Journal of Critical Care 53 (2019) 176–182

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Impact of timing to source control in patients with septic shock: A prospective multi-center observational study

Hongjung Kim, MD [a,1], Sung Phil Chung, MD, PhD [b,1], Sung-Hyuk Choi, MD, PhD [c], Gu Hyun Kang, MD, PhD [d], Tae Gun Shin, MD, PhD [e], Kyuseok Kim, MD, PhD [f], Yoo Seok Park, MD, PhD [g], Kap Su Han, MD, PhD [h], Han Sung Choi, MD, PhD [i], Gil Joon Suh, MD, PhD [j], Won Young Kim, MD, PhD [k], Tae Ho Lim, MD, PhD [a,*,2], Byuk Sung Ko, MD, PhD [a,*,2], for the Korean Shock Society (KoSS) Investigators

[a] Department of Emergency Medicine, Hanyang University Medical Center, 222-1, Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea
[b] Department of Emergency Medicine, Gangnam Severance Hospital, 211, Eonju-ro, Gangnam-gu, Seoul 06273, Republic of Korea
[c] Department of Emergency Medicine, Korea University Guro Hospital, 148, Gurodong-ro, Guro-gu, Seoul 08308, Republic of Korea
[d] Department of Emergency Medicine, Hallym University Kangnam Sacred Heart Hospital, 1, Singil-ro, Yeongdeungpo-gu, Seoul 07441, Republic of Korea
[e] Department of Emergency Medicine, Samsung Medical Center, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea
[f] Department of Emergency Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Republic of Korea
[g] Department of Emergency Medicine, Severance Hospital, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea
[h] Department of Emergency Medicine, Korea University Anam Hospital, Korea University, 73, Inchon-ro, Seongbuk-gu, Seoul 02841, Republic of Korea
[i] Department of Emergency Medicine, Kyunghee University Hospital, 23, Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Republic of Korea
[j] Department of Emergency Medicine, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea
[k] Department of Emergency Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea

ARTICLE INFO

Keywords:
Septic shock
Infection control
Emergency service
Hospital

ABSTRACT

Purpose: Current guidelines recommend that rapid source control should be adopted in patients not >6–12 h after sepsis is diagnosed. However, evidence level of this guideline is not specified, and there is no previous study on patients with septic shock visiting the emergency department (ED). Therefore, we aimed to assess the impact of rapid source control in patients with septic shock visiting the ED.
Materials and methods: In a prospective, observational, multicenter, registry-based study in 11 EDs, Cox proportional hazards model was used to assess the independent effect of source control and time to source control on 28-day mortality.
Results: Cox proportional hazard models revealed that 28-day mortality was significantly lower in patients who underwent source control (HR 0.538 (0.389–0.744), $p < .001$). However, no significant association between the performance of source control after 6 h or 12 h from enrollment and 28-day mortality was noted.
Conclusions: Patients with septic shock visiting the ED who underwent source control showed better outcomes than those who did not. We failed to demonstrate the performance of rapid source control reduced the 28-day mortality in septic shock patients. Further studies are required to determine the impact of rapid source control in sepsis and septic shock.

1. Introduction

Despite recent advances in treatment, sepsis is still a disease that is highly burdened by public health cost [1]. Sepsis remains a major health problem with high mortality, affecting aging populations with more comorbidities [2,3]. Furthermore, patients who survive sepsis often have long-term physical, psychological, social, and cognitive disabilities with significant health care and social implications, increasing social costs [2,4].

Source control includes performing all physical measures in patients with septic shock to eliminate sources of infection, to control contamination, and to restore the patients' anatomy and function [5]. Surviving Sepsis Campaign (SSC) recommends that an anatomically specific diagnosis of infection requiring the performance of rapid source control should be established as early as possible in patients with sepsis or septic shock [6]. In 2016, the SSC recommended the target time (no more

Abbreviations: ED, emergency department; SSC, Surviving Sepsis Campaign; ICU, intensive care unit; KoSS, Korean Shock Society; HR, hazard ratio; CI, confidence interval.

* Corresponding author.
E-mail addresses: kuedchoi@korea.ac.kr (S.-H. Choi), pys0905@yuhs.ac (Y.S. Park), suhgil@snu.ac.kr (G.J. Suh), erthim@gmail.com (T.H. Lim), postwinston@gmail.com (B.S. Ko).

[1] Hongjung Kim and Sung Phil Chung contributed equally to this work.
[2] Byuk Sung Ko and Tae Ho Lim contributed equally to this work.

https://doi.org/10.1016/j.jcrc.2019.06.012
0883-9441/

than 6–12 h after the diagnosis of sepsis or septic shock) of the performance of source control was sufficient for most cases. It was a strong recommendation, but the grading system of the evidence level was not specific and the evidence of the effectiveness of performing source control is lacking.

A few previous studies were conducted to investigate the impact of performing rapid source control in patients with sepsis or septic shock, and these studies showed inconsistent results regarding timing of source control and outcomes [7,8]. The previous studies had focused on patients with sepsis or septic shock who were admitted in the intensive care unit (ICU) or general wards. Patients with sepsis or septic shock are hospitalized commonly through the emergency department (ED), but there is no study conducted that investigates on the relationship between the performance of rapid source control and prognosis of patients with sepsis and septic shock in the ED [9,10]. Therefore, we aimed to assess the impact of performing rapid source control in patients with septic shock visiting the ED. The hypothesis of this study was that delays in the performance of source control in patients with septic shock would worsen patients' outcomes.

2. Materials and methods

2.1. Study design and population

We conducted a prospective, observational, multicenter, registry-based study to investigate the impact of time in performing source control in patients with septic shock visiting the ED. We analyzed the data from the Korean Shock Society (KoSS) septic shock registry from October 2015 to December 2017. This study was approved by the institutional review boards of each participating institute, and informed consent was obtained before data collection.

The methodology of the KoSS septic shock registry has been reported previously [11-15]. Patients who visited the ED and met the following inclusion criteria were included in this study: suspected or confirmed infection and evidence of refractory hypotension or hypoperfusion [16-18]. Hypotension was defined as having the following values: a systolic blood pressure <90 mmHg, a mean arterial pressure <70 mmHg, or a decrease in systolic blood pressure of >40 mmHg[19] Refractory hypotension was defined as a persistent hypotension after the administration of intravenous fluid (20–30 mL/kg or at least 1 L of crystalloid solution administered over 30 min), or the need for the administration of vasopressors to maintain a normal blood pressure after intravenous fluid administration [11]. Hypoperfusion was defined as having a serum lactate concentration of greater than or equal to 4 mmol/L [19,20]. Patients who signed a “do not attempt resuscitation” order before the ED arrival or at the time of diagnosis, met the inclusion criteria 6 h after the ED arrival, were transferred from the other hospitals without meeting the inclusion criteria upon the ED arrival, or were directly transferred from the EDs to the other hospitals were excluded.

2.2. Data collection

All data were collected anonymously using standardized web-based report forms by research coordinators or clinicians at each participating hospital. Data were centrally reviewed at the coordinating hospital to control quality of data. For this study, the following patients' demographic and clinical data were retrieved from the KoSS registry: age, sex, initial vital signs, initial lactate, lactate clearance, result of blood culture and identified resistant bacteria, comorbidities, source of infection, treatment bundles, types of source control, time to source control, and severity score such as Sequential Organ Failure Assessment (SOFA) score upon enrollment [21] or Acute Physiology and Chronic Health Evaluation II score [22] using the worst parameters within 24 h of the ED arrival.

Results of blood culture (called bacteremia in this study) were documented as positive or negative. Identified resistant bacteria were defined as those with an identified organism with in vitro resistance to administered empirical antibiotics on body fluid culture. Comorbidities were documented such as HTN, DM, cardiac disease, cerebrovascular accident, chronic lung, renal, liver disease. Source of infection was consisted of urinary tract, respiratory tract, gastrointestinal tract, hepatobiliary and pancreas, and the other origins. Treatment bundles were selected such as administration of vasopressor within 6 h, lactate clearance and 3 h bundles; 1) Measure lactate level, 2) Obtain blood cultures prior to administration of antibiotics, 3) Administer broad spectrum antibiotics, and 4) Administer 30 mL/kg crystalloid for hypotension or lactate 4 mmol/L [19]. “Time zero” of treatment bundles was defined as the time of triage in the ED [23]. The types of source control were consisted of emergency surgery, percutaneous drainage, endoscopic intervention, removal of infected device, and others. Time to source control was defined as the time from the enrollment to initiation of source control. The decision to perform source control procedure or surgery was at the discretion of the physician.

The primary outcome of this study was 28-day mortality. The secondary outcomes were rate of admission to the ICU, length of ICU and hospital stay, application and duration of use of mechanical ventilators and length of stay in the ICU.

2.3. Statistical analysis

The descriptive results were presented as frequencies and percentages for categorical variables and medians and interquartile ranges for continuous variables that do not follow a normal distribution. To compare continuous variables, we used the Mann-Whitney *U* test. To compare categorical variables, we used chi-squared test or Fisher's exact test, as appropriate.

The Cox proportional hazards model was used to assess the independent effect of source control and time to source control on 28-day mortality, with multivariable adjustment for confounding variables significant in univariate analysis. Variables yielding p below 0.2 by univariate analysis were entered into backward multivariable analysis. If variables had multicollinearity, only one variable was used as covariate.

Two-sided test was performed. Statistical tests were considered with significance defined as p value <.05. We used Statistical Package for the Social Sciences, version 20.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

A total of 2250 patients were eligible in KoSS septic shock registry from November 2015 to December 2017 and thus were included in this study (Fig. 1). 123 patients were lost to follow up after discharge before 28 day. The 28-day mortality rate was 21.3% (452 of 2127 patients).

The demographic and clinical characteristics and are shown in Table 1. The median age was 70 years (60–78), and 1316 (58.5%) patients were male. There was no statistical difference in positive result of blood culture (Survival group vs Non-survivor group; 43.3% vs 38.7%, $p = .081$) and identified organisms in vitro resistance to administered empirical antibiotics on body fluid culture (Survival group vs Non-survivor group; 9.1% vs 9.7%, $p = .696$) between survivor and non-survivor group according to 28-day mortality.

The respiratory tract (24.9%) was the most common site of infection, followed by the urinary tract (18.8%) and gastrointestinal tract (13.0%).

3.2. Source control

Out of the 2250 patients included in this study, 524 (23.3%) underwent source control. The following interventions were the types of source control performed: percutaneous drainage ($n = 301$, 57.4%),

emergency surgery ($n = 103$, 19.7%), endoscopic intervention ($n = 78$, 14.9%), removal of infected device ($n = 32$, 6.1%), and others ($n = 10$, 1.9%). The proportion of the performance of source control in the survivor group was 26.9%, which was significantly higher from that in the non-survivor (13.9%) group ($p < .001$).

The Cox proportional hazards model was used to assess the effect of source control on 28-day mortality, with multivariable adjustment for confounding variables The variables used as covariates in multivariable analysis were $p < .2$ in univariate analysis (Table S1). In multivariable analysis, performance of source control (Adjusted Hazard ratio (HR), 0.538; 95% confidence interval (CI), 0.389–0.744) and body temperature (Adjusted HR, 0.738; 95% CI, 0.677–0.805) were significantly associated with a decreased risk of 28-day mortality (Table 2). Age (Adjusted HR, 1.012; 95% CI, 1.004–1.020), respiratory rate (Adjusted HR, 1.017; 95% CI, 1.002–1.033), lactate concentration (Adjusted HR, 1.117; 95% CI, 1.087–1.148), SOFA score (Adjusted HR, 1.163; 95% CI, 1.129–1.199), and chronic lung disease (Adjusted HR, 1.387; 95% CI, 1.008–1.906) were significantly associated with an increased risk of 28-day mortality.

As shown in Table 3, there was no difference in treatment bundles between patients who underwent source control and patients who did not. Patients who underwent source control were younger and had higher initial lactate concentration and more positive results of blood culture. Hepatobiliary and pancreas infection was the most common source of infection (49.2%) in patients who underwent source control. On the other hand, respiratory tract was the most common source of infection (30.8%) in patients who did not.

Secondary outcomes measurements between source control and non-source control groups are shown in Table S2. The rate of applying mechanical ventilator was lower in patients who underwent source control (24.0% vs. 29.0%, $p = .028$) than those patients who did not. However, there was no association between source control and duration of use of mechanical ventilator. Other comparisons of the secondary outcomes between source control and non-source control groups are summarized in Table S2.

3.3. Time to source control

Median of time to source control in patients with septic shock visiting the ED was 13.3 h (5.9–37.0) (Table S3). Source control was initiated in 134 patients (25.6%) within 6 h, 115 patients (21.9%) over 6 h, but within 12 h, and 275 patients (52.5%) over 12 h. There was no statistical difference in median of time to source control between 28-day survivors (Median 13.6, IQR 6.0–42.5) and non-survivors (Median 10.4, IQR 4.4–25.9) ($p = .082$). There was no statistical difference in positive result of blood culture(bacteremia) and in inappropriate administration of empirical antibiotics(resistant bacteria) between patients who underwent source control within and after 6 h or 12 h (Within 6 h vs

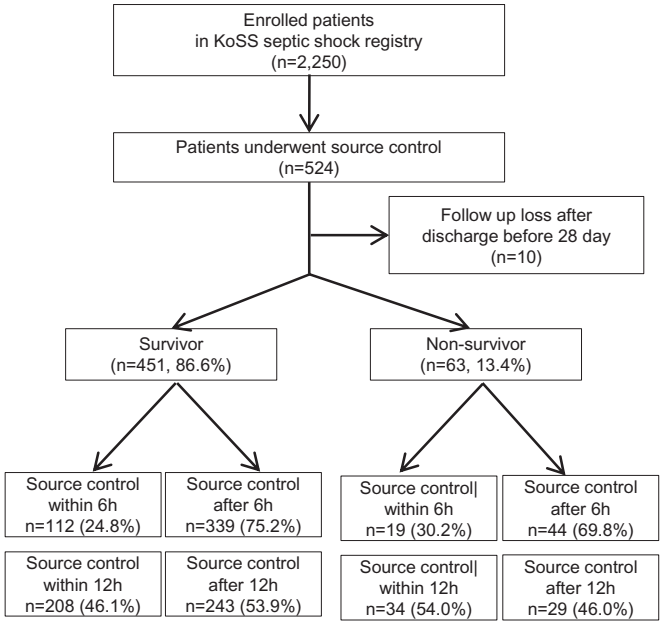

Fig. 1. Flowchart of the study population.

Table 1
Demographic and clinical characteristics of the patients ($n = 2250$).

	All patients (n = 2250)
Age (year)	70 (60–78)
Male	1316 (58.5%)
Vital sign	
Body temperature (°C)	37.6 (36.7–38.6)
Systolic BP (mmHg)	93 (79–116)
Diastolic BP (mmHg)	57 (48–69)
Heart rate (bpm)	109 (92–126)
Respiratory rate (rpm)	20 (18–24)
Lactate concentration (mmol/L)	3.3 (1.9–5.4)
SOFA score	6 (4–8)
APACHE score	19 (13–25)
Bacteremia[a]	940 (41.8%)
Resistant bacteria[b]	207 (9.2%)
Comorbities	
HTN	927 (41.2%)
DM	683 (30.4%)
Cardiac disease	298 (13.2%)
Cerebrovascular accident	275 (12.2%)
Chronic lung disease	179 (8%)
Chronic renal disease	167 (7.4%)
Chronic liver disease	254 (11.3%)
Source of infection	
Urinary tract	423 (18.8%)
Respiratory tract	560 (24.9%)
GI tract	292 (13.0%)
Hepatobiliary and pancreas	405 (18.0%)
Others[c]	570 (25.3%)
Treatment variables	
Measure lactate within 3 h	2103 (93.5%)
Blood culture prior to administration of antibiotics[d]	1589 (70.6%)
Administration of antibiotics within 3 h	1481 (65.8%)
IV fluid administration (≥30 mL/kg) within 3 h	1619 (72%)
Administration of vasopressor within 6 h	1856 (82.5%)
Lactate clearance[e]	853 (37.9%)
Source control	524 (23.3%)
Time to source control (h)[f]	13.3 (5.9–37.0)
Source control after 6 h [f]	390 (74.4%)
Source control after 12 h [f]	275 (52.5%)
Type of source control	
Surgery	103 (19.7%)
Percutaneous catheter drainage	301 (57.4%)
Endoscopic intervention	78 (14.9%)
Removal of infected device	32 (6.1%)
Others	10 (1.9%)
28-day mortality	452 (20.1%)

Categorical data are expressed as number (percentage) and continuous data are expressed as median (interquartile range).
SOFA Sequential Organ Failure Assessment, *HTN* hypertension, *DM* diabetes mellitus.
The value of the lactate clearance variable was lost in 33 (2%) of 28-day survivors and 3 (0.7%) of 28-day Non-survivors. The value of the 28-day mortality variable was lost in 123 of 2250 (5.5%).

[a] Bacteremia indicates a positive blood culture.
[b] Resistant bacteria were defined as those with an identified organism with in vitro resistance to an administered antibiotics on body fluid culture/
[c] Others include soft tissue/bone/joint infection, mixed infection origin, unknown origin, or others except for infection mentioned on the table and above.
[d] Obtain blood cultures prior to administration of empirical antibiotics within 3 h from triage in the Emergency Department.
[e] Normalization of lactate within 6 h.
[f] Time to source control was defined as the time from the enrollment to initiation of source control.

Table 2
Cox proportional hazard regression model of risk factors for 28-day mortality in total patients ($n = 2250$).

	Adjusted HR	p
Age (year)	1.012 (1.004–1.020)	0.002
Male	0.963 (0.780–1.188)	0.724
Body temperature (°C)	0.738 (0.677–0.805)	<0.001
Heart rate (bpm)	1.004 (1.000–1.008)	0.049
Respiratory rate (rpm)	1.017 (1.002–1.033)	0.030
Lactate concentration (mmol/L)	1.117 (1.087–1.148)	<0.001
SOFA score	1.163 (1.129–1.199)	<0.001
Comorbidities		
DM	1.039 (0.843–1.281)	0.718
Chronic lung disease	1.387 (1.008–1.906)	0.044
Chronic renal disease	1.038 (0.741–1.453)	0.829
Source of infection		
Urinary tract	1	
Respiratory tract	2.297 (1.578–3.344)	<0.001
GI tract	1.946 (1.273–2.973)	0.002
Hepatobiliary and pancreas	1.322 (0.829–2.109)	0.242
Others[a]	2.089 (1.431–3.052)	<0.001
Treatment variables		
Blood culture prior to administration of antibiotics[b]	0.926 (0.750–1.143)	0.472
IV fluid administration (≥30 mL/kg) within 3 h	0.980 (0.793–1.211)	0.851
Lactate clearance[c]	0.718 (0.556–0.928)	0.011
Source control	0.538 (0.389–0.744)	<0.001

Adjusted hazard ratios and 95% confidence intervals (CIs) for 28-day mortality in total patients.
The covariates of Cox proportional hazard regression model adopted the variables with a p of <0.2 in the univariate analysis shown in Table S1.
SOFA Sequential Organ Failure Assessment.
[a] Others include soft tissue/bone/joint infection, mixed infection origin, unknown origin, or others except for infection mentioned on the table and above.
[b] Obtain blood cultures prior to administration of empirical antibiotics within 3 h from triage in the Emergency Department.
[c] Normalization of lactate within 6 h.

Table 3
Demographic and clinical characteristics of patients who underwent and who did not undergo source control (n = 2250).

	Patients with source control ($n = 524$)	Patients without source control ($n = 1726$)	p
Age (year)	68 (58–76)	70 (61–78)	0.008
Male	319 (60.9%)	997 (57.8%)	0.213
Vital sign			
Body temperature (°C)	37.6 (36.6–38.6)	37.6 (36.7–38.6)	0.998
Systolic BP (mmHg)	94 (80–116)	92 (78–115)	0.460
Diastolic BP (mmHg)	58 (50–70)	57 (48–69)	0.159
Heart rate (bpm)	106 (91–125)	109 (92–126)	0.266
Respiratory rate (rpm)	20 (18–22)	20 (18–24)	0.002
Lactate concentration (mmol/L)	3.8 (2.0–5.6)	3.1 (1.8–5.3)	0.005
SOFA score	6 (4–8)	6 (4–8)	0.696
APACHE score	19 (14–25)	19 (13–25)	0.765
Bacteremia[a]	306 (58.4%)	634 (36.7%)	<0.001
Resistant bacteria[b]	54 (10.3%)	153 (8.9%)	0.388
Comorbidities			
HTN	213 (40.6%)	714 (41.4%)	0.775
DM	152 (29%)	531 (30.8%)	0.446
Cardiac disease	57 (10.9%)	241 (14%)	0.082
Cerebrovascular accident	42 (8%)	233 (13.5%)	0.002
Chronic lung disease	23 (4.4%)	156 (9%)	<0.001
Chronic renal disease	33 (6.3%)	134 (7.8%)	0.215
Chronic liver disease	81 (15.5%)	173 (10%)	0.001
Source of infection			
Urinary tract	67 (12.8%)	356 (20.6%)	<0.001
Respiratory tract	28 (5.3%)	532 (30.8%)	<0.001
GI tract	69 (13.2%)	223 (12.9%)	0.783
Hepatobiliary and pancreas	258 (49.2%)	147 (8.5%)	<0.001
Others[c]	102 (19.5%)	468 (27.1%)	0.001
Treatment variables			
Measure lactate within 3 h	484 (92.4%)	1619 (93.8%)	0.260
Blood culture prior to administration of antibiotics[d]	383 (73.1%)	1206 (69.9%)	0.371
Administration of antibiotics within 3 h	349 (66.6%)	1132 (65.6%)	0.507
IV fluid administration (≥30 mL/kg) within 3 h	370 (70.6%)	1249 (72.4%)	0.562
Administration of vasopressor within 6 h	430 (82.1%)	1426 (82.6%)	0.739
Lactate clearance[e]	186 (35.5%)	667 (38.6%)	0.114
28-day mortality	63 (12.3%)	389 (22.5%)	<0.001

Categorical data are expressed as number (percentage) and are compared using the chi-squared test; continuous data are expressed as median (interquartile range) and are compared using the Mann–Whitney *U* test.
SOFA Sequential Organ Failure Assessment, *HTN* hypertension, *DM* diabetes mellitus.
The value of the lactate clearance variable was lost in 4 (0.8%) of patients who underwent source control and in 33 (1.9%) of patients who did not. The value of the 28-day mortality variable was lost in 10 (1.9%) of patients who underwent source control and 113 (6.5%) of patients who did not.
[a] Bacteremia indicates a positive blood culture.
[b] Resistant bacteria were defined as those with an identified organism with in vitro resistance to an administered antibiotics on body fluid culture.
[c] Others include soft tissue/bone/joint infection, mixed infection origin, unknown origin, or others except for infection mentioned on the table and above.
[d] Obtain blood cultures prior to administration of empirical antibiotics within 3 h from triage in the Emergency Department.
[e] Normalization of lactate within 6 h.

after 6 h; Bacteremia (51.5% vs 60.8%, $p = .060$), Resistant bacteria (7.5% vs 11.3%, $p = .210$) and Within 12 h vs after 12 h; Bacteremia (55.4% vs 61.1%, $p = .189$), Resistant bacteria (11.2% vs 9.5%, $p = .501$). Treatment bundles had no statistical difference between early vs. late source control group except measurement lactate within 3 h and lactate clearance (Table S4).

The Cox proportional hazards model was used to assess the effect of time to source control on 28-day mortality, with multivariable adjustment for confounding variables. The variables used as covariates in multivariable analysis were $p < .2$ in univariate analysis (Table S3, Table 4). In multivariable analysis, source control performed after 6 h and 12 h were not associated with 28-day mortality (Adjusted HR, 1.418; 95% CI, 0.724–2.779; $p = .309$ and Adjusted HR, 1.263; 95% CI, 0.626–2.548; $p = .514$).

Secondary outcome measurements in the time to source control divided by 6 h and 12 h are shown in Table S4. The rate of applying mechanical ventilator was higher in patients who underwent source control within 6 h than after 6 h (30.6% vs 21.8%, $p = .040$) and higher in patients who underwent source control within 12 h than after 12 h (30.1% vs 18.5%, $p = .002$). However, duration of use of mechanical ventilator was not significantly different between the source control group within and after 6 h or 12 h. Other comparisons of the secondary outcomes between the source control group within and after 6 h or 12 h are summarized in Table S4.

3.4. Subgroup analysis in patients who underwent source control with Sepsis-3 septic shock

Out of the 2250 patients included in this study, 1049 (46.6%) were eligible for Sepsis-3 septic shock (hypotension, the need for vasopressors, and lactate concentration > 2 mmol/L despite adequate intravenous fluid administration) [24]. Among them, 281 (26.8%) patients underwent source control. In multivariable analysis, source control performed after 6 h and 12 h were not associated with 28-day mortality in Sepsis-3 septic shock (Adjusted HR, 1.309; 95% CI, 0.612–2.797; $p = .488$ and Adjusted HR, 1.344; 95% CI, 0.612–2.951; $p = .462$) (Tables S5 and S6).

3.5. Subgroup analysis in patients who underwent percutaneous catheter drainage

Percutaneous catheter drainage was the most common source control measure in this study ($n = 301$, 57.4%). In multivariable analysis, source control performed after 6 h and 12 h were not associated with 28-day mortality in patients who underwent percutaneous catheter drainage (Adjusted HR, 1.085; 95% CI, 0.479–2.455; $p = .845$ and Adjusted HR, 1.040; 95% CI, 0.437–2.471, $p = .930$) (Table S7, Table S8).

4. Discussion

This study revealed lower 28-day mortality in septic shock patients who underwent source control after adjusting the confounding factors. However, this study found no association between the time to source control and 28-day mortality. One prospective, observational study including 1011 patients with severe sepsis or septic shock found that performance of source control within the first 6 h was associated with 16% lower 28-day mortality [7]. This study was different from our study in that it was conducted in ICU patients with severe sepsis and septic shock. Another recent prospective, observational study including 3663 patients with severe sepsis and septic shock found that mortality was lower in septic patients who underwent source control than in those patients who did not; however, the time to source control could not be linked to survival in the study [8].

The result of this study is interesting because the SSC in 2016 recommended that the target time (no >6–12 h after the establishment of the diagnosis) of performance of source control was sufficient for most cases [6]. It was based on several studies that demonstrated the importance of the performance of rapid source control [25-30]. However, these studies included only single disease entity such as necrotizing fasciitis, peptic ulcer perforation, and cholangitis. The definition of rapid source control was also defined differently depending on each study [25,28,31-33].

New paradigm of sepsis suggested that the best approach to treatment is to minimize the time it takes for microorganisms to develop into septic shock [34]. This concept supported the current concept of rapid clearance of pathogen in patients with sepsis and septic shock. Kumar et al. discussed the rapid administration of antibiotics; however, they did not mention the performance of source control [34]. Although it is reasonable to assume that the performance of rapid source control is essential to increase survival in patients with septic shock, it has not been fully proved through data.

It is clear that the performance of source control improves the prognosis of patients with septic shock. In this study, 28-day mortality was reduced in patients who underwent source control compared to patients who did not (HR, 0.538; 95% CI, 0.389–0.744). One study found the source of infection in 80% of patients of surgical ICU who died of sepsis or septic shock through macroscopic findings in the autopsies, suggesting that the need for performing source control might be underassessed [35].

Failure of many attempts to demonstrate the association between the optimal time of the performance of source control and mortality

Table 4
Cox proportional hazard regression model of risk factors for 28-day mortality in patients who underwent source control (n = 524) measures.

	Adjusted HR	p		Adjusted HR	p
Source control			Source control		
Source control performed after 6 h[a]	1.418 (0.724–2.779)	0.309	Source control performed after 12 h[a]	1.263 (0.626–2.548)	0.514
Time to source control (h)[a]	0.994 (0.988–1.001)	0.082	Time to source control (h)[a]	0.994 (0.987–1.001)	0.109
Type of source control			Type of source control		
Surgery	1		Surgery	1	
Percutaneous catheter drainage	1.351 (0.538–3.389)	0.522	Percutaneous catheter drainage	1.403 (0.56–3.515)	0.470
Endoscopic intervention	0.175 (0.020–1.536)	0.116	Endoscopic intervention	0.186 (0.021–1.626)	0.128
Removal of infected device	2.047 (0.540–7.761)	0.292	Removal of infected device	2.058 (0.537–7.888)	0.292
Others	0.945 (0.134–6.679)	0.955	Others	0.956 (0.134–6.852)	0.965
Body temperature (°C)	0.767 (0.603–0.976)	0.031	Body temperature (°C)	0.771 (0.605–0.983)	0.036
Respiratory rate (rpm)	0.995 (0.937–1.056)	0.859	Respiratory rate (rpm)	0.997 (0.939–1.059)	0.920
Lactate concentration (mmol/L)	1.058 (0.977–1.146)	0.163	Lactate concentration (mmol/L)	1.052 (0.973–1.138)	0.200
SOFA score	1.254 (1.140–1.379)	<0.001	SOFA score	1.253 (1.138–1.380)	<0.001
Bacteremia[b]	0.566 (0.301–1.065)	0.078	Bacteremia[b]	0.568 (0.301–1.07)	0.080
Chronic lung disease	4.966 (2.091–11.79)	<0.001	Chronic lung disease	4.835 (2.039–11.464)	<0.001
Source of infection			Source of infection		
Urinary tract	1		Urinary tract	1	
Respiratory tract	3.533 (0.785–15.897)	0.100	Respiratory tract	3.321 (0.725–15.217)	0.122
GI tract	3.360 (0.837–13.482)	0.087	GI tract	3.328 (0.829–13.362)	0.090
Hepatobiliary and pancreas	1.632 (0.476–5.599)	0.436	Hepatobiliary and pancreas	1.56 (0.453–5.371)	0.481
Others[c]	2.376 (0.637–8.854)	0.197	Others[c]	2.387 (0.639–8.919)	0.196
Treatment variables			Treatment variables		
Blood culture prior to administration of antibiotics[d]	0.775 (0.416–1.444)	0.422	Blood culture prior to administration of antibiotics[d]	0.807 (0.436–1.494)	0.495
Administration of antibiotics within 3 h	0.749 (0.397–1.414)	0.373	Administration of antibiotics within 3 h	0.744 (0.393–1.408)	0.364
Lactate clearance[e]	0.400 (0.174–0.921)	0.031	Lactate clearance[e]	0.398 (0.173–0.918)	0.031

Adjusted hazard ratios and 95% confidence intervals (CIs) for 28-day mortality in patients who underwent source control.
The covariates of Cox proportional hazard regression model adopted the variables with a p of <0.2 in the univariate analysis shown in Table S3.
SOFA Sequential Organ Failure Assessment.
[a] Time to source control was defined as the time from the enrollment to initiation of source control.
[b] Bacteremia indicates a positive blood culture.
[c] Others include soft tissue/bone/joint infection, mixed infection origin, unknown origin, or others except for infection mentioned on the table and above.
[d] Obtain blood cultures prior to administration of empirical antibiotics within 3 h from triage in the Emergency Department.
[e] Normalization of lactate within 6 h.

could be due to various types of source control, diverse disease entities, and varying clinical decisions. First, as an example of disease entities, when intra-abdominal infection becomes complicated, it often requires more than one performance of source control [36], therefore increasing morbidity, hospital stay, and mortality [37,38]. Hence, initial performance of rapid source control to treat the intra-abdominal infection could not guarantee a successful eradication of the infection. Second, clinical decision could delay the performance of source control, leading to the occurrence of favorable outcomes. For example, certain disorders, such as necrotizing pancreatitis, require time to be anatomically defined; hence, the need for a clinical intervention is also delayed [39]. Third, there are various types of source control, and there may be limitations to study them together.

This study has several limitations. There may be other confounding factors that we did not measure. Possible confounding factors related to source control are the number of attempts in the performance of source control, technical success of source control, and complications of source control. The number of attempts of source control may be important, because the unstable patient condition does not allow complete source control intervention. It can make clinicians to do only bridging intervention first and complete source control could be performed later. In our registry, 57.4% of patients who underwent source control received percutaneous catheter drainage. Some of them could be just "bridging intervention". Furthermore, Even if the rapid source control was performed, a good prognosis cannot be achieved if the removal is unsuccessful or if fatal complications of intervention were made. There is no data about occurrence of fatal complication during intervention in our data. Finally, there were no data on patients who required source control, but did not undergo. It could make the outcome of patients who did not undergo source control to be worsened.

However, this study also has corresponding strengths. First, we prospectively enrolled a large cohort of patients with septic shock from a multicenter. Variables were predefined to minimize the difference of judgment among individual investigators. Second, this is the first study to investigate the effect of the performance of source control in patients with septic shock visiting the ED.

5. Conclusion

Among the patients who visited the ED with septic shock, those who underwent source control showed better outcomes than those who did not. But, we failed to demonstrate the performance of rapid source control reduced the 28-day mortality in septic shock patients. Well-designed clinical trials including patients with severe sepsis and septic shock and the number, technical success and needs of the performance of source control should be investigated to determine the impact of the performance of rapid source control.

Acknowledgements

The authors thank the KoSS participants and participating physicians, investigators and staff for making this research possible. More information about the study and how to access KoSS data is at www.shockkr.com.

Authors' contributions

HK and SPC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and contributed substantially to drafting and revising the manuscript. HK and SPC contributed equally to this work. THL and BSK contributed substantially to the design of the study, interpretation of results, revisions of the manuscript for critically important intellectual content and final approval of the version to be published. THL and BSK contributed equally to this work. SHC, GHK, TGS, KSK, YSP, KSH, HSC, GJS, WYK contributed to the acquisition, analysis and interpretation of the data. All authors have approved the submitted version. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Ethic approval and consent to participate

This study was approved by the institutional review boards of each participating institute, and informed consent was obtained before data collection.

1) Asan Medical Center (S2015-1918-0002)
2) Gangnam Sacred Heart Hospital (2015-11-142)
3) Gangnam Severance Hospital (3-2015-0227)
4) Hanyang University Hospital (HYUH 2015-11-013-022)
5) Korea University Anam Hospital (HRPC2016- 184)
6) Korea University Kuro Hospital (KUGH15358-001)
7) Samsung Medical Center (SMC2015-09-057-057)
8) Seoul National University Hospital (J-1408-003-599)
9) Seoul National University Bundang Hospital (B-1409/266-401)
10) Severance Hospital (4-2015-0929)
11) Seoul National University Boramae Hospital (IRB-16-2014-36)

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interests

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.012.

References

[1] Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. Am J Respir Crit Care Med 2016;193(3):259–72.
[2] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801.
[3] Vincent JL, Marshall JC, Ñamendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med 2014;2(5):380–6.
[4] Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 2010;304(16):1787–94.
[5] Marshall JC, al Naqbi A. Principles of source control in the management of sepsis. Crit Care Clin 2009;25(4):753–68.
[6] Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45(3):486–552.
[7] Bloos F, Thomas-rüddel D, Rüddel H, et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care 2014;18(2):R42.
[8] Martínez ML, Ferrer R, Torrents E, et al. Impact of source control in patients with severe sepsis and septic shock. Crit Care Med 2017;45(1):11–9.
[9] Perman SM, Goyal M, Gaieski DF. Initial emergency department diagnosis and management of adult patients with severe sepsis and septic shock. Scand J Trauma Resusc Emerg Med 2012;20:41.
[10] Rivers EP, Ahrens T. Improving outcomes for severe sepsis and septic shock: tools for early identification of at-risk patients and treatment protocol implementation. Crit Care Clin 2008;24(3 Suppl:S1–47).
[11] Shin J, Hwang SY, Jo IJ, et al. Prognostic value of the lactate/albumin ratio for predicting 28-day mortality in critically ill sepsis patients. Shock 2018;50(5):1.
[12] Shin TG, Hwang SY, Kang GH, et al. Korean shock society septic shock registry: a preliminary report. Clin Exp Emerg Med 2017;4(3):146–53.
[13] Choi A, Park YS, Shin TG, et al. Prognostic performance of disease severity scores in patients with septic shock presenting to the emergency department. Am J Emerg Med 2019;67(6):1054–9.

[14] Ryoo SM, Kang GH, Shin TG, et al. Clinical outcome comparison of patients with septic shock defined by the new sepsis-3 criteria and by previous criteria. J Thorac Dis 2018;10(2):845–53.
[15] Ko BS, Kim K, Choi SH, 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(1):1–7.
[16] Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015;372(14):1301–11.
[17] Quinlan M. A randomized trial of protocol-based care for early septic shock. J Emerg Med 2014;47(2):256–7.
[18] Bailey M, Bellomo R, Peter A, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371(16):1496–506.
[19] Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign. Crit Care Med 2013;41(2):580–637.
[20] Casserly B, Phillips GS, Schorr C, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the surviving sepsis campaign database. Crit Care Med 2015;43(3):567–73.
[21] Vincent J-L, Moreno R, Takala J, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22(7):707–10.
[22] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Apache II: a severity of disease classification system. Crit Care Med 1985;13(10):818–29.
[23] Levy MM, Evans LE, Rhodes A. The surviving Sepsis Campaign bundle: 2018 update. Crit Care Med 2018;46(6):997–1000.
[24] Sterling SA, Puskarich MA, Glass AF, Guirgis F, Jones AE. The impact of the sepsis-3 septic shock definition on previously defined septic shock patients. Crit Care Med 2017;45(9):1436–42.
[25] Moss RL, Musemeche CA, Kosloske AM, Guzzetta PC, Upp JR. Necrotizing fasciitis in children: prompt recognition and aggressive therapy improve survival. J Pediatr Surg 1996;31(8):1142–6.
[26] Buck DL, Vester-Andersen M, Møller MH. Danish clinical register of emergency surgery. Surgical delay is a critical determinant of survival in perforated peptic ulcer. Br J Surg 2013;100(8):1045–9.
[27] Chao W-N, Tsai C-F, Chang H-R, et al. Impact of timing of surgery on outcome of Vibrio vulnificus-related necrotizing fasciitis. Am J Surg 2013;206(1):32–9.
[28] Wong C-H, Chang H-C, Pasupathy S, Khin L-W, Tan J-L, Low C-O. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am 2003;85–A(8):1454–60.
[29] Karvellas CJ, Abraldes JG, Zepeda-Gomez S, et al. The impact of delayed biliary decompression and anti-microbial therapy in 260 patients with cholangitis-associated septic shock. Aliment Pharmacol Ther 2016;44(7):755–66.
[30] Azuhata T, Kinoshita K, Kawano D, Komatsu T, Sakurai A, Chiba Y. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care 2014;18(3):R87.
[31] Kobayashi L, Konstantinidis A, Shackelford S, et al. Necrotizing soft tissue infections: delayed surgical treatment is associated with increased number of surgical debridements and morbidity. J Trauma Inj Infect Crit Care 2011;71(5):1400–5.
[32] Sartelli M, Catena F, Ansaloni L, et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW study. World J Emerg Surg 2014;9:37.
[33] Tellor B, Skrupky LP, Symons W, High E, Micek ST, Mazuski JE. Inadequate source control and inappropriate antibiotics are key determinants of mortality in patients with intra-abdominal sepsis and associated bacteremia. Surg Infect (Larchmt) 2015;16(6):785–93.
[34] Kumar A. An alternate pathophysiologic paradigm of sepsis and septic shock: implications for optimizing antimicrobial therapy. Virulence 2014;5(1):80–97.
[35] Torgersen C, Moser P, Luckner G, et al. Macroscopic postmortem findings in 235 surgical intensive care patients with sepsis. Anesth Analg 2009;108(6):1841–7.
[36] Lopez N, Kobayashi L, Coimbra R. A comprehensive review of abdominal infections. World J Emerg Surg 2011;6(1):7.
[37] Marshall JC. Intra-abdominal infections. Microbes Infect 2004;6(11):1015–25.
[38] Koperna T, Schulz F. Relaparotomy in peritonitis: prognosis and treatment of patients with persisting intraabdominal infection. World J Surg 2000;24(1):32–7.
[39] Hartwig W, Maksan S-M, Foitzik T, Schmidt J, Herfarth C, Klar E. Reduction in mortality with delayed surgical therapy of severe pancreatitis. J Gastrointest Surg 2002;6(3):481–7.