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Long length of stay in the ICU associates with a high erythrocyte transfusion rate in critically ill patients

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Abstract

Objective: This study aimed to evaluate epidemiology and outcome among critically ill patients under a restrictive transfusion practice.

Methods: One hundred sixty-nine patients who were admitted to the intensive care unit (ICU) between March 2016 to December 2017 and remained in the ICU $>$ 24 hours were retrospectively included.

Results: Hemoglobin levels on admission were $<$12 g/dL in 85% and $<$9 g/dL in 37.9% of patients. The median admission hemoglobin level was decreased on the last day of the ICU stay. Erythrocyte transfusion was required for 34% of patients. Transfused patients had high Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores, more requirement for invasive mechanical ventilation, vasopressors, and dialysis, long ICU and hospital stays, low hemoglobin levels, and high hospital and ICU mortality rates. Multivariate analysis showed that the likelihood of transfusion increased from 6.6 to 25.8 fold when the ICU stay extended from $\geq$7 to $\geq$15 days. Age, vasopressor use, dialysis, and erythrocyte transfusion $\geq$5 units were predictors of mortality.

Conclusion: Patients receiving transfusion are severely ill and have more life support therapies. The number of erythrocyte units transfused, age, and organ support therapies are independent predictors of mortality.

Keywords

Anemia, intensive care unit (ICU), mortality, red blood cell transfusion, sequential organ failure assessment (SOFA) score, dialysis, vasopressor

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Introduction

Anemia is a common problem in critically ill patients. Approximately two thirds of patients who are admitted to the intensive care unit (ICU) present with hemoglobin levels <12 g/dL[1,2] and even 26% of patients have hemoglobin levels <9 g/dL.[3] The main cause of anemia is the result of three important abnormalities related to the host inflammatory responses, including dysregulation of iron metabolism, impaired proliferation of erythroid progenitor cells, and a blunted erythropoietin response.[4] Another essential cause is phlebotomy for diagnostic laboratory testing and an average of 40 mL of blood is drawn for a 24-hour period with 4.6 samples per patient in critically ill patients.[2] The number of blood samplings and blood volume increases with the severity of disease, which reaches 70 mL per day.[5] Hemodilution from large-volume resuscitation is another important reason for decreased hemoglobin levels in critically ill patients.[6] Although a small number of patients who are admitted to the ICU have normal hemoglobin levels, nearly all patients become anemic over the course of the ICU stay.[1,2] Therefore, red blood cell (RBC) transfusion is commonly required for critically ill patients. Patients who are anemic on ICU admission and who stay longer at the ICU have more RBC transfusions.[1,3] The proportion of patients who are transfused increases to 85% in those with an ICU length of stay (LOS) longer than 7 days.[5] A restrictive strategy for blood transfusion is suggested for critically ill patients where the target hemoglobin level is maintained between 7 and 9 g/dL. The recommended transfusion threshold for hemoglobin is <7 g/dL without undesired effects on mortality.[7,8]

This study aimed to determine the epidemiology of anemia and RBC transfusion. This study also aimed to examine the effect of blood transfusion on the clinical outcomes of critically ill patients who were under a restrictive transfusion regime in a tertiary medical intensive care unit.

Material and methods

This retrospective observational study was conducted in a nine-bed closed medical ICU in a tertiary-level hospital. All patients aged ≥18 years who were admitted to the ICU between March 2016 to December 2017 and stayed in the ICU for longer than 24 hours were included. A restrictive strategy for RBC transfusion was followed in the ICU. Hemoglobin levels were maintained in the range of 7.0 to 9.0 g/dL. Patients were transfused when hemoglobin levels were <7 g/dL, unless patients had coronary diseases, acute cerebrovascular events, heart failure, and severe hypoxemia where hemoglobin levels were maintained at ≥8 g/dL.[9]

Exclusion criteria were an age of <18 years, pregnancy, brain death, imminent death (within 24 hours), multitrauma, and terminal disease states. For patients with multiple ICU admissions, the first admission was used. Each patient's medical records and electronic laboratory database files were used to obtain information. The study protocol was approved by the ethics review board of Düzce University. Informed consent was not required because this was a retrospective study.

Admission diagnoses were classified as follows. A diagnosis of infection included admission for primarily a sepsis-related diagnosis, which included lung, gastrointestinal, urinary tract, central nervous system, soft tissue, and catheter-related infections. A cardiac diagnosis encompassed heart failure, acute coronary syndrome, rhythm problems, and cardiac arrest not precipitated by an underlying disease, such as sepsis or respiratory failure. A diagnosis of neurological disease included motor neuron and neuromuscular diseases, status epilepticus,

intracranial bleeding, and a cerebrovascular accident. A diagnosis of lung disease included chronic obstructive pulmonary disease and asthma exacerbation, pulmonary embolism, and pneumothorax. Surgery encompassed any planned or unplanned surgery. A gastrointestinal disease included any gastrointestinal disease.

The following parameters were recorded: demographics, comorbidities, admission diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores calculated from data gathered within 24 hours, RBC transfusions, and requirement for invasive mechanical ventilation (IMV), dialysis, and vasoactive drugs during the ICU stay. Hemoglobin levels that were measured on admission (within 6 hours), and at 24 hours, 48 hours, 72 hours, and 7 days after ICU admission were recorded. Hemoglobin levels that were measured on the last day of the ICU stay were also included. Laboratory results that were measured in the first 24 hours of admission were noted in the files. LOS in the ICU and hospital were recorded. Patients were followed up until hospital discharge or death, whichever came first.

Statistical analysis

Results are shown by median and interquartile range or number and percentage. The significance of differences was determined by the Mann–Whitney U test for continuous variables. The chi-square test was used to test statistical significance for categorical variables. The Wilcoxon test was used to compare baseline hemoglobin levels with hemoglobin levels that were measured on the last day of the ICU stay. Hemoglobin levels over time were compared by using repeated measure analysis of variance, followed by Tukey's honestly significant difference test for pairwise comparisons.

To determine the relative risks for RBC transfusion and mortality, forward stepwise logistic regression models were developed and variables yielding p values <0.1 were included in the models. Colinearity between variables was checked before modelling and all variables were included in the models thereafter, irrespective of the level of significance in the univariate model. Kaplan–Meier survival curves, which described the survival distribution for transfused and non-transfused patients were compared with using a log-rank test statistic. A p value of <0.05 was considered to indicate statistical significance. Statistical analysis was performed using the Statistical Package for the Social Sciences version 21 (IBM Corp., Armonk, NY, USA).

Results

The study included 169 patients and the main admission diagnosis was infection. The median APACHE II and SOFA scores were 22 (17–29) and 7 (4–11), respectively. The median hemoglobin level was decreased on the last day of ICU stay compared with that on the day of ICU admission ($p<0.001$). A total of 85% of patients had hemoglobin levels <12 g/dL and 37.9% of patients had hemoglobin levels <9 g/dL on admission to the ICU. A transfusion was provided to 34% of patients with a median of 3 units (1–4 units). Transfused patients were more severely ill, with higher APACHE II ($p=0.039$) and SOFA ($p=0.023$) scores, a higher rate of IMV ($p=0.042$), vasopressor use ($p=0.043$), and dialysis ($p=0.005$), and they spent a longer time in the ICU ($p<0.001$) and hospital ($p<0.001$) than non-transfused patients (Table 1). However, transfused patients had lower hemoglobin levels from the day of ICU admission until the last day of the ICU stay compared with non-transfused patients (all $p<0.001$). RBC transfusions were provided to 17% of

Table 1. Characteristics and outcomes of transfused and non-transfused critically ill patients.

Parameters	All patients n = 169	No transfusion n = 111	Transfusion n = 58	p[†]
Age, (years)	74 (63–83)	74 (63–83)	73 (63–82)	0.326
Male, n (%)	89 (42.7)	60 (54.1)	29 (50)	0.690
APACHE II	22 (17–29)	22 (16–27)	25 (19–32)	0.039
SOFA	7 (4–11)	6 (3–10)	9 (5.5–11)	0.023
Source of admission, n (%)				0.308
Emergency room	97 (57.4)	68 (61.3)	29 (50)	0.160
Hospital floor	72 (42.6)	43 (38.7)	29 (50)	
Comorbid condition, n (%)				
Diabetes mellitus	55 (32.5)	35 (31.5)	20 (34.5)	0.412
Chronic heart failure	51 (32)	42 (37.8)	12 (20.7)	0.023
Cerebrovascular disease	32 (18.9)	18 (16.2)	14 (24.1)	0.212
Chronic renal failure	36 (21.3)	19 (17.1)	17 (29.3)	0.066
Coronary artery disease	37 (21.9)	28 (25.2)	9 (15.5)	0.147
COPD	42 (24.9)	32 (28.8)	10 (17.2)	0.069
Admission diagnosis, n (%)				
Infection	107 (63.2)	70 (63.1)	37 (63.8)	0.926
Neurological disease	17 (10.1)	14 (12.6)	3 (5.2)	0.127
Postoperation	17 (10.1)	8 (7.3)	9 (15.5)	0.078
Lung disease	14 (8.3)	12 (10.8)	2 (3.4)	0.083
Others[‡]	14 (8.3)	7 (6.2)	7 (12.1)	0.220
Hemoglobin, (g/dL)				
HB0	10.8 (9.4–12.7)	11.6 (10.5–13.7)	9.1 (7.8–10.3)	<0.001
HB24	10.0 (9.1–11.6)	10.9 (9.6–12.8)	8.9 (7.9–9.9)	<0.001
HB48	9.9 (8.6–11.5)	11 (9.5–12.3)	8.7 (7.7–9.5)	<0.001
HB72	9.9 (8.8–11.3)	10.8 (9.6–12.1)	8.8 (7.8–9.4)	<0.001
HB7[¶]	9.6 (8.4–10.7)	10.3 (9.1–12)	9.0 (8.1–9.8)	<0.001
HBlast	9.6 (8.4–10.8)	10.3 (9.2–11.9)	8.3 (7.6–9.1)	<0.001
IMV, n (%)	107 (63.3)	65 (58.6)	42 (72.4)	0.042
Vasopressor, n (%)	97 (57.4)	58 (52.3)	39 (67.2)	0.043
Dialysis, n (%)	40 (23.7)	19 (17.1)	21 (36.2)	0.005
ICU length of stay, (days)	6 (4-15)	5 (3-8)	16 (6-25)	<0.001
>3 days of ICU stay	134 (79.3)	82 (73.9)	52 (89.7)	0.011
≥7 days of ICU stay	82 (48.5)	40 (36)	42 (72.4)	<0.001
≥15 days of ICU stay	45 (26.6)	14 (12.6)	31 (53.4)	<0.001
Hospital length of stay, (days)	14 (7.8–25.3)	10.8 (6–19)	24.5 (11–43)	<0.001
ICU mortality, n (%)	57 (33.7)	32 (28.8)	25 (43.1)	0.046
Hospital mortality, n (%)	70 (41.4)	38 (34.2)	32 (55.2)	0.009

[†]p indicates statistical significance between transfused and non-transfused patients

[‡]Others include electrolyte abnormalities (n = 5), cardiovascular disease (n = 4), hyperosmolar coma (n = 2), and gastrointestinal disease (n = 3)

[¶]The median hemoglobin level on the last day of the ICU stay was significantly decreased compared with that on the day of ICU admission ($p < 0.001$)

Abbreviations: ICU, intensive care unit; HB, hemoglobin; HB0, admission HB level; HB24, HB measured 24 hours after admission; HB48, HB measured 48 hours after admission; HB72, HB measured 72 hours after admission; HB7, HB measured on the seventh day of ICU stay; HBlast, HB measured on the last day of ICU stay; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; IMV, invasive mechanic ventilation; COPD, chronic obstructive pulmonary disease

patients who stayed ≤3 days, but were provided to 51% of patients who stayed ≥7 days and to 68.9% of patients who stayed ≥15 days. Hemoglobin levels over time, which were analyzed by repeated measure analysis of variance, showed a significant decline in transfused and non-transfused patients ($p < 0.001$, Figure 1). Because a sufficient number of patients received dialysis, which could affect hemoglobin levels and transfusion, the data were re-analyzed by excluding these patients. The significant differences between transfused and non-transfused patients with p values <0.05 were similar to the original results including all patients, except for ICU mortality (32.4% vs. 18.5%, p=0.085) and the APACHE II score (23 [16–29] vs. 20 [14–24], $p = 0.089$).

ICU and hospital mortality rates were significantly higher in patients who received a transfusion than in those who did not receive a transfusion ($p = 0.046$, $p = 0.009$, respectively) (Table 1). The main causes of death were sepsis-related organ failure (70.2%), acute cardiac events/cardiac failure (12.3%), cerebrovascular reasons (5.3%), bleeding (3.5%), and others (8.7%). The mortality rate significantly increased when the number of transfusions reached ≥5 units per patient compared with ≤4 units per patient (71.4% vs. 34.1%, $p = 0.014$). Although transfused patients had a high ICU mortality rate, Kaplan–Meier analysis did not show any significant difference in survival patterns during the ICU stay between transfused and non-transfused patients (Figure 2).

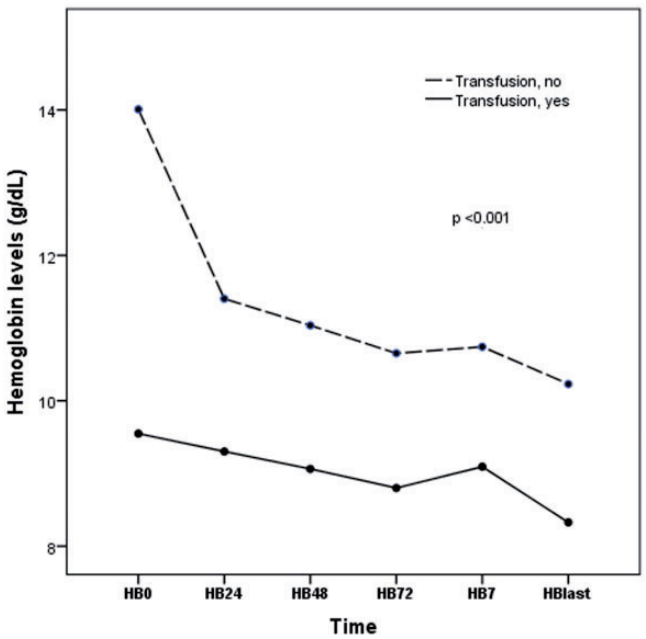

Figure 1. Hemoglobin evaluation patterns among transfused and non-transfused patients. Transfused patients had low hemoglobin levels from the first day of intensive care unit admission until the last day of the intensive care unit stay. HB, hemoglobin; HB0, admission HB level; HB24, HB measured 24 hours after admission; HB48, HB measured 48 hours after admission; HB72, HB measured 72 hours after admission; HB7, HB measured on the seventh day of intensive care unit stay; HBlast, HB measured on the last day of intensive care unit stay.

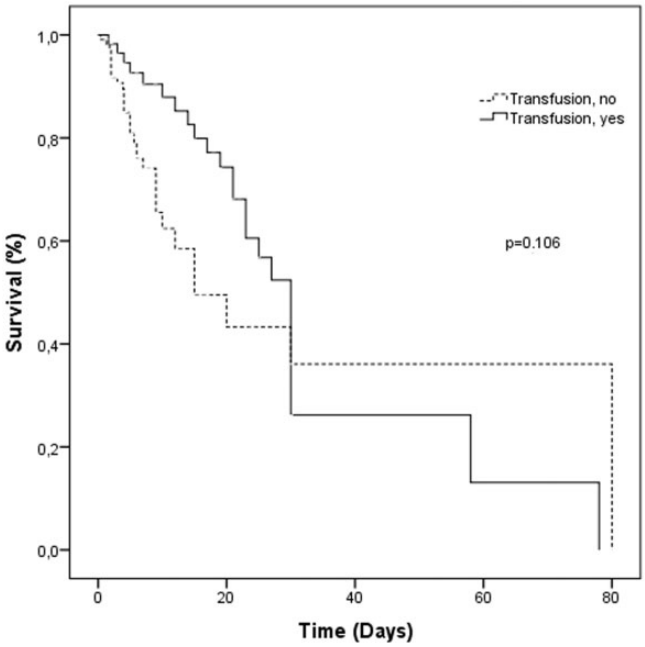

Figure 2. Kaplan–Meier long-rank statistic for testing the survival distribution between transfused and non-transfused critically ill patients during the intensive care unit stay. There was no significant difference in survival patterns.

Non-survivors had significantly higher APACHE II and SOFA scores (both $p < 0.001$), and a higher rate of IMV, dialysis, and vasopressor use (all $p < 0.001$) than did non-survivors (Table 2). Hemoglobin levels over time were not different between survivors and non-survivors, except for the last day of the ICU stay ($p < 0.001$).

Logistic regression analysis showed that the ICU LOS was a predictor of transfusion. The likelihood of transfusion increased from 6.58 (95% confidence interval [CI], 2.67–16.26) to 25.75 (95% CI, 7.51–88.30) fold when the ICU LOS was extended from ≥ 7 to ≥ 15 days. Logistic regression analysis for ICU mortality showed that age (odds ratio [OR], 1.04; 95% CI, 1.01–1.08; $p = 0.028$), vasopressor use (OR, 10.9; 95% CI, 3.00–36.69; $p < 0.001$), dialysis (OR, 3.72; 95% CI, 1.36–10.22; $p = 0.011$), and units transfused ≥ 5 (OR, 7.19; 95% CI, 1.35–38.23; $p = 0.021$) were predictors of mortality. Exclusion of patients who had dialysis from regression analysis did not change any prognostic factors.

Discussion

In this study, 85% of patients had hemoglobin levels < 12 g/dL and a continuous decrease in hemoglobin levels over time was observed. These findings are consistent with previous studies as follows. Two prospective multicenter studies conducted by Corwin et al. and Vincet et al.[1,2] showed a progressive decline in hemoglobin levels over 28 days in critically ill patients, irrespective of admission hemoglobin levels. Rodriguez et al.[10] reported that almost 95% of patients became anemic after 3 days in the ICU. The reasons for an increased incidence of anemia in severely ill patients are multifactorial. One reason is that phlebotomy is performed for

Table 2. Clinical characteristics of ICU survivors and non-survivors.

Parameters	Survivors (n = 112)	Non-survivors (n = 57)	p
Age, (years)	72 (62–80)	78 (65–86)	0.009
Male, n (%)	63 (56.3)	26 (45.6)	0.126
APACHE II	19 (14–25)	27 (22–36.5)	<0.001
SOFA	5 (3–9)	11 (8–14)	<0.001
Source of admission, n (%)			0.926
Emergency room	67 (56.8)	33 (57.9)	
Hospital floor	51 (43.2)	24 (41.2)	
Comorbid condition, n (%)			
Diabetes mellitus	33 (29.5)	22 (38.6)	0.231
Chronic heart failure	33 (29.5)	21 (36.8)	0.331
Cerebrovascular disease	24 (21.4)	8 (14)	0.246
Chronic renal failure	20 (17.9)	16 (28.1)	0.125
Coronary artery disease	20 (17.9)	17 (29.8)	0.075
COPD	26 (23.2)	16 (28.1)	0.490
Admission diagnosis, n (%)			
Infection	60 (53.6)	47 (82.5)	<0.001
Neurological disease	11 (9.8)	6 (10.3)	0.885
Postoperation	16 (14.3)	1 (1.8)	0.013
Lung disease	13 (11.6)	1 (1.8)	0.036
Others‡	12 (10.7)	2 (3.6)	0.144
Hemoglobin, (g/dL)			
HB0	11.2 (9.5–12.9)	10.3 (8.9–12.3)	0.110
HB24	10.2 (9.0–12.2)	9.8 (9.1–11.5)	0.282
HB48	9.9 (8.7–11.6)	9.7 (8.5–11.4)	0.519
HB72	9.9 (8.7–11.3)	9.8 (8.8–11.1)	0.448
HB7	9.5 (8.5–11.4)	9.6 (8.3–10.3)	0.570
HBlast	9.9 (8.7–11.1)	8.7 (7.5–10.4)	<0.001
IMV, n (%)	50 (44.6)	57 (100)	<0.001
Vasopressor, n (%)	43 (38.4)	54 (94.7)	<0.001
Dialysis, n (%)	12 (10.7)	28 (49.1)	<0.001
Transfusion, n (%)	33 (29.5)	25(43.9)	0.046
ICU length of stay, (days)	6 (4–10)	9 (4–22)	0.092
Hospital length of stay, (days)	14 (8–26)	14 (5–24)	0.280

‡Others include electrolyte abnormalities (n = 5), cardiovascular disease (n = 4), hyperosmolar coma (n = 2), gastrointestinal disease (n = 3)

Abbreviations: ICU, intensive care unit; HB, hemoglobin; HB0, admission HB level; HB24, HB measured 24 hours after admission; HB48, HB measured 48 hours after admission; HB72, HB measured 72 hours after admission; HB7, HB measured on the seventh day of ICU stay; HBlast, HB measured on the last day of ICU stay; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; IMV, invasive mechanic ventilation; COPD, chronic obstructive pulmonary disease

laboratory studies. The daily sampling volume ranges between 40 to 70 mL per day and blood sampling can account for 30% of the total blood transfused.[2,5] The phlebotomy volume is independently associated with the likelihood of transfusion, and even small increments in phlebotomy (3.5 mL per day) can increase the risk

of transfusion as much as two fold.[11] Other causes are blood loss from gastrointestinal bleeding, a decreased erythrocyte life span due to hemolysis and disseminated intravascular coagulation, and decreased erythrocyte production or ineffective erythropoiesis secondary to an increased inflammatory state.[4,10] As patients stay longer in the ICU, the exposure time to these factors increases and this can raise the incidence of anemia. Therefore, transfusion is extremely common in a long ICU LOS and increases up to 85% in patients who stay longer than 1 week in the ICU.[1,2,5,11] The current study showed a transfusion rate of 17% in patients who stayed $\leq$3 days and it increased to 51% in patients who stayed $\geq$7 days and to 68.9% in patients who stayed $\geq$15 days. Additionally, the likelihood of transfusion increased from 6.6 to 25.8 fold when the ICU LOS was extended from $\geq$7 to $\geq$15 days.

The present study showed that patients who received a transfusion at any time during the ICU stay had higher APACHE II and SOFA scores and lower hemoglobin levels on admission than did non-transfused patients. The current results are consistent with other previous studies as follows. A study performed by Vincet et al.[3] showed that transfused patients had significantly higher SAPS II and SOFA scores compared with non-transfused patients. Another multicenter study that included 1136 patients showed that transfused patients had meaningfully low hemoglobin levels on ICU admission together with high APACHE II and SOFA scores that were calculated from the first day's data.[2] A low hemoglobin level on admission was shown to be associated with the severity of disease.[1] Patients with high disease severity indices generally have more organ failure and more release of cytokines.[12] Because production and life span of erythrocytes are negatively affected by cytokines, anemia in patients with severe diseases is not surprising.[1,2] These patients require more life support therapies, such as renal replacement therapy, vasopressors, and IMV, as found in patients during their ICU stay in the current study.[2,11] Additionally, patients with high illness severity scores stay longer in the ICU than do those with low scores.[13] A long ICU LOS is associated with more transfusion, which has been discussed above.

The transfusion rate in the current study is lower than that in many other studies where transfusion rates have been reported to be as high as 85%.[5,11] This low transfusion rate is apparently due to the use of a restrictive transfusion strategy in the ICU. A restrictive transfusion strategy is associated with significantly less units of blood transfusion without any effect on mortality.[7,8] The present study showed a high mortality rate in patients who had an erythrocyte transfusion of $\geq$5 units compared with patients who had an erythrocyte transfusion of $\leq$4 units. The current study results are compatible with other studies where the mortality rate rose exponentially as the units of transfusion increased.[1,2,14] Additionally, these studies showed that the number of transfused units increased as the ICU stay lengthened, similar to the present study where transfused patients had a long ICU stay.

Although transfusion is necessary and provides therapeutic benefit to most patients, it is an intervention without inherent risk in critically ill patients. Transfusion is associated with increased risks of infectious complications and immunological reactions, such as hemolytic reactions, allergic reactions, and febrile nonhemolytic reactions, and circulatory fluid overload.[15] Diagnosis of these complications could be unrecognized because of confounding physiological alterations related to the primary admission diagnosis. Therefore, strategies should be implanted in the ICU for minimizing blood loss to avoid transfusion. One of these strategies is to decrease the number

of phlebotomies for diagnostic laboratory testing without compromising quality of care.[11] The use of small-volume or pediatric tubes for phlebotomy in the ICU can reduce blood loss by 33% to 80%.[16] The waste of blood from indwelling catheter lines can be decreased by reinfusing waste blood back to the patients either by a three-way stopcock or closed blood conservation devices.[17] Another strategy is cell salvage during surgery, especially elective cardiac and orthopedic surgeries, which reduce the requirement of transfusion in these patients.[18] A further strategy is using non-invasive monitoring, such as pulse oximetry, end-tidal CO_2 monitoring, and oximeters capable of measuring hemoglobin in selected patients, which may decrease the number of phlebotomies.[16] Furthermore, excessive volume infusion during resuscitation can be avoided to prevent dilutional anemia. Infusion protocols using techniques, such as an echocardiogram or passive leg-raising, may help physicians to introduce adequate fluids to patients.[19]

This study has some limitations. First, this was a retrospective study that was conducted at a single center with a limited number of patients. Second, transfusion-related complications, such as allergic reactions, transfusion-associated circulatory overload, and transfusion-related acute lung injury, were not included, which might have affected mortality and ICU LOS. Third, the amount of blood volume that was removed by phlebotomy was not measured. Therefore, the effect of phlebotomy on the occurrence of anemia and the transfusion rate could not be studied.

In conclusion, this study shows that one third of critically ill patients have RBC transfusion during their ICU stay. Transfused patients are more severely ill, have lower hemoglobin levels, stay longer in the ICU, and have a higher mortality rate than non-transfused patients. The differences between transfused and non-transfused patients do not change when patients on dialysis in whom the risk of transfusion is supposed to be high are excluded from statistical analysis. The odds of transfusion exponentially increase when the ICU length of stay increases from $\geq$1week to $\geq$2 weeks. The number of erythrocyte units transfused is a predictor of mortality along with age and organ support therapies. Therefore, blood transfusion should be considered as a sign of underlying disease severity in the ICU and should be added to risk scores. Transfusions themselves may increase the mortality rate in certain patient groups and can be associated with serious complications. Recommendations for blood-saving measures should be implemented in department's policies.

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