INTRODUCTION

Acute kidney injury (AKI) after orthotopic liver transplantation (OLT) is associated with increased length of hospital stay, morbidity, and mortality\textsuperscript{1,4} as well as the development of chronic kidney injury.\textsuperscript{1,3,5,6} Algorithms for identification of patients with high risk to develop AKI and preventive strategies need to be implemented. Although various studies have indicated many risk factors, the incidences of AKI have exhibited a wide range due to differences in AKI definition, which makes it difficult to compare the results and identify truly predictive factors.

Background: Acute kidney injury (AKI) is frequently observed after orthotopic liver transplantation (OLT) even in patients with previously normal renal function. In this study, we investigated the impact of factors such as graft steatosis, post-reperfusion syndrome (PRS), and hepatic ischemia reperfusion injury (HIRI) on the development of AKI after OLT in adult patients.

Methods: We retrospectively examined consecutive adult patients who underwent OLT at our institution between July 2011 and June 2017. AKI was diagnosed based on the criteria proposed by the International Kidney Disease Improving Global Outcomes (KDIGO) workgroup. Peak aspartate aminotransferase (AST) level within 72 hours after OLT was used as a surrogate marker for HIRI. Graft steatosis was diagnosed by histopathological examination using specimens biopsied intraoperatively at the end of transplantation procedure and categorized as <10%, 10%-20%, 20%-30%, and ≥30% of hepatic steatosis.

Results: Out of 386 patients, 141 (37%) developed AKI (KDIGO stage 1: 71 patients; stage 2: 29 patients; stage 3: 41 patients). Multivariable logistic regression analysis revealed that cold ischemic time (P = .012) and HIRI (P = .007) were independent risk factors for post-OLT AKI. Multivariable analysis also revealed that graft steatosis was associated with HIRI but not directly with AKI. PRS was not associated with HIRI or AKI in the multivariable analyses.

Conclusion: Our results indicate that greater severity of liver graft injury during transplantation negatively affects renal function after OLT. As expected, the severity of liver graft steatosis contributes to accelerated liver injury occurring during the transplantation procedure.
factors of AKI. Furthermore, the recent increase in the use of extended criteria donor grafts has led to more frequent development of AKI after OLT. Therefore, the characteristics and mechanisms of AKI in the era of accepting extended criteria donor organs need to be analyzed using universal criteria. In the present study, AKI was diagnosed and classified based on the AKI criteria proposed by the International Kidney Disease Improving Global Outcomes (KDIGO) workgroup.

Several studies have shown that extended criteria donor grafts lead to AKI through hepatic ischemia-reperfusion injury (HIRI) and/or post-reperfusion syndrome (PRS), which can be related to level of steatosis in the liver graft. A large registry study revealed the detrimental effects of macrovesicular steatosis of liver grafts by showing that higher steatosis was independently associated with impaired graft survival. Therefore, the association among graft steatosis, PRS, HIRI, and AKI needs to be investigated to determine the pathophysiological mechanism of AKI after OLT. Furthermore, in order to identify modifiable risk factors and to implement preventive strategies, the impact of intraoperative parameters such as low blood pressure and/or the use of vasopressors on the development of HIRI, PRS, and AKI need to be thoroughly investigated.

To determine the association of graft steatosis, PRS, HIRI, and AKI, we evaluated the effects of graft steatosis on PRS and HIRI together with recipient and donor variables. We also identified independent perioperative predictive factors for AKI development.

2 | METHODS

2.1 | Patient selection

We retrospectively identified 496 consecutive patients who underwent OLT using grafts from donation after brain death at our institution between July 2011 and June 2017. Of these, 110 patients were excluded from this study for the following reasons: recipient age <18 years (n = 58), re-transplantation (n = 33), urgent OLT for acute liver failure (n = 15), combined liver-kidney transplantation (n = 3), and early patient death within 48 hours (n = 1). Finally, 386 patients were included in the study (Figure 1). Clinical data were collected retrospectively from the registration database as well as from clinical records and stored anonymously. The Model for End-Stage Liver Disease (MELD) score was calculated using the data analyzed immediately before OLT. Cold ischemia time (CIT) was defined as the time from liver cold perfusion in the donor until removal from ice for implantation. Warm ischemia time (WIT) was defined as the time period from removal from ice until portal vein reperfusion. Intraoperative needle biopsy of the liver graft was routinely performed between the graft reperfusion and closing of the abdominal incision. After formalin fixation, the biopsied specimens were stained using the periodic acid-Schiff (PAS) staining technique. The degree of macrovesicular steatosis, which was evaluated for all of the biopsied specimens by two pathologists in our institution, was semiquantified and defined as the percentage of hepatocytes in which fat droplets accumulation resulted in displacement of the nucleus. The data on the percentage of macrovesicular steatosis were retrospectively collected from the histological reports. This study was conducted in accordance with the Helsinki Declaration and was approved by the local institutional internal review board. Informed consent from the patients in this study was waived by the institutional internal review board according to Swedish legislation.

2.2 | Definition of PRS, HIRI, and AKI

PRS was defined as at least a 30% decrease in mean arterial pressure occurring during the first 5 minutes after liver graft reperfusion and lasting longer than 1 minute. Peak aspartate aminotransferase (AST) level within 72 hours post-OLT was used as a surrogate marker of HIRI. HIRI was defined when AST was ≥2500 U/L, moderate HIRI was defined when AST was 2500-5000 U/L, and severe HIRI was defined when AST was >5000 U/L.
AKI after OLT was defined based on the AKI criteria proposed by the KDIGO workgroup, and Stage 1 was defined as 1.5-1.9 times the baseline serum creatinine (SCr) level in 7 days or a ≥26 µmol/L increase in 48 hours when compared with the baseline level. Stage 2 was defined as 2.0-2.9 times baseline in 7 days, and Stage 3 was defined as ≥3.0 times baseline or an increase to ≥354 µmol/L or the initiation of renal replacement therapy. The baseline SCr was defined as the SCr level immediately before LT, which was routinely evaluated in our institution.

2.3 | Immunosuppressive regimens

All patients received induction immunosuppressive treatment consisting of basiliximab perioperative and on day 4 after LT. Solumedrol was started at 1 g on the day of the operation with subsequent tapering to 5-10 mg at 2 months and 2.5-5 mg at 1 year after transplantation. The detrimental effect of calcineurin inhibitors, especially tacrolimus, on kidney function has been well documented. In our institution, we have implemented a renal-sparing immunosuppressive regimen that delays perioperative tacrolimus use; tacrolimus was initiated on post-operative day 4 and adjusted to maintain the initial trough level of 6-10 ng/mL. Mycophenolate mofetil was started on post-operative day 1 with the standard dose of 1 g twice daily.

2.4 | Statistical analysis

Data are expressed as means (± standard deviations, SD) or medians (interquartile range [IQR]) as appropriate. Significant differences were determined using one-factor analysis of variance for normally distributed data, Wilcoxon’s signed-rank tests for skewed data, and Fisher’s exact tests or chi-squared tests for dichotomous data. Univariate and multivariable logistic regression analyses were used to assess the association of several parameters with the incidence of HIRI and AKI. Analyses were performed using JMP Pro 14 (SAS Institute). A P-value less than .05 was considered significant.

3 | RESULTS

3.1 | Pre-transplant patient demographics

The median recipient age was 54 years with preoperative median SCr levels of 70 µmol/L and MELD scores of 13.2. The median donor age was 60 years with mean body mass index (BMI) of 25.4 kg/m². Out of 386 patients, 141 (37%) developed AKI (KDIGO stage 1:71 patients; stage 2:29 patients; stage 3:41 patients) (Table 1). In the No AKI group, the rate of recipients with pre-transplant diabetes, donor BMI, donor AST level, and donor creatinine level were lower compared with each AKI stage group.

3.2 | Intraoperative Factors

The graft and perioperative factors are listed in Table 2. In the stage 3 AKI group, the graft-to-recipient weight ratio (GRWR) was largest, the rate of macrovesicular steatosis ≥30% was greatest, CIT, WIT, and operative time were longest, and bleeding volume was largest. Regarding factors during the post-reperfusion period, systolic blood pressure was lowest, and noradrenalin dose and lactate level at the end of operation were highest in the stage 3 AKI group. Peak AST levels within 72 hours after OLT, a surrogate marker of HIRI, increased as AKI post-OLT became more severe.

3.3 | Correlation of Steatosis, HIRI, and AKI

Figure 2 demonstrates the correlation of steatosis, HIRI, and AKI. As the graft macrovesicular steatosis became more severe, the rate and severity of HIRI increased (P < .0001, Figure 2A). The incidence of severe HIRI was 4%, 12%, 17%, and 60% in the patients with steatosis of <10%, 10%-20%, 20%-30%, and ≥30%, respectively. Subsequently, as HIRI became more severe, the rate and severity of AKI increased (P < .0001, Figure 2B). The incidence of AKI was 27%, 55%, and 87% in the no HIRI, moderate HIRI, and severe HIRI groups. Figure 2C shows the correlation between graft steatosis and AKI development. The incidence of AKI was 31%, 60%, 52%, and 67% in the patients with steatosis of <10%, 10%-20%, 20%-30%, and ≥30%, respectively (P = .0003).

3.4 | Impact of AKI development on 1-year outcomes

We analyzed patient survival rate at 1-year post-LT in AKI stage 2 and 3 patients. At 1-year post-LT, the patient survival rate was lower in AKI stage 2 and 3 patients than those with AKI stage <2 (91.7% vs 94.2%), although statistically insignificant (P = .51).

3.5 | Multivariable analysis of risk factors for HIRI development

Univariate analysis for the development of HIRI, which was defined as peak AST ≥2500 U/L, demonstrated 12 variables as risk factors, including two recipient demographic characteristics (MELD score and insulin-dependent diabetes), two donor characteristics (male donor and BMI), three graft characteristics (GRWR, graft steatosis, and CIT), two surgical characteristics (WIT and operative time), and three post-reperfusion characteristics (PRS, total noradrenalin dose, and lactate level at the end of the operation) (Table 3). Among these 12 variables, multivariable analysis showed that graft steatosis, CIT, WIT, and lactate level at the end of the operation were independent risk factors for the development of HIRI.
3.6 Multivariable analysis of risk factors for AKI development

Univariate analysis showed that three recipient variables (MELD score, SCr level, and pre-transplant non-insulin-dependent diabetes), two donor variables (male donor and BMI), two graft characteristics (graft steatosis and CIT), four surgical variables (WIT, operative time, bleeding volume, and blood transfusion), and three post-reperfusion characteristics (total noradrenaline dose, lactate level at the end of operation, and HIRI) were risk factors for AKI (Table 4). Among these variables, multivariable analysis identified two independent predictive factors for the development of AKI, namely CIT and HIRI.

4 DISCUSSION

The main results of the present study were (a) 37% of OLT recipients transplanted in our center, developed AKI, which was diagnosed using the revised criteria of the KDIGO workgroup, and half of them...
presented with stage 2 or 3 AKI; (b) the degree of graft steatosis was associated with the development and severity of HIRI; (c) HIRI development, especially severe HIRI, was an independent predictor of AKI; and (d) PRS, together with the doses of vasopressors during post-reperfusion periods, were not identified as independent risk factors.

AKI is a multifactorial disorder, and various factors have been reported to be associated with AKI development. Among them,
### TABLE 3  Risk factors for the development of HIRI (n = 93): univariate and multivariable analyses

| Variable                      | Univariate analysis | Multivariable analysis |
|-------------------------------|---------------------|------------------------|
|                               | OR  | 95% CI | P-value | OR  | 95% CI | P-value |
| **Recipient**                 |     |        |         |     |        |         |
| Age at LT, years              | 0.997 | 0.98-1.01 | .70    |     |        |         |
| Sex, male                     | 1.39  | 0.82-2.42 | .23    |     |        |         |
| BMI, kg/m²                    | 1.03  | 0.98-1.08 | .25    |     |        |         |
| MELD score                    | 0.96  | 0.92-0.99 | .01    | 0.95 | 0.88-1.01 | .09    |
| Creatinine, µmol/L            | 1.00  | 0.99-1.01 | .98    |     |        |         |
| Albumin, g/dL                 | 1.40  | 0.98-2.01 | .07    |     |        |         |
| Hepatitis C                   | 0.83  | 0.47-1.40 | .48    |     |        |         |
| **Diabetes**                  |     |        |         |     |        |         |
| None                          | 1.00  |        |        |     |        |         |
| Non-insulin dependent         | 1.67  | 0.68-3.86 | .25    | 1.13 | 0.21-6.09 | .89    |
| Insulin dependent             | 0.48  | 0.22-0.98 | .04    | 0.34 | 0.11-1.30 | .12    |
| **Donor**                     |     |        |         |     |        |         |
| Age, years                    | 0.996 | 0.98-1.01 | .58    |     |        |         |
| Sex, male                     | 2.22  | 1.36-3.68 | .001   | 1.90 | 0.84-4.29 | .12    |
| BMI, kg/m²                    | 1.13  | 1.08-1.19 | <.001  | 1.08 | 0.99-1.17 | .07    |
| **Cause of death**            |     |        |         |     |        |         |
| Trauma                        | 1.00  |        |        |     |        |         |
| CVA                           | 0.79  | 0.41-1.57 | .49    |     |        |         |
| Other                         | 0.65  | 0.28-1.54 | .33    |     |        |         |
| AST, U/L                      | 1.00  | 1.00-1.00 | .75    |     |        |         |
| Creatinine, µmol/L            | 1.00  | 0.99-1.00 | .89    |     |        |         |
| Sodium, mmol/L                | 1.03  | 0.98-1.08 | .32    |     |        |         |
| **Perfusion solution**        |     |        |         |     |        |         |
| UW                            | 1.00  |        |        |     |        |         |
| HTK                           | 0.94  | 0.57-1.53 | .79    |     |        |         |
| **Surgical data**             |     |        |         |     |        |         |
| GRWR                          | 1.84  | 1.29-2.69 | <.001  | 1.44 | 0.83-2.39 | .17    |
| **Graft Steatosis**           |     |        |         |     |        |         |
| <10%                          | 1.00  |        |        |     |        |         |
| ≥10%, <20%                    | 4.80  | 2.05-11.18 | <.001  | 6.24 | 1.45-26.93 | .01    |
| ≥20%, <30%                    | 8.08  | 3.37-20.37 | <.001  | 5.96 | 1.49-23.90 | .01    |
| ≥30%                          | 33.77 | 8.98-220.17 | <.001 | 45.09 | 3.84-529.43 | .002  |
| CIT, h                        | 1.004 | 1.002-1.006 | <.001 | 1.005 | 1.001-1.009 | .02  |
| WIT, min                      | 1.04  | 1.02-1.06 | <.001  | 1.04 | 1.01-1.08 | .01    |
| Operative time, min           | 1.003 | 1.001-1.005 | .009 | 0.997 | 0.992-1.001 | .17  |
| Bleeding volume, L            | 1.01  | 0.98-1.03 | .65    |     |        |         |
| Blood transfusion, unit       | 1.01  | 0.99-1.03 | .36    |     |        |         |
| **Post-reperfusion period**   |     |        |         |     |        |         |
| PRS                           | 2.64  | 1.04-6.39 | .04    | 2.27 | 0.61-8.55 | .24    |
| Noradrenalin dose, µg/kg       | 1.01  | 1.00-1.03 | .04    | 0.98 | 0.96-1.01 | .22    |
| Lactate, mmol/L               | 1.15  | 1.04-1.28 | .008   | 1.21 | 1.01-1.47 | .04    |

Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; CVA, cerebral vascular accident; GRWR, graft-to-recipient weight ratio; HIRI, hepatic ischemia-reperfusion injury; HTK, Histidine-tryptophan-ketoglutarate; MELD, Model for End-Stage Liver Disease; OR, odds ratio; PRS, post-reperfusion syndrome; SBP, systolic blood pressure; UW, University of Wisconsin; WIT, warm ischemia time.
especially in the era when marginal donor grafts are increasingly accepted, the deleterious impact of extended criteria donor graft has been demonstrated in several studies.1-3,7 In the present study, graft steatosis was significantly associated with the development of HRI, which was then identified as an independent predictive factor of AKI development. In contrast, multivariable analysis revealed that graft steatosis itself was not an independent predictor of AKI, which suggests that steatotic livers did not directly cause AKI but had indirect effects through the development of HRI, which is linked with systemic inflammatory response. This seems to be an important finding of this study to elucidate the pathophysiological mechanism of post-OLT AKI.

In the present study, even the mildest degree of steatosis (steatosis of 10%-20%) had a significant impact on HRI development compared with steatosis of <10%. As the degree of steatosis became more severe, the association with HRI development became stronger. These results confirmed that even at its mildest degree, graft steatosis had effects on liver graft and patient outcomes, although most of those patients recovered from HRI. Similar associations between liver steatosis and post-OLT HRI have been seen in rodent models.13 In the clinical setting, the use of moderately or severely steatotic grafts remains controversial, and post-OLT outcomes vary depending on the presence of other risk factors. Salizzoni et al showed that macrovesicular steatosis had detrimental effects on post-OLT outcomes when combined with further risk factors such as prolonged ischemic time (>10 hours), high donor age, and hepatitis C-positive recipients.18 In our study, longer CIT was an independent risk factor for both HRI and AKI, suggesting that the use of steatotic liver grafts needs to be cautiously decided when it is predicted that CIT will be long. Several studies have shown that liver grafts with low or moderate macrovesicular steatosis can be safely used in recipients without additional risks.17-19 Considering the mortality rate of patients on the waiting list, accurate estimation of risks for AKI and further strategies for preserving kidney functions seem to be important to avoid wasting liver grafts. In this study, even mild steatosis was identified as a risk factor of HRI, which is inconsistent with previous studies.18,19 This inconsistency seems to be caused by the low prevalence of moderate or severe steatosis among our cohort. Regarding severe macrovesicular steatosis (>60%), many studies have demonstrated high primary non-function rate and impaired graft survival.19-22 However, McCormack et al reported that 60-day mortality and 3-year patient survival rate were comparable between the severe steatosis group and matched control group in well-controlled cases, although the proportion of patients with long-term ICU and hospital stay was significantly higher for patients who received severely steatotic grafts.12 Out of 386 cases in this study, only 5 patients received a liver graft of ≥60% macrovesicular steatosis. Although the 6-month survival rate for these patients was 100%, four of the five patients developed severe HRI and all of them developed AKI. This finding suggests that careful risk management and preventive strategies of HRI and AKI seem to be required from the perspective of risk management and cost effectiveness associated with post-operative AKI although moderately steatotic livers should not be discarded without careful evaluation of the other factors like donor age or predicted CIT.

Chen et al reported three independent risk factors for post-OLT AKI, including RBC transfusion, pre-transplant hypoalbuminemia (≤3.5 g/dL), and large doses of vasopressors.6 Blood transfusion and vasopressors are administered depending on patient status such as bleeding volume or hypotension. In particular, large doses of vasopressors are commonly administered at the time of severe hypotension or PRS, which causes the reduction of the renal blood flow through the constriction of renal arteries. In our study, intraoperative blood transfusion and post-reperfusion use of noradrenalin were significantly associated with AKI development by univariate analysis, but not by multivariable analysis. These results are consistent with those of several previous studies5,22 and suggest that the use of blood transfusion and/or vasopressors itself might not lead to the development of AKI. Hypoalbuminemia was also common in our study, and 83% of the patients presented with an albumin level of ≤3.5 mg/dL. However, pre-OLT albumin levels were comparable between patients with and without AKI in our study. On the contrary, the pre-OLT albumin level was highest in stage 3 AKI patients. This might be caused by pre-LT albumin infusion and/or the bias of selecting donors; marginal donor grafts might be likely to be allocated to patients in stable pre-OLT condition with normal albumin levels. However, this result and its mechanism need to be further investigated.

Kalisvaart et al showed that PRS was an independent risk factor for post-OLT AKI.10 Although PRS is known to be an early indicator of HRI, the impact of PRS on AKI development is still controversial. Leithead et al reported that post-reperfusion hemodynamic instability might not be a causal factor and instead might be a clinical manifestation of the post-reperfusion inflammation.7 In our study, univariate analysis showed that PRS was associated with HRI, but not with AKI. These results suggest that PRS might not have direct effects on the development of post-OLT AKI.

Although several studies have reported that pre-OLT SCr level is an important predictor of post-OLT AKI development,24 the impact of pre-OLT SCr level on AKI development is still controversial.2,9,25,26 In our study, pre-OLT SCr level was not associated with AKI development in the multivariable analysis. This inconsistency was partly due to the difference in AKI definition, especially that pre-transplant SCr level was a key component in diagnosing AKI in most diagnostic criteria, including KDIGO criteria. In OLT candidates, renal dysfunction was commonly caused by the impairment of liver function, including hepatorenal syndrome. However, in this study, the presence of underlying kidney disease and the cause of pre-OLT SCr elevation could not be identified. Therefore, further studies are needed to precisely evaluate this association. Several studies reported that a pre-transplant high MELD score is associated with AKI development.1,24,26 In contrast, the univariate analysis revealed that MELD score was conversely associated with the development of both HRI and AKI. This result might mean again that marginal donor grafts were likely to be allocated to recipients in stable conditions with lower MELD scores. The effect of pre-OLT MELD score on AKI development is strongly influenced by clinical decisions and the allocation system. Therefore, prospective studies are needed for further analyses.
The current study has several limitations. First, this was a retrospective single-center study, which means that post-OLT laboratory testing, including AST and SCr testing, was added when needed clinically. This variability could influence the diagnosis of HIRI and AKI. However, in this study, HIRI was defined using peak AST level within 72 hours post-OLT, not within 24 hours, which minimized the effect of variation of blood sampling timing. Second, SCr level is known to have several drawbacks as a marker of kidney function, especially...
among OLT recipients, because Scr level is influenced by many other factors such as medications, malnutrition, and edema. Furthermore, AKI was defined only by the increase in Scr level, and urine output was not available as it was in many previous studies, although the KDIGO AKI criteria include both Scr and urine output. Finally, HIRI was diagnosed using peak AST level, which could be elevated by other factors such as drug-induced hepatopathy. Furthermore, AST is not specific to the liver, but can be released by other organs such as the heart or muscles. However, at the present, peak AST level post-OLT has been commonly used as a surrogate marker of HIRI and time frame of 72 hours post-OLT was consistent with previous reports.2,15

In summary, HIRI induced by steatotic liver graft and long CIT was associated with post-OLT AKI development rather than pre-OLT recipient demographics or surgical factors. Although we should not discard mildly or moderately steatotic livers only for that reason, cautious evaluation of expected outcomes and preventive strategy to suppress post-perfusion inflammatory response would be of importance. To prevent AKI development in the era of enhancing donor pools, further strategies of suppressing HIRI, such as machine perfusion for steatotic liver grafts, need to be further examined and implemented.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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How to cite this article: Tokodai K, Lannsjö C, Kjaernet F, et al. Association of post-reperfusion syndrome and ischemia-reperfusion injury with acute kidney injury after liver transplantation. Acta Anaesthesiol Scand. 2020;64:742–750. https://doi.org/10.1111/aas.13556