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Original Contribution

Derivation of a screen to identify severe sepsis and septic shock in the ED-BOMBARD vs. SIRS and qSOFA☆

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ABSTRACT

Study objective: To predict severe sepsis/septic shock in ED patients.
Methods: We conducted a retrospective case-control study of patients ≥18 admitted to two urban hospitals with a combined ED census of 162,000.
Study cases included patients with severe sepsis/septic shock admitted via the ED. Controls comprised admissions without severe sepsis/septic shock. Using multivariate logistic regression, a prediction rule was constructed. The model's AUROC was internally validated using 1000 bootstrap samples.
Results: 143 study and 286 control patients were evaluated. Features predictive of severe sepsis/septic shock included: SBP ≤ 110 mm Hg, shock index/SI ≥ 0.86, abnormal mental status or GCS < 15, respirations ≥ 22, temperature ≥ 38C, assisted living facility residency, disabled immunity.
Two points were assigned to SI and temperature with other features assigned one point (mnemonic: BOMBARD). BOMBARD was superior to SIRS criteria (AUROC 0.860 vs. 0.798, 0.062 difference, 95% CI 0.022–0.102) and qSOFA scores (0.860 vs. 0.742, 0.118 difference, 95% CI 0.081–0.155) at predicting severe sepsis/septic shock. A BOMBARD score ≥ 3 was more sensitive than SIRS ≥ 2 (74.8% vs. 49%, 25.9% difference, 95% CI 18.7–33.1) and qSOFA ≥ 2 (74.8% vs. 33.6%, 41.2% difference, 95% CI 33.2–49.3) at predicting severe sepsis/septic shock. A BOMBARD score ≥ 3 was superior to SIRS ≥ 2 (76% vs. 45%, 32% difference, 95% CI 10–50) and qSOFA ≥ 2 (76% vs. 29%, 47% difference, 95% CI 25–63) at predicting sepsis mortality.
Conclusion: BOMBARD was more accurate than SIRS and qSOFA at predicting severe sepsis/septic shock and sepsis mortality.

1. Background

Experts recommend screening adults for sepsis using systemic inflammatory response syndrome (SIRS) criteria or the quick sequential sepsis-related organ failure assessment (qSOFA) score [1-3]. These screens may not be applicable in the emergency department (ED). Nearly 18% of all ED patients have ≥two SIRS criteria [4]. Only 26% of ED patients with ≥two SIRS criteria have an infection with the majority of these patients not admitted to the hospital [4]. The initial qSOFA score was derived in studies that primarily included inpatients and a subset of ED patients arriving by ambulance [2]. Studies that analyzed the qSOFA score in populations entirely comprised of ED patients found that qSOFA has poor sensitivity at predicting severe sepsis and septic shock [5-9]. Askim analyzed the qSOFA score and SIRS criteria in ED patients with suspected infections and found a qSOFA score ≥ 2 detected only 32% of cases of severe sepsis while ≥2 SIRS criteria were present in 74% of cases [5]. Hwang found a qSOFA ≥ 2 score on ED arrival was only 39% sensitive in predicting sepsis mortality in ED patients with severe sepsis and septic shock [6]. Park found that a qSOFA score ≥ 2 was only 53%

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sensitive in detecting in-hospital mortality in patients admitted via the ED with a suspected infection [7]. In a prospective study of ED patients with suspected infection and ≥SIRS criteria, Quinten found that a qSOFA score ≥ 2 only detected 19% of patients with severe sepsis, 78% of patients with septic shock, and 63% of sepsis deaths [8]. A recent meta-analysis found a qSOFA score ≥ 2 to be more specific but less sensitive than a SIRS score ≥ 2 at predicting sepsis mortality concluding that both tools are limited in their ability to risk stratify ED patients with infections [10]. Because current tools have limitations in predicting severe sepsis/septic shock and outcome related to sepsis in ED patients, we chose to perform this study. Specifically, our goal was to derive more accurate ED criteria for predicting severe sepsis, septic shock, and sepsis mortality.

2. Methods

2.1. Study design and setting

This study was conducted at two hospitals. Hospital A was a level 1 urban trauma center with a 2015 annual census of 82,500 patients per year with 65% of hospital admissions occurring via the ED. Hospital B was an urban community hospital with a 2015 annual census of 79,500 patients per year with 84% of hospital admission occurring via the ED.

2.2. Study participants

This was an observational case-control study of consecutive admitted patients with severe sepsis/septic shock and admitted patients without severe sepsis/septic shock. *Study cases* consisted of consecutive patients ≥18 years old diagnosed with severe sepsis and septic shock (ICD10 codes R65.20, R65.21) between October 1, 2015 and December 31, 2015 who were admitted to the study hospitals via the ED. Hospital abstractors used the Centers for Medicaid and Medicare Services (CMS) SEP-1 measure set for defining septic shock and severe sepsis (versions 5.0–5.1 during study) which use Sepsis-2 consensus definitions [11,12]. Study cases were included only if an infection was proven or suspected (antibiotics administered or suspected infection in inpatient notes) within 48 h of admission [13]. *Control cases* consisted of patients ≥18 years old admitted to the study hospital via the ED without severe sepsis/septic shock. Two control cases were randomly chosen from patients admitted on the same date as each study case. Patients with infection or features of sepsis beginning >48 h after admission, admitted to a dedicated chest pain center, designated as trauma-alert patients, transferred from another hospital, or not admitted via the ED were excluded. Only the first presentation of sepsis was included for each study patient.

This proposal was approved by the hospitals' Institutional Review Board.

2.3. Definitions and data collection

Data collection was completed by study authors using a standard data collection spreadsheet. Prior to data collection, consensus definitions were created for admission diagnostic categories, and disabled immune system (diabetes, transplant, cancer [active hematologic cancer or metastatic cancer], renal failure, severe liver disease [cirrhosis, chronic alcoholism, hepatitis due to alcohol, high INR due to liver disease], absent spleen, sickle cell disease, and immune medication use [steroids, chemotherapy, immune modulators]). Charts with templated ED history and physical examination components were used at both study hospitals. Features on the examination are circled if present or crossed out if absent. Free written text can be added to describe physical examination features at the discretion of the treating physician. Mental status was documented as normal if terms present on the templated ED physical examination were circled or written including, “alert”, “oriented X 3”, or “normal mental status” and no features of abnormal mental status were documented. Mental status was documented as abnormal if any of these items (alert, oriented X 3, normal mental status) were crossed out or if the terms confusion, abnormal mental status, not oriented, or disoriented were written on the ED physical examination record. Specific areas of each medical record that were reviewed included the index ED and inpatient record including all triage and ED vital signs (all of which are entered into an electronic health record), the ED and inpatient admission history and physical exam, clinical summary, laboratory results, electronic prescriptions, and consultant records for the index visit. Prior to record review, a three-hour training session took place that emphasized definitions and uniform chart reviews. Initially, study abstractors simultaneously abstracted 20 charts to ensure uniformity. After 52% of charts were reviewed, data abstraction and data entry were evaluated by principal investigators and coding rules were re-reviewed with abstractors. The principal investigators arbitrated all coding questions on an ongoing basis. Any disagreements were settled by consensus of the two principal investigators and study abstractor.

For each patient, age, sex, primary ED admitting diagnosis, final inpatient diagnosis, suspected source of infection, date of admission/discharge/death, duration of hospitalization (excluding patients who died), initial temperature, systolic blood pressure (SBP), heart rate (HR), shock index/SI (HR/SBP), respiratory rate (RR), oxygen (O_2) saturation, mental status (abnormal defined as altered mental status or Glasgow coma scale/GCS < 15, white blood cell and band count, lactate, end-tidal CO_2, and outcome were recorded. Initial vital signs that were absent were imputed as normal. Absent initial historical features were imputed as absent. All repeated vital signs (temperature, BP, HR, RR), GCS, and every documented mental status was reviewed over the first 3 h of each patient's ED course. Standard practice was to obtain and repeat vitals based on a patient's triage Emergency Severity Index (ESI) [14]. Hospital guidelines recommend that patients with an ESI of 1 have vital signs repeated every 5 to 15 min, an ESI of 2 have vital signs repeated at least every hour, and an ESI of 3 have vital signs repeated at least every 2 h. For each repeated set of vital signs, missing values were pulled forward from the most recent previous value to calculate composite scores.

2.4. Statistical analysis

Clinical features were compared between severe sepsis/septic shock and non-sepsis groups using the Mann Whitney *U* test for continuous and ordinal variables and χ^2 analysis or Fisher's exact test for categorical variables. Continuous and ordinal variables were dichotomized to categorical variables after constructing a receiver operating characteristic (ROC) curve and choosing the optimum cut-off. Calculated cutoffs from ROC analysis and published sepsis related cutoffs for heart rate (≥90), shock index (>0.9), temperature (≥38 °C), systolic blood pressure (<90 mm Hg), SIRS criteria, and qSOFA scores were compared between groups (MedCalc Statistical Software v18.2.1 - MedCalc Software bvba, Ostend, Belgium, 2018).

Using multivariate logistic regression with a purposeful selection model building strategy, a clinical prediction rule was constructed to predict severe sepsis/septic shock [15-17]. Initially, plausible variables plus all univariate variables with a p value ≤ .25 were included in the logistic regression model. Variables that initially did not contribute to the model (p > .10) were eliminated. Then, coefficients of variables in the new model were compared to coefficients in the original model. If a change of coefficients ($\Delta\beta$) was >20% for any retained feature (with vs. without the deleted variable), the deleted variable was added back to the model. The variance inflation factor (VIF) was calculated to assess for multicollinearity between final variables [14-16]. A VIF of 5 or greater is indicative of collinearity [18]. Bootstrap sampling was used to assess the internal validity of the model and estimate its performance in a simulated cohort. The AUROC for this model was calculated on the bootstrap sample and then again in the full data set. This process was repeated 1000 times to calculate an overall bootstrap optimism-corrected or "average" AUROC for the model.

The area under the receiver operating characteristic curve (AUROC) was compared between the New Model, SIRS criteria, and qSOFA criteria in predicting severe sepsis/septic shock and sepsis mortality using the method of Delong. AUROCs were considered worthless at 0.5, failed at 0.5 to 0.6, poor at 0.6 to 0.7, adequate at 0.7 to 0.8, good at 0.8 to 0.9, and excellent at 0.9 or higher. Calibration or the agreement between observed and predicted severe sepsis/septic shock rates was analyzed using the Hosmer & Lemeshow goodness-of-fit statistic, with a p value > .05 indicative of a well-calibrated test. Sensitivity and specificity of initial rules at predicting severe sepsis/septic shock, sepsis mortality, and all-cause mortality were compared using McNemar's test.

The maximum New Prediction rule, maximum or worst SIRS criteria (wSIRS), and maximum or worst qSOFA (wqSOFA) scores were calculated during the initial 3 h of each patient's ED stay. The AUROC of the maximum value of each criteria or score in predicting severe sepsis/septic shock was compared using the method of Delong. Sensitivity and specificity of maximum rules at predicting severe sepsis/septic shock and sepsis mortality were compared using McNemar's test.

The time from arrival to calculation of initial and worst scores/criteria was compared using Friedman's test. Paired comparison of criteria/scores was performed using the Wilcoxon signed-rank test (e.g. initial BOMBARD score time vs. initial SIRS criteria time, initial BOMBARD time vs. initial qSOFA score, initial SIRS criteria time vs. initial qSOFA score time).

Interrater reliability of chart abstraction for retained features was performed with a second reviewer abstracting 45 charts (10.5% of all cases) comprised of 15 study cases and 30 control cases. An intraclass correlation coefficient (continuous data) was consider excellent at ≥0.75, good at 0.60–0.74, fair at 0.40–0.59, and poor if <0.40. A kappa coefficient (nominal and ordinal data) was considered almost perfect at 0.81–1, showed substantial agreement at 0.61–0.80, moderate agreement at 0.41–0.60, fair agreement at 0.21–0.40, slight agreement at 0.01–0.20 and less than chance at <0.

2.5. Sample size calculation

Others have found SIRS criteria to be 52% sensitive in detecting severe sepsis/septic shock [19]. A study with 120 severe sepsis/septic shock patients and 240 controls would be needed to have >80% power to detect a 15% absolute difference (67% vs. 52%) in sensitivity between SIRS criteria and newly derived criteria. Prior studies have found that the AUROC for the qSOFA score in predicting sepsis related organ dysfunction and sepsis mortality was 0.81 [2,7]. A study with 137 severe sepsis/septic shock patients and 274 controls would be needed to have 80% power to detect an 8% improvement (0.065 increase, 0.875 vs. 0.810) in AUROC for newly derived criteria. To ensure these goals were attained, it was estimated that at least 140 cases and 280 controls would need to be enrolled.

3. Results

Data was originally collected from 186 study patients and 372 control patients. Forty-three cases and 86 matched controls were excluded because they were transfers from another hospital [23], direct admissions [10], or had onset of infection >48 h after admission [10]. Sixteen controls were replaced because they were transfers from another hospital [11] or trauma alerts [5]. Of the 143 study patients, 99 (69%) were admitted to hospital A and 44 (31%) were admitted to hospital B. Overall, 77 (54%) cases were classified as septic shock and 66 (46%) were classified as severe sepsis. Admitting diagnostic categories and infection sources are listed (Tables 1, 2).

Presenting features that differed between severe sepsis/septic shock and control cases included assisted living facility residency, a disabled immune system, mental status (altered mental status or Glasgow coma scale < 15), systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), shock index (SI), serum WBC count, respiratory distress (RDS), temperature, and oxygen saturation. Age, gender and initial end-tidal CO_2 did not differ between groups (Table 3).

Ten control patients had missing ED temperatures. Based on subsequent inpatient temperatures, the ED temperature was imputed as <38 °C in each case. Using the initial vital signs and assessment in the ED, the optimum cutoff for discriminating between severe sepsis/septic shock and controls included: GCS ≤ 14 vs. >15, SBP ≤ 110 vs. >110 mm Hg, HR > 100 vs. ≤100 beats per minute, RR ≥ 22 vs. <22 breaths per minute, temperature > 37.2 vs. ≤37.2 °C, SI ≥ 0.86 vs. <0.86, oxygen saturation ≤ 96 vs. >96%. Individual AUROCs for predicting severe sepsis/septic shock were adequate for SBP, HR, and SI (0.717, 0.706, and 0.765), poor for GCS, respiratory rate and temperature (0.622, 0.690, and 0.600) and failed for oxygen saturation (0.586).

Logistic regression resulted in 7 features predictive of severe sepsis/septic shock including: SI ≥ 0.86, SBP ≤ 110 mm Hg, RR ≥ 22 breaths per minute, temperature ≥ 38 °C, GCS < 15 or altered mental status, assisted living facility residency, and history of a disabled immune system. None of the retained features demonstrated multicollinearity (all variance inflation factors < 2). The Hosmer & Lemeshow test indicated good agreement between observed and predicted probabilities of severe sepsis/septic shock (chi-square goodness-of-fit = 2.414, p = .878). To create a total score, features were weighted by rounding the regression coefficient to the nearest integer. Rise in temperature and shock index were assigned two points each and all other features assigned one point (Table 4). The optimum cutoff for detecting severe sepsis/septic shock was ≥3 total points. A mnemonic (BOMBARD) was constructed to aid in remembering features (Table 5).

The AUROC of the derived model did not differ from the calculated bootstrap optimism-corrected AUROC (0.860, 95% Confidence Interval/CI 0.824 to 0.892 vs. 0.859, 95% CI 0.823 to 0.895).

The intraclass correlation coefficient for the chart abstraction of temperature, systolic BP, RR, and SI was 1.0. The kappa statistic for the chart abstraction of a history of disabled immune system and GCS < 15 or altered mental status was 1.0. The kappa statistic for abstraction of

Table 1
ED admitting diagnosis.

	Severe sepsis/septic shock N = 143	Non-sepsis N = 286
Infection	98	38
Neurological	15	52
Cardiovascular	11	77
Pulmonary	7	28
Gastrointestinal	6	43
Genitourinary	3	6
Metabolic	2	8
Orthopedic	1	10
Other[a]	0	24

[a] Category of "Other" included diagnoses of generalized weakness, falling, dehydration, venous thromboembolism, burn, thrombocytopenia, anemia, gynecological disorders, drug or alcohol intoxication, and minor trauma.

Table 2
Severe sepsis/septic shock source of infection.

Source	N (%)[a]
Respiratory	56 (39%)
Urinary tract	34 (24%)
Gastrointestinal	24 (17%)
Skin and soft tissue	16 (11%)
Cardiovascular, valve, bloodstream[b]	9 (6%)
Bone or joint	4 (3%)
Unknown	3 (2%)
Central Nervous System	1 (1%)

[a] Number adds up to >143 due to multiple infections in four patients.
[b] Includes bacteremia, central venous access infection, valvular infection, and parasitemia (malaria).

Table 3
Comparison of features and outcome between severe sepsis/septic shock and non-sepsis groups.[a,b]

Feature	Sepsis N = 143 (%)	Non-sepsis N = 286 (%)	Differences in 95% CI
Age - median years	65 (46.5–78)	64.5 (49–80)	
Male gender	82 (57.3)	138 (48.3)	9 ([−1] - 18.7)
Resident of an assisted living facility	33 (23.1)	27 (9.4)	13.7 (6.4–21.8)
Disabled immune system	88 (61.5)	125 (43.7)	17.8 (7.8–27.2)
Duration of admission - median days[c]	9 (5–15)	4 (2–6)	
Mortality	38 (26.6)	5 (1.7)	24.9 (18–32.7)
Initial GCS < 15	55 (39.2)	47 (16.4)	22.8 (13.8–31.8)
Initial GCS < 15 or not “alert”	60 (42)	50 (17.5)	24.5 (15.3–33.6)
Initial ED systolic blood pressure (SBP) – median mm Hg	117 (99–138)	141 (122–164)	
Initial SBP ≤ 110 mm Hg	59 (37.8)	28 (9.4)	28.4 (19.9–37.1)
Initial ED heart rate (HR) – median beats per minute	104 (87–125)	88 (76–101)	
Initial HR > 90 beats per minute	104 (72.7)	126 (44.1)	28.6 (18.9–37.3)
Initial HR > 100 beats per minute	84 (58.7)	72 (25.2)	33.5 (23.7–42.5)
Initial ED respiratory rate (RR) – median respirations per minute	20 (18–26)	18 (16–20)	
Initial RR ≥ 22 respirations per minute	65 (45.5)	36 (25.2)	20.3 (10.7–29.7)
ED respiratory (Resp) distress - dyspnea	48 (33.6)	44 (15.4)	18.2 (9.6–27.1)
Initial shock index/SI (HR/SBP) – median SI	0.89 (0.66–1.16)	0.62 (0.5–0.77)	
Initial shock index ≥ 0.9	70 (49)	32 (11.1)	37.9 (28.8–46.6)
Initial shock index ≥ 0.86	80 (55.9)	36 (12.6)	43.4 (34–51.9)
Initial temperature – median centigrade (°C)	36.9 (36.6–38.1)	36.8 (36.6–37)	
Initial temperature > 38 °C or <36 °F	48 (33.6)	20/276 (7.2)	26.4 (18.3–34.9)
Initial temperature ≥ 38 °C	38 (26.6)	10/276 (3.5)	23.1 (15.9–31)
Initial oxygen saturation (%)	97 (95–99)	98 (96–99)	
Initial oxygen saturation ≤ 92%	23 (16.1)	16 (5.6)	10.5 (4.4–17.7)
Initial oxygen saturation ≤ 96%	64 (43.2)	82 (28.7)	14.5 (4.9–24.1)
Initial lactate - media mg/dl	2.25 (1.5–3.8)	1.4 (1–1.9)	
Lactate > 2 mmol/L	72/128 (56.3)	13/53 (24.5)	31.8 (16.2–44.5)
Initial white blood cell/WBC count – median cells/mm^3	12,700 (9000–17,400)	8500 (6600–9100)	
WBC count ≥ 12,000 cells/mm^3 or <4000 or band count > 10%	88 (61.5)	74 (25.9)	35.6 (25.8–44.5)
WBC count ≥ 12,300 cells/mm^3	77 (53.8)	57 (19.9)	33.9 (24.3–42.9)
End-tidal CO_2 – median mm Hg	29 (23–36)	31 (25–41)	
SIRS positive (≥2 criteria)	70 (49)	25 (8.7)	40.3 (31.4–48.9)
qSOFA positive (≥2 criteria)	48 (33.6)	13 (4.5)	29.1 (21.3–37.4)
BOMBARD positive (≥3 criteria)	107 (74.8)	50 (14.3)	60.5 (51.6–67.8)

[a] Median and interquartile range for continuous data.
[b] 55 sepsis patients and 30 control patients had $ETCO_2$ measured in the ED. 128 sepsis and 66 Control patients had lactate measured in the ED. Ten Control patients did not have ED temperatures recorded. Temperatures in these cases were imputed as normal during derivation of the new decision rule and calculation of SIRS criteria. 18 sepsis and ten control patients had band counts measured.
[c] Excluding patients who died during admission.

assisted living facility residency was 0.85. The kappa for a positive BOMBARD score (≥3) was 0.95.

3.1. Initial criteria-scores

Accuracy of the initial BOMBARD score for predicting severe sepsis/septic shock was significantly greater than that of the initial SIRS criteria (AUROC 0.860 vs. 0.798, 0.062 difference, 95% CI 0.022 to 0.102).

Table 4
Retained and *non-retained* logistic regression variables.

Feature	Regression coefficient	Odds ratio (95% confidence interval)
Temperature ≥ 38 °C	1.9	7 (2.9–19.6)
Shock index ≥ 0.86 (Heart rate/systolic blood pressure)	1.7	4.4 (2.3–8.3)
Respiratory rate ≥ 22 breaths per minute	1.1	3.1 (1.7–5.6)
Disabled immune system	1	2.8 (1.6–4.8)
Resident assisted living facility	0.9	2.6 (1.2–5.5)
Systolic blood pressure ≤ 110 mm Hg	0.8	2.1 (1–4.6)
Glasgow coma scale < 15 or altered mental status	0.6	1.9 (1–3.5)
Initial oxygen saturation ≤ 92%	*0.8*	*2.2 (0.8–5.8)*
Respiratory distress	*0.2*	*1.2 (0.6–2.5)*
Initial heart rate > 100 beats per minute	*0.1*	*1.2 (0.6–2.3)*
Age ≥ 80 years	*−0.5*	*(0.3–1.1)*

Accuracy of the initial BOMBARD score for predicting sepsis/septic shock was significantly greater than that of the initial qSOFA score (AUROC 0.860 vs. 0.742, 0.118 difference, 95% CI 0.081 to 0.155) [Table 6, Fig. 1]. Receiver operator characteristics of initial BOMBARD, SIRS, and qSOFA are listed (Table 6).

An initial BOMBARD score ≥ 3 was more sensitive than initial SIRS criteria ≥ 2 [74.8% vs. 49%, difference 25.9%, 95% CI 18.7 to 33.1] and a qSOFA score ≥ 2 [74.8% vs. 33.6%, 41.2% difference, 95% CI 33.2 to 49.3] at predicting severe sepsis/septic shock. Initial SIRS criteria ≥ 2 were more sensitive than an initial qSOFA score ≥ 2 at predicting severe sepsis/septic shock (49% vs. 33.6%, 15.4% difference, 95% CI 9.5 to 21.3) [Table 6].

An initial BOMBARD score ≥ 3 was more sensitive than initial SIRS criteria ≥ 2 (76.3% vs. 44.7%, 31.6% difference, 95% CI 16.8 to 46.4) and

Table 5
BOMBARD screening criteria for severe sepsis/septic shock.[a,b]

B	**B**P (systolic BP) ≤ 110 mm Hg
O	**0**.86 or higher shock index (heart rate/systolic blood pressure)
M	**M**ental status altered or Glasgow coma scale < 15
B	**B**reathing at ≥22 respirations per minute
A	**A**ssisted living facility resident
R	**R**ise in temperature ≥ 38 °C (100.4 °F)
D	**D**isabled immune system

[a] Two points were given for (O) 0.86 or higher shock index and for (R) rise in temeprature > or = 38C. All other features were assigned 1 point each for a maximum total of 9 points. This screen is positive if the total is ≥3 points
[b] Zero (0.86) was replaced with letter O in the mnemonic.

Table 6
Comparison of operating characteristics and accuracy of initial criteria at predicting severe sepsis/septic shock.[a]

	BOMBARD ≥ 3	SIRS ≥ 2	qSOFA ≥ 2
Sensitivity[b]	74.8% (66.9–81.7%)	49% (40.5–57.4%)	33.6% (25.9–41.9%)
Specificity	82.5% (77.6–86.7%)	91.3% (87.4–94.3%)	95.5% (92.4–97.6%)
Positive predictive value	68.2% (62.1–73.7%)	73.7% (65–80.8%)	78.7% (67.4–86.8%)
Negative predictive value	86.7% (83.1–89.7%)	78.1% (75.2–80.8%)	74.2% (71.8–76.4%)
AUROC[c,d]	0.860 (0.824–0.871)	0.798 (0.757–0.835)	0.742 (0.698–0.783)

[a] 95% confidence interval in parentheses.
[b] McNemar's test: An initial BOMBARD score ≥ 3 was more sensitive than initial SIRS criteria ≥ 2 [74.8% vs. 49%, difference 25.9%, 95% CI 18.7 to 33.1] and a qSOFA score ≥ 2 [74.9% vs. 33.6%, 41.2% difference, 95% CI 33.2 to 49.3] at predicting severe sepsis/septic shock. Initial SIRS criteria ≥ 2 were more sensitive than an initial qSOFA score ≥ 2 at predicting severe sepsis/septic shock (49% vs. 33.6%, 15.4% difference, 95% CI 9.5 to 21.3).
[c] Area under the receiver operating characteristic curve Receiver Operator Curve.
[d] Accuracy of the BOMBARD score for predicting severe sepsis/septic shock was significantly greater than that of the SIRS criteria (AUROC 0.860 vs. 0.798, 0.062 difference, 95% CI 0.022 to 0.102). Accuracy of the BOMBARD score for predicting sepsis/septic shock was significantly greater than that of the qSOFA score (AUROC 0.860 vs. 0.742, 0.118 difference, 95% CI 0.081 to 0.155).

an initial qSOFA score ≥ 2 (76.3% vs. 28.9%, 48.7% difference, 95% CI 32.5 to 64.8) at predicting sepsis mortality. Initial SIRS criteria ≥ 2 were more sensitive than an initial qSOFA score ≥ 2 at predicting sepsis mortality (SIRS 44.7% vs. qSOFA 28.9%, 15.8% difference, 95% CI 4.2 to 27.4) [Table 7].

An initial BOMBARD score ≥ 3 was more sensitive than initial SIRS criteria ≥ 2 (72.1% vs. 44.2%, 27.9% difference, 95% CI 14.5 to 41.3) and an initial qSOFA score ≥ 2 (72.1% vs. 27.9%, 44.2% difference, 95% CI 29.3 to 59) at predicting all-cause mortality. Initial SIRS criteria ≥ 2 were more sensitive than an initial qSOFA score ≥ 2 at predicting all-cause mortality (SIRS 44.2% vs. qSOFA 27.9%, 16.3% difference, 95% CI 5.2 to 27.3).

3.2. Maximum criteria-scores

The worst BOMBARD (wBOMBARD) score or maximum score within 3 h of arrival was more accurate for predicting severe sepsis/septic shock than the worst SIRS criteria (wSIRS) [AUROC 0.886 vs. 0.809, 0.077 difference, 95% CI, 0.039 to 0.116]. wBOMBARD was more accurate for predicting severe sepsis/septic shock than the worst qSOFA score (wSOFA) [AUROC = 0.886 vs. 0.789, 0.098 difference, 95% CI, 0.065 to 0.130]. Accuracy of wSIRS criteria was equivalent to wqSOFA score for predicting severe sepsis/septic shock (AUROC 0.809 vs. 0.789 respectively, 0.02 difference, 95% CI, −0.027 to 0.068).

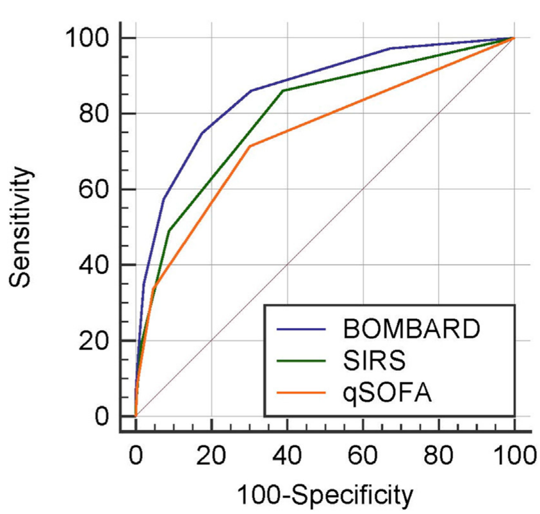

Fig. 1. Area Under the Receiver Operating Curve (AUROC) comparison between Initial BOMBARD, SIRS, and qSOFA criteria.

A wBOMBARD score ≥ 3 was more sensitive than wSIRS criteria ≥ 2 (86% vs. 81.1%, 4.9% difference, 95% CI, 1.4 to 8.4) and a wqSOFA score ≥ 2 (86% vs. 49.7%, 36.4% difference, 95% CI, 28.5 to 44.3) at predicting severe sepsis/septic shock. wSIRS criteria ≥ 2 were more sensitive than a wqSOFA score ≥ 2 at predicting severe sepsis/septic shock (81.1% vs. 49.7%, 31.5% difference, 95% CI, 23.9 to 39.1).

The sensitivity of a wBOMBARD score ≥ 3 was statistically similar to that of the wSIRS criteria ≥ 2 at predicting sepsis mortality (86.8% vs. 76.3%, 10.5% difference, 95% CI, 0.8 to 20.3). This study had 23% power to detect an 11% difference between sensitivities of wBOMBARD and wSIRS criteria in predicting sepsis mortality. Assuming a mortality rate of 26.6%, a study with at least 1448 patients with severe sepsis and septic shock patients would be needed to have 80% power (alpha 0.05) to detect an 11% difference (the observed difference) in sensitivity between the wBOMBARD and wSIRS criteria in predicting sepsis mortality. A wBOMBARD score ≥ 3 was more sensitive than the wqSOFA score ≥ 2 at predicting sepsis mortality (86.8% vs. 55.3%, 31.6% difference, 95% CI, 16.8 to 46.4).

3.3. Timing of criteria-scores

The median time from ED arrival to initial SIRS criteria calculation (62 min, 38 to 98 min - 25th to 75th percentile) was greater than the time from ED arrival to initial BOMBARD and initial qSOFA score calculations (10 min, 5 to 18 min - 25th to 75th percentile each) for all patients ($p < .001$ for both comparisons).

The median time from ED arrival to wSIRS criteria calculation (71 min, 48 to 105 min - 25th to 75th percentile) was greater than the median time from ED arrival to wBOMBARD (15 min, 7 to 44 min - 25th to 75th percentile) and wqSOFA score calculation (14 min, 7 to 38 min - 25th to 75th percentile) for all patients ($p < .001$ for both comparisons).

4. Discussion

Current recommendations to screen patients in the ED for sepsis rely on tools that have not proven useful in ED populations [2,4-10]. While the BOMBARD score was found to be more accurate with a higher sensitivity than other criteria, it was derived by comparing admitted severe sepsis/septic shock cases to non-sepsis patients. For this reason, BOMBARD might be less useful in a general ED population of patients with the majority being discharged from the ED. Rather, it would be useful in determining if patients likely to be admitted to the hospital are at risk for severe sepsis/septic shock and sepsis mortality.

SIRS criteria were derived from a consensus conference that selected “rapidly available” and “easy to define” features from the acute

Table 7
Comparison of sensitivity and specificity and accuracy of initial criteria at predicting sepsis mortality.[a]

	BOMBARD ≥ 3	SIRS ≥ 2	qSOFA ≥ 2
Sensitivity[b]	76.3% (59.8–88.6%)	44.7% (28.6–61.7%)	28.9% (15.4–45.9%)
Specificity	67.3% (62.4–71.9%)	80.1% (75.7–83.9%)	87.2% (83.5–90.4%)
AUROC[c,d]	0.732 (0.687–0.773)	0.667 (0.621–0.712)	0.663 (0.616–0.707)

[a] 95% confidence interval in parenthesis.
[b] McNemar's test: An initial BOMBARD score ≥ 3 was more sensitive than initial SIRS criteria ≥ 2 and an initial qSOFA score ≥ 2 at predicting sepsis mortality (BOMBARD 76.3% vs. SIRS 44.7%, 31.6% difference, 95% CI 16.8 to 46.4; BOMBARD 76.3% vs. qSOFA 28.9%, 48.7% difference, 95% CI 32.5 to 64.8). Initial SIRS criteria ≥ 2 were more sensitive than an initial qSOFA score ≥ 2 at predicting sepsis mortality (SIRS 44.7% vs. qSOFA 28.9%, 15.8% difference, 95% CI 4.2 to 27.4).
[c] Area under the receiver operating characteristic curve Receiver Operator Curve.
[d] The accuracy (AUROC) of the BOMBARD score was equivalent to SIRS criteria for predicting sepsis mortality (0.732 vs. 0.667, 0.065 difference, 95% CI −0.008 to 0.142). The BOMBARD score was more accurate than the qSOFA at predicting sepsis mortality (0.732 vs. 0.663, 0.069 difference, 95% CI 0.008 to 0.131). The accuracy of SIRS criteria was equivalent to the qSOFA score for predicting sepsis mortality (0.667 vs. 0.663, 0.005 difference, 95% CI – 0.071 to 0.080).

physiology and chronic health evaluation (APACHE) database of patients within intensive care units [20-22]. qSOFA criteria were derived from a study where the majority of cases comprised inpatients with a minority of patients enrolled from EDs and prehospital EMS encounters [2]. Thus, neither SIRS criteria or qSOFA scores should be expected to be an optimum screen for a population comprised entirely of ED patients.

Many ED studies have evaluated qSOFA scores and SIRS criteria in those already identified as having a severe infection, severe sepsis or already suspected of having an infection. This may lead to missing cases not initially suspected of having an infection [5,6,7,10,23-31]. We chose a broader group of control patients with and without infection since sepsis can occur in patients who do not initially appear to have an infection. Comparison to a population of patients that initially included those not felt to have infection is supported by the fact that nearly one third of sepsis patients in our study were admitted with non-infectious diagnoses and 13% of control patients had a primary infectious diagnosis on admission. Using a control population of patients with suspected infections would not have changed two important results in the study population: sensitivity of BOMBARD in detecting severe sepsis/septic shock and sensitivity in detecting sepsis mortality.

Study patients were identified by their international classification of diseases, clinical modification (ICD-10-CM) diagnostic codes defined by CMS and the National Center for Health Statistics [32-34]. Since October 2015, this classification has used the Sepsis-2 definitions for severe sepsis (evidence of organ dysfunction) and septic shock (lactate ≥4 mm/L or hypotension unresponsive to fluids) [32-36]. While newer, Sepsis-3, definitions have been proposed, they are not used to assign ICD-10 codes or track CMS quality measures (SEP-1, version 5.3) related to sepsis [10,37,38]. Regardless of which definitions are used to define sepsis and septic shock, our criteria were more sensitive than SIRS criteria and the qSOFA score in detecting sepsis related mortality.

5. Limitations

We did not directly analyze whether patients had features of severe sepsis or septic shock in the ED. Similar to authors who defined the qSOFA score, we identified study patients by their final discharge diagnostic codes and the presence of an infection or suspicion of infection within the first two days of admission [2]. Accordingly, the BOMBARD score was not constructed to detect severe sepsis/septic shock in the ED but to predict the presence of or the development of sepsis/septic shock in the ED or hospital, a final discharge diagnosis of severe sepsis/septic shock, and sepsis mortality.

Similar to studies that derived SIRS criteria and the qSOFA score, our study relied on retrospective data to identify features associated with sepsis [2,20-22]. Without prospective, standardized data collection, it is possible that historical and physical examination features might not be uniformly documented. Reviewers were not blinded to patient outcomes and diagnoses. Prospective validation studies should ensure that features are uniformly analyzed and documented and reviewers are blinded to final outcomes if possible.

The original derivation study of the qSOFA score, assigned a point for a GCS of ≤13. Others have defined the neurologic abnormality within qSOFA as an altered mental status [7,38-41], an abnormal Modified Early Warning System score [42], a GCS < 15 [43-45], or a GCS < 15 exclusive of dementia or mental retardation [5]. We used any alteration in mental status or a GCS < 15 regardless of baseline mental status in our definitions of BOMBARD and qSOFA. Limiting the neurologic component to only a GCS of <14, only a GCS < 15, only an examination finding of an altered mental status or excluding patients with a baseline abnormal mental status potentially could diminish the sensitivity of both scores.

Our derived score has more features than SIRS criteria and the qSOFA score. Unlike these screens, the BOMBARD score includes historical features. A more complex score might be more difficult to remember and calculate. Use of a shock index 0.86 might increase the complexity of calculating the BOMBARD score. We considered moving the shock index to 0.9 or 1.0 as these cutoffs have been found to predict admission to an intensive care unit, blood loss, requirement for surgery in trauma, and mortality from a variety of diseases [46-56]. Post hoc analysis of our data showed that raising the cutoff from 0.86 to 0.9 would decrease sensitivity of criteria for detecting severe sepsis/septic shock from 74.8% to 71.3% and sensitivity for predicting sepsis mortality from 76.3% to 68.4%. For this reason, the shock index cutoff of 0.86 was retained within the BOMBARD model.

Similar to the qSOFA derivation study, we measured the initial and the worst or highest score for derived criteria (BOMBARD), qSOFA and SIRS [2]. While vital signs were not repeated uniformly across all patients, each hospital used the ESI as a guide to monitor patients [14]. It is uncertain if non-uniform repeat vital sign assessment affected calculation of serial criteria/scores.

For 10 control cases, absent ED temperatures were imputed as <38 °C based on inpatient temperatures. Temperatures were documented a median of 1 h and 12 min (range 0 to 7 h) after hospital admission in these cases. With one exception, each of these control cases had six to 15 temperatures <38 °C recorded over the first 72 h of their hospital admission. The exception was a burn patient with smoke inhalation who had six normal temperatures over the first 7 h of their admission with a 7th temperature recorded as 38 °C 8 h after admission. All subsequent temperatures were recorded as normal during their five-day hospital admission and no infections were identified or empirically treated during their hospital stay. Moreover, post hoc analysis with these 10 control cases deleted would not have altered the main findings our study. The BOMBARD score for predicting severe sepsis/septic shock would still be significantly greater than that of the SIRS criteria (AUROC 0.862 vs. 0.809, 0.054 difference, 95% CI 0.014 to 0.094). Accuracy of the BOMBARD score for predicting sepsis/septic shock would be significantly greater than that of the qSOFA score (AUROC 0.862 vs.

0.744, 0.119 difference, 95% CI 0.082 to 0.156). Superior sensitivity of BOMBARD for predicting sepsis/septic shock and sepsis mortality would be unchanged if only controls were deleted.

BOMBARD scores, qSOFA scores and SIRS criteria were calculated for a maximum of 3 h after arrival at the hospital for each patient. This time cutoff was chosen because the study hospitals' median times from door to decision to admit was 150 min or less and by that time, care for the majority of patients had transitioned to admitting physicians.

This study was conducted from October to December during the early influenza season. It is possible that diagnostic scores might differ during influenza or other infectious outbreaks.

Interrater reliability of chart abstraction was excellent or almost perfect for all BOMBARD features. Interrater reliability of the clinical assessment of BOMBARD features was not performed. Others have found that vital signs and prediction scores based on physiologic variables have good to excellent interrater reliability [2,57-59]. A review of 52 studies that evaluated the interrater reliability of the GCS showed that kappa values were ≥0.6 in 85% of good quality studies [60]. Ideally, clinical features should be collected prospectively with repeated measures by multiple individuals to assess interrater reliability.

Our study did not assess physician clinical judgment. Before implementation of a clinical decision tool, researchers should assess whether that tool improves clinical judgment [61,62]. Others have noted that prediction tools often improve sensitivity in detecting pathology at the expense of worsened specificity [62,63]. This may lead to unnecessary testing, treatment, and admission rates [63].

6. Conclusion

A clinical prediction rule was developed to identify ED patients with severe sepsis/septic shock or who develop severe sepsis/septic shock in the hospital. This rule was more accurate and more sensitive than SIRS criteria and qSOFA scores at predicting severe sepsis/septic shock and sepsis mortality. Prospective validation in larger, more diverse ED settings is needed before this tool can be recommended for clinical use.

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Declarations of interest

None.

Author contributions

SGR and DC conceived the study.

SGR, DC, DB, JGB, and SFI designed the trial with input from all authors.

SGR, DC, JGB, SFI, DB, EH, and BG supervised the conduct of the trial, data collection/abstraction.

SGR, DB, EH, BG, KC, MD, RK, RL, AI, PP, and SP collected data.

SGR analyzed the data and performed statistical analysis.

SGR drafted the manuscript and all authors participated substantially to its revision.

All authors take responsibility for the paper as a whole.

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