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Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past

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ABSTRACT

Coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus strain disease, has recently emerged in China and rapidly spread worldwide. This novel strain is highly transmittable and severe disease has been reported in up to 16% of hospitalized cases. More than 600,000 cases have been confirmed and the number of deaths is constantly increasing. COVID-19 hospitalized patients, especially those suffering from severe respiratory or systemic manifestations, fall under the spectrum of the acutely ill medical population, which is at increased venous thromboembolism risk. Thrombotic complications seem to emerge as an important issue in patients infected with COVID-19. Preliminary reports on COVID-19 patients' clinical and laboratory findings include thrombocytopenia, elevated D-dimer, prolonged prothrombin time, and disseminated intravascular coagulation. As the pandemic is spreading and the whole picture is yet unknown, we highlight the importance of coagulation disorders in COVID-19 infected patients and review relevant data of previous coronavirus epidemics caused by the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV).

1. COVID-19 and coagulation disorders

A novel coronavirus strain disease, Coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has recently emerged in Wuhan, China and rapidly spread throughout China and subsequently worldwide [1,2]. Currently, more than 600,000 cases have been diagnosed and over 25,000 infected people have died [3]. Patients usually present with fever (> 80%), cough (> 60%), and myalgia or fatigue (> 40%) [1,4]. Males are more commonly affected (~60% of cases) with a median age of approximately 50 years [1,4,5]. The complete spectrum of presentations and complications associated with COVID-19 is not fully elucidated. Clinical manifestations range from asymptomatic or very mild to severe illness, sepsis and death. While the current state of evidence suggests that most COVID-19 illness is mild, the study by Guan et al. suggests severe illness occurs in 16% of cases [4,6]. As the pandemic is still in progression, with an incomplete picture and potential treatments in preliminary stages only, we sought to review the available literature relevant to

coagulation disorders in patients infected by the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) to raise awareness about these potential complications in patients with COVID-19.

Thrombotic complications seem to emerge as an important issue in patients with COVID-19. Preliminary reports on COVID-19 pandemic outcomes have shown that infected patients commonly develop thrombocytopenia (36.2%) and may have elevated D-dimer (46.4%) [4], while these rates are even higher in patients with severe COVID-19 disease (57.7% and 59.6%, respectively) [4]. Emerging data support that patients infected by this novel coronavirus are at risk of developing disseminated intravascular coagulation (DIC) [4,7,8]. Increased D-dimer and fibrin degradation products levels, and prolonged prothrombin time have been associated with poor prognosis in patients affected by the novel coronavirus [8]. Tang et al. reported that 15 out of 21 non-survivors (8% of the total cohort) developed overt DIC (≥5 points) according to the International Society on Thrombosis and Haemostasis diagnostic criteria [8]. A meta-analysis by Lippi and

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colleagues identified significantly lower platelet count in patients with severe disease (mean difference: $-31 \times 10^9/L$, 95% CI: -35 to $-29 \times 10^9/L$) and thrombocytopenia was associated with fivefold higher odds of having severe disease (OR: 5.13; 95% CI: 1.81–14.58) [9]. Lastly, a recent report investigated the prognostic factors of 28-day mortality of severely affected COVID-19 patients and the association between mortality and the administration of low molecular weight heparin (LMWH) for at least seven days. Elevated D-dimer, prolonged prothrombin time and increased age were associated with higher- while higher platelet count was associated with lower 28-day mortality. The use of anticoagulant therapy resulted in lower mortality in patients with sepsis-induced coagulopathy score ≥ 4 (LMWH: 40.0% vs No-LMWH: 64.2%, $p = 0.029$), lower mortality in patients with D-dimer over sixfold the upper limit of normal (LMWH: 32.8% vs No-LMWH: 52.4%, $P = 0.017$), but there was no overall benefit for patients on LMWH (LMWH: 30.3% vs No-LMWH: 29.7%, respectively, $p = 0.910$) [10].

Both thrombocytopenia and elevated D-dimer can be explained by the excessive activation of the coagulation cascade and platelets. Viral infections elicit the systemic inflammatory response and cause an imbalance between procoagulant and anticoagulant homeostatic mechanisms [11]. Multiple pathogenetic mechanisms are involved, including endothelial dysfunction, von Willebrand factor elevation, Toll-like receptor activation, and tissue-factor pathway activation [11–13]. Platelets, upon antigen recognition, become activated and interact with white blood cells to facilitate pathogen clearance through white blood cell activation and clot formation [14]. Platelets are key mediators of inflammation and sensors of infectious agents through the interaction of cell surface receptors and pathogens (pathogen pattern recognition receptors) or immune system derivatives (immunoglobulin Fc receptors and complement receptors). The activation of and the interactions between macrophages, monocytes, endothelial cells, platelets and lymphocytes play a critical role in the procoagulant effect of viral infections [12,15].

2. SARS-CoV-1 and coagulation disorders

In 2003, a different coronavirus epidemic caused by the SARS-CoV-1 virus had emerged in Guangdong, China and had subsequently spread in another 26 countries [16–18]. Similarly to COVID-19, SARS-CoV-1 had been associated with thrombotic complications and hematologic manifestations [19–23]. Nicholls et al. reported histological findings compatible with edema and fibrin thrombi within the pulmonary vasculature in a SARS-CoV-1 infected patient [24]. Additionally, thrombi have been identified in pulmonary, bronchial, and small lung veins of postmortem SARS-CoV-1 infected lung autopsies, suggesting a prothrombotic effect of the SARS-CoV-1 virus, mainly affecting the pulmonary vasculature [19,21,25]. A study from Singapore, involving postmortem autopsies of eight confirmed SARS-CoV-1 cases, identified pulmonary embolism in four patients, deep vein thrombosis in three patients, and widespread multi-organ infarcts due to thrombi in two patients [26]. Multiple organ thrombosis, associated with polyangiitis and microcirculation disturbance was also reported in an autopsy study on a 57-year old SARS-CoV-1 patient [27]. In addition, ischemic strokes have been described in five out of 206 patients infected with SARS-CoV-1 in a study by Umaphathi et al., while approximately 30% of critically ill patients had venous thromboembolism [20]. SARS-CoV-1 has also been associated with fetal complications (oligohydramnios, intrauterine growth delay, and small fetal size) due to placental circulation dysfunction, mainly attributed to intervillous and subchorionic fibrin deposition, avascular and fibrotic villi formation, and prothrombotic tendency [28].

Laboratory parameters associated with the coagulation cascade and normal clot formation have been investigated and identified as commonly disturbed in SARS-CoV-1 patients. Ng et al. reported a SARS-CoV-1 case complicated by overt pulmonary artery thrombosis and associated with prolonged prothrombin time, prolonged activated

partial thromboplastin time, elevated D-dimer, and worsening thrombocytopenia [19]. A retrospective analysis of 157 SARS-CoV-1 infected patients revealed the presence of thrombocytopenia (55%) with lowest platelet count at one week after the onset of symptoms, reactive thrombocytosis (49%) with a peak during the third week (median = 17 days), and prolonged activated partial thromboplastin time (63%) over the first two weeks [22]. Similarly, Yang and colleagues reported increased thrombopoietin levels in SARS-CoV-1 patients in the convalescent phase compared to normal controls (290 ± 53 pg/ml vs 228 ± 17 pg/ml, respectively) with a concomitant increase in platelet count [29]. Lee et al. described a cohort of 156 SARS-CoV-1 infected healthcare workers, medical students, and family members (secondary and tertiary cases), and reported high rates of thrombocytopenia on presentation (44.8%), prolonged activated partial-thromboplastin time (42.8%), and elevated D-dimer (45.0%). However, the aforementioned variables were not associated with the composite outcome of intensive care unit admission or death [30]. The clinical value of low platelet count has been assessed in a diagnostic model, which included thrombocytopenia (in addition to myalgia, fever, diarrhea, rhinorrhea/sore throat, and lymphopenia) and effectively detected SARS-CoV-1 with 100% sensitivity and 86.3% specificity [31]. Lastly, SARS-CoV-1 has been associated with the presence of anticardiolipin antibodies in patients with post-SARS osteonecrosis and with positive lupus anticoagulant test in children [32,33].

The effect of SARS-CoV-1 on the coagulation cascade has been investigated in an *in vitro* model containing peripheral blood mononuclear cells. Interestingly, a panel of genes that reveal a procoagulant effect has been reported to be highly expressed in SARS-CoV-1 infected mononuclear cells, including fibrinogen (FGB, FGG), SERPINS (D1 and A3), factors II, III and X [34]. In addition, thromboxane synthase (TBXAS) gene and Toll-like receptor 9 (TLR9) have also been identified as targets of the SARS-CoV-1 [34]. Increased thromboxane production promotes vasoconstriction, platelet aggregation, and endothelial dysfunction [35,36]. The TLR9 receptor is expressed in platelets and – upon ligand binding – promotes platelet activation, degranulation, and aggregation through the Interleukin-1 receptor-associated kinase 1 (IRAK1) and protein kinase B (Akt/PKB) pathways [37].

Analysis of the effects of SARS-CoV-1 in human hepatoma cells (Huh7) revealed upregulation in the expression of five genes associated with the coagulation pathway, namely the tissue factor pathway inhibitor 2 (TFPI2), early growth response 1 (EGR1), plasminogen activator inhibitor 1 (PAI1/SERPINE1), the phospholipid scramblase 1 (PLSCR1), and thrombospondin 1 (THBS1) [38]. TFPI2 inactivates the tissue factor-VIIa complex and thrombin generation, but its expression upregulation most probably corresponds to a counteractive mechanism that inhibits overt coagulation cascade activation in response to inflammation [38,39]. PAI1 gene upregulation inhibits fibrinolysis and promotes fibrin deposition during inflammatory states [40].

SARS-CoV-1 nucleocapsid protein has also been considered as one of the important determinants of SARS prothrombotic state. Han et al. proposed that the nucleocapsid protein induces the human fibrinogen-like protein-2 (HFGL2) prothrombinase gene through activation of the C/EBP- α transcription factor [41]. In contrast to this finding, Siu and colleagues reported no upregulation of HFGL2 expression in human embryonic kidney (HEK293) cells [42].

Dysregulation of the urokinase pathway and other associated prothrombotic genes have also been implicated in the pathogenesis of SARS-CoV-1 related coagulation disorders. In a SARS-CoV-1 infected mouse model procoagulant genes expression (thrombin, VII, XI, XII), plasminogen activators expression (PLAU,PLAT) and urokinase pathway dysregulation have been associated with fatal SARS-CoV-1 infection [43,44].

3. MERS-CoV and coagulation disorders

In 2012, another coronavirus had been initially reported in Saudi

Arabia and was identified as the virus responsible for the so-called “Middle East respiratory syndrome” (MERS-CoV). MERS-CoV disease, similar to COVID-19 and SARS-CoV-1 disease, was associated with thrombotic complications and hematologic manifestations. However, available data are scarce compared to COVID-19 and SARS-CoV-1.

Thrombocytopenia was identified in 36% of 47 laboratory confirmed MERS-CoV cases in Saudi Arabia [45]. A retrospective study by Hwang et al. reported relatively lower platelet count in MERS-CoV patients compared to negative controls (platelet count: $164 \pm 76.57 \times 10^3/\mu\text{L}$ vs. $240 \pm 79.87 \times 10^3/\mu\text{L}$, respectively) [46]. Kim et al. reported mild thrombocytopenia as a common finding during the first week, without any difference between patients with mild or severe disease [47]. Similar to COVID-19 non-survivors, DIC is one of the major complications reported in fatal MERS-CoV cases [8,48,49]. Algahtani and colleagues reported a case of MERS-induced DIC, intracerebral hemorrhage, and multiorgan failure, which occurred two weeks post-admission in an otherwise stable patient [50]. Al-Abdallat et al. reported a fatal case associated with DIC, hyperkalemia, ventricular tachycardia, and cardiac arrest [49].

The effect of the MERS-CoV on the coagulation cascade has also been demonstrated experimentally in transgenic mice expressing the human dipeptidyl peptidase 4 (hDPP4), which is considered as the cell binding and entry receptor of the virus. Histopathologic examination revealed microthrombi present on day 4 of infection in the pulmonary vasculature and parenchymal consolidation, alveolar edema, and cellular infiltrates as the main findings of the MERS-CoV infection [51]. On this basis, Algaissi and colleagues investigated the effects of increased soluble hDPP4 expression induction and the potential therapeutic effects of recombinant hDPP4 administration. The MERS-CoV infection associated lung histopathologic findings were milder in both groups compared to controls [52].

4. Conclusion

The dysregulation of the coagulation cascade and the subsequent formation of intra-alveolar or systemic fibrin clots are prominent findings in coronavirus infections associated with severe respiratory disease, and have been demonstrated in both humans and animal models. They can be attributed to the prothrombotic response, which attempts to prevent diffuse alveolar hemorrhage, but can instead result in overt clot formation with detrimental effects in patient recovery and survival.

5. Authorship

Conception and study design: Dimitrios Giannis

Data acquisition: Dimitrios Giannis, Ioannis A. Ziogas, Panagiota Gianni

Writing – original draft: Dimitrios Giannis, Ioannis A. Ziogas

Writing – review & editing: Dimitrios Giannis, Ioannis A. Ziogas, Panagiota Gianni

Final approval of the manuscript: Dimitrios Giannis, Ioannis A. Ziogas, Panagiota Gianni

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Declaration of Competing Interest

None.

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