The Association between Red Blood Cell Transfusion and Hospital Mortality in Critically Ill Surgical Patients: The Multi-center Thai University-Based Surgical Intensive Care Units Study (THAI-SICU Study)

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Objective: *Red blood cell transfusion (RBCT) is commonly prescribed to critically ill patients with anemia. Nevertheless, the benefits of RBCT in these patients, particularly critically ill surgical patients, are still controversial. The aim of this study is to explore the association between RBCT and hospital mortality in Thai critically ill surgical patients.*

Material and Method: *This study was a part of the multi-center, prospective, observational study, which included adult patients admitted to the SICUs after surgery. Patients were categorized into transfusion and no transfusion groups according to whether they received RBCT during SICU stay or not. The multiple logistic regression analysis was performed to determine whether RBCT was an independent risk factor for hospital mortality. The patients were also matched between two groups based on the propensity score for RBCT requirement and were then compared.*

Results: *There were 2,531 patients included in this study. The incidence of RBCT in SICU was 40.3%. Overall, there was no association between RBCT in SICU and hospital mortality (adjusted OR 1.33, 95% CI 0.83-2.11) except in the subgroup of patients with age of ≤65 years old (adjusted OR 1.99, 95% CI 1.03-3.84). However, when the amount of RBCT was more than 1,200 mL, it was independently associated with increased hospital mortality (adjusted OR 2.55, 95% CI 1.35-4.81). In the propensity-score matching cohort, there was no association between RBCT in SICU and hospital mortality (adjusted OR 1.56, 95% CI 0.88-2.77) except when the amount of RBCT was more than 600 mL (601-1,200 mL, adjusted OR 3.14, 95% CI 1.47-6.72 and >1,200 mL, adjusted OR 3.58, 95% CI 1.36-9.48).*

Conclusion: *RBCT should be considered as a life-saving intervention but with potential risks of adverse events. Identifying patients who will likely gain benefit from RBCT and implementing the restrictive transfusion strategy may be the keys to improve outcomes.*

Keywords: *Blood transfusion, Critical care, Mortality, Outcomes, Surgical patients*

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Approximately one-third of patients admitted to the intensive care unit (ICU) have encountered anemia, which is defined as hemoglobin levels of less than 10 g/dL, and the incidence will rise in those who have longer ICU stay[1,2]. Anemia theoretically contributes to a risk of decreased global oxygen delivery, especially to the vital organs such as brain and heart and may result in increased mortality in critically ill patients[3-6]. Consequently, 30 to 40% of patients admitted to ICU receive at least 1 unit of pack red blood cells (PRBC) transfused during their ICU stay[1,2,7-9]. Nonetheless, there has still been controversy whether red blood cell transfusion (RBCT) would really improve outcomes in critically ill patients[1,2,7-9]. It has been demonstrated that RBCT is associated with increased mortality risk in most critically ill patients[1, 7] but not in some patient populations such as patients with sepsis[8,9] or surgical patients[2].

In surgical patients, the association between RBCT and outcomes has been investigated in the recent

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single-center retrospective study[2]. The authors found that blood transfusion was associated with decreased risk of in-hospital death in patients admitted to their surgical ICU (SICU), especially in some subgroups such as patients aged between 66 and 80 years old, patients following non-cardiovascular surgery, patients with higher severity of illness, or patients with septic shock[2]. The large, national, multi-center prospective observational cohort including 4,654 adult patients admitted to nine tertiary care-based SICUs in Thailand with the aim to investigate the outcomes and the incidences of adverse events in these patients has been recently published[10]. With this large well-collected database[10], the aim of the present study is to explore the association between RBCT and hospital mortality in Thai critically ill surgical patients.

Material and Method

Study design

This present study was a part of the multi-center, prospective, observational study, the THAI-SICU study[10], which was performed in nine tertiary care-based SICUs across the nation between April 2011 and November 2012. The THAI-SICU study was registered with the ClinicalTrials.gov with the identifier reference of NCT01354197. Full details of the study could be found in publication elsewhere[10]. In brief, the aim of the THAI-SICU study was to report adverse events and outcomes in a large scale of patients admitted to SICUs across the nation. The study included all adult patients age 18 years old or more and admitted to the SICUs and excluded patients who had their SICU stay for less than six hours, those who were moribund cases, cardiac, neurosurgical and medical patients as well as foreigners (due to language barrier). An informed consent was obtained from each participant or their next of kin. This present study included all adult patients admitted to the SICUs after surgery and excluded those admitted to the SICUs without undergoing surgery, those with a history of massive blood transfusion prior to SICU admission and those whose blood transfusion data were missing or incomplete. Massive blood transfusion was defined as transfusion of 10 units or more of PRBC within 24 hours, transfusion of 4 units or more of PRBC within 1 hour with an anticipation of on-going need, or replacement of 50% or more of the total blood volume within 3 hours[11].

Data collection

The demographic data including age, gender, co-morbidities, sites and types of surgery (whether elective or emergency surgery), the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Sequential Organ Failure Assessment (SOFA) score, numbers of organ dysfunction and hemoglobin level at SICU admission and discharge were collected. Organ dysfunction was defined as a SOFA score of 2 or more on any of the respiratory, the coagulation, the hepatobiliary, or the renal component and 1, 3, or 4 on the cardiovascular component. All included patients were followed up daily until they were discharged from the SICUs or until 28 days after their SICU admission. RBCT prescribed during SICU stay in each patient was monitored. Patients were then categorized into RBCT or no RBCT groups according to whether they received RBCT during SICU stay or not. In addition, the amount of PRBC transfused was also recorded and were categorized according to the amount of transfusion e.g. $\leq$300 mL, 301-600 mL, 601-1,200 mL and >1,200 mL. All included patients were prospectively monitored for adverse events which occurred during their SICU stay including ICU acquired sepsis, acute kidney injury (AKI), acute lung injury/acute respiratory distress syndrome (ALI/ARDS), and myocardial infarction. ICU acquired sepsis was defined as clinically suspected infection with antibiotics given or positive culture from sterile site plus systemic inflammatory response syndrome with or without organ failure or unstable hemodynamics; AKI as increasing in serum creatinine level of more than 0.3 mg/dL from baseline; ALI/ARDS as the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) ratio of equal or less than 300 for ALI and PaO_2/FiO_2 ratio of equal or less than 200 for ARDS plus bilateral infiltration on chest x-ray and no evidence of left atrial hypertension by clinical signs or pulmonary artery occlusion pressure of equal or less than 18 mmHg; myocardial infarction as at least 2 of the following criteria: (1) positive troponin-T, (2) ischemic symptoms of more than 20 minutes, (3) ECG alterations[10]. Duration of SICU and hospital stay as well as patient's status (whether alive or dead) at SICU and hospital discharge was also collected.

Study endpoints and subgroup analysis

The primary endpoint of this study was the association between RBCT during SICU stay and the hospital mortality. This association was also determined in the prior defined subgroups including age of $\leq$65 versus >65 years old, APACHE II score of $\leq$15 versus >15 and hemoglobin levels at SICU admission of $\geq$8 versus <8 g/dL. The secondary endpoints were the

associations between RBCT and the adverse events occurred during SICU stay as well as the SICU mortality.

Statistical analysis

For categorical variables, they were presented as numbers with percentages and were compared between groups using Pearson's Chi-square or the Fisher's exact test when appropriated. For continuous variables, they were tested for the distribution normality using the Kolmogorov-Smirnov test, were presented as mean with standard deviation (SD) or median with interquartile range (IQR), and were compared between groups using unpaired t-test or Mann-Whitney U test when appropriated.

Clinical and outcome variables were compared between RBCT and no RBCT groups. In order to reduce the bias related to RBCT requirement, the propensity score[12] for the requirement of RBCT in SICU in each patient was determined. The propensity score was calculated using the logistic regression model based on RBCT status, that was whether they received RBCT during SICU stay or not, as the dependent variable. Variables introduced in the model included the prior defined variables including age, gender, the APACHE II score, the SOFA score and hemoglobin level at SICU admission as well as the variables that were statistically significant at a *p*-value of equal or less than 0.2 in the univariate analysis.

To determine the association between the RBCT in SICU and the hospital mortality, the multiple logistic regression analysis was performed, in which the hospital mortality was entered as the dependent variable. Variables considered for entering in the logistic regression model were the prior defined variables including age, gender, the APACHE II score, the SOFA score, RBCT status, the amount of RBCT (as categorical variable) and the propensity score for RBCT requirement as well as the variables that were statistically significant at a p-value of equal or less than 0.2 in the univariate analysis. The similar models were also performed in the prior defined subgroups. In addition, to determine the association between the adverse events occurred during SICU stay as well as the SICU mortality and the RBCT, similar multiple logistic regression models were performed.

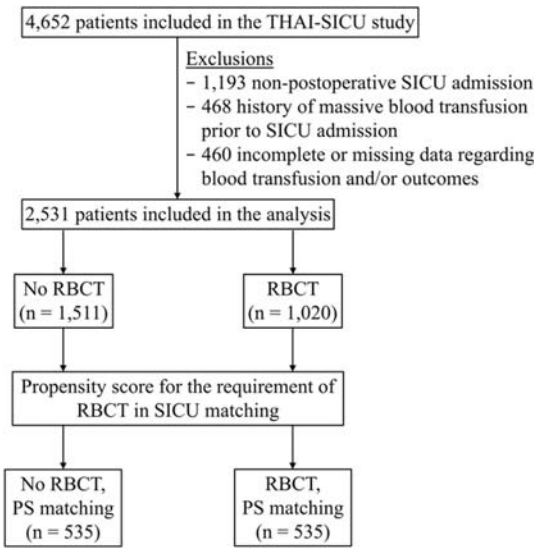
For the propensity-score matching cohort, a greedy matching technique[12] was used to match each patient in the RBCT group with one in the no RBCT group on the basis of the propensity score for RBCT requirement described earlier. The best-matched propensity score was five digits long. Once a match was made, that patient was removed from the pool. This process was sequentially repeated using four-, three-, two-, and then one-digit matching according to the propensity scores. If the patients in the RBCT group could not be matched with one in the no RBCT group at this point, they were then excluded from the cohort. In the propensity-score matching cohort, the association between the RBCT in SICU and the hospital mortality was subsequently analyzed using the multiple logistic regression analysis described earlier.

Data were analyzed using PASW Statistics 18 for Windows software (SPSS Inc., Hong Kong). All statistics were two-tailed analysis and a *p*-value of less than 0.05 was considered as statistically significant.

Results

A total of 4,652 patients were included in the THAI-SICU study (Fig. 1). Of these, 2,121 patients were excluded (1,193 patients as non-postoperative SICU admission, 468 as having a history of massive blood transfusion prior to SICU admission and 460 as having incomplete or missing data regarding blood transfusion and/or outcomes). Therefore, the total of 2,531 patients was included in the study. There were 1,020 (40.3%) patients received at least 1 unit of RBCT during their SICU stay.

Table 1 presented the demographic data and clinical outcomes of patients stratified according to RBCT status in SICU (i.e. RBCT versus no RBCT



PS = propensity score; RBCT = red blood cell transfusion; SICU = surgical intensive care unit

Fig. 1 The overall study flow.

Table 1. Demographic data and clinical outcomes of the entire cohort stratified according to the red blood cell transfusion status in surgical intensive care unit

	All (n = 2,531)	No RBCT (n = 1,511)	RBCT (n = 1,020)	*p*-value
Age; year	66 (54, 76)	65 (54, 75)	67 (53, 77)	0.029
Male	1,438 (56.8%)	863 (57.1%)	575 (56.4%)	0.712
Co-morbidity				
Hypertension	1,332 (52.6%)	833 (55.1%)	499 (48.9%)	0.002
Diabetes	581 (23.0%)	365 (24.2%)	216 (21.2%)	0.080
Malignancy	362 (14.3%)	213 (14.1%)	149 (14.6%)	0.719
Coronary artery disease	282 (11.1%)	190 (12.6%)	92 (9.0%)	0.005
Chronic renal failure	255 (10.1%)	152 (10.1%)	103 (10.1%)	0.975
Respiratory disease	223 (8.8%)	140 (9.3%)	83 (8.1%)	0.326
Stroke	159 (6.3%)	96 (6.4%)	63 (6.2%)	0.857
Vascular disease	155 (6.1%)	74 (4.9%)	81 (7.9%)	0.002
Congestive heart failure	57 (2.3%)	30 (2.0%)	27 (2.6%)	0.271
Site of surgery				
Lower abdomen	895 (35.4%)	552 (36.5%)	343 (33.6%)	0.134
Upper abdomen	840 (33.2%)	485 (32.1%)	355 (34.8%)	0.156
Spine and extremities	363 (14.3%)	192 (12.7%)	171 (16.8%)	0.004
Head and neck	298 (11.8%)	186 (12.3%)	112 (11.0%)	0.309
Thoracic and vascular	263 (10.4%)	134 (8.9%)	129 (12.6%)	0.002
Other Sites	202 (8.0%)	111 (7.3%)	91 (8.9%)	0.151
Emergency surgery	793 (31.3%)	317 (21.0%)	476 (46.7%)	<0.001
EBL; mL	350 (150, 700)	300 (100, 600)	400 (200, 850)	<0.001
EBL >600 mL	642 (25.4%)	322 (21.3%)	320 (31.4%)	<0.001
APACHE II score	10 (6, 13)	8 (6, 11)	12 (9, 16)	<0.001
SOFA score at SICU admission	2 (0, 4)	1 (0, 3)	3 (1, 5)	<0.001
Number of organ failure at SICU admission	0 (0, 1)	0 (0, 1)	1 (0, 1)	<0.001
Hb at SICU admission; g/dL	10.8 (9.6, 12.0)	11.3 (10.3, 12.5)	9.8 (8.9, 11.0)	<0.001
RBCT in SICU; mL	-	-	513 (286, 903)	NA
Adverse events in SICU				
Sepsis	349 (13.8%)	85 (5.6%)	264 (25.9%)	<0.001
Acute kidney injury	303 (12.0%)	71 (4.7%)	232 (22.7%)	<0.001
ALI/ARDS	71 (2.8%)	12 (0.8%)	59 (5.8%)	<0.001
Myocardial infarction	28 (1.1%)	7 (0.5%)	21 (2.1%)	<0.001
Hb at SICU discharge; g/dL	10.6 (9.7, 11.7)	10.9 (10.0, 12.1)	10.1 (9.3, 11.1)	<0.001
SICU LOS; day	1 (1, 3)	1 (1, 2)	3 (1, 5)	<0.001
Hospital LOS; day	14 (9, 24)	13 (8, 21)	16 (10, 27)	<0.001
SICU mortality	103 (4.1%)	19 (1.3%)	84 (8.2%)	<0.001
Hospital mortality	174 (6.9%)	47 (3.1%)	127 (12.5%)	<0.001

ALI/ARDS = acute lung injury/acute respiratory distress syndrome; APACHE II = Acute Physiology and Chronic Health Evaluation II score; EBL = estimated blood loss; Hb = hemoglobin level; LOS = length of stay; RBCT = red blood cell transfusion; SICU = surgical intensive care unit; SOFA = Sequential Organ Failure Assessment score

groups). Patients in the RBCT group seemed to be more critically ill than those in the no RBCT group in terms of older (67 [53-77] years old versus 65 [54-75] years old, $p = 0.029$), higher APACHE II score (12 [9-16] versus 8 [6-11], $p<0.001$), higher SOFA score (3 [1-5] versus 1 [0-3], $p<0.001$), more number of organ failure (1 [0-1] versus 0 [0-1], $p<0.001$) and lower hemoglobin level at SICU admission (9.8 [8.9-11.0] g/dL versus 11.3 [10.3-12.5] g/dL, $p<0.001$). Patients in the RBCT group received median 513 (IQR 286-903) mL of PRBC transfused during their SICU stay. In terms of clinical outcomes, patients in the RBCT group had higher hospital mortality (12.5% versus 3.1%, $p<0.001$) and higher SICU mortality (8.2% versus 1.3%, $p<0.001$) as

well as higher incidence of all adverse events in SICU (all $p<0.001$), longer LOS both in SICU (3 [1-5] days versus 1 [1-2] days, $p<0.001$) and in hospital (16 [10-27] days versus 13 [8-21] days, $p<0.001$) than those in the no RBCT group. Table 2 represented the final model of the propensity score for the requirement of RBCT in SICU, which was determined based on the RBCT status (i.e. RBCT versus no RBCT).

The multiple logistic regression analysis revealed that, overall, there was no association between RBCT in SICU and hospital mortality in the entire cohort (adjusted odds ratio [OR] 1.33, 95% confidence interval [CI] 0.83-2.11, $p = 0.236$) as well as in the prior defined subgroups except in the subgroup of age ≤65 years old (adjusted OR 1.99, 95% CI 1.03-3.84, $p = 0.041$) (Fig. 2). The associations between RBCT in SICU and hospital mortality as well as clinical outcomes were further analyzed according to the amount of PRBC transfused (Table 3). RBCT of more than 1,200 mL was independently associated with increased hospital mortality in the entire cohort (adjusted OR 2.55, 95% CI 1.35-4.81, $p = 0.004$) and in the prior defined subgroups of age >65 years old (adjusted OR 2.76, 95% CI 1.26-6.07, $p = 0.012$), APACHE II score ≤15 (adjusted OR 2.51, 95% CI 1.03-6.15, $p = 0.043$), APACHE II score >15 (adjusted OR 2.58, 95% CI 1.21-5.49, $p = 0.014$), and hemoglobin level at SICU admission ≥8.0 g/dL (adjusted OR 2.80, 95% CI 1.43-5.50, $p = 0.003$) while RBCT of more than 600 mL was independently associated with increased hospital mortality in the subgroup of age ≤65 years old (RBCT 601-1,200 mL, adjusted OR 2.92, 95% CI 1.29-6.62, $p = 0.010$ and RBCT >1,200 mL, adjusted OR 2.81, 95% CI 1.14-6.97, $p = 0.025$). Regardless of the amount of PRBC transfused, RBCT in SICU was not associated with increased hospital mortality in the subgroup of patients with hemoglobin level at SICU admission <8.0 g/dL. For the secondary outcomes, RBCT of more than 1,200 mL was independently associated with increased SICU mortality. Regardless of the amount of transfusion, RBCT in SICU was independently associated with the development of AKI. RBCT of more than 300 mL was independently associated with the development of ALI/ARDS and RBCT between 301

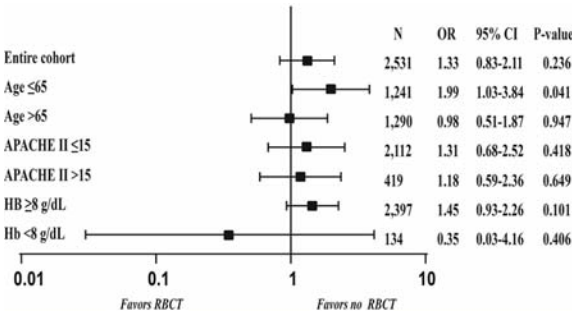


Fig. 2 The adjusted odds ratios (OR) and 95% confidence interval (CI) of the hospital mortality associated with red blood cell transfusion (RBCT) in surgical intensive care unit (SICU) in the entire cohort and the prior defined subgroups.

Table 2. The final model of the binary logistic regression used to calculate the propensity score for the requirement of red blood cell transfusion in surgical intensive care unit

	Coefficient	SE	Wald	OR (95% CI)	*p*-value
Age; per year	0.01	0.00	2.84	1.01 (1.00-1.01)	0.092
Hypertension	-0.26	0.11	5.86	0.77 (0.62-0.95)	0.016
Upper abdomen	0.29	0.12	5.70	1.33 (1.05-1.68)	0.017
Spine and extremities	0.69	0.15	20.48	2.00 (1.48-2.69)	<0.001
Thoracic and vascular	0.61	0.17	12.66	1.84 (1.32-2.58)	<0.001
Other sites	0.67	0.19	11.84	1.95 (1.33-2.85)	0.001
Emergency surgery	0.57	0.12	23.01	1.77 (1.40-2.23)	<0.001
EBL >600 mL	0.80	0.12	46.89	2.23 (1.77-2.81)	<0.001
APACHE II score; per point	0.07	0.01	42.07	1.07 (1.05-1.09)	<0.001
Hb at SICU admission; per g/dL	-0.52	0.03	243.73	0.59 (0.56-0.63)	<0.001
SICU LOS; per day	0.31	0.03	144.62	1.37 (1.30-1.44)	<0.001
Constant	2.73	0.42	43.34	-	-

APACHE II = Acute Physiology and Chronic Health Evaluation II score; CI = confidence interval; EBL = estimated blood loss; Hb = hemoglobin level; LOS = length of stay; OR = odds ratio; SE = standard error of the coefficient; SICU = surgical intensive care unit

Table 3. The association between the red blood cell transfusion in surgical intensive care unit and the hospital mortality as well as the adverse events stratified according to amount of transfusion*

	Amount of RBCT in SICU; adjusted OR (95% CI)*			
	≤300 mL	301-600 mL	601-1,200 mL	>1,200 mL
Primary outcome				
Hospital mortality				
Entire cohort	1.08 (0.57-2.06)	1.18 (0.65-2.17)	1.43 (0.78-2.64)	2.55 (1.35-4.81)[a]
Subgroups				
Age ≤65 years	1.27 (0.46-3.51)	1.46 (0.57-3.74)	2.92 (1.29-6.62)[b]	2.81 (1.14-6.97)[b]
Age >65 years	0.84 (0.36-1.97)	1.01 (0.48-2.11)	0.97 (0.43-2.18)	2.76 (1.26-6.07)[b]
APACHE II score ≤15	1.13 (0.49-2.61)	0.97 (0.42-2.24)	2.07 (0.95-4.51)	2.51 (1.03-6.15)[b]
APACHE II score >15	0.82 (0.29-2.31)	1.41 (0.63-3.17)	0.95 (0.43-2.14)	2.58 (1.21-5.49)[b]
Hb ≥8 g/dL	1.14 (0.59-2.18)	1.29 (0.70-2.40)	1.58 (0.84-2.98)	2.80 (1.43-5.50)[a]
Hb <8 g/dL	NA	NA	0.66 (0.05-9.39)	0.67 (0.05-9.94)
Secondary outcomes				
SICU mortality	1.07 (0.40-2.81)	1.67 (0.72-3.85)	1.92 (0.85-4.34)	3.42 (1.47-7.94)[a]
Sepsis	1.34 (0.84-2.13)	1.93 (1.26-2.97)[a]	2.30 (1.46-3.62)[a]	1.06 (0.62-1.81)
Acute kidney injury	2.47 (1.57-3.89)[a]	2.19 (1.39-3.46)[a]	4.52 (2.87-7.11)[a]	3.63 (2.12-6.20)[a]
ALI/ARDS	1.33 (0.45-3.94)	2.39 (1.01-5.68)[b]	3.59 (1.58-8.17)[a]	2.89 (1.18-7.05)[b]
Myocardial infarction	2.53 (0.75-8.57)	2.67 (0.84-8.49)	1.90 (0.48-7.50)	2.97 (0.76-11.71)

* No RBCT was as a reference, [a] *p*-value of <0.01, [b] *p*-value of <0.05
ALI/ARDS = acute lung injury/acute respiratory distress syndrome; APACHE II = Acute Physiology and Chronic Health Evaluation II score; CI = confidence interval; Hb = hemoglobin level at SICU admission; OR = odds ratio; RBCT = red blood cell transfusion; SICU = surgical intensive care unit

and 1,200 mL was independently associated with the development of sepsis. There was no such association with the development of myocardial infarction.

Table 4 showed the demographic data and clinical outcomes of 1,070 patients of the propensity-score matching cohort. There were 535 patients in the RBCT group matched with 535 in the no RBCT group. There was no significant difference in almost all baseline demographic data between the two groups. When compared with those in the no RBCT group, the incidence of AKI was significantly higher (13.5% versus 7.5%, $p = 0.001$) and the SICU LOS was significantly longer (2 [1-3] days versus 1 [1-2] day, $p<0.001$) in the RBCT group but the hospital mortality was not significantly different between groups (7.3% in the RBCT group versus 5.2% in the no RBCT group, $p = 0.165$). The multiple logistic regression analysis demonstrated that there was no association between RBCT in SICU and hospital mortality (adjusted OR 1.56, 95% CI 0.88-2.77, $p = 0.126$), however, such association was statistically significant when the amount of RBCT was more than 600 mL (601-1,200 mL, adjusted OR 3.14, 95% CI 1.47-6.72, $p = 0.003$ and >1,200 mL, adjusted OR 3.58, 95% CI 1.36-9.48, $p = 0.010$) (Table 5).

Discussion

The main result of this large prospective, observational cohort of surgical patients admitted to SICU was that, overall, RBCT in SICU was not associated with increased hospital mortality except in the subgroup of patients whose age was equal to or less than 65 years. Nevertheless, it was demonstrated that such association between RBCT in SICU and hospital morality was depended on the amount of PRBC transfused. The patient population in this study was comparable to those in the previous studies[1,2,7-9] in terms of general patient characteristics except severity of illness and mortality, which both were lower in this study. The transfusion rate in this study was 40.3%, which was comparable to the previous reports ranged from 30 to 40%[1,2,7-9].

It has still been debated whether RBCT increases mortality in critically ill patients. In the former observation studies[1,7], it was demonstrated that RBCT was independently associated with increased mortality in critically ill patients. On the other hand, the contradictory finding was reported in other studies[2,8,9]. Overall, this study could not demonstrate that RBCT was associated with increased hospital mortality in

Table 4. Demographic data and clinical outcomes of the propensity-score matching cohort stratified according to red blood cell transfusion status in surgical intensive care unit

	All (n = 1,070)	No RBCT (n = 535)	RBCT (n = 535)	*p*-value
Age, year	66 (53, 76)	66 (54, 76)	66 (53, 76)	0.740
Male	579 (54.1%)	290 (54.2%)	289 (54.0%)	0.951
Co-morbidity				
Hypertension	575 (53.7%)	292 (54.6%)	283 (52.9%)	0.581
Diabetes	247 (23.1%)	125 (23.4%)	122 (22.8%)	0.828
Malignancy	143 (13.4%)	70 (13.1%)	73 (13.6%)	0.788
Coronary artery disease	109 (10.2%)	62 (11.6%)	47 (8.8%)	0.130
Chronic renal failure	133 (12.4%)	89 (16.6%)	44 (8.2%)	<0.001
Respiratory disease	94 (8.8%)	51 (9.5%)	43 (8.0%)	0.388
Stroke	65 (6.1%)	31 (5.8%)	34 (6.4%)	0.701
Vascular disease	65 (6.1%)	27 (5.0%)	38 (7.1%)	0.159
Congestive heart failure	23 (2.1%)	11 (2.1%)	12 (2.2%)	0.833
Site of surgery				
Lower abdomen	368 (34.4%)	188 (35.1%)	180 (33.6%)	0.607
Upper abdomen	331 (30.9%)	172 (32.1%)	159 (29.7%)	0.390
Spine and extremities	184 (17.2%)	83 (15.5%)	101 (18.9%)	0.145
Head and neck	110 (10.3%)	44 (8.2%)	66 (12.3%)	0.027
Thoracic and vascular	113 (10.6%)	58 (10.8%)	55 (10.3%)	0.765
Other Sites	92 (8.6%)	51 (9.5%)	41 (7.7%)	0.275
Emergency surgery	338 (31.6%)	166 (31.0%)	172 (32.1%)	0.693
EBL, mL	400 (200, 800)	400 (150, 800)	400 (200, 800)	0.326
EBL >600 mL	308 (28.8%)	162 (30.3%)	146 (27.3%)	0.280
APACHE II score	10 (7, 13)	10 (7, 14)	10 (7, 13)	0.679
SOFA score at SICU admission	2 (1, 4)	2 (1, 4)	2 (0, 4)	0.177
Number of organ failure at SICU admission	0 (0, 1)	1 (0, 1)	0 (0, 1)	0.174
Hb at SICU admission, g/dL	10.4 (9.4, 11.4)	10.4 (9.4, 11.3)	10.4 (9.4, 11.5)	0.844
RBCT in SICU, mL	99 (0, 390)		390 (262, 630)	
Adverse events in SICU				
Sepsis	131 (12.2%)	61 (11.4%)	70 (13.1%)	0.401
Acute kidney injury	112 (10.5%)	40 (7.5%)	72 (13.5%)	0.001
ALI/ARDS	24 (2.2%)	9 (1.7%)	15 (2.8%)	0.215
Myocardial infarction	11 (1.0%)	4 (0.7%)	7 (1.3%)	0.363
Hb at SICU discharge, g/dL	10.2 (9.4, 11.2)	10.2 (9.3, 11.1)	10.2 (9.4, 11.3)	0.405
SICU LOS, day	2 (1, 3)	1 (1, 2)	2 (1, 3)	<0.001
Hospital LOS, day	15 (10, 25)	14.5 (10, 24)	16 (10, 25)	0.241
SICU mortality	37 (3.5%)	14 (2.6%)	23 (4.3%)	0.132
Hospital mortality	67 (6.3%)	28 (5.2%)	39 (7.3%)	0.165

ALI/ARDS = acute lung injury/acute respiratory distress syndrome; APACHE II = Acute Physiology and Chronic Health Evaluation II score; EBL = estimated blood loss; Hb = hemoglobin level; LOS = length of stay; RBCT = red blood cell transfusion; SICU = surgical intensive care unit; SOFA = Sequential Organ Failure Assessment score

critically ill surgical patients except in patients whose age of equal or less than 65 years. Theoretically, one of detrimental effects of anemia is that it can put patients at risk of inadequate oxygen delivery to organ tissues, especially to the vital organs such as brain and heart. It has been shown that anemia is one of the potential risks associated with increased mortality in patients with underlying cardiovascular diseases[3,4] as well as in surgical patients underwent either cardiac[6] or non-cardiac surgery[5]. Therefore, RBCT to restore hemoglobin levels to normal values or higher as one of measures to improve oxygen delivery should theoretically reduce morbidity and mortality, especially in high-risk critically ill patients[13]. Nevertheless, the

Table 5. The association between red blood cell transfusion in surgical intensive care unit and the hospital mortality of the propensity-score matching cohort*

	OR	95% CI	*p*-value
RBCT in SICU	1.56	0.88-2.77	0.126
RBCT in SICU; stratified according to amount of RBCT			
≤300 mL	0.80	0.32-2.02	0.635
301-600 mL	0.76	0.30-1.96	0.573
601-1,200 mL	3.14	1.47-6.72	0.003
>1,200 mL	3.58	1.36-9.48	0.010

* No RBCT was as a reference.
CI = confidence interval; OR = odds ratio; RBCT = red blood cell transfusion; SICU = surgical intensive care unit

issues regarding potentially harmful effects including infectious complications, transfusion-related acute lung injury, hemolytic transfusion reactions, transfusion-associated graft-versus-host disease, transfusion-associated circulatory overload, anaphylaxis and post-transfusion purpura have been well described[14]. In addition, RBCT has been shown to increase the risk of nosocomial infection, developing multi-organ dysfunction syndrome and ARDS as well as increased mortality in most critically ill patients[15]. For all of these reasons, RBCT should be considered as a life-saving therapy not without risks and this may explain, in part, the discrepancy of the results among studies that compared strategies of transfusion versus no transfusion in the most critically ill patients[1,2,7-9]. The most appropriate strategy may be to identify and restrict RBCT to patients who will likely gain benefit from a transfusion.

Since the landmark study compared the restrictive versus the liberal RBCT strategies in critically ill patients, the TRICC study[16], was published in 1999; there have been numerous studies investigating these two strategies in the broad patient population. A growing body of evidence supports the safe practice of the restrictive transfusion strategy in most critically ill patients, such as patients with septic shock[17] or postoperative non-cardiac high-risk patients[18], and may be even associated with better outcome in patients with acute gastrointestinal hemorrhage[19]. Nevertheless, it should be emphasized that the restrictive transfusion strategy might increase risk of death in some patient populations such as those who underwent non-emergency cardiac surgery[20] or major surgery for abdominal cancer[21]. Even though this study design did not allow comparing the restrictive versus the liberal transfusion strategies on patient outcomes, this study clearly demonstrated that the hospital mortality was independently associated with the amount of RBCT in SICU. RBCT of more than 1,200 mL in SICU significantly increased hospital mortality in the entire cohort and all the *prior* defined subgroups except that of hemoglobin level at SICU admission <8.0 g/dL and RBCT of more than 600 mL in the *prior* defined subgroup of age ≤65 years. These could be implied that RBCT might be harmful in the subgroup of younger patients but in the subgroup with low hemoglobin levels at SICU admission. This study could not thoroughly explain why younger patients had higher risk from allogeneic blood transfusion but this finding was supported by the results from the TRICC trial[16] that younger patients (age of less than 55 years old) had significant higher survival rate with the restrictive transfusion strategy. When compared with older patients, younger patients might have higher cardiovascular reserve to anemia and they might have more exaggerated immunological response when they received allogeneic blood transfusion (as discussed later). Altogether, the harmful effects from blood transfusion might be outweighed the beneficial effects in younger patients. On the other hand, this study showed that, regardless of the amount of PRBC transfused, RBCT did not associate with increased hospital mortality in subgroup of patients with low hemoglobin levels at SICU admission. Nonetheless, this should be interpreted with caution as the number of patients with hemoglobin levels of less than 8 g/dL in this study was only 134 (5.3%) of 2,531, which might result in an inadequate statistical power to detect significant association. However, the indications for each RBCT as well as the pre-transfusion hemoglobin levels were not recorded in this study. It, therefore, could not be concluded that the amount of RBCT per se or patient severity of illness reflected by the indications for RBCT caused increased mortality.

The postulated hypothesis related to adverse outcomes following allogeneic blood transfusion, the transfusion-related immunomodulation (TRIM)[22-24], deserves some discussion. The clinical syndrome of TRIM could be represented as either immunosuppression or pro-inflammation. The immunosuppressive effects following transfusion of RRBC may potentiate the risks of infection in recipients following allogeneic blood transfusion. This study demonstrated that the amount of PRBC transfused was independently associated with the development of sepsis in SICU. The recent meta-analysis[25] also demonstrated that the risk of serious infection could be attenuated with the restrictive transfusion strategy, especially in patients undergoing orthopedic surgery and septic patients. On the other side of the clinical syndromes of TRIM, it could be represented as pro-inflammation or immune activation. This may lead to the development of organ dysfunction following allogeneic blood transfusion, particularly acute lung injury[26], acute kidney injury[27] as well as myocardial and cerebral ischemia[28]. This study also showed that the amount of PRBC transfused in SICU was associated with an increased risk of development of AKI and ALI/ARDS but myocardial infarction. Nevertheless, the use of leukoreduced PRBCs[29] or fresh stored PRBCs[30] in an attempt to attenuate TRIM seems not to affect the outcomes. At present, it has been still controversy that such adverse events following allogeneic blood transfusion would result in adverse outcomes, specifically, increased mortality or not.

There are some limitations in this study that should be addressed. Firstly, as a prospective observational study design, even though all known parameters that could influence the outcomes, such as comorbidity or severity of illness (e.g. the APACHE II score and the SOFA score), were included in the multiple logistic regression analysis to determine the association between the RBCT in SICU and the hospital mortality, there was a possibility that some confounding parameters might not be included. Secondly, as mentioned earlier, the indications for transfusion of PRBCs as well as the pre-transfusion hemoglobin level were not recorded. These might also indicate the severity of illness and might importantly affect the outcomes of patients. However, the probability for the RBCT requirement was calculated as the propensity score for each patient and was introduced in the multiple logistic regression analysis as well as in the propensity-score matching cohort as a mean to adjust baseline severity of illness in each patient. Thirdly, only RBCT in SICU were considered in the analysis, blood transfusion prior to SICU admission, during surgery in the operating room, as well as after SICU discharge were not taken into account. Lastly, only critically ill surgical patients were included in this study, the results might not be able to extrapolate to critically ill medical patients or less critically ill patients.

Conclusion

In this large cohort of critically ill surgical patients, it was demonstrated that, overall, RBCT in SICU was not associated with increased hospital mortality except in subgroup of patients whose age was equal to or less than 65 years. Nonetheless, the association of the RBCT in SICU and the hospital mortality was evidenced when the amount of RBCT was taken in to account. Blood transfusions should be considered as a life-saving intervention in those anemic, critically ill patients but with some potential risks. To identify the patients who will likely gain benefit from RBCT and to implement the restrictive transfusion strategy may be the important keys to improve outcomes in these patients.

What is already known on this topic?

Anemia is one of the potential risk factors of increased morbidity and mortality in critically ill patients. Blood transfusion is the most common intervention for management of patients with anemia. Incidence of blood transfusion in critically ill patients is approximately 30 to 40%. Nevertheless, the benefits of RBCT in these patient populations, particularly critically ill surgical patients, are still controversial.

What this study adds?

Overall, RBCT in most critically ill surgical patients was not associated with increased hospital mortality except in subgroup of patients whose age was equal to or less than 65 years. However, the associations of the RBCT in SICU and the hospital mortality as well as other adverse events including sepsis, AKI, and ALI/ARDS were demonstrated when the amount of RBC transfusion was considered. The major keys to improve outcomes in this patient population should be to identify patients who will likely get benefit from blood transfusion and to implement of the restrictive transfusion strategy.

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Potential conflicts of interest

None.

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ความสัมพันธ์ระหว่างการได้รับการให้เลือดและการเสียชีวิตในโรงพยาบาลในผู้ป่วยหนักทางศัลยกรรม: การศึกษาสหสถาบันในหออภิบาลผู้ป่วยหนักทางศัลยกรรมของโรงพยาบาลมหาวิทยาลัยในประเทศไทย (THAI-SICU Study)

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วัตถุประสงค์: *ผู้ป่วยหนักทางศัลยกรรมที่มีภาวะซีดมักได้รับการให้เลือด แต่ยังไม่มีหลักฐานที่ชัดเจนถึงประโยชน์จากการได้รับการให้เลือดในผู้ป่วยกลุ่มนี้ จุดประสงค์ของการศึกษานี้ คือ เพื่อหาความสัมพันธ์ระหว่างการได้รับการให้เลือดและการเสียชีวิตในโรงพยาบาลในผู้ป่วยหนักทางศัลยกรรม*

วัสดุและวิธีการ: *การศึกษานี้เป็นส่วนหนึ่งของการศึกษาสหสถาบันในหออภิบาลผู้ป่วยหนักทางศัลยกรรมของโรงพยาบาลมหาวิทยาลัยในประเทศไทย (THAI-SICU study) ที่รวบรวมผู้ป่วยที่เข้ารับการรักษาในหออภิบาลภายหลังการผ่าตัด ผู้ป่วยจะถูกแยกเป็นกลุ่มที่ได้รับและไม่ได้รับการให้เลือด โดยพิจารณาจากการได้รับหรือไม่ได้รับการให้เลือดในระหว่างที่เข้ารับการรักษาในหออภิบาลตามลำดับ ความสัมพันธ์ระหว่างการได้รับเลือดและการเสียชีวิตในโรงพยาบาลจะถูกวิเคราะห์ด้วยวิธีการวิเคราะห์การถดถอยพหุคูณ นอกจากนี้ผู้ป่วยในสองกลุ่มจะถูกจับคู่กลุ่มตัวอย่างด้วยคะแนนความน่าจะเป็นของการได้รับการให้เลือดและทำการเปรียบเทียบ*

ผลการศึกษา: *ข้อมูลผู้ป่วยทั้งหมด 2,531 รายที่รวบรวมในการศึกษานี้ อุบัติการณ์การได้รับการให้เลือดเท่ากับร้อยละ 40.3 โดยรวมไม่พบความสัมพันธ์ระหว่างการได้รับเลือดในการรักษาในหออภิบาลและการเสียชีวิตในโรงพยาบาล (adjusted OR 1.33, 95% CI 0.83-2.11) ยกเว้นในกลุ่มผู้ป่วยที่อายุน้อยกว่าหรือเท่ากับ 65 ปี (adjusted OR 1.99, 95% CI 1.03-3.84) แต่ทั้งนี้การได้รับการให้เลือดระหว่างการรักษาในหออภิบาลจะเพิ่มอัตราการเสียชีวิตในโรงพยาบาลอย่างมีนัยสำคัญ เมื่อได้รับการให้เลือดปริมาณมากกว่า 1,200 มิลลิลิตร (adjusted OR 2.55, 95% CI 1.35-4.81) สำหรับกลุ่มผู้ป่วยที่ได้รับการจับคู่ด้วยคะแนนความน่าจะเป็นของการได้รับการให้เลือดพบว่า ไม่พบความสัมพันธ์ระหว่างการได้รับเลือดในการรักษาในหออภิบาลและการเสียชีวิตในโรงพยาบาล (adjusted OR 1.56, 95% CI 0.88-2.77) ยกเว้นเมื่อได้รับการให้เลือดปริมาณมากกว่า 600 มิลลิลิตร (601-1,200 มิลลิลิตร, adjusted OR 3.14, 95% CI 1.47-6.72 และ >1,200 มิลลิลิตร, adjusted OR 3.58, 95% CI 1.36-9.48)*

สรุป: *การให้เลือดในผู้ป่วยวิกฤตศัลยกรรมนั้นมีประโยชน์ แต่ก็มีความเสี่ยงที่จะเกิดภาวะไม่พึงประสงค์เช่นกัน การพิจารณาว่าผู้ป่วยรายใดที่น่าจะได้รับประโยชน์จากการให้เลือด รวมถึงการนำแผนการจำกัดการให้เลือดมาใช้น่าจะเป็นปัจจัยที่สำคัญที่ทำให้ผลลัพธ์ของการดูแลผู้ป่วยดีขึ้น*