experience more severe exacerbations and are more likely to die than individuals with smoking history and without airflow obstruction. This emphasizes that COPD severity within a population is a continuous variable and that, over time, this illness is not trivial among those not considered clinically severe enough to be included in a treatment trial. The challenge for the future will be to conduct appropriate treatment trials in this less severe population that is also commonly encountered in our clinical practice (13). ■

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References

1. Daniels M, Hill AB. Chemotherapy of pulmonary tuberculosis in young adults; an analysis of the combined results of three Medical Research Council trials. *BMJ* 1952;1:1162–1168.
2. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, *et al.*; REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491–1502.
3. De Soyza A, Calverley PMA. Large trials, new knowledge: the changing face of COPD management. *Eur Respir J* 2015;45:1692–1703.
4. Celli BR, Wedzicha JA. Update on clinical aspects of COPD. Reply. *N Engl J Med* 2019;381:2485–2486.
5. Walker S, Fingleton J, Weatherall M, Beasley R. Limited generalizability of UPLIFT findings to clinical practice. *Thorax* 2013;68:1066–1067.
6. Halpin DMG, Kerkhof M, Soriano JB, Mikkelsen H, Price DB. Eligibility of real-life patients with COPD for inclusion in trials of inhaled long-acting bronchodilator therapy. *Respir Res* 2016;17:120.
7. Çolak Y, Nordestgaard BG, Lange P, Vestbo J, Afzal S. Prognosis of patients with chronic obstructive pulmonary disease not eligible for major clinical trials. *Am J Respir Crit Care Med* 2022;206:271–280.
8. Hardin M, Silverman EK, Barr RG, Hansel NN, Schroeder JD, Make BJ, *et al.*; COPDGene Investigators. The clinical features of the overlap between COPD and asthma. *Respir Res* 2011;12:127.
9. Menezes AMB, Montes de Oca M, Pérez-Padilla R, Nadeau G, Wehrmeister FC, Lopez-Varela MV, *et al.*; PLATINO Team. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest* 2014;145:297–304.
10. Calverley PMA, Walker PP. ACO (asthma-COPD overlap) is independent from COPD: the case in favor. *Diagnostics (Basel)* 2021;11:1189.
11. Jenkins C, FitzGerald JM, Martinez FJ, Postma DS, Rennard S, van der Molen T, *et al.* Diagnosis and management of asthma, COPD and asthma-COPD overlap among primary care physicians and respiratory/allergy specialists: a global survey. *Clin Respir J* 2019; 13:355–367.
12. Thakur N, Lovinsky-Desir S, Appell D, Bime C, Castro L, Celedón JC, *et al.* Enhancing recruitment and retention of minority populations for clinical research in pulmonary, critical care, and sleep medicine: an official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2021;204:e26–e50.
13. Martinez FJ, Agusti A, Celli BR, Han MK, Allinson J, Bhatt SP, *et al.* Treatment trials in young patients with chronic obstructive pulmonary disease and pre-chronic obstructive pulmonary disease patients: time to move forward. *Am J Respir Crit Care Med* 2021; 205:275–287.

Turning the Page on Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome due to Severe COVID-19

The role of venovenous extracorporeal membrane oxygenation (ECMO) in the management of severe acute respiratory distress syndrome (ARDS) has been assessed by randomized controlled trials, meta-analyses, and a *post hoc* Bayesian analysis (1–6). This body of literature supports the beneficial effect of this intervention for severe ARDS refractory to protective mechanical ventilation. Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can develop ARDS being ECMO a therapeutic option for severely affected patients. Given that the mentioned evidence precedes the ongoing pandemic, the effectiveness of ECMO in COVID-19–related ARDS represents an important priority to be addressed.

Early reports during the pandemic suggested an alarmingly high mortality with ECMO in patients with COVID-19 (7). These studies were limited by the inclusion of unselected populations and the lack of adequate controls. Shaefi and colleagues conducted an emulated target trial using observational data to assess the efficacy of ECMO versus conventional mechanical ventilation in the context of COVID-19 (Table 1) (8). They included patients with severe hypoxemia and observed a reduction in mortality with ECMO (hazard ratio, 0.55; 95% confidence interval, 0.41–0.74). More recently, Urner and colleagues performed an emulated target trial including patients with severe hypoxemia, also observing a reduction of 60-day mortality associated with ECMO (relative risk, 0.78; 95% confidence interval, 0.75–0.82) (Table 1) (9).

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Table 1. Emulated Target Trials Assessing the Efficacy of Extracorporeal Membrane Oxygenation in Patients with Acute Respiratory Distress Syndrome from Severe COVID-19

	Shaefi *et al.*	Urner *et al.*	Hagaje *et al.*
Data source	STOP-COVID dataset including data on critically ill patients with COVID-19 among 68 hospitals in the United States	COVID-19 Critical Care Consortium including data on critically ill patients with COVID-19 from more than 48 countries	Database of Critically ill patients with COVID-19 in France, Belgium, and Switzerland
Population	Adults $<$70 yr old; IMV $\leqslant$ 7 d; $PaF_{IO_2} < 100$	Adults of all ages; PaO_2:$FiO_2 < 80$	Adults $<$70 yr old; IMV $\leqslant$ 7 d; PaO_2:$FiO_2 < 80$ or $Pa_{CO_2} > 60$; SAPS II $\leqslant$ 90
Methodology	Emulated target trial using sequential trials approach	Emulated target trial estimating adherence-adjusted mortality rates	Emulated target trial using sequential trials approach
Outcome	Hospital mortality up to 60 d	Hospital mortality up to 60 d	Survival at 90 d
Main results	Lower mortality in patients treated with ECMO (HR, 0.55; 95% CI, 0.41–0.74)	Lower mortality in patients treated with ECMO (RR, 0.78; 95% CI, 0.75–0.82)	Primary analysis: 90-d survival on ECMO 63% vs. 65% in the conventional arm; only in high-volume centers: survival 78% on ECMO vs. 64% in the conventional arm
Subgroups analyzed	No observed difference of treatment effects when considering severity of hypoxemia or time from IMV	ECMO more beneficial if profound hypoxemia, early during the course of IMV, or higher intensity of mechanical ventilation	ECMO more beneficial if profound hypoxemia, early during the course of IMV, or in high-volume centers

Definition of abbreviations: CI = confidence interval; COVID-19 = coronavirus disease; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; IMV = invasive mechanical ventilation; RR = relative risk; SAPS = Simplified Acute Physiology Score; STOP-COVID = Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19.

In contrast to other evidence-based treatments for severe ARDS, ECMO is a resource-intense intervention, and its deployment requires an experienced team (10). The efficacy and safety of this intervention relies on diverse technical factors, and it is reasonable that optimal delivery is provided in high-volume centers. Acknowledging that ECMO is a complex intervention, the assessment of its efficacy outside the rigorously controlled setting of a randomized experiment provides key complementary information on how ECMO performs in a real-world scenario. Perhaps this poses an ideal example of how data from randomized controlled trials and observational studies can serve as complementary tools for causal inference (11).

In this issue of the *Journal*, Hajage and colleagues (pp. 281–294) report the results of an emulated target trial to estimate the effect of ECMO on 60-day mortality compared with conventional mechanical ventilation in critically ill adults with COVID-19 (12). Inclusion criteria were similar to those for a hypothetical randomized trial (Table 1). The authors used a sequential trials approach, emulating a target trial in each day of invasive mechanical ventilation. The authors adjusted for confounding at the initiation of each "trial" and used time-dependent inverse probability of censoring weighting to account for patient censoring in the control group when deviating from the treatment strategy (i.e., received ECMO). Among 2,858 patients who met eligibility criteria for the target trial, 269 patients received ECMO. The estimated survival probability on ECMO at Day 7 was 87%, compared with 83% under the alternative strategy, but worsened at Day 90 (63% on ECMO vs. 65% in the conventional arm). Importantly, this near reversal of the efficacy of ECMO at 90 days was no longer apparent when only high-volume ECMO centers were included (survival was 78% on ECMO vs. 64% in the conventional arm).

The study by Hajage and colleagues addresses a very important question in our field, and the use of an emulated target trial methodology is opportune. Emulating randomized controlled trials using large observational datasets is an increasingly used technique for the assessment of comparative effectiveness between treatments when conducting a randomized experiment is not feasible ethically, timely, or both (13). Many of the key steps (definition of eligibility criteria, treatment strategies, follow-up period, and outcomes) of a randomized experiment can be emulated using observational data. Furthermore, the use of this methodology aids in the use of an explicit causal language avoiding ambiguous terms (e.g., association) when the underlying scientific question implies causal inference (14).

The critical remaining limitation when emulating a target trial using observational data is that the treatment allocation is not random. To ensure conditional exchangeability (i.e., comparability between patients in both treatment arms), it is indispensable that the dataset used contains information on baseline confounders. If conditional exchangeability cannot be ensured between treatment arms, the validity of the target trial becomes threatened (13). Hajage and colleagues used sophisticated methods to adjust for confounding and to account for artificial informative censoring. Despite these efforts, the question remains of which unmeasured confounders could have not fully been accounted for. Why were those patients in the control group not cannulated despite meeting criteria for ECMO? This is a crucial question, considering that many of the centers included in this study have experience with ECMO. It is possible that unmeasured confounding could bias the results of this target trial in both possible directions, thus favoring ECMO or the conventional

treatment arm. Predicting the direction and magnitude of this potential bias is not an easy task.

The results of the study by Hajage and colleagues should be interpreted in the context of two other emulated target trials assessing the effectiveness of ECMO for ARDS due to severe COVID-19 (8, 9). Taken together, these studies suggest a potential beneficial role of ECMO for severe COVID-19. In contrast to the other target trials, the study by Hajage and colleagues points toward a reduction of the observed benefit when assessing a longer time span of mortality. This unique observation was further explored by the authors, and ECMO remained consistently beneficial when performed in high-volume centers or where ECMO services had been organized. Importantly, this highlights the notion that ECMO is a complex intervention and the importance of an experienced team for its optimal deployment, as suggested by previous literature (15–17). Additional lessons obtained by the study of Hajage and colleagues and shared with other target trials are that ECMO seemed to be most effective in patients with profound hypoxemia and when used early throughout the course of invasive mechanical ventilation. These are key lessons to guide clinical decision making and patient selection (18).

In summary, evidence provided by randomized controlled trials and emulated target trials points toward a beneficial effect of ECMO for patients with severe ARDS due to COVID-19 and other risk factors. A higher benefit is seen when selecting patients earlier in the course of invasive ventilation, with severe hypoxemia, or receiving a higher intensity of mechanical ventilation (9). The study by Hajage and colleagues also reinforces the notion that ECMO is a team effort and likely best delivered in specialized centers. Moving forward, it is now time to turn the page on the question of ECMO versus non-ECMO for ARDS due to severe COVID-19. Future studies will hopefully help us determine optimal ventilation and liberation strategies, safe anticoagulation practices, and the role for early mobilization. Ongoing studies will also provide key insights on long-term outcomes beyond mortality, such as functional recovery and cognitive function. ■

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References

1. Combes A, Peek GJ, Hajage D, Hardy P, Abrams D, Schmidt M, *et al.* ECMO for severe ARDS: systematic review and individual patient data meta-analysis. *Intensive Care Med* 2020;46:2048–2057.
2. Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Jüni P, *et al.* Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *JAMA* 2018;320: 2251–2259.
3. Aoyama H, Uchida K, Aoyama K, Pechlivanoglou P, Englesakis M, Yamada Y, *et al.* Assessment of therapeutic interventions and lung protective ventilation in patients with moderate to severe acute respiratory distress syndrome: a systematic review and network meta-analysis. *JAMA Netw Open* 2019;2:e198116.
4. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med* 2019;7:163–172.
5. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, *et al.*; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018;378:1965–1975.
6. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, *et al.*; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;374:1351–1363.
7. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): pooled analysis of early reports. *J Crit Care* 2020;58:27–28.
8. Shaefi S, Brenner SK, Gupta S, O'Gara BP, Krajewski ML, Charytan DM, *et al.*; STOP-COVID Investigators. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. *Intensive Care Med* 2021;47:208–221.
9. Urner M, Barnett AG, Bassi GL, Brodie D, Dalton HJ, Ferguson ND, *et al.*; COVID-19 Critical Care Consortium Investigators. Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure: comparative effectiveness study. *BMJ* 2022;377:e068723.
10. Brodie D, Slutsky AS, Combes A. Extracorporeal life support for adults with respiratory failure and related indications: a review. *JAMA* 2019; 322:557–568.
11. Lodi S, Phillips A, Lundgren J, Logan R, Sharma S, Cole SR, *et al.*; INSIGHT START Study Group and the HIV-CAUSAL Collaboration. Effect estimates in randomized trials and observational studies: comparing apples with apples. *Am J Epidemiol* 2019;188: 1569–1577.
12. Hajage D, Combes A, Guervilly C, Lebreton G, Mercat A, Pavot A, *et al.* Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: an emulated target trial analysis. *Am J Respir Crit Care Med* 2022; 206:281–294.
13. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016;183: 758–764.
14. Hernán MA. The C-word: scientific euphemisms do not improve causal inference from observational data. *Am J Public Health* 2018; 108:616–619.
15. Barbaro RP, Odetola FO, Kidwell KM, Paden ML, Bartlett RH, Davis MM, *et al.* Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality: analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med* 2015;191: 894–901.
16. Riera J, Roncon-Albuquerque R Jr, Fuset MP, Alcántara S, Blanco-Schweizer P; ECMOVIBER Study Group. Increased mortality in patients with COVID-19 receiving extracorporeal respiratory support during the second wave of the pandemic. *Intensive Care Med* 2021;47: 1490–1493.
17. Barbaro RP, MacLaren G, Boonstra PS, Combes A, Agerstrand C, Annich G, *et al.*; Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* 2021;398:1230–1238.
18. Bullen EC, Teijeiro-Paradis R, Fan E. How I select which patients with ARDS should be treated with venovenous extracorporeal membrane oxygenation. *Chest* 2020;158:1036–1045.