Apples and oranges

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Apples and oranges: making international comparisons of COVID-19 observational studies in the intensive care unit.

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Multiple observational cohorts describing the outcome of patients with COVID-19 from across the world have been published.[1-3] Typically, these have reported regional or national cohorts and no two countries have had the same experience. The reasons for this are complex and difficult to quantify. Nonetheless, to be able to draw meaningful inferences from these data we must tackle the issues associated with international comparison.

Initial reports of outcomes in COVID-19, which emerged from China early in the pandemic, reported a range of ICU mortality (0-78%).[3] Case series from North America and Europe have been equally variable (ICU mortality 0-85%).[3] A major issue has been the large number of patients in these series who had incomplete outcomes at the time of reporting, a factor which has commonly resulted in mortality being over- or underestimated. An example of this can be found in the UK Intensive Care National Audit and Research Centre (ICNARC) data. Early reports from March estimated ICU mortality to be 48%, when 79% of 775 patients had an incomplete outcome. In the latest report, from 31st July 2020, ICU mortality had fallen to 40% in 10,341 patients with complete outcomes.[4] Table 1 summarises current European data on COVID-19 mortality, highlighting the range of outcome measures reported. Another key difference is the status of the health systems in which these patients have been managed, in particular the degree of 'stress' which those systems were under.[5] This is more difficult to adjust for. Variations in clinical decision-making between healthcare systems, reflected in the characteristics of patients admitted to ICUs and in the modes of ventilation employed, also confound direct comparison. This is potentially evident when comparing ICU admissions between the UK and Germany, where the median age of patients receiving invasive mechanical ventilation was 72 years in a large German series[2] versus 60 years in the latest ICNARC report.[4] However, ICU mortality was similar, emphasising the role of admission criteria. Regardless, the wide variation observed suggests the possibility that some factors are modifiable. Therefore, it is important that we can make comparisons between countries and systems.

Beyond careful epidemiological analysis, there are several ways in which we may improve comparisons. The most obvious is multinational collaboration. Indeed, it is difficult to see how we can mount an effective response to a global pandemic without it. The fight against COVID-19 has already produced some commendable examples, including the work of the Coalition for Preparedness Innovations (CEPI), of the Global Alliance for Vaccines and Immunizations (GAVI), and the of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). However, global comparative data on the outcomes from COVID-19 are lacking as a single observational study has not been reported to date. An issue with the current reports is the inconsistency of the hospital, ICU and individual patient level data definitions. Similarly, there are often fundamental differences in the design of these studies. Together these limitations make linkage or comparison difficult, which limits our ability to generate sufficiently robust data to form conclusions. While a single global study may be logistically and politically improbable, there are simpler measures which may ease the task of generating international data with fewer limitations.

First, the development of harmonised case report forms and data dictionaries would permit straightforward comparison of studies. This approach would also allow investigators to create tiers of data collection. This is of real importance in resource limited settings, in which the advanced monitoring, diagnostics, and research infrastructure required to perform extensive study protocols are not available. The use of core outcomes in ICU observational studies should also be addressed, for example the WHO Working Group on the Clinical Characterisation and Management of COVID-19 Infection outcome set.[6] Second, the inclusion of measures of system stress and resource availability have been largely missing from published studies to date. These are essential to understand the observational data collected in the midst of a pandemic. For example, evidence of national variation in ICU outcome has been described during the first wave of the COVID-19 pandemic in England.[7] Here, the authors hypothesised that this may have occurred as the result of local strain or resource-constraints in the face of a surge. Likewise, a recent study from Brazil has highlighted disparities in the outcomes of hospitalised patients between the south of the country and the economically poorer north.[8] In practice this may mean collecting hospital and unit level information on resource availability and staffing over time, in addition to patient-level data. Third, integrating ICU observational studies with those that capture patients before and after admission to critical care, as well as linkage to clinical trial data, would be advantageous. This would better characterise patients and would reduce the replication of data collection. Another benefit would be the ability to assess the influence of variations in clinical decision-making on ICU outcome, which hinder the comparison of existing studies. Furthermore, the effective linkage of large observational studies and clinical trials would allow investigators to better explore sub-group effects and identify heterogeneity of treatment effect, such as was identified in the RECOVERY dexamethasone study.[9]

Current reports of ICU outcome for patients with COVID-19 vary between countries. The reasons for this are unknown but are unlikely to be attributable to differences in the virus or host-response alone. Understanding those that are modifiable would be a major step forward in improving care. This virus does not respect borders, nor can we.

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Country	Last day of patient inclusion	Hospitalisation			ICU			Ventilated		
		Number of patients	Socio-demographic	Case fatality**	Number of patients	Socio-demographic*	Case fatality**	Number of patients	Socio-demographic	Case fatality**
Belgium	June 14	16,628*	53% male/ median 71y*	21%	1,696*	n/a/ median 66y	n/a	n/a	n/a	n/a
France	July 28 (hosp.)/ June 2 (ICU)	107,010*	53% male/ median 72y*	20%	4,007*	73% male/ 19% >75y	23%	n/a	n/a	n/a
Germany	April 19	10,021**	52% male/ median 72y**	22%	n/a	n/a	n/a	1,727**	66% male/ median 71y**	53%##
Netherlands	Aug 4	11,700**	n/a	17%	2,950*	73% male/ 14% >75y	29%#; 31%##	n/a	n/a	n/a
UK: England, Scotland, Wales	April 19	20,133*	60% male/ median 73y*	39%	3,001*	n/a	54%	1,658*+	median 61y*	69%##
UK: England, N. Ireland, Wales	July 30	n/a	n/a	n/a	10,624*	70% male/ median 60y	40%#; 45%##	7,425*	72% male/ median 60y*	48%#

* all patients (including those still in hospital); ** dead as % of discharged dead or alive; # in ICU; ## in hospital; + invasive ventilation only

Table 1. Euorpean mortality outcomes for COVID-19

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