4. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med* 2010;363:2233–2247.
5. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, *et al.*; National Heart Lung and Blood Institute (NHLBI) Severe Asthma Research Program (SARP). Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest* 2018;128:997–1009.
6. Morrison CB, Edwards CE, Shaffer KM, Araba KC, Wykoff JA, Williams DR, *et al.* SARS-CoV-2 infection of airway cells causes intense viral and cell shedding, two spreading mechanisms affected by IL-13. *Proc Natl Acad Sci USA* 2022;119:e2119680119.
7. Bonser LR, Eckalbar WL, Rodriguez L, Shen J, Koh KD, Ghias K, *et al.* The type 2 asthma mediator IL-13 inhibits severe acute respiratory syndrome coronavirus 2 infection of bronchial epithelium. *Am J Respir Cell Mol Biol* 2022;66:391–401.
8. Wang L, Liu C, Yang B, Zhang H, Jiao J, Zhang R, *et al.* SARS-CoV-2 ORF10 impairs cilia by enhancing $CUL2^{ZYG11B}$ activity. *J Cell Biol* 2022; 221:e202108015.
9. Holtzman MJ, Byers DE, Alexander-Brett J, Wang X. The role of airway epithelial cells and innate immune cells in chronic respiratory disease. *Nat Rev Immunol* 2014;14:686–698.
10. Keeler SP, Agapov EV, Hinojosa ME, Letvin AN, Wu K, Holtzman MJ. Influenza A virus infection causes chronic lung disease linked to sites of active viral RNA remnants. *J Immunol* 2018;201:2354–2368.
11. Singanayagam A, Footitt J, Marczynski M, Radicioni G, Cross MT, Finney LJ, *et al.* Airway mucins promote immunopathology in virus-exacerbated chronic obstructive pulmonary disease. *J Clin Invest* 2022;132:e120901.
12. Chen G, Sun L, Kato T, Okuda K, Martino MB, Abzhanova A, *et al.* IL-1β dominates the promucin secretory cytokine profile in cystic fibrosis. *J Clin Invest* 2019;129:4433–4450.
13. Zuo W, Zhang T, Wu DZ, Guan SP, Liew AA, Yamamoto Y, *et al.* $p63^{+}Krt5^{+}$ distal airway stem cells are essential for lung regeneration. *Nature* 2015;517:616–620.
14. Vaughan AE, Brumwell AN, Xi Y, Gotts JE, Brownfield DG, Treutlein B, *et al.* Lineage-negative progenitors mobilize to regenerate lung epithelium after major injury. *Nature* 2015;517: 621–625.
15 . Hernandez BJ, Cain MP, Lynch AM, Flores JR, Tuvim MJ, Dickey BF, *et al.* Intermediary role of lung alveolar type 1 cells in epithelial repair upon Sendai virus infection. *Am J Respir Cell Mol Biol* 2022;67: 389–401.
16. Ray S, Chiba N, Yao C, Guan X, McConnell AM, Brockway B, *et al.* Rare $SOX2^{+}$ airway progenitor cells generate $KRT5^{+}$ cells that repopulate damaged alveolar parenchyma following influenza virus infection. *Stem Cell Reports* 2016;7: 817–825.
17. Taylor MS, Chivukula RR, Myers LC, Jeck WR, Waghray A, Tata PR, *et al.* A conserved distal lung regenerative pathway in acute lung injury. *Am J Pathol* 2018;188:1149–1160.

Understanding Sex-based Differences in Intensive Care Unit Mortality: Moving Beyond the Biology

Many observational studies have pointed to survival differences between critically ill men and women with varying directionality depending on the disease state (1–3). Women, as compared with men, have displayed worse outcomes in coronary artery disease, cardiac surgery, and after cardiac arrests (4, 5). However, women are more likely to survive than men with certain conditions such as chronic obstructive pulmonary disease and respiratory viral diseases (6, 7).

Although the interplay between the patient's biological and immunological factors has been speculated as the potential unmeasured drivers for observed sex-based differences in care outcomes (8, 9), the potential contributions of systemic and implicit biases and cognitive errors have been largely understudied. Other factors historically overlooked, such as care environment, caseload, and team dynamics, are being independently investigated and increasingly recognized as important determinants of outcome, particularly for those at a high baseline risk of death (10–12). Similarly, exploring the variation in intensive care unit (ICU) mortality outcomes by the sex of the patient will require dedicated investigation that transcends the lens of acute physiology and comorbidity and other host factors.

In this issue of the *Journal*, Modra and colleagues (pp. 1353–1360) report their findings from a large, cross-sectional study of adult patients admitted to ICUs in Australia and New Zealand. Modra and colleagues took a deep dive into understanding variation in hospital mortality in men and women on the basis of how frequently a given condition occurred within each sex. The primary exposure variable was "sex balance", defined as the percentage of patients in a diagnostic group who were women, and the primary outcome was sex difference in adjusted hospital mortality by ICU admission diagnosis. The study was large, encompassing over 1.4 million ICU admissions between 2011 to 2020 in the ANZICS APD (Australia and New Zealand Intensive Care Society Adult Patient Database) (13). Using mixed-effects logistic regressions, the authors adjusted for severity of illness, hours of hospitalization before ICU admission, and year of admission, with hospital site as a random effect.

The key findings were that women displayed better risk-adjusted survival than men in sepsis, respiratory disorders, and in the combined category of metabolic/renal and hematological disorders. On the other hand, women fared worse than men in burns and cardiovascular disorders, with the most marked sex difference

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observed in the cardiac surgery diagnosis category. The most striking finding was the inverse association between sex balance (defined as the percentage of patients in a diagnostic group who were women) and sex differences in mortality: in diagnostic groups in which there was a lower percentage of women, the women were more likely to die and vice-versa for men. A key strength of the study is the consistency with which this inverse association was observed across a variety of sensitivity analyses, that included dividing the population by hospitals rather than admission diagnosis and adjusting for baseline limitations of care. The authors also evaluated whether patients presenting with less common illnesses spent more time in the hospital before being admitted to the ICU—and they did. This raises the question as to whether preconceived notions of lower probability conditions in a given sex contributed to delayed recognition by clinicians and whether those delays contributed to worse outcomes. Additional strengths of the study were the completeness of the dataset, which included over 90% of all ICU admissions in Australia and New Zealand with minimal missing data, and the quality of the data extracted.

The findings by Modra and colleagues should give pause to clinicians, educators, researchers, and trialists as they imply that variation in ICU mortality is not solely explained by biology but perhaps, because of systemic, implicit, and cognitive biases. Notably, these biases are hurting our patients when they are diagnosed with a condition more prevalent in the opposite sex. The authors clearly show us the limits of our heuristic algorithms and when cognitive biases (e.g., ascertainment, anchoring, and availability biases) are more likely to influence our decision-making, contributing to a delay in diagnosis (e.g., longer pre-ICU admission stays), delay in care (e.g., higher severity of illness on ICU admission), and ultimately resulting in higher adjusted mortality within that diagnosis.

Implicit and cognitive biases in medicine and their impact on patient care and outcomes have long been recognized (14). Despite this, long-term solutions to mitigate bias are still lacking. Given their pervasive nature, successful interventions will entail a multifaceted approach at the individual clinician degree (encouraging individual education and role-modeling) and the institutional degree (increasing workforce diversity and providing rapid solutions to tackle discriminatory behavior). Prior work in medicine and other fields has shown the benefit of diverse teams, especially when dealing with complex tasks such as patients who are critically ill. Diverse teams bring diverse heuristics, knowledge, and representation, resulting in higher quality research and enhanced recruitment into clinical trials (15). Beyond organizational change, there are opportunities within medicine to develop objective, sex-agnostic clinical tools such as biomarkers for pain (16).

There are several notable limitations to the study that should be considered. The study only included patients in the ICU and could not comment on pre-ICU care. In addition, who is admitted to the ICU is complicated and hospital-dependent. Lastly, the study was limited to a binary definition of sex and was unable to study transgender and nonbinary patients in the ICU; these sexual and sex minority groups may experience even more profound medical marginalization, poor representation in or complete exclusion from clinical studies, and as a result, worsened health outcomes (17).

Modra and colleagues have shone a critical spotlight on an insidious problem in medicine that should galvanize the medical community to design solutions and further studies in this field. Moving forward, this study raises urgent questions surrounding the influence of cognitive and implicit biases on medical decision-making for the sexual- and sex-diverse critically ill patient populations and the patients who are not critically ill who are hospitalized or presenting across other clinical domains. ■

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References

1. Todorov A, Kaufmann F, Arslani K, Haider A, Bengs S, Goliasch G, *et al.*; Swiss Society of Intensive Care Medicine. Gender differences in the provision of intensive care: a Bayesian approach. *Intensive Care Med* 2021;47:577–587.
2. Modra L, Higgins A, Vithanage R, Abeygunawardana V, Bailey M, Bellomo R. Sex differences in illness severity and mortality among adult intensive care patients: a systematic review and meta-analysis. *J Crit Care* 2021;65:116–123.
3. Valentin A, Jordan B, Lang T, Hiesmayr M, Metnitz PG. Gender-related differences in intensive care: a multiple-center cohort study of therapeutic interventions and outcome in critically ill patients. *Crit Care Med* 2003;31:1901–1907.
4. Johnston A, Mesana TG, Lee DS, Eddeen AB, Sun LY. Sex differences in long-term survival after major cardiac surgery: a population-based cohort study. *J Am Heart Assoc* 2019;8:e013260.
5. Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. *Crit Care* 2012;16:R92.
6. Lisspers K, Larsson K, Janson C, Ställberg B, Tsiligianni I, Gutzwiller FS, *et al.* Gender differences among Swedish COPD patients: results from the ARCTIC, a real-world retrospective cohort study. *NPJ Prim Care Respir Med* 2019;29:45.
7. Nguyen NT, Chinn J, De Ferrante M, Kirby KA, Hohmann SF, Amin A. Male gender is a predictor of higher mortality in hospitalized adults with COVID-19. *PLoS One* 2021;16:e0254066.
8. Zellweger R, Wichmann MW, Ayala A, Stein S, DeMaso CM, Chaudry IH. Females in proestrus state maintain splenic immune functions and tolerate sepsis better than males. *Crit Care Med* 1997;25:106–110.
9. Remmers DE, Cioffi WG, Bland KI, Wang P, Angele MK, Chaudry IH. Testosterone: the crucial hormone responsible for depressing myocardial function in males after trauma-hemorrhage. *Ann Surg* 1998; 227:790–799.

10. Viglianti EM, Bagshaw SM, Bellomo R, McPeake J, Wang XQ, Seelye S, *et al.* Hospital-level variation in the development of persistent critical illness. *Intensive Care Med* 2020;46:1567–1575.
11. Kadri SS, Sun J, Lawandi A, Strich JR, Busch LM, Keller M, *et al.* Association between caseload surge and COVID-19 survival in 558 U.S. hospitals, March to August 2020. *Ann Intern Med* 2021; 174:1240–1251.
12. Kelly Costa D, Liu H, Boltey EM, Yakusheva O. The structure of critical care nursing teams and patient outcomes: a network analysis. *Am J Respir Crit Care Med* 2020;201:483–485.
13. Modra LJ, Higgins AM, Pilcher DV, Bailey MJ, Bellomo R. Sex differences in mortality of ICU patients according to diagnosis-related sex balance. *Am J Respir Crit Care Med* 2022;206:1353–1360.
14. Sabin JA. Tackling implicit bias in health care. *N Engl J Med* 2022;387: 105–107.
15. Denby KJ, Szpakowski N, Silver J, Walsh MN, Nissen S, Cho L. Representation of women in cardiovascular clinical trial leadership. *JAMA Intern Med* 2020;180:1382–1383.
16. Niculescu AB, Le-Niculescu H, Levey DF, Roseberry K, Soe KC, Rogers J, *et al.* Towards precision medicine for pain: diagnostic biomarkers and repurposed drugs. *Mol Psychiatry* 2019; 24:501–522.
17. Liu M, Sandhu S, Keuroghlian AS. Achieving the triple aim for sexual and gender minorities. *N Engl J Med* 2022;387:294–297.

Evidence for Early Cystic Fibrosis Transmembrane Conductance Regulator Modulator Treatment for Children with Cystic Fibrosis Keeps Growing

Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies have led to dramatic improvements in clinical outcomes for many persons with cystic fibrosis (CF) eligible for these medications (1). In the 2020 U.S. Cystic Fibrosis Foundation Patient Registry, median lung function improved across all age groups, reflecting for the first time a reversal of the historically described annual decline in lung function (2). Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), the most recently developed CFTR modulator, results in clinical improvements larger than those with lumacaftor/ivacaftor (LUM/IVA) or tezacaftor/ivacaftor (TEZ/IVA) and similar to those with ivacaftor, which is only approved for a small population with responsive *CFTR* variants (1). ELX/TEZ/IVA was approved by the Food and Drug Administration for patients 12 years and older with at least one *F508del-CFTR* allele in the United States in 2019, and regulatory approvals followed in other countries, including the European Union (2020), Canada (2020), and Australia (2021). In June 2021, ELX/TEZ/IVA was approved by the Food and Drug Administration for children ages 6 to 11 years after a phase 3 open-label study demonstrating safety and efficacy (3). Although this study demonstrated substantial improvements in clinical outcomes, it was designed primarily to evaluate safety and did not include a control group.

In this issue of the *Journal*, Mall and colleagues (pp. 1361–1369) report results from a phase 3b randomized, double-blind, placebo-controlled study of ELX/TEZ/IVA in 121 children with CF, 6 to 11 years of age, and heterozygous for *F508del-CFTR* and a minimal function *CFTR* variant (4). Children were included if they had an elevated baseline lung clearance index ($LCI_{2.5}$) of $\geq$7.5, suggestive of small airway disease. Participants were randomized to receive either ELX/TEZ/IVA or placebo for 24 weeks. ELX/TEZ/IVA resulted in a significant improvement in $LCI_{2.5}$, the primary study outcome, with a between-groups difference of -2.26 units ($P < 0.001$). Reduction in sweat chloride (-51.2 mmol/L, $P < 0.0001$); improvement in percent predicted forced expiratory volume in 1 s ($ppFEV_1$) (11.0%, $P < 0.0001$); and improvement in scores on the Cystic Fibrosis Questionnaire–Revised, respiratory domain (5.5 points, $P = 0.0174$), were also observed and were similar to changes seen in the open-label study. Notably, less improvement on the Cystic Fibrosis Questionnaire–Revised, respiratory domain, was noted in this age range compared with adolescents and adults treated with ELX/TEZ/IVA, despite impressive improvements in lung function and sweat chloride, possibly because of relatively mild symptom scores at baseline (5, 6). Thus, in clinical practice, children and caregivers may not notice a substantial difference in symptoms after starting therapy, despite benefits to lung health.

Results from this study add information about the potential benefits of ELX/TEZ/IVA in this age range. Additionally, important comparisons related to adverse events were made between the treatment and placebo groups, providing additional insights into safety and benefits. Headache and rash were reported more frequently with ELX/TEZ/IVA, compared with placebo, whereas cough, abdominal pain, and pulmonary exacerbations were decreased relative to placebo, likely reflecting overall improvement in underlying CF disease. No new safety concerns were identified compared with previous clinical trials. Adverse events related to mental health or behavior changes were not measured in this trial, although concerns around mental health effects have been raised in older age groups.

As in several other recent clinical trials of CFTR modulators in younger children (7, 8), $LCI_{2.5}$ served as the primary outcome rather than $ppFEV_1$, which has generally been used as the primary efficacy outcome in studies of adolescents and adults (5, 6). Increases in $LCI_{2.5}$ appear more sensitive for the detection of early lung disease and may detect improvements in small airway disease that are not captured with $ppFEV_1$ measurements. The impact of

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