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Factors Associated with Development of Acute Kidney Injury After Liver Transplantation

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ABSTRACT

Background: Early post-liver transplant (LT) acute kidney injury (AKI) has been associated with worse short-term and long-term outcomes, but the incidence and risk factors in our population are unknown. **Methods:** We designed a prospective, single-center, longitudinal cohort study to determine the incidence of AKI during the immediate postoperative period of LT, and to identify the risk factors associated with AKI after LT. Pre-operative and intraoperative variables were analyzed to determine if there was any correlation with the development of post-operative AKI. **Results:** Eighty-six patients were included in the final analysis; from them, 45 (52%) developed AKI in the following 30 days after LT. The presence of hepatic encephalopathy prior to LT was the factor most strongly associated with the development of AKI (Relative Risk 3.67, 95% Confidence Interval 1.08-8.95). Other factors associated with AKI development were male gender and a higher serum lactate during surgery. **Conclusion:** AKI was a frequent complication that significantly worsened the prognosis of LT recipients and was associated with an increased 30-day mortality rate. The presence of hepatic encephalopathy strongly predicted the development of severe AKI. (REV INVEST CLIN. 2022;74(2):90-6)

Keywords: Renal failure. Transplantation. Encephalopathy. Dialysis.

INTRODUCTION

End-stage liver disease (ESLD) occurs when liver failure is irreversible and liver transplantation (LT) is the only potential curative treatment. Worldwide, ESLD is a common cause of morbidity and mortality[1,2]. Cirrhosis, which is defined as the histological development of advanced liver fibrosis, is commonly seen in patients with chronic liver injury from a variety of etiologies. As progressive liver damage occurs, liver disease may proceed to ESLD, which reflects a patient with decompensated cirrhosis. The major complications of this

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decompensation include variceal bleeding, ascites, encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatopulmonary syndrome. Remarkably, once liver decompensation occurs, the 5-year mortality without LT is as high as 85%, underscoring the life-saving implications of LT[3].

LT has evolved dramatically over the past 50 years; currently, it is performed at hundreds of medical centers in over 80 countries, including Mexico. The clinical benefits of LT are undisputable and survival outcomes related to this procedure have improved enormously, yielding 1-year patient survival rates above 80%[4]. However, even if this life-saving procedure confers the best therapeutic option for patients with ESLD, complications that arise soon after LT continue to implicate a major clinical problem.

The liver actively interacts with many body systems, so the patient who receives a liver graft faces a huge set of physiological challenges. During the immediate postoperative period, the liver is subject to a wide variety of insults, including hypotension, hypoxia, graft rejection, and ischemia; meanwhile, other tissues, including kidneys, lungs, and central nervous system, also suffer during the post-LT period. Accordingly, one of the most frequent complications seen after LT is acute kidney injury (AKI)[5,6].

Any event resulting in kidney hypoperfusion during LT might predispose the patient to develop AKI[6]. Furthermore, reperfusion after unclamping of the portal vein is followed by a series of insults to the whole body, including hemodynamic instability and a characteristic ischemia-reperfusion sequence that leads to the release of toxic components by the graft, including proinflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha. In turn, these cytokines trigger an inflammatory response that subsequently damages renal tissue, particularly producing tubular injury, which further increases the risk of developing AKI[7].

Early post-transplant AKI, even if transient, has been associated with increased graft rejection, longer intensive care unit (ICU) stays, greater hospital costs, and higher mortality rates[8-10]. Furthermore, it has been reported that a 50% increase in serum creatinine (sCr) from baseline within a week after LT is associated with the development of chronic kidney disease (CKD) within 1 year after LT and with increased long-term all-cause mortality[11,12]. Altogether, these findings underscore the huge detrimental effect of AKI after LT.

In our institution, the LT program began about 35 years ago with a growing number of transplants each year, reaching an average of 50 procedures per year (approximately 1/week) in the past 5 years, which represents an active program for a relatively small hospital (about 250 beds). However, the incidence and predisposing factors for developing AKI immediately after LT had been scantly studied. Therefore, the aim of the present study was to identify the incidence of AKI during the immediate postoperative period of LT, and the preoperative and intraoperative risk factors that correlate with the development of AKI.

METHODS

We designed a prospective, single center, longitudinal cohort study to determine the incidence and to identify the risk factors associated with AKI after LT. The study was conducted at *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (INCMNSZ). All patients who underwent LT from July 2017 until July 2019 were enrolled if they fulfilled the inclusion criteria: age ≥ 18 years old and agreement to sign the informed consent. Patients with some type of kidney disease at the time of the LT, either AKI or any chronic renal disease, were excluded.

Prior to LT, patients were required to present to the emergency department to be evaluated by the LT team; at the same visit, blood samples were taken for pre-operative assessment. All relevant clinical data were obtained from the medical charts and corroborated with the patient if needed: age, gender, etiology of hepatic disease, MELD-Na score, Child-Pugh stage, current diuretic usage, and whether or not patients presented ascites or encephalopathy prior to LT. Laboratory data included: hemoglobin, platelets, sCr, BUN, total bilirubin, ALT, AST, serum albumin, prothrombin time, and INR. During LT surgery, the following parameters were collected: cold-ischemic time, total bleeding during surgery, maximum serum lactate, and maximum dose of norepinephrine used.

After LT, we assessed sCr every 24 h until day 5, and then, as required by each patient. Urine samples for biomarkers were collected at 6, 12, 24, 48, and 72 h after LT. AKI was defined and classified based on the Kidney Disease Improving Global Outcomes guidelines[13]. We did not include the oliguria criteria to classify AKI in our patients; this was decided in accordance to the International Ascites Club, which recommends only using the sCr to classify AKI in cirrhotic patients[14].

Urinary KIM-1 levels were analyzed using a commercially available enzyme-linked immune absorbent assay kit (BioAssay Works H-RENA-E-001). All procedures were performed according to the manufacturer's instructions. Urinary HSP72 levels were evaluated by Western blot analysis. Briefly, 10 µL of urine was loaded in 8.5% SDS-PAGE gels and transferred onto PVDF membranes. The membranes were blocked with 5% blotting-grade reagent, incubated overnight at 4°C with the antibody against HSP72 (Enzo Life Sciences, ADI-SPA-810F), washed with TBS-tween, and incubated with the secondary antibody IgG goat-anti-mouse HRP (Santa Cruz, SC-2005). Proteins were detected using a chemiluminescence kit (Millipore), and the bands were scanned for densitometric analysis.

For statistical analysis, patients were dichotomized as follows: Group 1 included patients who did not develop AKI during the post-operative period together with patients who developed AKI stage 1. Group 2 included patients who developed AKI stages 2 or 3 after LT. For descriptive purposes, continuous variables were summarized as arithmetic means and standard deviations (SD) and were analyzed by a double-sided *t*-test; categorical variables were comprised as frequencies and proportions and were analyzed by χ^2 test. Finally, we performed a multivariate analysis by using a multinominal logistic regression model to estimate the relative risk (RR) (with 95% Confidence Interval [CI]) for developing AKI stages 2 or 3 after LT. Statistical significance was predetermined to be present for values of $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc, Chicago, IL).

This study was performed in accordance with the Declaration of Helsinki, and the principles of good clinical practice. All patients provided written informed consent to participate, and the study was previously approved by the scientific and bioethical committees of INCMNSZ.

Table 1. Etiology of liver disease that led to end-stage liver disease (ESLD)

ESLD Etiology	(n = 86) n (%)
Hepatitis C Virus	24 (28%)
Autoimmune Hepatitis	11 (13%)
Primary Biliary Cholangitis	9 (10%)
Non-alcoholic Steatohepatitis (NASH)	5 (6%)
Other less frequent causes	21 (24%)
Cryptogenic etiology	16 (19%)

RESULTS

During enrollment period, 105 patients underwent LT at the INCMNSZ. Of them, 86 patients were included for the final analysis, and 19 patients were excluded from the study. Nine because they had both, chronic liver and kidney disease and went into liver and kidney transplantation simultaneously, eight because they had already some level of AKI before LT and one who died during the procedure. From the 86 included patients, the mean age was 49.8 years (± 11.8), median age was 52 (range 18-69). The most frequent etiologies of hepatic disease are presented in table 1. Consistent with the universe of patients who are attended in our institution, the most frequent causes of liver disease were hepatitis C, autoimmune hepatitis, and primary cholangitis. In 19% of the patients, the etiology of the liver failure was unknown.

From the 86 included patients, 45 (52%) developed AKI in the following 30 days after LT. Of them, 11 (13%) developed AKI stage 1; 22 (26%) AKI stage 2, and 12 (14%) AKI stage 3. Nine patients (10.4%) required renal replacement therapy (RRT), which was given by intermittent hemodialysis; mean duration of

Table 2. Univariate analysis for baseline and intra-operative variables and development of AKI stages 2-3

Variable	No AKI & AKI 1 (n = 52)	AKI 2 & AKI 3 (n = 34)	p
Mortality at 30 days	3 (5.7%)	7 (20.5%)	0.036
Age	49.1 (± 12.1)	50.9 (± 10.7)	0.485
Gender			
Male	18 (34.6%)	22 (64.7%)	0.006
Female	34 (65.4%)	12 (35.2%)	
Child-Pugh			
A	7 (13.5%)	26 (50%)	
B	4 (11.8%)	11 (32.3%)	
C	19 (36.5%)	19 (55.9%)	0.194
History of hepatic encephalopathy			
No	34 (65.4%)	10 (29.4%)	0.004
Yes	18 (34.6%)	24 (70.6%)	
History of ascites			
No	34 (65.4%)	28 (82.3%)	0.213
Yes	18 (34.6%)	6 (17.7%)	
Furosemide/Spironolactone treatment			
No	22 (42.3%)	7 (20.6%)	0.037
Yes	30 (57.7%)	27 (79.4%)	
MELD Na	20.7 (± 5.09)	22.4 (± 5.18)	0.128
Serum Creatinine	0.77 (± 0.25)	0.83 (± 0.26)	0.44
BUN	16.8 (± 10.5)	16.3 (± 8.2)	0.249
Total bilirubin	5.7 (± 5.2)	6.1 (± 5.9)	0.782
Serum albumin	2.9 (± 0.61)	2.8 (± 0.64)	0.65
ALT	97.5 (± 61)	134.4 (± 87.2)	0.569
AST	193.3 (± 138.3)	202.2 (± 152.4)	0.93

(Continues)

Table 2. Univariate analysis for baseline and intra-operative variables and development of AKI stages 2-3 *(continued)*

Variable	No AKI & AKI 1 (n = 52)	AKI 2 & AKI 3 (n = 34)	p
INR	1.7 (± 0.42)	1.7 (± 0.93)	0.91
Hemoglobin	11.9 (± 2.8)	11.7 (± 2.1)	0.696
Platelets	102 (± 77.8)	82 (± 71.8)	0.234
Maximum lactate during surgery	5.9 (± 1.97)	7.2 (± 3.3)	0.012
Maximum dose of NE during surgery	0.63 (± 0.41)	0.8 (± 0.68)	0.103
Cold-ischemia time (min)	401.6 (± 116.5)	396.5 (± 90.6)	0.83
Bleeding during surgery (mL)	3110 (± 2139)	3690 (± 903)	0.511

RRT was 6.8 days. Patients who developed AKI stage 1 returned to their baseline renal function within a few days after LT, and their outcomes were similar to those of patients who did not develop AKI.

After a follow-up of 30 days, 10 of the 86 patients (11.6%) died; 2 of them did not develop AKI; 3 developed AKI stage 2; and 5 patients developed AKI stage 3. Of note, 80 of 86 (93%) patients who developed AKI presented this complication in the first 5 days after LT; none of the patients who developed AKI stages 2 o 3 did it after the first 5 days. Development of AKI stages 2 or 3 were correlated with a higher all-cause mortality at 30 days (5.7% vs. 20.5%, *p*= 0.036). Urinary KIM-1 and HSP72 were increased in patients who developed AKI stages 2 or 3, but because the development of AKI was so early, most of them after LT, the elevations detected were not useful to predict a sCr increase.

As mentioned before, since AKI stage 1 is a minor complication that is reversed, to study the factors associated with AKI after LT, we decided to pool all patients without AKI with those with AKI stage 1 in one group, and patients who developed AKI stages 2 or 3 in another group. The decision to merge patients with AKI 1 to patients without AKI was taken after an interim statistical analysis. As shown in table 2, at the univariate analysis, males developed AKI 2-3 significantly more frequently than females (64.7% vs. 35.2%, p = 0.006); furthermore, patients who presented with hepatic encephalopathy prior to LT were more likely to develop AKI 2-3 after LT than patients without encephalopathy (70% vs. 29%; p = 0.004). Interestingly, treatment with diuretic scheme, including furosemide and spironolactone, was also associated with a higher incidence of AKI 2-3. The rest of the studied variables at the time of LT were similar between patients from both groups. The only intra-operative variable associated with developing AKI 2-3 was a higher lactate plasma concentration during surgery (p = 0.012).

As shown in Table 3, the multivariate analysis revealed that the presence of hepatic encephalopathy prior to LT was the factor more strongly associated with the development of AKI (RR 3.67; 95% CI 1.08-8.95). Male gender was also strongly correlated with the development of AKI (RR 3.11; 95% CI 1.07-1.83). Finally, the maximum concentration of lactate during surgery was marginally associated with the development of AKI (RR 1.4; 95% CI 1.28-10.55). Diuretic treatment with furosemide plus spironolactone did not remain significantly associated with AKI 2-3 in the multivariate analysis.

DISCUSSION

Post-transplant AKI is typically due to a combination of factors, which include those related to the recipient, to the donor, to surgical events, and to early post-transplant immunosuppression. Any degree of renal dysfunction after LT portends poor long-term

Table 3. Multivariate analysis of the variables that reached significant differences at the univariate analysis; table present the relative risk (RR) and 95% confidence interval (95% CI) for developing AKI grades 2 or 3

Variable	RR	95% CI	p
Male gender	3.11	1.07-1.83	0.018
History of hepatic encephalopathy	3.67	1.08-8.95	0.005
Furosemide/Spironolactone treatment	2.43	0.73-8.07	0.149
Lactate > 6.0 mmol/L	1.4	1.28-10.55	0.009

survival and is associated with an increased mortality[10]. Patients with decompensated cirrhosis are more susceptible to perioperative kidney ischemia and are more prone to develop AKI after LT. This is likely due to renal vasoconstriction induced by the activation of endogenous vasoactive systems released during and after the transplant[15].

In the present study, we observed that in our program, half of patients developed some degree of AKI in the following days after LT. Almost all of them developed AKI in the first 5 days, except for 6 patients who developed AKI stage 1 between days 5 and 30 of LT, probably more related to nephrotoxic drugs or to other conditions different to hemodynamic factors inherent to transplant surgery. These results are in line with those reported by prior series[11,16]; remarkably, postoperative AKI is significantly higher after LT than is after almost any other surgery, including cardiovascular surgery, where postoperative AKI develops in around 10% of patients[17,18].

Even when AKI is a well-recognized complication following LT, the predisposing factors associated with this complication have not been well identified, and there is some discrepancy on which factors contribute to the development of AKI. In 2015 Hilmi et al., retrospectively analyzed predisposing factors associated with post-LT AKI; as their results suggest, female sex, higher Child-Pugh score, obesity, and pre-existing diabetes mellitus were all correlated with post-LT AKI[8]. On the other hand, Romano et al., analyzed the three components of the MELD score individually and reported that pre-LT INR but neither sCr, nor bilirubin, were strongly associated with post-LTAKI[19]. Contrasting with the results of the aforementioned studies, we found males to be more likely to develop AKI, and we did not find pre-LT INR to be associated with an increased incidence of AKI. In our study, male gender, hepatic encephalopathy, and a higher peak-lactate concentration during surgery were strongly associated with the development of AKI. It should be underscored that we classified patients who developed AKI stage 1 along with those who did not develop AKI; by doing this, we could identify which factors predispose patients to develop a severe form of kidney injury (AKI 2-3). Therefore, conclusions from our results should be made cautiously, especially when comparing our results with other studies that analyzed for any stage of AKI.

Of the predisposing factors identified in our study, pre-transplant hepatic encephalopathy was the one associated with the highest RR (3.67) for developing stage 2-3 AKI; these results suggest that decompensation of liver disease is a determinant factor for post-transplant AKI. Furthermore, a higher peak-lactate concentration during surgery was correlated with AKI stages 2-3 post-LT; we consider that this is a direct reflection of the hypoperfusion suffered by kidneys during LT surgery; accordingly, patients with higher hypoperfusion reached higher lactate levels and therefore, were more likely to develop AKI 2-3. Although our results contrast with those reported by Hilmi et al., regarding which gender predisposes to AKI, the fact that males are more likely to develop AKI than females has been reported previously, although not in the setting of LT[20,21]. However, the exact pathophysiologic mechanism that increases the risk of AKI in males, whether or not is related to testosterone, remains to be fully understood.

At our institution, every patient who will undergo a LT receives immunosuppression with Basiliximab administered in a two-dose regimen, with the first dose being administered early after reperfusion of graft, and the second dose administered 4 days after the surgery. Therefore, it is possible that the incidence

and severity of AKI will differ from that reported at institutions that use calcineurin inhibitors as the main immunosuppressive treatment immediately after LT. However, a previous study reported that Basiliximab was not associated with either improved or worsened kidney function after LT[22].

It is possible that the heterogeneity of the reported predisposing factors associated with AKI at the post-LT period might be explained because of the analyzed population. To the best of our knowledge, there is no international study analyzing predisposing factors for developing AKI in this setting, with most studies reporting retrospective cohorts from single institutions. To address this problem, we consider that multicentric, ideally multinational studies should be conducted in order to identify predisposing risk factors for AKI in LT.

Limitations of our study are its single-center nature and the relatively short follow-up period, which makes impossible to determine the long-term implications of developing AKI after LT, and its relationship with developing CKD. Furthermore, we did not analyze if variables in surgical techniques protect or predispose to the development of AKI (such as the preservation of the vena cava). Finally, we acknowledge that grouping patients without AKI along with those who developed AKI stage 1 is not a common practice, and this grouping was performed after an interim statistical analysis which might be considered as a statistical flaw.

In summary, we have performed what is probably the largest prospective study analyzing the risk factors predisposing to AKI after LT in a Latin-American population. As our results confirm, this is a frequent complication that significantly worsens prognosis of recipients and is associated with an increased 30-day mortality rate. The presence of hepatic encephalopathy strongly predicts the development of severe AKI.

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