CORRESPONDENCE

ECMO for Severe Acute Respiratory Distress Syndrome

TO THE EDITOR: In the trial conducted by Combes et al. (May 24 issue),[1] a large number of patients who had been randomly assigned to the control group later crossed over to receive extracorporeal membrane oxygenation (ECMO). The rate of the key secondary outcome (a composite of death or treatment failure) was significantly lower in the ECMO group than in the control group.

The conclusions of this analysis are problematic. First, despite the severity of the acute respiratory distress syndrome (ARDS) and the illness trajectory, the patients in the control group who crossed over were younger than those who did not cross over, they had a lower incidence of renal-replacement therapy at randomization, and they had survived the first several days of illness. Second, a lack of improvement in gas exchange may not predict outcome in patients with ARDS, especially in those undergoing prone positioning.[2] Third, rank-preserving structural-failure time models that are used to analyze crossover lose accuracy with the relative length of time that patients who cross over receive the investigational treatment.[3] The patients who crossed over had a similar length of time undergoing ECMO as those who had been initially assigned to receive ECMO. We believe that the more rigorous, per-protocol or as-treated analysis provides necessary balance to the secondary analysis: mortality at 60 days was 40% among patients who received ECMO and 42% among those who did not receive ECMO.

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Dr. Shanholtz reports that the University of Maryland was initially a site in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial but was removed for administrative reasons. No other potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1808731

TO THE EDITOR: Since 2011, England and Scotland have commissioned and organized the unified evidence-based provision[1,2] of ECMO for adult patients with severe respiratory failure. Any patient who meets the criteria[3] is referred to one of the designated severe respiratory failure centers, at which advice regarding improvements to conventional therapy is offered by telephone. For patients whose condition is deteriorating and who do not have a response to such measures, a mobile, intensive care–led ECMO team is dispatched to

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assess, stabilize, and transport the patient to the severe respiratory failure center, if appropriate. The majority of locally assessed patients who are transferred to the center undergo cannulation at the referring hospital by the commissioned team and receive mobile ECMO during transportation.

Over the past 3 years, the rate of survival to discharge from the intensive care unit among the last 700 consecutive patients who received ECMO support is 81%, which is substantially higher than the survival rate in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, despite equivalent disease severity and ventilation interventions in the patients.[4] We propose that this finding reflects the effect of a nationally structured, governance-based, collegial approach to the treatment of patients at specialized severe respiratory failure centers, whereby conventional therapies can be maximized and patients can be transitioned rapidly to ECMO support when appropriate, thus avoiding its application in extremis.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1808731

TO THE EDITOR: We believe that the most important finding of the EOLIA trial is that when ECMO is used as a rescue therapy, it provides a remarkably high probability of survival among patients with ARDS in whom imminent death seems almost inevitable, as noted in the editorial accompanying the article.[1] The investigators found that mortality was 43% among patients with hemodynamic instability who had an arterial oxygen saturation of 80% or less for more than 6 hours despite maximum therapeutic measures, even with the inclusion in the analysis of six patients who had undergone cardiopulmonary resuscitation. We believe that this is a solid argument in favor of the use of ECMO when the indications for this treatment are considered in similarly critical situations.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1808731

THE AUTHORS REPLY: Shanholtz et al. raise important points regarding the patients in the control group who crossed over to ECMO. First, we agree that the composite end point could favor the ECMO group, and we interpreted this point with caution in the Discussion section of our article. Second, Shanholtz et al. suggest that the patients in the control group who crossed over were less ill at randomization than those who did not cross over. We note that the two groups did not differ significantly with respect to age and that they had similar scores indicating the severity of illness. In addition, the patients who crossed over had more severe ARDS than those who did not cross over, including lower respiratory-system compliance (21.3 ml vs. 27.1 ml per

centimeter of water) and higher plateau pressures (31.7 cm vs. 28.5 cm of water) and driving pressures (20.2 cm vs. 16.6 cm of water).

In assessing the efficacy of ECMO, the critical question is how sick the patients were at crossover rather than at randomization. In the 24 hours before crossover, the median pH among the patients had dropped to 7.18, the inotrope score had increased by a factor of 9, and the lactic acid level had increased to 3.2 mmol per liter; 26% of the patients had had a cardiac arrest, 20% had had right heart failure, and 17% had received venoarterial ECMO during cardiopulmonary resuscitation. Given these data, we believe that a per-treatment analysis would not be very meaningful. The rank-preserving structural-failure time analysis both preserves the randomization and assesses overall survival (not the composite end point, as suggested by Shanholtz et al.). Finally, Ouwens et al. found that a rank-preserving structural-failure time model can have several solutions under certain extreme conditions.[1] This was not a problem with our data set, which provided a unique solution.

Patel et al. describe the organization of ECMO services in England and Scotland, which enroll highly selected patients with respiratory failure (including patients with asthma). Thus, it is difficult to compare that population of patients, in terms of severity of illness or outcomes, with patients with severe ARDS, who were included in the EOLIA trial. In addition, for acceptance into the program in England and Scotland, it is necessary that patients have both a reversible pathologic condition and sufficient physiological reserve to survive critical illness,[2] which represents a clear potential bias.

In response to Muñoz and colleagues: we agree that ECMO as rescue therapy may be a viable option for patients in whom ECMO was not initiated early. We note that the survival rate, not the mortality, was 43% among patients who crossed over to ECMO when the arterial oxygen saturation of 80% or less for more than 6 hours despite maximum therapeutic measures.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1808731

THE EDITORIALISTS REPLY: Patel et al. and Muñoz et al. raise two interesting points regarding the EOLIA trial. First, Patel et al. mention the possibility that standardized referral to and treatment at a subspecialty center may provide better outcomes with ECMO than those observed in the EOLIA trial. Although the reported rate of survival with ECMO in this system is high, such outcomes are likely to be related to multiple factors and reflect the careful selection of patients as well as the direct effect of ECMO. As such, these data add to the many positive case reports of high survival rates among patients who undergo ECMO, but they are not directly comparable to data from a randomized, controlled trial. We do, however, agree that the early recognition of severe ARDS and evidence-based treatment will maximize the chances of survival and that this may be best accomplished at specialized centers.

The second point, raised by Muñoz et al., is the relatively high survival rate among patients in the EOLIA trial who were not randomly assigned to the ECMO group but who had subsequent deterioration in their condition and underwent cannulation. It is remarkable and gratifying that so many of these very sick patients survived. Together, these letters highlight the important and ongoing questions of who should receive ECMO and when.

The primary end point in the EOLIA trial did not reach statistical significance. However, many have emphasized the trend toward a survival benefit in the ECMO group, the significant benefit with respect to the secondary end points, and the possibility that the primary end point might have reached significance if the trial had reached full enrollment. For these reasons, it is tempting to advocate for more aggressive early deployment of

ECMO. However, regardless of the statistical issues surrounding early termination of the trial, we believe that caution is appropriate before the enthusiastic adoption of an intervention on the basis of an equivocal result, be it positive or negative. Even positive critical care trials have famously failed to be replicated,[1,2] and the current list of evidence-based interventions for patients with ARDS may yet need revision as new data become available. We therefore continue to advocate for a consensus-based approach to severe ARDS that consists of careful lung-protective ventilation including low tidal volumes, prone positioning, and paralysis with the use of ECMO as a rescue therapy if these interventions do not stabilize the patient's condition.

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Since publication of their editorial, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1808731

Lung Cancer with a High Tumor Mutational Burden

TO THE EDITOR: Hellmann and colleagues (May 31 issue)[1] found that tumor mutation burden assessed with the commercial assay FoundationOne CDx helped to predict the response to immune checkpoint inhibitor therapy in patients with non–small-cell lung cancer (NSCLC), irrespective of programmed death ligand 1 (PD-L1) expression. Guidelines regarding turnaround times for tests to detect predictive genomic alterations (e.g., *EGFR*, *ALK*, *ROS1*, and *BRAF* V600E) and immune biomarkers such as PD-L1 immunohistochemical findings recommend targets of 3 workdays from a request for testing to receipt by a reference laboratory and testing results within 10 workdays.[2-4] This workflow is currently acceptable to most medical oncologists.[3]

We wonder whether assays that determine tumor mutation burden can be introduced into routine clinical practice within these turnaround-time specifications. The FoundationOne CDx assay profiles gene mutation, copy number, and rearrangement data as well as tumor mutation burden and microsatellite instability.[5] Among recent NSCLC samples from our institution submitted for testing with this assay, 90% were received by the laboratory in 3 workdays or less and results of 50% were provided in 10 workdays or less. These findings indicate that results are achievable within guideline-specified turnaround times in some cases, although further improvements in turnaround time are needed.

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Dr. Costa reports receiving consulting fees and honoraria from Pfizer, AstraZeneca, and Takeda. No other potential conflict of interest relevant to this letter was reported.

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