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## Review

## Neutrophils and COVID-19: The road so far

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## ABSTRACT

The SARS-Cov2 infection triggers a multisystem inflammatory disorder, known as COVID-19, a pandemic disease. This disease is characterized by acute respiratory distress syndrome, cytokine-driven hyperinflammation, and leukocytes count changes. The innate immune response has been linked to COVID-19 immunopathogenesis (e.g., dysfunctional IFN response and myeloid inflammation). In this regard, neutrophils have been highlighted as essential effector cells in the development of COVID-19. This review summarized the significant finds about neutrophils and its effector mechanisms (e.g., neutrophils enzymes and cytokines, neutrophil extracellular traps) in COVID-19 so far.

## 1. Introduction: COVID-19

COVID-19 (Coronavirus disease 2019) is an infectious inflammatory disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) [1], a new type of coronavirus identified in China in December 2019 after several patients were diagnosed with nonspecific pneumonia [2]. The coronavirus outbreak began in Wuhan, the capital of Hubei province, and quickly spread across continental dimensions, turning Covid-19 into a pandemic disease [3].

Coronaviruses are single-stranded RNA viruses that are characterized by having corona-like projections on their surface. There are four main proteins in the structure of these microorganisms, including the spike protein (S), which is related to the host cell mechanism of invasion [4]. The SARS-CoV-2 is the third virus of the  $\beta$  coronavirus group to demonstrate the capacity to infect humans with pandemic potential [5]. SARS-CoV and the MERS-CoV (Middle Eastern respiratory syndrome coronavirus) were responsible for previous relevant outbreaks of respiratory disease in 2003 [6,7] and 2012 [8,9], respectively.

Human-to-human transmission occurs through direct contact or respiratory droplets from infected individuals, whether symptomatic or asymptomatic [10–12]. Several reports have suggested that other forms of transmission, such as the fecal-oral route [13–16] and intrauterine vertical transmission, may also happen [17,18]. However, more studies need to be carried out to confirm this form of transmission.

The clinical features of COVID-19 may appear after an incubation

period of around 5–14 days [19]. Some early symptoms resemble those of other viral respiratory infections, such as those caused by influenza viruses. However, dyspnea and high fever define the main clinical difference between COVID-19 and common cold [20]. Additionally, when compared to the influenza virus, SARS-CoV-2 infection presents greater chances of progressing to severe and critical infections, which require oxygen therapy and ventilatory support [21]. Elderly patients and those with chronic conditions have higher risks of rapid progression to acute respiratory distress syndrome (ARDS) and multiple organ failure, often resulting in death. These features demonstrate a systemic aspect of this infection, which is accompanied by an intense inflammatory process [22–24].

## 2. COVID-19 and inflammation

The COVID-19 infection starts by exposure to microdroplets present in the exhalations of infected individuals. Then, the SARS-CoV-2 spreads to the bronchioles and alveolar spaces [25], entrancing into the host cells (e.g., endothelial, epithelial, and smooth muscle cells) by binding the angiotensin-converting enzyme (ACE)-2, a metallopeptidase present on the cell surface [26–29].

In the lung, SARS-CoV-2 infects the alveolar cells (type I and II pneumocytes and alveolar macrophages) and then starts intracellular replication in pulmonary tissues. Type I and III interferons (IFN) production is an early defense mechanism in the alveolar cells [25].

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However, recent researchers have found deficient expression of these cytokines, besides the upregulated expression of chemokines and interleukins [30,31]. In normal human bronchial epithelial (NHBE) cells culture, the cytokine profile includes the IFNs deficiency and elevated expression of CCL20, CXC-type chemokines, IL-1 $\beta$ , IL-6, and tumor necrosis factor (TNF) [31]. The type I and III IFN absence shows that, although SARS-CoV-2 is sensitive to IFN antiviral effect, the virus can inhibit its induction [31–34]. This ability may come from, at least, one mechanism of blocking the activation of the IFN signaling pathway at an early step following the nuclear transport of interferon regulatory factors (IRF) [35]. Furthermore, the recruitment of leukocytes, a hallmark of inflammation, is strongly related to the chemokine profile. For example, CCL2 and CCL8 recruit monocytes/macrophages, CXCL16 is a chemoattractant of NK cells, CXCL8 is the principal neutrophil chemoattractant, and CXCL9 and CXCL10 chemoattract T cells. Thus, the chemokine profile may be a driver of the signature pathology of SARS-CoV-2 [36].

The immune features between moderate and severe disease are modified after ten days of infection when severely ill patients remain with high proinflammatory cytokines [37]. Furthermore, deregulated inflammatory response to an infection may result in the cytokine storm syndrome, which is associated with severe COVID-19 [38,39]. This syndrome is characterized by high levels of interleukins, TNF- $\alpha$ , G-CSF, MCP-1, and MIP-1 $\alpha$ , which are higher in intensive care unit patients than non-intensive care unit patients [37,40,41]. Additionally, the inflammasome NLRP3, a multiprotein complex crucial to the host defense, is highly activated in COVID-19 patients. Inflammasome-induced cytokines IL-1 $\beta$  and IL-18 also contribute to cytokine storm, and sustained NLRP3 inflammasome activation is directly associated with the disease's severity [42–44]. The cytokines milieu recruits immune cells and activate T helper type 1 (Th1) response, which is related to the activation of a specific immune response. Moreover, Th1 cells stimulate IL-6 production by inflammatory monocytes in severe COVID-19 and contribute to the cytokine storm [45]. However, Th2 cytokines are also presented in COVID-19 serum patients and may impair the Th1-inflammatory response [40]. Thereby, chemokines/cytokines milieu comprises a possible therapeutic target for COVID-19 [46].

Peripheral blood immune cells (PBMcs) of COVID-19 patients present low T cell number and frequency in both CD4<sup>+</sup> and CD8<sup>+</sup> populations, which are more activated. On the other hand, monocytes are increased, but they present a reduction in HLA-DR expression compared with the control group (non-infected) [37]. Additionally, in severe COVID-19, patients present a reduced number of B cells and natural killer (NK) cells associated with severe T cell depletion, and a high neutrophil population [37,40,47–49]. This neutrophilia occurs after seven days symptoms onset [50].

### 3. Neutrophils in COVID-19

Neutrophils are the most abundant immune cells in human blood. They account for approximately 50–70% of all leukocytes. Besides serving as first responders to many infections, neutrophils have critical homeostatic functions being also implicated in chronic inflammatory diseases [51]. These polymorphonuclear cells play a protective role during bacterial or fungal infections; however, their role in viral infections is not fully understood [52,53]. Although the evidence is limited, it has been suggested that neutrophils enhance antiviral defenses by interaction with other immune cell populations, virus internalization and killing mechanism, cytokines release, degranulation, oxidative burst, and neutrophil extracellular traps (NETs) [53,54].

Neutrophils are present in many lung diseases associated with ARDS, as reported in infections by influenza virus and SARS-CoV-1 [55]. A bioinformatic study presented data indicating that neutrophil activation and degranulation are highly activated processes in the SARS infection [56]. Recently, the recruitment of this polymorphonuclear (PMN) was observed in the immune response triggered by SARS-CoV-2.

Furthermore, neutrophilia has been described as an indicator of severe respiratory symptoms and a poor outcome in patients with COVID-19 [57–59].

Several studies have reported that neutrophil-to-lymphocyte ratio (NLR), a clinical inflammation biomarker, is increased and predicts severe illness in the early stage of SARS-CoV-2 infection [59–62]. Higher D-dimer and C-reactive protein (CRP) levels follow NLR's increase in these patients [63,64]. Also, increased NLR has been considered an independent risk factor for mortality in hospitalized patients [41,65,66], related to some comorbidities (e.g., diabetes and cardiovascular disease) [67]. A study observed that COVID-19 diabetes patients with higher NLR had heavier severity and more extended hospital stay [68]. This fact supports the idea that pre-existing chronic inflammation contributes to COVID-19 severity [65,69].

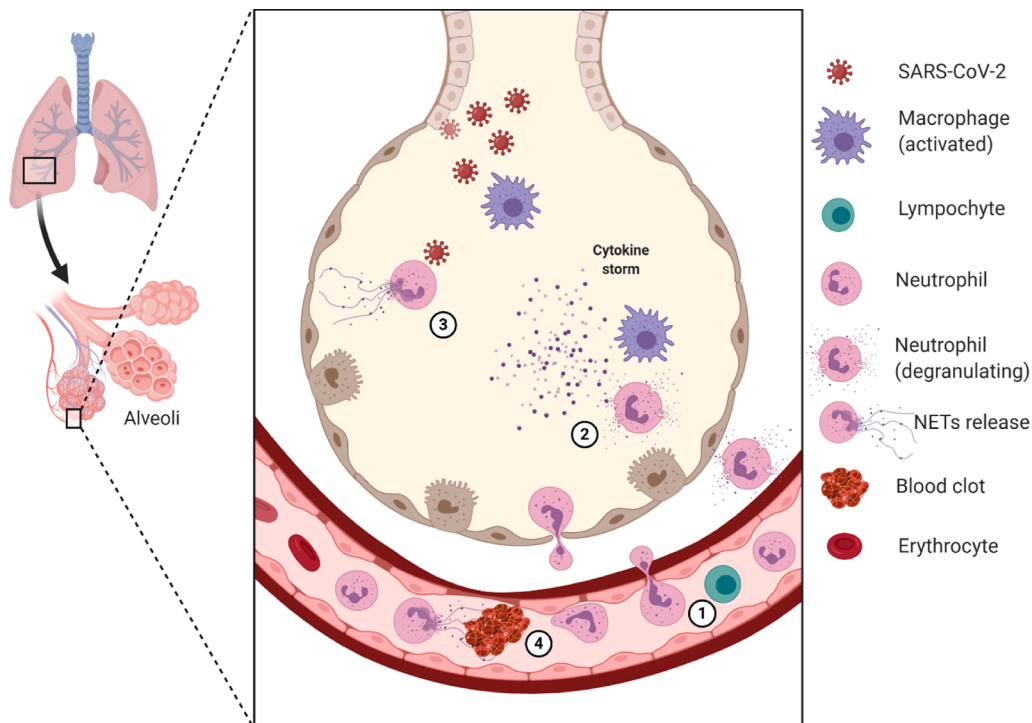
In addition to the NLR, neutrophil to CD4<sup>+</sup> lymphocyte ratio (NCD4LR) has been associated with the negative conversion time (NCT) of SARS-CoV-2. A study found that high NCD4LR indicates worse immune function and prolonged virus clearance [70]. Another biomarker involving this PMN, the neutrophil count to albumin ratio (NAR), has been described as a new predictor of mortality in COVID-19 patients [71]. Therefore, the NCD4LR and NAR values also could be used as clinical markers for COVID-19 progression in addition to the NLR [41].

Besides, the increase of neutrophils is not reported only in the bloodstream but also in the lungs [72]. PMN infiltration in pulmonary capillaries with extravasation to alveolar space and neutrophilic mucositis was observed in lung autopsies obtained from patients who died from COVID-19, indicating inflammation in the entire lower respiratory tract [73,74]. Moreover, immature phenotype and/or dysfunctional mature neutrophils have been described in severe COVID-19 patients [75,76]. These studies indicate that the increased infiltration of immature and/or dysfunctional neutrophil contributes to the imbalance of the lungs' immune response in severe cases.

Respiratory epithelium infection by SARS-CoV-2 leads to cell secretion of multiple cytokines, chemokines, and DAMPs, as previously described [31,77]. Transcriptional analysis of bronchoalveolar lavage fluid (BALF) from COVID-19 patients reported high levels of CXCL-2 and CXCL-8, chemokines that facilitate the PMN recruitment to the site of infection [78–82]. Although the neutrophils could present a protective role, extensive and prolonged activation of these leukocytes can lead to detrimental effects in the lungs and result in pneumonia and/or ARDS [83,84]. Wang and colleagues [50] also demonstrated that neutrophilia coincides with lung injury in severe COVID-19 patients.

It has been described that neutrophils play a pivotal role in the development of ARDS caused by influenza infection [55]. In COVID-19, neutrophils accumulation generates toxic molecules that might contribute to ARDS's physiopathology [85]. Respiratory burst from activated neutrophils induces ROS release, such as superoxide radicals and H<sub>2</sub>O<sub>2</sub>, leading to oxidative stress that contributes to the cytokine storm and blood clots formation in SARS-CoV-2 infection [86,87]. Moreover, decreased expression of the antioxidant enzyme superoxide dismutase 3 (SOD3) in the lung tissue of old patients with COVID-19 was also reported [88]. Therefore, excessive oxidative stress induced by PMN infiltration is related to the alveolar damage, thrombosis, and severity in COVID-19 [87]. In addition to ROS formation, neutrophil elastase has been implicated in COVID-19 pathogenesis [89–91]. This proteolytic enzyme, which is stored in azurophilic granules, is secreted to degrade antigens. Nevertheless, an imbalance of the elastase and other proteinases induces damage in the alveolar-capillary barrier, resulting in tissue injury and edema formation [92].

Furthermore, persistently activated neutrophils contribute to maintaining the inflammatory state in the lungs by cytokine release, as observed in MERS and SARS-CoV-1 infections [93]. Similar findings were described in SARS-CoV-2 infection by Parackova and colleagues [76] that reported the neutrophils as drivers of hyperinflammation by enhanced degranulation of primary granules and pro-inflammatory cytokines release. Taken together, these molecules secreted by PMN can



**Fig 1.** The neutrophil role in the lung tissue during infection by SARS-CoV-2. (1) The neutrophil-to-lymphocyte ratio (NLR) is elevated in the bloodstream. (2) The migrated neutrophils contribute to storm cytokines formation and release other mediators (e.g., elastase neutrophilic). (3) SARS-CoV-2 infection promotes neutrophil extracellular traps release, which can contribute to lung damage and (4) immunothrombosis. These many steps may be potential therapeutic targets. Several other cells and mediators are involved in COVID-19 immunopathology, but they are suppressed in this figure to highlight the neutrophil role. The figure was created with BioRender.com [119].

cause severe damage in alveolar tissue, independently of the virus cytopathic effect.

Additionally, Meizlish and colleagues [94] identified neutrophil activators (IL-8 and G-CSF) and effectors (resistin, lipocalin-2, and hepatocyte growth factor) as early biomarkers of severe COVID-19 patients. The authors also demonstrated a positive association between high levels in immature granulocytes and neutrophil counts with increased mortality [94]. These data highlight the neutrophil role in the severity of COVID-19 disease.

Viral infection can also induce the release of neutrophils extracellular traps (NETs) by neutrophils [95]. The NETs mechanism was first described by Brinkmann and colleagues in 2004 [96]. These traps consist of chromatin fibers associated with enzymes such as neutrophil elastase, cathepsin G, and myeloperoxidase [97,98]. NETs are known to immobilize and degrade bacteria, fungi, viruses, being a critical effector mechanism to contain infections [99]. However, NETs can act as a double-edged sword of immunity [98], having a pro- or anti-inflammatory effect [100,101]. Schauer and colleagues [102] reported that an aggregate of NETs can degrade cytokines and chemokines, reducing inflammation. This anti-inflammatory effect has also been demonstrated in the ocular microenvironment [103]. On the other hand, NETs can promote tissue damage, having already been shown that NETs and platelets' interaction can cause endothelial damage in infections by *Escherichia coli* [104]. NETs can also participate in the pathogenesis of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, where elevated levels of NETs have been seen in serum and synovial fluid, respectively, in patients with these diseases [105,106].

Studies have been reported an elevated level of NETs in patients with COVID-19 [107–109], and an increased plasma NETs is correlated with increased COVID-19 severity [109], besides contributing to lung injury and microvascular thrombosis [107]. The vascular occlusion caused by NETs is not only reported in lung tissue [110] but also in kidney and liver [111], which suggests that NETs thrombotic effects may be related to systemic and harmful effects of COVID-19. This relationship between NETs and thrombosis may also be related to complement system activation. Indeed, C3 [112] and C5 [113] inhibition dampen NET release in

COVID-19 patients. Since coagulation disorders are a worse prognosis to COVID-19 [114–116], and both NETs and complement proteins are associated with these thrombotic events [113], therapies that focus on this triple complement-NETs-coagulation axis may be a therapeutic opportunity.

At the transcriptional level, Wang and collaborators [50] demonstrated activation of several NETs-associated in COVID-19 patients. They hypothesized that some of them could be related to negative regulation of NK and T cell, dampening antiviral response [50]. In severe COVID-19, Veras and colleagues [109] demonstrated that neutrophils, both circulating and lung-infiltrating, release high levels of NETs. The authors also present data that demonstrate a NETs release directly induced by SARS-CoV-2 [117]. This SARS-CoV-2-induced NETs release is PAD-4-dependent [109]. PAD4 is critical to NET formation because it promotes a process of hypercitrullination of histones, resulting in chromatin decondensation [118]. The SARS-CoV-2-activated neutrophils can also induce apoptosis in lung epithelial (A549 cells), reinforcing neutrophil role in COVID-19 immunopathology and other coronavirus infections [109].

#### 4. Conclusions

The literature related to neutrophil and COVID-19 so far demonstrated a crucial role of these polymorphonuclear cells in the pathogenesis of COVID-19 (Fig. 1). Despite the immune system modulation needs being tightly controlled to avoid immunosuppression, the different neutrophil mechanisms (e.g., neutrophils enzymes and cytokines, NETs) are potential targets to treat COVID-19, mainly the severe cases.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



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