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Factors associated with the need for intraoperative packed red cells transfusion in pediatric liver transplant patients

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ABSTRACT

Background: Massive hemorrhage is one of the most common problems encountered during a liver transplantation procedure. Correction of the blood loss using packed red cells (PRC) is essential during the procedure to improve outcome. This retrospective study aims to investigate preoperative and intraoperative factors that may predict the PRC need.

Materials and methods: Thirty-four patients who underwent pediatric liver transplantation procedure within 2010-2018 were included in this study. Their medical record was examined and the data was analyzed using a comparison of mean and regression model.

Results: The mean bleeding in this study was found to be 906.62±674.30 mL, while the mean PRC transfusion was 566.71±307.30 mL. Correction of blood loss was also compensated with other means such as a crystalloid or colloid fluid.

Conclusion: This study statistically demonstrated that pre-operative weight, as well as bleeding volume, significantly affect the PRC transfusion requirement (p <0.05). However, other factors such as hemoglobin and surgical duration may also be clinically significant factors to predict PRC transfusion need.

Keywords: *liver transplantation, pediatric, predictor, transfusion, packed red cells*

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INTRODUCTION

The first liver transplantation procedure was done by Thomas Starzl in the University of Colorado in 1963[1] and has become the therapeutic modality for end-stage liver disease. In Indonesia, liver transplantation was first introduced in 2010. One of the major problem during liver transplantation is intraoperative massive bleeding.[2]

Rigorous hemodynamic monitoring and timely administration of blood products are essential to improve surgical outcome.[3] Intraoperative administration of packed red cells (PRC) often predicts postoperative mortality. However, it is unclear whether the post-operative mortality is attributed to worse patients' baseline condition, more complex surgical procedure, or immunomodulation effects of blood transfusion.[4] For these reasons, efforts to control bleeding and predict the amount of PRC needed have become a cornerstone in perioperative patient management of liver transplantation.

Pediatric patients possess difference physiologic characteristics compared to adult patients where a small amount of blood loss can produce significant hemodynamic changes. Impaired liver function will only further complicate these problems.[3] Previous studies have identified predicting factors to the intraoperative need for PRC transfusion in liver transplantation such as body weight and height, physical status, previous surgery, preoperative hemoglobin and thrombocyte, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), albumin, and pediatric end-stage liver disease (PELD) score.[5,6] However, pediatric liver transplant patients may have different characteristics. This study aims to identify factors associated with the need for intraoperative PRC transfusion in pediatric patients undergoing liver transplantation in Cipto Mangunkusumo Hospital.

MATERIALS AND METHODS

This is a retrospective study taken from the medical records of pediatric patients (0-18 years of age) underwent liver transplantation in Cipto Mangunkusumo Hospital between 2010 and 2018. All patients who qualified for inclusion and exclusion criteria were enrolled in this study. The study protocol was approved by the Health Research Ethics Committee of the University of Indonesia.

Patients who died intraoperatively and patients with the incomplete medical record were excluded from the analysis. The need for intraoperative PRC transfusion was divided into 3 groups: low (<40 mL/kg), moderate (40-60 mL/kg), and high (>60 mL/kg). Variables analyzed for the need for intraoperative PRC transfusion are listed in Table 1.

Data were tabulated and analyzed using Statistical Package for Social Sciences (SPSS) version 21.0.

Table 1 List of independent variables

Demographical data	Laboratory data	Calculated data	Intraoperative dada
Age (month)	Preoperative hemoglobin	PELD[a]	Bleeding volume
Gender	Preoperative thrombocyte		Surgery duration
Etiology of liver transplantation	Preoperative PT/aPTT		
History of bleeding	Preoperative INR		
Body Weight (kg)	Preoperative albumin		
Body Height (cm)			

PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; PELD: pediatric end-stage liver disease
[a]PELD score was calculated using the PELD calculator from the United Network of Organ Sharing (UNOS).

Table 2 Demographical data of the subjects

Variables	Results
Age (month), mean±SD	18.59 ± 13.04
Body weight (kg), mean±SD	9.01 ± 2.12
Body height (cm), mean±SD	73.51 ± 7.50
Gender	
Male, n(%)	18 (53)
Female. n(%)	16 (47)
Transplantation etiology	
Extrahepatic, n(%)	18 (53)
Intrahepatic, n(%)	16 (47)
History of previous bleeding (%)	0
History of malnutrition	
Yes, n(%)	13
No, n(%)	21
Preoperative data	
Hemoglobin (g/dL), mean±SD	8.93 ± 1.04
Thrombocyte (cells/μL), mean±SD	164,500 ± 76,114
Albumin (g/dL), mean±SD	2.97 ± 0.44
Total Bilirubin (mg/dL), mean±SD	17.80 ± 9.43
PT, mean±SD	1.19 ± 0.20
aPTT, mean±SD	1.47 ± 0.28
INR, mean±SD	1.25 ± 0.20
PELD Score, mean±SD	14.24 ± 6.33
Intraoperative data	
Surgical duration (minutes), mean±SD	696.38 ± 110.60
Bleeding volume (mL), mean±SD	906.62 ± 674.30
PRC transfused (mL), mean±SD	566.71 ± 307.30
PRC transfusion profile	
Low, n(%)	17 (50)
Moderate, n(%)	8 (23.5)
High, n(%)	9 (26.5)

PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; PELD: pediatric end-stage liver disease; SD: standard deviation; PRC: packed red cells

Kruskal-Wallis and Mann-Whitney tests were used to analyze numerical data. Chi-square test was used to compare categorical data. A p-value of <0.05 was considered significant.

RESULTS

As many as 34 pediatric patients in Cipto Mangunkusumo Hospital undergoing liver transplant from 2010-2018 were enrolled in this study. The mean age of pediatric liver transplantation patients was 18.59±13.04 years. Most of the patients were male (53%) and stunted (62%). None had a previous history of bleeding.

The most common cause of liver transplantation is extrahepatic biliary atresia (50%), followed by liver cirrhosis (35.3%). Other etiologies for liver transplantation include Allagile syndrome, Budd-Chiari syndrome, Caroli disease, and choledochal duct cyst. The demographic data of all subjects are displayed in Table 2.

A non-parametric comparison of the transfusion requirement for each independent variables was described in Table 3. Patients with high transfusion requirement (>60 mL/kg BW) have higher bleeding volume compared to patients with low and moderate transfusion requirement (p <0.05).

An ordinal regression model was conducted to predict factors that may affect transfusion requirement (Table 4). This model resulted in four variables that potentially affect transfusion requirement (p <0.05) i.e. age, weight, duration of surgery and bleeding volumes. The four variables were used to construct a multivariate analysis model in Table 5.

The multivariate analysis model in Table 5 demonstrated that weight and bleeding volume were significant predictors to transfusion requirement. A higher body weight predicted less transfusion requirement while higher bleeding volume predicted higher transfusion requirement.

DISCUSSION

This study demonstrated that the mean anthropometric data for pediatric liver transplantation were 18.59 months, with 9.01 kg in weight, and 73.51 cm in height. These findings were consistent with previous studies were most pediatric liver transplantation patients were aged <2 years old.[7-9] The main indications for liver transplantation in pediatric patients are cholestatic diseases, mainly biliary atresia.[8,9]

According to the European Liver Transplant Registry, 74% of recipients under 2 years of age and more than 40% of older children had cholestasis. A substantial percentage of these patients were malnourished (28%), signifying the severity of the

Table 3 Comparison of the means of variables affecting transfusion requirement

Independent variables	Transfusion requirement	Mean	SD	*Chi-square*	p-value[a]
Age	Low	28.12	16.30	4.844	0.89
	Moderate	14.34	2.92		
	High	16.35	13.00		
Weight	Low	10.87	2.41	6.521	0.39
	Moderate	8.20	1.14		
	High	8.56	1.94		
Height	Low	78.00	8.00	3.684	0.159
	Moderate	72.72	5.72		
	High	71.82	7.63		
Hemoglobin	Low	9.25	0.84	0.884	0.643
	Moderate	8.76	0.90		
	High	8.88	1.20		
Thrombocyte	Low	160,000	79,844	0.828	0.661
	Moderate	158,111	84,451		
	High	170,000	74,353		
PT	Low	1.13	0.17	1.509	0.470
	Moderate	1.17	0.22		
	High	1.22	0.20		
aPTT	Low	1.56	0.17	1.128	0.569
	Moderate	1.41	0.33		
	High transfusion	1.46	0.27		
INR	Low	1.19	0.18	1.853	0.396
	Moderate	1.22	0.21		
	High	1.20	0.21		
Albumin	Low	3.03	0.22	1.764	0.414
	Moderate	2.80	0.33		
	High	3.02	0.54		
PELD score	Low	13.62	5.97	0.306	0.858
	Moderate	15.22	4.84		
	High	14.00	7.39		
Surgery duration	Low	623.86	89.35	6.741	0.34
	Moderate	675.56	59.40		
	High	741.53	122.20		
Bleeding volume	Low	543.75	275.73	10.410	0.005
	Moderate	536.11	287.03		
	High	1273.53	759.75		

PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; PELD: pediatric end-stage liver disease; SD: standard deviation; PRC: packed red cells; [a]Kruskal-Wallis test

underlying disease that warrants liver transplantation. The clinical complications of malnutrition in children with chronic liver disease caused by cholestasis are very wide and include growth failure, rickets, bleeding, and life-threatening infections. Malnutrition is also shown as one of the main factors hats negatively affects affecting survival, and growth after transplant.[7] Our study showed that patients with moderate transplant requirement have higher mean of body weight at 10.87 kg compared to patients with high transplant requirement at 8.56 kg prompting that nutritional status may have some effect in predicting transfusion requirement. Although statistical test failed to show significance,

Table 4 Univariate analysis of independent variables affecting transfusion requirement

Independent variables	Estimated correlation coefficient (95% CI)	p-value
Age	-0.570 (-0.114-0.000)	0.049
Weight	-0.408 (-0.753-(-0.062))	0.021
Height	-0.088 (-0.179-0.004)	0.060
Hemoglobin	-0.208 (-0.832-0.417)	0.515
Thrombocyte	1.647 x10-6(-6.91x10-6–1.021x10-5)	0.706
PT	1.907 (-1.579-5.393)	0.284
aPTT	-0.685 (-3.037-1.668)	0.569
INR	2.520 (-0.983-6024)	0.159
Albumin	0.262 (-1.222-1.754)	0.729
PELD Score	-0.002 (-0.103-0.100)	0.973
Duration of surgery	0.013 (0.003-0.024)	0.010
Bleeding volume	0.003 (0.001-0.005)	0.007
Gender		
Male	15.211 (-2.837-33.259)	0.288
Female	-	
Malnourished		
No	0.482 (-0.822-1.786)	0.469
Yes	-	

PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; PELD: pediatric end-stage liver disease; SD: standard deviation; PRC: packed red cells; CI: Confidence Interval

Table 5 Multivariate analysis model using ordinal regression

Independent variables	Estimated correlation coefficient (95% CI)	p-value
Age	0.000 (-0.112-0.112)	0.998
Weight	-1.003 (-1.810-(-0.195)	0.015
Duration of surgery	0.011 (-0.000-0.23)	0.072
Bleeding volume	0.005 (0.002-0.009)	0.003

CI: Confidence Interval

this difference can be considered clinically significant for children under 2 years of age.

Massive bleeding is defined as the loss of more than 50% of blood volume in the first 3 hours of surgery. Pediatric population is especially vulnerable to massive bleeding due to an immature hemostatic mechanism such as low coagulant and procoagulant concentration as well as relatively dysfunctional fibrinogen.[10] This study demonstrated that massive bleeding occurred in 31 out of 34 cases (91%).

This result demonstrated that liver transplant is a complex procedure with a substantial bleeding risk that may affect surgical outcome. Blood transfusion is associated with severe complications such as hypothermia, abnormalities in electrolytes, immunological complications, coagulopathy, transfusion reaction, and postoperative mortality.[11] Monitoring of bleeding in pediatric patients becomes problematic due to the ability of pediatric patients to physiologically compensate for arterial blood pressure after 25-40% blood loss. For this reason, signs and symptoms of hypovolemia cannot be used as a predictor of early blood loss.[10] Nacoti, *et al*. reported that bleeding volume and allogeneic red cell transfusion affected patient and transplant outcome.[12]

It is also interesting to note that there was a discrepancy in the bleeding volume and the transfused PRC volume reported in this study. The mean bleeding volume was 906.652 ± 674.30 mL while the mean PRC transfusion was 566.71 ± 674.30 mL. This finding may be attributed to the relatively low mean preoperative hemoglobin that did not prompt aggressive transfusion. The use of other crystalloid or colloid fluid intraoperatively may also be attributed to this discrepancy. The method of predicting blood loss in the operating theatre by counting the gauze used and the blood pooled in the suction may also give rise to underestimation or overestimation of the blood loss.

Based on the need for PRC transfusion, most patients fell on the high (>60 mL/kg) transfusion requirement. Ulukaya, *et al.* stated that the mean PRC transfusion requirement from a living donor was 18.6 ± 19.1 mL/kg.[13] This difference may be attributed to the novelty of the liver transplant procedure in Cipto Mangunkusumo Hospital. The procedure has only been conducted for less than a decade with the frequency of 1-2 times in a month. A rigid transplantation selection criteria that were applied further limit the number of pediatric patients with chronic liver disease that were eligible to receive transplantation.

Patients with high transfusion requirement have a relatively longer duration of surgery (741.53 ± 122.20 minutes) compared to patients with moderate transfusion requirement (675.56 ± 59.40 minutes). The bleeding volume will increase as the surgery continues. Jin et al also demonstrated that preoperative hemoglobin and duration of surgery significantly differed between patients needing a massive transfusion and those needing a non-massive transfusion.[14]

The decision to do blood transfusion including PRC is made based on multiple considerations. Prediction of blood loss is one major factor in decision making. Intraoperative laboratory parameters may be used as guidance but may also hinder decision making due to the time lapse between blood drawing and the results.

This study demonstrated that body weight and bleeding volume significantly affect PRC transfusion. It should be noted that univariate and multivariate analysis with ordinal regression has low reliability with a small sample size. The previous study has described preoperative hemoglobin and duration of surgery were significantly associated with massive bleeding and fluid correction requirement for pediatric liver transplantation patient.[14]

This study observed that anthropometric parameter such as body weight, height, and malnutrition was not significantly associated with PRC transfusion requirement. Peripheral blood and coagulation profile such as hemoglobin, thrombocyte, PT/aPTT, INR, and albumin were not found statistically significant as well. The nature of the retrospective study left ample of opportunities for incomplete data.

CONCLUSION

This study concluded that there were significant differences in the means of bleeding volume between patients needing low, moderate, and high PRC transfusion. Preoperative body weight and bleeding volume were found to be significantly associated with PRC requirement.

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REFERENCES

1. Meirelles RFJ, Sevalaggio P, Rezende MB, *et al.* Liver transplantation: history, outcomes, and perspectives. *Einstein.* 2015; 13(1): 149-152. DOI: 10.1590/S1679-45082015RW3164
2. Groenland THN, Porte RJ, Metselaar HJ. Liver transplantation and risk of bleeding. *Curr Opin in Organ Transplantation.* 2007; 12(3): 287-293. DOI: 10.1097/MOT.0b013e32814e6bb0
3. Devi AS. Transfusion practice in orthotopic liver transplantation. *Indian J Crit Care Med.* 2009; 13(3): 120-128. DOI: 10.4103/0972-5229.58536
4. Rana A, Kaplan B, Jie T, *et al.* A critical analysis of early death after adult liver transplants. *Clin Transplant.* 2013; 27(4): E448-53. DOI: 10.1111/ctr.12186
5. Weismuller TJ, Fikatas P, Schmidt J, *et al.* Multicentric evaluation of a model for end-stage liver disease-based allocation and survival after liver transplantation in Germany—limitations of the 'sickest first'-concept. *Transpl Int.* 2011; 24: 91–99. DOI: 10.1111/j.1432-2277.2010.01161.x
6. Farmer DG, Vernick RS, McDiarmid SV, *et al.* Predictors of outcomes after pediatric liver transplantation: an analysis of more than 800 cases. *J Am Coll Surg.* 2007; 204(5): 904-14. DOI: 10.1016/j.jamcollsurg.2007.01.061
7. Pawlowska J. The importance of nutrition for pediatric liver transplant patients. *Clin Exp Hepatol.* 2016; 2(3): 105-108. DOI: 10.5114/ceh.2016.61665
8. Fieldman AG, Mack CL. Biliary atresia: clinical lessons learned. *J Ped Gastroenterol Nutrition.* 2015; 61(2): 167-175. DOI: 10.1097/MPG.0000000000000755
9. Jin SJ, Kim SK, Choi SS, *et al.* Risk factors for intraoperative massive transfusion in pediatric liver transplantation: a multivariate analysis. *Int J Med.* 2017; 14(2): 173-180. DOI:10.7150/ijms.17502
10. Blain S, Paterson N. Paediatric massive transfusion. *BJA Edu.* 2015; 18(8): 269-275. DOI: 10.1093/bjaed/mkv051
11. Turan A, Yang D, Bonilla A, *et al.* Morbidity and mortality after massive transfusion in patients undergoing non-cardiac surgery. *Can J Anaesth.* 2013; 60(8): 761-770. DOI: 10.1007/s12630-013-9937-3
12. Nacoti M, Cazzaniga S, Lorusso F, *et al.* The impact of perioperative transfusion of blood products on survival after pediatric liver transplantation. *Pediatr Transplantation.* 2012; 16: 357-366. DOI: 10.1111/j.1399-3046.2012.01674.x
13. Ulukaya S, Acar L, Ayanoglu HO. Transfusion requirements during cadaveric and living donor pediatric liver transplantation. *Pediatr Transplantation.* 2005; 9: 332-337. DOI: 10.1111/j.1399-3046.2005.00284.x
14. Jin SJ, Kim SK, Choi SS, *et al.* Risk factors for intraoperative massive transfusion in pediatric liver transplantation: a multivariate analysis. *Int J Med.* 2017; 14(2): 173-180. DOI: 10.7150/ijms.17502