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Venovenous Bypass Is Associated With a Lower Incidence of Acute Kidney Injury After Liver Transplantation in Patients With Compromised Pretransplant Renal Function

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BACKGROUND: Although the hemodynamic benefits of venovenous bypass (VVB) during liver transplantation (LT) are well appreciated, the impact of VVB on posttransplant renal function is uncertain. The aim of this study was to determine if VVB was associated with a lower incidence of posttransplant acute kidney injury (AKI).

METHODS: Medical records of adult (≥18 years) patients who underwent primary LT between 2004 and 2014 at a tertiary hospital were reviewed. Patients who required pretransplant renal replacement therapy and intraoperative piggyback technique were excluded. Patients were divided into 2 groups, VVB and non-VVB. AKI, determined by the Acute Kidney Injury Network criteria, was compared between the 2 groups. Propensity match was used to control selection bias that occurred before VVB and multivariable logistic regression was used to control confounding factors during and after VVB.

RESULTS: Of 1037 adult patients who met the study inclusion criteria, 247 (23.8%) received VVB. A total of 442 patients (221 patients in each group) were matched. Aftermatch patients were further divided according to a predicted probability AKI model using preoperative creatinine (Cr), VVB, and intraoperative variables into 2 subgroups: normal and compromised pretransplant renal functions. In patients with compromised pretransplant renal function (Cr ≥1.2 mg/dL), the incidence of AKI was significantly lower in the VVB group compared with the non-VVB group (37.2% vs 50.8%; $P = .033$). VVB was an independent risk factor negatively associated with AKI (odds ratio, 0.1; 95% confidence interval, 0.1–0.4; $P = .001$). Renal replacement in 30 days and 1-year recipient mortality were not significantly different between the 2 groups. The incidence of posttransplant AKI was not significantly different between the 2 groups in patients with normal pretransplant renal function (Cr <1.2 mg/dL).

CONCLUSIONS: In this large retrospective study, we demonstrated that utilization of intraoperative VVB was associated with a significantly lower incidence of posttransplant AKI in patients with compromised pretransplant renal function. Further studies to assess the role of intraoperative VVB in posttransplant AKI are warranted. (Anesth Analg 2017;125:1463–70)

Acute kidney injury (AKI) occurs frequently after liver transplantation (LT) and affects long-term posttransplant renal function and survival of recipients.[1-3] Renal perfusion pressure is pivotal to renal function in the perioperative period. Complete cross-clamping of the inferior vena cava (IVC) during LT surgery causes a number of hemodynamic changes: reduced blood return to the heart, decreased cardiac output, low systemic blood pressure, and increased renal venous pressure. These hemodynamic changes further lead to a decrease in renal perfusion pressure and an increase in the incidence of posttransplant AKI.[4-10] Venovenous bypass (VVB) is designed to divert blood from the cross-clamped IVC to the heart and mitigate these potentially disastrous changes.[4] While the hemodynamic benefits of VVB are well appreciated,[11,12] the impact of VVB on posttransplant renal function is uncertain.[11-13]

Previous studies investigating the impact of VVB on posttransplant renal function have generated conflicting results, making interpretation of their findings difficult. In addition, previous studies may be outdated since most of them were performed 20 or 30 years ago[4,5,7-10] and LT has advanced significantly since then. For example, implementation of the organ allocation system based on the Model for End-Stage Liver Disease (MELD) has made a major impact on patient renal function. An increasing number of patients presenting to LT today have compromised pretransplant renal function.[14,15] However, the role of compromised pretransplant

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Study: The impact of venovenous bypass on perioperative outcomes in liver transplantation. Approved by Alison Moore, MPH, MD, Chair, South General Institutional Review Board, 11000 Kinross Ave, Suite 211, Los Angeles, CA 90095. http://ohrpp.research.ucla.edu.

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renal function in the development of posttransplant AKI in patients who undergo VVB is not known. Furthermore, previous studies used various terms and definitions to describe renal dysfunction and AKI, making comparison between the studies impossible. Finally, the definition of AKI has continuously evolved in past few decades. In 2007, the Acute Kidney Injury Network (AKIN) introduced a new AKI definition.[16,17] Since then, this definition has been rapidly adopted by the transplant and hepatology communities.[17,18] Compared with older ones, the AKIN definition has several advantages including high sensitivity and the use of early (48 hours) diagnostic criteria. There is evidence suggesting that early diagnosis can lead to early interventions, which in turn can lead to better outcome.[17] Until today, no study has used the AKIN definition to investigate effect of VVB on posttransplant AKI in LT.

The present study took advantage of a large perioperative LT database collected over 10 years at a single institution to revisit this topic. The purpose of the study was to investigate if intraoperative VVB was associated with a significantly lower incidence of AKI as determined by the AKIN criteria.

METHODS

We conducted a retrospective study of LT between January 2004 and May 2014 at the University of California Los Angeles Medical Center. The institutional review board approved the study protocol (IRB# 15-000343) and waived the need for consent from participants. Adult (≥18 years) patients who underwent primary LT using classic technique during the study period were identified. Patients who developed renal failure and required renal replacement therapy before LT were excluded from the analysis. Patients who did not undergo complete cross-clamping (eg, piggyback technique) were also excluded from the analysis.

Standard anesthetic management at our institution that was used during the study period has been published in detail elsewhere.[14] Briefly, patients were induced and maintained with intravenous and inhalational anesthetics combined with fentanyl and muscle relaxants. In addition to standard monitors, intraarterial catheter and pulmonary artery catheter were placed. Transesophageal echocardiography was utilized as needed. Vasopressors and fluids were used to maintain intraoperative hemodynamic stability. Red blood cells and frozen fresh plasma was administered via a rapid infusion device.

VVB was selectively used in LT patients. The decision to utilize VVB was jointly made between the attending surgeon and anesthesiologist. While there was no standard protocol for utilizing VVB, the conditions prompting the discussion for VVB included coronary artery disease, nonischemic cardiac diseases, severe portal hypertension, moderate or severe portal pulmonary hypertension, acute liver failure, potential hemodynamic instability, potential massive blood loss, and failure to tolerate a trial of cross-clamping of the IVC. The majority of VVB was achieved by surgical cut-down on the saphenous veins for venous outflow and the axillary vein for venous return. The portal vein was also cannulated to decompress the splanchnic circulation if technically possible. Non–heparin-bonded silastic circuits were utilized. A designated perfusionist was responsible for setting up and running VVB.

Patients' demographics, comorbidity, etiology of liver disease, MELD scores, and baseline laboratory values were prospectively collected. Intraoperative variables included duration of surgery, transfusion of red blood cell and frozen fresh plasma, requirement of vasopressors, and postreperfusion syndrome. Donor data were collected by chart review. Postoperative variables included need for renal replacement therapy within 30 days after LT and patient survival. An investigator blinded to the baseline characteristics, intraoperative management, and postoperative outcomes collected the data regarding application of VVB and related parameters. Baseline laboratory values were those collected immediately before surgery. Postoperative serum creatinine (Cr) levels were measured daily after LT. Patients were divided into 2 groups: VVB and non-VVB. Posttransplant AKI was defined by the AKIN criteria (a percentage increase in Cr by >1.5-fold from preoperative level or an absolute increase in Cr ≥0.3 mg/dL within 48 hours).[16] The urine output was not included as a diagnostic creation in the study.

Data were reported as a median (interquartile range) for continuous variables, or percentages for categorical variables. Statistical analysis comparing the 2 groups was performed by using Student *t*, Mann-Whitney *U*, Pearson, or Fisher exact tests. The VVB and non-VVB groups were matched by propensity scores. Factors used to generate the propensity scores were those that occurred before VVB and had potential to influence either the decision to utilize VVB or the incidence of AKI. Patients were matched with nearest-neighboring matching in a 1:1 ratio without replacement. The caliper was defined as 0.2. Absolute standardized difference was calculated.[19] An absolute standardized difference less than 10% was considered to support the assumption of balance between the 2 groups.[20] Comparisons of the VVB and non-VVB groups after match were performed by using unpaired tests. A logistic regression of AKI model was constructed using VVB, pretransplant Cr (as a continuous variable), and intraoperative factors that were selected based on the important effects on posttransplant AKI. Based on this model, a predicted probability of AKI was graphed to show the relationship between predicted probability of AKI and pretransplant Cr/VVB. Independent risk factors were identified using a multivariable logistic regression model that included important intraoperative variables. Odds ratio and 95% of confidence interval were calculated. Survival analysis was done with the use of the Kaplan–Meier method with a log-rank test. All tests were performed using SPSS, version 22.0 (IBM, Armonk, NY), with $P < .05$ considered to be statistically significant.

RESULTS

A total of 1548 adult patients underwent primary LT with complete ICV cross-clamping technique during the study period. Of 1548 patients, 511 were excluded due to preoperative renal failure, leaving 1037 included in the analysis (Figure 1). The median age of the study population was 56 years (interquartile range, 50–62) and 67.4% were male. The majority of patients were Caucasian (51.6%), followed by Asian (17.4%) and Hispanic (16.0%). The median MELD score at the time of transplantation was 32 (25–38). VVB was utilized in 247 patients (23.8%) of the study population. The number and percentage of VVB cases in each year were

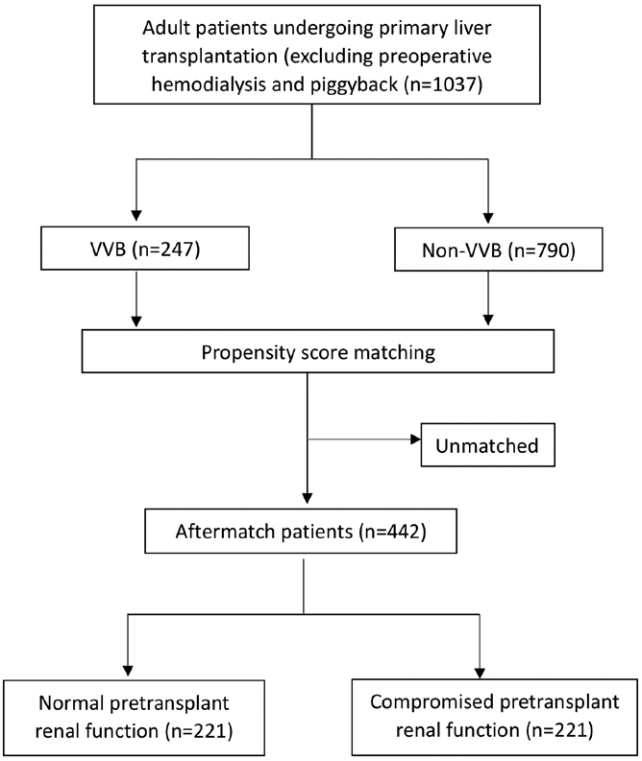

Figure 1. Flowchart of 1037 adult patients, 221 patients who underwent intraoperative VVB were matched with 221 patients who did not undergo VVB. VVB indicates venovenous bypass.

consistent, showing no significant trend during the study period. The median time for VVB was 93 (69–118) minutes, and the median flow was 2000 (1600–2100) mL/min.

As shown in Table 1, patients with VVB had more severe liver disease with higher MELD scores and a higher incidence of comorbidities including encephalopathy, coronary artery disease, diabetes mellitus, variceal bleeding, ascites, lower baseline hematocrit, higher baseline INR, and higher baseline Cr compared with non-VVB patients. Propensity scores generated by 11 preoperative variables eliminated all significant differences that existed before match between the 2 groups (Table 2). After propensity match, there were a total 442 patients, 221 in the VVB group and 221 in the non-VVB group.

The overall incidence of posttransplant AKI was 54.9% for the entire studied patient population (n = 1037). The incidence of AKI in the VVB and non-VVB groups before match was 56.5% and 49.8% and 51.1% and 55.2% after match, respectively. There were no significant differences between the VVB and the non-VVB groups either before or after match.

The logistic model of AKI is presented in Supplemental Digital Content, Table 1, http://links.lww.com/AA/B886. The relationship between predicted probability of AKI and pretransplant Cr/intraoperative VVB is shown in Figure 2. As shown in Figure 2, pretransplant Cr levels were correlated with predicted probability of AKI. As pretransplant Cr levels increased, the predicted probability of posttransplant AKI decreased (Figure 2). The relationship between VVB and predicted probability of AKI was more complex. When pretransplant Cr was low, VVB was associated with similar or even higher predicted probability of AKI. In contrast, when pretransplant Cr was high, VVB was associated with a lower predicted probability of posttransplant AKI. The cutoff point of Cr was 1.2 mg/dL. Therefore, aftermatch patients were divided into 2 subgroups: normal pretransplant renal function (baseline Cr <1.2 mg/dL) and compromised pretransplant renal function (baseline Cr ≥1.2 mg/dL). The association between VVB and posttransplant AKI was separately tested in each of the 2 patient subpopulations. Comparison showed that AKI was not significantly different between the VVB and non-VVB groups in patients with normal pretransplant renal function. However, in patients with compromised pretransplant renal function, the incidence of AKI was significantly lower in the VVB group compared with that in the non-VVB group (37.2% vs 50.8%; $P = .033$; Figure 3).

Intraoperative factors that remained significantly different between the VVB and non-VVB groups after match (Table 3) were included in a multivariable model to identify risk factor for posttransplant AKI. VVB was confirmed as a sole factor that was negatively associated with posttransplant AKI in patients with compromised pretransplant renal function (odds ratio, 0.1; 95% confidence interval, 0.1–0.4; $P = .001$, Table 4).

Posttransplant renal replacement therapy in 30 days (38.5% vs 45.7%; $P = .344$) and 1-year recipient survival (12.3% vs 18.8%, log-rank test $P = .149$, Figure 4) were not significantly different between the VVB and non-VVB groups in patients with compromised pretransplant renal function.

DISCUSSION

In this retrospective study of 1037 adult patients, we found that post-LT AKI defined by the AKIN definition was common and the use of intraoperative VVB was associated with

Table 1. Baseline Characteristics Before Matching (n = 1037)

	Venovenous Bypass (n = 247)	Non–Venovenous Bypass (n = 790)	Absolute Standardized Differences	*P*
Age (y)	57 (51–62)	56 (50–62)	8.96	.221
Gender (male, %)	68.4	67.1	2.78	.697
Race				
Caucasian (%)	54.4	50.7		
Asian (%)	15.8	17.9	.30	.601
Others (%)	29.8	31.4		
Body mass index (kg/m^2)	28.1 (24.1–32.3)	27.2 (24.2–30.9)	8.00	.179
Model for End-Stage Liver Disease score	31 (25–37)	27 (24–33)	39.30	<.001
Encephalopathy (%)	45.3	23.1	48.13	<.001
Hypertension (%)	30.9	32.9	4.50	.557
Coronary artery disease (%)	12.1	5.9	21.79	.002
Diabetes mellitus (%)	29.8	23.4	14.52	.047
Variceal bleeding (%)	35.4	25.2	22.33	.003
Ascites >1 L (%)	48.9	32.2	34.52	<.001
Laboratory values				
Hematocrit (%)	29 (26–31)	30 (27–35)	30.82	<.001
International normalization ratio	1.7 (1.4–2.2)	1.4 (1.2–1.8)	37.86	<.001
Serum creatinine (mg/dL)	1.3 (0.9–2.0)	1.0 (0.7–1.5)	32.84	<.001

P values represent the results of Student *t* tests or χ^2 tests.

Table 2. Baseline Characteristics After Matching (n = 442)

	Venovenous Bypass (n = 221)	Non–Venovenous Bypass (n = 221)	Absolute Standardized Differences	*P*
Age (y)	57 (51–62)	56 (50–63)	5.59	.473
Gender (male, %)	69.2	66.5	5.78	.541
Race				
Caucasian (%)	55.7	51.0		
Asian (%)	15.8	17.3	8.70	.633
Others (%)	28.6	31.7		
Body mass index (kg/m^2)	28.0 (24.2–32.2)	27.6 (24.4–31.9)	0.80	.634
Model for End-Stage Liver Disease score	28 (25–36)	30 (27–35)	2.10	.919
Encephalopathy (%)	44.8	45.2	0.80	.924
Hypertension (%)	30.0	33.2	7.00	.468
Coronary artery disease (%)	12.2	11.3	2.80	.768
Diabetes mellitus (%)	30.3	28.5	3.95	.676
Variceal bleeding (%)	35.3	34.4	1.89	.842
Ascites >1 L (%)	48.4	48.9	1.00	.924
Laboratory values				
Hematocrit (%)	29 (26–31)	28 (25–32)	8.34	.619
International normalization ratio	1.7 (1.4–2.2)	1.6 (1.3–2.2)	0.56	.565
Serum creatinine (mg/dL)	1.3 (0.9–2.0)	1.2 (0.8–2.0)	1.01	.925

P values represent the results of Student *t* tests or χ^2 tests.

a lower incidence of posttransplant AKI in selected patients. Specifically, in patients with compromised pretransplant renal function, the incidence of posttransplant AKI was significantly lower in VVB patients compared with that in non-VVB patients.

Our findings have important clinical implications. Today, an increasing number of patients presenting to LT have compromised pretransplant renal function and are subject to develop posttransplant AKI.[15] In addition, these patients are older, have more acuity of liver disease, have higher MELD scores, and have more comorbidities.[15,21] The intraoperative course is more difficult for these high-risk patients, with fewer being able to tolerate the dynamic hemodynamics during LT.[14] Although piggyback technique has some hemodynamic advantages by partially occluding the IVC, it has many surgical drawbacks and is not always feasible for the high-risk patients.[6] As classic LT technique with complete IVC cross-clamp remains as a preferred technique in many centers, our findings suggest that the use of VVB in the high-risk patients may be beneficial.

Previous studies evaluating the potential benefits of VVB have limitations in addition to being outdated and lack of uniform definitions. The additional limitations included small sample size, selection bias not adjusted, no control groups, and reports on patient cohorts that had significantly lower medical acuity. The current study is the first to include more than 1000 patients from a single center. Even after dividing patients into 2 populations, each subset still had more than 400 patients. This allowed us to mitigate the selection bias inherent in comparing all patients with and without VVB. Because utilization of VVB is a clinical decision based on patient characteristics and the projected intraoperative course during LT, patients who received VVB were significantly different from those did not receive VVB. Without properly controlling for these differences, results are difficult to interpret. We used propensity match to minimize the selection bias and achieved a good comparability between the 2 groups. In addition to using propensity match, we also used multivariable logistic regression

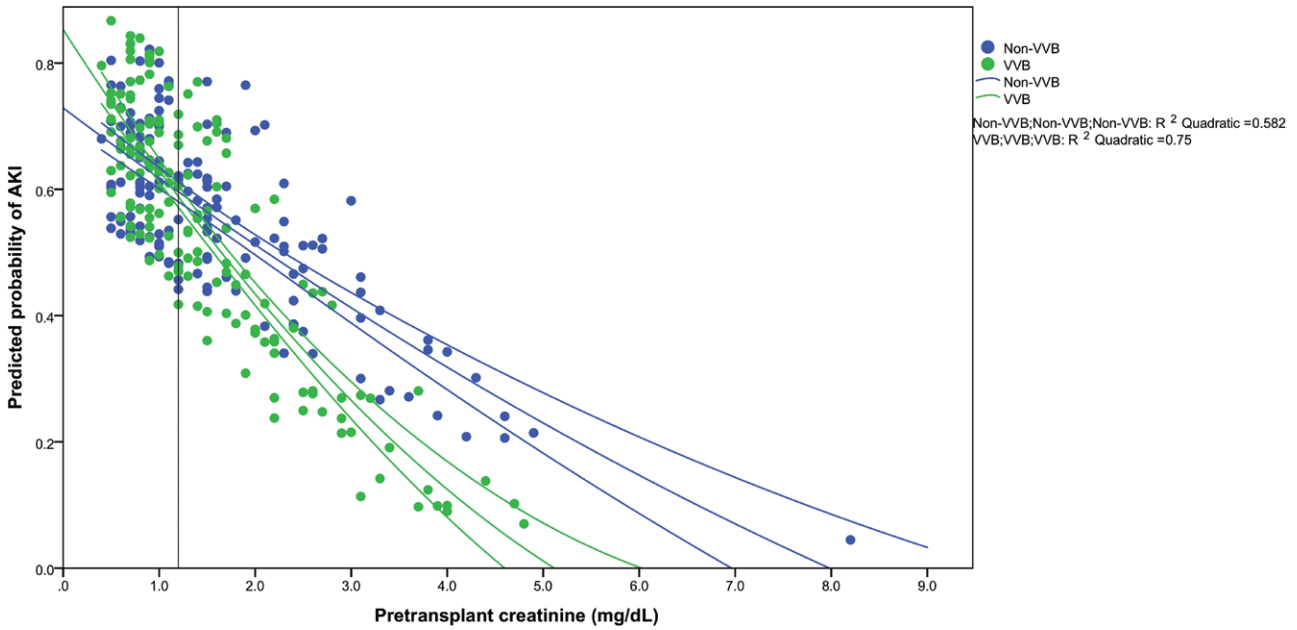

Figure 2. The relationship between posttransplant AKI and pretransplant Cr/intraoperative VVB was constructed using the model following model: AKI = a + b1*VVB + b2*pretransplant Cr + b3*VVB*pretransplant Cr + b4*cold ischemia time + b5*the use of intraoperative pressor infusion + b6*intraoperative transfusion + b7*presence of postreperfusion syndrome. Based on this model, this figure was graphed to show the relationship between the relationship between predicted probability of AKI and pretransplant Cr/intraoperative VVB. The green line indicates the VVB group and the blue line indicates the non-VVB group. 95% confidence of intervals was also provided for each group. A reference line showed pretransplant creatinine at 1.2. AKI indicates acute kidney injury; Cr, creatinine; VVB, venovenous bypass.

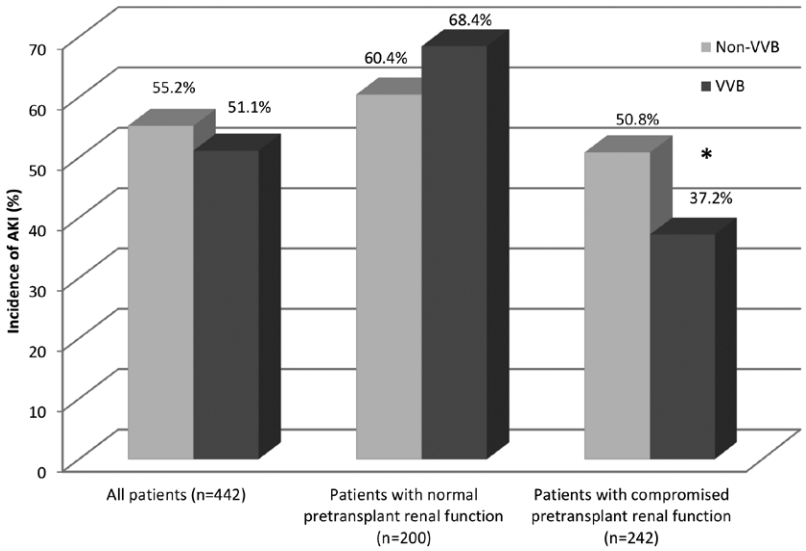

Figure 3. The incidence of AKI was compared in different groups in aftermatch patients. AKI was not significantly different in overall patients and patients with normal pretransplant renal function. However, in patients with compromised pretransplant renal function, the incidence of AKI was significantly lower in the VVB group compared with that in the non-VVB group (37.2% vs 50.8%; *P* = .033). AKI indicates acute kidney injury; VVB, venovenous bypass.

to control intraoperative cofounding factors that occurred during or after VVB. Many of the intraoperative variables that were included in our logistic model were as risk factors for posttransplant AKI in previous studies. The association between VVB and a lower incidence of AKI was demonstrated in both our analyses.

Pretransplant renal function plays an important role in development of posttransplant AKI. As we showed in this study, VVB was associated with significantly lower posttransplant AKI in the subset of recipients with compromised pretransplant renal function. Although the exact mechanism of this selective renal protection is not completely understood, the following may be postulated. First, it has been shown that patients with compromised pretransplant renal function are more sensitive to renal insults during LT.[1] In addition, VVB only partially diverts the blood from the cross-clamped IVC with partially restored RRP. Therefore, the protective effect of VVB for kidney may be partial as well. This selective protection may also contribute to our findings that VVB was only associated with significantly lower incidence of posttransplant AKI, but not renal replacement therapy in 30 days after LT. VVB requires priming the circuit, which has potential effect of hemodilution and lower postoperative serum Cr levels. We are not sure whether this hemodilution plays a significant role on low incidence of postoperative AKI in the VVB group because

Table 3. Comparison of Intraoperative Characteristics After Propensity Match (n = 442)

	Non–Venovenous Bypass (n = 221)	Venovenous Bypass (n = 221)	*P*
Cold ischemia time (min)	385 (305–489)	439 (318–552)	.007
Warm ischemia time (min)	40 (35–47)	42 (37–48)	.016
Surgery time (min)	288 (256–332)	289 (342–426)	<.001
Requirement of vasopressors (%)	62.1	75.2	.004
Red blood cell transfusion (unit)	13 (8–18)	19 (11–30)	<.001
Fresh frozen plasma transfusion (unit)	17 (10–24)	22 (15–34)	<.001
Postreperfusion syndrome (%)	13.6	27.2	.002

P values represent the results of Student *t* tests or χ^2 tests.

Table 4. Analysis of Intraoperative Risk Factors of Acute Kidney Injury in Patients With Compromised Pretransplant Renal Function (n = 242)

	Univariate Analysis		Multivariable Analysis	
Intraoperative Variable	Odds Ratio (95% Confidence Interval)	*P*	Odds Ratio (95% Confidence Interval)	*P*
Cold ischemia time	1.0 (0.9–1.0)	.547		
Warm ischemia time	1.0 (0.9–1.0)	.829		
Surgery time	1.0 (0.9–1.0)	.506		
Requirement of vasopressors	1.1 (0.6–1.9)	.708		
Postreperfusion syndrome	1.1 (0.5–2.3)	.760		
Transfusion of red blood cells	1.0 (0.9–1.0)	.013		
Transfusion of fresh frozen plasma	1.0 (0.9–1.0)	.024		
Use of intraoperative venovenous bypass	0.6 (0.3–0.9)	.033	0.1 (0.1–0.4)	.001

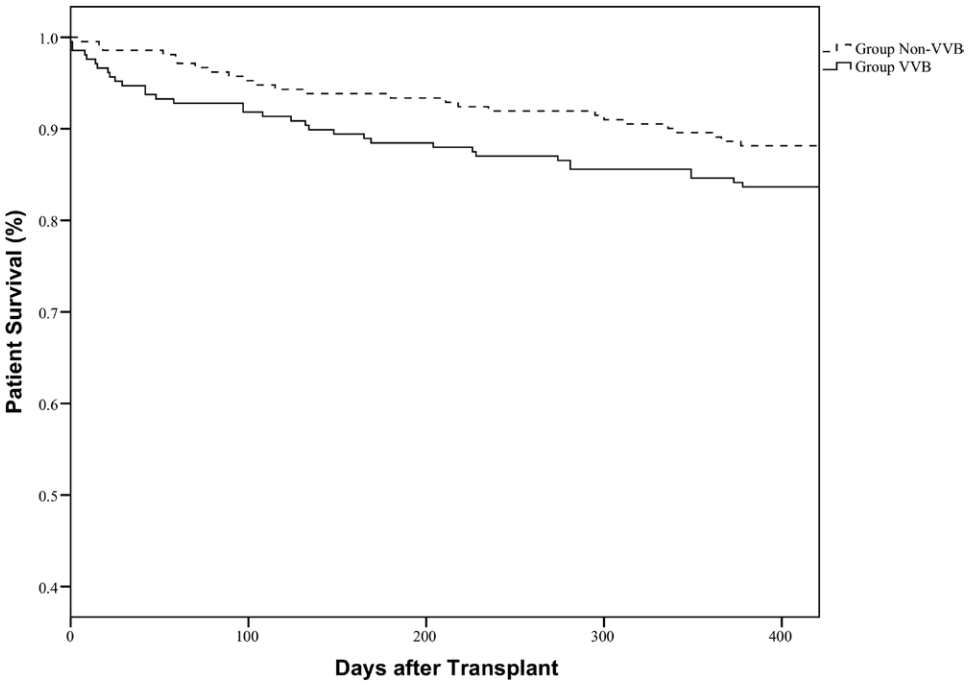

Figure 4. Kaplan–Meier survival analysis showed that 1-y mortality was not significantly different between the VVB and non-VVB groups in patients with compromised pretransplant renal function (n = 242). VVB indicates venovenous bypass.

effect of VVB renal protection remained after blood transfusion was controlled in a multivariable model. Finally, the selective protection is also reflected by the conflicting results in previous studies, where contrary results were often seen in different studies, when different methods, markers, and definitions were used, or the same markers were measured in different perioperative stages.[8]

The fact that the kidneys with normal pretransplant function (Cr <1.2 mg/dL) were not "protected" by VVB is interesting. First, the overall incidence of AKI was higher in patients with normal pretransplant renal function compared with compromised renal function in our study. Our findings seem contradictory to previous studies showing preoperative renal dysfunction is a risk factor for postoperative renal injury or failure. If renal injury is measured in a "late" or "permanent" term, preoperative renal dysfunction is an obvious risk factor. However, the AKIN definition requires the diagnosis of AKI in only 2 days. In addition, it heavily focuses on relative, not absolute, changes in Cr. Therefore, it is possible that under the AKIN definition, patients with relatively normal pretransplant renal function are at a higher risk of posttransplant AKI compared with those with

compromised pretransplant renal function.[21] Our hypothesis is supported by recent studies showing that the AKIN definition overestimates the incidence of AKI in patients with low baseline Cr and underestimate the incidence in patients with high baseline Cr.[22] The diagnosis using AKIN criteria has additional challenges in patients with chronic kidney disease and end-stage liver disease.[23,24] Many factors can affect baseline Cr levels in patients with end-stage liver disease. For example, ascites, fluid overload, and decreased muscle mass are very common in patients with end-stage liver disease and are associated with low Cr levels. Finally, VVB was selectively used in patients with more comorbidities including renal dysfunction. Although we used propensity to match patients with and without VVB, it remained possible that some cofounding factors were unmatched. These postulations can be answered only by prospective studies with randomized designs in the future.

Despite stabilizing hemodynamics and offering potential renal protection, the use of VVB is not without additional risks and costs. Performing VVB requires extra time and may increase the graft cold ischemia time that is associated with poorer graft function.[25] Furthermore, complications associated with VVB that have been reported include air emboli, thromboembolism, hypothermia, hematoma, lymphocele, and infection.[12,26] Because VVB is associated with risks and the benefit is seen only in selected patients, the use of VVB should not recommended for all patients. A decision of using VVB should be considered after benefits and risks are carefully evaluated.

The limitations of this study merit comments. As a retrospective study, it is subject to the usual inherent biases in such studies. Furthermore, the use of VVB was not standardized. Although we used robust propensity match and logistic regression to minimize the selection bias and the impact of confounding factors, potential bias or confounding by indication still remains. It is likely that the average treatment effect of the treated, not the average treatment effect, was estimated due to the match process. In this study, the urine output was not used. It is common that patients with liver disease are oliguric with avid sodium retention but maintain a relatively normal glomerular filtration rate, or have an increased urine output because of diuretic treatment. Therefore, it is widely accepted that the diagnosis of AKI in patients with liver diseases fully depends on the kinetic changes in serum Cr, as applied in our research.[2,17] Finally, the selection of VVB is center specific; therefore, generalization of our findings requires caution.

In conclusion, in this large retrospective study, we demonstrated that intraoperative VVB was associated with the significantly lower incidence of AKI in selected patients after LT. Further studies, preferably in randomized controlled designs, to assess the role of intraoperative VVB in posttransplant AKI, are warranted.

DISCLOSURES

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Contribution: This author helped provide substantial contribution to the design of the study, acquisition, analysis, and interpretation of data, drafting and revising the study, and final approval of the study to be published.
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