DOI: http://doi.org/10.4038/jccp.v51i1.7884

Critically Ill COVID-19

Dilshan Priyankara W D[1], Mahroof M R[2]

Journal of the Ceylon College of Physicians, 2020, **51**, 31-35

Introduction

Novel Coronavirus disease 2019 (COVID-19) first reported in December 2019 in China, has disseminated globally affecting more than 210 countries leading to significant morbidity and mortality[1]. At the time of writing, more than 5 million cases have been identified with 347,000 deaths causing a major health care burden globally[2]. Sri Lanka has 1097 confirmed cases, with 9 deaths to date[3].

As the COVID-19 pandemic spread across the world, many countries have faced a huge challenge in providing adequate care for these patients. This is due to the rapid surge of patients requiring intensive care at a given time, with a large proportion of them needing prolong intensive care unit (ICU) care for multiorgan support. Many countries have increased the surge capacity of the ICUs by converting post-anaesthesia care units and operating rooms to ICU models and by postponing elective non-urgent operations to redeploy skilled staff, in order to increase the capacity to face the challenge of providing critical care support[4]. The following review on the critically ill COVID-19 patients is based on literature from Italy, China, USA and United Kingdom, where the disease has had a major impact on critical care setting.

Critically ill COVID-19

In a review of 72 314 case records from China, most cases were classified as mild (81%)[5]. However, 14% had severe symptoms (i.e. dyspnoea, respiratory frequency 30/min, blood oxygen saturation 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio 50% within 24 to 48 hours). 5% were critically ill, having respiratory failure, septic shock, and/or multiple organ dysfunction or failure[5]. In most available literature, severity of COVID-19 is categorised as non-severe and severe. Approximately 25% of severe COVID-19 infections and about 5% of overall cases required intensive care support[6,7,8]. ICU admission rate was high as 32% in Wuhan China in the early part of the pandemic[7]. The differences in ICU admission rates might be due to the differences in demand and supply of intensive care facilities in different parts of the world.

It is still a conundrum how to identify who would develop severe illness, in terms of their clinical or biochemical profiles. Males and older patients (median age > 60 years), required ICU care than the others[9,10]. Further, patients with hypertension, diabetes mellitus and cardiac disease experienced severe disease[9,10]. Lymphopenia, lower levels of $CD3^+$ and $CD4^+$, high interleukin-6 (IL-6), high D-dimer levels, high lactate dehydrogenase and elevated serum creatinine levels were seen in critically ill COVID-19 patients and some of these factors were associated with higher incidence of mortality[11]. Children and pregnant mothers generally had mild disease[12]. Interestingly, Kass et al. reported that obesity is a main risk factor among critically ill young patients[13].

Prolonged hypoxia, multiorgan failure and sepsis are recognised causes of mortality among critically ill COVID-19 patients. The exact case fatality rate (CFR) in COVID-19 is difficult to ascertain, as the pandemic is still on-going and the true number of infected patients may be underestimated worldwide. The estimated CFR

[1] *Consultant Intensivist, National Hospital of Sri Lanka,* [2] *Consultant Intensivist and Anaesthetist, Addenbrooke's Cambridge University Hospitals, NHS Foundation Trust, Cambridge, UK.*

Correspondence: WDDP, e-mail: dilsh123@gmail.com

http://orcid.org/0000-0002-6739-0950

Received 12 May 2020, accepted 23 May 2020.

ranges between 1% to 7% with the fatality rate rising with age, and it is well below 1% among children[14,15]. Overall CFR of 2.3% (1023 deaths among 44 672 confirmed cases) was reported from China[5]. In the same study no deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and in those aged 80 years and older had a 14.8% CFR[5].

ICU admission

The commonest indication for ICU admission is for respiratory support, out of which almost two-thirds fulfilled Berlin criteria for ARDS[16]. Acute hypoxaemic respiratory failure induced by viral pneumonitis was the classic finding in almost all the cases requiring ventilatory support[16]. Other complications include shock (30%), myocardial dysfunction (20-30%), and acute kidney injury (10-30%)[16,17]. Most patients have bilateral opacities on chest radiograph and CT chest[6,9]. In the subgroup of CT-positive COVID-19 patients, ground-glass opacities were present in 58/58 (100%), both multilobe and posterior involvement were present in 54/58 (93%), and bilateral pneumonia was reported in 53/58 (91%) patients[18].

Whilst some patients presented to the ICU with hyper-acute respiratory failure needing multiorgan support, the majority showed a gradual deterioration needing ICU care at day 9-10 post-onset of symptoms,[19]. Unfortunately, mortality was as high as two thirds (66%) among COVID-19 patients who required invasive mechanical ventilation[20].

Respiratory phenotypes

It has been argued that applying conventional ventilator management strategies of ARDS are not really helpful in managing all COVID-19 infected lungs[21]. Gattinoni et al. have observed different respiratory phenotypes among critically ill COVID-19 patients[21]. A considerable minority of critically ill patients do not show overt features of dyspnoea despite significant hypoxemia, a phenomenon referred to as ‘silent hypoxia’. These patients are presumed to have good lung compliance (low elastance), low ventilation-perfusion ratio, low recruitability (low to moderate positive end expiratory pressure (PEEP) based ventilation) and low lung weight (less oedema) on CT scans which was classified as the ‘L phenotype’. These patients appear to have modestly reduced pulmonary compliance even when intubated and it is relatively easy to ventilate their lungs. It is likely that loss of hypoxic pulmonary vasoconstriction leads to hypoxia in these patients (low ventilation/perfusion ratio). Some patients may deteriorate to a more classical clinical picture of ARDS and they are classified as ‘type H’. Type H phenotypes have low compliance (high elastance), high right to left shunt, high recruitability (good response to PEEP), and high lung weight (more oedema). Moreover, there are concerns of patient-induced lung injury caused by high work of breathing efforts to increase minute ventilation in response to hypoxia[22]. Hence, early neuromuscular blockade may be crucial to prevent large tidal volumes and over distension of lungs.

Cytokine storm

Cytokine release causing a cytokine storm is hypothesised to contribute to those with severe multiple organ dysfunction. However, the cytokine profile including interleukin-6 levels are different in patients with COVID-19 compared to typical ARDS described in literature. Qin et al. reported mean IL-6 levels of 25 (SD: 10-55) pg/mL among critically ill COVID-19 patients and some case reports showed that IL-6 levels ranged from 7-125 pg/mL[23]. In contrast, typical ARDS patients had much higher values; mean IL-6 levels ranging from 282 (111-600) pg/mL to 1618 (517-3205) pg/mL[24]. Therefore, knowing the underlying pathophysiological mechanism and the host immune response on organ dysfunction is crucial in implementing immunomodulators to treat the disease at the correct time of the illness.

Thrombotic risk

COVID-19 infection has been associated with high risk of arterial and venous thrombosis in critically unwell patients. Thomas et al. reported a cumulative incidence of 30% for arterio-venous thrombosis in the critically ill[25]. Additionally, a high prevalence of acute pulmonary embolism has been reported in patients with COVID-19 (23%, [95%CI, 15-33%])[26]. Patients with pulmonary embolus were more likely require ICU care and mechanical ventilation than those without pulmonary embolus. In a tertiary care centre in France, out of 106 pulmonary CT angiograms performed for COVID-19 patients over a one-month period 32/106 (30%) demonstrated acute pulmonary embolus[27]. This rate of pulmonary embolus is higher than usually encountered in non-COVID-19 critically ill patients managed in ICU set up[28]. A higher D-dimer threshold of 2660 μg/L detected in all patients with CT evidence of pulmonary embolus could indicate activation of an on-going thrombotic process[27].

Extrapolation of above data may support the pulmonary behaviour in severe COVID-19 patients with significant hypoxaemia and preserved compliance, consistent with pulmonary shunting and endothelial dysfunction. They tend to produce a mild inflammatory response with significant ventilatory perfusion mismatch by a mechanism different to classic ARDS. Identification of pulmonary phenotypes and pathophysiology is helpful in individualising oxygenation and ventilation strategies in these patients. Non-invasive ventilator strategies such as facial continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) may be worth considering prior to invasive mechanical ventilation. NIV improves oxygenation and it is really useful especially in the presence of overwhelming hypoxia. While on NIV it is essential to monitor for the work of breathing, as high work of breathing would necessitate invasive ventilation[21].

Prone position ventilation has shown to reduce mortality in moderate to severe ARDS patients especially when used early[29]. A cross-sectional survey done by Sartini et al. demonstrated that proning COVID-19 patients while on NIV showed a reduction in respiratory rate and improvement in oxygenation[30]. Yet, because of the differences in pulmonary pathology observed in COVID-19 compared to classic ARDS, (especially in L type patients) patient selection, the time to initiate and the duration of prone ventilation still remain to be deciphered. Inhaled prostaglandin I_2 (epoprostenol) and strict attention to fluid balance may help better ventilation of lungs. Additionally, vigilance is needed for secondary ventilator – associated pneumonia which is common and may change the pulmonary phenotypic features.

Performing tracheostomy carries a high risk for the health care workers as it is an aerosol-generating procedure. However, as these patients require long ICU stay requiring invasive ventilation, tracheostomy would facilitate weaning off mechanical ventilation. Therefore, the timing of tracheostomy should be individualised to balance the ventilator weaning and staff protection.

Other treatment modalities

Extra corporeal membrane oxygenation (ECMO) is a rescue therapy for severe respiratory failure refractory to advanced invasive mechanical ventilation, and has been used in some centres for patients with severe ARDS. There is paucity of evidence worldwide on the benefit of using veno-venous extra-corporeal membrane oxygenation (VV-ECMO) in COVID-19 with ARDS. Zeng et al. published a retrospective analysis of ECMO in COVID-19 which showed that almost 50% of patients who received ECMO died due to sepsis[31]. Furthermore, pooled analysis of ECMO data in COVID-19 did not show promising results on survival[32].

It is accepted that all critically ill patients should receive venous thromboembolic prophylaxis with either low molecular weight heparin or unfractionated heparin unless contraindicated. Furthermore, systemic anti-coagulation may play a crucial role to prevent clotting of extracorporeal circuits used for haemodiafiltration. Despite that, the benefit of using therapeutic anti-coagulation still remains to be proven.

In the absence of a specific treatment against COVID-19 infection, drugs that are shown to be effective against other medical conditions have been tried by the clinicians. Hydroxychloroquine, azithromycin, antiviral agents such as lopinavir-ritonavir, favipiravir, remdesivir (extended compassionate use based on Ebola data), and immunomodulators such as tocilizumab, the anti-C5a antibody IFX-1, intravenous immunoglobulin (IVIG) and convalescent plasma are some of the treatments being tried in COVID-19 patients with no promising results[33-36]. Nonetheless, there are on-going trials on some of the therapies world-wide giving hope for the future. Currently in the UK, RECOVERY, REMAP-CAP and GenOMICC trials are underway and are expected to announce interim results in July 2020.

Major causes of death

Progressive refractory hypoxia and multiple organ dysfunction are the major causes of death among critically ill COVID-19 patients. Secondary bacterial sepsis is an important contributing factor to mortality in these patients. Withdrawal of prolonged organ support due to futility of care in elderly patients may impede deciphering the exact nature of ultimate cause of death in some patients. The actual cause of death may be influenced by the resource allocation for ICU facilities, availability of ICU beds and access to other critically important supportive resources[36].

Conclusion

Intensive care services face an enormous challenge due to the pressure from a large number of people requiring organ support within a short time frame during the COVID-19 pandemic. COVID-19 infection related viral pneumonitis leading to acute respiratory failure is the main indication for ICU admissions worldwide. Identification of different respiratory phenotypes would help in individualising therapies in patients with respiratory failure. There is no proven therapy for COVID-19 as yet, availability of which could lead to significant improvements in both morbidity and mortality. The real challenge ahead of us is enormous at present.

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