COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect* 2020;26:1622–1629.
11. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, *et al.*; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015;373:415–427.
12. Musher DM, Roig IL, Cazares G, Stager CE, Logan N, Safar H. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. *J Infect* 2013;67:11–18.
13. Musher DM, Jesudasen SS, Barwatt JW, Cohen DN, Moss BJ, Rodriguez-Barradas MC. Normal respiratory flora as a cause of community-acquired pneumonia. *Open Forum Infect Dis* 2020;7: ofaa307.
14. Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2004;39:165–169.

Identifying Survivors of Sepsis at Risk for Adverse Cardiovascular Outcomes

For many years, infections have been recognized as precipitants of incident cardiovascular disease (1). Several epidemiologic studies have reported higher long-term risk of heart failure, myocardial infarction, stroke, coronary revascularization, and atrial fibrillation after viral illness, pneumonia, and sepsis (2–5). The mechanisms underlying the increased risk of cardiovascular disease after sepsis remain incompletely understood, and point-of-care approaches to identify high-risk patients who may benefit from targeted interventions are appealing and much needed.

In this issue of the *Journal*, Garcia and colleagues (pp. 557–565) analyzed the association between serum troponin levels and 1-year cardiovascular events in a multicenter cohort of 14,046 adult survivors of sepsis hospitalization who had no prior cardiovascular diagnosis (6). Patients were categorized into three tertiles based on peak troponin levels measured within the first 14 days of hospital admission, and their association with a composite cardiovascular outcome of atherosclerotic cardiovascular disease (defined as acute myocardial infarction, ischemic stroke, or coronary revascularization), acute heart failure, and atrial fibrillation was assessed. Among the 14,046 patients included in the primary analysis, 6,403 (45.6%) had an elevated troponin level. In unadjusted and multivariable analysis, elevated troponin levels were associated with a "dose-dependent" risk increase in incident cardiovascular events that ranged from 1.37-fold (95% confidence interval, 1.2–1.55) for the lowest tertile to 1.77-fold (95% confidence interval, 1.56–2.00) in the highest tertile. These findings remained robust across multiple sensitivity analyses that included using only patients without missing data (i.e., complete cases), using different imputation strategies for missing data, using troponin as a continuous variable instead of *a priori* defined tertiles, and exclusion of cardiovascular events that occurred during hospitalization. In addition, the authors used eValues to assess the potential effect of unmeasured confounders (7). For example, the eValue for the association of peak troponin in the highest tertile and 1-year cardiovascular events was 2.94, indicating that residual confounding could explain the observed association only if there existed an unmeasured covariate with a relative risk association of at least 2.94.

Numerous previous studies have demonstrated an increased risk of cardiovascular events in survivors of sepsis (2–5). However, many of these studies, particularly those using administrative data, were limited in their ability to identify preexisting cardiovascular disease. We commend Garcia and colleagues on their efforts to identify patients with preexisting cardiovascular disease. They leveraged the advantages of a large integrated healthcare system and performed a 5-year look back using outpatient and inpatient records to identify presepsis comorbidities in addition to 3 months of medication data to identify current use of antihypertensives, statins, and antiplatelet drugs. The data sources used to identify preexisting chronic disease and length of the look-back period are indeed important, as shorter look back periods and use of single data sources (e.g., inpatient or outpatient data) underestimate the prevalence of chronic health conditions and consequently overestimate the hazard of incident cardiovascular disease (8, 9). This is particularly relevant for atrial fibrillation, which is often missed even during periods of intensive monitoring (10).

One common critique of composite outcomes, which are more commonly used in cardiovascular clinical trials than not, is that individual components are often unreasonably combined, inconsistently defined, and inadequately reported, which makes their interpretation challenging (11, 12). In the current study, Garcia and colleagues used a composite endpoint of atherosclerotic cardiovascular disease, acute heart failure, and atrial fibrillation diagnosis. Of the 2,012 (14.3%) patients who experienced the outcome, more than two-thirds (1,425 or 70.8%) had a new diagnosis of atrial fibrillation, and among the complete case subgroup, 27.2% (2,164/7,965) had an episode of atrial fibrillation during hospitalization. New onset atrial fibrillation is the most common arrhythmia encountered in ICUs and particularly prevalent among patients with sepsis (10, 13). It is associated with increased length of stay and hospital death (14), but its significance for long-term mortality and implications for subsequent treatment are debated (15), perhaps because many view "this type" of atrial fibrillation as a distinct and reversible manifestation of critical illness with unique predisposing factors (16). Because persistent inflammation and immunosuppression are common among survivors of sepsis (17), cardiovascular outcomes such as atrial fibrillation should be studied in this context, and this approach may broaden the number of candidate treatment strategies beyond anticoagulation and rhythm control (18).

Supported by the National Institute of General Medical Sciences grant K23GM132688 (F.B.M.) and Agency for Healthcare Research and Quality R01 HS026725 (H.C.P.).

Originally Published in Press as DOI: 10.1164/rccm.202105-1322ED on June 17, 2021

Elevated troponin levels are found in approximately 50% of critically ill patients and have been associated with adverse outcomes (19, 20). Hence, elevated troponin levels may be useful for future risk stratification in survivors of sepsis as suggested by this study. However, the appropriate troponin cutoff levels remain to be determined. There are legitimate concerns that indiscriminate troponin testing or use of highly sensitive assays will return many positive results of uncertain clinical significance that may result in subsequent procedures and treatments of questionable therapeutic value (21). Among the 39,590 eligible patients in this study, only a third had troponins drawn during hospitalization and were ultimately included in this study (*see* Figure 1 in the article by Garcia and colleagues). Speculating about the factors behind the clinical decision to obtain a troponin level versus not is intriguing, and one wonders how the 25,544 patients who did not have a troponin level measured differed from patients included in this study who did and had "normal" levels. Comparing cardiovascular outcomes in such groups will be necessary on the path forward to validating troponin and determining appropriate cutoff values for long-term cardiovascular risk prognostication in survivors of sepsis.

In conclusion, the association of increased troponin levels with adverse incident cardiovascular outcomes after sepsis is an intriguing finding that may signal a significant step toward identifying survivors of sepsis at high-risk for these outcomes. Future studies will show whether troponin levels alone or perhaps in combination with other biomarkers (e.g., markers of persistent inflammation or immunosuppression) will accurately identify patients that may benefit from targeted preventative interventions after hospital discharge. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Florian B. Mayr, M.D., M.P.H.
VA Pittsburgh Healthcare System
Pittsburgh, Pennsylvania
and
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Hallie C. Prescott, M.D., M.Sc.
University of Michigan
Ann Arbor, Michigan
and
VA Center for Clinical Management Research
Ann Arbor, Michigan

ORCID IDs: 0000-0002-2298-9011 (F.B.M.); 0000-0002-8442-6724 (H.C.P.).

References

1. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;351:2611–2618.
2. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang C-CH, *et al.* Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA* 2015;313:264–274.
3. Ou S-M, Chu H, Chao P-W, Lee Y-J, Kuo S-C, Chen T-J, *et al.* Long-term mortality and major adverse cardiovascular events in sepsis survivors. A nationwide population-based study. *Am J Respir Crit Care Med* 2016;194: 209–217.
4. Vallabhajosyula S, Jentzer JC, Geske JB, Kumar M, Sakhuja A, Singhal A, *et al.* New-onset heart failure and mortality in hospital survivors of sepsis-related left ventricular dysfunction. *Shock* 2018;49:144–149.
5. Yende S, Linde-Zwirble W, Mayr F, Weissfeld LA, Reis S, Angus DC. Risk of cardiovascular events in survivors of severe sepsis. *Am J Respir Crit Care Med* 2014;189:1065–1074.
6. Garcia MA, Rucci JM, Thai KK, Lu Y, Kipnis P, Go AS, *et al.* Association between troponin I levels during sepsis and postsepsis cardiovascular complications. *Am J Respir Crit Care Med* 2021;204:557–565.
7. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. *JAMA* 2019;321:602–603.
8. Bhavsar NA, Pura J, Navar AM, Hellkamp A, Muntner P, Maciejewski M, *et al.* Impact of look back period length on associations when using electronic health record data for epidemiologic research [abstract]. *Circulation* 2021; 143:AP112.
9. Reges O, Weinberg H, Hoshen M, Greenland P, Rayyan-Assi H, Avgil Tsadok M, *et al.* Combining inpatient and outpatient data for diagnosis of non-valvular atrial fibrillation using electronic health records: a validation study. *Clin Epidemiol* 2020;12:477–483.
10. Moss TJ, Calland JF, Enfield KB, Gomez-Manjarres DC, Ruminski C, DiMarco JP, *et al.* New-onset atrial fibrillation in the critically ill. *Crit Care Med* 2017;45:790–797.
11. Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. *BMJ* 2010;341:c3920.
12. Armstrong PW, Westerhout CM. Composite end points in clinical research: a time for reappraisal. *Circulation* 2017;135:2299–2307.
13. Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bögelein D, *et al.* Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care* 2010;14:R108.
14. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011;306:2248–2254.
15. Bosch NA, Cimini J, Walkey AJ. Atrial fibrillation in the ICU. *Chest* 2018;154: 1424–1434.
16. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L.; Canadian Critical Care Trials Group. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. *J Crit Care* 2012;27:326.e1–326.e8.
17. Yende S, Kellum JA, Talisa VB, Peck Palmer OM, Chang CH, Filbin MR, *et al.* Long-term host immune response trajectories among hospitalized patients with sepsis. *JAMA Netw Open* 2019;2:e198686.
18. Zhou X, Dudley SC Jr. Evidence for inflammation as a driver of atrial fibrillation. *Front Cardiovasc Med* 2020;7:62.
19. Lim W, Cook DJ, Griffith LE, Crowther MA, Devereaux PJ. Elevated cardiac troponin levels in critically ill patients: prevalence, incidence, and outcomes. Am J Critical Care Official Publ Am Assoc Critical-care Nurses 2006;15:280–288.
20. Docherty AB, Sim M, Oliveira J, Adlam M, Ostermann M, Walsh TS, *et al.* Early troponin I in critical illness and its association with hospital mortality: a cohort study. *Crit Care* 2017;21:216.
21. Siuba MT, Farkas JD. Against another nonspecific marker of perfusion. *Ann Am Thorac Soc* 2019;16:1334–1335.