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SHORT REPORT

INFECTIOUS DISEASES

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Eosinopenia is a reliable marker of severe disease and unfavourable outcome in patients with COVID-19 pneumonia

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Abstract

Background and Aim: Viral pneumonia is the most relevant clinical presentation of COVID-19 which may lead to severe acute respiratory syndrome and even death. Eosinopenia was often noticed in patients with COVID-19 pneumonia, but its role is poorly investigated. The aim of the present study was to investigate the characteristics and clinical outcomes of patients with COVID-19 pneumonia and eosinopenia.

Methods: We revised the records of consecutive patients with COVID-19 pneumonia admitted to our ER-COVID-19 area in order to compare clinical characteristics and outcomes of patients with and without eosinopenia. We considered the following clinical outcomes: 4-weeks survival; need for intensive respiratory support; and hospital discharge.

Results: Out of first 107 consecutive patients with pneumonia and a positive COVID-19 nasopharyngeal swab, 75 patients showed undetectable eosinophil count (absolute eosinopenia). At 4 weeks, 38 patients (38.4%) had required intensive respiratory treatment, 25 (23.4%) deceased and 42 (39.2%) were discharged. Compared with patients without absolute eosinopenia, patients with absolute eosinopenia showed higher need of intensive respiratory treatment (49.3% vs 13.3%, $P < .001$), higher mortality (30.6% vs 6.2%, P .006) and lower rate of hospital discharge (28% vs 65.6%, $P < .001$). Binary logistic regression analyses including neutrophil, lymphocyte, eosinophil, basophil and monocyte counts showed that absolute eosinopenia was an independent factor associated with 4-weeks mortality, need for intensive respiratory support and hospital discharge.

Conclusions: Absolute eosinopenia is associated with clinical outcomes in patients with COVID-19 pneumonia and might be used as a marker to discriminate patients with unfavourable prognosis.

1 | INTRODUCTION

The clinical course of COVID-19 is variable with different and heterogeneous symptoms. Viral pneumonia is the most relevant clinical presentation of COVID-19 infection which may lead to severe acute respiratory syndrome (SARS) and even death.[1,2] COVID-19 has a significant impact on the hematopoietic system, and lymphopenia is a well-known characteristic in patients with COVID-19 infection.[1] The dysregulation of hematologic and immunologic systems seems to play a key role in the pathological process of COVID-19 infection and, finally, in evolution of disease. Some authors provided demonstration about impairment of immune response especially of T lymphocytes and the derangement of excessive inflammatory response.[3] Remarkable eosinopenia was often noticed both in patients with and without severe disease but its role is poorly investigated.[3,4]

The aim of the present study was to investigate the characteristics and clinical outcomes of patients with COVID-19 pneumonia and eosinopenia.

2 | METHODS

Since 27 February 2020 following a regional alert about outbreak in Lombardia (Italy), our hospital set up a dedicated area in our emergency department (ER-COVID-19 area), where patients underwent diagnostic procedures, appropriated treatments and, then, transferred to COVID-19-dedicated wards, Intensive Units or discharged. We revised the records of consecutive patients with COVID-19 pneumonia admitted to our ER-COVID-19 area in order to compare demographic, biochemical, radiological and clinical characteristics at hospital admission and outcomes of patients with and without eosinopenia. We excluded patients younger than 18 years old and patients transferred from other hospitals.

We considered the following clinical outcomes: 4-weeks survival; need for intensive respiratory support (high-flow nasal cannula oxygen support, non-invasive ventilation and/or mechanical ventilation); and hospital discharge. The study was performed according to the Declaration of Helsinki, and written informed consent was obtained from all the patients. All data were anonymised.

Qualitative and quantitative data are reported as frequencies and means ± standard deviation (min-max) or median and range as appropriated, respectively. Non-parametric test was used to compare independent groups. Univariate and multivariate analyses were performed by logistic regression analyses. Sensitivity, specificity, predictive values and likelihood ratios were calculated by conventional formulas in order to predict in-hospital mortality.

Two-sided statistical tests were used for all analyses; a P value of <.05 was considered significant.

Jamovi software was used for statistical analyses.

3 | RESULTS

Out of first 107 consecutive patients with pneumonia and a positive COVID-19 nasopharyngeal swab, 75 patients showed undetectable eosinophil count (absolute eosinopenia) at hospital admission, whereas 32 patients exhibited a mild reduction or normal values of eosinophil count.

Patients with absolute eosinopenia were older and had higher age-adjusted Charlson comorbidity index (an accurate score to define the weight of comorbidity) with respect to patients without absolute eosinopenia. A clinically severe disease with lower values of pulse oxymeter saturation was more frequent in patients with absolute eosinopenia who showed a significantly higher values of C-reactive protein and lower counts of lymphocytes, basophils, monocytes and platelet than patients without absolute eosinopenia (Table 1).

What's known

- COVID-19 has a significant impact on the hematopoietic system. Lymphopenia and eosinopenia are frequently observed in patients with and without severe COVID-19. However, the relationship between eosinopenia and clinical outcomes is unknown.

What's new

- The present study confirms that eosinopenia is frequent in patients with COVID-19 pneumonia.
- Absolute eosinopenia is significantly associated with unfavourable clinical outcomes, namely need of intensive respiratory treatment and mortality and its relationship is independent from other leukocytes.
- Absolute eosinopenia showed good sensitivity and negative predictive values in predicting unfavourable outcomes suggesting that it is a useful marker in patients with COVID-19 pneumonia.

At 4 weeks, 38 patients (38.4%) had required intensive respiratory treatment, 25 (23.4%) deceased and 42 (39.2%) were discharged. The need of intensive respiratory treatment and mortality were significantly worse in patients with absolute eosinopenia compared with patients without absolute eosinopenia (49.3% vs 13.3%, $P < .001$ and 30.6% vs 6.2%, P .006, respectively), whereas the rates of hospital discharges were significantly lower in patients with absolute eosinopenia with respect to those without (28% vs 65.6%, $P < .001$) (Table 1).

Binary logistic regression analysis was performed including neutrophil, lymphocyte, eosinophil, basophil and monocyte counts. All variables were dichotomised according to their median values, and the multivariate analysis showed that absolute eosinopenia was an independent factor associated with 4-weeks mortality [OR 5.65 (95% CI: 1.16-27.6); $P = .032$]; need for intensive respiratory support [OR 4.09 (95% CI: 1.16-14.3); $P = .028$]; and hospital discharge [OR 3.55 (95% CI: 1.36-9.27); $P = .01$] (Table 2).

To evaluate the prognostic performance of absolute eosinopenia in predicting all three clinical outcomes (mortality; need for intensive respiratory support; and hospital discharge), we calculated the standard indices of accuracy.

Sensitivity, specificity positive and negative predictive values, positive and negative likelihood ratios for absolute eosinopenia in predicting 4-weeks mortality were 92%, 37%, 31%, 94%, 1.5 and 0.2, respectively.

Sensitivity, specificity positive and negative predictive values, positive and negative likelihood ratios for absolute eosinopenia in predicting need for intensive respiratory support were 89%, 43%, 49%, 87%, 1.6 and 0.2, respectively.

Sensitivity, specificity positive and negative predictive values, positive and negative likelihood ratios for absolute eosinopenia in

TABLE 1 Demographic, clinical, biochemical characteristics at baseline and clinical outcomes in 107 patients with COVID-19 pneumonia stratified according to absolute eosinopenia[a]

Variables	Whole population	Patients with absolute eosinopenia	Patients without absolute eosinopenia	
Characteristics at baseline	**(n = 107)**	**(n = 75)**	**(n = 32)**	***P* value**
Age (y)	64.3 ± 15.3 (18-96)	66.3 ± 14.8 (20-96)	59.8 ± 15.7 (18-86)	.046
Sex (female)	32 (29.9%)	20 (26.6%)	12 (37.5%)	.26
High respiratory rate (>20 min)	29 (27.1%)	24 (32%)	5 (15.6%)	.09
Pulse oxymeter saturation at room air (%)	92.2 ± 6.1 (65-100)	91.6 ± 5.8 (65-98)	93.9 ± 6.8 (65-100)	.002
Fever (>37.5°C)	99 (92.5%)	70 (93.3)	29 (90.6%)	.63
Clinically severe disease at admission[c]	52 (48.6%)	43 (57.3%)	9 (29.3%)	.011
CAaCI score[b]	3.2 ± 2.4 (0-9)	3.5 ± 2.4 (0-9)	2.5 ± 2.2 (0-7)	.045
Haemoglobin (g/dL)	14.0 ± 1.8 (9.3-19)	14.2 ± 2.8 (9.3-19)	13.8 ± 1.9 (10-16.6)	.73
White blood cell count (10^9/L)	6.3 ± 3.1 (1.9-18.6)	6.2 ± 2.9 (2.9-18.6)	6.7 ± 3.5 (1.9-17.9)	.42
Neutrophil count (10^9/L)	4.7 ± 3.0 (0.9-16.5)	4.7 ± 2.7 (1.3-16.5)	4.8 ± 3.6 (0.9-15.9)	.62
Lymphocyte count (10^9/L)	1.06 ± 0.5 (0.18-3.2)	0.99 ± 0.4 (0.18-3.2)	1.24 ± 0.5 (0.25-2.1)	.005
Eosinophil count (10^9/L)	0.01 ± 0.03 (0.0-0.15)	0.0 ± 0.0 (0.0-0.0)	0.04 ± 0.04 (0.1-0.15)	<.001
Basophil count 10^9/L)	0.014 ± 0.015 (0.0-0.09)	0.011 ± 0.013 (0.0-0.09)	0.020 ± 0.016 (0.0-0.07)	<.001
Monocyte count (10^9/L)	0.51 ± 0.2 (0.11-1.31)	0.47 ± 0.27 (0.11-1.31)	0.62 ± 0.27 (0.14-1.25)	.002
Platelet count (10^6/L)	171 ± 56 (68-329)	157 ± 50 (68-314)	203 ± 60 (100-329)	<.001
C-reactive protein (mg/dL)	7.1 ± 7.09 (<0.01-37.1)	8.2 ± 7.16 (0.29-37.1)	4.6 ± 6.3 (<0.01-30.0)	<.001
Clinical outcomes				
Death	25 (23.4%)	23 (30.6%)	2 (6.2%)	.006
Need for intensive respiratory treatments [b]	38 (38.4%)	34 (49.3%)	4 (13.3%)	<.001
Hospital discharge	42 (39.2%)	21 (28%)	21 (65.6%)	<.001

[a]Data are reported as frequencies or means ± standard deviation (min-max). Non-parametric tests (Mann-Whitney, χ^2 test or Fischer's exact tests) were used to compare groups.

[b]CAaCI: age-adjusted Charlson comorbidity index.

[c]Clinically severe disease: concurrent presence of: fever >38°C; lower respiratory symptoms (cough, difficulty breathing, shortness of breath, high respiratory rate) and radiographic evidence of lung infiltrates consistent with interstitial pneumonia or Acute Respiratory Distress Syndrome.

[d]Eight agonic patients treated by palliation were excluded from this analysis.

[e]Need for intensive respiratory treatments includes: high-flow nasal cannula oxygen support, non-invasive ventilation and/or mechanical ventilation.

predicting hospital discharge were 50%, 17%, 28%, 34%, 0.6 and 3.0, respectively.

4 | DISCUSSION

Eosinopenia has been reported, as lymphopenia, in the 2003 Coronavirus outbreak[5] and is a characteristic of COVID-19 pneumonia.[6] The role of eosinopenia in COVID-19 disease remains unknown. Some authors postulated a relationship between CD8 T-cell depletion and eosinophil consumption caused by SARS-CoV-2.[7] Indeed, the low production of IL-5 by CD8+ T lymphocytes might be involved in eosinophil proliferation and activation in blood. Decrease in circulating eosinophils was observed in acute infection, and some eosinophil granule proteins (such as eosinophil-cationic-protein, eosinophil-peroxidase and eosinophil-derived neurotoxin) show antiviral activity.[8] Therefore, eosinopenia might be associated with high viral load in patients with severe disease and unfavourable prognosis.

The rate of absolute eosinopenia was 70% in our study. The prevalence of eosinopenia varies in different studies. Zhang et al[6] reported a rate of 53% in their population. Conversely, Du et al[7] noted that 81% patients had absolute eosinopenia in a series of 85 fatal patients of COVID-19. Probably, the high rate of eosinopenia reflects the characteristics of our population which included patients with a more severe disease with a diagnosis of COVID-19-related pneumonia. All together, these data suggest that absolute eosinopenia could be more frequent in patients with severe COVID-19.

Our investigation, for the first time, showed a strong relationship between absolute eosinopenia and clinical outcomes. Indeed, mortality and need of intensive respiratory treatment in patients with absolute eosinopenia were higher compared with patients without absolute eosinopenia. On the other hand, the absence of eosinopenia is associated with favourable outcome such as hospital discharge.

TABLE 2 Logistic regression analysis including neutrophil, lymphocyte, eosinophil, basophil and monocyte counts to identify leukocytes independently associated with: (A) mortality; (B) need for intensive respiratory treatment; (C) hospital discharge in patients with COVID-19 pneumonia

	A mortality			
Variables	**Cut-offs (median values)**	**Odds ratio**	**95% confidence interval**	***P* value**
Neutrophil count (10^9/L)	4.0 10^9/L	4.77	(1.56-14.5)	.006
Lymphocyte count (10^9/L)	1.0 10^9/L	2.06	(0.70-6.04)	.18
Eosinophil count (10^9/L)	0.0 10^9/L	5.65	(1.15-27.6)	.032
Basophil count 10^9/L)	0.01 10^9/L	1.25	(0.38-4.11)	.71
Monocyte count (10^9/L)	0.5 10^9/L	1.65	(0.53-5.11)	.18
	B need of intensive respiratory treatment[a]			
		Odds ratio	**95% confidence interval**	***P* value**
Neutrophil count (10^9/L)	4.0 10^9/L	2.64	(0.98-7.10)	.054
Lymphocyte count (10^9/L)	1.0 10^9/L	1.17	(0.43-3.2)	.74
Eosinophil count (10^9/L)	0.0 10^9/L	4.09	(1.16-14.3)	.028
Basophil count 10^9/L)	0.01 10^9/L	2.05	(0.63-6.67)	.23
Monocyte count (10^9/L)	0.5 10^9/L	3.86	(1.33-11.2)	.013
	C Hospital Discharge			
		Odds ratio	**95% confidence interval**	***P* value**
Neutrophil count (10^9/L)	4.0 10^9/L	0.47	(0.18-1.19)	.11
Lymphocyte count (10^9/L)	1.0 10^9/L	0.76	(0.29-1.97)	.57
Eosinophil count (10^9/L)	0.0 10^9/L	0.28	(0.11-0.73)	.010
Basophil count 10^9/L)	0.01 10^9/L	0.34	(0.08-1.44	.14
Monocyte count (10^9/L)	0.5 10^9/L	0.49	(018-1.29)	.15

[a]Eight agonic patients treated by palliation were excluded from this analysis.

Moreover, at multivariate analyses including all major cells produced by hematopoietic system, absolute eosinopenia resulted as independent factor associated with all three clinical outcomes, namely survival, severity of disease (need of respiratory support) and favourable outcome (hospital discharge). This finding support the hypothesis that eosinopenia could have an independent role in the evolution of COVID-19 infection with respect to other leukocytes. However, further studies are required to explore the certain role of eosinopenia on impairment of immune response in patients with COVID-19 pneumonia and to confirm whether eosinopenia and the changes in eosinophil count during the course of COVID-19 might represent an independent predictor of unfavourable outcome in different populations.

Standard indices of accuracy revealed that absolute eosinopenia showed good sensitivity and negative predictive values in predicting both 4-weeks mortality and the need of intensive respiratory treatment, whereas the prognostic performance of absolute eosinopenia was weak in predicting hospital discharge.

Nevertheless, our results support the clinical usefulness of absolute eosinopenia as a marker to predict patients with unfavourable outcomes in an emergency setting, although these findings should be validated in independent cohorts.

DISCLOSURE

None of Authors has anything to disclose. We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

AUTHOR CONTRIBUTIONS

M Cazzaniga and L Fumagalli conceived the study. All listed authors did participate providing for data recording, retrieval and analysis. M Cazzaniga and L Fumagalli performed statistical analyses; M Cazzaniga and L Fumagalli drafted the manuscript. M Cazzaniga and L Fumagalli takes responsibility for the paper as a whole.

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