001
PT (s)	24.40 (17.30, 33.40)	21.85 (16.50, 32.68)	0.299
APTT (s)	53.80 (43.00, 67.00)	51.75 (40.73, 64.50)	0.140
FIB (g/L)	1.28 (0.97, 2.04)	1.39 (1.00, 2.07)	0.499
INR	2.24 (1.45, 3.29)	1.88 (1.34, 3.09)	0.203

(Continues)

TABLE 1 | (Continued)

Characteristics	Non-CKD group ($n=313$)	CKD group ($n=130$)	p
SCr (mol/L)	64.00 (55.00, 75.00)	76.00 (64.25, 93.00)	<0.001
EGFR (mL/min/1.73 m^2)	113.01 (99.08, 124.11)	97.60 (73.78, 111.35)	<0.001
MELD score	24.00 (22.00, 34.00)	22.00 (22.00, 28.00)	0.327
Surgical technique			
Standard	207 (66.13)	90 (69.23)	0.668
Piggyback	62 (19.81)	21 (16.15)	
Split liver	44 (14.06)	19 (14.62)	
Donor hepatic steatosis NG ≥ 1	100 (36.50%)	40 (37.38%)	0.872
Donor hepatic steatosis NG ≥ 2	15 (5.45%)	9 (8.41%)	0.285

Abbreviations: ALB, albumin; ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; EGFR, estimated glomerular filtration rate; FIB, fibrinogen; HCT, hematocrit; IBIL, indirect bilirubin; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end stage liver disease; PLT, platelets; PT, prothrombin time; SCr, serum creatinine; TBIL, total bilirubin; WBC, white blood cell.

TABLE 2 | Comparison of intraoperative variable differences.

Characteristics	Non-CKD group ($n=313$)	CKD group ($n=130$)	p
Duration of surgery (min)	430.69 ± 84.57	453.9 ± 109.19	0.032
Duration of anesthesia (min)	533.77 ± 87.37	558.6 ± 112.66	0.027
Anhepatic phase (min)	46.00 (40.00, 53.00)	46.50 (40.00, 55.00)	0.373
Cold ischemia time (h)	6.00 (5.67, 8.00)	6.00 (6.00, 8.00)	0.534
Urine volume (mL/kg/h)	2.69 (1.81, 4.09)	2.25 (1.32, 3.43)	0.009
Red blood cell (mL)	1250.00 (750.00, 1787.50)	1500.00 (750.00, 2125.00)	0.046
Plasma (mL)	2050.00 (1075.00, 2800.00)	2000.00 (1200.00, 3000.00)	0.451
Cryoprecipitate (mL)	30.00 (20.00, 40.00)	30.00 (20.00, 40.00)	0.818
Albumin (mL)	250.00 (200.00, 300.00)	250.00 (150.00, 300.00)	0.946
Blood loss (mL)	1500.00 (800.00, 2400.00)	1500.00 (1000.00, 2500.00)	0.242
Recombinant human coagulation factor (mg)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.092
Terlipressin (mg)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.577
Sodium bicarbonate (mL)	0.00 (0.00, 250.00)	150.00 (0.00, 250.00)	0.004
Continuous pumping of norepinephrine	178 (80.18%)	64 (82.05%)	0.719
Continuous pumping of dopamine	59 (26.58%)	22 (28.21%)	0.780
Continuous pumping of epinephrine	151 (68.02%)	58 (74.36%)	0.295

diabetes, hepatic malignancy, elevated preoperative serum creatinine (SCr) levels, progression from postoperative AKI to AKD, AKD stages 2 and 3, and an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 within 30 days were independent risk factors for the progression of AKI to CKD following liver transplantation (all $p<0.05$). Conversely, higher preoperative hematocrit (HCT) levels and recovery from AKD were associated with a reduced risk of AKI progressing to CKD ($p<0.05$, Table 5).

3.5 | Prognostic Outcomes of Patients in the CKD and Non-CKD Cohorts

Within 1 year post-surgery, the CKD cohort experienced a total of 67 readmissions, which was statistically significant ($p<0.05$). However, the rate of ICU readmissions did not differ significantly between the CKD and non-CKD groups ($p>0.05$). Mortality within one year post-surgery was observed in six patients (1.4%) in the CKD group, compared to 1 patient (0.2%) in

TABLE 3 | Comparison of postoperative variable differences.

Characteristics	Non-CKD group ($n=313$)	CKD group ($n=130$)	p
AKI stages 2 and 3	170 (54.31%)	75 (57.69%)	0.515
Recovering from AKI	301 (96.17%)	111 (85.38%)	<0.001
Recurrent AKI	29 (9.29%)	5 (3.85%)	0.050
AKD	145 (46.33%)	110 (84.62%)	<0.001
AKD stages 2 and 3	48 (15.34%)	62 (47.69%)	<0.001
Recovering from AKD	109 (75.17%)	68 (61.82%)	0.022
Recurrent AKD	60 (41.10%)	49 (44.95%)	0.538
Dialysis within 7 days	117 (37.78%)	41 (31.54%)	0.242
New hepatic dysfunction within 7 days	93 (30.00%)	53 (41.41%)	0.021
Hepatic artery stenosis within 1 year	23 (7.59%)	6 (4.72%)	0.280
Hepatic venous stenosis within 1 year	2 (0.64%)	1 (0.78%)	1.000
Portal vein stenosis within 1 year	11 (3.53%)	8 (6.20%)	0.208
Portal vein thrombosis within 1 year	2 (0.64%)	2 (1.54%)	0.366
Bile duct stenosis within 1 year	220 (70.29%)	88 (67.69%)	0.337
Recurrent hepatocellular carcinoma within 1 year	12 (3.85%)	7 (5.43%)	0.457
Medication within 7 days after surgery			
Pumping of norepinephrine	39 (17.57%)	12 (15.38%)	0.659
Pumping of dopamine	47 (21.17%)	21 (26.92%)	0.297
Pumping of aramine	13 (5.86%)	2 (2.56%)	0.398
CNI blood level exceedance	136 (43.45%)	68 (52.31%)	0.089
Replacement CNI	81 (25.88%)	58 (44.62%)	<0.001
Non-steroidal anti-inflammatory drug	95 (30.35%)	45 (34.62%)	0.379
Aminoglycoside antibiotic	22 (7.03%)	8 (6.15%)	0.739
Contrast agent	218 (69.65%)	88 (67.69%)	0.685
Hypoproteinemia within 30 days	23 (7.62%)	10 (7.94%)	0.910
SCr within 30 days (mol/L)	81.00 (65.00, 105.00)	131.00 (102.00, 185.00)	<0.001
EGFR < 60 mL/min/1.73 m^2 within 30 days	54 (19.15%)	73 (64.04%)	<0.001

Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury; CNI, calcineurin inhibitor; EGFR, estimated glomerular filtration rate; SCr, serum creatinine.

the non-CKD group, a difference that reached statistical significance ($p<0.005$) (Table 6 and Figure 2).

4 | Discussion

In this retrospective analysis conducted at our institution, we investigated the incidence, risk factors, and 1-year prognosis of AKI progressing to CKD in patients following liver transplantation. Our findings reveal that 29.3% of patients who experienced AKI post-liver transplantation subsequently developed CKD. The CKD cohort demonstrated higher rates of readmission and mortality within the first year post-surgery. The progression from AKI to CKD after liver transplantation is influenced by multiple factors. Our study identified preoperative diabetes, hepatic malignancy, elevated preoperative serum creatinine (SCr) levels, progression from postoperative AKI to AKD, AKD stages 2 and 3, and an eGFR of less than 60 mL/min/1.73 m^2 within 30 days as independent risk factors for theprogression of AKI to CKD. Conversely, no independent associations were found between preoperative blood urea nitrogen (BUN), preoperative eGFR, preexisting cirrhosis (including its etiology), intraoperative blood transfusion, urine output, sodium bicarbonate administration, and the progression from postoperative AKI to CKD. While these factors demonstrated statistical significance in univariate analysis, they are more likely indicative of renal impairment rather than direct causal determinants of the progression from AKI to CKD following transplantation. Additionally, these findings may be influenced by confounding effects in multivariate analysis and complex interactions among

TABLE 4 | Collinear diagnosis.

Characteristics	VIF	Tolerance
Age (≥ 65 years)	1.239	0.807
Hepatic malignancy	1.515	0.660
Cirrhosis	1.174	0.852
Preoperative diabetes	1.160	0.862
HCT	1.740	0.575
BUN (mmol/L)	1.313	0.761
SCr (mol/L)	2.284	0.438
EGFR (mL/min/1.73 m^2)	1.922	0.520
Duration of surgery (min)	13.435	0.074
Duration of anesthesia (min)	13.592	0.074
Urine volume (mL/kg/h)	1.219	0.820
Red blood cell (mL)	1.667	0.600
Sodium bicarbonate (mL)	1.188	0.841
Recovering from AKI	1.128	0.821
AKD	1.522	0.657
AKD stages 2 and 3	2.559	0.391
Recovering from AKD	1.145	0.874
New hepatic dysfunction within 7 days	1.171	0.854
Replacement CNI within 7 days	1.233	0.811
Readmission for treatment within 180 days	1.092	0.916
SCr within 30 days (mol/L)	1.914	0.522
EGFR < 60 mL/min/1.73 m^2 within 30 days	1.682	0.595

Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury; BUN, blood urea nitrogen; CNI, calcineurin inhibitor; EGFR, estimated glomerular filtration rate; HCT, hematocrit; SCr, serum creatinine.

TABLE 5 | Univariate and multivariate regression analysis.

	Univariate		Multivariate		
Parameters	**OR**	***p***	**OR**	**95% CI**	***p***
Preoperative diabetes	2.11	0.005	2.62	1.32–5.21	0.006
Hepatic malignancy	1.79	0.008	1.95	1.06–3.57	0.031
Higher preoperative HCT levels	0.03	0.025	0.00	0.00–0.26	0.010
Higher preoperative SCr levels	1.02	< 0.001	1.02	1.01–1.03	0.003
AKD	6.37	< 0.01	3.99	1.94–8.23	< 0.001
AKD stages 2 and 3	5.03	< 0.001	2.48	1.33–4.61	0.004
Recovery of AKD	0.61	0.025	0.49	0.27–0.86	0.014
EGFR < 60 mL/min/1.73 m^2 within 30 days	7.76	< 0.001	3.03	1.70–5.40	< 0.001
Age (≥ 65 years)	2.14	0.038			
Cirrhosis	1.92	0.039			
BUN (mmol/L)	1.11	< 0.001			
EGFR (mL/min/1.73 m^2)	0.99	< 0.001			
Duration of surgery (min)	1.03	0.019			
Duration of anesthesia (min)	1.01	0.014			
Urine volume (mL/kg/h)	0.86	0.014			
Red blood cell (mL)	1.01	0.006			
Sodium bicarbonate (mL)	1.01	0.031			
Recovering from AKI	0.23	< 0.001			
New hepatic dysfunction within 7 days	1.63	0.025			
Replacement CNI within 7 days	2.31	< 0.001			
SCr within 30 days (mol/L)	1.01	< 0.001			

variables. Our study has identified specific preoperative risk factors, including diabetes mellitus, hepatic malignancy, and elevated preoperative serum creatinine (SCr) levels, as well as postoperative risk factors, such as the transition from AKI to AKD, AKD stages 2 and 3, and an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 within 30 days post-transplantation, as predictors of AKI-to-CKD progression in liver transplant recipients. These predictive markers facilitate the early identification of high-risk patients, thereby enabling the timely implementation of targeted preventive strategies, such as intensive glycemic control and enhanced renal function monitoring and protection protocols.

AKD in hospitalized patients has been identified as an independent risk factor for the development of new-onset CKD [23]. In alignment with this, our study revealed that the progression from AKI to AKD, particularly advancing to AKD stages 2-3, constitutes an independent risk factor for the progression of postoperative AKI to CKD. Notably, the risk of progression to CKD in patients with postoperative AKD and those at AKD stages 2 and 3 was 3.99 and 2.48 times higher, respectively, compared to patients without AKD. This

observation suggests that certain patients either fail to achieve kidney function recovery within 3 months post-surgery or experience subsequent renal damage after initial recovery. This perpetuates a pathological process whereby AKI progresses to AKD and ultimately culminates in CKD. An eGFR of less than 60 mL/min/1.73 m^2 within the first month following surgery may serve as a significant indicator of kidney function status during the diagnostic window for AKD, thereby constituting an independent risk factor for CKD. Previous studies have established that the severity of AKI is a significant risk factor for the development of CKD. AKI not only facilitates the onset and progression of CKD but also predisposes patients to recurrent episodes of AKI, thereby establishing a bidirectional relationship between these two conditions [24–26].

Repeated and severe episodes of AKI can lead to renal interstitial fibrosis and a subsequent decline in renal function, ultimately resulting in CKD [27, 28]. Furthermore, baseline serum creatinine (SCr) levels may serve as predictors for the occurrence and progression of AKI [29]. Our study demonstrated that for each 1 μmol/L increase in preoperative SCr levels, the risk of postoperative AKI progressing to CKD following liver transplantation increases by a factor of 1.02. Additionally, we observed that recovery from AKD may mitigate the risk of postoperative AKI progressing to CKD. If timely interventions are implemented after the transition from AKI to AKD to gradually restore kidney function, the progression to CKD can be prevented, and the patient may ultimately avoid developing CKD. This finding presents a novel avenue for the prevention and management of CKD.

Despite some controversies, numerous cohort studies and meta-analyses have demonstrated a significant correlation between the severity and duration of AKI and the subsequent development of CKD and ESRD [30, 31]. In patients without liver transplants who experience AKI, approximately 25% progress to CKD following an AKI episode [32, 33]. Another study reported a cumulative CKD incidence of 30% over a 5-year follow-up period in individuals with AKI [34, 35]. The severity of AKI is a robust predictor of CKD progression, with higher stages of AKI correlating with an increased risk of CKD development. Both the prolonged duration and increased frequency of AKI episodes substantially elevate the risk of CKD. Specifically, patients experiencing AKI for more than 10 days have a 2.97-fold higher risk of developing CKD compared to those with an AKI duration of less than 2 days [35, 36]. Notably, the duration of AKI following cardiac surgery or gastrectomy has been identified as an independent risk factor for the subsequent development of CKD [37–39]. However, our findings indicate that the severity of AKI is not directly correlated with the onset of new CKD, consistent with results reported in the Journal of Hepatology in 2022 [23]. We propose that this discrepancy may stem from our exclusion of patients with pre-existing CKD prior to surgery. Notably, when AKD was included as a variable in the multivariate risk factor analysis model for CKD, AKD emerged as the most significant independent risk factor for CKD, surpassing AKI. This inclusion may have also affected the evaluation of the relationship between AKI and CKD. Consequently, future research should

TABLE 6 | Prognosis comparison.

Characteristics	Non-CKD group ($n = 313$)	CKD group ($n = 130$)	p
Readmission within 1 year	76 (25.00%)	67 (53.17%)	< 0.001
ICU readmission	5 (1.64%)	5 (3.97%)	0.270
Died within 1 year	1 (0.32%)	6 (4.62%)	0.004

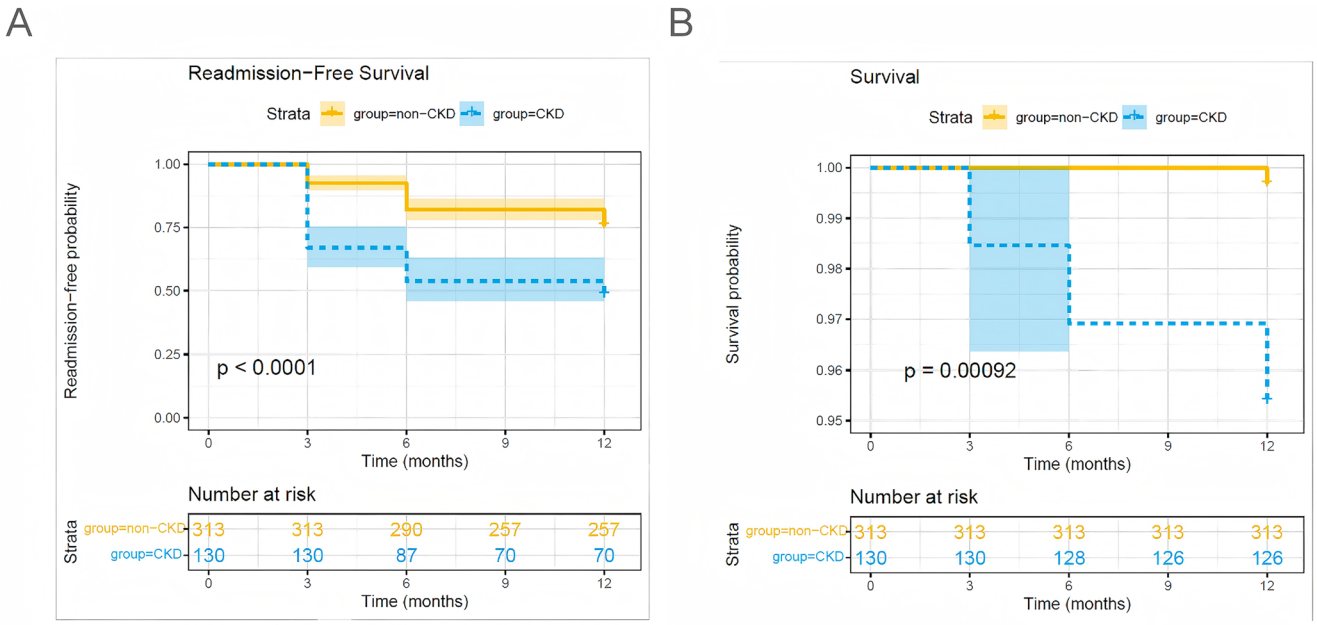

FIGURE 2 | Survival analysis of the non-CKD group and CKD group. (A) Depicts readmission—free survival over 12 months, with CKD group having lower probability ($p < 0.0001$); (B) shows survival probability, where CKD group has lower probability ($p = 0.00092$), both illustrating CKD impacts on post—surgery outcomes within 1 year.

explore these relationships to more accurately evaluate the risk associations between AKI, AKD, and CKD.

Preoperative diabetes has been recognized as an independent risk factor for CKD following liver transplantation [26, 40]. Research by Jha V et al. highlights a correlaton between diabetes and both the onset and progression of CKD, while studies by Lee et al. reveal that preoperative diabetes mellitus serves as an independent risk factor for the development of CKD within ten years post-liver transplantation [41, 42]. Among diabetic patients, AKI is identified as a factor that doubles the risk of progression to CKD stage 4 and significantly reduces patient survival. Experimental animal models suggest that nutrient-sensing pathways in the kidneys are altered under diabetic conditions, impairing the kidney's autophagic response, a process known to play a protective role in AKI [43]. The present study found that patients with preoperative diabetes exhibited a 2.62-fold increased risk of postoperative progression to CKD compared to non-diabetic patients, corroborating previous research findings.

Elevated preoperative hemoglobin levels have been shown to confer protection against the onset of CKD in patients following liver transplantation [10]. HCT can partially reflect hemoglobin trends. Patients presenting with low preoperative hemoglobin levels are susceptible to ischemia–reperfusion injury, attributed to trauma and circulatory instability. Consequently, higher preoperative HCT levels may reduce the risk of AKI progressing to CKD in the postoperative period. However, even minor variations in HCT can reflect significant changes in the internal physiological environment, making quantitative interpretations of HCT levels contentious.

Hypotension and the administration of high-dose vasoactive drugs have been identified as risk factors for AKI [44]. Intraoperative hypotension is frequently implicated in the onset of AKI, with reductions in systolic blood pressure being associated with an increased incidence of AKI episodes and the development of CKD [45–47]. The extensive use of vasopressors has been strongly correlated with the emergence of AKI [48]. Unfortunately, the regulation of blood pressure and the administration of vasoactive drugs during the perioperative period are dynamic processes, and as such, pertinent data on hypotension and vasoactive drug dosages were not collected in the study cohort of liver transplantation at our institution. Nevertheless, no significant differences were observed between the non-CKD and CKD groups concerning the infusion of vasoactive drugs during the perioperative period. This finding suggests that the overall extent of hypotension and vasoactive drug use may have a limited impact on the progression from AKI to CKD following liver transplantation. We attribute this outcome to the expertise and practices of leading liver transplantation teams both domestically and internationally. During the intraoperative phase, the anesthesiologist meticulously regulates blood pressure and administers goal-directed fluid therapy to maintain hemodynamic stability and ensure adequate renal perfusion. Concurrently, the reduced ischemic duration of the hepatic-free interval, averaging 46 min, minimizes the period of renal hypoperfusion, thereby offering additional protection to renal function.

This study's primary strength lies in its focus on a specific cohort of patients experiencing the progression from AKI to CKD following liver transplantation. It also aids in the early identification of individuals at risk for renal function deterioration, thereby enabling timely risk assessment and personalized treatment strategies. Furthermore, we systematically collected extensive clinical data throughout the perioperative period. Nonetheless, our study has several limitations. Notably, we excluded anesthesia duration and surgery duration from the multivariate logistic regression analysis due to high collinearity (VIF > 10), which enhances the stability and reliability of our findings. However, these variables are significantly associated with postoperative renal function, and anesthesia duration is an independent risk factor for postoperative AKI [49, 50]. Consequently, this aspect of the findings was not captured in our analysis. In future research, we aim to develop a predictive model to further investigate the relationship between anesthesia and surgery duration and postoperative CKD. Second, although we included most perioperative variables pertinent to liver transplantation, we did not account for potential factors related to postoperative infections and readmissions following patient discharge, which may have influenced our results. Third, the study is limited by its single-center retrospective design.

5 | Conclusions

Our findings indicate that the independent risk factors contributing to the progression from AKI to CKD following liver transplantation include preoperative diabetes, the presence of hepatic malignancy, elevated preoperative serum creatinine (SCr) levels, postoperative AKI leading to AKD, AKD stages 2 and 3, and an eGFR of less than 60 mL/min/1.73 m^2 within 30 days post-transplantation.

Author Contributions

Liping Li, Jinxuan Dai, and Yiqian Liu contributed equally to this study. Chaojin Chen, Chenfang Luo, Weifeng Yao, Yanling Wang, and Xiaoyun Li conceived and designed the experiments. Liping Li, Jinxuan Dai, Siyang Zeng, and Jing Yang performed the experiments. Liping Li, Jinxuan Dai, and Yiqian Liu analyzed the data and drafted the article. Chaojin Chen and Chenfang Luo guided the study, and all authors reviewed the manuscript. Chaojin Chen and Chenfang Luo confirmed that he has full access to the data in the study and has final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available upon reasonable request. Researchers interested in accessing the data should contact the corresponding author for further information. Please be advised that access to the data will be contingent upon approval from

the research team and adherence to ethical and legal standards. We are dedicated to fostering transparency and reproducibility in research and advocate for responsible data-sharing practices.

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