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Sepsis as 2 problems: Identifying sepsis at admission and predicting onset in the hospital using an electronic medical record–based acuity score☆,☆☆

Michael Rothman [a,*], Mitchell Levy [b], R. Philip Dellinger [c], Stephen L. Jones [d], Robert L. Fogerty [e], Kirk G. Voelker [f], Barry Gross [g], Albert Marchetti [h], Joseph Beals IV [a]

[a] PeraHealth, Inc, 6302 Fairview Rd, Suite 310, Charlotte, NC, 28203
[b] Alpert Medical School at Brown University, Providence, RI
[c] Cooper Medical School of Rowan University, Cooper University Health, Camden, NJ
[d] Houston Methodist Hospital, Weill Cornell Medical College, Houston, TX
[e] Yale School of Medicine, New Haven, CT
[f] Sarasota Memorial Hospital, Sarasota, FL
[g] Riverside Regional Medical Center, Newport News, VA
[h] Rutgers New Jersey Medical School, MedERA, Inc., Newark, NJ

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ABSTRACT

Purpose: Early identification and treatment improve outcomes for patients with sepsis. Current screening tools are limited. We present a new approach, recognizing that sepsis patients comprise 2 distinct and unequal populations: patients with sepsis present on admission (85%) and patients who develop sepsis in the hospital (15%) with mortality rates of 12% and 35%, respectively.

Methods: Models are developed and tested based on 258 836 adult inpatient records from 4 hospitals. A "present on admission" model identifies patients admitted to a hospital with sepsis, and a "not present on admission" model predicts postadmission onset. Inputs include common clinical measurements and the Rothman Index. Sepsis was determined using *International Classification of Diseases, Ninth Revision,* codes.

Results: For sepsis present on admission, area under the curves ranged from 0.87 to 0.91. Operating points chosen to yield 75% and 50% sensitivity achieve positive predictive values of 17% to 25% and 29% to 40%, respectively. For sepsis not present on admission, at 65% sensitivity, positive predictive values ranged from 10% to 20% across hospitals.

Conclusions: This approach yields good to excellent discriminatory performance among adult inpatients for predicting sepsis present on admission or developed within the hospital and may aid in the timely delivery of care.

1. Introduction

Sepsis is a complex illness with controversies embedded in its classification, epidemiology, presentation, diagnosis, and treatment. The past 3 decades have witnessed significant developments in the definition and conceptual understanding of the pathobiology of this condition [1-3]. Over this time, the reported incidence of inpatient sepsis, especially severe sepsis (infection-induced organ dysfunction or tissue hypoperfusion), has increased, whereas related case-rate mortality has decreased [4-8]. These trends are variously attributed to heightened awareness, enhanced screening [9-11], improved critical care services, proliferation of treatment bundles, and vigorous application of early goal-directed therapies [6-8,12]. Simultaneously, the health care ecosystem has evolved [13,14], with a growing emphasis on case identification [6,8] driven by changes in diagnostic coding practices and policy-based regulations that mandate hospital sepsis protocols [15]. Collectively, these changes have produced a "denominator effect," transforming sepsis populations into larger, less severely ill groups of patients, many of whom are not easily distinguished from the general patient populations [4,6,8,16].

An important distinction can be drawn between patients with sepsis present on admission to the hospital (POA) and patients who develop sepsis in the hospital, that is, not present on admission (NPOA).

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* Corresponding author at: PeraHealth, 6302 Fairview Rd, Suite 310, Charlotte, NC, 28203, USA. Tel.: +1 845 223 3900; fax: +1 845 223 5814.

E-mail addresses: mrothman@perahealth.com (M. Rothman), mitchell_levy@brown.edu (M. Levy), dellinger-phil@cooperhealth.edu (R.P. Dellinger), sljones2@houstonmethodist.org (S.L. Jones), robert.fogerty@yale.edu (R.L. Fogerty), kirk-voelker@smh.com (K.G. Voelker), barry.gross@rivhs.com (B. Gross), albertmarchetti@yahoo.com (A. Marchetti), jbeals@perahealth.com (J. Beals).

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Significant differences in incidence and mortality are associated with these 2 modalities; around 85% of sepsis cases are POA with a mortality rate of 12%, and 15% of sepsis cases are NPOA with a mortality rate of 35% [11].

In all cases, early identification is essential for effective disease management [17]. Once sepsis is identified, early administration of antibiotics is critical [18], with one study showing that for each hour of delay following documented hypotension, survival decreased 7.6% [19].

Early detection of sepsis can be difficult. Frequently, clinicians must differentiate sepsis from other acute conditions that can obscure its presence with analogous signs or symptoms. In addition, clinicians must confirm their suspicions with supportive data that are often elusive. For example, two thirds of severe sepsis cases have negative blood cultures; one third have negative cultures from all tested sites [20,21]. Moreover, the systemic inflammatory response syndrome (SIRS) criteria which have long been part of sepsis definitions are nonspecific, which handicaps their use as diagnostic indicators [3,13,22-24], and so the traditional definition of sepsis, predicated on SIRS, has limited prognostic value [3], prompting the proposal of new definitions and approaches to sepsis identification [3,25].

In light of the need to rapidly and effectively identify patients on or at risk of progressing along the sepsis spectrum, various tools leveraging electronic medical record (EMR) data have been developed [22,26-29]. Often, such efforts focus on specific patient care locations, such as the emergency department or intensive care units (ICUs). For patients outside the ICU, recent interest has centered around the Quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) score as a severity screen for patients with suspected infection (already receiving antibiotics) [25]. The goal of the present work is to advance these efforts by developing a model for early identification while distinguishing between sepsis present on admission and sepsis developed in the hospital, without restrictions based on hospital location.

2. Methods

2.1. Data

Institutional Review Board approvals and data from adult admissions were obtained from 4 hospitals:

- 161 527 admissions (January 2010-December 2014) from Sarasota Memorial Hospital (SMH), Sarasota, FL; Allscripts Sunrise Clinical Manager EMR system
- 78 726 admissions (February 2013-December 2014) from Yale–New Haven Hospital (YNHH), New Haven, CT; Epic EMR system
- 18 583 admissions (October 2013-September 2014) from Riverside Regional Medical Center (RRMC), Newport News, VA; Siemens Soarian EMR system
- 132 821 admissions (July 2011-August 2015) from Houston Methodist Hospital (HMH), Houston, TX; Allscripts Sunrise Clinical Manager EMR system. Data from HMH were limited to *International Classification of Diseases, Ninth Revision* (ICD-9) codes with present on admission indicators and discharge disposition information.

For SMH, YNHH, and RRMC, Rothman Index (RI) scores from each patient's stay were obtained, along with the constituent elements behind each RI score. The RI is an established EMR-based general acuity score used at multiple hospitals; it is automatically calculated in real time for each inpatient using vital signs, nursing assessments, and selected laboratory results [30]. It should be noted that the range of the RI scale is from 100 to −91, with a value of 100 representing a patient who is unimpaired. Almost all patients admitted to a hospital have an RI score less than 85. An RI of 65 is the average acuity level for patients discharged to a skilled nursing facility. Patients with an RI of 40 are considered for transfer to the ICU. Zero is the lowest score typically seen on a medical-surgical unit. Negative scores are sometimes present in the ICU, and scores less than −20 are rare. A distinguishing characteristic of the RI is its use of nursing assessment data. Nursing assessments have been shown to be a valid source of longitudinal clinical data [31]. In addition, we obtained ICD-9 data along with a wide range of clinical information (Table 1). In some cases, data access was opportunistic, according to data availability from each hospital, leading to some variation in data set size and time frame.

Note that urine bilirubin rather than serum bilirubin is used, as the measurement in urine is far more commonly available. Urine bilirubin is reported as a qualitative measure (eg, large, medium, small, none) and hence treated as a binary variable: if there is no bilirubin present in the urine, the value is 0; if any is present, the value is 1.

2.2. Incidence, onset, and model construction

Given the profound distinction between POA and NPOA sepsis populations which has been noted by others [11], the present approach entailed building 2 models to (1) identify patients admitted with sepsis, severe sepsis, or septic shock quickly and accurately for timely and appropriate treatment and (2) predict the risk of postadmission sepsis, severe sepsis, or septic shock prior to onset.

Sepsis incidence was determined by ICD-9 codes 995.91 (sepsis), 995.92 (severe sepsis), and 785.52 (septic shock). The use of ICD-9 codes is imperfect owing to inevitable variations and inconsistencies in coding practice, but lacking a criterion standard for sepsis diagnoses, the use of such codes is an established method for retrospective identification [3,4,32,33]. Mortality is also used as an outcome, as this is an unambiguous end point for assessing the ability of a tool to identify high-risk patients [25].

To develop and test the NPOA model's ability to predict likelihood of sepsis prior to onset, we focused on those patients identified by ICD-9 codes as having NPOA sepsis. As there is no established method to determine the true actual "onset" time of sepsis for this population, we

Table 1
Data elements included in initial analysis

Vital signs	**Orders**	**Laboratory tests**
Temperature	Heparin	*Creatinine*
Diastolic blood pressure	Recombinant human erythropoietins	*Sodium*
Systolic blood pressure	Colony-stimulating factors (last 60 d)	*Chloride*
Pulse oximetry	Anti-infectives (antibiotics, non-HIV antivirals, antifungals)	*Potassium*
Respiration rate		*BUN*
Heart rate		*WBC*
Assessments	**Diagnoses**	*Hemoglobin*
Cardiac	ICD-9 (ICD-10) codes	WBC bands
Respiratory	Diagnosis present on admission flag	Platelet count
Gastrointestinal	Medical or surgical admission (based on MS-DRG)	Lactate
Genitourinary	Diabetes diagnosis	aPTT
Neurological	End-stage renal disease diagnosis	Bilirubin
Skin	**Other**	Glucose
Safety	Fluid I/O	C-reactive protein
Peripheral vascular	Administration of antibiotics	Procalcitonin
Food/Nutrition	X-ray showing infiltrates	INR
Psychosocial	Patient on ventilator	Microbiological cultures
Musculoskeletal	Sex	NBRC
Braden score	Discharge disposition	
Heart rhythm	Location (ICU or non-ICU)	

Italicized items are included in RI score computations. aPTT indicates activated partial thromboplastin time; I/O, intake and output; INR, international normalized ratio; NBRC, nucleated red blood cells; MS-DRG, Medicare severity diagnosis related group.

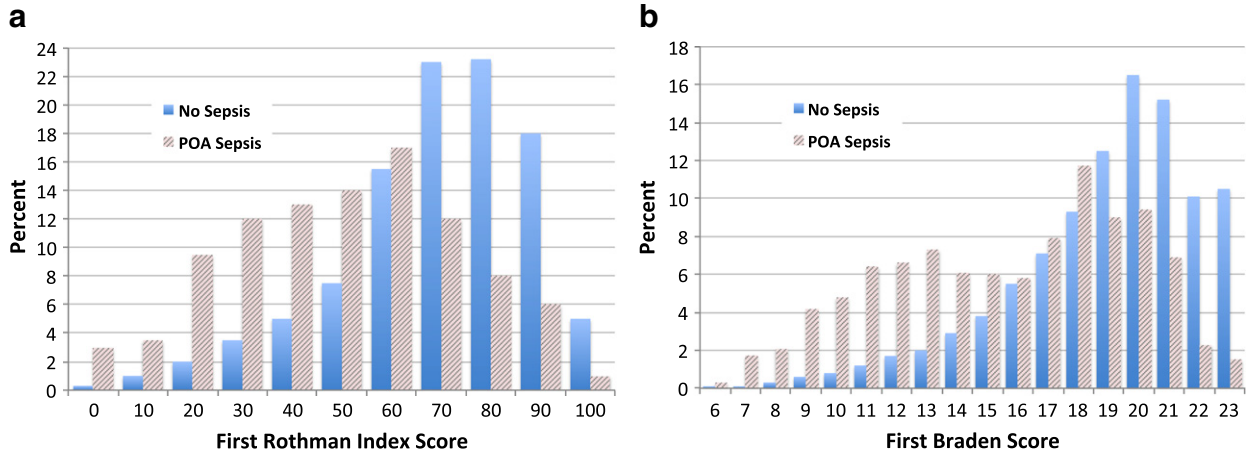


Fig. 1. Initial data points as a function of sepsis on admission. A, First RI scores. B, First Braden scores.

designate the time of the first order for anti-infectives, a practical and identifiable event that reflects physician concern, as a key reference point related to onset. NPOA model results are thus reported in relation to the time of anti-infective orders.

The qSOFA score has recently been proposed as a predictor of death in patients with suspected infection. The qSOFA score is calculated from 0 to 3, with 1 point awarded for each of altered mental status (eg, Glasgow Coma Scale score ≤ 13), respiratory rate greater than or equal to 22 per min, and systolic blood pressure less than or equal to 100 mm Hg [25]. For the comparison with the qSOFA score, both onset and qSOFA are defined to conform with the parameters used in the development of qSOFA [25]. Onset is the first of either orders for antibiotics or culture sampling, with the condition that an order for antibiotics must be followed within 24 hours by culture sampling and culture sampling, if done first, must be followed by orders for antibiotics within 72 hours. A qSOFA score greater than or equal to 2 is considered to be an indicator of sepsis risk. Only SMH data were used for this analysis owing to limitations on available culture sampling information from other sites.

Frequency and mortality are analyzed as functions of POA and NPOA sepsis using data from all 4 hospitals and published data from 21 Kaiser Permanente hospitals in Northern California, which also included patients coded with septicemia (ICD-9 038.*xx*) [34].

Model construction uses a combination of univariate analysis and stepwise logistic regression using SMH data. To build the model, 2014 SMH data were supplemented by including all sepsis patients from 2010 through 2014 to provide a stronger sepsis signal for model training purposes. For the POA model, 50% of the data were used for training, and for the NPOA model, 20% of the data were used for training. However, testing for SMH was done on the portion of the data not used in the training, and not supplemented with earlier years of sepsis patients.

Hence, the POA training set consists of 11 899 patients without sepsis and 1917 patients with at least 1 sepsis diagnosis, whereas the test data set consists of 11 691 patients without sepsis and 380 patients with at least 1 sepsis diagnosis (ICD-9). Distributions of initial candidate variables were examined as a function of having or not having any POA sepsis diagnosis. Inclusion of a variable in the model was based on the extent to which it could provide discriminatory evidence of POA sepsis (Fig. 1).

The NPOA training set consisted of data points from 17 452 patients without sepsis and 456 patients with at least 1 NPOA sepsis diagnosis, and the test data set consisted of data points from 17 803 patients without sepsis and 67 patients with at least 1 sepsis diagnosis. In contrast to the POA model, which uses only values of variables at admission, the NPOA model includes all points in the training data set with a new point generated whenever new data are received; that is, there is a new calculation for each time stamp associated with the arrival of new data. Thus, for patients who do not develop sepsis, all points generated throughout their admission are included as nonseptic. For patients developing sepsis, points prior to 24 hours before the first anti-infective order are designated as nonseptic; and those after, as septic.

The complete data sets from YNHH and RRMC were used strictly for model testing. Missing inputs associated with any variable used in either model were imputed to have normal values in keeping with common practice when computing clinical risk scores [25].

The models were assessed by testing their ability to identify (POA model) or predict (NPOA model) patients anywhere on the sepsis spectrum, including sepsis, severe sepsis, and septic shock. Patients were assessed as a whole, regardless of location within the hospital, and also as a function of whether or not they were in an ICU on admission (POA model) or when an anti-infective was ordered (NPOA model). In addition, both models are assessed as predictors of in-hospital mortality, as this is considered a more likely outcome for infected patients with sepsis than for those without [25].

The *C* statistic for each model is reported. However, as the *C* statistic alone does not always adequately reflect the efficacy of predictive clinical models [35,36], a further assessment is done by selecting several operating points and determining the associated sensitivity, specificity, and positive predictive value (PPV). Model calibration was evaluated with the Hosmer-Lemeshow goodness-of-fit test [37].

3. Results

3.1. Incidence and mortality rates

Important differences in incidence and mortality rates for sepsis, severe sepsis, and septic shock were observed between POA and NPOA patients (Table 2). The POA group accounted for 77% to 93% of sepsis diagnoses across hospitals, with an average 12% mortality rate. The

Table 2
Incidence of sepsis diagnoses (sepsis, severe sepsis, septic shock) and associated mortality rates

Onset category	Hospital	Unique admissions	% of total admissions	% of septic diagnoses	Mortality rate
	RRMC	1090	5.8%	93.1%	15.5%
	YNHH	4222	5.2%	83.6%	12.3%
POA	SMH	3926	2.4%	88.5%	12.2%
	HMH	5322	4.0%	77.0%	13.9%
	KPNC	50 520	10.5%	91.8%	10.4%
	RRMC	81	0.5%	6.9%	46.9%
	YNHH	826	1.0%	16.4%	35.2%
NPOA	SMH	511	0.3%	11.5%	34.6%
	HMH	1588	1.2%	23.0%	37.9%
	KPNC	4488	0.9%	8.2%	23.0%

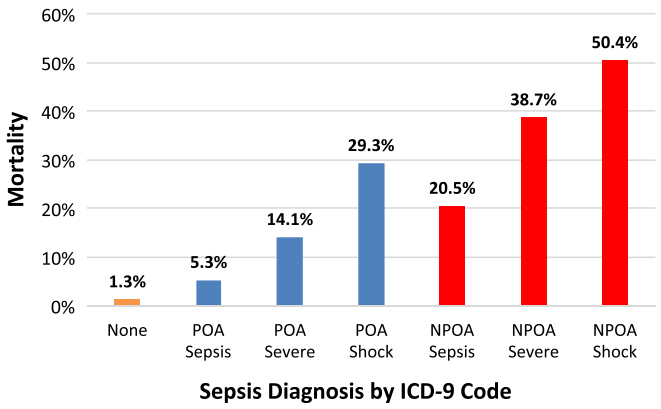


Fig. 2. Mortality rates by sepsis-related ICD-9 codes at SMH.

NPOA group accounted for 7% to 23% of sepsis diagnoses across hospitals, with an average 35% mortality rate.

Within the POA and NPOA populations, important distinctions between the type of sepsis coded (ie, sepsis, severe sepsis, septic shock) and the associated mortality rates was also found, as shown for 5 years of SMH data in Fig. 2.

Final inputs and associated odds ratios for both the POA and NPOA models are given in Table 3. For the POA model, a 10-point lower RI score translates to a 25% increase in the likelihood of sepsis (95% confidence interval [CI], 22%-28%) [computation, $1 - (0.972^{10})$], a 1-degree-higher temperature increases likelihood by 68% (61%-75%), a 5-point-lower Braden score by 30% (20%-39%), and so on. Note that the impact of any variable is a function of both the odds ratio and the size of a possible change in that variable.

3.2. POA model performance

The POA model is well calibrated as measured by the Hosmer-Lemeshow goodness-of-fit test. Table 4 reports the *C* statistics for the train and test data sets across facilities as assessed for all patients as a group as well as for test subpopulations based on whether or not the first location on admission was an ICU.

For any desired sensitivity or specificity, an operating point on the receiver operating characteristic curve can be chosen, and corresponding predictive values can be determined. For the POA model, we choose 2 such points with sensitivities of 50% and 75% for all patients (Table 5). These operating points are also used to find the sensitivity, specificity, and PPV for identifying septic patients who are admitted directly to the ICU and those who are not. We also validate the model by using these operating points to ascertain how well the sepsis model identifies patients who expire in the hospital.

Recent mention of the qSOFA as a potential sepsis screening tool (although not yet prospectively validated in that regard) prompted a comparison of qSOFA with the reported POA and NPOA models [3,24]. As previously described and in keeping with the development approach used for qSOFA, a modified definition of onset is used to identify the target population for both qSOFA and the POA model in this comparative analysis.

For the subset of patients with onset (as evidence of infection) prior to or within 6 hours of inpatient admission (thereby including anti-infectives orders in the ED), the POA model performance at 2 operating points (determined from all patients) is compared with the first qSOFA score available for each patient. Only patients whose first location on admission is not an ICU are included in this analysis. The same operating points are also used to compare the POA model to qSOFA as a predictor of in-hospital mortality, as shown in Table 6.

3.3. NPOA model performance

The NPOA model is well calibrated as measured by the Hosmer-Lemeshow goodness-of-fit test. For this predictive model, the *C* statistics obtained across facilities are shown in Table 7. The subpopulations in and out of ICU are determined based on the patient's location at the time an anti-infective is ordered.

The NPOA model was derived using data points throughout each patient's admission, and hence, the AUC values correspond to the

Table 3
Model input variables with point estimates of odds ratios

POA model inputs			NPOA model inputs		
Variable (first value)	Point estimate	95% Wald confidence	Variable	Point estimate	95% Wald confidence
RI score	0.972	0.967-0.976	RI score	0.962	0.961-0.963
Temperature	1.676	1.606-1.749	Heart rate	1.014	1.013-1.015
Braden	0.93	0.906-0.955	Diastolic BP	0.99	0.99-0.991
Heart rate	1.017	1.014-1.02	Creatinine	1.283	1.271-1.295
Systolic BP	0.986	0.983-0.989	INR	0.849	0.826-0.873
Diastolic BP	0.987	0.983-0.992	Bilirubin	6.313	5.92-6.731
GU assmt not met	1.323	1.153-1.518	Currently in ICU	2.876	2.786-2.969
WBC	1.023	1.015-1.032	Admitted through ED	1.204	1.169-1.24
Creatinine	1.168	1.126-1.212	Male	1.086	1.055-1.118
Admitted through ED	2.241	1.946-2.581			
Male	1.641	1.445-1.864			

Model coefficients for each variable are found from the natural log of the corresponding odds ratio. The constants from the regression equations are −49.96 for the POA model and −1.14 for the NPOA model. Missing inputs were imputed with normal values for each variable. As an example, for SMH, vital signs were always present in the data for both models. For the POA model, imputed values were used for WBC (13%), creatinine (17%), Braden (18%), RI (20%), and genitourinary assessments (35%). For the NPOA model, imputed values were used for creatinine (19%), INR (35%), and bilirubin (39%).

Table 4
Train and test *C* statistics for the POA model as a function of patient location

Data set	Hosp.	All Inpatients	Non-ICU	ICU
POA train	SMH	0.908 (0.901-0.915)	–	–
	SMH	0.911 (0.897-0.924)	0.908 (0.894-0.923)	0.897 (0.847-0.947)
POA test	YNHH	0.894 (0.889-0.900)	0.897 (0.891-0.903)	0.814 (0.788-0.841)
	RRMC	0.869 (0.857-0.881)	0.860 (0.846-0.875)	0.865 (0.841-0.890)

Numbers in parentheses are 95% confidence intervals.

Table 5
POA model performance at 2 operating points

POA sepsis prediction	Hosp.	All inpatients	Non-ICU	ICU
Operating point at 50% sepsis sensitivity	SMH	0.50, 0.96, 29%	0.49, 0.96, 28%	0.59, 0.91, 44%
	YNHH	0.49, 0.96, 34%	0.49, 0.96, 34%	0.39, 0.93, 37%
	RRMC	0.39, 0.97, 40%	0.29, 0.98, 36%	0.62, 0.91, 47%
Operating point at 75% sepsis sensitivity	SMH	0.75, 0.88, 17%	0.75, 0.88, 16%	0.76, 0.78, 29%
	YNHH	0.73, 0.88, 21%	073, 0.89, 20%	0.65, 0.80, 27%
	RRMC	0.64, 0.89, 25%	0.55, 0.92, 23%	0.85, 0.73, 30%
Mortality prediction	**Hosp.**	**All inpatients**	**Non-ICU**	**ICU**
Operating point at 50% sepsis sensitivity	SMH	0.30, 0.95, 8.5%	0.32, 0.95, 7.7%	0.23, 0.87, 21%
	YNHH	0.32, 0.95, 13%	0.31, 0.95, 12%	0.36, 0.92, 33%
	RRMC	0.33, 0.96, 17%	0.30, 0.97, 13%	0.37, 0.87, 23%
Operating point at 75% sepsis sensitivity	SMH	0.59, 0.87, 6.5%	0.59, 0.87, 5.5%	0.60, 0.78, 28%
	YNHH	0.56, 0.87, 9.1%	0.56, 0.87, 8.2%	0.60, 0.79, 24%
	RRMC	0.59, 0.88, 12%	0.57, 0.90, 8.6%	0.62, 0.69, 18%

Resulting values ordered as follows: sensitivity, specificity, PPV.

effectiveness with which the model discriminates between points associated with septic vs nonseptic states. However, to illuminate the utility of the NPOA model, it is also evaluated by patient admission. For each admission, we identify the first time the predicted probability of sepsis is above a given value. In each instance that the model flags a patient, we compute the time between the first order for an anti-infective and the time the patient was flagged. Performance of the model was assessed against all patients as well as for subpopulations based on whether the order for anti-infectives was placed while the patient was in or out of the ICU.

Different model output levels reflect the trade-off between the confidence with which they are identified as septic and how far in advance of an anti-infective order they are identified. Fig. 3 illustrates the relationship between PPV and median time prior to onset for 4 different model outputs (corresponding to an 80%, 60%, 40%, and 20% likelihood of sepsis), for all patients (Fig. 3A), for patients with onset outside of the ICU (Fig. 3B), and for patients with onset in the ICU (Fig. 3C). Patients are also assessed using qSOFA outside the ICU where it is designed to be applied according to whether or not at least 2 qSOFA criteria are met (Fig. 3B).

For each model output point, the percentage of sepsis patients correctly identified can be broken out over time relative to the order for anti-infectives. This is explicitly shown in Fig. 4 for the population of all YNHH patients. It is evident that a model output corresponding to a 20% probability of correct identification (where lower probability implies a lower PPV) allows more patients to be identified early relative to the order for anti-infectives than a model output with a higher probability of being correct (high associated PPV).

The predictive statistics of the NPOA model at 4 different SMH sepsis likelihoods are detailed in Table 8 for both prediction of sepsis as well as the prediction of in-hospital mortality.

4. Discussion

The principal goal of the current research is to construct a practical model to identify sepsis on admission or predict its onset during hospitalization. The model uses structured information that is commonly available for adult inpatients in the EMR.

The POA and NPOA versions of the model have advantages over previously reported models in their broadened use of EMR data. Some included data elements, such as blood pressure and temperature, are common to all SIRS-based models, and sex has also been included in some models [6,26]. However, other variables such as the genitourinary nursing assessment and Braden score (both elements of the RI) have not been included previously. Indeed, the use of the RI, a general measure of patient acuity that encompasses vital signs, nursing assessments, and laboratory findings, represents a novel approach to sepsis screening and prediction. As a general acuity measure, the RI enhances the ability to detect or predict sepsis, severe sepsis, or septic shock, as these conditions are characterized by general deterioration.

The approach pursued in this work to separately examine POA and NPOA sepsis reveals important distinctions between these populations and concomitant differences in the practicability of identifying sepsis on admission vs that developed in the hospital. Identifying sepsis on admission—without any prior knowledge of infection or cultures—appears to be a tractable problem. We measured performance on all patients and

Table 6
POA model performance at 2 operating points compared with qSOFA

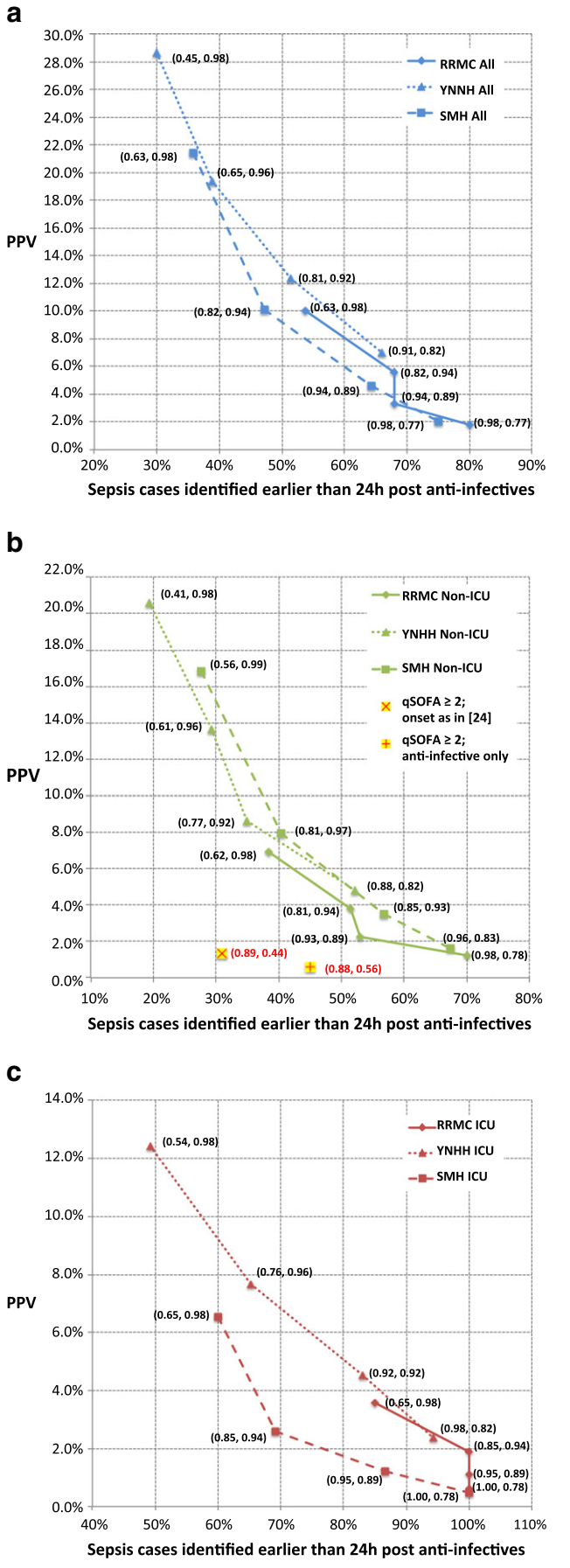
Target condition	Patient population	POA model *50% sensitivity*	POA model *75% sensitivity*	qSOFA
POA sepsis	SMH: non-ICU	0.54, 0.88, 35%	0.78, 0.69, 24%	0.15, 0.90, 16%
Mortality	SMH: non-ICU	0.44, 0.83, 5.1%	0.70, 0.65, 3.8%	0.60, 0.90, 11%

Resulting values ordered as follows: sensitivity, specificity, PPV.

Table 7
Train and test *C* statistics for the NPOA model as a function of patient location

Data set	Hosp.	All inpatients	Non-ICU	ICU
NPOA train	SMH	0.850 (0.847-0.852)	–	–
NPOA test	SMH	0.884 (0.880-0.888)	0.872 (0.866-0.877)	0.911 (0.906-0.916)
	YNHH	0.821 (0.818-0.825)	0.801 (0.797-0.806)	0.860 (0.855-0.865)
	RRMC	0.814 (0.809-0.819)	0.819 (0.814-0.825)	0.802 (0.791-0.812)

Numbers in parentheses are 95% confidence intervals.



then separately for patients where the first order for an anti-infective was in the ICU or not in the ICU to facilitate comparisons with models limited to patients in the ICU. Generally, model results were good to excellent independent of the location of the patient at the time of the first anti-infective order. Whether patients are first admitted to ICU units or non-ICU units, it is possible to identify three quarters of patients with any form of sepsis with a reasonable number of false positives for the importance of the alert, limiting alarm fatigue (PPV about 33% in the ICU and 20% outside of the ICU). Variation in the reported PPV values between hospitals is due in part to the variation in POA incidence rates (eg, SMH and RRMC differ by a factor of 2), which in turn reflects the different patient populations each hospital serves. The ultimate clinical value of the POA model will depend on the proportion of patients admitted with sepsis who currently fail to receive timely recognition and therapy. A tool such as the POA model, run once at admission and which can effectively highlight 75% of all sepsis cases, has the potential to offer valuable clinical decision support by raising suspicion of sepsis and encouraging consideration of sepsis therapies.

In contrast to sepsis present on admission, predicting NPOA sepsis without prior knowledge of infection is a considerably more daunting problem. The challenge is 3-fold. Part of the difficulty lies in distinguishing the clinical indicators of sepsis from those of comorbidities that share many of the same signs and symptoms. Indeed, the NPOA sepsis model's higher PPV values for predicting mortality (as seen in Table 8) are a reflection of the fact that detecting the clinical deterioration that precedes death is an easier task than distinguishing the deterioration characteristics uniquely linked to sepsis. Finding an appropriate reference point for establishing onset is another part of the challenge. Using the order for anti-infectives as a target is straightforward in principle but less meaningful in actual practice because such orders are extremely common. Approximately 60% of patients in the SMH data set had such an order, suggesting that they rarely denote a point at which "life-threatening organ dysfunction caused by a dysregulated host response to infection" commences, in keeping with the Third International Consensus Definition of sepsis [3]. It is therefore reasonable to interpret such orders as a suggestive reference point that serves as a surrogate for suspicion of infection rather than an absolute indicator of onset time. Finally, the extremely small target population exacerbates the operational difficulty of providing adequate sensitivity while maintaining an acceptably low false-positive rate. What we observe across all 3 hospitals in Fig. 3 is that seeking higher confidence, as reflected by a higher PPV, results in sepsis patients being identified at later times relative to the probable point of onset suggested by the order for anti-infectives. This reflects the fact that identification becomes easier as physiological derangement progresses over time. The upper leftmost point in Fig. 3A indicates that 45% of all NPOA sepsis cases are flagged with a PPV of 30%. Of those flagged, 30% are prior to or within 24 hours after the anti-infective order. These would represent early warnings. Forty-four percent of patients are flagged 6 days or more following the anti-infective order (rightmost bar in Fig. 4). The utility of these warnings is less clear. Integration of the model with clinical workflow is needed to determine the most effective mode of use; this might include early warning alerts or serve as evidence for clinical decision support in cases of uncertain sepsis determination. This work depends on the integrity of ICD-9 codes as an indicator of sepsis. As we see in Fig. 2, increased sepsis acuity (from sepsis to severe sepsis to septic shock) corresponds to increased mortality. In addition, it is apparent that each form of POA sepsis has a lower associated mortality rate than its NPOA counterpart. The observation that the data bear out the expected correspondence lends credibility to the use of ICD-9 codes, however imperfect, as an indicator of sepsis incidence and type.

Fig. 3. Positive predictive value for a sepsis alert versus the percentage of septic patients identified "early" - in this case any time prior to, or with 24-hours after, the order for anti-infectives. Graph A shows this relationship for all patients for each hospital. Graph B includes only those patients outside the ICU at the time of the anti-infective order. Graph C includes only patients in the ICU at the time of the anti-infective order. Numbers in parentheses are sensitivity and specificity. See discussion for further elucidation of the term *early* in this context.

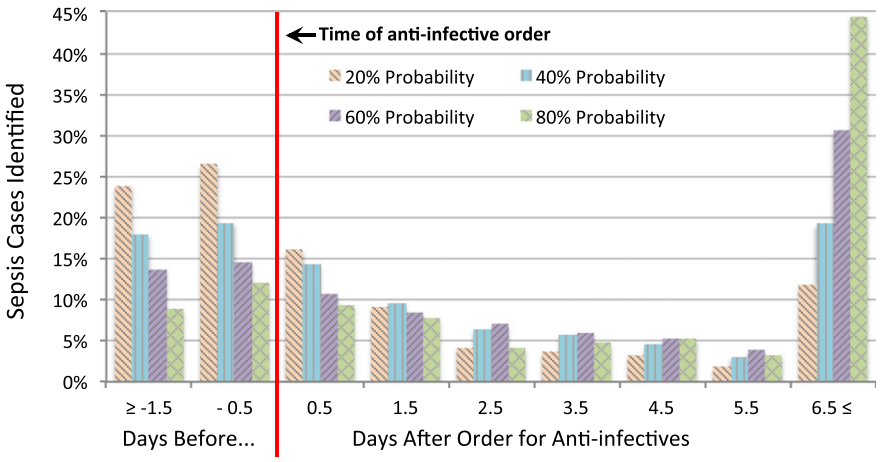


Fig. 4. Distribution of all YNHH sepsis cases correctly identified in the days before and after the order for anti-infectives as a function of model output probability. Labels indicate midpoints, for example, "2.5" contains sepsis patients identified between 2 and 3 days after the order for anti-infectives.

Assessing the ability of both models to predict mortality recognizes that the presence of sepsis is associated with an elevated risk of mortality and provides an additional dimension to validation. For example, the recently derived "quick" SOFA or qSOFA score depends on trying to predict risk of mortality in a subpopulation of patients suspected to have infection [25]. When we test qSOFA at admission, it performs reasonably in predicting mortality, the measure for which it was developed. However, comparisons with qSOFA on the subset of the population meeting infection criteria highlight the excellent performance of the POA model for detection of sepsis. The POA model demonstrated sepsis sensitivity 3 to 5 times higher than qSOFA (depending on the POA model's operating point) with a PPV 50% to 100% higher. This superior performance is not surprising given that the POA model incorporates the RI, which itself spans a wide range of physiologic components, as well as demographic inputs, compared with qSOFA's 3 inputs.

4.1. Limitations

The training and test data sets were limited by reliance on hospital ICD-9 coding to identify sepsis, severe sepsis, and septic shock when determining the target populations. Intrafacility and interfacility variations are inevitable in the way that coding is conducted, and hence, recorded codes in an administrative database are an imperfect representation of the true incidence of sepsis within a patient population.

In addition, our selection of orders for anti-infectives as the signal for onset also entails an approximation. Although this data element captures physician awareness and concern regarding patient infection, dependency on this criterion rather than a detailed retrospective chart review introduces an element of ambiguity regarding the true onset time presumed for any particular patient.

Table 8
NPOA model performance for sepsis and mortality prediction at 4 model output levels

NPOA sepsis prediction	Hosp.	All inpatients	Non-ICU	ICU
Model output 80% probability	SMH	0.58, 0.99, 21%	0.56, 0.99, 17%	0.67, 0.99, 6.5%
	YNHH	0.45, 0.98, 29%	0.41, 0.98, 21%	0.54, 0.98, 12.4%
	RRMC	0.63, 0.98, 10%	0.62, 0.98, 7.0%	0.65, 0.98, 3.6%
Model output 60% probability	SMH	0.82, 0.97, 10%	0.81, 0.97, 7.9%	0.87, 0.97, 2.6%
	YNHH	0.65, 0.96, 19%	0.61, 0.96, 14%	0.76, 0.96, 7.7%
	RRMC	0.82, 0.94, 5.6%	0.81, 0.94, 3.8%	0.85, 0.94, 1.9%
Model output 40% probability	SMH	0.88, 0.93, 4.6%	0.85, 0.93, 3.5%	1.00, 0.93, 1.2%
	YNHH	0.81, 0.92, 12%	0.77, 0.92, 8.6%	0.92, 0.92, 4.5%
	RRMC	0.94, 0.89, 3.3%	0.93, 0.89, 2.3%	0.95, 0.89, 1.1%
Model output 20% probability	SMH	0.97, 0.82, 2.1%	0.96, 0.83, 1.6%	1.00, 0.83, 0.5%
	YNHH	0.91, 0.82, 7.0%	0.88, 0.82, 4.8%	0.98, 0.82, 2.4%
	RRMC	0.98, 0.77, 1.8%	0.98, 0.78, 1.2%	1.00, 0.78, 0.6%
NPOA mortality prediction	**Hosp.**	**All inpatients**	**Non-ICU**	**ICU**
Model output 80% probability	SMH	0.26, 0.99, 38%	0.24, 0.99, 37%	0.21, 0.99, 35%
	YNHH	0.39, 0.98, 36%	0.36, 0.99, 34%	0.33, 0.99, 31%
	RRMC	0.41, 0.98, 32%	0.38, 0.98, 30%	0.39, 0.98, 30%
Model output 60% probability	SMH	0.48, 0.98, 24%	0.47, 0.98, 23%	0.45, 0.98, 23%
	YNHH	0.62, 0.96, 27%	0.60, 0.97, 25%	0.57, 0.97, 24%
	RRMC	0.64, 0.95, 21%	0.62, 0.95, 20%	0.63, 0.95, 20%
Model output 40% probability	SMH	0.68, 0.94, 15%	0.67, 0.94, 14%	0.67, 0.94, 14%
	YNHH	0.81, 0.92, 18%	0.79, 0.92, 17%	0.78, 0.92, 16%
	RRMC	0.82, 0.90, 15%	0.81, 0.90, 13%	0.81, 0.90, 14%
Model output 20% probability	SMH	0.89, 0.83, 7.7%	0.89, 0.83, 7.5%	0.88, 0.84, 7.2%
	YNHH	0.92, 0.83, 10%	0.91, 0.83, 9.6%	0.91, 0.83, 8.9%
	RRMC	0.92, 0.79, 8.2%	0.92, 0.79, 7.8%	0.92, 0.79, 8.0%

Resulting values ordered as follows: sensitivity, specificity, PPV.

The methodology represents a compromise. The training data were from a single hospital, using 1 year of data supplemented by an additional 4 years of sepsis data to increase the signal. However, it is possible that sepsis treatment patterns changed over the 5-year period and have affected the performance of the model.

Furthermore, others have suggested that general early warning systems, such as Modified Early Warning System (MEWS) or National Early Warning Score (NEWS), may have utility in predicting mortality in infected patients [38]. We have not explicitly addressed these considerations, which may be the subject of further work.

5. Conclusions

Analysis of data from 4 hospitals shows that addressing sepsis is facilitated by recognizing 2 distinct patient populations: those who are admitted with sepsis and those who develop sepsis during their hospital stay. Consequently, 2 models were developed: one to determine the likelihood of sepsis on admission and the other to predict onset of sepsis postadmission. Both models yield good to excellent discriminatory performance and are applicable to all adult patients regardless of admission route or inpatient location. Furthermore, the model that predicts the development of sepsis in the hospital is also effective at identifying patients at high risk of death. By design, the use of readily available clinical real-time data from the EMR makes these models suitable for automated monitoring and practical for clinical implementation and may improve care. Approaches to implementation and prospective assessment of outcomes are subjects of further research.

Contributors

All authors meet the requirements for authorship. Michael Rothman is the guarantor and was responsible for data management and analysis.

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Michael Rothman conducted the data analysis and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

The authors will provide access to the RI score to qualified researchers without cost.

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