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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 (OR1.53, 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.

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 modifiable 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. Log 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 characters, 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,

Table 1
Demographic and clinical characteristics by severe outcome status.[*]

|	All patients N = 733	No Severe Outcomes N = 296 (40.4%)	Severe Outcomes N = 437 (59.6%)	P-value (n[1])
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	
Demographics				
Age (mean)	65 (±16)	62 (±17)	67 (±15)	<0.001
Sex, Male (%)	372 (50.8)	146 (39.2)	226 (60.8)	0.324
Race or Ethnic Group				0.77
White	72 (9.8)	29 (9.8)	43 (9.8)	
Hispanic or Latino	260 (35.5)	109 (36.8)	151 (34.6)	
Black or African American	280 (38.2)	109 (36.8)	171 (39.1)	
Asian	22 (3.0)	7 (2.4)	15 (3.4)	
Other[2]	99 (13.5)	42 (14.2)	57 (13.0)	
Body Mass Index (kg/m^2)	29.39 (± 7.81)	28.51 (±7.61)	29.03 (±7.94)	0.598 (n=693)
Comorbidities and risk factors				
Comorbidities				
Anemia[3]	304 (41.5)	114 (38.5)	190 (43.5)	0.125
Diabetes Mellitus	357 (48.7)	130 (43.9)	227 (51.9)	0.078
Hypertension	559 (76.3)	211 (71.3)	348 (79.6)	0.008
Hyperlipidemia	366 (49.9)	130 (43.9)	236 (54.0)	0.009
Coronary Artery Disease	202 (27.6)	73 (24.7)	129 (29.5)	0.165
Heart Failure	117 (16.0)	32 (10.8)	85 (19.5)	0.003
Asthma	112 (15.3)	42 (14.2)	70 (16.0)	0.309
COPD	88 (12.0)	31 (10.5)	57 (13.0)	0.317
Chronic Kidney Disease	271 (37.0)	94 (31.9)	177 (40.6)	0.031
Cancer	145 (19.8)	56 (18.9)	89 (20.4)	0.359
Immunosuppressed	83 (11.3)	32 (10.8)	51 (11.7)	0.368
Current/Former smoker	235 (38.9)	81 (32.8)	154 (43.1)	0.029
Laboratory Parameters				
Hemoglobin (g/dL)	11.15 (±2.94)	11.22 (±2.99)	11.10 (±2.91)	0.658
Hgb min (g/dL)	9.53 (±2.81)	9.98 (±2.91)	9.23 (±2.70)	<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)
Ferritin/Transferrin	13.78 (±31.07)	9.00 (±10.51)	17.19 (±39.45)	0.729 (n=125)
D-dimer (ug/mL)	4.22 (±5.33)	2.75 (±3.61)	5.21 (±6.03)	<0.001 (n=586)
MCV (fL)	89.71 (±8.44)	88.49 (±8.25)	90.53 (±8.48)	0. 003
WBC (k/uL)	9.32 (±9.13)	8.91 (±10.96)	9.77 (±7.66)	0.002 (n=730)
IL-6 (pg/mL)	149.44 (±242.11)	40.76 (±33.65)	195.63 (±276.34)	0. 027 (n=57)
CRP (ug/mL)	13.24 (±10.77)	8.26 (±7.79)	16.68 (±11.19)	<0.001 (n=541)
Platelet (k/uL)	245.84 (±130.61)	252.64 (±129.08)	241.25 (±131.57)	0.676 (n=730)
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 (±179.75)	49.07 (±55.45)	81.31 (±227.82)	<0.001 (n=700)
Creatinine (mg/dL)	2.51 (±3.06)	2.12 (±2.50)	2.77 (±3.37)	<0.001 (n=730)
Anemia on Admission	438 (59.8)	162 (54.7)	276 (63.2)	0.038
Length of Stay**				
Mean (days)	11 (±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. [1]n reports counts of available values and frequencies reported. If no n is written, n = 733, whole sample.[2]Other category includes all patients who either declined to answer, fit in to none of the categories, or information was unavailable.[3]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.

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 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%) than no anemia and moderate-severe anemia groups. Overall, although rates of mortality and severe composite outcomes increased with increasing anemia severity, the differences were not significant.
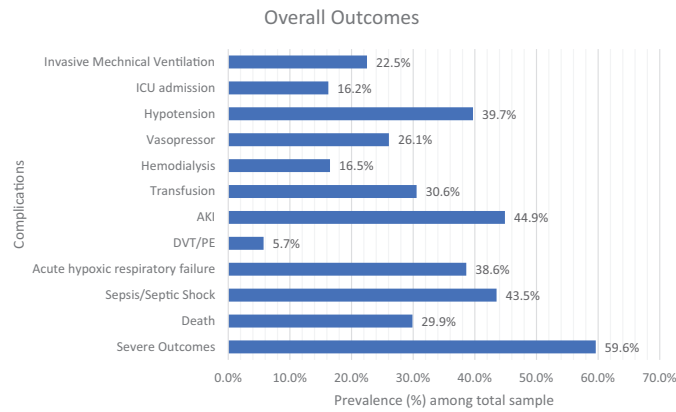
Fig. 1. Prevalence of clinical outcomes in our total sample cohort. Representation of prevalence of disease outcomes in total sample cohort. ICU admission signifies admission to the traditional Intensive Care Units, and may not reflect the true prevalence for need of intensive cares since patients admitted to make-shift ICUs and higher level care floors could not be accurately counted. Hypotension was defined as systolic blood pressure < 100 and diastolic blood pressure < 60, or a mention of hypotension in the physician notes. AKI was defined as an elevation in creatinine by ≥0.3 mg/dL within 48 h or increase in serum creatinine to ≥1.5 times baseline, or urine volume < 0.5 mL/kg/h for six hours according to the KDIGO guidelines [30]. DVT/PE: Deep Vein Thrombosis/Pulmonary Embolism, ICU: Intensive Care Unit, AKI: Acute Kidney Injury.

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 [1.008–2.303], $p = 0.046$, Model I). 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

Table 2
Demographics and patient characteristics by anemia status on admission (no anemia, mild, and moderate-severe anemia)

	No Anemia N = 295 (40.2)	Anemia N = 438 (59.8)	P-value†	Mild N = 105 (14.3)	Mod-Severe N = 333 (45.5)	P-value‡ (n¹)
	Mean (SD) Or n (%)	Mean (SD) Or n (%)		Mean (SD) Or n (%)	Mean (SD) Or n (%)	
Demographics						
Age (years)	63 (±16)	66 (±16)	0.009	67 (±15)	66 (±16)	0.032
Sex, Male	163 (55.3)	209 (47.7)	0.045	54 (51.4)	155 (46.5)	0.018
BMI (kg/m²)	30.59 (±7.80)	27.69 (±7.61)	<0.001	28.65 (±7.02)	27.39 (±7.78)	<0.001(n = 693)
Comorbidities						
Anemia	56 (19.0)	248 (56.5)	<0.001	36 (34.3)	212 (63.7)	<0.001
Iron supplementation	27 (9.2)	160 (36.5)	<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	25 (8.5)	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
Clinical Outcomes						
Length of Stay*	9 (±12)	12 (±13)	0.012	10 (±10)	12 (±13)	0.001 (n = 502)
Prolonged Stay*	40 (18.2)	89 (31.6)	0.022	14 (20.6)	75 (35.0)	0.005 (n = 502)
Transfusion	19 (6.4)	205 (46.8)	<0.001	16 (15.2)	189 (56.8)	<0.001

¹n reports counts of available values and frequencies reported. If no n is written, n = 733, whole sample. Abbreviations: ED: Emergency Department, DM: Diabetes Mellitus, HTN: Hypertension, HLD: Hyperlipidemia, CAD: Coronary Artery Disease, HF: Heart failure CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, PE/DVT: Pulmonary Embolism/Deep Vein Thrombosis. †: P- value for the test comparing anemia vs. no anemia. ‡: P-value for the test comparing three categories of no anemia, mild, and moderate-severe anemia.

(a)

Clinical Interventions

(b)

Clinical Outcomes
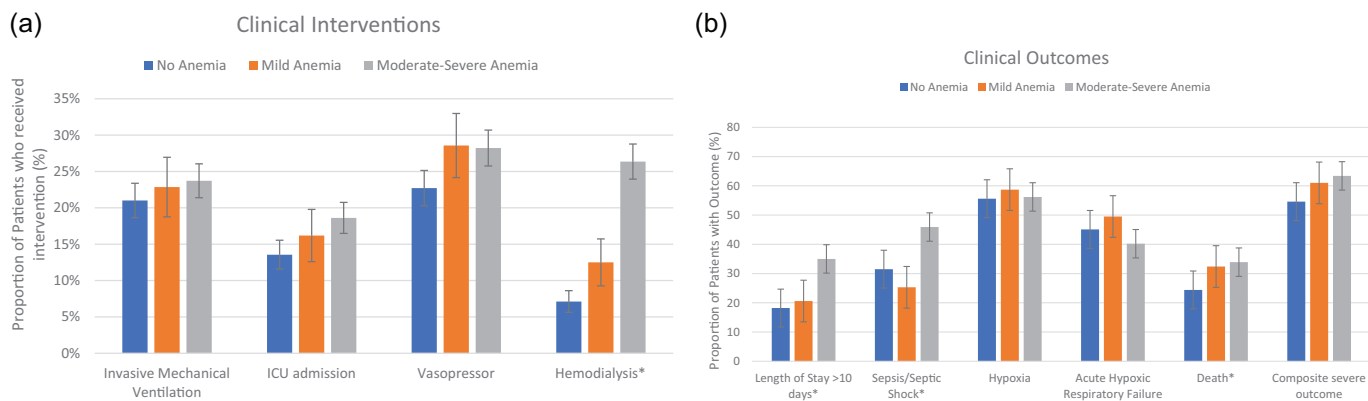
Fig. 2. a) Prevalence of clinical interventions among patients without anemia and different severities of anemia. *Chi-square *p* < 0.05. Error bars are of standard errors calculated based on sample statistics. Moderate-severe anemia patient group was significantly more likely to receive hemodialysis 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 ane-mia 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]. An-other 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
Logistic regression models of the composite endpoint of severe outcomes

	Unadjusted Model			Adjusted Model I			Adjusted Model II		
	OR	95% CI	P-value	aOR[1]	95% CI	P-value	aOR[1]	95% CI	P-value
Demographics									
Age > 65	1.989	1.427–2.772	<0.001	1.715	1.171–2.510	0.006	1.727	1.180–2.528	0.005
BMI	1.006	0.984–1.028	0.601						
Male Sex	1.179	0.850–1.635	0.325	1.271	0.897–1.801	0.176	1.287	0.908–1.824	0.156
Comorbidities									
DM	1.346	0.967–1.873	0.078	1.050	0.709–1.555	0.807	1.053	0.711–1.559	0.796
HTN	1.654	1.137–2.408	0.009	1.129	0.693–1.840	0.627	1.121	0.694–1.842	0.622
HLD	1.556	1.119–2.165	0.009	1.373	0.935–2.015	0.105	1.370	0.933–2.011	0.109
Heart Disease	1.443	1.009–2.063	0.044	0.952	0.626–1.448	0.818	0.953	0.626–1.451	0.822
Asthma	1.274	0.798–2.032	0.310						
COPD	1.314	0.768–2.249	0.318						
Kidney Disease	1.472	1.035–2.093	0.031	1.122	0.740–1.700	0.588	1.101	0.724–1.674	0.652
Cancer	1.221	0.797–1.870	0.360						
Lab Findings									
Hemoglobin	0.988	0.937–1.041	0.645						
Ferritin*	1.000	1.000–1.000	0.001						
D-dimer*	1.134	1.077–1.194	<0.001						
WBC	1.047	0.990–1.107	0.107						
CRP*	1.096	1.066–1.128	<0.001						
Platelet	0.999	0.998–1.001	0.392						
ALT**	1.003	0.999–1.007	0.096						
AST	1.006	1.003–1.010	0.001	1.007	1.002–1.011	0.002	1.007	1.002–1.011	0.002
Creatinine***	1.087	1.011–1.170	0.025						
Classifications									
Anemia (on admission) vs. none	1.411	1.019–1.954	0.038	1.403	0.969–2.032	0.073			
Anemia Severity									
Mild vs. none	1.383	0.872–2.200	0.168				1.297	0.792–2.125	0.301
Mod-Sev vs. none	1.441	1.045–1.985	0.026				1.532	1.048–2.230	0.028

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.[1]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.

Table 4

Logistic regression models of mortality outcome

	Unadjusted Model			Adjusted Model I			Adjusted Model II		
Demographics	OR	95% CI	P-value	aOR[1]	95% CI	P-value	aOR[1]	95% CI	P-value
Age > 65	2.790	1.914–4.065	<0.001	2.277	1.481–3.501	<0.001	2.295	1.492–3.529	<0.001
BMI	0.986	0.962–1.012	0.293						
Male Sex	1.311	0.920–1.870	0.134	1.535	1.029–2.288	0.036	1.557	1.044–2.323	0.030
Comorbidities									
DM	1.266	0.887–1.808	0.194	0.856	0.565–1.299	0.465	0.860	0.567–1.303	0.476
HTN	2.738	1.720–4.358	<0.001	2.157	1.181–3.939	0.012	2.163	1.187–3.942	0.012
HLD	1.643	1.148–2.351	0.007	1.392	0.924–2.097	0.113	1.390	0.922–2.095	0.116
Heart disease	1.458	1.003–2.120	0.048	0.677	0.429–1.069	0.094	0.676	0.428–1.069	0.094
Asthma	1.156	0.715–1.868	0.554						
COPD	1.338	0.778–2.302	0.292						
CKD	1.889	1.309–2.725	0.001	1.257	0.801–1.974	0.320	1.234	0.784–1.942	0.364
Cancer	1.298	0.833–2.024	0.250						
Lab Findings									
Hemoglobin	0.972	0.914–1.034	0.365						
Ferritin*	1.000	1.000–1.000	<0.001						
D-dimer*	1.142	1.101–1.185	<0.001						
WBC	1.027	0.986–1.070	0.199						
CRP*	1.080	1.058–1.103	<0.001						
Platelet	0.998	0.006–0.999	0.006	0.997	0.995–0.999	0.005	0.997	0.995–0.999	0.005
ALT**	1.001	1.000–1.003	0.095						
AST	1.004	1.000–1.008	0.048	1.004	1.000–1.008	0.033	1.004	1.000–1.008	0.033
Creatinine***	1.091	1.025–1.161	0.006						
Classifications									
Anemia (on admission) vs. none	1.541	1.079–2.200	0.017	1.523	1.008–2.303	0.046			
Anemia Severity									
Mild vs. none	1.496	0.913–2.451	0.011				1.406	0.823–2.404	0.212
Mod-Sev vs. none	1.587	1.118–2.253	0.010				1.671	1.090–2.563	0.019

Model I: 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.[1]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 heterogenous, 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 and thus prevent vasodilation, further compounding peripheral tissue ischemia. Indeed, a meta-analysis by Taneri et al. showed that severity of disease and prognosis of patients with COVID-19 may depend on lower Hb levels as severe cases had significantly lower hemoglobin levels [13], a possible explanation for why anemic patients have higher rate of mortality and severe adverse events.

In addition, our subgroup analysis demonstrated that anemia acquired during hospitalization was independently associated with severe COVID-19 outcomes. Patients infected with COVID-19 may develop anemia through several possible mechanisms. Cavezzi et al. hypothesized that viral entry through receptors located on erythrocytes may induce hemolysis, resulting in hemolytic anemia [17]. Anemia may be a result of severe infection due to alteration of iron homeostasis by the innate immune system, implicated by the pathological value of ferritin observed in severe COVID-19 cases. The innate immune system reduces iron's bioavailability by pro-inflammatory cytokine pathways that up-regulate hepcidin, an iron regulatory protein that blocks iron release 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

Table 5
Subgroup Analysis: Logistic Regression analysis of the composite endpoint of severe outcomes in patients with no anemia on admission who later become anemic

	Unadjusted Model			Adjusted Model I		
	OR	95% CI	*P-value*	aOR[1]	95% CI	*P-value*
Demographics						
Age > 65	2.361	1.470–3.791	*<0.001*	2.792	1.527–5.103	*0.001*
BMI	1.000	0.970–1.031	*0.993*			
Male Sex	1.349	0.847–2.147	*0.207*	1.479	0.847–2.585	*0.168*
Comorbidities						
DM	1.236	0.768–1.991	*0.382*	1.120	0.624–2.010	*0.704*
HTN	1.397	0.854–2.286	*0.182*	0.876	0.450–1.704	*0.695*
HLD	1.497	0.939–2.387	*0.089*	1.243	0.688–2.246	*0.469*
Heart Disease	1.328	0.764–2.309	*0.313*	0.888	0.441–1.786	*0.738*
Asthma	1.160	0.559–2.406	*0.689*			
COPD	1.661	0.684–4.031	*0.261*	1.272	0.414–3.910	*0.673*
Kidney Disease**	1.616	0.883–2.956	*0.119*			
Cancer	1.330	0.636–2.781	*0.448*			
Lab Findings						
Ferritin*	1.000	1.000–1.000	*0.017*			
D-dimer*	1.135	1.062–1.212	*<0.001*			
WBC	1.152	1.080–1.229	*<0.001*	1.139	1.061–1.222	*<0.001*
CRP*	1.108	1.062–1.156	*<0.001*			
Platelet	1.000	0.998–1.002	*0.913*			
ALT***	1.004	0.999–1.009	*0.091*			
AST	1.008	1.002–1.014	*0.005*	1.007	1.001–1.013	*0.015*
Creatinine	1.325	0.995–1.764	*0.054*	1.132	0.934–1.372	*0.204*
Classifications						
Becoming anemic vs. none	1.693	1.062–2.701	*0.027*	1.737	1.033–2.922	*0.037*

Total subgroup n = 295, a subset of sample who did not have anemic hemoglobin levels on admission. [1]Adjusted Odds Ratio. *Variables with 20% or missing values were not included in the multivariable model: ferritin, D-dimer, CRP due to too many missing values. **Chronic Kidney Disease was not included in multivariable models because of the high correlation with creatinine which appeared to be the highest predictive variable in bivariate analysis. *** 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.

York; hence our results may have limited generalizability. However, as anemia is a global condition with higher prevalence in developing countries, our findings may have potential implications. Secondly, the study was performed during the peak of the pandemic, in which contactless interviews and shortened notes were the norm and limited the amount of information from chart review. Similarly, not all laboratory studies were performed on all patients, and values were missing in laboratory parameters. Lastly, our main limitation was that we could not separate acute from chronic anemia, and did not account for the etiology of anemia including hemoglobinopathies and sickle cell disease, which limits our interpretation. Nonetheless, our study suggests that moderate-severe anemia on admission regardless of its etiology poses as a risk for severe outcomes in COVID-19.

Future research would benefit from an inclusion/exclusion criteria of laboratory values to help distinguish anemia by etiology and strengthen the multivariable regression analysis. Furthermore, a thorough look at all treatments including medications could further control for the differences in outcomes.

5. Conclusion

Anemia is a global disease associated with the prognosis of many clinical diseases, including diseases with respiratory compromises, 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.

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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