Sultan Qaboos University Med J, May 2022, Vol. 22, Iss. 2, pp. 163–166, Epub. 26 May 22
Submitted 16 Aug 21
Revision Req. 21 Oct 21; Revision Recd. 2 Nov 21
Accepted 24 Nov 21
https://doi.org/10.18295/squmj.1.2022.001

EDITORIAL

COVID-19, Obstructive Airway Disease and Eosinophils

A complex interplay

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Eosinopenia is associated with a high risk of serious disease during infection with the severe acute respiratory syndrome coronavirus 2, the causative agent of COVID-19. Persistent eosinopenia correlates with low rates of recovery, while the resolution of eosinopenia predicts improvement.[1] Eosinophils have an important role in the pathogenesis of chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). In COPD, eosinopenia is associated with poorer patient outcomes and short-term readmission after discharge.[2] Eosinophils also play a key role in allergic diseases, including asthma. Moreover, many patients with asthma can have intentionally induced eosinopenia by biological drugs. In addition, persistent peripheral eosinopenia indicates poor survival in sepsis.[3] In this context, the role of eosinophils remains a puzzle in COVID-19, especially among those with severe disease or an associated obstructive lung disease. It is unclear if they directly play a pathobiological role in sepsis and lung injury or whether they are just sentinel cells that are harbingers of danger.

The incidence of eosinopenia in COVID-19 patients has been shown to vary from 50.8% to 94%.[3–5] A lower prevalence of 26.93% was noted in a study from Spain, possibly due to a large sample size and the study period spanning through the course of the pollen season.[6] Eosinopenia on admission is associated with a higher risk of severe disease and intensive care unit admissions. Yan *et al*. noted that eosinophil levels were significantly low in COVID-19 patients with critical disease and the eosinophil counts remained low or progressively declined in those with fatal outcomes.[7] Similarly, in another study, maximum reduction in eosinophils was observed on the fourth day from onset and these patients with low eosinophil counts were more likely to have fever, fatigue, dyspnoea and worse lesions in their computed tomography scan than those with normal counts.[8] Peripheral eosinophil counts typically return to near normal levels as patients recover from moderate-to-severe infection suggesting that normalisation of the blood eosinophil count indicates recovery.[9] On admission, a low eosinophil count was found to improve continuously, reaching significantly higher levels in survivors than among non-survivors with a greater increase indicating a better outcome.[10] Surprisingly, the prognostic utility of peripheral eosinophil counts varied with patient race and ethnicity.[11] In contrast, increased levels of eosinophils were noted among patients with severe COVID-19 in a large cohort. However, this observation cannot be generalised as a different technique was used and low density eosinophils were counted.[12] Thus, the current evidence suggests a protective role for eosinophils in mortality and length of hospital stay among patients with COVID-19.

There is mixed evidence regarding the prevalence of asthma in patients with COVID-19 or the effect of asthma and its treatment on the progression of the disease.[13] Theoretically, patients with asthma could be at a higher risk considering their increased susceptibility to common respiratory virus-associated exacerbations. The prevalence of asthma was markedly lower among those diagnosed with COVID-19 compared to the general population of Wuhan, China.[14] In a group of 140 hospitalised patients from Wuhan, no cases of asthma and allergic rhinitis were reported while the prevalence of asthma and allergic rhinitis in the province was 4.2% and 9.7%, respectively.[5] A low incidence of 2.1% was noted in severe asthma patients from Belgium and none of them experienced a severe disease course or death.[15] Similarly low incidence was reported from Italy, Russia and Australia.[16] However, contradictory data were reported from Germany and the United States, where higher asthma prevalence was noted among patients with COVID-19.[16] Though asthma was not a risk factor for poor prognosis, higher mortality was observed among those who had experienced an acute exacerbation in the previous year.[17] Since eosinopenia is a biomarker for the severity of COVID-19, the eosinophil reduction/depletion induced by anti-interleukin (IL)-5 and anti-IL-5 receptor blocking monoclonal antibodies raises a real concern. However, reports on the safety of

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patients using the monoclonal antibodies for asthma or atopic dermatitis are reassuring.[14,15,18] A study from Spain on 545 patients receiving different biologics for severe asthma found no increased risk, no greater disease severity or higher mortality.[18] A large study on asthmatics, with infection confirmed by polymerase chain reaction testing, did not find anti-IL-5 biologics to increase the risk of infection or worsen outcomes. In contrast, systemic corticosteroids were an independent risk factor for the highest COVID-19 severity and all-cause mortality.[19] Nevertheless, there is clear evidence that asthma presents a lesser risk for developing severe COVID-19 and the current medications, including inhaled corticosteroids and biologics, remain safe for use.[9,15,18]

Available data certainly suggests a higher risk for severe COVID-19 in COPD patients. An early case series on COVID-19 from China reported a higher prevalence of COPD in patients with severe presentation and worse outcomes.[20] A meta-analysis of studies in Chinese and English languages showed that the pre-existing COPD is associated with a four-fold increase in the risk of developing severe COVID-19.[21] The prevalence of COPD among hospitalised COVID-19 patients ranges from 0% to 10% in China, 2.4% to 14% in New York City and 5.6% to 9.2% in Italy.[22] In COPD, higher blood eosinophil counts predict a positive response to corticosteroids and eosinopenia is associated with worsening of symptoms and severity of exacerbations.[2]

Eosinophils remain in the blood only for about 8 to 12 hours before they migrate into tissues, where they are active for several days.[9] They have potent pro-inflammatory effects and participate in inflammation, immunoregulation and provide a defence against many diseases including viral infections.[4] Proliferation, development and activation of eosinophils are controlled by IL-5, IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF).[23] The immune mechanism of eosinopenia in COVID-19 remains unclear. It is likely to be multifactorial, involving inhibition of the main steps in the eosinophil life cycle, apoptosis induced by type 1 interferon during acute infection or association with eosinophil consumption by their antiviral actions.[1,24] It is also unclear if it is indeed eosinopenia that leads to poor outcomes or if eosinopenia is a manifestation of impaired GM-CSF signalling, IL-33 secretion or the diminished expression of its receptor, ST2, in the airway epithelium.[25] Thus, eosinopenia could either be the sign of host exhaustion trying to clear the COVID-19 virus or a primary risk factor for a severe infection.[24,26] It is not clear whether the COVID-19 virus could involve the bone marrow and cause the decrease of peripheral blood eosinophils. Nevertheless, increased production of neutrophils in bone marrow leading to a reduction in eosinophil production has also been reported.[8,27] To re-iterate, it is still not clear whether eosinopenia is the result of direct virus targeting or the result of generally impaired immunity.[14]

Considering the anti-viral effects of eosinophils, the reported eosinopenia in COVID-19 patients is of special interest.[28] Studies have indicated a potential role of eosinophils in promoting viral clearance and antiviral host defence. Respiratory virus infections are associated with asthma exacerbation in children and adults, among which rhinovirus is the most common agent.[14] Asthma was identified as the single most common comorbid condition among hospitalised individuals with influenza A virus subtype haemagglutinine-1 neuraaminidase-1 (H1N1) infection, with rates of asthma ranging from 10% to 32%.[29] Interestingly, there are no reports regarding asthma exacerbation due to COVID-19. There were only a few reports on asthma exacerbation during the severe acute respiratory syndrome and Middle East respiratory syndrome epidemics as well. Though biological agents that induce eosinopenia reduce asthma exacerbations, patients enduring these conditions have not been reported to have increased viral infections.[1] In fact, a large population-based cohort study showed that patients with nonallergic asthma had a higher risk of severe COVID-19 when compared to those with allergic asthma.[30] Eosinophils in the respiratory tract might represent a "double-edged sword"—promoting antiviral responses on the one hand and resulting in an exaggerated host response leading to tissue damage on the other.[9]

This lack of susceptibility to COVID-19 in patients with pre-existing asthma and allergic airway disease appears in contrast with the established link between these chronic respiratory conditions and susceptibility to common respiratory viruses, especially rhinoviruses.[6] However, rhinoviruses use intercellular adhesion molecule-1 as an entrance into respiratory epithelial cells which is overexpressed in allergic airways. In contrast, corona viruses use another host cell receptor, the angiotensin-converting enzyme 2 (ACE2). The expression of ACE2 on ACE inhibitors is increased in patients with COPD, diabetes mellitus and hypertension explaining their higher risk of developing COVID-19. On the other hand, lower expression of ACE has been noted in the airways of asthmatic patients which reduces the chances of a COVID-19 infection. Moreover, inhaled steroids can down regulate ACE2 receptors and suppress cytokine production and corona virus replication.[31] The use of inhaled corticosteroids was found to be associated

with a decreased level of ACE2 and transmembrane protease serine 2 gene expression from sputum in asthmatic patients.[32] An inhaled steroid, ciclesonide, reduced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ribonucleic acid replication as well as host inflammation in the lungs in *in-vitro* studies.[33]

Conclusion

Eosinopenia, that might also represent a low T2 immune status, is associated with poor outcomes in asthmatic and possibly in non-asthmatic COPD patients. However, it is unclear if the eosinophils directly contribute to the pathobiology of SARS-CoV2 lung injury or not. There is even less clarity around the role of lung eosinophils as this has not been extensively investigated. Eosinophils are unlikely to be directly involved in lung injury as the use of anti-eosinophil biologics has not been associated with poor outcomes in asthma patients with COVID-19. Eosinophil numbers in peripheral blood are likely to be just a biomarker of the biological activity of T helper 2 cytokines. There is very little information on their numbers or activity in the airways in patients with COVID-19. The general consensus is to continue to manage airway diseases, both asthma and COPD, as per current guidelines with the appropriate use of corticosteroids and bronchodilators and judicious use of biologics as indicated.

AUTHORS' CONTRIBUTIONS

BJ conceptualised and wrote out the draft of the initial manuscript. BJ and PN contributed to the literature review. PN performed a critical review and both the authors approved the final version of the manuscript.

References

1. Lindsley AW, Schwartz JT, Rothenberg ME. Eosinophil responses during COVID-19 infections and coronavirus vaccination. J Allergy Clin Immunol 2020; 146:1–7. https://doi.org/10.1016/j.jaci.2020.04.021.
2. Kerkhof M, Chaudhry I, Pavord ID, Miravitlles M, Kook Rhee C, Halpin DMG, et al. Blood eosinophil count predicts treatment failure and hospital readmission for COPD. ERJ Open Res 2020; 6:00188–2020. https://doi.org/10.1183/23120541.00188-2020.
3. Al Duhailib Z, Farooqi M, Piticaru J, Alhazzani W, Nair P. The role of eosinophils in sepsis and acute respiratory distress syndrome: a scoping review. Can J Anesth/J Can Anesth 2021; 68:715–26. https://doi.org/10.1007/s12630-021-01920-8.
4. Soni M. Evaluation of eosinopenia as a diagnostic and prognostic indicator in COVID-19 infection. Int J Lab Hematol 2021; 43:137–41. https://doi.org/10.1111/ijlh.13425.
5. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020; 75:1730–41. https://doi.org/10.1111/all.14238.
6. Valverde-Monge M, Canas JA, Barroso B, Betancor D, Ortega-Martin L, Gómez-López A, et al. Eosinophils and Chronic Respiratory Diseases in Hospitalized COVID-19 Patients. Front Immunol 2021; 12:1–10. https://doi.org/10.3389/fimmu.2021.668074.
7. Yan B, Yang J, Xie Y, Tang X. Relationship between blood eosinophil levels and COVID-19 mortality. World Allergy Organ J 2021; 14:1–12. http://doi.org/10.1016/j.waojou.2021.100521.
8. Xie G, Ding F, Han L, Yin D, Lu H, Zhang M. The role of peripheral blood eosinophil counts in COVID-19 patients. Allergy 2021; 76: 471–82. https://doi.org/10.1111/all.14465.
9. Rosenberg HF, Foster PS. Eosinophils and COVID-19: diagnosis, prognosis, and vaccination strategies. Semin Immunopathol 2021; 43: 383–92. https://doi.org/10.1007/s00281-021-00850-3.
10. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol 2020; 146: 89–100. https://doi.org/10.1016/j.jaci.2020.05.003.
11. Glickman JW, Pavel AB, Guttman-Yassky E, Miller RL. The role of circulating eosinophils on COVID-19 mortality varies by race/ethnicity. Allergy 2021; 76: 925–7. https://doi.org/10.1111/all.14708.
12. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature 2020; 584:463–9. https://doi.org/10.1038/s41586-020-2588-y.
13. Garcia-Moguel I, Diaz Campos R, Alonso Charterina S, Fernandez Rodriguez C, Fernandez Crespo J. COVID-19, severe asthma, and biologics. Ann Allergy Asthma Immunol 2020; 125:357–9.e1. https://doi.org/10.1016/j.anai.2020.06.012.
14. Liu S, Zhi Y, Ying S. COVID-19 and Asthma: Reflection During the Pandemic. Clin Rev Allergy Immunol 2020; 59:78–88. https://doi.org/10.1007/s12016-020-08797-3.
15. Hanon S, Brusselle G, Deschampheleire M, Louis R, Michils A, Peché R, et al. COVID-19 and biologics in severe asthma: data from the Belgian Severe Asthma Registry. Eur Respir J 2020. 56:1–4. https://doi.org/10.1183/13993003.02857-2020.
16. Ramakrishnan RK, Al Heialy S, Hamid Q. Implications of pre-existing asthma on COVID-19 pathogenesis. Am J Physiol Lung Cell Mol Physiol 2021; 320: L880–91. https://doi.org/10.1152/ajplung.00547.2020.
17. Lee SC, Son KJ, Han CH, Jung JY, Park SC. Impact of comorbid asthma on severity of coronavirus disease (COVID-19). Sci Rep 2020; 10:1–9. https://doi.org/10.1038/s41598-020-77791-8.
18. Rial MJ, Valverde M, Del Pozo V, González-Barcala FJ, Martínez-Rivera C, Muñoz X, et al. Clinical characteristics in 545 patients with severe asthma on biological treatment during the COVID-19 outbreak. J Allergy Clin Immunol Pract 2021; 9:487–9.e1. https://doi.org/10.1016/j.jaip.2020.09.050.
19. Adir Y, Humbert M, Saliba W. COVID-19 risk and outcomes in adult asthmatic patients treated with biologics or systemic corticosteroids: Nationwide real-world evidence. J Allergy Clin Immunol 2021; 148:361–7.e13. https://doi.org/10.1016/j.jaci.2021.06.006.
20. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382:1708–20. https://doi.org/10.1056/NEJMoa2002032.
21. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. J Med Virol 2020; 92: 1915–21. https://doi.org/10.1002/jmv.25889.
22. Leung JM, Niikura M, Yang CWT, Sin DD. COVID-19 and COPD. Eur Respir J 2020; 56:1–9. https://doi.org/10.1183/13993003.02108-2020.
23. Aoki A, Hirahara K, Kiuchi M, Nakayama T. Eosinophils: Cells known for over 140 years with broad and new functions. Allergol Int 2021; 70: 3–8. https://doi.org/10.1016/j.alit.2020.09.002.

24. Tanni F, Akker E, Zaman MM, Figueroa N, Tharian B, Hupart KH. Eosinopenia and COVID-19. J Am Osteopath Assoc 2020; 120:504–8. https://doi.org/10.7556/jaoa.2020.091.

25. Krishack PA, Hollinger MK, Kuzel TG, Decker TS, Louviere TJ, Hrusch CL, et al. IL-33-mediated Eosinophilia Protects against Acute Lung Injury. Am J Respir Cell Mol Biol 2021; 64:569–78. https://doi.org/10.1183/23120541.00188-2020.

26. Jesenak M, Banovcin P, Diamant Z. COVID-19, chronic inflammatory respiratory diseases and eosinophils-Observations from reported clinical case series. Allergy 2020; 75:1819–22. https://doi.org/10.1183/23120541.00188-2020.

27. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

28. Phipps S, Lam CE, Mahalingam S, Newhouse M, Ramirez R, Rosenberg HF, et al. Eosinophils contribute to innate antiviral immunity and promote clearance of respiratory syncytial virus. Blood 2007; 110:1578–86. https://doi.org/10.1182/blood-2007-01-071340.

29. Santillan Salas CF, Mehra S, Pardo Crespo MR, Juhn YJ. Asthma and severity of 2009 novel H1N1 influenza: A population-based case-control study. J Asthma 2013; 50:1069–76. https://doi.org/10.3109/02770903.2013.834505.

30. Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA, Jr., Liang L. Association of asthma and its genetic predisposition with the risk of severe COVID-19. J Allergy Clin Immunol 2020; 146:327–9.e4. https://doi.org/10.1016/j.jaci.2020.06.001.

31. Lovinsky-Desir S, Deshpande DR, De A, Murray L, Stingone JA, Chan A, et al. Asthma among hospitalized patients with COVID-19 and related outcomes. J Allergy Clin Immunol 2020; 146:1027–34.e4. https://doi.org/10.1016/j.jaci.2020.07.026.

32. Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, et al. COVID-19-related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids. Am J Respir Crit Care Med 2020; 202:83–90. https://doi.org/10.1164/rccm.202003-0821OC.

33. Matsuyama S, Kawase M, Nao N, Shirato K, Ujike M, Kamitani W, et al. The Inhaled Steroid Ciclesonide Blocks SARS-CoV-2 RNA Replication by Targeting the Viral Replication-Transcription Complex in Cultured Cells. J Virol 2021; 95:e01648–20. https://doi.org/10.1128/JVI.01648-20.