Comparison of Blood Counts and Markers of Inflammation and Coagulation in Patients With and Without COVID-19 Presenting to the Emergency Department in Seattle, WA

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ABSTRACT

Objectives: We compared complete blood count (CBC) with differential and markers of inflammation and coagulation in patients with and without coronavirus disease 2019 (COVID-19) presenting to emergency departments in Seattle, WA.

Methods: We reviewed laboratory values for 1 week following each COVID-19 test for adult patients who received a standard severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription polymerase chain reaction (RT-PCR) test before April 13, 2020. Results were compared by COVID-19 status and clinical course.

Results: In total 1,027 patients met inclusion criteria. Patients with COVID-19 (n = 155) had lower leukocytes (P < .0001), lymphocytes (P < .0001), platelets (P < .0001), and higher hemoglobin (P = .0140) than those without, but absolute differences were small. Serum albumin was lower in patients with COVID-19 (P < .0001) and serum albumin, neutrophil to lymphocyte ratio (NLR), and red cell distribution width (RDW) were each associated with disease severity. NLR did not differ between patients with COVID-19 and those without (P = .8012).

Conclusions: Patients with COVID-19 had modestly lower leukocyte, lymphocyte, and platelet counts and higher hemoglobin values than patients without COVID-19. The NLR, serum albumin, and RDW varied with disease severity, regardless of COVID-19 status.

Key Points

- Patients with SARS-CoV-2 presenting to the ED had lower leukocyte, lymphocyte, and platelet counts than COVID-19–negative patients.
- Serum albumin, RDW, and the neutrophil to lymphocyte ratio were associated with disease severity in both COVID-19–positive and COVID-19–negative patients presenting to the ED.
- None of the changes in laboratory findings identified are sufficiently specific for COVID-19 to alleviate the need for robust testing for the virus.

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 in Wuhan, China, and progressed to a pandemic resulting in over 1.7 million global deaths by the end of 2020.1,2 The clinical disease caused by SARS-CoV-2, coronavirus disease 2019 (COVID-19), has a wide range of clinical manifestations, ranging from asymptomatic to severe pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure.3 Diagnostic testing for the virus is most commonly performed by amplification of viral RNA from nasopharyngeal or lower respiratory tract specimens via reverse transcription polymerase chain reaction (RT-PCR). Early and ongoing limitations on testing hampered disease control efforts. Given the breadth of clinical presentations and widely divergent clinical progression, identifying changes in routine laboratory tests that support the diagnosis and management of patients with COVID-19 is critical.
Early reports from China identified an exaggerated inflammatory response (cytokine storm) as one of the distinct features of SARS-CoV-2 infection, at least in a subset of patients. Significant elevations in serum C-reactive protein (CRP), interleukin 6 (IL-6), ferritin, procalcitonin, fibrinogen, and other acute phase reactants have since been consistently described in patients with severe COVID-19. Lymphopenia was singled out as a hallmark of COVID-19 when the first descriptive studies from Wuhan showed that over 80% of patients with COVID-19 had low lymphocyte counts. Other alterations noted on analysis of CBC include leukopenia, eosinopenia, monocytosis, neutrophilia, and thrombocytopenia. The magnitude of lymphopenia and thrombocytopenia in patients with COVID-19 has been associated with more severe outcomes including admission to the intensive care unit (ICU), ARDS, and death. Some have proposed using the neutrophil to lymphocyte ratio (NLR), an established metric of overall inflammation, as well as other ratios of hematologic laboratory values as surrogate markers of disease severity in COVID-19.

Additionally, a subset of patients with COVID-19 have alterations in coagulation factors manifesting as slightly prolonged prothrombin times (PT), activated partial thromboplastin times (PTT), and increased D-dimer levels, with some COVID-19 patients presenting with coagulopathy and disseminated intravascular coagulation. The topic of hematologic and other laboratory alterations in COVID-19 is of considerable interest and has been well reviewed. While numerous reports have summarized patterns of laboratory markers in COVID-19 patients and/or identified laboratory markers that correlate with disease severity, comparisons of these markers between patients with and without COVID-19 are infrequent.

We sought to detail differences in CBC with differential in patients with COVID-19 presenting to emergency departments (EDs) affiliated with the University of Washington in Seattle, one of the first metropolitan areas in the United States to encounter SARS-CoV-2 and having one of the first laboratories to receive emergency use authorization from the United States Food and Drug Administration for diagnostic SARS-CoV-2 RT-PCR testing (March 1, 2020). Our data reflect an early time point in the course of the pandemic in the United States, during which differences in treatment approaches between COVID-19 patients is likely to be limited. Importantly, we offer comparison to patients without COVID-19 stratified by clinical course, which captures the diversity of individuals presenting to EDs in the United States.

**Materials and Methods**

This study was approved by the University of Washington Human Subjects Division Institutional Review Board (STUDY00009972) and was limited to adult patients (≥18 years old) who received a SARS-CoV-2 RT-PCR test at one of the University of Washington hospitals in Seattle, before April 13, 2020, the date on which routine screening for COVID-19 was enacted at our institution. Patients were stratified by SARS-CoV-2 status, mortality, and sending location of laboratory results. Patients with results originating from an ED location only were assigned to the ED clinical course. Patients with results from an ED location and an inpatient location (but not ICU) were assigned to the admitted clinical course. Finally, patients with results from an ED location and an ICU location at any point during their admission were assigned to the critical clinical course. Results from patients in locations with ICU, intensive, or critical in the location name were classified as ICU. Results from patients in a special care unit at one of the local hospitals were also classified as originating from an ICU. To better capture early laboratory alterations associated with illness severity that could be used to stratify those at increased risk of poor outcome, patients who died within 15 days of their last SARS-CoV-2 test were put in their respective critical group; this added 20 patients to the critical COVID-19–negative group and 18 patients to the critical COVID-19–positive group, respectively. Two patients with COVID-19 and 35 patients without COVID-19 died outside of the 15-day window from their last COVID-19 test and were not included in the analysis.

Patients with laboratory values originating from locations or wards of the University of Washington’s affiliated cancer center were excluded due to the high prevalence of patients with leukemia and lymphoma. Similarly, patients from locations including the word oncology were excluded. Select laboratory results were extracted from the Department of Laboratory Medicine and Pathology’s data warehouse for 1 week following each SARS-CoV-2 PCR test. Demographics, International Classification of Diseases-Tenth Revision (ICD-10) diagnostic codes, and mortality data were pulled from the health care system’s shared electronic data warehouse. No values outside of an assay’s reportable range were included and all values were exact (no greater or less than results). Results were organized and analyzed using RStudio version 1.2.1335.

For most laboratory tests, such as CBC, we defined the presentation value as the first test sent from an ED location for each patient (or as the first value identified within 1 day of the patient’s first set of tests). For some markers, we also evaluated the highest documented
(maximum) and lowest documented (minimum) values, in addition to the presentation levels. Continuous variables were tested for normality using the D’Agostino-Pearson omnibus normality test. Due to the frequency of nonparametric distributions in the selected laboratory values, the Mann-Whitney U test and Kruskal-Wallis test were used for continuous variables. Fisher exact test was used in comparison of categorical variables. For pairwise comparisons, the Wilcoxon signed rank test was used. We set the significance level (α) at P = .05. Statistical analysis was performed using GraphPad Prism8.

Results

A total of 1,027 patients met criteria for evaluation, comprising 155 patients in the SARS-CoV-2 detected and 872 patients in the SARS-CoV-2 not detected groups Table I. The median age of patients with COVID-19 was 65 years; 41% were female. The cohort of patients without COVID-19 was younger, with a median age of 56 years (P < .0001); 44% were female. Only patients with COVID-19 in the admitted group were significantly older than corresponding patients without COVID-19 (median age 70 vs 64 years, P = .031). More patients with COVID-19 identified as Hispanic or Latino (28% vs 8%; P < .0001; odds ratio [OR], 4.33; 95% confidence interval [CI], 2.85-6.60), but other demographics were not significantly different between patients with COVID-19 compared to those without. A total of 31 of 155 (20%) patients with COVID-19 and 44 of 872 (5%) patients without COVID-19 died within 15 days of their last SARS-CoV-2 test. The frequency of different ICD-10 diagnostic codes at the time of testing for SARS-CoV-2 were similar between patients with and without COVID-19. Cough, fever, and shortness of breath were within the top 20 diagnostic codes regardless of COVID-19 status concordant with the symptom-driven testing in place at the time (Supplemental Table 1; all supplemental materials can be found at American Journal of Clinical Pathology online).

Several significant differences in basic CBC data were noted between the COVID-19–positive and COVID-19–negative patient groups Table II, including platelet and WBC counts Figure 2. A number of other parameters showed differences between groups that reached statistical significance, but for many of these (including hemoglobin, RBC count, and RDW) the differences were relatively small. Lymphocyte count was notably lower in patients with COVID-19 overall (median, 1.06 vs 1.43 × 10^9/L, P < .0001), predominantly attributable to lower median lymphocyte counts in patients with the

| Characteristic | COVID-19 Positive | COVID-19 Negative | P Value |
|----------------|-------------------|-------------------|-------|
| Total patients | 872 (89)          | 618 (71)          |       |
| Women          | 56 (65)           | 441 (71)          |       |
| Men            | 306 (35)          | 177 (29)          |       |
| Male           | 52 (60)           | 45 (7)            |       |
| Female         | 34 (36)           | 40 (68)           |       |
| Age, y         | 65 (69)           | 61 (67)           |       |
| <60            | 483 (56)          | 307 (50)          |       |
| ≥60            | 389 (44)          | 311 (50)          |       |
| White          | 569 (66)          | 441 (71)          |       |
| Female         | 282 (65)          | 227 (51)          |       |
| Male           | 287 (35)          | 214 (49)          |       |
| Age, y         | 65 (69)           | 61 (67)           |       |
| <60            | 438 (50)          | 344 (56)          |       |
| ≥60            | 441 (50)          | 274 (44)          |       |
| Hispanic or Latino | 61 (7) | 31 (5) | <.0001 |
| Race unknown or declined | 6 (1) | 3 (0) |       |
| Abbreviations  |                  |                   |       |
| COVID-19, coronavirus disease 2019 |                  |                   |       |
| ED, emergency department |                  |                   |       |
| Neg, negative |                  |                   |       |
| Pos, positive |                  |                   |       |
| RT-PCR, reverse transcription polymerase chain reaction |                  |                   |       |
| SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 |                  |                   |       |
| Data are No. (%) except where indicated. Bold values indicate significance P < .05. All patients who died within 15 days of their last SARS-CoV-2 RT-PCR test were put in their respective critical course.
Figure 1: Flow diagram showing patient selection process. Patients who had at least 1 positive SARS-CoV-2 RT-PCR test at any point were assigned to the detected group. Patients who never had a positive or inconclusive SARS-CoV-2 test were assigned to the not detected group. Those patients who had only an inconclusive SARS-CoV-2 test were excluded from analysis. Patients were stratified for disease severity according to sending location of laboratory results. Patients with only ED locations were classified as ED COVID-19–negative or ED COVID-19–positive, depending on whether they fell into the SARS-CoV-2 detected or not detected group. In a similar manner, patients with laboratory testing submitted from only an inpatient ward (not ICU locations) were classified as admitted COVID-19–negative or admitted COVID-19–positive. Lastly, patients with laboratory results submitted from an ICU at some point during their clinical course or died within 15 days of their last SARS-CoV-2 test were classified as critical COVID-19–negative or critical COVID-19–positive. Patients with SARS-CoV-2 detected (n = 2) or not detected (n = 35) were excluded. COVID-19, coronavirus disease 2019; ED, emergency department; ICU, intensive care unit; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
## Table 2: Comparison of CBC Data by COVID-19 Status and Clinical Course

| Analyte or Ratio | Overall by COVID-19 Status | ED Course by COVID-19 Status | Admitted Course by COVID-19 Status | Critical Course by COVID-19 Status | Between Courses |
|------------------|---------------------------|-----------------------------|----------------------------------|----------------------------------|----------------|
|                  | Neg (n = 872) | Pos (n = 155) | Mann-Whitney P | Neg (n = 618) | Pos (n = 59) | Mann-Whitney P | Neg (n = 129) | Pos (n = 38) | Mann-Whitney P | Neg (n = 125) | Pos (n = 58) | Mann-Whitney P | Kruskal-Wallis COVID-19 Neg P | Kruskal-Wallis COVID-19 Pos P |
| Hemoglobin, g/L  | 129 (28.0) | 134 (28.5) | **.0140** | 131 (26.8) | 139 (24.5) | **.0096** | 127 (31.0) | 128 (28.8) | **.3882** | 117 (27.0) | 132 (30.8) | **.016** | <.0001 | .0596 |
| Hematocrit, %    | 39 (8.00)  | 40 (7.50)  | .0610 | 40 (7.00)  | 42 (7.00)  | .0514 | 38.5 (8.00) | 42 (6.75)  | .1028 | 37 (8.00)  | 40 (8.75)  | **.110** | <.0001 | .2122 |
| RBCs, x10^9/L    | 4.38 (0.88) | 4.53 (0.98) | **.0430** | 4.47 (0.79) | 4.64 (0.83) | **.0160** | 4.28 (0.95) | 4.305 (1.14) | .5549 | 3.94 (0.92) | 4.445 (0.89) | **.022** | <.0001 | .433 |
| WBCs, x10^9/L    | 8.53 (5.21) | 6.48 (3.22) | <.0001 | 7.9 (4.32)  | 7.62 (4.90) | <.0001 | 11.6 (5.44) | 7.32 (4.90) | <.0001 | 11.19 (7.83) | 7.235 (3.96) | <.0001 | <.0001 | .2599 |
| Platelets, x10^9/L | 245 (119)  | 191 (95.50) | <.0001 | 254 (113.75) | 207 (89.50) | <.0001 | 235 (122.00) | 169.5 (99.00) | <.0001 | 227 (114.00) | 184 (105.00) | .1106 | <.0001 | .4266 |
| Neutrophils, x10^9/L | 4.38 (4.92) | 3.57 (4.07) | <.0001 | 4.39 (3.74) | 3.89 (2.01) | <.0001 | 7.91 (6.29)  | 4.205 (2.60) | <.0001 | 76 (7.48)  | 5.725 (4.51) | **.0008** | <.0001 | .021 |
| Lymphocytes, x10^9/L | 143 (11.1) | 106 (8.7)  | <.0001 | 159 (10.4)  | 132 (9.3)  | **.0086** | 108 (9.2)  | 9.655 (4.7)  | .2766 | 1 (1.05)  | 0.86 (0.77)  | .1954 | <.0001 | .002 |
| Basophils, x10^9/L | 0.04 (0.04) | 0.01 (0.02) | <.0001 | 0.04 (0.04) | 0.02 (0.02) | <.0001 | 0.04 (0.04) | 0.01 (0.02) | <.0001 | 0.03 (0.04) | 0.01 (0.02) | <.0001 | .1329 | .6332 |
| Eosinophils, x10^9/L | 0.08 (0.16) | 0.01 (0.04) | <.0001 | 0.1 (0.17)  | 0.02 (0.10) | <.0001 | 0.03 (0.13) | 0.01 (0.06) | .0035 | 0.02 (0.11) | 0 (0.01)  | <.0001 | <.0001 | <.0001 |
| Monocytes, x10^9/L | 0.64 (0.38) | 0.54 (0.39) | <.0001 | 0.62 (0.34) | 0.52 (0.34) | <.0001 | 0.68 (0.49) | 0.6 (0.39)  | .0332 | 0.73 (0.54) | 0.505 (0.42) | **.017** | .2211 | .6537 |
| Nucleated RBCs, x10^9/L | 0 (0.00)  | 0 (0.00)  | <.0001 | 0 (0.00)   | 0 (0.00)   | <.0001 | 0 (0.00)   | 0 (0.00)   | <.0001 | 0 (0.00)   | 0 (0.00)   | <.0001 | <.0001 | .1803 |
| Immature granulocytes, x10^9/L | 0.03 (0.05) | 0.03 (0.03) | **.0074** | 0.03 (0.03) | 0.02 (0.02) | **.007** | 0.05 (0.08) | 0.025 (0.04) | .046 | 0.05 (0.12) | 0.04 (0.07) | <.0001 | .015 |
| RDW, %           | 13.8 (2.23) | 13.4 (2.60) | **.0354** | 13.5 (2.10) | 12.8 (1.95) | **.0066** | 13.9 (2.20) | 13.45 (2.55) | .0722 | 14.6 (2.60) | 14.05 (2.78) | **.0342** | <.0001 | .076 |
| PNR              | 41.7 (32.94) | 40.4 (29.26) | .3900 | 46.98 (33.08) | 55.05 (34.07) | .0690 | 29.88 (26.88) | 37.06 (19.89) | **.010** | 29.12 (25.65) | 32.42 (26.47) | **.0263** | <.0001 | <.0001 |
| PLR              | 170.4 (142.40) | 201.8 (157.43) | .1035 | 158.4 (114.62) | 166.5 (128.04) | .7800 | 225.3 (171.15) | 191.8 (151.07) | .2537 | 206 (251.94) | 244.1 (180.96) | .3950 | <.0001 | .0049 |
| NLR              | 3.971 (5.75) | 4.074 (5.65) | .8012 | 3.196 (3.92)  | 2.871 (2.57)  | .0940 | 7.216 (11.36) | 4.538 (4.33)  | .052 | 8.433 (13.01) | 7.405 (7.14)  | .1910 | <.0001 | <.0001 |

COVID-19, coronavirus disease 2019; ED, emergency department; Neg, negative; NLR, neutrophil to lymphocyte ratio; PNR, platelet to neutrophil ratio; Pos, positive; RDW, red cell distribution width.

*Data are median (interquartile range). Bold values indicate significance at P = .05.

aData are median (interquartile range). Bold values indicate significance at P = .05.

bn = 617 for nucleated RBC in ED COVID-19 Neg group and n = 57 for critical COVID-19 Pos group.

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lowest disease severity (ED group only). While lymphocyte counts were lower in those patients with COVID-19 with a more severe clinical course, this finding did not appear to be specific to COVID-19 (Table 2). Lymphocyte counts were not significantly different among patients admitted to standard inpatient care (admitted course) or critical care (critical course) based on their COVID-19 status (P = .2766 and P = .1954, respectively). Similarly, while 53% and 55% of patients with COVID-19 in the admitted and critical courses were lymphopenic in the ED, similar rates of lymphopenia were observed among admitted and critical COVID-19–negative patients (Supplemental Table 2). While there was a higher likelihood of identifying lymphopenia in patients with COVID-19 overall (45% vs 27%; P < .0001; OR, 2.26), this was largely attributable to differences in the least-severe patient group (ED only, 31% vs 19%; P = .0393; OR, 1.9).

Interestingly, we found similar patterns with all leukocyte populations, including significantly lower neutrophil counts among patients with COVID-19 compared to the comparison group across all clinical courses. Median counts of eosinophils and basophils were also significantly lower overall in patients with COVID-19 across the clinical course. Median monocyte counts were lower overall for patients with COVID-19 (0.54 vs 0.64 × 10^9/L, P < .0001), but without much variation by clinical course (Table 2). Platelet counts were lower overall in patients with COVID-19 compared to those without COVID-19 (Figure 2) and rates of thrombocytopenia were higher (Supplemental Table 2). However, median platelet counts for patients with COVID-19 who followed a critical course were not significantly different from their non-COVID-19 comparison group (P = .11). Additionally, median platelet count did not vary with COVID-19 illness severity (Kruskal-Wallis P = .4266).

The median platelet to lymphocyte ratio (PLR), platelet to neutrophil ratio (PNR), and NLR were not significantly different overall between patients with COVID-19 and those without (P = .10, P = .39, and P = .80, respectively; Figure 2). However, each of these ratios demonstrated a trend of increasing (PLR and NLR) or decreasing (PNR) with illness severity, regardless of COVID-19 status. Considering just patients with COVID-19, the median values for PNR, PLR, and NLR were significantly different by clinical course (Kruskal-Wallis P < .0001 to P = .0049).

Testing for inflammatory markers such as CRP and IL-6 was not as widespread among the ED patients in our dataset (Supplemental Tables 3 and 4). Patients with COVID-19 had a CRP test more often; 61 (39%) COVID-19–positive patients vs 97 (11%) of COVID-19–negative patients. Overall, median maximum CRP levels were significantly higher in patients with COVID-19 (94 vs 28.4 mg/L, P < .0001) driven by substantial elevations in the critical COVID-19–positive group. The data are similarly limited for IL-6; 29 (19%) of patients with COVID-19 had an IL-6 level measured and only 3 patients (less than 1%) in the comparison group had an IL-6 level measured in our dataset. Maximum IL-6 levels increased dramatically with illness severity in COVID-19 (median for admitted COVID-19–positive patients 35 ng/L vs 215 ng/L in the critical COVID-19–positive group, Supplemental Figure 1).

A large majority of patients with and without COVID-19 had a test for serum albumin in our dataset (144 [93%] and 717 [82%], respectively). Minimum albumin levels were lower overall in patients with COVID-19 (33 g/L vs 39 g/L, P < .0001) and decreased with increasing illness severity. Patients with COVID-19 were more likely to have a minimum albumin value below the reference interval (55% vs 24%; P < .0001; OR, 3.79; Supplemental Table 4). The presentation albumin for patients with COVID-19 admitted to a hospital was compared to the minimum value when possible. In both settings, albumin on presentation was significantly higher than minimum values (P < .0001, absolute differences 4 and 5 g/L, for admitted COVID-19–positive and critical COVID-19–positive groups, respectively). Patients without COVID-19 in the corresponding clinical courses had similar but less-pronounced decreases.

PT and PTT were only performed in a subset of patients (Supplemental Table 3 and Supplemental Figure 2). Maximum PT/international normalized ratio [INR] values in patients with COVID-19 were not significantly different from the comparison group and tended to be lower (median 14.2 s/INR 1.1 vs 14.4 s/INR 1.1, P = .86 and P = .83, respectively). Maximum PTT values were significantly higher overall in patients with COVID-19 (median 36 s vs 32 s, P = .0031). Patients with COVID-19 were significantly more likely to have an elevated maximum PTT compared to COVID-19–negative patients (52% vs 33% of those tested; P = .0053; OR, 2.20; 95% CI, 1.31-3.72). However, anticoagulants that could prolong the PTT, such as heparin, were not recorded. The presentation PT and PTT for patients with COVID-19 admitted to a hospital was compared to the maximum value when possible. For both PT/INR and PTT, presentation values were significantly lower than maximum values in admitted patients (P < .0001 for both), although absolute differences were not large (0.15 s and 0.9 s for PT, 1 s and 5 s for PTT, admitted COVID-19–positive and critical COVID-19–positive groups, respectively). Notably, this finding was also present in patients without
COVID-19 in the critical course but not evident for those in the admitted course.

D-dimer testing was concentrated in the critical COVID-19–positive group (66% of all D-dimer tests in patients with COVID-19), while approximately 10% of patients without COVID-19 in each clinical course had a D-dimer value. Overall, maximum D-dimer values in patients with COVID-19 were not different from those without COVID-19 (920 µg/L and 680 µg/L fibrinogen equivalent units, respectively, \( P = .1972 \)). However, an elevated D-dimer was present in 80% of all patients with COVID-19 tested (28 of 35 patients), which was significantly higher than the rate in patients without COVID-19 (57%, 52 of 91; \( P = .0225 \); OR, 3; 95% CI, 1.25-7.53).

**Discussion**

We present a description of changes in laboratory tests associated with SARS-CoV-2 infection...
in a cohort of patients in the United States, with a COVID-19–negative comparison group stratified by clinical acuity. Concordant with what has been previously published, our findings suggest that laboratory alterations seen in COVID-19 are related to disease severity but highlight that these alterations may not be specific to pathogenic mechanisms distinct to COVID-19.\(^6,15,16\)

Regarding WBC counts, ED patients with COVID-19 were overall more likely to be leukopenic (16% vs 5%, \(P < .0001\)) and lymphopenic (45% vs 27%, \(P < .0001\)) compared to those without COVID-19 in the ED. Among patients with COVID-19, leukocyte counts increased significantly with illness severity, driven largely by an increase in neutrophils. Rates of absolute neutrophilia also increased significantly with disease severity (3% up to 34%, ED to critical courses; \(P < .0001\); OR, 15). Meanwhile, lymphocyte counts and illness severity were inversely related; the ED COVID-19–positive group had significantly higher lymphocyte counts than either the critical COVID-19–positive or admitted COVID-19–positive groups. This finding supports the use of lymphocyte count as a marker...
that may flag patients with COVID-19 more likely to require admission to the hospital. However, a low lymphocyte count alone is not sufficiently sensitive or specific to predict COVID-19 status (sensitivity of 45% and specificity of 73% in our dataset). Our findings are similar to those recently published by Pozdnyakova et al., who found critically ill patients with COVID-19 had lower leukocyte counts compared to ICU patients without COVID-19, but higher rates of neutrophilia and lymphopenia compared to patients with COVID-19 who did not require critical care.

SARS-CoV-2 is similar to the original SARS-CoV in its tendency to cause lymphopenia, and the higher neutrophil counts and higher rates of neutrophilia in patients with severe COVID-19 were also observed in SARS-CoV and MERS-CoV infections. Lieberman and colleagues have shown an inverse correlation between SARS-CoV-2 viral transcripts and neutrophil and B-cell related transcripts in nasopharyngeal specimens. This finding, in combination with the data of Liu et al showing increasing levels of circulating neutrophils over
time in both severe and nonsevere COVID-19 infections, suggests neutrophilia and lymphopenia may lag behind the periods of highest viral replication and presumed infectivity.

Several prior studies have suggested the NLR is a useful marker of disease severity in COVID-19.²⁴¹ Our data support the utility of NLR to stratify patients but, importantly, our data show the association of NLR with disease severity is not unique to patients with COVID-19 (Figure 2). Overall, the NLR may be useful as a proxy for disease severity as a measure of a patient’s overall inflammatory state and may help stratify those at risk of needing a higher level of hospital care.¹²

Other hematologic laboratory values responsive to inflammation include hemoglobin and RDW. Interestingly, anemia was less common in patients with COVID-19 (P = .075) and did not vary with illness severity (Figure 2), fitting the muddled picture in the literature; most analyses similar to our study show no significant change in hemoglobin with worsening disease.⁵² However, a small meta-analysis found a significant association between decreased hemoglobin concentrations and severity of COVID-19.²³ The lack of consistent impact on RBC levels is somewhat surprising, as inflammatory cytokines blunt erythropoiesis (anemia of inflammation).²⁴ The hemoglobin data in our study represent early time points in the disease course for COVID-19 (all coming from the ED) and may be too early to detect any changes in erythropoiesis or erythrophagocytosis due to the disease.

Higher values of RDW are thought to reflect a proinflammatory state and have been associated with more severe illness in the critical care literature.²⁵²⁶ RDW increased steadily, and significantly, with disease severity in both patients with and without COVID-19 in our dataset. This finding is concordant with the findings of Foy et al²⁷ showing increased mortality risk with increasing RDW in patients with COVID-19. Somewhat surprisingly, we found patients with COVID-19 tended to have lower RDWs compared to patients without COVID-19 overall (P = .035), and this held true for each level of acuity examined (Figure 2). Also, patients with COVID-19 were no more likely than patients without COVID-19 overall to have an abnormally high RDW (35% vs 36%, P = .9278). As such, RDW holds utility as an indicator of general illness severity but is not specific to COVID-19.

The reason for the slightly higher platelet counts in our study compared to some others is unclear.²⁸²⁹ It
may represent heterogeneity in our patient subgroups or reflect local differences in disease characteristics, as our median platelet count is similar to those reported in case series from the Seattle, WA, area. Lastly, Qu et al found that hospitalized patients with COVID-19 presenting with an elevated platelet count had worse outcomes and that PLR was a risk factor for prolonged hospitalization. Platelet counts may increase due to the inflammatory milieu, and a slight increase in platelet count in our critical group may be confounding the statistical analysis.

The non-CBC analytes in our dataset were not uniformly available for all patients, but several trends of interest will be discussed further. We observed significant increases in CRP and IL-6 in patients with COVID-19 and corresponding changes in acute phase reactants, including ferritin, fibrinogen, and albumin, compared to patients without COVID-19. Serum albumin in particular showed a dramatic decrease with increased illness severity in patients with COVID-19 and was lower than the comparison group for each clinical course (Supplemental Figure 1). Patients in our critical COVID-19–positive group were over 47 times more likely to have a low minimum albumin compared to their peers in the ED COVID-19–positive group (OR, 47.05; 95% CI, 13.95-158.7), suggesting this common laboratory parameter may have utility as a marker of disease severity in COVID-19.

Much has been made of coagulopathy in association with COVID-19 due to the high rates of thrombotic complications in reports from Wuhan with focus shifting to a microthrombotic pathology as described in one of the first autopsy studies. Our dataset was not specifically focused on investigating markers of coagulation and we did not collect information regarding rates of anticoagulation, thus limiting interpretations. However, our data fit the findings in the literature in which small to negligible increases in PT and significantly longer aPTTs are noted in patients with COVID-19. Aside from the use of prophylactic or therapeutic anticoagulation, especially heparin, one potential explanation for the prolonged PTT we observed is the presence of a lupus anticoagulant, antibodies against phospholipids formed in hyperinflammatory states. Lupus anticoagulant have been reported in 45% to 91% of patients with COVID-19.

Interpretation of D-dimer levels poses several challenges. Our study fits with numerous others showing that D-dimer levels increase with disease severity in COVID-19, but the use of this marker and an indicator of thrombotic tendency in COVID-19 is fraught due to its correlation with systemic inflammation. Our data did not show a significant difference in D-dimer levels between patients with and without COVID-19 overall (P = .1972). However, this finding is confounded by differences in test acquisition by clinical course between COVID-19–negative and –positive groups. Over half (65%) of D-dimer tests in our COVID-19–negative group were ordered in the ED course, where the analyte is frequently used to rule out pulmonary thromboembolism (compared to 17% of D-dimer tests in the COVID-19–positive group). In contrast, orders for D-dimer in COVID-19–positive patients were enriched in the critical course (66%). While an elevated D-dimer is an indication of fibrinolysis, this is not an uncommon finding in hospitalized patients, particularly those that are critically ill. The choice of comparison group colors the interpretation of D-dimer elevation observed in COVID-19.

Similar to our data, Helms et al found lower D-dimer levels in patients with COVID-19 in the ICU compared to matched patients with ARDS. Meanwhile, Qu et al compared D-dimer levels in severe cases of COVID-19 to admitted patients with community acquired bacterial pneumonia (CAP) and found higher D-dimers in patients with COVID-19. This was despite the fact that markers of inflammation, including CRP and erythrocyte sedimentation rate, were higher in patients with CAP. In most of the patients with COVID-19 they followed, D-dimer decreased along with CRP following treatment. However, in a subset of patients with COVID-19, D-dimer levels remained elevated, suggesting the presence of thrombi and possibly the need for more aggressive anticoagulation.

Our study has a number of limitations. It is a retrospective, observational analysis of a narrow geographic region during a specific period of time. Pediatric patients (younger than 18 years) and those likely to have a neoplastic diagnosis, including leukemias and lymphomas, were excluded. As we approximated clinical course from origin of laboratory order instead of directly reviewing the medical record for each patient, there is a risk of incomplete or miscategorization of patients. While we chose a significance level of P = .05, many of the laboratory values are likely correlated, thus the statistical significance of those close to this cutoff should be interpreted with caution. Lastly, non-CBC laboratory tests are not uniformly represented in our dataset and thus conclusions are limited by the possibility of ascertainment bias from differences in ordering practices.

**Conclusions**

Our data bolster existing reports regarding laboratory alterations in patients with COVID-19. Overall, the
laboratory findings we identified in COVID-19 patients are similar to those previously described, but our findings offer context to laboratory alterations in COVID-19 by providing direct comparison to patients without the disease at 3 different levels of acuity, a comparison lacking in the existing literature. As outlined, some laboratory alterations may be related to disease severity; however, additional, larger, prospective studies in more diverse cohorts are suggested to confirm the impressions in this retrospective, observational study. We emphasize that none of the changes in laboratory findings identified in this study are sufficiently specific for COVID-19 to alleviate the need for robust testing for the virus.

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