Eosinopenia and COVID-19
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Context: Early diagnosis of coronavirus disease 2019 (COVID-19) and patient isolation are important for both individual patient care and disease containment. The diagnosis is confirmed by testing for the presence of nasopharyngeal viral RNA with a polymerase chain reaction assay, which has limited availability, variable turnaround time, and a high false-negative rate. The authors report that a rapid laboratory test, the eosinophil count, readily obtained from a routine complete blood cell count (CBC), may provide actionable clinical information to aid in the early recognition of COVID-19 in patients, as well as provide prognostic information.

Objective: To investigate the diagnostic and prognostic value of eosinopenia in COVID-19–positive patients.

Methods: The eosinophil results of routine CBC from the first 50 admitted COVID-19–positive patients were compared with the eosinophil results of 50 patients with confirmed influenza infection at the time of presentation to the emergency department at Coney Island Hospital in Brooklyn, New York. The number of patients with 0 eosinophils on the day of presentation was also compared between the 2 groups. Furthermore, the eosinophil counts in the 50 COVID-19 patients were reviewed for the first 5 days of their hospital stay and before discharge, along with the outcome (deceased vs discharged), and trends in eosinophil data were compared based on the outcome.

Results: On the day of presentation, 30 patients in the COVID-19 group (60%) and 8 patients in the influenza group (16%) had an eosinophil count of 0. An additional 14 patients in the COVID-19 group had 0 eosinophils during the following 2 days; the total number of patients in the COVID-19 group who had 0 eosinophils on admission or during the ensuing 2 days was 44 (88%). In addition, 18 of 21 deceased patients in the COVID-19 group (86%) who initially presented with eosinopenia remained eosinopenic compared with 13 of 26 survivors (50%).

Conclusion: The absence of an eosinophil count in a CBC can aid in early diagnosis of COVID-19. It may be a useful tool in deciding whether to promptly isolate a patient and initiate specific therapies while waiting for confirmatory test results. Persistent eosinopenia after admission correlated with high disease severity and low rates of recovery.

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Coney Island Hospital, part of the New York City Health and Hospitals system, serves a diverse population in Brooklyn, New York. Brooklyn and the broader New York City metropolitan area experienced a sharp incline in COVID-19 cases during March and April 2020.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), was first noted as a cluster of cases of pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.1 The emergence of SARS-CoV-2, following SARS-CoV outbreak in 2002-2003 and Middle East respiratory syndrome (MERS-CoV) in 2012, marked the third introduction of a highly pathogenic and large-scale epidemic coronavirus into the human population in the 21st century. Since then, COVID-19 has spread globally and was declared a pandemic by the World Health Organization on March 11, 2020.2 Community transmission was first detected in the United States in February 2020, with all 50 states reporting cases of COVID-19 by mid-March 2020.2 New York City experienced a particularly sharp increase in COVID-19 cases and deaths during March and April 2020.

COVID-19 primarily spreads through respiratory droplets. Common clinical presentations of COVID-19 include fever, cough, dyspnea, myalgia, rhinorrhea, chest pain, and diarrhea.3 However, in severe cases, the disease can progress to multiorgan dysfunction syndrome, including acute respiratory distress syndrome, acute renal failure, septic shock, coagulopathy, and death.3,4 The clinical diagnosis of COVID-19 is confirmed by laboratory testing with a reverse-transcription polymerase chain reaction (RT-PCR) assay, which remains a challenge due to limited test availability, variable turnaround time, and the unreliable availability of rapid RT-PCR kits. In many hospitals, test results may take days to return. A recent article in *Annals of Internal Medicine* based on literature review and pooled analysis of 7 previously published studies (n=1330) found that PCR performance varied by time since symptom onset or SARS-CoV-2 exposure using samples from the upper respiratory tract.5 On the day of symptom onset, typically day 5 after exposure, the median false-negative rate was 38%; this decreased to 20% on day 8 (3 days after symptom onset) and then began to increase again, from 21% on day 9 to 66% on day 21.5

Laboratory parameters, such as lymphopenia and elevated concentrations of liver enzymes, C-reactive protein, lactate dehydrogenase, ferritin, and D-dimer, have been associated with COVID-19 and some, such as elevated levels of C-reactive protein and D-dimer, have been linked to the severity of the disease.3,6,7 One report observed a progressive decline in the lymphocyte count in nonsurvivors compared with more stable levels in survivors.8

In our early care of patients with COVID-19, we observed that many manifested low or absent eosinophil counts at the time of admission. We embarked on a study to corroborate this impression, assess its prevalence, and compare it with a viral infection (influenza) that may have a similar presentation to help us determine whether this observation has relevance in classifying patients at the time of presentation with disease that requires hospitalization.

**Methods**

This study was reviewed and approved by the institutional review board of the Biomedical Research Alliance of New York.

**Study Design and Participants**

We performed a retrospective medical record review of the first 50 confirmed COVID-19 cases (COVID-19 group) admitted to the hospital, as well as 50 randomly selected patients with confirmed influenza (influenza group [control]). The COVID-19 group consisted of patients who presented to the emergency department with clinical or laboratory abnormalities raising the concern for COVID-19 and who were sufficiently ill to merit hospitalization. All of these patients had a positive PCR test for COVID-19. Patients in the control group tested positive for influenza on PCR testing for
the presence of nasopharyngeal viral RNA during the influenza season (January-March 2020).

**Data Collection**

We collected the following patient data: age, sex, and eosinophils on the complete blood cell count (CBC) performed at presentation, during the subsequent 5 days, and on the last day of the hospital stay (for patients who required longer hospitalizations). Patients with baseline eosinophilia were excluded from the study. Eosinophils were determined by the Coulter counter. Its lower limit of detection of eosinophils is 0. The accuracy and reproducibility are close to 100% (laser-based SYSMEX machine). In the hospital’s laboratory, the normal absolute eosinophil count range is 100 to 400/µL.

For the purpose of this study, we looked at the absolute eosinophil count from the initial CBC count at the time of presentation to the emergency department in the COVID-19 group and the influenza control group to address our primary question, which was whether the absence of eosinophils was predictive of COVID-19 and prognosis. A set of medical records for both groups was generated electronically based on either positive PCR result for COVID-19 or positive rapid influenza swab tests. The CBC results were not part of the selection process in either group.

**Statistical Analysis**

Categorical variables between groups were compared using the Pearson $\chi^2$ test.

**Results**

There were 29 men (58%) and 21 women (42%) in the COVID-19 group and 21 men (42%) and 29 women (58%) in the influenza group. The mean ages of patients in the 2 groups were similar (59 and 59.5 years, respectively).

The first CBC obtained on the day of presentation revealed that 30 patients in the COVID-19 group (60%) had absent eosinophils, compared with 8 patients in the influenza group (16%) ($P<.001$; Table).

In addition to the 30 patients who had 0 eosinophils on the day of presentation, of the remaining 20 patients in the COVID-19 group, 17 demonstrated a low absolute eosinophil count (mean, 23/µL; range, 10-60/µL) on the initial CBC. Two patients (4%) presented with a normal absolute eosinophil count, and 1 patient (2%) presented with an elevated eosinophil count.

Of the 20 patients in the COVID-19 group who had measurable eosinophils on presentation, 14 had 0 eosinophils on a subsequent CBC within the next 48 hours. For these patients, the mean time to an eosinophil count of 0 from presentation to 48 hours was 22.6 hours (range, 11.17-36.73 hours).

In the COVID-19 group, 23 patients (46%) died during hospitalization. The average age of those who died was 68.7 years compared with 56.7 years for those who survived. Of the 30 patients in the COVID-19 group who had a 0 absolute eosinophil count at presentation, 17 (56.7%) died. Of the 17 patients in the COVID-19 group who had a low but detectable eosinophil count at the time of presentation, 4 (23.5%) died.

**Table.**

Demographic and Initial Eosinophil Data of Patients in the COVID-19 Group and Influenza Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>COVID-19 Group (n=50)</th>
<th>Influenza Group (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>59.0</td>
<td>59.5</td>
</tr>
<tr>
<td>Median age, y</td>
<td>64</td>
<td>72</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>29:21</td>
<td>21:29</td>
</tr>
<tr>
<td>Mean eosinophil count on presentation, /µL</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>No. (%) of patients with eosinophil count of 0 at presentation</td>
<td>30 (60.0)</td>
<td>8 (16.0)</td>
</tr>
</tbody>
</table>

Next, we evaluated a trend in eosinophil counts in relation to the outcomes. In the COVID-19 group, 21 of 23 deceased patients (91%) and 26 of 27 survivors (96%) had eosinopenia (absolute eosinophil count <100/μL) on presentation. In the deceased group, 18 of 21 (86%) remained eosinopenic before death. In the survivor group, eosinophil counts remained low in 13 of 26 patients (50%) (Figure).

Discussion
When we first began caring for patients with COVID-19, the turnaround time for PCR testing was 5 or more days. We noted the presence of an unusual number of patients with absent eosinophils among those who were confirmed to have COVID-19. In the current study, we confirmed our observation, which suggests that while waiting for a PCR report in suspected cases, an absent eosinophil count could identify likely COVID-19–positive cases and, in particular, cases in which there may be a higher risk of mortality.

The pathophysiology for eosinopenia in COVID-19 remains unclear, but it may be multifactorial. Mechanisms may include inhibition of eosinophil egress from the bone marrow, blockade of eosinophilo-poesis, reduced expression of chemokine receptors/adhesion factors, and/or direct eosinophil apoptosis induced by type 1 interferons released during the acute infection.

Whether the acquired eosinopenia associated with COVID-19 directly contributes to the disease course or is a marker of severe disease has not yet been determined, but it is notable that pulmonary eosinophilia is not part of the pathologic findings in the lung so far attributed to SARS-CoV-2.

We found that an absence of eosinophils at the time of presentation was present in 60% of the COVID-19 group and in 16% of the influenza group. In the first 50 admitted COVID-19 patients, 94% displayed eosinopenia on their first CBC. Our findings are consistent with a recent report from China that noted that the rate of eosinopenia in COVID-19–positive patients was 79% compared with 36% in COVID-19–negative patients. Using the results from a routine CBC to help identify COVID-19 hours or days before a confirmatory PCR test is available could be sufficiently reliable to direct early institution of therapy. This could include therapies that prove to be effective in specifically treating patients with this virus, guiding the intensity of isolation strategies, or instituting therapies directed at preventing severe complications, such as anticoagulation therapy.

Eosinopenia is not unique to COVID-19, but we demonstrated that it is more prevalent in COVID-19.
than it is in influenza infection. Furthermore, we found an absence of eosinophils in 60% of our COVID-19 patients at presentation. An additional 28% of the COVID-19 group had absent eosinophils on CBC within 48 hours of their presentation. In COVID-19, a disease that has substantial symptom overlap with influenza, eosinopenia could help to distinguish which patients likely have COVID-19 with actionable reliability.

Our data show that persistent eosinopenia correlates with the severity of COVID-19. In our observation, the trend of the eosinophil count may help predict disease severity and the likelihood of recovery. Our data also show that improvement in and recovery of eosinophil counts corresponds to a better prognosis.

Our study is limited by its relatively small sample size and relies on early observational data from a single center. In addition, the majority of patients with influenza did not merit hospital admission, so they reflect a population of lower medical acuity than the study group. Because many patients were not admitted, repeated eosinophil data were limited and, therefore, the ability to compare eosinophil count trends in those patients was limited. This is the second study that we are aware of that calls attention to the presence of low or absent eosinophils in patients presenting with COVID-19 symptoms.10 Examining other populations of patients with COVID-19 will help validate or refute this observation. Future studies could determine whether strategies to rapidly identify patients with COVID-19 with the goal of early institution of treatments results in improvements in prognosis.

Conclusion
The existing COVID-19 PCR diagnostic test has limitations, limited availability, variable turnaround time, and a high false-negative rate. An eosinophil count of 0 in patients requiring hospitalization can assist in the early recognition of COVID-19 and be used to direct therapeutic decisions while confirmatory PCR tests are still in process. These findings may be especially helpful during seasons when influenza infection is prevalent and symptom-based patient classification may lack specificity in diagnosing COVID-19. Poor improvement of eosinophil counts after admission was also correlated with high disease severity and with low rates of recovery.

References

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