A Comparative Analysis of Sepsis Identification Methods in an Electronic Database*

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Objectives: To evaluate the relative validity of criteria for the identification of sepsis in an ICU database.

Design: Retrospective cohort study of adult ICU admissions from 2008 to 2012.

Setting: Tertiary teaching hospital in Boston, MA.

Patients: Initial admission of all adult patients to noncardiac surgical ICUs.

Interventions: Comparison of five different algorithms for retrospectively identifying sepsis, including the Sepsis-3 criteria.

Measurements and Main Results: 11,791 of 23,620 ICU admissions (49.9%) met criteria for the study. Within this subgroup, 59.9% were suspected of infection on ICU admission, 75.2% of admissions had Sequential Organ Failure Assessment greater than or equal to 2, and 49.1% had both suspicion of infection and Sequential Organ Failure Assessment greater than or equal to 2 thereby meeting the Sepsis-3 criteria. The area under the receiver operator characteristic of Sequential Organ Failure Assessment (0.74) for hospital mortality was consistent with previous studies of the Sepsis-3 criteria. The Centers for Disease Control and Prevention, Angus, Martin, Centers for Medicare & Medicaid Services, and explicit coding methods for identifying sepsis revealed respective sepsis incidences of 31.9%, 28.6%, 14.7%, 11.0%, and 9.0%. In-hospital mortality increased with decreasing cohort size, ranging from 30.1% (explicit codes) to 14.5% (Sepsis-3 criteria). Agreement among the criteria was acceptable (Cronbach's alpha, 0.40–0.62).

Conclusions: The new organ dysfunction-based Sepsis-3 criteria have been proposed as a clinical method for identifying sepsis. These criteria identified a larger, less severely ill cohort than that identified by previously used administrative definitions. The Sepsis-3 criteria have several advantages over prior methods, including less susceptibility to coding practices changes, provision of temporal context, and possession of high construct validity. However, the Sepsis-3 criteria also present new challenges, especially when calculated retrospectively. Future studies on sepsis should recognize the differences in outcome incidence among identification methods and contextualize their findings according to the different cohorts identified. (*Crit Care Med* 2018; 46:494–499)

Key Words: critical care; organ failure; sepsis

***See also p. 640.**

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Sepsis is a major and economically significant disease in the ICU, costing over $20 billion in the United States in 2011 (5.2% of all U.S. hospital costs) (1), with costs growing to over $23 billion in 2013 (6.2% of all U.S. hospital costs) (2). The European Society of Intensive Care Medicine/Society of Critical Care Medicine Third International Consensus Definitions for Sepsis and Septic Shock task force (the Sepsis-3 task force) recently defined sepsis as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" (3). Analyzing retrospective databases, the authors proposed and evaluated new clinical criteria for detection of sepsis: an increase of greater than or equal to 2 Sequential Organ Failure Assessment (SOFA) score points in a defined temporal context of suspected infection (3, 4). These new criteria were further validated in a dataset of 184,875 adults in ICUs across Australia and New Zealand (5). Although the utility of the Sepsis-3 criteria for clinical care is still being deliberated upon (6), to date, little research has focused on application of the new criteria to identify septic patients in electronic health records (EHRs).

The penetration of EHRs has dramatically increased in the United States, from 9.4% in 2008 to 83.8% in 2015, a nine-fold increase (7). Research using EHRs is becoming progressively more important and has the potential for making decision-making more precise, more robust, and more personal. Past criteria for sepsis using EHRs mainly used administratively assigned billing codes, with the research focused on the epidemiology of sepsis (8, 9). The criteria as proposed by the Sepsis-3 task force offer an attractive operational definition of sepsis in retrospective observational research because they are objectively quantifiable, incorporate an approximation for the start time of clinical concern as opposed to classifying entire hospitalizations, and are based directly on the physiologic data rather than captured indirectly via administrative codes. Our study aims to examine previously employed administrative criteria for retrospective identification of patients with sepsis and compare these with the new Sepsis-3 criteria.

MATERIAL AND METHODS

Study Population

Study data were acquired from the Medical Information Mart in Intensive Care (MIMIC)-III database v1.4 (10). MIMIC-III is a large, openly available deidentified dataset comprised of patients admitted to the Beth Israel Deaconess Medical Center (BIDMC, Boston, MA). The database encompasses admissions between 2001 and 2012. Use of the MIMIC-III database was approved by Institutional Review Boards of BIDMC and Massachusetts Institute of Technology. Data extraction adhered to the original Sepsis-3 study as closely as possible (3, 4). We focused on ICU admissions from years 2008 to 2012 for three reasons: antibiotic prescriptions are only recorded from 2003 onward; explicit sepsis codes were introduced at BIDMC in 2004; the group of admissions between 2008 and 2012 are easily identifiable in the database (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D208; **Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D208).

A total of 23,620 ICU admissions were analyzed; of these, we excluded three nonadults, 7,536 secondary (or greater) admissions for patients to avoid repeated measures, 2,298 admissions to the cardiothoracic surgical service since their postoperative physiologic derangements do not translate to the same mortality risk as the other ICU patients, and 18 admissions with missing data. We excluded patients suspected of infection more than 24 hours before ICU admission as MIMIC-III only contains ICU data (excludes 1,250 patients), and more than 24 hours after ICU admission as we chose to focus the majority of patients who are admitted to the ICU with sepsis (excludes 824 patients). The final cohort contained 11,791 patients.

Outcomes

As in Seymour et al (4), our primary outcome was hospital mortality and the secondary outcome was a composite of hospital mortality and/or prolonged (≥3 d) ICU length of stay (LOS).

Variables

In our study, we precisely replicated the Sepsis-3 task force (3, 4) definition of suspected infection as the acquisition of a body fluid culture temporally contiguous to administration of antibiotics. Other data extracted included patient demographics and all necessary variables for calculating SOFA scores (11), which were calculated using data from the first 24 hours of the ICU stay. The Sepsis-3 criteria for sepsis were extracted as suspected infection with associated organ dysfunction (SOFA ≥ 2). Five other definitions of sepsis were extracted: 1) explicit criteria: the presence of at least one of the two proposed *International Classification of Diseases*, 9th revision (ICD-9), codes explicitly mentioning sepsis (995.92, severe sepsis and 785.52, septic shock); 2) Angus methodology: ICD-9 codes for sepsis as proposed by Angus et al (8); 3) Martin methodology: ICD-9 codes proposed by Martin et al (9); 4) the Centers for Medicare & Medicaid Services (CMS) criteria: an adaptation of the CMS Severe Sepsis and Septic Shock Management Bundle (National Quality Forum no. 0500) which uses a combination of diagnostic ICD-9 codes, Systemic Inflammatory Response Syndrome (SIRS) criteria, and specific thresholds for organ dysfunction (12); and 5) the Centers for Disease Control and Prevention (CDC) complete surveillance criteria, which use suspicion of infection criteria that are identical to Sepsis-3 along with organ dysfunction criteria that are similar (but not identical) to SOFA (13).

Analysis

Demographics for the cohort were extracted. The cohort was also grouped by survival at hospital discharge, and statistical comparison between these groups was done using the two sample *t* test, Pearson's X^2 test, or the Mann-Whitney-Wilcoxon *U* test, as indicated. We evaluated SOFA against primary and secondary outcomes. The discrimination of SOFA was evaluated using the area under the receiver operator characteristic (AUROC) curve. We compared the population identified by the Sepsis-3 criteria with other populations identified by three methods: visually, using Cronbach's alpha, and via their relationship to the primary and secondary outcomes. Statistical significance was set at the 0.001 level as in Seymour et al (4).

As MIMIC-III is open to the public, our study is completely accessible, reproducible, and available online (14).

RESULTS

Demographics of the population studied are provided (**Table 1**). Of the 11,791 patients, 75.2% (9,323) had a SOFA score greater than or equal to 2 during their first ICU day. Median age was 64.5 years (Q1–Q3, 51.1–78.5 yr), and mean body mass index (BMI) was 28.7 kg/m^2 (SD, 8.4 kg/m^2). Median ICU LOS was 1.9 days (Q1–Q3: 1.1–3.5 d), and hospital mortality was 10.8%. All demographic items had significant differences between survivors and nonsurvivors except gender and BMI.

Hospital mortality was higher for patients with SOFA greater than or equal to 2 (13.2%) than those with SOFA less than 2 (3.6%); the secondary outcome, a composite of in-hospital mortality and/or ICU LOS greater than or equal to 3

TABLE 1. Demographics of the Cohort for All 11,791 ICU Stays, as Well as Demographics for Stays When Grouped into Survival and Nonsurvival at Hospital Discharge

Variables	All Patients (*n* = 11,791)	Survivors (*n* = 10,514)	Nonsurvivors (*n* = 1,277)	*p*
Age (yr), median (25–75th percentiles)	64.5 (51.1–78.5)	63.3 (50.0–77.5)	74.9 (61.8–83.7)	< 0.001
Male, *n* (%)	6,478 (54.9)	5,795 (55.1)	683 (53.5)	0.28
Body mass index (kg/m^2), mean ± SD	28.7 ± 8.4	28.7 ± 8.2	28.1 ± 10.1	0.17
Race, *n* (%)				< 0.001
White	8,497 (72.1)	7,630 (72.6)	867 (67.9)	
Black	1,110 (9.4)	1,036 (9.9)	74 (5.8)	
Hispanic	457 (3.9)	424 (4.0)	33 (2.6)	
Elixhauser index	1 (–1 to 6)	0 (–1 to 6)	5 (0–10)	< 0.001
Systemic Inflammatory Response Syndrome	3 (2–3)	3 (2–3)	3 (3–4)	< 0.001
Sequential Organ Failure Assessment	3 (2–5)	3 (1–5)	6 (4–10)	< 0.001
Mechanical ventilation, *n* (%)	4,149 (35.2)	3,273 (31.1)	876 (68.6)	< 0.001
ICU length of stay (d), median (25–75th percentiles)	1.9 (1.1–3.5)	1.9 (1.1–3.2)	2.4 (1.1–5.6)	< 0.001
30-d mortality, *n* (%)	1,619 (13.7)	375 (3.6)	1,244 (97.4)	< 0.001
Hospital mortality, *n* (%)	1,277 (10.8)	0 (0)	1,277 (100)	< 0.001

Systemic Inflammatory Response Syndrome (score ranges between 0 and 4), Sequential Organ Failure Assessment (score ranges between 0 and 24), Elixhauser index: summarizes the degree of comorbid burden for the patient with higher scores indicate higher levels of comorbidity (score ranges between –36 and 51).

days, occurred in two fifths (41.2%) of patients. Patients suspected of infection had higher hospital mortality (12.5% vs 8.3%). Examining only these patients, SOFA had an AUROC of 0.74 (95% CI, 0.72–0.76; primary outcome) and 0.69 (95% CI, 0.68–0.70; secondary outcome).

The Sepsis-3 criteria identified the largest cohort of patients (49.1%, 5,784 cases), followed by CDC (31.9%, 3,761), Angus (28.6%, 3,368), Martin (14.7%, 1,734), CMS (11.0%, 1,302), and explicit (9.0%, 1,062). The in-hospital mortality rate was highest in explicit (31.4%), followed by CMS (27.2%), Martin (23.4%), CDC (18.6%), Angus (17.7%), and Sepsis-3 (14.7%). **Figure 1** shows these trends graphically. The rankings for the composite outcome of mortality and long ICU LOS were similar, with the exception of the CDC and Martin criteria being transposed (**Table 2**).

Figure 2 shows three-set Venn diagrams for the criteria assessed. Figure 2*A* compares Sepsis-3, Angus, and Martin. All three criteria were satisfied by 1,420 patients (12%), whereas 5,488 patients (46.2%) did not satisfy any. Very few patients were identified by Martin alone (0.5%, 58), and similarly few for Angus (3.4%, 399). Figure 2*B* compares Sepsis-3, CDC, and CMS: 51.5% satisfied at least one criterion; 9.0% satisfied all three criteria. The majority of patients who satisfied CDC also satisfied Sepsis-3 (3,521 patients, 93.6%), and similarly those who satisfied CMS usually also satisfied Sepsis-3 (1,228 patients, 94.3). The explicit criteria, not shown in Figure 2, were entirely subsumed by Angus criteria and almost entirely subsumed by Martin criteria (**Supplemental Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/D208). Cronbach's alpha for Sepsis-3 varied from acceptable (0.40–0.49 vs explicit, CMS, Martin) to good (0.62 vs Angus and 0.76 vs CDC) (**Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/D208).

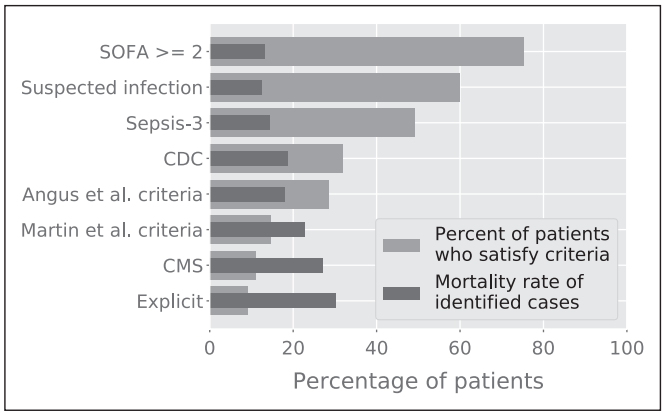

Figure 1. Percentage of patients detected by the criteria are shown in the *wider light gray bar,* and the mortality rate of these patients is shown in the *thinner dark gray bar.* Actual values are available in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/D208). CDC = Centers for Disease Control and Prevention, CMS = Centers for Medicare & Medicaid Services, SOFA = Sequential Organ Failure Assessment.

DISCUSSION

Current large-scale EHR sepsis identification frequently rests on administrative coding primarily done for billing. In contrast, the Sepsis-3 criteria primarily rely on the assembly of

TABLE 2. Percentage of Patients Identified by the Various Sepsis Criteria and the Outcome Frequency for the Subgroups Identified

Criteria	Patients Who Satisfy Criteria, *n* (%)	In-Hospital Mortality for Positive Cases (%)	In-Hospital Mortality for Negative Cases (%)	Composite Outcome for Positive Cases (%)	Composite Outcome for Negative Cases (%)
Sequential Organ Failure Assessment ≥ 2	8,869 (75.2%)	13.20	3.60	41.20	19.20
Suspected of infection	7,061 (59.9)	12.50	8.30	46.30	19.90
Sepsis-3	5,784 (49.1)	14.50	7.30	50.00	21.90
Centers for Disease Control and Prevention	3,761 (31.9)	18.60	7.20	61.10	23.80
Angus et al (8)	3,368 (28.6)	17.90	8.00	61.20	25.50
Martin et al (9)	1,734 (14.7)	22.70	8.80	60.10	31.50
Centers for Medicare & Medicaid Services	1,302 (11.0)	27.20	8.80	64.70	32.10
Explicit	1,062 (9.0)	30.10	8.90	70.70	32.20

The composite outcome is defined as in-hospital mortality and/or ICU length of stay ≥ 3 days.

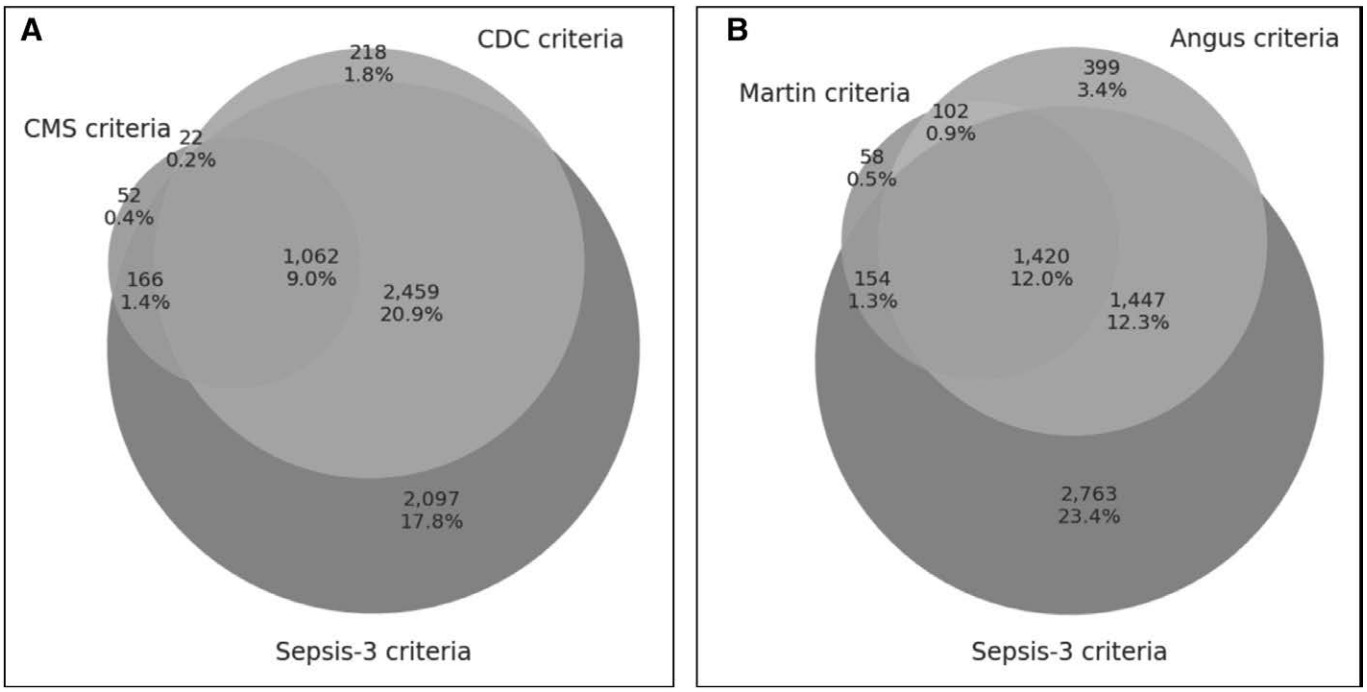

Figure 2. Venn diagrams comparing overlap in populations identified by criteria presented. **A**, Martin et al (8), Angus et al (9), and Sepsis-3 criteria: 6,343 patients (53.8%) were captured by at least one criterion, whereas 1,420 patients (12.0%) satisfied all criteria. **B**, Centers for Medicare & Medicaid Services (CMS), Centers for Disease Control and Prevention (CDC), and Sepsis-3 criteria: 6,076 patients (51.5%) satisfied at least one of the criteria, whereas 1,062 patients (9.0%) satisfied all criteria.

contributory data elements based on physiology, via the SOFA score, and clinical practice, via the definition of suspicion of infection.

We calculated the AUROC of SOFA for both the primary outcome (hospital mortality) and the secondary outcome (composite outcome of ICU LOS greater than or equal to 3 d or hospital mortality). Our reported AUROC of 0.74 for SOFA against in-hospital mortality is similar to that of Seymour et al (0.74) (4) and Raith et al (0.75) (5), though it is worth noting that our AUROC of SOFA against the secondary outcome (0.69) was lower than that of Raith et al (0.74) (5). These results give confidence in our replication of the Sepsis-3 criteria.

We found important disparities in the identification of sepsis using the various approaches. When examining different methodologies for retrospectively identifying patients with sepsis, cohort sizes varied from small (explicit: 1,062 patients, 9.0% of the entire cohort) to almost half of all

patients (Sepsis-3: 5,784 patients, 49.1% of the entire cohort). Among purely administrative definitions (Angus, Martin, explicit), we found similar disparities (Fig. 1). Iwashyna et al (15) assessed variance in cohort sizes for only these administrative criteria and further performed an expert chart review of a subset of these records. The authors found that the explicit criteria identified a pure cohort (100% positive predictive value) but missed the vast majority of septic patients (9.2% sensitivity). Iwashyna et al (15) also found that the Angus methodology identified a larger population of septic patients (50.3% sensitivity) but at a cost of fidelity (70.7% PPV). Our results appear consistent with the conclusions of Iwashyna et al (15) in that mortality rate ran roughly in reverse order of cohort size, and we are able to extend their results to the CMS, CDC, and Sepsis-3 criteria. This could imply that the more restrictive cohorts represent sicker, higher risk segments of the population. Sepsis-3 identified the largest cohort in our study, and this cohort mostly encapsulated those identified by other criteria (Fig. 2). Only 4.8% of patients were identified by the approaches of Angus and Martin but not by Sepsis-3 (Fig. 2*A*), and only 2.2% were identified only by the methodologies from CMS and CDC (Fig. 2*B*). We posit that Sepsis-3, in general, identifies a larger and likely less "pure" cohort of septic patients, but one that still remains at higher risk of mortality (14.5% vs 7.3%) and higher risk of composite mortality/excess LOS (50.0% vs 21.9%).

Another advantage of the Sepsis-3 criterion is the temporal context it provides. All other criteria used billing (ICD-9) codes which are typically assigned on hospital discharge and are not time stamped within the stay. Consequently, these administrative criteria are only capable of identifying sepsis for entire hospitalizations and cannot be used to assess the time course of the disease. In contrast, the algorithm for Sepsis-3 requires the delineation of a time point at which the patient may be septic (suspected of infection with associated organ failure). This time point could be useful in retrospective assessment of the trajectory of the patient's illness. It is worth noting that this defined onset time may occur later in the course of the illness than optimally desirable for clinical detection (6), and alternative criteria may be necessary depending on the desired application.

Lastly, Sepsis-3 is also advantageous as it better aligns with the contemporary understanding of the pathophysiology of sepsis. Angus et al (16) have proposed a framework to assess sepsis criteria, and Seymour et al (13) provided a case study using this framework. Briefly, the Sepsis-3 criteria for sepsis demonstrate content validity (agreement with contemporary understanding of sepsis), construct validity (agreement with similar previously used definitions), and criterion validity (identification of a cohort at risk of death). We provide a more detailed assessment in the **Supplemental Material** (Supplemental Digital Content 1, http://links.lww.com/CCM/D208), and we refer the interested reader there.

Overall, Sepsis-3 appears to present usable and viable criteria for retrospectively identifying septic patients in EHRs for the three reasons discussed: 1) it is consistent with other criteria, 2) it is timely, and 3) it satisfies many forms of validity. However, there are some limitations to the Sepsis-3 criteria. Both the Sepsis-3 and the CDC criteria rely on treatments as surrogates for organ failure. More importantly for Sepsis-3, the retrospective definition of suspicion of infection is entirely dependent the actions of the clinician. As a result, the test lacks "meta-reliability," that is, it is susceptible to changes unrelated to the biology of the patient.

Organ failure as captured by SOFA (and used by Sepsis-3) also has limitations. The neurologic component uses the Glasgow Coma Scale, which has known issues regarding interrater reliability and use/scoring in intubated and/or sedated patients (17). The respiratory component requires an arterial blood gas and uses a low Pa_{O_2}/F_{IO_2} ratio as a marker of severity of illness. This measurement requires a known, specialized source of oxygen for accurate measurement of F_{IO_2} and thus is variably accurate across different treatment regimens (18). Finally, the cardiovascular component is primarily determined by the type and rate of vasopressor administration, and not on the degree of organ failure; thus scoring is susceptible to the clinician's propensity for certain interventions. The cardiovascular component of SOFA is scored as 2 if a patient is administered low-dose dopamine, though this is infrequently done in contemporary clinical practice. All of these issues are rooted in the inherent difficulty of quantifying the level of organ dysfunction when patients are intensively treated. In the absence of advances in direct quantification of organ function, carefully conceived simplifications of current criteria could improve robustness to variation in clinical practice and may improve construct validity. For example, instead of quantifying the level of organ dysfunction based on the type and dose of vasopressor (as is done in SOFA), criteria could be simplified to use of any vasopressor (such as in the CDC definition).

Our study has several limitations. First, our results are limited to a single tertiary medical center. Second, we excluded patients suspected of infection more than 24 hours before or after ICU admission, and our results are limited to patients admitted to the ICU with sepsis. We did not address the use of the SIRS criteria for sepsis identification as these criteria are not intended to independently identify septic patients (19). Finally, knowledge of sepsis continues to develop, and the evaluation in this work rests vulnerably upon universal agreement of what sepsis is, how it is defined clinically, and precisely how the applicable terminologies are documented.

CONCLUSIONS

Current identification of sepsis within the United States, outside of individual chart review, frequently relies on proxies such as administrative coding primarily done for billing. The advent of large EHR databases allows for finer grained classification of sepsis using new methods based on patient physiology. Taking advantage of a publicly available EHR, we have demonstrated that administrative and physiology-based approaches result in cohorts of severely ill patients with variable outcome frequencies. Among methods assessed here, the Sepsis-3 criteria identified the largest, healthiest cohort. As more clinical research is performed on routinely collected

patient data, it becomes progressively more important to develop standardized criteria that can identify sepsis in a consistent, reliable, and usable manner.

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This article is dedicated to the memory of Sean A. Yemen, MD.

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