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The relationship between preoperative creatinine clearance and early outcomes of adult patients undergoing deceased donor liver transplant

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Abstract

Introduction: Preoperative renal dysfunction is detected in many patients undergoing liver transplants (LTs), which is significant in determining the potential surgical outcome.
Objectives: This study aimed to assess the renal dysfunction of the recipient before LT and its short-term impact after the surgery.
Patients and Methods: We reviewed the records of eligible 148 consecutive adult LT recipients from deceased donors between March 2019 and November 2021. Liver re-transplant, combined kidney-liver transplants, pre-existing kidney transplant, and renal replacement therapy before transplant were excluded. Patients who underwent LTs were divided into two groups based on their pre-LT creatinine clearance as calculated by the Cockcroft-Gault formula; group I (creatinine clearance <70 mL/min) and group II (creatinine clearance ≥ 70 mL/min). Then, the relationship between pretransplant renal function and early LT outcomes, including 3- and 12-month survival, and selected post-transplant variables were assessed.
Results: Of the 148 patients, 73 (49.3%) had preoperative creatinine clearance less than 70 mL/min. Warm ischemia time (min) was considerably higher in group II ($P=0.048$).
However, group I had significantly delayed peak total bilirubin levels after surgery ($P=0.03$) as well as post-LT longer hospitalization ($P<0.001$) and more readmissions ($P=0.002$) compared to group II. No significant differences in 3- and 12-month survival rates were observed between the two groups ($P=0.383$ and $P=0.766$, respectively).
Conclusion: Renal dysfunction before LT did not significantly influence short-term survival after the surgery but did negatively affect hospital stay and readmission post-transplant.

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Introduction

Renal insufficiency is a critical parameter among waiting list liver transplant (LT) recipients. About 33% of patients undergoing LT have evidence of preexisting kidney dysfunction. The development of renal dysfunction before LT is a complex, multifactorial, and crucial matter (1). Measuring the glomerular filtration rate (GFR) based on inulin clearance is generally the most accurate method to evaluate kidney function. However, interpreting inulin clearance results in cirrhosis patients is challenging due to their fluctuating renal function. Furthermore, impaired exogenous marker clearance could occur in patients presenting with pleural effusion, ascites, and severe edema, which may result from an abnormal volume of distribution (2).

Key point

Renal dysfunction is a major clinical problem in waiting-listed liver transplant (LT) recipients, with reported incidence from 3% to 20%. Accurate assessment of renal impairment and its early diagnosis before LT is of great importance for treatment strategy and prognosis. Little is known about the significance of renal dysfunction before LT on early post-LT outcomes. The results of this type of research are needed to revise the guidelines.

Cystatin C, a small peptide produced by all nucleated cells, can be an ideal marker for assessing kidney function in cirrhotic patients (3). Cystatin C is more accurate than serum creatinine. However, its higher cost and limited availability make it less practical for routine monitoring.

In the clinical setting, the serum creatinine

test is easily accessible. Despite underestimating kidney dysfunction in patients with chronic liver disease (4), serum creatinine is commonly used as a biomarker for estimating GFR.

Kidney function can be estimated easily with serum creatinine-based equations like Cockcroft-Gault (CG). This equation is the simplest and most commonly used method for estimating kidney function (5).

Accurate assessment of kidney function before LT is of considerable importance in predicting prognosis and surgical outcomes (6). However, the importance of the preoperative calculated CG formula in evaluating early outcomes after LT is not well known.

Objectives

This study aimed to assess the short-term outcomes of LT in cirrhotic patients with different degrees of pre-transplant kidney dysfunction compared to those with normal kidney function.

Patients and Methods

This retrospective study included 148 consecutive adult patients who underwent deceased donor LT at Mashhad university organ transplant center between March 2019 and November 2021.

Exclusion criteria were as follows: liver re-transplant, combined kidney-liver transplant, pre-existing kidney transplant, transplants resulting from acute liver failure, and history of pre-transplant renal replacement therapy.

A total of 148 patients were allocated into two groups depending on their renal function before LT, which was calculated by estimated creatinine clearance (CCr) using the CG formula: [[140 – age (y)] × weight (kg)]/[72 × serum Cr (mg/dL)] (multiply by 0.85 for women). Pre-LT renal dysfunction was defined by creatinine clearance lower than 70 mL/min (group I).

Liver transplant was performed using either the standard technique or the piggyback. The University of Wisconsin solution was used to prepare liver grafts.

Anesthesia was performed using standard intravenous induction: fentanyl (1-2 μg/kg), propofol (0.5-2 mg/kg), followed by neuromuscular block succinylcholine or cisatracurium, tracheal intubation, and ventilation with isoflurane 0.6% to 1.2% in the air–oxygen mixture 40% to 50% then supplemented with cisatracurium bolus administration and the remifentanil infusion (0.05-0.3 μg/kg/min) or bolus fentanyl. The anesthesiologist had discretion in the use of inotropes and vasopressors depending on the patient's hemodynamic condition. Methylprednisolone was administered to all patients before portal venous reperfusion. Packed red blood cells (PRBCs) were transfused to achieve hematocrit levels in the 25% to 30% range.

Intraoperative clinical coagulopathies were corrected by replacing the coagulation component based on thromboelastography guidance. At the end of the surgery, tracheal extubation was performed for all patients.

After surgery, recipients in both groups received triple immunosuppressive therapy based on the calcineurin inhibitor tacrolimus, the antimetabolite mycophenolate mofetil or azathioprine, and short-term steroid.

We analyzed patient demographic characteristics. In addition, intraoperative variables; recipient warm ischemia time (rWIT) referred to the duration from the donor's liver removed from the preservation solution until the portal vein reperfused and divided to short rWIT ≤30 min, the acceptable rWIT duration ranges from 30 to 50 minutes, and the prolonged rWIT more than 50 minutes; also, PRBCs and blood component transfusion; operative time; surgical technique, and final arterial pH were also evaluated. Postoperative variables included peak day and value of serum total bilirubin, alanine aminotransferase, aspartate aminotransferase, transfusion units of PRBC and fresh frozen plasma (FFP), length of stay in the intensive care unit (ICU) and hospital, occurrence of reoperation, readmission, 180-day survival, and one-year survival.

Statistical analysis

Data are shown as mean values (standard deviation). Numbers and percentages are used to report categorical variables. Statistical analysis was performed with SPSS software version 16 and using the Mann-Whitney U test and chi-square test with a significant P value ≤ 0.05.

Results

This retrospective study included 148 patients whose mean age was 48 years, mostly men (52.7%). Regarding renal function before LT, 73 patients (49.3%) had renal insufficiency (group I), while 75 cases (50.7%) had normal renal function (group II). The most common causes of LT were autoimmune hepatitis (31.1%) and hepatitis B infection (23.6%). Table 1 shows the demographic and preoperative data of the patients.

Group I had significantly older age and more comorbidities such as diabetes compared to the other group ($P < 0.001$, $P = 0.041$, respectively). Likewise, Table 2 shows the relationship between recipients' demographic data and creatinine clearance (mL/min/1.73 m^2).

There was no significant difference in preoperative hemoglobin levels between the two groups. However, group I had significantly higher numbers of intraoperative and postoperative PRBC transfusion units.

Furthermore, later peak serum total bilirubin levels, longer postoperative hospital stays, and higher hospital readmissions were significant in group I.

The results of our study showed that rWIT differed significantly between study groups such that group II had prolonged rWIT compared with an acceptable rWIT of 30 to 50 minutes in the other study group. However, the units of PRBC transfused were significantly higher during and after the surgery in group I.

There were no significant differences in terms of

Table 1. Demographic and preoperative data of the liver transplant recipients (N = 148)

Parameter	Result
Age, years	48.33 (15.54)
Males%	52.7%
Body mass index, kg/m^2	25.08 (5.56)
Underlying liver disease	
Autoimmune hepatitis	46 (31.1%)
Hepatitis B virus	35 (23.6%)
Cryptogenic	27 (18.2%)
NASH	9 (6.1%)
Hepatitis C virus	4 (2.7%)
Hepatocellular carcinoma	1 (0.7%)
Other	26 (17.6%)
MELD score	18.58 (5.34)
Child-Pugh Score	
A	12 (8.1%)
B	77 (52%)
C	59 (39.9%)
Coexisting disease (yes%)	89 (60.1%)
DM	42 (28.4%)
Ascites	36 (24.3%)
Encephalopathy (grade III/IV)	3 (2%)
HTN	2 (1.4%)
Other	6 (4.1%)
Preoperative variables	
Creatinine clearance, mL/min/1.73 m^2	77.09 (35.74)
Hemoglobin, g/dL	11.76 (2.10)
Platelet count, per microliter	108.72 (78.80)
International normalized ratio	1.61 (0.74)
Partial thromboplastin time, Sec	40.02 (9.48)
Serum albumin, g/dL	3.05 (0.56)
Total bilirubin, mg/dL	7.75 (7.10)
Serum creatinine, mg/dL	1.22 (0.61)

Abbreviations: NASH, Nonalcoholic steatohepatitis; HCC, Hepatocellular carcinoma; MELD, Model for end-stage liver disease; DM, Diabetes mellitus; HTN, Hypertension.
Values are expressed as mean (SD) or number (percent). Statistically significant ($P < 0.05$).

survival rates at both the 180-day and 1-year between groups (Table 3).

Discussion

As the main finding, there was no significant difference in the 180-day and one-year survival rates between groups with and without pre-LT renal dysfunction. However, recipients with impaired renal function before LT had longer postoperative hospital stays and more frequent readmissions.

The study by Cullaro et al analyzed data on 78,640 liver and simultaneous liver-kidney transplants from 2002 to 2017. This study indicated that renal dysfunction before LT affects post-LT mortality, regardless of the cause of the dysfunction (7).

On the other hand, the study by Wadei and colleagues performed a retrospective analysis of data from 2871 primary LT cases, grouping patients into 5-year periods from 1998 to 2018, and reported that kidney dysfunction before LT had less effect on survival after the transplant in contemporary transplants, which is consistent with our results (8).

A review of the two studies found that in the first study, the authors neither excluded simultaneous liver-kidney transplantation recipients nor assessed the effect of the transplant year (era) on survival outcomes. The effect of the LT era on outcomes may be because the demographics of the LT waiting list have changed significantly over time. In the last decade, the average age of waitlist patients has increased from 51.2 to 55.7 years (9), and the proportion of LT candidates aged 65 and above on the list has risen from 8.9% to 20.8% (10). Moreover, non-alcoholic steatohepatitis cirrhosis has emerged as one of the major causes of LT (11).

In our results, group I was characterized by a higher prevalence of the recipient's age and comorbidities like diabetes. However, 180-day and 1-year survival did not significantly differ between the groups.

This could be attributed to significant progress in LT immunosuppressive therapy, surgery, and anesthesia techniques, particularly in anesthesia monitoring, coagulation, and fluid management over the past few years (12). In the past years, few articles have been published on whether kidney dysfunction before the LT affects survival after surgery. Furthermore, the negative consequences of prolonged rWIT are well-known (13). However, it is still difficult to definitively conclude the association between short rWIT and decreased perioperative blood transfusion. The reasons are as follows; First, various factors lead to blood loss and the necessity of blood transfusion during LT, such as preoperative coagulation abnormalities, difficult hepatic resection, marginal LT, and intense fibrinolysis (14). Second, different surgical transplant techniques, such as piggyback or standard, may affect rWIT (13). Furthermore, the role of acceptable versus prolonged rWIT on perioperative blood loss and transfusion in LT patients is less studied. Of note, in our study, in the renal dysfunction group with an acceptable rWIT of 30 to 50 minutes, the number of PRBC units transfused perioperatively was significantly higher than in another group with a prolonged rWIT. In our study, the total BIL peak day early after LT was significantly later in the renal dysfunction group. However, this variable seems to be within acceptable limits in both study groups.

Table 2. Relationship between recipients' demographic data and creatinine clearance (mL/min/1.73 m^2)

Variable	Group I (n=73) CLCr < 70	Group II (n=75) CLCr ≥ 70	*P* value
Characteristics of recipients			
Age, years	53.79 (13.81)	43.01 (15.37)	<0.001[a]
Males%	25.7%	27%	0.876[b]
BMI, kg/m^2	25.63 (5.42)	24.55 (5.69)	0.130[a]
Underlying liver disease			0.174[b]
AIH	14.2%	16.9%	
HBV	13.5%	10.1%	
Cryptogenic	10.1%	8.1%	
NASH	4.7%	1.4%	
HCV	1.4%	1.4%	
HCC	0	0.7%	
Other	5.4%	12.2%	
MELD score	19.50 (6.13)	17.68 (4.28)	0.087[a]
Child-Pugh score			0.056[b]
A	4.1%	4.1%	
B	20.9%	31.1%	
C	24.3%	15.5%	
Coexisting disease (yes%)	34.4%	25.7%	0.041[b]
DM	18.9%	9.5%	
Ascites	12.8%	11.5%	
Encephalopathy (grade III/IV)	1.4%	0.7%	
HTN	0	1.4%	
Other	1.4%	2.7%	

Abbreviations: BMI, Body mass index; AIH, Autoimmune hepatitis; HBV, Hepatitis B virus; NASH, Nonalcoholic steatohepatitis; HCV, Hepatitis C virus; HCC, Hepatocellular carcinoma; MELD, Model for end-stage liver disease; DM, Diabetes mellitus; HTN, Hypertension.
Values are expressed as means (SD) or number (%). [a] Mann-Whitney U; [b] Chi-square test. Statistically significant ($P < 0.05$).

Conclusion

Patients with pre-existing kidney dysfunction before LT had longer postoperative stays in the hospital and were more likely to be readmitted. However, their short-term survival following LT was not significantly affected.

Limitations of the study

The main limitation of this study in a single center investigation. We suggest larger studies on this aspect of LT individuals.

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Authors' contribution

Conceptualization: Soheila Milani.
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Investigation: Soheila Milani, Masoomeh Tabari, Mandana Jahanian, Monir Mirzadeh.
Methodology: Soheila Milani, Maryam Emadzadeh, Mandana Jahanian.
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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research adhered to the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of Mashhad University of Medical Sciences (Ethical code#IR.MUMS.MEDICAL.REC.1401.139). Informed consents were obtained at the point of patient admission. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

Table 3. Relationship between perioperative recipient variables and creatinine clearance (mL/min/1.73 m²)

	Group I (n=73) CLCr < 70	Group II (n=75) CLCr ≥ 70	*P* value
Preoperative variables			
Creatinine clearance, mL/min/1.73 m ²	46.01(11.92)	107.34(22.77)	<0.001[a]
Hemoglobin, g/dL	11.40 (2.20)	12.11 (1.95)	0.052[a]
Platelet count, per microliter	98.10(53.43)	119.05(96.64)	0.731[a]
International normalized ratio	1.65 (0.76)	1.56 (0.72)	0.571[a]
Partial thromboplastin time (s)	39.25 (9.94)	40.77(9.01)	0.129[a]
Serum albumin (g/dL)	3.01(0.56)	3.09 (0.55)	0.646[a]
Total bilirubin (mg/dL)	5.91 (6.75)	8.25(8.50)	0.070[a]
Serum creatinine (mg/dL)	1.68(0.53)	0.77(0.22)	<0.001[a]
Donor risk index	1.20(0.18)	1.25(0.23)	0.653[a]
Intraoperative variables			
Warm ischemia time, min	48.69(10.51)	52.54(12.69)	0.048[b]
PRBC transfusion, units	2.05(1.47)	1.50(1.47)	0.010[a]
FFP, units	1.67(1.13)	1.62(1.21)	0.713[a]
Cryo, units	0.82 (1.17)	0.49 (0.99)	0.067[a]
Fibrinogen concentrate, g	0.45 (0.72)	0.50 (0.79)	0.799
PLT transfusion, units	0.027 (0.23)	0.026 (0.23)	0.985[a]
Operative time, min	358.83(57.01)	358.93(56.07)	0.099[b]
Surgical Tech, Standard/Piggyback %	27.7 / 21.6%	33.1 / 17.6 %	0. 253[c]
Last arterial pH	7.33 (0.07)	7.37 (0.05)	0.104[a]
Postoperative variables			
Total BIL max (mg/dL)	6.67(4.32)	7.60(5.28)	0.371[a]
Total BIL max (day)	2.42(3.05)	1.72 (1.76)	0.038[a]
ALT max, UI/L	646.32 (700.85)	606.88(519.93)	0.533[a]
ALT max, day	1.78(1.67)	1.58(1.11)	0.715[a]
AST max, UI/L	920.42(991.52)	851.58(781.20)	0.808[a]
AST max, day	1.56(1.52)	1.49(0.97)	0.527[a]
PRBC transfusion, units	1.73(2.09)	0.97(1.43)	0.009[a]
FFP, units	2.15(7.05)	0.58(1.36)	0.051[a]
ICU stay, day	6.48 (2.93)	5.98(3.27)	0.084[a]
Re-operation, yes%	5.4%	6.1%	0.866[c]
Hospital discharge, day	22.7(6.22)	19.36(6.36)	<0.001[a]
Hospital Readmission, yes%	49.3%	24%	0.002[c]
180-day survival (%)	87.7%	92%	0.383[c]
1-Year survival (%)	83.6%	85.3%	0.766[c]

Abbreviations: PRBC, Packed red blood cell; FFP, Fresh frozen plasma; Cryo, Cryoprecipitate; PLT, Platelet; BIL, Bilirubin; ALT, Alanine aminotransferase; AST, Aspartate transaminase; ICU, Intensive care unit.
Data presents as frequency (%) or mean (standard deviation).
[a] Mann-Whitney test; [b] *t* test; [c] Chi-square test. Statistically significant ($P < 0.05$).

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