

## Mechanical Ventilation in COVID-19: Interpreting the Current Epidemiology

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Right now the world is scrutinizing every cohort and every outcome for COVID-19 patients, particularly the most critically ill who are receiving mechanical ventilation. The numbers that have been published are all over the place, and some of them – such as very high mortality – are causing panic. Two major issues are at play in these epidemiological studies. The first is when to intubate, and assessment of the rates of intubation and mechanical ventilation for hospitalized patients in cohorts from across the world. The second is the reported mortality for patients who receive mechanical ventilation. Presentation and interpretation of the data for both of these issues is not straightforward, and never has been. However, there are ways we can improve assessment of these cohort studies.

### **The decision to ventilate**

“He claimed that the Americans had put their patients in the respirators far too early - certainly they would not have been ventilated in Copenhagen. It’s no wonder they survived, he claimed, because they didn’t need treatment in the first place (1).” That is not a quote from 2020, but is from Dr. Henry Lassen in 1952. He and his team were dealing with an overwhelming polio epidemic and a high rate of respiratory failure among his patients and he was scrutinizing data from California. It turns out that the same debate we are now having regarding early versus late(r) use of mechanical ventilation and when patients need to receive mechanical ventilation has been going on since the birth of intensive care seventy years ago (2).

Conscientious writers and editors have always insisted on describing patients as having “received” mechanical ventilation, rather than having a “need” for mechanical ventilation because we have never fully agreed on who is in need. What may have seemed like quibbling

over semantics now has large repercussions. What we are seeing in the current publications on COVID-19 are different rates of invasive mechanical ventilation across the world that have always existed, but these differences are now writ large because it is a particularly high-stakes game of world-wide data interpretation and a desperation to learn as much as possible from the experiences of others. In a sampling of some of the larger epidemiologic studies of COVID-19 patients to date, rates of invasive mechanical ventilation among patients admitted to ICUs range from 29.0% in one Chinese study (3) to 89.9% in a US study (4) and anywhere from 2.3% of patients admitted to the hospital up to 33.1% (Table 1).

Many issues, unrelated to the virus itself, are embedded in these epidemiological reports. First, is the clinical decision-making, which has always varied, even when dealing with “classic” acute respiratory distress syndrome (ARDS). For example, in the Lung Safe study (of non-COVID-19 patients) despite everyone meeting inclusion criteria for ARDS, 15% of patients were receiving non-invasive ventilation on the first two days after enrolment in the cohort (5). In a study of variation by Mehta et al looking at patients who had what were termed “strong evidence” conditions for receiving noninvasive ventilation, the authors found huge variability in use of this modality across California hospitals, ranging from 18.6% of patients in the lowest quartile of hospitals up to 42.0% in the highest quartile, with similar variability in receipt of invasive mechanical ventilation (6). We have never been able to agree on triggers for ventilatory support, even with diseases that are much better known and understood than COVID-19.

Second is availability of resources; the focus of the greatest concern right now. Availability of resources has always varied between countries (7), influencing thresholds for admission to ICU,

perception of “need” for mechanical ventilation and duration of continued invasive life-supporting therapies (8, 9). However, what is linked with variability in resources, and is perhaps the most important piece that gets little air time, is the expectations and preferences for care that are often driven by cultural norms (10). This variability in preferences is intertwined with resources and always will be a huge factor in understanding the data coming out of different countries; for example, in 2008 Gray et al published a large randomized controlled trial comparing non-invasive ventilation to conventional oxygen therapy for patients with acute cardiogenic pulmonary edema. The trial was “negative” for its primary outcome – there was no difference in 7-day mortality between the groups. But if you look more closely, it becomes apparent that among those who died within 7 days, only 30% were placed on a ventilator when they began to fail their treatment (11). This study was done in the UK, with about 7-fold fewer ICU beds than in the US (7); as a practitioner in the US, I have always found this trial difficult to interpret; what would have happened if patients had received mechanical ventilation? Is it possible there was a signal that was lost without the use of this rescue support? We cannot know. And we also do not know how much of those decisions not to place patients on ventilators was due to patient and family preference versus availability of ventilators at the time.

Transparency regarding resources, preferences and clinical decision-making can aid the reader in interpretation of data. Basic information, such as the country/location of the study and the relative availability of ICU beds should be included wherever possible; for example, care patterns when only 1% of a hospital’s beds are ICU beds will likely be different than in a hospital where they constitute 20% of hospitals beds; providing such information in the methods of a

study will help readers understand the data. Similarly, information on care preferences, such as how many patients preferred not to receive mechanical ventilation (due to age, comorbidity, or other personal preference) would aid in interpreting data such as when reporting that only 20.2% of those who died with COVID-19 received this intervention (12). And transparency regarding clinical practices such as approach to the use of invasive mechanical ventilation matters. As an example, the recent paper by Goyal et al provided the information that they used an “early intubation strategy” as an explanation for their high (33.1%) rate of mechanical ventilation among hospitalized patients (13); even more information regarding their thresholds for intubation would be helpful. In other words, the more contextualization for the reader, the better.

### **Mortality for patients who receive mechanical ventilation**

What is the mortality for the patients who receive mechanical ventilation with COVID-19? In the United Kingdom, newspaper headlines in the last few weeks are that 65% of patients who receive mechanical ventilation are dying, and the recent *JAMA* paper published on New York patients initially included an abstract stating that the mortality for mechanically ventilated patients was 88% (4). But denominators being used matter. In data from the UK and from New York, the denominators excluded people who were still in the ICU on a ventilator (4, 14). In a study from Italy, those in the ICU were included in the denominator (15), and the abstract for the data by Richardson et al has since been corrected to report the percentage of patients alive, dead, and still in the ICU to try to avoid this mis-interpretation. We need to know the outcome for everyone before we can draw firm conclusions. It may be higher than we hope; but

excluding all those still receiving care is causing confusion to readers with less understanding of epidemiological principles. We need to ensure uncertainty is presented either in a form that clearly highlights the large pool of individuals still without clear outcomes, or by presenting estimated mortality using the range of possible numbers assuming best and worst-case scenarios; right now those ranges look wide due to the large number of people still being cared for in ICUs (Table 2). What we can say from these data is that it appears that many patients who receive mechanical ventilation may receive it for a prolonged period of time, requiring extensive follow-up to know their ultimate outcomes.

Headlines extolling very high mortality have consequences beyond the shock value; doctors and nurses may read them and feel that what they are doing is futile. When 80 or 90% of the patients you are risking your life to take care of are dying, it's harder to continue. Patients and families may panic; if you hear that someone you love has been moved to the ICU, appropriate concern turns into terror. And less resourced countries will wonder whether they should even bother trying to procure ventilators to care for these patients. This sort of mis-interpretation of the current data does no one any service.

It is not the job of the scientific community to police the press. However, epidemiological studies are being scrutinized by people without scientific backgrounds in a way that has rarely occurred. Therefore, it is important that we provide data that is as accurate as possible, but also presented to limit the ability of readers to seize on a specific number that only tells part of the story. It may be more important than before to ask a "non-scientific reader" to look at an abstract, or read a manuscript before it goes to press; and editors who have more expertise

than most researchers in clear communication of results must help scientific writers ensure transparent presentation of results, setting aside any focus on generating headlines or publicity.

The goal of using invasive mechanical ventilation for COVID-19 patients is universal: to save lives. Our goal is to reduce mortality to ensure it is low for everyone, irrespective of age or comorbidities, or frailty, with judicious implementation of invasive ventilation when it is deemed necessary (Figure 1, black line). But, some aspects of human physiology are also universal; the mortality for patients placed on ventilators who are in their 80s and 90s, or with severe comorbidities has always been very high even in the best of times and best of circumstances. In an epidemiological study from 2010, 50% of those age 85 and above who were ventilated in the US died in the hospital (16). Certain patterns will start to replicate themselves across countries and cultures that will become most apparent when we ultimately combine all these data to look at averages, removing the extremes; there will likely be differential benefit from mechanical ventilation across age groups and those with different comorbidities or severe frailty; we are unlikely to be able to reduce mortality to the same flat rate for all with the use of mechanical ventilation (Figure 1, blue line).

The decision to place a COVID-19 patient on a ventilator is not clear-cut and neither are the outcomes. We will never fully understand how or why these data from each country look so different. But recognizing when patterns of care and outcomes reported fall outside of one's own norms are essential to make the best use of these data for real-time care. So while we scrutinize these reports and extract what is universal and can be applied to our understanding and care of patients locally, we need to recognize and report on the enormous drivers of

differences, and be vigilant in presentation of data to minimize confusion in interpretation. The variability of findings has always existed in studies of mechanical ventilation for critically ill patients. COVID-19 is not an exception, merely an amplifier of these differences.

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## Figure Legend

**Figure 1.** Mortality with use of invasive mechanical ventilation (IMV) for COVID-19 patients. The red line represents the expected increasing mortality associated with COVID-19 as age or number and severity of comorbidities increases; the black line represents the idealized ability to reduce mortality to the same low rate for all, irrespective of patient characteristics. The blue line represents the likely, differential impact of IMV with more benefit for those who are younger and healthier at baseline and less benefit for those who are older and with more underlying health issues.

**Table 1. Comparison of rates of invasive mechanical ventilation in a sample of epidemiology studies of COVID-19 patients**

Study	Location	Hospitalized n	ICU admission n	Invasive Mechanical Ventilation		
				n	% of ICU patients	% of hospitalized patients
Richardson (4)	New York City	5,700	1,281	1,151	89.9	20.2
Petrilli (17)	New York City	1,999	534*	445	83.3	22.3
Goyal (13)	New York City	393	NA	130	NA	33.1
ICNARC (14)	United Kingdom	NA	3,883	2,291**	59.0	NA
Grasselli (15)	Lombardy, Italy	NA	1,300***	1,150	88.5	NA
Zhou (18)	Wuhan, China	191	50	32	64.0	16.8
Wang (3)	Wuhan, China	NA	344	100	29.1	NA
Guan (19)	China	1,099	55	25	45.5	2.3

ICU = intensive care unit; NA = not available

\*excludes 116 patients deemed “critically ill” who were discharged to hospice or died without either intensive care or mechanical ventilation

\*\*within first 24 hours

\*\*\*1,591 admitted to ICU but only 1,300 with respiratory support information

**Table 2. Reported data on mechanical ventilation/ICU patients and outcomes for selected cohorts with possible range of ICU/hospital mortality accounting for patients still receiving care. Lower bound assumes everyone receiving care survives; upper bound assumes they all die**

Study	Location	Total, n	Died, n	Survived to ICU discharge, n	Still receiving care, n	Range of possible mortality, %
Richardson (4)	New York City	1,151	282	38 (hospital)	831	24.5-96.7
ICNARC (14)	United Kingdom	2,291*	698**	355	1,238	30.5-84.5
Grasselli (15)***	Lombardy, Italy	1,581	405	256	920	25.6-83.8

ICU = intensive care unit

\*mechanically ventilated within first 24 hours

\*\*received “advanced organ support; may include patients who received mechanical ventilation after the first 24 hours

\*\*\*all patients in ICU, not just mechanically ventilated

Figure 1

