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Review Article

Is COVID-19 associated thrombosis caused by overactivation of the complement cascade? A literature review

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 is responsible for the current COVID-19 pandemic resulting in an escalating number of cases and fatalities worldwide. Preliminary evidence from these patients, as well as past coronavirus epidemics, indicates that those infected suffer from disproportionate complement activation as well as excessive coagulation, leading to thrombotic complications and poor outcome. In non-coronavirus cohorts, evidence has accumulated of an interaction between the complement and coagulation systems, with one amplifying activation of the other. A pressing question is therefore if COVID-19 associated thrombosis could be caused by overactivation of the complement cascade? In this review, we summarize the literature on thrombotic complications in COVID-19, complement activation in coronavirus infections, and the crosstalk between the complement and coagulation systems. We demonstrate how the complement system is able to activate the coagulation cascade and platelets, inhibit fibrinolysis and stimulate endothelial cells. We also describe how these interactions see clinical relevance in several disorders where overactive complement results in a prothrombotic clinical presentation, and how it could be clinically relevant in COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus (CoV) responsible for the current COVID-19 pandemic. The deterioration of organ function following infection from the disease has largely been attributed to a maladaptive immune response [1], of which the complement system is an integral part [2]. In addition to complement activation, COVID-19 patients also suffer from excessive coagulation, leading to thrombotic complications and poor clinical outcome [3]. In non-CoV cohorts, there is evidence of interactions between the complement and coagulation systems, resulting in an amplification of their otherwise targeted responses [4,5,14–23,6,24–30,7–13]. However, it is not known whether this process occurs and could explain the thrombotic complications in COVID-19. In this review, we summarize the literature on thrombotic complications in COVID-19, complement activation in CoV infections, and the crosstalk between the complement and coagulation system.

2. The complement system

The complement system is part of the innate immune response [31,32] and made up of serine proteases that share the same ancestral genes as coagulation proteins [33]. Much like the coagulation system, its activation involves the interaction of plasma and membrane-bound proteins. The function of the complement system is carried out by opsonization, generating pro-inflammatory mediators, and activating the membrane attack complex (MAC, also known as the terminal complement complex C5b-9) [34]. This activation generally follows three pathways, each triggered by different agents, which converge in the formation of C3 convertase. C3 convertase then cleaves C3 into C3b, a potent opsonin, and C3a, an anaphylatoxin [34]. Further propagation of C3b also results in the generation of C5 convertase, which cleaves C5 to C5a and C5b. C5b forms a complex with other complement proteins that make up the C5b-9 membrane attack complex (MAC). Deposition of MAC on cell membranes leads to calcium influx and cell lysis, but can also activate intracellular signaling at lower doses [34]. The complement system is also regulated by complement control proteins, including C1-inhibitor (CI-INH), decay-accelerating factor (DAF), C4-binding protein (C4BP), factor H and other [34,35].

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3. Complement-mediated thrombosis

3.1. Complement and the coagulation cascade

One of the principal driving forces behind the coagulation cascade is the exposure to tissue factor, which initiates the intrinsic coagulation pathway. C5a has been shown to increase tissue factor activity in both circulating form [4] and on endothelial cells [5]. This is supported by ex-vivo studies that have showed that inhibition of C3 or C5 leads to reduced expression of tissue factor [6,7]. The same reaction can be seen on mast cells, where the complement system is able to induce the expression of tissue factor and promote a prothrombotic phenotype [8]. Other studies have also shown that MASP-1 and MASP-2, a group of serine proteases that initiate the lectin complement pathway, can cleave prothrombin to form activated thrombin [9], and autonomously activate fibrinogen and factor XIII (fibrin stabilizing factor) [10,11]. MASP-1 knockout mice show significantly longer tail-bleeding times compared to controls, highlighting the possible clinical significance of these results [36]. Complement system inhibitors are also able to inhibit the coagulation cascade [12,13]. C1 esterase inhibitor (C1-INH) can inhibit factor XII [14] and thrombin [15], and C4b-binding protein (C4BP) has been shown to inhibit protein S, a co-factor for the activated protein-C pathway of coagulation inhibition. Thus, the complement system is capable of activating the coagulation cascade (Table 1, Fig. 1).

3.2. Complement and platelets

Early murine studies showed that C3- and C5 deficient mice have prolonged tail-bleeding times and reduced platelet function [16], lending support to the notion that complement activates platelets. More recent studies have highlighted how MAC is able to activate platelets and enhance platelet aggregation [17–19], and that C3 deficiency in mice reduces thrombus incidence, fibrin deposition and platelet activation [20]. The assembly of MAC on human platelets has also been shown to result in a dose-dependent increase in the binding of coagulation factors Va and Xa, which increases platelet prothrombinase activity and initiates the release of the prothrombotic factor V from alpha-granules [21,22]. Moreover, removal of external Ca^{2+} from this reaction seems to inhibit the MAC-initiated release of the platelet alpha-granule storage pool, suggesting that the effects that lead to increased platelet prothrombinase activity are mediated by influx of Ca^{2+} across the MAC pore [22]. Other studies have further demonstrated that platelets have receptors for C3a that can mediate their activation [37]. Thus, both C3 and the MAC of the complement system appear capable of activating platelets. This has seen clinical relevance in trauma patients, where complement activation has been shown to increased platelet aggregation [23,24]. In summary, evidence points to a relationship between complement and platelets on multiple levels that can result in disproportionate platelet activation, as well the release of platelet-derived microparticles that further stimulates this reaction (Table 1, Fig. 1).

Table 1
Complement-mediated coagulopathy: molecular interactions.

Complement substrate	Effect on hemostasis
C3a	Platelet activation
C5a	Increased tissue factor activity
	Increased expression of endothelial P-selectin
	Increased expression of PAI-1 on mast cells
MAC (C5b-9)	Platelet activation
	Increased binding of coagulation factors Va and Xa
	Increased release of factor V from platelet alpha-granules
	Induces endothelial cells to secrete von Willebrand factor
MASP 1	Activates thrombin
	Activates TAFI
	Activates factor XII
	Activates fibrinogen
MASP 2	Activates thrombin
C1-INH	Inhibits factor XII
	Inhibits thrombin
	Inhibits plasmin
C4BP	Inhibits protein S

Abbreviations: C = complement factor; MAC = membrane attack complex; MASP = mannan-binding lectin serine protease; C1-INH = C1 esterase inhibitor; C4BP = C4b-binding protein; PAI-1 = plasminogen activator inhibitor-1; TAFI = thrombin-activatable fibrinolysis inhibitor.

3.3. Complement and fibrinolysis

Fibrinolysis is the enzymatic breakdown of fibrin in blood clots. In a study by Brown et al., C1-INH in its native state was found to inhibit plasmin [27], which could lead to decreased fibrinolysis and increased thrombus formation. Similarly, complement factors have been shown to stimulate the expression of plasminogen activator inhibitor-1 (PAI-1) by mast cells, further inhibiting fibrinolysis and thereby presumably promoting thrombosis [8]. In vitro-studies have also showed that MASP-1 is able to activate thrombin-activated fibrinolytic inhibitor (TAFI), an inhibitor of fibrinolysis [10,11]. Thus, evidence shows that fibrinolysis can be regulated by both complement factors and complement inhibitors, through limitation of the formation of plasminogen to plasmin and stimulating endogenous fibrinolysis inhibitors, respectively (Table 1, Fig. 1). In addition to this, factors of fibrinolysis are able to modify complement activity as well. Probably the most important finding is that plasmin can activate C3 and C5 independently of C3 convertase [38–41], yielding functional MAC. This means that plasmin bridges thrombosis and the immune response by liberating C5a and inducing MAC assembly [42]. Plasmin, therefore, in addition to thrombin, also seems to be a key C5a generating enzyme.

3.4. Complement and endothelial activation

Evidence supports the hypothesis that the endothelium is a key target organ of COVID-19 [43]. This is of interest as studies have shown that complement factors can stimulate endothelial activation. Probably the most important finding in this context is that MAC is able to induce endothelial cells to secrete von Willebrand factor [28], which seems to be accompanied by an increase in prothrombinase activity. While the precise mechanism behind this remains unclear, the assembly of MAC on endothelial cell membranes appears to result in an influx of Ca^{2+} across the plasma membrane, which in turn leads to an increase in endothelial cytosolic Ca^{2+} and secretion of platelet adhesive von Willebrand factor [28]. This capacity of MAC to induce exposure of prothrombinase enzyme complex may contribute to fibrin deposition associated with immune endothelial injury [29]. C5a has also been found to induce a dose-dependent expression of endothelial P-selectin similar to that of thrombin [30]. This is important for the recruitment and aggregation of platelets to areas of vascular injury through platelet-fibrin and platelet-platelet binding. Thus, the complement system can also induce thrombosis by inducing endothelial cells to release von Willebrand factor and express P-selectin (Table 1, Fig. 1).

3.5. Clinical examples of complement-mediated thrombosis

Clinically relevant interplay between the complement and coagulation system is seen in several disorders (“complementopathies”) where complement overactivation results in a prothrombotic state. Paroxysmal nocturnal hemoglobinuria (PNH) is a hematological disorder associated with an acquired deficiency in the synthesis of glycophosphatidylinositol that renders erythrocytes susceptible to complement-mediated destruction [44]. PNH is also associated with an increased risk of thrombosis linked to complement-mediated platelet

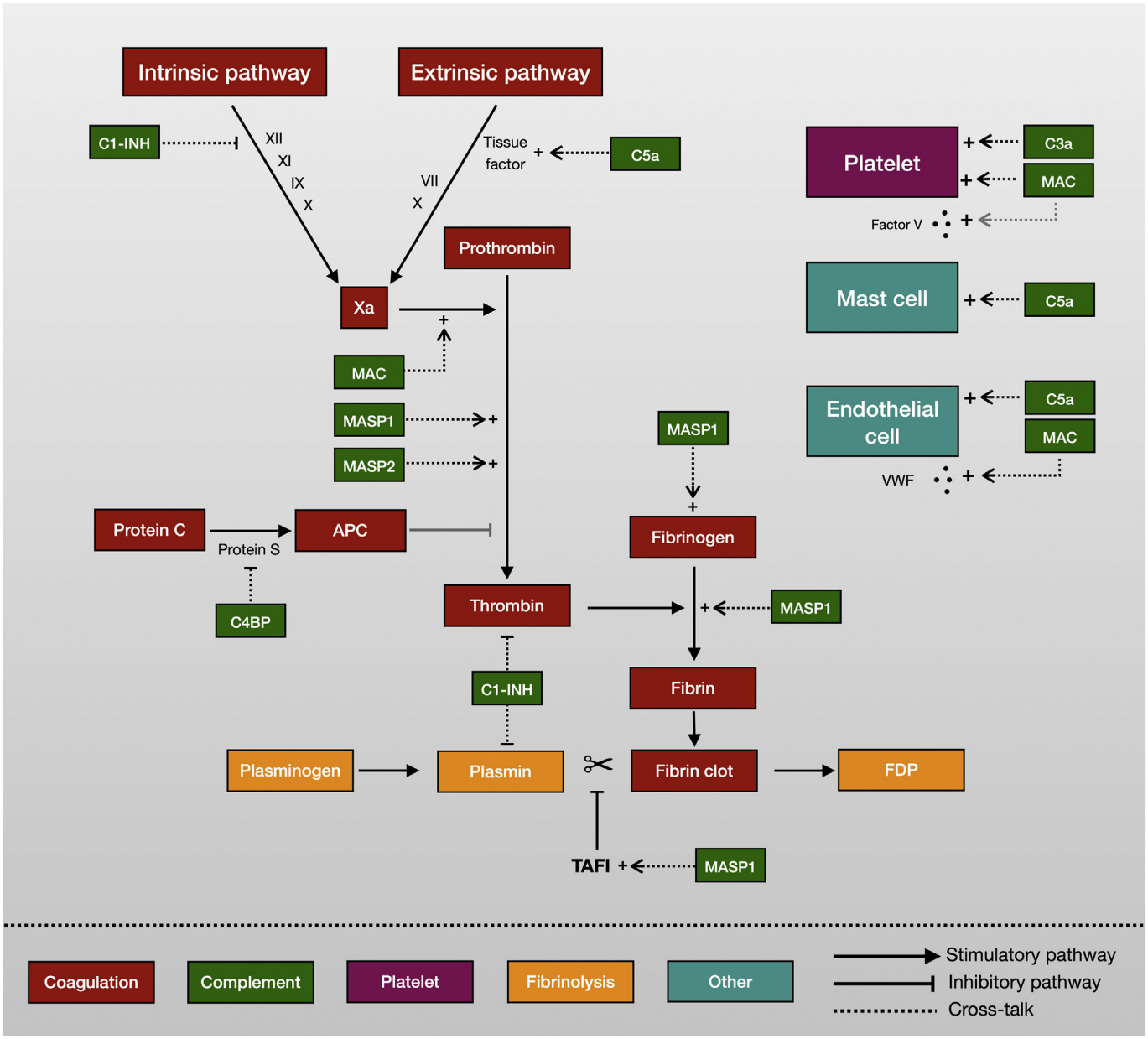

Fig. 1. Schematic overview of complement-mediated coagulopathy.

activation [45]. Atypical hemolytic uremic syndrome (aHUS) is another rare disease caused by excessive activation of the complement system, due to production of anti-factor H autoantibodies or genetic mutations in complement regulatory proteins, that results in platelet activation and thrombotic microangiopathy [46]. Moreover, complement deposition on platelets has been linked to the severity and infarct volume in acute stroke [47]. Increased complement deposition on platelets is also seen in systemic lupus erythematosus (SLE) patients with a history of venous thromboembolism [48]. Together, these disorders demonstrate that increased complement activity leads to thrombotic events.

Eculizumab has been a therapeutic revolution for patients with aHUS and PNH. The agent, an anti-C5 antibody that blocks formation of MAC and C5a generation, has been shown to reduce thromboembolic events in patients with PNH [49] and aHUS [50]. It has also shown clinical benefit in treating thrombotic microangiopathy secondary to sepsis-induced DIC [51], as well as provide potential benefits in anti-phospholipid syndrome [36].

4. Thrombosis and hypercoagulability in COVID-19

Growing evidence from multiple studies indicates that COVID-19 patients suffer from excessive coagulation, leading to increased thrombosis and poor clinical outcome [3]. In particular, the incidence of venous thromboembolism (VTE) among COVID-19 patients in intensive care units (ICU) appears to be higher compared to those reported in other ICU-cohorts [52]. In an early study from Wuhan, 25% of hospitalized COVID-19 patients developed VTE [53]. A similar incidence of 31% was reported in a later European study of 184 patients with severe COVID-19 [54]. A third study noted increased VTE in COVID-19 patients with ARDS compared with a matched historic non-CoV ARDS cohort [55]. In addition, the largest COVID-19 autopsy study to date found pulmonary embolism (PE) in 21% of the patients and deep vein thrombosis (DVT) in 40% [56]. In addition to VTE, ischemic stroke has been recognized as a complication to severe COVID-19 [57]. In a current preprint study of 2132 patients, COVID-19 was found to be independently associated with an increased risk of stroke compared to a

matched Influenza group [58]. A recent pooled analysis of 11,685 COVID-19 patients also found that 20% had a documented myocardial injury [59].

From a laboratory standpoint, blood hypercoagulability is frequently encountered in COVID-19 patients [60,61]. D-dimer has gained particular attention as a predictor of poor outcome, with several studies concluding that increased D-dimer values correlate to injury severity and death [61–68]. D-dimer levels also seem to gradually increase during the diseases course [61]. Pooled results from a recent meta-analysis also revealed that prothrombin time and D-dimer levels were significantly higher in patients with severe compared to those with mild COVID-19 [69]. Similar results have been reported for activated partial thromboplastin time [3]. In an Italian study of 22 patients admitted to the ICU due to COVID-19 associated respiratory failure, cases also showed markedly hypercoagulable thromboelastometry profiles, as reflected by shorter Clot Formation Time (CFT) in and higher Maximum Clot Firmness (MCF), indicative of hypercoagulability rather than consumptive coagulopathy [68].

5. Complement activation in coronavirus infections

In a rodent study of SARS-CoV, which is closely related to SARS-CoV-2, Gralinski and colleagues reported increased complement activity and found that C3-deficient mice exhibited less respiratory dysfunction (despite equivalent viral loads in the lung), fewer neutrophils and inflammatory monocytes, and reduced lung pathology and lower cytokine and chemokine levels in both the lungs and sera compared to controls [70]. This showed that the complement system is an important host mediator of SARS-CoV-induced disease and that complement activation regulates a systemic proinflammatory response to SARS-CoV infection. In another rodent model of MERS-CoV, increased concentrations of C5a and C5b-9 were found in sera and lung tissues, and blockade of the C5a-C5aR axis lead to the decreased tissue damage, as manifested by reduced apoptosis and T cell regeneration in the spleen [71]. This highlighted the fact that excessive complement activation contributed to the dysregulated host immune responses that contribute to the severe outcome of MERS-CoV infection as well. While these studies suggest that complement activation regulates a systemic inflammatory response to CoV pneumonia, data on the role of complement activation in the development of specifically SARS-CoV-2 have been scarce. However, in recent paper that examined skin and lung tissues from 5 patients with severe COVID-19 characterized by respiratory failure (n = 5) and purpuric skin rash (n = 3), significant deposits of C5b-9, C4d, and (MASP)-2 were found in the microvasculature of lung tissue, consistent with systemic activation of the alternative and lectin-based complement pathways. The purpuric skin lesion samples showed a similar deposition of C5b-9 and C4d [72]. This means that at least a subset of sustained, severe COVID-19 may be accompanied by activation of complement pathways and an associated procoagulant state. Further supporting these findings, a recent preprint reported that N proteins of SARS-CoV, MERS-CoV and SARS-CoV-2 were found to bind to MASP-2, resulting in aberrant complement activation and aggravated inflammatory lung injury. Complement hyperactivation was also detected, and a suppressive effect was observed when two deteriorating COVID-19 patients were treated with an anti-C5a monoclonal antibody [73]. Another preprint measured erythrocyte-bound C3b, iC3b, C3dg and C4d using flow cytometry in patients. Here, the amount of erythrocytes with bound complement activation products was markedly elevated in hospitalized COVID-19 patients compared to with healthy donors, and continued to increase during the first 7 days. Moreover, COVID-19 erythrocytes bound viral spike protein, suggesting activation of the classic pathway of complement and immune complex deposition on the erythrocytes [74]. Thus, preliminary evidence from COVID-19 patients, as well as other CoV infections, indicates that the disease results in disproportionate complement activation (Table 2).

6. Discussion

The aim of this study was to review the literature on complement activation following CoV pneumonia, as well as the crosstalk between the complement and coagulation systems. In short, evidence suggests a range of interactions between the two, with activation of one amplifying activation of the other independent of their respective established pathways. For example, complement factors are able to increase tissue factor activity [4–8], form activated thrombin from prothrombin [9–11], increase platelet activity and aggregation [17–20,37], increase prothrombinase activity and the release of platelet-derived procoagulant granules [21,22], as well as stimulate endothelial cells to release von Willebrand factor and express P-selectin [28–30]. Complement also regulates fibrinolysis, with complement cascade inhibitors demonstrating the ability to inhibit plasmin [27], and complement factors able to activate the fibrinolysis inhibitors PAI-1 and TAFI [8,10,11]. This collectively suggests that increased complement activity leads to increased coagulation cascade activity and platelet aggregation, i.e. a prothrombotic state, which is exemplified by a number of complementopathies where inappropriate activation of the complement pathways result in thrombotic complications that can be reduced using complement-inhibitors. In the case of COVID-19, evidence is accumulating of an incidence of VTE, stroke and myocardial injury that is higher than matched ICU cohorts [52,53,68,54–61]. Intriguingly, early evidence from COVID-19, as well as previous studies on SARS-CoV and MERS-CoV, also indicates that the complement system is overactivated and contributes to the dysregulated host immune response [70–74]. Although several similarities exist with known complementopathies, there are yet no studies that have examined if there is an interaction between the complement and coagulation system in COVID-19. Based on the material provided in this review, such an interaction would presumably lead to increased thrombosis, and might therefore explain the prothrombotic state seen in these patients.

Abbreviations

aHUS	atypical hemolytic uremic syndrome
ARDS	acute respiratory distress syndrome
C1-INH	C1-inhibitor
C4BP	C4b-binding protein
CoV	coronavirus
COVID	coronavirus disease
DAF	decay-accelerating factor
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ICU	intensive care unit
MAC	membrane attack complex
MASP	mannan-binding lectin serine protease
MERS	Middle East respiratory syndrome
PAI-1	plasminogen activator inhibitor-1
PE	pulmonary embolism
PNH	paroxysmal nocturnal hemoglobinuria
SARS	severe acute respiratory syndrome
SLE	systemic lupus erythematosus
TAFI	thrombin activatable fibrinolysis inhibitor
TAT	thrombin-antithrombin complex
VTE	venous thromboembolism

Author contributions

Conceptualization: AFS, BMB. Methodology: AFS. Data curation: AFS. Data interpretation: AFS, BMB. Writing—original draft preparation: AFS. Writing—review and editing: AFS, BMB. Supervision: BMB.

Table 2
Key studies on complement activation in coronavirus pneumonia.

Reference	CoV type	Key finding
Gralinski [70]	SARS-CoV	Relative to controls, SARS-CoV-infected C3−/− mice exhibited less respiratory dysfunction (despite equivalent viral loads in the lung), fewer neutrophils and inflammatory monocytes in the lungs, and reduced lung pathology and lower cytokine and chemokine levels in both the lungs and the sera.
Jiang [71]	MERS-CoV	Complement was excessively activated in MERS-CoV-infected mice through observations of increased concentrations of C5a and C5b-9 in sera and lung tissues, respectively. Blockade of the C5a-C5aR axis lead to the decreased tissue damage.
Magro [72]	SARS-CoV-2	In the examination of tissue from 5 patients with severe COVID-19, significant deposits of C5b-9, C4d and MASP-2 were found in the pulmonary microvasculature. Purpuric skin lesions of 3 patients also showed deposition of C5b-9 and C4d.
Gao [73][a]	SARS-CoV-2 SARS-CoV MERS-CoV	The N proteins of SARS-CoV, MERS-CoV and SARS-CoV-2 were found to bind to MASP-2, resulting in aberrant complement activation and aggravated inflammatory lung injury. Complement hyper-activation was also observed in COVID-19 patients, and a suppressive effect was observed when the deteriorating patients were treated with anti-C5a monoclonal antibody.
Lam [74][a]	SARS-CoV-2	Compared to healthy donors, the amount red blood cells with bound C3b and C4d were markedly elevated in hospitalized COVID-19 patients, and had increased even further by day 7.

Abbreviations: CoV = coronavirus, COVID = coronavirus disease, MASP = mannan-binding lectin serine protease, MERS = Middle East respiratory syndrome, SARS = severe acute respiratory syndrome.
[a] Preprint not yet peer-reviewed.

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Declaration of competing interest

None.

Statement

The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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