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High-performance detection and early prediction of septic shock for alcohol-use disorder patients

Jacob Calvert [a], Thomas Desautels [a], Uli Chettipally [b, c], Christopher Barton [c], Jana Hoffman [a], Melissa Jay [a], Qingqing Mao [a], Hamid Mohamadlou [a], Ritankar Das [a, *]

[a] Dascena Inc., Hayward, CA, USA
[b] Kaiser Permanente South San Francisco Medical Center, South San Francisco, CA, USA
[c] Department of Emergency Medicine, University of California San Francisco, San Francisco, CA, USA

HIGHLIGHTS

- At 93% sensitivity, *InSight* reduces false alarms by >80% over other detection tools.
- *InSight*'s diagnostic odds ratio is >30X those of MEWS, SAPS II, SIRS for detection.
- *InSight* outperforms comparable methods for septic shock prediction hours before onset.

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ABSTRACT

Background: The presence of Alcohol Use Disorder (AUD) complicates the medical conditions of patients and increases the difficulty of detecting and predicting the onset of septic shock for patients in the ICU.
Methods: We have developed a high-performance sepsis prediction algorithm, *InSight*, which outperforms existing methods for AUD patient populations. *InSight* analyses a combination of singlets, doublets, and triplets of clinical measurements over time to generate a septic shock risk score. AUD patients obtained from the MIMIC III database were used in this retrospective study to train *InSight* and compare performance with the Modified Early Warning Score (MEWS), the Simplified Acute Physiology Score (SAPS II), and the Systemic Inflammatory Response Syndrome (SIRS) for septic shock prediction and detection.
Results: From 4-fold cross validation, *InSight* performs particularly well on diagnostic odds ratio and demonstrates a relatively high Area Under the Receiver Operating Characteristic (AUROC) metric. Four hours prior to onset, *InSight* had an average AUROC of 0.815, and at the time of onset, *InSight* had an average AUROC value of 0.965. When applied to patient populations where AUD may complicate prediction methods of sepsis, *InSight* outperforms existing diagnostic tools.
Conclusions: Analysis of the higher order correlations and trends between relevant clinical measurements using the *InSight* algorithm leads to more accurate detection and prediction of septic shock, even in cases where diagnosis may be confounded by AUD.

1. Introduction

Alcohol Use Disorder (AUD) encompasses alcohol dependency, abuse, and addiction [1]. In the United States, AUD affects over 18 million people, and can lead to increased severity of illness for a variety of conditions [2,3]. AUD is estimated to be present in between 10% and 33% of patients in the Intensive Care Unit (ICU) [2]. AUD patients have increased hospital stays by 2.4 days on average, and are up to 8% more likely to experience unplanned rehospitalization within 30-days of discharge [4,5]. According to the World Health Organization, "In 2012, about 3.3 million net deaths, or 5.9% of all global deaths, were attributable to alcohol consumption. 139 million net DALYs (disability-adjusted life years), or 5.1% of the global burden of disease and injury, were attributable to alcohol consumption." [6] Through increased complications [7] and longer

* Corresponding author. Dascena Inc., 1135 Martin Luther King Drive, Hayward, CA 94541, USA.
E-mail address: ritankar@dascena.com (R. Das).

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length of stays, AUD increases costs and burdens on the health care system [8,9].

Sepsis has been one of the leading causes of death in the United States for over a decade [10,11]. It is a major public health concern, costing over $20 billion per year in the U.S. alone [12]. New definitions for sepsis and septic shock have recently been introduced, in an effort to simplify and streamline the clinical diagnoses of sepsis [13]. While these new definitions may prove useful and eventually find wide adoption, they are currently still under debate. Therefore for the purposes of this manuscript we have utilized the standard definitions of sepsis, severe sepsis, and septic shock, which are summarized in Table 1.

Patients with AUD are 1.7 times more likely to develop any healthcare associated infection, including sepsis, than patients who do not have AUD [18]. In particular, AUD is known to complicate and exacerbate infections and sepsis in hospitalized patients [19,20]. Although the relationships between AUD, septic shock, and infections are still being explored, increased sepsis mortality in patients with AUD may be impacted by the effects of AUD on cortisol and cytokine production [21]. The exact pathophysiologic mechanisms for the increased risk of sepsis and adverse outcomes in the AUD patient have not clearly been elucidated but a number of potential mechanisms (specific and general) have been suggested. These include the compromise of cellular immune function [22] and the alteration in the ratio of T1 helper cells to T2 helper cells [23]. Abuse of alcohol also directly affects the functioning of macrophages [24]. Complicating the recognition of emerging septic shock, AUD patients often suffer from chronic hypertension [25]. Therefore hypotension, which correlates with septic shock [17], may be difficult to identify among patients in the AUD subpopulation. Additionally, lactate, a common biomarker test which is used in the recently proposed updated septic shock definition [13,26], may be inaccurate for AUD patients [27] because patients with AUD often suffer from chronic lactic acidosis [28,29]. While this study was not meant to explore or explain the pathophysiologic mechanisms of sepsis and failure in AUD patients, it does recognize and attempt to correlate the clinical presentation of these patients and propose methods to identify those at risk for sepsis and septic shock before they have fully manifested themselves.

The higher costs and increased risks from sepsis and septic shock in the AUD population, in conjunction with suboptimal existing septic shock diagnostic screening performance, demonstrate the need for improved risk scoring systems for septic shock in AUD patients. Here, we analyze the performance of a risk scoring system, *InSight*, when detecting and predicting septic shock onset for AUD patients. We have determined to use septic shock as the gold standard for the *InSight* program because accurate identification and prediction of septic shock is crucial for the timely administration of antibiotics and supportive treatments to reduce mortality [30]. Additionally, the onset time of septic shock is well defined, and thus provides a clear time point for predictive assessment. We will demonstrate that *InSight* outperforms existing methods in discriminating between septic shock and non-septic shock patients, as well as providing early warning of impending septic shock onset.

2. Methods

2.1. Data set

The Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) III database [31] was queried to obtain the 29,083 patients used in *InSight* training and testing. MIMIC III contains de-identified patient records collected from Beth Israel Deaconess Medical Center during the years 2001–2012. We filtered a total of 61,532 MIMIC III ICU stays to obtain patients aged 15 or more years with admission to any of the intensive care units (the age filter primarily excludes neonatal ICU patients and a handful of pediatric cases), and with at least one observation of the following measurements: blood oxygen saturation, heart rate, pH, pulse pressure, respiration rate, systolic blood pressure, temperature, and white blood cell count. We also recorded the presence of ICD-9 codes for septic shock (785.52) and of alcohol abuse and related conditions (291.X, 291.XX, 303.XX, 305.XX, 357.5, 425.5, 535.3X, 571.2, and 571.3, where X denotes a wildcard).

2.2. Gold standard

Patients were assigned outcomes of septic shock upon meeting the following, hierarchical definition. Septic shock was identified using the following criteria: (1) SIRS criteria score $\geq$ 2, [16] (2) presence of an infection-related ICD-9 code, (3) organ dysfunction, (4) systolic blood pressure below 90 mmHg for at least 1 hour, and (5) total fluid replacement $\geq$1200 mL or $\geq$20 mL/kg for 24 hours. Combined with the requirement that patients have an AUD-related ICD-9 code, a total of 270 ICU stays were associated with AUD patients who also contracted septic shock, giving a prevalence of 0.9%. This prevalence is reasonable since septic shock and AUD prevalences are roughly 10% each and, assuming independence, a 1% net prevalence would be expected.

2.3. InSight training, score assignment, and comparison with MEWS and SIRS

InSight performs multidimensional analysis on streams of patient measurements. When working with these patient time-series data, we used a standard time resolution of one hour. We used the most recent value of measurements that were not updated by the end of each hour period. For singlet measurements, we fit a continuous function approximating the measurement value-conditioned probability distribution of the gold standard outcome. Doublets and triplets of measurement trends were binned according to heuristic tables. These tables associate a bin's empirical septic shock risk with ranges of measurement values, similar to the calculation of Modified Early Warning Score (MEWS) [32]. In the next step, we estimated the correlation between each feature and septic shock for AUD patients. The features were weighted by these correlations, then all of the measurements, singlet, doublet, and triplet trends were summed. Finally, these aggregates were combined through logistic regression, in order to assign risk scores which best reflect training data. This process and

Table 1
Classification of sepsis, severe sepsis, and septic shock.

Classification	Clinical indication
Sepsis [14,15]	Documented or suspected infection Dysregulated host response SIRS criteria are common indicator
Severe sepsis [16]	Sepsis-induced organ dysfunction or tissue hypoperfusion
Septic shock [17]	Severe sepsis with hypotension despite adequate fluid resuscitation