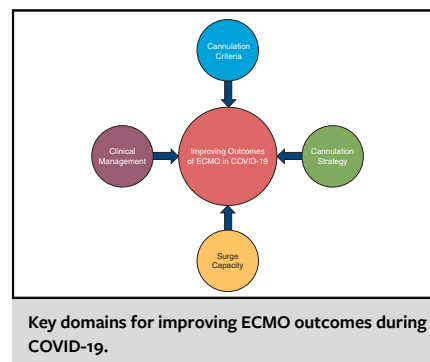


Extracorporeal membrane oxygenation support during the coronavirus disease 2019 pandemic: Outcomes and technical considerations



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Over the course of 18 months, global spread of coronavirus disease 2019 (COVID-19) has led to nearly 4 million deaths.¹ Severe acute respiratory syndrome coronavirus 2 (the novel coronavirus identified as the cause of COVID-19) targets the respiratory system and mortality during COVID-19 is related to the development of acute respiratory distress syndrome, accompanied by a severe cytokine storm, with subsequent cardiopulmonary collapse.^{2,3} Early in the pandemic, it was noted that the utility of mechanical ventilation was limited in cases of severe respiratory failure with reports of nearly 90% mortality⁴ and the role of extracorporeal membrane oxygenation (ECMO) was questionable. Although initial reports showed poor outcomes with ECMO during COVID-19, expert consensus supported its use in selected patients.⁵ A year and half into the pandemic, ECMO continues to be employed not so uncommonly, with more than 8000 cases noted in the Extracorporeal Life Support Organization (ELSO) registry.⁶ Observational studies indicate that ECMO can be a viable method of mechanical support with refractory respiratory failure from COVID-19.⁷⁻¹⁰ Addressing key domains such as standardizing cannulation criteria and technical considerations surrounding circuit deployment, cannulation strategies, patient selection, and management from experiences thus far during the pandemic can further improve outcomes of this lifesaving modality (Figure 1).



CENTRAL MESSAGE

ECMO has served as an essential and lifesaving modality in appropriately selected patients with severe respiratory failure from COVID-19.

See Commentary on page 83.

EARLY EXPERIENCES AND GUIDELINES

During March 2020, the first case series of 12 patients with severe COVID-19 placed on ECMO was reported from Wuhan, China.⁵ In that brief report, poor outcomes were noted with 5 deaths and an additional 4 patients experiencing poor neurologic outcomes. A pooled analysis of 4 centers from surrounding regions with patients supported by ECMO yielded similarly unpromising outcomes with no differences in comparison to conventional therapy (odds ratio, 2.0; 95% confidence interval [CI], 0.49-8.16; $P = .99$).¹¹ These preliminary and small reports portended a gloomy and potentially very limited role for ECMO in patients with COVID-19.

Notwithstanding unpromising early results, initial guidance for ECMO use during COVID-19 was provided by ELSO.¹² That document underscored use of antecedent measures such as prone positioning, neuromuscular blockade, and high-positive end-expiratory pressure for patients with severe hypoxia defined by a ratio of arterial oxygen tension (P_{aO_2}) to inspired oxygen fraction (F_{iO_2}) <150 mm Hg. In those with progressive hypoxia ($P_{aO_2} - F_{iO_2} <80$ mm Hg for 6 hours or <50 mm Hg for 3 hours) or acidosis ($pH < 7.25$ with hypercapnia; ie, arterial carbon

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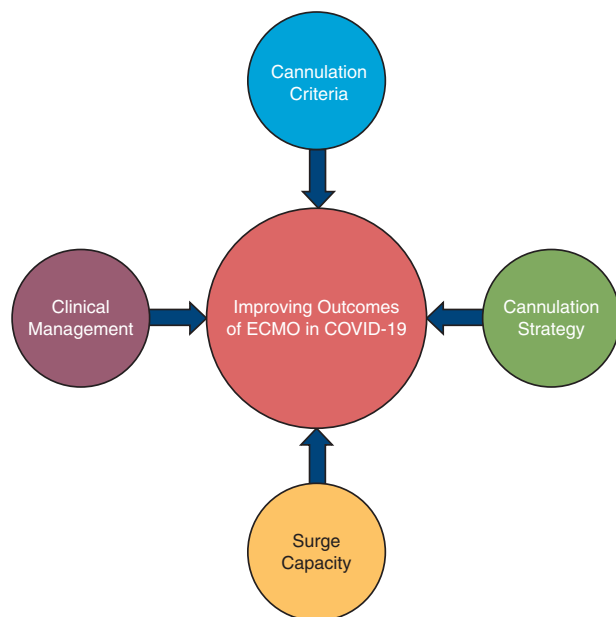


FIGURE 1. Key domains for improving extracorporeal membrane oxygenation (ECMO) outcomes during coronavirus disease 2019 (COVID-19).

dioxide tension ≥ 60 mm Hg for 6 hours) without contraindications, ECMO was recommended. ECMO was also recommended for patients with hypoventilation and acidosis (pH < 7.25 , arterial carbon dioxide tension ≥ 60 mm Hg for 6 hours) in the absence of severe hypoxia (Pao₂:Fio₂ ≥ 150 mm Hg).¹² With these guidelines and an exponentially rising burden of cases, ECMO was commonly employed in North America and Europe.

PATIENT CHARACTERISTICS AND OUTCOMES WITH ECMO DURING COVID-19

Several studies from around the world with at least 200 cases have reported in-hospital mortality ranging from 37% to 54% (Figure 2). During September 2020, clinical outcomes from the global ELSO registry were reported.⁷ This largest-to-date, observational analysis comprised 1035 patients from 213 hospitals across 36 countries placed on ECMO between January 16 and May 1, 2020. In this cohort, patients had a mean age of 49 years (range, 41-57 years), 47% were obese with a body mass index >30 , and only 30% were free of comorbidities. Prone positioning and neuromuscular blockade were used in majority of patients before ECMO placement and pre-ECMO Pao₂:Fio₂ was 72 mm Hg (range, 59-94 mm Hg). Overall, 90-day in-hospital mortality was noted to be 37.4% (95% confidence interval, 34.4%-40.4%) with 30% of the patients being discharged home or to an acute rehabilitation center. Tracheostomy was performed in 444 patients. In multivariable analysis, advanced age, immune-compromised status,

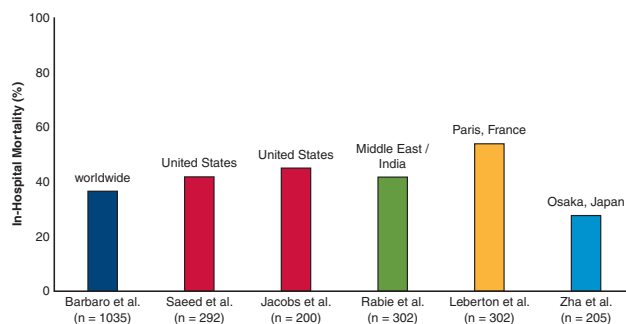


FIGURE 2. In-hospital mortality during extracorporeal membrane oxygenation for coronavirus disease 2019 in studies with at least 200 cases.

chronic respiratory disease, lower Pao₂:Fio₂ ratio, pre-ECMO cardiac arrest, and renal injury were noted to be associated with death.⁷

To gain additional insight into ECMO characteristics and outcomes within the United States, we formed and reported results from the COVID-19 ECMO Working Group.⁸ During the study period from March 1 to September 30, 2020, 292 patients were supported by ECMO across 17 participating centers.⁸ Similar to the worldwide ELSO report, patients had a mean age of 49 years (range, 39-57 years), 38% did not have comorbidities, and pre-ECMO Pao₂:Fio₂ was 77 mm Hg (range, 63-101 mm Hg). More than half (56%) were transferred from another hospital. Biomarkers of inflammation and coagulation were highly elevated before ECMO placement (C-reactive protein, 21 mg/dL [range, 9-45 mg/dL], ferritin, 1187 ng/mL [range, 683-1095 ng/mL], and D-dimer 8.6 μ g/mL [range, 2.6-963 μ g/mL]). In this cohort, 280 (96%) of the patients were placed on venovenous (VV)-ECMO and 66% of the cannulations were performed at the bedside or in an intensive care unit procedure room. Heparin was used in 71% of the patients for anticoagulation, followed by argatroban and bivalirudin. Bleeding requiring transfusion (74%), renal failure requiring replacement therapy (46%), and secondary infections (55%) were commonly observed adverse events. Overall, 90-day in-hospital mortality was 42% (95% confidence interval, 36%-47%), which persisted after exclusion of patients in overlapping centers from the ELSO report. The most common cause of death was multi-organ failure and stroke occurred in 10% of the cases. In a key observation, it was noted that patients who died were placed on ECMO nearly 4 days later in comparison to those that were eventually discharged or transferred alive. Thus, close monitoring of tenuous mechanically ventilated patients for early ECMO placement within 48 to 72 hours after presentation has an essential role in improving outcomes.⁸

A centralized ECMO referral network was formed by a group of 17 hospitals in the Ile-de-France (Greater Paris) region. This group carried out a 4-step process to prepare inventory, standardize workflow and ECMO criteria, form a

centralized communications hub with daily e-mailed reports, and conduct weekly meetings and sharing of information with local and international groups. ECMO criteria were similar to those proposed by the ELSO guidance document and the ECMO to Rescue Lung Injury in Severe ARDS trial,¹³ with exclusion of patients older than age 70 years, presence of serious comorbidities, cardiac arrest, refractory multiorgan failure or Simplified Acute Physiology Score-II >90, irreversible neurologic injury, or ongoing ventilation beyond 10 days. This group dispatched a mobile team composed of a cardiovascular surgeon and a perfusionist to a patient's bedside for cannulation with verification by ultrasonography and chest radiograph. Results are reported from a group of 302 patients placed on ECMO from March 8 to June 3, 2020. Patients had a mean age of 52 years (range, 45-58 years), 78% were men with a pre-ECMO Pao₂:Fio₂ of 61 mm Hg (range, 54-70 mm Hg). Prone positioning and neuromuscular blockage were utilized in more than 90% of patients. Overall, the 90-day in-hospital mortality was 46%. Center experience, evident by hospitals managing at least 30 VV-ECMO cases in the prior year, was noted to be independently associated with improved survival.⁹ Additional collaborative reports have also been reported from Southern California, the Middle East, India, and Japan showing similar outcomes with rapid deployment of mobile units¹⁴ and establishment of new centers under expert guidance.^{10,15}

Numerous additional observational studies from around the world have also reported ECMO outcomes during COVID-19.^{10,16-21} A recent meta-analysis of 22 reports with 1896 cases from December 1, 2019, to January 10, 2021, showed a pooled in-hospital mortality of 37.1% (95% CI, 32.3%-42.0%).²² In that pooled analysis, the average ECMO support time was 15.1 days, increasing age was associated with poorer survival, and renal complications were commonly reported during device support.²²

In complement to the studies mentioned above, estimates pertaining to the effectiveness of ECMO during COVID-19 with comparative groups have also been reported. The Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 investigators utilized a multicenter cohort of 68 centers in the United States to compare survival in patients with severe hypoxic respiratory failure from COVID-19 who were and were not initiated on ECMO during the first 7 days of admission to an intensive care unit. The study design emulated a clinical trial with intensive care unit time matching and after adjustment for covariates, those patients receiving ECMO had lower mortality (hazard ratio, 0.55; 95% CI, 0.41-0.74). ECMO remained associated with better survival across subgroups of progressive baseline hypoxia.²³ The Lille Intensive Care COVID-19 group from France compared the outcomes with ECMO use between patients with acute respiratory distress

syndrome from COVID-19 versus historical controls with influenza. Patients with COVID-19 had a lower Simplified Acute Physiology Score-II score (58 [range, 37-64] vs 68 [range, 26-34]; $P = .039$) and were cannulated later at 6 versus 3 days ($P = .004$). Despite these differences, patients with COVID-19 and influenza had similar 28-day mortality (43.3% vs 50% [$P = .63$]).²⁴

Given the weight of the observations provided by the studies mentioned above, ECMO appears to be a suitable platform in appropriately selected patients. However, because nearly half of the patients may not survive despite ECMO support, judicious use of this supportive and highly resource-intensive modality is critical. To further assist with patient selection, ELSO released an updated consensus document with recommended indications and contraindications in adult patients. Advanced age, significantly frailty, prolonged ventilation (ie, >10 days), overt baseline comorbidities with end organ dysfunction, severe multiorgan failure, uncontrolled bleeding, inability to take blood products or anticoagulation therapy, and ongoing cardiopulmonary resuscitation remain important absolute contraindications to ECMO.²⁵ Relative contraindications such as use in patients older than age 65 years and in those with a body mass index ≥ 40 may require additional study and case-by-case discussions.

TECHNICAL CONSIDERATIONS

COVID-19 presents a unique set of conditions for ECMO use related to the highly contagious nature of the virion, surge potential, prolonged support times, a hyperinflammatory state,²⁶ and possibility for mixed cardiopulmonary failure. Given these challenges, certain key technical aspects pertaining to cannulation, circuit deployment, and management are highlighted below.

Cannulation Strategies

A simple method of cannulation proposed early in the pandemic was through the right internal jugular and femoral veins (Figure 3, A). Because this type of cannulation can be accomplished with minimal imaging and personnel and provide high flows with limited mixing in the right atrium, it was indeed the most applied method. Ninety percent of the patients were cannulated through the femorojugular approach in the Parisian experience and nearly half (47%) in the US-based ECMO COVID-19 Working Group cohort were supported in this manner.^{8,9}

To avoid 2 separate sites of cannulation and evade femoral involvement to promote mobility, cannulation can also be performed through a single dual-lumen cannula. At Montefiore Medical Center, we used the single, dual-lumen cannula (Medtronic Inc, Minneapolis, Minn) (Figure 3, B), which was placed at the bedside using ultrasound guidance with the distal tip positioned into the inferior vena cava. Use of the Protek Duo TandemHeart

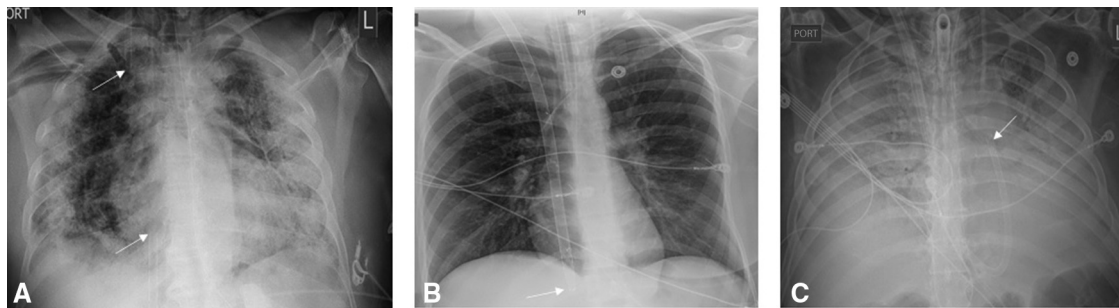


FIGURE 3. Chest radiographs of patients with severe coronavirus disease 2019 pneumonia on venovenous extracorporeal membrane oxygenation through cannulas in the right femoral and right jugular veins (A), a single, dual-lumen cannula with tip positioned in the inferior vena cava and right atrial junction (B), and a single, dual-lumen cannula with tip positioned in the main pulmonary artery (C). Arrows indicate cannula tip.

cannula (CardiacAssist Inc, Pittsburgh, Pa) was reported by the group from Advocate Christ Medical Center and Rush University Medical Center in Chicago, Ill (Figure 3, C).¹⁶ In the operating room, the right internal jugular vein was accessed and the distal tip of the cannula was placed in the main pulmonary artery under fluoroscopic and echocardiographic guidance. In their initial experience with 40 patients, this group reported a highly promising survival to discharge of 73%.¹⁶ Superiority of neck-only cannulation is plausible because it increases mobility and directed flow into the pulmonary artery allows for right ventricle support. However, these advantages are balanced by the simplicity of the 2-cannula femorofemoral or femorojugular approach. Further studies are needed to compare the

outcomes and complications of dual, single, and directed cannulation methods.

Circuit Deployment

At Advent Health Orlando, an intensive care unit procedure room was established with standardization of cannulation strategy, equipment, and personnel (Figure 4). Using the femorojugular approach, the surgeon and surgical assistant were able to cannulate within 5 to 7 minutes, leading to swift establishment of ECMO support. There was rapid availability of anesthesia staff, and imaging modalities such as fluoroscopy and transesophageal echocardiography were accessible within the room. Due to standardization, supplies and personal protective equipment were easily

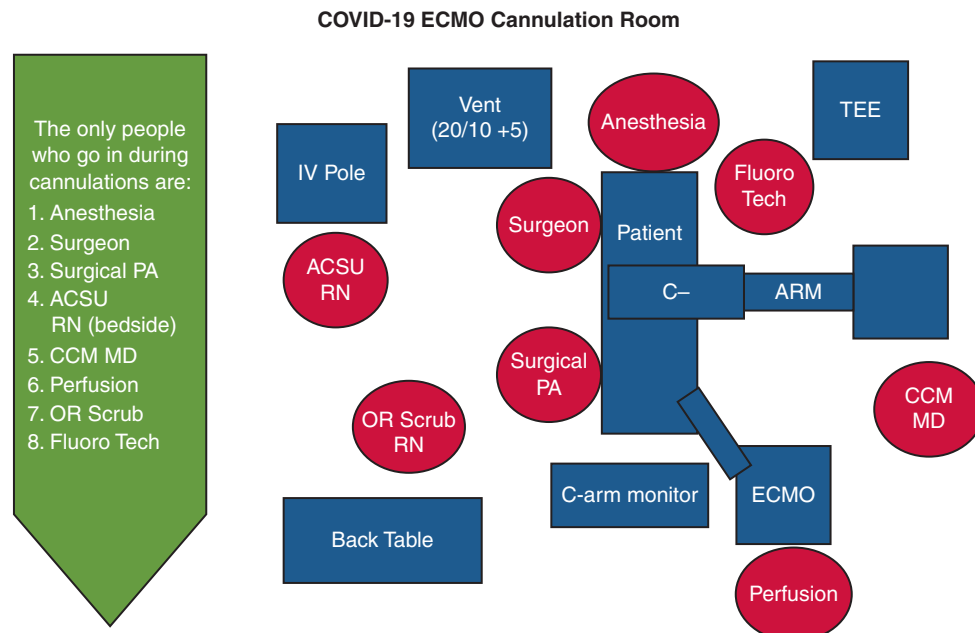


FIGURE 4. Schematic of coronavirus disease 2019 (COVID-19) extracorporeal membrane oxygenation support (ECMO) cannulation room at the Advent Health Transplant Institute in Orlando, Fla. Vent, Ventilator; TEE, transesophageal echocardiography; IV, intravenous; PA, physician assistant; ACSU, acute care surgical unit; RN, registered nurse; ARM, C-shaped arm; CCM, critical care unit; MD, physician/surgeon; OR, operating room; Fluoro Tech, fluoroscopy technician.

TABLE 1. Recommendations for extracorporeal membrane oxygenation (ECMO) placement, management, and operations during the coronavirus 2019 (COVID-19) pandemic

Criteria for ECMO placement
<p>Inclusions</p> <ul style="list-style-type: none"> - Progressive hypoxia ($P_{aO_2}:F_{iO_2} < 80$ mm Hg for 6 h or < 50 mm Hg for 3 h) or acidosis ($pH < 7.25$ with hypercapnia; ie, $P_{aCO_2} \geq 60$ mm Hg for 6 h) despite prone positioning, neuromuscular blockade and high positive end expiratory pressure.¹² - Hypoventilation and acidosis ($pH < 7.25$, $P_{aCO_2} \geq 60$ mm Hg for 6 h) in the absence of severe hypoxia ($P_{aO_2}: F_{iO_2} \geq 150$ mm Hg).¹² <p>Exclusions</p> <ul style="list-style-type: none"> - Advanced age, significant frailty, prolonged mechanical ventilation (> 10 d), overt baseline comorbidities, severe multiorgan failure, and ongoing cardiopulmonary resuscitation.²⁵
<p>Circuit deployment and cannulation strategy</p> <ul style="list-style-type: none"> - Close monitoring of tenuous patients such as those with a $P_{aO_2}:F_{iO_2}$ ratio ≤ 100 mm Hg for early ECMO within 48-72 h of presentation. - Standardization of cannulation procedures. - Designation of an ECMO placement area with stocked supplies and rapid availability of preappointed multispecialty staff. - Dual-lumen neck cannulation with avoidance of femoral cannulation, when feasible, to promote mobility.
<p>Device and patient management</p> <ul style="list-style-type: none"> - Close vigilance for cannula malposition, migration, erosion, or thrombosis. - Anticipate circuit reconfiguration depending on clinical trajectory. - Radiograph and/or ultrasound-based imaging to reconfirm cannula tip position to improve low flows. - Standard anticoagulation with direct or indirect thrombin inhibitors and judicious blood product use. - Confirmation of adequate anticoagulation to avoid thrombosis, especially during weaning stages. - Determination of goals of care and futility thresholds.
<p>Surge Capacity</p> <ul style="list-style-type: none"> - Daily reassessment of available resources, active cases, staffing, intensive care unit beds, and diversion policies with a multidisciplinary team.

accessible and complications such as a bradycardia or hypoxic arrest were more manageable.

Reconfiguration

Depending on clinical trajectory, circuit reconfiguration should be anticipated during COVID-19 infection. With clinical improvement, cannulas can be consolidated to a single catheter in the neck to improve mobility and promote ambulation. For those initially supported by venoarterial ECMO, if there is cardiac recovery with persistent respiratory failure conversion to a VV-ECMO configuration can be performed. Patients initially supported by VV-ECMO may develop right ventricular or biventricular failure, in which cases a right ventricular assist device or an arterial cannula can be added to the circuit to transition to venoarterial ECMO support. In the ECMO COVID-19 Working Group experience, circuit reconfiguration was reported in 7% of cases.⁸

Circuit Management and Anticoagulation Therapy

ECMO support times can be highly prolonged during COVID-19, reaching as far as several months.²⁵ During these lengthy support times, it is critical to remain vigilant about cannula malposition, migration, erosion, and thrombosis. Volume management may improve low flows; however, in such cases radiograph and/or ultrasound-based imaging should be considered to confirm appropriate

cannula tip positioning. If there is site erosion, an alternative vessel should be cannulated before onset of irreversible skin breakdown and infection.

Although severe COVID-19 infection is characterized and as a hyperinflammatory and prothrombotic state, current guidelines recommended standard anticoagulation with judicious blood product use. At current time, no single anticoagulation agent is recommended and use of unfractionated heparin is reported in most centers. Adequate anticoagulation must be confirmed to avoid thrombosis, especially during weaning stages with lower flow rates.²⁵ Due to prolonged support times, circuit exchanges are not uncommon and were reported to occur in more than 10% of cases.⁸

Surge Case Capacity

A tier-based surge capacity system has been proposed and can be adopted by centers to provide adequate ECMO support with appropriate case selection during the COVID-19 pandemic.²⁵ Central to this system is establishment of a center's active case capacity load at baseline with contingency planning of thresholds for expanded and crises capacity levels. In addition, a daily reassessment of available resources, active cases, staffing and intensive care unit beds is essential for maintaining operations. If the system is within capacity, then ECMO can be offered with judicious patient selection based on usual criteria to COVID-19

and non-COVID-19 cases. Once cases reach expanded capacity levels, then prioritization can be given to younger patients with single-organ failure. ECMO criteria can be restricted at near saturation of expanded capacity. If the system is saturated, ECMO, which requires significant staffing and allocation of supplies, may no longer be appropriate and resources should be concentrated to usual care. At crisis levels, it is important to consider termination of futile cases to increase capacity. This schema balances allocation of resources to saving lives of patients with severe respiratory failure while maintaining the quality of care of all patients.

CONCLUSIONS

Despite pessimism stemming from early reports, ECMO has served as an essential lifesaving modality during the COVID-19 pandemic. To further improve outcomes, it remains paramount to develop risk score models for optimal patient selection, create preemptive clinical protocols for close monitoring of tenuous patients to provide early ECMO, standardize cannulation procedures, determine optimal cannulation strategies, anticipate technical issues surrounding circuit management, perform daily assessments of case capacity, and develop diversion policies with a multidisciplinary team (Table 1).⁸ As the pandemic smolders, centers must reappraise local and regional pathways for providing ECMO coverage to care for the sickest patients with cardiopulmonary failure from COVID-19 and beyond.

Conflict of Interest Statement

Dr Silvestry is a consultant for Abbott Laboratories, Medtronic, Syncardia, and Abiomed outside of the submitted work. The other author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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