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Hematologic Involvement as a Predictor of Mortality in COVID-19 Patients in a Safety Net Hospital

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ABSTRACT

Introduction. COVID-19 affects the hematologic system. This article evaluated the impact of hematologic involvement of different blood cell line parameters of white blood cells including absolute neutrophil count (ANC), hemoglobin, and platelets in COVID-19 patients and their association with hospital mortality and length of stay (LOS).

Methods. This was a retrospective study of 475 patients with confirmed positive COVID-19 infection and hematologic abnormalities in the metropolitan New York City area.

Results. Elevated absolute neutrophil count (OR: 1.20; 95% CI: 1.02-1.42; $p < 0.05$) increased days of hematologic involvement (OR: 4.44; 95% CI: 1.42-13.90; $p < 0.05$), and persistence of hematologic involvement at discharge (OR: 2.87; 95% CI: 1.20-6.90; $p < 0.05$) was associated with higher mortality. Higher hemoglobin at admission (OR: 0.77; 95% CI:0.60-0.98; $p < 0.001$) and platelets peak (OR: 0.995; 95% CI: 0.992-0.997; $p < 0.001$) were associated with decreased mortality. Patients with higher white blood cell peak (B = 0.46; SE = 0.07; $p < 0.001$) and higher hemoglobin at admission (B = 0.05; SE = 0.01; $p < 0.001$) were associated with higher LOS. Those with higher hemoglobin nadir (B = -0.06; SE = 0.01; $p < 0.001$), higher platelets nadir (B = -0.001; SE = < 0.001; $p < 0.001$), and hematologic involvement at discharge or death (B = -0.06; SE = 0.03; $p < 0.05$) were associated with lower LOS.

Conclusions. These findings can be used by clinicians to better risk-stratify patients with hematologic involvement in COVID-19 and tailor therapies potentially to improve patient outcomes.

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INTRODUCTION

Coronavirus Disease (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was declared a pandemic crisis in March 2020 by the World Health Organization.[1] COVID-19 has claimed over 2 million lives and has had a profound public health impact worldwide.[2] The spectrum of COVID-19 disease varies from asymptomatic to severe cases requiring Intensive Care Unit (ICU) level of care and intubation. Severe COVID-19 commonly is complicated by development of multiorgan involvement,[3,4] including hematologic and hematopoietic dysfunction.[5] Studies of hematologic involvement in COVID-19 demonstrated its manifestation mostly in the form of thromboembolic events[6] with an unadjusted mortality of 24 - 50%.[7,8]

Several risk factors are described for severe COVID-19 disease, including older age, hypertension, diabetes mellitus type 2, morbid obesity, and chronic lung disease.[6] There are mixed findings for male gender where some report an increased association for severe COVID-19 disease,[9] while others do not report an association.[10] Race and ethnicity also has mixed findings where some report that Hispanics have a higher incidence of infection[11] and African-Americans have a higher mortality rate in COVID-19[12,13] while others do not report an association.[14,15] Some report that lack of health insurance was associated with increased SARS-CoV-2 infection.[12] The authors were not aware of any studies on the impact of many demographic variables for COVID-19 patients with hematologic involvement.

Anemia and abnormalities of iron metabolism markers may be associated with increased mortality in patients with COVID-19.[5,16] Similarly, thrombocytopenia is a common feature in patients with severe COVID-19.[17] The presence of elevated hematologic inflammatory markers (i.e., pro-inflammatory cytokines) and neutrophil-to-lymphocyte ratio may be indicators for severity of COVID-19 disease.[18] However, other key hematologic variables such as absolute neutrophil count (ANC) have not been studied as a predictor for mortality and disease severity in COVID-19. A meta-analysis of Chinese studies summarizing the impact of COVID-19 on all blood cell lines found an association between COVID-19 and increased hypercoagulability.[5] Another meta-analysis of Chinese studies that compiled laboratory findings in patients with COVID-19 suggested that increased white blood cells (WBC), low platelets, and high interleukin-6 (IL-6) levels may be useful clinically in predicting severe and fatal COVID-19.[7] The impact of hematologic involvement in all blood cell lines parameters and its association with COVID-19 disease mortality and length of stay (LOS) have not been well investigated.

This paper describes hematological involvement in patients with COVID-19. The authors conducted multivariate analyses for the association of demographics and different blood cell lines parameters of WBC including absolute neutrophil count (ANC), hemoglobin, and platelets to study their association with COVID-19 mortality and LOS in patients with hematological involvement.

METHODS

Study Subjects. This was a retrospective study of 475 patients with confirmed COVID-19 and hematologic involvement that were admitted to a safety-net hospital in suburban New York City from March 1, 2020 through May 15, 2020. All patients were 18 years of age or older. Diagnosis of COVID-19 was confirmed by a positive reverse transcriptase polymerase chain reaction (RT-PCR) showing SARS CoV-2 RNA. Hematologic involvement was defined as the abnormal laboratory value of any of the following blood cell lines components: WBC including ANC, hemoglobin, and platelets. All patients were followed until

completion of their hospital course whether alive or deceased. Ethical approval was received from the hospital Institutional Review Board to conduct this study. A waiver for informed consent was received due to the retrospective nature of the study.

Variables. Demographic variables were age (years), gender (male/female), and race/ethnicity (Caucasian, Hispanic, African American, East Asian, and Southeast Asian (i.e., Indian, Afghan, Pakistani, Bangladeshi, Thai), and Other). Insurance status had categories of private, uninsured, or emergency Medicaid (i.e., Medicaid issued during this hospitalization), regular Medicaid, and Medicare.

Comorbidities were obesity (body mass index (BMI) ≥ 30.0 kg/m^2), sickle cell disease, other hematologic disorders, excluding those that are included in the Charlson Comorbidity Index (CCI), and use of immunosuppressive medications in the past six months such as chemotherapy, steroids, disease-modifying antirheumatic drugs, and others (i.e., tacrolimus, sirolimus, JAK-inhibitors). The CCI was calculated (range: 0 - 37), which predicts a 10-year survival rate based on a series of comorbid conditions of age, history of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular accident, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, chronic liver disease, diabetes mellitus, renal disease, solid tumor, leukemia, lymphoma, and AIDS status.[19,20]

Disease severity indicators were Intensive Care Unit (ICU) level of care (defined as hospitalization in a critical care area, use of vasopressor medication, or supplemental oxygen use with requirement of a fraction of inspired oxygen (FiO_2) above 55%), Quick Sepsis Related Organ Failure Assessment (qSOFA) score (range: 0 - 3) upon admission (identifies non-ICU high risk patients and estimates their mortality based on a 3-point scoring),[21] invasive mechanical ventilation upon admission, and highest supplemental oxygen requirement during hospitalization (none, low $FiO_2 \leq 55\%$, high $FiO_2 > 55\%$, and use of invasive mechanical ventilation).

Treatment and management included the use of any vasopressor medication, any antibiotic, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARBs), antiviral (remdesivir), antimalarial, any steroid medication regardless of dosage, convalescent plasma from COVID-19 survivor donors, interleukin inhibitors (anti-IL-6 monoclonal antibodies - tocilizumab), and therapeutic dosage of anticoagulant medications.

Number of organs involved was defined as the sum of organs that were impaired or involved during admission. This involved organs of neurological system, renal system, cardiovascular system, liver organ system, endocrine system, musculoskeletal system, and hematologic system.

Hematologic involvement was considered if one of the following parameters were present: hemoglobin more than 16.0 g/dL or less than 12.0 g/dL, WBC less than 4,000 k/mm^3 or more than 11,000 k/mm^3, ANC of less than 1.80 k/mm^3 or more than 7 k/mm^3, and platelet count less than 150 k/mm^3 or more than 450 k/mm^3. Authors collected the WBC peak and nadir, ANC nadir, platelet peak and nadir, and hemoglobin at admission and nadir. Peak and nadir were defined as the highest and the lowest recorded value during the hospitalization respectively, regardless of normal or abnormal. WBC proportion days involved was defined as the total number of days that WBC count was abnormal divided by the total number of days of hospitalization. ANC proportion days involved was calculated by dividing the total number of days that ANC was abnormal by the total number of days of hospitalization. Days-to-hematologic-involvement was defined as the total number of days from admission until the first day of hematologic involvement. Persistent hematologic involvement at the time of discharge or death also was recorded. The outcome variables were mortality and LOS. Admission levels of lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), ferritin, D-dimer, C-reactive protein (CRP), fibrinogen, prothrombin time (PT) peak level, and International Normalized Ratio (INR) peak level also were collected and described.

Statistical Analysis. Mean and standard deviation were used to describe the continuous variables. Frequency and percentage were used to describe the categorical variables. Two models were used to analyze the separate outcome variables of mortality and LOS. Model 1 consisted of univariate analyses that included demographic, comorbidities, disease severity, and treatment management variables. Model 2 consisted of a multivariate analysis that included all the significant variables in the univariate analyses from Model 1 and added hematology variables. Mortality was analyzed with logistic regression. LOS was analyzed with linear regression. Logarithmic transformations were calculated for the skewed variables. The p values were two-sided. IBM® SPSS Statistics version 26 was used for the analyses (IBM® SPSS Statistics for Windows®. Version 26. Armonk, NY: IBM® Corporation; 2019).

RESULTS

Table 1 describes the sample characteristics. Mean age was approximately 61 years, more than one-third were female, slightly less than two-thirds were those from either African American or Hispanic race/ethnicity, more than one third had regular Medicaid, and more than a third met criteria for obesity. Almost two thirds of patients that met the criteria of ICU level of care, and less than 10% of patients were intubated on the day of admission. Slightly over a third of patients with hematologic involvement required mechanical ventilation, and only 10% of patients did not require supplemental oxygen during the admission. The mean CCI was 3.0 (the CCI score of 3 signifies that there is a 77% 10-year survival)[20] and the mean qSOFA was 1.5 (the qSOFA score of 2 signifies 3-to-14-fold increase in in hospital mortality)[21]. The mean number of organs involved was 4.8 organs. The most frequent interventions were antibiotics, antimalarial medications, and steroids. Mortality was at 42.9% and mean length of stay was 12.8 days.

Table 1. Sample characteristics of 475 COVID-19 patients.

Variables	Mean (SD) or Frequency (%)
Demographics	
Mean age (years)	60.9 (15.75)
Sex (female)	171 (36.0)
Race/ethnicity	
Caucasian	125 (26.3)
African American	115 (24.2)
Hispanic	198 (41.7)
East Asian	16 (3.4)
Southeast Asian	11 (2.3)
Other	10 (2.1)
Insurance	
Private	103 (21.7)
Uninsured/emergency Medicaid	98 (20.6)
Regular Medicaid	179 (37.7)
Medicare	95 (20.0)
Comorbidities	
Sickle cell disease (yes)	3 (0.6)
Other hematologic disorders (yes)	3 (0.6)
Immunosuppressive medications at home (yes)	24 (5.1)
Obese (yes)	177 (37.3)
CCI [mean]	3.0 (2.45)
qSOFA [mean]	1.5 (0.65)
Disease severity	
ICU (yes)	301 (63.4)
Intubation admission (yes)	41 (8.6)
Oxygen requirement hospitalization	
None	48 (10.1)
Low FiO_2 (< 55%)	130 (27.4)
High FiO_2 (> 55%)	127 (26.7)
Ventilation	170 (35.8)
Treatment management	
Vasopressor (yes)	117 (24.6)
Antibiotic (yes)	454 (95.6)
NSAID (yes)	118 (24.8)
ACEi/ARBS (yes)	61 (12.8)
Antiviral (yes)	14 (2.9)
Antimalarial (yes)	392 (82.5)
Steroid (yes)	206 (43.4)
Convalescent plasma (yes)	50 (10.5)
Interleukin inhibitor (yes)	72 (15.2)
Anticoagulant (yes)	121 (25.5)
Organ involvement	
Mean number organs involved	4.8 (1.62)
Hematology	
Mean white blood cell peak	16.4 (11.45)
Mean white blood cell nadir	6.7 (3.80)
Mean absolute neutrophil count nadir	6.2 (3.92)
Mean hemoglobin admission	12.8 (2.36)
Mean hemoglobin nadir	10.5 (2.56)
Mean platelets peak	350.7 (154.67)
Mean platelets nadir	191.6 (92.52)
Mean white blood cell proportion days involved	0.4 (0.30)
Mean absolute neutrophil count proportion days involved	0.2 (0.19)
Mean days to hematology involvement	2.2 (2.37)
Hematology persistent involvement at discharge (yes)	367 (77.3)
Mean lactate dehydrogenase	663.8 (504.63)
Mean erythrocyte sedimentation rate	69.9 (32.60)
Mean interleukin level (pg/mL)	179.8 (496.07)
Mean ferritin level (ng/mL)	1,612.1 (1,919.01)
Mean D-dimer (µg/ml)	4.6 (5.71)
Mean C-reactive protein (mg/L)	18.2 (10.62)
Mean fibrinogen (mg/dL)	565.1 (209.10)
Mean prothrombin time peak (seconds)	16.0 (5.45)
Mean international normalized ratio peak	1.3 (1.09)
Outcomes	
Mortality (yes)	204 (42.9)
Mean length of stay (days)	12.8 (13.17)

Abbreviations: SD, standard deviation; CCI, Charlson Comorbidity Index; qSOFA, quick Sepsis Related Organ Failure Assessment; ICU, intensive care unit; FiO_2, fraction of inspired oxygen; NSAID, nonsteroidal anti-inflammatory drug; ACEi, Angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers.

The following variables were missing data and are only shown for descriptive purposes: lactate dehydrogenase level (n = 295), erythrocyte sedimentation rate (n = 133), interleukin (n = 67), ferritin (n = 300), D-dimer (n = 252), C-reactive protein (n = 301), fibrinogen (n = 161), prothrombin time peak (n = 357), and international normalized ratio peak (n = 365).

Table 2 shows logistic regression analyses for mortality. In the univariate analyses shown in Model 1, increased age, insurance of regular Medicaid and Medicare, increased CCI, increased qSOFA, ICU care, intubation at admission, oxygen requirement during hospitalization of high FiO_2 and ventilation, vasopressor, antiviral, steroid, and increased number organs involved each were associated significantly with increased odds for mortality. Hispanic race/ethnicity was associated significantly with decreased odds for mortality. In the multivariate analysis shown in Model 2, increased age, insurance of regular Medicaid, oxygen requirement during hospitalization of ventilation, increased number organs involved, increased absolute neutrophil count nadir, increased days to hematology involvement, and hematology persistent involvement at discharge each were associated significantly with increased odds for mortality. Increased platelets peak and increased hemoglobin admission were associated significantly with decreased odds for mortality.

Table 2. Logistic regression analyses for mortality.

Variables	Model 1 Univariate OR (95% CI)	Model 2 Multivariate OR (95% CI)
Demographics		
Age (years)	1.05 (1.04, 1.07)***	1.04 (1.01, 1.08)*
Sex (female)	0.98 (0.67, 1.44)	---
Race/ethnicity		
Caucasian	1.00	1.00
African American	0.78 (0.47, 1.30)	0.37 (0.13, 1.03)
Hispanic	0.56 (0.35, 0.88)*	0.66 (0.26, 1.68)
East Asian	1.31 (0.46, 3.73)	0.22 (0.03, 1.54)
Southeast Asian	0.85 (0.25, 2.92)	0.39 (0.05, 3.20)
Other	4.07 (0.83, 19.91)	10.67 (0.93, 122.22)
Insurance		
Private	1.00	1.00
Uninsured/emergency Medicaid	0.94 (0.52, 1.70)	1.21 (0.40, 3.68)
Regular Medicaid	1.75 (1.06, 2.91)*	3.68 (1.41, 9.61)**
Medicare	3.64 (2.02, 6.54)***	2.35 (0.68, 8.16)
Comorbidities		
Sickle cell disease (yes)	2.67 (0.24, 29.69)	---
Other hematologic disorders (yes)	2.67 (0.24, 29.69)	---
Immunosuppressive medications at home (yes)	1.92 (0.84, 4.42)	---
Obese (yes)	0.96 (0.66, 1.40)	---
CCI	1.30 (1.19, 1.41)***	1.03 (0.84, 1.26)
qSOFA	1.66 (1.24, 2.22)**	0.72 (0.42, 1.24)
Disease severity		
ICU (yes)	17.89 (10.03, 31.91)***	2.22 (0.38, 12.88)
Intubation admission (yes)	7.54 (3.27, 17.40)***	0.44 (0.11, 1.80)
Oxygen requirement hospitalization		
None	1.00	1.00
Low FiO_2 (< 55%)	1.92 (0.40, 9.08)	1.75 (0.32, 9.56)
High FiO_2 (> 55%)	15.94 (3.71, 68.61)***	7.82 (0.86, 70.91)
Ventilation	107.33 (24.69, 46.63)***	98.43 (8.84, 1,095.89)***
Treatment management		
Vasopressor (yes)	14.37 (8.19, 25.22)***	2.41 (0.83, 7.04)
Antibiotic (yes)	2.50 (0.90, 6.93)	---
NSAID (yes)	1.34 (0.88, 2.03)	---
ACEi/ARBS (yes)	0.84 (0.49, 1.46)	---
Antiviral (yes)	5.09 (1.40, 18.50)*	2.33 (0.29, 18.65)
Antimalarial (yes)	1.10 (0.68, 1.79)	---
Steroid (yes)	1.50 (1.04, 2.16)*	0.95 (0.44, 2.04)
Convalescent plasma (yes)	1.15 (0.64, 2.07)	---
Interleukin inhibitor (yes)	1.49 (0.90, 2.47)	---
Anticoagulant (yes)	1.00 (0.66, 1.52)	---
Organ involvement		
Number organs involved	2.94 (2.43, 3.57)***	1.69 (1.21, 2.36)**

Table 2. Logistic regression analyses for mortality. *continued.*

Variables	Model 1 Univariate OR (95% CI)	Model 2 Multivariate OR (95% CI)
Hematology		
White blood cell peak	---	0.70 (0.08, 6.30)
White blood cell nadir	---	0.93 (0.06, 15.59)
Absolute neutrophil count nadir	---	1.20 (1.02, 1.42)*
Hemoglobin admission	---	0.77 (0.60, 0.98)*
Hemoglobin nadir	---	1.25 (0.99, 1.57)
Platelets peak	---	0.995 (0.992, 0.997)***
Platelets nadir	---	1.00 (0.999, 1.01)
White blood cell proportion days involved	---	1.17 (0.27, 5.12)
Absolute neutrophil count proportion days involved	---	2.35 (0.24, 22.55)
Days to hematology involvement	---	4.44 (1.42, 13.90)*
Hematology persistent involvement at discharge (yes)	---	2.87 (1.20, 6.90)*

Abbreviations: OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; qSOFA, quick Sepsis Related Organ Failure Assessment; ICU, intensive care unit; FiO_2, fraction of inspired oxygen; NSAID, nonsteroidal anti-inflammatory drug; ACEi, Angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers.
*p < 0.05, **p < 0.01, ***p < 0.001, Model 2 Nagelkerke R Square = 0.76.

Table 3 shows linear regression analyses for LOS. In the univariate analyses shown in Model 1, ICU care, oxygen requirement during hospitalization of high FiO_2 and ventilation, vasopressor, antibiotic, NSAID, steroid, convalescent plasma, interleukin inhibitor, anticoagulant, and increased number organs involved each were associated significantly with increased LOS. East Asian race/ethnicity was associated significantly with decreased LOS. In the multivariate analysis shown in Model 2, steroid, convalescent plasma, interleukin inhibitor, white blood cell peak, increased platelets peak, and increased hemoglobin admission each were associated significantly with increased LOS. Increased white blood cell nadir, increased platelets nadir, increased hemoglobin nadir, increased white blood cell proportion days involved, increased absolute neutrophil count proportion days involved, and hematology persistent involvement at discharge each were associated significantly with decreased LOS.

Table 3. Linear regression analyses for length of stay.

Variables	Model 1 Univariate B (SE)	Model 2 Multivariate B (SE)
Demographics		
Age (years)	-0.001 (0.001)	---
Sex (female)	-0.07 (0.04)	---
Race/ethnicity		
Caucasian	Reference	Reference
African American	-0.07 (0.05)	-0.03 (0.03)
Hispanic	0.01 (0.04)	-0.03 (0.03)
East Asian	-0.23 (0.10)*	-0.03 (0.06)
Southeast Asian	0.02 (0.11)	-0.01 (0.07)
Other	0.19 (0.12)	0.03 (0.07)
Insurance		---
Private	Reference	
Uninsured/emergency Medicaid	0.07 (0.05)	
Regular Medicaid	-0.05 (0.05)	
Medicare	0.01 (0.05)	
Comorbidities		
Sickle cell disease (yes)	-0.28 (0.21)	---
Other hematologic disorders (yes)	0.31 (0.21)	---
Immunosuppressive medications at home (yes)	-0.06 (0.08)	---

Table 3. Linear regression analyses for length of stay. *continued.*

Variables	Model 1 Univariate B (SE)	Model 2 Multivariate B (SE)
Comorbidities		
Obese (yes)	-0.03 (0.04)	---
CCI	-0.004 (0.01)	---
qSOFA	0.02 (0.03)	---
Disease severity		
ICU (yes)	0.25 (0.03)***	0.05 (0.06)
Intubation admission (yes)	-0.07 (0.06)	---
Oxygen requirement hospitalization		
None	Reference	Reference
Low FiO_2 (< 55%)	0.09 (0.06)	0.02 (0.04)
High FiO_2 (> 55%)	0.25 (0.06)***	-0.01 (0.07)
Ventilation	0.34 (0.06)***	-0.11 (0.07)
Treatment management		
Vasopressor (yes)	0.17 (0.04)***	-0.03 (0.03)
Antibiotic (yes)	0.22 (0.08)**	0.09 (0.05)
NSAID (yes)	0.08 (0.04)*	0.03 (0.02)
ACEi/ARBS (yes)	-0.04 (0.05)	---
Antiviral (yes)	0.15 (0.10)	---
Antimalarial (yes)	0.08 (0.04)	---
Steroid (yes)	0.31 (0.03)***	0.06 (0.03)*
Convalescent plasma (yes)	0.50 (0.05)***	0.12 (0.04)**
Interleukin inhibitor (yes)	0.37 (0.04)***	0.07 (0.04)*
Anticoagulant (yes)	0.29 (0.04)***	0.04 (0.03)
Organ involvement		
Number organs involved	0.07 (0.01)***	0.01 (0.01)
Hematology		
White blood cell peak	---	0.46 (0.07)***
White blood cell nadir	---	-0.27 (0.09)**
Absolute neutrophil count nadir	---	-0.01 (0.01)
Hemoglobin admission	---	0.05 (0.01)***
Hemoglobin nadir	---	-0.06 (0.01)***
Platelets peak	---	0.001 (< 0.001)***
Platelets nadir	---	-0.001 (< 0.001)***
White blood cell proportion days involved	---	-0.14 (0.04)**
Absolute neutrophil count proportion days involved	---	-0.21 (0.07)**
Days to hematology involvement	---	0.02 (0.04)
Hematology persistent involvement at discharge (yes)	---	-0.06 (0.03)*
Constant	---	0.54 (0.10)***

Abbreviations: B, unstandardized beta; SE, standard error; CCI, Charlson Comorbidity Index; qSOFA, quick Sepsis Related Organ Failure Assessment; ICU, intensive care unit; FiO_2, fraction of inspired oxygen; NSAID, nonsteroidal anti-inflammatory drug; ACEi, Angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers.
*p < 0.05, **p < 0.01, ***p < 0.001, Model 2 adjusted R Square = 0.65.

DISCUSSION

Results showed that increased age was associated with increased mortality. This finding was consistent with other studies that found increased age as an independent predictor of mortality in COVID-19.[14,15] This study had a large percentage of minorities consisting of Hispanics and African Americans and did not find an association of race/ethnicity with mortality. Some studies showed higher mortality among these minorities.[11,12] However, other studies that adjusted for many covariates did not find an association of Hispanics and African Americans with mortality.[14,15] Results found that regular Medicaid, but not those uninsured who were eligible for emergency Medicaid, had an association with increased mortality. The authors were not aware of any research of regular Medicaid status with COVID-19 mortality. However, studies done in other diseases found increased mortality in patients who have regular Medicaid.[22,23] Patients who have regular Medicaid were often of lower socioeconomic class, have barriers to care, and have increased burden of comorbidities.[24] Uninsured patients tend to be younger and healthier as many of them are undocumented in the country for work.[25] This could be a reason why there was no association of uninsured with mortality.

This study did not find a significant association between obesity and mortality. This was like other studies that did not find an association with obesity and mortality at BMI ≥ 30.[26] Studies that reported an association of obesity with mortality found this association for severe obesity at BMI ≥ 40.[27,28] This study found that mechanical ventilation was associated with higher odds for mortality, and this was consistent with other studies.[4] Results demonstrated that patients who developed hematologic involvement adjusted for other organ compromise and had increased mortality. Although previous research for hematologic involvement in COVID-19 showed increased mortality, these studies did not adjust for other organ involvement.[17,29,30] This study showed increased mortality adjusted for all other organ involvement.

The results demonstrated that increased ANC had higher odds for mortality. These results were consistent with findings of all COVID-19 patients reporting higher ANC associated with mortality.[31] Other studies in COVID-19 found neutrophilia to be a risk factor for development of Acute Respiratory Distress Syndrome and mortality,[29,32] suggesting that innate immune cell response might be the cause of pathogenesis in the pulmonary system.[33] This likely was related to the hyperinflammatory response in COVID-19 carried out mostly by neutrophils.[34,35] As part of the innate immunity response, neutrophils are recruited to the lungs by proinflammatory cytokines and form neutrophil extracellular traps (NETs). NETs consist of an extracellular network of DNA fragments, microbicidal proteins, and oxidant enzymes like myeloperoxidase (MPO) and neutrophils elastase (NE), whose function is to capture and eliminate viral particles.[34-36] Sustained NETs formation can induce a cascade of inflammatory reactions that ultimately causes tissue damage and cell death via the MPO and NE release.[34,35] This also was corroborated with reports of lung autopsies that showed neutrophil infiltration within lung capillaries and extravasation of neutrophils into the alveolar space in COVID-19.[37]

In this study, higher WBC peak was associated with higher LOS and an increased WBC nadir was associated with decreased LOS. In COVID-19, patients with leukocytosis tended to have more severe disease, more ICU admissions, and higher LOS.[38] One possibility of why patients with increased WBC nadir had decreased LOS was that the WBC nadir was in the normal range signifying a milder disease. Another possibility is that decreased WBC nadir often was caused by lymphopenia that in COVID-19 studies has been associated with more severe disease.[39]

This study found that patients with higher hemoglobin on admission was associated with decreased mortality. Studies in COVID-19 patients report that patients with baseline anemia on presentation had increased odds of mortality[16] and the more severe the degree of the anemia the higher odds of mortality.[30] The proposed pathophysiology is that patients with anemia have decreased oxygen delivery to peripheral tissues, leading to worsening organ function.[40] Also, the increased inflammatory state due to the cytokine storm makes iron unavailable for erythropoiesis resulting in anemia of inflammatory disease. This ultimately creates a deficit in organ perfusion during the increasing demand of oxygen secondary to the hyper-metabolic state of the COVID-19 disease.[16,40] Patients in this study who had higher hemoglobin nadir had lower LOS. This finding was similar to a study in COVID-19 patients that showed a significantly negative correlation between hemoglobin and LOS.[41] This also was consistent with other medical conditions where low hemoglobin was an independent risk factor for increased LOS.[42]

High platelet peak was associated with decreased mortality and increased LOS. There were no studies of platelet peak and its association with mortality or LOS in COVID-19. However, studies showed that having low platelets in COVID-19 patients was associated with increased mortality.[17,43,44] Thrombocytopenia can develop in COVID-19 patients through two possible approaches.[45,46] One approach is by affecting hematopoiesis. The virus can enter the bone marrow platelet precursors and platelets through their surface receptors and induce growth inhibition and apoptosis.[45,46] Another approach is by generation of antibodies. The antibodies that form in response to interaction of the host cells and the virus bind to surface antigens on platelets and are recognized by reticuloendothelial system which ultimately leads to platelets destruction.[45,46] This study found that patients with higher platelets nadir had decreased LOS. Previous research related to platelets and LOS showed an increased LOS if patients developed delayed thrombocytopenia after 14 days of admission.[44] The platelet nadir mean in this study was within normal range. The results suggested that our patients with higher platelets nadir had a milder disease and therefore a decreased LOS.

The results showed that increased days to hematologic involvement was associated with higher mortality. Other studies reported a similar association of abnormal hematologic parameters positively associated with mortality.[38,41,44] Patients that took longer to have WBC or ANC involvement had decreased LOS. The data on WBC or ANC and LOS were limited to a study that showed no association between ANC and

LOS.[47] In this study, it took an average of 2.2 days for hematologic involvement. The authors propose that a decrease in LOS with abnormalities in WBC and ANC later during hospitalization were likely no longer COVID-19 related and manifestations of a milder form of the illness.

This study found that treatment with convalescent plasma, interleukin inhibitors, or steroids were associated with increased LOS. The data on LOS and treatment of COVID-19 were limited. A study of interleukin inhibitor treatment for COVID-19 also had increased LOS for those receiving tocilizumab.[48] A study from China found increased LOS with steroid treatment; however, the study did not focus on those with hematologic involvement.[47] Data from COVID-19 patients administered convalescent plasma showed decreased LOS when convalescent plasma was applied early in the course of the disease.[49,50] This study's findings may differ since the sample was collected at the time when convalescent plasma was experimental and was started on patients with severe disease late in their course after they did not respond to other therapies. A possible reason for the findings may pertain to treatment with these therapies as indications for more severe cases that would have an increased LOS regardless of their administration.

Patients that had hematologic involvement at discharge had higher mortality and lower LOS than those who recovered to normal hematologic values. The authors propose that these patients likely were critically ill. This was consistent with other studies showing hematologic abnormalities being associated with increased mortality[16,17,29-32,43,44] and a decreased LOS.

This study had some limitations. First, it was done in a single center safety net hospital with a large minority population and may not be representative of other hospitals in the U.S. However, inclusion of a large proportion of minorities in the study group allowed a better description of the COVID-19 experience in this population. Second, data were collected from patients admitted during the peak of the pandemic in New York, where treatment management standards frequently were changing based on new guidelines. This could have affected patients' outcomes. Third, although guideline-based criteria were used for defining each hematologic cell line dysfunction, universally accepted criteria for hematologic organ system involvement were not available. We chose involvement as abnormalities in laboratory values for at least one cell line. Fourth, the retrospective nature of our study prevented any causative analysis. Fifth, there were some patients where the baseline information on hematologic parameters were not available.

In conclusion, patients with increased ANC, increased days to any hematologic involvement, and persistence of hematologic involvement at discharge were associated with increased odds for mortality while increased hemoglobin on admission and increased platelets peak were associated with decreased odds for mortality. Hematologic parameters consistent with milder disease (increased WBC nadir, increased hemoglobin nadir, and increased platelets nadir) or critical illness (hematologic involvement at discharge) were associated with shorter LOS. Hematologic parameters consistent with more severe form of the disease (increased WBC peak) were associated with longer LOS. These findings can be used by clinicians to risk-stratify patients with hematologic involvement in COVID-19 better and tailor therapies potentially to improve patient outcomes.

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