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REVIEW

Impaired coagulation, liver dysfunction and COVID-19: Discovering an intriguing relationship

Damiano D'Ardes, Andrea Boccatonda, Giulio Cocco, Stefano Fabiani, Ilaria Rossi, Marco Bucci, Maria Teresa Guagnano, Cosima Schiavone, Francesco Cipollone

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Abstract

Coronavirus disease 2019 (COVID-19) is, at present, one of the most relevant global health problems. In the literature hepatic alterations have been described in COVID-19 patients, and they are mainly represented by worsening of underlying chronic liver disease leading to hepatic decompensation and liver failure with higher mortality. Several potential mechanisms used by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to cause liver damage have been hypothesized. COVID-19 primary liver injury is less common than secondary liver injury. Most of the available data demonstrate how liver damage in SARS-CoV-2 infection is likely due to systemic inflammation, and it is less likely mediated by a cytopathic effect directed on liver cells. Moreover, liver alterations could be caused by hypoxic injury and drugs (antibiotics and non-steroidal anti-inflammatory drugs, remdesivir, tocilizumab, tofacitinib and dexamethasone). SARS-CoV-2 infection can induce multiple vascular district atherothrombosis by affecting simultaneously cerebral, coronary and peripheral vascular beds. Data in the literature highlight how the virus triggers an exaggerated immune response, which added to the cytopathic effect of the virus can induce endothelial damage and a prothrombotic dysregulation of hemostasis. This leads to a higher incidence of symptomatic and confirmed venous thrombosis and of pulmonary embolisms, especially in central, lobar or segmental pulmonary arteries, in COVID-19. There are currently fewer data for arterial thrombosis, while myocardial injury was identified in 7%-17% of patients hospitalized with SARS-CoV-2 infection and 22%-31% in the intensive care unit setting. Available data also revealed a higher occurrence of stroke and more serious forms of peripheral arterial disease in COVID-19 patients. Hemostasis dysregulation is observed during the COVID-19 course. Lower platelet count, mildly increased prothrombin time and increased D-

dimer are typical laboratory features of patients with severe SARS-CoV-2 infection, described as "COVID-19 associated coagulopathy." These alterations are correlated to poor outcomes. Moreover, patients with severe SARS-CoV-2 infection are characterized by high levels of von Willebrand factor with subsequent ADAMTS13 deficiency and impaired fibrinolysis. Platelet hyperreactivity, hypercoagulability and hypofibrinolysis during SARS-CoV-2 infection induce a pathological state named as "immuno-thromboinflammation." Finally, liver dysfunction and coagulopathy are often observed at the same time in patients with COVID-19. The hypothesis that liver dysfunction could be mediated by microvascular thrombosis has been supported by post-mortem findings and extensive vascular portal and sinusoidal thrombosis observation. Other evidence has shown a correlation between coagulation and liver damage in COVID-19, underlined by the transaminase association with coagulopathy, identified through laboratory markers such as prothrombin time, international normalized ratio, fibrinogen, D-dimer, fibrin/fibrinogen degradation products and platelet count. Other possible mechanisms like immunogenesis of COVID-19 damage or massive pericyte activation with consequent vessel wall fibrosis have been suggested.

Key Words: COVID-19; SARS-CoV-2; Liver; Coagulation

Core Tip: Evidence in the literature suggests a contribution of the severe acute respiratory syndrome coronavirus 2 to the pathophysiology of liver injury, atherothrombosis and coagulation disorders. This minireview explores the possible mechanisms by which these alterations are generated during coronavirus disease 2019 according to current knowledge.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is, at present, one of the most relevant global health problems, declared a pandemic on March 11, 2020 by the World Health Organization[1]. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel positive-sense single-stranded RNA betacoronavirus[2,3]. The pulmonary manifestation of COVID-19, including pneumonia and acute respiratory distress syndrome, are well known, but it is necessary to emphasize that the coronavirus deleterious effects are also exerted on many other organ systems and are responsible for extrapulmonary manifestations[4].

SARS-CoV-2 can cause both direct and indirect cardiovascular sequelae (myocardial injury, acute coronary syndromes, cardiomyopathy, acute cor pulmonale, arrhythmias and cardiogenic shock), acute kidney injury and gastrointestinal symptoms, such as diarrhea, nausea, vomiting, abdominal pain and anorexia[4]. Neurological complications include headaches, dizziness, ageusia, myalgia, anosmia up to stroke, Guillain-Barré and encephalopathy, and dermatological signs have also been described (petechiae, urticaria, vesicles, erythematous rash, livedo reticularis)[4]. Hepatobiliary manifestations can be observed especially in patients with severe presentations of COVID-19 and occur mainly with increased plasma levels of transaminases and bilirubin[4]. Thromboembolic events have also been described in COVID-19, such as acute limb ischemia, which can occur in patients without existing peripheral arterial disease and in those receiving thromboprophylaxis. Acute abdominal-thoracic aortic thrombosis and mesenteric ischemia are less common but associated with significant morbidity and mortality[5]. Several studies have also demonstrated increased rates of deep vein thrombosis and pulmonary embolism in COVID-19 patient[5-7]. Acute cerebrovascular disease, including ischemic stroke, and disseminated intravascular coagulation are also severe thrombotic complications of COVID-19 that must not be forgotten[5].

This article aims to explore the possible mechanisms underlying hepatic and hemocoagulative alterations in COVID-19 through the search of published, readily accessible, peer-reviewed, full articles related to this topic written in English and found on PubMed.

COVID-19 AND LIVER

Pathophysiology

SARS-CoV-2 has the capacity to infect cells through the angiotensin-converting enzyme 2 (ACE2) receptor that is mainly expressed on the type 2 alveolar cells[8]. The ACE2 receptor is mainly present in the liver, lung, heart, renal and gastrointestinal system[9]. Regarding hepatic involvement, the level of ACE2 expression in cholangiocytes (59.7%) is higher than hepatocytes (2.9%)[10]. SARS-CoV-2 cell entry is mediated by its S protein, which specifically interacts with the host cell ACE2 and transmembrane serine protease 2[11]. The major expression of ACE2 in cholangiocytes reveals that SARS-CoV-2 may cause bile duct dysfunction. Cholangiocytes play critical roles in liver regeneration and immune responses, indicating that viral immunologic injury might be important in liver injury in COVID-19[12].

Even if there is a substantial difference in ACE2 receptor expression between the liver and biliary tract, the liver is not unaffected by the SARS-CoV-2 infection. In fact, current data have shown that in patients with COVID-19 aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase levels are increased, while alkaline phosphatase and gamma glutamyl transferase, representatives of bile duct injury, did not increase significantly[12]. Indeed, in the literature many clinical findings and hepatic alterations are described, and there are several reported potential mechanisms used by the virus to cause liver disease.

Most of the available data demonstrate that hepatic injury during SARS-CoV-2 infection is more likely due to systemic inflammation, and it is less likely mediated by a cytopathic effect directed on liver cells. Viral RNA can be detected in liver tissue of patients with COVID-19, but infection of liver cells has not yet been demonstrated[13]. During a viral infection, the innate and the acquired immune systems recognize pathogen associated molecular patterns and specific viral antigens and release inflammatory molecules, such as cytokines and chemokines, that activate macrophages and T cells to clear the virus and kill infected cells. In patients affected by COVID-19, high levels of inflammatory cytokines have been observed, and this context could cause significant liver damage when SARS-CoV-2 infects host hepatocytes. The most involved inflammatory molecules are tumor necrosis factor, interleukin-2 (IL-2), IL-6, IL-7, IL-18, granulocyte-colony stimulating factor, interferon-γ and ferritin[14]. An early hypercytokinemia could lead to multiorgan injuries, including the liver (Figure 1). The literature demonstrates that worse outcomes of COVID-19 are more common in patients with early cytokine elevation[15].

Another potentially harming mechanism is represented by hypoxic injury. The complex vascularization of the liver makes it particularly exposed to circulatory alterations that could be generated in cardiac, circulatory, respiratory failure or in septic shock, causing decreased perfusion of the liver[12]. About 1.1%-20.0% of COVID-19 patients are affected by septic shock, and 23.0% of patients have heart failure[16].

Drugs are also involved with damage mechanisms, particularly causing drug induced liver injury. Antibiotics and non-steroidal anti-inflammatory drugs, which are one of the most common causes of drug induced liver injury in the general population, can contribute to liver damage in COVID-19 patients when used to treat bacterial superinfection, myalgias or fever. Furthermore, drug induced liver injury has been shown in 15.2% of patients receiving remdesivir and in 37.2% of patients in treatment with lopinavir/ritonavir[17]. Finally, dexamethasone, tocilizumab and tofacitinib, used to treat COVID-19, could potentially create hepatic injury *via* pre-existing chronic liver disease reactivation, especially hepatitis B virus[18].

Clinical characteristics

During SARS-CoV-2 infection, patients can be asymptomatic or present clinical symptoms such as fever, dry cough, headache, dyspnea and fatigue and up to acute respiratory distress syndrome, shock and cardiac failure[19,20]. Hepatic involvement can occur through all the pathophysiological pathways previously investigated and still other studies are needed to better characterize them. In current reports, COVID-19 primary liver injury is less common than secondary liver injury[21,22]. SARS-CoV-2 liver involvement is mainly represented by worsening of underlying chronic liver disease, leading to hepatic decompensation and acute-on-chronic liver failure, with higher mortality. Symptoms mainly reported in the literature associated to liver injury and gastrointestinal involvement are diarrhea, nausea, vomiting and loss of appetite. Abnormal liver function was also observed with the increase of AST, ALT, lactate dehydrogenase and bilirubin and the decrease of albumin[21-25].

According to the current data, hepatic dysfunction is significantly higher in critically ill patients and is associated with a poor outcome, underlining its importance in clinical settings. Elevated liver enzymes are observed predominantly in severe and critical cases of COVID-19. For example, increased AST was observed in 62% of patients in the intensive care unit (ICU) compared to 25% in non-ICU patients[23]. Chen *et al*[21] reported that AST, ALT, alkaline phosphatase, gamma glutamyl transferase and bilirubin levels were significantly higher in non-survivors than in survivors. Also hypoalbuminemia was found significantly lower in deceased patients rather than in surviving patients. Furthermore, according to Bangash *et al*[24] the mortality rate in patients with underlying chronic liver disease was 0%-2%. According to the literature data, liver injury is most common in critically ill patients who have diabetes and hypertension[22,25].

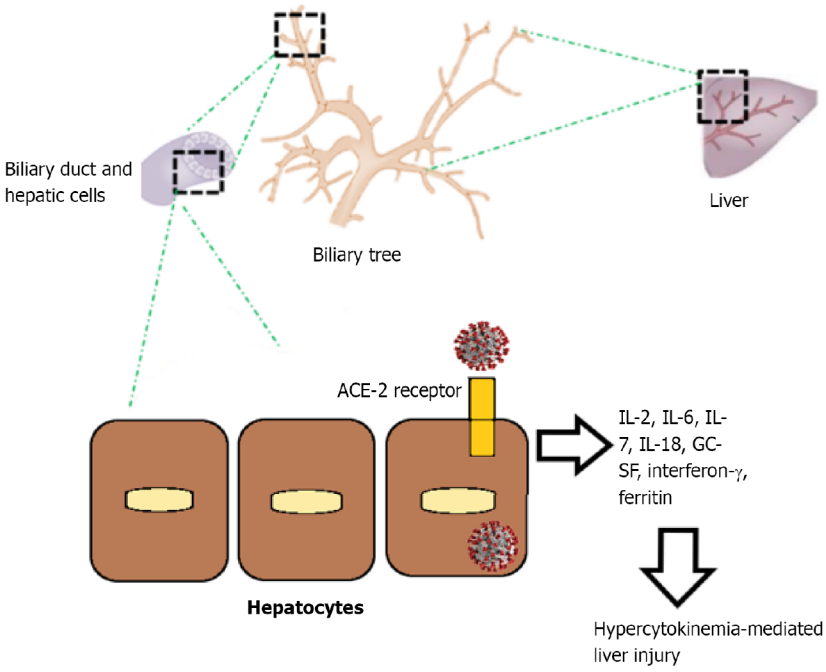

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Figure 1 Structure of severe acute respiratory syndrome coronavirus 2 hepatic receptors that induce hepatic injury mediated by cytokine storm. Inflammatory mediators secreted by lymphocytes and macrophages aggravate inflammatory responses causing hepatic damage. IL: Interleukin; GC-SF: Granulocyte colony stimulating factor; ACE-2: Angiotensin-converting enzyme 2.

The fact that liver injury in COVID-19 is mostly hepatocellular rather than cholestatic is demonstrated by the more frequent elevation of ALT, AST and lactate dehydrogenase than of alkaline phosphatase and gamma glutamyl transferase. The latter two did not increase significantly, and jaundice is uncommon[12,26]. Moreover, the current data demonstrate that AST could represent an important hepatocellular injury marker because its elevation is associated with a major mortality risk[27]. According to a meta-analysis, the pooled prevalence of abnormal liver functions (12 studies, 1267 patients) was 19%, and in subgroup analysis patients with severe COVID-19 had higher rates of abdominal pain and abnormal liver function including increased ALT and AST[28].

In a hospital setting, drugs also have to be considered in liver injury; moreover COVID-19 critically ill patients are treated with multiple drugs, such as antibiotics, immunosuppressants and antiviral and antipyretic agents that are associated to abnormal liver function, especially when used in patients with severe COVID-19[23,29]. In the literature, drug induced liver injury has been shown to result in AST and ALT elevation and reactivation of pre-existing chronic liver disease, above all hepatitis B virus infection[17,18]. Indeed, a retrospective study has shown that patients with chronic hepatitis B virus hepatitis had a worse prognosis for COVID-19 and for a higher mortality and a higher incidence of acute-on-chronic liver failure[30]. In a trial by Goldman *et al*[31] comparing remdesivir treatment for either 5 d or 10 d, severe but not life-threatening ALT/AST elevations were reported in 4%-6% of patients and life-threatening AST/ALT elevations in 2%-3% of patients.

COVID-19 AND COAGULATION DISORDERS

Clinical characteristics

SARS-CoV-2 infection can induce multiple vascular district atherothrombosis by simultaneously affecting cerebral, coronary and peripheral vascular beds. Data in the literature highlight how the virus can trigger an exaggerated immune response, which added to the cytopathic effect of the virus can induce endothelial damage and a prothrombotic dysregulation of hemostasis[32-34]. Nowadays, there are several reports and original papers on cases of venous thromboembolism and pulmonary embolism related to COVID-19[35-40].

Incidence of symptomatic and confirmed venous thrombosis in COVID-19 patients hospitalized in the ICU can reach 30%-40%[41]. Data from a study performed in China demonstrated that 25% of COVID-19 patients developed lower extremity deep vein thrombosis without venous thromboembolism prophylaxis[42]. A work by Klok *et al*[36] described pulmonary embolisms in 25 of 184 ICU patients with COVID-19 (13.6%), 72% of which were in central, lobar or segmental pulmonary arteries, despite standard dose pharmacological prophylaxis[36,43]. In Italy, Lodigiani *et al*[35] showed thromboembolic

events (venous and arterial) in 7.7% of patients admitted with COVID-19, corresponding to a cumulative rate of 21.0%.

There are currently fewer data for arterial thrombosis. A study from Wuhan showed that about 12% of patients displayed Hs-troponin I above the threshold of 28 pg/mL[14]. Other data revealed that myocardial injury was diagnosed in 7%-17% of patients hospitalized with SARS-CoV-2 infection and 22%-31% in the ICU setting[16,25]. Dysregulated inflammatory response enhances atherosclerotic plaque disruption[21,44-46]. Previous studies demonstrated that influenza and community-acquired pneumonia are related to an increased risk of myocardial infarction, within the first 7 d of diagnosis and even after hospitalization[47]. Regarding cerebrovascular disease, occurrence of stroke in COVID-19 patients ranges between 2.7% and 3.8%, and these subgroup of patients often displayed comorbidities such as hypertension and were older on average[48,49]. Moreover, there are some reports documenting more serious forms of peripheral arterial disease in patients with SARS-CoV-2 infection[50].

Laboratory findings

Hemostasis dysregulation has been described as an early pathological change in the COVID-19 course. Lower platelet count, mildly increased prothrombin time and increased D-dimer are typical laboratory features of patients with severe SARS-CoV-2 infection, and they are correlated to poor outcomes[51]. Those changes have been described as "COVID-19 associated coagulopathy"[52-54]. Moreover, patients with severe SARS-CoV-2 infection are characterized by high levels of IL-6, thus leading to a subsequent increase in proteins such as fibrinogen and von Willebrand factor (vWF)[55]. High lactate dehydrogenase and ferritin values are other laboratory findings of patients with severe COVID-19 infection, resembling a thrombotic microangiopathy[51,55,56]. Furthermore, complement components C5b-9, C4d and mannose-binding lectin-associated serine protease 2 have been detected in the small vessels of the lung due to complement-associated microvascular injury[57]. High levels of vWF and subsequent ADAMTS13 deficiency seem to be other typical findings of severe COVID-19 infection[52,58,59]. Decreased levels of ADAMTS13 can induce increased platelet-endothelial interaction generating a thrombotic microangiopathy-like state[52,60-63].

Recent data demonstrate that fibrinolysis is impaired in patients with severe COVID-19[64,65]. Critical COVID-19 patients are characterized by low levels of plasminogen, as for a consumptive state [65]. Nougier *et al*[66] reported elevated levels of plasminogen activator inhibitor 1 and low levels of tissue plasminogen activator, along with high thrombin generation, thus demonstrating a significant imbalance between inhibitor and activator factors of fibrinolysis.

Pathogenetic mechanisms

Platelet hyperreactivity, hypercoagulability and hypofibrinolysis induce a pathological state that has been named "immuno-thromboinflammation" during SARS-CoV-2 infection[67]. SARS-CoV-2 binds to the ACE2 receptor on the surface of endothelial and arterial smooth muscle cells, inducing a cytopathic effect and a subsequent endothelial injury[68]. As it is well known, endothelial damage triggers platelet activation, adhesion to the subendothelial matrix and aggregation, thus generating a platelet plug[69]. Moreover, a release of vWF, inefficient cleavage of ultralarge vWF catalyzed by ADAMTS13, direct contact with activating surfaces in the subendothelial matrix, loss of heparan sulfates at the surface of injured blood vessels, disrupted generation of nitric oxide, prostaglandin E2 and prostaglandin I2 and loss of surface expression of ectonucleotidases occur[70,71]. Platelet activation may represent a consequence of the production of a consistent level of thrombin after initiation of coagulation[64].

Furthermore, high IL-6 levels can induce megakaryocytopoiesis generation and platelet formation, which could play a role to generate a hypercoagulability state, in particular within the lung. Intriguing, SARS-CoV-2 can bind directly to platelets since they express both ACE2 and transmembrane serine protease 2 on their surface[72]; this binding can favor platelet activation and the release of clotting factors, inflammatory molecules and leukocyte-platelet aggregates[72].

In patients affected by severe COVID-19 pneumonia, levels of tissue factor (TF) on monocytes are higher than normal, together with P-selectin expression and the amount of platelet-neutrophil and platelet-monocyte aggregates[2]. Therefore, platelet activation due to adenosine diphosphate, thrombin and collagen stimulation is enhanced in these patients. Platelet hyperactivation induced by SARS-CoV-2 infection induce the release of inflammatory molecules such as cytokines, chemokines, growth factors and even procoagulant factors like fibrinogen and vWF[73]. This mechanism seems to generate a vicious cycle since inflammatory molecules worsen endothelial injury by decreasing nitric oxide availability and enhancing oxidative stress and/or favoring leukocyte-endothelial interaction[74,75].

Endothelial injury triggers the release of TF in the blood stream. Moreover, TF can derive from macrophage/monocyte cells and through their microparticles, as a consequence of macrophage activation syndrome shown in patients with severe COVID-19 infection[76]. SARS-CoV-2 can directly induce macrophage activation, which can even occur as a consequence of the inflammatory hyperactivation (cytokine storm), as demonstrated by high levels of interferon-g, C-C motif chemokine ligand 2 and C-X-C motif chemokine 9 and 10 detected in critical COVID-19 patients[77,78].

Neutrophils can also be activated both directly by SARS-CoV-2 and by other inflammatory cells, thus generating neutrophil extracellular traps that may activate Factor XII and the intrinsic pathway of coagulation[79]. Hemostasis dysregulation in SARS-CoV-2 infection is also characterized by a decreased

activity of endogenous anticoagulants like antithrombin, TF pathway inhibitor and anticoagulation proteins C and S[78,80]. Endothelial injury and platelet hyper-activation in severe COVID-19 patients enhance the release of plasminogen activator inhibitor 1 (PAI-1)[81]. High levels of PAI-1 can further inhibit fibrinolysis, thus worsening the thrombotic burden[82,83]. Therefore, as the pulmonary inflammation progresses, there is consumption of plasminogen, along with high levels of PAI-1 and depletion of tPA, thus inducing a state of hypofibrinolysis and allowing perpetuation of prothrombotic state[84].

In patients with SARS-CoV-2 infection, the presence of antiphospholipid antibodies has been demonstrated, which may directly induce endothelial cell activation and enhance TF expression by monocytes, thus contributing to the procoagulant and prothrombotic state[85-87]. Particularly, antiphospholipid antibodies can bind to the platelets and trigger their activation decreasing levels of inhibitors such as activated protein C and antithrombin and increasing clotting factors such as FXa and thrombin [88-90].

SARS-CoV-2 can dysregulate the ACE pathway by its binding to the ACE2 receptor on tissues; high levels of angiotensin (Ang) II favor PAI-1 and TF expression, thus promoting hypercoagulability and impairing fibrinolysis[60]. Furthermore, Ang II receptors on platelets can induce platelet activation and aggregation[91]. Ang 1,7 levels are lower in COVID-19 patients who develop severe disease[92]. Ang 1,7 is a vasoprotective molecule by mediating vasodilation and blocking platelet aggregation through nitric oxide release[93-95]. Therefore, low Ang 1,7 levels can contribute to the procoagulant state in COVID-19 infection. Finally, obesity is a main risk factor for thrombosis due to adipocytokine-mediated mechanisms, increased inflammatory molecules, Ang II/Ang 1,7 imbalance, reactive oxygen species-mediated endothelial dysfunction and lipid and glucose metabolism changes[96-98].

RELATIONSHIP BETWEEN COVID-19, LIVER AND COAGULATION

Liver dysfunction and coagulopathy are often observed in patients with COVID-19. Japanese researchers found that patients with high ALT had higher levels of D-dimer and fibrin/fibrinogen degradation products. In particular elevation of ALT and D-dimer were identified simultaneously[99]. Moreover D-dimer was independently associated to ALT elevation[99].

This study suggests the hypothesis that liver dysfunction could be mediated by microvascular thrombosis, and intrahepatic microvascular thrombosis could theoretically play a role in this physiopathological context. This hypothesis is supported by post-mortem findings by Sonzogni *et al* [100] who found marked derangement of intrahepatic blood vessels with aspects of intravascular thrombosis, suggesting a possible liver damage linked to thrombotic processes. Other evidence has shown a correlation between coagulation and liver damage in COVID-19. In fact, a Chinese study on COVID-19 patients demonstrated the association between AST and ALT values with coagulopathy, identified through laboratory markers such as prothrombin time, international normalized ratio, fibrinogen, D-dimer and platelet count[101]. Pathological findings are consistent with a vascular-related damage caused by impaired blood flow, with lesions similar to histological characteristics of hepatopulmonary syndrome and in obliterative portal venopathy[100]. Indeed it has been shown a diffuse network of sinusoids decorated by CD34 suggesting an abnormal hepatic circulation of blood[100].

A likely explanation could be related to increased hepatic blood flow: this aspect may be linked to heart distress or to thrombotic phenomena in portal and sinusoidal vessels[100]. The abnormal high levels of transaminases in some patients whose liver sample were analyzed post-mortem could be explained by extensive vascular portal and sinusoidal thrombosis, leading to confluent parenchymal necrosis and hepatic cells accelerating apoptosis[100]. Attention must be paid to the evidence of massive pericyte activation in liver samples obtained post-mortem[100]. Pericytes are involved in the recruitment of inflammatory cells in liver injury, and their transformation in myofibroblast-like cells leads to the production of abundant amounts of extracellular matrix proteins and to the consequent vessel wall fibrosis[100].

CONCLUSION

Liver abnormalities and coagulopathy are physiopathological characteristics of COVID-19 that represent the most relevant global health problem. Hypercoagulability, hypofibrinolysis and platelet alterations during SARS-CoV-2 infection induce a sort of "immuno-thromboinflammation," while mildly increased prothrombin time and increased D-dimer are typical laboratory features of patients with severe SARS-CoV-2 infection, described as "COVID-19 associated coagulopathy." These phenomena are clinically relevant with manifestations of thrombosis in a large variety of anatomic districts. Moreover, hepatic alterations are mainly represented by worsening of underlying chronic liver disease leading to hepatic decompensation and liver failure with higher mortality, and they appear to be mediated more by systemic inflammation, direct cytopathic effect on liver cells, hypoxic injury and drugs. Liver dysfunction and coagulopathy are also observed at the same time in patients with COVID-19, probably mediated by microvascular thrombosis, immunological mechanisms and pericyte activation. More data

are needed to better investigate the relevant relationship between coagulation, liver dysfunction and COVID-19 with the aim to understand more deeply the physiopathological mechanisms of SARS-CoV-2 and to evaluate new therapeutic strategies to prevent mortality.

FOOTNOTES

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