Negative Prognostic Impact of Renal Replacement Therapy in Adult Living-donor Liver Transplant Recipients: Preoperative Recipient Condition and Donor Factors


ABSTRACT

Background. In deceased-donor liver transplantation settings, post-transplantation acute renal failure with the induction of renal replacement therapy (RRT) is known to have negative effects on graft and patient survivals. However, the impact of RRT in living-donor liver transplantation (LDLT) has not been well investigated. The aim of this study was to elucidate risk factors requiring RRT and prognostic factors after its induction.

Methods. Clinical data on the consecutive 113 adult patients who underwent LDLT from March 2002 to May 2013 were retrospectively reviewed. They were divided into 2 groups: RRT (n = 33) and Non-RRT (n = 80). The primary reasons for receiving RRT were hepatorenal syndrome (n = 17), sepsis (n = 12), and renal hypoperfusion (n = 4).

Results. Although there were no significant differences in age or sex, the Model for End-Stage Liver Disease (MELD) score was significantly higher in the RRT group than in the Non-RRT group (23 ± 13 vs 16 ± 7; P = .002). The graft-recipient weight ratio (GRWR) was significantly lower in the RRT group (0.86 ± 0.3 vs 0.99 ± 0.2; P = .025). The 1- and 5-year patient survival rates were significantly higher in the Non-RRT group than in the RRT group (respectively, 91.3% and 84.3% vs 42.9% and 25.5%; P < .001). In multivariate analysis, independent risk factors for receiving RRT were MELD score >20 (P = .044) and GRWR <0.7 (P = .039). In the RRT group, donor age >50 years (P = .042) and preoperative serum creatinine level >1.5 mg/dL (P = .049) were significant prognostic risk factors.

Conclusions. In adult LDLT patients, the induction of RRT after LDLT was a negative predictor of survival. In addition to the preoperative recipient’s condition, donor factors including graft size and donor age influenced prognosis after the induction of RRT.

A CUTE renal failure (ARF) is common in the perioperative period of deceased-donor liver transplantation (DDLT) [1,2] and is associated with prolonged hospitalization, significant financial costs, and increased mortality rates, especially in the intensive care unit setting [3–5]. Although some of the patients who suffered from ARF needed renal replacement therapy (RRT), ARF with the induction of RRT had negative effects on graft and patient survivals after DDLT [6,7]. Most of the analyses regarding RRT after LT have been performed in the DDLT but not the living-donor liver transplantation (LDLT) setting.

The reasons for induction of RRT after DDLT are multifactorial: hepatorenal syndrome (HRS) due to liver failure, drug-induced toxicity, septic episodes, and intraoperative hemodynamic instability [8–10]. In contrast, only...
a few studies on RRT after LDLT have been reported [11,12], and the usefulness and appropriate indication of RRT in LDLT remain unclear.

LDLT differs greatly from DDLT in terms of graft liver size, graft ischemia time, surgical process, and complexity [13]. Particularly in adult LDLT, graft size mismatching with partial liver transplantation can cause various problems, including ARF, when the graft can not sustain excessive portal blood perfusion [14].

The aim of the present study was to clarify the usefulness of RRT in LDLT and to determine prognostic risk factors for patients who received RRT after LDLT. This study also focused on evaluating the clinical characteristics and prognosis of patients who developed ARF and received RRT before or after LDLT.

PATIENTS AND METHODS

Patients

Among the 139 patients who underwent LDLT at Mie University Hospital from March 2002 to May 2013, 113 were adults. The indications for these 113 LDLT patients included hepatocellular carcinoma (n = 48), liver cirrhosis (n = 35), primary biliary cirrhosis (n = 15), acute liver failure (n = 10), and others (n = 5). The transplanted liver grafts included left lobe grafts (n = 41), right lobe grafts (n = 53), right lobe with middle hepatic vein (n = 17), and posterior segment graft (n = 2). All LDLTs were performed after obtaining full informed consents from the patients and were approval by the Liver Transplantation Committee of Mie University Hospital. The exclusion criterion for this study was LDLT patients who had undergone morphologic renal alteration for chronic renal insufficiency (n = 1). Graft selection process and the details of the surgery were described elsewhere [15]. The mean follow-up was 58.4 months (range, 3–132 months).

Immunosuppression

The immunosuppression protocol consisted of tacrolimus and low-dose steroids as described elsewhere [16]. The target whole-blood trough level for tacrolimus was 10 ng/mL (range, 8–12 ng/mL). The hemodiafiltration system was continuously monitored with a personal bedside console (ACH-10; Asahi Medical, Tokyo, Japan).

Statistical Analyses

Categoric variables were compared with the use of the chi-square test. Continuous data were compared with the use of the Mann-Whitney test. Patient survival after liver transplantation was analyzed with the use of the Kaplan-Meier survival method and the log-rank tests. Variables with a P value of < .1 in the univariate analysis were entered in a multivariate analysis using a stepwise forward Cox regression procedure. All statistical analyses were performed with Statview 5.0 (Hulinks, Tokyo, Japan).

RESULTS

Characteristics of Patients With and Without RRT

Among the 113 patients who received LDLT, RRT was introduced preoperatively and/or postoperatively in 33 (29.2%; RRT group) and was not in 80 (Non-RRT group; Table 1). Although there were no significant differences in recipients’ age or sex, the Model for End-Stage Liver Disease (MELD) score (23.2 ± 13.3 vs 15.8 ± 7.5; P = .0021) and Child-Pugh score (11.0 ± 2.1 vs 9.0 ± 2.5; P = .0003) were higher in the RRT group, and this group included more cases with acute liver failure as the primary hepatic disorder (8/33 vs 2/80; P = .0002). Regarding the donor and
operative factors, there were no significant differences in donors’ age, sex, or graft type; however, the graft weight (528 ± 143 vs 613 ± 136; P = .010) and the graft-recipient weight ratio (GRWR; 0.857 ± 0.24 vs 0.986 ± 0.19; P = .025) were significantly lower in the RRT group.

Patient Survival Rates in Adult LDLT Patients

The 1- and 5-year patient survival rates were significantly lower in the RRT group than in the Non-RRT group (respectively, 91.3% and 84.3% vs 42.9% and 25.5%; P < .00001; Fig 1).

Risk Factors for Induction of RRT

Uni- and multivariable analyses for the induction of RRT are summarized in Table 2. Statistically significant variables in the univariable analyses were MELD score >20, GRWR <0.7, hepatocellular carcinoma, vascular complication, and hepatitis C virus positivity. In multivariable analysis, independent risk factors for receiving RRT were MELD score (P = .044) and GRWR (P = .039; Table 2).

Primary Reasons for Receiving RRT

Among the 33 patients who received RRT, 10 (30.3%) had RRT already induced before LDLT (Pre-RRT), and 23 (69.7%) received it only after LDLT (Post-RRT). All of the patients who started RRT before LDLT continued RRT after LDLT. The primary reasons for receiving RRT are summarized in Table 3. All 10 patients in the Pre-RRT group suffered from HRS, being associated with the co-morbid conditions of acute liver failure (n = 5) and MELD score >30 (n = 5). In the Post-RRT group, the most frequent reason was sepsis (52.2%), followed by HRS (30.4%) and renal hypoperfusion (17.4%).

Duration of RRT in LDLT Patients

Durations of RRT in all LDLT patients are shown in Fig 3, according to patient survival. The median duration of RRT in the 11 patients who survived after RRT (Survivor) was 10.5 days, and that in the 22 patients who did not survive (Nonsurvivor) was 9 days. The rate of patients who needed RRT for 14 days was 36.4% (4/11) in the Survivor group and 45.5% (10/22) in the Nonsurvivor group, showing no significant difference between the 2 groups (P = .618).

Risk Factors Affecting Survival of RRT Patients

Uni- and multivariable analyses for the survival in RRT patients are summarized in Table 4. Statistically significant variables in the univariable analysis were donor age >50 years, serum creatinine (Cr) before LDLT >1.5 mg/dL, prothrombin time (international normalized ratio) before LDLT >1.2, and hepatitis C virus positivity. In multivariate analysis, independent risk factors for the survival in RRT patients were donor age >50 years (P = .0423) and Cr >1.5 mg/dL (P = .0493; Table 4).

![Fig 1. Survival rates of adult living-donor liver transplantation patients. The 1- and 5-year survival rates in renal replacement therapy (RRT) patients were significantly lower than those in Non-RRT patients (respectively, 91.3% and 84.3% vs 42.9% and 25.5%; P < .00001).](image)

### Table 2. Uni- and Multivariate Analysis of Risk Factors for Induction of RRT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score &gt;20</td>
<td>1.61</td>
<td>1.003-1.122</td>
<td>.044</td>
</tr>
<tr>
<td>GRWR &lt;0.7</td>
<td>0.39</td>
<td>0.007-0.888</td>
<td>.039</td>
</tr>
<tr>
<td>HCC</td>
<td>0.57</td>
<td>0.531-2.273</td>
<td>.944</td>
</tr>
<tr>
<td>Vascular complication</td>
<td>1.03</td>
<td>0.899-7.534</td>
<td>.145</td>
</tr>
<tr>
<td>HCV positive</td>
<td>2.01</td>
<td>0.598-9.247</td>
<td>.827</td>
</tr>
</tbody>
</table>

Abbreviations: MELD, the model for end-stage liver disease; GRWR, the graft-recipient weight ratio; HCC, hepatocellular carcinoma; HCV, hepatitis C.

### Table 3. Primary Reasons for Receiving RRT

<table>
<thead>
<tr>
<th>Group</th>
<th>Reason</th>
<th>[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RRT (n = 10)</td>
<td>Hepatorenal syndrome</td>
<td>100 (100%)</td>
</tr>
<tr>
<td></td>
<td>Renal hypoperfusion</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Post-RRT (n = 23)</td>
<td></td>
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</tbody>
</table>

*Including 5 patients with acute hepatic failure and 5 patients with high MELD score more than 30.
DISCUSSION

ARF before DDLT has been reported to worsen the prognosis of the patients, the mortality of whom reaches 60%–70% even after undergoing DDLT [14,17]. Occurrence of ARF after DDLT also is an important risk factor for mortality [18]. Moreover, the yearly survival rate among patients undergoing RRT for ARF after DDLT was 45%, whereas it was 96% in the patients without using RRT, and postoperative ARF was the most significant independent risk factor for death during the 1st year after DDLT [19]. Meanwhile, in LDLT patients, the 1-year patient survival rate was 63.9% in patients with RRT and 94.1% in those without RRT [11]. Our data also revealed that survival rates in the RRT group were significantly lower than those in the Non-RRT group. These data indicate that the status requiring RRT after LDLT as well as DDLT remains a negative prognostic factor.

In the present study, the risk factors for induction of RRT were MELD score >20 and GRWR <0.7, which reflected preoperative status including renal function and graft size. In the DDLT setting, the risk of RRT after DDLT was correlated with preoperative conditions including RRT before DDLT, diabetes, and preoperative Cr >1.5 mg/dL [20]. Differing from DDLT, LDLT graft size mismatching is an important issue, especially in adult patients. Small-for-size graft in LDLT affects the balance between vasoconstriction and vasodilatory factors, and leads to ARF [21,22]. Utsumi et al [12] also reported the relationship between small-for-size grafts (GRWR <0.7) and severe ARF after LDLT. One of the causes of ARF after adult LDLT might be persistent portal hypertension and a hyperdynamic state in the patients with a small-for-size graft.

We investigated the prognosis of patients receiving RRT before or after LDLT, because we hypothesized that the early induction of RRT for LDLT recipients could improve their prognosis after LDLT. However, the timing of

Table 4. Uni- and Multivariate Analysis of Risk Factors Affecting Survival of RRT Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age &gt;50 years old</td>
<td>1.89</td>
<td>1.003–1.411</td>
<td>.0423</td>
</tr>
<tr>
<td>Cr &gt;1.5 mg/dL (before LDLT)</td>
<td>1.33</td>
<td>1.001–4.359</td>
<td>.0491</td>
</tr>
<tr>
<td>PT-INR (before LDLT)</td>
<td>2.76</td>
<td>0.508–2.741</td>
<td>.1534</td>
</tr>
<tr>
<td>HCV positive</td>
<td>1.35</td>
<td>0.415–5.698</td>
<td>.3476</td>
</tr>
</tbody>
</table>

Abbreviations: Cr, creatinine; PT-INR, prothrombin time–international normalized ratio.
induction of RRT did not influence their prognosis. Zand et al [20] also reported that there was no statistically significant difference in prognosis between RRT patients before and after DDLT, though the number of RRT patients before DDLT was small. Ikegami et al [11] reported excellent outcomes in the patients who started RRT before LDLT. The reason for their excellent results was thought to be the fact that the majority of the patients with RRT before LDLT had ARF with acute HRS, but not end-stage cirrhosis with chronic renal failure. In the present study, one-half of the Pre-RRT patients had ARF and the remaining patients suffered from end-stage liver disease with high MELD score. Additionally, some of them had a history of bacterial and/or viral infection (data not shown). The preoperative patient’s condition, including the etiology of LDLT, but not the timing of induction of RRT might be an important prognostic factor in LDLT patients.

Regarding the duration of RRT after liver transplantation, Townsend et al [23] reported that DDLT recipients who had died within 1 year had undergone RRT significantly longer than survivors. In the LDLT setting, among patients who survived >1 year, the duration of RRT did not influence their prognosis [11]. Our results also suggested that the duration of RRT was not related to prognosis, though the number of patients who underwent RRT <14 days was small. These results suggested that the prognostic risk factor in recipients requiring RRT was not only severe ARF but also other systemic diseases, eg, sepsis, rejection, or surgical complications.

In the RRT patients of our study, Cr >1.5 mg/dL and donor age >50 years were independent risk factors for survival, which means that both recipient and donor factors affected prognosis after RRT. Pre-DDLT renal insufficiency is reported to be an important predictor of post-DDLT morbidity and mortality, including sepsis, duration of the intensive care unit stay, need for post-DDLT RRT, and overall costs [3,6]. We previously reported [24] that older-donor (donor age >50 years) liver graft had impaired regenerative activity in LDLT. The insufficiency of graft liver regeneration might influence ARF after LDLT. Most of the cases of severe ARF requiring RRT in LDLT resulted from systemic disease. During the perioperative management, we have to consider not only ARF but also systemic conditions, including graft liver functions.

In conclusion, the induction of RRT after adult LDLT was a negative predictor of survival. In addition to the recipient’s preoperative condition, donor factors including graft size and age influenced prognosis after the induction of RRT.

REFERENCES