renal subscore. Again, although in some cases the adjusted scores were less poorly calibrated than the original score, differences in performance between Black and white patients remained. The results of these analyses suggest that other factors associated with Black versus white race were contributing to the calibration errors.

This study is timely, of critical importance in the midst of the COVID-19 pandemic, and reinforces the necessity of examining each component of our public health and acute healthcare delivery systems for race-based disparities and inequities. The large size and multicenter nature of the population as well as the study's rigorous statistical approach and well-conceived sensitivity analyses are important strengths. However, the use of a non–COVID-19 patient population and the focus solely on mortality prediction scores rather than also evaluating full CSC scoring systems makes interpretation of these results in light of the pandemic or comparison to other studies, such as that by Gershengorn and colleagues (6), challenging.

Given concerns that scoring systems may be biased against nonwhite persons as well as the overwhelming evidence of higher prevalence and worse outcomes associated with COVID-19 among nonwhite communities, authors of some CSCs have proposed the use of correction factors that give credits to minoritized or disadvantaged groups. One example is the Area Deprivation Index, which uses a person's address to rank their degree of socioeconomic disadvantage (5, 8, 9), although this does not explicitly address the racial differences in calibration identified in this study. The use of such correction factors in CSCs is just one example of several potential approaches to address the systematic racial disparities identified by Dr. Ashana and colleagues. This important study highlights the crucial need for more research, validation, and refinement of CSC scoring systems to ensure that they achieve their goals of equitable distribution of resources while maximizing lives or life-years saved. ■

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

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Immunocompromised Patients with Acute Respiratory Failure: "Don't Wait to Intubate"?

In this issue of the *Journal*, Dumas and colleagues (pp. 187–196) report the results of their meta-analysis using individual data of over 11,000 immunocompromised patients from 24 studies (1), a huge amount of work representing the most comprehensive overview to date. They report that approximately one out of two immunocompromised adult patients with acute respiratory failure requiring invasive mechanical ventilation die, that clinical outcomes have improved over the years, that time to intubation and duration of mechanical ventilation are related to impaired outcome, and that early intubation is associated with better outcome. These are clinically relevant messages.

Similar to most other critically ill patient groups, the prognosis of immunocompromised patients has improved over recent decades. This

Originally Published in Press as DOI: 10.1164/rccm.202103-0813ED on May 4, 2021

may reflect general improvements in the fields of critical care, hematology, and oncology but may also indicate a shift in admission criteria and policy as indicated by a lower nonpulmonary Sequential Organ Failure Assessment score in immunocompromised patients admitted to the ICU over time. Clearly, physicians have become less reluctant to admit these patients to the ICU. Also, in this specific group of patients on invasive mechanical ventilation, V_T was found to be lower over time (*P* value for trend: <0.001) and the positive end-expiratory pressure levels higher (*P* value for trend: <0.001), which could also explain some of the improved outcomes.

Importantly, and independently from these improvements in general management, the authors show that in immunocompromised patients and patients with acute respiratory failure, early intubation is associated with better outcomes. Previous large trials from the same group have shown that in immunocompromised patients, the results from noninvasive ventilation (NIV) and high-flow nasal cannula are substantially different compared with nonimmunocompromised patients, with no benefit from NIV of high-flow nasal cannula (2, 3). Nevertheless, noninvasive modalities have become the most common first-line ventilation strategies in these patients (4). Hence, it is important to ascertain that there is no obvious harm from this practice. The current study indicates that in the subgroup of patients who ultimately need invasive mechanical ventilation, delayed intubation is associated with higher mortality. This difference already became apparent 6 hours after ICU admission, and this effect became more pronounced when the time from ICU admission to intubation was longer.

The results of this study need to be interpreted with some caution. First, only 24 out of 43 eligible studies were included because individual patient data could not be obtained for 19 studies. Nevertheless, data from a wide range of centers and experience and not only highly specialized centers were used, increasing the generalizability of the results. Second, all included studies except three were nonrandomized cohort studies, albeit generally of acceptable quality. Third, because this study describes observational data, cause–effect relationships are troublesome and bias by indication, confounding factors, and baseline differences may play a role. Finally, it is important to emphasize that this study focused only on patients who ultimately needed intubation and invasive ventilation. Patients successfully treated with noninvasive strategies were not included in this study. Consequently, this study does not directly evaluate the role of noninvasive strategies in immunocompromised patients with acute respiratory failure, and this may introduce an important source for selection bias. For example, it is conceivable that patients who deteriorated during a noninvasive strategy and required intubation simply represent a worse prognosis group than the patients who were intubated early. Late intubation happens in patients who get worse over time, and therefore this implies a selection of patients who deteriorate and thus may have an impaired outcome. Other studies in other patient cohorts have also shown that failure of noninvasive strategies is associated with worse outcomes. For example, in LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure), NIV failure in patients with acute respiratory distress syndrome was associated with a substantial increase in the risk of death, with mortality rates higher than for severe acute respiratory distress syndrome managed with invasive mechanical ventilation (5).

This selection bias may be partially addressed by using statistical models. The authors performed appropriate sensitivity analyses and propensity score matching aimed to correct for these issues by adjusting for potential confounders, including the severity of hypoxemia assessed by using the Pa_{O_2}/Fi_{O_2} ratio as a marker of hypoxemia severity and by using the nonpulmonary Sequential Organ Failure Assessment score as a marker of other organs' dysfunction. Nevertheless, there is still need for caution, as patients who failed the noninvasive strategies may simply be different from patients who did not fail, and this difference may not have been captured in the chosen confounders that were adjusted for. Unfortunately, but not surprising in data retrieved from large cohorts, important clinical information at the time of intubation (e.g., respiratory rate or oxygen saturation) was not available.

In conclusion, this study confirms that the clinical outcome of immunocompromised patients has improved over the years and, in addition, convincingly demonstrates that late intubation in immunocompromised patients, in the subgroup that ultimately does need invasive ventilation, is associated with a worse prognosis. Clearly, a proportion of patients will improve with a noninvasive ventilation strategy, and these patients should not be intubated. This implies that only in hindsight, we have not provided optimal treatment to those patients who do not improve and need intubation later on. How should this be dealt with in clinical practice? Persevering with noninvasive strategies in patients who do not improve may be harmful, especially in patients with a high respiratory drive, which is possibly associated with an increased risk of patient self-inflicted lung injury. Early identification of patients at high risk for failure of noninvasive strategies is a clear priority. Ideally, validated criteria predictive for failure of noninvasive strategies would be helpful in the decision to intubate early. In LUNG SAFE (4), noninvasive ventilation failure was predicted by the percentage increase of Pa_{CO_2} and a decline of Pa_{O_2}/Fi_{O_2} ratio. Several scoring systems based on clinical and laboratory parameters have been proposed but not yet validated in immunocompromised patients. Until then, careful frequent bedside assessment of the response to noninvasive strategies is essential in this patient group, and a lower threshold to intubate early should be applied to patients who fail to improve. ■

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

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A Phase-2 NIH-sponsored Randomized Clinical Trial of Rituximab in Scleroderma-associated Pulmonary Arterial Hypertension Did Not Reach Significance for Its Endpoints

End of Story? Not So Fast!

In this issue of the *Journal*, Zamanian and colleagues (pp. 209–221) report the results of a randomized placebo-controlled clinical trial (RCT) of rituximab in scleroderma-associated pulmonary arterial hypertension (SSC-PAH), a common form of PAH (1). The protocol excluded patients with significant interstitial lung disease, and all patients were on at least two PAH therapies, including epoprostenol. This NIH-sponsored trial showed acceptable drug safety and tolerability but failed to reach significance for the primary (6-min-walk distance [6MWD] change from baseline at 24 weeks) and secondary endpoints, which included a change in pulmonary vascular resistance. However, a closer look suggests that rituximab may be a promising adjuvant therapy for patients with SSC-PAH, opening important questions for the future.

Most clinicians do not understand how long and complicated an RCT can be. More than 75% of the RCT funding comes from industry (2), where large teams of employees and consultants design the protocol, which goes through several regulatory stages before it even reaches clinicians at participating centers, a process that can take years. In investigator-driven trials, all the work is completed by the principal investigator and his or her small team. The study received funding from the NIH/National Institute of Allergy and Infectious Diseases and the NIH Autoimmunity Centers of Excellence and, after years of planning, started enrolling in 2010 and closed in 2019. Three years into the trial, only 30 patients had been recruited, forcing the steering committee to change the protocol and decrease the original target sample size from 80 to 60, decreasing the power to only 50% (to detect a change in 6MWD $>$33 m), contributing to the failure to detect significance in the endpoints.

There are at least two obvious reasons for this difficulty in recruiting: *1*) as a publicly funded trial, it had to compete with industry trials, which typically compensate more, both at the physician (3) and occasionally the patient level (4), creating a bias against enrolling in trials with less direct (trial cost) and indirect (consulting fees or institutional grants) funding (5); and *2*) the trial included two right heart catheterizations that decrease enthusiasm on the patient side, although this is critical and necessary to assess treatment effects on the pulmonary circulation.

All the patients were already on approved PAH therapies compared with the original RCTs that led to the approval of prostacyclin (6), bosentan (7), and sildenafil (8), in which the drug was compared with placebo. In those trials, the placebo-corrected 6MWD was 47, 44, and 45 m, respectively. In this trial, this was 25.1 m. There was, however, variability in the group responses, with 38% of patients on rituximab having a $>$50-m increase in 6MWD compared with 15% on placebo.

In a *post hoc* analysis, the authors used machine learning and found that of the many serum biomarkers they tested, a panel of cytokines (low levels of RF [rheumatoid factor], IL2, and IL17) predicted response to rituximab. Because this is a publicly funded trial, the raw data are deposited in www.import.org and open to anyone for analysis, in contrast to industry trials, for which data are typically not publicly available. We asked the authors to provide us the endpoints for the subsets of patients that did and did not have this biomarker profile, now shown in Figure 1A. In patients that had the biomarker, the placebo-corrected 6MWD (24 wk) was +101 m, whereas the placebo-corrected Δpulmonary vascular resistance was −2.56 Wood units, suggesting a significant improvement. Through a precision medicine (PM) lens, one would conclude that, in fact, rituximab may be a very effective therapy for a subset of patients with SSC-PAH. The trial design, however, prohibits such an analysis because these subgroups were not prospectively defined and thus are suffering from potential bias. There is one exception to that rule: when the biomarker is genetically driven (i.e., allocated in the drug–placebo group patients at the time of conception by Mendelian distribution) because this is immune to selection biases. In fact, some cancer drugs have been approved for patient subgroups based on *post hoc* analysis of genetic biomarkers, even though they were not prospectively assigned as "potential drug-response" predictors (9, 10).

The response to rituximab in patients with the biomarker is too robust to ignore. Can the responder–nonresponder separation have a

Supported by Canadian Institutes of Health Research Foundation grants.

Originally Published in Press as DOI: 10.1164/rccm.202103-0612ED on April 15, 2021