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Low Mean Arterial Blood Pressure is Independently Associated with Postoperative Acute Kidney Injury After Living Donor Liver Transplantation: A Propensity Score Weighing Analysis

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Background: As end-stage liver disease progresses, renal blood flow linearly correlates with mean arterial blood pressure (MBP) due to impaired autoregulation. We investigated whether the lower degree of postoperative MBP would predict the occurrence of postoperative acute kidney injury (AKI) after liver transplantation.

Material/Methods: This retrospective study enrolled 1,136 recipients with normal preoperative kidney function. Patients were categorized into two groups according to the averaged postoperative MBP: <90 mmHg ($MBP_{below90}$) and ≥90 mmHg (MBP_{over90}). The primary endpoint was occurrence of postoperative AKI, defined by the creatinine criteria of the Kidney Disease Improving Global Outcomes. The logistic regression model with inverse probability treatment weighting (IPTW) of propensity score was used to compare the risk of postoperative AKI between two groups.

Results: $MBP_{below90}$ group (83.0±5.1 mmHg) showed higher prevalence and risk of postoperative AKI (74.2% versus 62.6%, $p<0.001$; IPTW-OR 1.34 [1.12–1.61], $p=0.001$) compared with MBP_{over90} group (97.3±5.2 mmHg). When stratified by quartiles of baseline cystatin C glomerular filtration ratio (GFR), the association between $MBP_{below90}$ and postoperative AKI remained significant only with the lowest quartile (cystatin C GFR ≤85 mL/min/1.73 m^2; IPTW-OR 2.24 [1.53–3.28], $p<0.001$), but not with 2^{nd}–4^{th} quartiles.

Conclusions: Our results suggest that maintaining supranormal MBP over 90 mmHg may be beneficial to reduce the risk of post-LT AKI, especially for liver transplant recipients with cystatin C GFR ≤85 mL/min/1.73 m^2.

MeSH Keywords: **Acute Kidney Injury • Arterial Pressure • Liver Transplantation • Renal Circulation**

Abbreviations: **ESLD** – end-stage liver disease; **MBP** – mean arterial blood pressure; **AKI** – acute kidney injury; **LT** – liver transplantation; **IPTW** – inverse probability treatment weighting; **HRS** – hepatorenal syndrome; **POD** – postoperative day; **aOR** – adjusted odds ratio; **KDIGO** – The Kidney Disease: Improving Global Outcomes; **GFR** – glomerular filtration rate; **BMI** – body mass index

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Background

Postoperative acute kidney injury (AKI) is a major cause of morbidity and mortality following surgery [1,2]. AKI occurrence depends on pre-existing renal function [3,4], the complexity of the surgery [1,5,6]. and perioperative management, including hemodynamic optimization [7,8]. Avoiding perioperative hypotension and optimizing mean arterial blood pressure (MBP) have been known to prevent injury to the kidney, which is the most sensitive organ to these conditions [7,9]. Studies have suggested an MBP of 55–60 mmHg as a threshold point for the autoregulation plateau of renal blood flow to prevent postoperative AKI [4,8,10,11], however, those findings were extrapolated from patients undergoing noncardiac surgery and healthy animals. For critically ill patients (e.g., patients with sepsis or septic shock, especially those with chronic hypertension), a target MBP up to 80–95 mmHg has been associated with favorable outcomes, including a reduction in renal failure and mortality [12,13], presumably because renal autoregulation is impaired in those patients [14–16].

Patients with end-stage liver disease (ESLD) also experience impaired renal autoregulation. Although the mechanisms leading to autoregulation failure are not entirely clear, evidences from both animal and human studies have shown that the renal autoregulation curve shifts to the right and becomes linearized as ESLD progresses [17,18]. Hence, at a given MBP level, renal blood flow might be markedly lower than normal. Even small changes in MBP may directly affect renal blood flow, thus making patients with ESLD vulnerable to kidney injury during hemodynamic fluctuation.

In this regard, postoperative AKI occurs in up to 80% of patients after liver transplantation (LT), with an adverse impact on the outcome of LT [19,20]. In addition, clinical studies have demonstrated that raising MBP up to "supranormal" levels was associated with a reversal of hepatorenal syndrome (HRS) regardless of the type of vasoactive therapy [18,21–25]. Thus, we hypothesized that raising MBP would also have a favorable impact on the occurrence of postoperative AKI following LT in the same manner, as it did for septic shock and HRS. However, studies on how MBP influences kidney outcomes after LT are scarce. Thus, we aimed to determine the association between postoperative MBP and occurrence of postoperative AKI after LT using population data from our large-volume center.

Material and Methods

This retrospective observational study was approved by our institutional review board. We reviewed consecutive patients who underwent living-donor LT between July 2011 and October 2015. Patients who were older than 20 years of age were included and a total of 1,292 patients were identified. As to include the patients only with normal kidney functions, we excluded patients who had chronic kidney disease (CKD, n=15). CKD was defined as positive when patients were already diagnosed by nephrologist prior to LT candidacy. To exclude the patients who had any possibility of being diagnosed as HRS, those with preoperative creatinine >1.5 mg/dL, which was adapted from HRS diagnostic criteria [26], were excluded (n=69). We also excluded patients who did not have preoperative cystatin C glomerular filtration rate (GFR) data (n=72). In all, 1,136 patients were enrolled.

Anesthesia and hemodynamic monitoring were performed in accordance with our institutional standard [27]. Briefly, we maintained anesthesia with sevoflurane or desflurane, a mixture of 50% O_2 and 50% air, and a continuous infusion of fentanyl. Arterial pressure was monitored using radial and femoral arterial catheters. For advanced hemodynamic monitoring, a pulmonary arterial catheter was inserted and connected to a Vigilance device (Vigilance II, Edwards Lifesciences LLC). According to the patient's blood pressure and hemodynamics, either fluid or vasoactive drugs were given by the attending anesthesiologist. In cases of low systemic vascular resistance, a continuous infusion of norepinephrine, vasopressin, or terlipressin was used to maintain MBP. We attempted to maintain intraoperative MBP above the preoperative level. After surgery, patients were transferred to the intensive care unit in an intubated state. Patients were sedated with remifentanil and usually extubated on postoperative day 1.

We collected the patients' preoperative and early postoperative MBP values. MBP was calculated using the following equation: MBP=(systolic blood pressure +2×diastolic blood pressure)/3. Preoperative MBP was defined as the averaged blood pressure value measured during the week before surgery. Early postoperative MBP was defined as the averaged MBP value until the postoperative day 1. Because a single measurement of MBP would not accurately represent MBP status, we derived the MBP automatically. Using our institution's electronic medical record system (Asan Biomedical Research Environment), a total of 35,467 preoperative MBP and 33,185 early postoperative MBP values were collected and then averaged for each patient to represent preoperative and early postoperative MBP variables.

The preoperative characteristics and perioperative variables were also collected. Preoperative characteristics included age, sex, body mass index (BMI), Model for End-Stage Liver Disease (MELD) score, heart rate, comorbidities (hypertension, diabetes mellitus), hypertension medication, etiology of liver cirrhosis, and donor age. Preoperative laboratory variables included serum creatinine, cystatin C GFR, serum albumin, and total bilirubin. Intraoperative variables included units of transfused

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Table 1. Perioperative variables according to the development of postoperative acute kidney injury.

	AKI (n=777, 68.4%)	No AKI (n=359)	Total (n=1136)	*P* value
Perioperative MBP				
Preoperative MBP	81.6±9.4	84.2±9.4	82.4±9.5	<0.001
Early postoperative MBP	89.3±8.6	92.0±8.8	90.2±8.8	<0.001
Increase in MBP after surgery	8.2 [0.9; 14.7]	8.4 [0.9; 14.7]	8.3 [0.9; 14.7]	0.998
Demographics				
Age (years)	53.2±8.3	52.7±7.4	53.0±8.0	0.311
Sex, male	575 (74.0%)	284 (79.1%)	859 (75.6%)	0.074
Body mass index (kg/m^2)	24.4±3.5	23.6±2.8	24.1±3.4	<0.001
Diabetes mellitus	161 (20.7%)	68 (18.9%)	229 (20.2%)	0.538
Hypertension	78 (10.0%)	48 (13.4%)	126 (11.1%)	0.119
Heart rate	72.9±11.8	72.3±10.9	72.7±11.5	0.393
MELD score	14.1±6.3	12.4±6.8	13.6±6.5	<0.001
Preoperative vasopressor use	32 (4.1%)	12 (3.3%)	44 (3.9%)	0.765
Donor age	28.4±8.6	27.2 ±8.1	28.0±8.4	0.031
Hypertension medication				
Angiotensin II receptor antagonist	21 (5.9%)	47 (6.1%)	68 (6.0%)	1.000
Angiotensin-converting-enzyme inhibitor	1 (0.3%)	2 (0.3%)	3 (0.3%)	1.000
Calcium channel blocker	34 (9.5%)	80 (10.3)	114 (10.0)	0.746
Beta blockers	50 (14.0%)	119 (15.3%)	169 (14.9%)	0.602
Etiology of liver cirrhosis				
Hepatitis B virus	445 (57.3%)	245 (68.2%)	690 (60.7%)	0.001
Hepatitis C virus	64 (8.2%)	23 (6.4%)	87 (7.7%)	0.338
Alcohol abuse	161 (20.7%)	46 (12.8%)	207 (18.2%)	0.002
Biliary cirrhosis	29 (3.7%)	12 (3.3%)	41 (3.6%)	0.876
Others	97 (12.5%)	38 (10.6%)	135 (11.9%)	0.412
Preoperative laboratory variables				
Creatinine (mg/dL)	0.7±0.2	0.7±0.2	0.7±0.2	0.471
Cystatin C GFR (ml/min/1.73 m^2)	102.7±28.5	112.7±37.4	105.9±31.9	<0.001
Albumin (g/dL)	3.1±0.5	3.3±0.5	3.2±0.6	<0.001
Total bilirubin (mg/dL)	4.7±7.6	4.3±8.1	4.5±7.8	0.469
Perioperative variables				
Transfused pRBC (units)	6 [2; 12]	4 [0; 8]	5 [1; 10]	0.001
Intraoperative vasopressor uses	724 (93.2%)	327 (91.1%)	1051 (92.5%)	0.317
Severe post-reperfusion syndrome	90 (11.6%)	35 (9.8%)	125 (11.0%)	0.424
Graft-to-recipient weight ratio	1.1±0.2	1.2±0.2	1.1±0.2	0.006
Total ischemic time (min)	129.8±30.8	130.0±51.9	129.9±38.7	0.941
Postoperative vasopressor use (days)	0 [0; 1]	0 [0; 0]	0 [0; 1]	<0.001
Use of FK506	696 (89.6%)	329 (91.6%)	1025 (90.2%)	0.333
Trough level of FK506 (ng/mL)	6.2±2.5	6.2±2.4	6.2±2.5	0.737
Outcome variables				
Renal replacement therapy	8 (2.2%)	50 (6.4%)	58 (5.1%)	0.004
3-month CKD	30 (3.7%)	7 (2.0%)	37 (3.3%)	0.132
Overall CKD	190 (24.5%)	47 (13.1%)	237 (20.9%)	<0.001
Hospital stay (days)	28 [23; 38]	32 [24; 47]	30 [24; 44]	<0.001
Intensive care unit stay (days)	2 [2; 4]	3 [2; 5]	3 [2; 5]	<0.001

Values are expressed as mean±SD, median [IQR], or numbers (percent). AKI – acute kidney injury; MBP – mean arterial blood pressure; MELD – model for end-stage liver disease; GFR – glomerular filtration rate; pRBC – packed red blood cells; CKD – chronic kidney injury.

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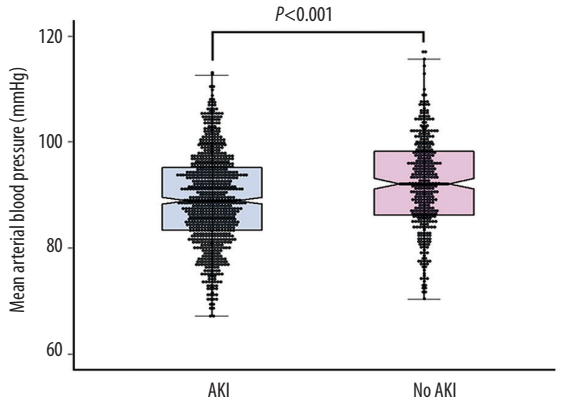

Figure 1. Comparison of early postoperative mean arterial blood pressure according to the occurrence of postoperative AKI. Boxes represent median with interquartile range and the whiskers the 95th percentile. AKI – acute kidney injury.

packed red blood cell, severe post-reperfusion syndrome, graft-to-recipient body weight ratio, and total ischemic time. Severe post-reperfusion syndrome was defined as the need for more than 30 μg of epinephrine during the reperfusion period.

The primary outcome in our study was the occurrence of postoperative AKI. The Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria were used to determine AKI [28]. KDIGO classification diagnosis of AKI is based on changes in serum creatinine within 1–7 postoperative days (POD) from baseline creatinine. KDIGO classification is further divided into three stages; stage 1 as an increase in creatinine ≥0.3 mg/dL within 48 hours or 1.5–1.9 times baseline within 7 days; stage 2 as an increase in creatinine of 2.0–2.9 times baseline within 7 days; stage 3 as an increase in creatinine of 3.0 times baseline or ≥4.0 mg/dL, with an acute increase of at least 0.5 mg/dL, or the need for renal replacement therapy within 7 days. For consecutive creatinine data in the same POD, the highest level of each day was selected for data collection. The secondary outcome was development of stage 3 or higher CKD, which was defined when the estimated GFR decreased to <60 mL/min/1.73 m^2 in two consecutive occasions at least three months apart [29].

Variables are expressed as numbers and percentages, means ± standard deviation, or medians with interquartile ranges (IQR) if skewed. We categorized all patients into two groups based on the early postoperative MBP: less than 90 mmHg ($MBP_{below90}$) and greater than 90 mmHg (MBP_{over90}). Intergroup comparisons were performed using the chi-squared test or Fisher's exact test for categorical variables, and the Student's *t*-test or Mann-Whitney U test for continuous variables as appropriate. Multivariate logistic regression was applied to determine whether the association of early postoperative MBP with postoperative AKI was independent of confounding variables. Variables with *p* values of <0.1 in the univariate analysis were included for multivariable analysis. To further decrease the effect of potential confounding in this observational study, we also rigorously adjusted for significantly different characteristics by performing weighted logistic regression modeling with inverse probability treatment weighting (IPTW) [30]. Weights for MBP_{over90} group were the inverse of 1 – propensity score, and weights for $MBP_{below90}$ were the inverse of propensity score. We calculated propensity scores without regard to results from multivariate logistic regression modeling. All preoperative and perioperative covariates represented in Table 1 were included in a full non-parsimonious model. Discrimination of the model was assessed by C-statistics and calibration was evaluated with the Hosmer-Lemeshow statistics. We stratified patients according to the baseline cystatin C GFR (quartile 1 [Q1] versus quartiles 2–4 [Q2–4]) to examine the association between baseline kidney function and the effect of early postoperative MBP on postoperative AKI. IPTW-weighted logistic regression modeling was applied for each subgroup. To present the relationship between early postoperative MBP and postoperative AKI, we conducted multivariable generalized logistic regression analysis with logit model using significant independent risk factors from multivariable analysis to plot predicted probability and relative risk. We considered *p* values <0.05 to be statistically significant. Statistical analyses were performing using SPSS version 22 (IBM, New York, NY, USA) or R version 3.3.2 (*http://www.R-project.org/*).

Results

A total of 1,136 patients were evaluated. Table 1 lists the preoperative characteristics and perioperative variables for these patients according to the development of AKI. Postoperative AKI occurred in 777 (68.4%) patients. Of them, 466 patients (41.0%) were classified with stage 1 AKI, 233 patients (20.5%) with stage 2 AKI, and 78 patients (6.9%) with stage 3 AKI. Patients who developed postoperative AKI had lower early postoperative MBPs (89.3±8.6 versus 92.0±8.8, $p<0.001$; Figure 1). Other variables, including BMI, MELD score, donor age, hepatitis B cirrhosis, alcoholic cirrhosis, cystatin C GFR, serum albumin concentration, units of transfused packed red blood cells, and graft-to-recipient body weight ratio differed between patients who developed postoperative AKI and patients who did not ($p<0.05$).

To compare the incidence of postoperative AKI according to early postoperative MBP, patients were divided into two groups by their early postoperative MBP: MBP_{over90} and $MBP_{below90}$. Table 2 shows the perioperative variables according to these groups. The optimum cutoff value of 90 mmHg was derived from

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Table 2. Perioperative variables according to early postoperative mean arterial blood pressure.

	MBP_{over90} (n=567)	$MBP_{below90}$ (n=569)	Total (n=1136)	*P* value
Perioperative MBP				
Preoperative MBP	85.6±9.4	79.2±8.4	82.4±9.5	<0.001
Early postoperative MBP	97.3±5.2	83.0±5.1	90.2±8.8	<0.001
Increase in MBP after surgery	12.7[5.2; 18.9]	4.9[–1.9; 10.3]	8.3[0.9; 14.7]	<0.001
Demographics				
Age (years)	51.8±8.1	54.2±7.8	53.0±8.0	<0.001
Sex, male	453 (79.9%)	406 (71.4%)	859 (75.6%)	0.001
Body mass index (kg/m^2)	24.2±3.1	24.0±3.6	24.1±3.4	0.100
Diabetes mellitus	98 (17.3%)	131 (23.0%)	229 (20.2%)	0.019
Hypertension	79 (13.9%)	47 (8.3%)	126 (11.1%)	0.003
Heart rate	72.5±11.2	72.9±11.8	72.7±11.5	0.636
MELD score	13.1±6.6	14.0±6.3	13.6±6.5	<0.001
Preoperative vasopressor use	24 (4.2%)	20 (3.5%)	44 (3.9%)	0.636
Donor age	27.4±8.6	28.6 ±8.3	28.0±8.4	0.023
Hypertension medication				
Angiotensin II receptor antagonist	40 (7.1%)	28 (4.9%)	68 (6.0%)	0.164
Angiotensin-converting-enzyme inhibitor	2 (0.4%)	1 (0.2%)	3 (0.3%)	0.998
Calcium channel blocker	67 (11.8%)	47 (8.3%)	114 (10.0%)	0.058
Beta blockers	80 (14.1%)	89 (15.6%)	169 (14.9%)	0.521
Etiology of liver cirrhosis				
Hepatitis B virus	361 (63.7%)	329 (57.8%)	690 (60.7%)	0.050
Hepatitis C virus	38 (6.7%)	49 (8.6%)	87 (7.7%)	0.272
Alcohol abuse	105 (18.5%)	102 (17.9%)	207 (18.2%)	0.856
Biliary cirrhosis	12 (2.3%)	28 (4.9%)	41 (3.6%)	0.027
Others	61 (10.8%)	74 (13.0%)	135 (11.9%)	0.281
Preoperative laboratory variables				
Creatinine (mg/dL)	0.7±0.2	0.7±0.2	0.7±0.2	0.017
Cystatin C GFR (ml/min/1.73 m^2)	107.9±31.2	103.9±32.5	105.9±31.9	0.011
Albumin (g/dL)	3.2±0.6	3.1±0.5	3.2±0.6	<0.001
Total bilirubin (mg/dL)	4.4±7.8	4.7±7.8	4.5±7.8	0.022
Perioperative variables				
Transfused pRBC (Units)	5 [0; 10]	6 [2; 12]	5 [1; 10]	0.006
Intraoperative vasopressor uses	510 (89.9%)	541 (95.1%)	1051 (92.5%)	0.002
Severe post-reperfusion syndrome	50 (8.8%)	75 (13.2%)	125 (11.0%)	0.024
Graft-to-recipient weight ratio	1.1±0.2	1.1±0.3	1.1±0.2	0.381

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Table 2 continued. Perioperative variables according to early postoperative mean arterial blood pressure.

	MBP_{over90} (n=567)	$MBP_{below90}$ (n=569)	Total (n=1136)	*P* value
Total ischemic time (min)	128.9±45.2	130.9±30.9	129.9±38.7	0.071
Postoperative vasopressor use (days)	0 [0; 0]	0 [0; 1]	0 [0; 1]	<0.001
Use of FK506	518 (91.4%)	4.5±39.4	1025 (90.2%)	0.120
Trough level of FK506 (ng/mL)	6.2±2.4	507 (89.1%)	6.2±2.5	0.238
Outcome variables				
Acute kidney injury	355 (62.6%)	422 (74.2%)	777 (68.4%)	<0.001
Grade 1	227 (40.0%)	239 (42.05)	466 (41.0%)	0.539
Grade 2	95 (16.8%)	138 (24.3%)	233 (20.5%)	0.002
Grade 3	33 (5.8%)	45 (7.9%)	78 (6.9%)	0.202
3-month CKD	18 (3.2%)	19 (3.3%)	37 (3.3%)	1.000
Overall CKD	115 (20.3%)	122 (21.4%)	237 (20.9%)	0.684
Hospital stay (days)	30 [24;41]	31 [24;47]	30 [24;44]	0.108
Intensive care unit stay (days)	3 [2; 4]	3 [2; 5]	3 [2; 5]	0.002

Values are expressed as mean±SD, median [IQR], or numbers (percent). MBP – mean arterial blood pressure; MELD – model for end-stage liver disease; GFR – glomerular filtration rate; pRBC – packed red blood cells; CKD – chronic kidney injury.

Table 3. Prevalence and odds ratio of acute kidney injury according to the early postoperative mean arterial blood pressure.

	Incidence of acute kidney injury	Odds ratio	*P* value	IPTW adjusted odds ratio	*P* value
Overall (n=1136)					
Early postoperative MBP ≥90 mmHg	355/567 (62.6%)	1 (reference)	< 0.001	1 (reference)	0.001
Early postoperative MBP <90 mmHg	422/569 (74.2%)	1.71 (1.33–2.21)		1.34 (1.12–1.61)	
Cystatin C GFR ≤85 ml/min/1.73m² (n=290)					
Early postoperative MBP ≥90 mmHg	84/127 (66.1%)	1 (reference)	0.007	1 (reference)	< 0.001
Early postoperative MBP <90 mmHg	131/163 (80.4%)	2.10 (1.23–3.59)		2.24 (1.53–3.28)	
Cystatin C GFR >85 ml/min/1.73 m² (n=846)					
Early postoperative MBP ≥90 mmHg	271/440 (61.6%)	1 (reference)	0.002	1 (reference)	0.157
Early postoperative MBP <90 mmHg	291/406 (71.7%)	1.58 (1.18–2.11)		1.16 (0.94–1.43)	

Values are expressed as numbers (present) or odds ratio (95% confidence interval). Model discrimination was assessed with C-statistics (overall, C=0.7169; GFR ≤85, C=0.7521; GFR >85, C=0.7309), and model calibration was assessed with Hosmer-Lemeshow statistics (overall, χ^2=6.0478, df=8, p=0.6419; GFR ≤85, χ^2=5.458, df=8, p=0.7077; GFR >85, χ^2=5.2234, df=8, p=0.7335). OR – odds ratio; CI – confidence interval; MBP – mean blood pressure; GFR – glomerular filtration rate; MBP – mean arterial blood pressure; GFR – glomerular filtration rate; IPTW – inverse probability of treatment weighing.

receiver operating curve analysis (area under the curve=0.588, p<0.001). Additionally, other studies of patients with HRS [18,21–25], septic shock [13,31], and cardiac surgery [32] recommended a value of 90 mmHg for the prevention of kidney injury. The average early postoperative MBP values for the MBP_{over90} and $MBP_{below90}$ groups were 97.3 ± 5.2 mmHg (range: 90–117 mmHg) and 83.0 ± 5.1 mmHg (range: 67–89 mmHg), respectively. When MBP was compared with preoperative and early postoperative MBP values, the degrees of the increases in MBP after surgery were 12.7 mmHg (IQR: 5.2–18.9 mmHg)

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Table 4. Multivariable analysis of risk factors associated with postoperative acute kidney injury after liver transplantation defined by KDIGO criteria.

	Univariable			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Male sex	0.75	0.56–1.02	0.063			
Body mass index	1.08	1.04–1.12	<0.001	1.09	1.04–1.13	<0.001
Hypertension	0.72	0.49–1.06	0.097			
Early postoperative MBP (by decrease of 10 mmHg)	1.44	1.24–1.66	<0.001	1.36	1.16–1.59	<0.001
MELD score	1.04	1.02–1.07	<0.001			
Cystatin C GFR (by decrease of 10 ml/min/1.73 m^2)	1.10	1.06–1.15	<0.001	1.05	1.01–1.10	0.016
Albumin	0.42	0.33–0.54	<0.001	0.52	0.40–0.68	<0.001
Hepatitis B cirrhosis	0.61	0.47–0.79	<0.001			
Alcoholic cirrhosis	1.77	1.25–2.55	0.002	1.44	0.99–2.12	0.062
Donor age	1.02	1.00–1.03	0.039			
Transfused packed red blood cell (by unit)	1.04	1.02–1.05	<0.001	1.02	1.00–1.04	0.021
Graft-to-recipient weight ratio	0.50	0.30–0.84	0.008			

KDIGO – the Kidney Disease: Improving Global Outcomes; OR – odds ratio; CI – confidence interval; MBP – mean arterial blood pressure; MELD – model for end-stage liver disease; GFR – glomerular filtration rate.

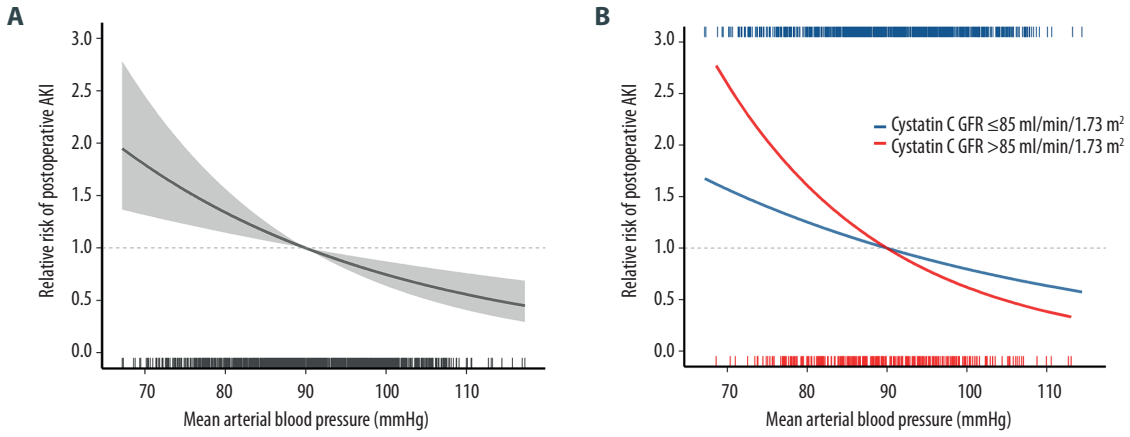

Figure 2. Relative risk plot showing the relationship between early postoperative mean blood pressure and postoperative acute kidney injury (AKI) of overall patients (**A**). When stratified by the baseline kidney function, a steeper relative risk gradient is observed in patients with lower baseline kidney function (cystatin C GFR ≤85 mL/min/1.73 m^2) than patients with higher baseline kidney function (cystatin C GFR >85 mL/min/1.73 m^2, (**B**). Estimates are adjusted for independent confounders from multivariable generalized logistic regression model. The solid lines and translucent band depict relative risk and 95% confidence intervals of those estimates. AKI – acute kidney injury; GFR – glomerular filtration ratio.

and 4.9 mmHg (IQR: –1.9–10.3 mmHg) for the MBP_{over90} and $MBP_{below90}$ groups, respectively (p<0.001).

The incidence of postoperative AKI was significantly different between the two groups: 62.6% (355/567) for the MBP_{over90} group and 74.2% (422/569) for the $MBP_{below90}$ group (p < 0.001). The odds ratio (OR) and IPTW-adjusted OR of $MBP_{below90}$ for predicting postoperative AKI were 1.71 (95% confidence interval [CI]: 1.33–2.21, p<0.001) and 1.34 (95% CI: 1.12–1.61, p=0.001) when compared with MBP_{over90} (Table 3). Multivariable logistic regression with backward selection showed the significance of early postoperative MBP for predicting postoperative AKI (OR: 1.36; 95% CI: 1.16–1.59 by a decrease of 10 mmHg, p<0.001; Table 4). Other independent compounders of the final model

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were BMI, cystatin C GFR, serum albumin concentration, and units of transfused packed red blood cells. Figure 2A shows the relative risk of postoperative AKI after adjustment for independent confounders.

To examine the association between baseline kidney function and the effect of MBP on AKI, we stratified patients according to cystatin C GFR (Q1 versus Q2–4). The quartiles of cystatin C GFR were 70.5±11.6 mL/min/1.73 m^2 (Q1), 95.1±5.3 mL/min/1.73 m^2 (Q2), 112.3±5.4 mL/min/1.73 m^2 (Q3), and 146.1±28.9 mL/min/1.73 m^2 (Q4). Among patients with the lowest quartile (Q1, cystatin C GFR ≤85 mL/min/1.73 m^2), $MBP_{below90}$ was still significantly associated with postoperative AKI (IPTW-adjusted OR: 2.24, 95% CI: 1.53–3.28, $p<0.001$; Table 3). However, among patients with higher baseline kidney function (Q2–4: cystatin C GFR >85 mL/min/1.73 m^2), $MBP_{below90}$ was not significantly associated with postoperative AKI (IPTW-adjusted OR: 1.16, 95% CI: 0.94–1.43, $p=0.157$). In multivariate-adjusted relative risk plot, patients with lower baseline kidney function (Q1) had a steeper relative risk gradient than patient with higher baseline kidney function (Q2–4, Figure 2B).

Three-month CKD and overall CKD after surgery were not different between MBP_{over90} and $MBP_{below90}$ (18/567 [3.2%] versus 19/569 [3.3%], $p=1.000$ and 115/567 [20.3%] versus 122/569 [21.4%], $p=0.684$, respectively).

Discussion

In this retrospective observational study, we found that the degree of early postoperative MBP was independently associated with postoperative AKI after living-donor LT even after adjusted by IPTW of propensity score. The IPTW-adjusted odd ratio of $MBP_{below90}$ for predicting postoperative AKI was 1.34 (95% CI: 1.12–1.61, $p=0.001$) when compared with MBP_{over90}. In multivariate analysis, a 10 mmHg decrease of MBP was associated with 1.36-fold increased risk of postoperative AKI. Notably, despite MBP was maintained at a relatively high level (90.2±8.8 mmHg), the risk of AKI was still affected by the degree of MBP. This association between MBP and postoperative AKI remained significant only in patients with lower baseline cystatin C GFR ≤85 mL/min/1.73 m^2.

In patients with ESLD, renal blood flow is known to be critically dependent on blood pressure [18]. Normal renal blood flow autoregulation curve has a sigmoid shape with a plateau, which operates at a renal perfusion pressure greater than 55–60 mmHg [4,8]. However, the autoregulation curve is altered and even lost in patients with ESLD. Although the mechanisms leading to autoregulation failure are not entirely clear, several factors have been identified, including an activated sympathetic nervous system [17,18], decreased myogenic responses of the renal vascular smooth muscle [33], and an activated renin-angiotensin system [11,34]. As a result, autoregulation curve shifts to the right and becomes linearized as ESLD progresses [17,18]. Therefore, the renal blood flow of a patient with ESLD is markedly lower at the same given level of MBP when compared with normal patients. Moreover, because MBP is linearly correlated with renal blood flow, even a small change of MBP can directly affect renal blood flow [17]. A previous study by Stadlbauer et al. demonstrated that the renal blood flow of normal patients was approximately 1,000 mL/min/g at an MBP of 70 mmHg, whereas renal blood flow for patients with ESLD was approximately 200–800 mL/min/g at the same MBP level [18]. Hence, for patients with ESLD who are scheduled for LT, renal hypoperfusion and ischemic kidney injury may not be prevented unless the MBP is kept at a high level.

An MBP increase is tightly correlated with an improvement in renal function for patients with HRS, which is the most severe form of renal dysfunction in patients with ESLD. Clinical studies on HRS have documented the clinical significance of increasing MBP. A previous randomized trial by Sharma et al., which was originally designed to observe the effect of different types of vasoconstrictors, eventually demonstrated that high MBP (83.0±8.5 mmHg versus 76.7±8.3 mmHg, $p=0.023$) is a strong predictor of therapeutic response regardless of the type of vasoconstrictor used [23]. In another similar randomized trial, patients in the highest quartile according to MBP increase (15.9–20.9 mmHg from baseline values) showed a greater treatment response to vasoconstrictor therapy regardless of therapy type [24]. A meta-analysis confirmed those parallel associations between MBP and improvement of kidney function in ESLD patients with HRS [25]. Among patients with a baseline MBP of ≥77 mmHg, there was also significant correlation between an increase of MBP and a change of creatinine ($\rho=-0.83$, $p<0.001$). The author stated that raising MBP might be required to maximize renal flow optimization and thus protect renal function in ESLD patients with HRS.

Our study indicated that the importance of increasing MBP is not only limited to the setting of HRS but is also applicable to post-LT status. According to our data, MBP has a significant impact on postoperative AKI in patients with normal preoperative creatinine levels as well as in patients with HRS. Similar results may have been found for both ESLD patients with normal creatinine and patients with HRS because the renal autoregulation curve has already started to alter in the early stages of ESLD, even before developing HRS [18]. Hence, factors affecting renal perfusion pressure, such as MBP and BMI, may have been independently associated with postoperative AKI in our study, as well as studies regarding HRS [21,24]. In addition, even if LT is performed successfully, renal autoregulation seems to return to normal only after a few weeks [35]. In a previous study of ESLD patients with and without HRS,

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renal function declined even during first week after LT and recovered to preoperative levels after more than a week [36]. Thus, perioperative MBP needs to be tightly regulated to maintain proper renal blood flow because the return of normal renal autoregulation cannot be guaranteed until weeks after LT.

Another remarkable aspect of our results is that supranormal levels of MBP helped to prevent the occurrence of postoperative AKI. This result is also in line with previous studies regarding MBP and HRS [21–24]. A meta-analysis demonstrated that improvement in renal function were observed not only when MBP increased from low to normal, but also when MBP increased from normal to "supranormal" [25]. Those previous studies stated that an MBP of >90 mmHg might be needed to minimize renal injury in patients with ESLD. Supranormal MBP is also recommended for patients with septic shock and for cardiac surgery, when renal autoregulation impairment frequently develops [13,31,32]. Our receiver operating curve analysis showed the best MBP cutoff value for predicting postoperative AKI to be 90 mmHg, which is a supranormal level. Also, the degree of MBP increase from preoperative values was highest in our MBP_{over90} group (12.7 mmHg, IQR: 5.2–18.9 mmHg), which is similar to the value in a previous study regarding MBP increases and HRS [24]. In that previous study, the group with the greatest MBP increase showed an MBP increase from 15.9 mmHg to 20.9 mmHg; this group also demonstrated the greatest creatinine reduction. Other previous studies showed that an increase of approximately 10 mmHg – from normal to supranormal – was needed to demonstrate a clinical difference in patients with HRS [21,22].

The effect of MBP on postoperative AKI was more prominent in patients with lower cystatin C GFR values. Considering that our study cohort did not have HRS, our result suggests a possibility that not only the patients with HRS but also the patients with even mild renal impairment (cystatin C GFR ≤85 mL/min/1.73 m^2), consequently much wider spectrum of cirrhotic patients, may benefit from maintaining adequate MBP to avoid further injuries to the kidney. In addition, we demonstrated that cystatin C GFR was an independent risk factor for postoperative AKI. We included cystatin C GFR in the multivariable analysis instead of creatinine because cystatin C GFR is known to better reflect the renal function of patients with ESLD [37]. In this regard, our study showed that preoperative creatinine levels were not different between patients with and without postoperative AKI (0.7±0.2 mg/dL for both groups, p=0.471). However, cystatin C GFR was significantly higher in patients who developed postoperative AKI (112.7±37.4 mL/min/1.73 m^2 versus 102.7±28.5 mL/min/1.73 m^2, p<0.001). Moreover, cystatin C GFR was significantly correlated with preoperative MBP (r=0.184, p<0.001). We speculated that preoperative MBP within a week before LT may affect preoperative baseline renal function as measured by cystatin C GFR. BMI and albumin levels were also found to be independent risk factors for postoperative AKI. This finding agrees with previous results: the increased intra-abdominal pressure of obese patients was found to negatively affect renal perfusion pressure [38], and preoperative and postoperative low albumin levels were found to be independent risk factors for AKI after LT [39,40].

There are several limitations to our study. First, although we conducted an observational analysis of over 1,000 patients, causality could not be determined. Thus, a randomized study is warranted to confirm our observations. Second, we did not collect intraoperative MBP. We have intraoperative hand-written medical record. But, due to the lack of accuracy in demonstrating precise blood pressure, which might be very important in studies like ours, we decide to not to use those hand-written intraoperative blood pressures. Rather, we included units of packed red blood cells and intraoperative use of vasopressor as intraoperative variables, because episodes of hypotension mostly occurred due to massive bleeding. Third, because this was a single-center study, our institutional perioperative strategy might influence the occurrence of postoperative AKI. Finally, because we only included patients who underwent living-donor LT and had normal preoperative creatinine levels, our results cannot be generalized to other populations.

Conclusions

Our results demonstrate that lower postoperative MBP values may increase the likelihood of postoperative AKI in liver transplant recipients with normal baseline kidney function. Even when MBP is maintained at a relatively high level, the risk of AKI is still affected by the degree of MBP increase. Maintaining a supranormal MBP may be beneficial to reduce the risk of postoperative AKI after LT especially in patients with baseline cystatin C GFR ≤85 mL/min/1.73 m^2.

Conflict of interests

None.

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