Association of Phlebotomy on Blood Product Transfusion Requirements During Liver Transplantation: An Observational Cohort Study on 1000 Cases

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INTRODUCTION

A significant decrease in blood loss and blood product requirements has been observed during orthotopic liver transplantation (OLT) during the past 2 decades. This achievement could be explained through the increasing experience, improvements in surgical and anesthetic techniques, and a better understanding of the various hemostatic abnormalities encountered during OLT.

Transfusion of blood products is associated with mortality and morbidity. To reduce bleeding and transfusion of blood products, one must understand the physiology and coagulation abnormalities associated with cirrhosis. Patients with cirrhosis and portal hypertension have an altered blood volume distribution. The cirrhotic liver causes a blood flow impediment in the portal vein and an increased secretion of compensatory vasoactive substances that increases splanchnic pooling.

METHODS

The present study evaluated the impact of phlebotomy on bleeding, transfusion rate, renal dysfunction, and mortality in 1000 consecutive OLTs. Two groups were defined and compared using phlebotomy. Multivariate logistic and linear regression models were used to determine predictors of bleeding, red blood cell (RBC) transfusion, renal dysfunction, and mortality. Results. A mean of 0.7 ± 1.5 RBC units was transfused per patient for 1000 OLTs, 75% did not receive any RBCs, and the median and interquartile range (25–75) were 0 for all blood products transfused. The phlebotomy was associated with decreased transfusion (RBCs, plasma, platelets, cryoprecipitate, albumin), with less bleeding, and with an increased survival rate, both 1 mo and 1 y. Phlebotomy was not associated with renal dysfunction. Conclusions. The practice of phlebotomy to lower portal venous pressure was associated with reduced blood product transfusions and blood loss during liver dissection without deleterious effect on renal function.

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conventional strategy for optimizing cardiac output was limited to generous intravenous fluid administration (crystalloid, colloid, plasma)—to maintain arterial pressure and end-organ perfusion—during periods of caval compression and clamping. This approach has been increasingly questioned and replaced on the basis of our improved understanding of the physiology of end-stage liver disease. This hypothesis may partly explain the decreased need for blood transfusion when a low central venous pressure (CVP) is maintained. In our previous study, a low CVP was achieved by phlebotomy and adhering to restrictive fluid management before the anhepatic phase. The phlebotomy consisted of withdrawing blood from the introducer of the pulmonary artery catheter without any crystalloid or colloid volume replacement at the beginning of the case while CVP was monitored. Avoiding hemodilution led to a preservation of the coagulation factors level. Typically, because portal venous pressure cannot be measured reliably intraoperatively, CVP is often used as a surrogate measure. Fluid restriction to reduce portal congestion requires liberal use of vasopressors, and the concern of systemic—and especially renal—hypoperfusion is often raised; but, unfortunately, there are a limited amount of data available on this issue, and the published evidence is contradictory.

The primary outcome of this study was to confirm the short-term effect of the phlebotomy on blood product requirements in adult liver transplant recipients (on a larger scale than our previous 100 patients). The secondary objectives were to study the influence of phlebotomy on bleeding, renal dysfunction, and survival. Our hypothesis was that phlebotomy would decrease transfusion rate and blood loss and would be associated with an increased survival, potentially at the expense of renal function.

MATERIALS AND METHODS

Design
An observational cohort study was conducted on 1000 consecutive patients undergoing liver transplantation at the Centre hospitalier de l’Université de Montréal from October 2002 to May 2019 without any exclusion. This observational study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies. An informed and written consent was not necessary according to our review ethics board (REB#15.113).

Intraoperative Management
Coagulation disorders diagnosed from conventional tests were not treated preemptively with blood products in the absence of overt bleeding either before or at the time of transplantation. Such disorders were only treated if diffuse intraoperative nonsurgical bleeding was observed: plasma was transfused if the international normalized ratio (INR) value was >1.5 (at a dose of 10–15 mL/kg), platelets if platelet count was <30 × 10^9/L (at a dose of 1 apheresis of a pool of 5 units), and cryoprecipitate if fibrinogen was <2 g/L (at a dose of a pool of 5 units). Red blood cell (RBC) units were transfused when hemoglobin (Hb) concentration was between 60 and 70 g/L. The first 300 patients received aprotinin as an antifibrinolytic, and the last 700 received tranexamic acid (30 mg/kg as a bolus and 16 mg/kg/h as an infusion until graft reperfusion). All livers were procured from brain death donors. Anesthesiologists have attempted to lower CVP by about 33% using phlebotomy (7–10 mL/kg) and by restricting volume infusion or a combination of both techniques, as previously described. CVP was monitored from the pulmonary artery catheter. Criteria for phlebotomy were an Hb concentration >85 g/L and a normal renal function (baseline creatinine value ≤104 μmol/L). This technique was well described in previous reports. No venovenous bypass was used, and >96% of the transplantations were performed using a total vena cava replacement technique. Transesophageal sonography was not used except for very few cases, neither rotational thromboelastometry.

Data Collection, Exposures, and Outcomes
Baseline population characteristics, including baseline laboratory values, and intraoperative and postoperative data were prospectively collected with a standardized report form during and after each OLT. Collected intraoperative data included duration of surgery, baseline and prehepatic CVP, volume of fluid resuscitation, type of fluid used, volume of phlebotomy performed, blood products transfused, volume of cell saver reinfused, and intraoperative bleeding. Mortality at 1 mo and 1 y was collected. Renal dysfunction was evaluated with acute kidney injury (AKI) score (0 = increase creatinine <1.5 times from baseline, 1 = increase between 1.5 and 1.9 times from baseline, 2 = increase between 2.0 and 2.9 times from baseline, 3 = increase ≥3 times from baseline) at day 2 and 7 postoperatively. The incidence of continuous venovenous hemodialysis (CVVH) and hemodialysis was evaluated at day 7 (data were collected only for the last 486 OLTs, data retrieval for the first 514 OLTs was not possible because data were not numerized). The outcomes of interest were the quantity of blood products transfused intraoperatively (RBC, plasma, platelets, cryoprecipitate, and albumin) total blood lost (measured from the cell saver minus irrigating fluid plus sponges), mortality at 1 mo and 1 y, renal dysfunction (AKI at day 2 and 7), and incidence of CVVH and hemodialysis at day 7 from patients who benefited from phlebotomy and the ones who did not.

Statistical Analysis
Continuous variables are reported as means with standard deviations or medians with interquartile range for skewed distributions and discrete variables as proportions. Univariate mixed logistic regression models were used to assess the association of a total of 22 variables with (1) transfusion of ≥1 RBC units; (2) blood loss (binary using the median, 900 mL); (3) blood loss (continuous variable); (4) AKI at day 2 (binary, no = AKI score 0, yes = AKI score (1 + 2 + 3)); (5) AKI at day 7 (binary, no = AKI score 0, yes = AKI score (1 + 2 + 3)); (6) incidence of CVVH at day 7 (binary yes or no); (7) hemodialysis at day 7 (binary yes or no); and (8) mortality at 1 y (binary). For the analysis of renal dysfunction, patients who were already on CVVH or dialysis and the ones who had renal transplantation were excluded. Phlebotomy was considered as a binary variable: yes or no. A mixed logistic and linear multivariate model was used by incorporating the significant factors identified in the univariate analysis. Statistical analyses were performed using SPSS version 26.

RESULTS
A total of 1000 OLTs were performed on 908 patients during the study period (826 patients had 1 OLT, 72 had 2 OLTs, 10 had 3 OLTs). Five hundred thirty-six patients underwent phlebotomy, and 464 patients did not. In the phlebotomized group,
493 ± 200 mL was withdrawn with a minimum of 100 mL and a maximum of 1200 mL. Table 1 compares demographic and health characteristics for both groups. There were no demographic differences between the groups except for gender, and there were more men in the phlebotomy group (70% versus 62%, P = 0.007). The phlebotomy group was healthier in terms of baseline Hb, INR, platelet count, fibrinogen, creatinine, bilirubin score, model of end-stage liver disease–Na score, and percentage of hepatocellular carcinoma. The baseline CVP was the same for the groups but was lower in the phlebotomy group just before vena cava clamping (7.6 ± 3.4 versus 8.7 ± 4.4, P < 0.001). The mean intraoperative transfusion of RBC units for all 1000 cases was 0.7 ± 1.5. The median and the interquartile range (2.5–7.5) were 0 for all blood products transfused. A total of 74.6% of patients did not receive any RBC units. Patients who were transfused with RBC units received a mean of 2.6 ± 2.0 RBC units (median, 2 [1–3]). Table 2 depicts transfusion rate, bleeding, and survival for both groups. The phlebotomy group had less transfusion of crystalloid and all blood products (RBCs, plasma, platelet, cryoprecipitate, and albumin) and less bleeding (1109 ± 1076 versus 1700 ± 1709 mL, P < 0.001; median, 800 mL [500–1300] versus 1100 mL [700–2200]). Interestingly, the final Hb value was higher in the phlebotomy group (1063 ± 956 versus 1358 ± 1226 mL, P = 0.002) in the group that underwent phlebotomy than those who did not have phlebotomy (29.8%). Demographic values were the same for both groups. The group of phlebotomy was healthier in terms of baseline Hb, INR, and CTP score. The baseline CVP was the same but was lower at the time of clamping vena cava in the group phlebotomy. Blood losses were lower (1063 ± 956 versus 1358 ± 1226 mL, P = 0.002) in the group that underwent phlebotomy, and there was less transfusion of RBCs, plasma, and cryoprecipitate as well.

Of the patients who were candidates for phlebotomy (Table 4), Table 5 shows the sickest patients in terms of INR value and CTP score (according to the median). Again, transfusions of blood products and blood loss were less in the phlebotomy group.

Table 6 separates the phlebotomy group according to the volume of blood withdrawn using the median: 450 mL. Patients with a large volume of blood removed had decreased blood product transfusions and blood loss.

Table 3 demonstrates the evolution of the renal function between patients who had phlebotomy and the ones who did not. Creatinine values (baseline, day 2, and day 7) were higher in the no phlebotomy group. Also, we can see the proportion of patients in each category of AKI (0 to 3) at day 2 and 7 postoperatively. Patients who underwent phlebotomy needed less CVVH and conventional hemodialysis on day 2 and day 7.

Table 4 resumes baseline characteristics and perioperative variables for patients who were candidates for phlebotomy (baseline Hb ≥85 g/L and creatinine value ≤104 µmole/L). Of these 348 patients, 410 had phlebotomy (70.2%), and 174 did not have phlebotomy (29.8%). Demographic values were the same for both groups. The group of phlebotomy was healthier in terms of baseline Hb, INR, and CTP score. The baseline CVP was the same but was lower at the time of clamping vena cava in the group phlebotomy. Blood losses were lower (1063 ± 956 versus 1358 ± 1226 mL, P = 0.002) in the group that underwent phlebotomy, and there was less transfusion of RBCs, plasma, and cryoprecipitate as well.

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### Table 1

| Variables | Total (N=1000) | Phlebotomy (n=536) | No phlebotomy (n=464) | P |
|-----------|----------------|-------------------|-----------------------|---|
| **Baseline characteristics** | | | | |
| Gender (male) (%) | 66 | 70 | 62 | 0.007 |
| Age (y) | 51.9 ± 11.4 | 51.9 ± 11.0 | 52.1 ± 11.4 | 0.196 |
| Weight (kg) | 78 ± 18 | 78 ± 18 | 77 ± 18 | 0.021 |
| Height (cm) | 169 ± 9 | 170 ± 10 | 169 ± 9 | 0.122 |
| Preoperative hemoglobin (g/L) | 105 ± 24 | 114 ± 23 | 90 ± 18 | <0.001 |
| Preoperative INR value | 1.9 ± 1.0 | 1.6 ± 1.3 | 1.9 ± 0.9 | <0.001 |
| Preoperative platelet count (×10^9 pl/L) | 94 ± 61 | 98 ± 59 | 89 ± 64 | 0.019 |
| Preoperative fibrinogen (g/L) | 2.16 ± 1.26 | 2.33 ± 1.19 | 2.01 ± 1.30 | 0.009 |
| Preoperative creatinine (µmol/L) | 102 ± 73 | 91 ± 72 | 115 ± 73 | <0.001 |
| Preoperative bilirubin (µmol/L) | 126 ± 150 | 96 ± 116 | 169 ± 176 | <0.001 |
| CTP score | 9.9 ± 2.6 | 9.0 ± 2.5 | 10.6 ± 2.4 | <0.001 |
| MELD-Na score | 22.4 ± 8.5 | 20.4 ± 7.5 | 24.1 ± 8.0 | <0.001 |
| Retransplantation (REDO) (%) | 11 | 7 | 16 | <0.001 |
| HCC (%) | 12 | 16 | 8 | <0.001 |
| **Intraoperative variables** | | | | |
| CVP at the start of surgery (mm Hg) | 13.2 ± 4.9 | 12.9 ± 4.7 | 13.4 ± 5.1 | 0.112 |
| CVP before vena cava clamping (mm Hg) | 8.1 ± 3.9 | 7.6 ± 3.4 | 8.7 ± 4.4 | <0.001 |
| Threshold for RBC transfusion | 61 ± 11 | 61 ± 9 | 61 ± 11 | 0.985 |
| Length of surgery (min) | 248 ± 66 | 246 ± 64 | 251 ± 67 | 0.219 |
| Blood reinfused from cell saver (%) | 77 | 78 | 76 | 0.784 |
| **Intraoperative fluid management** | | | | |
| Intraoperative crystalloid (mL) | 4001 ± 1618 | 3851 ± 1509 | 4178 ± 1723 | 0.002 |
| Albumin 5% (mL) | 219 ± 728 | 154 ± 594 | 295 ± 853 | 0.002 |
| Synthetic colloid (mL) | 381 ± 403 | 387 ± 392 | 373 ± 415 | 0.598 |
| Intraoperative urine output (mL) | 414 ± 309 | 435 ± 293 | 401 ± 347 | 0.060 |

Continuous variables expressed as mean ± SD.
CTP, Child-Turcotte-Pugh; CVP, central venous pressure; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model of end-stage liver disease; RBC, red blood cell; REDO, 2 liver transplantations or more.
Table 2. Blood loss, transfusion, and mortality data per transplantation

| Variables                        | Total (N = 1000) | Phlebotomy (N = 536) | No phlebotomy (n = 464) | P     |
|----------------------------------|------------------|----------------------|-------------------------|-------|
| % without RBC transfusion        | 75               | 91                   | 53                      | <0.001|
| RBC transfusion (unit/pt)        | 0.7 ± 1.5        | 0.2 ± 1.0            | 1.3 ± 1.9               | <0.001|
| Final hemoglobin (g/L)           | 94 ± 20          | 100 ± 21             | 87 ± 17                 | <0.001|
| Plasma transfusion (unit/pt)     | 0.4 ± 1.6        | 0.1 ± 1.0            | 0.7 ± 2.0               | <0.001|
| Platelet transfusion (unit/pt)   | 0.3 ± 1.7        | 0.1 ± 1.1            | 0.6 ± 2.1               | <0.001|
| Cryoprecipitate transfusion (unit/pt) | 0.8 ± 2.9        | 0.4 ± 1.9            | 1.2 ± 3.7               | <0.001|
| Blood loss (mL)                  | 1382 ± 1434      | 1109 ± 1076          | 1700 ± 1709             | <0.001|
| Survival rate at 1 mo (%)        | 95.3             | 95.9                 | 94.8                    | 0.483 |
| Survival rate at 1 y (%)         | 87.6             | 91.3                 | 84.4                    | 0.008 |

Continuous variables expressed as mean ± SD. RBC, red blood cell.

Table 7 (A–F) shows logistic regression and multivariable analysis to find variables linked to the following: A, transfusion of ≥1 RBC units; B, bleeding of more than the median (900 mL); C, bleeding (as a continuous variable); D, AKI (1 + 2 + 3) at day 2; E, AKI (1 + 2 + 3) at day 7; and F, mortality at 1 y.

In Table 7, for A, 3 variables were linked to transfusion of ≥1 RBC units: baseline Hb, phlebotomy, and plasma transfusion. For each increase of 1 g/L of baseline Hb from the mean, the risk of transfusing at least 1 RBC decreased by 3.8%. When phlebotomy was performed, the risk decreased by 73%. The risk increased by 110% when plasma was transfused.

**FIGURE 1.** Percentage of patients by the number of RBCs transfused for groups with or without phlebotomy. Series 1: phlebotomy. Series 2: no phlebotomy. RBC, red blood cell.
### TABLE 3.
Evolution of the creatinine in postoperative and AKI

| Variables                        | Total (N = 1000) | Phlebotomy (N = 536) | No phlebotomy (n = 464) | P     |
|----------------------------------|------------------|----------------------|-------------------------|-------|
| Baseline creatinine (µmol/L)     | 102 ± 73         | 91 ± 72              | 115 ± 73                | <0.001|
| Creatinine value at day 2 (µmol/L) | 133 ± 72         | 121 ± 69             | 143 ± 74                | <0.001|
| AKI at day 2 (% of patients in each category) | 0 = 68.5%        | 0 = 69.4%            | 0 = 67.3%               |       |
|                                  | 1 = 13.1%        | 1 = 12.4%            | 1 = 14.0%               |       |
|                                  | 2 = 12.9%        | 2 = 12.6%            | 2 = 13.3%               |       |
|                                  | 3 = 5.5%         | 3 = 5.6%             | 3 = 5.3%                |       |
| Creatinine value at day 7 (µmol/L) | 106 ± 73         | 98 ± 70              | 115 ± 76                | <0.001|
| AKI at day 7 (% of patient in each category) | 0 = 84.1%        | 0 = 86.6%            | 0 = 81.3                |       |
|                                  | 1 = 6.5%         | 1 = 5.1              | 1 = 8.1                 |       |
|                                  | 2 = 5.8%         | 2 = 4.9              | 2 = 6.8                 |       |
|                                  | 3 = 3.6%         | 3 = 3.3              | 3 = 3.8                 |       |
| AKI (1 + 2 + 3) at day 2         | 32%              | 31%                  | 33%                     | 0.689 |
| AKI (1 + 2 + 3) at day 7         | 16%              | 13%                  | 19%                     | <0.001|
| CVVH within 7 d                 | 6%               | 3%                   | 9%                      | <0.001|
| Hemodialysis within 7 d         | 3%               | 1%                   | 6%                      | <0.001|

0 = increase creatinine <1.5 times from baseline
1 = increase creatinine between 1.5 and 1.9 times from baseline.
2 = increase creatinine between 2.0 and 2.9 times from baseline.
3 = increase creatinine ≥3.0 times from baseline.

AKI, acute kidney injury; CVVH, continuous venovenous hemodialysis.

### TABLE 4.
Baseline characteristics and perioperative variables for patients who had criteria to have a phlebotomy (Hb value ≥85 g/L and starting creatinine ≤104 µmole/L)

| Variables                        | Total (N = 584) | Phlebotomy (n = 410) | No phlebotomy (n = 174) | P     |
|----------------------------------|-----------------|----------------------|-------------------------|-------|
| Baseline characteristics          |                 |                      |                         |       |
| Gender (male) (%)                 | 67              | 69                   | 61                      | 0.077 |
| Age (y)                          | 51 ± 11         | 51 ± 11              | 52 ± 11                 | 0.255 |
| Weight (kg)                      | 78 ± 18         | 78 ± 18              | 76 ± 18                 | 0.116 |
| Height (cm)                      | 170 ± 9         | 170 ± 9              | 169 ± 9                 | 0.304 |
| Preoperative Hb (g/L)             | 117 ± 20        | 120 ± 20             | 107 ± 19                | <0.001|
| Preoperative INR value            | 1.9 ± 1.0       | 1.6 ± 1.3            | 1.9 ± 0.9               | <0.001|
| Preoperative platelet count (×10^12 pl/L) | 96 ± 61         | 99 ± 61              | 90 ± 61                 | 0.114 |
| Preoperative fibrinogen (g/L)     | 2.29 ± 1.30     | 2.38 ± 1.22          | 2.11 ± 1.30             | 0.124 |
| Preoperative creatinine (µmol/L)  | 71 ± 16         | 70 ± 16              | 72 ± 16                 | 0.410 |
| Preoperative bilirubin (µmol/L)   | 108 ± 129       | 106 ± 111            | 119 ± 160               | 0.061 |
| CTP score                         | 9.3 ± 2.5       | 7.5 ± 2.5            | 10.5 ± 2.6              | 0.049 |
| MELD-Na score                     | 20.5 ± 8.2      | 20.3 ± 7.9           | 20.9 ± 8.9              | 0.461 |
| Intraoperative variables         |                 |                      |                         |       |
| CVP at the start of surgery (mmHg) | 12.8 ± 4.6      | 12.8 ± 4.7           | 12.7 ± 4.5              | 0.712 |
| CVP before vena cava clamping (mmHg) | 7.8 ± 3.6      | 7.6 ± 3.4            | 8.3 ± 4.0               | 0.037 |
| Length of surgery (min)          | 245 ± 61        | 247 ± 63             | 241 ± 54                | 0.243 |
| Blood loss (mL)                  | 1151 ± 1051     | 1063 ± 956           | 1358 ± 1226             | 0.002 |
| Blood reinfused from cell saver (%) | 75              | 78                   | 69                      | 0.153 |
| Intraoperative fluid management   |                 |                      |                         |       |
| % without RBC transfusion        | 88              | 93                   | 75                      | <0.001|
| RBC transfusion (unit/pt)        | 0.3 ± 0.9       | 0.1 ± 0.7            | 0.6 ± 1.2               | <0.001|
| Final Hb value (g/L)             | 100 ± 20        | 102 ± 20             | 95 ± 19                 | <0.001|
| Plasma transfusion (unit/pt)     | 0.2 ± 0.8       | 0.1 ± 0.6            | 0.3 ± 1.1               | 0.001 |
| Platelet transfusion (unit/pt)   | 0.2 ± 1.2       | 0.1 ± 1.1            | 0.3 ± 1.5               | 0.195 |
| Cryoprecipitate transfusion (unit/pt) | 0.4 ± 1.9      | 0.3 ± 1.6            | 0.7 ± 2.6               | 0.030 |
| Intraoperative crystalloid (mL)   | 3917 ± 1419     | 3889 ± 1445          | 3984 ± 1356             | 0.456 |
|Albumin 5% (mL)                   | 196 ± 620       | 178 ± 663            | 241 ± 501               | 0.259 |
| Synthetic colloid (mL)           | 373 ± 392       | 365 ± 390            | 391 ± 398               | 0.482 |
| Intraoperative urine output (mL)  | 460 ± 304       | 459 ± 283            | 462 ± 351               | 0.901 |
| Survival rate at 1 mo (%)        | 99              | 99                   | 97                      | 0.645 |
| Survival rate at 1 y (%)         | 93              | 95                   | 86                      | 0.037 |

CTP, Child-Turcotte-Pugh; CVP, central venous pressure; Hb, hemoglobin; INR, international normalized ratio; MELD, model of end-stage liver disease; RBC, red blood cell.
### TABLE 5.
Baseline characteristics and perioperative variables for patients who had an Hb value ≥85 g/L, starting creatinine ≤104 µmole/L, INR >1.5, and CTP score >10

| Variables                               | Total (N = 156) | Phlebotomy (n = 92) | No phlebotomy (n = 64) | P     |
|-----------------------------------------|-----------------|---------------------|------------------------|-------|
| **Baseline characteristics**            |                 |                     |                        |       |
| Gender (male) (%)                       | 65              | 71                  | 58                     | 0.004 |
| Age (y)                                 | 50 ± 11         | 49 ± 12             | 52 ± 11                | 0.435 |
| Weight (kg)                             | 79 ± 19         | 85 ± 23             | 77 ± 16                | 0.187 |
| Height (cm)                             | 170 ± 9         | 170 ± 9             | 169 ± 9                | 0.328 |
| Preoperative Hb (g/L)                   | 107 ± 17        | 108 ± 15            | 98 ± 13                | 0.670 |
| Preoperative INR value                  | 2.4 ± 1.1       | 2.3 ± 1.1           | 2.4 ± 0.9              | 0.962 |
| Preoperative platelet count (×10^9/L)   | 81 ± 53         | 79 ± 63             | 82 ± 57                | 0.969 |
| Preoperative fibrinogen (g/L)           | 1.5 ± 0.9       | 1.4 ± 0.8           | 1.5 ± 1.1              | 0.206 |
| Preoperative creatinine (µmol/L)        | 70 ± 16         | 66 ± 17             | 73 ± 16                | 0.464 |
| Preoperative bilirubin (µmol/L)         | 196 ± 170       | 184 ± 128           | 198 ± 211              | 0.078 |
| CTP score                               | 12.0 ± 1.1      | 11.7 ± 1.2          | 12.1 ± 1.2             | 0.381 |
| MELD-Na score                           | 25 ± 7          | 24 ± 6              | 26 ± 7                 | 0.414 |
| **Intraoperative variables**            |                 |                     |                        |       |
| CVP at the start of surgery (mm Hg)     | 14.8 ± 5.2      | 15.2 ± 6.5          | 14.4 ± 5.1             | 0.712 |
| CVP before vena cava clamping (mm Hg)   | 9.1 ± 3.7       | 8.9 ± 2.8           | 10.1 ± 4.0             | 0.078 |
| Length of surgery (min)                 | 251 ± 61        | 253 ± 61            | 250 ± 63               | 0.716 |
| Blood loss (mL)                         | 1495 ± 1268     | 1143 ± 824          | 2363 ± 1908            | <0.001|
| Blood reintroduced from cell saver (%)  | 81              | 89                  | 74                     | <0.001|
| **Intraoperative fluid management**     |                 |                     |                        |       |
| % without RBC transfusion               | 76              | 94                  | 50                     | <0.001|
| RBC transfusion (unit/pt)               | 0.5 ± 1.1       | 0.1 ± 0.2           | 1.3 ± 1.6              | <0.001|
| Final Hb value (g/L)                    | 92 ± 16         | 92 ± 15             | 91 ± 17                | 0.419 |
| Plasma transfusion (unit/pt)            | 0.4 ± 1.2       | 0.1 ± 0.5           | 1.0 ± 2.0              | <0.001|
| Platelet transfusion (unit/pt)          | 0.2 ± 1.2       | 0.1 ± 1.1           | 0.3 ± 1.5              | 0.195 |
| Cryoprecipitate transfusion (unit/pt)   | 0.4 ± 1.9       | 0.3 ± 1.6           | 0.7 ± 2.6              | 0.030 |
| Intraoperative crystalloid (mL)         | 3960 ± 1492     | 3933 ± 1574         | 3992 ± 1379            | 0.614 |
| Albumin 5% (mL)                         | 202 ± 491       | 98 ± 317            | 363 ± 648              | <0.001|
| Synthetic colloid (mL)                  | 440 ± 438       | 448 ± 430           | 427 ± 451              | 0.779 |
| Intraoperative urine output (mL)        | 390 ± 293       | 382 ± 234           | 401 ± 365              | 0.153 |
| Survival rate at 1 mo (%)               | 97              | 98                  | 95                     | 0.081 |
| Survival rate at 1 y (%)                | 89              | 94                  | 81                     | <0.001|

CTP, Child-Turcotte-Pugh; CVP, central venous pressure; Hb, hemoglobin; INR, international normalized ratio; MELD, model of end-stage liver disease; RBC, red blood cell.

### TABLE 6.
Baseline characteristics and perioperative variables for patients who had a volume of phlebotomy higher or lower than the median (450 mL)

| Variables                               | Volume of phlebotomy <450 mL (256 patients) | Volume of phlebotomy ≥450 mL (279 patients) | P     |
|-----------------------------------------|---------------------------------------------|-------------------------------------------|-------|
| Starting Hb (g/L)                       | 114 ± 21                                    | 119 ± 21                                  | 0.607 |
| Starting INR value                      | 1.7 ± 0.9                                   | 1.6 ± 0.8                                 | 0.431 |
| Starting platelet count (×10^9/mL)      | 101 ± 64                                    | 96 ± 55                                   | 0.415 |
| Starting fibrinogen (g/L)               | 2.30 ± 1.14                                 | 2.41 ± 1.27                               | 0.563 |
| Starting bilirubin (µmol/L)             | 99 ± 111                                    | 100 ± 109                                 | 0.967 |
| CTP score                               | 9.4 ± 2.5                                   | 8.9 ± 2.4                                 | 0.020 |
| MELD-Na                                 | 21.0 ± 7.5                                  | 21.3 ± 8.6                                | 0.677 |
| Starting CVP, (mm Hg)                   | 13.6 ± 4.6                                  | 12.5 ± 4.7                                | 0.800 |
| CVP at clamping (mm Hg)                 | 8.0 ± 3.3                                   | 7.3 ± 3.5                                 | 0.638 |
| Blood loss (mL)                         | 1200 ± 1227                                 | 1025 ± 911                                | 0.034 |
| RBC transfused (unit/pt)                | 0.28 ± 1.04                                 | 0.15 ± 0.87                               | 0.003 |
| Plasma transfused (unit/pt)             | 0.22 ± 1.16                                 | 0.07 ± 0.77                               | 0.001 |
| Platelet transfused (unit/pt)           | 0.21 ± 1.35                                 | 0.05 ± 0.67                               | <0.001|
| Cryoprecipitate transfused (unit/pt)    | 0.60 ± 2.49                                 | 0.11 ± 0.94                               | <0.001|
| Final Hb value (g/L)                    | 98 ± 20                                     | 101 ± 21                                  | 0.396 |

CTP, Child-Turcotte-Pugh; CVP, central venous pressure; Hb, hemoglobin; INR, international normalized ratio; MELD, model of end-stage liver disease; RBC, red blood cell.
TABLE 7. Summary of the logistic and linear regression model and odds ratios

| Variables | Odds ratio | Lower  | Upper  | P    |
|-----------|------------|--------|--------|------|
| A: Transfusion ≥1 RBC units | Hb          | 0.962  | 0.942  | 0.980 | <0.001 |
|           | Phlebotomy  | 0.267  | 0.122  | 0.560 | <0.001 |
|           | Plasma      | 2.096  | 1.581  | 3.022 | 0.05   |
| B: Blood loss (binary) | Fibrinogen  | 0.892  | 0.542  | 0.872 | 0.002  |
|           | Creatinine  | 1.007  | 1.001  | 1.013 | 0.027  |
|           | Plasma      | 3.374  | 1.680  | 15.092| 0.016  |
| C: Blood loss (continuous) | Fibrinogen  | −193.145| −310.949| −75624| 0.001  |
|           | Bilirubin   | 1.492  | 0.527  | 2.456 | 0.03   |
|           | Baseline CVP| 27.849 | 1.274  | 54.424| 0.041  |
|           | INR         | 353.145| 151.472| 554.817| <0.001 |
| D: AKI (1 + 2 + 3) at day 2 | Creatinine  | 0.985  | 0.976  | 0.9922| <0.001 |
| E: AKI (1 + 2 + 3) at day 7 | Creatinine  | 0.978  | 0.970  | 0.986 | <0.001 |
| F: Mortality at 1 y | Phlebotomy  | −2.498 | −1.554 | −4.014| <0.001 |

AKI, acute kidney injury; CVP, central venous pressure; Hb, hemoglobin; INR, international normalized ratio; RBC, red blood cell.

DISCUSSION

Intravenous fluid loading may result in an increased blood loss because of an increased portal venous pressure and an increased splanchnic venous congestion while providing minimal or no support for cardiac output. In contrast, intravenous vasoconstrictors alter the splanchnic circulation and may decrease portal hyperemia and splanchnic venous congestion besides supporting arterial blood pressure. In addition, a restrictive intravenous fluid volume management during the dissection phase was proven to minimize venous congestion and reduce blood loss. A reduction of CVP and therefore portal pressure—can be helpful in minimizing surgical venous bleeding because of reduced engorgement of collateral vessels. Methods to lower CVP include phlebotomy.

Overall, patients who underwent phlebotomy as part of their intraoperative OLT care required fewer transfusions (RBCs, plasma, platelets, and cryoprecipitate) and had less blood loss than the patients who did not have phlebotomy. Additionally, the percentage of surgeries without RBC transfusion was higher, and the final Hb concentration was higher as well. Predictably, the CVP at the time of vena cava clamping was lower in the phlebotomy group. Most importantly, the survival rate after 1 year was also better.

Phlebotomy and intravenous fluid restriction are often accompanied by continuous infusion of vasopressors to maintain acceptable blood pressure during OLT surgery. Nonetheless, there is a concern about hypovolemia, hypotension, and vasopressors causing an ischemic renal insult. Schroeder and Kuo compared outcomes at 2 different transplant centers with contrasting OLT clinical protocols, involving low versus normal CVP. In this comparison, the low CVP center had lower transfusion rates; however, unfortunately, postoperative renal impairment, need for dialysis, and mortality within 30 days after surgery were all increased. In another study, Carrier et al looked at AKI after OLT on postoperative days 2 and 7. They did not find any association between the use of vasopressors and the incidence of postoperative AKI, and they concluded that the use of vasopressors might be beneficial in liver transplant patients to offset the negative hemodynamic effects of an imbalance in intravenous fluid management strategy.

Postoperative acute renal failure is a serious concern in OLT. The actual magnitude of this clinical problem is hard to know because of the different definitions and criteria being used in various studies (Risk Injury, Failure, Loss of Function, End-Stage Disease; Kidney Disease Improving Global Outcomes; Acute Kidney Injury Network). Serum creatinine is considered an “imperfect gold standard” for the diagnosis of AKI. Physiopathological classification of AKI includes prerenal and acute postrenal (obstruction) nephropathy and intrinsic acute kidney disease. In OLT, the incidence of AKI ranges from 8% to 94% in various data sets, and 8% to 17% of the patients receive renal replacement therapy. In our series, patients received vasopressin—a drug that is known to redistribute blood volume from the splanchnic to blood volume redistribution on a regular basis. Unfortunately, we do not have the exact quantity of the different vasopressors used in this series. Regression logistics in Table 7 (D and 6E) show the results of the variables linked to the incidence of AKI on postoperative days 2 and 7. The baseline creatinine value is the only variable we found linked to AKI (1 + 2 + 3). For the analysis of variables to the outcomes, CVVH and dialysis, both outcomes were combined. Sixteen patients were excluded from the analysis because they already were on CVVH or dialysis or had a kidney transplant at the same time of their OLT. With these exclusions and the first 514 OLTs, it was impossible to make a logistic regression; there were too few events (CVVH and dialysis). It is difficult to interpret the intergroup differences in terms of creatinine, incidence of AKI, use of CVVH, and need for dialysis. The phlebotomy group had a better (lower) baseline creatinine concentration, and this persisted through the periooperative period. Intraoperative hypotension—an AKI risk factor—was not studied specifically in this cohort. We concluded with certainty, however, that—based on our data set—phlebotomy does not seem to be linked to AKI, CVVH, or dialysis.

Blood loss was a secondary outcome in this study, and it was lower in the phlebotomy group. Notably, however, this group was healthier at baseline, including less abnormal laboratory values of coagulation-related parameters. With the logistic and linear regressions, phlebotomy was not linked to blood losses of ≥900 mL (binary) or blood losses analyzed as a continuous variable. This agrees with our previous report. Moreover, a technique aimed at reducing blood loss will prove
to be effective with surgeries with large blood loss that is not the case in our center. Phlebotomy was the only variable linked to postoperative survival at 1 y. These results confirm the previous reports where phlebotomy was associated with a decreased death rate of 30%, 58%, 61%, and 135%, 29–32

In addition, a retrospective study—including some members of our research group—found that phlebotomy was associated with less bleeding and fewer RBC units transfusions during liver resection.33 Our findings confirm their results, including that large volume phlebotomy (≥450 mL) was associated with less blood loss than smaller volume phlebotomy (Table 6). Phlebotomy is an effective medical intervention to decrease portal venous pressure21 that is best used as a part of a multipronged evidence-based clinical strategy for liver transplantation. In our cohort, the blood loss difference was 690 mL between the phlebotomy and the no phlebotomy groups. This difference was a significant factor in our transplant center where the typical blood loss is about 1500 mL, but it may be less relevant in other settings where the average blood loss is 5 to 10 L.

There are some limitations to this study. This is an observational study from a single center for a long time period with a low transfusion rate. Despite increased bleeding and transfusions over time, survival improved, probably because of improved patient care. This phenomenon was explained in a previous report.28 The kind and amount of vasopressors used peripheratively are not reported. Two kinds of antifibrinolytics were used in this series. The first 300 OLTs received aprotinin, and the last 700 received tranexamic acid. Contrary to what Mangano et al24 reported for cardiac surgery, the incidence of AKI at day 7 (postoperative) was the same, that is, 10%. In a previous article comparing aprotinin and tranexamic acid, we did not find any change in bleeding and transfusion rate.29 As mentioned earlier, this study is not a randomized controlled study. Use of the matching propensity score could have controlled this weakness, but a major determinant of feasibility of phlebotomy is the clinical impression of the anesthesiologist. This clinical impression is difficult to quantify, and we know that anesthesiologists all work differently. 3,4,28 A total of 584 patients underwent phlebotomy and the no phlebotomy groups. This difference was a significant factor in our transplant center where the typical blood loss is about 1500 mL, but it may be less relevant in other settings where the average blood loss is 5 to 10 L.

Table 5 shows the sickest patients in terms of INR (INR value and CTP score. The phlebotomy group had a decrease in blood product transfusion (RBC, plasma, platelets, cryoprecipitate) and blood loss and saw an improvement in 1-y survival. Additionally, our data indicate that these benefits did not come at the cost of impaired postoperative renal function. A prospective randomized trial is needed to further evaluate the effectiveness and safety during OLT. This study provides insight that might inform the design of such a trial.

CONCLUSIONS
In this series of 1000 consecutive OLTs, patients received a mean of 0.7 RBC units, and 75% of them did not receive any RBC transfusions. Patients who benefited from the phlebotomy had a decrease in blood product transfusion (RBC, plasma, platelets, cryoprecipitate) and blood loss and saw an improvement in 1-y survival. Additionally, our data indicate that these benefits did not come at the cost of impaired postoperative renal function. A prospective randomized trial is needed to further evaluate the effectiveness and safety during OLT. This study provides insight that might inform the design of such a trial.

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