Hour-1 Bundle Adherence Was Associated With Reduction of In-Hospital Mortality Among Patients With Sepsis In Japan

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Research

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Abstract

Background: The updated Surviving Sepsis Campaign guidelines recommend a 1-hour window for completion of a sepsis care bundle, however, the effectiveness of the hour-1 bundle has not been fully evaluated. The present study aimed to evaluate the impact of hour-1 bundle completion on clinical outcomes in sepsis patients.

Methods: This is a multicenter, prospective, observational study conducted in 17 intensive care units in tertiary hospitals in Japan. We included all adult patients who were diagnosed as having sepsis by Sepsis-3 and admitted to the ICUs from July 2019 to August 2020. Impacts of hour-1 bundle adherence and delay of adherence on risk-adjusted in-hospital mortality were estimated by multivariable logistic regression analyses.

Results: The final study cohort included 178 patients with sepsis. Among them, 89 received bundle-adherent care. Completion rates of each component (measure lactate level; obtain blood cultures; administer broad-spectrum antibiotics; administer crystalloid, apply vasopressors) within 1 hour were 98.9%, 86.2%, 51.1%, 94.9%, and 69.1%, respectively. Completion rate of all components within 1 hour was 50.3%. In-hospital mortality was 18.0% in patients with and 30.3% in patients without bundle-adherent care (p=0.054) Adjusted odds ratio of non-bundle-adherent versus bundle-adherent care for in-hospital mortality was 2.32 (95% CI 1.09–4.95) using propensity score. Non-adherence to obtaining blood cultures and administering broad-spectrum antibiotics within 1 hour were related to in-hospital mortality (2.65 [95% CI 1.25–5.62] and 4.81 [95% CI 1.38–16.72], respectively). Adjusted odds ratio for 1-hour delay in achieving hour-1 bundle components for in-hospital mortality was 1.28 (95% CI 1.04–1.57) by logistic regression analysis.

Conclusion: Completion of the hour-1 bundle was associated with lower in-hospital mortality. Obtaining blood cultures and administering antibiotics within 1 hour may have been the components most contributing to decreased in-hospital mortality.

Introduction

Sepsis is now defined “as life-threatening organ dysfunction caused by a dysregulated host response to infection” [1]. Although tremendous progress in medical management has been made over the past few decades, sepsis remains a leading cause of death and enormously impacts global health systems, with approximately 11 million sepsis-related deaths reported in 2017 [2].

Multidisciplinary intensive care has been mainly required as sepsis is a fatal disease, and no specific medicines have been developed to resolve it. The care bundle has recently become a key factor in multidisciplinary intensive care. In the Surviving Sepsis Campaign (SSC) guidelines, to improve awareness and outcomes of sepsis, time-dependent bundles such as time to antibiotic administration have become one of the key components [3–6]. The updated 2018 SSC guidelines recommend a 1-hour window for completion of a sepsis care bundle following the recognition of sepsis to be a reasonable

approach instead of within 3 hours from triage or recognition of sepsis [7]. This update has been significantly debated and remains controversial [8].

The effectiveness of the hour-1 bundle has not been fully evaluated because fundamentally, initiation of earlier treatment does not negatively affect the disease. A recent study did not show an association between completion of the hour-1 bundle components within 1 hour and lower mortality, whereas they did show an association between care completed within 3 hours and lower mortality [9]. In addition, a randomized controlled trial in the pre-hospital setting that assessed early antibiotic use in patients with suspected infection showed that it failed to reduce mortality [10]. Therefore, our aim was to prospectively evaluate adherence to the hour-1 care bundle. We also evaluated the association between completion of the hour-1 bundle and patient outcomes.

Materials And Methods

Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of all participating institutions in the Japanese Association for Acute Medicine (JAAM) study group. Osaka University, the representative for the JAAM Multicenter Assessment for Sepsis Treatment and Outcome (MAESTRO) study, was responsible for the overall approval (IRB number 18323).

Design and setting

This multicenter, prospective, observational study, JAAM MAESTRO (UMIN000036349), was conducted in 17 intensive care units (ICUs) in Japan from July 2019 to August 2020.

Participants

Patients were eligible for this study if they met the following criteria: 1) were older than 16 years; 2) fulfilled the Sepsis-3 criteria [6], i.e., had a proven or suspected infection and an acute increase of 2 or more points in Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) score; and 3) were diagnosed as having only new-onset infection.

Exclusion criteria included 1) patients with cardiopulmonary arrest on hospital arrival; 2) patients with the limitation of sustained life care or post-cardiopulmonary arrest resuscitation status at the time of sepsis diagnosis; 3) patients deemed ineligible as study participants by a research director; and 4) patients transferred from other hospitals.

Data collection

Data were extracted from the MAESTRO database and compiled by the MAESTRO investigators. Collected variables included relevant patient information such as demographics, comorbidities, vital

signs, laboratory data, and site of infection. We also obtained data on adherence to sepsis care bundles (specifically, the hour-1 bundle).

In-hospital mortality was identified as the primary outcome. Secondary outcomes were the number of ventilator-free days and ICU-free days, length of hospital stay, and condition at discharge.

Data collection was conducted as part of the clinical routine workup. The MAESTRO site investigators recorded all data throughout the patient's hospital stay. In the case of missing data, the MAESTRO committee requested a reconfirmation of data extraction from the MAESTRO investigators.

Data definitions

Sepsis care bundles were defined according to SSC guidelines [11] as whether all bundle components were achieved within the appropriate time frame (i.e., 1 hour) and if they adhered to the indications. Thus, if a component of the bundle was not applicable, we treated achievement of the other components as completion of the bundle (i.e., in cases where administration of crystalloid and application of vasopressor were not indicated), and adherence was defined when the other three components were completed. For all patients, bundle initiation time was defined as the time of sepsis recognition in the emergency department, ward, or ICU. Sepsis recognition was based on clinical judgement, by which the physician-in-charge suspected sepsis at the initial evaluation. The timestamp was recorded in the database by the physician-in-charge.

Analysis

We divided the patients into two groups, those receiving bundle-adherent care (bundle-adherent group) and those not receiving it (non-bundle adherent group). We performed univariate analyses of the characteristics of the patients in whom the hour-1 bundle was or was not completed within 1 hour. Continuous data are expressed as mean (SD) or median (interquartile range), depending on normality. Categorical variables are shown as proportions. We also evaluated the time to completion of each component of the hour-1 bundle.

The impact of non-adherence to the hour-1 bundle on risk-adjusted in-hospital mortality was estimated using an inverse probability of treatment weighting analysis with a propensity score. The propensity score for adherence to the hour-1 bundle was determined using a logistic regression with the following covariates as independent variables, which were specified *a priori* based on clinical experience and prior studies: patient age, sex, admission source (emergency department, ward, or in ICU), Charlson comorbidity index (CCI), mechanical ventilation use, and each organ score within the SOFA. In addition, after replacing time to completion of each component of the hour-1 bundle as a continuous variable, we performed a multivariable logistic regression analysis, adjusted for clinically plausible and relevant confounders equal to the covariates, to calculate the propensity score. No assumptions were made on these data because the number of missing data was low.

Sensitivity analysis

Because two components (measure initial lactate level and begin rapid administration of crystalloid) in the hour-1 bundle were completed in almost all of the patients, we performed the same analyses excluding these two components. Two-tailed p values < 0.05 were considered to indicate significance. All statistical analyses were performed using STATA software version 15.0 (Stata Corp, College Station, TX, USA).

Results

Among 180 patients, 178 individuals who met all eligibility criteria entered the final analyses. Of them, 89 patients received bundle-adherent care (Figure 1). Baseline characteristics and comorbidities were similar between the two groups, with the exception of body temperature and mechanical ventilation use (Table 1). We show time to completion of each component of the hour-1 bundle as a supplemental table (Table S1). Two components (measure initial lactate level [98.9%] and begin rapid administration of crystalloid [94.9%]) were completed in 1 hour in almost all patients. The rate of completion of all components within 1 hour was 50.3%. In-hospital mortality was 18.0% in the bundle-adherent group and 30.3% in the non-bundle-adherent group (p=0.054) (Table 2). The number of ventilator-free days and ICU-free days and length of hospital stay were not different between the two groups.

The adjusted odds ratio (OR) of the non-bundle-adherent group versus bundle-adherent group for in-hospital mortality was 2.32 (95% CI 1.09–4.95) using an inverse probability of treatment weighting analysis with a propensity score (Figure 2). Among the components of the hour-1 bundle, non-adherence to obtaining blood cultures (OR 2.65 [95% CI 1.25–5.62]), broad spectrum antibiotics (OR 4.81 [95% CI 1.38–16.72]), and administration of crystalloid (OR 13.97 [95% CI 2.19–89.31]) within 1 hour were associated with increased in-hospital mortality among the patients with sepsis. In addition, the adjusted OR for 1-hour delay of achievement of the components of the hour-1 bundle for in-hospital mortality was 1.28 (95% CI 1.04–1.57) using a multivariable logistic regression analysis (Figure 3). The results were similar in a sensitivity analysis that excluded components with adherence rates that were too high (Supplemental Figure S1).

Discussion

Our study showed that approximately one-half of the patients with sepsis received care that adhered to the hour-1 bundle, and their outcomes were significantly improved when the hour-1 bundle was completed within 1 hour. However, among the hour-1 bundle components, only obtaining blood cultures and administration of antibiotics may have contributed to the decreased in-hospital mortality.

Since the original studies of care bundle effectiveness were published [12, 13], there have been mainly negative opinions about its implementation [8, 14, 15]. In fact, our previous descriptive study did not prove the effectiveness of the 3-hour bundle [16]. However, few studies have directly investigated its effectiveness. Sepsis is different from other emergent conditions such as acute coronary syndrome, stroke, or trauma in terms of disease onset although appropriate and timely detection and treatment

should be essential in improving the outcome of sepsis. A recent retrospective cohort study showed no association between completion of hour-1 bundle components within 1 hour and lower mortality, whereas bundle completion within 3 hours was associated with lower mortality [9]. In that study, the hour-1 bundle was completed in only 8% of the patients, whereas it was completed in half of the patients in the present study. Facilities with high bundle adherence rates may have better outcomes because of the multidisciplinary nature of the treatment. A better understanding and implementation of the hour-1 bundle may be important for health care personnel to achieve an improvement in patient prognosis. For example, early goal-directed therapy (EGDT) has never been well known, and its effectiveness compared with usual care was only demonstrated as it became better known. However, after most physicians came to understand it, the prognosis of sepsis treated with usual care based on EGDT knowledge and the Surviving Sepsis Campaign Guideline has been equal to or better than that for EGDT itself [17]. It is natural in health care research for results to change as education is disseminated. Thus, it may be a while until we see the effects of the hour-1 bundle.

Among the components of the hour-1 bundle, only obtaining blood cultures and administration of antibiotics may have contributed to the decreased in-hospital mortality in the present study. These time-dependent factors were similarly significant whether they were dichotomized in 1 hour after diagnosis or as continuous variables every hour. A systematic review of seven observational studies in the Japanese clinical practice guidelines for management of sepsis and septic shock 2020 showed no significant difference in outcomes with administration of antibiotic within 1 hour compared to later. Therefore, it was given a weak recommendation: initiation of antibiotics as early as possible, but not necessarily within 1 hour. However, we validated and agree with the importance of the hour-1 bundle as reported in previous studies [12, 13]. The study of a quality indicator such as time to antibiotic can influence the standardization of medical practice. However, education on sepsis care was not disseminated from previous studies that did not show an association with early antibiotic administration [16]. Actually, the results are more greatly influenced by strong clinical variables such as a certain treatment if clinically more important known or unknown (unmeasured) variables than a quality measurement such as time to antibiotic are assessed. It is most important that two groups with similar severity of illness receive similar treatments before looking at differences in time to antibiotic. Otherwise, non-adherent patients might experience worse outcomes because it may have been difficult to diagnose sepsis or its severity than in adherent patients [18, 19]. The non-adherent patients had more unknown sources of infection, fewer fevers, and lower ventilator use. Thus, time to antibiotic might not have been a cause but a result.

The resuscitation protocol of the hour-1 bundle such as maintenance of fluid volume and application of vasopressors will continue to be controversial. Adherence to the administration of crystalloid and lactate measurement were both very high in the present study. However, it is difficult to assess clinical effectiveness of a resuscitation protocol only from these results. Further study of fluid resuscitation and balance is needed.

Our study has several limitations. First, this study included convenience samples but not consecutive ones, which might have led to selection bias. Second, our adherence rate was very high. Regarding

generalizability, as triage and the path of emergency care and intensive care are influenced by the health care system in each country, the current findings may not be applicable in different countries. Third, due to the nature of observational studies, the possibility remains that the prognosis was better for the patients who received bundle-adherent care within an hour than for those who could not receive it within this time. In any case, we reconfirmed that the time of antibiotic administration is a key component in the treatment of sepsis.

Conclusions

We showed an association between completion of the hour-1 bundle and lower in-hospital mortality. Among the components of the hour-1 bundle, obtaining blood cultures and administering antibiotics may have contributed the most to the decrease of in-hospital mortality.

Abbreviations

SSC: Surviving Sepsis Campaign; JAAM: Japanese Association for Acute Medicine; MAESTRO: Multicenter Assessment for Sepsis Treatment and Outcome; ICU: intensive care units; SOFA: Sequential Organ Failure Assessment; CCI: Charlson comorbidity index; EGDT: early goal-directed therapy

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of all participating institutions in the Japanese Association for Acute Medicine (JAAM) study group, Japan (IRB No. 18323 from Osaka University, the representative for MAESTRO).

Consent for publication

Not applicable

Availability of data and materials

The statistical codes and full dataset are available from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

The statistical codes and full dataset are available from the corresponding author.

Authors’ contributions

YU conceived and designed this study; contributed to acquisition, analysis, interpretation of the data, and drafting the manuscript. TA conceived and designed this study; contributed to analysis and interpretation of the data; and was responsible for drafting, editing, and submission of the manuscript. HO was responsible for the study design; and contributed to acquisition, analysis, and interpretation of the data. SG had a significant influence on the study design and interpretation of the data. SF and SK had a major influence on the interpretation of the data and critical appraisal of the manuscript. All of the authors contributed to the acquisition of data, reviewed, discussed, and approved the final manuscript.

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Tables

Table 1 Patient characteristics

	Non-bundle-adherent group	Bundle-adherent group	p Value
	n=89	n=89	
Age	75 (67-84)	75 (69-82)	0.946
Sex, male	62 (70%)	58 (65%)	0.522
BMI (kg/m^2)	21 (18-24)	22 (19-25)	0.327
Charlson comorbidity index	1 (1-4)	1 (0-2)	0.073
Site of infection			0.092
Lung	42 (47%)	40 (45%)	
Abdomen	15 (17%)	18 (20%)	
Urinary tract	12 (13%)	19 (21%)	
Bone soft tissue	6 (7%)	6 (7%)	
Cardiovascular	0 (0%)	2 (2%)	
Other unidentified	14 (16%)	4 (4%)	
Glasgow Coma Scale	13 (10-14)	13 (9-15)	0.509
Respiratory rate (/min)	22 (19-30)	20 (16-30)	0.144
Systolic blood pressure (mmHg)	96 (74-119)	92 (69-132)	0.776
Diastolic blood pressure (mmHg)	50 (41-70)	56 (42-72)	0.371
Mean blood pressure (mmHg)	65 (53-86)	69 (51-94)	0.687
Heart rate (bpm)	105 (87-122)	111 (91-129)	0.259
Body temperature (°C)	37.3 (36.3-38.5)	38.2 (36.9-39.1)	0.002
Lactate (mmol/L)	3.7 (2.1-5.6)	3.7 (1.8-5.3)	0.624
White blood cell count (×10^3/μL)	12.3 (7.7-17)	9.7 (5.6-14.3)	0.049
Platelet count (×10^4/μL)	18.3 (13.8-25.4)	16.3 (11.8-22.5)	0.137
Total bilirubin (mg/dL)	0.8 (0.6-1.2)	0.9 (0.6-1.5)	0.176
Creatinine (mg/dL)	2 (1-3.8)	1.4 (1.1-2.6)	0.178
Glucose (mg/dL)	141 (100-231)	154 (108-200)	0.976
CRP (mg/dL)	11.3 (5.3-22.2)	10.6 (2.9-21.9)	0.501
24-hour urine volume (mL)	945 (430-1700)	1220 (641-1703)	0.279
FDP (μg/mL)	13.4 (8.1-32.6)	12.3 (6.5-27.4)	0.233

D-dimer (μg/mL)	5.8 (2.9-12.3)	6.3 (2.4-11.6)	0.439
APACHE II score	24 (18-28)	24 (18-27)	0.587
SOFA score	8 (6-10)	8 (5-10)	0.357
Mechanical ventilation use	26 (29%)	44 (49%)	0.006

BMI body mass index, *CRP* C-reactive protein, *FDP* fibrin/fibrinogen degradation products, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment

Table 2 Primary and secondary outcomes in the two groups

	Non-bundle-adherent group	bundle-adherent group	p Value
	n=89	n=89	
In-hospital mortality	27 (30.3%)	16 (18.0%)	0.054
Ventilator-free days	19 (0-28)	21 (0-28)	0.696
ICU-free days	15 (0-22)	18 (0-23)	0.24
Length of hospitalization (days)	19 (10-42)	21 (10-46)	0.827

ICU, intensive care unit

Figures

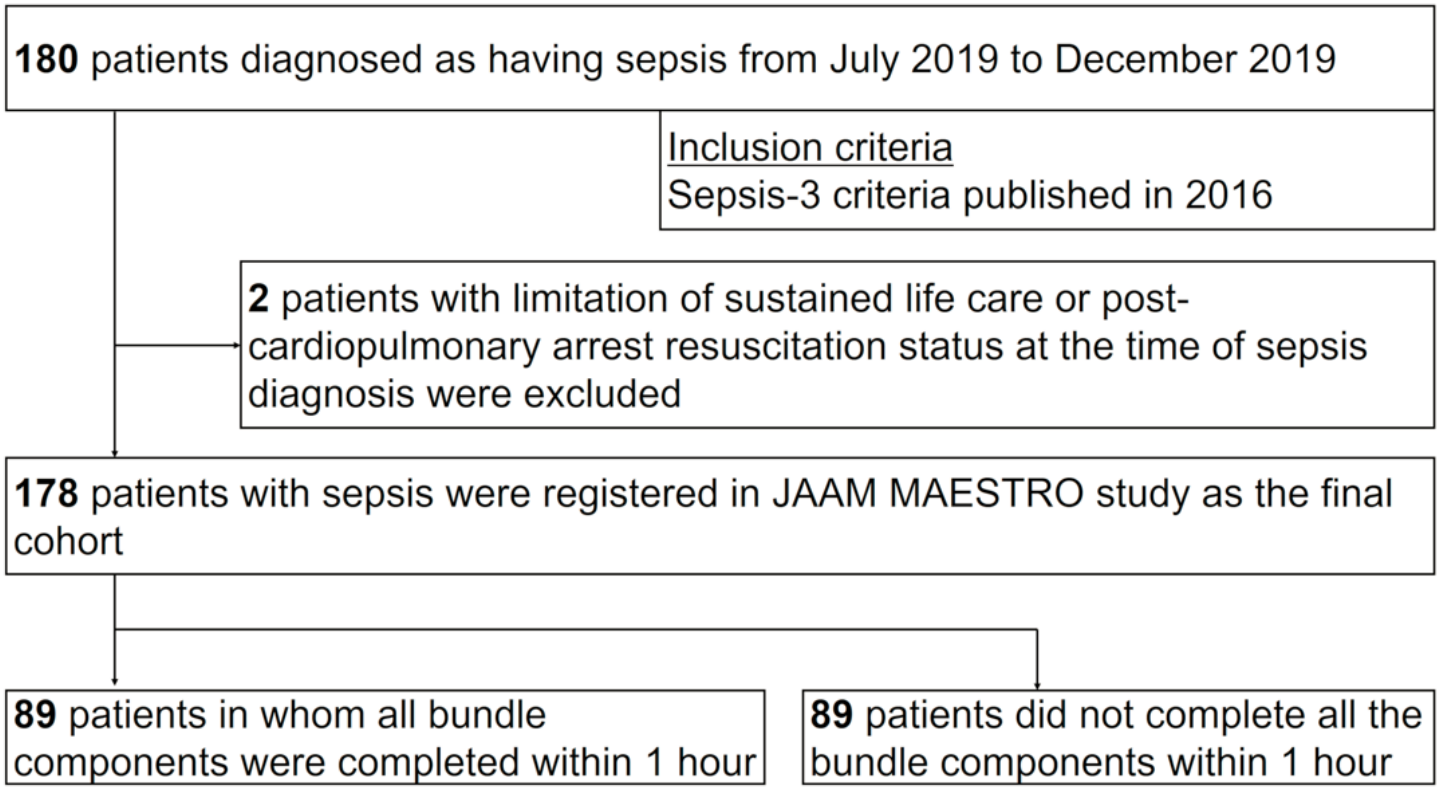

Figure 1

Patient flow diagram. JAAM MAESTRO Japanese Association for Acute Medicine Multicenter Assessment for Sepsis Treatment and Outcome

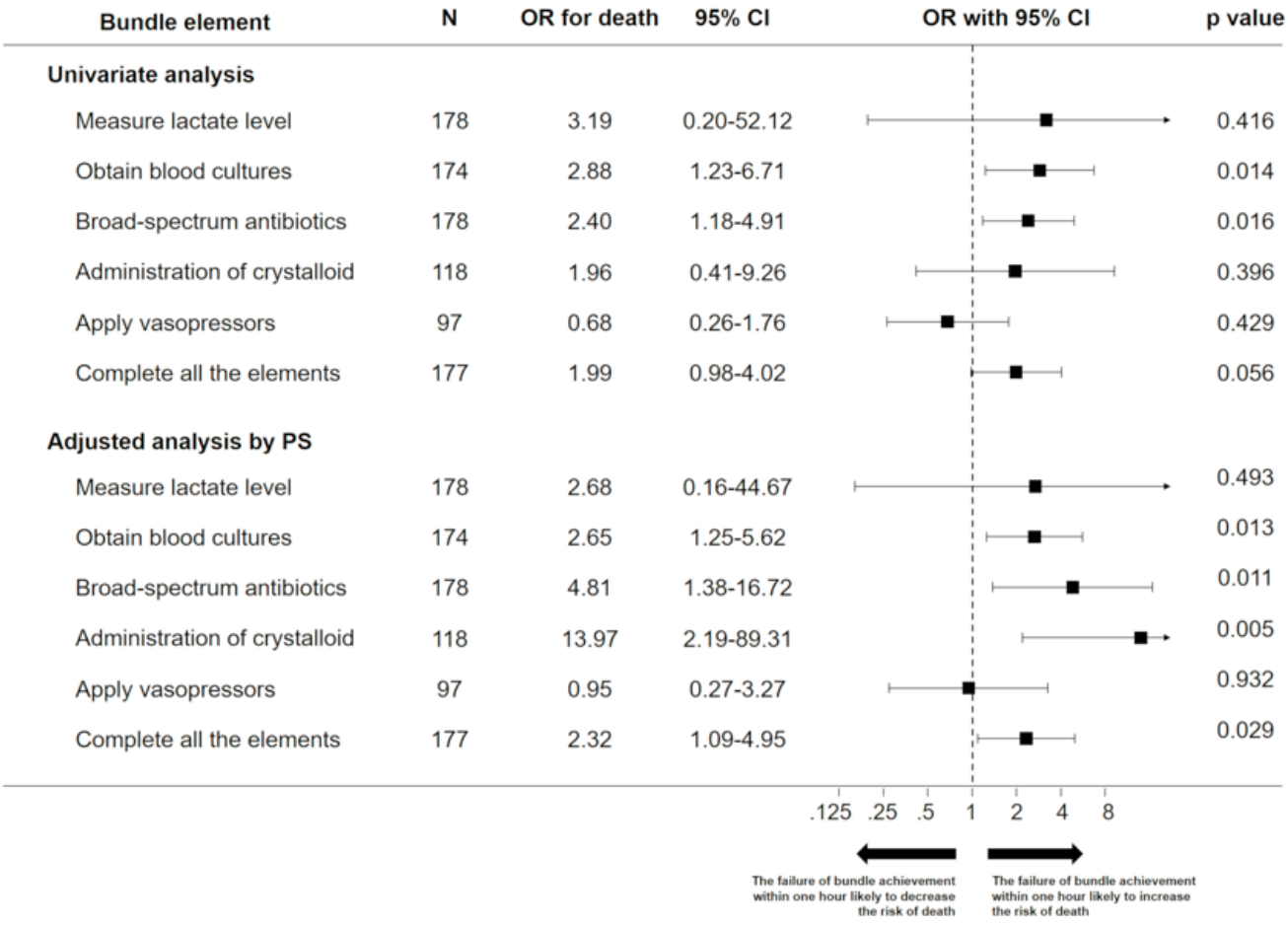

Figure 2

Association between mortality and adherence to each bundle component within 1 hour. Univariate and multivariate-adjusted ORs with 95% CIs for mortality risk are represented as forest plots. Inverse probability of treatment weighting analysis with propensity score was used as the adjustment method. OR odds ratio, CI confidence interval, PS propensity score

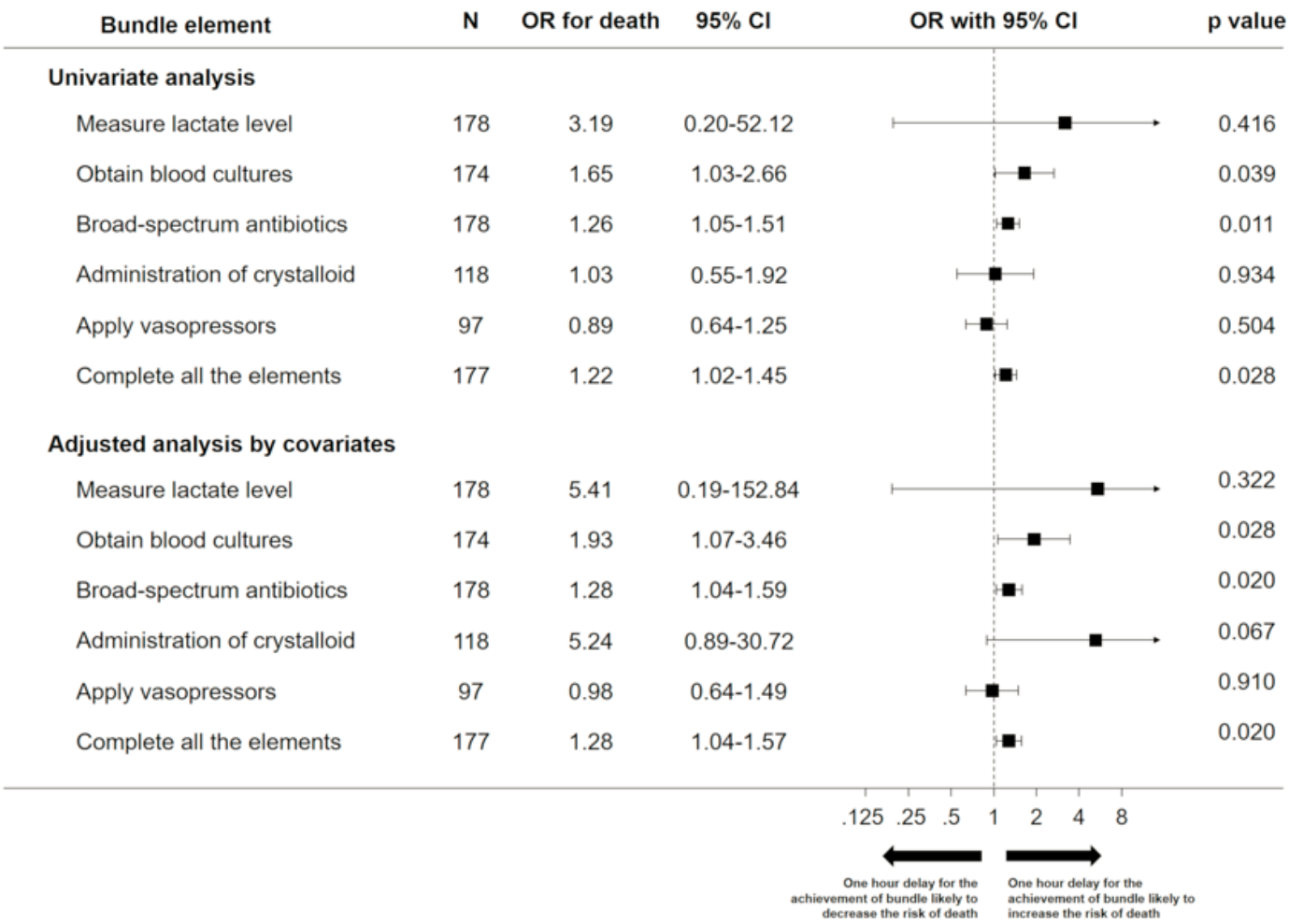

Figure 3

Association between the increase in mortality and 1-hour delay in the achievement of each bundle component. Univariate and multivariate-adjusted ORs with 95% CIs for mortality risk are represented as forest plots. Regression analyses were adjusted by including several clinically plausible and relevant confounders as covariates. OR odds ratio, CI confidence interval

Supplementary Files

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