Editorial

Critical care outcomes from COVID-19: patients, interventions, healthcare systems and the need for core datasets

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In this issue of *Anaesthesia*, Taylor et al. report on the factors associated with mortality in patients with COVID-19 admitted to ICU [1]. First, it is worth emphasising that only a minority of patients who have died in the pandemic have done so in ICU: 9% of those in the UK, with a third of deaths occurring outside hospital and six in seven hospital deaths occurring on the wards [2]. The average age of patients admitted to ICU in the UK is 10 years lower than for all hospitalised patients and more than 20 years younger than patients who have died from COVID-19: 61 vs. 73 vs. 83 y [3–5]. Despite only a minority of patients hospitalised with COVID-19 being admitted to ICU, there has been an enormous focus on critical care during the pandemic and this is appropriate.

The problems

Early in the pandemic, the high mortality of patients with COVID-19 admitted to ICU was noted, and in China and North America mortalities of >60% were reported, including >90% in those receiving mechanical ventilation [6, 7]. In the first 6 months of the pandemic, global mortality in ICU fell to approximately 35% [8]. There are several potential explanations: first, variability in presentations, type of respiratory support received and specific treatment strategies (a common factor in ICU but amplified during the COVID-19 pandemic); second, an issue with the 'denominator' of the mortality fraction as many early observational studies reported ICU mortality when most patients were still receiving ICU treatment meaning their outcomes were unknown [8, 9]; third, the role of underlying comorbidities and perceived disease reversibility; and fourth, the incremental understanding of the pathophysiology of COVID-19. Undoubtedly, improved learning about the disease allied with improved management and therapeutics has enabled ICUs to save many lives that a few months earlier would have been lost. Importantly, this has been achieved by collaboration and experience sharing within and between countries [10, 11] and by rapidly executed and disseminated high quality research [12, 13].

What then does the work of Taylor et al. tell us? They have undertaken a meta-analysis of published studies to explore the association between admitted patients' characteristics and ICU outcome. The factors they report to be associated with mortality are generally expected and in line with those in large primary care studies examining all-cause mortality from COVID-19 [14, 15]. Essentially, an older patient with more comorbidities, greater disease severity (most markedly lung injury and renal impairment), indices of inflammation and organ dysfunction is more likely to die in ICU – regardless of sex or BMI.

In terms of methodology, the analysis is constrained by the data available, and these are heterogeneous and fragmentary. There are numerous sources of heterogeneity. First, there is inevitably variation in what is meant by intensive care: an ICU in Yemen or Iran or some parts of Africa [16–18] is unlikely to be the same, in terms of staffing, infrastructure and facilities, as an ICU in Wuhan or many European, Australasian or North American countries. Second, it is likely that the underlying characteristics of patients admitted to different ICUs will differ. Those in a lower income country are more likely to be younger and fitter, though perhaps with chronic disease from endemic non-COVID-19 infection; and those in higher income countries older and more likely to have the chronic diseases associated with surfeit such as obesity, diabetes, hypertension and ischaemic heart disease. Also, admission to ICU may not be solely an expression of organ dysfunction or disease severity but may depend on other factors including local resources, biases and timing of presentation during the pandemics (i.e. the chance of being admitted to ICU may differ at the peak of a pandemic surge compared with one of the tails). All these factors affect patient selection – and crucially baseline characteristics of the patients admitted to ICU – and their association with outcome. Third, in locations with differing ICU 'capabilities' (e.g. number of ICU beds per capita, staff or treatments available), the criteria for ICU admission (or non-admission) are likely to vary, as will the ability to provide critical care support for the period of several weeks or months, which is often required to achieve survival in COVID-19 induced severe respiratory or multiorgan failure. This will mean that disease severity on admission, treatments offered, and their duration or withdrawal will have an unpredictable impact on outcome. Fourth, it is likely that surges (which have occurred at different times in different countries) have altered provision of ICU and while in some settings it is self-evident that this has altered ICU admission criteria, capability [19, 20] and therefore outcomes, this effect is more subtle in other counties [21]. Fifth, and intriguingly, it is not clear that the same disease has been treated either over time or by location: it is quite possible that different variants lead to subtly different disease patterns that may alter presentation and mortality and while this remains a matter of debate it is quite plausible for this to impact differentially on ICU survival. Sixth, the data collected and reported between studies differ, but perhaps even more importantly there is lack of consistency in definitions within datasets, for example definitions of comorbidities, hypoxia, renal failure, respiratory, cardiovascular or neurological support and ICU itself.

The fragmented nature of data available means several unmeasured factors are likely to impact on outcome. These may be external (e.g. national wealth; critical care provision per capita; level of social deprivation; access to primary care); pandemic-related (e.g. degree of systemic stress in the healthcare system); or patient-related (comorbidities; frailty; natural history and treatment received). While age, comorbidities or smoking status have been reported to influence ICU outcome, other variables require qualification. For example, the association between lower PaO_2/F_IO_2 ratio and greater mortality has previously been well documented in other studies of acute respiratory distress syndrome, but there are many factors that influence this ratio at baseline and its clinical impact. For example, PaO_2/F_IO_2 ratio depends on the F_IO_2 administered, the ventilation settings and patient positioning (prone or supine) [22]. Changes in PaO_2/F_IO_2 ratio following treatment will modify outcome: for two patients with identical PaO_2/F_IO_2 ratios at baseline the outcome may differ depending on whether it improves or not following prone positioning or as a consequence of a change in ventilatory settings [23]. Furthermore, patients with a very low PaO_2/F_IO_2 ratio may have a survival chance of up to 70% if they are a candidate for extracorporeal membrane oxygenation (ECMO) [24] but a very low chance of survival if they are not. As COVID-19 is a single disease and yet mortality varies widely, it is conceivable that the factors associated with survival reside within the treatment provided. Unfortunately, none of these factors – although generally but variably reported in observational studies – have been examined in the meta-analysis by Taylor et al.

The nature of the analysis likely prevents full exploration of the interaction of factors too. For instance, are alterations in total white cell count, neutrophils, lymphocyte, platelets and levels of D-dimers and ferritin all independently associated with poor outcome or to what extent do they co-vary as discrete measures of systemic inflammation? The effects of hypertension and angiotensin converting enzyme inhibitors are still unclear as a mechanism to explain mortality rather than susceptibility.

Two other factors are important for interpretation. As not all patients included in the meta-analysis required invasive mechanical ventilation, it is uncertain whether the identified risk factors apply equally to patients who: underwent invasive ventilation without ever receiving non-invasive respiratory support; received invasive ventilation after failed non-invasive respiratory support; and who improved and did not undergo mechanical ventilation. Finally, heterogeneity in centre effect (including case volume) is a very important consideration given that even within the UK the hazard ratio of death varies widely among different centres and this variation is greater than the effects that can be attributed to a specific therapeutic intervention [25].

Taylor et al. have unavoidably performed an analysis based on population characteristics of the cohorts included. Analysis of patient-level data would enable more thorough analysis including multivariable adjustment, but this requires access to detailed data from large numbers of patients, which is consistently defined, collected and curated. Such data are likely only available to national datasets [26]. One of the largest of these is the UK's Intensive Care National Audit and Research Centre (ICNARC) which has a well-established dataset and processes and collects data from all patients in all ICUs in England, Wales and Northern Ireland [27]. As a result of the high burden on ICUs of the pandemic in the UK, including two near-overwhelming peaks, ICNARC has been able to undertake analyses in approximately 36,000 patients [27]. The results bear comparison to those of Taylor et al. Amongst the factors reported by ICNARC as impacting on ICU survival in the first wave were age (mortality approximately doubling every 12 y above age 60); ethnicity; degree of social deprivation; and extent of physiological disturbance on admission to ICU. The ICNARC report (3 June 2021) shows similar 28-day hospital mortality in different quartiles on BMI. [27] Unlike Taylor et al., the ICNARC data consistently reports a lower mortality in women, in line with primary care studies [14, 15] and large-scale population data. Of note, the ICNARC data documents a fall in mortality in the Spring of 2020, [21] which then rose again in late 2020 and early 2021, coinciding with the period when ICUs again became overburdened in the peak of the second wave [27]. At the peak of the first wave, the baseline characteristics of patients admitted to UK ICUs altered, with a reduction in average age and a change in disease characteristics, perhaps suggesting that care could not be provided for all patients [21]. The ICNARC dataset provides a model for how data should be collected, but even this is limited as the dataset captures only the most extreme levels of comorbidity (e.g. liver disease requires biopsy-proven cirrhosis and renal disease ongoing renal replacement) meaning lesser but perhaps significant comorbidities are not included and cannot be factored into analyses.

There are numerous national or large regional ICU databases panning at least four continents. During the COVID-19 pandemic there have been reports from numerous rapidly convened networks. It is likely that no two datasets are the same. This prevents reliable pooling of data that is needed for a better understanding of what is happening across ICUs globally, whether in this pandemic or in other circumstances. The variation in datasets between individual studies based outside databases is wider still.

The solutions

How then can we do better? There is a need for harmonisation of data definition, collection and reporting both in studies and by those organisations collecting population-level data. Achieving this will require significant collaboration and most likely in some cases, humility, to modify long-used definitions and accept new ones. In this context, wider availability of accurate data beyond basic demographic data, to include physiological data, treatments received, and minimal outcomes data is an essential starting point. The ultimate aim is to report large scale data in a timely fashion, using 'real-life' data. For example, in the field of peri-operative medicine, some progress has been made in a similar initiative: two projects working independently to similar goals (the standardised endpoints for peri-operative medicine (StEP) and core outcome measures for peri-operative and anaesthetic care (COMPAC)) have combined as the StEP-COMPAC initiative to standardise definitions for specific outcome measures used in anaesthetic and peri-operative care studies [28]. The process involves systematic evidence review, stakeholder consultation and Delphi consensus processes. One example of how this might work is the risk stratification in COVID-19 patients in the ICU collaboration (RISC-19-ICU – https://www.risc-19-icu.net) based in Switzerland and supported by the Swiss Society of Intensive Care Medicine. The RISC-19-ICU registry "*aims to collect and make accessible an anonymised minimal dataset to characterize patients that develop life-threatening critical illness due to COVID-19*". The initiative lists (as of June 2021) 94 institutions from 16 counties across Europe, North and South America, which are participating.

Further issues for ICU – particularly relevant during a pandemic – are how to capture resource availability and how this may impact on the options available to patients, who should analyse these data, and how this information can be shared. The expansion in the use of machine learning and artificial intelligence can help with some of these questions. We congratulate Taylor et al. for their analysis of patient factors associated with outcome in patients with COVID-19 admitted to ICU. We also note that outcome from ICU may be impacted by factors other than patient and disease characteristics: these include the type of ICU, interventions undertaken (or withheld), the socio-economic setting of the healthcare service and the extent of systemic stress in that system. In the future, regular reporting in a manner akin to ICNARC's regular reports, using a core outcome set and harmonisation of data definition, collection and reporting on a much broader basis – including physiological and clinical data acquired in ICU – is likely to be not only beneficial, but necessary if we are to better understand this pandemic, the next one and the major health challenges that affect ICUs across the world.

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