Intensive Care Med (2021) 47:337–341
https://doi.org/10.1007/s00134-020-06329-3

WHAT'S NEW IN INTENSIVE CARE

Twenty articles that critical care clinicians should read about COVID-19

Jennifer L. Y. Tsang[1,2,3*], Alexandra Binnie[4,5,6*] and Robert A. Fowler[7,8,9,10]

Infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first identified in December 2019 and has since become a worldwide pandemic, challenging and sometimes overwhelming healthcare systems as well as causing more than a million deaths thus far. In just 10 months, over 80,000 indexed publications have appeared that reference SARS-CoV-2 and the associated Coronavirus disease 2019 (COVID-19). In this article, we highlight 20 papers that are of particular relevance to the critical care clinician. The papers are divided into four broad topics: manifestations of severe COVID-19 disease, pharmacological therapy for COVID-19, ventilatory support for COVID-19 acute respiratory distress syndrome (ARDS), and healthcare system and worker stress. This list is not designed to be comprehensive but rather to give the reader an overview of important early papers and their findings.

Manifestations of severe COVID-19 disease

COVID-19-associated ARDS is the hallmark of severe COVID-19 infection. Although it fulfills clinical criteria for ARDS, there may be important differences between COVID-19 ARDS and "classical" ARDS. A prospective study by Graselli et al. of 301 patients with COVID-19 ARDS highlighted several important differences. Firstly, mean static compliance was higher in COVID-19 ARDS (42 vs 31 mL/cm H_2O) relative to classical ARDS, although most patients had static compliance within the 95% confidence interval (CI) for classical ARDS [1]. Secondly, in COVID-19 ARDS static compliance and PaO_2/FiO_2 ratios did not correlate, indicating that hypoxemia is not closely tied to lung stiffness in these patients, unlike in classical ARDS. Finally, D-dimer levels were markedly elevated in COVID-19 ARDS (median 1880 ng/mL) and higher D-dimer levels correlated with increased dead space ventilation and higher mortality. In the subset of patients who underwent CT angiogram, those with D-dimer levels above the median showed evidence of bilateral hypoperfusion. All of these data suggest a role for intravascular pathology in COVID-19 ARDS.

An autopsy study from Ackermann et al. shed additional light on the differences between COVID-19 ARDS and classical ARDS [2]. The authors compared 7 lungs from patients with COVID-19 ARDS with 7 lungs from patients with influenza-associated ARDS. All of the lungs showed diffuse alveolar damage with perivascular T-cell infiltration; however, the COVID-19 lungs also showed widespread thrombosis with microangiopathy and angiogenesis, confirming the presence of pulmonary vascular disease in patients with COVID-19 ARDS.

Early COVID-19 ARDS can present with relatively preserved aeration on chest imaging in spite of severe hypoxemia. In some patients this, early, high-compliance phenotype evolves into a low-compliance phenotype with poor aeration. Gattinoni et al. described these 2 clinical presentations as the "L-type" (Low elastance, high compliance, preserved aeration) and "H-type" (High elastance, low compliance, poor aeration) phenotypes. Although they likely describe a continuous and dynamic spectrum of disease, the concept of inhomogeneous phenotypes of COVID-19-ARDS illustrates important clinical descriptions and may have therapeutic implications.

Thrombosis is another frequent complication of COVID-19. Bilaloglu et al. reported on thrombotic complications in a retrospective cohort of COVID-19 patients from New York [3]. Out of 3334 hospitalized patients, 16% suffered at least one thrombotic event (6.2% venous

*Correspondence: alexandra.binnie@williamoslerhs.ca; alexandra.binnie@williamoslerhs.ca
[1] Niagara Health, St. Catharines, Ontario, Canada
[4] Intensive Care Department, William Osler Health System, Etobicoke, Ontario, Canada
Full author information is available at the end of the article
Jennifer L. Y. Tsang and Alexandra Binnie contributed equally to this work.

vs 11.1% arterial), whilst amongst 829 ICU patients, the rate was 29.4% (13.6% venous vs 18.6% arterial). Age, sex, Hispanic ethnicity, coronary artery disease, prior MI, and higher D-dimer levels at hospital presentation were all associated with risk for thrombotic events. The occurrence of a thrombotic event was independently associated with increased mortality.

Panigada et al. quantified the hypercoagulability of COVID-19 in 24 critically-ill patients using plasma markers and thromboelastography [4]. Although platelet counts, prothrombin time, and activated partial thromboplastin time were near-normal, fibrinogen and D-dimer levels were dramatically increased. Thromboelastography revealed a state of hypercoagulability, as indicated by decreased clotting times and increased velocity of clot formation. Studies of anticoagulation for the prevention and treatment of COVID-19 and its complications are underway.

Other extra-pulmonary manifestations of COVID-19 infection have been reported including neurologic complications (stroke, encephalopathy, anosmia), cardiac complications (acute coronary syndrome, myocarditis, arrhythmia, Takotsubo cardiomyopathy), renal complications (acute kidney injury), hepatic complications (transaminitis), and gastrointestinal complications (diarrhea, nausea and vomiting, anorexia). Gupta et al. summarized the data on these diverse complications and explored the relationship between the virus, its direct cytotoxic effects, its effects on the renin–angiotensin–aldosterone systems, its effects on the endothelium, and the diverse manifestations of COVID-19 disease [5].

The concept of "cytokine storm" in severe COVID-19 disease has also received widespread attention. Although it is imprecise, the term "cytokine storm" implies a hyperactive immune response leading to host tissue damage. Early studies reported that patients with COVID-19 ARDS had higher levels of interleukin-6 (IL-6), a key inflammatory cytokine, relative to those with milder COVID-19 disease. However, in the broader context of ARDS, it appears that IL-6 levels in COVID-19 patients are not particularly high. Sinha et al. compared the data on IL-6 levels in COVID-19 ARDS relative to "classical" ARDS [6]. On average, IL-6 levels were 10–40x higher in "classical ARDS", casting doubt on whether IL-6 levels are a major contributor to COVID-19 severity. This may explain why IL-6-targeted therapies have yet to show convincing benefit (see below), although further studies are ongoing.

Pharmacological therapy for COVID-19

International efforts have translated into extraordinary progress in identifying and testing potential therapies for COVID-19 (Fig. 1). One of the most important studies to date was the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Trial, which compared dexamethasone to standard of care in hospitalized COVID-19 patients. Dexamethasone reduced mortality from 25.7% to 22.9% overall, and from 41.4% to 29.3% amongst patients requiring invasive mechanical ventilation (IMV) [7]. A follow-up meta-analysis confirmed the beneficial effects of corticosteroids in critically ill patients using data pooled from 7 randomized control trials (RCTs) of corticosteroids vs placebo or standard of care [8]. The authors reported a summary odds ratio of 0.66 (95% confidence interval (CI) 0.48–1.01; $p < 0.001$) for mortality in ICU patients with the use of corticosteroids.

Other immunomodulatory therapies have so far failed to show convincing benefit. Tocilizumab, a monoclonal antibody that blocks the interleukin-6 receptor, appeared beneficial in early observational studies. However, a recent RCT from Stone et al. did not show benefit amongst 243 patients with COVID-19 and lower respiratory tract involvement [9]. The hazard ratio for intubation or death in the treatment group was 0.83 (CI 0.38–1.81) and there was an increase in the percentage of patients with worsening of disease at 14 days. Additional data on tocilizumab is expected shortly.

Remdesivir is a viral RNA synthesis inhibitor that has received attention as a potential antiviral therapy for COVID-19. The Adaptive COVID-19 Treatment Trial (ACTT-1) trial studied remdesivir vs placebo in hospitalized patients with COVID-19 and lower respiratory tract involvement [10]. Patients who received remdesivir ($n = 541$) had a median recovery time of 11 days, compared to 15 days for placebo ($n = 521$). The hazard ratio for mortality at day 29 was 0.73 (95% CI 0.52–1.03), however no benefit was observed amongst patients receiving invasive or non-invasive ventilation.

Remdesivir, along with three other repurposed antiviral drugs, was also studied in the WHO-SOLIDARITY Trial, a multinational platform trial that randomized 11,266 adults from one to four drugs: hydroxychloroquine, lopinavir/ritonavir, remdesivir, or interferon-β1a [11]. Outcomes were hospital mortality, initiation of ventilation, and duration of hospitalization. None of the four drugs showed benefit amongst patients requiring IMV. Amongst patients not requiring IMV, the most promising was remdesivir, with a hazard ratio for mortality of 0.86 (95% CI 0.67–1.39). Studies of remdesivir are ongoing to determine whether specific patient subgroups may benefit in terms of mortality.

Finally, convalescent plasma showed promise in early observational studies of COVID-19, but RCT data have been less convincing. Simonovich et al. reported the results of the largest RCT to date, involving 333 patients with COVID-19 pneumonia who were randomized to

convalescent plasma vs placebo in a 2:1 ratio [12]. No mortality difference was observed between the two groups (11% vs 11.4%) and there were no significant differences in clinical outcomes. Additional RCTs of convalescent plasma are underway, as are studies of monoclonal and polyclonal antibody preparations.

Ventilatory support in patients with ARDS secondary to COVID-19

One of the mainstays of ARDS management is invasive mechanical ventilation (IMV). Ferrando et al. published a multicentre observational cohort study of 742 patients with COVID-19-ARDS on IMV during the first wave of the pandemic [13]. In this cohort, the average PaO_2/FiO_2 ratio at the time of intubation was 120 with a compliance of 35 ml/cmH_2O, plateau pressure of 25 cmH_2O, and positive end-expiratory pressure (PEEP) of 12 cmH_2O. Duration of ventilation was prolonged, with an average of only 4 ventilator-free days at day 30. Mortality at 28 days was 32% but was lower for patients with mild ARDS (24%) relative to those with moderate or severe ARDS (29% and 39%, respectively).

Many centres are using high flow nasal oxygen (HFNO) to try and reduce the need for IMV. Although there are no RCT data available, Zucman et al. published a retrospective single-centre study of 62 COVID-19 patients treated with HFNO during the first wave of the pandemic: 34% succeeded on HFNO, 63% required intubation, and 3% died on HFNO after a decision not to intubate [14]. A ROX index $[(SpO_2/FiO_2)/\text{Respiratory Rate}] \geq 5.37$ within 4 h of initiation of HFNO predicted a lower risk of intubation and showed reasonable discrimination (sensitivity 0.66, specificity 0.83). It is still unclear, however, whether HFNO actually reduces the need for IMV.

Prone positioning is also widely used to treat hypoxemia in COVID-19 ARDS, including in awake patients.

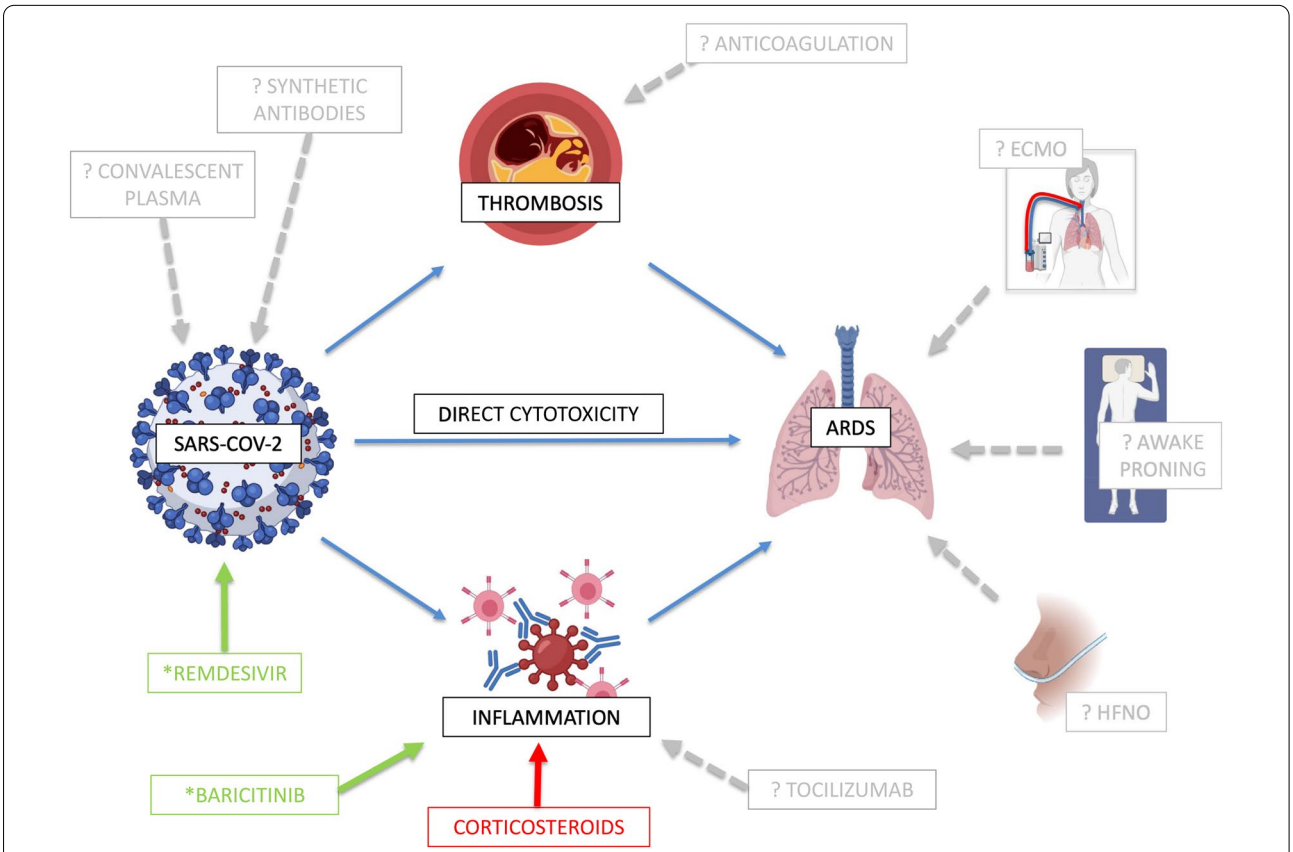

Fig. 1 COVID-19-ARDS: potential mechanisms and therapeutic options. Infection with the SARS-CoV-2 virus has direct cytotoxic effects on the lung as well as indirect effects via thrombosis and inflammation. Only one therapy has shown mortality benefit (red) in randomized control studies of COVID-19-ARDS, which is corticosteroids. Two additional therapies have shown reduced time to resolution of symptoms (green): remdesivir and baricitinib (data not included in article). Therapeutic options that are under investigation (grey) include convalescent plasma, synthetic antibodies with antiviral activity, tocilizumab, and anticoagulation. Ventilatory options for COVID-19 ARDS are also under investigation, including high flow nasal oxygen (HFNO), extracorporeal membrane oxygenation (ECMO), and proning, but have not yet been proven to be beneficial in randomized studies. *Figure created using BioRender.com and Powerpoint*

Its utility in reducing the need for IMV and improving mortality are uncertain. Ferrando et al. published a prospective multicentre observational study of 199 COVID-19 patients receiving HFNO, of whom 55 participated in awake proning [15]. Patients treated with proning showed a trend towards later intubation (median = 1 day), but no reduction in IMV or 28 day mortality. Once again, randomized data are not yet available.

For COVID-19 patients on IMV with severe hypoxemia, extracorporeal membrane oxygenation (ECMO) is sometimes used as a rescue strategy. Schmidt et al. published a retrospective review of 83 patients with COVID-19 who received ECMO between March and May 2020 [16]. At 60 days post-ECMO initiation, 6% of patients were still on ECMO, 45% had been discharged from the ICU, 31% had died, and 18% were in the ICU but off ECMO. The authors noted that these outcomes were similar to previous cohorts of non-COVID-19-ARDS patients treated with ECMO.

Finally, Menk et al. described the evolving standard of care for COVID-19 ARDS [17]. The authors advocated lung protective ventilation with tidal volumes ≤ 6 mL/kg of predicted body weight, limitation of driving pressure to ≤ 15 cmH_2O, individualized PEEP titration, conservative fluid management, and veno-venous ECMO for severe, untreatable hypoxemia. Most of these recommendations are extrapolated from studies of patients with "classical" ARDS. Until COVID-19-specific data are available, however, it is reasonable to adopt these recommendations as best practice.

Healthcare organization and healthcare worker stress

The impact of the COVID-19 pandemic on hospital systems, healthcare workers, patients, and their families has been profound. Healthcare systems have struggled to provide care to large numbers of severely ill patients. Rimmelé et al. published a multicentre retrospective observational study of 9809 patients with COVID-19 in French ICUs between January and April, 2020 [18]. They reported increased mortality in the regions of France with the highest rates of COVID-19 (Paris and the north-east), as well as during periods with potentially fewer healthcare workers. These data highlight the dangers of overwhelming healthcare systems.

Managing patient surges has been a major challenge for hospitals and ICUs worldwide. Aziz et al. published guidelines to help anticipate ICU needs in the event of a surge, including estimates of equipment and supplies per ICU patient admitted [19]. They also provided recommendations on managing shortages of mechanical ventilators, shortages of ICU staff, protecting staff against COVID-19, patient triage, and supporting families and staff.

Finally, the pandemic has taken a heavy toll on healthcare workers. Azoulay et al. published a cross-sectional cohort study of 1058 French ICU healthcare workers during the first wave of the pandemic [20]. Symptoms of mental health disorders were common, including anxiety (50.4%), depression (30.4%), and peritraumatic dissociation (32%). Nurses reported more symptoms than physicians, and females reported more symptoms than males. Other determinants of mental health issues included fear of being infected, inability to rest, inability to care for family, struggling with difficult emotions, regrets about restrictions in visitation policies, and witnessing hasty end-of-life decisions. Healthcare worker distress may lead to higher rates of burnout and should be a focus of healthcare systems as we look to the 2nd wave and beyond.

In the first year of the COVID-19 pandemic, the international critical care community has mobilized rapidly to develop a dynamic and ever-increasing body of knowledge. Enormous advances have been made in characterizing COVID-19 disease and identifying therapeutic options. Urgent research priorities in critical care include greater pathophysiological understanding of COVID-19; ongoing evaluation of direct antiviral, anti-inflammatory, and immune-focused treatments; optimal thromboembolism prevention; optimal management of invasive and non-invasive ventilation; determining the influence of oxygenation and ventilation strategies on viral dispersion in healthcare environments; long-term outcomes of patients with COVID-19; and long-term effects of the pandemic on hospital systems and healthcare workers.

Author details
[1] Niagara Health, St. Catharines, Ontario, Canada. [2] Department of Medicine, McMaster University, Hamilton, Ontario, Canada. [3] Niagara Regional Campus, Michael G. DeGroote School of Medicine, McMaster University, St. Catharines, Ontario, Canada. [4] Intensive Care Department, William Osler Health System, Etobicoke, Ontario, Canada. [5] Faculty of Medicine and Biomedical Sciences, University of Algarve, Faro, Portugal. [6] Algarve Biomedical Centre, Faro, Portugal. [7] Department of Medicine, University of Toronto, Toronto, Ontario, Canada. [8] University of Toronto Interdepartmental Division of Critical Care Medicine, Toronto, Ontario, Canada. [9] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada. [10] Tory Trauma Program, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

Author contributions
JT and AB identified potential articles. All authors selected topics and articles for inclusion. JT and AB prepared the first draft. All authors reviewed the article and approved the final version.

Compliance with ethical standards

Conflicts of interest
R.F. is a lead investigator for Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial (CATCO). J.T., R.F., and A.B. are site investigators for CATCO and

REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia). A.B. is also a site investigator for the RAPID study (Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation Versus Standard Care). The authors have received research funding from the Canadian Institutes of Health Research (R.F., J.T., A.B.), Mohawk MedBuy non-profit (J.T., A.B.), and Canadian Critical Care Trials Group (J.T., A.B.).

Publisher's Note

Received: 9 November 2020 Accepted: 30 November 2020
Published online: 3 January 2021

References

1. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G et al (2020) Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med 8(12):1201–1208. https://doi.org/10.1016/S2213-2600(20)30370-2
2. Ackermann M, Verleden SE, Kuehnel M et al (2020) Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 383:120–128. https://doi.org/10.1056/NEJMoa2015432
3. Bilaloglu S, Aphinyanaphongs Y, Jones S et al (2020) Thrombosis in hospitalized patients with COVID-19 in a New York City Health System. JAMA 324:799–801. https://doi.org/10.1001/jama.2020.13372
4. Panigada M, Bottino N, Tagliabue P et al (2020) Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J ThrombHaemost 18:1738–1742. https://doi.org/10.1111/jth.14850
5. Gupta A, Madhavan MV, Sehgal K et al (2020) Extrapulmonary manifestations of COVID-19. Nat Med 26:1017–1032. https://doi.org/10.1038/s41591-020-0968-3
6. Sinha P, Matthay MA, Calfee CS (2020) Is a "cytokine storm" relevant to COVID-19? JAMA Intern Med 180:1152–1154. https://doi.org/10.1001/jamainternmed.2020.3313
7. RECOVERY Collaborative Group, Horby P, Lim WS et al (2020) Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med. https://doi.org/10.1056/NEJMoa2021436
8. WHO Rapid evidence appraisal for COVID-19 therapies (REACT) Working Group, Sterne JAC, Murthy S, et al (2020) Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 324:1330–1341. https://doi.org/10.1001/jama.2020.17023
9. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS et al (2020) Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 383(24):2333–2344. https://doi.org/10.1056/NEJMoa2028836
10. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC et al (2020) Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 383(19):1813–1826. https://doi.org/10.1056/NEJMoa2007764
11. WHO Solidarity Trial Consortium (2020) Repurposed antiviral drugs for Covid-19—interim WHO solidarity trial results. N Engl J Med. NEJMoa2023184–15. https://doi.org/10.1056/NEJMoa2023184
12. Simonovich VA, Burgos Pratx LD, Scibona P et al (2020) A randomized trial of convalescent plasma in COVID-19 severe pneumonia. N Engl J Med NEJMoa2031304. https://doi.org/10.1056/NEJMoa2031304
13. Ferrando C, Suárez-Sipmann F, Mellado-Artigas R, Hernández M, Gea A, Arruti E et al (2020) Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Int Care Med 46(12):2200–2211. https://doi.org/10.1007/s00134-020-06192-2
14. Zucman N, Mullaert J, Roux D et al (2020) Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure. Intensive Care Med 46:1924–1926. https://doi.org/10.1007/s00134-020-06177-1
15. Ferrando C, Mellado-Artigas R, Gea A et al (2020) Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Crit Care 24:597. https://doi.org/10.1186/s13054-020-03314-6
16. Schmidt M, Hajage D, Lebreton G et al (2020) Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. Lancet Respir Med 8:1121–1131. https://doi.org/10.1016/S2213-2600(20)30328-3
17. Menk M, Estenssoro E, Sahetya SK, Neto AS, Sinha P, Slutsky AS et al (2020) Current and evolving standards of care for patients with ARDS. Int Care Med 46(12):2157–2167. https://doi.org/10.1007/s00134-020-06299-6
18. Rimmelé T, Pascal L, Polazzi S, Duclos A (2020) Organizational aspects of care associated with mortality in critically ill COVID-19 patients. Int Care Med 46(7):1303. https://doi.org/10.1007/s00134-020-06249-2
19. Aziz S, Arabi YM, Alhazzani W et al (2020) Managing ICU surge during the COVID-19 crisis: rapid guidelines. Intensive Care Med 46:1303–1325. https://doi.org/10.1007/s00134-020-06092-5
20. Azoulay E, Cariou A, Bruneel F, Demoule A, Kouatchet A, Reuter D et al (2020) Symptoms of anxiety, depression and peritraumatic dissociation in critical care clinicians managing COVID-19 patients: a cross-sectional study. Am J RespirCrit Care Med 202(10):1388–1398. https://doi.org/10.1164/rccm.202006-2568OC