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EDITORIAL

Mortality among elderly patients with COVID-19 ARDS—age still does matter

Mortality rates in elderly coronavirus disease 2019 (COVID-19) patients have been a major concern throughout the COVID-19 pandemic. According to data from the World Health Organization,[1] the overall mortality rate for COVID-19 is estimated to be around 2%, but the mortality rate increases dramatically for elderly patients. For example, the mortality rate for patients over the age of 80 has been estimated to be as high as 15—20%. This is at least in part due to the fact that elderly patients are more likely to have underlying health conditions such as heart disease, diabetes, and respiratory illness, which can increase the severity of COVID-19 symptoms. In addition to age, other factors that may increase mortality risk in elderly COVID-19 patients include sex, obesity, and the presence of certain comorbidities such as hypertension or chronic kidney disease. The mortality rate increases drastically for patients who require admission to an intensive care unit (ICU), especially for those who need mechanical ventilation.

In this issue of *Pulmonology*, Cilloniz et al. report on an analysis of the conveniently-sized observational study in critically ill COVID-19 patients in 55 ICUs in Spain, named the CIBERESUCICOVID study.[2] In this analysis she studied risk factors for mortality in a cohort of 5090 ventilated patients of which 1525 (27%) were aged ≥70 years. Overall in-hospital mortality in patients aged ≥70 years was twice that in patients aged <70 years: 50 versus 23%. Factors that had an independent association with higher in-hospital mortality in patients aged ≥70 years were ventilation at ICU admission, age, chronic heart disease, chronic renal failure, platelet count, and previous admission within the last 30 days. Of note, use of systemic steroids had an independent association with lower in-hospital mortality.

It is worth noting that mortality rates for COVID-19 can vary widely between countries and regions, depending on factors such as healthcare infrastructure and access to treatment. The could also be true for patients that require admission to an ICU. However, one recent analysis of the PRoVENT-COVID study, a nationwide multicenter observational study in the 22 ICUs in the Netherlands, performed in the first three months of the national outbreak of COVID-19, showed a remarkably similar pattern for mortality in elderly patients.[3,4] The PRoVENT-COVID study focused on key ventilator parameters, including tidal volume, positive end-expiratory pressure, driving pressure, and respiratory system compliance, and the use of rescue therapies for refractory hypoxemia in the first days of mechanical ventilation, but also reported on pulmonary and extrapulmonary complications, hospital- and ICU stay, and mortality amongst four age groups (<58, 58—65, 66—72, and >72 years). No meaningful differences were found in ventilation parameters and in the use of rescue therapies in the first days of ventilation. Older patients, however, received more often a tracheostomy, developed more frequently acute kidney injury and myocardial infarction, stayed longer in the ICU and in the hospital, and had higher mortality rates, e.g., in-hospital mortality increased from 16.6, to 27.7, 44.3, and 55.6%. The mortality rate in the oldest group in the Dutch study was fairly comparable to that in the Spanish study, on which Cilloniz et al. report in this issue of *Pulmonology*.[2]

It is also worth noting that we may be looking at the results of 'triage'.[5] Indeed, the decision to admit an elderly patient to an ICU for e.g., ventilation is often individualized, based on the specific clinical situation, in collaboration with the patient and their family, and with input from a multidisciplinary team of healthcare providers. ICU triage for elderly patients involves assessing the patient's overall health status, the severity of their illness, and the potential benefits and risks of ICU care.[6,7] Some factors to consider when triaging elderly patients to an ICU include:

1. overall health status—elderly patients with multiple comorbidities or poor functional status may have a lower chance of benefiting from ICU care; however, patients who are otherwise healthy and have a good baseline functional status may be good candidates for ICU admission;
2. severity of illness—severity of illness is a key factor in determining whether ICU care is necessary; however,

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patients with severe illness, such as respiratory failure, may benefit from ICU care regardless of age;
3. potential benefits and risks—elderly patients may be at higher risk of complications, such as delirium or infection, and may have a longer recovery time; however, ICU care may also provide life-saving interventions and improve outcomes; and
4. goals of care—the patient's goals of care should also be taken into consideration; quality of life may be more important than prolonging life for some elderly patients, and they may prefer to forego aggressive interventions.

Could there have been a policy early in the COVID-19 pandemic to keep elderly patients away from ICUs? Hospitals worldwide were confronted with surges of patients with an at that time unknown disease, with initially reportedly extremely high mortality rates. We also may have selected patients with the best survival rates, excluding older patients from ICU care more than usual. And if this is true, could it be that there are differences between countries and regions? The PRoVENT-COP investigators will use individual patient data from four recently published large observational COVID-19 studies,[8] including the Spanish study reported on in this issue of Pulmonology[2] and the Dutch study mentioned above,[3,4] and 2 large observational studies of ARDS from the pre-COVID era to answer this question.[7]

Mortality rates for elderly ICU patients in general can vary depending on a variety of factors, including the underlying medical conditions of the patient, the severity of their illness, and the quality of care they receive. However, research has consistently shown that advanced age is a significant predictor of mortality in ICU patients. One study found that ICU mortality rates increased with age, with patients over the age of 80 having a significantly higher risk of death than younger patients.[6,7] The study also found that elderly patients who required ventilation had a higher mortality risk than those who did not. Another study published found that the mortality rate for elderly ICU patients was high, with nearly half of patients over the age of 80 dying within 1 year.[9] Elderly patients who have pre-existing health conditions, such as heart disease or dementia, are at an even higher risk of mortality. And again, it is important to note that mortality rates for elderly ICU patients can vary depending on the specific ICU and hospital setting, as well as the quality of care provided. In some countries, elderly patients may easier, or earlier choose to forego aggressive medical interventions like ventilation, which definitely affects the overall mortality risk, but also the outcome of ICU care due to changes in case-mixes.[10]

Is COVID-19 ARDS different from other forms of ARDS, and does this translate in differences in outcomes among the elderly? While the pathophysiology of ARDS in COVID-19 patients is similar to 'classic' ARDS, there are some differences:

1. time course—COVID-19 ARDS may have a more prolonged course than non-COVID ARDS, with some patients requiring ventilation for several weeks;
2. hypoxemia—COVID-19 ARDS is associated with more severe hypoxemia than non-COVID ARDS, even in patients with relatively preserved lung compliance;
3. lung compliance—in COVID-19 ARDS, the lungs may be stiffer than in non-COVID ARDS, albeit that this was recently challenged;[11,12]
4. blood clotting—COVID-19 ARDS is associated with a higher risk of blood clotting in the lungs and other organs;
5. inflammatory response—COVID-19 ARDS is associated with a particularly strong inflammatory response, with elevated levels of cytokines and other inflammatory mediators, which may contribute to other complications; and
6. treatment response—studies showed that COVID-19 ARDS responds well to steroids; of note, this was confirmed in the CIBERESUCICOVID study, wherein patients that used corticosteroids had a 39% decrease in the risk of death?

In the current analysis of the CIBERESUCICOVID study a multivariable analysis was performed to determine which factors had an independent association with outcome.[2] The CIBERESUCICOVID-investigators could have considered doing a propensity matched analysis, a statistical method used to compare two or more groups of individuals with similar characteristics in order to draw conclusions about the effects of e.g., age or steroid use. This method is increasingly used in observational studies, as this type of analysis can help to control for potential confounding factors and reduce bias in a study, allowing for more accurate conclusions about the effects of the intervention being studied.

The findings of this analysis of CIBERESUCICOVID study are an important part of the information surrounding COVID-19. Even now that the pandemic appears to be over, at least in many countries, this information remains important: the world will face more frequent outbreaks of (respiratory) infections, and lessons from previous epidemics help guide steps to take in the next epidemic.[13]

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