LETTER TO THE EDITOR

Eosinopenia is associated with greater severity in patients with coronavirus disease 2019

To the Editor,

The novel coronavirus (SARS-CoV-2)-infected pneumonia, now known as coronavirus disease 2019 (COVID-19), which began in Wuhan, China, since late December 2019, has now become a public health emergency of international concern. Previous studies indicated that the clinical condition of patients worsened in a short period of time, while a national survey of 1099 cases with COVID-19 suggested that 5% required intensive care and 1.36% succumbed to severe infection. Despite that the available articles have described the clinical features of COVID-19 patients, it is important to emphasize that partial critically ill patients showed poor therapeutic efficiency and worse prognosis and thus clinical diagnosis research is still warrant.

Based on accumulating data, patients with severe COVID-19 show a trend toward eosinopenia, which raises the concern whether eosinopenia is associated with the disease severity. Eosinophil, initially identified as a key effector cell of allergy, has now been demonstrated to possess antiviral capacities and serve to amply immune response and thus dampen inflammation. It is currently not known whether COVID-19 patients with eosinopenia are also more likely to develop into critically illness. This updated analysis aimed to investigate the association between eosinopenia and COVID-19 severity.

This single-center, retrospective study reports 51 laboratory-confirmed COVID-19 patients admitted to Wuhan Tongji Hospital between February 9, 2020, and February 16, 2020, and electronic medical records including demographics, clinical symptoms and signs, underlying comorbidities, laboratory features on admission were reviewed and analyzed. Severity of COVID-19 was defined based on the guideline issued by Chinese National Health Committee, and eosinopenia is defined as eosinophil absolute number <0.02 × 10⁹. This study was approved by the local ethics review board, and informed consents from patients with COVID-19 were waived for use of the de-identified data.

Demographics and partial clinical characteristics of COVID-19 patients stratified by eosinophil status are shown in Table 1. Of 51 patients, 18 (35.3%) patients showed a decrease in eosinophil absolute number. Compared with normal eosinophil group, eosinopenia patients presented serious vital signs on admission, with faster heart rate (101 vs 87 beats/min, \( P = .001 \)) and relatively higher temperature (36.4 vs 36°C, \( P = .012 \)), and a greater proportion of eosinopenia patients were categorized into a severe condition (66.7% vs 27.3%, \( P = .006 \)).

Of 51 patients, the majority experienced lymphopenia and abnormality of neutrophil in the blood routine test (Table S1). Compared with patients with normal eosinophil range, eosinopenia patients tended to presented a lower trend in lymphocyte count (0.86 vs 1.22 × 10⁹/L, \( P = .005 \)), monocyte absolute number (0.29 vs 0.56 × 10⁹/L, \( P = .003 \)) and proportion (8.1% vs 9.7%, \( P = .01 \)) but a higher neutrophil proportion (75% vs 66.5%, \( P = .043 \)). Furthermore, absolute number of eosinophils were positively correlated with lymphocyte count (Figure 1A), similar to reports by Zhang et al and Qian et al, where the correlation was also statistically significant on 3 or more days afterward in Zhang’s study (\( r = 0.479, P < .001 \)).

Following the inflammatory markers, eosinopenia patients have higher high sensitive C-reactive protein (50.5 vs 24.6 mg/L, \( P = .022 \)) and procalcitonin (0.085 vs 0.05 ng/dL, \( P = .048 \)) concentrations. Particularly, high sensitive C-reactive protein levels inversely correlated with absolute number of eosinophils

FIGURE 1 Correlation between eosinophil and lymphocyte counts (×10⁹/L) (A) and correlation between eosinophil counts (×10⁹/L) and high sensitive C-reactive protein levels (mg/L) (B) in blood from COVID-19 patients. Spearman's test was used to evaluate the correlation. hsCRP, high sensitive C-reactive protein
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(Figure 1B). Also, in eosinopenia group, elevated aspartate aminotransferase (39 vs 22 U/L, \( P = .004 \)), blood glucose (6.83 vs 5.68 mmol/L, \( P = .01 \)), creatine kinase (135 vs 60 U/L, \( P = .041 \)), and lactate dehydrogenase (35.6 vs 221 U/L, \( P = .01 \)) were found, whereas lower levels of total cholesterol (3.05 vs 3.83 mmol/L, \( P = .001 \)) and triglycerides (0.77 vs 1.38 mmol/L, \( P = .056 \)) were more common in these cases.

To identify the effect of eosinophil on COVID-19 severity, we obtained the odds ratio (OR) after conducting the logistic regression analysis (Table S2). Given blood test was influenced by age, gender, and other traditional risk factors, we constructed adjusted models and obtained the adjusted OR. Notably, after controlling confounding factors, the association between eosinopenia and COVID-19 severity remained significant (adjusted OR 10.260, 95%CI: 1.953, 56.5).

### TABLE 1 Demographic and partial characteristics of patients with laboratory-confirmed COVID-19

| Overall \((n = 51)\) | Without eosinopenia \((n = 33)\) | With eosinopenia \((n = 18)\) | \(P\) value |
|----------------------|----------------------------------|-------------------------------|------------|
| **Demographics**     |                                  |                               |            |
| Age (years)          | 63 (51, 68)                      | 63 (54, 68)                   | .844       |
| Gender/Female        | 21 (41)                          | 14 (42.4)                     | .806       |
| Systolic blood pressure (mm Hg) | 134 (118, 149)               | 134 (117, 149)                | .730       |
| Diastolic blood pressure (mm Hg) | 82 (75, 93)                | 79 (71, 92)                   | .108       |
| Respiratory rate     | 20 (20, 21)                      | 20 (18, 21)                   | .097       |
| Heart rate (beats per minute) | 92 (83, 102)                    | 87 (78, 99)                   | .001       |
| Temperature on admission (°C) | 36 (35.8, 36.5)             | 36 (35.8, 36.3)               | .012       |
| **Severity\(^a\)-No.** | 21 (42.3)                       | 9 (27.3)                      | .006       |
| Smoking history      | 19 (37)                          | 13 (39.4)                     | .669       |
| **Onset symptoms**   |                                  |                               |            |
| Fever                | 40 (78)                          | 26 (78.8)                     | .933       |
| Fatigue              | 37 (72.5)                        | 26 (78.8)                     | .176       |
| Dry cough            | 30 (58.8)                        | 21 (63.6)                     | .344       |
| Nasal congestion     | 7 (13.7)                         | 5 (15.2)                      | .689       |
| Shortness of breath  | 23 (45.1)                        | 15 (45.5)                     | .945       |
| Rhinorrhea           | 3 (5.9)                          | 1 (3.0)                       | .241       |
| Muscle ache          | 12 (23.5)                        | 7 (21.2)                      | .597       |
| Diarrhea             | 15 (29.4)                        | 12 (36.4)                     | .140       |
| More than one sign or symptom | 40 (78.4)                     | 27 (81.8)                     | .426       |
| **Comorbidities**    |                                  |                               |            |
| Any                  | 35 (68.6)                        | 24 (72.7)                     | .393       |
| Hypertension         | 21 (41.2)                        | 15 (45.5)                     | .401       |
| Diabetes             | 9 (17.6)                         | 8 (24.2)                      | .094       |
| Cerebrovascular disease | 4 (7.8)                          | 1 (3.0)                       | .083       |
| Coronary artery disease | 5 (9.8)                         | 5 (15.2)                      | .082       |
| Respiratory diseases | 8 (15.7)                         | 5 (15.2)                      | .887       |
| Cancer               | 7 (13.7)                         | 4 (12.1)                      | .652       |
| Chronic kidney disease | 1 (2.0)                         | 1 (3.0)                       | .456       |
| Chronic liver disease | 8 (15.7)                         | 6 (18.2)                      | .507       |
| **Clinical outcomes**|                                  |                               |            |
| Discharge            | 45 (88.2)                        | 31 (93.9)                     | .168       |
| Death                | 6 (11.8)                         | 2 (6.1)                       | .222       |

Note: Results were presented as median (IQR) for continuous variables and number (%) for categorical variables. Parameters between with and without eosinopenia groups were tested by the Mann-Whitney \( U \) test (continuous variables) or chi-square test (categorical variables). A two-sided \( \alpha \) of <0.05 was considered statistically significant.

\(^a\)Severe cases at admission met at least one of the following items: (a): breathing rate ≥30/min; (b) oxygen saturation at rest state ≤93%; and (c) partial pressure of arterial oxygen (PaO\(_2\))/fraction of inspired oxygen (FiO\(_2\)) ≤300 mm Hg (1 mm Hg = 0.133 kPa).
53.899, \( P = .006 \). (We found an error when analyzing our data again, and we revised the supplementary Table S2. Please see the attachment. Although we revised this table, we did not change the direction of our research and the effect of eosinophil became even more powerful in the revised models.)

Formerly, eosinophils were regarded as an intermediary factor in the propagation and potentiation of allergic-type process within the host.\(^6\) With the concept emerging, that eosinophils are participating in maintaining immune regulatory systems, eosinophils were increasingly believed to be positioned centrally within inflammatory networks by producing inflammatory and homeostatic mediators. As comprehensively illustrated in “LIAR hypothesis,”\(^8\) eosinophils were responsible for local immunity and tissue repair. In animal models, eosinophils were even reported to possess antiviral activity,\(^9\) but it has not been clinically confirmed in humans. In the present study, the findings suggest that eosinopenia was inversely related to inflammatory markers and could be associated with the severity of COVID-19. As shown by recent evidence, eosinopenia was very frequent in COVID-19\(^6,10,11\) and could be applied in the early prediction of severity before clinical symptoms have significantly deteriorated, which may help clinicians in identifying potentially severe cases and greatly improve the prognosis of patients with COVID-19. As suggested, eosinopenia may have an important prognostic value in COVID-19 patients, especially in patients with typical radiological images and clinical manifestation.\(^5,12-14\)

The pathophysiology for eosinopenia in COVID-19 could be multifactorial, involving the suppressed eosinophil egress from the bone marrow, inhibition of eosinophilopoiesis, reduced eosinophil-driving cytokines or direct interferon-induced apoptosis.\(^15,16\) It has been speculated that eosinophil exhaustion was associated with neutralization of virus with eosinophil-derived enzymes, but from another perspective, eosinophil may be just a coincidence when neutralizing virus with eosinophil-derived enzymes, but from another perspective, eosinophil might be important for antiviral activity or there is an IL-33 pathway that gets activated and eosinopenia is just coincidence, needs further investigation. Patients included in our study were not accompanied with allergic diseases (eg, asthma). One possible reason may be our small sample size, but future larger sample research is needed to identify the effect of SARS-CoV-2 on allergic disorders.

**KEYWORDS**
COVID-19, eosinophils, infections, inflammation, virus

**CONFLICTS OF INTEREST**
None reported.

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