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Review

Pathological effects of SARS-CoV-2 on hematological and immunological cells: Alterations in count, morphology, and function

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ABSTRACT

The novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19 outbreak, spread rapidly and infected more than 140 million people with more than three million victims worldwide. The SARS-CoV-2 causes destructive changes in the immunological and hematological system of the host. These alterations appear to play a critical role in disease pathology and the emerging of clinical manifestations. In this review, we aimed to discuss the effect of COVID-19 on the count, function and morphology of immune and blood cells and the role of these changes in the pathophysiology of the disease. Knowledge of these changes may help with better management and treatment of COVID-19 patients.

1. Background

In December 2019, the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) emerged from Wuhan, China and rapidly spread over more than 200 countries. Eventually, the World Health Organization (WHO) officially declared Coronavirus Disease-2019 (COVID-19) a pandemic on March 11, 2020 [1,2]. SARS-CoV-2 is highly contagious and it has so far infected more than 140 million patients with more than three million victims across the world [3]. COVID-19 mostly involves the lower respiratory tract causing respiratory symptoms ranging from mild respiratory illness to acute respiratory distress syndrome (ARDS) [4]. The most common reported symptoms of COVID-19 patients are fever, cough, dyspnea, myalgia or fatigue, and sputum production [5].

Infection with SARS-CoV-2 causes crucial hematological and immunological changes in patients, which are involved in the pathophysiology of the disease [6,7]. The immune system has an essential role in the control and eradication of viral infections. However, an insufficient or over-responsive immune system may cause serious adverse conditions [8,9]. Inflammatory cells like macrophages are recruited in almost all viral infections and release cytotoxic cytokines, lipid mediators, metalloproteinases, and reactive oxygen species that induce tissue damage [9]. In severe cases of COVID-19, elevated levels of cytokines and chemokines (IL1α/β, IP-10, MCP-1) promote hyper inflammation in the lungs and underlies ARDS. Furthermore, postmortem analysis has shown infiltration of inflammatory cells such as macrophages and lymphocytes in the lung tissue of COVID-19 patients [5,10,11]. Several studies have found a decreased number of CD8 + and NK cells and functional exhaustion of these cells due to overexpression of inhibitory markers like NKG2A and PD-1 [12–14].

The most common hematological changes in covid-19 patients include lymphopenia [15,16], neutrophilia [17,18], eosinopenia [19,20], mild thrombocytopenia [15], and thrombocytosis with a lower frequency. The leukocyte count varies between different cases and may be normal, reduced [15,20,21], or increased [3,22]. In some studies, the lymphocyte count is proposed as an indicator for classification of disease severity besides pulmonary imaging as the main test for classification of disease type [23,24]. The platelet count is another indicator of disease severity and prognosis and can reflect the pathophysiological alterations in COVID-19 patients in the early stages [25]. A combination of thrombocytopenia, prolonged prothrombin time (PT) and increased D-dimer is indicative of disseminated intravascular coagulation (DIC) in COVID-19 patients. In addition, deposition of fibrin and thrombin in the pulmonary microvasculature is a factor that contributes to ARDS and coagulopathy in patients dying from COVID-19 [26,27].

Daily global reports warn that the number of patients is rising

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sharply. Moreover, a lack of information about different aspects of the disease is still a serious obstacle despite all efforts [28]. Hence, the study of the pathophysiology of disease and the effect of the virus on the immune cells and other blood cells, besides improving our knowledge about the disease, can also help to choose effective treatment strategies. In this comprehensive study, we reviewed the destructive effects of COVID-19 on the quality and quantity of immune and blood cells and discussed the role of these changes in the pathophysiology of the disease.

2. NK cells

2.1. Alteration in count

While many studies have reported findings related to the NK cell function in COVID-19, the exact role of these cells in defense against SARS-CoV-2 and the pathophysiology of the disease is not defined. In SARS-CoV-2 infected patients, the frequency of NK cells in the blood is decreased [13,29–32], or increased [33], or does not show any significant changes [34]. A similar NK cell reduction was reported in SARS-CoV-1 infection previously [35]. After recovery, the NK cell count returns to normal levels in severe COVID-19 patients [33,36]. In addition, the NK cell frequency has the potential to predict COVID-19 severity. The NK cell frequency is lower in patients with ARDS and pneumonia compared to those with a mild phenotype of the disease, which suggests an indirect link between the NK cells count and disease severity in COVID-19 patients [12]. It is still unclear whether NK cell reduction is because of cell death resulting from SARS-CoV-2 or infiltration of inflammatory NK cells into infected organs (particularly the lung) [37]. However, it is unlikely that SARS-CoV-2 induces cell death in NK cells similar to what is observed in other viral infections like influenza [38] because NK cells lack the entry receptor, angiotensin-converting enzyme 2 (ACE-2) [39]. In a study, analysis of the bronchoalveolar lavage fluid (BLAF) of ARDS patients showed no CD16 +CD57 + mature NK cells in the lung tissue, suggesting that the reduction of circulatory NK cells is not a consequence of the migration of these cells into infected lungs [12]. On the contrary, the single cell landscape of bronchoalveolar immune cells in two recent studies reported an increased frequency of NK cells in BALF of COVID-19 patients [40,41]. Therefore, more studies are needed to determine the etiology of NK cell reduction in COVID-19 patients.

2.2. Alteration in cell surface markers and function

While several studies have investigated the potential responses of NK cells during COVID-19, there are still many debates in this regard. In a cohort study by Demaria et al. [12], the frequency of NK group 2 member A (NKG2A) expressing NK cells was lower in ARDS patients compared to healthy controls while the NKG2A density on the surface of NK cells was up-regulated. Likewise, other regulatory molecules such as programmed cell death protein-1 (PD-1), CD244 (also known as 2B4), and CD39 were upregulated in COVID-19 patients. More importantly, the levels of cytotoxic effector molecules including granzyme A and perforin decreased in the patients [12,32]. Besides, isolated NK cells from BALF of patients had higher expression of NKG2A, CD39, and PD-1 molecules, even higher than those observed in NK cells derived from blood samples. Interestingly, incubation of NK cells isolated from ARDS patients with monalizumab, an anti-NKG2A monoclonal antibody, unleashed their cytotoxic functions and killing ability [12]. In a study comparing mild and severe forms of COVID-19 patients, Zheng et al. [31] found a significant reduction in the frequency of NK and CD8 + T cells in severe COVID-19 patients. In addition, they reported higher expression levels of inhibitory receptor NKG2A in NK and CD8 + T cells in the severe form of the disease. The expression level of CD107a (a degranulation marker of NK cell) [29] and production of IFN-γ and TNF-α are lower in severe COVID-19 patients [31]. Accordingly, it is hypothesized that NK and CD8 + T cells have an exhausted phenotype in severe COVID-19 patients, which might be due to NKG2A over-expression (Table 1) [31]. To evaluate the possible role of SARS-CoV-2 spike protein (SP) in altering the NK cell function, an in vitro study explored NK cell responses towards lung epithelial cells transfected with spike protein. The results showed that the spike protein might induce chemo-attraction and IFN-γ production of NK cells [42]. Furthermore, CD107a degranulation marker decreased in SP1 transfected cell culture. Further analysis exhibited that the HLA-E/NKG2A/CD94 interaction may be a possible mechanism for the reduction in NK cell cytotoxicity functions [42]. These studies emphasize the exhausted phenotype of NK cells with over-expression of inhibitory molecules and describe NKG2A as a potential cause for this exhaustion during COVID-19 infection. In addition, the data suggests that the exhausted phenotype of NK cells can be a prognostic factor for a more severe phenotype of COVID-19.

3. Lymphocytes

3.1. Alteration in count

Lymphopenia following SARS-CoV-2 infection has been reported in many studies [43–49]. About 85% of patients who need to be hospitalized have lymphopenia [45,50] with a decrease in both T and B lymphocytes [44,45,51–54]. However, a study noted that the lymphocyte count remained in the normal range in mild COVID-19 patients [55]. The B cell count is not affected by SARS-CoV-2 infection [47,55,56] even in the severe phase [55]. A decrease in lymphocyte populations can be used as a predictive parameter for determining the severity of the disease and the risk of death in patients with SARS-CoV-2 infection [43,50,52–55,57,58]. However, a recent systematic review found that a low lymphocyte level was correlated with a poor prognosis in general but the association between lymphocyte subsets and the mortality rate of COVID-19 patients was not significant [59]. Possible mechanisms that may cause lymphopenia include bone marrow suppression [45,52,60], direct infection of lymphocytes with SARS-CoV-2 [44,45,59–62], pulmonary entrapment [44,59,60,62] high amounts of inflammatory cytokines [44,52,58,60] that prevent T cell proliferation and survival [44,45,63], the destructive effects of SARS-CoV-2 on the lymphatic tissue such as the thymus and spleen [51,52], epigenetic changes in lymphocytes [52] and dendritic cell dysfunction leading to T cell apoptosis [45].

In the disease course, a dynamic alteration is seen in the lymphocyte count. According to a recent study, during the disease progression, the lowest level of B cells and CD4+ T cells is seen in the second week after the onset of symptoms, whereas the CD8+ T cells show the lowest level in the third week after the onset of symptoms [58]. In addition, in the recovery phase, the T cell population is larger compared to the acute phase of infection [58] but a sustained lymphopenia with decreased CD3+, CD4+, and CD8+ T cells is found in more severe cases of COVID-19 [46]. After treatment and in the convalescent phase of the disease, the lymphocyte count gradually returns to the range of COVID-19 mild cases [46,64].

3.1.1. B lymphocytes and SARS-CoV-2 infection

The data on B-lymphocytes is still conflicting and needs further investigation. A study on the total B cells and its different subsets indicated that the frequency and the absolute number of total B cells did not change considerably in COVID-19 patients relative to healthy controls [65]. The results of this study showed that transitional B cells and antibody secreting cells (plasmablast/plasma cell) increased in COVID-19 patients whereas the memory B cells reduced significantly indicating a positive correlation with disease severity (Table 1) [65]. Other studies also reported that the number or proportion of plasma cells increased in COVID-19 patients [52,65–67].

3.1.2. T lymphocyte subset and SARS-CoV-2 infection

A decrease in both CD4+ and CD8+ T cells is reported in COVID-19 patients with different disease severities, which is more significant in

Table 1
Alterations in NK cells and lymphocytes in COVID-19 patients.

Demaria et al. [12]	10 healthy 10 paucisymptomatic COVID-19 34 pneumonia 28 ARDS	Blood BALF	NK	Expression of CD39, PD-1, and NKG2A in Severe COVID-19 patients↑ KIR2DL1/S1 expression in ARDS↑ CD16 + CD57+ in BALF of ARDS↓ CD39, PD-1, and NKG2A in BALF of Severe COVID-19 patients↑
Varchetta et al. [14]	32 patients 25 healthy	Blood	NK CD8+T	Mature NK↑ Expression of Tim-3 and CD69 in NK and CD8+T↑ NK exhaustion (IFN-γ ↓), FcεRIγ$^-$ CD56$^+$ CD57$^+$ (mature NK)↑
Osman et al. [29]	78 controls and 10 COVID-19	Blood	NK	NK count↓ Cytotoxic activity↓ Serum NK activating cytokines↓
Wan et al. [30]	123 patients	Blood	NK, WBC Lymph, Plt	NK, WBC, Lymph, Plt count in severe comparing to mild patients↓
Zheng et al. [31]	55 mild 13 severe	Blood	NK CD8+ T	NK and CD8+ T count↓ NK and CD8+ T exhausted
Li et al. [32]	16 mild 16 severe	Blood	NK, NKT CD4+ T CD8+ T	NK, CD4+ T, CD8+ T, and NKT count and percentages in severe patients ↓ Regulatory molecules CD244 and PD-1 on T and NK in severe patients↑ Serum perforin and granzyme A ↓
Yan et al. [33]	11 convalescent 11 controls	Blood	NK, CD8+T Tfh	NK counts↑, Effector memory CD8+ T counts↑ Tim-3+ Tfh like cell counts ↑ CD226+ Tfh like cell counts ↓ ICOS+ Tfh like cell counts↓
Gil-Etayo et al. [44]	55 patient 21 control	Blood	T cell	Percentage of Th1, Th2, Th17 ↓ Th2 activity ↑ (78% of died patient have over-reactive Th2 response)
Gutierrez-Bautista et al. [45]	144 patient 42 control	Blood	T cell	Significantly reduction in Th1 subset HLA-DR and CD38 expression on CD8+ T cell ↓ Active CD4+ T cell in severe case ↑ Exhausted profile in CD4+ and CD8+ of died case ↑
Shi et al. [48]	54 patient 16 control	Blood	B cell T cell NK cell	The count of B cell, T cell and NK cell ↓ in sever case The % of B cell and NK cell ↑ (in patient relative to control) The percentage of CD8+ T cell ↓ (associated with severity) IL-2R and JAK/STAT expression↓ (lead to T cell reduction)
Sosa-Hernández et al. [65]	52 patient 7 control	Blood	B cell	severe cases relative to mild cases: CD19+ B cells ↑ Transitional B cells ↓ in severe cases Memory B cell ↓ in severe and critical cases Ab-secreting cell ↑ (associated with severity)
Shuwa et al. [66]	58 acute patients 83 convalescent patients	Blood	B cell T cell	IL-6 production by B cell during acute phase ↑ cytotoxic activity of CD8+ in convalescent phase ↑ CXCR5/CXCR3 expression in acute phase ↓

severe and critical patients [43,45,51,52,54,57,58,60]. Histological analysis of deceased COVID-19 patients showed that the CD4+ and CD8+ T cells decreased in the spleen and lymph nodes of these patients [68].

3.1.2.1. CD4+ T cells. The absolute count of Th1, Th2, Th17, Th22, and Treg is reduced in COVID-19 patients [45]. The Th subset differentiation and Th1/Th2 coordination can determine the COVID-19 severity and outcome [44]; for instance, it has been observed that a high percentage of exhausted Th2 cells is associated with a high rate of mortality in COVID-19 patients (Table 1) [44]. Furthermore, the memory T cells also decrease in COVID-19 patients, which can be one of the reasons why infected individuals are not immune to the virus after infection [52].

Th1 cells play a vital role in anti-viral response and induce proliferation and activation of cytotoxic T cell, which leads to removal virus-infected cells [45]. On the other hand, Th2 cytokines are reported to be high in COVID-19 patients [45,51,61]; these cytokines have a suppressive effect on inflammatory Th1 response and induce antibody response [44,45].

Reduction of Treg cells [52,54] and exhaustion of CD4+ and CD8+ T cells in COVID-19 [52,54,68] patients exacerbate the inflammatory status and cause more damage to the lung [46,54]. On the other hand, intense inflammatory cytokines may promote lymphopenia and lymphocyte exhaustion [52] creating a damage cycle all together. A possible reason for Treg cell reduction is direct infection with SARS-CoV-2 or migration of these cells to the lungs [52]. In addition, a decrease in IL-2 level is seen in bronchoalveolar lavage of severe COVID-19 patients, which may lead to Treg apoptosis [52].

3.1.2.2. CD8+ T cells. One study found that only CD8+ T cells reduced in asymptomatic COVID-19 patients and the other subsets of lymphocytes in these patients were similar to healthy individuals [58]. It may indicate that CD8+ T cells are more susceptible to SARS-CoV-2 infection [48,51,52,55,63] and their reduction in the early phase of infection may predict the need for ICU admission [69]. Interestingly, a study found that the baseline levels of ACE2 and TMPRSS2 in the lung tissue were negatively related to the level of CD8+ T cells that reside in the lungs before infection [70]. This finding may indicate why some people are more susceptible to more severe infections with the SARS-CoV-2 [70]

since the presence of cytotoxic cells in the lungs can play an important role in rapid containment of the infection in the early stages of the virus infection [70]. Moreover, this study revealed that the baseline level of chemokines attracting CD8+ T cells to the lung had a negative correlation with ACE2 and TMPRSS2 expression levels, which, in return, exacerbates the lack of cytotoxic cells [70]. However, it has been observed that the level of these chemokines increases following the SARS-CoV-2 infection resulting in the migration of CD8+ T cells and other cytotoxic cells to the lungs [70].

3.2. Alteration in cell surface markers and function

Although ACE2 is not expressed on lymphocytes, CD147 may act as an alternative receptor for SARS-CoV2 entry, which is expressed on B cells as well as CD4+ and CD8+ T cells [51]. In addition, CD26 (DPP4) is also suggested to be an entry receptor for SARS-CoV-2 on T cells (but does not exist on B cells) [51]. However, the exact role of these receptors is not yet proven warranting further research [51].

3.2.1. CD4+ T cells

The percentage of CD4+ T cells that express HLA-DR and CD38 is also elevated in severe disease, which indicates the activation of these cells [45,56,68]. Increased expression of HLA-DR may be due to a high level of inflammatory cytokines in these patients and therefore it does not indicate specific activation of these cells (Table 1) [45]. A recent study found that the expression of OX40 and 4–1BB increased on CD4+ and CD8+ T cells of COVID-19 patients, respectively. Both markers indicate the active phenotype of these cells and increase more in severe cases [56]. The expression of PD-1 and TIM-3 as exhaustion markers on T lymphocytes increases in severe COVID-19 patients, which is associated with a poor prognosis [51,52,56,68,71].

It has been reported that SARS-CoV-2 specific CD4+ T cells cannot efficiently generate am interferon response, specifically in ICU patients [71]. Additionally, it has been shown that in critical patients admitted to the ICU, the neutralizing antibody titer is not concordant with the level of CD4+ T lymphocytes indicating discordance between B cells, as major participants in the humoral response, and CD4+ T cells [71].

3.2.2. CD8+ T cells

Generally, most studies have reported a hyperactive status in CD4+ and CD8+ T cells [51,63,68,69]. A recent study found that the expression of CD38 and HLA-DR on CD8+ T cells reduced following SARS-CoV-2 infection, which is possibly associated with Th1 dysfunction [45]. However, on the opposite side, it has been revealed that the cytotoxicity of these cells is increased in COVID-19 patients for compensating their count reduction [47,52,69]. In this regard, some studies reported increased expression of HLA-DR, CD38, GrA, GrB, and perforin on CD8+ T cell in SARS-CoV-2 infected patients [47,66,72].

4. Neutrophils

4.1. Alteration in count

Neutrophils, as the innate immune cells, are the first cells that are recruited in inflammations. They have important roles in defense against COVID-19 [73]. Neutrophils are recruited to the lungs of COVID-19 patients, and neutrophilia acts as a prognostic factor of ARDS in these patients [22,74–77].

The neutrophil to lymphocyte ratio (NLR) as the prognostic value is used to predict the severity of disease in the early stage of COVID-19 [25,34,78–85]. Some studies reported that diabetic patients with COVID-19 had higher NLRs [6,76,86,87]. A study found that the neutrophil to CD4 + lymphocyte ratio (NCD4LR) provided a better prediction of virus negative conversion time [49]. Another study showed that the neutrophil count to albumin ratio (NAR) could be a predictor of the mortality rate of COVID-19 patients [88]. Infiltration of neutrophils in pulmonary capillaries and alveolar space is reported in some studies; moreover, in infiltration of immature and/or dysfunctional neutrophils has been observed severe cases of COVID-19 [89–92].

4.2. Alteration in cell surface markers and function

BALF analysis of COVID-19 patients has shown increased levels of some chemokines such as CXCL2 and CXCL8 leading to recruitment of PMNs to lungs. Although neutrophils are important in defense against viruses, neutrophilia can cause lung injury and ARDS [17,93–99]. A study reported an increase in the expression of some genes such as Cathepsin G, IFNγR1, ATP6AP2, CD36 that induce neutrophil apoptosis and downregulation of the TGFB gene in macaques model of COVID-19 infection [78].

Degranulation of neutrophils and release of some proteolytic enzymes such as elastase can cause more injury to lung capillaries and result in edema formation [100]. The level of calprotectin, as a neutrophil activation marker, is correlated with the severity of COVID-19 disease. In addition, it has positive correlations with C-reactive protein, ferritin, lactate dehydrogenase, absolute neutrophil count, and platelet count. Therefore, calprotectin, as an inflammatory marker, can activate neutrophils and lead to their degranulation and phagocytosis. Furthermore, cross-talk between neutrophils and platelets and calprotectin can cause artery and vein thrombosis in COVID-19 [101]. A study revealed strong associations between markers of hyperactive neutrophils (calprotectin and cell-free DNA) and D-dimer [102]. Neutrophils and platelets interact closely [103] via P-selectin and its ligand (PSGL-1) [104,105]. Platelets induce the release neutrophil extracellular traps (NET) from neutrophils in viral infections [106,107]. Neutrophils and platelets are entrapped in the fibrin meshwork in alveolar capillaries of SARS-COV-2 patients. these neutrophils are destructed to some extent and form NETs [77,89,102,108,109].

4.2.1. NETosis during COVID-19 infection

NET is composed of chromatin fibers and citrullinated histones, some special enzymes such as neutrophil elastase, myeloperoxidase, and cathepsin G [110]. The NETosis process can act as a double-edged sword; although it is an essential mechanism for virus entrapment, excessive NET formation increases inflammation, autoimmunity, vascular disease, and thrombosis [102,111–114]. COVID-19 patients may develop thromboembolism and arterial thrombosis [95,115]. NETs are associated with the severity of COVID-19 disease and can trigger macrophages to produce more IL-1β precursors [116]. An active form of IL-1β can help with NET formation in vivo and in vitro [117,118]. The NET–IL1β loop is activated in severe COVID-19. An enhanced production of NETs and IL1β can accelerate respiratory decompensation, formation of micro thrombi, and aberrant immune responses. Importantly, IL1β induces IL6 [119], and IL6 is considered as a promising target for COVID-19 treatment [31,120]. NETs can activate the coagulation cascade by acting as a scaffold for VWF and tissue factor (TF) and also by activating the contact pathway. NETs also has an inhibitory effect on anticoagulant pathway such as protein C and tissue factor pathway inhibitors (TFPI) Fig. 1 [111,121]. Some studies found evidence for NETosis in COVID-19 patients, such as aggregation of neutrophils and platelets in the blood, presence of cell-free DNA and MPO-DNA complex [102,109,112,121–125]. Elevated levels of soluble platelet derived factors that trigger NETosis, including PF4 and RANTES can be observed as the prognosis of the severity of the disease in these patients Table 2 [121]. One study found that the branch length of the NETs released by neutrophils was larger in COVID-19 patients compared to healthy controls [112]. NETs are positively correlated with ARDS [121], multi-organ failure and mortality [122] but NET formation normalizes during convalescence after COVID-19 [121]. NET levels are also significantly higher in the tracheal aspirate fluid than in plasma samples in COVID-19 patients [121]. NET is related to the complement system, and inhibition of C3 and C5 can reduce NET formation [126,127].

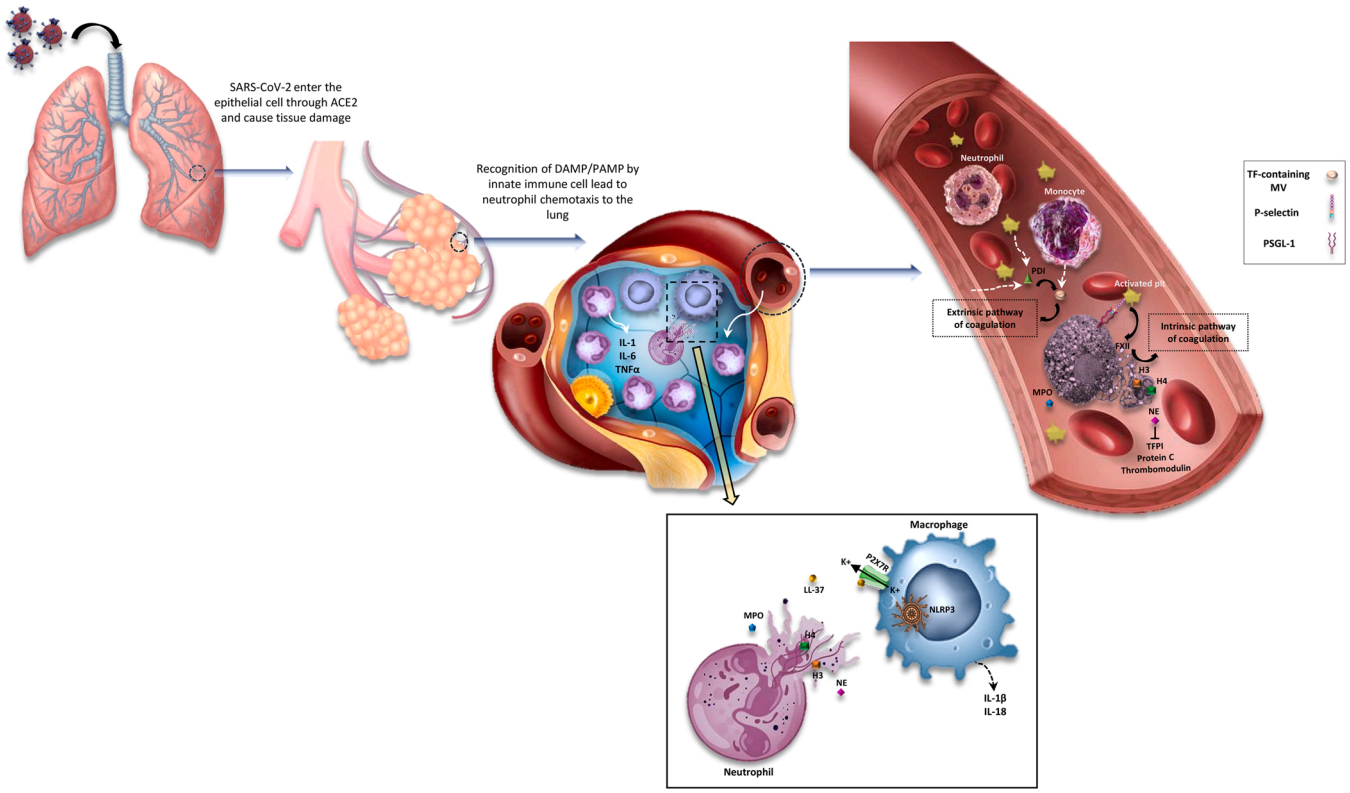

Fig. 1. Role of neutrophils in hypercoagulable state of COVID-19 patients. After the entrance of the SARS-CoV2 virus into the respiratory system, it enters the epithelial cells through ACE2 and causes some damages. This virus travels to the alveoli of the lungs and innate immune cells are recruited. Monocytes activate by identifying PAMPs and DAMPs and neutrophils are recruited and cytokine storm occurs by producing some inflammatory cytokines such as IL-6, IL-1b, TNF-α. Therefore, infiltration of neutrophils occurs, which produce NETs. The NETosis process has some connections with macrophages in the tissue. NETs are composed of MPO, NE, H3, H4, LL37, etc. LL37 activates the p2x7r channel on macrophages and then the efflux of K^+ ions occur. Hence, NLRP3 inflammasome activates and macrophages produce some cytokines such as IL-1b and IL-18 that can help neutrophils to produce more NETs. On the other hand, the neutrophils that produce NETs can link to platelets in the blood through PSGL1 and p-selectin on the platelets and activate them. These activated platelets release poly p and PDI. PDI, as an enzyme, causes the release of TF micro- vesicles from activated monocytes. Not only this TF activates the extrinsic pathway of coagulation but also adheres to the NETs. VWF adheres to these NETs too, and they can form a scaffold for thrombosis happening. Also, the intrinsic pathway can be activated by activating factor XII on this scaffold. NE extraction of neutrophils inhibits some inhibitory factors of the coagulation system such as protein C, thrombomodulin, and TFPI. Finally, all of the above cause thrombosis in the veins or arteries of COVID19 patients.

Therefore, targeting some parts of the NET formation, thrombosis, or complement system can be a good therapeutic approach for reducing the mortality of COVID-19 patients [128].

5. Eosinophil alterations in COVID-19 patients

Eosinophils account for 1–3% of circulating leukocytes and have some roles in antiviral responses [129]. Some studies found that more than half the patients admitted with COVID-19 had eosinopenia (defined as an absolute eosinophil count$<0.02 * 10^9$ cells/L) [83,95,130,131]. This eosinopenia is correlated with the severity of COVID-19 disease [129,132,133]. A low eosinophil count will normalize over time (Table 2) [83]. No eosinophil enrichment has been found in the pulmonary tissue of patients with COVID-19 in postmortem analyses [134]. Type 2 immune response, including type 2 cytokines (IL-4, IL-13, etc.) and accumulation of eosinophils, might provide potential protective effects against COVID-19 [135]. However, there is controversy over the protective or exacerbating role of eosinophils during SARS-CoV-2 infection [129].

6. Monocytes/macrophages

Monocytes and macrophages are the main cells of the mononuclear phagocyte system (MPS) that play an important role in both innate and adaptive immune systems [136]. The presence of these two cell populations in all phases of SARS-CoV-2 infection can act as a double-edged sword that can ameliorate infection or exacerbate it [136]. They are the main players in the innate anti-viral immunity. They can also trigger systemic inflammation, pro-coagulant syndrome and cytokine release syndrome (CRS) leading to ARDS and multi organ failure in COVID-19 patients [136–140]. Monocytes and tissue macrophages express a broad set of membrane receptors and secretory elements that mediate their role in both anti-viral and inflammatory responses [136]; the balance between these two responses and the contribution of other immunity mechanisms can determine the severity and outcome of SARS-CoV-2 infection [136].

6.1. Alteration in count and morphology

The absolute number of total monocytes and their frequencies are not affected by SARS-CoV-2 virus [141–145]; however, some studies found a decrease in the number of monocytes in critical patients [146,147] and an increase in mild cases [147]. Based on previous studies, it can be concluded that monocytes increase their antiviral response in the early stages, which may indicate a good prognosis. However, in the severe stages of the disease, a decrease occurs in monocytes, suggesting the destructive effects of the virus on monocytes [146]. In patients with SARS-CoV-2 infection, the monocyte distribution width (MDW) shows a higher value compared to healthy individuals. Moreover, among infected individuals, those requiring ICU admission have significantly higher

Table 2
Quantitative and qualitative changes in granulocytes due to SARS-CoV-2 infection.

Author (year)	Sample size (case/control)	Sample	Parameter studied	Study findings
Yufei et al. (2020) [79]	191 COVID19 patients and 50 healthy individuals as control	Blood (retrospective study)	Neutrophil Lymphocyte	NLR and CRP↑ lymphocyte percentage↓ Neutrophilia
Xie et al. (2021) [83]	227 pneumonia patients and 97 hospitalized COVID19 patients	Blood	Eosinophil	Eosinopenia in COVID19 patients CRP level in pneumonia patients↑
Shi et al. (2021) [101]	172 hospitalized COVID19 patients	Serum Plasma	Neutrophil	Serum and plasma calprotectin↑ Positive correlation of calprotectin and NET release
Middleton et al. (2020) [121]	33 COVID19 patients,17 age and sex matched healthy adults	Whole blood Autopsy of lung specimen	Neutrophil NETosis Platelet	Plasma NET↑ MPO-DNA complexes↑ PMN granularity↓ Co-localization of Cit H3 with platelets and thrombosis Platelet-neutrophil aggregations
Kong et al. (2020) [122]	210 COVID19 patients (retrospective cohort study)	Blood	Neutrophil Lymphocyte	NLR↑ Neutrophilia Lymphopenia APPt and D-dimer↑
Sun et al. (2020) [133]	63 confirmed COVID-19 patients	Throat swab or sputum, Urine Blood Stool	Eosinophil	Leukopenia Lymphopenia Eosinopenia in moderate and severe form of COVID19

Table 3
Alterations in monocytes, macrophages and dendritic cells in COVID-19 patients.

Author (year)	Sample size (case/ control)	Sample	Parameter studied	Study findings
Sánchez-Cerrillo (2020) [138]	64 COVID-19 cases 22 Non-COVID-19	Blood Bronchial sample	DCs Monocytes	DCs and monocytes ↓ (blood samples). $CD1^{+}c$ DCs and monocyte ↑ (bronchial sample). CD40 on monocyte and pDCs in blood ↓ and on bronchial sample ↑
Gatti (2020) [141]	30 COVID-19 cases 20 healthy control	Blood	Monocyte	Monocytes number → patients = control NC monocyte↓ in severe cases. INT monocyte and CD11b ↑ in moderate case HLA-DR ↓ in severe cases.
Matic (2020) [142]	57 COVID-19 patients 5 healthy control	Blood	DCs Monocyte Macrophage	Monocyte/ macrophage ↓. C monocyte ↑ / INT and NC monocyte ↓. Co-expressing of CD23 & CD38 on INT and NC monocytes.
Peruzzi (2020) [143]	40 COVID-19 patients 8 healthy control	Blood	DCs Monocytes	Total monocytes → patients = controls. NC monocyte ↓ and T and C monocyte ↑. HLA-DR ↓ and CD11b / CD64 ↑
Silvin (2020) [144]	13 COVID-19 cases 12 flu-like cases	Blood	Monocyte	Total monocytes → severe cases = controls. INT monocyte ↑ in mild cases. NC monocyte ↓ in severe cases CD11b+ C monocyte ↑/ HLA-DR expression ↓ (in severe cases)
Zhang (2021) [145]	34 COVID-19 patients Unknown number of healthy control	Blood	Monocyte	Atypical monocyte ↑ C monocytes ↓ / INT & NC monocyte ↑ ACE2 on monocyte of patients ↓
Bedin (2021) [151]	32 COVID-19 cases 30 healthy control	Blood	Monocytes	Monocyte CD169 ↑ during active infection. Monocyte CD169 in mild cases > severe cases Monocyte CD169 lower in cases with producing IgG against SARS-CoV-2

MDW values relative to patients with mild symptoms [148]. Therefore, MDW can be considered a prognostic parameter along with other laboratory parameters for predicting unflavored outcomes [148].

6.2. Alteration in morphology

Large monocytes with vacuolated cytoplasm are seen specifically in COVID-19 patients [145]. Meanwhile, the results of several studies have confirmed a change in the frequency of different subsets of monocytes in COVID-19 patients [143]; A study showed that the non-classical (NC) monocytes could determine the severity of the disease; NC monocytes below 4% indicate more severe disease and the recovery phase also occurs when the NC monocytes start to increase [144]. Two studies reported a mixed phenotype expressing both M1 and M2 macrophage markers in this specific population (Table 3) [142,145]. Nonetheless, there is a profound contradiction in the results of studies on each cell population, and more research is needed to draw a definitive conclusion about the changes in each monocyte subset.

6.3. Alteration in cell surface markers and function

Comparison of COVID-19 patients with healthy individuals shows a significant reduction in HLA-DR expression on monocytes of COVID-19 patients, which has a direct relationship with the severity of symptoms [92,143,147,149]. The high amounts of IL-6 and CRP in COVID-19 patients can downregulate the HLA-DR expression on classical monocytes [143,144]. Impaired HLA-DR expression leads to less antigen presentation and lower anti-viral response by T cells [143,149]. On the other hand, the expression of some functional markers such as CD64 and CD11b increases on monocytes, which is independent of COVID-19 severity [143]. Moreover, one study reported an increase in CD38

expression on monocytes in critical patients, which indicates the enhanced inflammatory status of monocytes [147]. A recent study found reduced CD4 expression on monocytes in severe COVID-19 patients [146]. CD40 expression as an activation marker in blood monocytes has a propensity to decrease in all monocyte subtypes in critically ill patients; however, this reduction is not associated with IL-6 and other inflammatory elements (Table 3) [138].

Monocytes, macrophages (particularly M1), and dendritic cells have a transporting role for SARS-CoV-2 as they bind to the virus by their lectin-binding receptors such as CD169 and carry it to local lymph nodes. Through this transportation, the virus gains access to the lower respiratory tract and even other tissues through the bloodstream [136, 149,150]. When SARS-CoV-2 disseminates in the body and reaches other organs, resident tissue macrophages evoke an inflammatory response and cause some dysfunction in the related organ [136]. During the early phase of infection with SARS-CoV-2, overexpression of CD169 on monocytes has been observed; however, its expression decreases in the severe phase of the disease (Table 3) [151]. Under inflammatory conditions, it has been shown that mononuclear phagocytes can activate platelets and produce procoagulant factors such as tissue factors [136, 137], factor 5, and factor 13, which indicates their role in hyper-coagulation and generation of thrombo-embolism (Fig. 2) [136]. Furthermore, a recent study reported an increase in monocyte-platelet aggregation (MPA) in COVID-19 patients compared to healthy individuals and a positive relationship between MPA and the severity of disease [152]. These MPAs can be one of the underlying mechanisms for increased risk of thrombotic complications in COVID-19 patients [152].

On the opposite side of the pathological processes that are driven by these cells, the recovery process also depends on macrophages in COVID-19 infection [136]. M2-macrophages can reduce inflammation by producing some lipid metabolites such as resolvins, protectins, and maresins [136]. Besides, secretion of elastase, collagenase, TGFβ, and IGF-1 and blotting out the necrotic cells is a cooperative mechanism done by macrophages resulting in recovery [136]. It has been shown that the number and function of monocytes are restored in the course of COVID-19 remission [147].

7. Platelets

Platelets, in addition to being the major cells in thrombosis and homeostasis, are also involved in inflammatory processes and immune responses [153–157]. Adverse changes in the platelet count and function are responsible for coagulation drawbacks and thrombotic complications in COVID-19 patients and increase the risk of lethal outcomes [156,158–162].

7.1. Alteration in count

Thrombocytopenia is a common occurrence in COVID-19 patients [158,161–164]. The platelet count shows a decreasing trend throughout the disease progression proportional to the severity of the COVID-19 disease [25,158,161–166]. However, it gradually begins to increase after admission in survivors [25,166]. Several retrospective studies showed a more severe reduction in the platelet count in non-survivor COVID-19 patients compared to survivors [25,167]. A low platelet count at the onset of infection can indicate a poor prognosis and a higher chance of mortality [25,166]. A decrease in the platelet count in COVID-19 patients may be associated with several factors including hyper activation of platelets and platelet consumption [25,155,162,168, 169]. However, some studies found that the platelet count increased or did not change in COVID-19 patients [153,156–158,166,170]. Elevated levels of IL-6 and other inflammatory cytokines as characteristic inflammatory conditions in COVID-19 patients may promote platelet biogenesis through increasing thrombopoietin production by hepatocytes [153,157,158,170].

An increase in the mean platelet volume (MPV) is directly related to the severity of COVID-19 disease and the rate of platelet activation [155, 162,166,168]. However, a prospective study of asymptomatic children that tested positive for SARS-CoV-2 infection found a high MPV even without any clinical signs (Table 4) [154]. A possible underlying

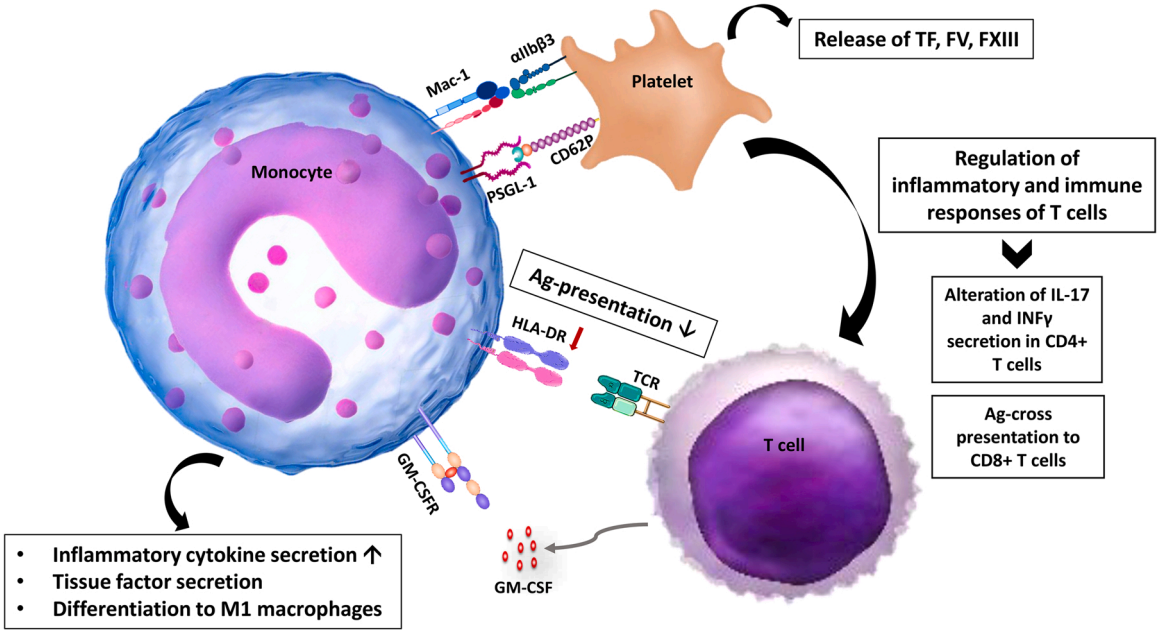

Fig. 2. Interaction between Monocytes-Platelets-T cells in COVID-19 patients. In COVID-19 patients, the relationship between platelets, monocytes, and T cells exacerbates the cytokine storm, enhances coagulopathies, and diminished the antiviral response of T lymphocytes. As shown figure, the monocyte-platelet interaction through Mac-1/αIIbβ3 and PSGL-1/CD62P leads to the release of TF, FV, and FXIII from platelets. On the other hand, activated platelets can affect the T cell responses by altering some CD4+ T cell functions and Antigen presentation to CD8+ T cells. Moreover, excessive secretion of GM-CSF by T cells exacerbates cytokine release and TF production by monocytes and differentiates them toward M1 pro-inflammatory macrophages. A decrease in the HLA-DR expression on monocytes results in more attenuation of the T cell response due to a decrease in antigen presentation.

Table 4
Morphological, functional, and count alterations in red blood cells and platelets of COVID-19 patients.

Author (year) [Ref.]	Sample size (case/control)	Sample	Parameter studied	Study findings
Gumus et al. (2021) [154]	55 children infected with COVID-19 and 60 healthy children	Blood	Platelet Lymphocyte	MPV↑ Lymphopenia
Manne et al. (2020) [156]	41 COVID19 patients	Blood	Platelet	platelet-neutrophil, -monocyte, and -T-cell aggregates↑ Platelet hyperactivity TPO levels↑ Expression of P-selection on plt↑
Si Zhang et al. (2020) [162]	422 COVID19 patients and 201 non COVID19 patients	Blood	Platelet	Thrombocytopenia PCT↓ MPV,PDW,PT,INR, APPT,D-dimer and FDPs↑ PTA↓ Plt hyperactivity Releasing factor V and XIII from platelets
Yang et al. (2020) [164]	1476 consecutive patients with COVID-19	Blood	Platelet	Thrombocytopenia
Paola Canzano et al. (2021) [169]	46 consecutive COVID-19 patients	Blood	Platelet	Expression of p-selectin on plt↑ Granulocyte-plt and monocyte-plt aggregations, Plt activation
Venter et al. (2020) [177]	37 COVID-19 patients	Blood	RBC Platelet	Serum ferritin↑ CRP↑ P-selectin concentrations on plt↑ Plt hyperactivity Erythrocyte-platelet aggregations
Yuan et al. (2020) [180]	117 COVID19 patients	Blood	RBC	RBC and Hb↓
Henry et al. (2020) [181]	49 COVID19 patients	Blood	RBC RDW	progressive increase of RDW
Berzuini et al. (2021) [182]			RBC	Mild to severe anemia, morphology alterations such as polychromasia and basophilic stippling, Rouleaux formation spherocytes, schistocyte Retic count↑

mechanism for a high MPV in COVID-19 patients may be an increase in the release of young platelet in response to platelet destruction after infection and cytokines such as IL-6 [154,157]. A study reported that MPV/platelet count ratio (MPR) had a correlation with COVID-19 severity as the patients with elevated MPR were more prone to severe pneumonia and were at a high risk of death [157].

7.2. Alteration in morphology and coagulation parameters

A short report showed the presence of macro thrombocytes and platelet aggregation in peripheral blood smears of ICU COVID-19 patients while such a manifestation was not observed in stable non-ICU patients [170]. Macro thrombocytes indicate the increased turnover of platelets [168,170] leading to PDW elevation [168]. An autopsy examination showed an increased number of megakaryocytes in the lungs and bone marrow of dead COVID-19 patients [159]. The morphology of BM megakaryocyte indicates the active platelet biogenesis. Moreover, electron microscopy examination of these cells has shown the presence of small amounts of virions in megakaryocytes [159].

Severe thrombocytopenia causes some abnormalities in the results of PT, APTT, INR, D-dimer, and FDP measurement in COVID-19 patients [158,161–163]. The levels of D-dimer [158,161, 166,171–173] and fibrinogen [166,172,174] and the fibrinogen-albumin ratio (FAR) [171] are higher in severe COVID-19 patients and the platelet count and albumin level were lower in these patients compared to non-severe patients [25,169,171]. It has been reported that a high level of fibrinogen in COVID-19 patients can make platelets more active and intensify coagulopathies [162,174].

7.3. Alteration in cell surface markers and function

7.3.1. Platelet and map kinase pathway

An in vitro study showed direct infection of platelets by SARS-CoV-2 through ACE2 and TMPRSS2 expression on platelets [162] while other studies did not report such a finding [156,169,175]. The effect of SARS-CoV-2 on platelets is mediated by activation of the MAPK pathway and production of thromboxane A2, which has been shown to increase in COVID-19 patients [156,162,174]. Activation of the MAPK pathway rearranges the platelet cytoskeleton, which subsequently results in the reinforcement of platelet secretory profile, clot retraction, and platelet aggregation [156,162]. Enhanced platelet-leukocyte aggregates are seen in COVID-19 patients [153,156,162,176] and makes platelets respond to IL-6 by assembling the IL-6R subunits and subsequently activates them significantly [175].

7.3.2. Platelet and hyper activation

Hyper activation of platelets following the SARS-CoV-2 infection is reported by several studies [153,156,157,169]. It can occur in several ways including TLR response to DAMP released from damaged tissues and stimulation of complement receptors on platelets leading to thrombosis and platelet depletion [163,175]. Moreover, Fc receptor activation on platelets may be involved in antibody-mediated platelet count reduction in COVID-19 patients [163,175]. There are reports of the increased expression of αIIbβ3 integrin [153,162] and CD62P (P-selectin) on the platelets of COVID-19 patients, indicating the active state of these cells (Table 4) [156,162,174,177]. TF release by damaged endothelial cells together with decreased levels of nitric oxide and prostacyclin are the possible causative mechanisms of this hyper activation [169]. CD62P (P-selectin) expression as a marker of platelet activation increases in COVID-19 patients, especially in severe ones [153,156,157,162,169,174]. Enhancement of CD62P expression results in augmentation of its interaction with PSGL-1 on leukocytes, which causes platelet-leukocyte aggregation [153,156,162,169]. Furthermore, SARS-CoV-2 and its spike protein can trigger the secretion of factor V, factor XIII, PF4, IL-1β, IL-8, and TNFα from platelets (Table 4) [162]. The PF4 level is significantly elevated in COVID-19 patients and is correlated with disease severity [162]. It has been found that spike protein (S1, not S2) can increase αIIbβ3 integrin activation and CD62P expression on platelets in the presence or absence of agonist stimulation [153,162].

7.3.3. Platelets and other blood cells

The platelet-monocyte and platelet-neutrophil interactions play an auxiliary role in tissue factor secretion, micro-thrombosis formation, and ARDS in COVID-19 [175]. The interrelation between platelets and neutrophils can promote the formation of neutrophil extracellular traps (NETs) [153,158,174], resulting in platelet activation and thrombotic complications in COVID-19 patients [158]. In addition, the platelet-monocyte aggregation has been shown to increase in COVID-19

patients, particularly in severe patients, and is associated with the mortality rate [169,174]. In vitro and in vivo observations indicate that adhesion of platelets to monocytes induces TF expression on monocytes [174,178], which is mediated by CD62P adhesion molecule and αIIbβ3 integrin and subsequently contributes to hyper-coagulation in COVID-19 patients [174]. Aggregation of platelets and T cells is increased in COVID-19 patients, which may affect the T cell inflammatory and immune response [156]. In addition, the platelet-to-lymphocyte ratio is higher in patients with SARS-CoV-2 infection compared to non-infected individuals [179].

7.3.4. Platelets and endothelial cells

Activation of endothelial cells, monocytes, granulocytes, and platelets after viral infection may lead to the secretion of pro-coagulant macrovesicles (MVs) containing phosphatidyl serine (PS) and TF, which plays a role in triggering the coagulation cascade [169]. It has been shown that TF-containing MVs are more abundant in the plasma of COVID-19 patients compared to healthy individuals [169]. According to a prospective study of COVID-19 patients, platelets, monocytes, and granulocytes that express tissue factor are higher in COVID-19 patients compared to healthy subjects [169]. In COVID-19, ACE2 expression on endothelial cells causes some damage to these cells, which in turn leads to an increased expression of VonWillebrand factor and a hyper coagulation state in the patients [158,163,175]. Destructed endothelial cells increase platelet adhesion and activation through collagen-GPIV interaction [175] and cause platelet aggregation in the lungs [25,167,168]. On the other hand, due to lung damage, the function of lung megakaryocytes may be impaired and they may no longer be able to produce platelets efficiently [25,155,158,164–166,170]. Moreover, megakaryocyte secretions, which contain cytokines, may cause further injury to the lungs [170]. Adverse immune mechanisms such as autoantibodies against platelets and immune complexes may result in platelet loss [25,158].

8. Red blood cells

8.1. Alteration in count and morphology

COVID-19 as a viral infection causes some changes in erythrocytes and their hematological markers. One study found that red blood cell counts were lower in COVID-19 patients compared to normal individuals. It is suggested that inhibition of hematopoiesis by this virus in the bone marrow of patients causes anemia [180]. Anisocytosis, some changes in the lipid and protein membrane of circulating RBCs, erythrophagocytosis, and hemophagocytosis by macrophages engulfed with both erythroblasts and mature erythrocytes are reported in COVID-19 patients [181]. Polychromasia and basophilic stippling can be seen in the blood film of patients, probably as a consequence of an increased reticulocyte count [182]. Huge rouleaux formations and auto agglutination are reported in the blood film too [182]. Spherocytes and schistocytes are also observed, probably as a result of membrane damage induced by fibrin strands occurring in vascular thrombosis with microangiopathy [183]. Another common observation is the presence of high percentages of stomatocytes, knizocytes, and cup-shaped erythrocytes in the blood smear of COVID-19 patients. These morphological changes are associated with COVID-19-related anemia [182,184]. One study reported a few mushroom-shaped cells in the blood film [185]. Red blood cell distribution width (RDW) is increased in severe COVID-19 patients so it can be used as a significant predictor and prognostic factor for the severity and kidney damage of COVID-19 patients [181]. The hemoglobin (Hb) concentration tends to decrease during COVID-19. Therefore, a mild to severe anemia may ensue [186]. There are reports of coated RBCs with some complement proteins such as C3b/iC3b/C3dg. C4d is also seen on the RBCs of COVID-19 patients [187].

9. Conclusions

In conclusion, the SARS-CoV-2 infection can change immunological and hematological cells in different aspects. These changes appear to play a critical role in disease pathology and the emerging of clinical manifestations. Infection with SARS-CoV-2 contributes to lymphopenia, neutrophilia, eosinopenia, and mild thrombocytopenia. Severe thrombocytopenia in COVID-19 patients causes abnormalities in the results of PT, APTT, INR, D-dimer, and FDP measurements. Hyperactivation of platelets and development of DIC are observed in COVID-19 patients. Furthermore, SARS-CoV-2 and its spike protein can trigger the secretion of factor V, factor XIII, PF4, IL-1β, IL-8, and TNFα from platelets. Accordingly, SARS-CoV-2 can induce coagulopathy and thrombosis in infected patients. COVID19 as a viral infection causes some changes in erythrocytes and its related hematological markers. Anisocytosis, echinocytosis, spherocytosis, schistocytes, stomatocytes, knizocytes, polychromasia, basophilic stippling, and huge rouleaux formation may appear in the blood film of patients. In addition, the hemoglobin (Hb) concentration tends to decrease during COVID19 disease, therefore, mild to severe anemia may occur in the patients. The virus can cause attenuated immune responses or uncontrolled inflammatory responses, which lead to improper defense against the virus and damage to the host respectively. Neutrophils, as first responders to inflammation, can trigger inflammation and lung injury by production of proteolytic enzymes, ROS, and NET. Furthermore, inflammatory cells like monocytes and macrophages are associated with systemic inflammation, procoagulant syndrome, and cytokine release syndrome, which can result in ARDS condition and multi-organ failure in COVID-19 patients. Large monocytes (high MDW) with vacuolated cytoplasm are another feature of SARS-CoV-2 infection. The presence of DC-SIGN, L-SIGN, and CD147 along with ACE2 expression on DCs makes these cells a vulnerable target for SARS-CoV-2 entry and infection. HLA-DR and co-stimulatory molecules such as CD80 and CD86 are downregulated in DCs following infection with SARS-CoV-2 virus and can subsequently affect the T cell responses and even cause their apoptosis. The absolute count of CD4+ and CD8+ T cells is lower in severe patients. The effect of SARS-CoV-2 on lymphocyte function is a controversial subject and further studies are needed. Lymphocyte morphology is also affected by SARS-CoV-2 and atypical lymphocytes with plasmacytoid features are common in the blood smear of COVID-19 patients. The SARS-CoV-2 can turn normal NK and CD8+ T cells, which are important to eliminate the virus, to exhausted phenotype, which makes the patients prone to other viral infections. Considering these changes may help to manage and treat COVID-19 patients better.

Author contributions

EA: Originated the study, Drafted the manuscript. AO: final approval of the version to be published. ZB: Made substantial contributions to the conception. EZ: revised article for important intellectual content. All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Ehsan Ahmadi: Originated the study, acquired data, Drafted the manuscript. **Azadeh Omidkhoda:** Made substantial contributions to the conception and substantively revised manuscript. **Zahra Bagherpour:** Acquired data and Design some part of the work. **Elmira Zarei:** Design some part of the work. All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Data Availability

Not applicable.

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