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Relationship between low hemoglobin levels and mortality in patients with septic shock

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Background: Hemoglobin levels are a critical parameter for oxygen delivery in patients with shock. On comparing target hemoglobin levels upon transfusion initiation, the correlation between the severity of decrease in hemoglobin levels and patient outcomes remains unclear. We evaluated the association between initial hemoglobin levels and mortality in patients with septic shock treated with protocol-driven resuscitation bundle therapy at an emergency department.

Methods: Data of adult patients diagnosed with septic shock between June 2012 and December 2016 were extracted from a prospectively compiled septic shock registry at a single academic medical center. Patients were classified into four groups according to initial hemoglobin levels: ≥9.0 g/dl, 8.0–8.9 g/dl, 7.0–7.9 g/dl, and <7.0 g/dl. The primary endpoint was 90-day mortality.

Results: In total, 2,265 patients (male, 58.3%; median age, 70.0 years [interquartile range, 60 to 78 years]) with septic shock were included. For the four groups, 90-day mortality rates were as follows: 29.1%, 43.0%, 46.5%, and 46.9% for ≥9.0 g/dl (n=1,808), 8.0–8.9 g/dl (n=217), 7.0–7.9 g/dl (n=135), and <7.0 g/dl (n=105), respectively (P<0.001). Multivariate logistic regression showed that initial hemoglobin levels were an independent factor associated with 90-day mortality and mortality proportionally increased with decreasing hemoglobin levels (odds ratio [OR], 1.88; 95% confidence interval [CI], 1.36 to 2.61 for 8.0–8.9 g/dl; OR, 1.97; 95% CI, 1.31 to 2.95 for 7.0–7.9 g/dl; and OR, 2.35; 95% CI, 1.52 to 3.63 for <7.0 g/dl).

Conclusions: Low hemoglobin levels (<9.0 g/dl) were observed in approximately 20% of patients with septic shock, and the severity of decrease in these levels correlated with mortality.

Key Words: anemia; mortality; septic shock

INTRODUCTION

Low hemoglobin levels are frequently observed in patients with septic shock and may have several underlying causes, including reduced red blood cell (RBC) production due to systemic inflammatory response and increased RBC destruction due to hemolysis and bleeding [1]. In these patients, low hemoglobin levels may augment tissue oxygenation impairment by decreasing arterial oxygen concentration. Therefore, maintenance of adequate blood hemoglobin levels has been proposed as a strategy to diminish shock-induced tissue damage [2].

Although immediate hemoglobin correction <7.0 g/dl is one of the goals of transfusion, the critical hemoglobin concentration in critically ill patients at which oxygen delivery get

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impaired, tissue hypoxia ensues, and the risk of adverse outcomes increases has not been determined yet. In patients with septic shock, targeting a hematocrit value of 30% in those with a low central venous oxygen saturation during the first 6 hours of resuscitation [3] has been proposed [4]. However, blood transfusion has been associated with increased mortality in subgroups of critically ill patients, both in cohort studies and in randomized trial [5-8]. In a recent study investigating optimal hemoglobin levels in cases of septic shock, transfusion thresholds of 7 g/dl and 9 g/dl were compared and similar 90-day mortality rates were observed [9]. Current Surviving Sepsis Campaign guidelines recommend that RBC transfusion should be performed only when hemoglobin levels decrease to <7.0 g/dl in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage [10].

Low hemoglobin levels at the time of admission to the emergency department (ED) may indicate insufficient tissue oxygenation and may reflect that inflammation is more severe in such patients than in those with septic shock with normal hemoglobin levels. However, it remains unclear whether the severity of decrease in these levels correlates with patient outcomes. Therefore, we aimed to evaluate the association between initial hemoglobin levels and mortality in patients with septic shock treated with protocol-driven resuscitation bundle therapy at a hospital's ED.

KEY MESSAGES

- In patients with septic shock, low hemoglobin levels are frequently observed due to several underlying mechanisms.
- Hemoglobin levels are a critical parameter for oxygen delivery in patients with shock.
- In patients with septic shock, mortality increases with decreasing initial hemoglobin levels.

MATERIALS AND METHODS

Setting and Study Population

Asan Medical Center has an annual ED patient volume of approximately 110,000 patients and serves as a tertiary referral center in Seoul, Korea. All adult patients (aged ≥18 years) with septic shock in ED and treated with protocol-driven resuscitation bundle therapy were consecutively enrolled, and their data were prospectively collected from the center's septic shock registry. Septic shock was defined as the presence of refractory hypotension (mean arterial pressure ≤70 mmHg) requiring treatment with vasopressors or blood lactate concentration ≥4 mmol/L despite sufficient fluid loading. Patients with a "do not attempt resuscitation" status and those who were transferred to another hospital during the initial resuscitation phase were not included. A single-center, retrospective, observational, and registry-based study was, therefore, conducted to analyze consecutive patients with septic shock diagnosed from June 1, 2012, to December 31, 2016. Study protocol was approved by the Institutional Research Ethics Committee (No. 2015-1253) and informed consent requirement waived due to the retrospective nature of the study.

Management

All patients with septic shock were treated with protocol-driven resuscitation bundle therapy, if indicated, including initial crystalloid bolus infusions, blood culture, broad-spectrum antibiotics, vasopressors, lung-protective ventilation, glucocorticoids, and surgical intervention. In accordance with the Surviving Sepsis Campaign guidelines, blood culture was obtained, empirical antibiotic therapy initiated, and initial lactate levels determined within 3 hours of shock recognition. No specific transfusion protocol was followed during the study, with transfusion being performed at the discretion of the treating physician.

Data Collection and Definition

There are many factors affecting mortality in patients with septic shock, but this study focused on patient's factors. Demographic and clinical data including age, sex, previous medical history, symptoms, initial vital signs, site of infection, and the first laboratory values at the time of admission were retrieved from the septic shock registry [11-15]. Data on initial hemoglobin levels at the time of admission to ED and on whether blood transfusions were performed were also examined to determine the relationship between hemoglobin and mortality. Hemoglobin was applied as a continuous variable, and patients were stratified into four groups according to initial hemoglobin levels: ≥9.0 g/dl, 8.0–8.9 g/dl, 7.0–7.9 g/dl, and <7.0 g/dl. Hemoglobin levels <9.0 g/dl were defined as low. In addition, multivariable analysis was performed by adding the Sequential Organ Failure Assessment (SOFA) score to adjust the severity of patients with septic shock. The primary endpoint was 90-day mortality.

Statistical Analysis

Statistical analyses were performed using IBM SPSS ver. 23.0

(IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR) if the assumption of a normal distribution was violated. Categorical variables were expressed as numbers and percentages. To adjust for confounding variables and assess possible effect modification, multivariate logistic regression analyses were performed. Results were reported as odds ratio (OR) and 95% confidence interval (CI). All tests were two-sided, and a P-value <0.01 was considered significant.

RESULTS

A total of 2,265 adult patients with septic shock were enrolled in the ED septic shock registry during the study period. The median age was 70.0 years (IQR, 60 to 78 years), and 58.3% patients were male. Hypertension was the most common comorbidity, observed in 41.2% of patients. Initial low hemoglobin levels (<9.0 g/dl) were observed in 457 patients (20.2%). The characteristics of each group are detailed in Table 1. For the four groups, 90-day mortality rates were as follows: 29.1%,

Table 1. Baseline and clinical characteristics of study patients according to initial hemoglobin levels

Characteristics	Total cohort (n=2,265)	Hb ≥9.0 g/dl (n=1,808)	Hb 8.0–8.9 g/dl (n=217)	Hb 7.0–7.9 g/dl (n=135)	Hb <7.0 g/dl (n=105)	P-value
Age (yr)	70.0 (60.0–78.0)	71.0 (60.0–78.0)	68.0 (59.0–77.0)	69.0 (59.0–78.0)	65.0 (55.0–72.0)	<0.001
Male	1,321 (58.3)	1,060 (58.6)	116 (53.5)	77 (57.0)	68 (64.8)	0.254
Comorbid disease						
Hypertension	933 (41.2)	762 (42.1)	89 (41.0)	52 (38.5)	30 (28.6)	0.046
Diabetes mellitus	690 (30.5)	544 (30.1)	69 (31.8)	41 (30.4)	36 (34.3)	0.795
Cerebrovascular accident	278 (12.3)	234 (12.9)	26 (12.0)	12 (8.9)	6 (5.7)	0.094
Chronic pulmonary disease	180 (7.9)	156 (8.6)	12 (5.5)	9 (6.7)	3 (2.9)	0.075
Chronic renal disease	167 (7.4)	130 (7.2)	17 (7.8)	15 (11.1)	5 (4.8)	0.265
Infection						0.206
Respiratory	563 (24.9)	452 (25.0)	59 (27.2)	32 (23.7)	20 (19.0)	
Urinary	427 (18.9)	359 (19.9)	36 (16.6)	17 (12.6)	15 (14.3)	
Gastrointestinal	293 (12.9)	238 (13.2)	24 (11.1)	21 (15.6)	10 (9.5)	
Hepatobiliary and pancreas	408 (18.0)	319 (17.6)	42 (19.4)	24 (17.8)	23 (21.9)	
Soft tissue	61 (2.7)	52 (2.9)	4 (1.8)	3 (2.2)	2 (1.9)	
Others	114 (5.0)	78 (4.3)	16 (7.4)	10 (7.4)	10 (9.5)	
Mixed	262 (11.6)	205 (11.3)	24 (11.1)	17 (12.6)	16 (15.2)	
Unknown	137 (6.0)	105 (5.8)	12 (5.5)	11 (8.1)	9 (8.6)	
Laboratory finding						
White blood cell count (10^3/μl)	10.55 (5.37–17.15)	11.01 (6.00–17.48)	8.80 (3.30–14.42)	7.90 (2.47–14.86)	6.34 (0.64–18.40)	<0.001
Hemoglobin (g/dl)	11.1 (9.3–12.8)	11.7 (10.5–13.1)	8.5 (8.2–8.7)	7.6 (7.3–7.7)	6.3 (5.6–6.6)	<0.001
Hematocrit (%)	33.6 (28.6–38.4)	35.4 (31.8–39.5)	25.9 (25.0–26.8)	22.8 (22.0–23.7)	19.0 (17.0–20.7)	<0.001
Platelet (10^3/μl)	148.0 (83.0–227.8)	155.5 (98.0–234.0)	105.0 (49.5–173.0)	89.0 (40.0–194.0)	62.0 (26.0–199.3)	<0.001
PT (INR)	1.26 (1.13–1.47)	1.24 (1.12–1.43)	1.34 (1.17–1.58)	1.37 (1.20–1.61)	1.42 (1.27–1.61)	<0.001
Creatinine (mg/dl)	1.34 (0.92–2.14)	1.33 (0.92–2.13)	1.38 (0.89–2.19)	1.33 (0.96–2.26)	1.30 (0.99–2.01)	0.904
CRP (mg/dl)	12.4 (4.5–21.9)	11.92 (3.82–21.64)	13.76 (6.32–22.12)	13.25 (5.00–22.73)	14.51 (7.61–23.45)	0.035
CRP >0.6 mg/dl	2,102 (92.8)	1,674 (92.6)	205 (94.5)	123 (91.1)	100 (95.2)	0.468
Severity score						
SOFA score	8.0 (6.0–11.0)	8.0 (5.0–10.0)	9.0 (6.0–11.0)	9.0 (6.0–11.0)	9.0 (6.0–12.0)	<0.001
APACHE II score	19.0 (13.0–25.0)	18.0 (13.0–24.0)	21.0 (16.0–28.0)	20.0 (16.0–25.0)	24.0 (18.0–30.0)	<0.001

Values are presented as median (interquartile range) or number (%).
Hb: hemoglobin; PT: prothrombin time; INR: international normalized ratio; CRP: C-reactive protein; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation.

43.0%, 46.5%, and 46.9% for ≥9.0 g/dl (n=1,808), 8.0–8.9 g/dl (n=217), 7.0–7.9 g/dl (n=135), and <7.0 g/dl (n=105), respectively, (P<0.001); 90-day mortality increased with decreasing initial hemoglobin levels. Analyses of white blood cell and platelet counts and prothrombin time revealed that the group with low hemoglobin levels had decreased leukocyte and platelet counts and increased prothrombin time (Table 1).

Patients with septic shock were treated with bundle therapy

Table 2. Treatment and outcomes of study patients according to initial hemoglobin levels

Treatment	Total cohort (n=2,265)	Hb ≥9.0 g/dl (n=1,808)	Hb 8.0–8.9 g/dl (n=217)	Hb 7.0–7.9 g/dl (n=135)	Hb<7.0 g/dl (n=105)	P-value
Fluid resuscitation <3 hr	1,630 (72.0)	1,302 (72.1)	156 (71.9)	98 (72.6)	74 (70.5)	0.985
Antibiotic administration <3 hr	1,479 (65.3)	1,171 (64.8)	141 (65.0)	95 (70.4)	72 (68.6)	0.525
Vasopressor use	2,001 (88.4)	1,597 (88.4)	193 (88.9)	121 (89.6)	90 (85.7)	0.802
Central line insertion <6 hr	1,382 (61.0)	1,110 (61.4)	125 (57.6)	90 (66.7)	57 (54.3)	0.172
Mechanical ventilator	628 (27.7)	498 (27.5)	64 (29.5)	29 (21.5)	37 (35.2)	0.114
Renal replacement therapy <24 hr	209 (9.2)	172 (9.5)	16 (7.4)	8 (5.9)	13 (12.4)	0.254
Transfusion <6 hr						
pRBC	174 (7.7)	28 (1.5)	31 (14.3)	45 (33.3)	70 (66.7)	<0.001
FFP	99 (4.4)	58 (3.2)	11 (5.1)	10 (7.4)	20 (19.0)	<0.001
PC	144 (6.4)	59 (3.3)	31 (14.3)	18 (13.3)	36 (34.3)	<0.001
Outcome						
28-Day mortality[a]	452 (21.1)	325 (19.1)	56 (27.3)	35 (26.7)	36 (35.0)	<0.001
90-Day mortality[b]	612 (32.5)	433 (29.1)	80 (43.0)	53 (46.5)	46 (46.9)	<0.001

Values are presented as number (%).
Hb: hemoglobin; pRBC: packed red blood cell; FFP: fresh frozen plasma; PC: platelet concentrates.
[a]A total of 126 patients (108 in Hb ≥9.0 g/dl, 12 in Hb 8.0–8.9 g/dl, 4 in Hb 7.0–7.9 g/dl, and 2 in Hb <7.0 g/dl) were lost to follow-up; [b]A total of 308 patients (267 in Hb ≥9.0 g/dl, 19 in Hb 8.0–8.9 g/dl, 16 in Hb 7.0–7.9 g/dl, and 6 in Hb <7.0 g/dl) were lost to follow-up.

Table 3. Odds ratios for 90-day mortality rates calculated using univariate and multivariate logistics analyses

Characteristics	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (yr)	1.020 (1.012–1.028)	<0.001	1.027 (1.018–1.036)	<0.001
Female sex	0.759 (0.622–0.926)	0.007		
Comorbid disease				
Hypertension	0.969 (0.796–1.179)	0.752		
Diabetes mellitus	1.221 (0.995–1.500)	0.056		
Cerebrovascular accident	1.154 (0.859–1.552)	0.342		
Chronic pulmonary disease	1.532 (1.100–2.134)	0.012	1.522 (1.072–2.161)	0.019
Chronic renal disease	1.426 (1.008–2.018)	0.045		
Laboratory finding				
Hemoglobin (g/dl)	0.888 (0.853–0.923)	<0.001		
Hemoglobin range (g/dl)				
≥9.0	Reference		Reference	
8.0–8.9	1.835 (1.345–2.505)	<0.001	1.883 (1.358–2.611)	<0.001
7.0–7.9	2.113 (1.438–3.104)	<0.001	1.966 (1.309–2.953)	0.001
<7.0	2.151 (1.425–3.249)	<0.001	2.349 (1.519–3.630)	<0.001
Initial SOFA score	1.199 (1.160–1.239)	<0.001	1.199 (1.160–1.241)	<0.001
pRBC transfusion <6 hr	0.712 (0.611–0.830)	<0.001		

OR: odds ratio; CI: confidence interval; SOFA: Sequential Organ Failure Assessment; pRBC: packed red blood cell.

including fluid therapy, empirical antibiotics, and vasopressors. Intubation, mechanical ventilation, and renal replacement therapy results are summarized in Table 2. No significant differences were observed among the four groups for bundle therapy. Not surprisingly, transfusion frequency was higher in patients with low hemoglobin levels (Table 2).

Multivariate logistic regression analyses revealed that age, chronic pulmonary disease and initial SOFA score were associated with 90-day mortality rate (Table 3). Initial hemoglobin levels were independently associated with 90-day mortality, and mortality proportionally increased with decreasing hemoglobin levels (OR, 1.88; 95% CI, 1.36 to 2.61 for 8.0–8.9 g/dl; OR, 1.97; 95% CI, 1.31 to 2.95 for 7.0–7.9 g/dl; and OR, 2.35; 95% CI, 1.52 to 3.63 for <7.0 g/dl). However, there was no statistical correlation between RBC transfusion within 6 hours and 90-day mortality rate. Further analysis about the association of 28-day mortality and hemoglobin level were summarized in Supplementary Table 1.

DISCUSSION

Anemia is a common problem in critically ill patients. The present study showed that approximately 20% of patients with septic shock who visited ED had low hemoglobin levels (<9 g/dl). A large observational study including 3,534 patients from European intensive care units reported mean hemoglobin levels at admission to be 11.3 g/dl, with 29% patients having levels <10 g/dl [16]. In a prospective cohort study [17], 55% of all patients had hemoglobin levels <9 g/dl, a higher rate than that observed in the present septic shock cohort. One possible explanation is the fact that blood loss (due to trauma, surgical procedures, or occult gastrointestinal bleeding), one of the most common cause of anemia in critically ill patients, is less common in patients with septic shock. Sepsis is a complex pathophysiological process, and possible underlying mechanisms include microcirculation alterations, decreased RBC production, pre-existing chronic anemia, hemodilution, and increased RBC destruction due to alterations in RBC membranes.

Current guidelines recommend that the transfusion threshold should be hemoglobin levels <7 g/dl, aiming at levels between 7 g/dl and 9 g/dl in patients without myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease [10]. However, there are limited data supporting these recommendations [10], and many clinicians do not comply with these, despite findings from the transfusion requirements in septic shock trial, which compared transfusion thresholds of 7 g/dl and 9 g/dl, showing similar 90-day mortality rates (45% vs. 43%) in patients with septic shock [9].

In the present study, we found that percentage of patients with 90-day mortality increased with decreasing initial hemoglobin levels. Moreover, multivariate logistic regression analysis revealed that initial hemoglobin levels were independently associated with 90-day mortality and mortality proportionally increased with decreasing hemoglobin levels. These data suggest that, apart from being a therapeutic target, initial hemoglobin levels may also be a prognostic factor. This hypothesis is consistent with the results from a recent small observational study by Muady et al. [1] reporting that hemoglobin levels on admission independently correlate with survival (OR, 0.83; 95% CI, 0.75 to 0.92). Furthermore, a study of patients with community-acquired pneumonia found that hemoglobin levels <10 g/dl were independently associated with 90-day mortality [18]. Although it is known that lower hemoglobin levels in the setting of increased oxygen demand, frequently observed in septic shock cases, may play a negative role and augment organ dysfunction, the prognostic relevance of low hemoglobin levels may alternatively be explained by the fact that it may also reflect older age or a high rate of comorbidities.

Although this study showed that transfusion had no significant association with mortality, previous studies investigating the correlation between blood transfusion and mortality in sepsis found conflicting results [19-21]. As previously mentioned, at the hospital where this study was conducted, decision regarding a blood transfusion relies on the treating physician's discretion rather than on a specific transfusion protocol. Thus, it would be actively administration of blood products in more severely ill patients. The present study revealed poor patient outcomes associated with low hemoglobin levels at presentation. However, due to the observational nature of our study, these results do not support definite conclusions about optimal hemoglobin levels and about an optimal blood transfusion strategy for patients with septic shock. Another limitation of this study that is worth mentioning is its retrospective design, which necessarily impacted data collection, analysis, and interpretation. Although this was addressed through an adjusted multivariate analysis, the potential for bias due to an unmeasured confounder remains. For example, the initial patient's condition may affect mortality, but the physician's management, such as appropriate selection of empirical antibiotics, may also affect patient's mortality. However, data beyond the contents of the registry could not be evaluated. Additionally, this cohort comprised patients from a single medical center; thus, the results may be influenced by re-

ferral bias. Conversely, the consecutive enrollment of patients with septic shock with a prospective registry reflects a real-world scenario, free of typically observed inclusion biases.

In this study, low hemoglobin levels (<9.0 g/dl) were observed in approximately 20% of patients with septic shock, and the severity of decrease in these levels correlated with mortality. However, transfusion itself was not an independent factor affecting mortality. These findings suggest that initial hemoglobin levels may play a role as a prognostic factor and that a better understanding of the etiology of low hemoglobin levels may prompt the investigation of new preventive therapeutic strategies.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: WYK. Data curation: SMJ, YJK. Formal analysis: YJK, SMR. Methodology: SMR, WYK. Project administration: WYK. Visualization: SMJ, YJK. Writing - original draft: SMJ. Writing - review & editing: WYK.

SUPPLEMENTARY MATERIALS

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Supplementary Table 1. ORs for 28-day mortality rates calculated using univariate and multivariate logistics analyses

Characteristics	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (yr)	1.019 (1.010–1.027)	<0.001	1.024 (1.014–1.033)	<0.001
Female sex	0.752 (0.607–0.932)	0.009		
Comorbid disease				
Hypertension	1.040 (0.843–1.284)	0.714		
Diabetes mellitus	1.258 (1.009–1.568)	0.041		
Cerebrovascular accident	1.246 (0.918–1.691)	0.157		
Chronic pulmonary disease	1.930 (1.373–2.713)	<0.001	1.999 (1.388–2.880)	<0.001
Chronic renal disease	1.457 (1.017–2.088)	0.040		
Laboratory finding				
Hemoglobin (g/dl)	0.919 (0.882–0.958)	<0.001		
Hemoglobin range (g/dl)				
≥9.0	Reference		Reference	
8.0–8.9	0.440 (0.288–0.671)	<0.001	1.599 (1.126–2.269)	0.009
7.0–7.9	0.699 (0.421–1.163)	0.168	1.368 (0.890–2.103)	0.153
<7.0	0.679 (0.388–1.188)	0.175	2.499 (1.590–3.930)	<0.001
Initial SOFA score	1.243 (1.201–1.287)	<0.001	1.249 (1.204–1.294)	<0.001
pRBC transfusion <6 hr	0.712 (0.606–0.836)	<0.001		

OR: odds ratio; CI: confidence interval; SOFA: Sequential Organ Failure Assessment; pRBC: packed red blood cell.