Impact of 1-Hour Bundle Achievement in Septic Shock

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Research

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Abstract

Background: Evidence supporting the association between 1-hour bundle achievement and patient outcomes is limited and inconsistent. Hence, this study aimed to address the impact of 1-hour bundle achievement on outcomes in septic shock patients.

Methods: A prospective multicentre observational study of septic shock patients with a protocolised resuscitation bundle therapy at emergency departments was conducted from October 2015 to December 2018. In-hospital mortality according to 1-hour bundle achievement from shock recognition were compared using multivariable logistic regression analysis. Patients were also divided into six groups according to the time of bundle achievement and outcomes were compared to examine the difference in outcome for each group over time: group 1 (≤1 h; reference), 2 (1–2 h), 3 (2–3 h), 4 (3–4 h), 5 (4–5 h), and 6 (5–6 h).

Results: In total, 1,612 patients with septic shock were included and in-hospital mortality was 18.2%. The 1-hour bundle was achieved in 461 (28.6%) patients. In multivariate analysis, the group achieving 1-hour bundle did not show a significant difference in in-hospital mortality compared to those who did not achieve 1-hour bundle (odds ratio = 0.74, confidence interval: 0.522–1.049, $p = 0.091$). However, groups 2, 3, 4, 5, and 6 showed significantly lower odds ratios of in-hospital mortality compared to those who did not achieve the bundle elements (odds ratio = 0.733, 0.604, 0.541, 0.532, and 0.458, respectively; $p = 0.042$, 0.001, < 0.001, 0.001, and < 0.001, respectively). There was no significant difference in in-hospital mortality over time for each group compared to that of group 1 used as a reference.

Conclusion: One-hour bundle achievement was not associated with improved outcomes in septic shock patients with protocolised resuscitation bundle therapy. However, groups achieving 2-, 3-, 4-, 5-, and 6-hour bundle were associated more with improved outcome than those who did not. Further clinical trials are needed to clarify the clinical implications of 1-hour bundle achievement.

Introduction

An estimated 48.9 million cases of sepsis have been reported, accounting for 19.7% of all global deaths [1, 2]. The incidence of sepsis increases with advanced age, comorbidities, and immunocompromised status [3, 4]. This may also be due to increased detection of early sepsis as a result of intensive sepsis education and awareness campaigns. Despite advances in recent critical care, sepsis remains a serious disease with high mortality and morbidity.

Early identification and management is essential in septic patients. In 2005, the Surviving Sepsis Campaign (SSC) suggested a protocolised bundle therapy to facilitate implementation at the bedside with a defined target [5, 6]. SSC bundles were revised from 6-hour to 3-hour bundles in 2015. The current guideline states that this resuscitation bundle therapy should be initiated within the first hour after the recognition of sepsis and septic shock, named the 1-hour bundle [7]. This recommendation is based on a study that reported a significant reduction in mortality associated with timely completion of 3-hour

bundles [8]. Although this study did not address the direct effect of the 1-hour bundle, it provided supporting evidence. However, there are concerns regarding the lack of evidence supporting the cut-off of 1 h and a concern about the 1-hour bundle causing hasty management decisions, inappropriate fluid administration, and indiscriminate use of broad-spectrum antibiotics [9, 10]. Evidence supporting the individual elements of the bundle varies from low to moderate [7]. To the best of our knowledge, no study has examined the validity of the 1-hour bundle in sepsis and septic shock.

Therefore, we aimed to evaluate the impact of 1-hour bundle achievement in patients with septic shock visiting the emergency department (ED). We hypothesised that 1-hour bundle achievement does not lead to significantly better outcomes than 2-hour or 3-hour bundle achievements.

Material And Methods

Study Population

A prospective multicentre observational study was conducted involving 10 Korean university-affiliated hospital EDs using data from the Korean Shock Society septic shock registry from October 2015 to December 2018. Patients aged ≥ 19 years who met the inclusion criteria (evidence of refractory hypotension or hypoperfusion in patients with suspected or confirmed infection) were included [11, 12]. Hypotension was defined as systolic blood pressure (SBP) < 90 mmHg, mean arterial pressure (MAP) < 70 mmHg, or an SBP decrease of > 40 mmHg. Refractory hypotension was defined as persistent hypotension despite the administration of fluid challenge (30 mL/kg of crystalloid fluid) or the requirement of vasopressors to maintain an SBP of ≥ 90 mmHg or a MAP of ≥ 70 mmHg. Hypoperfusion was defined as the presence of serum lactate levels ≥ 4 mmol/L. Patients were excluded if they had given “do not attempt resuscitation” orders, met the inclusion criteria 6 h after arrival at the ED, were transferred from other hospitals and did not meet the inclusion criteria on arrival at the ED, or were transferred directly from the ED to other hospitals. The institutional review board of each institution approved the study protocol, and informed consent was obtained from all patients before data collection. In this registry, information regarding the time of lactate measurement, blood culture, antibiotic administration, fluid administration, and use of vasopressors was recorded. A detailed description of the registry has been presented elsewhere [13–15].

In addition to the general septic shock registry described above, this study also used a specific design. In our registry, overall cohorts were composed of patients who visited the ED directly or were transferred from another hospital. We included only patients who visited the ED directly to eliminate confusion; in the case of transferred patients, bundle treatment (antibiotics, fluid administration, and vasopressors) would have already been initiated in the previous hospital. We also only included patients who were enrolled for refractory hypotension because data regarding infusion of 30 mL/kg of crystalloid fluid of patients enrolled for hypoperfusion were missing in our registry. Patients with missing information on any bundle component were excluded. Patients with missing information on their outcomes were also excluded.

Definitions and Outcomes

Based on the SSC guidelines, the 1-hour bundle is composed of the following five elements: measuring the lactate level, obtaining blood culture prior to administration of antibiotics, administering broad-spectrum antibiotics, beginning rapid administration of 30 mL/kg crystalloid fluid for hypotension or lactate ≥ 4 mmol/L, and administering vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain MAP at ≥ 65 mmHg within 1 h from time zero [7].

Patients were divided into six groups according to the interval from recognition of sepsis and septic shock to bundle achievement: group 1 (≤ 1 h; reference), 2 (1–2 h), 3 (2–3 h), 4 (3–4 h), 5 (4–5 h), and 6 (5–6 h). We defined the recognition of sepsis and septic shock as the time of completion of fluid administration of 30 mL/kg crystalloid fluid.

If any of the five elements was not achieved within the specified time, bundle achievement was defined as failed.. The outcomes of all groups were compared to those of the reference group. The outcomes of achieving each of the five individual elements in the bundle were also compared with those of the reference group. The decision to perform each element of the bundle was made by the treating physician. However, all the participating hospitals adhered to the recommendations of the SSC guidelines. The primary outcome of this study was in-hospital mortality; the secondary outcomes were 28-day and 90-day mortality.

Statistical Analysis

Continuous variables were analysed as means ± standard deviation or medians with interquartile ranges, as appropriate, and categorical variables were analysed as absolute or relative frequencies. The student's *t*-test or Wilcoxon rank-sum test were used to compare continuous variables, and the Chi-squared test or Fisher's exact test were used for categorical variables.

The univariate and multivariable logistic regression analyses of each hour bundle achievement for predicting outcomes were conducted (1-hour bundle achievement group vs. failed group, 2-hour bundle achievement group vs. failed group, etc). Multivariable logistic regression analysis was used to assess the bundle achievement of each group on in-hospital mortality, with adjustment for confounding variables that were significant on univariate analysis. Variables yielding $p < 0.2$ on univariate analysis were entered in a backward fashion in the multivariable analysis.

Patients were also divided into six groups according to the interval to bundle achievement, and outcomes were compared to examine the linear relationship in outcome for each group over time: group 1 (≤ 1 h; reference), 2 (1–2 h), 3 (2–3 h), 4 (3–4 h), 5 (4–5 h), and 6 (5–6 h). Comparisons of each group with the reference group were analysed using a multivariable logistic model.

A two-sided *p*-value < 0.05 was considered statistically significant, and the Bonferroni-corrected threshold for statistical significance was computed and applied in each category. All statistical analyses were

performed using SAS version 9.4 (SAS Institute; Cary, NC) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participant Characteristics

A total of 1,777 patients with refractory hypotension visited the ED directly during the study period. Of these, 165 patients with missing information on bundle achievement were excluded (Fig. 1). Finally, 1,612 patients were included. The baseline characteristics of 1,612 patients with bundle data are shown in Table 1. The mean patient age was 69 years. Of the total patients, 913 (56.6%) were males. In-hospital mortality was 18.2% (n = 293) and the 28-day mortality rate was 18.1%. The median time from ED visit to shock recognition was 87 min (interquartile range, 26–150 min). The 1-hour bundle was achieved in 461 patients (28.6%). The mean age in the 1-hour bundle achieved group was significantly lower than in those who failed 1-hour bundle achievement (68 vs. 70 years, $p = 0.013$). The mean initial SBP was not significantly different between the 1-hour bundle achieved group and those who failed ($p = 0.136$). The median lactate level in the 1-hour bundle achieved group was significantly lower than that in those who failed (2.5 mmol/L vs. 2.9 mmol/L, $p < 0.001$). A significantly lower proportion of in-hospital mortality was observed in the group that achieved a 1-hour bundle (13.8% vs. 19.9%, $p = 0.004$). The comparisons of baseline characteristics between the groups that succeeded or failed to achieve the 2-hour and 3-hour bundles are shown in Additional Tables 1 and 2, respectively. Univariate logistic regression analysis of each bundle was performed to predict in-hospital mortality. Achievement of a 1-hour bundle was significantly associated with in-hospital mortality ($p = 0.005$) (Table 2). There was also a significantly lower odds ratio (OR) of 2-, 3-, 4-, 5-, and 6-hour bundle achievement for in-hospital mortality (OR = 0.64, 0.603, 0.574, 0.569, and 0.511, respectively; p = 0.001, < 0.001, < 0.001, < 0.001, and < 0.001, respectively). Old age, Sequential Organ Failure Assessment score, and Acute Physiologic Assessment and Chronic Health Evaluation score was associated with in-hospital mortality in the univariate analysis.

Table 1
Comparison of and clinical characteristics of groups that succeeded or failed to achieve the 1-hour bundle

Variables	All patients (n = 1,612)	1-hour bundle achieved (n = 461)	1-hour bundle failed (n = 1151)	*p* value
Age, years	69 (60–77)	68 (60–76)	70 (60–78)	0.013
Male, n (%)	913 (56.6)	255 (55.3)	658 (57.1)	0.497
Initial vital signs				
SBP, mmHg	90 (76–110)	91 (77–111)	89 (75–109)	0.136
DBP, mmHg	55 (47–66)	56 (48–67)	54 (46–65)	0.058
Heart rate, bpm	111 (94–128)	111 (94–128)	110 (93–128)	0.626
Respiratory rate, breaths/min	20 (18–23)	20 (18–24)	20 (18–22)	0.111
Body temperature, ℃	38 (36.9–38.9)	38.1 (37.1–38.9)	37.9 (36.8–38.9)	0.041
Comorbidities, n (%)				
Hypertension	638 (39.5)	184 (39.9)	454 (39.4)	0.861
Diabetes mellitus	426 (26.4)	105 (22.7)	321 (27.8)	0.035
Cardiac disease	215 (13.3)	81 (17.6)	134 (11.6)	< 0.001
COPD	116 (7.2)	40 (8.7)	76 (6.6)	0.145
CKD	114 (7.1)	33 (7.2)	81 (7)	0.931
Chronic liver disease	172 (10.6)	57 (12.4)	115 (10)	0.163
Infection site, n (%)				
Respiratory	373 (23.1)	123 (26.7)	250 (21.7)	0.032
Urinary tract	342 (21.2)	93 (20.2)	249 (21.6)	0.517
Gastrointestinal tract	216 (13.4)	48 (10.4)	168 (14.6)	0.025
Hepato-biliary & pancreas	270 (16.7)	85 (18.4)	185 (16.1)	0.25

APACHE 2 Acute Physiology and Chronic Health Evaluation 2, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *SOFA* Sequential Organ Failure Assessment

Variables	All patients (n = 1,612)	1-hour bundle achieved (n = 461)	1-hour bundle failed (n = 1151)	*p* value
Others	79 (4.9)	20 (4.3)	59 (5.1)	0.508
Lactate, mmol/L	2.72 (1.7–4.5)	2.5 (1.7–3.5)	2.9 (1.7–4.9)	< 0.001
SOFA	6 (4–8)	6 (4–8)	6 (4–8)	0.75
APACHE 2	19 (13–25)	19 (13–25)	19 (13–26)	0.147
Positive blood culture, n (%)	731 (45.3)	208 (45.1)	523 (45.4)	0.907
Outcomes, n (%)				
In-hospital mortality	293 (18.2)	64 (13.8)	229 (19.9)	0.004
28-day mortality (n = 1,492)	270 (18.1)	57 (13.3)	213 (20.1)	0.002
90-day mortality (n = 1,327)	387 (29.1)	102 (26.1)	285 (30.5)	0.111

APACHE 2 Acute Physiology and Chronic Health Evaluation 2, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *SOFA* Sequential Organ Failure Assessment

Table 2
Univariate logistic regression for in-hospital mortality

	Unadjusted OR	95% CI of OR	*p* value
Age, years	1.028	1.017–1.038	< 0.001
Male	1.415	1.090–1.838	0.009
SBP, mmHg	1.000	0.995–1.004	0.891
DBP, mmHg	0.998	0.991–1.005	0.574
Heart rate, bpm	1.005	1.000-1.010	0.064
Respiratory rate, breaths/min	1.074	1.050–1.098	< 0.001
Body temperature, ℃	0.663	0.598–0.734	< 0.001
Comorbidities			
Hypertension	1.018	0.786–1.319	0.891
Diabetes mellitus	0.970	0.727–1.294	0.834
Cardiac disease	1.108	0.770–1.595	0.579
COPD	1.403	0.894–2.202	0.140
CKD	1.516	0.970–2.369	0.068
Chronic liver disease	1.219	0.824–1.802	0.322
Infection site			
Respiratory	2.233	1.699–2.936	< 0.001
Urinary tract	0.338	0.225–0.509	< 0.001
Gastrointestinal tract	1.259	0.884–1.793	0.202
Hepato-biliary & pancreas	0.674	0.464–0.978	0.037
Others	0.493	0.235–1.036	0.062
Lactate, mmol/L	1.291	1.238–1.346	< 0.001
SOFA	1.236	1.183–1.290	< 0.001
APACHE 2	1.083	1.068–1.098	< 0.001
Positive blood culture	1.019	0.791–1.314	0.883

APACHE 2 Acute Physiology and Chronic Health Evaluation 2, *CI* confidence interval, *CKD* chronic kidney disease; *COPD* chronic obstructive pulmonary disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *OR* odds ratio, *SOFA* Sequential Organ Failure Assessment

	Unadjusted OR	95% CI of OR	*p* value
Bundle achievement			
1-hour bundle	0.649	0.481–0.877	0.005
2-hour bundle	0.64	0.496–0.827	0.001
3-hour bundle	0.603	0.465–0.783	< 0.001
4-hour bundle	0.574	0.434–0.759	< 0.001
5-hour bundle	0.569	0.419–0.773	< 0.001
6-hour bundle	0.511	0.369–0.707	< 0.001

APACHE 2 Acute Physiology and Chronic Health Evaluation 2, *CI* confidence interval, *CKD* chronic kidney disease; *COPD* chronic obstructive pulmonary disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *OR* odds ratio, *SOFA* Sequential Organ Failure Assessment

Multivariable logistic regression analysis of 1-hour bundle and the effect of hourly delay in bundle achievement

The adjusted OR of 1-hour bundle achievement was 0.74 in predicting in-hospital mortality on multivariable logistic regression, but it was not significant (confidence interval [CI]: 0.522–1.049, $p = 0.091$) (Table 3). Two-hour bundle achievement was significantly associated with lower in-hospital mortality (OR = 0.733, CI: 0.543–0.988, $p = 0.042$); 3-, 4-, 5-, and 6- bundle achievements were also associated with lower in-hospital mortality (OR = 0.604, 0.541, 0.532, and 0.458, respectively).

Table 3
Multivariable analysis of bundle achievements to predict in-hospital mortality

	Multivariable logistic regression analysis	*p* value
1-hour bundle achievement	0.74 (0.522–1.049)	0.091
2-hour bundle achievement	0.733 (0.543–0.988)	0.042
3-hour bundle achievement	0.604 (0.446–0.819)	0.001
4-hour bundle achievement	0.541 (0.391–0.751)	< 0.01
5-hour bundle achievement	0.532 (0.372–0.761)	0.001
6-hour bundle achievement	0.458 (0.312–0.672)	< 0.01

Variables such as respiratory tract, urinary tract, hepatobiliary, pancreatic, and other infection, age, male sex, heart rate, respiratory rate, body temperature, CKD, infection site, lactate, and SOFA score were adjusted as covariates in multivariable analysis. *CI* confidence interval, *OR* odds ratio, *CKD* chronic kidney disease, *SOFA* Sequential Organ Failure Assessment

Multivariable analyses were performed to examine the effect of hourly delay in bundle achievement, with the 1-hour bundle achievement group as the reference group. There were 461 patients in group 1 (reference group), and were 384, 253, 143, 97, and 53 patients in groups 2–6, respectively. There was no significant difference in in-hospital mortality or trend over time between the 1-hour and 2-, 3-, 4-, 5-, and 6-hour bundle groups on multivariable analysis (Fig. 2).

Multivariable analyses were conducted to predict the 28-day mortality of each group, with the 1-hour bundle achievement group as the reference group. There was no significant difference in 28-day mortality between the 2-, 3- 4-, 5-, and 6-hour bundle groups and the reference group on multivariable analysis (Fig. 3). On multivariable analysis, there was no significant difference in 90-day mortality between the groups (Fig. 4).

Analysis of the effect of individual element achievement on the outcome

Antibiotics were administered in 50% of patients within 1 h of shock recognition (Additional Table 3). Within 2 h, 73% of patients received antibiotics. Blood culture was performed in 73% of patients within

1 h. Lactate measurement was conducted in 95% of patients within 1 h. Vasopressors were administered to 54% of patients within 1 h. More than 90% of patients achieved each element within 4 h. The numbers of individual elements achieved in a specific time are summarised in Additional Table 3.

Patients who received antibiotics within 1 h did not show a significant difference in in-hospital mortality compared to those who did not in multivariable logistic regression analysis (OR = 0.791, CI: 0.582–1.076, $p = 0.136$) (Additional Table 4). Patients who were administered antibiotics within 2, 3, 4, 5, and 6 h also did not show different in-hospital mortality rates than those who were not ($p = 0.074$, 0.05, 0.096, 0.396, and 0.356, respectively). Patients in whom blood culture was conducted within 1 and 2 h did not show a significant difference in in-hospital mortality compared to those for whom it was not ($p = 0.228$ and 0.087, respectively). Patients who underwent blood culture within 3, 4, 5, and 6 h had significantly lower in-hospital mortality rates than those who did not ($p = 0.003$, 0.007, 0.016, and 0.005, respectively). Lactate measurement performed within 5 h was significantly associated with lower in-hospital mortality compared to those for whom it was not ($p = 0.029$). However, achievement of lactate measurement within other time limits (1, 2, 3, 4, or 6 h) did not show a significant difference in in-hospital mortality. Patients who received vasopressors within 3, 4, 5, and 6 h had significantly lower in-hospital mortality rates than those who did not ($p = 0.019$, 0.036, 0.005, and 0.002, respectively). However, 1- and 2-hour achievement of vasopressor administration did not show significant differences in in-hospital mortality ($p = 0.567$ and 0.302, respectively). There was no significant difference in in-hospital mortality or trend over time between the 1-hour (reference) and 2-, 3-, 4-, 5-, or 6-hour bundles regarding antibiotics, blood culture, lactate measurement, or vasopressor achievement in multivariable analysis (Additional Figs. 1, 2, 3, and 4).

Discussion

In this study, we found that the achievement of a 1-hour bundle was not independently associated with improved outcomes in patients with septic shock in the ED. No linear association was observed between the time delay in bundle achievement and outcomes. However, 2-, 3-, 4-, 5-, and 6-hour bundle achievement were all associated with improved outcomes compared to those who did not achieve the bundle elements. Among bundle elements, antibiotic and vasopressor administration were less frequently achieved (50% and 54%, respectively). More than 90% of patients achieved each element within 4 h. In the analysis of individual bundle elements, blood culture and vasopressor achievement within 3, 4, 5, and 6 h were associated with improved outcomes. However, antibiotic administration and lactate measurement within a specific hour did not show differences in outcomes, despite lactate measurement within 5 h showing improved outcomes. No linear association or trend was observed between delay in individual element achievement and outcome.

To the best of our knowledge, this is the first study to address the impact of 1-hour bundle achievement on the outcomes of patients with septic shock. Several studies have addressed individual elements of bundle treatment in sepsis or septic shock, but no study has investigated the impact of whole bundle achievement. Our study population was a prospective multicentre study with a large sample size. Our

registry had all information regarding bundle elements, especially time variables, although it was not constructed to examine the impact of 1-hour bundle achievement. There are controversies regarding the 1-hour bundle treatment, and this study may be the basis for future research and may help clinicians in sepsis care.

The effectiveness of bundle therapy in sepsis and septic shock treatment is controversial [10, 16–18]. In a single-centre retrospective study, the group that failed to achieve severe sepsis and septic shock performance measure bundle (SEP-1) had a higher crude mortality than the group that achieved well, but no significant difference was found after adjusting for clinical variables and disease severity [19]. There were five elements in SEP-1, similar to those in the 1-hour bundle, but the time limits were 3 h and 6 h. In a study by Baghdadi et al., timely lactate measurement was associated with reduced mortality, but full SEP-1 adherence was not associated with improved outcome in patients with hospital-onset or community-onset sepsis [20]. According to one systematic review, no high- or moderate-level evidence shows that SEP-1 or its haemodynamic interventions improve the survival rate of adults with sepsis [21]. In a study analysing the effect of the 3-hour bundle of sepsis care on 49,311 patients in 149 hospitals in New York, rapid bundle completion was associated with reduced in-hospital mortality [8]. A longer time to bundle completion was associated with higher rates of risk-adjusted in-hospital mortality. However, as the time to achieve bundle treatment was delayed, outcomes were not significantly different in our study despite the bundle achievement group showing significantly better outcomes than the failed group when comparing 2 groups (i.e., 2-hour achievement vs. 2-hour failure). Our study consisted of five bundle treatment elements and the study in New York consisted of three elements (blood culture, lactate level measurement, and antibiotic administration); hence, comparison would be difficult. In a study of paediatric patients, Evans et al. reported lower in-hospital mortality in the group that completed sepsis bundle therapy within 1 h than in the group that did not [22]; however, individual elements (antibiotics, blood culture, and fluid) of bundle achievement within 1 h were not related to patient prognosis. Our study also showed that individual elements of bundle achievement within 1 h were not associated with patient outcomes.

Our study has several limitations. First, our data were not constructed to investigate 1-hour bundle treatment. Patients included in this analysis were admitted between October 2015 and December 2018; therefore, clinicians were likely unaware of this study or the intent of the data collection. Therefore, the achievement rate of the 1-hour bundle was low (28.6%). It was not part of a performance improvement initiative, as we analyzed retrospective data. Performance improvement examining a 1-hour bundle would be better to conclude it’s prognostic value. It is difficult to conclude that there is no effect of 1-hour bundle achievement. Second, it is not clear whether there was start of rapid administration of 30 mL/kg crystalloid fluid within 1 h of shock recognition because we defined the time of shock recognition as completion of the amount of fluid administration. However, it is likely that start of rapid fluid administration might be achieved within 1 h because the median time from ED triage to fluid completion was 87 min. Third, the inherent limitations of a registry-based observational study should be acknowledged. Although our registry collected all variables related to bundle treatment elements, we cannot exclude the influence of unmeasured confounders that may have affected the results despite

adjustment for the differences in the baseline risk factors with multivariable analysis. Fourth, the differences in the outcomes of each participating hospitals were not addressed. Finally, we did not examine the impact of bundle achievement in patients with sepsis, as our study population consisted of septic shock patients.

Conclusions

The 1-hour bundle was achieved by 28.6% of septic shock patients who were treated with a protocolised bundle therapy in the ED and 1-hour bundle was not independently associated with improved outcomes. No linear association was observed between the time delay in bundle achievement and patient outcome. However, 2-, 3-, 4-, 5-, and 6-hour bundle achievement were all associated with improved outcomes compared to those who failed in comparison between the 2 groups. Further randomised controlled trials on the clinical implications of 1-hour bundle achievement in patients with septic shock are needed before making strong recommendations.

Abbreviations

ED: emergency department; CI: confidence interval: MAP: mean arterial pressure: systolic blood pressure: OR: odds ratio; SEP-1: severe sepsis and septic shock performance measure bundle; SSC: Surviving Sepsis Campaign.

Declarations

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Authors' contributions

BSK, WYK (Won Young Kim) and THL designed the study; SHC, KK, TGS and SMR performed the data analysis; YJK, YSP and WYK (Woon Yong Kwon) contributed to data interpretation, writing, and approval of the final manuscript; HSC, SPC, GJS and HK R has contributed to data collection, data interpretation, and editing of text. DHS performed the statistical analysis. BS, WYK and THL drafted the manuscript. All authors participated in the interpretation of the results. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

Ethics approval and consent to participate: The institutional review board of each institution approved the study protocol, and informed consent was obtained from all patients before data collection.

Consent for publication

Not applicable

Competing interests

The authors have no conflicts of interest to report.

References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395:200–11.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
3. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. Crit Care. 2006;10:R42.
4. Kaukonen K-M, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311:1308–16.
5. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care—reasons for caution. N Engl J Med. 2014;370:1673–6.
6. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304–77.
7. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med. 2018;44:925–8.
8. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376:2235–44.

9. Marik PE, Farkas JD, Spiegel R, Weingart S. Rebuttal From Drs Marik, Farkas, Spiegel et al. Chest. 2019;155:17.
10. Marik PE, Farkas JD, Spiegel R, Weingart S, Aberegg S, Beck-Esmay J, et al. POINT: should the Surviving Sepsis Campaign guidelines be retired? Yes. Chest. 2019;155:12–4.
11. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372:1301–11.
12. Investigators P. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683–93.
13. Ko BS, Kim K, Choi S-H, Kang GH, Shin TG, Jo YH, et al. Prognosis of patients excluded by the definition of septic shock based on their lactate levels after initial fluid resuscitation: a prospective multi-center observational study. Crit Care. 2018;22:47.
14. Jung SM, Kim Y-J, Ryoo SM, Kim WY. Relationship between low hemoglobin levels and mortality in patients with septic shock. Acute Crit Care. 2019;34:141.
15. Ryoo SM, Han KS, Ahn S, Shin TG, Hwang SY, Chung SP, et al. The usefulness of C-reactive protein and procalcitonin to predict prognosis in septic shock patients: A multicenter prospective registry-based observational study. Sci Rep. 2019;9:1–8.
16. Levy MM, Rhodes A, Evans LE, Antonelli M, Bailey H, Kesecioglu J, et al. COUNTERPOINT: should the Surviving Sepsis Campaign guidelines be retired? No. Chest. 2019;155:14–7.
17. Freund Y, Khoury A, Möckel M, Karamercan M, Dodt C, Leach R, et al. European Society of Emergency Medicine position paper on the 1-hour sepsis bundle of the Surviving Sepsis Campaign: expression of concern. Eur J Emerg Med. 2019;26:232–3.
18. Murri R, Taccari F, Palazzolo C, Fantoni M, Cauda R. IDSA did not endorse the Surviving Sepsis Campaign guidelines. Clin Infect Dis. 2018;
19. Rhee C, Filbin M, Massaro AF, Bulger A, McEachern D, Tobin KA, et al. Compliance with the national SEP-1 quality measure and association with sepsis outcomes: a multicenter retrospective cohort study. Crit Care Med. 2018;46:1585.
20. Baghdadi JD, Brook RH, Uslan DZ, Needleman J, Bell DS, Cunningham WE, et al. Association of a care bundle for early sepsis management with mortality among patients with hospital-onset or community-onset sepsis. JAMA Intern Med. 2020;180:707–16.
21. Pepper DJ, Jaswal D, Sun J, Welsh J, Natanson C, Eichacker PQ. Evidence Underpinning the Centers for Medicare & Medicaid Services' severe sepsis and septic shock management bundle (SEP-1) A systematic review. Ann Intern Med. 2018;168:558–68.
22. Evans IVR, Phillips GS, Alpern ER, Angus DC, Friedrich ME, Kissoon N, et al. Association between the New York sepsis care mandate and in-hospital mortality for pediatric sepsis. JAMA. 2018;320:358–67.

Figures

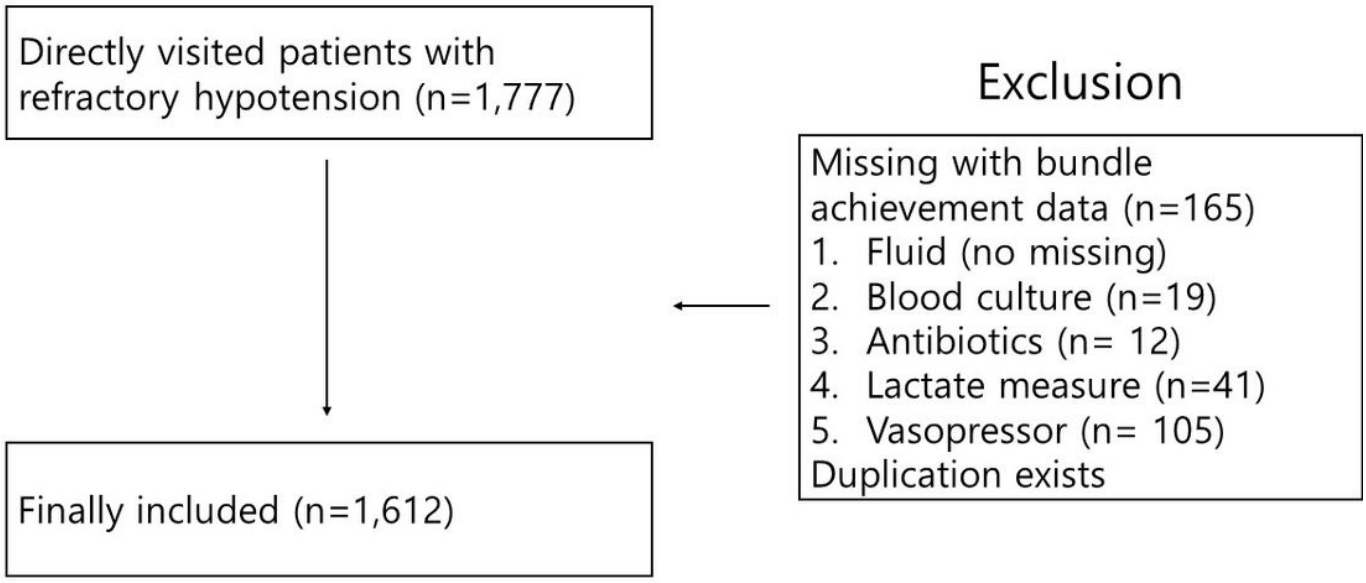


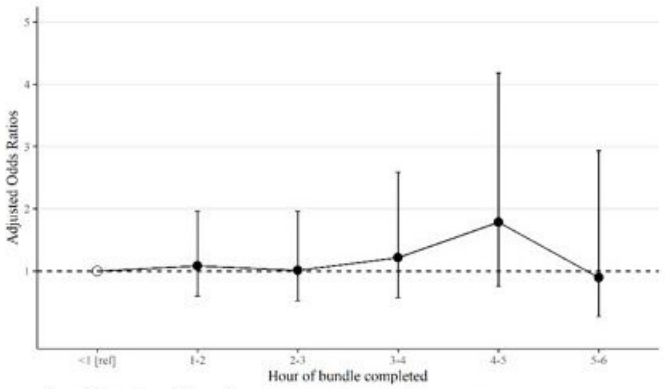
Figure 1

Patient selection flow diagram

Directly visited patients with refractory hypotension (n=1,777)
Exclusion
Missing with bundle achievement data (n=165)
1. Fluid (no missing)
2. Blood culture (n=19)
3. Antibiotics (n= 12)
4. Lactate measure (n=41)
5. Vasopressor (n= 105)
Duplication exists
Finally included (n=1,612)

Figure 1

Patient selection flow diagram

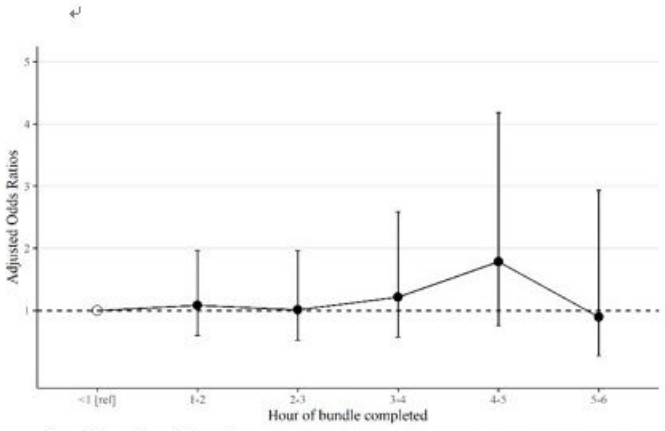


* Adjusted odds ratios are significantly different from 1 ($P < 0.01$).

Group	OR	Lower	Upper	p-value
<1 vs 1-2	1.084	0.599	1.961	0.726
<1 vs 2-3	1.010	0.521	1.960	0.968
<1 vs 3-4	1.213	0.569	2.587	0.511
<1 vs 4-5	1.782	0.759	4.180	0.081
<1 vs 5-6	0.893	0.272	2.935	0.806

Figure 2

Adjusted odds ratios of each group for in-hospital mortality in multivariable logistic analysis



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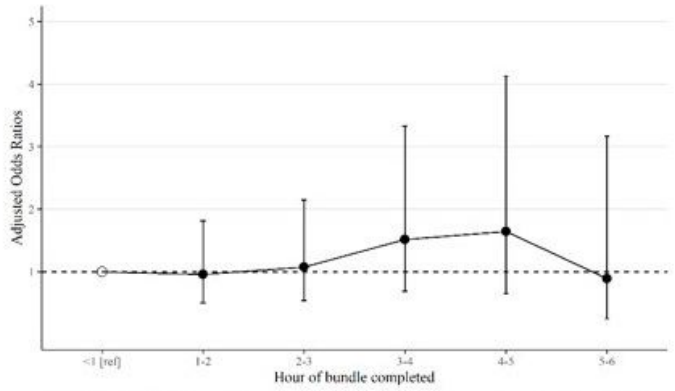

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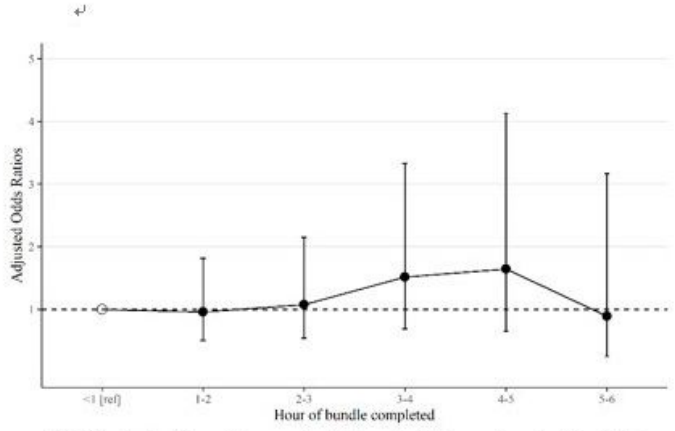
Group	OR	Lower	Upper	p-value
<1 vs 1-2	0.957	0.504	1.815	0.859
<1 vs 2-3	1.075	0.538	2.148	0.786
<1 vs 3-4	1.515	0.690	3.329	0.174
<1 vs 4-5	1.643	0.654	4.127	0.164
<1 vs 5-6	0.890	0.250	3.165	0.812

Figure 3

Adjusted odds ratios of each group for 28-day mortality in multivariable logistic analysis



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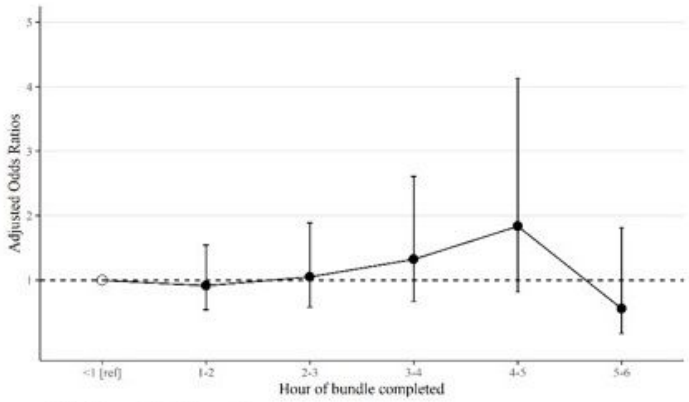

Group	OR	Lower	Upper	p-value
<1 vs 1-2	0.914	0.541	1.544	0.659
<1 vs 2-3	1.049	0.582	1.889	0.835
<1 vs 3-4	1.322	0.670	2.607	0.289
<1 vs 4-5	1.835	0.816	4.126	0.053
<1 vs 5-6	0.556	0.171	1.813	0.201

* Adjusted odds ratios are significantly different from 1 ($P < 0.01$).

Figure 4

Adjusted odds ratios of each group for 90-day mortality in multivariable logistic analysis

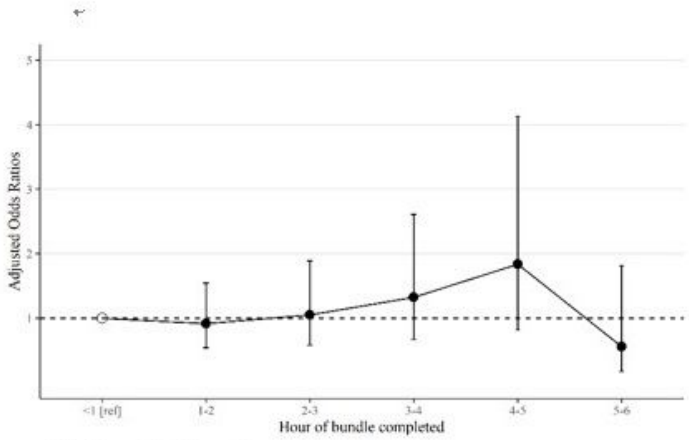

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Figure 4

Adjusted odds ratios of each group for 90-day mortality in multivariable logistic analysis

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