Kidney Function After Liver Transplantation in a Single Center

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Background: Renal dysfunction in the peri-transplant period appears to complicate both short- and long-term outcome of liver transplantation (LT). The aim of this study was to analyze the impact of selected clinical features in the peri-liver transplant period, as well calcineurin inhibitor, particularly tacrolimus given after LT, on kidney function in a single liver transplant center’s experience.

Material/Methods: A total 125 consecutive liver-grafted individuals (82 M, 43 F), mean age 50±13 y (with alcohol-related liver disease in 48 (38%) patients) were included into the study. Their clinical data were collected in the database until 46 months of follow-up, and the Python packages Pandas (version 0.22.0) and scikit-learn (version 0.21.3) were used for data analysis.

Results: More advanced liver disease as judged by Child-Pugh class and MELD score differed significantly patients with preserved (serum creatinine SCR <1.5 mg/dL) and impaired (SCR ≥1.5 mg/dL) kidney function before LT. Older age and higher SCR pre-LT were associated with higher levels of SCR after LT in 2 time-points. SCR before LT was correlated with delta SCR for the highest and last recorded value (P<0.0001). Higher amounts of transfused colloids during surgery were associated with increased delta SCR for the highest value (P=0.019) after grafting in logistic regression analysis. There were no associations between SCR after LT and duration of anhepatic phase, urine output ≤100 mL/h, or post-reperfusion syndrome during transplantation (all P>0.05). There were no associations between SCR after LT and tacrolimus trough levels in analyses of correlations and linear regression analyses (all P>0.05).

Conclusions: We found that pretransplant serum creatinine was the only factor affecting kidney function after LT in our liver transplant center. The restricted fluid policy was safe and effective in terms of long-term renal function. The role of kidney-saving immunosuppressive protocols in preserving renal function long-term after LT was also confirmed.

Keywords: Creatine • Liver Transplantation • Renal Insufficiency, Chronic

Abbreviations: AKI – acute kidney injury; CKD – chronic kidney disease; CNI – calcineurin inhibitor; GFR – glomerular filtration rate; ICA – International Club of Ascites; MELD – Model of End-Stage Liver Disease; Na – serum sodium; LT – liver transplantation; SCR – serum creatinine; TAC – tacrolimus

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Background

Despite the major progress in liver transplantation, renal dysfunction (RD) before and after liver transplantation (LT) is still a factor complicating both short- and long-term outcomes of LT, increasing health care costs. Acute kidney injury (AKI), with reported incidence ranging from 10% to 20% in the pretransplant setting, may reach even 64% after LT, with a known impact on morbidity and mortality [1-13]. The development of RD before and/or after liver grafting is complicated and multifactorial. However, currently available methods of assessing RD in the setting of liver cirrhosis are not sufficient or practical enough [14]. Thus, in clinical practice, serum creatinine (Scr) testing is widely available and inexpensive, although the limitations of Scr are well known. In cirrhotic patients, lower levels of Scr are related to sarcopenia, decreased production of creatine by the liver, and potentially increased tubular secretion [15]. Notably, many cirrhotic patients have actively fluctuating renal function or normal renal function despite existing histological findings in the kidneys [16].

Serum creatinine is an over-weighted component of model for end-stage liver disease (MELD) score, but MELD score cannot distinguish between acute and chronic kidney dysfunction [5,17]. The spectrum of renal dysfunction before LT varies from minimal increase in serum creatinine to full-blown renal failure requiring renal replacement therapy (RRT) [17]. To emphasize the impact of kidney dysfunction on liver-transplant patient survival, post-transplant sepsis and longer intensive care unit (ICU) stay [18], the International Ascites Club (IAC) redefined the criteria of RD in cirrhotic individuals and introduced the concept of acute kidney injury (AKI) [19,20] as well as chronic kidney disease (CKD) and acute-on-chronic kidney disease [21] to include both functional and structural renal diseases [18-20]. Subsequently, more precise criteria of AKI and CKD were introduced [22]. Impaired renal function at transplantation was associated with a higher risk of CKD after transplantation [18,19,23-25]. Giusto et al found the dominant role of lower pre-transplantation estimated glomerular filtration rate (GFR) being the only independent risk factor of CKD after LT [26]. Additionally, pretransplant AKI is associated with post-transplant morbidity, including post-LT AKI, which then predisposes to post-transplant CKD. Risk factors of post-LT AKI were identified [27] and post-LT AKI itself is a risk factor of 30-day mortality in liver graft recipients and can lead to CKD in a substantial proportion of affected individuals [1,18,28]. Thus, prevention of pre-LT or early post-transplant AKI is essential to reduce the burden of CKD after grafting [29]. Of note, the prevalence of CKD in LT recipients ranges from 20% up to 80%, and 10 years after grafting, patients have a 30% to 50% risk of chronic kidney disease development [7,18,28]. In this cohort, the risk of death is 4 times higher [30]. Development of arterial hypertension, episodes of severe infections, and reduced glomerular filtration rate may help to estimate the risk of post-LT CKD [23,26]. Arterial hypertension after LT occurs in more than 50% of recipients, which is significantly higher than in the general population [31], similar to the higher prevalence of CKD after LT [32]. However, the complexity of post-LT CKD development reflects the Renal Risk index, developed and validated by Sharma et al, which consists of 14 patient-specific factors, even without the role of immunosuppressive regimen [17].

Calcineurin inhibitors (CNI)-based immunosuppressive regimens, including cyclosporine, and mainly tacrolimus (TAC), play important roles in long-term liver graft outcome. However, CNI nephrotoxicity is still considering a major contributing factor for chronic kidney dysfunction, with up to 20% of liver graft recipients developing chronic renal disease within 3 years of LT [25,33]. These findings highlight the importance of wide-ranging strategies to balance the risk of liver graft rejection and chronic RD with the known impact of both on LT results.

Thus, the aim of this study was to analyze the impact of selected clinical features in the peri-grafting period on kidney function, including renal function before LT and surgery characteristics. The second end-point of the analysis was the role of immunosuppressive TAC-based regimen on Scr after the procedure.

Material and Methods

This was a retrospective, single-center, observational study including 126 consecutive liver transplant recipients. This cohort consisted of 82 males and 44 females, mean age 51±13 and 49±13, respectively. There were no patients with end-stage renal disease and/or treated with renal replacement therapy. In 37.5%, LT candidate history of arterial hypertension was known, but already reduced, with no pharmacotherapy; the only drugs used in this population were non-selective beta-blockers, none were treated with blockers of the renin-angiotensin system. The indications for LT were: alcoholic liver disease (ALD) in n=48 (38%) of patients, followed by viral chronic hepatitis in 40 (32%) individuals, and autoimmune liver diseases (primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis) in 35 patients (28%). Three (2.4%) individuals were transplanted due to acute liver failure, and 11 (8.8%) were re-transplanted. Mean MELD in ALD individuals was 16.69±10.21 points, 17.73±10.12 points in viral patients, and 16.14±8.40 points in autoimmune patients. Renal dysfunction before LT was defined as serum creatinine (Scr) ≥1.5 mg/dL, similar to Wong et al [20]. All patients were transplanted between Sep 2015 and Feb 2017, and 95% of recipients received a tacrolimus-based immunosuppressive regimen. During the follow-up period of 1417.43±139.70 days in...
females and 1371.84±168.75 days in males (until March 2019), 10 (12.5%) liver graft recipients died.

Ethics

The study protocol was approved by the Ethics Committee of the Medical University of Warsaw (AKBE/130/2020) and conformed with the ethics guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

Statistics

Data are presented as mean±standard deviation (SD) and median±interquartile range (IQR). The Pearson’s correlation coefficients were calculated in order to investigate the relationship between SCr and the remaining variables. For numeric variables, the Mann-Whitney U test was performed. Normally distributed data, as well as randomly and independently distributed non-numeric data, were assessed with the Z test. The linear regression model was also used. For data analysis, the Python packages Pandas (version 1.1.0) and scikit-learn (version 0.23.2) and NumPy (version 1.18.5) and SciPy (version 1.4.1) were used. A P value <0.05 was considered statistically significant.

Results

The analyzed cohort of patients consisted of 82 males and 44 females. Their selected clinical features before LT are presented in Table 1. There were no significant differences between groups in age, sex, MELD, Child-Pugh class, baseline SCr, or serum sodium.

Before LT, there were 26 individuals with SCr level ≥1.5 mg/dL and 100 individuals with SCr <1.5 mg/dl in the entire cohort of liver graft recipients. Their clinical characteristics are summarized in Table 2. Patients with impaired and preserved renal function in respect to pretransplant SCr differed significantly in MELD score and Child-Pugh classes.

The mean volume of crystalloids and colloids transfused during surgery were 4019±1094.41 mL and 1033.98±492.50 mL, respectively. The mean anhepatic phase lasted 98.26±37.45 minutes. In n=28 (22.4%) of grafted individuals, post-reperfusion syndrome occurred. There were 110 (88%) individuals with oliguria during surgery, and 12 individuals required intra-operative dialysis. There were 72 patients with hypotonia (MAP £80 mmHg) immediately before LT, with an indication to catecholamine usage in 60 of them (F17, M43). The mean highest SCr during the entire observation period was 1.66±0.94 mg/dL (1.35±0.47 in females and 1.83±1.09 mg/dL in males) and at the last recorded follow-up period it was – 1.07±0.32 mg/dL (in females 0.94±0.29, and in males 1.15±0.31 mg/dL).

Table 1. Selected clinical features of the study group.

|          | Before LT | Females (n=44) | Males (n=82) |
|----------|-----------|---------------|--------------|
| Age (years) | 48.75±12.57 | 50.62±13.17    |
| Child-Pugh class (points) | B-9 | B-9 |
| MELD (points) | 19.19±9.05 | 15.80±8.55    |
| Serum creatinine (mg/dL) | 1.07±0.72 | 1.24±0.77    |
| Serum sodium (mmol/L) | 138.87±4.21 | 137.61±4.43   |

MELD – Model of End-Stage liver Disease; Data presented as median±IQR.

Table 2. Clinical differences between liver graft candidates in respect to baseline SCr.

|          | SCr ≥1.5 mg/dL | SCr <1.5 mg/dL | p-Value |
|----------|----------------|---------------|---------|
| Age (years) | 60±19.5 | 57±19 | 0.146   |
| Gender |       |       |         |
| F | 7 | 37 | 0.337 |
| M | 19 | 63 |       |
| MELD (points) | 28±13.25 | 14±9.5 | 0.0000000597 |
| Child-Pugh class (CPC) | C | B | 0.0026 |
| ALD | 7/26 | 21/100 | 0.518 |
| HBV, HCV | 5/26 | 34/100 | 0.147 |
| Autoimmune (PBC, PSC, AIH) | 6/26 | 29/100 | 0.548 |

AIH – autoimmune hepatitis; SCr – serum creatinine; PBC – primary biliary cholangitis; PSC primary sclerosing cholangitis. Data presented as median±IQR.
The factor most strongly associated with highest Scr after surgery during the observational period was the age of the recipients at LT, but not sex (p=0.09), and their Scr level before LT. In patients with preserved renal function before LT, there was a trend to intravenous administration of lower amounts of colloids during LT. The roles of arterial pressure (p=0.985) and aminopressors usage (p=0.13) were not significant. Tacrolimus blood trough level was also not a significant factor (P=0.47).

Data are presented in Table 3.

This trend was also observed for the last recorded Scr during the whole follow-up period of 46 months. However, the trend of benefit of lower colloids infusion during surgery reached statistical significance, with the role of hypotension during surgery (MAP ≤80 mmHg) (p=0.013) and the positive trend of catecholamines usage (P=0.076). The role of tacrolimus blood trough level was also not prominent (P=0.458). Data are summarized in Table 4.

When we analyzed data regarding the impact of selected features on the changes of highest Scr (D Scr) during follow-up, only Scr before LT and the amount of intravenously administered colloids during surgery were associated with changes of creatinine level. However, the role of hypotonia and catecholamines usage was minor (both P>0.05). Data are presented in Table 5.

We found an impact of pre-LT Scr on changes in the last creatinine value as well as a role of pre-LT serum sodium (P=0.077) was also found (Table 6). However, the clinical course of surgery and tacrolimus blood trough level were not significantly different between groups (all p>0.05). A Pearson correlation matrix model is presented on Figure 1.

### Table 3. Factors associated with the highest Scr during the whole analyzed period.

|                          | Scr ≥1.5 mg/dL | Scr <1.5 mg/dL | p-Value   |
|--------------------------|----------------|----------------|-----------|
| Age (years)              | 58±15          | 48±22.75       | 0.0008    |
| Serum sodium             | 138.35±5.375   | 139.3±5.9      | 0.398     |
| Scr before LT (mg/dL)    | 1.08±0.36      | 0.7±0.27       | 0.0000184 |
| Colloids (mL)            | 1050±600       | 925±600        | 0.0996    |
| Crystalloids (mL)        | 4000±1000      | 4000±1000      | 0.28      |
| Anhepatic phase duration (minutes) | 93±45         | 90±53          | 0.22      |
| Hypotonia (MAP ≤80 mmHg) (% of patients) | 52            | 52             | 0.985     |
| Catecholamines usage during LT (n of patients) | 20            | 16             | 0.13      |
| Urine output during LT (≤100 mL/hour) (n of patients) | 34            | 40             | 0.442     |
| Tacrolimus blood trough level (ng/mL) | 8.35±8.925    | 8.8±5.4        | 0.47      |

Scr – serum creatinine; MAP – mean arterial pressure. Data presented as median±IQR.

### Table 4. Factors featuring the last recorded Scr during follow-up period.

|                          | Scr ≥1.5 mg/dL | Scr <1.5 mg/dL | p-Value   |
|--------------------------|----------------|----------------|-----------|
| Age (years)              | 63±13          | 54±19.5        | 0.007     |
| Serum sodium before LT (mmol/l) | 137.4±5.20   | 139.1±5.8     | 0.32      |
| Scr before LT (mg/dL)    | 1.22±1.08      | 0.87±0.43      | 0.0037    |
| Colloids (mL)            | 1500±900       | 900±600        | 0.018     |
| Crystalloids (mL)        | 4200±1000      | 4000±1000      | 0.23      |
| Anhepatic phase (minutes) | 110±40        | 90±50          | 0.36      |
| Hypotonia (MAP ≤80 mmHg) (% of individuals) | 89            | 46             | 0.016     |
| Catecholamines usage during LT (n of patients) | 7             | 24             | 0.076     |
| Tacrolimus blood trough level (ng/mL) | 7.4±6.55      | 9.4±6.8       | 0.458     |

Scr – serum creatinine; MAP – mean arterial pressure. Data presented as median±IQR.
In the present study, we found that SCr level before liver transplantation was the only risk factor for renal dysfunction after LT pretransplant and intra-operatively. In this single-center study of LT recipients, we did not find as many individuals with significant renal dysfunction as previously described in the literature. Moreover, the results questioned the leading role of CNI as a major nephrotoxic agent and showed good long-term control of both graft and kidney functions in our experience.

Table 5. Some characteristic impacted increasing or decreasing the highest level of SCr during observation.

|                         | Δ crea (+) | Δ crea (-) | p-Value |
|-------------------------|-----------|-----------|---------|
| Age (years)             | 55±21     | 58±8      | 0.064   |
| Serum sodium before LT (mmol/L) | 139±5.65  | 139±6.1   | 0.35    |
| SCr before LT           | 0.85±0.35 | 2.21±1.59 | 0.00000153 |
| Colloids (mL)           | 1200±300  | 900±600   | 0.019   |
| Crystalloids (mL)       | 4000±1000 | 4200±500  | 0.22    |
| Anhepatic phase         | 91±50     | 91±72.5   | 0.49    |
| Hypotonia (MAP ≤80 mmHg) (% of individuals) | 52 | 54 | 0.905 |
| Catecholamines usage during LT (n of patients) | 28 | 7 | 0.091 |
| Tacrolimus blood through level (ng/mL) | 8.9±6.3 | 8±7.05 | 0.18 |

Crea – creatinine; MAP – mean arterial pressure; SCr – serum creatinine. Data presented as median±IQR.

Table 6. The features impacted the changes in the last recorded SCr during follow-up period.

|                         | Δ crea (+) | Δ crea (-) | p-Value |
|-------------------------|-----------|-----------|---------|
| Age                     | 54.5±18.5 | 56.5±14.75 | 0.34    |
| Serum sodium before LT (mmol/L) | 138.5±4.9  | 140.65±4.8 | 0.077   |
| SCr before LT (mg/dL)   | 0.79±0.315 | 1.245±1.195 | 0.000000122 |
| Colloids (mL)           | 1000±700  | 950±500   | 0.38    |
| Crystalloids (mL)       | 4000±1000 | 4000±1000 | 0.40    |
| Anhepatic phase (min)   | 90±50     | 85±47.5   | 0.28    |
| Hypotonia (MAP ≤80 mmHg) (% of individuals) | 54 | 46 | 0.511 |
| Catecholamines usage during LT (n of patients) | 21 | 9 | 0.872 |
| Tacrolimus blood through level (ng/mL) | 9.35±6.4 | 8.6±9.3 | 0.257 |

SCr – serum creatinine; MAP – mean arterial pressure. Data presented as median±IQR.

Figure 1. Pearson correlation matrix. MELD – Model of end-stage liver disease; PRS – post-reperfusion syndrome; RR – arterial pressure; SCr – serum creatinine; Tacro – tacrolimus blood trough level.

Discussion

In the present study, we found that SCr level before liver transplantation was the only risk factor for renal dysfunction after LT pretransplant and intra-operatively. In this single-center study of LT recipients, we did not find as many individuals with significant renal dysfunction as previously described in the literature. Moreover, the results questioned the leading role of CNI as a major nephrotoxic agent and showed good long-term control of both graft and kidney functions in our experience.
Post-transplant renal dysfunction is one of the most important and common complications experienced by LT recipients, leading to increased morbidity and mortality [17,33,34]. Major risk factors contributing to post-LT end-stage renal disease include recipient factors at LT as well as immunosuppression-related adverse effects [17]. However, many of the risk factors that predict chronic kidney disease after LT are associations, and not always causative [7,17]. Thus, early identification of patients at risk as well as their modification before, during, and after LT are challenging because of the narrow window of opportunity [17].

Renal dysfunctions, both AKI and CKD, in liver graft recipients, are clearly associated with post-LT morbidity and mortality [35]. Of note, RD after LT is associated with prolonged hospitalization and significant increase in hospitalization costs and ICU readmissions, and was reported to be the major risk factor for cardiac events [14]. However, despite the previously reported widely increasing problem of more severely ill cirrhotic patients with more comorbidities, our results did not reflect this trend in respect to MELD score and RD. However, more advanced liver dysfunction as judged by MELD score and Child-Pugh class were features distinguished significantly by patients with impaired or preserved renal function in the present study, similar to findings of Weber et al [18]. Of note, normal creatinine levels in the study group may be center-specific, reflecting the number of patients without comorbidities resulting in RD (eg, diabetes and NAFLD) as well as the number of individuals with HCC and well-preserved liver function, and the number of patients without significant liver function impairment or ascites (eg, in primary sclerosing cholangitis (PSC) or with alveococcosis). Wong et al found an association between the severity of ascites and increasing prevalence of AKI despite minimal baseline liver and renal dysfunction [36].

Serum creatinine before liver transplantation was the only factor associated with the levels of Scr after grafting as well as changes of creatinine levels over time. Both findings were in line with the results of recently published data of Bassegoda et al, who found that CKD commonly developed after an episode of AKI in cirrhotic individuals [37]. Baseline serum creatinine was among the factors associated with AKI progressing to CKD, but not with the etiology of kidney injury [37]. Our findings are also consistent with those of Wong et al, who showed that baseline serum creatinine might be a risk factor of AKI [20], with higher Scr associated with higher risk of AKI development and progression to CKD with reduced survival [20]. Of note, renal dysfunction defined as Scr >1.5 mg/dl lasting longer than 2 weeks was reported to be associated with the risk of CKD after liver transplantation at 1 year [19,23,24], with no role of the origin of RD. It is postulated that progression of renal damage after AKI might be related to a maladaptive repair in the tubular, vascular, and interstitial compartments of the kidney, leading to interstitial fibrosis [38]. Although the authors did not show the impact of age on delta Scr in the 2 analyzed time-points, this effect was observed for the highest and last recorded Scr. The postulated maladaptive regeneration might be derivative of age. Recipient age together with preoperative kidney function were the risk factors of CKD in the study of Kalisvaart et al [39].

Liver transplantation is a major surgery associated with intraoperative massive fluid shift. The higher amounts of intravenously administered colloids were associated with higher levels of Scr as well as increased delta Scr in the present study. However, our liver transplant center used a restrictive fluid/volume policy during grafting to decrease blood transfusion requirements, as previously described [40]. Lekerika et al [40] and the present study found that this strategy was effective in terms of kidney function, probably due to reduced bleeding during LT. Moreover, blood loss during surgery was independently associated with the risk of post-LT AKI in the study of Zongyi et al [27] as well as in previously published research [20,23]. The role of intraoperative blood loss was also found to be a significant risk factor of chronic RD 1 year after LT in univariate regression analysis of 500 cases [41]. Recently, Mrzljak et al published Crostians’ data regarding early AKI after LT, indicating the negative role of red blood cell transfusion [42]. The majority of patients developed AKI within the first 2 days after LT; thus, the major determinant of AKI development had to be procedure-related, with kidney hypoperfusion, large intraoperative fluid shifts, and blood loss. Red blood cells transfusion might indicate a pro-inflammatory state and increasing concentration of nephrotoxic free hemoglobin and iron [42-44]. Thus, intraoperative volume shifts might be a contributor to post-LT renal dysfunction, as suggested by Mrzljak et al [42]. Additionally, recipient transfused with crystalloid only had less intraoperative ascites and blood loss, with more stable hemodynamics and early extubation [45].

The highest and last recorded tacrolimus blood trough levels were not associated with Scr during the long follow-up period in the present study. Although calcineurin inhibitors in the post-LT immunosuppressive regimen have been associated with nephrotoxicity [18], it is postulated that their role may be overestimated [46]. The results of the present study are in keeping with these suppositions [47,48]. Notably, kidney-saving immunosuppressive regimens based on induction and delayed TAC introduction with lower TAC doses/blood trough levels have been applied in our center, in line with the recent recommendations [49]. We believe that more attention should be paid to acquired interstitial/post-inflammatory changes in the kidneys after LT.

The most important finding of the present study is the Scr level in the end of observation period; after 46 months of follow-up,
the last recorded Scr was within normal ranges in the entire cohort. This is the achievement reflecting our center’s experience with immunosuppressive kidney-sparing protocols as well as with CNI therapy. Of note, in one of the largest studies, with 69,321 participants, 16.5% of recipients of non-renal organs developed chronic kidney disease, and among them, RRT or renal transplant were required in 28.9% [30]. Again, among the other factors, recipients age and pretransplant kidney function were risk factors for post-surgery CKD [30].

Although the presented results are encouraging in terms of long-term kidney function in liver graft recipients, our study has certain limitations, including the lack of proper collection of some important data affecting long-term kidney function, such as arterial hypertension or diabetes mellitus development after LT in the analyzed cohort. However, the main goal of the study was to analyze the selected peri-transplant features causing peri-operative hemodynamic insult to the kidney.

Conclusions

We found less renal dysfunction in our single liver transplant center than previously reported, and pretransplant serum creatinine was the only factor significantly associated with post-LT kidney function. A restricted fluid policy is safe and effective in terms of short- and long-term renal function. We confirmed the role of kidney-saving immunosuppressive protocols in preserving long-term renal function. A rational drug use policy might reduce CNI-associated nephrotoxicity. Some other important factors, such as arterial hypertension or diabetes mellitus development after LT, may affect long-term kidney function, but the main goal of the study was to analyze the selected peri-transplant features causing peri-operative hemodynamic insult to the kidney.

Our results show the experience of a high-volume LT center with long-term treatment using drugs with a narrow therapeutic window.

Conflict of Interest

None.

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