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COMMENTARY

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COVID-19, ECMO, and respiratory infection: A new triad?

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In December 2019, the initial outbreak of COVID-19 started in Wuhan, China, which rapidly escalated to an international scale within weeks.[1] This ultimately resulted in it being declared as a global pandemic by the World Health Organization (WHO) in March 2020.[2] This highly contagious respiratory infection has since mutated and evolved to enable viral survival in the host.[3] Treatment pathways for the virus have also changed and improved, accompanied by more knowledge of the disease pathogenesis. For example, May 2020 saw the introduction of the broad-spectrum antiviral medication Remdesivir, followed by the FDA's approval of monoclonal antibodies such as Bamlanivimab in November 2020.[4] The employment of extracorporeal membrane oxygenation (ECMO) as supportive therapy for COVID-19-related ARDS has also been advocated for by the WHO and Extracorporeal Life Support Organization (ELSO).[5] This rescue therapy[6] is primarily recommended as a last resort, subsequent to unavailing results from conventional therapies[7] for COVID-19 patients with a limited number of co-morbidities who do not have severe multisystem organ failure.[8] Yet, according to the ELSO Registry, the in-hospital mortality rate remains as high as 47%.[9] This sparks some questions on the use of this therapy in COVID-19 patients with ARDS. Whilst there are some studies to suggest the clinical benefit of ECMO,[10] there is also concern over potential increased mortality and morbidity of up to 65% in some cases.[11] Thus, this area requires more clinical data to scientifically draw evidence-based guidelines and recommendations on the use of ECMO for severe COVID-19 ARDS, a topic that remains poorly documented in the literature.

In this issue of the *Journal of Cardiac Surgery*, Shih et al.[12] shared the results from a single-center retrospective, observational cohort study, finding that patients with COVID-19 with ARDS (the latter diagnosed using the Berlin criteria) who were placed on ECMO, had high rates of secondary bacterial and respiratory coinfections. This was demonstrated by over 50% of the cohort being diagnosed with an infection by Day 15 and 60.8% (30 patients) developing coinfections throughout the course of treatment. These patients were also found to have a longer duration of extracorporeal life support (ECLS), ECMO (34 vs. 15.5 days on average), and intensive care unit days (44 vs. 31 days on average) than patients who did not suffer any coinfection. However, interestingly, they did not find the mortality rates of these patients to be significantly superior to their non-coinfected counterparts. The authors attributed this to diligent care from the multidisciplinary specialist team. This study comprised of 44 patients, with a range of characteristics including pre-existing co-morbidities such as malignancy, chronic obstructive pulmonary disease, diabetes mellitus, and hypertension. The primary outcome of the study was deemed as freedom from coinfection following initial ECMO cannulation, whereas secondary outcomes were bloodstream and respiratory cultures, frequency of positive cultures, and patients with polymicrobial infection, amongst others. The commonest organism found in positive respiratory cultures was found to be methicillin-resistant *Staphylococcus aureus* and the commonest organism found in positive blood cultures was *Enterococcus faecalis*.

Shih et al. establish in their study, that ECMO treatment was associated with high rates of coinfection, despite the overall survival rate remaining non-inferior compared to patients who were not coinfected. Whilst in Shih et al.'s study, there was no significant difference in mortality between coinfected and non-coinfected patient groups, Barbaro et al. found a large interquartile range of 33%–92% for mortality rates across ECMO centers,[13] with 82.3% mortality specifically in COVID-19 patients with ARDS undergoing ECMO.[14] On the other hand, a systematic literature review found that the use of veno-venous ECMO in acute severe respiratory failure was associated with a 60-day reduced mortality compared to conventional mechanical ventilation.[15] While some studies have demonstrated that ECMO leads to an increased coinfection rate in other respiratory diseases caused by *Klebsiella pneumoniae*, *S. aureus*,

Haemophilus influenza, and *Streptococcus pneumoniae*,[16] Vuylsteke argued the tool cannot be blamed for the increased mortality but rather, it is a question of health professionals' responsibilities to determine when to use it to benefit patients most.[17] It has also been found that severe COVID-19 ARDS patients requiring ECMO are prone to contracting late-onset ventilation-associated pneumonia (VAP), commonly caused by inducible AmpC-cephalosporinase-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*.[18] Also, it is important to note the high relapse rate from VAP despite antimicrobial therapy, which can cause further health complications.[18]

This study by Shih et al. proposes some pioneering results on the topic of coinfection in COVID-19 patients with ARDS on ECMO, nevertheless, several significant limitations should also be acknowledged. First, despite obtaining statistically significant results for some categorical variables, it is important to note that the small-sized cohort of 44 patients may restrict the reliability of the study. This could also prevent the findings from being extrapolated and may render it difficult to determine if the outcome is a true finding or based on chance. Thus, this study may be underpowered to identify differences in particular secondary infections. Perhaps the small sample size may also explain the lack of statistically significant results for the majority of categorical variables, inflammatory markers ($p = .85$) and ferritin levels ($p = .17$).[12] As a result, the authors could replicate the study with an amplified data set consisting of a larger number of patients. This would increase the accuracy of their findings as well as aid in identifying outliers, ultimately providing a smaller margin of error.

Moreover, although the inflammatory marker levels were not a significant factor in the sub-analysis of the study, the fact that this data set was incomplete remains a point of critique. Having a complete, thorough testing protocol for inflammatory markers around the dates of positive cultures can serve as a useful tool to understand patients' disease states, by comparing values to their baseline. The lack of completeness of such information in the data collection phase of the study could have affected the monitoring of patients on ECMO. Evidence suggests that COVID-19 patients receiving ECMO who have hyperinflammation characterized by raised ferritin levels have an increased risk of mortality.[19] This is supported by the fact that COVID-19 infection is characteristically well-known to induce pathological processes such as progressive hypoxic dyspnea[20] and inflammatory cytokine storms.[21] Thus, this further accentuates the need to regularly monitor patients' inflammatory markers such as lactate dehydrogenase, C-reactive protein, ferritin, and lactic acid levels.[22]

Second, the single-center nature of this study may challenge the generalizability and external validity of the findings. Since this study specifically investigated critically ill patients with similar demographics (41% Hispanic ethnicity, 75% male gender) at a well-established ECMO facility, the results may be skewed to this population. To increase the representativeness of their results, the authors could further their research by investigating trends at multiple ECMO centers. This would provide them with comparable data sets and the opportunity to better assess a potential correlation between ECMO and coinfection rates in COVID-19 patients with ARDS. Undertaking a multi-center study could also help reduce any deviation in results as well as skewness from similar patient demographics that may have arisen in their single-center study.[23]

Third, lies the limitation of being a retrospective study. This can render the findings prone to recall, misclassification and selection biases. As well as this, there may have been some confounding variables not accounted for. For example, the association between COVID-19 ARDS and acquiring bacterial or respiratory coinfections is little known in the scientific community; the paucity of evidence further highlights the need for more research in this area.[24] It can therefore be difficult to decipher correlation and cause in the study. Determining the cause of infection in COVID-19 patients with ARDS on ECMO can be challenging because the infection may be caused by many factors including COVID-19 infection itself pre-disposing patients to catching a superinfection,[25] ARDS as, this weakens the immune response,[26] the use of immunosuppressants,[27] catheter-associated bloodstream infections,[28] and invasive respiratory ventilators,[29] amongst many other confounding factors. Also, as mentioned by Shih et al. in their study, vancomycin, and either a cephalosporin or penicillin were used at the start of ECMO cannulation. It is common practice to administer empirical antibiotic prophylaxis to patients when initiating ECMO treatment.[30] However, research suggests that this routine protocol may increase patients' likelihood of suffering hospital-acquired infections and developing multi-drug resistant organisms (MDROs).[31] For example, exposure to β-lactams inactive against *P. aeruginosa*, is associated with carbapenem-resistant *P. aeruginosa* isolation, caused by OprD gene repression or inactivation.[32] This notion of confounding variables is further highlighted by the Kaplan–Meier analysis performed in the study to ascertain differences in survival rates. A drawback of this method is the inability to estimate the difference in magnitude of the survival-predictor relationship and most importantly, the incapacity to be used for multivariate analysis. Thus, this can make it difficult to evaluate causation versus correlation. Shih and colleagues may wish to pursue a large, prospective cohort study to better calculate the incidence of bacterial and respiratory coinfections with ease, as well as being able to tailor their methodology to collect specific patient exposure data.

Fourthly, another key criticism of this study is the lack of consideration for positive urine cultures or viral coinfections amongst the cohort. By omitting these potentially confounding variables, may have led to inaccuracies in measuring outcomes. For example, if a patient tested positive for urosepsis, an omitted positive urine culture could have ruled in a urinary tract infection earlier. Another misunderstanding that may have been masked in the data collection phase, is the cause of the secondary bacterial and respiratory infections. Shih et al.[12] state that the average duration of ECLS was longer in patients who developed a coinfection than in those who did

not. Studies suggest that ECLS itself and receiving ECMO treatment can serve as pre-disposers to catching secondary infections.[33]

Finally, information on patient follow-up post-discharge from hospital is limited in this study. This makes it difficult to assess the post-discharge quality-of-life (QoL) of patients who survived the acute phase of ECMO support for COVID-19 and coinfection. Therefore, the authors may wish to explore this further by conducting studies to specifically evaluate the recovery period. This is supported by the wider literature, which suggests that COVID-19 ARDS and ECMO survivors often experience chronic complications and poor health-related QoL due to a range of factors including physical and psychological stresses.[34]

In general, Shih et al.'s demonstration that ECMO is associated with high rates of coinfection in COVID-19 patients with ARDS, appears to suggest there may be a limited clinical benefit of this rescue therapy. However, considering the small sample size, other study limitations, and the advantages of ECMO outlined in the literature, it is important to further this study on a wider scale to increase the generalizability of any recommendations made.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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