



ROLE OF EOSINOPHIL COUNT, CRP AND SERUM FERRITIN LEVELS AS MARKERS OF SEVERITY IN COVID-19 ILLNESS.

Pathology

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ABSTRACT

INTRODUCTION: Coronavirus disease-2019 (COVID-19) is a systemic infection which has a significant impact on the hematopoietic system and hemostasis. Definitive diagnosis requires a laboratory confirmation test with presence of specific clinical characteristics. Patients critically ill with COVID-19 presents with hyper inflammation, and the associated biomarkers may be beneficial for risk stratification. During the disease course, Eosinophil count and CRP may help to effectively differentiate the suspected COVID-19 patients from others attending the fever clinic with flu like symptoms. Ferritin is a key mediator of immune dysregulation and act as a crucial factor influencing the severity of COVID-19.

RESULT: 19 patients in the COVID-19 group (73%) and 4 patients in the COVID-19 negative group (16.6%) had eosinopenia. Eosinopenia and elevated C-reactive protein present with a positive predictive value at 70.7%. 14 patients with severe COVID-19 revealed elevated levels of ferritin as compared with patients having non-severe disease

CONCLUSION: The combination of eosinopenia and elevated CRP can effectively distinguish suspected COVID-19 patients from other patients attending the flu clinic with COVID-19 like initial symptoms. An elevated serum CRP and ferritin were associated with poor outcome and critical phase of disease. Our study is helpful in classifying patients at the time of presentation with disease that requires hospitalization and initial therapy. The utmost importance of our study reflects about early isolation of cases.

AIM and Objective:

- To study the role of Eosinophil count in risk stratification of patients presenting in flu clinic.
- To correlate the severity of disease with levels of eosinopenia, elevated CRP and Serum Ferritin.

KEYWORDS

COVID-19, CRP, Eosinopenia, Serum Ferritin

INTRODUCTION:

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] COVID-19 has spread globally and was declared a pandemic by the World Health Organization on March 11, 2020.^[2] COVID-19 may present with varying degrees of disease severity, from asymptomatic or mild upper respiratory illness to multiple organ failure with fatal outcome. SARS-CoV-2 is more contagious than SARS-CoV or the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Eventually, isolation of suspected cases is of highest importance to stop the epidemic spreading.^[3] Fever occurs in the majority (83% to 98%) of diagnosed COVID-19 patients.^[4]

Accurate diagnosis of COVID-19 requires a high degree of clinical understandings with laboratory confirmation test of SARS-CoV-2 infection testing with a reverse-transcription polymerase chain reaction (RT-PCR) assay and typical pulmonary computed tomography abnormality. It remains a challenge due to limited test availability, variable turnaround time, and the unreliable availability of rapid RT-PCR kits. In Most of the hospitals, it may take days. 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]

The initial screening for COVID-19 mostly starts from fever clinics. Therefore, it is essential for the fever clinic to triage suspected COVID-19 patients from other patients properly with similar symptoms. Laboratory findings, 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^[6, 7, 8] Progressive decline in the lymphocyte count in non survivors has been reported as compared with more stable levels in survivors.^[9]

In our early care of COVID-19 patients, we observed that many manifested low or absent eosinophil counts at the time of admission so studied the pattern along with hs-CRP levels and Serum ferritin levels as a triage for screening suspected patients, proved to be helpful in classifying patients at the time of presentation with disease that requires hospitalization and initial therapy. The utmost importance of our study reflects about early isolation of cases.

MATERIAL AND METHODS:

A prospective study was done for two months in June and July 2020 in our tertiary health care center. 50 patients who visited the Flu Clinic were taken under study, their clinical and laboratory data was analyzed. Eosinophil count was studied from the complete blood count. According to data received eosinophil levels distinguished into two groups depending upon levels less than and more than $0.02 \times 10^9/L$. Based on RT-PCR testing for SARS-CoV-2 infection, SARS-CoV-2 positive patients considered as cases and SARS-CoV-2-negative patients as controls. CRP and Ferritin levels of two groups were also compared and analyzed over time. Sensitivity, specificity, positive predictive value and negative predictive value calculated based on data received for eosinopenia and for combined effects of CRP and Serum ferritin.

STATISTICAL ANALYSIS:

Sensitivity, specificity and positive and negative predictive values were evaluated using standard statistical methods. $P < 0.05$ was considered as significant statistical difference. Comparison was made using Chi square. The statistical analyses were performed using SPSS version 22 for windows.

RESULTS AND OBSERVATIONS:

50 adult patients who visited the Flu Clinic were studied into the study. Based on RT-PCR testing for COVID-19 infection, two groups were formed COVID-19 positive patients as cases (26) and COVID-19 negative patients as controls (24).

The eosinophil count was analyzed in both the groups. All patients

were divided into two major group according to the eosinophil count less than $0.02 \times 10^9/L$ and more than $0.02 \times 10^9/L$. According to the data received for sensitivity, specificity, positive predictive value and negative predictive value for eosinopenia was 73.07%, 83.33%, 82.6% and 74.07% respectively. (Table 1)

Table 1: Diagnostic performance of eosinophil count on two study groups:

	CASES (26)	CONTROL (24)
Eosinophil count ($<0.02 \times 10^9/L$)	19	04
Eosinophil count $>0.02 \times 10^9/L$	07	20

CRP and Serum ferritin levels of COVID-19 group were compared and analyzed over time during hospital stay. Diagnostic performance of Serum Ferritin levels and CRP levels on patients with COVID-19 (n = 26). Raised ferritin levels more than 400 $\mu g/L$ were found in 14 patients while 12 were showing normal levels. While out of 26 cases 16 patients presented with raised CRP levels ($\geq 4mg/L$). The combined diagnostic performance of Serum Ferritin levels and CRP levels on patients with COVID-19 (n = 26).

Out of total 19 cases of low eosinophils levels 12 also show high CRP levels. (Table 2).

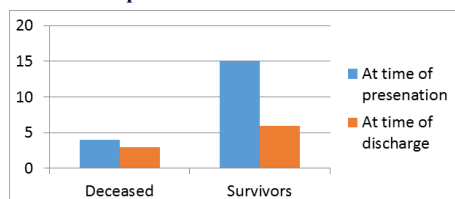
Table 2: Combined diagnostic performance of Serum Ferritin levels and CRP levels on patients with COVID-19 (n = 26)

	Eosinophil levels ($<0.02 \times 10^9/L$)	Eosinophil levels ($>0.02 \times 10^9/L$)	Total
CRP elevated	12	04	16
CRP normal	07	03	10
Total	19	07	26

From the combined data of serum ferritin and CRP levels sensitivity, specificity, positive predictive value and negative predictive value for eosinopenia was 63.16%, 42.85%, 75.0% and 30.0% respectively.

We evaluated a trend in eosinophil counts in relation to the outcomes Eosinopenia trend presentation to final disposition in deceased vs survivor patients with COVID-19 shows the prognosis of cases, Survivors had an effect over the eosinophil levels at the time of discharge while the deceased were having still low eosinophil levels.

Figure 1: Eosinopenia trend presentation to final disposition in deceased vs survivor patients with COVID-19.



DISCUSSION:

In our study, we confirmed our observation, which suggests that in suspected cases instead of waiting for a RT-PCR report, an absent eosinophil count could identify likely COVID-19-positive cases and specifically higher risk of mortality cases. The pathophysiology for eosinopenia in COVID-19 remains unclear, but it may be multifactorial. Mechanisms may include inhibition of eosinophil regress from the bone marrow, blockade of eosinophilopoiesis, reduced expression of chemokine receptors/ adhesion factors, and/or direct eosinophil apoptosis induced by type I interferons released during the acute infection.^[10] 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 73.07% of the suspected patients. Our findings are consistent with a 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.^[11]

Eosinopenia has been shown to be a useful maker of sepsis at the admission to intensive care units, which is highly sensitive in distinguishing between non infection and infection, and be more specific than C-reactive protein.^[12] At the time of the pandemic

eosinopenia alone may serve as an early diagnostic marker of COVID-19. Hs-CRP was usually tested along with eosinophil test, as it enhances the specificity.^[13] A few studies that tested eosinophil showed that eosinopenia occurred in 52% to 53% of confirmed COVID-19 patients. This relatively stable range of the presentation of eosinopenia (52%-53%) in confirmed COVID-19 cases may serve to further justify its usefulness in predicting COVID-19, especially when used with other parameters like hs-CRP or the optimal eosinophil cutoff value be established.

Results from a routine CBC can help screen COVID-19 cases before a confirmatory PCR test report, which is helpful in early institution of therapy. This could include therapies that prove to be effective in specifically treating patients, guiding the intensity of isolation strategies, or therapies in prevention of severe complications, such as anticoagulation therapy.

CONCLUSION:

Low eosinophil count can effectively distinguish suspected COVID-19 patients from other patients attending the flu clinic with COVID-19 like initial symptoms, which were later confirmed by RT-PCR. Persistent eosinopenia after admission with an elevated serum CRP and ferritin were correlated with poor outcome and critical phase of the disease.

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