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Original Article
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Red Blood Cell Transfusion Beyond Restrictive Thresholds in Patients With Septic Shock and an Elevated Lactate Level: A Multicenter Observational Study

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ABSTRACT

Background: Few studies have examined real-world transfusion practices in patients with septic shock. It is unclear whether red blood cell (RBC) transfusion benefits patients with an elevated lactate level. This study investigated transfusion practices and explored lactate as a physiological marker for guiding transfusion decisions.
Methods: This observational study used data from a prospective, multicenter registry of patients with septic shock, provided by the Korean Shock Society, from November 2015 to December 2022. The initial hemoglobin (Hb) value and RBC transfusion status within six hours of emergency department visits were recorded. The in-hospital mortality rate was assessed based on the Hb level. The association between RBC transfusion and in-hospital mortality was analyzed using multivariable logistic regression, stratified by Hb groups and lactate level subgroups.
Results: Among the 8,711 patients included, 884 (10.1%) received an RBC transfusion. Of these, 510 patients (57.7%) received a transfusion at an Hb level ≥ 7 g/dL. In the Hb 7.0–8.9 g/dL and Hb ≥ 9.0 g/dL groups, the transfusion group had a higher heart rate and a greater percentage of patients meeting the Sepsis-3 criteria for shock compared to the non-transfusion group. The initial lactate level was significantly higher in the transfusion group compared to the non-transfusion group in the Hb ≥ 9.0 g/dL group (median 5.3 mmol/L vs. 3.5 mmol/L). No significant association was found between RBC transfusion and in-hospital mortality in the Hb < 7.0 g/dL group (adjusted odds ratio [aOR], 0.86; 95% confidence interval [CI], 0.54–1.37) and the Hb 7.0–8.9 g/dL group (aOR, 0.79; 95% CI, 0.59–1.06).

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Yoo KH, Cho Y. Data curation: Cho Y, Yoo KH. Formal analysis: Cho Y, Yoo KH. Funding acquisition: Cho Y, Shin TG. Investigation: Yoo KH, Suh GJ, Kwon WY, Choi SH, Chung SP, Kim WY, Kim K, Park YS, Shin TG, Ko BS, Lim TH. Methodology: Cho Y. Writing - original draft: Yoo KH, Cho Y. Writing - review & editing: Cho Y, Shin TG.

However, in the Hb ≥ 9.0 g/dL group, RBC transfusion was associated with an increased in-hospital mortality rate (aOR, 1.99; 95% CI, 1.34–2.93). The benefits of transfusion were not confirmed by the analysis based on the lactate level.

Conclusion: RBC transfusions were frequently administered beyond restrictive thresholds in patients with septic shock, particularly in those with an elevated lactate level. However, RBC transfusion in patients with an elevated lactate level was not associated with decreased in-hospital mortality.

Keywords: Sepsis; Septic Shock; Erythrocyte Transfusion; Lactate; In-Hospital Mortality

INTRODUCTION

Patients with septic shock often have anemia, which is associated with a poor outcome.[1-3] Red blood cells (RBCs) play a critical role in oxygen transport, and RBC transfusion has been used in patients with septic shock to improve tissue oxygenation.[4] Transfusions in critically ill patients are also associated with risks, such as circulatory overload, transmission of infectious diseases, and hypersensitivity reactions.[5,6] Therefore, a careful balance between the benefits and risks is essential for each patient. Current guidelines recommend a restrictive transfusion strategy in patients with sepsis with a hemoglobin (Hb) threshold of 7 g/dL.[7,8] However, few studies have examined real-world transfusion practices in patients with septic shock, particularly regarding adherence to these guidelines.

The guidelines recommend that decisions regarding RBC transfusion should not solely rely on the Hb level, but should also consider individual patient-specific factors and overall clinical condition.[7,8] However, specific recommendations for alternative physiological transfusion triggers have not been provided. This stems from the limited research into alternative transfusion triggers, compared to the extensive evidence supporting Hb transfusion thresholds. In septic shock, an elevated lactate level indicates inadequate perfusion, and recovery from this condition is critical.[9,10] However, few studies have reported whether RBC transfusion is beneficial for patients with septic shock and an elevated lactate level.

This study examined RBC transfusion practices in patients with septic shock and investigated the differences in in-hospital mortality rates based on the transfusion status across groups with a different Hb level. Additionally, we explored the relationship between transfusion and mortality based on the lactate level in patients with septic shock. We aimed to investigate transfusion practices in patients with septic shock and to examine whether lactate can be used as a physiological marker to trigger transfusion.

METHODS

Data source and study cohort

An observational study was conducted using data from a multicenter registry of the Korean Shock Society (KoSS), prospectively collected between October 2015 and December 2022. The KoSS is a collaborative research network dedicated to improving the diagnosis and management of septic shock. The registry includes data collected from patients with septic shock who presented to the emergency departments (EDs) of 16 teaching hospitals in South Korea.[11]

The inclusion criteria for patients in the KoSS registry were: age ≥ 19 years, visit to participating ED with suspected or confirmed infection, and evidence of refractory hypotension or hypoperfusion.[12,13] Hypotension was defined as systolic blood pressure < 90 mmHg, mean arterial pressure (MAP) < 70 mmHg, or a reduction of > 40 mmHg in systolic blood pressure.[14] Refractory hypotension was defined as persistent hypotension following administration of intravenous fluid (≥ 1L over 30 minutes or 20–30 mL/kg) or the requirement for vasopressors after fluid resuscitation. Hypoperfusion was defined as a serum lactate level ≥ 4 mmol/L. This differs from the Sepsis-3 definition of septic shock, as the KoSS registry began prior to the implementation of the Sepsis-3 definition.[15] Patients who were classified as "Do Not Attempt Resuscitation" at the time of the ED visit, diagnosed more than six hours after the ED visit, or transferred to another hospital during ED treatment were excluded.[16]

Patients with a missing initial Hb value in the registry were excluded. Patients with septic shock were divided into three groups based on their initial Hb level: Hb < 7.0 g/dL, Hb 7.0–8.9 g/dL, and Hb ≥ 9.0 g/dL. Group classification was based on an Hb level of 7 g/dL for the restrictive transfusion threshold and 9 g/dL for the liberal transfusion threshold.

Data collection

Demographic and clinical data including age, sex, initial Hb and lactate levels, initial vital signs, medical history, and infection focus were extracted from the KoSS registry. The severity of illness was assessed using the Sequential Organ Failure Assessment (SOFA) score[17] and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score at the time of patient enrollment. The presence of septic shock, as defined by the Sepsis-3 criteria, was also determined. Sepsis-3 shock refers to sepsis with persistent hypotension requiring vasopressors to maintain a MAP ≥ 65 mmHg and a serum lactate level > 2 mmol/L, despite adequate fluid resuscitation.[15]

During the initial period following an ED visit, patients with septic shock often present with unstable vital signs, reflecting the acute phase. During this critical period, fluid resuscitation, administration of antibiotics, and vasopressor therapy are essential interventions that can significantly reduce mortality.[18] The KoSS registry includes variables regarding whether RBC transfusions were administered within six hours and 24 hours of the ED visit. To assess whether RBC transfusion during the acute resuscitation phase was associated with patient outcomes, the independent variable in this study was defined as the administration of RBC transfusion within the first six hours of the ED visit.

To account for the overall quality of septic shock management, we also collected data on adherence to the sepsis resuscitation bundle. These data included the time to antibiotic administration (categorized as < 1 hour, 1–3 hours, or ≥ 3 hours from the ED visit), whether at least 30 mL/kg of crystalloid fluid was administered within 3 hours, the achievement of a MAP > 65 mmHg (typically with vasopressors within 6 hours), and whether source control interventions, such as emergency surgery or percutaneous drainage, were performed.

The primary outcome of this study was in-hospital mortality.[19] First, whether in-hospital mortality differed between the transfusion and non-transfusion groups based on the Hb level was assessed. Subsequently, this outcome was examined within subgroups categorized by the lactate level.

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Statistical analysis

Categorical variables are presented as counts and percentages. Fisher's exact test was used to compare categorical variables between two groups. The normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution are presented as means and standard deviations, whereas those with a non-normal distribution are presented as medians and interquartile ranges (25th to 75th percentiles). The Student's *t*-test or the Wilcoxon rank-sum test was applied based on the results of the test for normality.

To evaluate the association between RBC transfusion within six hours and in-hospital mortality, multivariable logistic regression analyses were performed. The model was adjusted for potential confounding factors that might influence in-hospital mortality. These covariates included age, sex, SOFA score, APACHE II score, initial lactate level, and compliance with the sepsis bundle, specifically: timing of antibiotics, adequate fluid administration, use of vasopressors to maintain MAP > 65 mmHg, and source control. The results are presented as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). All statistical analyses were conducted using R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria) with the R Studio interface. Statistical significance was determined using two-sided, unpaired tests with a P value < 0.05.

Ethics statement

This study was approved by the Institutional Review Boards of Hanyang University Hospital (HYUH 2015-11-013-022), and informed consent was obtained before data collection. The study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

Basic characteristics of transfused patients

Of the 8,715 patients registered in the KoSS registry, four with missing Hb data were excluded, resulting in 8,711 being included in the analysis (**Fig. 1**). Among these, 535 patients had Hb < 7.0 g/dL, 1,599 had Hb 7.0–8.9 g/dL, and 6,577 had Hb ≥ 9.0 g/dL. The percentage of patients who received an RBC transfusion was 10.1% (884/8,711). For patients with Hb < 7.0 g/dL, Hb 7.0–8.9 g/dL, and Hb ≥ 9.0 g/dL, 69.9% (374/535), 23.1% (370/1,599), and

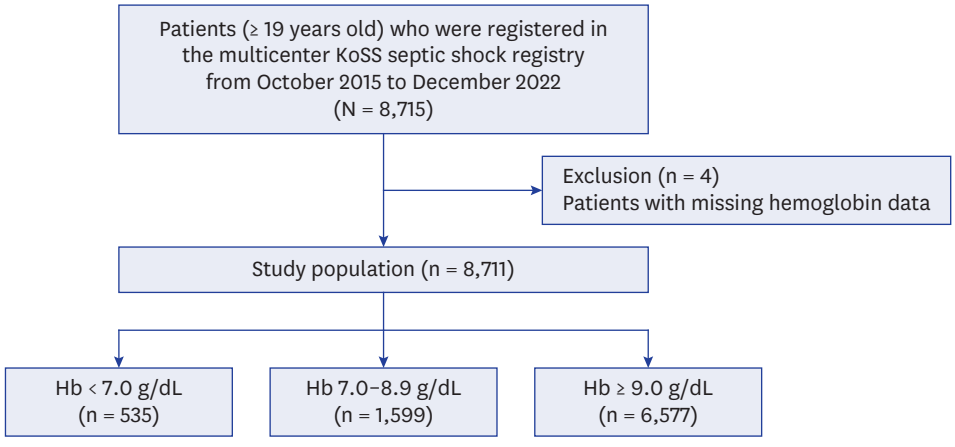

Fig. 1. Study flow diagram.
KoSS = Korean Shock Society, Hb = hemoglobin.

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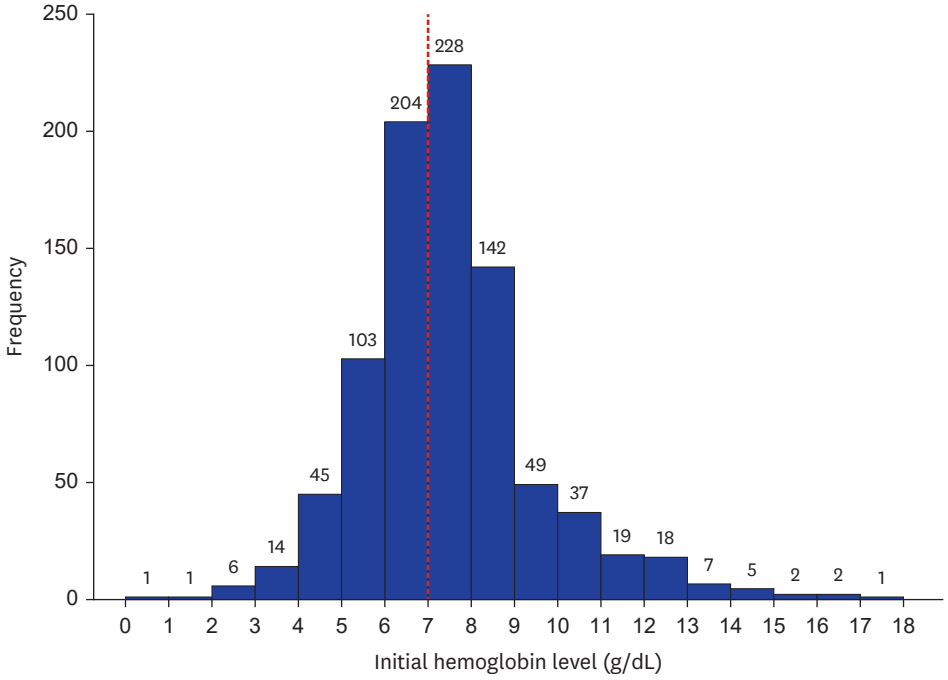

Fig. 2. Initial hemoglobin level of transfused patients with septic shock.

2.1% (140/6,577), respectively, received an RBC transfusion. Among the 884 patients who received an RBC transfusion, 510 (57.7%) were transfused at an Hb level ≥ 7 g/dL, exceeding the restrictive threshold (**Fig. 2**). Furthermore, 15.8% (140/884) of the patients who received an RBC transfusion were transfused at an Hb level ≥ 9.0 g/dL, which exceeds the liberal transfusion threshold.

To identify the factors associated with RBC transfusion, the baseline characteristics were compared between the transfusion and non-transfusion groups (**Table 1**). For the patients in the Hb 7.0–8.9 g/dL and Hb ≥ 9.0 g/dL groups, the transfusion group was younger than the non-transfusion group, whereas the Hb < 7.0 g/dL group had a higher percentage of females in the transfusion group. The severity of illness, as indicated by the SOFA score and the APACHE II score, was higher in the transfusion group than in the non-transfusion group across all groups of Hb level. In all groups, the initial Hb level was lower in the transfusion group than in the non-transfusion group. In terms of comorbidities, there was a greater percentage of patients with hematological malignancies in the transfusion group than in the non-transfusion group. For patients with metastatic cancer, this tendency was only in the Hb ≥ 9.0 g/dL group.

In the Hb 7.0–8.9 g/dL and Hb ≥ 9.0 g/dL groups, the transfusion group had a higher heart rate and a greater percentage of patients met the Sepsis-3 criteria for shock compared to the non-transfusion group. Notably, the initial lactate level was similar between the transfusion and non-transfusion groups in the Hb < 7.0 g/dL (median 3.4 mmol/L vs. 3.3 mmol/L, $P = 0.496$) and Hb 7.0–8.9 g/dL (3.2 mmol/L vs. 3.2 mmol/L, $P = 0.281$) groups. However, the initial lactate level was significantly higher in the transfusion group compared to the non-transfusion group in the Hb ≥ 9.0 g/dL group (median 5.3 mmol/L vs. 3.5 mmol/L, $P < 0.001$). The proportion of patients with sepsis from gastrointestinal infections was higher in the transfusion group across all Hb levels. Regarding sepsis treatment, a higher

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Table 1. Comparison of characteristics between non-transfused and transfused septic patients within 6 hours of emergency department visit, stratified by hemoglobin levels

Variables	Hb < 7.0 g/dL			Hb 7.0–8.9 g/dL			Hb ≥ 9.0 g/dL		
	No transfusion (n = 161)	Transfusion (n = 374)	*P* value	No transfusion (n = 1,229)	Transfusion (n = 370)	*P* value	No transfusion (n = 6,437)	Transfusion	*P* value
Age, yr	67.0 (59.0–75.0)	67.0 (57.0–75.0)	0.589	69.0 (60.0–77.0)	67.0 (59.0–75.0)	0.003	71.0 (62.0–79.0)	69.0 (58.0–77.0)	0.018
Female, sex	57 (35.4)	178 (47.6)	0.010	558 (45.4)	167 (45.1)	0.953	2,685 (41.7)	65 (46.4)	0.262
Initial hemoglobin	6.3 (5.8–6.7)	6.1 (5.3–6.5)	0.001	8.2 (7.8–8.6)	7.8 (7.4–8.3)	< 0.001	11.6 (10.3–13.0)	10.4 (9.6–11.9)	< 0.001
Severity score									
SOFA score	6.0 (4.0–8.0)	7.0 (5.0–10.0)	0.001	6.0 (4.0–9.0)	7.0 (5.0–9.0)	0.010	6.0 (4.0–8.0)	7.0 (4.5–10.0)	< 0.001
APACHE II score	25.0 (18.0–30.0)	26.0 (20.0–33.0)	0.027	22.0 (17.0–28.0)	25.0 (19.0–31.0)	< 0.001	19.0 (14.0–25.0)	25.0 (19.0–32.0)	< 0.001
Initial vital sign									
Systolic BP, mmHg	85.0 (76.0–99.0)	84.0 (75.0–95.0)	0.317	86.0 (77.0–96.0)	85.0 (76.0–95.0)	0.643	86.0 (76.0–99.0)	86.0 (74.0–99.0)	0.975
Heart rate, beats/min	104.6 ± 22.6	108.4 ± 21.2	0.060	102.0 (88.0–117.0)	107.0 (90.0–123.0)	0.004	103.0 (88.0–120.0)	111.5 (96.0–130.0)	< 0.001
Respiratory rate, breaths/min	20.0 (18.0–24.0)	20.0 (18.0–24.0)	0.886	20.0 (18.0–24.0)	20.0 (18.0–24.0)	0.707	20.0 (18.0–25.0)	21.0 (19.5–28.0)	0.050
Severity of shock									
Initial lactate, mmol/L	3.4 (2.1–5.7)	3.3 (2.1–7.3)	0.496	3.2 (1.7–5.4)	3.2 (1.9–5.9)	0.281	3.5 (2.0–5.6)	5.3 (3.1–8.4)	< 0.001
Sepsis-3 shock	102 (63.4)	228 (61.0)	0.629	684 (55.7)	235 (63.5)	0.008	3,548 (55.1)	108 (77.1)	< 0.001
Comorbidities									
Hypertension	53 (32.9)	133 (35.6)	0.621	499 (40.6)	148 (40.0)	0.856	2,833 (44.0)	52 (37.1)	0.121
Diabetes mellitus	54 (33.5)	110 (29.4)	0.358	429 (34.9)	109 (29.5)	0.052	2103 (32.7)	38 (27.1)	0.173
Cardiovascular disease	18 (11.2)	33 (8.8)	0.423	181 (14.7)	45 (12.2)	0.234	951 (14.8)	19 (13.6)	0.809
Cerebrovascular disease	15 (9.3)	27 (7.2)	0.483	142 (11.6)	43 (11.6)	1.000	859 (13.3)	9 (6.4)	0.016
Chronic lung disease	11 (6.8)	16 (4.3)	0.280	66 (5.4)	13 (3.5)	0.172	551 (8.6)	14 (10.0)	0.541
Hematologic malignancy	28 (17.4)	95 (25.4)	0.044	154 (12.5)	76 (20.5)	< 0.001	288 (4.5)	14 (10.0)	0.006
Metastatic cancer	61 (37.9)	147 (39.3)	0.773	485 (39.5)	166 (44.9)	0.070	1582 (24.6)	54 (38.6)	< 0.001
Chronic kidney disease	20 (12.4)	27 (7.2)	0.066	151 (12.3)	37 (10.0)	0.269	546 (8.5)	13 (9.3)	0.758
Chronic liver disease	19 (11.8)	34 (9.1)	0.346	140 (11.4)	37 (10.0)	0.509	641 (10.0)	18 (12.9)	0.255
Infection focus									
Respiratory	55 (34.2)	113 (30.2)	0.417	400 (32.5)	117 (31.6)	0.752	2,046 (31.8)	42 (30.0)	0.714
Urinary tract	38 (23.6)	75 (20.1)	0.358	303 (24.7)	76 (20.5)	0.109	1,745 (27.1)	21 (15.0)	0.001
Gastrointestinal	21 (13.0)	86 (23.0)	0.009	204 (16.6)	88 (23.8)	0.002	1,116 (17.3)	54 (38.6)	< 0.001
Hepatobiliary and pancreas	34 (21.1)	74 (19.8)	0.726	279 (22.7)	59 (15.9)	0.006	1,361 (21.1)	19 (13.6)	0.028
Soft tissue, bone, and joint	12 (7.5)	21 (5.6)	0.436	52 (4.2)	21 (5.7)	0.256	228 (3.5)	7 (5.0)	0.351
Blood stream	6 (3.7)	22 (5.9)	0.399	62 (5.0)	14 (3.8)	0.403	183 (2.8)	4 (2.9)	1.000
Unclear focus	20 (12.4)	36 (9.6)	0.357	80 (6.5)	28 (7.6)	0.479	418 (6.5)	7 (5.0)	0.602
Treatment									
Antibiotics[a]			0.047			0.409			0.513
< 1 hr	19 (11.8)	62 (16.6)		173 (14.1)	59 (15.9)		922 (14.3)	18 (12.9)	
1–3 hr	71 (44.1)	188 (50.3)		602 (49.0)	187 (50.5)		3,214 (49.9)	77 (55.0)	
≥ 3 hr	71 (44.1)	124 (33.2)		454 (36.9)	124 (33.5)		2,301 (35.7)	45 (32.1)	
Fluid > 30 mL/kg within 3 hr	118 (73.3)	265 (70.9)	0.602	887 (72.2)	280 (75.7)	0.204	4,751 (73.8)	111 (79.3)	0.173
MAP > 65 mmHg[b]	159 (98.8)	368 (98.4)	1.000	1,197 (97.4)	365 (98.6)	0.235	6,232 (96.8)	134 (95.7)	0.460
Source control[c]	35 (21.7)	75 (20.1)	0.643	280 (22.8)	88 (23.8)	0.725	1,545 (24.0)	48 (34.3)	0.007

Continuous variables were presented as mean ± standard deviation if normally distributed, and as median (25–75%) if not normally distributed. Categorical variables were presented as number (%).
Hb = hemoglobin, SOFA = Sequential Organ Failure Assessment, APACHE = Acute Physiologic Assessment and Chronic Health Evaluation, BP = blood pressure, MAP = mean arterial pressure.
[a]Time from emergency department visit to antibiotic administration; [b]Vasopressor use within 6 hours of enrollment to achieve MAP > 65 mmHg; [c]Source control intervention (e.g., emergency surgery, percutaneous drainage, endoscopic intervention, or removal of infected device, and other procedures).

Table 2. Comparison of mortality rates between non-transfused and transfused septic patients within 6 hours of emergency department visit, stratified by hemoglobin levels

Variables	Hb < 7.0 g/dL			Hb 7.0–8.9 g/dL			Hb ≥ 9.0 g/dL		
	No transfusion (n = 161)	Transfusion (n = 374)	*P* value	No transfusion (n = 1,229)	Transfusion (n = 370)	*P* value	No transfusion (n = 6,437)	Transfusion (n = 140)	*P* value
In-hospital mortality	59 (36.6)	155 (41.4)	0.336	363 (29.5)	112 (30.3)	0.795	1,373 (21.3)	66 (47.1)	< 0.001
28-day mortality	51 (31.7)	133 (36.6)	0.428	341 (27.7)	117 (31.6)	0.15	1306 (20.3)	61 (43.6)	< 0.001

Categorical variables were presented as number (%).

proportion of patients in the transfusion group received early antibiotic administration within the Hb < 7 g/dL group, while the proportion of patients who underwent source control was more frequently performed in the transfusion group among patients with Hb ≥ 9.0 g/dL. Otherwise, there were no significant differences in sepsis treatment between the transfusion and non-transfusion groups.

RBC transfusion and mortality

First, the in-hospital mortality rate between the transfused and non-transfused groups for each Hb level group was compared (**Table 2**). There was no significant difference in in-hospital mortality between the transfused and non-transfused groups in the Hb < 7.0 g/dL group (41.4% vs. 36.6%, $P = 0.336$) and the Hb 7.0–8.9 g/dL group (30.3% vs. 29.5%, $P = 0.795$). However, in the Hb ≥ 9.0 g/dL group, the transfused group had an in-hospital mortality rate that was more than double that for the non-transfused group (47.1 vs. 21.3%, $P < 0.001$). A similar trend was observed for the 28-day mortality rate (**Table 2**).

Fig. 3 presents the results of the multivariable logistic regression analyses. In the Hb < 7.0 g/dL group (aOR, 0.86; 95% CI, 0.54–1.37) and the Hb 7.0–8.9 g/dL group (aOR, 0.79; 95% CI, 0.59–1.06), there was no significant association between RBC transfusion and in-hospital mortality. However, in the Hb ≥ 9.0 g/dL group, RBC transfusion was associated with an increased in-hospital mortality rate (aOR, 1.99; 95% CI, 1.34–2.93).

To investigate the role of lactate, we examined the association between RBC transfusion and in-hospital mortality within subgroups defined by lactate levels, < 2 mmol/L, 2–3.9 mmol/L, and ≥ 4 mmol/L was assessed (**Fig. 3**). In the Hb < 7.0 g/dL group and the Hb 7.0–8.9 g/dL group, there was no significant difference in in-hospital mortality rates according to RBC transfusion status for any lactate level group. In the Hb ≥ 9.0 g/dL group, in-hospital mortality did not differ significantly between groups based on RBC transfusion status for the lactate level < 2 mmol/L group (aOR, 0.69; 95% CI, 0.10–3.09). However, RBC transfusion was associated with an increased in-hospital mortality rate for the lactate level groups 2–3.9 mmol/L (aOR, 3.54; 95% CI, 1.65–7.44) and ≥ 4 mmol/L (aOR, 1.70; 95% CI, 1.06–2.74).

DISCUSSION

In this study, we found that for 57.7% of patients with sepsis and septic shock the restrictive transfusion threshold of 7 g/dL for Hb was not followed. Overall, transfusions were more commonly administered to patients with more severe conditions, and the Hb ≥ 7.0 g/dL transfusion group had a higher percentage of patients with sepsis-3 shock. Notably, in the Hb ≥ 9.0 g/dL group, the lactate level was significantly higher in the transfusion group compared to the non-transfusion group. However, no improvement in in-hospital mortality was observed in the transfusion groups across the Hb < 7.0 g/dL, Hb 7.0–8.9 g/dL, and

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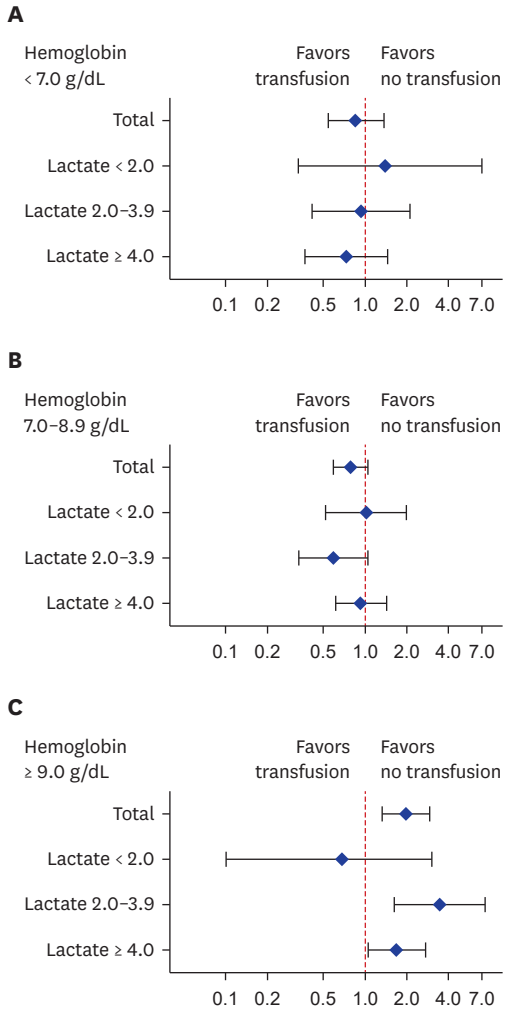

	In-hospital mortality No./total No. (%)		
	aOR (95% CI)	No transfusion	Transfusion
A			
Total	0.86 (0.54–1.37)	59/161 (36.6)	155/374 (41.4)
Lactate < 2.0	1.41 (0.33–6.94)	4/36 (11.1)	22/83 (26.5)
Lactate 2.0–3.9	0.94 (0.42–2.13)	17/54 (31.5)	41/125 (32.8)
Lactate ≥ 4.0	0.74 (0.37–1.46)	38/71 (53.5)	92/166 (55.4)
B			
Total	0.79 (0.59–1.06)	363/1,229 (29.5)	112/370 (30.3)
Lactate < 2.0	1.03 (0.52–1.98)	62/367 (16.9)	18/101 (17.8)
Lactate 2.0–3.9	0.60 (0.33–1.05)	85/356 (23.9)	23/120 (19.2)
Lactate ≥ 4.0	0.93 (0.61–1.42)	216/506 (42.7)	71/149 (47.7)
C			
Total	1.99 (1.34–2.93)	1,373/6,437 (21.3)	66/140 (47.1)
Lactate < 2.0	0.69 (0.10–3.09)	163/1,562 (10.4)	2/15 (13.3)
Lactate 2.0–3.9	3.54 (1.65–7.44)	328/2,012 (16.3)	15/36 (41.7)
Lactate ≥ 4.0	1.70 (1.06–2.74)	882/2,863 (30.8)	49/89 (55.1)

Fig. 3. Adjusted odds ratios of in-hospital mortality for transfusion vs non-transfusion by hemoglobin and lactate level groups. The multivariable logistic regression model was adjusted for age, sex, Sequential Organ Failure Assessment score, Acute Physiology and Chronic Health Evaluation II score, and compliance with the sepsis bundle (Specifically: timing of antibiotics, adequate fluid administration, use of vasopressors to maintain MAP > 65 mmHg, and source control interventions).
aOR = adjusted odds ratio, CI = confidence interval.

Hb ≥ 9.0 g/dL groups, and the benefits of transfusion were not confirmed in the analysis based on the lactate level.

The transfusion guidelines of the European Society of Intensive Care Medicine for non-bleeding critically ill adults recommend a restrictive transfusion threshold (7 g/dL) rather than a liberal transfusion threshold (9 g/dL) for critically ill adult patients with sepsis and septic shock.[7] This recommendation is based on the evidence that, although there was no difference in outcomes between restrictive and liberal thresholds, the restrictive transfusion strategy significantly reduced the amount of transfused blood. The TRISS trial, published in 2014, is a landmark randomized controlled trial (RCT) on transfusion thresholds in patients with septic shock.[20] This study involved 998 patients with septic shock and an Hb level ≤ 9 g/dL. A single unit of leuko-reduced RBCs was transfused to patients with an Hb level ≤ 7 g/dL (lower threshold) or ≤ 9 g/dL (upper threshold) during their stay in the intensive care unit (ICU). The 90-day mortality rates were statistically similar between the

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two groups (43.0% vs. 45.0%, $P = 0.44$). However, the lower-threshold group received a median of one unit of blood, whereas the higher-threshold group received a median of four units of blood during their stay in the ICU. When these patients were followed up for more than one year, there was no difference in the mortality rate or health-related quality of life between the groups.[21] A meta-analysis that analyzed 1,516 patients from three RCTs also found no difference in 28–30 day mortality between the lower and higher Hb threshold groups (pooled OR, 0.99; 95% CI, 0.67–1.46).[22] Guidelines for various critically ill patients, including those with sepsis, recommend restrictive transfusion strategies (low Hb threshold, 7–8 g/dL).[7,8,23]

However, in clinical practice, RBC transfusions are often administered at an Hb level higher than the recommended thresholds. More than 50% of the patients with septic shock in our study received transfusions at an Hb level > 7 g/dL. However, studies investigating transfusion practices, specifically in patients with septic shock, are limited. The InPUT Study, an international prospective cohort study on transfusion practices in ICUs, included 3,643 patients across 233 ICUs in 30 countries.[24] The study reported that the median Hb level at the time of transfusion varied widely among the ICUs, ranging from 5.2 g/dL to 13.1 g/dL. Notably, only 16% of the patients in the ICUs had a median Hb level below 7 g/dL at the time of transfusion. However, detailed information on subgroups of patients with septic shock is unavailable. In a study conducted on 154 critically ill patients admitted to the ICU from the EDs of five university hospitals in Korea, 46.1% (71/154) who received an RBC transfusion had an Hb level ≥ 7.0 g/dL.[25] In the subgroup of 86 patients with sepsis, 31 (36%) received a transfusion, with 64.5% of them receiving a transfusion at an Hb level ≥ 7.0 g/dL. In these two studies, elevated lactate level, tachycardia, and hypotension were reported as the physiological triggers for transfusion.[24,25] In our study, this trend was not observed in patients with an Hb level < 7 g/dL. However, in the Hb ≥ 7.0 g/dL group, the transfusion group had a faster heart rate and a higher percentage of patients with sepsis-3 shock compared to the non-transfusion group, reflecting a more pronounced shock state. Additionally, in the Hb ≥ 9.0 g/dL group, the lactate level was higher in the transfusion group compared to the non-transfusion group. Overall, our data show that transfusions were more frequently administered to patients with an elevated lactate level and more severe shock.

Subsequently, we examined whether the in-hospital mortality rate differed in patients with a higher Hb level, contrary to the guidelines and recommendations. In the Hb < 7.0 g/dL and Hb 7.0–8.9 g/dL groups, there was no difference in the in-hospital mortality rate between the transfusion and non-transfusion groups. However, in the Hb ≥ 9.0 g/dL group, even after adjusting for confounding factors, the transfusion group had worse outcomes. This could be explained by the direct harmful effects of transfusions. Alternatively, transfusions may have been administered to patients with more severe conditions who were expected to have poorer prognoses and were potentially influenced by unmeasured confounding factors. Regardless, better outcomes were not observed in the transfusion group compared to the non-transfusion group in any patients. Furthermore, when we assessed the in-hospital mortality rate according to the lactate level, a marker of severe shock and low perfusion, no favorable outcomes were observed in the transfusion group. In patients with Hb ≥ 9.0 g/dL and lactate ≥ 2 mmol/L, the transfusion group had even worse outcomes. Although transfusions were more commonly administered in patients with elevated lactate levels, this was not associated with improved clinical outcomes.

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This study should be interpreted with the following limitations. First, the analysis was conducted based on Hb levels measured at the time of the ED presentation and RBC transfusions performed within the first six hours after the ED visit. However, considering that a patient's Hb level may change even during this acute phase, it is possible that the initially measured Hb level may not fully reflect the hematological status at the time of RBC transfusion or decision-making regarding transfusion. Moreover, evaluating the amount of transfusion and corresponding changes in Hb concentration could provide a more dynamic perspective. Unfortunately, such analyses were not feasible in this study because of the lack of relevant data within the registry. Therefore, there are limitations to interpreting the physiological impact or effectiveness of individual transfusions in each patient. Second, we were unable to adjust for potential confounding related to specific clinical indications for transfusion. This limitation arose due to a lack of information regarding whether transfusions were administered to improve oxygen delivery, blood management in preparation for invasive procedures, or active bleeding. According to previous literature, the proportion of transfusions attributable to bleeding in patients with sepsis was 20.6%, and large-scale studies reporting transfusion practices in critically ill patients have documented that non-bleeding accounted for 75.2–81.8% of transfusions.[24,26,27] In sepsis, the primary purpose of transfusion was predominantly to improve oxygen delivery. Nevertheless, the inability to adjust for potential confounding factors based on transfusion indications may have resulted in residual confounding bias. The relatively large patient population may have mitigated this limitation. Third, this study did not prospectively apply restrictive or liberal transfusion thresholds. From the registry data, we used the initial Hb level and whether RBC transfusion was performed within six hours as independent variables. However, these data are valuable in assessing transfusion practices. Fourth, this study focused on patients with acute sepsis in EDs, and the outcomes of patients with sepsis in hospital wards and ICUs may differ. Additionally, as this multicenter study was conducted in Korea, the results for patients with septic shock in other countries may vary. Further studies are required to elucidate these discrepancies.

This study found that transfusions were frequently administered to patients with septic shock, despite not following restrictive transfusion thresholds. Additionally, transfusions were more commonly administered to patients with a higher lactate level and more severe shock. However, no improvement in in-hospital mortality was observed across various lactate and Hb levels.

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