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REVIEW ARTICLE

Hyperviscosity syndrome in COVID-19 and related vaccines: exploring of uncertainties

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Abstract

Hyperviscosity syndrome (HVS) recently emerged as a complication of coronavirus disease 2019 (COVID-19) and COVID-19 vaccines. Therefore, the objectives of this critical review are to establish the association between COVID-19 and COVID-19 vaccines with the development of HVS. HVS may develop in various viral infections due to impairment of humoral and cellular immunity with elevation of immunoglobulins. COVID-19 can increase blood viscosity (BV) through modulation of fibrinogen, albumin, lipoproteins, and red blood cell (RBC) indices. HVS can cause cardiovascular and neurological complications in COVID-19 like myocardial infarction (MI) and stroke. HVS with or without abnormal RBCs function in COVID-19 participates in the reduction of tissue oxygenation with the development of cardio-metabolic complications and long COVID-19. Besides, HVS may develop in vaccine recipients with previous COVID-19 due to higher underlying Ig concentrations and rarely without previous COVID-19. Similarly, patients with metabolic syndrome are at the highest risk for propagation of HVS after COVID-19 vaccination. In conclusion, COVID-19 and related vaccines are linked with the development of HVS, mainly in patients with previous COVID-19 and underlying metabolic derangements. The possible mechanism of HVS in COVID-19 and related vaccines is increasing levels of fibrinogen and immunoglobulins. However, dehydration, oxidative stress, and inflammatory reactions are regarded as additional contributing factors in the pathogenesis of HVS in COVID-19. However, this critical review cannot determine the final causal relationship between COVID-19 and related vaccines and the development of HVS. Prospective and retrospective studies are warranted in this field.

Keywords COVID-19 · Hyperviscosity syndrome · COVID-19 vaccination

Introduction

Hyperviscosity syndrome (HVS) is a group of symptoms induced by high blood viscosity (BV) including bleeding, headache, visual disturbances, seizure, vertigo, and coma [1]. HVS is characterized by the triad of mucosal bleeding, visual changes, and neurological deficits [1]. The main cause of HVS is Waldenstrom macroglobulinemia, which is an abnormal proliferation of plasma cells and lymphoplasmacytoid cells [2]. HVS is also caused by polycythemia, leukemia, multiple myeloma, sepsis, and sickle cell anemia [3]. As a result, HVS is caused by an increase in the number of red blood cells (RBCs) or a deformity in RBC shape, as well as an increase in serum proteins [3]. Normal BV is typically between 1.4 and 1.8 centipoise (cp), and symptoms of HVS develop when BV exceeds 4.0 cp [4].

HVS recently emerged as a complication of coronavirus disease 2019 (COVID-19) and COVID-19 vaccines [5]. Therefore, the objectives of this critical review are

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to determine the association between COVID-19 and/or COVID-19 vaccines with the development of HVS.

Hyperviscosity syndrome and viral infections

HVS can occur in a variety of viral infections, including human immunodeficiency virus type 1 (HIV-1) infections, as a result of impaired humoral and cellular immunity and an increase in immunoglobulin (IgG) [6]. The underlying mechanisms of HVS in patients with HIV-1 are related to the direct activation of B cells by HIV-1, alteration of T cells-mediated B cell regulation, chronic exposure to the antigens of HIV-1 and high IL-6 [6]. However, hyper-activation of B cells with high production of IgG could be the main mechanistic pathway of HVS in HIV-1 infection [7]. According to Jin et al., HVS was linked to the formation of myeloma-associated IgG1paraprotein against HIV-1 p24 antigen in HIV-1 patients [8].

As well, HVS has been demonstrated in patients with acute respiratory viral infections, including influenza complicated by pneumonia [9]. A study involving 232 patients with influenza and acute respiratory viral infections showed significant alterations in the microcirculation, intravascular homeostasis, hypercoagulation, augmentation of fibrinolytic activity, and an increase in BV [9]. Generally, Sloop and colleagues revealed that severe infections increase BV with the development of HVS due to inflammation-induced hypergammaglobulinemia and elevation of acute-phase reactants that increase BV [10]. High BV or HVS fosters aggregation of RBCs with an increasing risk of thrombosis due to augmentation of vascular resistance, which impedes peripheral tissue perfusion [10]. Of note, previous acute infection and chronic bronchitis within two months caused by influenza infection predispose to the risk of acute ischemic stroke, and influenza vaccine did not offered a protection against the development of acute ischemic stroke [11]. This observation suggests that HVS could be a possible risk factor for the development of acute ischemic stroke in patients with influenza infection.

Furthermore, indices of blood viscosity are increased in patients with hepatitis B virus (HBV) infection who are at risk for the development of HVS [12]. A study of 55 patients with HBV infection illustrated that RBCs aggregation index, hematocrit, and whole BV were higher compared with control groups and unrelated to the state of oxidative stress and hemorheology indices [12]. Of interest, HVS is implicated in the pathogenesis of septic shock in parallel with high fibrinogen levels [13]. Van et al. reported that soluble fibrinogen-like protein 2 (sFGL2) is increased in patients with HBV infection [14]. Therefore, high sFGL2 plasma levels could be the potential cause of HVS in HBV infection. These findings indicated that HVS may be developed in various viral infections and contribute to the development of complications.

Hyperviscosity syndrome and immunoinflammatory disorders

It has been reported that HVS is linked with acute inflammatory disorders since BV is sensitive to acute-phase reactants [15]. Therefore, HVS is high in subpopulations with high C-reactive protein and erythrocyte sedimentation rate (ESR) as compared with subpopulations with low CRP and ESR [15]. HVS has been shown to develop in patients with rheumatoid arthritis due to the formation of immunocomplexes which affect RBCs deformability and vascular resistance [15]. HVS in rheumatoid arthritis can be developed with a level of IgG less than in Waldenstrom macroglobulinemia [16]. It developed in patients with rheumatoid arthritis due to the formation of an intermediate complex from the aggregation of Ig, RBCs aggregation, and high fibrinogen levels [17]. However, HVS in rheumatoid arthritis is rare in treated patients, so treating with plasmapheresis and immunosuppressive agents can reduce the risk of development of HVS [17]. Likewise, HVS in rheumatoid arthritis is significantly correlated with high activity of rheumatoid factor [18].

Furthermore, HVS may be the presenting feature in patients with systemic lupus erythematosus (SLE) due to hyper-paraproteinemia and monoclonal gammopathy [19]. Besides, HVS is also developed in IgG4-related disorders, which are systemic fibro-inflammatory disorders characterized by elevation of Ig, including IgG4 [20].

Of interest, CD169 macrophages contribute to the process of bone marrow erythropoiesis and maturation of RBCs. Over-activation of CD169 macrophages may be associated with the development of polycythemia [21]. Thus, depletion of CD169 macrophages reduces bone marrow erythroblasts and prevents erythropoietic recovery from anemia [21]. According to Asano et al., CD169 macrophages control and modulate immunological responses in the circulating fluid by recruiting monocytes and producing chemokines [22]. CD169 macrophages are activated during immunological disorders, tumor growth, and viral infections to produce immunological tolerance and antiviral effects [23–25]. As a result, in immunological diseases, activated CD169 macrophages may increase BV via boosting erythropoiesis.

Indeed, there is a close relationship between HVS and inflammation due to the increase in acute-phase reactant fibrinogen, whose level is correlated with increasing blood viscosity [26]. Gordy et al. revealed that fibrinogen-related proteins are increased during the immune response to various inflammatory stimuli [27]. Fibrinogen and fibrinogen-related proteins play a critical role in neutralizing invading pathogens [28]. In turn, exaggerated immune responses and

high levels of fibrinogen-related proteins are associated with the development of HVS.

These observations indicated that high BV or HVS is linked with underlying immunoinflammatory disorders.

Hyperviscosity syndrome and COVID-19

Effects of COVID-19 on blood viscosity

COVID-19 is a pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leading to worldwide crisis with high morbidity [29]. Till late January 2022, the total number of infected cases reached more than 370 million, with about 5 million confirmed deaths. In general, the clinical presentation of COVID-19 is mild in the majority of cases, though 15% of COVID-19 patients presented with pulmonary and extra-pulmonary manifestations including headache, fever, dry cough, sweating, and fatigue [30, 31]. About 5% of COVID-19 patients may develop severe and critical outcomes due to the development and propagation of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) that require intensive care unit admission [32].

SARS-CoV-2 exploits different receptor types to enter the affected cells. The angiotensin-converting enzyme 2 (ACE2) is a pioneer one related in the pathogenesis of SARS-CoV-2 infection [33]. This interaction induces down-regulation of ACE2, which is necessary for conversion of pro-inflammatory/vasoconstrictor angiotensin II (AngII) to vasodilator/anti-inflammatory Ang1-7 [34]. In severe cases, SARS-CoV-2 infection may result in an exaggerated immune response, hyperinflammation, and hypercytokinemia, as well as a cytokine storm [35, 36]. Therefore, SARS-CoV-2-induced upregulation of AngII may provoke the development of HVS in COVID-19 through the induction of inflammatory changes and vasoconstriction.

It has been shown that SARS-CoV-2 infection is associated with microcirculation failure in hospitalized patients with severe COVID-19 characterized by weak peripheral pulses, cold extremities, and metabolic acidosis [37]. Microcirculation dysfunction/failure has been linked to severe sepsis because of increased RBC aggregation, decreased RBC deformability, and alterations in RBC physiology/morphology [38, 39]. Endothelial dysfunction, coagulation problems, and cytokine storm were observed to contribute to the development of microcirculation failure in septic COVID-19 patients by Colantuoni et al. [40]. A study that included 7 hospitalized COVID-19 patients compared to 7 non-COVID-19 septic patients and 7 healthy control illustrated that RBCs deformability was reduced in both COVID-19 patients and non-COVID-19 septic patients compared to the controls ($P < 0.05$) [41]. Moreover, RBCs aggregation was higher in COVID-19 patients compared to 7 non-COVID-19 septic patients without significant changes in BV and fibrinogen levels [37]. This small sample study does not give any concrete clues about normal BV and fibrinogen levels in COVID-19. A retrospective study involving 41 COVID-19 patients revealed that estimated BV was higher in COVID-19 patients than in the control group [41].

Enhanced RBCs aggregation with reduction of RBCs deformability in COVID-19 is increased in both stasis and low-shear flow [37] that together with increasing fibrinogen level may increase BV and development of HVS. Of note, acute viral infections are linked with development of HVS due to hypergammaglobulinemia and elevation of acute-phase reactants which might cause thromboembolic disorders and cardiovascular complications [42]. Increasing of BV and development of HVS in COVID-19 could be related to different mechanisms including exaggerated immune response, endothelial dysfunction, hypoxia, coagulation disorders [41].

Similarly, changes in RBCs morphology/function, platelet hyper-reactivity, high ferritin, and P-selectin activity in COVID-19 could contribute in the development of HVS [43]. As well, psychological stress, fever, and dehydration may increase BV and compensatory increment in the release of arginine vasopressin in COVID-19 patients [44]. High arginine vasopressin triggers release of pro-inflammatory cytokines through activation of nuclear factor kappa B (NF-κB) and nod-like receptor pyrin 3 (NLRP3) inflammasome which participate in increasing of BV [44]. Both of NF-κB and NLRP3 inflammasome induce asymmetry of RBCs membrane with reduction of RBCs deformability in normal and sickle RBCs [45, 46]. In addition, NF-κB and NLRP3 inflammasome are highly activated in COVID-19 [47] and could a potential causes for reduction of RBCs deformability in COVID-19.

Of note, CD169 macrophages are involved in the maturation of RBCs and development of polycythemia [21]. CD169 monocytes are expressed in 93.7% of COVID-19 patients and could be of diagnostic benefits [48]. Therefore, SARS-CoV-2-induced CD169 macrophages/monocytes may cause polycythemia and elevation of BV in COVID-19.

Exaggerated immune response and release of pro-inflammatory cytokines mainly IL-6 are linked with development of cytokine storm and multi-organ injury [49]. Panigada et al. observed that IL-6 is regarded as a powerful activator for synthesis of fibrinogen in COVID-19 [50]. Also, dysregulation of RAS with high AngII in COVID-19 may induce expression and synthesis of fibrinogen [35, 51]. Fibrinogen activates RBC membrane integrinαvβ3 receptors resulting in the activation of RBCs aggregation with subsequent development of HVS [50]. As well, hypoalbuminemia is linked with increasing of blood viscosity and development of HVS [52]. Serum albumin is inversely correlated with

D-dimer and CRP, and hypoalbuminemia is associated with an increased risk of development of coagulopathy in COVID-19 patients by a reduction in the anticoagulant and antiplatelet effects of albumin [53]. A retrospective study involving 113 COVID-19 patients illustrated that a high fibrinogen/albumin ratio was associated with a high risk of thrombosis, disease severity, and poor clinical outcomes [54]. As a result, the BV is augmented and reaches 4.2 cp. Therefore, hyperfibrinogenemia and hypoalbuminemia may increase BV and participate in the development of HVS and thrombotic events in COVID-19. Notably, severe COVID-19 is associated with the development of arterial and venous thromboembolic events due to direct SARS-CoV-2 cytopathic effects and associated endothelial dysfunction, platelet activation, coagulation activation, and inhibition of the fibrinolytic pathway [55]. Furthermore, downregulation of ACE2 with dysregulation of RAS together with exaggerated pro-inflammatory cytokines may initiate endothelial dysfunction by reduction of prostacyclin and nitrous oxide (NO) [56]. Felicetti et al. recently illustrated that thrombotic events may increase the risk of development of HVS [57]. These observations suggest a mutual interaction between HVS and thrombotic events in COVID-19.

Moreover, SARS-CoV-2 may directly affect RBCs morphology through binding of membrane CD147 receptor and Band3 protein on the RBCs [58, 59]. These changes hamper functional capacity for oxygen transport by RBCs leading to development of tissue hypoxia [59]. Besides, Foy and colleagues revealed that RBC distribution width and other indices were severely affected in SARS-CoV-2 infection and linked with COVID-19 severity and poor clinical outcomes [60]. In addition, extreme hypoxia and acidosis induce alteration in RBCs morphology [61]. These observations suggest that direct SARS-CoV-2-induced RBCs dysmorphology and associated metabolic acidosis and hypoxia may induce progression of HVS in COVID-19.

Furthermore, lipoproteins can affect blood viscosity since low-density lipoprotein (LDL) is positively correlated, while high-density lipoprotein (HDL) is negatively correlated with BV [62]. HDL is necessary for RBCs morphology and deformability; thus, reduction of HDL may reduce RBCs life span by increasing osmotic fragility and reduction of RBCs deformability [63]. In COVID-19, there is a noteworthy alteration in lipoprotein serum levels, and low HDL levels are associated with COVID-19 severity [64, 65]. Therefore, reduction of HDL in SARS-CoV-2 infection can increase BV with the development of HVS in COVID-19.

Moreover, SARS-CoV-2 infection-induced oxidative stress may trigger elevation of BV [66]. It has been reported that high oxidative stress can induce abnormal hemorheological changes with a reduction of RBCs deformability and the induction of thrombotic changes [67]. In COVID-19, severe oxidative stress triggers endothelial dysfunction and thromboembolic complications [66]. Thus, alterations in RBC fragility and deformability together with endothelial dysfunction by SARS-CoV-2 infection-induced oxidative stress could cause HVS in COVID-19.

Interestingly, RBCs morphology and functions are affected in COVID-19 with the development of abnormal erythrocrine function [68]. Development of abnormal RBCs may contribute to the progression of endothelial dysfunction and vascular injury by increasing oxidative stress [69]. RBCs from COVID-19 patients induce expression and upregulation of endothelial arginase with the production of reactive oxygen species (ROS), reduction of endothelial NO and development of endothelial dysfunction [69]. Therefore, SARS-CoV-2 infection-induced oxidative stress could in part be mediated by the development of abnormal RBCs in COVID-19.

Moreover, COVID-19 is commonly associated with psychological stress and sympathetic outflow [70]. Of interest, psychological stress increases circulating AngII as well, AngII promotes psychological stress through augmentation of sympathetic activation [71]. Likewise, AngII receptor blockers attenuate stress pressor in young adults [71]. Thus, COVID-19-induced psychological stress may augment the dysregulated RAS by increasing AngII with subsequent development of HVS.

Taken together, COVID-19 can increase BV through modulation of fibrinogen, albumin, lipoproteins, and RBC indices (Fig. 1).

Complications of hyperviscosity in COVID-19

COVID-19 HVS has been linked with various cardiovascular and neurological complications such as myocardial infarction (MI) and stroke [72, 73]. The incidence of MI in COVID-19 has increased by up to 5% [74]. That could be due to the development of HVS. In addition, increasing of RBCs aggregation and SARS-CoV-2 infection-induced endothelial dysfunction and immunothrombosis may elevate BV in COVID-19 [75]. These changes increase the risk of the development of MI in surviving COVID-19 patients due to the development of coronary microangiopathy [76].

HVS in COVID-19 causes poor tissue perfusion, peripheral vascular resistance, and thrombosis [77]. Low-shear areas are susceptible to thrombosis due to reduction in dispersion of clotting factors and attenuation of shear-induced release of antithrombotic molecules like NO and prostacyclin [77]. Remarkably, most of the COVID-19 patients with BV greater than 3.5cp had coagulation disorders [78]. Herein, there is a close relationship between HVS and thrombotic events in COVID-19. Maier and coworkers reported 15 critical COVID-19 with thrombotic complications. All patients had a BV greater than 3.5cp (the normal range is 1.4–1.8 cp) as tested by a traditional

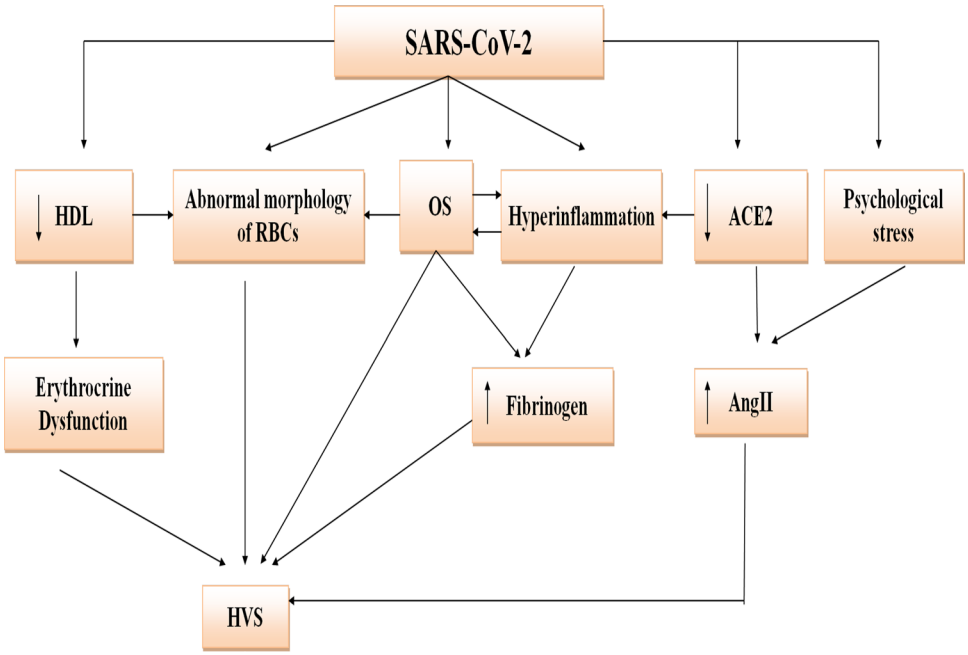

Fig. 1 Proposed mechanism of hyperviscosity syndrome in COVID-19: SARS-CoV-2 through induction of the downregulation of angiotensin-converting enzyme 2 (ACE2), psychological stress, hyperinflammation, oxidative stress (OS), abnormal morphology of red blood cells (RBCs), and reduction of high density lipoprotein (HDL). These changes increase fibrinogen, angiotensin II (AngII), and the induction of erythrocrine dysfunction with the subsequent development of hyperviscosity syndrome (HSV)

capillary viscometer. The high BV was correlated with thrombotic events ($r = 0.84$, $P < 0.01$) [78]. Further, a case series reported by Truong et al. showed symptoms of HVS were more evident in COVID-19 patients with BV greater than 4.2 cp [75]. These findings suggest that higher BV is linked with more severe HVS in COVID-19.

Furthermore, HVS may lead to complications like acute kidney injury, glucose intolerance, skeletal muscle ischemia, and myocardial necrosis [79]. As well, HVS leads to pulmonary hypoperfusion and the development of ventilation-perfusion mismatch. These changes cause silent hypoxemia with the propagation of high pulmonary vascular resistance [80].

Indeed, HVS is linked with the development of post-COVID-19 syndrome (long COVID-19), which is the persistence of symptoms like dyspnea, fatigue, cognitive dysfunction, and headache following recovery from COVID-19 [81]. Long-term COVID-19 is associated with immunosuppression and cardio-pulmonary fibrosis due to upregulation of transforming growth factor beta (TGF-β) [82]. Prolonged inflammatory changes and high blood viscosity in patients with long COVID-19 can reduce tissue perfusion and cellular metabolism [83]. As mentioned above, prolonged abnormal RBCs function following COVID-19 may cause tissue hypoxia and subnormal cell metabolism with accentuation of long COVID-19 [69].

Taken together, HVS with or without abnormal RBCs function in COVID-19 participates in reduction of tissue oxygenation with the development of cardio-metabolic complications and long COVID-19 (Fig. 2).

Hyperviscosity and COVID-19 vaccination

COVID-19 vaccine was developed on the 8th of April 2020 to control the spread of SARS-CoV-2 infection and limit morbidity and mortality caused by COVID-19 [84]. Following COVID-19 vaccination, some reports showed that the BV was increased because of the induction of Ig [85]. HVS may develop after COVID-19 vaccination, leading to immunopathological changes [86]. HVS is correlated with the concentration of Ig, though the lowest normal Ig concentrations are 545 mg/dl, while the lowest BV is 1.5 cp [86]. The BV will be 2.6 cp when Ig concentrations reach 6160 mg/dl [85]. Of note, symptoms of HVS are developed when BV exceeds 4.0 cp [4].

Surprisingly, HVS can develop in vaccine recipients who have previously received COVID-19 due to higher underlying Ig concentrations, and only rarely in those who have never received COVID-19 [85]. Thus, screening for previous COVID-19 is essential before induction of COVID-19 vaccination to prevent the development of HVS and related hemorheological adverse effects. Alongside, use of contraceptives may augment the risk of development of HVS after COVID-19 vaccination [87]. Therefore, we suggest taking the risk into consideration for patients taking contraceptives at the time of COVID-19 vaccination.

Different studies revealed that metabolic alterations in patients with metabolic syndrome increase BV and the risk for development of HVS [88]. Metabolic syndrome

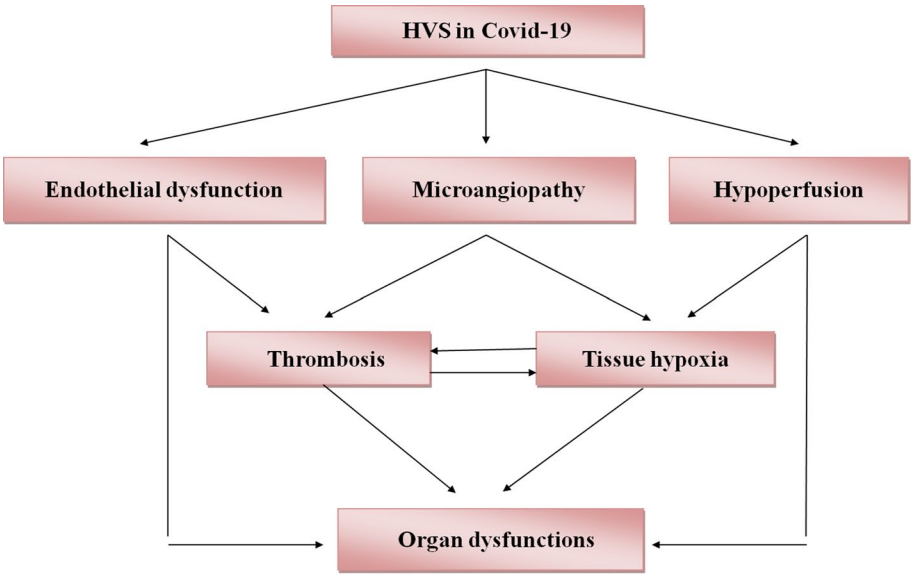

Fig. 2 Complications of hyperviscosity in COVID-19: Hyperviscosity (HVS) in COVID-19 induces the development of endothelial dysfunction, microangiopathy, and hypoperfusion with the development of thrombosis and tissue hypoxia, which ultimately cause organ dysfunction

is linked with systemic inflammation and oxidative stress which affect the microcirculation by increasing of BV due to reduction of RBCs deformability [89]. Therefore, patients with metabolic syndrome are at the highest risk for propagation of HVS after COVID-19 vaccination. Joob and Wiwanitkit confirmed that COVID-19 vaccination increases the risk of development of HVS in patients with metabolic syndrome [90]. The BV is increased by 2.7 times in healthy subjects and by 2.99 in patients with metabolic syndrome following COVID-19 vaccination [91]. This increment in BV did not reach the state of HVS in both healthy subjects and patients with metabolic syndrome, which might be due to the validity of the method in the assessment of blood viscosity [91].

Generally, BV in healthy COVID-19 vaccine recipients is increased by 2.4 cp [92]. However, COVID-19 vaccine-induced HVS is common in patients with metabolic syndrome due to high underlying metabolic disorders which increase BV [93]. Sookaromdee et al. proposed that underlying chronic liver diseases with high bilirubin levels may cause HVS after COVID-19 vaccination since hyperbilirubinemia is linked with the development of HVS [93]. Patients with underlying metabolic disorders have a higher chance of developing HVS following COVID-19 vaccination. Thus, close monitoring of blood viscosity in COVID-19 vaccine recipients is necessary to prevent post-vaccine complications [94].

Interestingly, oxidative stress can induce a reduction in RBCs deformability with a subsequent elevation of BV [95]. In obesity, high oxidative stress and fibrinogen together with prolonged low-grade inflammation are linked with the development of HVS [96, 97]. Therefore, depending on these findings, obese patients are at high risk for the development of HVS after COVID-19 vaccination. Pivonello and colleagues suggested that the immune response in obese patients against the COVID-19 vaccine is low due to impaired reactivity of T and B cells [98]. Therefore, a delay in immune response may reduce Ig concentrations following COVID-19 vaccination, and this may affect the development of HVS in obesity. Of note, the immune response in obese patients was low following the influenza vaccine [99]. These findings are premature to draw a final association between COVID-19 vaccination and the risk of HVS, and thus, prospective and retrospective studies are warranted in this regard.

The present review had many limitations, including the rarity of prospective studies that evaluate BV in COVID-19 at the time of admission and discharge. Also, most studies were speculative in their explanation of HVS in COVID-19 and COVID-19 vaccination. Despite these limitations, the present critical review revealed that HVS is an important mechanistic pathway in the development of complications in COVID-19 and related vaccines.

Conclusions

COVID-19 and related vaccines are linked with the development of HVS mainly in patients with previous COVID-19 and underlying metabolic derangements. The possible mechanism of HVS in COVID-19 and related vaccines is increasing levels of fibrinogen and immunoglobulins. Dehydration, oxidative stress, and inflammatory reactions are regarded as additional contributing factors in the pathogenesis of HVS in COVID-19. However, this critical review cannot determine the final causal relationship between COVID-19 and related vaccines and the development of HVS. Prospective and retrospective studies are warranted in this field.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Consent for publication This article does not contain any studies with human or animal subjects.

Ethics approval and consent to participate This article does not contain any studies with human or animal subjects.

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