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New-Onset Atrial Fibrillation as a Sepsis-Defining Organ Failure

To the Editor:

The Sepsis-3 (Third International Consensus Definitions for Sepsis and Septic Shock) task force defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). The concept of organ dysfunction was operationalized through the Sequential Organ Failure Assessment (SOFA) score, which assigns points to measures of six organ systems. The SOFA measure intended to represent cardiovascular dysfunction is calculated from blood pressure and vasopressor dose but does not consider other measures of cardiac dysfunction, such as new arrhythmias, during sepsis. However, the extent to which other potential measures of cardiac dysfunction with plausible sepsis-related mechanisms (2, 3), such as new-onset atrial fibrillation (AF) (4), may improve prognostication consistent with the conceptual model of Sepsis-3 is unclear. We hypothesized that new-onset AF during sepsis is a readily observable life-threatening organ dysfunction due to a dysregulated response to infection, and we tested this hypothesis by exploring the additional prognostic value of considering new AF during sepsis as a form of cardiovascular dysfunction within the current framework of Sepsis-3.

Methods

We used the MIMIC-III database (Medical Information Mart for Intensive Care III) (5, 6) from 2008 through 2012 to recreate methods used to derive the Sepsis-3 definition. Adult intensive care unit (ICU) patients with suspected infection were identified by concurrent orders for antibiotics and cultures (7). We identified new-onset AF temporally related to suspected infection (48 h before to 24 h after suspected infection) using previously validated (8) hourly nurse-documented cardiac rhythm.

We used univariable and multivariable logistic regression to evaluate predictive ability of new-onset AF (as a binomial variable) for hospital mortality. Multivariate models were analogous to those used to adjust for presepsis prognosis within the Sepsis-3 model (age, age squared, sex, race/ethnicity, Elixhauser comorbidity index score, Elixhauser comorbidity index score squared) and prognosis associated with sepsis-associated organ dysfunction (maximum SOFA score) (7). We evaluated the change in C-statistic and net reclassification improvement after adding new-onset AF to the Sepsis-3 model. We used β-coefficients for maximum SOFA score and new-onset AF to compare the number of SOFA "points" that new-onset AF may represent if considered as a form of sepsis-associated cardiac dysfunction. We performed a subgroup analysis to evaluate differences in mortality risk associated with new-onset AF among patients receiving vasopressors (SOFA score ≥ 2) or not (SOFA score <2). To determine which components of the SOFA score captured increased risk associated with new-onset AF, we evaluated the change in β-coefficient of new-onset AF after the addition of each SOFA component to the unadjusted model. To identify patients in whom new-onset AF may signal the onset of sepsis, we evaluated the number of patients with new-onset AF coincident with or antecedent to a change in SOFA greater than or equal to 2 (Sepsis-3 criteria).

All tests were two sided with α of 0.05. SAS version 9.4 software (SAS Institute Inc.) was used for statistical analyses. This study was designated by the Boston University Institutional Review Board as not human subjects research.

Results

Of the 9,528 patients with suspected infection, 233 (2.5%) developed new-onset AF after ICU admission (Table 1). New-onset AF was associated with increased hospital mortality in an unadjusted model (odds ratio [OR], 2.54; 95% confidence interval [CI], 1.94–3.32) and when added to the Sepsis-3 model (β-coefficient, 0.58; OR, 1.78; 95% CI, 1.34–2.38) (Table 2). Similarly, each 1-point increase in the maximum SOFA score was associated with an increased risk of hospital mortality in an unadjusted model (OR, 1.18; 95% CI, 1.16–1.20) and in the Sepsis-3 model that included new-onset AF (β-coefficient, 0.16; OR, 1.18; 95% CI, 1.16–1.19). Adding new-onset AF to

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Table 1. Demographics, severity of illness, and outcomes among patients with suspected infection

Characteristic	No New-Onset Atrial Fibrillation (*n* = 9,295)	New-Onset Atrial Fibrillation (*n* = 233)
Age, yr, mean (SD)	66.3 (16.5)	74.1 (12.8)
Female sex, *n* (%)	4,330 (46.6)	95 (40.8)
Race/ethnicity, *n* (%)		
Black	977 (10.5)	15 (6.4)
White	6,794 (73.1)	184 (79.0)
Hispanic	294 (3.2)	5 (2.1)
Asian	233 (2.5)	8 (3.4)
Other	245 (2.6)	3 (1.3)
Unknown	752 (8.1)	18 (7.7)
Hospital length of stay, d, median (25th, 75th quartiles)	9.7 (5.7–16.9)	11.0 (6.1–18.8)
ICU length of stay, d, median (25th, 75th quartiles)	3.9 (1.9–8.6)	4.9 (2.5–11.5)
ICU admission Elixhauser score (van Walraven modification), mean (SD)	9.6 (7.8)	10.2 (7.2)
Maximum daily SOFA score in the 48 h before to 24 h after suspected infection, mean (SD)	8.3 (3.8)	10.2 (4.1)
Died in hospital, *n* (%)	1,872 (20.1)	91 (39.1)
Died in ICU, *n* (%)	1,303 (14.0)	75 (32.3)

Definition of abbreviations: ICU = intensive care unit; SD = standard deviation; SOFA = Sequential Organ Failure Assessment.

the Sepsis-3 model increased the C-statistic (0.722 vs. 0.720; $P = 0.031$) and improved the net reclassification improvement by 1.3% (95% CI, 0.4–3.1%) for hospital mortality. New-onset AF showed similar associations with mortality among patients with cardiovascular SOFA scores less than 2 (OR, 1.72; 95% CI, 1.14–2.59) or greater than or equal to 2 (OR, 2.41; 95% CI, 1.63–3.56; P for interaction = 0.21). Addition of the cardiovascular SOFA score component to the unadjusted model decreased the β-coefficient of new-onset AF from 0.93 to 0.8 (13.7% change). Addition of the other SOFA components decreased the β-coefficient by less than 10%. New-onset AF developed in 33 patients coincident with or antecedent to meeting Sepsis-3 criteria.

Table 2. Nested model coefficients

Model	Variable	β-Coefficient	Odds Ratio (95% CI)	*P* Value
Unadjusted maximum SOFA score	Maximum SOFA score (per 1-point increase)	0.17	1.18 (1.16–1.20)	<0.001
Unadjusted new-onset AF	New-onset AF	0.93	2.54 (1.94–3.32)	<0.001
Sepsis-3 model	Maximum SOFA score	0.17	1.18 (1.16–1.20)	<0.001
	Age (per 1-yr increase)	0.004	1.02 (1.02–1.03)	0.66
	Age × age	0.0001	NA	0.14
	Female vs. male	−0.02	0.98 (0.88–1.09)	0.68
	Ethnicity/race			<0.001
	White vs. black	0.26	1.30 (1.08–1.57)	
	Hispanic vs. black	0.02	1.02 (0.70–1.49)	
	Asian vs. black	0.02	1.02 (0.69–1.50)	
	Other vs. black	0.24	1.28 (0.87–1.87)	
	Unknown vs. black	0.83	2.30 (1.81–2.94)	
	Elixhauser score (per 1-point increase)	0.06	1.05 (1.04–1.06)	<0.001
	Elixhauser score × Elixhauser score	−0.0007	NA	0.025
Sepsis-3 with new-onset AF	New-onset AF	0.58	1.78 (1.34–2.38)	<0.001
	Maximum SOFA score	0.16	1.18 (1.16–1.19)	<0.001
	Age (per 1-yr increase)	0.004	1.02 (1.02–1.03)	0.77
	Age × age	0.0001	NA	0.14
	Female vs. male	−0.02	0.98 (0.88–1.10)	0.76
	Ethnicity/race			<0.001
	White vs. black	0.26	1.30 (1.07–1.57)	
	Hispanic vs. black	0.02	1.02 (0.70–1.49)	
	Asian vs. black	0.01	1.02 (0.69–1.50)	
	Other vs. black	0.25	1.29 (0.88–1.88)	
	Unknown vs. black	0.84	2.31 (1.81–2.95)	
	Elixhauser score (per 1-point increase)	0.06	1.05 (1.04–1.06)	<0.001
	Elixhauser score × Elixhauser score	−0.0007	NA	0.025

Definition of abbreviations: AF = atrial fibrillation; CI = confidence interval; NA = not applicable; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock; SOFA = Sequential Organ Failure Assessment.

Discussion

Our findings suggest that new-onset AF during suspected infection meets the Sepsis-3 conceptual criteria of an acute organ (cardiac) dysfunction associated with a high risk of mortality. Among critically ill patients, new-onset AF showed small improvements in prognostic validity as compared with the Sepsis-3 model and potentially identified "sepsis" before Sepsis-3 criteria in a small number of ICU patients. New-onset AF was associated with increased mortality proportionate to an increase in SOFA score of ~4 points.

Our findings have limitations. Our ICU cohort likely underestimated the number of patients who developed new-onset AF before meeting Sepsis-3 sepsis criteria, because our patients likely had higher SOFA scores than a non-ICU population. Similarly, the rate of new-onset AF in our study was lower than previous estimates of rates of new-onset AF in critically ill patients with sepsis (4), likely due to cases of new-onset AF that occurred before ICU admission that were coded as preexisting AF using our algorithm. Thus, our findings likely represent conservative estimates. Further studies should examine how new-onset AF may affect prognostic validity outside the ICU.

Our study highlights strengths of the conceptual model of Sepsis-3, as well as limitations of the SOFA score as an operational sepsis definition. The concept that sepsis may be defined as organ dysfunction related to a dysfunctional response to infection provides a framework for including new information within the Sepsis-3 definition. However, the SOFA score was not intended to provide an account of all organ dysfunction or to provide the best predictive model during sepsis; it was chosen to represent sepsis-associated organ dysfunction for its simplicity and familiarity (1). Similar to new-onset AF, there are possibly other infection-associated, life-threatening manifestations of organ dysfunction that incrementally improve prognostication and thus may be considered as "sepsis-defining organ dysfunction" and included in future concepts of "sepsis." Given plausible mechanisms linking infection to new-onset AF (2, 3) and the high risk of death among patients with new-onset AF and suspected infection, we suggest that future sepsis investigators continue to explore new-onset AF as a potentially sepsis-defining sign of cardiac dysfunction.

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Against Another Nonspecific Marker of Perfusion

To the Editor:

We read with interest the article by Frencken and colleagues and the accompanying editorial by Bonk and Meyer regarding the use of high-sensitivity troponin (hs-Tn) in pneumonia (1, 2). We applaud the authors on their publication of useful manuscripts regarding this emerging topic.

Elevated troponin levels are found in nearly half of critically ill patients, using standard troponin assays (3). Thus, it comes as little surprise that 85% of critically ill patients with pneumonia would have an elevated hs-Tn level. The challenge facing clinicians has to do with how to use these data. The pathophysiology of troponin elevation in this context is multifactorial (e.g., including inflammatory injury to myocytes, as

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