

Perioperative risk factors of progressive chronic kidney disease following liver transplantation: analyses of a 10-year follow-up single-center cohort

Kyungho Lee¹, Junseok Jeon¹, Jong Man Kim², Gaabsoo Kim³, Kyunga Kim⁴, Hye Ryoung Jang¹, Jung Eun Lee¹, Jae-Won Joh², Suk-Koo Lee², Woosong Huh¹

¹Division of Nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

²Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

³Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

⁴Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea

Purpose: The incidence of chronic kidney disease (CKD) has been increasing due to improved survival after liver transplantation (LT). Risk factors of kidney injury after LT, especially perioperative management factors, are potentially modifiable. We investigated the risk factors associated with progressive CKD for 10 years after LT.

Methods: This retrospective cohort study included 292 adult patients who underwent LT at a tertiary referral hospital between 2000 and 2008. Renal function was assessed by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula. The area under the curve of serial eGFR (AUC_{eGFR}) was calculated for each patient to assess the trajectory of eGFR over the 10 years. Low AUC_{eGFR} was considered progressive CKD. Linear regression analyses were performed to examine the associations between the variables and AUC_{eGFR}.

Results: Multivariable analysis showed that older age (regression coefficient = -0.53, $P < 0.001$), diabetes mellitus (DM) (regression coefficient = -6.93, $P = 0.007$), preoperative proteinuria (regression coefficient = -16.11, $P < 0.001$), preoperative acute kidney injury (AKI) (regression coefficient = -14.35, $P < 0.001$), postoperative AKI (regression coefficient = -3.86, $P = 0.007$), and postoperative mean vasopressor score (regression coefficient = -0.45, $P = 0.034$) were independently associated with progressive CKD.

Conclusion: More careful renoprotective management is required in elderly LT patients with DM or preexisting proteinuria. Postoperative AKI and vasopressor dose may be potentially modifiable risk factors for progressive CKD.

[Ann Surg Treat Res 2020;99(1):52-62]

Key Words: Renal insufficiency, Kidney failure, Liver transplantation, Risk factors

INTRODUCTION

The incidences of acute kidney injury (AKI) and AKI requiring

renal replacement therapy post liver transplantation (LT) are common as 41% and 7%, respectively [1]. Because of improved survival of recipients after LT, the prevalence of chronic kidney

Received January 10, 2020, Revised March 28, 2020,
Accepted April 28, 2020

Corresponding Author: Woosong Huh

Division of Nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea

Tel: +82-2-3410-3443, Fax: +82-2-3410-0064

E-mail: woosong.huh@samsung.com

ORCID: <https://orcid.org/0000-0001-8174-5028>

Copyright © 2020, the Korean Surgical Society

© Annals of Surgical Treatment and Research is an Open Access Journal. All articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

disease (CKD) after LT has been increasing. Significant CKD occurs in up to 25% of patients after LT [2,3]. In addition, posttransplantation CKD is independently associated with high mortality and morbidity, which has elicited concerns in posttransplantation management. Prevention of renal injury has emerged as a priority for transplant physicians [2-4].

Although studies have reported the risk factors for renal injury after LT, most have dealt with reversible AKI rather than irreversible, progressive CKD, a sustained decline in estimated glomerular filtration rate (eGFR) over long-term follow-up [5,6]. Moreover, there have been conflicting results of direct association between perioperative AKI and post-LT CKD [7,8]. To date, only a limited number of studies has evaluated post-LT long-term renal outcome, which has important implications for patient management. The etiology of AKI after LT can be multifactorial in origin. Perioperative factors such as hemodynamics, intraoperative blood loss, administered dose of vasopressors, and amount of blood products transfused may affect posttransplantation renal function [9,10]. If these causes are shown to affect long-term renal outcomes, they could be more important for clinicians than other factors because they are thought to be correctable by modification of perioperative patient care.

The purpose of this study was to evaluate the risk factors associated with progressive CKD in LT recipients with a focus on perioperative variables. We analyzed an association between a variety of demographic, clinical, and laboratory variables and area under the curve of serial eGFR (AUC_{eGFR}) with 10-year follow-up longitudinal data of renal function.

METHODS

Study population

This retrospective cohort study was performed at Samsung Medical Center, Seoul, Korea. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the priori approval by Samsung Medical Center, Institutional Review Board (No. IRB2014-12-115). All adult (the age of 18 or more) patients who underwent deceased donor or living donor LT due to parenchymal liver disease without malignancy between January 2000 and December 2008 with follow-up data available before December 2018 were screened for inclusion. This period was chosen as a period of relevant clinical practice experience and to ensure that 10-year follow-up information would be complete for all patients. The exclusion criteria were as follows: (1) patients who underwent LT twice or more (retransplantation); (2) simultaneous liver-kidney transplant recipients (criteria for simultaneous liver-kidney transplantation was end-stage renal disease [ESRD] on dialysis or $eGFR < 30 \text{ mL/min/1.73 m}^2$ for at least 12 weeks); (3) patients with a survival or follow-up of 6 months or less.

Data collection

Serum creatinine concentrations from the time of transplantation until 10 years after LT, death, or dialysis or kidney transplantation were collected. Assessment of kidney function was based on the eGFR using the Modification of Diet in Renal Disease 4-variable formula [11].

The Acute Kidney Injury Network criteria were used to define perioperative acute renal dysfunction [12]. "Stage 1" was defined as an increase of creatinine by $\geq 0.3 \text{ mg/dL}$ or 1.5–1.9 times, "stage 2" as an increase of creatinine 2.0–2.9 times, and "stage 3" as an increase 3 times.

Patients' final renal function was classified according to the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation CKD classification [13]: CKD stage 1 ($eGFR \geq 90 \text{ mL/min/1.73 m}^2$), CKD stage 2 ($eGFR 60\text{--}89 \text{ mL/min/1.73 m}^2$), CKD stage 3 ($eGFR 30\text{--}59 \text{ mL/min/1.73 m}^2$), CKD stage 4 ($eGFR 15\text{--}29 \text{ mL/min/1.73 m}^2$), and CKD stage 5 ($eGFR < 15 \text{ mL/min/1.73 m}^2$).

The multiple eGFR values for individual patients during the follow-up period were combined into a single index for statistical analysis. We used the calculated area under the curve of serial eGFR (AUC_{eGFR}) value as an index of long-term renal function after LT. The initial 6 months after LT were excluded from calculation because there were many episodes of reversible

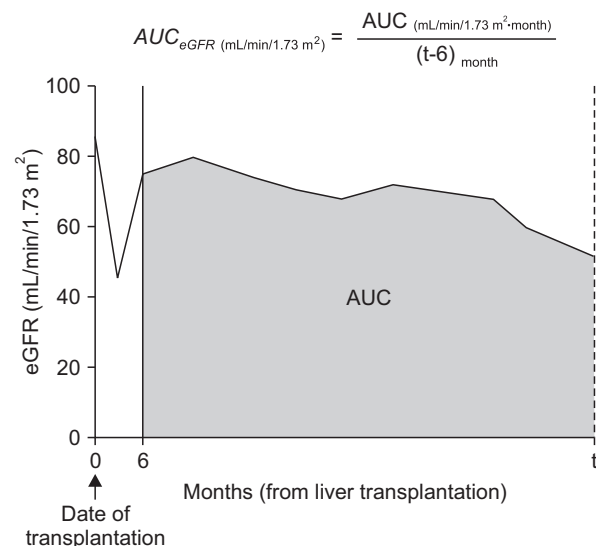


Fig. 1. An example of serial changes in eGFR after transplantation and calculation of AUC_{eGFR} . Month 0 corresponds to the time of transplantation. The initial 6 months following transplantation were excluded from AUC calculation. AUC was divided by individual follow-up duration (t). In patients who died or were lost to follow-up within 10 years, "t" corresponds to survival duration or follow-up duration, respectively. In other cases (patients who survived 10 years or more after transplantation with complete follow-up), "t" corresponds to 120 (months). AUC, area under the curve; eGFR, estimated glomerular filtration rate.

AKI, and serum creatinine concentration in that period is known to be an inaccurate representation of renal function because of the severely reduced muscle mass related to liver dysfunction. Because not all patients survived until the end of the 10-year follow-up, the AUC_{eGFR} was adjusted to account for individual survival durations. An example calculation of the AUC_{eGFR} is illustrated in Fig. 1. The average number of creatinine values used to calculate AUC_{eGFR} for each patient was 18.6.

The etiology of liver disease, episodes of AKI, diagnosis of diabetes mellitus and hypertension, prothrombin time expressed as international normalized ratio (INR), and model for end-stage liver disease (MELD) score were recorded as potential pretransplantation risk factors for deterioration of long-term renal function. Pretransplantation CKD was defined as $eGFR < 60 \text{ mL/min/1.73 m}^2$ (CKD stage 3 or greater) with a duration of more than 3 months.

The following intraoperative risk factors were recorded: hemodynamics (baseline blood pressure, lowest blood pressure, and duration of hypotension including intraoperative cardiac arrest); amount of blood loss; amount of blood products transfused (RBCs, fresh frozen plasma [FFP], platelet concentrate, cryoprecipitate, and cell salvaged blood); and dose of administered vasopressors. Intraoperative hypotension was defined as systolic blood pressure (SBP) $< 80 \text{ mmHg}$. To estimate intraoperative blood loss, we calculated lost red cell mass (in mL) using the equation described by Bang et al [14]. Vasopressor requirements were measured using the following equation: Vasopressor score = (dopamine dose [$\mu\text{g/kg/min}$] $\times 1$) + (dobutamine dose [$\mu\text{g/kg/min}$] $\times 1$) + (epinephrine dose [$\mu\text{g/kg/min}$] $\times 100$) + (norepinephrine dose [$\mu\text{g/kg/min}$] $\times 100$) + phenylephrine dose [$\mu\text{g/kg/min}$] $\times 100$) [15].

The following postoperative variables were recorded: dose of vasopressors administered within postoperative 36 hours, the highest AST concentration within postoperative 72 hours, the highest creatinine concentration within postoperative 3 days for assessment of postoperative AKI, presence of renal-replacement therapy, the occurrence of early allograft dysfunction (defined as the presence of 1 or more of 3 variables, including a peak serum AST or alanine aminotransferase concentration higher than 2,000 U/L within first 7 postoperative days, a serum bilirubin concentration of 10 mg/dL or higher on postoperative day 7, and an INR of 1.7 or higher on postoperative day 7 [16]), use of nephrotoxic antimicrobial agents (defined as the administration of one of the following antimicrobial agents for 7 days or more within postoperative 30 days; aminoglycosides, vancomycin, teicoplanin, colistin, ganciclovir, acyclovir, and amphotericin B). Immunosuppressive regimens and trough concentrations for individual patients were also recorded.

Donor data, including donor type (deceased donor or living donor), donor age, donor body mass index, cold ischemic time, warm ischemic time, and fatty change rates, were recorded and

analyzed.

Intraoperative patient care

Intraoperative fluid therapy consisting of crystalloids and 5% albumin was administered as determined appropriate by the anesthesiologist. The transfusion and coagulation management guidelines at our institution were as follows. The hemoglobin concentration was maintained at $> 8 \text{ g/dL}$. Two units of FFP were administered if the PT INR was > 3.0 . Three hundred milliliters of platelets were administered for patients with a platelet count $< 30,000/\mu\text{L}$. Cryoprecipitate was administered as either 1,200 or 2,400 mL if the serum fibrinogen concentration was $< 80 \text{ mg/dL}$ coupled with a platelet count of either $> 50,000$ or $< 50,000/\mu\text{L}$, respectively. The intraoperative vasopressors used during the study period were phenylephrine, ephedrine, epinephrine, norepinephrine, dopamine, and vasopressin. The vasopressor was given as a single agent or in combination and as either a bolus or continuous infusion. Inferior vena cava was partially clamped during the living donor LT. Anastomosis of the liver graft was performed with a piggyback technique without a venovenous bypass in deceased donor LT. Histidine-tryptophan-ketoglutarate solution was used as the liver preservation solution.

Immunosuppression

Basiliximab was used for induction therapy. A standardized maintenance immunosuppression protocol including calcineurin inhibitors, steroid, and mycophenolate mofetil was initiated within 24 hours of transplantation. The choice of calcineurin inhibitor between cyclosporine and tacrolimus was determined by a transplantation team. In cases receiving a cyclosporine-based regimen, cyclosporine was administered to an intended trough level of 250–300 ng/mL during the first week after transplantation, 200–250 ng/mL during the next 3 weeks, 150–200 ng/mL during the next 2 months, and 100–150 ng/mL thereafter. In cases receiving a tacrolimus-based regimen, tacrolimus was administered to an intended trough level of 12–15 ng/mL during the first 2 weeks after transplantation, 10–12 ng/mL during the next 2 weeks, 8–10 ng/mL for the next 2 months, and 5–8 ng/mL thereafter. Intravenous methylprednisolone 500 mg was administered during anhepatic phase and tapered gradually during 7 days. Steroid was gradually withdrawn in most patients by 3 months after LT if liver function is stable.

Statistical analyses

The categorical variables are presented as percentage, and the quantitative variables are presented as mean \pm standard deviation. All analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) and R (3.1.0; Vienna, Austria; <http://www.R-project.org>) software. The Jonckheere-

Terpstra test was performed to examine trends between the posttransplantation final CKD status and AUC_{eGFR} .

For risk factor analysis, linear regression analyses were performed to examine the associations between target variables (possible risk factors) and AUC_{eGFR} . Potential significant variables ($P < 0.2$) in the univariable analysis were chosen for multivariable analysis. The final multivariable model was fitted using the stepwise method with $\alpha = 0.1$ for both insertion and deletion.

To provide a sensitivity analysis of AUC_{eGFR} , logistic regression analysis for CKD upstaging and development of ESRD during 10-years of follow-up was performed.

Regression estimates and P-values are reported for the multivariable analysis. Statistical significance was defined as a 2-sided P-value < 0.05 . The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used to ensure the reporting of this observational study [17].

RESULTS

A total of 348 patients who underwent LT were evaluated for inclusion. Of these, 56 patients were excluded: 19 underwent retransplantation, 2 received simultaneous liver–kidney transplantation, and 35 died within 6 months after LT. The final cohort was comprised of 292 patients (Fig. 2), among whom 47 died and 245 survived during the 10-year follow-

up period, giving a 10-year survival rate after LT of 84%. The median follow-up period was 10 years (interquartile range, 10-10). Of the 292 patients, 74 (25%) finally had CKD stage 1, 138 (47%) had CKD stage 2, 51 (17%) had stage 3, 7 (2%) had stage 4, and 22 (8%) had stage 5. To determine if AUC_{eGFR} was significantly associated with CKD stage, we reclassified the 5 groups according to KDOQI CKD classification into 3 groups (CKD stage 1 + stage 2, CKD stage 3, CKD stage 4 + stage 5) and analyzed trends. AUC_{eGFR} significantly decreased with CKD

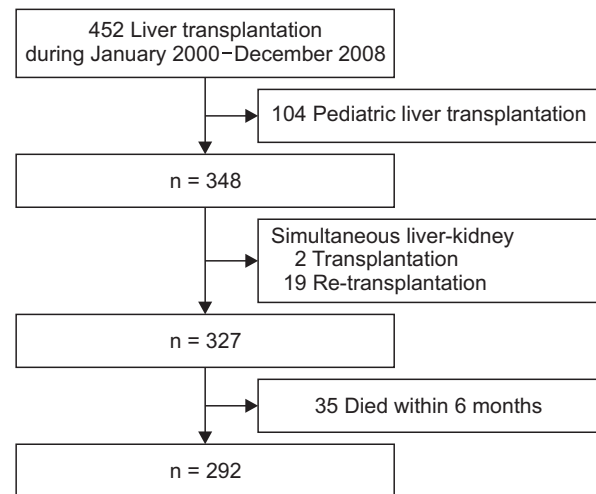


Fig. 2. The flow of study cohort.

Table 1. Baseline characteristics (before transplantation) of liver transplant recipients

Characteristic	Included patients (n = 292)	Excluded adult patients (n = 56)	P-value
Age (yr)	47 ± 9	46 ± 11	0.342
Male sex	213 (73)	44 (79)	0.380
Etiology of liver disease			0.142
Hepatitis B virus infection	241 (83)	41 (73)	
Hepatitis C virus infection	5 (2)	3 (5)	
Alcohol	10 (3)	3 (5)	
Toxicity	12 (4)	3 (5)	
Others	24 (8)	6 (11)	
MELD score	25 ± 10	30 ± 11	<0.001
Diabetes mellitus	54 (18)	8 (14)	0.451
Hypertension	23 (8)	8 (14)	0.128
Proteinuria	22 (8)	12 (21)	0.001
Baseline eGFR (mL/min/1.73 m ²)	86 (32)	84 (49)	0.704
AKI			
Stage 1	16 (5)	7 (13)	0.170
Stage 2	11 (4)	9 (16)	0.002
Stage 3	14 (5)	9 (16)	0.005
CKD stage 3	9 (3)	6 (11)	0.021
CKD stage 4–5	0 (0)	7 (13)	<0.001

Values are presented as mean ± standard deviation or number (%).

MELD, model of end-stage liver disease; eGFR, estimated glomerular filtrate rate; AKI, acute kidney injury; CKD, chronic kidney disease.

progression (CKD stage 1 + stage 2, 79.6 ± 15.1 , 95% confidence interval [CI], 77.6–81.6; CKD stage 3, 54.8 ± 12.6 , 95% CI, 51.3–58.3; CKD stage 4 + stage 5, 37.0 ± 18.9 , 95% CI, 30.1–43.9; $P < 0.001$ for trend.).

The average age at the time of LT was 47 ± 9 years. Coexisting conditions were present before LT in some patients; these included hypertension ($n = 23$, 8%) and diabetes mellitus ($n = 54$, 18%). The most common etiology of underlying liver disease was chronic hepatitis B ($n = 241$, 83%). The mean MELD score was 25 ± 10 . Pretransplantation AKI was present in 41 patients (14%), and CKD was present 9 (3%) of patients. All of CKD patients were CKD stage 3, and there were no patients with CKD stage 4–5. Cyclosporine was administered in 39 patients (13%), and tacrolimus was administered in 253 patients (87%). The baseline characteristics and comparison between included and excluded patients are summarized in Table 1.

Univariable analyses of the preoperative variables of progressive CKD after LT showed older age ($P < 0.001$), diabetes mellitus ($P < 0.001$), hypertension ($P = 0.020$), proteinuria ($P < 0.001$), pretransplantation AKI ($P = 0.009$), and pretransplantation CKD ($P < 0.001$) were associated with a low AUC_{eGFR} during the follow-up period (Table 2). Among the intraoperative variables, mean vasopressor score ($P = 0.001$), and maximum vasopressor score ($P = 0.040$) correlated negatively with AUC_{eGFR} (Table 2). Administration of higher dosage vasopressor during postoperative 36 hours ($P = 0.003$), perioperative continuous renal replacement therapy ($P < 0.001$), postoperative AKI within 3 days ($P < 0.014$), and administration of nephrotoxic antimicrobial agents ($P = 0.023$) were significantly related to low AUC_{eGFR} (Table 2). LT from a deceased donor was associated with low AUC_{eGFR} ($P = 0.047$) (Table 3).

The multivariable linear regression analysis identified older age (regression coefficient = -0.53 , $P < 0.001$), diabetes mellitus (regression coefficient = -6.93 , $P = 0.007$), pretransplantation proteinuria (regression coefficient = -16.11 , $P < 0.001$), pretransplantation AKI (regression coefficient = -14.35 , $P < 0.001$), pretransplantation CKD (regression coefficient = -29.36 , $P < 0.001$), postoperative mean vasopressor score (regression coefficient = -0.45 , $P = 0.034$) during the first 72 hours after LT, and postoperative AKI (regression coefficient = -3.86 , $P = 0.007$) as significant predictors of progressive CKD (Table 4). Further analysis of subgroups of patients without pretransplantation AKI nor CKD ($n = 242$) did not alter the significant risk factors (Table 4).

Time-dependent change in eGFR according to the significant risk factors in the multivariable analysis were presented in Fig. 3. The steep declines in eGFR during the first 3 days after LT were noted because of postoperative AKI. Subsequently, steep rises of eGFR were observed due to the recovery of renal function. After 6 months from LT, eGFR trajectories achieve stabilities and

highlight progressive declines with distinct degrees according to the risk factors described above.

The multivariable logistic regression analysis for CKD upstaging during the 10 years of follow-up showed that diabetes mellitus (odds ratio [OR], 7.65; 95% CI, 2.81–20.85; $P < 0.001$), postoperative mean vasopressor score (OR, 1.14; 95% CI, 1.00–1.30; $P = 0.049$), perioperative continuous renal-replacement therapy (OR, 13.70; 95% CI, 1.92–97.84; $P = 0.009$), and postoperative AKI (stage 1: OR, 4.72; 95% CI, 1.50–14.81; $P = 0.008$; stage 2: OR, 7.69; 95% CI, 1.51–39.27; $P = 0.014$; stage 3: OR, 19.63; 95% CI, 1.35–285.05; $P = 0.029$) were significant risk factors.

ESRD was occurred 17 of 292 patients during the 10-year follow-up. Proteinuria (OR, 6.57; 95% CI, 1.81–23.86; $P < 0.001$) and postoperative mean vasopressor score (OR, 1.08; 95% CI, = 1.00–1.15) were significantly associated with development of ESRD in the multivariable logistic regression analysis.

DISCUSSION

This cohort study including 292 consecutive LT recipients with 10-year follow-up data was performed to identify the risk factors for progressive CKD following LT. Factors associated with progressive CKD were recipient age, diabetes mellitus, pretransplantation proteinuria, pretransplantation renal dysfunction, postoperative AKI, and higher dose of vasopressor use immediately after the operation.

Many previous studies have addressed the burden of post-LT renal failure, most of which focused on postoperative AKI rather than CKD [5,6]. Although there have been several studies evaluating long-term renal outcome after LT [3,8], the follow-up period was usually less than 5 years. Our study is the only one to report predictors of 10-year renal outcome in LT recipients. Furthermore, there have been few studies dealing with perioperative risk factors, especially for CKD. Both intraoperative and immediate postoperative hemodynamic data including blood pressure, administered dose of vasopressor, amount of blood loss, and transfused amount of blood products were analyzed.

The development of CKD can be used as a clinical end point of renal outcome measurement. However, this requires longer follow-up duration and larger sample size. The number of patients who progressed to clinically relevant CKD ($eGFR < 30 \text{ mL/min/m}^2$) was 29, which was only 10% of our study population. Also, using only eGFR measures at the end of the follow-up period to define renal outcome would misclassify patients who experienced AKI long after the LT as progressive CKD. In such cases, it would be difficult to establish a direct causal relationship between renal outcome and perioperative events. Thus, we used an alternative eGFR-based single continuous variable, AUC_{eGFR} , as an outcome parameter.

Table 2. Univariable linear regression analysis of perioperative variables associated with AUCeGFR following liver transplantation (n = 292)

Variable	Value	Regression coefficient (SE)	P-value
Preoperative variables			
Age (yr)	47 ± 9	-0.66 (0.13)	<0.001
Male sex	213 (73)	1.68 (2.77)	0.544
Body mass index (kg/m ²)	24 ± 4	-0.01 (0.32)	0.970
Viral liver disease	258 (86)	4.28 (3.84)	0.267
MELD score	25 ± 10	-0.18 (0.12)	0.140
Diabetes mellitus	54 (18)	-12.40 (3.09)	<0.001
Hypertension	23 (8)	-10.62 (4.54)	0.020
INR	2.6 ± 3.6	0.31 (0.34)	0.375
Proteinuria		-27.24 (3.58)	<0.001
1+ or 2+	19 (7)		
3+ or 4+	3 (1)		
Pretransplantation AKI		-4.25 (1.62)	0.009
Stage 1	16 (5)		
Stage 2	11 (4)		
Stage 3	14 (5)		
Pretransplantation CKD (eGFR < 60)	9 (3)	-39.76 (6.74)	<0.001
Intraoperative variables			
Lowest systolic blood pressure (mmHg)	75 ± 16	0.05 (0.08)	0.493
Lowest diastolic blood pressure (mmHg)	38 ± 11	0.06 (0.11)	0.584
Duration of hypotension (min) ^{a)}	11 ± 33	-1.33 (0.87)	0.125
Mean vasopressor score	4.48 ± 2.98	-1.36 (0.41)	0.001
Maximum vasopressor score	7.83 ± 5.87	-0.43 (0.21)	0.040
Red blood cell transfusion (unit)	4 ± 4	-0.39 (0.33)	0.230
Fresh frozen plasma transfusion (unit)	8 ± 7	-0.23 (0.18)	0.199
Platelet concentrate transfusion (unit)	4 ± 5	-0.05 (0.23)	0.817
Cryoprecipitate transfusion (unit)	5 ± 5	-0.18 (0.27)	0.512
Salvaged blood cell transfusion (mL)	1653 ± 1687	-0.01 (0.01)	0.103
Intraoperative blood loss (mL)	1486 ± 1314	-0.01 (0.01)	0.176
Postoperative variables			
Vasopressor score postop 36 hr (mean)	3.54 ± 4.58	-0.79 (0.27)	0.003
Vasopressor score postop 36 hr (maximum)	5.12 ± 6.67	-0.52 (0.18)	0.005
Perioperative CRRT	35 (12)	-16.35 (3.67)	<0.001
Posttransplantation AKI		-4.35 (1.76)	0.014
Stage 1	59 (20)		
Stage 2	18 (6)		
Stage 3	6 (2)		
Peak postoperative serum AST	688 ± 1,151	-0.01 (0.01)	0.093
Early allograft dysfunction	100 (34)	-2.68 (2.59)	0.303
Use of nephrotoxic antimicrobial agents	99 (34)	-11.42 (2.52)	0.023
Cyclosporine (vs. tacrolimus)	39 (13)	-4.18 (3.62)	0.248
Average concentration of cyclosporine	65.07 ± 42.33	-0.13 (0.07)	0.069
Average concentration of tacrolimus	3.85 ± 1.75	1.00 (0.78)	0.206

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.

AUC_{eGFR}, under the curve of serial eGFR; SE, standard error; MELD, model of end-stage liver disease; INR, international normalized ratio; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; postop, postoperative; CRRT, continuous renal-replacement therapy.

^{a)}Hypotension was defined as systolic blood pressure <80 mmHg.

The vasopressor score was the sum of all vasopressors administered during the operation, as described by Zuppa et al. [15].

Acute Kidney Injury Network (AKIN) criteria were used to define acute renal dysfunction. "Stage 1" was defined as an increase of creatinine 1.5–1.9 times, "stage 2" as an increase of creatinine 2.0–2.9 times, and "stage 3" as an increase 3 times or more in the first 3 days after LT compared with pre-LT level.

Early allograft dysfunction was defined as the presence of 1 or more of the following: (1) a peak serum AST or alanine aminotransferase concentration higher than 2,000 U/L within first 7 postoperative days, (2) a serum bilirubin concentration of 10 mg/dL or higher on postoperative day 7, and (3) an INR of 1.7 or higher on postoperative day 7.

Use of nephrotoxic antimicrobial agents defined as administration of one of the following antimicrobial agents for 7 days or more, postoperatively; aminoglycosides, vancomycin, teicoplanin, colistin, ganciclovir, acyclovir, and amphotericin B.

Table 3. Univariable linear regression analysis of donor variables associated with AUC_{eGFR} following liver transplantation (n = 292)

Variable	Value	Regression coefficient (SE)	P-value
Deceased donor	54 (18)	-6.29 (3.16)	0.047
Donor age	34 ± 12	0.10 (0.11)	0.361
Donor body mass index (kg/m ²)	23 ± 3	-0.64 (0.44)	0.204
Cold ischemic time (min)	117 ± 111	-0.01 (0.01)	0.361
Warm ischemic time (min)	40 ± 23	0.05 (0.06)	0.396
Steatosis			
Total (%)	21.5 ± 17.7	0.02 (0.07)	0.741
Macro (%)	12.8 ± 12.1	0.08 (0.11)	0.482
Micro (%)	8.6 ± 9.1	-0.03 (0.14)	0.845

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.
 AUC_{eGFR} , under the curve of serial estimated glomerular filtration rate (eGFR); SE, standard error.

Table 4. Multivariable stepwise regression analysis of variables associated with AUC_{eGFR} following liver transplantation

Variable	Regression coefficient (SE)	P-value
Older age	-0.53 (0.11)	<0.001
Diabetes mellitus	-6.93 (2.55)	0.007
Pretransplantation proteinuria	-16.11 (3.46)	<0.001
Pretransplantation AKI	-14.35 (2.41)	<0.001
Pretransplantation CKD	-29.36 (6.05)	<0.001
Vasopressor score postop 36 hr (mean)	-0.45 (0.21)	0.034
Postoperative AKI	-3.86 (1.42)	0.007
Subgroup analysis of patients without preoperative AKI nor CKD (n = 242)		
Older age	-0.61 (0.12)	<0.001
Diabetes mellitus	-7.64 (2.85)	0.008
Pretransplantation proteinuria	-27.16 (4.83)	<0.001
Vasopressor score postop 36 hr (mean)	-0.34 (0.19)	0.048
Postoperative AKI	-4.56 (1.15)	<0.001

Variables with P-value <0.2 in univariable analysis were entered into the multivariable stepwise regression analysis.
 AUC_{eGFR} , under the curve of serial estimated glomerular filtration rate (eGFR); SE, standard error; AKI, acute kidney injury; CKD, chronic kidney disease.

The AUC_{eGFR} was calculated as a metric of GFR decline with longitudinal serum creatinine data. AUC_{eGFR} can represent long-term renal function in a simple way and has been used in other clinical studies [18,19]. We further analyzed AUC_{eGFR} trends according to final CKD stages, and there was significant statistical correlation, which indicates AUC_{eGFR} could be a surrogate marker for CKD progression. Some previous studies have used absolute GFR decrease or absolute serum creatinine threshold [3,8]. However, this is not the optimal method for assessing renal function because the time course of eGFR during follow-up in this population is unstable and non-linear. Furthermore, measuring renal function based on a single first and single last eGFR measurement could be less precise than alternative designs in which multiple measures are performed [20].

Similar to the findings from the general population, proteinuria and diabetes were associated with progressive

CKD [21]. Preexisting proteinuria and diabetes were present in 8% and 18% of patients in our study. Moreover, considering the high prevalence of viral hepatitis, HBV- or HCV- related glomerulonephritis, which is associated with poor renal outcome, may exist among proteinuric patients. Therefore, routine pretransplantation screening for proteinuria and diabetes could be an appropriate first step for assessing risk of post-LT CKD.

Importantly, we found that post-LT AKI was a strong predictor of progressive CKD. However, the causal relationship between AKI and CKD in post-LT patients or in general has been debated [8,22]. *In vitro* studies have demonstrated a prolonged inflammatory and remodeling response in renal tissues following a transient insult, providing a biological basis for transition from AKI to CKD [23,24]. However, among patients with post-LT AKI, reversible episodes of AKIs account for a large proportion [25]. These milder reversible cases cannot

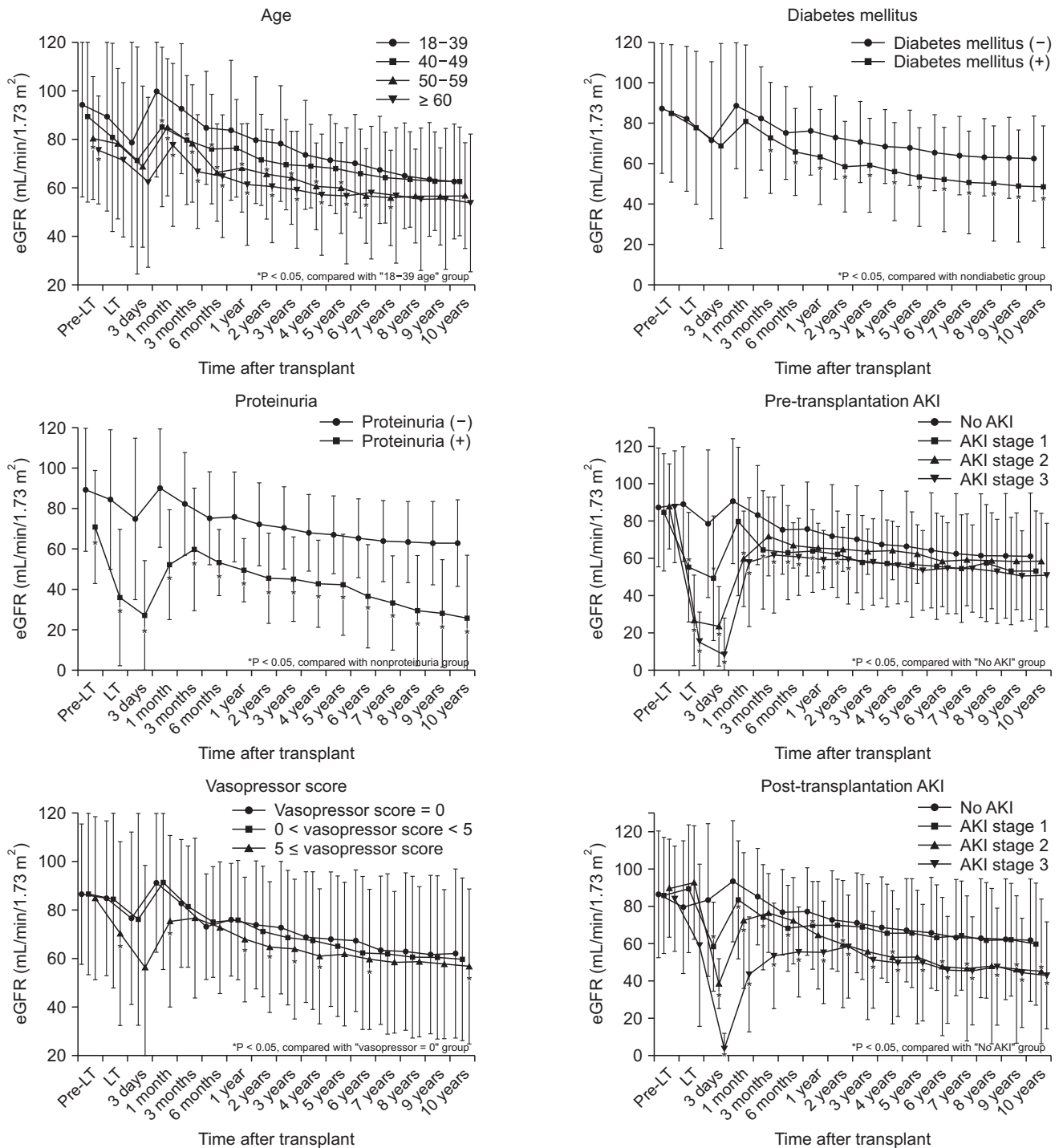


Fig. 3. Time-dependent changes in eGFR according to the risk factors in the multivariable analysis. Each dot represents average eGFR according to subgroups of patients (Bars represent standard deviation). AKI, acute kidney injury; eGFR, estimated glomerular filtration rate. *P < 0.05, compared with the reference group (t-test).

be explained by the aforementioned theory. Recently, there has been increasing recognition that even patients with complete recovery from AKI remain at risk for progressive CKD [26]. In these cases, AKI serves as a "failed renal stress test" rather than a causative factor in the development of CKD [27]. Regardless of

the nature of the relationship between AKI and CKD, patients who experienced the AKI could be recognized as high-risk patients for CKD. Our results support the need for regular follow-up of patients who experienced AKI during admission for transplantation in the period following discharge for earlier

detection of CKD development, even among those with AKI that may have recovered before discharge.

Perioperative hemodynamic instability is a well-recognized phenomenon, and vasoactive agents are often used during LT [28]. We showed that perioperative hypotension and blood loss do not appear to be independent predictors of long-term renal function. Instead, immediate postoperative vasopressor score was independently associated with progressive CKD. This result may indicate that prolonged administration of a high dose of vasopressor during the perioperative period is related with irreversible kidney damage after LT. In the vasodilatory condition, it makes physiologic sense to improve GFR by restoration of vascular resistance. It is uncertain, however, whether vasopressor can achieve these goals safely [29]. If a vasopressor is excessively administered, intrarenal vascular resistance would increase proportionately more than perfusion pressure, and overall blood flow would decrease [29]. If a patient is hypotensive, routine initiation or increasing the dose of vasopressor is not an advisable solution due to effects on the kidney. Although administration of vasopressor is required in sustained vasodilatory hypotension, judicious assessment of the patient's volume status and surveillance of other correctable causes (e.g., sedatives, analgesics, or hemorrhage) with efforts of correcting them would be reasonable. It is worth mentioning that vasopressor infusion under normal circulatory conditions or hypovolemic hypotension is more strongly associated with renal ischemia [10]. To our knowledge, this is the first study to demonstrate a relationship between perioperative vasopressor and post-LT CKD.

The absence of a significant relationship between transfused amount of blood products and progressive CKD after LT is inconsistent with results from previous studies. The intraoperative transfused amount of RBC has been reported as a strong risk factor for overall poor outcome in the general population and in people with renal dysfunction after LT [5,9]. The difference between our study and previous studies may relate to restrictive policy for use of intraoperative RBC transfusion with active use of autologous cell salvage.

Our study has several limitations. First, the study is subject to bias due to unknown or unmeasured confounders due to its retrospective nature. However, because it was a single-center study, we collected the data for many potential variables associated with progressive CKD. The precise values for the hemodynamic data during the operation were retrieved from the electronic medical records. Second, the effects of mammalian target of rapamycin (mTOR) inhibitors on renal outcome were not studied in our study. Nearly all patients received standard calcineurin inhibitor therapy without switching to alternative regimens because mTOR inhibitors have only become available recently in Korea. Further studies regarding renal outcome in patients with alternative

immunosuppressive regimens are required in the future. Third, our threshold for defining intraoperative hypotension was SBP <80 mmHg. A change in this threshold value may alter the incidence of hypotension, and this definition has not been validated for LT patients. However, there is no accepted single definition for intraoperative hypotension, and our threshold value has been used in previous studies [30]. Fourth, we did not use a clinical-endpoint such the onset of end-stage renal disease as a main outcome parameter. Although this has more clinical impact, this is a relatively late event in the course of CKD progression. Despite the 10-year long-term follow-up period of our study, ESRD only occurred in a few patients. Evaluation of outcomes other than ESRD with surrogate markers is needed in most clinical studies. Fifth, we used creatinine-based eGFR to assess renal function using MDRD formula. Since the serum creatinine concentration generally underestimates the degree of renal dysfunction in patients with liver disease and is affected by muscle mass, GFR estimation using serum cystatin C or measure of GFR using inulin clearance or isotopic clearance is desirable.

In this single-center study of LT recipients, age, diabetes mellitus, proteinuria, perioperative AKI, and administered dose of vasopressor were risk factors for CKD after LT. These findings indicate that postoperative AKI and vasopressor may be modifiable risk factors for progressive CKD. In postoperative patient care, risk stratification of patients based on the risk factors described above coupled with preventive strategies may improve long-term renal outcome in LT recipients.

ACKNOWLEDGEMENTS

The authors are grateful to all members and coordinators from the liver transplantation team of Samsung Medical Center for their support throughout this research work.

Fund/Grant Support

Kyungho Lee was supported by the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C1337).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ORCID iD

Kyungho Lee: <https://orcid.org/0000-0003-2627-0220>

Junseok Jeon: <https://orcid.org/0000-0003-2532-0177>

Jong Man Kim: <https://orcid.org/0000-0002-1903-8354>

Gaabssoo Kim: <https://orcid.org/0000-0002-9383-2652>

Kyunga Kim: <https://orcid.org/0000-0002-0865-2236>

Hye Ryoung Jang: <https://orcid.org/0000-0001-9856-6341>
 Jung Eun Lee: <https://orcid.org/0000-0002-4387-5291>
 Jae-Won Joh: <https://orcid.org/0000-0003-4823-6218>
 Suk-Koo Lee: <https://orcid.org/0000-0002-8503-2882>
 Woosong Huh: <https://orcid.org/0000-0001-8174-5028>

Formal Analysis: KL, JJ, KK
 Investigation: KL, JJ, KK
 Methodology: KL, HRJ, JEL
 Project Administration: WH
 Writing – Original Draft: KL, JJ, KK
 Writing – Review & Editing: JMK, GK, HRJ, JEL, JWJ, SKL, WH

Author Contribution

Conceptualization: KL, JMK, GK, JWJ, SKL, WH

REFERENCES

- Thongprayoon C, Kaewput W, Thamcharoen N, Bathini T, Watthanasuntorn K, Lertjitbanjong P, et al. Incidence and impact of acute kidney injury after liver transplantation: a meta-analysis. *J Clin Med* 2019;8:372.
- Bahirwani R, Reddy KR. Outcomes after liver transplantation: chronic kidney disease. *Liver Transpl* 2009;15 Suppl 2:S70-4.
- Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003;349:931-40.
- Kim HY, Lee JE, Ko JS, Gwak MS, Lee SK, Kim GS. Intraoperative management of liver transplant recipients having severe renal dysfunction: results of 42 cases. *Ann Surg Treat Res* 2018;95:45-53.
- Chen J, Singhapricha T, Hu KQ, Hong JC, Steadman RH, Busuttill RW, et al. Postliver transplant acute renal injury and failure by the RIFLE criteria in patients with normal pretransplant serum creatinine concentrations: a matched study. *Transplantation* 2011;91:348-53.
- Utsumi M, Umeda Y, Sadamori H, Nagasaka T, Takaki A, Matsuda H, et al. Risk factors for acute renal injury in living donor liver transplantation: evaluation of the RIFLE criteria. *Transpl Int* 2013;26:842-52.
- Hilmi IA, Damian D, Al-Khafaji A, Planinsic R, Boucek C, Sakai T, et al. Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes. *Br J Anaesth* 2015;114:919-26.
- Leithead JA, Ferguson JW, Bates CM, Davidson JS, Simpson KJ, Hayes PC. Chronic kidney disease after liver transplantation for acute liver failure is not associated with perioperative renal dysfunction. *Am J Transplant* 2011;11:1905-15.
- Rana A, Petrowsky H, Hong JC, Agopian VG, Kaldas FM, Farmer D, et al. Blood transfusion requirement during liver transplantation is an important risk factor for mortality. *J Am Coll Surg* 2013;216:902-7.
- Richer M, Robert S, Lebel M. Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. *Crit Care Med* 1996;24:1150-6.
- Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247-54.
- Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.
- National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 Suppl 1):S1-266.
- Bang SR, Ahn HJ, Kim GS, Yang M, Gwak MS, Ko JS, et al. Predictors of high intraoperative blood loss derived by simple and objective method in adult living donor liver transplantation. *Transplant Proc* 2010;42:4148-50.
- Zuppa AF, Nadkarni V, Davis L, Adamson PC, Helfaer MA, Elliott MR, et al. The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. *Crit Care Med* 2004;32:2318-22.
- Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl* 2010;16:943-9.
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453-7.
- Saliba F, Fischer L, de Simone P, Bernhardt P, Bader G, Fung J. Association between renal dysfunction and major adverse cardiac events after liver transplantation: evidence from an International Randomized Trial of Everolimus-Based Immunosuppression. *Ann Transplant* 2018;23:751-7.
- Yilmaz S, Yilmaz A, Häyry P. Chronic renal allograft rejection can be predicted by area under the serum creatinine versus time curve (AUCr). *Kidney Int* 1995;48:251-8.

20. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 2014;311:2518-31.
21. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013;382:260-72.
22. Rifkin DE, Coca SG, Kalantar-Zadeh K. Does AKI truly lead to CKD? *J Am Soc Nephrol* 2012;23:979-84.
23. Basile DP, Donohoe D, Roethe K, Osborn JL. Renal ischemic injury results in permanent damage to peritubular capillaries and influences long-term function. *Am J Physiol Renal Physiol* 2001;281:F887-99.
24. Basile DP, Leonard EC, Tonade D, Friedrich JL, Goenka S. Distinct effects on long-term function of injured and contralateral kidneys following unilateral renal ischemia-reperfusion. *Am J Physiol Renal Physiol* 2012;302:F625-35.
25. Northup PG, Argo CK, Bakhru MR, Schmitt TM, Berg CL, Rosner MH. Pretransplant predictors of recovery of renal function after liver transplantation. *Liver Transpl* 2010;16:440-6.
26. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012;81:477-85.
27. Kellum JA. Persistent acute kidney injury. *Crit Care Med* 2015;43:1785-6.
28. Xia VW, Du B, Braunfeld M, Neelakanta G, Hu KQ, Nourmand H, et al. Preoperative characteristics and intraoperative transfusion and vasopressor requirements in patients with low vs. high MELD scores. *Liver Transpl* 2006;12:614-20.
29. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. *Crit Care Med* 2008;36(4 Suppl):S179-86.
30. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007;107:213-20.