Bloodless living donor liver transplantation
Risk factors, outcomes, and diagnostic predictors

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Abstract
Massive bleeding is often unavoidable during liver transplantation (LT). However, blood transfusions are associated with risks and should be avoided whenever possible. This study compares preoperative factors and outcomes between non-transfusion and transfusion groups to identify variables that could be used to predict bloodless surgery in living donor liver transplantation (LDLT) patients.

We conducted a retrospective study of 87 LDLT patients. The group of patients who did not require packed red blood cell (PRBC) transfusion (non-PRBC group, n = 44) was compared with those who did (PRBC group, n = 43). We compared risk factors, fluid management, and outcomes between the groups and identified variables for prediction of transfusion during LDLT.

Compared with the PRBC group, the non-PRBC group had a lower model for end-stage liver disease (MELD) score (8.1 ± 1.1 vs 18.2 ± 8.8), international normalized ratio (INR) (1.16 ± 0.1 vs 1.80 ± 0.94), and partial thromboplastin time (PTT) (37.1 ± 6.3 vs 54.1 ± 24.0), but higher hemoglobin (Hb) (13.6 ± 1.6 vs 11.5 ± 2.2) and hematocrit (HCT) (39.1 ± 4.4 vs 32.6 ± 6.0). The non-PRBC group were more likely to receive colloid and albumin but had shorter intensive care unit (ICU) and hospital length of stay. The area under the receiver operating characteristic (ROC) curve of the MELD score was the highest (91%) using a cutoff value of 10.5.

Patients without PRBC transfusion during LDLT were in better condition preoperatively and had better outcomes. The MELD score is a significant predictor for PRBC transfusion.

Abbreviations: BIS = bispectral index, DDLT = deceased living donor liver transplantation, ECG = electrocardiography, Hb = hemoglobin, HCT = hematocrit, ICU = intensive care unit, INR = international normalized ratio, LDLT = living donor liver transplantation, LT = liver transplantation, MELD = Model for End-Stage Liver Disease, PRBC = packed red blood cell, PTT = partial thromboplastin time, ROC = receiver operating characteristic, TB = total bilirubin.

Keywords: blood transfusion, liver transplantation, living donor, predictor, red blood cell, risk factor

1. Introduction
The requirement for blood transfusion during liver transplantation (LT) following massive bleeding has been of significant concern since LT was first performed by Starzl et al in 1963. In addition to the risks posed by bleeding itself, patients requiring transfusion have more septic episodes, worse graft survival, and longer intensive care unit (ICU) and hospital stays.\textsuperscript{[1]} Transfusion itself is associated with a variety of complications: hemolytic and allergic reactions, transfusion-related acute lung injury, risk of infection, graft versus host disease, and immune sensitization.

Several studies have described anesthetic and surgical techniques that can be used to reduce the need for transfusion.\textsuperscript{[3–4]} However, bloodless LT remains uncommon and minimizing the need for blood transfusion during transplantation is an ongoing challenge.

Previous reports have identified a number of preoperative variables associated with increased risk of intraoperative hemorrhage during deceased donor liver transplantation (DDLT) and a consequent requirement for blood transfusion, including primary diagnosis, preoperative coagulation test results, and biochemical parameters.\textsuperscript{[5–7]} In contrast, no study has evaluated factors associated with requirements for blood transfusion during living donor liver transplantation (LDLT). Therefore, we investigated patients’ clinical and laboratory factors, outcomes, and diagnostic predictors associated with the need for blood transfusion in LDLT.

This study has 2 aims: first, to compare clinical factors and outcomes between LDLT patients who underwent PRBC transfusion and those who did not; and second, to determine factors that can be used to predict bloodless LDLT.

2. Methods
With the approval of the institutional review board of Pusan National University Yangsan Hospital (ID 05–2015-097), we retrospectively reviewed data from clinical records of 87 patients who underwent LDLT at Pusan National University Yangsan Hospital during a 3-year period from December 14, 2011 to December 23, 2014.
Table 1
Preoperative demographics and risk factors.

| Age (yr)     | Non-PRBC group (n = 44) | PRBC group (n = 43) | P value |
|--------------|-------------------------|---------------------|---------|
| 53.3 ± 5.4   | 50.5 ± 11.7             | .077                |
| 37.7 (70/16) | 29.14 (67/33)           | .070                |
| 8.1 ± 1.1*   | 18.2 ± 8.8              | < .001              |
| 12 (28)      | 92 (20)                 | .574                |
| 13.6 ± 6.2   | 32.6 ± 6.0              | < .001              |
| 9.0 ± 4.4*   | 91.9 ± 68.8             | .257                |
| 1.16 ± 0.7   | 1.8 ± 0.94              | < .001              |
| 37.1 ± 6.3*  | 54.1 ± 24.0             | < .001              |
| Serum creatinine (mg/dL) | 0.87 ± 0.4             | 0.78 ± 0.2 | .066 |

All measured values are presented as mean ± standard deviation or numbers of patients (%).

PRBC = packed red blood cells, MELD = model for end-stage liver disease, INR = international normalized ratio of prothrombin time, PTT = partial thromboplastin time.

2.1. Statistical analysis

Statistical calculations were performed using SPSS 13.0 (IBM Corp., Armonk, New York, USA). Categorical variables were analyzed using Pearson Chi-squared test. Parametrically distributed data were compared using unpaired Student t tests and non-parametrically distributed data were compared using the Mann–Whitney U test. A P value of less than .05 was defined as significant. The discriminatory power of preoperative risk factors for predicting a requirement for transfusion was assessed by the area under the receiver operating characteristic (ROC) curve. To identify variables that could predict the need for PRBC transfusion, a multiple logistic regression model was used.

3. Results

3.1. Preoperative risk factors

Preoperative patient demographics and clinical and laboratory variables for the entire group and the non-PRBC and PRBC groups are listed in Table 1. The non-PRBC group had a lower preoperative MELD score (8.1 ± 1.1 vs 18.2 ± 8.8), INR (1.16 ± 0.1 vs 1.8 ± 0.94), and PTT (37.1 ± 6.3 vs 54.1 ± 24.0), but higher Hb (13.6 ± 1.6 vs 11.5 ± 2.2) and HCT (39.1 ± 4.4 vs 32.6 ± 6.0) compared with the PRBC group.

3.2. Intraoperative fluid management

A mean of 3.5 units (± 5.5 units) of PRBCs were transfused across the whole group. Forty-four patients (51%) did not receive PRBCs; the remaining 43 patients received a mean of 7.1 units (± 6.0 units) of PRBCs. However, the non-PRBC group received greater amounts of colloid and albumin (Table 2).

3.3. Influence of PRBC transfusion on patient outcome

The PRBC group had an increased requirement for ICU care (P < .001) and an increased duration of hospital stay (P < .001). There were no statistically significant differences observed between the non-PRBC group and PRBC group for other patient outcomes (Table 3).

3.4. Factors predicting the need for PRBC transfusion

Among the preoperative risk factors, the MELD score, Hb, HCT, and INR had discriminatory power between the non-PRBC and
PRBC groups using ROC curve analysis. For the MELD score, the area under the ROC curve was the highest (91%) using a cutoff value of 10.5 (Fig. 1, Table 4). In the multiple logistic regression analysis with forward selection, the variables included in the final predictive model were MELD score, platelet count, sex, and creatinine. However, only the MELD score was found to be a statistically significant predictor of PRBC transfusion \((P < .001)\) (Table 5).

### Table 2

|                          | Entire group (n = 87) | Non-PRBC group (n = 44) | PRBC group (n = 43) | \(P\) value |
|--------------------------|-----------------------|-------------------------|---------------------|-------------|
| PRBC (units)             | 3.5 ± 5.5             | 0 *                    | 7.1 ± 6.0           | < .001      |
| FFP (units)              | 3.1 ± 4.7             | 0 *                    | 6.3 ± 4.9           | < .001      |
| Platelet (pheresis, units) | 1.4 ± 3.3            | 0 *                    | 2.7 ± 4.2           | < .001      |
| Colloid (mL)             | 195.4 ± 298.8         | 272.7 ± 331.6 *        | 116.3 ± 240         | .0138       |
| Albumin (20%, mL)        | 327.8 ± 224.2         | 234.1 ± 155.4 *        | 423.7 ± 244         | < .001      |

All measured values are presented as mean ± standard deviation.

* \(P < .05\) compared with the PRBC group.

### Table 3

|                          | Entire group (n = 87) | Non-PRBC group (n = 44) | PRBC group (n = 43) | \(P\) value |
|--------------------------|-----------------------|-------------------------|---------------------|-------------|
| ICU stay (days)          | 9.6 ± 6.7             | 7.3 ± 5.2 *             | 12.0 ± 8.4          | < .001      |
| Hospital stay (days)     | 31.6 ± 21.6           | 27.5 ± 14.7 *           | 35.8 ± 26.4         | < .001      |
| Postoperative mortality  | 4 (4.6)               | 0 (0)                   | 4 (9.3)             | .1305       |
| Postoperative surgical procedures |          |                        |                     |             |
| Re-procedure             | 6 (6.9)               | 1 (2.3)                 | 5 (11.6)            | .2149       |
| Bleeding control         | 9 (10.3)              | 4 (9.0)                 | 5 (11.6)            | 1           |

All measured values are presented as mean ± standard deviation.

ICU = intensive care unit, PRBC = packed red blood cell.

* \(P < .05\) compared with the PRBC group.

### Figure 1

Area under the receiver operating characteristic curve was used to identify the discriminatory power between the two groups. Hb = hemoglobin, HCT = hematocrit, INR = international normalized ratio of prothrombin time, MELD = model for end-stage liver disease.

4. Discussion

This study demonstrated a remarkable rate of bloodless LDLT (50.6%) achieved through the coordinated efforts of the anesthesiologist and surgeon over the last 3 years. We had well-defined criteria for PRBC transfusion and strictly adhered to them. Our PRBC transfusion criteria were not associated with adverse effects.
This retrospective study was conducted to analyze outcomes associated with a high rate of bloodless LDLT in patients undergoing LDLT. In addition, this study may have important implications as previous studies have analyzed factors associated with PRBC transfusion during DDLT, rather than LDLT.[9,10]

In an analysis of preoperative factors associated with the need for PRBC transfusion, we found that patients in the non-PRBC group were in a better condition preoperatively than those in the PRBC group, similar to results from other studies.[4,11] The non-PRBC group had a decreased requirement for ICU care and hospitalization. A limitation of this study is that we could not demonstrate the independent effects of PRBC transfusion on patient outcome.

Several reports[3,4] emphasize the difficulties in identifying generally applicable preoperative factors that can reliably predict the need for PRBC transfusion during LDLT. The results of these studies may be influenced by variability in surgical procedures and anesthetic protocols. In contrast, in our study of LDLT, the patients received the same anesthetic management and surgical treatment.

One of the main purposes of our study was to identify predictive preoperative factors for bloodless LDLT using strict PRBC transfusion criteria. First, our findings using ROC curve analysis suggested a positive point that can be used as a standard to determine the need for PRBC transfusion (MELD score, Hb, HCT and PTT/INR) (Fig. 1). Second, we demonstrated that the MELD score is a powerful predictive factor for PRBC transfusion during DDLT, rather than LDLT. In conclusion, patients in the non-PRBC group were in a better condition preoperatively. A requirement for PRBC transfusion was associated with an increased need for ICU care and longer hospital stays. We also found that the MELD score was a significant predictive factor of the requirement for PRBC transfusion. This study has important limitations; however, most of these stems from the selection of preoperative clinical variables and the small sample size. For effective clinical recommendation to be made based on the results of study, future studies should be performed that include larger samples and a greater number of risk factors.

The aim of the present study was to compare factors between patients treated with and without PRBC transfusion, and to identify significant predictors associated with requirements for PRBC transfusion, in patients treated using well-defined criteria for transfusion.

In conclusion, patients in the non-PRBC group were in a better condition preoperatively. A requirement for PRBC transfusion was associated with an increased need for ICU care and longer hospital stays. We also found that the MELD score was a significant predictive factor of the requirement for PRBC transfusion. Many studies report that blood transfusion can cause serious complications.[13] Reducing the need for blood transfusion is important in LDLT patients, who often have unstable hemodynamics and an imbalance in electrolytes during the operation. We were able to avoid PRBC transfusion in 50% of LDLT patients using strict criteria for PRBC transfusion. We hope that our findings are useful to other physicians who plan to attempt bloodless LDLT. Further large studies should be performed at multiple organizations, based on the findings of this study, to attempt to reduce blood transfusions during LT.

### Author contributions

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### Table 4

| Cut off value | Specificity | Sensitivity |
|--------------|-------------|-------------|
| MELD score   | 10.5        | 100.0       | 76.7        |
| Hb           | 11.5        | 93.2        | 58.1        |
| Hct          | 36.6        | 77.3        | 74.4        |
| INR          | 1.31        | 97.7        | 79.1        |

### Table 5

Results of logistic regression analysis with forward selection to detect predictors.

| Estimate  | Standard Error | Odds ratio | P value | MELD score | Platelet | Sex (based on a men) | Creatinine |
|-----------|----------------|------------|---------|------------|----------|---------------------|------------|
| 1.173     | 0.322          | 3.232      | <.001   |            |          | –2.050              | 2.267      |
| 0.014     | 0.008          | 1.014      | .072    |            |          |                     |            |
|           |                |            |         | –2.050     |          |                     |            |

MELD = model for end-stage liver disease score.
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