THERAPEUTIC ADVANCES in
Infectious Disease

Original Research

The utility of procalcitonin for identifying secondary infections in patients with influenza or COVID-19 receiving extracorporeal membrane oxygenation

Ther Adv Infect Dis

2024, Vol. 11: 1–9

DOI: 10.1177/20499361241255873

Kajal D. Patel, James K. Aden, Michal J. Sobieszczyk and Joseph E. Marcus

Abstract

Background: Identifying secondary infections in patients receiving extracorporeal membrane oxygenation (ECMO) presents challenges due to the ECMO circuit's influence on traditional signs of infection.

Objectives: This study evaluates procalcitonin as a diagnostic marker for secondary infections in patients receiving ECMO with influenza or COVID-19 infection.

Design: Single-center retrospective cohort study.

Methods: All adult patients receiving veno-venous ECMO with underlying influenza or COVID-19 from November 2017 to October 2021 were included. Patient demographics, time receiving ECMO, culture data, and procalcitonin levels were examined. The first procalcitonin within 3 days of infection was compared to negative workups that were collected at least 10 days from the last positive culture. Furthermore, we compared procalcitonin levels by the type of pathogen and site of infection.

Results: In this study, 84 patients with influenza or COVID-19 who received ECMO were included. A total of 276 procalcitonin labs were ordered in this cohort, with 33/92 (36%) of the secondary infections having an associated procalcitonin value. When comparing procalcitonin levels, there was no significant difference between the infection and negative workup groups [1 ng/mL (interquartile ranges, IQR: 0.4–1.2) *versus* 1.3 (0.5–4.3), $p = 0.19$]. Using 0.5 ng/mL as the cut-off, the sensitivity of procalcitonin was 67% and the specificity was 30%. In our cohort, the positive predictive value of procalcitonin was 14.5% and the negative predictive value was 84%. There was no difference in procalcitonin by type of organism or site of infection. Procalcitonin levels did not routinely decline even after an infection was identified.

Conclusion: While procalcitonin is a proposed potential diagnostic marker for secondary infections in patients receiving ECMO, this single-center study demonstrated low sensitivity and specificity of procalcitonin in identifying secondary infections. Furthermore, there was no association of procalcitonin levels with etiology of infection when one was present. Procalcitonin should be used cautiously in identifying infections in veno-venous ECMO.

Plain language summary

The utility of procalcitonin for identifying secondary infections in patients with influenza or COVID-19 receiving extracorporeal membrane oxygenation

Aim: To determine if procalcitonin performs well as a diagnostic marker in identifying additional infections in adult patients receiving ECMO with influenza or COVID-19. Background: It is very difficult to determine whether patients receiving ECMO have infections as both vital signs and laboratory markers have not shown good utility.

Correspondence to:
Joseph E. Marcus
Infectious Diseases Service, Department of Medicine, Brooke Army Medical Center, Joint Base San Antonio-Fort Sam Houston, 3551 Roger Brooke Dr, Fort Sam Houston, TX 78234-4504, USA

Department of Medicine, Uniformed Services University, Bethesda, MD, USA
joseph.e.marcus3.mil@health.mil

Kajal D. Patel
Department of Medicine, Brooke Army Medical Center, Joint Base San Antonio-Fort Sam Houston, TX, USA

James K. Aden
Biostatistics, San Antonio Uniformed Services Health Education Consortium, Joint Base San Antonio-Fort Sam Houston, TX, USA

Michal J. Sobieszczyk
Pulmonary Service, Department of Medicine, Brooke Army Medical Center, Joint Base San Antonio-Fort Sam Houston, TX, USA

Procalcitonin is a laboratory test sometimes used to identify infections, but its test performance is not known in this population. Methods: We performed a study of adult patient patients receiving ECMO to determine if there were differences in procalcitonin levels when patients had infections as compared to when they did not have infections. We also looked to see if procalcitonin levels routinely dropped after an infection was diagnosed. Results: Procalcitonin values were no different when patients had an infection as compared to when they did not have an infection. Using standard laboratory cut-offs, the procalcitonin sensitivity was 67%, and specificity was 30%. Procalcitonin levels did not routinely decline even after an infection was identified. Conclusions: Procalcitonin poorly differentiated patients with infections from those without infections and should be used with caution in patients receiving ECMO.

Keywords: diagnostic stewardship, extracorporeal membrane oxygenation, nosocomial infection, procalcitonin

Received: 5 October 2023; revised manuscript accepted: 2 May 2024.

Introduction

Patients receiving extracorporeal membrane oxygenation (ECMO) are at high risk for developing nosocomial infections. Recent studies have highlighted that patients with COVID-19 are at a particularly elevated risk of secondary infections compared to other indications for ECMO.[1,2] While existing literature has focused on the epidemiology and prognosis of ECMO-related infections, limited attention has been given to diagnostics. Identifying infections in patients receiving ECMO can be challenging due to the lack of universal definitions of infections in this population, concern about masking temperature changes with the ECMO circuit, and the systemic inflammatory response related to contact between the blood and the ECMO circuit.[3,4] Recent studies have shown low specificity to commonly used factors to determine infection, such as fever, leukocytosis, and elevated sepsis scores.[5] Due to the poor individual performance of common infectious markers, a third of ECMO centers perform surveillance cultures to monitor for infections.[6] There have been proposals to trial other markers of infection on ECMO due to the low sensitivity and specificity of each individual test.[7]

Procalcitonin, a biomarker believed to rise in response to bacterial infections and decline with effective treatment, has been used extensively in de-escalating antibiotics for community-acquired pneumonia.[8] Procalcitonin measurements are not affected by the ECMO circuit and are used clinically at certain institutions to assist in determining the presence of an infection.[9] This study evaluated the sensitivity and specificity of elevated procalcitonin during nosocomial infections and the subsequent changes in procalcitonin after an infection is identified.

Methods

This single-center retrospective cohort study assessed the real-world use of procalcitonin in identifying secondary infections among adult patients (age >18) who received ECMO for underlying COVID-19 or influenza between November 2017 to October 2021 at Brooke Army Medical Center. Brooke Army Medical Center is the sole ECMO facility in the Department of Defense and is a referral center for other military hospitals and civilian critically ill patients in South Texas. For this protocol, we excluded all patients admitted for a reason other than severe COVID-19 or influenza to standardize the population and minimize the effects of ischemia and surgery on procalcitonin values.[10] At this center, there are no prophylactic antibiotics nor use of surveillance cultures. Procalcitonin ordering was not protocolized and primary teams had sole discretion to order when they felt it was clinically indicated. All patients receiving standard precautions on ECMO with COVID-19 were on strict isolation (face shield, N95, gown) for 20 days after admission, while patients with influenza were on droplet precautions. All patients in this study received veno-venous ECMO configuration. This study followed the Strengthening the report of observa-

tional studies in epidemiology (STROBE) checklist for cohort studies (Supplemental Table 1).

We collected demographics for all patients who met the inclusion criteria. All infectious workups were performed at the discretion of the treatment team and were not protocolized. Additional data collected included the duration of ECMO support and survival to discharge. Infections were defined as a positive culture that the primary team treated with an antimicrobial. Infections were further characterized by the site of collection (as either bloodstream, respiratory, or urinary tract) as well as the characteristics of the causative pathogen.

Statistical analysis

The primary outcome of this study was to evaluate the sensitivity and specificity of elevated procalcitonin values in identifying confirmed infections. Any procalcitonin value greater than 0.5 ng/mL was considered positive. For this analysis, the procalcitonin values associated with infection were compared to procalcitonin values associated with a negative workup, which encompassed procalcitonin values from patients with no secondary infection, as well as those procalcitonin values collected at least 10 days from the most recent positive culture. Infection-associated procalcitonin values included those on the day of positive culture or in the 3 days following positive culture. For patients with infections, we trended procalcitonin values collected in the 10 days after the first positive culture to determine if they reliably dropped after diagnosis of an infection. For secondary outcomes, we compared the infection-associated procalcitonin value for gram-positive and gram-negative infections, as well as by site of infection. An analysis of covariance mixed model was performed to determine if there was a significant difference in decay to the procalcitonin value in the 10 days after an infection was identified for blood *versus* lung infections.

The analyzed values we reported as medians, interquartile ranges (IQR), and corresponding p values. We determined the significance of primary outcome analysis based on the Mann–Whitney U test. A p value less than 0.05 was considered indicative of statistical significance. This protocol was reviewed by the San Antonio Research and Human Protections Office and determined to be exempt.

Results

From November 2017 to October 2021, 214 patients received ECMO at Brooke Army Medical Center. Of these, 84 (36%) patients were diagnosed with influenza or COVID-19 on admission and were included in this study (Table 1). The population was predominantly male ($n = 65$, 77%), with a median age of 43 (IQR: 35–51). A total of 76% of the study population had an admission diagnosis of COVID-19, while the remaining 24% had an admission diagnosis of influenza. A total of 53 survived to discharge (63%), and the median time on ECMO was 17.3 (IQR: 9.7–34.3) days. Patients received a median of 2 [1–4] procalcitonin tests during their hospitalization.

We identified a total of 92 nosocomial infections, with 55 bloodstream infections, 32 respiratory infections, and 5 urinary tract infections. Of these secondary infections, organisms included 42 gram-positive bacteria, 41 gram-negative bacteria, 8 fungi, and 1 disseminated viral infection. A total of 33 (36%) nosocomial infections had a procalcitonin value taken within 72 h of positive culture. Of these procalcitonin values in the infection group, 19 (58%) procalcitonin were collected on the day of positive culture, 10 (32%) within 1 day of positive culture, and 4 (12%) collected 2–3 days after the positive culture. A total of 185 values met criteria for procalcitonin values with a negative infectious workup. A total of 58 procalcitonin values were collected between 3 days and 10 days from the most recent positive culture and were not included in comparisons between procalcitonin and secondary infection.

The median procalcitonin was 1.33 IQR [0.46–3.49]. There was no difference in median procalcitonin for those with influenza [1.12 (0.46–3.12)] as compared to those with COVID-19 [1.41 (0.5–3.85), $p = 0.45$]. The was no difference in median procalcitonin for those with infections [0.36 (0.35–1.38) *versus* 1.00 (0.48–2.37), $p = 0.30$] or negative infectious [1.48 (0.48–4.23) *versus* 1.19 (0.40–4.26), $p = 0.36$] workups between influenza and COVID-19 respectively. The median procalcitonin was lower in patients who survived hospital discharge as compared to those who died in the hospital [0.9 (0.3–2.3) *versus* 2.4 (0.9–5.7), $p < 0.0001$].

For the primary outcome, there was no significant difference between procalcitonin values

Table 1. Demographic information of 84 patients with COVID-19 or influenza who received extracorporeal membrane oxygenation at Brooke Army Medical Center during the study period.

	Count (*n*, %) or Median (IQR)
Female	19 (23%)
Age	43 (35–51)
Admission diagnosis	
Influenza	20 (24%)
COVID-19	64 (76%)
Survival to discharge	53 (63%)
Time on ECMO, days	17.3 (9.7–34.3)
Total infections	92
Bloodstream infections	55
Respiratory infections	32
Urinary tract infections	5
Infection rate/1000 ECMO days	
Total	48.0
Bloodstream infections	28.7
Respiratory infections	16.7
Urinary tract infections	2.6
Infectious organisms	
Gram-positive Bacteria	42 (46%)
Enterococcus faecalis	16 (38%)
Staphylococcus aureus	15 (36%)
Staphylococcus epidermidis	7 (17%)
Gram-negative Bacteria	41 (45%)
Pseudomonas aeruginosa	12 (29%)
Klebsiella oxytoca	4 (10%)
Klebsiella aerogenes	4 (10%)
Fungal	8 (9%)
Candida albicans	4 (50%)
Candida dubliniensis	1 (13%)
Candida tropicalis	1 (13%)
Viral	1 (1%)
Disseminated HSV	1 (100%)
Procalcitonin tests/patient, median [IQR]	2 [1–4]

ECMO, extracorporeal membrane oxygenation; HSV, Herpes simplex virus; IQR, interquartile ranges.

associated with patients with identified secondary infection compared to procalcitonin values in patients with negative infectious workups [median: 1 ng/mL (IQR: 0.4–1.2) *versus* 1.3 (0.5–4.3), $p = 0.19$] (Table 2 and Figure 1). The sensitivity was 66.7%, and the specificity was 30.3% when we used a cut-off value of 0.5 ng/mL for procalcitonin. For this cohort, the positive predictive value was 14.5%, while the negative predictive value was 83.5%. There was no difference in the ECMO day of procalcitonin between the procalcitonin values at time of secondary infection as compared to time without secondary infection [8 (4–21) *versus* 7 (2–20), $p = 0.49$]. Within the infectious group, there was no difference in median procalcitonin value in gram-positive infections [1.09 (0.43–2.70) *versus* 0.95 (0.4–1.29), $p = 0.35$] as compared to gram-negative infections. Finally, procalcitonin values associated with bloodstream infections [1.3 (0.45–2.70) *versus* 0.55 (0.4–1.38), $p = 0.35$] were no different from respiratory infections. The procalcitonin values were no different in those with a secondary infection who died as compared to those who survived hospital discharge [0.58 (0.36–2.26) *versus* 1.04 (0.66–2.02), $p = 0.34$]. There were eight procalcitonin values greater than 25, and none were associated with a secondary infection.

There were 41 secondary infections with serial procalcitonin values in the first 10 days after infection. These serial procalcitonin values were graphed individually (Figure 2) and showed no reliable decrease in trend following infection identification. When divided by admitting diagnosis and site of infection, there was again no clear distinction of a site where procalcitonin reliably decreased after diagnosis (Figure 3). An analysis of covariance showed no significant change in procalcitonin value in the 10 days after a secondary infection was identified, except for lung infections in patients with influenza, which showed significant increase in the 10 days after infection (slope estimate: 0.21, $p = 0.003$, Supplemental Table 2).

Discussion

This single-center study investigated the diagnostic utility of procalcitonin as a marker for identifying secondary infections in patients receiving ECMO with COVID-19 or influenza. This study did not find an association between

Table 2. Procalcitonin valves in cohort based on presence of infection, type of bacterial infection, and location of infection.

Type of infection	Median procalcitonin (IQR)	*p* Value
Secondary infection (*N* = 33)	1 (0.40–1.19)	0.19
No secondary infection (*N* = 185)	1.27 (0.47–4.26)	
Secondary infections		
Gram-positive infections (*n* = 42)	1.09 (0.43–2.70)	0.35
Gram-negative infections (*n* = 41)	0.95 (0.4–1.29)	
Bloodstream infections (*n* = 55)	1.3 (0.45–2.70)	0.35
Respiratory infections (*n* = 32)	0.55 (0.4–1.38)	

ECMO infections and procalcitonin levels, with a sensitivity of 67% and a specificity of 30%. Despite the frequent infections in this cohort, the positive predictive value for identifying a culture-positive infection with an elevated procalcitonin was 14.5%.

The utility of procalcitonin has been best described in community-acquired pneumonia, where its ability to increase with common respiratory bacterial pathogens and decrease with appropriate antibiotics allows its use both as a marker of infection as well as a tool to decrease antibiotic exposure without increasing patient harm.[11] However, patients with critical illness have shown less utility to serial procalcitonin with sensitivities below 80% and specificities below 30%.[12] Our study showed similar sensitivity and specificity compared to studies of critically ill patients. This finding may be due to systemic inflammatory changes associated with critical illness or different pathogens that cause infections in critically ill patients compared to community dwellers.[13,14]

Multiple studies have assessed the utility of procalcitonin in detecting secondary infection in both influenza and COVID-19, but the results have been varied and inconclusive. In cases of influenza, studies have linked admission procalcitonin levels to co-infection with bacterial pneumonia upon admission.[15] However, several studies evaluating procalcitonin in patients with COVID-19 have been less effective, with systematic reviews showing sensitivity of 60% and specificity of 71% at identifying secondary infections in patients not receiving ECMO.[16] Both studies demonstrate much better testing performance than this study. Similar to work with community-acquired pneumonia, procalcitonin may have better performance characteristics for identifying infections in community settings for viral illnesses as well.

Primary viral infection in patients on ECMO can present challenges in detecting infection due to the unreliable nature of traditional signs such as fever and temperature. Previous research has indicated that patients on ECMO experience a complex inflammatory response similar to systemic inflammatory response syndrome, characterized by elevated levels of proinflammatory cytokines and leukocyte activation.[17] This phenomenon is particularly evident in neonates receiving ECMO, where both respiratory failure and the ECMO circuit contribute to neutrophil and cytokine activation.[18] Consequently, conventional markers used to identify systemic inflammatory responses associated with infection cannot be considered reliable in ECMO patients. Most of the literature on the use of procalcitonin in patients receiving ECMO involves studies in pediatric populations. Early studies have shown that the kinetics of the assay used for procalcitonin are largely unaffected in pediatric patients receiving ECMO, which provided reassurance of using this assay for this population.[9] Further pediatric studies showed that using a cut-off of 0.5 ng/mL provided the best sensitivity (92%) and specificity (43%) in identifying a secondary bacterial process.[19]

The diagnostic utility of procalcitonin in adult ECMO patients is limited to several small studies

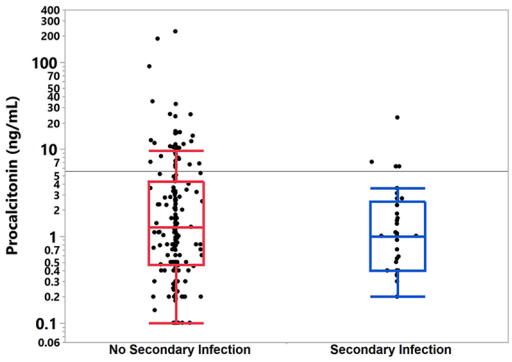

Figure 1. Box and Whisker plot of procalcitonin values in patients without and with secondary infections.

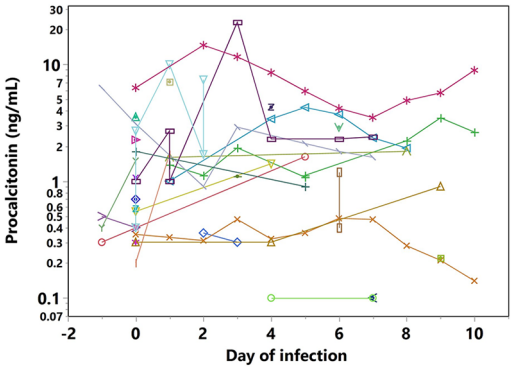

Figure 2. The trend of procalcitonin in patients with secondary infections.

in patients receiving ECMO for cardiac support (veno-arterial ECMO) as opposed to veno-venous ECMO seen in this study population. One study of 27 adult patients demonstrated procalcitonin was useful in identifying infection in veno-arterial ECMO (sensitivity: 89%, specificity: 50%).[20] In an additional study of 20 adult patients on veno-arterial ECMO, sensitivities and specificities of procalcitonin reached as high as 90% and 82%, respectively. These small studies provided limited data in selected patient populations suggestive of benefit of procalcitonin as a diagnostic marker in this population.[21] Alternatively, a final small study in veno-arterial ECMO with 38 patients did not find an association between procalcitonin and subsequent development of infection.[22] It is essential to study larger cohorts to demonstrate if the high sensitivity of veno-arterial ECMO and the low sensitivity of veno-venous ECMO seen in this study are related to patient factors or ECMO differences between the two populations.

Previous studies have suggested that the type of organism causing infection is associated with procalcitonin level.[23,24] However, in our study, no significant association was observed between procalcitonin levels and either the site of infection or the type of infectious organism. The lack of association with any specific type of infection argues against a clear physiologic mechanism for monitoring procalcitonin values in these patients. This study demonstrated greater procalcitonin levels in patients with in-hospital mortality, as reported in other studies in both ECMO and COVID-19.[22,25] It is possible that procalcitonin represents some underlying immune activation with a poor prognostic significance that may be confounding the results of this study, and future work is needed to explore a mechanism leading to elevated procalcitonin in patients receiving ECMO. However, the low sensitivity and specificity reported in this study suggest the need for further research to explore alternative markers or diagnostic strategies for identifying secondary infections in ECMO patients.

One reason procalcitonin is popular is that its values are thought to be dynamic and show rapid drops after appropriate infection treatment.[26] However, in our study, there was no decrease in procalcitonin values in the days after diagnosis of an infection. Previous work in bloodstream infections on ECMO has shown that most patients are only bacteremic for 1 day.[27] Despite the implication that patients improve when they are no longer bacteremic, there is no clear decrease in procalcitonin level. This discrepancy may be due to underlying inflammation leading to falsely elevated procalcitonin levels or related to the organisms that lead to bloodstream infections in this cohort having less impact on procalcitonin levels.

There are several limitations to this single-center retrospective study. At this ECMO center, there was no standardized protocol for selecting patients to collect procalcitonin values; therefore, only about a third of infections in this cohort had an associated procalcitonin value.

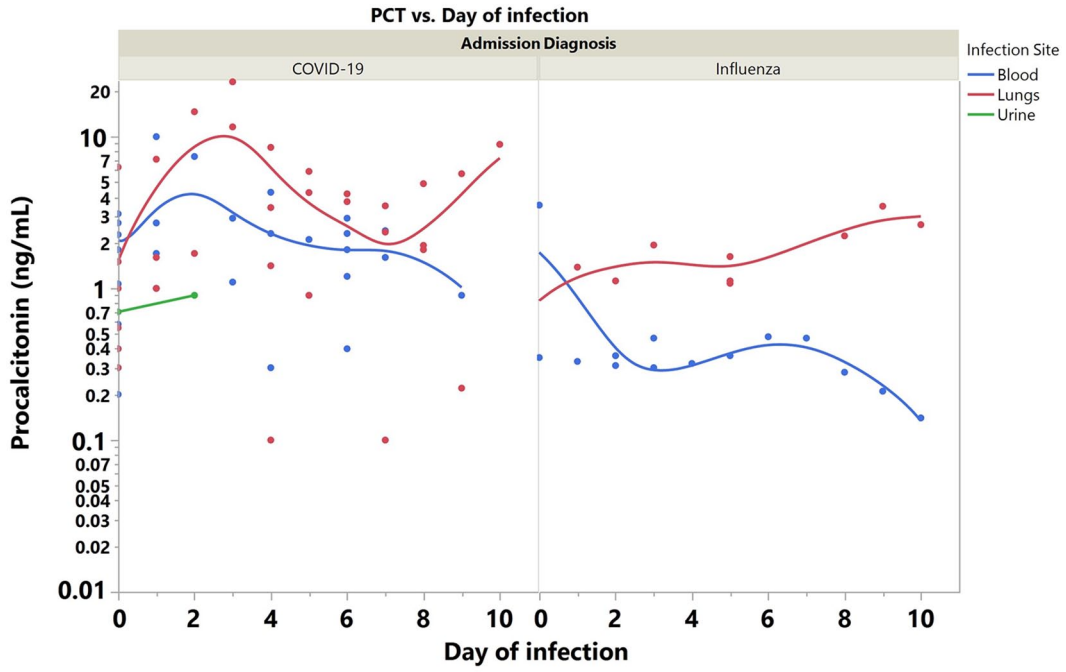

Figure 3. The trend of procalcitonin values in patients with infections at various sites (blood, lungs, urine) over 10 days.

Furthermore, some patients had a procalcitonin value on a day with no cultures and, therefore, may have been falsely part of the no-infection group. There was no protocol to start or stop antimicrobials based on procalcitonin values, and it is unknown if use of procalcitonin led to more or less antimicrobial use in this cohort. Another limitation is the study's focus solely on patients with primary respiratory failure due to viral illness requiring veno-venous extracorporeal membrane oxygenation, making it less applicable to patients on veno-arterial extracorporeal membrane oxygenation or those receiving veno-venous ECMO for other indications. ECMO settings were not collected, and it is possible that changes in ECMO settings between different patients may have affected procalcitonin measurements. Finally, there was no power calculation to calculate sample size for this study, and thus, it may be underpowered to find a difference between the infected and non-infected cohort. These limitations underscore the need for caution when interpreting the findings and suggest avenues for future research to address these constraints and broaden the applicability of the study's conclusions.

Conclusion

Our study evaluates the utility of procalcitonin in a large cohort of patients receiving veno-venous ECMO for COVID-19 or influenza and found low sensitivity and specificity for this test at identifying nosocomial infections. Procalcitonin alone does not have the specificity to rule in or the sensitivity to rule out secondary infections, and its use for diagnostic decision-making in this patient population is limited. In patients with severe viral acute respiratory syndrome requiring ECMO, there is a great need for better diagnostics to determine patients with potential secondary infections.

Declarations

Disclaimer

The views expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Defense Health Agency, Brooke Army Medical Center, the Department of Defense, nor any agencies under the U.S. Government.

Ethics approval and consent to participate
This study was deemed exempt by the San Antonio Institutional Review Board (21-13083), and informed consent was waived.

Consent for publication
N/A

Author contributions
Kajal D. Patel: Data curation; Formal analysis; Methodology; Writing – original draft.

James K. Aden: Formal analysis; Methodology; Writing – review & editing.

Michal J. Sobieszczyk: Data curation; Supervision; Writing – review & editing.

Joseph E. Marcus: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Data is available by contacting the corresponding author.

ORCID iD
Joseph E. Marcus https://orcid.org/0000-0002-1789-603X

Supplemental material
Supplemental material for this article is available online.

References

1. Tan C, Hota SS, Fan E, *et al.* Bloodstream infection and ventilator-associated pneumonia in patients with coronavirus disease 2019 (COVID-19) supported by extracorporeal membrane oxygenation. *Infect Control Hosp Epidemiol* 2023; 44: 1443–1450.
2. Marcus JE, Sams VG and Barsoumian AE. Elevated secondary infection rates in patients with coronavirus disease 2019 (COVID-19) requiring extracorporeal membrane oxygenation. *Infect Control Hosp Epidemiol* 2021; 42: 770–772.
3. Millar JE, Fanning JP, McDonald CI, *et al.* The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. *Crit Care (London, England)* 2016; 20: 387.
4. MacLaren G, Schlapbach LJ and Aiken AM. Nosocomial infections during extracorporeal membrane oxygenation in neonatal, pediatric, and adult patients: a comprehensive narrative review. *Pediatr Crit Care Med* 2020; 21: 283–290.
5. Lee DG, Sobieszczyk MJ, Barsoumian AE, *et al.* The utility of sepsis scores for predicting blood stream infections in extracorporeal membrane oxygenation. *Perfusion*. Epub ahead of print April 2023. DOI: 10.1177/02676591231168644.
6. Glater-Welt LB, Schneider JB, Zinger MM, *et al.* Nosocomial bloodstream infections in patients receiving extracorporeal life support: variability in prevention practices: a survey of the extracorporeal life support organization members. *J Intensive Care Med* 2016; 31: 654–669.
7. de Roux Q, Renaudier M, Bougouin W, *et al.* Diagnostic yield of routine daily blood culture in patients on veno-arterial extracorporeal membrane oxygenation. *Critical Care (London, England)* 2021; 25: 241.
8. Self WH, Balk RA, Grijalva CG, *et al.* Procalcitonin as a marker of etiology in adults hospitalized with community-acquired pneumonia. *Clin Infect Dis* 2017; 65: 183–190.
9. Bobillo S, Rodríguez-Fanjul J, Solé A, *et al.* Kinetics of procalcitonin in pediatric patients on extracorporeal membrane oxygenation. *Biomarker Insights* 2018; 13: 1177271917751900.
10. Falcoz PE, Laluc F, Toubin MM, *et al.* Usefulness of procalcitonin in the early detection of infection after thoracic surgery. *Eur J Cardio-Thoracic Surg* 2005; 27: 1074–1078.
11. Schuetz P, Briel M, Christ-Crain M, *et al.* Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. *Clin Infect Dis* 2012; 55: 651–662.
12. Luyt CE, Combes A, Reynaud C, *et al.* Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. *Intensive Care Med* 2008; 34: 1434–1440.

13. Leli C, Ferranti M, Moretti A, *et al.* Procalcitonin levels in gram-positive, gram-negative, and fungal bloodstream infections. *Dis Markers* 2015; 2015: 701480.

14. Vincent JL, Sakr Y, Singer M, *et al.* Prevalence and outcomes of infection among patients in intensive care units in 2017. *JAMA* 2020; 323: 1478–1487.

15. Pfister R, Kochanek M, Leygeber T, *et al.* Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. *Critical Care (London, England)* 2014; 18: R44.

16. Wei S, Wang L, Lin L, *et al.* Predictive values of procalcitonin for coinfections in patients with COVID-19: a systematic review and meta-analysis. *Virol J* 2023; 20: 92.

17. Wang S, Krawiec C, Patel S, *et al.* Laboratory evaluation of hemolysis and systemic inflammatory response in neonatal nonpulsatile and pulsatile extracorporeal life support systems. *Artif Organs* 2015; 39: 774–781.

18. Fortenberry JD, Bhardwaj V, Niemer P, *et al.* Neutrophil and cytokine activation with neonatal extracorporeal membrane oxygenation. *J Pediatrics* 1996; 128: 670–678.

19. Tan VE, Moore WS, Chopra A, *et al.* Association of procalcitonin values and bacterial infections in pediatric patients receiving extracorporeal membrane oxygenation. *Perfusion* 2018; 33: 278–282.

20. Pieri M, Greco T, De Bonis M, *et al.* Diagnosis of infection in patients undergoing extracorporeal membrane oxygenation: a case-control study. *J Thoracic Cardiovasc Surg* 2012; 143: 1411–1416.

21. Tanaka D, Pitcher HT, Cavarocchi NC, *et al.* Can procalcitonin differentiate infection from systemic inflammatory reaction in patients on extracorporeal membrane oxygenation? *J Heart Lung Transplant* 2014; 33: 1186–1188.

22. Kim DW, Cho HJ, Kim GS, *et al.* Predictive value of procalcitonin for infection and survival in adult cardiogenic shock patients treated with extracorporeal membrane oxygenation. *Chonnam Med J* 2018; 54: 48–54.

23. Guo SY, Zhou Y, Hu QF, *et al.* Procalcitonin is a marker of gram-negative bacteremia in patients with sepsis. *Am J Med Sci* 2015; 349: 499–504.

24. Li S, Rong H, Guo Q, *et al.* Serum procalcitonin levels distinguish Gram-negative bacterial sepsis from Gram-positive bacterial and fungal sepsis. *J Res Med Sci* 2016; 21: 39.

25. Lu M, Drohan C, Bain W, *et al.* Trajectories of host-response subphenotypes in patients with COVID-19 across the spectrum of respiratory support. *CHEST Crit Care* 2023; 1: 100018.

26. Samsudin I and Vasikaran SD. Clinical utility and measurement of procalcitonin. *Clin Biochem Rev* 2017; 38: 59–68.

27. Frankford SA, Sobieszczyk MJ, Markelz AE, *et al.* Clearance of blood stream infections in patients receiving extracorporeal membrane oxygenation: a retrospective single-center cohort study. *BMC Infect Dis* 2023; 23: 63.