Mechanical Ventilation in COVID-19: Interpreting the Current Epidemiology

The world is scrutinizing every cohort and every outcome for patients with coronavirus disease (COVID-19), 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 refers to 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 70 years ago (1,2).

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 worldwide 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 patients with COVID-19 to date, rates of invasive mechanical ventilation among patients admitted to ICUs range from 29.1% in one Chinese study (3) to 89.9% in a U.S. 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. For example, in the Lung Safe study (of patients without COVID-19), despite everyone meeting inclusion criteria for acute respiratory distress syndrome, 15% of patients were receiving noninvasive ventilation on the first 2 days after enrolment in the cohort (5). In a study of variation by Mehta and colleagues 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, which is a large 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 airtime, 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 and colleagues published a large randomized controlled trial comparing noninvasive 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, a maximum of 30% were placed on a ventilator when their treatment began to fail (11). This study was done in the United Kingdom with about sevenfold fewer ICU beds than in the United States (7). As a practitioner in the United States, 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 many of those decisions not to place patients on ventilators were due to patient and family preference versus availability of ventilators at the time.

Supported by a Canada Research Chair in Critical Care Organization and Outcomes, an Excellence in Research Award from the Department of Anesthesia at the University of Toronto, and the NIH (R01 DA042299; HL137816).

Originally Published in Press as DOI: 10.1164/rccm.202004-1385ED on May 13, 2020

Table 1. Comparison of Rates of Invasive Mechanical Ventilation in a Sample of Epidemiology Studies of Patients with COVID-19

Study	Location	Hospitalized (*n*)	ICU Admission (*n*)	Invasive Mechanical Ventilation		
				n	Percent of ICU Patients	Percent 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)	UK	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

Definition of abbreviations: COVID-19 = coronavirus disease; ICNARC = Intensive Care National Audit & Research Centre; 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.

Transparency regarding resources, preferences, and clinical decision-making can aid the reader in interpretation of data. Basic information, such as the country or 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 (because of 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). Furthermore, transparency regarding clinical practices such as the approach to the use of invasive mechanical ventilation matters. As an example, the recent paper by Goyal and colleagues 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 initially claimed that 65% of patients who receive mechanical ventilation are dying, and a paper published in the *Journal of the American Medical Association* on New York patients initially included an abstract stating that the mortality for mechanically ventilated patients was 88% (4). However, denominators being used matter. In data from the United Kingdom 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 and colleagues has since been corrected to report the percentage of patients alive, dead, and still in the ICU to try to avoid this misinterpretation. We need to know the outcome for everyone before we can draw firm conclusions. Mortality 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 because of 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

Table 2. Reported Data on Mechanically Ventilated ICU Patients and Outcomes for Selected Cohorts with Possible Range of ICU or Hospital Mortality Accounting for Patients Still Receiving Care

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)	UK	2,291*	698†	355	1,238	30.5–84.5
Grasselli (15)‡	Lombardy, Italy	1,581	405	256	920	25.6–83.8

Definition of abbreviation: ICNARC = Intensive Care National Audit & Research Centre.
Lower bound assumes everyone receiving care survives; upper bound assumes they all die.
*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 those mechanically ventilated.

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. Also, those individuals in countries with fewer resources will wonder whether they should even bother trying to procure ventilators to care for these patients. This sort of misinterpretation 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 "nonscientific 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 data 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 patients with COVID-19 is universal: to save lives. Our goal is to reduce mortality to ensure it is low for everyone, irrespective of age, comorbidities, or frailty, with judicious implementation of invasive ventilation when it is deemed necessary (Figure 1, black line). However, 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 United States 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 benefits 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 patient with COVID-19 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. However, 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. ■

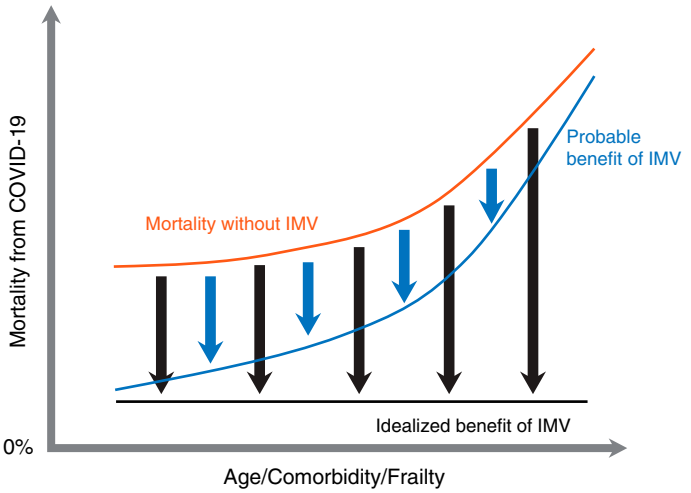

Figure 1. Mortality with use of invasive mechanical ventilation (IMV) for patients with coronavirus disease (COVID-19). The red line represents the expected increasing mortality associated with COVID-19 as age or number and severity of comorbidities increases; the black line represents the idealized 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.

Author disclosures are available with the text of this article at www.atsjournals.org.

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MicroRNAs as Biomarkers in Corticosteroid-Resistant/Neutrophilic Asthma: Still a Long Way to Go!

Asthma is a complex and heterogeneous disorder characterized by chronic airway inflammation with variable airflow obstruction that affects people of any age. It is associated with an earlier decline of lung function over time and, in some cases, reduced lung function growth during childhood/adolescence (1, 2). Antiinflammatory corticosteroids are the mainstay of asthma treatment from infancy to senescence, often combined with long-acting β-agonists in patients older than 6 years of age (3). In most subjects, corticosteroids allow clinical control of asthma (symptomatic treatment) and are also effective as disease-modifying therapy, inhibiting lung function decline in both children and adults (4, 5).

However, a clinically relevant proportion of individuals with asthma do not respond to corticosteroid treatment, even when administered at high doses. Severe steroid-resistant asthma affects 5–10% of adult patients, who disproportionately account for 50–80% of all asthma-associated healthcare costs (6). The epidemiology and prevalence of severe steroid-resistant asthma in children are unclear (7). In adults, severe asthma is classified based on the inflammatory profile as T2 high and T2 low. The latter is often characterized by neutrophilic inflammation, an indication of steroid resistance.

The molecular mechanisms leading to corticosteroid resistance are various and only partially understood (6). Their identification could pave the way for new treatment targets in asthma. Even better, unraveling the risk factors associated with the development of corticosteroid resistance over time could allow early targeted interventions and the implementation of preventive precision medicine ("precision prevention"). Complex interactions between genetic and environmental factors regulate corticosteroid resistance. The genetic factors include microRNAs (miRNAs), which are are small noncoding RNAs that intervene in gene expression regulation during inflammatory and immune responses, and are recognized as possible genetic modulators of steroid sensitivity in asthma (6).

In this issue of the *Journal*, Gomez and colleagues (pp. 51–64) and Li and colleagues (pp. 65–72) provide additional data about the role of miRNAs in corticosteroid-resistant asthma in children and neutrophilic adults, respectively (8, 9).

Li and coworkers identified seven circulating miRNAs associated with treatment response, quantified as the change in FEV_1% predicted after 4 years, in a cohort of nearly 500

Originally Published in Press as DOI: 10.1164/rccm.202004-1216ED on April 30, 2020