Central Asian Journal of Medical Sciences
CAJMS

Original Article

Cent Asian J Med Sci. 2021 Dec;7(4):339-345. https://doi.org/10.24079/CAJMS.2021.12.005

Renal Dysfunction After Liver Transplantation: a Single Center Study

Batsaikhan Batsuuri[1, 2], Fidel Lopez-Verdugo[3], Bat-Ireedui Badarch[2], Suvd Nergui[4], Ariunaa Togtokh[5], Shiirevnyamba Avirmed[1], Sergelen Orgoi[1, 2]

[1]Department of Surgery, School of Medicine, Mongolian National University of Medical Sciences; [2]Center of Transplantation, Liver Transplantation Team, The First Central Hospital of Mongolia; [3]Center for Global Surgery, University of Utah, Salt Lake City, Utah, United States; [4]Department of Nephrology, The First Central Hospital, Ulaanbaatar, Mongolia; [5]Department of Nephrology, School of Medicine, Mongolian National University of Medical Sciences

Submitted: September 26, 2021
Revised: October 5, 2021
Accepted: December 19, 2021

Corresponding Author
Shiirevnyamba Avirmed, PhD
Department of Surgery, School of Medicine, Mongolian National University of Medical Science, Ulaanbaatar, 14210 Mongolia
Tel: +976-9948-8523
E-mail: batsbats23@gmail.com

Objectives: Mongolia is known as one of the countries with a high prevalence of viral hepatitis infection and its related liver cirrhosis and HCC. Therefor, liver transplantation (LT) surgery increases from year to year in Mongolia. Our goal was to evaluate post-transplant renal dysfunction (PTRD) and to investigate the predicting factors for renal dysfunction after LT. **Methods:** The impact of graft ischemic time, peri- and postoperative blood product transfusion, perioperative hemodynamics, time to extubating, intensive care length of stay, incidence of chronic renal failure, and mortality and morbidity were examined alone and then as a combined outcome. **Results:** Early renal dysfunction was identified by measuring serum creatinine and glomerular filtration rate. In our investigation which was a study group of patients following liver transplantation (LT), the following renal dysfunctions were found: 39% of recipients in the study had renal dysfunction, while the rest had no renal dysfunction. The average creatinine level of the recipients who had a renal dysfunction after LT, was 0.825 ± 0.24 mg/dl and the glomerular filtration rate was 111 ± 36.3 ml/min, and statistically significant. **Conclusion:** Preoperative kidney function plays a crucial role for postoperative renal dysfunction.

Keywords: Renal Dysfunction, Liver, Transplantation

Introduction

In 2019, more than 34,270 liver transplants (LT) was performed worldwide, this means 6.02 LT per 1 million population [1]. The Liver Transplant Program in Mongolia started performing experimental surgery on pigs in 2007 with the support of the Mongolian Science Foundation. The first LT surgery in Mongolia on a human patient was successfully performed in September, 2011 with the collaboration of the Liver Transplant Team of the Asan Medical Center in South Korea. Since its establishment, by 2021 one hundred LTs among both adults and children were successfully performed in Mongolia.

The main causes of LT in other countries is cirrhosis (83.4%) and hepatocellular cancer (HCC) (3.0%)[2]. At the First Central Hospital of Mongolia, 67% of viral cirrhosis and 26% of HCC were counted as the primary causes for LT, which indicates

regional features. The incidence of HCC is high in developing and low-income countries of Asia and Africa [3, 4]. Mongolia has the highest HCC incidence in the world at 78.1 per 100,000 population [5].

Renal dysfunction is one of the most common complications of mortality and morbidity in cirrhotic patients [6]. Renal dysfunction occurs in every 5 patients with cirrhosis and occurs among 20 - 50% of the hospitalized patients with a primary diagnosis [7]. LT is an effective treatment method on cirrhotic patients with impaired renal function [8]. However, LT surgery itself is a risk factor for Post-Transplant Renal Dysfunction (PTRD). LT recipients experience a high incidence of PTRD [9,10]. The etiology of PTRD is thought to be multifactorial and includes exposure to high levels of toxic free-radicals, renal ischemia, use of nephrotoxic medications and the effects of end-stage liver disease (ESLD) on the kidney [11,12]. A better understanding of the predicting factors for PTRD can enable improved methods to prevent or ameliorate the injury. For example, initiation of calcineurin inhibitors (tacrolimus) could be delayed or the dosage can be adjusted in patients at high risk for PTRD [13]. Furthermore, long-term outcomes associated with early PTRD are largely unknown.

As a result, PTRD can lead to high morbidity and mortality in LT recipients [14]. The prevalence of renal failure after LT surgery varies in different centers according to published papers. For example, Thorsten F. et al. reported that acute kidney injury (AKI) after LT from cadaveric donors occurred in 36.8% of patients and renal failure in 25.7%. Pre-LT renal dysfunction assessed by serum creatinine (SCr) was the most important risk factor predicting severe forms of AKI [15]. According to the study of Hilmi et al., kidney failure after LT occurs to 52% of recipients of LT. Predisposing factors for development of AKI were female sex, weight (>100 kg), severity of liver disease (Child–Pugh score (CPS)), pre-existing diabetes mellitus, number of units of blood or fresh frozen plasma transfused during surgery and non-alcoholic steatohepatitis as the etiology of ESLD ($p \leq 0.05$) [16]. LT patients with impaired renal function have a 1-month survival rate of 47.5% and a 1-year survival rate of 46.4% [17]. Compared to similar studies done in other countries, the study conducted in Mongolia has a smaller sample size due to the number of LT surgeries performed. However, it is the first study to predict the risk factors for PTRD in LT patients in Mongolia.

The primary objectives of this study were to identify the predicting risk factors for PTRD in patients undergoing LT.

Materials and Methods

Research design and subjects

This is a hospital-based case control study. The study population included adult and pediatric patients who had chronic ESLD and who received living and cadaveric liver allografts at the Organ Transplant Center of the First Central Hospital of Mongolia between September 2011 and September 2020. Patients with fulminant hepatic failure were excluded from the study. We collected data at the preoperative, intraoperative, and postoperative time periods. Preoperative and intraoperative data was used to predict AKI and to construct the prediction model, whereas postoperative data was used to define the end point and outcome analysis.

The participants were divided into two groups. In the case group, patients with renal dysfunction after LT were selected (n = 39), and in the control group, patients without renal dysfunction (n = 61) were selected and included in the study on a voluntary basis.

Variables

The following preoperative variables were also included: patient characteristics, Model for End-Stage Liver Disease (MELD) score (serum bilirubin, International Normalized Ratio (INR), etiology), Child-Pugh scores (CTPS) [SCr, serum total bilirubin, serum albumin, INR, ascites, hepatic encephalopathy], SCr measured by the spectrophotometric modified method, serum lactate, ammonia level, serum bilirubin, preoperative co-morbidities, preoperative medications, and history of previous organ transplant. Intraoperative data were haemodynamics (systemic arterial pressure, central venous pressure, heart rate and cardiac output), arterial blood gases, serum lactate, urine output, blood products transfused, fluid balance, vasopressor agents, duration of the surgery, medications used during the surgery (combination of vasopressors, diuretics, and anti-fibrinolytic agent), as well as the type of liver allograft (right lobe, left lobe, extended left lobe of whole cadaveric allograft), and ischemia times (cold and warm). Postoperative data included daily SCr, sepsis, urine output, blood products transfused, fluid balance and occurrence of postoperative LT complications (bleeding, bile leak, primary graft failure, delayed graft function, rejection, or ischaemia-

reperfusion injury).

Procedures

PTRD was defined by the most recent definition, which uses a 50% increase in SCr from the baseline (preoperative value) or a 26.5 mmol litre^{-1} increase from baseline within 48 h without urine output [18]. Chronic kidney disease (CKD) was defined according to the criteria established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002 [19]. The KDOQI defined CKD as a glomerular filtration rate (GFR) of $<$ 60 ml min^{-1} 1.73 m^{-2}. We determined the estimated GFR (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) formula: eGFR = 186 $\times$ (SCr mg dl^{-1})$^{-1.154}$ $\times$ age $^{-0.0203}$ $\times$ 0.742 if patient is female $\times$ 1.21 if patient is African American [20].

The modified CPS was determined by the same consultant hepatologist and was usually updated every 3 – 6 months. SCr is measured at the time of hospital admission in preparation for the transplant; for the entire study, SCr was measured at the First Central Hospital's laboratory using the same method used since 2010.

Immunosuppression was provided per standard protocol: methylprednisolone (1 g) given before reperfusion of the graft followed by tacrolimus. The loading dose for tacrolimus is given by an IV in 0.025 mg/kg/day dose for 2 - 3 days. Oral dose loading guided by daily blood levels measured before giving the next dose with a targeted trough of 10-12 ng/dl. Patients were followed-up for minimal 12 months after LT.

Statistical analysis

The frequency distribution of the parameters in the group was determined by the Shapiro Wilk's test. Unpaired t-test was conducted to compare the mean between two independent groups. For categorical variables, chi-square test was carried out. A value of p less than 0.05 was considered statistically significant. The data collected using a quantitative method was entered to and analyzed using Statistical Packages for Social Sciences (SPSS) version 20 statistical software.

Ethical statement

Ethical approval for this study was obtained from the Mongolian National University of Medical Sciences Research Ethics Committee on January 01, 2021 (№2021/3-01). Informed consent was obtained from all participants.

Results

During the ten-year study period, one hundred LTs were performed on patients who were potentially eligible for inclusion in our study. Of those, 39 (39%) patients diagnosed with PTRD and were included in the study. One patient died within the first 24h after transplant and was excluded from the study since it did not meet the criteria used to define PTRD. Preoperative data, along with baseline characteristics for the 100 patients, are shown in Table 1. Of note, baseline renal function were associated with the development of early PTRD.

Of the total study participants (n = 100), the majority of the recipients of LT surgery at the First Central Hospital of Mongolia are male (55%) and the mean age of the study participants is 41 years. The mean MELD score of the surgical recipients was 14.9 ± 5.3, while the CTP score of 53% was "B".72% of LT recipients underwent surgery due to viral induced cirrhosis and 24% for HCC. Regarding to co-morbidity, diabetes mellitus accounted for 8.7% and essential hypertension for 6.5%.

The mean SCr level prior to LT was 0.70 ± 0.27 mg/dl and the GFR was 121.6 ± 61.3 ml/min. In comparison to the preoperative renal function parameters in the two groups, the average SCr of the recipients in the renal dysfunction group was slightly higher than the group without renal dysfunction (0.825 ± 0.24 vs. 0.625 ± 0.26). GFR was slightly lower than the group without renal dysfunction, which is statistically significant (111 ± 36.3 vs. 153 ± 68.5).

Donor type, graft type, graft weight, graft-to-recipient weight ratio (GRWR), and ischemic times were all not significant (Table 2). 93% of LT performed at the First Central Hospital of Mongolia were performed from living donors while the remaining 7% from brain-dead donors. In terms of graft type, 91% of living donors liver right lobes were transplanted, and the average graft weight was 756.6 ± 192.3 cc. The type and weight of transplanted liver appear to be statistically irrelevant to renal dysfunction. Total ischemia in the group with impaired renal function was slightly longer, 207 (171.5 - 235) minutes, while in the group without renal dysfunction was 193 (167 - 229) minutes.

Intraoperative data, along with descriptive statistics for the one hundred patients, are shown in Table 3. The mean arterial pressure (MAP) level at the beginning of the LT surgery was 80

Table 1. Demographics of recipients.

Variables	Case (n = 39)	Control (n = 61)	Total (n = 100)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age, mean (IQR)	43.1 ± 38.2	40.5 ± 41.5	41.3 ± 48.7	0.918
BMI (kg/m2)	24.7 ± 3.2	24.8 ± 3.8	24.7 ± 3.6	0.973
MELD score	14.2 ± 5.9	15.4 ± 4.9	14.9 ± 5.3	0.297
Pre-Liver transplantation serum creatinine	0.825 ± 0.24	0.625 ± 0.26	0.70 ± 0.27	0.001
Pre-Liver transplantation GFR	111 ± 36.3	153 ± 68.5	121.6 ± 61.3	0.001
	N (%)	N (%)	N (%)	
Gender				
Male	28 (71.8)	27 (44.3)	55 (55)	0.012
Female	11 (28.2)	34 (55.7)	45 (45)	
Child-Turcotte-Pugh				
Class A	8 (20.5)	8 (13.1)	16 (16)	0.657
Class B	21 (53.8)	32 (52.4)	53 (53)	
Class C	10 (25.6)	21 (34.4)	31 (31)	
Hypertension				
Yes	4 (10.8)	2 (3.7)	6 (6.5)	0.219
No	35 (89.2)	59 (96.3)	94 (93.5)	
Diabetes mellitus				
Yes	4 (10.8)	4 (7.4)	8 (8.7)	0.710
No	35 (89.2)	57 (92.6)	92 (91.3)	
Diagnosis				
Viral liver cirrhosis	26 (66.6)	46 (75.4)	72 (72)	
HCC	12 (30.7)	12 (19.6)	24 (24)	
Primary biliary cirrhosis	-	2 (3.2)	2 (2)	
Others	1 (2.5)	1 (1.6)	2 (2)	
Blood type				
O	14 (35.8)	19 (31.1)	33 (33)	
B	7 (17.9)	27 (44.2)	34 (34)	
A	14 (35.8)	13 (21.3)	27 (27)	
AB	4 (10.2)	2 (3.2)	6 (6)	

MELD: model for end-stage liver disease; GFR: Glomerular filtration rate.

mmHg while the minimum arterial pressure level was 52 mmHg. There was no difference between the groups (78 (69.5 - 86) vs. 81.5 (72.5 - 93.5)). No difference in central venous pressure (2 (1 - 3) vs. 2 (1 - 3.2)) was observed. Similarly, the average amount of urine excretion during LT did not differ between the groups 1459 cc (1094 - 1975) vs. 1560 cc (1166 - 1927).

Blood transfusions and blood products during LT surgery may indicate some degree of bleeding. On average, recipient surgery is transfused 4 (2-10) units of leucocyte-reduced red blood cells, 5 units of cytopheresed platelets, 10 units of inactivated fresh frozen plasma and 10 units of cryoprecipitate. Comparing the groups, there was no statistical significance between the group with renal dysfunction and without renal dysfunction. Baseline MAP, CVP, amount of ascites, urine output and intraoperative blood transfusions were all significantly less likely to be associated with PTRD.

Postoperative outcomes are shown in Table 4. LT recipients have an average of 33 hospital stay days. Vascular and biliary complications have not been shown to affect renal function. However, more leucocyte-reduced red blood cells, on average 3 (2 - 5.7) units, and inactivated fresh frozen plasma, on average 8 (4 - 15.2) units, were more likely to have transfused.

Table 2. Indications for liver transplantation.

Variables	Case (n = 39)	Control (n = 61)	Total (n = 100)	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Graft weigh (g)	740.8 ± 156.2	766.7 ± 212.8	756.6 ± 192.3	0.643
GRWR	0.97 ± 0.91	1.06 ± 1.26	1.04 ± 1.29	0.275
Cold ischemic time	118.1 ± 136.6	110.5 ± 138.9	112.3 ± 120.9	0.760
Warm ischemic time	81.7 ± 128.5	77.3 ± 83.5	80.9 ± 82.1	0.549
Total ischemic time	207.0 ± 221.6	193.1 ± 199.2	202.8 ± 209.1	0.757
Donor type	**N (%)**	**N (%)**	**N (%)**	
Live	38 (97.4)	55 (90.1)	93 (93)	0.414
Cadaveric	1 (2.5)	6 (9.8)	7 (7)	
Graft type				
Whole	1 (2.5)	6 (9.8)	7 (7)	
Right lobe	37 (94.8)	54 (88.5)	91 (91)	
Left lobe	-	1 (1.6)	1 (1)	
Extended right lobe	1 (2.5)	-	1 (1)	

GRWR: Graft-to-recipient weight ratio

Table 3. Intraoperative findings.

Variables	Case (n = 39)	Control (n = 61)	Total (n = 100)	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Baseline MAP	78.2 ± 77.8	81.5 ± 83.0	80.1 ± 80.5	0.172
Lowest MAP	53.5 ± 53.25	52.3 ± 50.25	52.1 ± 50.5	0.388
Lowest CVP	2 ± 2.0	2 ± 2.1	2 ± 2.0	0.664
Ascites	100 ± 115.0	250 ± 125	150 ± 118.2	0.277
Urinary output, cc	1459.0 ± 1534.5	1560.1 ± 1546.5	1540.9 ± 1531.0	0.912
Intraoperative RBC (units)	2 ± 0.5	6 ± 2.1	4 ± 2.5	0.077
Intraoperative FFP (units)	8 ± 1.6	11.5 ± 6.6	10 ± 8.3	0.670
Intraoperative cryo (units)	10 ± 5.2	10 ± 5.8	10 ± 5.9	0.559
	N (%)	**N (%)**	**N (%)**	
Pontaneous PSS, n (%)				
Yes	21 (53.8)	26 (42.6)	47 (47)	0.327
No	18 (46.2)	35 (57.4)	53 (53)	

MAP: mean arterial pressure; CVP: central venous pressure; PSS: portosystemic shunts; RBC: red blood cels; FFP: fresh frozen plasma.

Table 4. Postoperative outcomes.

Variables	Case (n = 39)	Control (n = 61)	Total (n = 100)	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Hospital stay (days)	32 ± 28.5	34 ± 29	33 ± 24	0.989
FFP (units)	8 ± 4.2	5.5 ± 2.5	6 ± 2.2	0.133
RBC (units)	3 ± 2.7	2.5 ± 1.6	3 ± 1.8	0.974
Platelets (units)	8 ± 1.2	15 ± 10.2	14 ± 5.3	0.111
Fluid balance POD1	1186.4 ± 1419.8	1067.9 ± 871.8	1119.23 ± 1136.28	0.168
Fluid balance POD3	-555.0 ± 1928.8	70.56 ± 1329.3	-197 ± 1633.71	0.807
Fluid balance POD7	-455.05 ± 1265.8	-445.38 ± 1126.9	-449.5 ± 1181.1	0.525
Immunosuppression protocol	**N (%)**	**N (%)**	**N (%)**	
Tacrolimus + MMF	37 (94.8)	55 (90.1)	92 (92)	
Tacrolimus	2 (5.1)	1 (1.6)	3 (3)	

*MMF: Mycophenolate mofetil

Discussion

The true incidence of PTRD after LT is not known due to different patient selections, different study methods and definitions of AKI. In some of the above-mentioned center studies, the incidence of AKI varies from 20 to 50%. In a very recent study by Hilmi et al. it was reported that the incidence of AKI following operative LT was 52% [15, 16]. In our study, PTRD occurred in 39% of LT recipients, which shows similar findings to other studies. Our center results show that PTRD group preoperative baseline renal function, meaning high SCr levels (0.825 ± 0.24) and low GFR (111 ± 36.3) compared to non-PTRD group (0.625 ± 0.26 and 153 ± 68.5) lead to PTRD.

One of the risk factors for PTRD in our study was male sex, which is not consistent with multiple previous studies of AKI done by other researchers. In regards to a sex, in men androgens have been implicated in the etiology and progression of cardiovascular and renal diseases, as testosterone stimulates the renin–angiotensin aldosterone system and the endothelin system, augmenting oxidative stress and end-organ damage. However, in cirrhotic males, testosterone production was reduced and oestradiol increased, which lead to increases in luteinizing hormone and follicle stimulating hormones. Combining these facts might be related to why there were more men than women in the renal dysfunction group [4].

Unexpectedly, none of the intraoperative and postoperative variables were predictive of PTRD, with the exception of total blood and fresh frozen plasma use. Blood use seems to be a strong overall marker of surgical complexity, as it is well known to correlate with the number of complications and overall survival following operative LT. Thus, blood use was a surrogate marker for intraoperative bleeding. In our study, intraoperative and postoperative blood transfusion was not a significant predictive factor for PTRD.

There are several limitations in the study. First, the sample size is a relatively small even though we included all the LT recipients who had surgery in Mongolia. Second, some of the variables including body mass index, preoperative laboratory values like bilirubin and prior bacterial infection and type of LT etc. were not included in the analysis. According to the study of Dagmar Kollmann et al. it was found that LT patients requiring renal replacement therapy who received donation from circulatory death or donation after brain death showed significantly lower patient survival in multivariate analysis [21]. In our study, donor type (live vs. cadaveric) did not show any statistically significant difference due to the small sample size. In addition, other studies found similar finding like our study that donor status (cardiac vs. brain dead donor) does not affect PTRD [9].

In the future, additional research is needed to see whether body mass index as well as the above mentioned preoperative laboratory values are a clinically meaningful predictor of patient reported outcomes of LT.

Conclusions

It is unquestionable that severe forms of PTRD, especially those that require renal replacement therapy, have a significant impact on patient survival rate. Preoperative kidney function plays a crucial role for postoperative renal dysfunction. It is pivotal to elucidate the risk factors for PTRD since its role in the clinical implication of the LT has a significant impact on patient outcomes. Our study is the first study to elucidate its role in Mongolian LT patients.

Conflict of Interest

The authors state no conflict of interest.

Acknowledgements

The authors thank the recipients who participated in this study, Fidel Lopez-Verdugo and Center for Global Surgery of the University of Utah for data handling.

References

1. Global Observatory on Donation and Transplantation. Retrieved from transplant-observatory. [accessed on 27 July 2019]. Available at: http://www.transplant-observatory.org/.
2. Vandana Khungar AN. Current Indications, contraindications, delisting criteria and timing for Transplantation, 3rd edition, 2015.
3. Sloan FA. Retrieved from cancer control opportunities in low- and middle-income countries. Washington DC: National Academies Press 2007.

4. Sung H, Jacques F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin 2021; 7: 209–49.
5. Jazag A. Status quo of chronic liver diseases including hepatocellular carcinoma in Mongolia. KJIM 2012; 27: 121-7.
6. Beate A, Frank L. Renal failure in patients with liver cirrhosis: novel classifications, biomarkers, treatment. Visc Med 2018; 34: 246-54.
7. Appenrodt B. Renal failure in patients with liver cirrhosis: novel classifications, biomarkers, treatment. Visc Med 2018; 34: 236-42.
8. Garcia-Tsao GP. Acute kidney injury in cirrhosis. Hepatology 2008; 48: 2064-77.
9. Wiesen PM. Incidence and risk factors for early renal dysfunction after liver transplantation. World J Transplant 2016; 10: 220–32.
10. Lee SK. Early postoperative renal dysfunction in the adult living donor liver transplantation. Transplant Proc 2007; 39: 1517-9.
11. Gainza FJ. Evaluation of acute renal failure in liver transplantation perioperative period: incidence and impact. Transplant Proc 2002; 34: 250–1.
12. Gonwa TA, Continued influence of perioperative renal function on outcome of orthotopic liver transplant in US: where will the MELD lead us? Am J Transplant 2006; 6: 2651–9.
13. Duvoux C. Immunosuppression in liver transplant recipients with renal impairment. Hepatoloty 2011; 54: 1041–54.
14. Varun SM. Renal failure and liver allocation: current practices and potential improvements. Adv Chronic Kidney Dis 2015; 22: 391–8.
15. Thorsten FAB. Renal damage after liver transplantation. Biosci Rep 2020; 31: 40-4.
16. Hilmi IA. Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes. Br J Anaesth 2015; 114: 919–26.
17. O'Riordan AWV. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. Am J Transplant 2007; 7: 168–76.
18. Wong FN. Working party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut 2011; 60: 702–9.
19. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002; 39: S1–S266.
20. Poge UG. MDRD equations for estimation of GFR in renal transplant recipients. Am J Transplant 2005; 5: 1306–11.
21. Dagmar K, Shuet FN, Roizar R, Bettina E, Gonzalo S. Renal dysfunction after liver transplantation: effect of donor type. Liver Transpl 2020; 26: 799-810.