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On-admission anemia predicts mortality in COVID-19 patients: A single center, retrospective cohort study

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Abstract

Objectives: We investigated the impact of anemia based on admission hemoglobin (Hb) level as a prognostic risk factor for severe outcomes in hospitalized patients with coronavirus disease 2019 (COVID-19).

Methods: A single-center, retrospective cohort study was conducted from a random sample of 733 adult patients (age ≥ 18 years) obtained from a total of 4356 laboratory confirmed SARS-CoV-2 cases who presented to the Emergency Department of Montefiore Medical Center between March–June 2020. The primary outcome was a composite endpoint of in-hospital severe outcomes of COVID-19. A secondary outcome was in-hospital all-cause mortality.

Results: Among the 733 patients included in our final analysis, 438 patients (59.8%) presented with anemia. 105 patients (14.3%) had mild, and 333 patients (45.5%) had moderate-severe anemia. Overall, 437 patients (59.6%) had a composite endpoint of severe outcomes. On-admission anemia was an independent risk factor for all-cause mortality, (Odds Ratio 1.52, 95% CI [1.01–2.30], \( p = 0.046 \)) but not for composite severe outcomes. However, moderate-severe anemia (Hb < 11 g/dL) on admission was independently associated with both severe outcomes (OR 1.53, 95% CI [1.05–2.23], \( p = 0.028 \)) and mortality (OR 1.67, 95% CI [1.09–2.56], \( p = 0.019 \)) during hospitalization.

Conclusion: Anemia on admission was independently associated with increased odds of all-cause mortality in patients hospitalized with COVID-19. Furthermore, moderate-severe anemia (Hb < 11 g/dL) was an independent risk factor for severe COVID-19 outcomes. Moving forward, COVID-19 patient management and risk stratification may benefit from addressing anemia on admission.

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1. Introduction

Since its discovery in December 2019 in Wuhan, China, the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) has rapidly evolved into a global pandemic with over 100 million confirmed cases worldwide and total deaths exceeding 2 million as of March 2021 [1]. Despite much progress that has been made over the past year to combat the pandemic including vaccinations which began in January 2021, efforts to respond to and understand the virus continue as reports of new coronavirus variants have emerged across the globe [2], posing a challenge for healthcare providers to predict the outcomes in COVID-19 patients.

Older age, male sex, and multiple comorbid conditions, including hypertension, diabetes, hypercholesterolemia, cardiovascular disease, and kidney disease have been associated with mortality and critical outcomes of COVID-19 [3–6]. Anemia is a global health concern affecting over 1.6 billion people, approximately 24.8% of the world’s population, and is often associated with common medical conditions and critical illness [7,8]. Anemia has been identified as a significant risk factor for mortality and hospitalization in several diseases, such as heart failure, chronic obstructive pulmonary disease, and myocardial infarction [9–11]. While iron deficiency anemia has been reported as a risk factor for lower respiratory tract infection in the pediatric population [12], little information regarding anemia as a risk factor for respiratory infection outcomes was available in the adult literature. However, anemia

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on admission has been implicated as a possible risk factor for severe COVID-19 outcomes, albeit without consistency [3,5,13,14]. In a recently published study, anemia was associated with higher rates of mortality in COVID-19 patients who displayed signs of immune-mediated alteration of iron homeostasis [15]. Furthermore, reduction in hemoglobin has been observed in critically ill patients [16,17], but the relationship between anemia and severe illness of COVID-19 remains poorly understood, with no studies looking at pre-existing history of anemia or iron deficiency anemia [18].

In this study, we investigated anemia based on admission hemoglobin level as a prognostic risk factor for severe COVID-19 outcomes in hospitalized patients. Additionally, we evaluated the association between increasing severities of anemia, anemia as a comorbidity, and reduction in hemoglobin levels during hospitalization with severe COVID-19 outcomes. Investigation of its association with severe cases of COVID-19 was warranted since anemia is a preventable and modificable factor.

2. Methods

2.1. Study design and data collection

We conducted a retrospective study of COVID-19 patients, confirmed by positive nasopharyngeal RT-PCR test for SARS-CoV-2, diagnosed at the Montefiore Health System from March 12 – June 15, 2020. From a total of 4356 identified COVID-confirmed patients who presented to the ED, we used arbitrary cutoffs of Hb values (9 g/dL and 13 g/dL) to divide patients and randomly sampled 250 patients from each group for a total of 750 patients. Sample size was determined from a preliminary study to compare inpatient admission rates between groups based on Hb cutoff values. We then used the WHO classification (Hb <12 g/dL for females, <13 g/dL for males) to identify patients who presented with anemia on admission and subclassified those cases of anemia as mild (Hb 11–12.9 g/dL in men and 11–11.9 g/dL in women) or moderate-severe (Hb < 11 g/dL) [19]. The data were obtained using Clinical Looking Glass (CLG), an electronic data support software used at Montefiore, and through manual review of electronic medical records.

We collected data on baseline demographics, clinical comorbidities, laboratory values pertaining to anemia and inflammation, in-hospital complications, clinical outcomes, and interventions given during the hospital course such as the use of vasopressors, invasive mechanical ventilation (IMV), hemodialysis, transfusions, and admission to the intensive care unit (ICU).

2.2. Definitions and outcomes

Our primary outcome was a composite endpoint of severe COVID-19 outcomes among the different anemia cohorts. We defined the composite endpoint as the occurrence of any events such as death, prolonged mechanical ventilation, acute hypoxic respiratory failure, and sepsis based on the WHO COVID-19 management guidelines [20] during the hospitalization. In brief, acute hypoxic respiratory failure was defined as clinical signs of pneumonia plus severe respiratory distress or O2 saturation < 90% on room air. Sepsis was defined as acute life-threatening signs of organ dysfunction caused by a documented infection, and a clinical diagnosis of sepsis or septic shock in the medical notes. Secondary outcome was all-cause mortality. Hospitalization was defined as admission to the hospital for at least 24 consecutive hours or death in the emergency department within 24 h of presentation.

2.3. Statistical analysis

We report demographic and clinical characteristics as frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. Sampling weights were utilized to take into account the change of classification for the post-stratified random samples on statistical tests. We used Chi-squared tests and t-test or the one-way analysis of variance (ANOVA) for categorical and continuous variables, respectively, to compare between patients with and without severe outcomes and between anemia statuses on admission. Logistic transformation was applied for non-normally distributed continuous variables. We employed multivariable logistic regression to evaluate the association of anemia on admission with each outcome – a composite endpoint of severe events (primary outcome) and all-cause mortality (secondary outcome) – while adjusting for potential confounding factors. Variables with p-value <0.1 on bivariate analysis or established clinical significance were included: age, sex, diabetes mellitus, hypertension, hyperlipidemia, heart disease, chronic kidney disease, levels of AST and platelet. For anemia on admission, binary anemia status and categorical anemia severity were each used in multivariable models. Odds ratios (ORs) with associated 95% confidence intervals (CIs) were estimated for effects of variables on each outcome. In addition, we performed two subgroup analyses for patients with no anemia on admission and patients with ferritin values prior to admission to investigate the associations of becoming anemic during hospitalization and pre-existing iron deficiency anemia with the composite endpoint of severe outcome. All tests of statistical significance were two-sided, and p-values <0.05 were considered statistically significant. Data were analyzed using Stata (16.1, StataCorp LLC, College Station, TX).

3. Results

From a total of 4356 patients with RT-PCR-confirmed SARS-CoV2 infections who presented to the emergency department, anemia was identified in 1887 (43.3%) patients. Among the randomly sampled 750 patients, 14 patients were excluded because they were discharged from the ED in less than 24 h. One patient remained admitted at the end of the data collection period and was excluded from analysis. Two patients with no prior medical records admitted with altered mental status were also excluded. We report the findings from a final cohort of 733 patients.

3.1. Baseline demographics, clinical characteristics, and outcomes

Baseline demographics and clinical characteristics are depicted in Table 1. The mean age was 65 (+16) years, with 372 (50.8%) men. Hypertension (76.3%) was the most common comorbidity, followed by hyperlipidemia (49.9%), diabetes mellitus (48.7%), and chronic kidney disease (37.0%). Baseline laboratory parameters were elevated for ferritin, D-dimer, and CRP. Overall, 219 (29.9%) patients died during hospitalization, and 437 (59.6%) reached the composite endpoint of severe outcomes (Fig. 1).

Patients with severe outcomes were older (p < 0.001, Table 1) with a higher rate of pre-existing comorbidities such as hyperlipidemia (p = 0.009), heart failure (p = 0.003), and chronic kidney disease (p = 0.031) but did not have a higher rate of history of anemia. Supplementary Table S1 depicts complications and management during hospitalization. More patients with severe outcomes received transfusion (p < 0.001), and the rates of all complications were higher in patients with severe outcomes (p < 0.003). Serum chemistry values showed significantly elevated acute phase reactants such as ferritin, D-dimer, and CRP (p < 0.001, Table 1). Indices of functional impairment of major organs such as AST and creatinine were also significantly elevated in the severe outcome group (p < 0.001). Based on admitting hemoglobin values, more patients in the severe outcome group met the diagnostic criteria for anemia on admission (63.2% vs. 54.7%, p = 0.038).

3.2. Comparisons between anemia status on admission

In our cohort, 438 (59.8%) of patients had hemoglobin levels corresponding to anemia diagnosis on admission. As shown in Table 2,
patients with anemia on admission were older, more likely female, and had significantly higher rates of comorbidities, including chronic kidney disease (49.1% vs. 19.3%, \( p < 0.001 \)), heart failure (21.0% vs. 8.5%, \( p < 0.001 \)), and cancer (25.3% vs. 11.5%, \( p < 0.001 \)). Not all patients with the comorbidity of anemia in the past presented with anemia on admission (248/304, 81.6%).

Anemia was mild in 105 (14.3%) patients and moderate-severe in 333 (45.5%) patients. Overall, rates of comorbidities were lowest in the no anemia group compared to each cohort of anemia severity, except for COPD (8.1% in no anemia, 6.7% in mild anemia, and 17.2% in moderate-severe anemia). The rate of prior history of anemia increased significantly with anemia severity (19% vs. 34.3% vs. 63.7%, \( p < 0.001 \)). With increasing severities of anemia on admission, patients showed elevated inflammatory markers such as D-dimer (\( p < 0.001 \)) and presented with lower albumin and higher creatinine on admission (\( p < 0.001 \), Supplementary Table S2).

Patients who presented with anemia on admission had a longer length of stay (\( p = 0.001 \), Supplementary Table S2) and a significantly higher rate of complications such as sepsis (43.4% vs. 31.5%, \( p = 0.015 \)) and hemodialysis (23.0% vs. 7.1%, \( p < 0.001 \)). Accordingly, anemic patients had significantly higher rates of mortality (33.6% vs. 24.4%, \( p = 0.017 \)) and severe outcomes (63.0% vs. 54.6%, \( p = 0.038 \)). When comparing different anemia severities, rates of adverse events such as prolonged stay, hypotension, and hemodialysis increased significantly with anemia severity (Fig. 2a, b). However, the mild anemia group had highest rate of hypoxia (55.6% in no anemia, 58.7% in mild anemia, and 56.2% in moderate-severe anemia) and acute respiratory failure (45.1% vs. 49.5% vs. 40.2%, \( p < 0.001 \) vs. moderate-severe anemia groups. Overall, although rates of mortality and severe composite outcomes increased with increasing anemia severity, the differences were not significant.

**Table 1**

| Demographic and clinical characteristics by severe outcome status.* |
|-----------------------------------------------|
| All patients | No Severe Outcomes (n = 296 (40.4%)) | Severe Outcomes (n = 437 (59.6%)) | P-value |
|---------------|-------------------------------------|-------------------------------------|---------|
| Demographics  |                                      |                                      |         |
| Age (mean)    |                                    | 62 (±17)                            | \( < 0.001 \) |
| Sex, Male (%) |                                    | 146 (39.2)                          | 0.324 |
| Race or Ethnic Group |          |                                      |          |
| White         | 72 (9.8)                            | 29 (9.8)                            |          |
| Hispanic or Latino | 260 (35.5)   |                                     |          |
| Black or African American | 280 (38.2) |                                     |          |
| Asian         | 22 (3.0)                            | 7 (2.4)                             | 0.77    |
| Other | 99 (13.5)                            | 42 (14.2)                           |          |
| Body Mass Index (kg/m²) | 29.39 (± 7.81) |                                     |          |
| Comorbidities and risk factors | | | |
| Anemia | 304 (41.5)                            | 114 (38.5)                           | 0.029 |
| Diabetes Mellitus | 357 (48.7)   |                                    |          |
| Hypertension | 559 (76.3)                            | 211 (71.3)                           | 0.008 |
| Hyperlipidemia | 366 (49.9) |                                    |          |
| Coronary Artery Disease | 202 (27.6) |                                    |          |
| Heart Failure | 117 (16.0)                            | 32 (10.8)                            | 0.003 |
| Asthma | 112 (15.3)                            | 42 (14.2)                            |        |
| COPD | 88 (12.0)                             | 31 (10.5)                            |          |
| Chronic Kidney Disease | 271 (37.0) |                                     |          |
| Cancer | 145 (19.8)                            | 56 (18.9)                            | 0.359 |
| Immunosuppressed | 83 (11.3) |                                     |          |
| Current/Former smoker | 235 (38.9) |                                     |          |
| Laboratory Parameters | | | |
| Hemoglobin (g/dL) | 11.15 (±.94) | 11.22 (±.99) | 0.658 |
| Hgb min (g/dL) | 9.53 (±.81) | 9.98 (±.91) | 0.923 (±.70) | <0.001 (n = 728) |
| Hgb Max (g/dL) | 11.85 (±2.57) | 11.95 (±2.50) | 11.79 (±2.62) | 0.671 (n = 728) |
| Ferritin (ng/mL) | 1716 (±4713) | 1043 (±1339) | 2142 (±5891) | <0.001 (n = 573) |
| Transferrin (mg/dL) | 153.87 (±57.50) | 156.60 (±59.98) | 151.93 (±54.23) | 0.301 (n = 125) |
| D-dimer (ug/mL) | 13.78 (±331) | 9.00 (±10.51) | 17.19 (±39.45) | 0.729 (n = 125) |
| MCV (FL) | 89.71 (±8.44) | 87.49 (±8.25) | 90.51 (±8.48) | 0.003 |
| WBC (k/ul) | 9.32 (±13) | 8.91 (±10.96) | 9.77 (±7.66) | 0.002 (n = 730) |
| CRP (mg/dL) | 149.44 (±242.11) | 10.76 (±33.65) | 195.63 (±276.34) | 0.027 (n = 57) |
| Platelets (k/ul) | 13.24 (±10.77) | 8.26 (±7.79) | 16.88 (±11.18) | <0.001 (n = 541) |
| Albumin (g/dL) | 3.58 (±0.61) | 3.71 (±0.58) | 3.48 (±0.61) | <0.001 (n = 712) |
| ALT (U/L) | 48.19 (±140.26) | 37.46 (±61.68) | 55.39 (±173.87) | 0.013 (n = 712) |
| AST (U/L) | 68.23 (±79.75) | 49.07 (±55.45) | 81.31 (±227.82) | <0.001 (n = 700) |
| Creatinine (mg/dL) | 2.51 (±0.36) | 2.12 (±0.30) | 2.77 (±0.37) | <0.001 (n = 730) |
| Anemia on Admission | 418 (59.8) | 102 (54.7) | 276 (63.2) | 0.018 |
| Length of Stay** | | | |
| Mean (days) | 12 (±13) | 7 (±7) | 16 (±16) | <0.001 (n = 502) |
| Prolonged stay (>11 days) | 129 (17.6) | 40 (13.8) | 89 (42.0) | <0.001 (n = 502) |

*All raw sample values are reported. P-values applied with sampling weights are reported. n reports counts of available values and frequencies reported. If no n is written, n = 733, whole sample. Other category includes all patients who either declined to answer, fit in to none of the categories, or information was unavailable. Comorbidities and risk factors Anemia is information on any medical history or prior diagnosis of Anemia, regardless of current admission hemoglobin status.

**Length of stay excludes patients who died during hospital stay. Abbreviations: ED: Emergency Department, DM: Diabetes Mellitus, HTN: Hypertension, HLD: Hyperlipidemia, CAD: Coronary Artery Disease, CHF: Chronic Heart failure CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease.
3.3. Independent risk factors for death and severe outcomes

Tables 3 depicts the results of the multivariable logistic regression analysis for severe outcomes. After controlling for confounders, anemia on admission was not predictive of severe outcomes (Model I), but moderate-severe anemia was significantly associated with increased odds of severe outcomes (OR 1.532, CI [1.048–2.230], *p* = 0.028, Model II). In the multivariable analysis for morality (Table 4), anemia on admission remained an independent risk factor for mortality (OR 1.523, CI [1.008–2.251], *p* = 0.028, Model II). Further analysis showed that moderate-severe anemia was significantly associated with increased risk of death in COVID-19 patients (OR 1.671, CI [1.090–2.563], *p* = 0.019, Model II).

In our subgroup analysis of patients who were not anemic on admission, becoming anemic during the hospitalization was significantly associated with an increase in the risk of having severe COVID-19 outcomes (OR 1.737, CI [1.033–2.922] *p* = 0.037, Table 5) after adjusting for confounders. Another subgroup analysis of patients with ferritin values prior to admission demonstrated that pre-existing iron deficiency anemia [21] was not significantly associated with severe outcomes of COVID-19 in an unadjusted regression analysis (Supplementary Table S3).

4. Discussion

Our single-center, retrospective study of 733 patients admitted with SARS-CoV2 in the greater New York City area showed that anemia on admission is predictive of higher rate of mortality in hospitalized patients with COVID-19, but was not significant for having severe outcomes during hospitalization. However, moderate-severe anemia on

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Table 2

Demographics and patient characteristics by anemia status on admission (no anemia, mild, and moderate-severe anemia)

| Demographics | No Anemia (n = 295) | Anemia (n = 438) | P-value<sup>‡</sup> | Mild (n = 105) | Mod-Severe (n = 333) | P-value<sup>‡</sup> |
|--------------|--------------------|-----------------|------------------|---------------|---------------------|------------------|
| Age (years)  | Mean (SD)          | Or n (%)        |                  | Mean (SD)     | Or n (%)            |                  |
| Sex, Male    | 63 (±16)           | 66 (±16)        | 0.009            | 67 (±15)      | 66 (±16)            | 0.032            |
| BMI (kg/m²)  | 30.59 (±7.80)      | 27.69 (±7.61)   | <0.001           | 28.65 (±7.02) | 27.39 (±7.78)       | <0.001           |
| Comorbidities|                   |                 |                  |               |                     |                  |
| Anemia       | 56 (19.0)          | 248 (56.5)      | <0.001           | 36 (34.3)     | 212 (63.7)          | <0.001           |
| Iron supplementation | 27 (9.2) | 160 (36.3) | <0.001 | 20 (19.0) | 140 (42.0) | <0.001 |
| DM           | 114 (38.6)         | 243 (55.5)      | <0.001           | 57 (54.3)     | 186 (55.9)          | <0.001           |
| HTN          | 199 (67.5)         | 360 (82.2)      | <0.001           | 86 (81.9)     | 274 (82.3)          | <0.001           |
| HLD          | 138 (46.8)         | 228 (52.1)      | 0.317            | 51 (48.6)     | 177 (53.2)          | 0.410            |
| CAD          | 55 (18.6)          | 147 (33.6)      | <0.001           | 36 (34.3)     | 111 (33.4)          | <0.001           |
| HF           | 25 (8.5)           | 92 (21.0)       | <0.001           | 23 (21.1)     | 20 (19.0)           | <0.001           |
| Asthma       | 34 (11.5)          | 78 (17.8)       | 0.058            | 18 (17.1)     | 60 (18.1)           | 0.115            |
| COPD         | 24 (8.1)           | 64 (14.6)       | 0.085            | 7 (6.7)       | 57 (17.2)           | 0.011            |
| CKD          | 57 (19.3)          | 214 (49.1)      | <0.001           | 38 (36.2)     | 176 (53.2)          | <0.001           |
| Cancer       | 34 (11.5)          | 111 (25.3)      | <0.001           | 18 (17.1)     | 93 (27.9)           | <0.001           |
| Immunosuppressed | 9 (3.1) | 74 (17.0) | <0.001 | 12 (11.4) | 62 (18.7) | <0.001 |
| Length of Stay* | 9 (±12) | 12 (±13) | 0.012 | 10 (±10) | 12 (±13) | 0.001 (n = 502) |
| Transfusion  | 40 (18.2)          | 89 (31.6)       | 0.022            | 14 (20.6)     | 75 (35.0)           | 0.005 (n = 502) |
|                | 19 (6.4)           | 205 (46.8)      | <0.001           | 16 (15.2)     | 189 (58.6)          | <0.001           |

*P-values*<sup>†</sup> were obtained using *χ*² tests for categorical variables and *t*-tests for continuous variables. CI: confidence interval. OR: Odds Ratio. *p* values were adjusted using Bonferroni correction unless noted otherwise. Continuous variables were compared using unpaired *t*-tests.

<sup>†</sup> *P*-value for the test comparing three categories of no anemia, mild, and moderate-severe anemia.

<sup>‡</sup> *P*-value for the test comparing three categories of no anemia, mild, and moderate-severe anemia.
Fig. 2. a) Prevalence of clinical interventions among patients without anemia and different severities of anemia. *Chi-square p < 0.05. Error bars are of standard errors calculated based on sample statistics. Moderate-severe anemia patient group was significantly more likely to receive hemodialysis than the other two groups. No statistically significant differences were observed in the rates of mechanical ventilation, ICU admission, or vasopressor use. However, ICU admission rate may not reflect the true prevalence for need of intensive cares since patients admitted to make-shift ICUs and higher-level care floors could not be accurately counted. b) Prevalence of clinical outcomes and diagnoses among patients without anemia and with different severities of anemia. *Chi square p < 0.05. Error bars are of standard errors calculated based on sample statistics. Moderate-severe anemia group had significantly higher rates of prolonged stay, sepsis/septic shock, and death compared to the other two groups. The rate of acute hypoxic respiratory failure was highest in the mild anemia group, and lowest in the moderate-severe anemia group. Although lacking statistical significance, the rate of composite severe outcomes increases with anemia severity.

admission was independently associated with both mortality and severe outcomes in COVID-19 patients. We additionally found that anemia acquired during the course of hospitalization was independently associated with severe COVID-19 outcomes. Our findings on the associations between anemia and death were similar to the findings from a recent study by Bellmann et al., who also reported anemia on admission as an independent predictor of mortality in 259 patients with COVID-19 (OR 3.729, CI[1.02–11.75], p = 0.001) but no association with functional iron deficiency [15]. Another recent study by Tao et al. reported anemia as an independent risk factor for severe COVID-19 in 222 patients (OR 3.47, [1.02–11.75], p = 0.046) [18], which differs from our findings, but their definition of severe cases had a higher cutoff of O2 saturation. Whereas both studies included all patients admitted with COVID-19, we report results from a

### Table 3

| Demographics       | Unadjusted Model | Adjusted Model I | Adjusted Model II |
|--------------------|------------------|------------------|------------------|
| Age > 65 ≤ 80      | 1.989            | 1.715            | 1.727            |
| BMI                | 1.006            | 1.053            | 1.121            |
| Male Sex           | 1.179            | 1.271            | 1.370            |
| Comorbidities      |                  |                  |                  |
| DM                 | 1.346            | 1.050            | 1.053            |
| HTN                | 1.654            | 1.129            | 1.121            |
| HLD                | 1.556            | 1.373            | 1.370            |
| Heart Disease      | 1.443            | 0.952            | 0.953            |
| Asthma             | 1.274            | 0.952            | 0.953            |
| COPD               | 1.314            | 0.952            | 0.953            |
| Kidney Disease     | 1.472            | 1.122            | 1.101            |
| Cancer             | 1.221            | 0.797            | 0.724            |
| Lab Findings       |                  |                  |                  |
| Hemoglobin         | 0.988            | 0.998            | 0.998            |
| Ferritin*          | 1.000            | 1.000            | 1.000            |
| D-dimer*           | 1.134            | 1.098            | 1.098            |
| WBC                | 1.107            | 1.107            | 1.107            |
| CRP                | 1.089            | 1.128            | 1.128            |
| Platelet           | 0.999            | 0.999            | 0.999            |
| ALT**              | 1.003            | 1.000            | 1.000            |
| AST                | 1.006            | 1.000            | 1.000            |
| Creatinine***      | 1.087            | 1.011            | 1.011            |
| Classifications    |                  |                  |                  |
| Anemia (on admission) vs. none | 1.411            | 1.403            | 1.403            |
| Anemia Severity    |                  |                  |                  |
| Mild vs. none      | 1.383            | 1.297            | 1.297            |
| Mod-Sev vs. none   | 1.441            | 1.532            | 1.532            |

Model I: Adjusted model for the association between anemia and composite endpoint of severe outcomes. Model II: Adjusted model for the association between different severities of anemia and composite endpoint of severe outcomes. **Adjusted Odds Ratio. *Variables with 20% or missing values were not included in the multivariable model due to too many missing values. **ALT was not included in multivariable models because of the high correlation with AST which appeared to be the highest predictive variable in bivariate analysis. ***Creatinine was not included in multivariable models because of the high correlation with CKD which appeared to be the highest predictive variable in bivariate analysis.
Anemia (on admission) vs. none 1.541 1.079–2.200 0.017 1.523 1.008–2.303 0.046

Model 1: Adjusted model for the association between anemia and all-cause mortality. Model II: Adjusted model for the association between different severities of anemia and all-cause mortality. ADJ = Adjusted Odds Ratio. *Variables with 20% or more missing values were not included in the multivariable model due to too many missing values. **ALT was not included in multivariable models because of the high correlation with AST which appeared to be the highest predictive variable in bivariate analysis. ***Creatinine was not included in multivariable models because of the high correlation with CKD which appeared to be the highest predictive variable in bivariate analysis.

cohort of patient population with higher prevalence of on-admission anemia (43.3% vs. 24.7%, 35.6%). Our sample size is larger than the total patients included in either study, and our patient population was more heterogeneous, with a higher comorbidity burden than either study.

Hemoglobin concentration is one of the most important markers of oxygen-carrying capacity in the blood. In the setting of respiratory compromise and increased oxygen demand in a hyper-metabolic state such as COVID-19, anemia can further reduce oxygen delivery to peripheral tissues. That SARS-CoV-2 directly infects cells expressing the ACE-2 enzyme has been observed in organs throughout the body [22], leading to significant complications such as septic shock and multiple organ dysfunction [5,23] as they may reduce the availability of ACE-2 receptors from macrophages. This leads to decreased intestinal iron absorption and cellular sequestration of iron in macrophages, [24] and an upregulation of cytosolic ferritin, which stores iron to prevent iron-mediated free radical damage [25]. The net result of decreased iron availability, elevated ferritin and hindered erythropoiesis may explain the association between severe COVID-19 and moderate-severe anemia. In COVID-19, marked hyperferritinemia has been reported with the development of cytokine storm characterized by significantly elevated IL-6, CRP, and other inflammatory markers in critically ill patients [26–28]. Our data also suggest that patients with severe outcomes had significantly elevated levels of acute-phase reactants, suggesting a state of inflammation. While our data suggest that being anemic in the ED alone is inconclusive to predicting severe outcomes of COVID-19, it seems warranted to assess whether moderate-severe anemia could be used as a reliable measure to help guide clinical management of COVID-19.

Our findings may have implications in guiding the management of COVID-19 patients hospitalized with or without anemia. Based on our study results, the timing of anemia and the severity of anemia could offer additional insights into COVID-19 patients' treatment. In the case of COVID-19 infection with mild anemia on presentation, O2 supplementation, in addition to general practice guidelines, may suffice. However, if the patients are moderate-severely anemic in the ED or become newly anemic during hospitalization, the use of steroids may prevent further deterioration, in addition to standard care using iron or blood transfusions. However, the current WHO and NIH guidelines based on the RECOVERY trial have a conditional recommendation against corticosteroids in patients with a mild course of COVID-19 [29]. Given our findings, early detection of anemic hemoglobin levels and their severity could be beneficial in considering the use of systemic steroids before disease progression.

Our study has several limitations. First, this study was conducted using the data from one integrated- delivery health system in New York City, which may limit the generalizability of the results. Second, the study was observational and cannot establish causality. Third, the study was conducted during the early phase of the COVID-19 pandemic when treatment guidelines were changing rapidly, which may have influenced the results. Despite these limitations, our study provides important insights into the association between anemia and COVID-19 outcomes.
Anemia is a global disease associated with the prognosis of many clinical diseases, including diseases with respiratory complications, such as COVID-19. We report that anemia on admission and particularly moderate-severe anemia was independently associated with all-cause mortality in patients hospitalized with COVID-19. Moderate-severe anemia was also predictive of severe outcomes in COVID-19 patients. Anemia on admission and changing hemoglobin levels throughout hospitalization may help further guide risk stratification and management of patients hospitalized with COVID-19. Additional studies addressing more inclusion of laboratory values and treatments received by patients should be the focus of future studies.

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Declaration of Interest
None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2021.03.083.

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