THE 28-DAY MORTALITY OUTCOME OF THE COMPLETE HOUR-1 SEPSIS BUNDLE IN THE EMERGENCY DEPARTMENT

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ABSTRACT—**Introduction:** The Surviving Sepsis Campaign published the Hour-1 Sepsis Bundle in 2018. The first-hour management of patients with sepsis in the emergency department (ED) is important, as suggested in the Hour-1 Sepsis Bundle. The objectives of the present study were to evaluate 28-day mortality and delayed septic shock with use of a complete and incomplete Hour-1 Sepsis Bundle in the ED. **Methods:** This prospective cohort study included adult patients with sepsis from March to July 2019. We followed the sepsis protocol used in the ED of a tertiary care hospital. **Results:** We enrolled 593 patients, with 55.9% in the complete Hour-1 Sepsis Bundle group. The 28-day mortality was 3.9% overall and no significant difference between the complete and incomplete Hour-1 Sepsis Bundle groups (3.6% vs. 4.2%, $P = 0.707$). Complete Hour-1 Sepsis Bundle treatment was not associated with 28-day mortality (adjusted $OR = 2.04$, 95% confidence interval $[CI] = 0.72–5.74$, $P = 0.176$) or delayed septic shock (adjusted $OR = 0.74$, 95% $CI = 0.30–1.78$, $P = 0.499$). Completion of each bundle did not affect outcomes of 28-day mortality and delayed septic shock. **Conclusions:** The complete Hour-1 Sepsis Bundle treatment in the ED was not significantly associated with 28-day mortality and delayed septic shock. **Trial registration:** The trial was registered in the Thai Clinical Trial Registry, TCTR 20200526013.

KEYWORDS—28-Day mortality, emergency department, hour-1 sepsis bundle, sepsis, septic shock

ABBREVIATIONS—ATB—antibiotic; ED—emergency department; EP—Emergency Physician; qSOFA—quick Sequential Organ Failure Assessment; SOFA—Sequential Organ Failure Assessment

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to serious infection (1). The Surviving Sepsis Campaign (SSC) has declared that sepsis is a global public health emergency. The SSC was established in 2002 and created sepsis treatment bundles to reduce mortality. Compliance with these Sepsis Bundles is associated with 25% reduction in the risk of death and cost (2). The most recently revised Hour-1 Sepsis Bundle was developed in 2018 and published in "SSC: International Guidelines for Management of Sepsis and Septic Shock: 2016" (3). The Suggestion in the Hour-1 Sepsis Bundle was the five suggestions to initiate the sepsis treatment within 1 h of presentation. Time zero in the emergency department (ED) is the time of triage:

1) Measure blood lactate level and re-measure if the initial lactate is >2 mmol/L,
2) Obtain blood culture specimens prior to administration of antibiotics,
3) Administer broad-spectrum antibiotics,
4) Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L,
5) Administer vasopressors if the patient is hypotensive during or after fluid resuscitation, to maintain mean arterial blood pressure ≥ 65 mm Hg (3).

The first-hour management of patients with sepsis in the ED is important, as suggested in the Hour-1 Sepsis Bundle (2). These recommendations emphasize early recognition, initiation of antimicrobial therapies, and provision of organ support (4). Multiple studies have shown a reduction in admission to the intensive care unit and lower mortality with the use of an Hour-3 Sepsis Bundle (5, 6). However, the Hour-1 Sepsis Bundle recommendation lacks supporting scientific evidence (5, 7). The implementation in a real-life ED setting has been controversial (5).

In the Tertiary care and university hospitals in Thailand, the sepsis protocols in the ED have been applied since 2015. The mortality rate of ED patients with sepsis was 5.65% in 2016. The latest 2019, an updated ED sepsis protocol emphasizes triage time as time zero as early recognition, initial investigation, empirical antimicrobials, and intravascular fluid administration by the first Emergency Physician (EP) in attendance. The initial sepsis management in the ED is performed by using a checklist in the ED sepsis protocol when the EP suspects sepsis. However, first-hour completion depends on multiple factors. Pre-treatment factors and the triage system affect the

time until the patient is attended by an EP and the time to treatment. Treatment factors involve individual and personalized treatment for multiple comorbid diseases. Overcrowding in the ED has an additional important effect on multiple processes in the ED. In the present study, we aimed to investigate the effect on patient outcomes of using a complete and an incomplete Hour-1 Sepsis Bundle in the ED.

METHODS

This trial was registered in the Thai Clinical Trial Registry (TCTR 20200526013) and approved by the ethics committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, in January 2019.

Study design and study site

This prospective cohort study was conducted in the ED of a tertiary care and university hospital in Thailand from March to July 2019. The ED receives approximately 60,000 visits annually.

We did not rely on the data of historical control because we planned to reduce bias from time trend, period, and environmental effect (differences in the development of sepsis management).

Study participants

Using ED sepsis protocol registration, patients aged 18 years or more who visited the ED were enrolled. The inclusion criteria were patients who were suspected of sepsis or septic shock. According to an EP using the ED sepsis protocol, they included by clinical judgment or two or more quick Sequential Organ Failure Assessment (qSOFA) scores. The exclusion criteria were:

1) patients with a do-not-resuscitate order,
2) patients who refused treatment,
3) patients who were referred in from or referred out to other hospitals,
4) patients who had received previous treatment for sepsis, and
5) patients with cardiac arrest on arrival to the ED.

Data collection and measurement

We collected baseline characteristics of patients including age, gender, and underlying illnesses. The pre-treatment information was vital signs at triage and qSOFA score. Initial patient information included initial lab results, SOFA score, diagnosis of sepsis or initial septic shock, source of sepsis, and appropriate spectrum of antibiotic. We review the hemoculture result, specimen culture, and antibiotic spectrum covering the suspected source pathogen. An appropriate antibiotic was defined as the patients had received antibiotics according to the type of pathogen, consideration of the previous antibiotic, and history of previous admission or treatment. The time from triage to each Hour-1 Sepsis Bundle and the overall completed protocols were recorded if patients were registered in a database of the ED sepsis protocol.

Clinical outcomes

The primary outcome was 28-day mortality. The secondary outcome was delayed septic shock within 48 h and Intensive care unit (ICU) admission.

Sample size and statistical analysis

The sample size was calculated using the equation for comparison of two independent proportions in cohort studies. The probability of type I error ($\alpha = 0.05$) and probability of type II error ($\beta = 0.10$) was included in the formula. The mortality in 2014 among patients with sepsis in the ED who were not treated with an ED sepsis protocol was 14.2%. In 2015, mortality decreased to 5.65% after an initiation of the ED sepsis protocol. The sample size for one sample was 278 and the sample size for two samples was 556 patients.

The sample characteristics were summarized using descriptive statistics, including number and percentage, mean and standard deviation (SD), and median and interquartile range (IQR). Continuous variables were compared between groups using an independent t test or Mann–Whitney

U test. Chi-square tests or Fisher's exact test was used for categorical data. Univariate analysis was performed for the association between the treatment group and outcome, and to identify candidate related factors for inclusion in multiple logistic regression analysis. Multivariate logistic regression analysis was performed to determine independently related factors associated with a significant outcome (P-value ≤ 0.05). The results of multivariate analysis were reported as the adjusted odds ratio (OR) and 95% confidence interval (CI). Statistical analyses were performed using Stata 16.1 (StataCorp LLC, College Station, TX).

RESULTS

Baseline characteristics

In this study, we enrolled 593 patients from ED sepsis protocol registration. A total of 332 (55.9%) patients were included in the complete Hour-1 Sepsis Bundle group (Fig. 1). Of the total, 182 (55.1%) were female patients and the most common underlying condition was hypertension (54.5%). Five hundred eighty-four (98.15%) patients were diagnosed with sepsis and 1.85% had initial septic shock. The two most common sources of infection were urinary tract infection (36.6%) and pneumonia (34.4%). Median time from triage to each Hour-1 Sepsis Bundle was different between the complete and incomplete groups, as shown in Table 1. The severity of sepsis, defined as qSOFA score ≥ 2 and initial venous lactate level ≥ 4, was greater in the incomplete Hour-1 Sepsis Bundle (Table 1).

Outcomes

Our results showed that the complete Hour-1 Sepsis Bundle did not affect 28-day mortality (adjusted OR = 2.04, 95% CI = 0.72–5.74, $P = 0.176$) (Table 2). Subgroup analysis of each completed bundle was not associated with 28-day mortality. The antibiotics administrated within 1 h (adjusted OR = 1.85, 95% CI = 0.51–6.71, $P = 0.343$), IV fluid 30 mL/kg (adjusted OR = 1.74, 95% CI = 0.26–11.65, $P = 0.568$), and vasopressors within 1 h (adjusted OR = 1.32, 95% CI = 0.37–4.80, $P = 0.669$) were shown in Table 3.

The complete Hour-1 Sepsis Bundle was not associated with the outcome of delayed septic shock (adjusted OR = 0.73, 95% CI = 0.30–1.78, $P = 0.499$) (Table 2). Subgroup analysis of each complete bundle did not affect delayed septic shock. The antibiotics within 1 h (adjusted OR = 2.11, 95% CI = 0.24–18.35, $P = 0.499$) and IV fluid 30 mL/kg (adjusted OR = 1.43, 95% CI = 0.23–8.80, $P = 0.700$) were shown in Table 3. Our cohort study also showed the complete Hour-1 Sepsis Bundle was associated with ICU admission (adjusted OR = 1.90, 95% CI = 1.15–3.12, $P = 0.012$) (Table 2). Univariable analysis of 28-day mortality outcome were shown in Table 4.

DISCUSSION

The SSC 2018 states that compliance with Sepsis Bundles can improve survival in patients with sepsis and septic shock (3). An important change in the SSC 2018 bundle is that the Hour-3 and Hour-6 bundles were combined into an ''Hour-1 Bundle''.

Data from our setting showed only 56.3% compliance with the Hour-1 Bundle. Most patients had non-shock sepsis
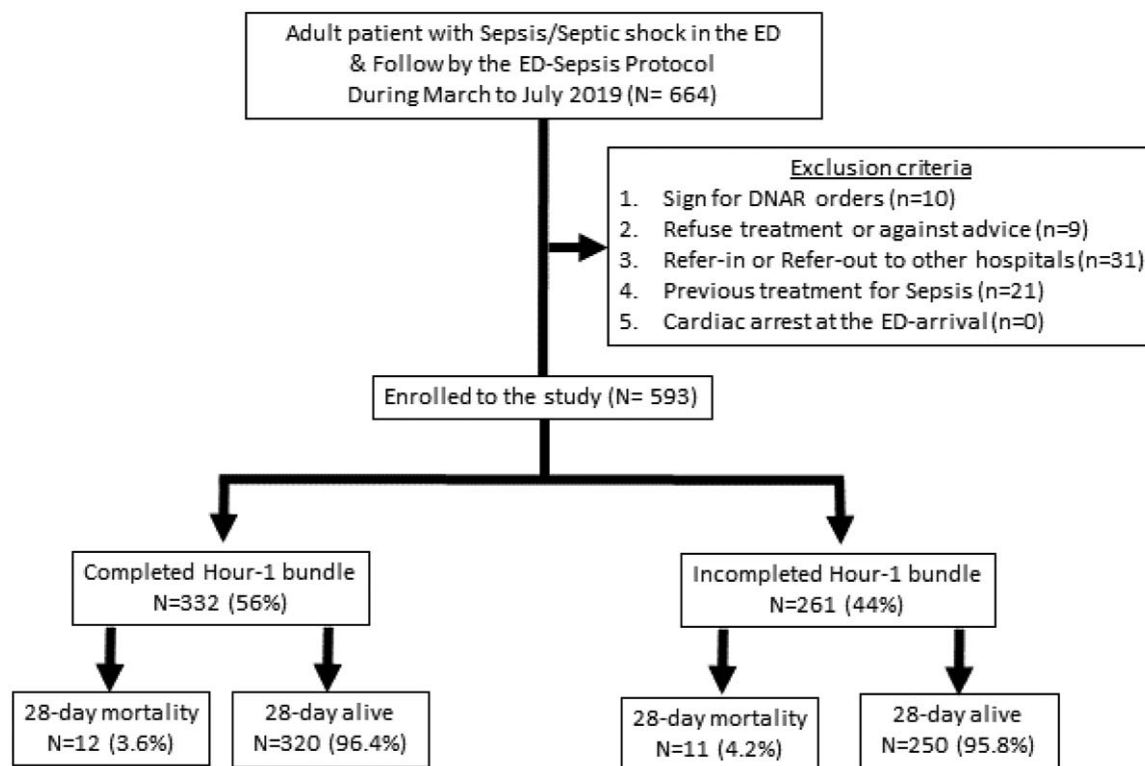
Fig. 1. **Study flow chart.** DNAR indicates do not attempt resuscitation; ED, emergency department; n, number.

(98.15%) and less severe sepsis. The 28-day mortality was 3.6% vs. 4.2% ($P = 0.166$) in the complete and incomplete Hour-1 Bundle groups. The complete Hour-1 Bundle did not affect 28-day mortality. Treatments in the incomplete Hour-1 Bundle were delayed but completed afterwards. The median time to obtaining blood culture specimens and measuring lactate levels was 60 (IQR 23, 81) min, and the time to antibiotics administration was 74 (IQR 54, 101) min. Most patients were initially treated within 1 to 3 h (complete Hour-3 bundle). This implies that there is no difference in mortality outcomes between the complete Hour-1 Bundle and Hour-3 Bundle in our setting.

Our findings are consistent with the results of Seymour et al., demonstrating that patients with septic shock who received the complete Hour-3 Bundle had improved mortality outcomes (8). There was no survival benefit in patients who did not have septic shock as cited in the SCC 2018 (8, 9). Hu et al. and Peltan et al. reported 28-day mortality was associated with Hour-3 Bundle but not with the Hour-1 Sepsis Bundle (10, 11). However, a systematic review and meta-analysis conducted in 2015 found no significant mortality benefit for administering antibiotics within 3 h of ED triage or within 1 h of shock recognition in severe sepsis and septic shock (12).

Filbin et al. reported no difference in hospital mortality before and after improvement in sepsis care quality, including administration of antibiotics within 1 h (13). The current data showed that receiving antibiotics during the first hours after triage had very little effect on 28-day mortality in patients with sepsis (non-shock). The Infectious Diseases Society of America (IDSA) has expressed concern regarding the variety of diseases that can mimic sepsis. IDSA revised the National Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Sepsis Quality Measure in 2020 to only recommend broad-spectrum antibiotics within 1 h in patients with septic shock, and appropriate empiric antibiotics as soon as possible in patients with sepsis but without shock (14).

In subgroup analysis, complete Hour-1 IV fluid 30 mL/kg in patients with hypotension or serum lactate ≥ 4 mmol/L was not associated with mortality, as in a study by Seymour et al. (8). In a large study that analyzed the independent effect of the fluid bolus (30 mL/kg) in the Sepsis Bundle, rapid completion of the fluid bolus had no effect on in-hospital mortality (15). However, patients who received more than 5 L of fluid during the first day of hospitalization had a significantly increased risk of death. Therefore, this may be harmful in some patients such as those with heart disease or renal failure (16–18). Personalized medicine could be important in addressing this issue.

Subgroup analysis showed that complete Hour-1 vasopressors in patients with septic shock were not associated with mortality, as in the study by Permpikul et al. (19). Although, our study included a small proportion of patients with initial septic shock (1.85%). Reports regarding vasopressors and IV fluids in septic shock are limited. Therefore, further investigation of these aspects in septic shock is suggested.

The complete Hour-3 Bundle did not affect the outcome of delayed septic shock, including in each bundle subgroup (antibiotics, IV fluid 30 mL/kg, and vasopressors). It is possible that our data was limited with respect to confounding factors of delayed shock, for example, patients' volume response, appropriate antibiotics, and source control.

TABLE 1. **Baseline characteristics between the complete and incomplete Hour-1 Sepsis Bundle groups**

Demographic data	All n = 593	Complete Hour-1 Bundle n = 332	Incomplete Hour-1 Bundle n = 261	P
Age (y), mean (SD)	69 (17.5)	70 (17.0)	68 (17.9)	0.108
Female, n (%)	327 (55.1)	182 (54.8)	145 (55.6)	0.858
Underlying conditions, n (%)				
Hypertension	323 (54.5)	193 (58.1)	130 (49.8)	0.043
Diabetes mellitus	215 (36.3)	117 (35.2)	98 (37.5)	0.562
Chronic kidney disease	155 (26.1)	94 (28.3)	61 (23.4)	0.174
Heart disease	138 (23.3)	91 (27.4)	47 (18.0)	0.007
Liver disease	60 (10.1)	37 (11.1)	23 (8.8)	0.350
Immunocompromised	212 (35.8)	110 (33.1)	102 (39.1)	0.134
Vital signs at triage, mean (SD)				
Systolic BP (mm Hg)	131 (31)	137 (30)	123 (31)	<0.001
Mean arterial BP (mm Hg)	91 (2)	95 (18)	86 (18)	<0.001
Heart rate (bpm)	108 (22)	108 (23)	108 (22)	0.966
Body temperature (°C)	38.3 (1)	38.3 (1)	38.3 (1)	0.557
Respiratory rate (bpm)	24 (5)	25 (5)	23 (4)	<0.001
Oxygen saturation (%)	96 (6)	95 (7)	97 (5)	0.001
qSOFA score, median (min, max)	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.438
qSOFA ≥ 2, n (%)	112 (18.9)	52 (15.7)	60 (23.0)	0.024
qSOFA = 0, n (%)	154 (26.0)	70 (21.1)	84 (32.2)	0.002
qSOFA = 1, n (%)	327 (55.1)	210 (63.3)	117 (44.8)	<0.001
qSOFA = 2, n (%)	95 (16.0)	46 (13.9)	49 (18.8)	0.105
qSOFA = 3, n (%)	17 (2.9)	6 (1.8)	11 (4.2)	0.081
Laboratory tests, median (IQR)				
White blood cell count (10^3)	10 (6.8,13.4)	9.85 (6.7,13.2)	10.2 (6.8, 14)	0.339
Serum creatinine (mg/dL)	1.0 (0.7, 1.5)	0.98 (0.7,1.5)	0.97 (0.7,1.4)	0.524
Initial serum lactate (mmol/L)	2 (1.6, 2.8)	2 (1.6, 2.7)	2 (1.6, 3.4)	0.156
Initial venous lactate ≥ 4, n (%)	65 (11)	11 (3.3)	54 (20.7)	<0.001
Positive hemoculture result, n (%)	89 (15)	45 (13.6)	44 (16.9)	0.263
SOFA* score, median (min, max)	1 (0, 11)	1 (0, 10)	1 (0, 11)	0.588
SOFA ≥ 2	270 (45.5)	154 (46.4)	116 (44.4)	0.638
Diagnosis, n (%)				
Sepsis	584 (98.2)	331 (99.7)	251 (96.2)	0.002
Initial septic shock	11 (1.9)	1 (0.3)	10 (3.8)	
Source of infection, n (%)				
Pneumonia	204 (34.4)	140 (42.2)	64 (24.5)	<0.001
Urinary tract infection	217 (36.6)	110 (33.1)	107 (41.0)	0.048
Diarrhoea, GI tract	60 (10.1)	30 (9.0)	30 (11.5)	0.324
Skin and soft tissue	34 (5.7)	13 (3.9)	21 (8.1)	0.032
Septicemia	60 (10.1)	31 (9.3)	29 (11.1)	0.477
Hepatobiliary tract	10 (1.7)	5 (1.5)	5 (1.9)	0.701
CNS infection	2 (0.3)	0 (0)	2 (0.8)	0.110
Unknown	6 (1.0)	3 (0.9)	3 (1.1)	0.767
Median time from triage to bundle (min), median (IQR)				
Triage to measure lactate level	32 (15, 56)	22 (14, 40)	60 (23, 81)	<0.001
Triage to obtain blood culture	32 (15, 56)	23 (14, 40)	60 (23, 81)	<0.001
Triage to ATB	50 (33, 71)	40 (30, 51)	74 (54, 101)	<0.001

ATB indicates antibiotic; BP, blood pressure; CNS, central nervous system; GI, gastrointestinal; IQR, interquartile range; qSOFA, quick Sequential Organ Failure Assessment; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.
*Change in SOFA score.

TABLE 2. **Primary and secondary outcomes in complete and incomplete Hour-1 bundle groups**

				Multivariate analysis	
Outcomes	All n = 593	Complete Hour-1 Bundle n = 332	Incomplete Hour-1 Bundle n = 261	Adjusted odds ratio* (95% CI)	P
Primary outcome					
28-Day mortality, n (%)	23 (3.9)	12 (3.6)	11 (4.2)	2.04 (0.72–5.74)	0.176
Secondary outcome					
Delayed septic shock, n (%)	28 (4.7)	10 (3.0)	18 (6.9)	0.73 (0.30–1.78)	0.499
ICU admission, n (%)	111 (18.8)	64 (19.3)	47 (18.0)	1.90 (1.15–3.13)	0.012

CI indicates confidence interval.
*Adjusted odds ratio with quick Sequential Organ Failure Assessment ≥ 2, initial venous lactate ≥ 4 mmol/L, appropriate spectrum of antibiotic.

TABLE 3. **Clinical outcomes in each Hour-1 Sepsis Bundle criteria**

Criteria	All n	Complete, each bundle n (%)	Incomplete, each bundle n (%)	Multivariate analysis Adjusted Odds ratio[*] (95% CI)	P
Primary outcome: 28-day mortality					
Antibiotics in 1 h	593	20/394 (5.1)	3/199 (1.5)	1.86 (0.52–6.71)	0.343
IV 30 mL/kg for hypotension or lactate ≥ 4 mmol/L	101	2/8 (25.0)	11/93 (11.8)	1.74 (0.26–11.65)	0.568
Vasopressors in 1 h for septic shock	62	7/29 (24.1)	6/33 (18.2)	1.32 (0.37–4.80)	0.669
Secondary outcome: delayed septic shock					
Antibiotics in 1 h	593	23/394 (5.8)	5/199 (2.5)	2.11 (0.24–18.35)	0.499
IV 30 mL/kg for hypotension or lactate ≥ 4 mmol/L	101	2/8 (25.0)	13/93 (14.0)	1.43 (0.23–8.80)	0.700

CI, confidence interval.
[*]Adjusted odds ratio with quick Sequential Organ Failure Assessment ≥ 2, initial venous lactate ≥ 4 mmol/L, appropriate spectrum of antibiotic.

This study reveals interesting practical information regarding a diagnosis of sepsis in the ED. Our findings showed that 81.1% of patients with qSOFA score < 2 had a definite diagnosis of sepsis in the ED. This supports that the sensitivity of qSOFA is too low for application in the ED and patients will be missed. There is no gold standard definition to trigger any resuscitative bundle (15). EPs require more clinical findings, not only a qSOFA score, to diagnose sepsis and to make the decision for initial resuscitation in patients with suspected sepsis, to avoid misdiagnoses and make fewer mistakes. Moreover, overcrowding in the ED, the triage system, and the complexity of underlying diseases in a tertiary hospital affect the complete Hour-1 Sepsis Bundle.

Limitations

This study has several limitations. Firstly, our study was conducted at a single center, Tertiary care medical school hospital. Our results may differ from those in primary care or rural hospitals. Secondly, the patient population in our study had community-acquired sepsis, and most did not have shock and had less severe sepsis. If we had only included patients with septic shock, treatment using the complete Hour-1 Sepsis Bundle may have affected the clinical outcomes. The sepsis mortality was very low so that the potential to show a survival benefit would be limited. A power analysis should be performed to determine if a large sample size would show a survival benefit. Thirdly, a variety of sepsis scores are used

TABLE 4. **Univariable analysis of 28-day mortality outcome**

	28-day mortality n = 23	28-day survival n = 570	P
Age (y), mean (SD)	70 (15)	69 (17)	0.852
Vital signs at enrollment, mean (SD)			
Systolic BP (mm Hg)	105 (27)	132 (31)	<0.001
Mean arterial BP (mm Hg)	78 (19)	92 (18)	<0.001
Heart rate (bpm)	116 (20)	107 (22)	0.058
Body temperature (°C)	37.9 (0.8)	38.3 (1.1)	0.849
Respiratory rate (bpm)	28 (5)	23 (5)	<0.001
Oxygen saturation (%)	93 (7)	96 (6)	0.064
qSOFA score, median (min, max)	2 (1, 3)	1 (0, 3)	<0.001
qSOFA ≥ 2, n (%)	15 (65.2)	97 (17.0)	<0.001
Laboratory results			
White blood cells (10^3), median (IQR)	10.7 (4.8, 13.7)	10 (6.9, 13.3)	0.712
Serum creatinine, median (IQR)	1.1 (0.8, 2.4)	1.0 (0.7, 1.4)	0.409
Initial venous lactate ≥ 4, n (%)	10 (15.4)	55 (84.6)	<0.001
Positive hemoculture, n (%)	4 (4.5)	85 (95.5)	0.744
SOFA score, median (IQR)	4 (0, 11)	1 (0, 10)	<0.001
SOFA ≥ 2, n (%)	18 (78.3)	252 (44.2)	0.001
Final diagnosis, n (%)			
Sepsis	20 (87.0)	562 (98.6)	0.001
Initial septic shock	3 (13.0)	8 (1.4)	
Delayed septic shock, n (%)	4 (17.4)	24 (4.2)	0.008
Source of infection, n (%)			
Pneumonia	9 (39.1)	195 (34.2)	0.626
Urinary tract infection	5 (21.7)	212 (37.2)	0.131
Diarrhoea, GI tract	5 (21.7)	55 (9.6)	0.059
Skin and soft tissue	2 (8.7)	32 (5.6)	0.533
Septicemia	2 (8.7)	58 (10.2)	0.818
Appropriate spectrum of Antibiotic	14 (60.9)	475 (83.3)	0.005
ICU admission	15 (65.2)	96 (16.9)	<0.001

BP indicates blood pressure; GI, gastrointestinal; ICU, intensive care unit; IQR, interquartile range; qSOFA, quick Sequential Organ Failure Assessment; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

for the diagnosis of sepsis, such as qSOFA, SOFA, and systemic inflammatory response syndrome. However, there is no standard recommendation or definition for triggering any resuscitative bundle. Fourthly, our compliance with the complete Hour-1 Sepsis Bundle was approximately 56.3%. Improved compliance might have an effect on patient outcomes. Further studies that include more data such as compliance with the protocol, hemodynamic and patient responsiveness, other supportive therapy, and the timing of other treatments, might be needed.

CONCLUSION

In summary, our cohort study showed that use of the complete Hour-1 Sepsis Bundle in the ED was not significantly associated with 28-day mortality and delayed septic shock.

ACKNOWLEDGMENTS

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