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Hospital Capacity Strain as a Window into the Value of ICU Admission

Some Answers, More Questions

Millions of patients are admitted to ICUs every year in the United States (1). ICU admission is costly, because ICU patients receive more expensive care, and building and staffing ICUs imposes high fixed costs (2). At the same time, ICU admission may not always provide value—there is wide variation in ICU admission practices across hospitals that is not tightly linked with better outcomes (3–6). We therefore urgently need to understand which patients benefit most from ICU care, and which aspects of ICU care drive this benefit, so we can use ICU and hospital resources more efficiently.

In this issue of the *Journal*, Anesi and colleagues (pp. 520–528) work to address these questions by analyzing the association between ICU triage and patient outcomes (7), using a previously validated instrumental variable in the form of hospital capacity strain (8). Their two cohorts included patients in 27 emergency departments—90,150 patients with sepsis and 45,339 with acute respiratory failure—who did not require life support (vasopressors or invasive mechanical ventilation) before ICU triage. These cohorts were chosen as archetypical patients whose need for and likely benefit from ICU admission were uncertain. The study's primary endpoint was hospital length of stay (LOS), using a "placement of death" approach in which in-hospital deaths or hospice discharges were assigned a LOS value equal to the 99th percentile of hospital LOS for the cohort. This primary outcome attempts to capture the fact that ICU care may modify LOS independent of mortality, while accounting for the effects of mortality censoring on LOS. The authors then analyzed the association between ICU admission and hospital LOS, using hospital capacity strain at the time of triage as an instrumental variable.

The primary finding was that ICU admission was associated with harm in patients with sepsis (1.32 d longer LOS), whereas it was associated with benefit in patients with acute respiratory failure (0.82 d shorter LOS). Secondary analyses suggested that these LOS changes were driven by higher mortality associated with ICU admission in patients with sepsis (odds ratio [OR], 1.48) and lower mortality in patients with acute respiratory failure (OR, 0.75). The results were generally consistent across sensitivity analyses. However, when code status at hospital admission was included as a covariate, the LOS and mortality results were attenuated, and the OR for mortality in patients with sepsis was no longer statistically significant.

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This study has several key strengths. Most importantly, the authors used granular electronic health record data from a large number of patients across many hospitals, with implications beyond just the generalizability of the findings. First, these data allowed analysis of the effects of patient-level triage, whereas prior studies largely addressed hospital-level triage practices (5, 6). Second, the granularity of the data allowed for cohort definitions and statistical risk adjustment using detailed physiologic data, rather than relying on administrative claims or diagnosis codes with well-described biases (9).

At the same time, the authors' instrumental variable approach requires careful interpretation (10). An instrumental variable is a characteristic—in this case hospital capacity strain at the time of each patient's ICU triage decision—that is randomly assigned between patients and associated with the outcome (hospital LOS) only via the exposure (ICU admission). As a result, an instrumental variable analysis attempts to mimic the effects of a randomized trial. Notably, while the associations between the instrumental variable and the exposure and, separately, the outcome can be directly measured, the randomness of the assignment can only be assessed via the association between the instrumental variable and observed confounders. Residual confounding therefore remains possible. In addition, the results of an instrumental variable analysis apply only to the statistically marginal population—those patients for whom the decision to admit to the ICU was influenced by hospital capacity strain at the time of triage. The size of this patient population cannot be directly measured, but in prior work the authors estimated that the marginal population was approximately 20% of the sepsis cohort and 35% of the acute respiratory failure cohort (8). Consequently, it would be incorrect to interpret this study to mean that when confronted with a random patient with sepsis not receiving vasopressors, choosing to admit the patient to the ICU will result in higher LOS or mortality.

Furthermore, we do not know the mechanisms underlying the observed associations between ICU admission and outcomes, which were in differing directions in in the sepsis and respiratory failure cohorts. A number of possibilities exist. First, capacity strain appears to modify practices around end-of-life discussions (11). If, during times of high hospital capacity strain, emergency department physicians were more likely to have goals-of-care discussions upstream of the triage decision in ways that altered downstream care and outcomes, residual confounding would have been introduced. Alternatively, goals-of-care conversations may have occurred downstream of the triage decision in ways that mediated or confounded the observed differences in outcomes. Second, patients admitted to the ICU with sepsis may have had longer LOS due to nonbeneficial increases in treatment intensity—for example, holding a patient in the ICU "one more day" for closer observation or treatment with vasopressors for mild hypotension (12). Third, patients admitted to the ICU with respiratory failure may have been more likely to receive appropriate treatment, such as with noninvasive ventilation or high-flow oxygen, reducing progression to intubation (13).

As the authors note, conducting a randomized controlled trial of ICU admission is likely ethically untenable. Moreover, even such a trial would be hampered by heterogeneity in care (including goals-of-care discussions) after initial randomization at triage. Anesi and colleagues, therefore, are to be commended for executing a complex and rigorous analysis, which is the best available option and meaningfully advances the field of ICU use research. Nevertheless, it would be premature to translate these findings into clinical triage guidelines. We first must understand how ICU care confers harm or benefit. This knowledge will help determine which patients may benefit from ICU admission. Moreover, these mechanistic studies may identify beneficial aspects of ICU care that are replicable outside the ICU setting, reducing the need for more resource-intensive ICU admission. ■

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Cystic Fibrosis: A Disease in Transformation, yet More Work to Be Done!

What have we learned from real-world experience about highly effective CFTR modulation and its impact on the lives of patients with cystic fibrosis? In 2019, the triple combination CFTR (cystic fibrosis transmembrane regulator) modulator elexacaftor-tezacaftor-ivacaftor (ETI) was approved for patients with cystic fibrosis (PwCF) aged 12 years and older with at least one copy of the *F508del* variant in the United States and several European countries based on supportive phase 3 efficacy and safety data (1, 2). Over the past 2 years, the international cystic fibrosis (CF) community has begun collecting and analyzing real-world experience with ETI based on several large and comprehensive post-approval observational studies evaluating its biologic and clinical impact on PwCF. In this issue of the *Journal*, two papers provide initial findings from complementary studies, one by Nichols and colleagues (pp. 529–539) focused on clinical outcomes (3), and the second by Graeber and colleagues (pp. 540–549) on CFTR channel function across multiple epithelia (sweat duct, airway, and intestine) (4). The findings are exciting and impactful, indicating that the CFTR channel function is likely approaching 50% normal levels and we are just beginning to understand the longer-term clinical impact of this biological milestone for PwCF.

Why is it so important to continue to collect prospective post-approval biological and clinical data? First, it allows us to understand the generalizability of the phase 3 findings across a broad range of ages (≥12 yr), geography, populations, disease severity, and comorbidities. The ETI phase 3 trials excluded patients with mild (FEV_1 > 90% predicted) and severe (FEV_1 < 40% predicted) lung disease and comorbidities such as active *Mycobacteria abscessus* and *Burkholderia cepacia* complex infections. In addition, phase 3 trials focused on a few key pulmonary endpoints, such as percent predicted FEV_1 ($ppFEV_1$), and not the multiple other organ systems affected by this genetic disease. In addition, the CF community needs to better understand the biologic basis of these remarkable changes in lung function and patient well-being. The international CF community should be commended for the foresight and commitment to collect real-world data and should serve as a model for other orphan genetic diseases as they develop new therapies.

What New Insights Have These Two Papers Provided?

These two papers have demonstrated that ETI leads to ∼50% functional correction of the CFTR protein channels in epithelial cells across multiple organs, leading to impressive clinical impacts for patients 12 years and older with at least one copy of the *F508del* variant (plus a small number of other ETI-responsive variants) (3, 4).

The article by Nichols and colleagues (3) reports the initial findings of a planned 6-month interim analysis of a 30-month observational study of PwCF who were 12 years and older with at least one *F508del* variant at the time of initiation of ETI (Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function [PROMISE], NCT04038047). These patients were assessed before drug initiation and at 1, 3, and 6 months after therapy. The outcomes being evaluated are changes in $ppFEV_1$, sweat chloride concentration (SCC), body mass index, and patient-reported outcomes (Respiratory Domain of the Cystic Fibrosis Questionnaire-Revised [CFQ-R, RD]). The PROMISE study has multiple substudies examining other disease manifestations, including airway microbiology, gastrointestinal (GI) symptoms, and glucose metabolism, which will be reported at a later date (5). Among the 487 study participants across 56 U.S. sites, ∼50% had received earlier generations of CFTR modulators, potentially reducing the magnitude of the ETI therapeutic impact. Yet, even with previous modulator exposure, the mean clinical changes at 6 months were remarkable in $ppFEV_1$ (9.79%; 95% confidence interval [CI], 8.76% to 10.76%), SCC (−41.7 mmol/L, 95% CI, −43.8 to −39.6), and CFQ-R increased (20.39 points; 95% CI, 18.3 to 27.50) (Figures 1 and 2 and Table 2) (3). Treatment effect was robust across all CFTR variant grouping, race, sex, age, and disease severity. These findings undertaken in real-world settings are comparable to the data from the phase 3 trials and set a new benchmark for clinical impact measures, surpassing the robust ivacaftor studies (6, 7). In addition, with the large study population and effect size, a modest correlation (at 6 mo) between sweat chloride and FEV_1 change was seen for the first time (Figure 4) (3).

The article by Graeber and colleagues (4) comes from five German CF centers and examines the effect of ETI on CFTR function in airway and intestinal epithelia, using CFTR biomarkers, SCC, nasal potential difference (NPD), and intestinal current measurement (ICM). The study included 107 patients with one or two *F508del CFTR* variants (55 with *F508del* and minimal function variant; 52

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