Association between anemia and ICU outcomes

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To the Editor: Anemia is a common finding among patients admitted to intensive care units (ICUs), nearly 60% of ICU patients had serum hemoglobin levels <12 g/dL at baseline, 30% of whom had serum hemoglobin levels <9 g/dL, over 95% of critically ill patients were anemic within 3 days of ICU admission.[1] Moreover, anemia may be aggravated or newly developed in critically ill patients during their ICU stay.

Severe anemia could result in a decline in oxygen delivery, and hence, it may affect heart, kidney, metabolic pathway, and brain function among critically ill patients.[2] As a result, anemia could be associated with worse outcomes during critical illnesses. The role of anemia in the prognosis of critically ill patients remains debated. While anemia has been reported to be associated with prolonged length of ICU or hospital stay and increased mortality rate among critically ill patients suffering from sepsis, cardiogenic shock, or trauma in some studies, in some other investigations these outcomes were not observed in patients with chronic obstructive pulmonary disease (COPD), cancer, and burn casualties. Therefore, we hypothesize that the effect of anemia on outcomes could vary in subgroups of critically ill patients based on primary diseases, and it is plausible that the pathogenesis of anemia may influence the prognosis of critically ill patients. Hence, we conducted a meta-analysis to find the relationship between anemia, either as a comorbid condition or a consequence of critical illness, and clinical outcomes to test this hypothesis.

We performed an electronic search in PubMed, Web of Science, and EMBASE from inception to September 2020 (Supplementary Digital Content, 1, http://links.lww.com/CM9/A708). We included cohort and case-control studies to investigate the association between anemia and ICU outcomes. Patients ≥18 years old who were admitted to the ICU were included. Anemia was defined as serum hemoglobin level <13 mg/dL in men and <12 mg/dL in women at entry or during the ICU stay. We excluded studies without an abstract, or those written in other languages other than English or Chinese. The outcomes of interest included mortality, length of ICU and hospital stay, and complications related to anemia. For all-cause mortality, we conducted subgroup analyses based on primary diagnoses in the ICU. Two reviewers screened the English and Chinese language search results independently. Any disagreement was resolved by discussion with a third author.

As a result, the electronic search yielded 3357 references. Ultimately, 28 studies (included eight case-control studies and 20 cohort studies) with a total of 28,285 patients were included in the final systematic review [Supplementary Digital Content, Table 1, http://links.lww.com/CM9/A708]. The study population was comprised of ICU admissions with diagnoses post-surgery, stroke, neoplasm, septic shock, hypovolemic shock, respiratory failure, cardiogenic shock, acute kidney injury, severe burns, COPD, cancer, severe brain injury, trauma, sepsis, and postoperative peritonitis. All studies had a high risk of bias. One of the major sources of bias was the type of study participants. Most studies only included patients with a specific disease, therefore, they could not represent all ICU patients. Also, anemia definition was different among studies [Supplementary Digital Content, Table 2, http://links.lww.com/CM9/A708].

Seventeen studies (15,499 participants, 54.7%) reported the association between anemia and all-cause mortality. Fourteen studies (15,167 participants, 54%) used odds ratio (OR) as the measurement of the association. In

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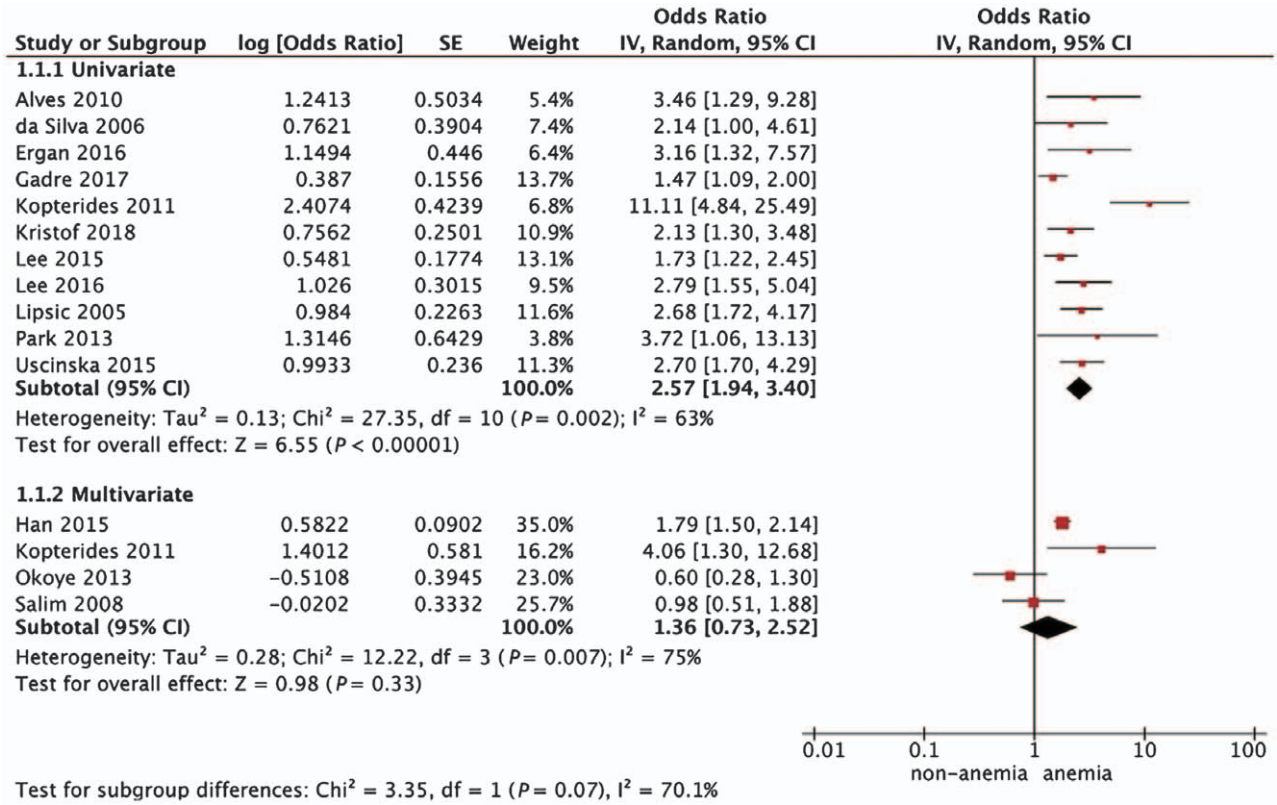

Figure 1: Forest plots representing anemia and all-cause mortality by odds ratio. Han 2015: adjusted factors included age, sex, body weight, systolic/diastolic blood pressure, primary diagnosis, chronic kidney disease, diabetes mellitus, non-hematologic/hematologic malignancy, previously diagnosed anemia, bleeding, need for mechanical ventilation, use of vasoactive and nonsteroidal anti-inflammatory drugs (NSAID), contrast media, and APACHE II score. Kopterides 2011: adjusted factors included simplified acute physiology score, performance status, septic shock on admission. Okoye 2013: adjusted factors included gender, mean hemoglobin on admission, coagulopathy on admission, head abbreviated injury score, injury severity score, packed red blood cells transfusion, packed red blood cells units, fresh frozen plasma units, platelet units, cryoprecipitate units. Salim 2008: adjusted factors included transfusion, anemia and transfusion interaction, head abbreviated injury score, age, gender, injury severity score, head injury, spinal column injury, systolic blood pressure, heart rate. SE: Standard error; CI: Confidence interval.

univariate analysis of pooled data, anemia was found to be associated with an increased risk of death. This was particularly noted in 11 out of 14 studies (10,060 participants, 39%) with OR of 2.57 and 95% confidence interval (CI) of 1.94–3.40, $I^2 = 63\%$ [Figure 1]. Four out of seventeen studies underwent multivariate analysis after adjusting for baseline characteristics. The results yielded a nonsignificant association between anemia and all-cause mortality (adjusted OR: 1.36, 95% CI 0.73–2.52, $I^2 = 75\%$) [Figure 1].

Subgroup analyses for patients with acute kidney injury, trauma, cancer, and peritonitis, sepsis, and those admitted in cardiac intensive care units showed anemia to be associated with a higher risk of all-cause mortality. This association was not observed for patients with traumatic brain injury [Supplementary Digital Content, Figure 4A–D, http://links.lww.com/CM9/A708].

We investigated the effect of anemia on ICU- and hospital-related mortality as well as mortality at 30-day, 90-day, and 6 years follow-ups.

The association between anemia and ICU mortality was reported in two studies involving 1158 (4%) participants. The univariate analysis showed a nonsignificant association between anemia and ICU mortality (OR: 1.78, 95% CI: 0.61–5.18, $I^2 = 66\%$), while multivariate analysis in one study involving 126 (0.4%) participants indicated that anemia was significantly associated with an increased odds of ICU mortality (OR: 4.06, 95% CI: 1.30–12.68) [Supplementary Digital Content, Figure 5A, http://links.lww.com/CM9/A708]. Subgroup analysis showed that among patients with COPD and cancer, there was no association between anemia and ICU mortality [Supplementary Digital Content, Figure 5B, http://links.lww.com/CM9/A708].

Four studies including 1967 participants (7%) reported the association between anemia and hospital mortality. These studies demonstrated a significantly increased pooled OR of 2.22 (95% CI: 1.39–3.56, $I^2 = 69\%$) of hospital mortality among anemic patients. In a multivariate analysis, one study, including 2807 (10%) participants, observed a significantly decreased risk of hospital death per unit increase in hemoglobin (OR: 0.89, 95% CI: 0.82–0.97) [Supplementary Digital Content, Figure 5C], http://links.lww.com/CM9/A708. Subgroup analysis showed patients in the cardiac ICU or those with peritonitis had a higher risk of hospital mortality when they were anemic [Supplementary Digital Content, Figure 5D, http://links.lww.com/CM9/A708]. However, for patients with COPD, there was no association between anemia and hospital mortality.

Two studies revealed that anemic patients had a significantly higher risk of 30-day mortality (RR: 3.10, 95% CI: 1.63–5.90; RR: 1.79, 95% CI: 1.08–2.97). The risk of 90-day mortality in patients with anemia was found to be significantly higher than those without anemia (RR: 2.60, 95% CI: 1.50–4.5 and HR: 1.68, 95% CI: 1.03–2.74). In 1 study involving 2145 participants (8%), a significant increase in 6-year mortality was observed among patients with anemia compared with the control population (OR: 1.79, 95% CI: 1.49–2.13).

Two studies showed there was no significant association between anemia and length of mechanical ventilation, ICU, or hospital stay. While one study revealed that patients with anemia had a significantly longer ICU stay (MD: 8.0, 95% CI: 5.93–10.07, Supplementary Digital Content, Table 3, http://links.lww.com/CM9/A708).

There was no significant association between anemia and progression of acute kidney injury (AKI) from stage I to III [Supplementary Digital Content, Table 3, http://links.lww.com/CM9/A708]. A significantly increased risk of AKI in patients with anemia was found in one study involving 2145 (12.02%) participants (HR: 1.76, 95% CI: 1.35–2.30); however, this was nonsignificant at six months follow-up based on another study [Supplementary Digital Content, Figure 2, http://links.lww.com/CM9/A708].

We assessed the reporting bias through visual interpretation of funnel plots only for all-cause mortality using univariate analysis [Supplementary Digital Content, Figure 3, http://links.lww.com/CM9/A708], and did not find reporting biases. We did not assess the reporting bias for the other outcomes included less than 10 studies, due to the low test efficiency.

In this study, we reported the results of a meta-analysis to examine the association between anemia and clinical outcomes. Our data indicate an increased risk of all-cause mortality in patients with anemia compared with a non-anemic population. In addition, patients with anemia in the ICU were more likely to develop AKI. Subgroup analyses showed that for patients with AKI, trauma, cancer, sepsis, and patients in the cardiac ICU, anemia was associated with a higher risk of all-cause mortality. However, this association was not observed among patients with traumatic brain injury. There was also no association between anemia with ICU mortality among COPD or cancer patients. Unlike patients with COPD, patients in the cardiac ICU or those with peritonitis had a higher risk of hospital mortality when they were anemic.

Anemia is a clinically relevant issue, commonly due to abnormal response to erythropoietin, iron or other vitamin deficiencies, inflammation or infection, hemorrhage, hemolysis, and frequent blood draws in ICUs.[3] Severe anemia could result in oxygen delivery and consumption mismatch, particularly within organs that primarily rely on oxidative metabolisms such as the kidney tubular epithelial and myocardial cells.[4] Renal tubular cells have limited glycolytic capacity, which increases their dependency on the maintenance of appropriate renal blood flow.[5] Our data support the relationship between anemia and its physiological function on several organs which could lead to higher mortality. There is no well-known mechanism to explain the association between anemia and mortality in ICU patients. Further research is required to characterize underlying mechanisms that explain our observed associations between anemia and higher mortality rates based on differences in underlying pathologies and injuries.

In conclusion, anemia among critically ill patients may be associated with a higher risk of mortality, it also could be more correlated with a higher incidence of complications, such as acute kidney injury. In the future, the occurrence of anemia at different time-points in relation to ICU admission, as well as degree and occurrence rate of anemia, duration of anemia, and whether blood transfusion should also be measured and recorded in future studies.

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Conflicts of interest

None.

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