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Role of myeloid-derived suppressor cells in viral respiratory infections; Hints for discovering therapeutic targets for COVID-19

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ABSTRACT

The expansion of myeloid-derived suppressor cells (MDSCs), known as heterogeneous population of immature myeloid cells, is enhanced during several pathological conditions such as inflammatory or viral respiratory infections. It seems that the way MDSCs behave in infection depends on the type and the virulence mechanisms of the invader pathogen, the disease stage, and the infection-related pathology. Increasing evidence showing that in correlation with the severity of the disease, MDSCs are accumulated in COVID-19 patients, in particular in those at severe stages of the disease or ICU patients, contributing to pathogenesis of SARS-CoV2 infection. Based on the involved subsets, MDSCs delay the clearance of the virus through inhibiting T-cell proliferation and responses by employing various mechanisms such as inducing the secretion of anti-inflammatory cytokines, inducible nitric oxide synthase (iNOS)-mediated hampering of IFN-γ production, or forcing arginine shortage. While the immunosuppressive characteristic of MDSCs may help to preserve the tissue homeostasis and prevent hyper-inflammation at early stages of the infection, hampering of efficient immune responses proved to exert significant pathogenic effects on severe forms of COVID-19, suggesting the targeting of MDSCs as a potential intervention to reactivate T-cell immunity and thereby prevent the infection from developing into severe stages of the disease. This review tried to compile evidence on the roles of different subsets of MDSCs during viral respiratory infections, which is far from being totally understood, and introduce the promising potential of MDSCs for developing novel diagnostic and therapeutic approaches, especially against COVID-19 disease.

1. Introduction

Respiratory viral infections (RVIs) are among the most important causes of mortality around the world [1–3]. Such viruses facilitate their proliferation by disrupting the body's overall homeostasis [4]. However, the appropriate antiviral immune responses from both innate and acquired types are crucial factors in restoring and preserving homeostasis of the body and thus preventing the viral proliferation [5]. Nevertheless, sometimes exaggerated and uncontrolled immune response following these infections, especially from the innate type, can cause severe inflammation and extensive and even irreparable immunopathogenic damage to the host respiratory system and moreover can inhibit protective antiviral immune responses [6–9]. One of the most interesting and well-described immunosuppressor cell type that has attracted a lot of attention is myeloid derived suppressor cell (MDSC). Its appellation to MDSC is because of the absence of surface marker molecules of natural killer (NK) cells, macrophages, T-cells or B-cells on this cell [10]. In fact, MDSCs are pathologically activated monocytes and neutrophils with remarkable immunosuppressive effects on both innate and adaptive immune responses [11], which were first described around 30 years ago

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[12]. These cells are a highly heterogeneous population of cells derived from immature myeloid progenitors [13] and are proved to play an important role in tumor growth by suppressing the antitumor immune responses [14]. MDSCs consist of several cell types from myeloid origin, including myeloid progenitors, immature granulocytes, immature macrophages and immature dendritic cells with the capability of producing arginase I and reactive oxygen and nitrogen species to suppress immune responses [15,16]. Also, MDSCs have been described as producers of some other factors including interleukin (IL)-10, transforming growth factor beta (TGF-β), and indoleamine 2,3-dioxygenase (IDO), all of which are protective immunity suppressors [17,18]. Frequency of MDSCs can increase considerably during various pathological circumstances like malignancy, infectious diseases, autoimmune diseases, inflammatory diseases and trauma [19–23].

MDSCs have shown specific immunosuppression potentials, which may give rise to disease severity and worsen the clinical condition in patients with different infectious diseases. Studies have indicated extensive proliferation and immunosuppressive function of MDSCs, and consequently a more complicated disease following several viral infections including simian immunodeficiency virus (SIV) [24], murine AIDS (LP-BM5) [25] and hepatitis C virus (HCV) [26]. Furthermore, available results suggest a direct role for MDSCs in exacerbating respiratory viral infections. Based on a study by De Santo et al., peripheral blood MDSCs of patients with influenza A virus (IAV) infection considerably suppress IAV-specific T cell responses through expression of arginase 1 and iNOS which results in higher IAV titer and increased mortality [27]. Their results also showed this immunosuppressive effect on IAV-specific T cells for lung-infiltrating and bone marrow-derived MDSCs of mice [27]. Extensive accumulation of MDSCs in the lungs of IAV-infected mice leads to the deviation from effective T-helper (Th)-1 antiviral immune responses toward probably non-effective responses [28]. Several recent studies also have shown the same immunosuppression pattern for other respiratory viruses like SARS-CoV-2, where excessive proliferation and activation of MDSCs result in decreased number and impaired function of NK cells and T cells [29–33]. In this review we focus on immunosuppressive functions of MDSCs in the respiratory system during viral respiratory infections and evaluating the potential for targeting these functions for therapeutic purposes.

2. Myeloid-derived suppressor cells (MDSCs)

Myeloid-derived suppressor cells constitute a highly heterogeneous population derived from myeloid progenitor and precursor, arrested in different stages of differentiation and characterized by their potent immunosuppressive effects on various T-cell responses [15]. These suppressive cells were recognized for the first time more than 20 years ago in tumors as natural suppressor cells [34], which eventually were called “myeloid-derived suppressor cells” in 2007 [12], according to both their myeloid origin and immunosuppressive effects.

Due to the rapid differentiation of bone marrow-derived MDSCs into mature dendritic cells, macrophages or granulocytes, MDSCs are present at extremely low levels during steady-state in healthy individuals [15]. But their counts significantly extend under pathological conditions such as cancers, infections and chronic inflammatory disorders due to partial blocking of differentiation into mature myeloid cells [15], likely as a compensatory mechanism, which might be associated with limiting bystander tissue damage in these conditions.

Despite the heterogeneous population of MDSCs with various phenotypes and functions, today, MDSCs are subdivided into two main subsets based on their surface markers, morphology and functions including: granulocytic or polymorph-nuclear MDSCs (PMN-MDSCs or G-MDSCs), showing a phenotype and morphology similar to neutrophils, and monocytic-MDSCs (M-MDSCs) with a phenotype similar to monocytes [35]. More recently, another subset of MDSCs identified in S. aureus-infected mice and it termed Eo-MDSC, owing to its phenotypic resemblance to eosinophils. Eo-MDSCs express cluster of differentiation (CD)-11b, Syglec-F, variable levels of CC chemokine receptor (CCR)-3 and low levels of IL-5Ra, as well as high levels of SSC-A [36].

In humans, MDSCs are most often classified as CD34+ cells, which express CD11b and CD33 but lacking markers of mature lymphoid and myeloid cells, particularly the major histocompatibility complex (MHC) class II molecule, HLA-DR, an important marker of mature lymphoid and myeloid cells. Today, the phenotypic characterizations of MDSCs, consisting of M-MDSCs and G-MDSCs, are relatively well defined in humans by means of flow cytometry (Table 1). In addition, another population of MDSCs, believed to be the precursors of total MDSC, have been classified as myeloid progenitors or early-MDSCs (E-MDSC), lacking lineage markers (CD3, CD4, CD8, CD19, CD20) and expressing CD33 and HLA-DR$^{-/lo}$ [37]. The phenotypic markers of human MDSCs are listed in Table 1.

2.1. Mechanisms of MDSC suppressive activity

MDSCs are known for their potent immunosuppressive activities, affecting both innate and adaptive immune responses via several mechanisms. These mechanisms are mainly contact-dependent, which are exerted by cell surface molecules and receptors or production and release of soluble factors [15].

The immunosuppressive impact of MDSCs on adaptive immunity is exerted by suppressing the activation, function and proliferation of T-cell, promoting T-cell anergy, and the formation and recruitment of regulatory T (Treg) cells. These immunosuppressive effects are employed through multiple mechanisms including: (1) depleting the microenvironment of important nutrients factors for T cell activation and proliferation such as L-arginine and L-tryptophan (L-Trp) by expressing high levels of Arginase-1 (Arg-1) [38,39] and indoleamine 2, 3 dioxygenase (IDO), respectively, (2) producing oxygen species such as nitric oxide (NO) [40,41], Radical Oxygen Species (ROS) and Peroxynitrite (ONOO-) (PNT) [42], and (3) producing immunosuppressive cytokines like TGF-b and IL-10, and eventually inducing the development and recruitment of Treg cells [43].

Furthermore, MDSCs also have the ability to interact and regulate the function of other immune cells such as innate immunity cells through several mechanisms including: (1) downregulation of IL-12 production by macrophages as well as driving macrophage polarization into suppressive M2-macrophages [44,45], (2) impairment of the development, function and cytotoxicity of NK cells [46,47], (3) impairment of the development and functions of dendritic cell (DC), as a bridge between innate and adaptive immunity, and (4) blocking the ability of DCs in inducing T cells to produce interferons (IFN)-γ [48,49]. These immunosuppressive effects of MDSCs are presented in further detail in Fig. 1.

2.2. Subset-specific mechanisms

Although the immunosuppressive activity is the main characteristic of all MDSCs, the nature of suppression can differ depending on their subpopulations. The G-MDSCs represent high ROS levels and low levels of NO, while M-MDSCs are the opposite. However, both subsets express elevated level of arginase 1 [50]. Interestingly, despite the different frequencies and mechanisms of action of G-MDSCs and M-MDSCs,

Table 1
Various phenotypic markers of human MDSCs.

Population	Molecular markers	References
Total MDSC	CD33+HLA-DR−	[37,129, 130]
	CD33+CD11b+CD14-	
G-MDSC	$CD33^{+}$ $CD11b^{+}$ $CD15^{+}$ $CD14^{-}$ $HLA\text{-}DR^{-}$ $CD66b^{+/-}$	
M-MDSC	$CD33^{+}$ $CD11b^{+}$ $CD14^{+}$ $CD15^{-}$ $HLA\text{-}DR^{low/-}$	
Early- MDSC	$Lin^{-}HLA\text{-}DR^{-}$ $CD33^{+}$ $CD11b^{+}$	
G-MDSC	$CD33^{+}$ $CD11b^{+}HLA\text{-}DR^{-}$ $CD15^{+}$ $CD14^{-}$	
M-MDSC	$CD33^{+}$ $CD11b^{+}HLA\text{-}DR^{-}$ $CD14^{+}CD15^{-}$	

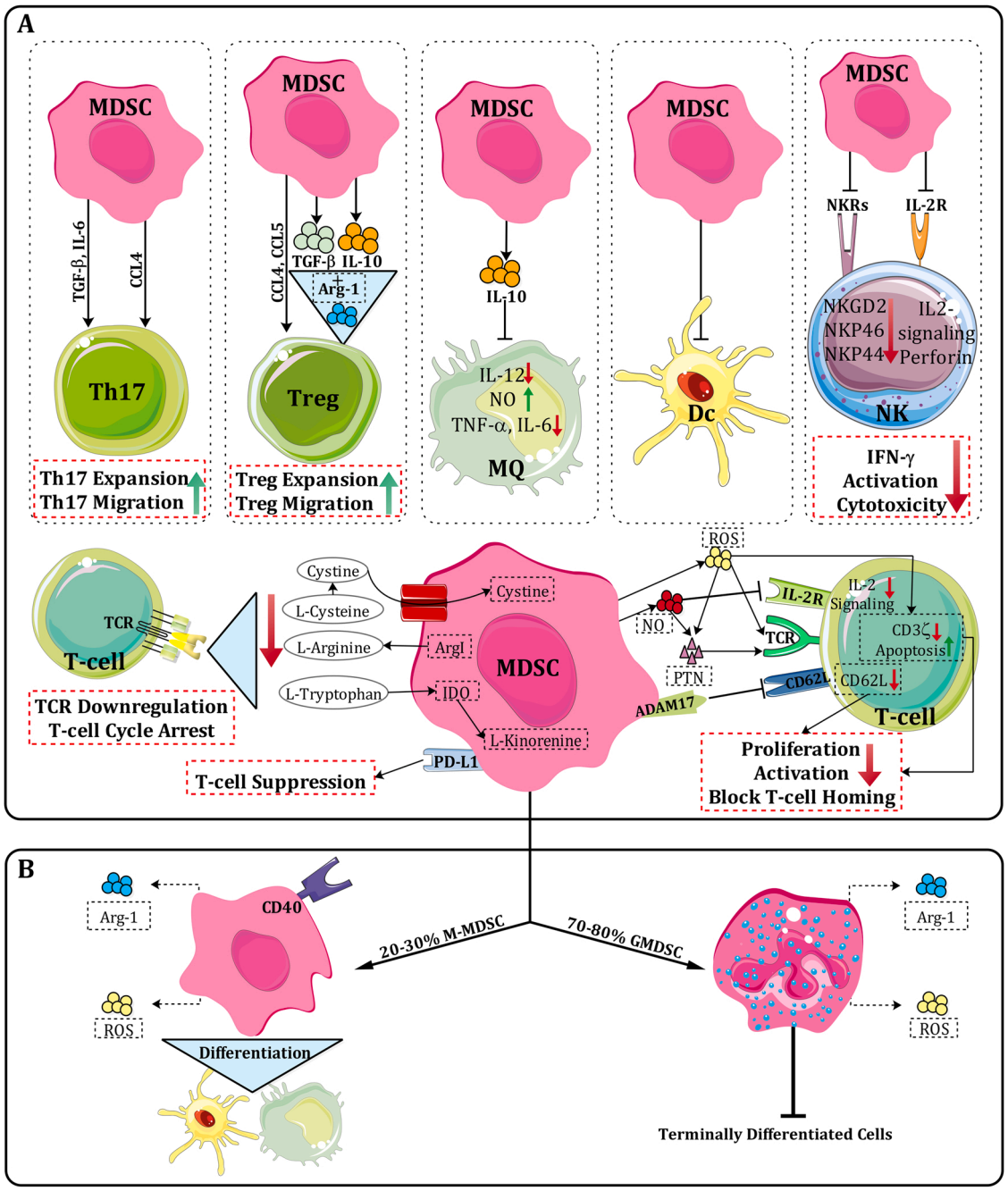

Fig. 1. Suppressive functions mediated by MDSCs in innate and adaptive immune responses; (A) Immune suppression by MDSC require cell-cell contact or soluble mediators, which use multiple mechanisms, including (1) eliminating the microenvironment of important nutrition factors for T cells (such as L-arginine, L-cysteine, and L tryptophan), which lead to suppression of T cells proliferation via G0/G1 cell cycle arrest, and also T cell anergy via downregulation of TCR ζ in CD4, CD8 and NKT cells [121,122]; (2) producing oxygen species such as NO, ROS, and PNT: the produced NO inhibit T cells functions via blocking the main signaling pathways coupled to the IL-2 receptor (IL-2R) [40,41]. Produced ROS induces T-cell apoptosis [42]. Moreover, produced peroxynitrite and Ros via inducing nitration of tyrosines in several sites of TCR and CD8 molecules leading to disrupt peptide–MHC–TCR interaction and induces unresponsiveness of T cells to specific antigens [42]; (3) producing immunosuppressive cytokines (TGF-band IL-10), (4) disruption of T cells homing through the ADAM17 expression, which downregulate L-selectin on naïve T cells and E-selectin on the vasculature [38,123]; (5) inducting T regulatory (Treg) cells via an IL-10-, TGF-β and ARG1-dependent mechanism [43], (6) attracting Tregs to inflammatory condition via production of CCL4 and CCL5 chemokines [124]. (7) Upregulation of PD-L1 on MDSCs surface [38,39]; (8) inducing, and also recruiting Th17 cells [125]. (B) Different subpopulations of MDSCs; despite the terminally differentiated G-MDSCs represent about 70–80% of all MDSCs [50], the immunosuppressive effects are considered equal in both populations, which is due to the more immunosuppressive activity of M-MDSCs per-cell basis, and also have the ability to differentiate into mature dendritic cells and macrophages, especially tumor-associated macrophages (TAMs) [126].

induction of T-cell hypo-responsiveness generally considered equal between both populations [15,50].

Despite several studies reported negative role of MDSCs in cancer immunity, recent investigations have shown that MDSCs play an important regulatory role in controlling inappropriate inflammatory immune responses to pathogens in various conditions, subsequently preventing autoimmune responses and tissue damages. In this respect, MDSCs display dual-effect; they exert beneficial and protective effects in the host via reducing immune-mediated pathology caused by collateral damage associated with potent anti-pathogen immune responses. On the

other hand, MDSCs inhibit or limit the formation of efficient immune responses against pathogens, so favoring the pathogens persistence and long-term infections. In the following we discuss the MDSC roles in lung disorders, particularly viral infections and coronavirus disease (COVID-19).

3. Lung-residing myeloid-derived suppressors

Innate immune cells such as resident macrophages, innate lymphoid cells (ILCs), dendritic cells, and NKs are crucial in providing the first defending line against inhaled pathogens and keeping the homeostasis within the lung [51]. Recently, newly identified cell types of innate immunity like MDSCs add other layers of complexity to the innate defence shields in the pulmonary mucosal environment. Despite enhancing our understanding of the regulatory and pathophysiological roles of MDSCs in mice model systems, their importance for human lung pathologies has remained poorly defined so far.

Rising evidence showed important roles of MDSCs during pathological conditions of the lungs including cancers, inflammatory and infectious diseases, respiratory viral infections, etc. Several factors involved in the recruitment and accumulation of MDSC-type cells in lung disorders including prostaglandins 2 (PGE2), GM-CSF, CCL2, IL-1β, IL-6, S100 protein family, Toll-like receptor (TLR) ligands like lipopolysaccharide (LPS), and allergens [52–55]. It has been shown that MDSCs perform could significant dual roles during inflammatory and infectious lung diseases such as protective potential against developing asthma by suppressing the Th2-mediated allergic inflammation [52,53], or through promoting T-cell dysfunction and blunt immune responses, may worsen the condition of some lung diseases such as chronic obstructive pulmonary disease (COPD) [56], tuberculosis (TB) [57], etc.

On the other hands, some studies showed different result in respiratory viral infections. During IAV infection, activation of TLR7 by the virus RNA induces MDSC differentiation, which subsequently inhibits the suppression of T-cell responses [28]. In Jα18$^{-/-}$ mice, selectively deficient in invariant NKT (iNKT) cells, IAV infection was showed to trigger MDSC activation, which restrained anti-IAV immune responses via the activity of arginase-1 and inducible iNOS. This MDSC expansion can lead to higher virus titer and increased mortality. Interestingly, the injection of iNKT cells in infected Jα18$^{-/-}$ mice resulted in the reduction of the total number of lung MDSC and the subsequent restoration of immunocompetence. These findings were extended to humans by showing the suppressive activity of CD11b^{+} cells from patients with recent IAV infections [27]. CD11b+Gr-1+ cells were shown to be expanded in response to highly pathogenic H5N1 and H1N1 influenza viruses, which contributes to T-cell suppression by expression of arginase-1 in the lungs and subsequently consumption of L-arginine.

These contradictory effects between various disease may result from different kinetic parameters of involved MDSCs and their downstream responses [27,58]. Collectively, growing data indicates that MDSCs as immunosuppressive myeloid cells playing crucial roles in inflammatory and infectious pulmonary diseases. Although MDSCs suppress inflammation in various lung diseases, they may also promote pathogen resistance by suppressing anti-pathogen immune responses and induce lung fibrosis under certain conditions. A better and comprehensive understanding of MDSCs biology, their precise mechanisms of actions, and their effects in various diseases will allow developing the most appropriate treatments in distinct conditions.

4. Role of MDSCs in coronavirus infection

In general, MDSCs may play dual roles in viral infections: (1) being detrimental to the host by immunosuppression and (2) being beneficial by dampening inflammation and preventing tissue damage [59,60]. Roles of MDSCs are subject to pathogen's virulence mechanisms, disease stage, and the pathology of infectious disease [59].

Various studies have demonstrated an increase in circulating MDSCs accompanied by lymphopenia and pyroptotic cell death in patients with COVID-19 [33,61,62]. Moreover, patients with severe COVID-19 admitted to the intensive care unit (ICU) had reduced frequency of innate and adaptive cytotoxic cells including NK cells and T-lymphocyte, which paralleled the MDSC expansion and high level of cytokines [63]. A positive correlation has been observed between the frequency of MDSCs with viral loads and hospitalization duration, whereas negatively associated with T cell and NK cell counts and serum albumin [31].

It has been shown that COVID-19 infections lead to impaired T cell and antibody responses to SARS-CoV-2 and subsequently high risk of cytomegalovirus co-infection in transplant recipients. The data has shown higher frequencies of M-MDSCs and G-MDSCs among COVID-19 patients, which negatively correlated with specific T cells frequencies and subsequent responses [62]. Rendeiro et al. [64] demonstrated a profound imbalance in COVID-19-related immunity, characterized by expansion of MDSCs, especially G-MDSCs, and T cell exhaustion that may offer avenues for more effective therapeutic options for COVID-19 patients. The finding suggested that G-MDSCs and other myeloid cells represent uncontrolled negative feedback, which ultimately contributes to the establishment of pan-immunosuppression and subsequent dysregulated adaptive immune responses. In another study, COVID-19 has been characterized by decline in the counts of myeloid and plasmacytoid dendritic cells (mDC and pDC) and increase in the number of MDSCs, as well as the redistribution of monocytes toward intermediate subsets [65].

Furthermore, a positive correlation between the increased viral load and the severity and progression risk was reported. Therefore, it provides another possible reason showing that MDSCs suppress the antiviral immune response in severe infection [66]. In a cohort study in Japan, it was reported that G-MDSCs were expanded transiently in survivors of severe COVID-19. The elevated G-MDSCs may prevent deleterious immune responses and serve as prognosticator in these patients [67]. In another study on patients with ARDS, significant elevation of LOX-1G-MDSCs was reported, which their potent immunosuppressive properties may prevent patients from resolving infection [68].

Some studies have demonstrated various mechanisms for suppressing T cells activities and subsequent immune responses. Although a significant decrease of both CD4^{+} and CD8^{+} T cells has been reported in patients with severe form of COVID-19 [69], which negatively correlated with their survival, the exact mechanisms are unknown so far. Impairing the proliferation of T cells by CD3ζ chain downregulation could be a potential mechanism, which has previously been shown concerning MDSCs for other disorders [70,71]. Significant elevated M-MDSCs has been reported, only in blood but not in respiratory mucosa, in both COVID-19 and influenza patients, which was associated with the severity of COVID-19 disease. The patients showed a lower count of T cells and significantly downregulated level of CD3ζ chain expression on CD+4 and CD+8T cells [72]. The data reported that isolated M-MDSCs from COVID-19 patients, through Arg-1–dependent mechanisms, suppressed T cell proliferation and IFN-γ production, which significantly associated with the severity of the disease [72]. A study by Sacchi et al. showed the abundance of MDSCs in the lungs of patients with COVID-19, proposing a potent association between the G-MDSC percentage and the fatal outcome of coronavirus disease. The results indicated that G-MDSCs, through iNOS- and TGF-β-mediated mechanisms, gave rise to the inhibition of IFN-γ production by T-cells and probably the suppression of virus elimination [30]. Moreover, GM-CSF was introduced as a key factor for driving the differentiation and recruitment of MDSCs [30]. In addition, it was reported that a significant increase of IL-6 in non-survivors was associated with decrease in G-MDSCs, suggesting that immune suppression, possibly mediated by expanded MDSCs, could be highly beneficial in managing inflammation.

In COVID-19-associated acute respiratory distress syndrome (ARDS) patients, T cell defects were correlated with the expansion of M-MDSCs. In these patients, enhanced activity of IDO and arginase were observed,

especially in severe forms of the disease, which can have a negative effect on T cell functions, mainly $CD8^{+}$T cells. The data showed a correlation between the increased activity of IDO and arginase with lymphopenia that could be explained by reduced T cells proliferation. Therefore, making up for arginine deficiency as the adjuvant therapy was suggested to restore normal T cell function and help virus clearance [29].

Another study demonstrated a reduction in the frequencies of both the population of MDSCs and the TGF-β at convalescent phase, which was associated with increasing the levels of inflammatory mediators in plasma. The data revealed that MDSCs increased up to 90% of total circulating mononuclear cells in severe diseases, 25% in mild diseases, and then reduced with recovery [33]. They suggested a dual role for MDSCs; one in exerting the early protective function during the acute COVID-19 phase, which decreases inflammation and T-cell hyperactivation, and the other in unfavorable significant suppression of protective immune responses. Some studies have shown a positive correlation between the noticeable increase of IL-6, IL-8 and GM-CSF levels with the expansion and differentiation of both subsets of MDSCs in patients with severe COVID-19 [30,33,67,72]. Moreover, a significant expansion of M-MDSC–like cell subset has been observed in patients with severe COVID-19 disease in an IL-6 and IL-10 cytokine-dependent manner [73].

Dean et al. measured a great number of accumulated $Arg1^{+}$G-MDSC expressing NOX-1 and NOX-2 (important for the ROS production) in the lungs of patients who died from COVID-19 complications. Their results showed that an increased level of Arg^{+}G-MDSCs impaired T cell receptors by decreasing T cell receptor ζ chain expression and hampering the function of endothelial cells [74]. In vulnerable populations with COVID-19, the expansion of CD33 MDSC has been reported. While sialylation is negligible for SARS-CoV-1, it has been revealed that spike glycans are sialylated in SARS-CoV-2. Release of SARS-CoV-2 sialylated secreted glycoproteins (SGP) would allow potential binding to CD33-related (CD33-r) Siglecs. Consequent CD33 MDSC activation would result in impairment of T cell and B cell responses via arginase 1, along with immunosuppressive cytokines TGF-β and IL-10. Moreover, these cells release NO and ROS, which would be associated with tissue damage. The interaction between viral SGP and CD33-r Siglecs requires testing to be confirmed or excluded. Genotyping of severe COVID-19 cases allows confirmation or rejection of this model of SARS-CoV-2 pathogenesis [75]. Monocytic MDSCs, identified by markers $CD14^{+}$ and $HLA\text{-}DR^{Low}$, showed a major increase in COVID-19 patients with immune dysregulation. Furthermore, elevated calprotectin (S100A8/S100A9) and accumulation of immature subsets of neutrophils with an immunosuppressive profile (G-MDSCs) were reported in blood and lungs of patients with severe COVID-19 infection [61,76,77]. Higher plasma level of S100A8/S100A9 was correlated with developing a severe form of COVID-19. S100A8 could significantly govern high inflammation in severe COVID-19 and COVID-19-associated ARDS through elevated pulmonary recruitment of both MDSC populations, mediated by stimulating the mobilization of TLR4-expressing MDSCs and TLR4/MD-2 pathways [55].

Collectively, it was shown that MDSCs suppressed proliferation and activities of T cells in severe COVID-19 cases by various mechanisms including: (1) enhancing the activity of IDO enzyme [29], (2) releasing Arginase-1 [72,74,75] and subsequently arginine depleting and reducing T cell proliferation, (3) reducing IFN-γ production, (4) downregulating the expression of T cell receptor ζ chain and subsequent impairing of T cell receptors [72,74], (5) production of the immunosuppressive cytokines TGF-β and IL-10 [30,33,75], or (6) iNOS-mediated mechanisms and subsequent inhibition of the IFN-γ production that can suppress virus elimination [30].

Furthermore, the significant expansion of both G-MDSCs and immature forms of neutrophils with immunomodulatory properties has been shown in the severe COVID-19 cases, revealing a strong polarity shift toward Th17 cells and enhancing their frequencies, while suppressing Th1 cells [78]. Previous studies have shown that G-MDSC could promote Th17 differentiation via NOS- and arginase-dependent mechanisms [79,80]. Beside the suppressive effect on T cell proliferation and activation, MDSCs are involved in downregulation of cytokine production by macrophages, impairment of NK-cell function, induction of Treg expansion, and less reported B-cell suppression [33,81,82].

On the other hand, platelet activation is contributing to thromboembolic complications during COVID-19 infection. Interestingly, Sacchi et al. [83] have introduced G-MDSC as a new player in platelet homeostasis that highlights a novel role of MDSC in driving the pathogenesis of COVID-19. The data substantiated that G-MDSCs, via decreasing L-arginine and subsequent inducing of GPIIb/IIIa complex (PAC-1) expression, could directly trigger the activation of platelets during COVID-19.

Unique metabolic profiles of immune cells like MDSCs were introduced as important reasons for different responses in SARS-CoV-2 patients than other infections; and their expansion could apply for distinguishing mild and severe COVID-19 from other viral diseases [84]. Interestingly, a significant increase in specific population of M-MDSC, i.e. CPT1a+VDAC1+DR-M-MDSCs, was found in patients with COVID-19, which express high levels of voltage-dependent anion channel (VDAC) and carnitine palmitoyltransferase 1a (CPT1a), a mitochondrial membrane enzyme that is associated with both inflammasome activation and ROS production [85,86], in association with the severity of disease. Since inflammasome activation is an important step in the pathogenesis of COVID-19 disease, CPT1a can play a potential role in contributing to SARS-CoV-2 pathogenesis by activation of inflammasome [87]. Moreover, a significant increase of G-MDSC, i.e. VDAC1+HKII+G-MDSCs, has been observed with concurrent high upregulation of Hexokinase II+ and VDAC, previously were known for preventing apoptosis [88]. Therefore, this unique metabolic signature of G-MDSCs and M-MDSCs in patients with severe COVID-19 leads to dysfunctional immune response and provides further information for predicting and tracking disease severity or designing metabolic therapeutic targets.

Collectively, these data emphasize the important roles of MDSC subsets and their related markers in COVID-19 disease (summarized in Table 2), which could be another key piece of the puzzle of enhancing our knowledge and subsequent progress toward developing novel therapeutic and diagnostic approaches against severe forms of COVID-19 disease.

5. Mechanisms of MDSC-mediated immunosuppression in viral infections

Several molecular mechanisms have been shown to be involved in MDSC-derived T-cell suppression including catabolism of L-arginine through arginase 1 and iNOS enzymes, ROS production, and secretion of immunosuppressive cytokines like TGF-β and IL-10 [81].

The main mechanisms applied by MDSCs to suppress T-cell function are described below:

5.1. L-Arginine metabolism

One of the first described mechanisms in MDSCs is depletion of amino acids, particularly arginine, which are required for T-cell function. Rodriguez et al. have shown that moderate decrease in L-arginine uptake influences T-cell survival, while deprivation of this amino acid from the culture medium inhibited T cell proliferation [11,89].

Arginase 1 and iNOS are two enzymes involved in L-arginine metabolism using L-arginine as a substrate to generate urea and L-ornithine or NO, respectively. L-arginine deficiency through arginase 1 activity dampens T cell proliferation by decreasing the expression of T cell receptor ζ chain (CD3ζ) and preventing the expression of cell-cycle regulators in T cells (cyclin D3 and cyclin-dependent kinase 4). In a study on hepatocellular carcinoma, methylglyoxal from MDSC was identified to be transferred to T cells and subsequently paralyze T cell function by

Table 2
MDSC subsets, their related markers and possible mechanisms of action in Covid-19 disease severity.

	MDSC subtypes	Mechanism of action and Outcome	Refs
MDSCs Populations in Covid-19 Patients	Massive expansion of MDSCs in patients with severe disease	Suppressed T-cell functions, probably by TGF- β secretion Lower frequency of precursor $CD8^+$ T cells with a parallel higher frequency of EM and terminally differentiated (TEMRA) $CD8^+$ T cells	[33]
	Significant evaluated M-MDSCs only in blood but not in respiratory mucosa,	Suppressed T cell proliferation and IFN-γ production in an Arg-1–dependent mechanism Significant downregulated expression of the CD3ζ chain on $CD4^+$ and $CD8^+$ T cells	[72]
	Transiently expansion of G-MDSCs only in severe cases	The elevated G-MDSCs may prevent deleterious immune responses and serve as prognosticator in these patients Improved clinical outcome	[67]
	Significantly increased of the G-MDSCs in non-survivors	Inhibiting SARS-CoV-2 specific T cell response inhibiting IFN-γ release by T cell via iNOS- and TGF-β-mediated mechanisms correlated with IL-6, IL-1β, TNF-α, and IL-8 plasma levels	[30]
	Significantly increased of the expansion of both MDSC subsets in severe disease	Lymphopenia decreased T cell proliferation and activity, especially in CD8 T cells mediated by enhanced activity of IDO and arginase	[29]
	Significantly increased levels of a specific Covid-19 population of M-MDSC expressing CPT1a and VDAC	Positive correlation with disease severity Dysregulated inflammation	[127]
	Significant increased MDSCs	Decreased number and Impaired function of NK cells and T cells	[30–32]
	Robust increased Specific Covid-19 Hexokinase II+ G-MDSC	Increased with severity	[127]
	Significant increased LOX-1 + G-MDSCs in patients with severe Covid-19 with ARDS	Potent immunosuppressive properties	[68]
	Increased frequency of CD14 +HLA-DRlo/neg MDSCs	Decreased T cell and NK cells counts Increased inflammation levels and viral loads	[31]
	Significant increased Arg^+G-MDSCs expressing NOX-1 and NOX-2	Decreased T cell receptor ζ chain (CD3ζ) Increased markers of endothelial cell dysfunction	[74]
	Extremely high-level increases CD33 MDSC numbers in severe Covid-19 infection	Impairment of T cell and B cell responses via arginase 1, along with immunosuppressive cytokines TGF-β and IL-10. Tissue damage by releasing NO and ROS	[75]
	Significant increasing of M-MDSC–like cell subset in sever disease	IL-10 cytokines Immunosuppressive effects	
	Expansion of MDSCs, especially G-MDSCs in sever Covid-19	T cell exhaustion Dysregulation of adaptive immune responses	[64]
	Significant increase of G-MDSCs-like $LOX\text{-}1^+$ LDGs cells in sever Covid-19	Impaired lymphocyte responses Increased activation and recruitment of neutrophils	[128]
	G-MDSC	Platelet activation Inducing GPIIb/IIIa complex (PAC-1) by decreasing L-arginine	[83]
	Significant increase of MDSCs in ICU patients with severe COVID-19	decreasing cytotoxic activity of innate and adaptive cells. Decreasing frequency of NK cells and T-lymphocyte	[63]

depletion of L-arginine, and by rendering L-arginine containing proteins non-functional through glycation. This arginine depletion is different from that of arginase activity and requires direct cell–cell contact. This finding needs to be investigated in other conditions [90]. Increased MDSC-derived nitric oxide (NO) production has been shown to inhibit IL-2 signaling in T cells by blocking the phosphorylation of JAK3 (Janus Kinase 3) and STAT (signal transducer and activator of transcription)-5, to reduce MHC class II expression or to induce T cell apoptosis [91,92]. In COVID-19 patients, levels of arginase 1 and IL-6 in plasma were found to be dependent on disease severity, ranging from lower levels in mild disease to higher concentrations in severe cases. Isolated M-MDSCs from these patients were shown to be functional and capable of suppressing the proliferation of T cells and the release of IFN-γ. When L-arginine was added to M-MDSC cocultures, the level of IFN-γ was restored [72].

Furthermore, L-arginine can enhance the survival capacity of T cells by controlling glycolysis and mitochondrial activity through interaction with transcriptional regulators (PSIP1, BAZ1B, and TSN) [89]. Mitochondrial dysfunction can facilitate the pathogenesis of Covid-19 by altering various host metabolic pathways like mitochondrial DNA (mtDNA)-induced inflammasome activation, and subsequent suppression of immune responses [93]. A link has been shown between L-arginine and improving mitochondrial function and reducing apoptosis of bronchial epithelial cells after injury [94]. Although arginine depletion and lymphocyte mitochondrial dysfunction have been extensively studied as an immunosuppressive mechanism of MDSC in malignancies [89], mechanistic strategies must be considered in coronavirus patients for strengthening these conclusions and developing therapeutic trials.

5.2. ROS

L-arginine deprivation can result in the generation of superoxide anion, which can further participate in the production of reactive nitrogen species (RNS) and other ROS. G-MDSCs show upregulated STAT3 and NADPH oxidase (Nox) activity, leading to the release of high levels of ROS. Beyond their role in immunosuppression, ROS prevents MDSC differentiation into mature cells. Cytokines such as TGF-β, IL-6, IL-3 and IL-10 are involved in the induction of ROS production by MDSCs.

The interaction of superoxide anion and NO forms peroxynitrites, which is associated with modification of TCR and CD8 molecules, making $CD8^+$ T-cells unable to bind phosphorylated MHC, rendering antigen-specific tolerance of $CD8^+$ T-cells in cancer. Superoxide anion can also participate in the formation of hydrogen peroxide (H_2O_2), which contributes to T-cell dysfunction [81,95].

NO is considered to exert both antiviral and pathogenic outcomes in viral infections. Akaberi et al. reported that NO prevented in vitro

replication of SARS-CoV-2 and targeted the activity of its protease [96]; yet, after the second step of COVID-19 disease, cytokine storm and the following free radical generation lead to organ damage [97].

5.3. Other less-investigated mechanisms

Mechanisms mediated through IL-10 and IDO are among the most commonly studied in cancer, autoimmune disorder, and chronic infection [98,99]. IL-10 produced by MDSCs and other cells can induce MDSC expansion in a positive feedback loop with immunosuppressive effects on T cell immunity. IL-10 can increase the expression of PD-1 and PD-L1 on MDSCs, limiting the immune response activation directly through interaction with immune cells that express the corresponding ligands. Moreover, IL-10 can impair the specific immune responses in an indirect way by promoting the expansion of Treg cells and by preventing the maturation and activation of DCs, NK cells, and macrophages [99].

In patients with mild COVID-19, monocytes were found to be the main producers of IL-10, while M-MDSCs dominantly produced IL-10 in severe cases of the disease [32]. It has also been reported that in the latter group of patients, suppressive monocytes promote a significant decline in the quantity and function of mucosal-associated invariant T (MAIT) cells through IL-10 [100].

IDO is a tryptophan catabolic enzyme in M-MDSCs that converts tryptophan (Try) into kynurenine (Kyn). This conversion exerts important immunosuppressive impacts through the activation of Treg cells and MDSCs, limiting the function of effector T cells and inducing T cell death. In COVID-19 patients, especially those with ARDS, higher IDO activity has been reported [29].

6. Therapeutic MDSC-targeted strategies

There are various strategies to target MDSCs, regarding their beneficial or deleterious role in different viral infections. In case of COVID-19, it is still unknown whether MDSCs have an anti-inflammatory effect or they are involved in exacerbating inflammation [30,59,60]. However, some studies provided rationale for targeting MDSCs and rescuing T cell responses in treating severe COVID-19 [30].

Several therapeutic strategies have already been proposed aimed at inhibition or elimination of MDSCs, which involved various steps of MDSCs accumulation and activities such as (1) preventing MDSC generation (e.g. bisphosphonates that decreases prenylation of MMP9), (2) inhibition of MDSC recruitment and migration from the bone marrow and circulation (e.g. CXCR −2 and CCR5 inhibitors, CSF1R antagonists); (3) depleting MDSCs (e.g. anti-GR1 antibody), (4) direct blocking of the suppressive activity of MDSCs (e.g. cyclooxygenase-2 (COX-2) inhibitors, STAT3 inhibitors, Phosphodiesterase-5 (PDE-5) inhibitors (tadalafil, sildenafil, and vardenafil)), (5) promoting MDSCs differentiation into mature and non-suppressive cells (e.g. 1,25-dihydroxyvitamin D3) [81,101].

It has been shown that the increased inflammatory responses in severe COVID-19 through depleting arginine lead to the impairment of T cells functions, endothelial cells, and ultimately pulmonary damage [74]. Therefore, arginase 1 inhibition and/or arginine supplementations have been suggested as adjuvant therapeutic interventions in patients with severe COVID-19 [29,74]. An in vitro study showed that arginine supplementation could significantly restore the proliferative capacity of T cells in COVID-19 patients, suggesting arginine supplementation as an efficient adjuvant therapy in COVID-19 ICU patients, which could decrease infection and mortality by reducing MDSC-induced immunosuppression and inducing virus clearance [29].

Furthermore, numerous studies have demonstrated that vitamin D deficiency correlates with a high level of CRP and exacerbated ARDS in COVID-19 infection. An association has also been supposed between vitamin D status with cytokine storm in COVID-19 patients [102]. Together, it seems that vitamin D plays a role in reducing unregulated inflammation and mortality in COVID-19. Similar to other immune cells, MDSCs express vitamin D receptors (VDRs) and can be influenced by vitamin D intervention. It has been shown that treatment with the active form of vitamin D via the VDR significantly decreases the immunosuppressive activity of MDSCs [103,104]. It also seems that vitamin D supplementation reduces the ARDS in COVID-19 patients by lowering hyperinflammatory responses, mediated by macrophages and MDSCs in the lungs of patients [104].

IL-6 is an important cytokine involved in the cytokine storm of COVID-19, which can mediate the expansion of MDSCs in COVID-19 patients [72]. A pilot study by Luo et al. assessed the effect of an IL-6 inhibitor (Tocilizumab) in COVID-19 patients and reported a gradual decrease of IL-6, good response and improvement of clinical outcomes in most patients [105]. Repeated doses of Tocilizumab were found to be safe and effective. Tocilizumab was suggested as an efficient drug for patients with severe COVID-19 with the ability to reduce mortality in severe cases [106]. However, in some trials, Tocilizumab did not affect the percentage of the MDSC subset and was not effective in preventing death or intubation of hospitalized patients with COVID-19 [32,107]. Despite this, Tocilizumab-treated COVID-19 patients had less severe infections than the placebo control group [107].

It is postulated that prostaglandin D2 (PGD2) acts as a central mediator of lymphopenia in Covid-19 disease through PGD2/DP1 and PGD2/DP2 signaling paths. In PGD2/DP2 pathway, PGD2 induces IL-13 release and subsequently upregulates M-MDSCs. This M-MDSC activation downregulates the virus-specific T cell response, leading to lymphopenia. Hence, an antagonist of the PGD2/DP2 receptors (e.g. Ramatroban) can prevent IL-13 secretion and serve as an immunotherapy for immune dysfunction and lymphopenia in Covid-19 patients [108,109].

In another study reveals that the expression of alarmin S100A8, as one of the main proteins of MDSCs, was augmented in both SARS-CoV-2 infections and a mouse coronavirus, which through bounding to TLR4 causing an abnormal antiviral immunity. The data reported that inhibition of this binding by Paquinimod could resolve the immune disorder, regain antiviral responses and contribute to virus elimination in mice, providing novel therapeutic interventions for Covid-19 [110]. Moreover, Resatorvid, as a selective TLR4 inhibitor, significantly reduced the proportion of aberrant immature neutrophils that were considered as MDSCs and improved the health status of coronavirus-infected mice [110]. Given that the S100A8-TLR4/MD-2 axis may induce MDSCs recruitment from bone marrow in COVID-19 [55], it is supposed that other effective drugs against this axis, such as Eritoran as a TLR4/MD-2 antagonist, can be considered for treating patients with severe COVID-19. Moreover, the therapeutic administration of Eritoran has been shown to improve the clinical symptoms and to decrease the levels of inflammatory chemokines/cytokines and mortality in IAV-infected mice [111].

As mentioned above, targeting chemokines such as CXCR2 (e.g., AZD5069) and CCR5 (e.g., leronlimab) could target recruitment and migration of MDSCs, introducing a potential therapeutic strategy for COVID-19. A study by Patterson et al. targeted the CCL5-CCR5 pathway using leronlimab, a CCR5 blocking antibody, in severe COVID-19 patients. The results showed a rapid reduction of plasma IL-6 and inflammation, restoration of T cell lymphocytopenia and the CD4/CD8 ratio, and reduction of SARS-CoV-2 plasma viremia following leronlimab-mediated CCR5 blockade. Consistent with the decrease of IL-6 level in plasma, single-cell RNA-sequencing exhibited declines in transcriptomic myeloid cell clusters expressing IL-6 and interferon-related genes [112] (Table 3).

Corticosteroids show beneficial effects for COVID-19 patients on short-term mortality and reducing the need for mechanical ventilation [113]. However, effective evidence related to corticosteroids to treat COVID-19 is still limited and reliable data and investigations to further knowledge on their benefit and harms are needed. Some COVID-19 patients treated with high-dose but no low dose of corticosteroids showed a prolonged viral shedding and decreased clearance, which may

Table 3
Therapeutic strategies to target MDSCs in Covid-19.

Therapeutic agents	Mechanism of action	Outcome	Model	Refs
Ramatroban	Targeting PGD_2/DP_2 pathway	Preventing MDSC upregulation	Proposed	[108, 109].
Tocilizumab	Inhibiting IL-6-IL-6R	Improving clinical outcomes Reducing mortality in severe cases Reducing severe infections, but not effective in preventing death Not affect the percentage of the MDSC subsets	Tested in human	[105,106] [32,107]
Paquinimod	Blocking S100A8/A9-TLR4 binding	Reducing aberrant neutrophils	Tested in mice	[110]
Resatorvid	Blocking TLR4 signaling	Reducing aberrant neutrophils	Tested in mice	[110]
Arginine supplementation	Probably through restoring the availability of arginine	Partial recovery of T cell proliferation	Tested in cell culture	[29]
Vit D	Direct targeting through VDR	decreasing the immunosuppressive activity of MDSCs	Proposed	[103,104]
Leronlimab	An inhibitor of CCR5 signaling	Reduction of IL-6 and inflammation Restoring T cell lymphocytopenia and the CD4/CD8 ratio A significant decrease in SARS-CoV-2 plasma viremia	Tested in human	[112]

reflect impaired antiviral immunity [114]. On the other hand, a significant increase in MDSCs expansion has been reported after corticosteroid treatments in other disorders [115,116], which is associated with immunosuppressive responses. Moreover, Covid-19 patients who received systemic treatment included systemic corticosteroids showed an enhanced quantification of both MDSC subsets including M-MDSCs and G-MDSCs in the blood samples [117,118], which were associated with the severity of Covid-19 [117].

According to up-regulated inhibitory receptors, such as PD-1, in various inflammatory cells isolated from severe COVID-19 patients [119], targeting the inhibitory receptors on MDSCs could be another effective approach in the treatment of COVID-19 and restoring immune dysregulation. Furthermore, targeting other molecules such as IDO enzyme, STAT3 pathway, and an inhibitor of the anaplastic lymphoma kinase (ALK) like LDK378 for preventing the MDSCs recruitment [120] and their metabolic mediators may be good candidates to induce MDSCs suppression and reverse virus-specific T cells responses.

Collectively, despite the ability of MDSCs in dampening excessive tissue inflammation at the early stages of the disease, MDSCs have shown a significant pathogenic role in COVID-19-associated lymphopenia of severe disease forms. Therefore, therapeutic approaches targeting MDSCs can be promising strategies to restore immune cells activities, control the unregulated inflammation, and reverse the suppressed anti-viral immune responses and augment them in COVID-19 patients at severe stages of the disease.

7. Conclusion

MDSCs play important roles in cancer, infectious and inflammatory lung disorders, particularly TB, asthma, COPD, PcP, as well as IAV and COVID-19 infections. While these heterogeneous populations of immune cells are characteristically categorized into monocytic and granulocytic subsets, both of them show highly suppressive attitude against T lymphocytes. The pathway of genesis, recruitment, activation and inhibitory functions of MDSCs may be distinct according to the type of disease, and they also may utilize multiple mechanisms, thereby the inhibition of one mechanism is not enough to thoroughly hamper the suppressive function of these cells. MDSCs are bilateral immune cells with both protective and harmful sides across different lung diseases. It seems axiomatic that besides preserving the protective responses against lung-resident pathogens, the immunopathology should be restricted. In this regard, the cellular modulators of MDSCs genesis and function should precisely be identified to dampen MDSCs in cases that they provoke the survival and progression of malignant cells, like lung cancer, or viral respiratory infections. In contrast, immunotherapy driven by expansion and activation of MDSCs may provide an interesting therapeutic method for restriction of host immune system from overreaction and thereby cytokine storm as may be found in different virus infections such as COVID-19 infection. Beside the highly investigated role of MDSCs in cancer progression, their role in other pathological contexts is less understood. Of note, recent studies have highlighted the similar attitude of MDSCs across distinct pathologies to that across cancer, making them a good candidate for developing immunoregulatory approaches applicable through a broad range of immunopathologies. Ultimately, more clinical evaluation is in demand to confirm the efficiency and safety of MDSC-based therapeutic approaches in viral respiratory infections.

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CRediT authorship contribution statement

Amir Ghaemi, Mohsen Keshavarz, Khadijeh Koushki, Maryam Salemi: Wrote the draft and revised it. **Seyed Mohammad Miri**: Depicted the figures and revised it. **Mohsen Keshavarz, Khadijeh Koushki, Maryam Salemi, Yaser Arjeini**: Collected the data and designed the tables. All the authors are read and approved submitted version.

Conflict of interest statement

The authors declare they have no conflict of interest.

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