Title

Supplementary Content: Evaluation of evolving sepsis criteria in discriminating suspected sepsis and mortality among adult patients admitted to the intensive care unit

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eAppendix 1. Discussion of Supplementary Methods

Method of Constructing the Baseline Risk Prediction Model

The baseline regression models for mortality and sepsis were constructed using all available variables at the time of intensive care unit (ICU) admission that related to the hospital, time of admission, and patient. The following parameters were included in both models:

Hospital Level

- Teaching Status (Yes, No, Unknown = No)
- Hospital size by number of beds (<100, 100-249, 250-500, >500, unknown)
- ICU Admission Source (direct admit, emergency department, floor/ward, operating room/procedural area, step-down unit, other/unknown)
- Type of specialty service admitted to (critical care versus non-critical care)
- Year of hospital discharge

Patient Level

- Age
- Gender (male, female/other/unknown)
- Ethnicity (Caucasian, African American, Hispanic, Asian, Native American, other/unknown)
- Body mass index ranges: 0-18.5, >18.5-25, >25-30, >30-35, >35-40, >40-50, >50
- Chronic comorbidities documented in history and physical: Acquired immunodeficiency syndrome (AIDS), hepatic failure, cirrhosis, leukemia, lymphoma, immunosuppression, metastatic cancer, diabetes, dialysis status, thrombolytic status (Yes, No, Unknown = No)
- Respiratory chronic comorbidity documented in history and physical: asthma, chronic obstructive pulmonary disease (COPD), home oxygen, respiratory failure, restrictive pulmonary disease, sarcoidosis, lung transplant (Yes, No)

- Cardiovascular chronic comorbidity documented: myocardial infarction (MI), congestive heart failure (CHF), angina, and thrombolytic therapy administration prior to ICU admission for MI patients (Yes, No)
- Acute Physiology Age Physiology Health Evaluation (APACHE) IVa scores

All variables were statistically significant ($p<0.01$) except for ethnicity African American, body mass index range unknown, teaching status, hospital discharge year 2011, ICU admission source other, and use of thrombolytic therapy administration prior to ICU admission for MI patients in the mortality model and ICU admission source step-down unit in the sepsis model. Most variables were significance at levels ($p<0.0001$). The baseline mortality model area under the receiver operator curve (AUROC) was 0.706 and the baseline sepsis model AUROC was 0.708.

eAppendix 2. Explanation of Study Design Decisions

A publicly available subset of the eICU Research Institute database known as the eICU Collaborative Research Database (known as the eICU-CRD) [1] was used to complete a comprehensive review of the content and structure of the data tables and to test code that was written in the R statistical programming language (https://www.r-project.org) prior to conducting analysis of the eICU Research Institute database.[2] Hospital level and patient level inclusion required that data be present in the following data tables (diagnoses, laboratory, vital sign, and ordered medications). Empty data tables in the eICU Research Institute and eICU Collaborative Research Database databases can occur for several reasons:

1. Some hospitals subscribe to episodic interventions models of care (example: curbside consultations) versus continuous, proactive monitoring (surveillance) models. In the former, these hospitals may choose NOT to build and maintain costly integration of patient information from health information systems.
2. Patients can be electronically admitted to an ICU but never arrive, user errors in

removing those patients (discharge versus delete) can result in patient records with no trended health information systems data.

3. End user error related to incorrect medical record entry can lead to patient records with no trended health information systems data for a period, usually discovered within the first day or two of admission.
4. Integration between health information systems can become compromised and fail, resulting in loss of data.
5. Hospitals not participating in APACHE and best practice data collection

eAppendix 3. Description of methods to determine criteria of measurement systems

Sepsis-related organ failure (SOFA)

Chronic health condition data is part of APACHE data collection, and these data are entered by trained critical care team members in the first 24 hours of ICU admission. Baseline SOFA scores were assigned for three chronic health conditions using the same methodology a study by Raith el al. (2017): 1) patients with chronic respiratory impairment were assigned 2 points; 2) patients with chronic hepatic failure were assigned 4 points; and 3) patients with chronic renal organ failure (defined as being on dialysis upon admission to the ICU) were assigned 4 points.[3] Baseline SOFA points were subtracted from the total SOFA score with a net score of 2 or more considered a positive SOFA score. We identified a SOFA score of ≥ 2 after accounting for baseline SOFA scores as being a positive score (Table 1e). PaO2 refers to partial pressure of oxygen in arterial blood, FiO2 to fraction of inspired oxygen, and SaO2 to peripheral arterial oxygen saturation. The PaO2/FIO2 ratio was used preferentially. If not available, the SaO2/FIO2 ratio was used. Vasopressor use was defined as any of these continuous intravenous medications present in the patient's record: epinephrine, norepinephrine, dopamine, or , phenylephrine (Table 1e).

eTable 1. Sepsis-related organ failure assessment (SOFA) score variables

SOFA score	1	2	3	4
Respiration				
PaO_2/FIO_2 (mm Hg)	< 400	< 300	< 220	< 100
SaO_2/FIO^2	221-301	142-220	67-141	< 67
Coagulation				
Platelets ×103/mm3	< 150	< 100	< 50	< 20
Liver				
Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular				
Hypotension (mm Hg)	MAP < 70	Any dose of vasopressor		
CNS				
Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal				
Creatinine (mg/dL) or urine output (mL/d)	1.2-1.9	2.0-3.4	3.5-4.9 or < 500	> 5.0 or < 200

PaO_2, partial pressure of oxygen in arterial blood; FiO2, fraction of inspired oxygen; mm Hg, millimeter of mercury; SaO_2, peripheral arterial oxygen saturation; mm^3, per cubic millimeter; mg/dL, milligrams per deciliter; MAP, mean arterial pressure; CNS, central nervous system.

Quick sepsis-related organ failure (qSOFA)

We identified a qSOFA score of ≥ 2 as being a positive score. Each variable below received 1 point if:

1) Change in mentation as measured by a Glasgow Coma Scale (GCS) < 15
2) Respiratory rate of ≥ 22 breaths per minute (bpm)
3) Systolic blood pressure ≤ 100 mmHg

Systemic inflammatory response syndrome (SIRS) criteria

1) Temperature > 38°C or < 36°C
2) Heart rate > 90 beats/minute
3) White blood cell > 12,000 or < 4,000 cu mm or 10% immature neutrophils (bands)
4) Respiratory rate > 20 breaths/minute) or hyperventilation ($PaCO_2$ < 32 mm Hg)

Description of methods to determine sepsis alert inflammation criteria

A total of 2.5 points is needed to meet the threshold for the inflammation criteria of the sepsis alert score. Each criterion below was assigned partial to 1 full point in differing incremental change based on how far values deviated from normal.

1) Heart rate values ranging from 81 to ≥ 109 beats per minute and respiratory rate values ranging from 15 to ≥ 29 breaths per minute. Only values within 2 hours were used.
2) Temperature values were assigned depending on how far they deviate from normal (hypothermia and hyperthermia). Any temperature < 33° C or > 41° C is considered NULL. Only values within 12 hours were used.
3) Serum glucose values ranging from 109 mg/dL to ≥ 182 mg/dL for non-diabetic patients and 251 to ≥ 460 mg/dL for patients with chronic health or active diagnosis of diabetes. Only values within 6 hours were used.
4) Mental Status active diagnosis of mental status change: Altered mental status, obtundation, stupor, and coma from ICD-9 codes 780.01 and 780.09 or ICD-10 code classes R40 and R41 assigned 1 point. Documentation within 24 hours is used.
5) INR values of 1.3-1.7 receive partial points and values of 1.8 or greater receive 1 point; values less than 1.3 are considered NA. Only values within 24 hours are used.
6) WBC and bands. Only values within 24 hours are used.
7) Lactate > 2 mmol/L assigned 1 point. Only values within 24 hours are used.

Description of methods to determine sepsis alert criteria for organ failure

Each organ failure criteria below are worth one point. After inflammation threshold is met, one organ failure point is needed for a positive sepsis alert score. Organ failure criteria are dichotomous (1 point or 0).

1) Mental Status- active diagnosis of mental status change: Altered mental status, obtundation, stupor, and coma from International Classification of Diseases ICD-9 codes 780.01and 780.09 or ICD-10 code classes R40 and R41.
2) Cardiovascular – Any one of the following: systolic blood pressure (SBP) < 90 mm Hg, mean arterial pressure (MAP) < 65 mm Hg, use of any dose of norepinephrine, epinephrine, phenylephrine, vasopressin, or dopamine.
3) Respiratory - Any one of the following: PaO_2 < 70 mm Hg on room air or PaO^2/FiO_2 ratio 200 when intubated
4) Metabolic acidosis - Any one of the following: pH 7.30, except with $PaCO_2$ > 50 or base deficit ≥ 5.0 mEq/L
5) Lactate > 2 mmol/L
6) Hematologic – Any two of the following: platelets < 100,000 microL, international normalized ratio (INR) > 1.5, or Activated Partial Thromboplastin clotting Time (aPTT) >

60 seconds

a. If warfarin was listed as a prior to admission (PTA) medication, all INR values were ignored. If warfarin was ordered after admission, any INR after the ordered warfarin start time was ignored.
b. If heparin was listed as a prior to admission (PTA) medication, all aPTT values were ignored. If heparin was ordered after admission, any aPTT obtained after the ordered heparin start time was ignored.

7) Liver failure – of labs obtained within a 24-hour period a bilirubin > 4 mg/dL or an alanine transaminase (ALT) > 80 IU/dL or aspartate aminotransferase (AST) > 80 IU/dL or serum albumin < 3.5 gm/dL or INR > 1.5 (unless on warfarin see above) equaled one point in the organ failure category.
8) For renal failure we converted urine output into 3-hour intervals to calculate the urine output per hour for 3 consecutive hours. The time since the last measurement was used to derive the rate. Any creatinine levels obtained within the first 24 hours of ICU admission (before or after ICU admission) were assessed. Of patients with one creatinine value during the first 24 hours of ICU stay 41.4% had a value obtained prior to ICU admission. Of patients with two values obtained during the first 24 hours of ICU stay, 12.5% had a value obtained prior to ICU admission. Approximately 93% had at least one creatinine level and nearly 60% had a creatinine level drawn prior to the ICU stay (baseline creatinine). Baseline creatinine were the lowest creatinine level obtained before the ICU stay started or the first value during first 24 hours of ICU stay.
9) Explanation of eTable 2: “Values within” indicates the timeframe that the algorithm looks for/accepts values. Lactate level and neurologic status could be used for either inflammation or organ failure criteria but not for both. We converted urine output into 3-hour intervals to calculate the urine output per hour for 3 consecutive hours. Criteria selection was based on a sepsis screening tools found in the literature and the clinical judgement of the principal investigator, an expert in sepsis screening.

eTable 2. Sepsis Algorithm Expanded Systemic Inflammatory Response Syndrome and Organ Failure Criteria (SIRS+OF)

Values within:	Sepsis alert for inflammation (light gray), organ failure criteria (dark gray), and both (white)
2 hours	Heart rate (HR) partial point for values > 81 beats per minute (bpm) and >/= 109 bpm assigned 1 point
	Respiratory rate (RR) partial point for values > 15 breaths per minute and >/= 26 per minute assigned 1 point (RR > 60 considered NA)

12 hours	Temperature values were assigned depending on how far they deviate from normal (hypothermia and hyperthermia). No points assigned for grossly abnormal temperature < 33 degrees C or > 46 degrees C.
6 hours	Partial point values up to 1 point were assigned for serum glucose values ranging from 109 mg/dL to >/= 182 mg/dL for non-diabetic patients (251 to >/= 460 mg/dL for diabetic patients)
24 hours	INR values of 1.3 to 1.7 assigned partial points and values of >/= 1.8 assigned 1 point
	WBC values less than 5 and greater than 9 cu mm assigned a partial point value and value >/= to 15 cu mm assigned 1 point. Bands >/= 7 to 12% partial points assigned and >/= 13% assigned 1 point
	Lactate >2 mmol/L assigned 1 point
	Altered mental status, obtundation, stupor, or coma from International Classification of Diseases (ICD -9) codes 780.01 and 780.09 or ICD-10 code classes R40 and R41 were assigned 1 point.
	PO2 < 70 mm Hg or PO2/FiO2 ratio 200 when intubated
	Platelets < 100,000 microL, INR > 1.5, or aPTT > 60 seconds
	SBP < 90 mm Hg, MAP < 65 mm Hg, use of any dose of norepinephrine, epinephrine, phenylephrine or vasopressin, or dopamine.
	pH 7.30, except with pCO2 > 50 or base deficit ≥ 5.0 mEq/L
	Bilirubin > 4 mg/dL or an ALT > 80 IU/dL or AST > 80 IU/dL or serum albumin < 3.5 gm/dL or INR > 1.5
	Urine output > 30 ml/hr or increase in creatinine of at least 12% from baseline

CV, cardiovascular; C, Celsius; mg, milligrams; dl, deciliter; INR, international normalized ratio; cc mm, cubic millimeters; PO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; mm Hg, millimeters of mercury; microL, microliter; PCO_2, partial pressure of carbon dioxide; IU, international units;

International Classification of Diseases ICD-9 and ICD-10 codes are stored in the Philip's eICU Research Institute database and associated with problem list entries in the eCareManager health information system by trained critical care team members (eTable 3). Using administrative data codes is an approach consistent with Seymour et al. (2016) Sepsis-3 study's management of non-electronic health record datasets where researcher used Angus ICD-9-CM diagnosis codes or prospective screening data to identify infection present on admission.[4, 5]

eTable 3. International Classification of Diseases 10th (ICD-10) revision codes and descriptions used to determine presence or absence of suspected sepsis in the first 24 hours of ICU admission

Suspected Sepsis: *Septic shock:* R65.21; *Severe sepsis:* R65.20; *Toxic shock syndrome:* A48.32;
Infection: *AIDS, HIV positive*: B20, Z21, R75; *Bacterial diseases:* A00-01, A03, A30-A31, A39, A42-A43, A48, A69, A75, A77-A79, B47, B95, B96, M60; *Bacterial zoonoses infections:* A02, A20-A28, A35; *Fungal infections:* B37-B44, B48; *Genito-urinary tract infections:* N15.1, N34, N39.0, N41, N70-N77; *Gastrointestinal infections: abscesses (appendicitis, cholecystitis, colitis, diverticulitis, gastroenteritis, hepatitis, peritonitis, perforation):* A04, A08, A09, B15-17, B19, K22.3, K35-K37, K57.01, K61, K63.0, K63.1, K65, K68, K75.0, K75.1, K81.0, K81.2, K82.2; *Infection related to device or procedure:* K68.11, T81.4XX, T80.212A, T84.5, T84.6, T84.7; *Intracranial/intraspinal infections:* A39, G06, G08; *Meningitis, myelitis, encephalitis, and encephalomyelitis:* G00-G04, G06, G08; *Pericarditis, endocarditis,*

myocarditis, thrombophlebitis: I30-I33, I38-I41, I80; *Pneumonia, all forms:* J12-J18; *Sepsis, septicemia, bacteremia:* R65, A40, A41, R78.81; *Skin, bone, joint infections:* A46, A66, A67, L03, L04, L08, L88, L89, M00, M01, M72.6, M86; *Sexually transmitted diseases:* A50-A54; *Tuberculosis: all forms:* A15, A17-A19; *Upper/lower respiratory infections (sinusitis, pharyngitis, tonsillitis, laryngitis, tracheitis, bronchitis):* A37, A38, J01-J06, J20-J22, J44.0, J44.1, J47.0, J47.1, J85, J86, J98.5; *Viral infections:* B25, B27, B33, B97, J11
Organ Failure: *Altered mental status, obtundation, stupor, coma, delirium, encephalopathy, anoxic brain damage:* F05, G93.1, G93.40, R40, R41; *Heart Failure:* I50.2; *Hematologic: DIC, TTP, thrombocytopenia:* D65, D69.59, D96.6; *Hepatic failure:* K72, K76; *Renal failure:* N17; *Respiratory failure:* J21, J80, J81, J96 (excluding J96.1, J96.12), R09.02, R09.1, R09; *Shock states (without trauma), hypotension:* E86, I95.89, I95.9, R57, T81

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; OF, organ failure; DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura. Adapted from Rincon, TA (2020).[6]

eTable 4. Sensitivity, Specificity, NPV, and PPV for Each Measurement System

Predictor – Suspected Sepsis	***Sensitivity (%)***	***Specificity (%)***	***NPV (%)***	***PPV (%)***
SIRS ≥ 2 criteria	89.0%	27.1%	90.5%	24.0%
qSOFA ≥ 2 score	82.0%	36.6%	88.7%	25.1%
SOFA ≥ 2 score	86.1%	35.6%	90.9%	25.7%
Sepsis-2 ≥ 3.5 score	81.6%	51.8%	91.6%	30.4%
Predictor - Mortality				
SIRS ≥ 2 criteria	93.1%	25.6%	97.3%	11.5%
qSOFA≥ 2 score	90.6%	35.2%	97.3%	12.7%
SOFA ≥ 2 score	94.3%	33.8%	98.3%	12.9%
Sepsis-2 ≥ 3.5 score	86.5%	48.2%	97.2%	14.8%

NPV; negative predictive value; PPV, positive predictive value; SIRS, systemic inflammatory response syndrome; qSOFA, quick SOFA; SOFA, sepsis-related organ failure assessment; Sepsis-2, modified algorithm based on sepsis-2 expanded SIRS and organ failure criteria.

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