doi: 10.2490/prm.20220015 Progress in Rehabilitation Medicine 2022; Vol. 7, 20220015

ORIGINAL ARTICLE

Rehabilitation Characteristics of Acute-stage COVID-19 Survivors Managed with Extracorporeal Membrane Oxygenation in the Intensive Care Unit

Tomoko Sakai, MD, PhD [a] Chisato Hoshino, MD, PhD [a] Megumi Nakano, MD [a] Yu Fujiwara, MD [a] and Atsushi Okawa, MD, PhD [b]

Objectives: This study aimed to describe the rehabilitation characteristics of patients with acute stage coronavirus disease managed with extracorporeal membrane oxygenation (ECMO) in the intensive care unit. **Methods:** This retrospective study enrolled coronavirus disease patients who underwent rehabilitation following ECMO between April 21, 2020, and August 20, 2021. The following patient data were evaluated: age, sex, weaning, peak C-reactive protein, lowest albumin level, white blood cell count, use of steroids and muscle relaxants, duration of respiratory management, ECMO management and rehabilitation, Medical Research Council (MRC) score, and Barthel index after sedation and at discharge. **Results:** ECMO was performed in 20 patients, and 16 were weaned successfully. The median durations of ECMO and respiratory management in survivors were 14.5 and 38 days, respectively. The median MRC scores after sedation and after rehabilitation therapy were 18 and 45, respectively. The median rehabilitation duration after sedation was 14 days. The MRC score after sedation showed significant correlations with the durations of ECMO and intubation. The median Barthel index values after sedation and at discharge were 0 and 30, respectively. **Conclusions:** Rehabilitation was important for patients with severe coronavirus disease because muscle weakness advanced in proportion with the durations of ECMO and ventilation management in the intensive care unit.

Key Words: COVID-19; extracorporeal membrane oxygenation; ICU-acquired weakness; Medical Research Council score; rehabilitation

INTRODUCTION

Patients with acute respiratory distress syndrome (ARDS) caused by coronavirus disease (COVID-19) require respiratory management, including lung recruitment, proning, neuromuscular blockade, and sedation. Extracorporeal membrane oxygenation (ECMO) is considered in COVID-19 patients when standard respiratory support does not improve respiratory function. For patients with severe COVID-19, the ventilator is managed at low-pressure settings to allow lung rest as per the "Extracorporeal Life Support Organization: COVID-19 interim guidelines" which recommends prolonged ECMO use in these patients.[1)] Sedation and analgesia are resumed depending on the patient's level of anxiety and discomfort, although sedation should be minimal. Moreover, the most important thing for the ECMO management, venous blood drainage of ECMO equipment must not be limited by the reason that the patient is anxious, moving, or coughing, and blood flow should be adequate to support systemic perfusion or gas exchange. Sufficient sedation is important to avoid an increase in the basal metabolism, and neuromuscular blockade with muscle relaxants and cooling may be necessary if venous drainage cannot be achieved.

Patients with severe COVID-19 are susceptible to sev-

Received: October 11, 2021, Accepted: February 15, 2022, Published online: March 31, 2022
[a] Department of Rehabilitation Medicine, Tokyo Medical and Dental University, Tokyo, Japan
[b] Department of Orthopedic Surgery, Tokyo Medical and Dental University, Tokyo, Japan
Correspondence: Tomoko Sakai, MD, PhD, Department of Rehabilitation Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan, E-mail: t_sakai.orth@tmd.ac.jp

eral potential complications, including intensive care unit-acquired weakness (ICU-AW).[2] ICU-AW commonly occurs during treatment in the ICU, and its well-recognized risk factors, independent of the etiology of ICU admission, are sepsis, multiorgan system failure, severe inflammatory response syndrome, prolonged sedation, prolonged mechanical ventilation, immobility, hyperglycemia, and use of glucocorticoids or neuromuscular blocking agents.[3] The acquisition of neuromuscular dysfunction during critical illness is associated with increased morbidity in adults, prolonged ICU stay and hospitalization, increased days of mechanical ventilation, and poor overall function and quality of life after discharge from hospital.[4–6] ICU-AW is also associated with increased mortality in critically ill adults.[7,8]

Literature studies of ECMO in COVID-19 patients report long median durations of ECMO of 13.9–20 days.[9–12] Moreover, successful native lung recovery has been reported after prolonged veno-venous (V-V) ECMO support (>28 days).[13] Based on these results, active rehabilitation should be performed in ECMO survivors when weaning from ECMO and during extubation of the ventilator to overcome post-intensive care syndrome (PICS). To date, there are few reports on rehabilitation in ICU patients, especially those on ECMO support, despite such patients reportedly being at risk of ICU-AW because of prolonged ECMO.[14,15] Therefore, this study aimed to describe the rehabilitation characteristics of patients with severe COVID-19 who were managed with ECMO in the ICU and to determine whether these survivors could successfully resume social life.

MATERIALS AND METHODS

Study Design and Setting

This was a single-center, retrospective, observational study. The Tokyo Medical and Dental University is a general acute care hospital with 814 beds located in Tokyo. For patients with a confirmed diagnosis of COVID-19, the hospital provided two dedicated general wards and an ICU. Patients in the COVID-19 ICU required oxygen therapy (>5 L/min) and underwent either intubation or treatment with respiratory management, including ECMO, according to the "Extracorporeal Life Support Organization: COVID-19 interim guidelines." Treatments also included medication for COVID-19 (remdesivir, dexamethasone, or baricitinib) and intensive care for ARDS, such as prone positioning, continuous renal replacement therapy (CRRT), and nitric oxide treatment. Patients were admitted to the COVID-19 ICU from the emergency center or were transported from other hospitals or from the in-house COVID-19 general wards. For patients with hypercoagulability, anticoagulants (internal use of rivaroxaban or intravenous administration of heparin) were provided according to the patients' D-dimer and C-reactive protein levels.

We formed a COVID-19 rehabilitation team consisting of one rehabilitation doctor and several physical therapists. From the time of admission to the COVID-19 ICU, rehabilitation therapy was prescribed by the rehabilitation doctor. Every morning, the rehabilitation doctor and physical therapists evaluated each patient's general status together with ICU doctors in a multidisciplinary approach, and rehabilitation was initiated depending on the patient's condition. To avoid hospital-acquired infections, doctors and physical therapists wore complete personal protective equipment (PPE) during rehabilitation therapy. The PPE included a disposable fluid-resistant long-sleeved gown, N95 mask, goggles or face shield, cap, and double gloves. Although donning and doffing complete PPE takes substantial time and effort, it is necessary to prevent disease transmission. Staff members were trained in the correct methods of wearing, removing, and disposing of PPE, including checking the fit of the N95 mask. During ECMO management with sedation, joint mobilization was performed with consideration for the safety of blood access or ECMO venous blood drainage. Electric muscle stimulation was attempted, avoiding blood access points and ECMO venous blood drainage in each thigh; however, because of the use of muscle relaxants and sedatives, muscle contraction was usually not obtained.

Immediately after patients emerged from sedation after ECMO support and respiratory condition improved with the mode of respirator getting lower, muscle facilitation and muscle training were initiated along with the evaluation of muscle strength. Safe mobilization was attempted considering muscle strength and respiratory function to avoid the development of life-threatening hypoxia or reintubation. Early mobilization or sitting on the side of the bed was attempted gradually to avoid increases in oxygen demand and was performed with control of oxygen saturation and monitoring of patient fatigue. Occasionally, a cycle ergometer with an automated mechanism was used to control the oxygen demand when even sit on bed was not available. The cycle ergometer was used passively (no effort by the patient) and actively.

Survivors were transferred from the ICU to the general ward immediately after their respiratory condition improved following extubation or ECMO treatment. In some cases, after extubation and when intensive care was completed, patients were returned to the hospital where they were previ-

ously admitted without active rehabilitation before departure.

Patients

To evaluate rehabilitation in patients with COVID-19 treated with ECMO, we retrospectively analyzed the data of all consecutive patients with COVID-19 admitted to the COVID-19 ICU who received ECMO management in our hospital together with rehabilitation between April 21, 2020, and August 20, 2021. COVID-19 was diagnosed based on a positive polymerase chain reaction test result for severe acute respiratory syndrome-coronavirus-2.

We recorded the following patient data: sex, age, body mass index (BMI), outcome (weaning), lowest albumin level, peak C-reactive protein (CRP) level, white blood cell (WBC) count from admission to the end of ECMO management, and the use of steroids and muscle relaxants. The outcome was weaning from ECMO. For the ECMO survivors (patients who were alive at the end of the study period after being weaned from ECMO), we investigated the duration of intubation, ECMO management, and rehabilitation, as well as the Medical Research Council (MRC) score and Barthel index after sedation. The MRC score was determined after terminating sedative drugs when the Richmond Agitation-Sedation Scale score ranged from −2 to 0. For patients transferred to rehabilitation hospitals from our hospital, the MRC score or Barthel index at discharge from our hospital was recorded. The Barthel index at 3 months after the end of ECMO management was determined at the outpatient facility or from medical charts.

Ethical Considerations

This study was approved by the Research Ethics Committee of Tokyo Medical and Dental University (M2018-073) and was conducted in accordance with the World Medical Association Declaration of Helsinki. The decision-making ability of some patients at the time of admission was compromised because they were intubated and sedated, and some were immediately intubated on admission because of low oxygen saturation. Patients identified a family member to provide consent on their behalf because written consent from COVID-19 patients was not directly obtained due to the risk of virus transmission. Written informed consent was obtained by mail from a family member who was selected as the key person or guardian (conservator) because visitors were not allowed to visit our hospital during the pandemic. In Japan, digital signatures are not considered to be legally binding.

Statistical Analysis

A minimum sample size of 29 patients was calculated based on a power of 80%, an α error of 5%, and an effect size of 0.5. The correlations between the MRC scores of ECMO survivors after sedation and other factors were assessed using Pearson's correlation coefficient. The analyzed factors were age, intubation duration, ECMO duration, maximum WBC count, maximum CRP level, lowest albumin level, and BMI. All statistical analyses were performed using Bell Curve for Excel 2016 (Social Survey Research Information, Tokyo, Japan). Statistical significance was set at $P < 0.05$.

RESULTS

In total, 132 COVID-19 patients were admitted to the ICU, and ECMO was performed in 20 of them (16 men, 4 women; mean age: 55.7 years) (**Table 1**). Among these 20 patients, 16 were successfully weaned from ECMO. The 16 successfully weaned patients had a median age of 56 years, a median peak WBC count of 20.45 × 103 cells/dL, a median lowest albumin level of 2.5 g/dL, and a median peak CRP level of 25.5 mg/mL. The comorbidities in survivors included hypertension in four patients, hyperlipidemia in two patients, diabetes mellitus in one patient, heart disease in one patient, and chronic renal dysfunction in one patient. The comorbidities in non-survivors included hyperlipidemia in two patients, diabetes mellitus in two patients, heart disease in one patient, malignant disease in one patient, and cerebrovascular disease in one patient.

The median duration of ECMO management in ECMO survivors was 14.5 days, and that of respiratory management was 38 days. The median MRC score after sedation in ECMO survivors was 18. In five cases, the MRC score after sedation was 0, and no muscle contraction was observed.

The median MRC score at discharge was 45, ranging from 6 to 54. Rehabilitation was performed for a median duration of 14 days, and eight patients were discharged from our ICU directly to other hospitals for further treatment after intensive care and rehabilitation.

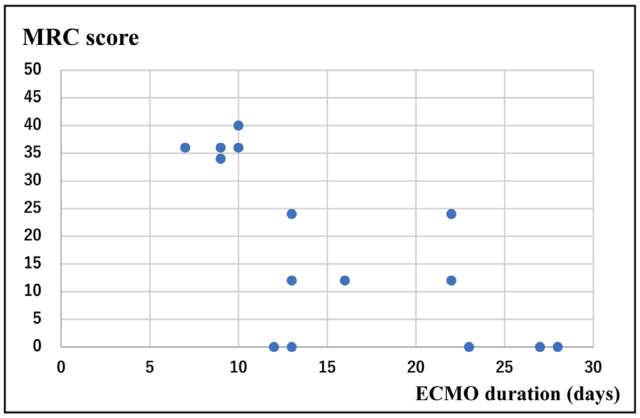
The MRC score after sedation showed significant negative correlations with ECMO duration ($P=0.0023$) and intubation duration ($P < 0.001$) (**Fig. 1**, **Table 2**). There was no significant correlation between MRC score after sedation and age, maximum WBC count, maximum CRP level, lowest albumin level, or BMI. Steroid pulse treatment and muscle relaxants were used in all cases. After sedation, the median initial Barthel index was 0 and that on discharge was 30. The median final Barthel index, which was obtained from

Table 1. Patients with severe COVID-19 with ECMO characteristics

No.	Age (years)	Sex (M/F)	ECMO	ECMO outcome	ECMO duration (days)	Intubation duration (days)	Peak CRP level (mg/mL)	Peak WBC count (10^3 cells/dL)	Lowest albumin level (g/dL)	MRC score after sedation	MRC score on discharge	Rehabilitation duration after sedation (days)	BMI (kg/m^2)	Barthel index after sedation	Barthel index on discharge	Barthel index at 3 months after ECMO
1	66	M	V-V	Not weaned	70	77	33.2	13.6	1.8				21.5			
2	52	M	V-V	Not weaned	62	63	35.8	13.1	2.3				31.9			
3	66	M	V-V	Not weaned	49	70	27.9	41.1	2.2				24.5			
4	66	M	V-V	Not weaned	18	29	33.4	15.6	2.5				21.8			
5	57	M	V-V	Weaned	22	29	47.3	42.6	2.2	12	30	13	23.9	0	5	100
6	54	M	V-V	Weaned	13	36	27.5	15.9	2.3	12	48	15	22.6	0	15	100
7	55	M	V-V	Weaned	10	20	41.5	40.0	1.5	40	54	9	22.1	0	80	100
8	33	F	V-V	Weaned	9	9	24.0	10.4	3.5	36	48	3	21.6	0	70	100
9	65	F	V-V	Weaned	9	16	33.7	20.0	2.2	34	44	20	20.1	0	35	100
10	57	M	V-V	Weaned	9	21	20.9	12.2	2.1	36	48	6	28.4	0	80	100
11	50	M	V-V	Weaned	10	14	26.6	15.7	2.9	36	48	27	26.4	0	25	100
12	60	M	V-V	Weaned	22	44	23.3	28.1	2.7	24	48	14	24.5	0	0	95
13	54	M	V-V	Weaned	23	48	37.9	35.0	1.4	0	15	20	30.3	0	0	N/A
14	70	M	V-V	Weaned	27	83	18.6	16.4	2.5	0	48	50	22.2	0	35	N/A
15	75	M	V-V	Weaned	28	44	36.3	37.2	1.6	0	6	8	26.6	0	0	N/A
16	44	F	V-A	Weaned	13	40	7.9	21.5	2.5	0	34	25	23.1	0	90	N/A
17	50	M	V-V	Weaned	13	29	22.4	12.1	2.5	24	44	14	24.3	5	35	N/A
18	57	M	V-V	Weaned	16	38	24.6	9.7	2.6	12	32	11	33.4	0	5	N/A
19	57	M	V-V	Weaned	12	49	30.4	23.5	2.6	0	20	37	26.9	0	5	N/A
20	26	F	V-V	Weaned	7	12	5.4	20.9	2.5	36	46	7	52.4	5	35	N/A
Weaned summary	56 (26–75)	12/4	15/1	Weaned	14.5 (7–28)	38 (9–83)	25.5 (5.4–47.3)	20.45 (9.7–42.6)	2.5 (1.4–3.5)	18 (0–40)	45 (6–54)	14 (3–50)	24.4 (20.1–52.4)	0 (0–5)	30 (0–90)	100 (95–100)

The bottom row of the table summarizes data for the ECMO 16 survivors (patients 5–20). Summary data are displayed as median (range) or as number.
F, Female; M, male; N/A, not available.

(a)



(b)

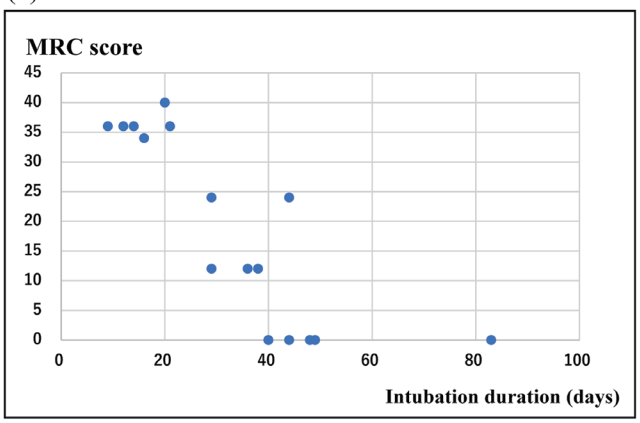


Fig. 1. Correlations between MRC score after sedation and ECMO duration (a) and intubation duration (b).

the patients' medical charts or via telephone interview with eight patients, was 100.

DISCUSSION

This study examined the rehabilitation characteristics of 16 patients with severe COVID-19 who were managed with ECMO in the ICU. Our results show that the median MRC score after sedation was 18. In 5 of the 16 cases, the MRC score after sedation was 0, and no muscle contraction was observed. The MRC score after sedation showed significant correlations with the duration of ECMO and duration of intubation.

Sixteen of 20 patients with severe COVID-19 were weaned from ECMO management in the ICU; the mortality rate was 20% in the present study. According to pre-pandemic historical data from the ELSO registry, V-V ECMO results in a mortality rate of approximately 40%, whereas veno-arterial (V-A) ECMO and extracorporeal cardiopulmonary resuscitation have mortality rates of 55% and 71%, respectively.[12] Our mortality rate was lower than that reported in previous studies, although our indication of ECMO was consistent with the guidelines. This result might depend on the patients' conditions and other treatments, such as CRRT or steroid pulse treatment.

The median duration of ECMO management was 14.5 days, which is almost the same as that reported in previous studies on ECMO in COVID-19.[12] For each patient, the duration depends on the recovery of the PaO_2/FiO_2 ratio; the longest duration of ECMO with successful weaning was 28 days.

In the present study, severe muscle weakness occurred after ECMO management in COVID-19 patients. The median MRC score after sedation after surviving ECMO was 18, and five patients had the lowest score of 0. After the interruption of sedation in these patients, it was difficult to assess the recovery of consciousness because they could not move their body. Initially, some patients could not close or open their eyes, nor could they move their eyebrows at will, even if they had a clear level of consciousness. In such cases, several days were required to determine whether the patient had a clear level of consciousness, which was determined by the patient's attempts to answer questions by moving their eyelids or eyebrows on request. For patients that were unable to move, we ruled out akinetic mutism based on the patients' attempts to respond to questions through changes in their facial expressions. Extreme muscle weakness in ECMO patients immediately after the termination of sedation should be taken into consideration for intubated patients after the interruption of sedation.

ICU-AW is reported to originate from critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or critical illness polyneuromyopathy (CIPM).[16] In a study of the

Table 2. Relationship between MRC score after sedation and factors in patients with severe COVID-19 requiring ECMO

	Age	ECMO period	Intubation duration	Peak level of CRP	Peak level of WBC	Lowest level of albumin	BMI
Correlation coefficient	0.0813	−0.3219	−0.5446	0.4309	0.2911	0.6597	−0.3899
P	0.0949	0.0023*	<0.001*	0.761	0.372	0.363	0.628

* P <0.05

neurophysiological characterization of muscular weakness in patients with severe COVID-19 in the ICU, CIP, CIM, and CIPM were the most frequently encountered neurological disorders based on the clinical or neurophysiological evaluation (4/6; 66%).[2] To diagnose ICU-AW, evaluation of electroneuromyography is recommended. However, we did not evaluate this parameter in our COVID-19 ICU because of noise in the electronic equipment in the ICU. Therefore, our ICU-AW cases were diagnosed by clinical means and not through a neurophysiological test.

In the current study, the only factors related to ICU-AW under ECMO support in COVID-19 patients were ECMO duration and intubation duration. The MRC score after sedation correlated with ECMO duration and intubation duration but not with other factors such as the peak WBC count, peak CRP, or lowest albumin level. The peak WBC count and peak CRP level were similarly very high. Elevated interleukin-6 levels at admission may be a predictive biomarker of ICU-AW in COVID-19 patients,[2] although it was not measured in our hospital. Almost all patients underwent steroid pulse treatment or neuromuscular blockage, and we could not investigate the correlation between steroid pulse treatment or neuromuscular blockage and the MRC score after sedation. The lowest albumin level was considered to be an indicator of nutritional status; however, the MRC score after sedation and the lowest albumin level were not correlated. This might be because albumin was always supplemented when it was low for the management of blood pressure or continuous hemodialysis during ECMO management; therefore, the albumin value was not an accurate indicator of nutritional status. Prealbumin levels were not checked during ECMO management.

The COVID-19 cases that involved longer ECMO duration were more severe than the others, and immobilization might not have been the main reason for the low MRC score after sedation. Although the severity of sepsis or other morbidities could be related to immobilization, early mobilization was impossible during ECMO management or sedation. We could not identify the factors directly related to muscle weakness in ECMO management; nevertheless, the patients who underwent longer durations of ECMO and intubation required rehabilitation because of muscle weakness. In recent reports on ICU treatment, to reduce the incidence of PICS, early mobilization in the ICU has been recommended as part of the ABCDEF bundle: awakening, breathing coordination, delirium monitoring and management, early mobilization, and family engagement and empowerment.[17–19] Early mobilization includes activities such as sitting, standing, ambulation, passive range-of-motion exercises, and ergometry. However, in ECMO patients, early mobilization cannot be performed because of the circumstances of lung rest, sedation, and the use of forcible ventilation during ECMO, as shown in the guidelines.[1]

The median rehabilitation duration in our hospital was 14 days. Despite the short duration of rehabilitation, recovery was achieved to some extent. The patients recovered gradually from muscle weakness; the median MRC score on discharge from our hospital was 45, whereas the median MRC score after sedation was 18. In patients where the MRC score after sedation was 0, MRC scores recovered to 6–48 on discharge. The median Barthel index increased from 0 after sedation to 30 on discharge. In eight early-stage cases, the final Barthel index was determined during outpatient visits or from medical charts at 3 months. The median Barthel index of these patients was 100. Survivors complained of muscle weakness, impaired handgrip, and nerve pain at 6 months after discharge,[20] although eight of our patients showed relatively good recovery. The recovery from axon damage in ICU-AW may be worse than that of myelin sheath injury in neuropathy.

ECMO was performed on patients with the most severe COVID-19 disease, and the survivors successfully recovered with comprehensive intensive care treatment. The range of muscle weakness varied, with some showing 0 in the MRC test, although some of these patients showed a maximum Barthel index within 3 months. However, it is uncertain whether patients can always recover from this muscle weakness, and the time that it takes to recover is unclear. Follow-up is necessary to determine the characteristics of PICS associated with COVID-19. Nevertheless, rehabilitation in patients with severe COVID-19 in the ICU is very important immediately after sedation is removed.

This study has several limitations. First, this was a single-center, retrospective, observational study of the characteristics of rehabilitation in patients with severe COVID-19. The sample size of this study was smaller than that required (n=29). We could not perform regression or subgroup analysis to evaluate the factors affecting the outcome of the MRC score in COVID-19 patients on ECMO because this was a pilot study with a small sample size. Therefore, a larger multicenter cohort study should be performed for a longer duration to validate the efficacy and validity of rehabilitation in COVID-19 cases from multiple viewpoints. Although relatively few patients were included in the current analysis, we believe that the present study is clinically meaningful because it provides information on the characteristics of

patients with COVID-19. The urgent need for rehabilitation should be emphasized to gain the good outcome in comprehensive COVID-19 treatment. Second, COVID-19 data vary by country, region, and governmental policy. The findings of this study may be peculiar to Japan or regions with similar governmental policies. Further long-term investigation is necessary to statistically identify the cause of ICU-AW in COVID-19 patients and to determine the outcomes of rehabilitation in ECMO survivors.

In conclusion, for 16 survivors of ECMO treatment in our COVID-19 ICU, the median ECMO duration was 14.5 days and the median MRC score after sedation was 18. To address ICU-AW and serious muscle weakness caused by long-term ECMO and intubation, intensive rehabilitation for ECMO survivors should start immediately after sedation. A further multicenter investigation with a relatively large sample size could help clarify the effect of rehabilitation in patients with COVID-19-related ARDS managed by ECMO.

ACKNOWLEDGMENTS

We sincerely thank all the doctors, physical therapists, and our colleagues in the Department of Rehabilitation Medicine, Tokyo Medical and Dental University, for their dedicated efforts in treating patients with COVID-19.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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