
Research and Applications

An investigation of sepsis surveillance and emergency treatment on patient mortality outcomes: An observational cohort study

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ABSTRACT

Objective: To determine the prevalence of initiating the sepsis 3-h bundle of care and estimate effects of bundle completion on risk-adjusted mortality among emergency department (ED) patients screened-in by electronic surveillance.

Materials and Methods: This was a multiple center observational cohort study conducted in 2016. The study population was comprised of patients screened-in by St. John Sepsis Surveillance Agent within 4 h of ED arrival, had a sepsis bundle initiated, and admitted to hospital. We built multivariable logistic regression models to estimate impact of a 3-h bundle completed within 3 h of arrival on mortality outcomes.

Results: Approximately 3% ED patients were screened-in by electronic surveillance within 4 h of arrival and admitted to hospital. Nearly 7 in 10 (69%) patients had a bundle initiated, with most bundles completed within 3 h of arrival. The fully-adjusted risk model achieved good discrimination on mortality outcomes [area under the receiver operating characteristic 0.82, 95% confidence interval (CI) 0.79–0.85] and estimated 34% reduced mortality risk among patients with a bundle completed within 3 h of arrival compared to non-completers.

Discussion: The sepsis bundle is an effective intervention for many vulnerable patients, and likely to be completed within 3 h after arrival when electronic surveillance with reliable alert notifications are integrated into clinical workflow. Beginning at triage, the platform and sepsis program enables identification and management of patients with greater precision, and increases the odds of good outcomes.

Conclusion: Sepsis surveillance and clinical decision support accelerate accurate recognition and stratification of patients, and facilitate timely delivery of health care.

Key words: cloud computing, decision support, clinical, emergency services, hospital, epidemiology, sepsis, early diagnosis

Key findings

- Approximately 3% emergency department (ED) patients triggered an electronic sepsis surveillance alert within 4 h of arrival and admitted to hospital; 69% of them had the 3-h bundle of care initiated.
- Most patients had the 3-h bundle completed within 3 h of ED arrival, with an associated 34% reduced mortality risk compared to non-completers.
- Patients who activated a sepsis escalation tiered alert, typically within 30 min of their first systemic inflammatory response syndrome (SIRS) alert, were more likely to have the 3-h bundle completed within 3 h of arrival compared with patients with only a SIRS alert activated within the 4-h period after arrival.

BACKGROUND AND SIGNIFICANCE

Sepsis is associated with approximately half the all-cause in-hospital deaths¹ and mortality risk increases with severity of illness.^{2–5} International clinical practice guidelines recommend early recognition of sepsis and early treatment, typified by formalizing a sepsis program with screening, risk stratification, and completion of the Surviving Sepsis Campaign bundle of care for patients with sepsis within 3 h: first, measure lactate level; second, obtain blood cultures prior to giving antibiotics; third, administer broad spectrum IV antibiotics, and fourth, for patients who have deteriorated into septic shock, resuscitate with intravenous (IV) fluids bolus.^{6,7} These program components comprise a sepsis clinical decision support (CDS) system, and when integrated into a provider's clinical workflow, a patient is more likely to survive sepsis.^{8–11}

Impact evaluations on sepsis bundles on outcomes have shown promise. Using 2010 data, a longitudinal retrospective quality improvement study suggested bundle compliance was associated with 30% reduced mortality risk.¹² In comparison, a multinational point-prevalence study involving 618 hospitals conducted in 2013 estimated 40% reduction in mortality risk when bundle compliance was achieved; however, only 20% patients actually had a bundle completed in a timely manner.¹³ A more recent observational cohort study examined the association between patient outcomes and bundle initiation among patients admitted from the emergency department (ED) from 2014 to 2016.¹⁴ The study, which included 149 hospitals with a mandated sepsis program, reported 82% bundle compliance within 3 h of initiation, rather from arrival time zero, and estimated mortality risk increased 4% per elapsed hour after bundle initiation. Moreover, the study concluded that rapid completion of the initial IV fluid bolus, if applicable, was not associated with improved mortality outcomes.

None of these studies, however, discussed the application of modern electronic surveillance to screen-in ED patients at-risk of sepsis and its relationship to initiating the 3-h bundle. Building upon early studies that showed a positive relationship between sepsis screening, CDS, and treatment interventions,^{15–19} the more recent gaps in literature caused us to examine the concept of electronic surveillance as an effective approach to continuously screen patients for sepsis-risk upon arrival to hospital and the intersection of timely intervention to improve outcomes.

OBJECTIVES

Therefore, to clarify the discrepancies in the above research, the objective of this study was to determine the prevalence and timing of initiating the sepsis bundle, and estimate the effect of bundle compliance associated with improved mortality outcomes among patients who activated an electronic sepsis surveillance alert within 4 h after ED arrival.

MATERIALS AND METHODS

The study site was 8 different hospitals in 2 distinct geographic regions in southwest USA. All facilities had an enterprise electronic health record (EHR) system (Millennium: Cerner Corporation, Kansas City, MO, USA) and a sepsis surveillance system with integrated CDS (St. John Sepsis Surveillance Agent: Cerner Corporation, Kansas City, MO, USA). While all hospitals shared the cloud-based sepsis surveillance system, each hospital had their own localized sepsis CDS. This configuration enabled common experiences in deployment and management of the surveillance system across hospitals while localizing the routing of alert notifications to defined providers and tailoring the sepsis CDS to meet requirements established by each hospital's sepsis program. The surveillance system was consistent with a human factors design for a binary (off/on) alarm system with user access to clinical information that may be cross-checked before responding with a medical decision. The surveillance system contained 2 alerts: (1) indications of systemic inflammatory response syndrome (SIRS) (proxy for sepsis) and (2) indications of sepsis (proxy for severe sepsis). The system operated continuously 24/7 to monitor patient diagnostics from ED arrival until hospital discharge. Localized positions and relationships between providers and patients were established to route alerts, orders, and documentation. The sepsis CDS was guided by the Surviving Sepsis Campaign resuscitation and management bundles, to include STAT lactate measurement, obtain cultures prior to antibiotics, early administration of antibiotics, and early administration of fluids in patients with severe sepsis or septic shock.

The hospitals had a common clinical workflow using an EHR open chart configuration, differentiating SIRS from sepsis alert activations. The ED triage assessment and clinical documentation were updated to prime the sepsis surveillance system. The system's SIRS alert notifications were delivered to a designated nurse. In comparison, sepsis alert notifications were delivered to both the nurse and provider. Regardless of alert type, acknowledgement of alert notifications was required by either accepting the alert or selecting a bypass option. This acknowledgement was a purposeful hard stop rule to encourage quality of care for at-risk patients. A sepsis screening form facilitated the clinical assessment, which included STAT or point-of-care lactate measurement. The form, developed to meet Surviving Sepsis bundle compliance, pulled-in details of the alerting criteria. The cross-check option allowed the nurse or provider to establish whether the alert met criteria or not, and if indicated, document the severity. A positive screen activated the sepsis bundle. Situation-Background-Assessment-Recommendation (SBAR) language to escalate care was applied for rapid response and code sepsis alert processes. The hospitals' sepsis program go-live occurred simultaneously in 2015. This study was approved by the Western Institutional Review Board.

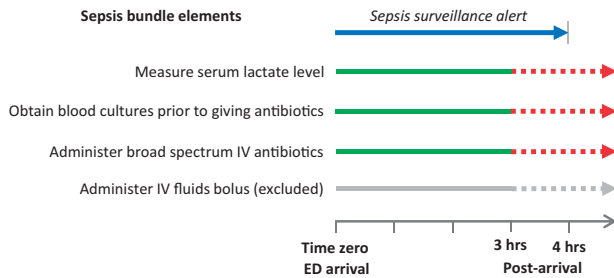


Figure 1. A flow diagram showing the relationship between sepsis surveillance and bundle elements.

Study design

This was a multiple center, observational cohort study. The study population included adults (≥ 18 years old) who arrived at the ED and admitted to the hospital over 90 consecutive days in 2016. The St. John Sepsis Surveillance Agent alert had activated within 4 h of ED arrival.²⁰ Patients were assessed for suspicion of infection, which required antibiotics be given within 72 h after cultures drawn, or cultures drawn within 24 h after antibiotic administration.^{21,22} These patients also had the 3-h bundle initiated, which included measurement of serum lactate. The bundle definition, however, was adapted to exclude administration of IV fluid bolus for patients in septic shock because the surveillance system was designed to detect at-risk patients of sepsis, rather than distinguishing septic shock specifically. Essentially, all patients screened-in by the surveillance system had lactates measured, cultures drawn, and antibiotics administered, but not necessarily given an IV fluid bolus (Figure 1). Two subgroups were established to distinguish bundle completion from non-completion. Completion of the bundle occurred when implementation followed the appropriate clinical protocolized process (ie, measure serum lactate, obtain cultures prior to administering antibiotics, and give antibiotics within 3 h after arrival); otherwise, the encounter was flagged as non-completion.

Definitions

The primary outcome was a composite of in-hospital death or referral to hospice at discharge. This primary outcome was proxy for in-hospital mortality. The primary exposure was time to bundle completion after ED arrival (ie, time zero).²³ Data source for all variables was the Millennium EHR system.

A sepsis 3-h bundle flag was created retrospectively. Bundle compliance was achieved when the 3 bundle elements were initiated and completed in proper sequence within 3 h of ED arrival; otherwise the bundle was considered incomplete. We calculated the time, in minutes, from arrival to first serum lactate measurement and first cultures drawn, which included blood, body fluid, bronchial, catheter tip, cerebrospinal fluid, fungal, ova and parasites, sputum, stool, tissue, urine, and wound. We calculated the time, in minutes, from arrival to first anti-infective antibiotics administered, which included ampicillin-sulbactam, azithromycin, cefepime, ceftriaxone, ciprofloxacin, clindamycin, fluconazole, fluticasone-salmeterol, levofloxacin, meropenem, piperacillin-tazobactam, and vancomycin. We also calculated the time, in minutes, from arrival to onset of infection, which was the earliest clinical event of either cultures drawn or antibiotics given.^{24,25}

Covariates included variables specified as potential confounders of patient outcomes. In addition to the types of surveillance alert(s) activated within the first 4 h after ED arrival, we included patient

demographics, severity of illness indicators, and subsequent admission to an intensive care unit (ICU), if applicable. We calculated the time, in minutes, from arrival to first activation of St. John Sepsis Surveillance Agent alert and an escalation alert, if triggered within 4 h after arrival.⁶ Alert activations at the patient level were grouped into 3 strata: SIRS alert only, SIRS $\Delta\uparrow$ sepsis escalation tiered alerts, and sepsis alert only. An alert activated when at least 3 SIRS criteria were present with alert notifications delivered to nursing, or 1 organ dysfunction and ≥ 2 SIRS criteria were present with alert notifications delivered to nursing and providers. The SIRS alert threshold included 3 of the following 5 SIRS criteria being satisfied: (1) temperature $>38.3^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; (2) heart rate >90 b.p.m.; (3) respiratory rate >20 b.p.m.; (4) white blood cell count $>12\,000$ cells/ mm^3 or <4000 cells/ mm^3 , or $>10\%$ immature (band) forms; or (5) glucose 140–200 mg/dL. The sepsis alert required at least 2 SIRS criteria and 1 organ dysfunction: (1) tissue perfusion: serum lactate >2.0 mmol/L; (2) cardiovascular system: systolic blood pressure <90 mm Hg and/or mean arterial pressure <65 mm Hg; (3) hepatic system: total bilirubin: ≥ 2.0 mg/dL and <10.0 mg/dL; and (4) renal system: serum creatinine: $\Delta\uparrow 0.5$ mg/dL from baseline. A look back period consisted of 12 h for serum lactate, 30 h for the other criteria, and 72 h for $\Delta\uparrow$ serum creatinine.²⁰ We calculated patient age, in years, upon admission. We calculated days from prior hospitalization discharge to current hospitalization; patients discharged within the previous 30 d and now returning to hospital were flagged.⁹ We calculated and categorized the Nation Early Warning Score (NEWS) composite score using the first vital signs and neurologic assessment documented, to include respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate, and level of consciousness.^{26,27} We calculated the corrected *apparent* Strong Ion Difference (SIDa) using the first laboratory results, where the corrected $\text{SIDa} = [(\text{Na}^+ + \text{K}^+ + 1.85) \text{ minus } \text{Cl}^-]$. Severe electrolyte abnormality and metabolic disturbance were indicated when the corrected $\text{SIDa} \leq 34.0$ or ≥ 48.0 mmol/L.^{9,28–31} We obtained and categorized the first serum lactate result.¹⁴ We calculated ED length of stay (LOS), in hours, from arrival to ED admission. We calculated hours elapsed from ED admission to ICU admission, if applicable, and were grouped into 3 strata: not admitted to ICU, admitted to ICU <4 h after ED admission, and ICU admission ≥ 4 h after ED admission. We flagged patients who were admitted to the ICU within 48 h of ED arrival.

Statistical analysis

Data were analyzed retrospectively. We performed bivariate analyses of patient characteristics by completion or non-completion of the bundle. Unadjusted bivariate analyses applied Fisher exact test and χ^2 test for dichotomous variables. The Mann–Whitney *U* test for independent samples was applied to estimate differences in medians and distributions.

Multivariable logistic regression (MLR) was used to estimate the effects of bundle completion on mortality outcomes, with adjustment for covariates and controlling confounders. Unadjusted and adjusted odds ratio (OR) with 95% confidence intervals (CIs) were reported for bundle completion and covariates. Two predictive models on the primary outcome were established. First, the baseline risk model included 4 parameters, to include bundle completion within 3 h of arrival, age, female sex, and admission to the ICU. Second, the fully-adjusted risk model incorporated the baseline model parameters, the St. John Sepsis Surveillance Agent alerts that activated within 4 h of arrival, and severity of illness covariates. We

used the area under the receiver operating characteristic (AUROC, *c*-statistic) to examine the clinimetric performance of the 2 MLR models, respectively. Accuracy comparisons were performed using the AUROC to discriminate the fully-adjusted model on the primary outcome vs the baseline model. AUROC output tables containing positive and negative predictive values were analyzed to potentially reclassify patients when holding specificity constant at 67%. We applied the Hanley–McNeil method for comparing AUC derived from same cases.³² We conducted a sensitivity analysis to compare NEWS categories, descriptively, with reference values in published literature.²⁷ In subgroup analysis, a MLR model estimated the effects of NEWS acuity, adjusted for age, on patient outcomes to include ICU admission <48 h after ED arrival; in-hospital mortality or hospice at discharge; and a composite of ICU, in-hospital mortality, or hospice. The age-NEWS adjusted ORs with 95% CIs were compared to reference parameter estimates.²⁷

A 2-tailed *P*-value <.05 was considered statistically significant. All analyses were conducted using SPSS v24 (IBM Corp., Armonk, NY, USA).

RESULTS

The St. John Sepsis Surveillance Agent screened-in approximately 3% (2172 of 75 958) ED patients within 4 h of arrival, which corresponded to 1 in 5 ($n=2172$ of 10 796, 20%) ED admissions. Alert reliability was 75% positive predictive value (PPV) ($n=1636$ of 2172 patients) on suspected infection. Serum lactate was measured among 92% ($n=1508$ of 1636) patients with suspected infection. By applying these criteria to bundle initiation and proxy for sepsis rule-in, alert reliability was 69% PPV ($n=1508$ of 2172 patients). Most patients ($n=862$, 57%) had the bundle completed within 3 h after arrival. Figure 2 illustrates a flow diagram of patient selection to this study.

Of the 1508 patients comprising the study population, 92% ($n=1383$) patients had the initial alert notification acknowledged by either a nurse or provider. The median time between notification and response completion was 29 min (interquartile range 18–100 min); 68% ($n=940$) responses were documented within 1 h after notification. Of the 1383 acknowledged alert notifications, 60% ($n=829$) had a documented source of suspected infection, 26% ($n=359$) had documented no identifiable source of infection, and 14% ($n=195$) responses selected the bypass option.

Table 1 describes characteristics of the study population ($n=1508$). The typical patient was 63 years old, slightly less likely to be female, and not hospitalized recently. The median NEWS composite score was 5 points (interquartile range 3–7 points). Approximately 1 in 3 ($n=481$, 32%) patients had NEWS ≥ 7 points in which nearly half ($n=215$ of 481, 45%) of them had NEWS ≥ 9 points, an indication of progressively severe physiologic deterioration. The median corrected SIDa was 42 mmol/L (interquartile range 40–44 mmol/L), which falls within the therapeutic normal range 40–46 mmol/L. About 1 in 11 ($n=132$, 9%) patients had very low SIDa (<38.0 mmol/L) in which 10% ($n=14$ of 132) patients had critically low SIDa (≤ 34.0 mmol/L). In contrast 5% ($n=77$) patients had very high SIDa (>48.0 mmol/L). The median serum lactate measure was 2.2 mmol/L (interquartile range 1.4–3.2 mmol/L). Severe tissue perfusion organ system involvement (ie, serum lactate ≥ 4.0 mmol/L) was indicated among 1 in 6 ($n=268$, 18%) patients. Most patients ($n=858$, 57%) activated a SIRS alert first in which 39% ($n=332$ of 858) patients subsequently triggered a sepsis escalation tiered alert within the 4-h post-arrival period. The median

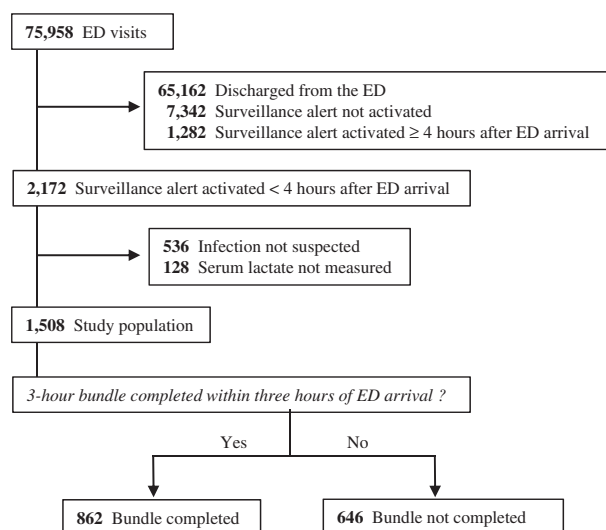


Figure 2. Patient selection schematic.

time between the first SIRS alert and sepsis escalation tiered alert was 26 min (interquartile range 13–59 min). A sepsis alert, therefore, was involved with approximately two-thirds ($n=982$, 65%) patients who triggered any type of surveillance alert within the 4-h period after ED arrival. Patients were likely to be admitted to hospital within 3 h of ED arrival, and 1 in 4 (26%) patients were admitted to the ICU during their hospitalization. Approximately 1 in 7 (14%) patients experienced an adverse outcome.

Characteristics of patients who had the bundle completed within 3 h of ED arrival were mostly similar to those who did not have the bundle completed, with exception of completers being associated with more severe physiologic deterioration upon arrival (ie, increasing NEWS composite score, SIRS Δ ↑sepsis escalation tiered alert activations, shorter ED LOS prior to admission, and a quicker admission to ICU). These patients were also more likely to have a sepsis diagnosis code documented at discharge.

Table 2 illustrates clinical process durations from ED arrival to surveillance alert and bundle clinical events. The median time from ED arrival to first surveillance alert was 71 min (interquartile range 41–116 min). The median time from arrival to completion of the bundle was 156 min (interquartile range 90–300 min). Despite cultures being drawn within 45 min of arrival, most patients ($n=996$, 66%) activated a surveillance alert before antibiotics were ordered. Process durations were accelerated among patients who had the bundle completed within 3 h of arrival when compared to patients who did not have the bundle completed. The noteworthy difference in clinical process reflected time elapsed between cultures drawn and antibiotic orders and administration, despite the timeliness of surveillance alerts.

In multivariable analysis (Table 3), the bundle completion was associated with 34% decreased mortality risk when applying the fully-adjusted model for acuity in surveillance alerts, age, female sex, readmission status, NEWS composite score, SIDa ≤ 34 mmol/L or SIDa ≥ 48 mmol/L, serum lactate measurement, and timing of ICU admission (adjusted OR 0.66, 95% CI 0.47–0.93). The fully-adjusted model displayed good fit (Hosmer and Lemeshow test $\chi^2=3.33$, $df=8$, $P=.91$) and achieved good discrimination on the mortality outcome (AUROC *c*-statistic = 0.82, 95% CI 0.79–0.85).

Table 1. Bundle completion by characteristics of patients

Parameters	Study population number (%)	Bundle completed within 3 h after ED arrival		P-value
		Yes	No	
Hospitalizations	1508 (100)	862 (57)	646 (43)	—
Age (years), median (IQR)	63 (51–75)	64 (51–75)	63 (51–75)	.45
Female	703 (47)	387 (45)	316 (49)	.13
First clinical results				
Recent discharge, <30 d	120 (08)	65 (08)	55 (09)	.50
NEWS score, points				.001
0–4	636 (42)	317 (37)	319 (49)	
5–6	391 (26)	230 (27)	161 (25)	
7–8	266 (18)	169 (19)	97 (15)	
9–20	215 (15)	146 (17)	69 (11)	
SIDa ≤34 or ≥48 mmol/L	91 (06)	55 (06)	36 (06)	.52
Serum lactate, mmol/L				.68
0.0 < 2.0	605 (40)	336 (39)	269 (41)	
2.0 < 3.0	466 (31)	273 (32)	193 (30)	
3.0 < 4.0	169 (11)	101 (12)	68 (11)	
4.0 ≤ 25.0	268 (18)	152 (17)	116 (18)	
Surveillance alert(s) activated within 4 h after arrival				.001
SIRS	526 (35)	275 (32)	251 (39)	
SIRS Δ↑ Sepsis	332 (22)	221 (26)	111 (17)	
Sepsis	650 (43)	366 (42)	284 (44)	
ED LOS (h), median (IQR)	2.8 (1.7–4.2)	2.6 (1.8–3.7)	3.1 (1.5–4.9)	.002
Timing of admission to ICU after ED admission				.001
None	1109 (74)	650 (76)	459 (71)	
<4 h	242 (16)	149 (17)	93 (14)	
≥4 h	157 (10)	63 (07)	94 (15)	
Expired or hospice	214 (14)	110 (13)	104 (16)	.073
LOS (d), median (IQR)	4.3 (2.7–7.2)	4.2 (2.5–7.1)	4.4 (2.7–7.2)	.44
Sepsis diagnosis code	941 (62)	585 (68)	356 (55)	.001

Note: Statistical measures report counts and percentage (%), if not otherwise indicated.

IQR: interquartile range; NEWS: National Early Warning Score; SIDa: *apparent* Strong Ion Difference; SIRS: systemic inflammatory response syndrome; ED: emergency department; LOS: length of stay; ICU: intensive care unit.

Table 2. Bundle completion by timing of clinical events

Parameters	Study population	Bundle completed within 3 h after ED arrival		P-value
		Yes	No	
Minutes between arrival and surveillance alert, median (IQR)	71 (41–116)	65 (36–100)	84 (50–137)	.001
Minutes between arrival and bundle elements, median (IQR)				
Serum lactate measured	42 (20–88)	34 (17–61)	68 (28–176)	.001
Microbiology cultures drawn	43 (17–91)	33 (13–62)	76 (28–197)	.001
Antibiotics ordered	101 (49–182)	63 (29–95)	203 (147–366)	.001
Antibiotics given	144 (87–249)	98 (67–132)	282 (206–515)	.001
Surveillance alert activated before antibiotics ordered, <i>n</i> (%)	996 (66)	440 (49)	556 (86)	.001

ED: emergency department; IQR: interquartile range.

Comparing the unadjusted to the fully-adjusted ORs, the observed effect of bundle completion moderated sepsis-risk associated with an increased likelihood of adverse outcome among patients experiencing moderate-to-severe physiologic deterioration. A similar effect, however, was not observed among patients recently discharged from the hospital and now returning to the ED, critical derangement of vital signs (NEWS ≥9 points), remarkable electrolyte abnormalities (SIDa ≤34 or ≥48 mmol/L), or severe tissue perfusion organ system involvement (serum lactate ≥4 mmol/L).

Analysis of positive and negative predictive values derived from the AUROC result output tables, the baseline risk model

AUROC *c*-statistic = 0.74, 95% CI 0.70–0.79 and fully-adjusted risk model AUROC *c*-statistic = 0.82, 95% CI 0.79–0.85 (*P* < .001). Holding specificity constant at 0.67 (ie, 33% false positive rate), sensitivity of the baseline model compared to the fully-adjusted model was 0.68 and 0.82, respectively. The fully-adjusted model correctly reclassified, in absolute terms, 3% patients from the baseline model, which translates to a relative improvement in sensitivity of Δ↑ 20% (see [Supplementary File, Tables S1 and S2](#)).

Sensitivity analysis included all patients in the study population. In subgroup analysis, each rise in the respective NEWS category was

Table 3. Odds ratios before and after adjustment for covariates on mortality

Parameters	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Bundle completed <3 h after ED arrival	0.76 (0.57–1.02)	0.66 (0.47–0.93)
Surveillance alert(s) <4 h after ED arrival		
SIRS (reference)	1.00	1.00
SIRS Δ ↑ Sepsis	2.18 (1.42–3.34)	1.60 (0.89–2.87)
Sepsis	2.47 (1.70–3.57)	1.78 (1.06–2.99)
Age, per one year	1.04 (1.03–1.05)	1.04 (1.03–1.05)
Female	1.07 (0.80–1.43)	1.06 (0.76–1.47)
First clinical results		
Recent discharge within 30 d	2.53 (1.65–3.89)	2.18 (1.34–3.56)
NEWS score, points		
0–4 (reference)	1.00	1.00
5–6	1.40 (0.94–2.09)	1.09 (0.70–1.70)
7–8	1.73 (1.13–2.66)	1.17 (0.72–1.89)
9–20	4.33 (2.92–6.43)	3.14 (1.98–4.98)
SIDa \leq 34 or \geq 48 mmol/L	2.31 (1.42–3.78)	2.17 (1.23–3.82)
Serum lactate (mmol/L)		
0.0 < 2.0 (reference)	1.00	1.00
2.0 < 3.0	1.02 (0.68–1.52)	0.71 (0.43–1.18)
3.0 < 4.0	1.36 (0.81–2.29)	0.74 (0.39–1.42)
4.0 < 25.0	4.22 (2.91–6.11)	2.32 (1.38–3.92)
Timing of admission to ICU		
None (reference)	1.00	1.00
<4 h after ED admission	4.61 (3.26–6.52)	2.51 (1.68–3.75)
\geq 4 h after ED admission	4.42 (2.96–6.62)	3.92 (2.52–6.08)

Notes: Mortality outcome is the composite of expired in-hospital or referral to hospice at discharge. Multivariable logistic regression; model constant = -5.570 . Model performance: Nagelkerke $R^2 = 0.28$; Hosmer and Lemeshow test $\chi^2 = 3.33$, $df = 8$, $P = 0.91$; AUROC c -statistic = 0.82, 95% CI (0.79–0.85).

ED: emergency department; SIRS: systemic inflammatory response syndrome; NEWS: National Early Warning Score; SIDa: *apparent* Strong Ion Difference; ICU: intensive care unit; OR: odds ratio; CI: confidence interval.

associated with an increased risk of adverse outcome when compared to the lowest category. The age-NEWS adjusted OR demonstrated a risk profile similar to the reference, and all parameter estimates fell inside the reference parameter OR 95% CI (see [Supplementary File, Tables S3 and S4](#)).

DISCUSSION

Approximately 3% ED patients activated an electronic sepsis surveillance alert within 4 h of arrival, in which 69% patients had a bundle initiated and admitted to hospital. Almost half the patients who activated a SIRS alert subsequently activated a sepsis escalation tiered alert too, usually within 30 min of their first alert. Thus, by initiating the bundle, regardless of alert acuity at first activation, was likely associated with reduced mortality risk for many sick patients because determining who might deteriorate into catastrophic septic organ failure remained elusive. Indeed, patients who had the bundle completed within 3 h of arrival had one-third (34%) reduction in mortality risk. Our study suggests a symbiotic relationship exists between a patient presenting to ED triage, electronic surveillance screening, and treatment effects on patient outcomes.

Given this is potentially the first study to integrate sepsis surveillance, sepsis risk stratification, and NEWS acuity categorization for patients within 4 h of ED arrival, we offer a unique contribution to the literature. Our study, nevertheless, has several limitations. First, since this was a multiple center observational cohort study involving

8 EDs in the southwest USA, the findings may not be applicable to other hospitals. Second, all hospitals shared an electronic surveillance system with alert notifications integrated into the clinical workflow, each hospital could localize their sepsis program and clinical processes to meet local needs. However, the study hospitals' sepsis programs, in general, were characteristically similar to a mandated sepsis program.^{9,23} Third, we relied upon clinimetric reliability of the St. John Sepsis Surveillance Agent and operational management of the system to select patients for the study population because sepsis has been underdiagnosed historically.³³ Fourth, by excluding administration of IV fluid bolus from the definition of the bundle covariate, measurement error may have been introduced into in the mortality risk model for a subgroup of patients in septic shock within 4 h of ED arrival. However, a recent study found no association between timing of bolus completion and in-hospital mortality among ED patients in septic shock.¹⁴ Fifth, the study design incorporated structured clinical and administrative data types, and applied a retrospective analysis of this data beginning almost 5 months after launch of the hospitals' sepsis management programs, which may have introduced informed presence and other selection bias associated with real-world clinical practice and processes.³⁴ Sixth, the study's Use Data were not specifically checked by study hospitals, which should be considered when interpreting study results. Use Data originated with the hospitals' EHR system, encounter data were extracted by a qualified data engineer, and the transformation of clinical event data was kept to a minimum. The fully-adjusted mortality risk model was not over-parameterized. Furthermore, to

ascertain face validity, we used published literature as a reference to compare patients' crude NEWS composite scores³⁵ and applied subgroup analysis of NEWS categorization by outcome.²⁷

Indeed, sepsis surveillance is an effective approach toward reducing mortality risk among vulnerable patients, despite others reporting to the contrary.^{36,37} A 2-stage sepsis CDS system, which surveillance is the front-end component, provides early recognition of patients at-risk of sepsis, facilitates diagnostic assessment and risk stratification, and supports medical decisions. Since surveillance is a component of a CDS system as well as a prompt for bundle initiation and completion, this association between surveillance and treatment is consistent with sepsis programs that incorporate a 2-stage CDS system into the clinical workflow.²⁴ Our study findings speak to the robustness of sepsis definition and clinical protocol,⁶ as shown by high alert reliability (ie, PPV) and functionality to validate alert data on-line and real-time, which encourages provider adoption necessary to achieve high response to surveillance alerts³⁸ and intervene as appropriate. In contrast, insufficiently parameterized surveillance systems may not realize acceptable clinimetric performance necessary for adoption.^{39,40}

In light of our findings, in addition to assessing readmission status, measurement of serum lactate and examining the corrected SIDA for electrolyte abnormalities, the NEWS tool is supportive and shows promise in a standardized triage assessment⁴¹; in particular, NEWS ≥ 7 points and escalation NEWS ≥ 9 point thresholds.⁴² These diagnostic factors form imperatives given the high prevalence of sepsis among ED patients and urgency in treatment.⁴³ Moreover, bundle completion may be facilitated by coupling alert notifications to clinical events, especially in medication administration processes during handoffs or transitions. An examination of unstructured clinical data types may add depth and context to further research and sepsis quality improvement initiatives. The 2016 SEP-3 guideline definition, applied against prior guidance among patients presenting to the ED, may also elevate our understanding of differential risk of sepsis and timeliness of interventions on patient health and wellness outcomes.⁴⁴⁻⁴⁶

CONCLUSION

Sepsis programs accelerate accurate recognition and stratification of patients, as well as facilitate the delivery of healthcare, thereby supporting robust diagnostic protocols to detect sepsis early in the care process and enabling providers to initiate aggressive treatments. Electronic surveillance and CDS, beginning at triage and effectively utilizing the ED tracking board for individualized patient management, establishes a platform for identifying and managing susceptible patients with greater precision, and may increase the odds of good outcome. The sepsis bundle of care is an effective intervention for many patients and likely to have the bundle completed within 3 h after arrival when monitored by surveillance with reliable 2-tier alert notifications integrated into clinical workflow. This being said, real-time monitoring and status of orders, particularly antibiotics, against time zero may improve bundle completion and outcomes, with an objective of placing the appropriate antibiotic orders within 2 h 30 min after ED arrival.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online. Data available from the

Dryad Digital Repository: <http://dx.doi.org/10.5061/dryad.gt5m884>.

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