



Active COVID-19 Infection Is Indicated by $WBC \leq 7.0$ and $PLT \leq 200$ at Presentation

Urgent message: Testing supplies were scarce in urgent care centers (and even some emergency rooms) early in the pandemic. Ingenuity, creative thinking, and teamwork can help fill gaps in resources in the midst of a crisis.

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Introduction

The impact coronavirus disease of 2019 (COVID-19) has had on individuals, businesses, and governments is unprecedented in many ways. Though widespread and frequent screening is recommended for better containment,¹ limited availability of testing supplies was a reality for many emergency and urgent care providers, particularly in low-resource settings.

Cytopenia was associated with COVID-19 in early studies.^{2,3} As complete blood count (CBC) is almost always known early in a visit, it could be a valuable tool.

This retrospective review of ED visits had the objective of characterizing the association between different cell counts and active COVID-19 infection. Specifically, we examined white blood cell (WBC) and platelet (PLT) counts at presentation. We hypothesized that patients who presented with COVID-19 would be more likely to have relative leukopenia and thrombocytopenia.

Methods

Following IRB approval, data were abstracted by retrospective review of our electronic medical records from all ED visits at three community hospitals, all sites of a



single emergency medicine residency program, from March 15, 2020 to April 15, 2020.

Included were all adult patients (age >18) presenting to the ED who had RT-PCR testing for SARS-CoV-2 (Abbott Molecular, Des Plaines, IL, USA) sent from the ED and subsequently admitted to the hospital. Excluded were those with history of liver or hematopoietic system disease and patients with missing data in the encounter. Abstracted data included demographics, chief complaints, ED vital signs, WBC count, PLT count, and result of COVID-19 testing.

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Table 1. Most Common Presenting Chief Complaints				
	n (%)	(+) COVID-19	(-) COVID-19	p-value*
Total	476 (100%)	241 (50.6%)	235 (49.4%)	
Fever/chills	179 (37.6%)	127 (52.7%)	52 (17.0%)	<0.001
SOB	178 (37.4%)	86 (35.7%)	92 (39.1%)	0.435
Cough	110 (23.1%)	79 (32.8%)	31 (13.2%)	<0.001
Weakness/fatigue	42 (8.8%)	30 (12.4%)	12 (5.1%)	0.005
Chest Pain/palpitations	37 (7.8%)	10 (4.1%)	27 (11.5%)	0.003
Altered mental status	29 (6.1%)	6 (2.5%)	23 (9.8%)	0.001
Abdominal/flank pain	21 (4.4%)	11 (4.6%)	10 (4.3%)	0.870
Nausea/emesis	21 (4.4%)	10 (4.1%)	11 (4.7%)	0.778
Diarrhea	12 (2.5%)	7 (2.9%)	5 (2.1%)	0.589
Myalgia	10 (2.1%)	7 (2.9%)	3 (1.3%)	0.216
URI/sore throat	9 (1.9%)	6 (2.5%)	3 (1.3%)	0.331
Dizziness	9 (1.9%)	6 (2.5%)	3 (1.3%)	0.331

Table 2. Presenting WBC and PLT Counts				
	All	(+) COVID-19	(-) COVID-19	p-value
WBC x 10 ⁹ /L (SD)	9.3 (5.0)	7.3 (3.5)	11.3 (5.5)	<0.001
PLT x 10 ⁹ /L (SD)	238 (107)	213 (95)	263 (113)	<0.001

Initial WBC and PLT counts of the presenting patient population who tested positive (+) or negative (-) for COVID-19 (significance set at 0.025 with Bonferroni correction (0.05/2)).

With power set at 0.80 and significance set at 0.05, a sample size of 340 patients would detect a 15% difference among variables related to a positive SARS-CoV-2 test. Differences between positive and negative patients were tested using Student's t-test and Chi-square test as appropriate. Significance was set at $p=0.05$ with Bonferroni correction when appropriate. Receiver operating characteristic (ROC) curve analysis was used to define optimum cutoff points for prediction of SARS-CoV-2 test results based on WBC and PLT counts. Sensitivity, specificity, positive, and negative likelihood ratios are reported with 95% confidence intervals. Selected variables were manually re-abstracted on 10% of random patients with a Kappa of 100%.

Results

Four hundred ninety-four patients met the inclusion criteria with 43.1% of cases from Site 1, 25.8% from Site 2, and 31.1% from Site 3. Patients with history of liver or hematopoietic system disease were excluded ($n=13$; cirrhosis ($n=4$), thrombocytopenia ($n=6$), multiple myeloma ($n=2$), lymphoma ($n=1$)). Five patients with encounters with missing data were also excluded.

SARS-CoV-2 was detected in 241 of 476 patients

(50.6%). The most common chief complaints were shortness of breath (29.6%), fever/chills (27.5%), and cough (10.7%). Diarrhea was not common and there were no reported symptoms of dysgeusia or anosmia (Table 1). Patients with COVID-19 were significantly younger (65.7 vs 70.4 years of age; $p=0.002$) and had higher incidence of fever/chills ($p<0.001$). Finally, COVID-19 patients had significantly lower presenting WBC (7.3 vs 11.3; $p<0.001$) and PLT counts (213 vs 263; $p<0.001$) (Table 2).

ROC curve analysis of initial WBC and PLT counts were both significant ($p<0.001$) with areas under the curve of 75% and 64.5%. Further analysis showed that with a presenting WBC count of $\leq 7.0 \times 10^9/L$ or less, a patient was likely to be positive for COVID-19 with sensitivity of 0.620 and specificity of 0.766. In addition, with presenting WBC $7.0 \times 10^9/L$, the positive likelihood ratio of testing positive for COVID-19 was 2.70 ($p<0.001$, 95% CI: 2.10 to 3.52) and the negative likelihood ratio was 0.54 ($p<0.001$, 95% CI: 0.43 to 0.59) (Table 3).

Similarly, with a presenting platelet count of $200 \times 10^9/L$ or less, a patient was likely to be positive for COVID-19 with sensitivity of 0.543 and specificity of 0.716, with a positive likelihood ratio of 1.82 ($p<0.001$, 95% CI: 1.00

Table 3. Positive and Negative Likelihood Ratios for COVID-19 Infection				
	n (%)	p-value*	+LR (95% CI)	-LR (95% CI)
WBC $\leq 7.0 \times 10^9/L$	276 (58%)	<0.001	2.70 (2.10 to 3.52)	0.54 (0.43 to 0.59)
PLT $\leq 200 \times 10^9/L$	278 (58.4%)	<0.001	1.82 (1.00 to 2.40)	0.92 (0.85 to 1.00)
WBC ≤ 7.0 and PLT ≤ 200	136 (28.6%)	<0.001	2.92 (2.06 to 4.23)	0.67 (0.61 to 0.76)

Positive (+LR) and negative (-LR) likelihood ratios for active COVID-19 infection given presenting WBC $\leq 7.0 \times 10^9/L$ or PLT $\leq 200 \times 10^9/L$ counts are shown, as well as the likelihood ratios for patients presenting with both WBC $\leq 7.0 \times 10^9/L$ and PLT $\leq 200 \times 10^9/L$ (*significance set at 0.017 with Bonferroni correction (0.05/3)).

to 2.40) and negative likelihood ratio of 0.92 ($p < 0.001$, 95% CI: 0.85 to 1.00). When combined, WBC $\leq 7.0 \times 10^9/L$ and platelet $\leq 200 \times 10^9/L$ gave a sensitivity of 0.437 and specificity of 0.849 with positive likelihood ratio of 2.90 ($p < 0.001$, 95% CI: 2.06 to 4.23) and negative likelihood ratio of 0.67 ($p < 0.001$, 95% CI: 0.61 to 0.76).

Discussion

We often have to make treatment and disposition decisions in real time, while waiting for a critical test. The strain of caring for critically ill patients can be augmented by limited resources as providers brace for additional surges. Any available data that could help decrease the cognitive burden of decision-making could be valuable as stress and burnout rose in response to

COVID-19.^{4,5}

Many clinicians and researchers have documented an association of leukopenia and thrombocytopenia with COVID-19 diagnosis and, often, an increased severity of illness.

Leukopenia is driven by lymphopenia, decrease of the lymphocytes. Angiotensin-converting enzyme expression in myeloid precursors causes macrophages to be more pro-inflammatory. This can then worsen immune response of target cells and cause consumption of T cells, especially CD4 and CD8 T cells.⁶ Thrombocytopenia in COVID-19 patients is thought to result from increased platelet consumption, low-grade disseminated intravascular coagulation, and in some cases a thrombotic microangiopathy. This is thought to be

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Table 4. Positive and Negative Likelihood Ratios for COVID-19 Infection with Traditional Cutoff Values				
	n (%)	p-value*	+LR (95% CI)	-LR (95% CI)
WBC $\leq 4.0 \times 10^9/L$	28 (5.9%)	0.023	2.44 (1.04 to 5.95)	0.94 (0.92 to 1.00)
PLT $\leq 150 \times 10^9/L$	80 (16.8%)	0.037	1.54 (1.00 to 2.27)	0.84 (0.84 to 1.00)
WBC ≤ 4.0 and PLT ≤ 150	18 (3.8%)	0.670	1.22 (0.45 to 3.34)	0.99 (0.96 to 1.03)

Positive (+LR) and negative (-LR) likelihood ratios for active COVID-19 infection using traditional cutoff values for leukopenia and thrombocytopenia of WBC $\leq 4.0 \times 10^9/L$ and PLT $\leq 150 \times 10^9/L$, respectively, are shown, as well as the likelihood ratios for patients presenting with both WBC $\leq 4.0 \times 10^9/L$ and PLT $\leq 150 \times 10^9/L$ (*significance set at 0.017 with Bonferroni correction (0.05/3)).

from endothelial damage releasing vWF multimers, activating platelets and increasing consumption.⁷ Others suggest the additional possibility of direct platelet stimulation by the SARS-CoV-2 spike protein.⁸

Our observation of significantly lower WBC and PLT counts in active COVID-19 infection is in agreement with previous studies.⁹⁻¹⁴ However, very few studies have shown the detailed association or, more important, the clinical implications. Our study suggests that the simple and rapidly available CBC, along with memorable cutoff points for presenting WBC and PLT counts, may provide the clinician with a useful tool for guiding clinical decision-making when tests are not easily available.

Limitations

There are several limitations to our study. The data reflect the conditions at the time of the study in three EDs in a single urban community and we cannot assert that our results would apply to a wider population.

In addition, we only examined patients who were symptomatic enough to be admitted, so it is unclear whether or not discharged patients with COVID-19 or those who did not require admission would have the same characteristics. The PCR test used to detect SARS-CoV-2 RNA (Abbott Molecular, Des Plaines, IL, USA) received Emergency Use Authorization (EUA) for a PCR test to detect SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swabs from patients with suspected COVID-19. Due to the EUA, manufacturer sensitivity and specificity are not provided. However, independent testing showed sensitivity at 93% and specificity at 100%.¹⁵

Finally, the traditional laboratory cutoff values that define leukopenia and thrombocytopenia are WBC $\leq 4.0 \times 10^9/L$ and PLT $\leq 150 \times 10^9/L$, respectively. Using those cutoff values gave likelihood ratios that trended in the same direction as our main results (Table 4). However, the sample sizes with traditional values were much smaller and resulted in less robust data, so we presented results primarily with cutoff values that were nontraditional but simple to remember, with stronger evidence.

Our study supports association between active COVID-

19 infection and presenting WBC and PLT counts that trend closer to the lower end of normal rather than actual leukopenia and thrombocytopenia as defined by traditional cutoffs. It is also important to note that the likelihood ratio should be used in the context of the pretest probability specific to the patient, which will vary widely.

Conclusions

In this multicenter community study of ED patients admitted over 1 month with suspected COVID-19, both the initial WBC and PLT counts were significantly lower in patients with active COVID-19 infection. Our study shows that a symptomatic patient with presenting WBC and PLT counts ≤ 7.0 and 200, respectively, is almost three times more likely to be positive for active COVID-19 infection. ■

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