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EDITORIAL

Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2

Chiara Robba[a], Denise Battaglini[a], Paolo Pelosi[a,b] and Patricia R. M. Rocco[c,d]

[a]Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy; [b]Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy; [c]Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; [d]Ministry of Science, Technology, Innovation and Communication, Brasilia, Brazil

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1. Introduction

In December 2019, an outbreak of viral pneumonia caused by a novel coronavirus (since named SARS-CoV-2) was identified in Wuhan, China. Within few months, this disease – now known as coronavirus disease 2019 (COVID-19) – spread worldwide, causing a global health emergency [1]. The classic routes for transmission of SARS-CoV-2 are airborne droplets and surface contamination. The clinical presentation of COVID-19 ranges from asymptomatic infection to severe respiratory failure, with fever, fatigue, and cough occurring in most cases [1]. However, the pathophysiology of SARS-CoV-2 infection is complex and is now known to involve activation of the immune and hematologic systems. Endotoxin and tumor necrosis factor (TNF-α) trigger the production of interleukin (IL)-6 and IL-8, which is followed by a cytokine storm. Further events lead to activation of the coagulation cascade through endothelial and tissue factor (TF) pathways, as well as systemic inflammatory activation [2]. Moreover, SARS-CoV-2 binds to angiotensin-converting enzyme-2 (ACE2) receptors, which are widely distributed not only in the lung alveolar epithelial cells and nasopharyngeal and oral mucosa but also in the endothelium and vascular smooth muscle cells, in the brain, in the gut, and in peripheral organs such as the liver and kidneys [3]. This suggests that the clinical spectrum of COVID-19 is not limited to local pneumonia, but rather represents a multisystem illness with involvement of different organs and potential for systemic complications [3].

In this context, we aim to briefly discuss the pathophysiology and clinical manifestations of multiple organ damage after SARS-CoV-2 infection. The current definition of SARS-CoV-2 infection may be incorrect since this disease is not only a respiratory infection. However, we believe the recently suggested redefinition of COVID-19 as 'MicroCLOTS' [4] is also inappropriate because it is not only – or even primarily – a vascular disease. We therefore propose a new nomenclature, which includes the concept of multiple organ damage: multiple organ dysfunction in SARS-CoV-2 (MODS-CoV-2) (Figure 1).

2. Lung impairment

A proportion of cases with SARS-CoV-2 infection experience severe respiratory failure with need for mechanical ventilation [1]. Although SARS-CoV-2 has been initially described and treated as acute respiratory distress syndrome (ARDS), COVID-19 represents a novel viral infection of the lower respiratory tract whose pathophysiology and treatment are still poorly understood. In this context, chest computed tomography (CT), focusing not only on pulmonary structure but also on perfusion, may help understand the pathophysiology and guide personalized mechanical ventilation strategies [5,6]. CT findings in COVID-19 vary among patients and with time and can be classified according to three broad phenotypes: multiple, focal, possibly overperfused ground-glass opacities; an overperfused-hypoperfused, patchy, ARDS-like pattern; or hypoperfused, inhomogeneously distributed atelectasis [6]. These phenotypes are attributed to different pathophysiological mechanisms and respiratory mechanics, thus requiring specific ventilatory strategies. Further, the importance of CT perfusion techniques must be emphasized for future CoVID-19 pulmonary assessment. Gattinoni et al. [7] described two phenotypes: L, characterized by low elastance, low ventilation-to-perfusion ratio, and low recruitability; and H, which presents with ARDS-like features. In phenotype L, the main cause of hypoxemia seems to be the impaired distribution of lung perfusion and shunting, and the use of moderate PEEP levels may be helpful to redistribute pulmonary blood flow from damaged to non-damaged lung areas. These patients are candidates for noninvasive ventilation, with low PEEP (max 10 cmH_2O) to reach oxygen saturation (SpO_2) values of 94–95%. In phenotype H, atelectasis is preponderant and moderate to high PEEP values can be used to promote lung recruitment, as can lateral or prone positioning. These patients probably require prompt intubation and invasive ventilation. Finally, evaluation of fibrotic development during the late stage (longer than 25 days) of non-resolving disease or follow-up in survivors must be considered by using chest CT. In summary, the use of personalized ventilator strategies based on respiratory mechanics and chest CT, focusing also on

CONTACT Patricia R. M. Rocco prmrocco@biof.ufrj.br Laboratory of Pulmonary Investigation, Carlos Chagas Filho Biophysics Institute, Federal University of Rio de Janeiro, Rio de Janeiro, RJ 21941-902, Brazil

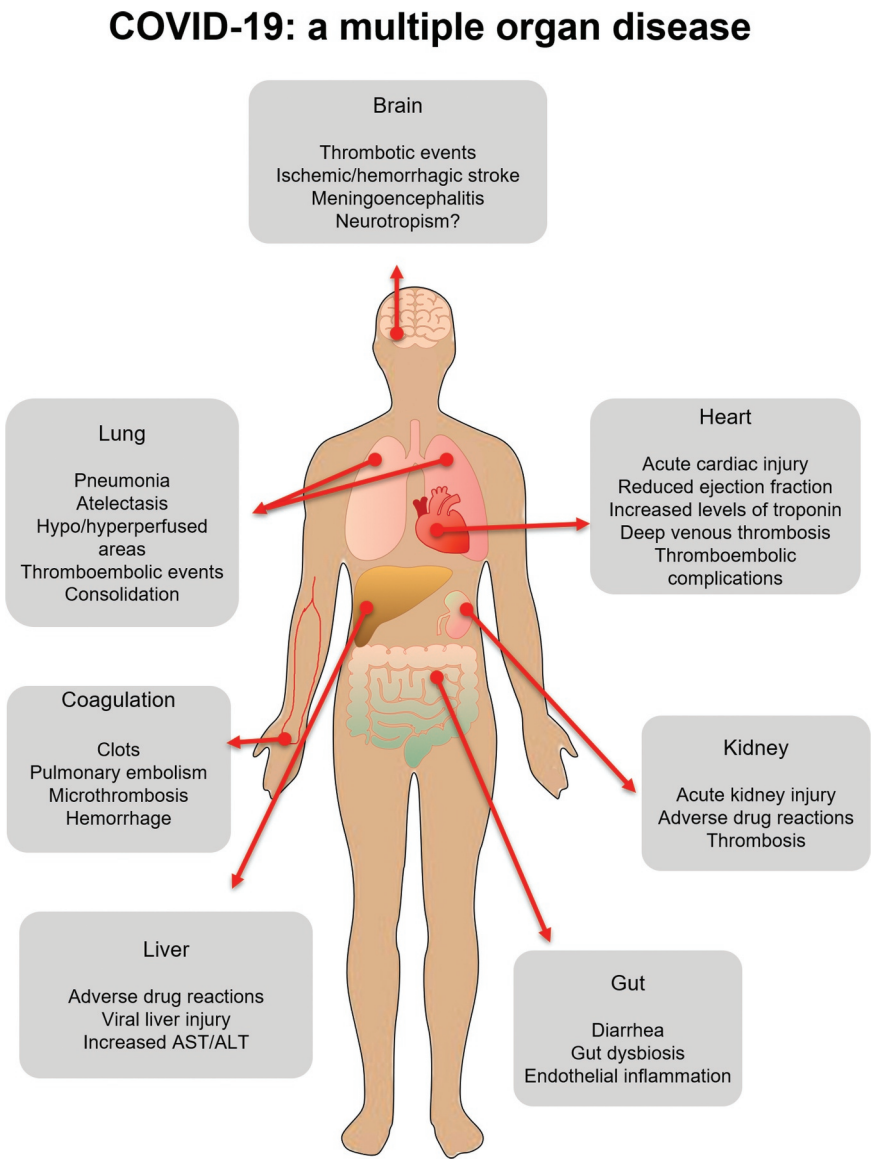

Figure 1. **MODS-CoV-2 features**. Possible organs involved in SARS-CoV-2 infection, including pulmonary, coagulation, cardiac, neurological, renal, hepatic, and gastrointestinal manifestations.

perfusion patterns, is warranted in all patients with severe COVID-19 who require mechanical ventilation [6].

3. Coagulation disorders

A high incidence of thromboembolic and hemorrhagic events has been observed in COVID-19 patients [1]. SARS-CoV-2 infection may lead to activation of the coagulation cascade due to an imbalance between platelet function, the regulatory mechanisms of coagulation, and fibrinolysis. Coagulation derangements seem to be associated with high levels of pro-inflammatory markers such as tumor necrosis factor (TNF-α), interleukin (IL)-6, and IL-8. A recent retrospective study [8] found that 17% of COVID-19 patients were at high risk for venous thromboembolic events (VTE) and 6% were at high risk of bleeding due to VTE prophylaxis, thus suggesting that severe COVID-19 patients are at high risk for both thrombosis and bleeding, either one of which can have a significant negative effect on outcomes. Deep vein thrombosis and pulmonary embolism can occur in COVID-19 patients with pneumonia despite the use of prophylactic low-molecular-weight heparin (LMWH) [9]. Strict monitoring of coagulation function is warranted as well as prophylactic/therapeutic anticoagulation and prompt diagnosis of complications. The Sepsis-Induced Coagulopathy (SIC) Score, able to predicts likelihood of sepsis-induced coagulopathy, has been evaluated in the COVID-19 pandemic given concerns that COVID-19 may cause thrombosis. Traditional coagulation tests, including activated partial thromboplastin time (aPTT) and prothrombin time (PT), should be checked daily; eventually, protein C, protein S, antithrombin (AT), tissue factor pathway inhibitor (TFPI), D-dimers, and coagulation factors can be further investigated. Rotational thromboelastography (TEG) and thromboelastometry (ROTEM) may also be useful. To reduce the risk of microthrombosis and pulmonary embolism, LMWH or unfractionated heparin should be promptly

administered, and treatment with antiplatelet agents (such as clopidogrel) can be considered depending on the patient's clinical conditions. However, careful attention must be paid to the risk of bleeding, and treatment should be individualized to each patient's risk profile [9].

4. Cardiovascular impairment

There is growing evidence suggesting an increased incidence of cardiac injury in COVID-19 patients [10]. In a recent report including 138 patients with COVID-19 found that 7.2% developed acute cardiac injury, with a higher incidence in those admitted to the intensive care unit (22%), which suggests an important effect of cardiac injury on clinical outcome [10]. The largest study published so far on cardiac injury after COVID-19 [11] reported an incidence of 19.7%. Patients with cardiac injury were older, had more comorbidities (such as hypertension), higher leukocyte counts, and higher levels of inflammatory biomarkers (C-reactive protein, procalcitonin, and creatinine) than those without cardiac involvement. Moreover, they were more likely to exhibit ground-glass opacities and densities at radiography and require noninvasive and invasive mechanical ventilation. Patients with cardiac injury also had a higher incidence of complications such as kidney injury, electrolyte disturbances, and coagulation disorders, with a correspondingly higher case fatality rate. In short, cardiac injury is a common finding and seems to be related to both the severity of the disease as well as patient comorbidities. Even though coronaviruses (including MERS-CoV) are known to cause acute myocarditis with direct viral infection of the myocardium [12], evidence of cardiac dysfunction and direct effects of SARS-CoV-2 on the heart requires further research. Moreover, the impact of COVID-19-related respiratory failure and the use of high PEEP on right heart failure should always be taken into account, as well as the possible late complications of COVID-19 pneumonia in patients with pulmonary fibrosis, including pulmonary heart disease and pulmonary hypertension [13]. Meanwhile, strict monitoring of cardiac function using bedside echocardiography, electrocardiography, and standard biomarkers – such as troponin and brain natriuretic peptide (BNP), which has shown to have prognostic value in COVID-19 patients [14] – is warranted.

5. Neurological manifestations

A possible involvement of the central and peripheral nervous system after SARS-CoV-2 infection has also been described, with patients reporting loss of sense of smell or taste, suggesting that the virus might spread from the olfactory epithelium to the brain [15]. Many neurological manifestations have been described recently, ranging from nonspecific signs and symptoms such as headache to epileptic seizures and the Guillain-Barré syndrome have also been recently reported [16]. The potential neurotropic mechanism of COVID-19 may also be due to viral passage from the systemic to the cerebral circulation through the microcirculation, followed by binding to ACE2 receptors in the capillary endothelium [17]. Additionally, neurological damage during the course of SARS-CoV-2 infection may be associated with coagulopathy, with a higher rate of systemic and local thrombotic events [1,18].

Ischemic or hemorrhagic stroke has been associated with increased D-dimer levels [18]. In a recent study of 58 COVID-19 patients, neurological involvement was detected in 14% at ICU admission and 67% after sedation hold, with agitation and confusion being the most common symptoms. Neuroradiological features consistent with meningoencephalitis were demonstrated in eight patients, and areas of small acute ischemic stroke and subacute ischemic stroke were noted. However, in all patients, RT-PCR assays of CSF samples were negative for SARS-CoV-2 [10]. Few studies and case reports have reported direct nervous system involvement after SARS-CoV-2 infection, either in addition to respiratory failure and systemic disease or as the primary clinical presentation [17]. A recent case report described acute necrotizing encephalopathy (ANE) in a patient with COVID-19 [19]. ANE has been previously described as a possible complication of influenza and other viral infections, with its pathogenesis apparently associated with an intracranial cytokine storm, resulting in blood-brain barrier disruption but with no direct viral invasion or para-infectious demyelination [2]. In summary, the neurotropic effect of SARS-CoV-2 requires elucidation, and the neurological features described are likely related to the effects of the systemic infection rather than a direct effect of the virus on the brain.

6. Liver and kidney injury

Some patients can have microemboli in the hepatic and renal vessels, as demonstrated on abdominal CT scan, as consequence of the prothrombotic state [20] resulting in liver and kidney damage. Liver and kidney damage in COVID-19 can be also drug-related. Lopinavir/ritonavir, oseltamivir, ribavirin, remdesivir, and chloroquine or hydroxychloroquine [21], which have been or are being tested as potential treatments for SARS-CoV-2 infection, are all metabolized in the liver, and most of their metabolites are subject to renal excretion. Liver and kidney damage can therefore have an important effect on the concentration, metabolism, and excretion of these medications, thus increasing the risk of toxicity and further hindering consensus as to therapeutic effects and optimal doses. A case report of a COVID-19 patient with liver injury described moderate microvesicular steatosis and mild lobular and portal activity in liver biopsy specimens [22]. However, whether the occurrence of liver dysfunction is related to a direct effect of the virus or to the adverse effect profile of any medications used is unclear [22]. Similarly, an increased incidence of acute renal injury has been described in COVID-19 patients and is associated with higher fatality [23]. Several mechanisms can be implicated: (1) hypertension, often observed in these patients, can result from a pro-inflammatory status, which may cause derangement of renal peripheral vascular resistance; (2) angiotensin II–induced hypertension can cause polarization of CD4 + T cells toward Th1 and Th17 phenotypes, thus increasing IFN-γ, IL-6, and IL-17 expression and CD8 + T cell counts in the kidney [23]; and (3) the innate immune response, including monocytes, macrophages, granulocytes, and dendritic cells, seems to be involved in the endothelial dysfunction observed in angiotensin II–induced hypertension [23]. In summary, evidence is lacking regarding the pathophysiology of hepatic and kidney damage in COVID-19, which are likely to be multifactorial and related to both direct and indirect effects of the infection on the liver and kidneys. Strict monitoring of organ-damage biomarkers, as well as serial imaging, are warranted in case of suspected involvement of these

organs in order to reduce morbidity and optimize medication regimens. COVID-19 patients may also present with gastrointestinal symptoms such as diarrhea, abdominal pain, and vomiting [24]. This is consistent with the fact that ACE2 receptors, a key target for SARS-CoV-2 infection, are highly expressed in the gastrointestinal tract as a whole and in the small bowel in particular. Alteration of the gut microbiota and endothelial inflammation can themselves contribute to spreading the virus [25]. Although evidence is lacking in this context, probiotics, prebiotics, and symbiotics are being employed to improve gut dysbiosis, and a specific probiotic has been suggested for COVID-19 patients [25].

7. Conclusions

Although initially described as a viral pneumonia, SARS-CoV-2 infection seems to present features of a multisystem disease, with impairment of several organs. Clinicians should be aware of potential systemic complications and their management when treating a disease which might be more correctly renamed SARS-CoV-2-associated multiple organ dysfunction syndrome. Research aiming to clarify the mechanisms, clinical features, and management of this disease is urgently needed. Future investigations should focus on exploring the pathophysiology of multiorgan dysfunction, new therapeutic targets, and treatment individualization with personalized approaches to management of 'multiorgan COVID-19' – MODSCoV-2.

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
2. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–1034.
3. Hamming I, Timens W, Bulthuis M, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203:631–637.
4. Ciceri F, Beretta L, Scandroglio AM, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc. 2020;15;Epub ahead of print. PMID:32353223.
•• **This work advanced the hypothesis of MicroCLOTS pathology as part of an atypical acute respiratory distress syndrome.**
5. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med. 2020;46:854–887.
6. Robba C, Battaglini D, Ball L, et al. Distinct phenotypes require distinct respiratory management strategies in severe COVID-19. Respir Physiol Neurobiol. 2020;103455. Online ahead of print. DOI:10.1016/j.resp.2020.103455
• **This article advanced the hypothesis of three distinct respiratory phenotypes characterizing COVID-19 patients.**
7. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;14:1–4.
8. Xu JF, Wang L, Zhao L, et al. Risk assessment of venous thromboembolism and bleeding in COVID-19 patients. Pulmonology. 2020. DOI:10.21203/rs.3.rs-18340/v1
9. Levi M, Thachil J, Iba T, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;S2352–3026:30145–30149.
10. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–1069.
11. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA cardiol. 2020 Mar 25;e200950. DOI:10.1001/jamacardio.2020.0950
12. Zhu H, Rhee JW, Cheng P, et al. Cardiovascular complications in patients with COVID-19: consequences of viral toxicities and host immune response. Curr Cardiol Rep. 2020;22:32.
13. Li J-W, Han T-W, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: a systemic review and meta-analysis. Prog Cardiovasc Dis. 2020;S0033–0620:30080–30083.
14. Gao L, Jiang D, Wen XS, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res. 2020;21:83.
15. Xydakis MS, Dehgani-Mobaraki P, Holbrook EH, et al. Smell and taste dysfunction in patients with COVID-19. Lancet Infect Dis. 2020;S1473–3099:30293.
16. Carod Artal FJ. Neurological complications of coronavirus and COVID-19. Rev Neurol. 2020;70:311–322.
17. McCray PB, Pewe L, Wohlford-Lenane C, et al. Lethal Infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. J Virol. 2007;81:813–821.
18. Zhang J, Song Y, Shan B, et al. Elevated level of D-dimer increases the risk of stroke. Oncotarget. 2018;9:2208–2219.
• **As suggested by this work, elevated D-dimer levels like in COVID-19 increase the risk of cerebrovascular disease.**
19. Poyiadji N, Shahin G, Noujaim D, et al. COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology. 2020;201187. DOI:10.1148/radiol.2020201187
20. Cate Ten H. Thrombosis management in times of COVID-19 epidemy; a Dutch perspective. Thromb J. 2020;18:7.
21. Battaglini D, Robba C, Ball L, et al. Emerging therapies for COVID-19 pneumonia. Expert Opin Investig Drugs. 2020:1–5. DOI:10.1080/13543784.2020.1771694
• **COVID-19 therapy remains supportive, as all drugs with potentially specific effect against SARS-CoV-2 infection are still investigational.**
22. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420–422.
23. Anders HJ, Bruchfeld A, Fernandez Juarez GM, et al. Recommendations for the management of patients with immune-mediated kidney disease during the severe acute respiratory syndrome coronavirus 2 pandemic. Nephrol Dial Transplant. 2020. DOI:10.1093/ndt/gfaa112
24. Poggiali E, Ramos PM, Bastoni D, et al. Abdominal pain: a real challenge in novel COVID-19 infection. Eur J Case Rep Intern Med. 2020;7:1632.
25. Ianiro G, Mullish BH, Kelly CR, et al. Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel. Lancet Gastroenterol Hepatol. 2020;5:430–432.