Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Update in COVID-19 in the intensive care unit from the 2020 HELLENIC Athens International symposium

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ABSTRACT

The 2020 International Web Scientific Event in COVID-19 pandemic in critically ill patients aimed at updating the information and knowledge on the COVID-19 pandemic in the intensive care unit. Experts reviewed the latest literature relating to the COVID-19 pandemic in critically ill patients, such as epidemiology, pathophysiology, phenotypes of infection, COVID-19 as a systematic infection, molecular diagnosis, mechanical ventilation, thromboprophylaxis, COVID-19 associated co-infections, immunotherapy, plasma treatment, catheter-related bloodstream infections, artificial intelligence for COVID-19, and vaccination. Antiviral therapy and co-infections are out of the scope of this review. In this review, each of these issues is discussed with key messages regarding management and further research being presented after a brief review of available evidence.

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Contents

1. Introduction

COVID-19 is an ongoing global pandemic caused by SARS-CoV-2. Elderly patients with underlying chronic diseases are considered of high risk for death, like immunocompromised but younger people without major underlying diseases may also present lethal complications [1]. COVID-19 must be regarded as a systemic disease involving multiple human systems due to the uncontrolled systematic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines and chemokines by immune effector cells, named "cytokine storm" [2]. For this reason, we propose the new definition as SARS-CoV-2 Multiple Organ Disease Syndrome (SARS-CoV-2 MODS) [3]. In this situation the treatment with immunomodulatory agents (corticosteroids, tocilizumab, anakinra, sarilumab, etc.) has been widely used, although more laboratory and clinical evidence is required [4]. A major problem of the coronavirus pandemic is the considerable burden imposed on National Health Systems worldwide due to the hyperacute outbreak and the proportional increase of patients requiring intensive care unit (ICU) support in an extremely limited period of time, while outcomes vary according to the burden of the disease in each country. The pandemic has caused also a major global social and economic disruption while misinformation about the virus has circulated through social and mass media.

In this article, through an International Webinar meeting which took place in Athens Greece on September 24th 2020, we report an update on information and knowledge on COVID-19 pandemic issues in the ICU.

2. General aspects

2.1. Epidemiology

COVID-19 infection, caused by SARS-CoV-2, has led to a global pandemic. The clinical and pathological features of acute infection have been extensively published, with a wide spectrum of disease seen, from asymptomatic infection to mild self-limiting symptoms to acute respiratory failure requiring invasive mechanical ventilation (MV) [5]. The most common clinical finding is fever, cough and fatigue with some laboratory findings such as increased serum ferritin, D dimers and C reactive protein (CRP) [6]. It affects more older adults and there is also a high fatality rate in this subset of patients. Acute respiratory distress syndrome (ARDS) is the primary cause of death in COVID-19 [7] and a recent scope review found that for COVID-19, $<$ 5% of patients were reported as experiencing bacterial/fungal coinfection at admission, but development of secondary infections during ICU admission is common [8,9].

Patients who do not develop a bacterial infection present high initial CRP levels and low procalcitonin (PCT) levels, decreasing progressively, with implications on antimicrobial stewardship. Therefore, empirical antimicrobial therapy with low serum PCT in ICU patients should not be indicated. CRP does not have predictive value for bacterial infections in ICU patients with SARS-CoV-2 infection. Consideration of superinfection and prompt appropriate use of antibiotics should be considered if PCT increase after some days of MV.

COVID-19 infection has shown a great variability in terms of mortality in different regions around the globe. An observational study conducted in the US found an excess of 122,300 (95% prediction interval, 116,800−127,000), more deaths than would typically be expected at the same time of the year [10]. Indirect deaths caused by cardiovascular events, delayed cancer care, or malnutrition may be a serious concern. Persistent symptoms after hospital discharge also represent a significant burden after acute COVID-19 in the ICU.

2.2. Pathophysiology

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA viruses of ~30 kb, only able to synthesise 34 proteins but creating a wide variety of signs and symptoms.

Coronaviruses, and especially SARS-CoV-2, penetrate the epithelial cells via the angiotensin converting enzyme 2 (ACE2). The serine transmembrane serine protease 2 in the host cell further promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein. After entry, SARS-CoV-2 can shut down the effective IFN type 1 antiviral pathway. The virus uses the intracellular machinery to multiply and disseminate into the airway [11].

The virus mainly spread from the lung but could disseminate to all tissues that express ACE2 (mainly small bowel and colon, brain, heart, kidney and skin); during autopsies, the virus is found in many organs [12]. Critically ill mechanically ventilated patients showed RNAemia for 17 days in median [13].

The absence of normal Th1 response leads to pyroptosis of the epithelial cell (with massive proinflammatory reactions, recruitment of blood monocytes into the lungs and neutrophils attraction and activation (Reactive Oxygen Species, proteases production and cell death by Neutrophil Extracellular Traps (NETosis)), leading to a "cytokine storm" [14]. The lack of cytokine at a transcriptional level in the blood, contrasting with high level of protein, suggest a compartmentalisation of the response starting into the lung and spreading into other tissues [11].

The abnormal Th2 response is unable to clear the pathogen and leads to an abnormal activation of CD8 + T cells with massive decrease, partial differentiation, and exhaustion. The CD4+ response is anarchic with plasmablast proliferation. The high level of production of SARS-CoV-2 antibodies contemporaneously to virus persistence is supposed to enhance the inflammatory reaction and to abrogate the wound healing response (MCP-1 and interleukin (IL)-8 production and pro-inflammatory monocytes/macrophage recruitment) [15].

Endothelium is activated, through the ACE2 receptor with expression of Tissue Factor, platelet activation and increased von Willebrand factor (VWF) and factor VIII (FVIII) levels, all of which contribute to thrombin generation and fibrin clot formation. Thrombin, in turn, causes inflammation through its effect on platelets which promote NET formation in neutrophils. It also activates endothelium through the protease-activated receptors (PAR) receptor, which leads to C5a release and monocyte activation. Vasculitis is associated with a prolonged procoagulant and anti-fibrinolytic states that explain the high risk of arterial and vein thrombosis [12,16].

2.3. The five phenotypes of infection

Presentation of COVID-19 is characterised by different clinical phenotypes [17], with different severity-of-illness and outcomes, with specific biomarkers.

Phenotype 1 is characterised by mild symptomatic patients without hypoxemia and radiological abnormalities. Phenotype 2 presents as hyper-inflamed and hypovolaemic patients, presenting mild hypoxemia and/or small opacities on chest X-ray. Exposed to rapid deterioration risk, close SpO2 monitoring is needed. Manifested as "Bronchopneumonia pattern" of Jin et al. [18]. These patients have a median IL-6 under 95 pg/mL.

Phenotype 3 is characterised by greater hypoxemia (PaO2/FiO2 $<$ 200), respiratory rates $>$ 25 per minute, IL-6 values $>$ 94 pg/mL, being a possible progression from type 2. An "organising pneumonia pattern" of Jin and "phenotype 1" of Robba et al. [19] is present.

Phenotype 4 and 5 are characterised by severe hypoxemia requiring intubation. Phenotype is characterised by hypoxic vasoconstriction, micro-embolic lesions, normal lung compliance, lower lobes oedema with ground glass opacities; consider iNO, prostacyclin, normal tidal. Computed tomography (CT) scan is consistent with as "progressive organising pneumonia pattern" of Jin, "type L" of Marini and Gattinoni [20] and "phenotype 1-2" of Robba. Phenotype 5 represents an advanced stage of ARDS, typically in patients with delayed intubation; it totally fits the severe ARDS criteria. Patients may benefit from positive end-expiratory pressure (PEEP) levels $>$ 12 cm H20, prone positioning, and low tidal volumes. CT documents the "diffuse alveolar damage pattern" of Jin, "type H" of Marini and "phenotype 2-3" of Robba. A comprehensive categorisation is required, based on physiology, CT scan findings and clinical presentation, to achieve a personalised treatment, indeed.\

2.4. COVID-19 is a systematic infection

As the ACE-II receptor to which SARS-COV-2 binds is widely found throughout the body, including the lung alveolar epithelial cells, enterocytes of the small intestine, arterial and venous endothelial cells and arterial smooth muscle cells [21], it should not be surprising that COVID-19 is a disease more than just the lungs.

After the lungs, the heart is the most frequently involved organ. A variety of pathologies can impair cardiac function, both primary (i.e. myocarditis) and secondary (myocardial infarction, arrhythmia, cytokine-induced suppression, etc.) [22]. Assessing the cause of cardiac involvement is complicated by the frequent comorbid heart disease in patients with severe disease and the variety of cardiotoxic medications that have frequently been used in combination (e.g. ritonavir, hydroxychloroquine, alpha interferon, high dose methylprednisolone, etc.) [23]. However, rates of myocarditis are quite significant and a cause for concern regarding long term consequences in COVID-19 survivors [24].

Widespread thrombotic disease in the venous and arterial system due to the endotheliitis, despite prophylactic low molecular weight heparin therapy [25], is the other hallmark of COVID-19. Primary neurological disease other than stroke is rare, and most renal disease is secondary to systemic insults rather than primary.

3. COVID-19 management

3.1. Molecular diagnosis

The prompt and reliable diagnosis of COVID-19 cases is challenging for several reasons and is mainly based on molecular assays. The aims of real-time RT-PCR are to perform early, rapid and accurate diagnostics and also guide patient care and management as well as epidemiological strategies.

The most common specimens used are nasopharyngeal and oropharyngeal samples, while tracheal aspirate, bronchial specimens or bronchoalveolar samples are occasionally collected from intubated patients. The molecular diagnosis nowadays mainly relies on real-time RT-PCR techniques, which are considered reference ones, as they present high sensitivity and specificity and are compatible with automation. In a lesser extent, other PCR assays, such as nested PCR, RT-LAMP, RT-iiPCR or the GenXPERT assay may be used [26].

The RNA extraction techniques were initially manual and later evolved to automated, with RT-PCR set up to be prepared manually and RT-PCR to be run in separate thermal cyclers. All these steps were later incorporated in fully automated instruments, such as the sample-to-result instrument NeuMoDx system.

A very recent evolution in the molecular diagnosis is the application of real-time RT-PCR in saliva, which can be effectively used for the detection of respiratory viruses [27]. Saliva has the obvious advantages to be easy to collect, unaffected by collection process, advantageous for individuals with physical or mental handicaps, stable at room temperature for extended periods, not dependent on swabs that are in shortage, of low-risk for exposing laboratorians to hazardous samples, can be obtained while social distancing and can reduce the need for personal protective equipment since it is self-collected.

3.2. Oxygenation and mechanical ventilation

The global pandemic manifested as COVID-19 pneumonia has raised important challenges to physicians working in ICUs. In fact, patients with COVID-19 pneumonia present heterogeneous clinical manifestations; further, significant proportion of these manifestations develop severe hypoxemic respiratory failure requiring invasive MV. Different factors have been identified to predict those patients who will require MV, like elevated IL-6 in the serum, deterioration of oxygenation (mainly PaO_2/FiO_2 lower than 100), presence of heart disease and older age [28].

At histopathological analysis, early presentation is characterised by lymphocytic alveolitis. Recent evidence reported pneumo and vascular lysis, alveolar cell infiltration, alveolar mucinosis, and further fibrosis [29,30]. It is mandatory to understand better the peculiarities of COVID-19 pneumonia pathophysiology, in order to optimise MV. Different radiologic phenotypes have been identified by CT scan [19]: phenotype 1 with multiple, focal over-perfused ground-glass opacities, associated with normally aerated areas; phenotype 2, with atelectasis and peri-bronchial opacities, heterogeneously distributed and hypo-perfused, associated with phenotype 1; phenotype 3, with patchy ARDS-like pattern, heterogeneously distributed, with hyper and hypo-perfused areas, associated with radiologic phenotype 1. Radiologic phenotype 1 is likely to be treated by non-invasive respiratory support, while phenotype 3 more often needs invasive MV. In ICU, among intubated critically ill patients, most of them are characterised by phenotype 1, and only a minority as phenotype 2 or 3. In normal lungs, the standard lung weight is around 800 g, while in traditional ARDS, the lung weight is on average around 1800 g, with an excess tissue mass of 1000 g. Similarly, in COVID-19 patients with phenotype 3, average lung weight is around 1600 g, with an excess tissue mass of 800 g. Thus, the excess tissue mass is similar in traditional ARDS as well as in COVID-19 pneumonia phenotype 3. In traditional ARDS, the distribution of regional perfusion is mainly distributed on the dependent lung regions, where atelectasis and the majority of non-aerated lung tissue is located. On the contrary, in COVID-19 pneumonia, the distribution of blood flow is non-gravitational, prevalent in non-dependent lung regions, with better aeration. Areas of hypoperfusion are distributed mainly in dependent lung non-aerated regions. Thus, hypoxia is mainly due to the following mechanisms: first, lower ventilation-perfusion ($\dot{V}_A/\dot{Q}$), in aerated (non-dependent) and poorly aerated lung regions due to increased perfusion; second, higher shunt in non-aerated lung tissue with micro-thrombosis and vascular lysis effect, which may be even partially protective; and, third, lower alveolar-capillary diffusion. It has been hypothesised that in patients with high compliance and low $\dot{V}_A/\dot{Q}$, hypoxemia is primarily due to the $\dot{V}_A/\dot{Q}$ mismatch related to the loss of the lung perfusion regulation, with a lower amount of non-aerated tissue and less alveolar recruitability. In contrast, in patients with lower compliance with a major loss of aeration, the recruitability and the response to PEEP has been suggested to be higher. The application of higher levels of PEEP is associated with larger recruitment in traditional ARDS as compared to severe COVID-19 pneumonia, radiological phenotype 1 or 3, but not with the respiratory mechanics. Traditional ARDS is characterised by a diffuse damage of the alveolar capillary membrane, leading to oedema and atelectasis in the most dependent lung regions, in supine position. Thus, traditional ARDS is characterised by increased excess tissue mass, highly recruitable by increasing levels of pressures. On the contrary, COVID-19 pneumonia is characterised by alveolar infiltration, leading to different increased excess tissue mass, yielding to phenotypes 1–3, less recruitable by increasing pressures. For these reasons, we suggest to minimise lung inflation at end inspiration and expiration, minimising oxygenation [31] and optimising the level of haemoglobin, according to the optimal oxygen transport [32]. Severe COVID-19 pneumonia is a typical "primary" ARDS, with pneumocytes and vascular lysis, to be ventilated at lower pressures both at end inspiration and expiration with minimal oxygenation. In conclusion, "less is more" in ventilating critically ill patients with severe COVID-19 pneumonia.

3.3. Thromboprophylaxis

COVID-19 infection with critical disease has been characterised by requiring MV, vasopressors for septic shock or having organ failure with need for close monitoring in the ICU. Patients with critical COVID-19 disease have been associated with increased inflammatory response, elevated D-dimer and abnormal coagulation parameters [33] consistent with systemic activation of haemostasis. Many of these patients present similar parameters used to define disseminated intravascular coagulation and sepsis-induced coagulopathy. Cohorts reporting mostly patients admitted to the ICU have shown a high prevalence of venous thromboembolic disease (VTE) of up to 31.27% [34]. The presence of microthrombosis in case series of autopsies also supports microangiopathy due to endothelial injury as part of the pathophysiology. It is unclear whether therapeutic anticoagulation would benefit patients with critical COVID-19 infection having a negative workup for VTE or other clear indication for such intervention. There is no evidence that therapeutic anticoagulation in microvascular thrombosis or systemic activation of haemostasis may improve survival. Elevated D-dimer has been associated not only with increased risk of VTE, but also with increased risk of bleeding [35]. Given the lack of evidence, different societies are providing recommendations based on expert opinions supporting the use of standard prophylaxis anticoagulation in patients with COVID-19 infection [36,37]. Patients with a negative clinical workup for VTE and critical COVID-19 infection should receive standard prophylaxis anticoagulation. Those patients with sudden decompensation and presumed VTE should be considered for therapeutic anticoagulation until further evaluation for VTE is performed to confirm or rule out VTE. There are currently multiple ongoing clinical trials to determine whether patients with critical COVID-19 disease without evidence of VTE would benefit of therapeutic anticoagulation, standard prophylaxis anticoagulation or intermediate dose anticoagulation. Evidence of frequent lung and kidney perfusion deficits in adults without acute respiratory failure [38] emphasises the importance of early interventions in SARS-CoV-2 infected subjects.

3.4. Immunotherapy

Pathogenesis of severe respiratory failure (SRF) caused by SARS-CoV-2 is dominated by a shift of the pro-inflammatory-anti-inflammatory balance towards pro-inflammatory responses characterised by high values of the ratio of IL-6 to IL-10 [39]. Progression from lower respiratory tract infection to SRF necessitating MV is taking place either through over-production of IL-1β and development of macrophage activation syndrome or through over-activation of the IL-6 receptor pathway leading to a unique pattern of monocyte dysregulation. In this pattern, the expression of the human leukocyte antigen DR on monocytes is decreased, which is associated with defective antigen presentation and subsequent lymphopenia. In parallel, monocytes maintain their potential for the over-production of pro-inflammatory cytokines [4]. This leads to the hypothesis that early treatment with a biological that can provide effective blockade of pro-inflammatory responses and enhance anti-inflammatory responses may prevent progression into SRF and MV. Results of the prospective Ana-COVID open-label trial in 41 patients have shown that early treatment with anakinra may achieve this goal [40]. Anakinra is the recombinant receptor of IL-1. Early recognition of the risk of a patient for progression into SRF using the biomarker suPAR (soluble urokinase plasminogen activator receptor) [41] and start of anakinra to prevent MV is the rational of the on-going SAVE trial (EudraCT number 2020-001466-11, www.clinicaltrials.gov NCT04357366).

Tocilizumab which blocks IL-6 receptor is also proposed [4] with intravenous use being suggested to be superior to subcutaneous administration [42]. Although the ROCHE press release of the first results from the phase III COVACTA trial is not favouring

early administration in all patients, some systematic reviews suggest potential mortality benefit in some cohorts with acute respiratory failure [43]. Sarilumab is also effective in blocking IL-6 receptors and may have similar effects. Promising results were provided with the use of low-dose dexamethasone in the RECOVERY trial. When given at 6 mg once daily either orally or intravenously for 10 days, significant decrease of mortality was found. The recommended patient population is either for patients with severe disease in need for oxygen (e.g. oxygen saturation less than 94%) or under MV [44]. The European Medicines Agency human medicines committee (CHMP) endorsed on 18th 2020 the administration of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 Kg) who require supplemental oxygen therapy (oxygenation requirements to maintain SpO_2 above 94% or who underwent MV). In all cases, the recommended dose is 6 mg once a day up to 10 days. Use of intravenous steroids is also recommended in the recent American Thoracic and European Respiratory Society guidance [45] for patients who underwent MV, require oxygen supplementation or require extracorporeal membrane oxygenation. It is also supported by recent meta-analyses [46], although more research is required on the interaction with antivirals, anticoagulation, specific subsets like diabetes or older than 70 years, suggesting the need for a precision prescription approach [47] to be more selective in reducing potential harm and optimise benefits. Finally, interactions between IL-6R blocking therapy and steroids need to be elucidated.

3.5. Plasma treatment

Plasma from patients who have overcome COVID-19 infection, referred to as convalescent plasma, is a treatment option, which has been recently approved by the Food and Drug Administration for use in patients with SARS-CoV-2 infection [48,49]. This approval was based on preliminary results from clinical studies that showed a significant clinical and biochemical improvement of patients, reduction in hospitalisation days and survival benefit [50].

In Greece, a Phase II clinical study for the use of convalescent plasma in hospitalised patients with COVID-19 (NCT04408209) has been performed. To date, 259 possible donors were tested for the presence of IgG/IgA antibodies against the spike protein of SARS-CoV-2 (S1 domain). Median time from the day of the first symptom or PCR positivity (for asymptomatic patients) till the day of screening was 62 days. IgG antibodies were detected in 229 (88%) donors. Plasmapheresis was performed in the first 74 donors, at a median time of 12 days (range: 8–19) after screening. There was a significant reduction in the titer of IgG and IgA antibodies between the days of screening and plasmapheresis [51]. This rapid reduction of anti-SARS-CoV-2 antibodies in this cohort has also been described in other studies [52] and reveals a time pattern of reduction. However, it remains unknown whether neutralising antibodies share the same model or if this reduction affects the host immunity against SARS-CoV-2. This result also suggests that, when indicated, plasmapheresis has to be performed as soon as the patient has recovered from COVID-19. Significant improved clinical outcomes with convalescent plasma therapy has been restricted to patients not requiring MV.

4. COVID-19 patients with specific conditions

4.1. CRBIs in COVID-19 era

During the times of COVID-19 patient surge, hospitals have been unprecedently challenged with acute lack of resources (ICU beds, equipment, disposables, trained ICU staff). ICUs were mainly focusing on managing crisis, dedicating less time to Healthcare-Associated Infections (HAI) surveillance and compliance with standard Infection Preventionists (IP) bundles [53]. ICU staff was challenged with new IP protocols, personal protective equipment (PPE) use (decreased comfort, donning & doffing of multiple PPE items), frequent patient pronation, time pressure, fatigue and emotional burden.

Recently published evidence reported increased Bloodstream Infection (BSI) rates associated with central lines with authors stating that COVID-19 is expected to have highest impact on central line-associated bloodstream infection (CLABSI) rates [53,54].

As multiple factors interfered with standard HAI prevention protocols, it was imperative to quickly recover ICU standards of care and "adapt recommendations to exceptional care conditions" [55]. Italian group (SIAARTI) responded to this challenge with Guidance on vascular approach in COVID-19 patients [56]. The effect of central line bundle enhancement was well demonstrated by Swiss researchers back in 2019 [57].

Moving forward, taking care of three key elements at all times will probably further minimise HAI risk: well-trained PEOPLE, high compliance to updated evidence-based PROTOCOLS and utilisation of reliable and easy to use TECHNOLOGY. Needless to say, maintaining sufficient stock is of paramount importance.

4.2. The vaccine

Scientists and pharmaceutic industry are racing to produce a safe and effective vaccine against SARS-CoV-2 by the year 2021. The procedure would require more than 15 years with the typical vaccine development pathway. In this rapidly evolving landscape, as of October 4th 2020, at least 92 candidate vaccines were in preclinical trials; 29 in Phase I; 14 in Phase II; 11 in Phase III, of which five products have already received limited approval [58]. Types of vaccines in Phase III development are as follows:

Weakened-inactivated SARS-CoV-2: Sinovac Biotech's Corona-Vac, and two inactivated SARS-CoV-2 vaccines by Sinopharm have gained limited approval in China. Sinopharm's products have been approved in United Arab Emirates for healthcare workers.

Viral vector vaccines: CanSino Biologics, together with the country's Academy of Military Medical Science, developed a vaccine based on adenovirus 5 (Ad5), which was already given limited approval in China [59]. The Gamaleya Research Institute has developed Gam-Covid-Vac, using a combination of Ad5 and Ad26. Renamed as Sputink-V, it was given limited approval in Russia before entering Phase III trials [60]. Johnson & Johnson, in partnership with the Beth Israel Deaconess Medical Center, is testing another Ad26 vaccine. AstraZeneca and the University of Oxford is testing a vaccine based on a chimpanzee adenovirus called ChAdOx1; safety concerns of potential neurotoxicity (transverse myelitis case) have suspended trials in some countries, whereas in others they resumed [61].

Nucleic acid vaccines: two messenger RNA (mRNA) vaccines; the first produced by Moderna in collaboration with the National Institute of Health [62] and the second by BioNTech, Pfizer and Fosun Pharma are in Phase III trials.

Protein-based vaccines: Novavax, in partnership with Coalition for Epidemic Preparedness Innovations, has manufactured such a vaccine.

Repurposed vaccines: The Bacillus Calmette-Guerin vaccine is in Phase III trial in Australia.

4.3. Artificial intelligence and COVID-19

The Artificial Intelligence (AI) and Data Science community has supported the global response to the COVID-19 outbreak, with the number of published AI and machine learning studies related to

COVID-19 exceeding 30 thousand. The contribution of AI to the fight against COVID-19 is briefly classified in (i) biomedicine and pharmacotherapy, (ii) modelling of the outbreak (identification, tracking and prediction), and (iii) detection and diagnosis. In biomedicine and pharmacotherapy deep, neural networks were used for DNA microarray and genomic sequence analysis, while in the modelling of the outbreak machine learning models like Long short-term memory (LSTM) have been used [63]. Regarding detection and diagnosis, studies have used machine learning algorithms to predict the criticality of COVID-19 positive patients using clinical features and identifying which of them have statistically significant hazard errors [64,65]. Other studies have used cough and/or breath sound data to identify COVID-19, as in [66]. The most popular AI-based COVID-19 identification approach is using chest X-ray or CT images with CNN models [67]. The conducted studies have shown the contribution of AI and data science to the fight against COVID-19 pandemic, however more standardised datasets and clinical validation of the models' performance are further needed.

5. Conclusion

Management and understanding of SARS-CoV2 infection has evolved during the six first months of the pandemic. In spite of early reports calling for ICU preparedness [68,69], many ICUs in Western countries were overwhelmed in March-April 2020, with patients exposed to adverse events due to compassionate administration of drugs with weak evidence [23], with need of implementing ICU admission triage algorithms [70] and lack of targeting management based on clinical phenotypes. Whereas some ICUs reported similar mortality to primary influenza pneumonia requiring MV [71], these conditions were responsible for a large amount in preventable deaths. Better understanding of early micro-thrombosis [38], refining strategies of oxygenation and intubation criteria (using high flow nasal therapy with awake prone position), and use of immunomodulatory agents have been associated with a shift in the management of critically ill patients, with a lower burden of deaths among hospitalised patients. Further research in form of randomised clinical trials is required to improve the understanding of the interactions between antivirals, steroids and other immunomodulatory agents, and to determine the effects on different subpopulations. Clinicians and researchers have focused on the acute phase of severe COVID-19, but continuing monitoring [45] after ICU and hospital discharge for long-lasting complications is advised. In addition, assessment of anxiety, sleep disturbances, depression and post-traumatic distress syndrome in ICU survivors needs to be investigated.

Disclosure of interest

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