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LETTER TO THE EDITOR

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# Anemia and COVID-19: A prospective perspective

To the Editor,

In a recent report, Tao et al.[1] described that anemia, diagnosed based on hemoglobin measured within the first 24 h after hospital admission, was independently associated with progression to severe coronavirus disease 2019 (COVID-19). In a recent meta-analysis, we reported a weighted mean difference (WMD) of −6.52 (95% CI, −9.2, −3.85) g/L in the hemoglobin of patients progressing to severe COVID-19 compared to those who did not.[2] This finding was confirmed in another recent prospective study, where we observed a significant trend toward lower hemoglobin values with progressively worse COVID-19 severity ($p = .017$).[3] Though the results of Tao et al. appear in line with such observations, significant differences between populations with respect to COVID-19 laboratory abnormalities have been noted. As such, these findings need to be validated in other heterogenous cohorts.[4] To that end, we evaluated anemia and its association with inflammatory biomarkers and disease outcomes in a prospective cohort of patients with COVID-19.

Adults presenting to the emergency department (ED) of the University of Cincinnati Medical Center with a positive standard-of-care reverse transcription-polymerase chain reaction test for SARS-CoV-2 were enrolled in this prospective observational study. Blood samples were collected by the ED during routine blood draws under an institutional review board-approved waiver of informed consent. A complete blood count with differential was performed using a Beckman Coulter UniCel DxH 800 Cellular Analysis System. Plasma ferritin and C-reactive protein (CRP) were assayed on a Behring Nephelometer II System (BN II; Siemens Medical Solutions USA, Inc.). Lactate dehydrogenase (LDH) was analyzed with the Dimension RxL Max Integrated Chemistry System (Siemens Medical Solutions USA, Inc.), whereas procalcitonin (PCT) was measured with the chemiluminescent immunoassay on a Diasorin Liaison XL (DiaSorin S.p.A.). Interleukin 6 (IL-6) was measured using a Meso Scale Discovery (MSD) U-Plex assay. The primary outcome was the development of severe COVID-19 within 30 days of index ED visit. Severe COVID-19 was defined as the need for intensive care unit (ICU) admission, need for mechanical ventilation, or death. Anemia was defined according to WHO criteria: <120 g/L in females and <130 g/L in males.[5] Laboratory values were compared between groups using the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables and performed using R (version 4.0.2), with a $p < .05$ considered statistically significant.

A total of 49 patients with laboratory-confirmed COVID-19 were included in this investigation, 17 (34.7%) of whom were diagnosed as having anemia at ED presentation. The baseline characteristics of patients with and without anemia are shown in Table 1. No differences in age, race, or sex were observed. A higher frequency of coronary artery disease ($p = .041$), heart failure ($p = .005$), diabetes ($p = .017$), chronic obstructive pulmonary disease (COPD) ($p = .015$), and chronic kidney disease ($p = .015$) were observed in patients with anemia. No statistically significant differences were observed in IL-6, CRP, LDH, ferritin, PCT, or lymphocyte count between patients with and without anemia (all $p > .05$; Table 1). Among the 17 patients with anemia, 10 (58.8%) developed nonsevere COVID-19 and 7 (41.2%) developed severe COVID-19, all 7 of which were admitted to the ICU. Three of the patients with anemia died (17.6%), whereas no patient without anemia died. No significant difference in the prevalence of anemia in patients with severe (43.8%) versus nonsevere COVID-19 (30.3%) within 30-days of index ED visit was observed ($p = .523$) (Table 2). Moreover, no difference in the frequency of mild, moderate, and severe anemias was found based on COVID-19 severity ($p = .773$) (Table 2). Further details of the Cincinnati ED Cohort by peak 30-day severity are presented in Table S1.

In this prospective study, anemia was a common finding, observed in one-third of patients with COVID-19 at ED presentation. Nonetheless, unlike the observations of Tao et al.,[1] we did not find anemia to be strongly associated with progression to severe COVID-19 disease. Moreover, we did not find anemia to be associated with significant elevations in inflammatory biomarkers. Given the lack of association with severe disease, we suspect that the anemia observed at this point in the disease course (i.e., at ED presentation) may be more reflective of anemia of chronic disease (ACD) due to the underlying comorbidities rather than a pathophysiologic process of COVID-19. This hypothesis requires further investigation. On the contrary, it is predictable that a decreased hemoglobin value would play a more significant role as a negative prognostic factor during later stages of hospitalization or in concomitance with clinical deterioration.

In a meta-analysis by Taneri et al.,[6] hemoglobin levels were found to be significantly lower in patients with severe COVID-19 as opposed to moderate cases (WMD, −4.08 g/L; 95% CI, −5.12 to 3.05 g/L), in agreement with the observations by Henry et al.[2] Taneri et al.,[6] however, also reported that lower hemoglobin levels were observed in patients with older age, a higher percentage of subjects with diabetes, hypertension, and overall comorbidities, suggesting that underlying comorbidities and ACD may play a role in this observation. In an interesting study by Bellmann-Weiler et al.,[7] 24.7% of COVID-19 patients had anemia at admission, similar to the rate observed in our study and that by Tao et al.[1] They further reported that functional iron deficiency, defined as transferrin saturation of less than 20% and serum ferritin greater than 100 µg/L, was observed in 80.0% of patients upon admission. The authors also observed anemia to be associated with significantly higher odds of in-hospital mortality (odds ratio, 3.73,

  

**TABLE 1** Patient demographics and inflammatory biomarker levels in COVID-19 patients with and without anemia

| Variable | Anemia | | *p* Value |
|---|---|---|---|
| | Present (*n* = 17) | Absent (*n* = 32) | |
| Age (years) | 60 (45–66) | 50.5 (39–65) | .265 |
| Sex | | | |
| Male | 9 (52.9%) | 20 (62.5%) | .555 |
| Female | 8 (47.1%) | 12 (37.5%) | |
| Race | | | |
| Black | 9 (52.9%) | 12 (37.5%) | .306 |
| Hispanic | 4 (23.5%) | 13 (40.6%) | |
| White | 4 (23.5%) | 4 (12.5%) | |
| Other | 0 (0.0%) | 3 (9.4%) | |
| Coronary artery disease | 5 (29.4%) | 2 (6.3%) | .041 |
| Heart failure | 7 (41.2%) | 2 (6.3%) | .005 |
| Hypertension | 10 (58.8%) | 15 (46.9%) | .551 |
| Hyperlipidemia | 5 (29.4%) | 8 (25%) | .746 |
| Diabetes | 11 (64.7%) | 9 (28.1%) | .017 |
| Chronic obstructive pulmonary disease | 6 (35.3%) | 2 (6.3%) | .015 |
| Asthma | 2 (11.8%) | 6 (18.8%) | .696 |
| Chronic kidney disease | 5 (29.4%) | 1 (3.1%) | .015 |
| Chronic liver disease | 4 (23.5%) | 3 (9.4%) | .217 |
| Cerebrovasculardisease | 0 (0.0%) | 1 (3.1%) | 1.000 |
| Cancer | 3 (17.6%) | 1 (3.1%) | .114 |
| Obesity | 6 (35.3%) | 12 (37.5%) | 1.000 |
| Acquired immunodeficiency (HIV, transplant) | 2 (11.8%) | 1 (3.1%) | .254 |
| Autoimmune disease | 0 (0.0%) | 2 (6.3%) | .537 |
| Current smoker | 6 (35.3%) | 4 (12.5%) | .075 |
| Inflammatory biomarkers | | | |
| Lymphocytes (×$10^3$/mm3) | 0.98 (0.85–1.24) | 0.97 (0.63–1.52) | .938 |
| C-reactive protein (mg/dl) | 5.48 (2.52–15.2) | 4.8 (0.91–11.13) | .196 |
| Procalcitonin (ng/ml) | 0.19 (0.06–2.26) | 0.10 (0.05–0.20) | .062 |
| Ferritin (ug/L) | 353 (114–575) | 721.5 (134.8–1422.5) | .136 |
| Lactate dehydrogenase (U/L) | 301 (271–357) | 368.5 (273–472.8) | .219 |
| Interleukin-6 (ng/L) | 34.75 (9.71–48.71) | 15.35 (4.5–23) | .052 |

*Note:* Data presented as frequency (%) or median (interquartile range).

95% CI, 1.74–78.0) but not an increased rate of ICU admission. Hyperferritinemia has been strongly associated with poor COVID-19 progression and increased mortality,[2,6] thus immune-mediated disruption of iron homeostasis in patients progressing to severe disease appears a strong possibility and thus the use of FID, as well as ferritin/transferrin ratio, as predictors of COVID-19 severity warrants further investigation.[7] However, we suspect that anemia in moderate and severe cases of COVID-19 is not driven by inflammation alone, but a combination of factors including direct cytopathic injury resultant from infection of circulating erythrocytes or their bone marrow precursors, indirect erythrocyte damage due to hemolytic anemia, and/or thrombotic microangiopathy, as evidenced by elevated LDH and low ADAMTS13.[3,8,9]

Differences between our findings and that of Tao et al. are likely explained by patient heterogeneity, that is, patient comorbidities and baseline demographics. For example, Tao et al. reported that COPD was present in 10.1% of patients with anemia and 0% without anemia. COPD is associated with ACD and is a risk factor for severe COVID-19.[10] Moreover, differences in the sample size, sampling procedure, and study design may also, in part, contribute to the differences observed. Our prospective cohort included patients who were discharged from the ED without hospital admission, whereas in Tao et al.'s retrospective

**TABLE 2** Anemia at emergency department presentation and maximum 30-day COVID-19 severity

| | COVID-19 30-day severity | | |
|---|---|---|---|
| | Nonsevere ($n$ = 33) | Severe ($n$ = 16) | $p$ Value |
| Anemia | 10 (30.3%) | 7 (43.8%) | .523 |
| Mild anemia | 6 (18.2%) | 3 (18.8%) | .773 |
| Moderate anemia | 4 (12.1%) | 3 (18.8%) | |
| Severe anemia | 0 (0.0%) | 1 (6.3%) | |

*Note:* Data presented as frequency (%). Mild anemia: 110–119 g/L for females and 110–129 g/L for males. Moderate Anemia: 80–109 g/L. Severe anemia: <80 g/L.

investigation, only hospitalized patients were included. Nonetheless, these results highlight the need for validation of COVID-19 research findings in multiple heterogenous cohorts. The prognostic value of anemia should be further investigated in future studies with larger cohorts and assessed over the course of illness.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

Brandon M. Henry and Giuseppe Lippi designed the study and interpreted the data. Justin L. Benoit and Stefanie W. Benoit collected and processed data. Maria H. S. de Oliveira analyzed the data and contributed to manuscript preparation. Brandon M. Henry drafted the manuscript. All authors revised the manuscript for important intellectual content.

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