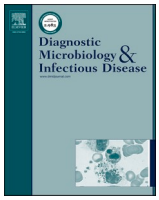
Diagnostic Microbiology & Infectious Disease 108 (2024) 116149

Contents lists available at ScienceDirect

Diagnostic Microbiology & Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio



Original Article

Impact of the empirical therapy timing on the clinical progress of septic shock patients

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ARTICLE INFO

Keywords:
Empirical therapy
One-month mortality
Septic shock
Timing of therapy

ABSTRACT

Aim: To evaluate the effect of timing of antimicrobial therapy on clinical progress of patients with septic shock.
Materials and Method: We included 204 adult patients diagnosed with septic shock according to Sepsis-3 criteria between March 2016 and April 2021. One-month survival was evaluated using univariate and logistic regression analysis.
Results: Antibiotic treatment was initiated within 1 h of the vasopressors in 26.4 % of patients. One-month mortality did not differ significantly between patients with and without empirical therapy coverage on etiological agents. Univariate factors that significantly affected one-month survival were starting antibiotics at the first hour, the unit where the case was diagnosed with septic shock, SOFA scores, qSOFA scores, and lactate level. In multivariate analysis, diagnosis of septic shock in the Emergency Service, SOFA score ≥11, qSOFA score of three and lactate level ≥4 were significantly associated with one-month mortality.
Conclusion: Training programs should be designed to increase the awareness of septic shock diagnosis and treatment in the Emergency Service and other hospital units. Additionally, electronic patient files should have warning systems for earlier diagnosis and consultation.

1. Introduction

Despite advances in sepsis management and targeted early treatment approaches, survival rates remain quite low. Mortality rates can increase from 20 % in sepsis to up to 80 % in septic shock (SS), according to different studies [1–3].

The initiation of broad-spectrum antibiotic treatment is strongly recommended to be performed within the first hour of SS, according to the 2018 update of the Surviving Sepsis Campaign [4]. Although it is a guideline recommendation [4], studies regarding the relationship between the timing of antimicrobial therapy initiation and survival in patients with SS according to the Sepsis-3 criteria are quite limited [5].

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https://doi.org/10.1016/j.diagmicrobio.2023.116149
Received 20 May 2023; Received in revised form 11 November 2023; Accepted 24 November 2023
Available online 29 November 2023

The recommendation for early antibiotics in SS is mainly based on a retrospective cohort study by Kumar et al. [6] conducted between 1989 and 2004 in the United States and Canada, which included 2731 SS patients diagnosed by the Sepsis-1 definitions [3]. They reported that the median time to start antimicrobial therapy after SS diagnosis was 6 h (min = 0.45–max = 13.51 h). Furthermore, mortality increased by 7.6 % for each hour of delay if antimicrobial therapy was started within the first 6 h after diagnosis [6].

The objective of this study was to analyze the impact of timing for empirical antimicrobial therapy on clinical outcomes, and to identify factors associated with one-month mortality (OMM) in a cohort of SS patients.

2. Materials and method

2.1. Selection of the patients

Patients who met the criteria of SS (sepsis with hypotension, use of adrenergic agents, and arterial lactate level of >2 mmol/L) and were consulted by the Department of Infectious Diseases and Clinical Microbiology consultants (DA and/or ORS) in a tertiary-care educational university hospital between March 2016 and April 2021 were prospectively recorded and retrospectively evaluated.

Septic shock (SS) was defined as sepsis with hypotension that required vasopressors to maintain a mean arterial blood pressure above 65 mmHg despite adequate fluid resuscitation. An elevated serum lactate concentration (arterial lactate level of >2 mmol/L) was added as an inclusion criterion for septic shock according to the 3rd International Sepsis and Septic Shock Consensus Statement [5].

In a previous analysis, the one-month survival rate of 263 patients with a preliminary diagnosis of SS, who were consulted by the Department of Infectious Diseases and Clinical Microbiology between December 2013 and March 2016, and whose treatment was started after 1 h (1 h), was 26.2 %. Our hypothesis was that starting treatment within 1 h would increase survival by 10 %. We calculated the required sample size as follows: incidence 1 (patients who started antibiotics after 1 h): 26.2 %, incidence 2 (patients who started antibiotics during the first hour): 36.2 %, type 1 error probability (alpha value): 0.05, type 2 error probability (beta value): 0.2, and we determined that 336 patients were required in both arms (a total of 672 patients).

2.2. Data collection and outcome measures

This study hypothesized that initiating antimicrobial therapy within 1 h of starting the vasopressor agent would increase survival rates by at least 10 %.

The case assessment forms contained data regarding demographical parameters such as age, gender, and underlying diseases, as well as the origin of infection (community-onset/nosocomial-infection related), the diagnosed unit and duration of hospitalization (Emergency Service/hospital wards). Additionally, the forms included scores related to SIRS (systemic inflammatory response syndrome), qSOFA (quick sequential organ failure assessment), and SOFA. Other variables included the infectious source, laboratory values (leukocyte count, C-reactive protein (CRP), procalcitonin, arterial lactate level, and SARS-CoV-2 PCR after March 2020), microbiological culture results within 24 h before and after SS diagnosis, initiation date and timing of vasopressor, coverage and timing of empirical antimicrobial therapy (the cohort was divided into two groups according to the Sepsis-3 criteria, as those that received the first antimicrobial treatment within 1 h (early) and those that received it after 1 h (late)), timing of Infectious Diseases consultation, supportive therapy (vitamin C and corticosteroid), and day 7–30 mortality rates. All data were retrieved from electronic or paper-based patient files.

Empirical antimicrobial therapy was considered "covered" if the antibiotic initiated during the first consultation matched the in vitro susceptibility of the pathogen deemed to be the likely cause of infection, as determined from routine bacterial cultures. The definition of nosocomial infection and infection sites were determined according to CDC criteria [7].

Inclusion criteria were:

- Meeting the Sepsis-3 criteria for septic shock, defined as qSOFA ≥ 2 or an increase of at least two points in the SOFA score plus hypotension, use of adrenergic agents, and arterial lactate level of >2 mmol/L [5]
- Age 18 years or older
- Hospitalization in the Emergency Service or other In-Hospital Units of our hospital between March 2016 and April 2021
- Consultation by the Department of Infectious Diseases and Clinical Microbiology consultants (DA and/or ORS)

Exclusion criteria were:

- Pregnancy
- Transfer from another Intensive Care Unit (ICU) or hospital after septic shock diagnosis (due to inability to analyze timing of antibiotics)
- Intraabdominal infection (due to confounding timing of surgery)
- Neutropenia (<500/mm^3).

2.3. Microbiological evaluation and sensitivity tests

Based on clinical findings of patient, clinical samples were taken for blood culture, urine (mid-stream, catheter, urostomy), respiratory (sputum, deep tracheal aspiration, bronchoscopic aspiration), tissue biopsy, cerebrospinal fluid, and/or drainage.

Peripheral/catheter blood cultures were inoculated into aerobic and anaerobic culture bottles (BacT/ALERT, BioMérieux, Durham, USA), and an automated microbial detection system (BacT/ALERT 3D, BioMérieux, Durham, USA) was used. Signal-positive blood culture samples, together with other samples such as urine and intra-abdominal fluid/pus, were inoculated into 5 % sheep blood agar and Eosin Methylene-blue Lactose Sucrose (EMB) agar (BioMerieux, France). Microbial identification was performed using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (VITEK MS, BioMérieux, France). Antibiotic sensitivity tests were performed using the VITEK2 (BioMérieux, France) system and evaluated according to EUCAST criteria [8]. Carbapenem minimum inhibitory concentration (MIC) levels were determined using gradient tests (E test, BioMérieux, France).

2.4. Ethics

The study was approved by the Local Institutional Review Board (approval no: 21-4.1T/27, 20 April 2021).

2.5. Statistical analysis

Statistical analysis was performed using the SPSS 25.0 program (SPSS Inc, Chicago, IL, USA). Univariate analysis was conducted on the variables for OMM. Chi-square test was used to compare categorical values between the two groups, while Student t-test was used for numerical values of independent groups. Binary logistic regression for OMM was performed using the enter method. OMM was the dependent variable, and variables with a p-value less than 0.05 in the univariate analysis were used as covariates. A p-value less than 0.05 was considered significant.

3. Results

3.1. General characteristics

A total of 204 patients, with a mean age of 64.5 ± 15.7 years (minimum age of 18 and maximum age of 117 and 37.2 % being female), met the study inclusion criteria. Of these patients, 51 % were over the age of 65. SS was diagnosed in 31.3 % (n = 64) of patients in the Emergency Service, and in 68.6 % (n = 140) in other In-Hospital Units. The three In-Hospital Units where our cohort was most commonly diagnosed with SS were the Cardiovascular Surgery Clinic (26.4 %), Neurosurgery Clinic (17.1 %), and Anesthesiology and Reanimation ICU (5.8 %), respectively.

Thirty-three (51.5 %) patients diagnosed with SS in the Emergency Service died without being transferred to any ICU in the hospital. The mean transfer time from the Emergency Service to ICUs was 12.7 ± 15.3 h (min = 1 – max = 59). The mean duration of hospitalization was 12.2 ± 16.1 days (min = 1–max = 113). Patients transferred from the Emergency Service to In-Hospital Units had significantly shorter hospital stays than other patients, except for those who died in the Emergency Service (10.2 ± 12.6 days [min = 1–max = 65]/31.6 ± 65.8 h [min = 5–max = 389], p = 0.0002). Approximately 38.2 % of all patients had community-onset SS, while 61.7 % had nosocomial infection-related SS.

The mean levels for leucocytes, CRP, procalcitonin, and lactate were 18,037 ± 11,187/mm^3, 15.3 ± 11.4 mg/dL, 23.8 ± 32.2 μg/L, and 5.9 ± 4.6 mmol/L, respectively. Among patients diagnosed with SS in the Emergency Service compared to the In-Hospital Units, the lactate level in arterial blood gas was significantly higher (6.9 ± 4.7 vs. 5.4 ± 4.5, p = 0.030).

Of the 204 patients, 170 (83.3 %) had at least one chronic disease. The three most common chronic diseases were diabetes mellitus (35.2 %), hypertension (34.8 %), and coronary artery disease (33.5 %).

All patients included in the study met the SIRS definition with a score of ≥2 at the beginning of the SS attack. Of the included patients, 62 (30.3 %) had a SIRS score of two, 83 (40.6 %) had a score of three, and 59 (28.9 %) had a score of four. The mean SIRS score was 2.98 ± 0.77 (range: 2–4).

The qSOFA score for SS patients diagnosed in the emergency service was 2.6 ± 0.4 (range: 2–3), while it was 2.7 ± 0.4 (range: 2–3) for patients diagnosed in In-Hospital Units (p = 0.084). The mean SOFA score at the beginning of the SS attack for the overall cohort was 11.4 ± 2.8 (range: 4–19). Furthermore, the SOFA score for SS patients diagnosed in In-Hospital Units and emergency services at the time of diagnosis was 11.2 ± 2.7 (range: 5–18) and 11.6 ± 3.1 (range: 4–19), respectively (p = 0.348).

3.2. Infection sites and etiological agents

The infection site was determined in 88.2 % of the patients. The three most common sites of infection were pneumonia (71.5 %), followed by urinary tract infection (UTI) (26.4 %), and bacteremia & fungemia (20.5 %). Patients diagnosed in In Hospital Units had significantly higher rates of pneumonia, catheter-related bloodstream infection (CRBSI), and other sites than those diagnosed in the Emergency Service (Table 1). Furthermore, patients with nosocomial infection-related SS had significantly higher rates of pneumonia, CRBSI, and other sites than those with community-onset SS (Table 1, p = 0.012, p = 0.017, p = 0.019).

In 50 % (n = 102) of the total cohort, bacterial cultures revealed at least one pathogen, with a total of 143 pathogens identified. The most common pathogens were *Staphylococcus* spp. (21.5 %), *Klebsiella* spp. (19.6 %), *Acinetobacter* spp. (17.6 %), and fungi (17.6 %). Multiple pathogens were found in 31.3 % of cases whose microbial cultures were positive. *E. coli* was more prevalent in the community-onset SS subgroup (p = 0.036), while *Acinetobacter* spp. (p = 0.014) and *Pseudomonas* spp. (p = 0.045) were more common in the nosocomial infection-related SS subgroup. There were no significant differences in the frequency of other pathogens between the two groups (Table 2).

Approximately 15.7 % and 42.1 % of the Gram-positive bacteria were identified as *S. aureus* and coagulase-negative staphylococci, while 33.3 % (2/6) and 100 % (16/16) of them were identified as methicillin-resistant (MRSA-MRCNS), respectively. Among Gram-negative bacteria, 44.2 % (31/70) were carbapenem-resistant and 41.4 % (29/70) were extended-spectrum beta-lactamase (ESBL) producer. Carbapenem resistance was found in 88.8 %, 60 %, 53.3 %, 33.3 %, and 7.1 % of *Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas* spp., *Enterobacter cloacae*, and *E. coli* isolates, respectively. Carbapenem-resistant Gram-negative pathogens were significantly more prevalent in nosocomial-infection-related SS than community-onset SS (p = 0.0001) (Table 2).

Table 1
Characteristics of infection sites according to diagnosed unit with septic shock.

	Emergency Service n = 64 (%)	In-Hospital Units n = 140 (%)	Total n = 204 (%)	p value
Pneumonia	38 (59)	108 (77.1)	146 (71.5)	0.009
UTI	19 (29.6)	35 [9]	54 (26.4)	0.481
Bacteremia and fungemia	9 [10]	33 (23.5)	42 (20.5)	0.119
SSTI	5 (7.8)	6 (4.2)	11 (5.3)	0.3
CRBSI	1 (1.5)	20 (14.2)	21 (10.2)	0.005
Other*	0 (0)	13 (9.2)	13 (6.3)	0.011
Not determined	8 (12.5)	16 (11.4)	24 (11.7)	0.825

(*: central nervous system [8], spondylodiscitis [2], mediastinitis [1], pericarditis [1], infective endocarditis [1] (UTI = urinary tract infection, SSTI = skin soft tissue infection, CRBSI = catheter-related bloodstream infection)

Table 2
Distribution of pathogens in terms of type of infection and in terms of type of resistance profile.

Pathogens	Community-acquired septic shock n = 38 (%)	Hospital-acquired septic shock n = 64 (%)	Total n = 102 (%)	p value
Staphylococcus spp.	7 (18.4)	15 (23.4)	22 (21.5)	0.625
Klebsiella spp.	7 (18.4)	13 (20.3)	20 (19.6)	1
Acinetobacter spp.	2 (5.2)	16 [9]	18 (17.6)	0.014
Fungi	5 (13.1)	12 (18.7)	17 (16.6)	0.586
Pseudomonas spp.	2 (5.2)	13 (20.3)	15 (14.7)	0.045
E.coli	9 (23.6)	5 (7.8)	14 (13.7)	0.036
Enterococcus spp.	4 (10.5)	5 (7.8)	9 (8.8)	0.723
Other*	11 (28.9)	17 (26.5)	28 (27.4)	0.821
Methicillin resistant *S. aureus*	2 (5.2)	0 (0)	2 (1.9)	0.136
Methicillin resistant coagulase negative staphylococcus	3 (7.8)	13 (20.3)	16 (15.6)	0.157
Ampicillin resistant *Enterococcus* spp.	1 (2.6)	2 (3.1)	3 (2.9)	1
Vancomycin resistant *Enterococcus* spp.	0 (0)	1 (1.5)	1 (0.9)	1
Carbapenem resistant Gram-negative pathogen	4 (10.5)	27 (42.1)	31 (30.3)	0.0001

(*:*C. striatum* (1/4), *Haemophilus influenzae* nontip b (3/1), *Serratia marcescens* (1/3), *Proteus mirabilis* (2/3), *Enterobacter cloacae* (0/3), Stenotrophomonas maltophilia (1/1), *Salmonella enteritidis* (1/0), *Citrobacter koseri* (1/0), *S. pneumoniae* (1/0), *S. mitis/oralis* (0/1), *M. tuberculosis* (0/1)]

3.3. Antimicrobial treatment

The most commonly used empirical antimicrobial regimens were meropenem+teicoplanin/vancomycin (19.1 %, $n = 39$), meropenem+teicoplanin/vancomycin-antifungal (15.1 %, $n = 31$), and meropenem+tigecycline-antifungal (13.2 %, $n = 28$). Colistin-including regimens were started in 19.1 % of patients, and antifungal-including regimens were started in 50 % of patients. The most commonly initiated empirical antifungal treatment was micafungin (66.6 %).

Among the culture-positive cohort, the coverage of empirical antimicrobial therapy on the etiological agents was 76.4 % (78/102). The etiological agents were sensitive to one empirical antimicrobial in 62.8 % (49/78) of cases, and to two empirical antimicrobials in 35.8 % (28/78) cases. Regarding OMM, no statistically significant difference was found between those infected with bacteria sensitive to one antibiotic vs. those sensitive to two antibiotics ($p = 0.797$).

Early treatment (within 1 h) was initiated in 26.4 % of the patients, while late treatment (after1 h) was present in 73.5 % (Table 3). For patients diagnosed in the Emergency Service and In-Hospital Units, antimicrobial treatment was started within the first hour in 25 % and 27.1 % of cases, respectively ($p > 0.05$).

In only 54.8 % of cases was an Infectious Diseases consultation requested within the first hour. However, of those who requested consultation within the first hour, antimicrobial treatment was started in the same timeframe in 55.3 % of cases. This was significantly higher than the 29.3 % of cases where consultation was requested after the first hour ($p = 0.0018$).

3.4. One-month mortality and associated factors

Overall, all-cause mortality rates at day 7 and day 30 (OMM) were 55.8 % (114/204) and 73 % (149/204), respectively. The OMM rate in the Emergency Service cohort was significantly vs. those transferred to the In-Hospital Units vs. those diagnosed with SS in the In-Hospital Units (Emergency Service: 33/33; transferred to the In-Hospital Units: 23/31; In-Hospital Units: 93/140; $p = 0.0016$).

Chi-square analysis resulted that the diagnosed unit (Emergency Service 8/64 vs. In-Hospital Units 47/140; $p = 0.001$), SOFA score (SOFA < 11 33/70 vs. SOFA ≥ 11 22/134, $p = 0.000002$), qSOFA score (qSOfA:2 27/58 vs. qSOFA: 3 28/146; $p = 0.00007$), lactate level (lactate: 2–4 mmol/l 38/100 vs. lactate > 4 mmol/L 17/104; $p = 0.000049$), and timing of antimicrobial therapy (during the 1st h 21/54 vs. after 1 h 34/150; $p = 0.021$) were significantly associated with OMM. Univariate analysis of all independent variables on OMM are shown in the Table 4.

3.5. Logistic regression analysis

Logistic regression analysis showed that the diagnosis of SS in the Emergency Service ($p = 0.005$, OR = 3.8, 95 % CI 1.4–9.6), a SOFA score of ≥11 ($p = 0.003$, OR = 3.1, 95 % CI 1.4–6.5), a qSOFA score of three ($p = 0.02$, OR = 2.5, 95 % CI 1.1–5.4), and a lactate level of ≥4 ($p = 0.027$, OR = 2.2, 95 % CI 1–4.6) were associated with OMM (Table 5).

Table 3
Starting time of antimicrobial therapy after vasopressor.

Timing of antimicrobial therapy	Number of patients n (%)
<30 min	11 (5.3)
30–60 min	43 [11]
60 min–3 h	23 (11.2)
3–6 h	42 (20.5)
6–12 h	26 (12.7)
12–18 h	11 (5.3)
18–24 h	3 (1.4)
>24 h	45 [12]

4. Discussion

The prevalence of sepsis in hospitalized patients ranges from 4.4 % to 92 %, and the prevalence of septic shock ranges from 0.8 % to 50 % in studies conducted in different countries across the globe [13]. One of the main key factors in sepsis management is initiating appropriate antimicrobial therapy as quickly as possible.

Pneumonia is the most commonly reported site of infection in sepsis patients, with a reported incidence of 13–64 % in the literature [10,14–16]. In our study, the rate of pneumonia was relatively higher at 71.6 %, which may be attributed to pneumonia being the most common infection site in our hospital. Additionally, the distribution of dominant hospital units, such as the Emergency Service, Cardiovascular Surgery Clinic, and Neurosurgery Clinic, within the study cohort [17,18] could have played a role. The incidence of pneumonia and CRBSI was found to be statistically significantly higher in In-Hospital Units than in the Emergency Service, and nosocomial infection-related SS was higher than community-onset SS, further supporting this aspect.

Consistent with the literature, *E. coli* was the most common microbiological pathogen in community-onset SS, while *Acinetobacter* spp. and *Pseudomonas* spp. were significantly more frequent in nosocomial infection-related SS. There was no significant difference in terms of other pathogens [11,12,19–24]. As expected, carbapenem-resistant Gram-negative pathogens were also significantly higher in nosocomial infection-related SS than in community-onset SS.

OMM rates range from 21.5 % to 85.5 % [9,25–34] in various studies around the world in Sepsis-3 criteria studies. In Turkey, Baykara et al. [9], Onal et al. [25] and Gursoy et al. [32] reported the OMM rates as 70.4 %, 75.9 % and 70.7 %, respectively [9,25,32]. Our study found a OMM rate of 73 %, which is within the overall OMM rates reported in the literature from Turkey.

The OMM rate is reported to be higher in patients with SS who have a higher qSOFA score [5,35,36]. In 2019, Nathan et al. [35] conducted a retrospective study of 353 critically ill malignancy patients with sepsis and SS. In patients with a qSOFA score of 2, the in-hospital mortality rate was 36 % (95 % CI: 29–44 %), compared to 67 % (95 % CI: 52–79 %) in patients with a qSOFA score of 3. Another study by Wu et al. found that 53.9 % of 206 SS patients had a qSOFA score of 2 or higher, while 63.8 % of patients who died within 90 days had a qSOFA score of 2 or higher [36]. In our study, multivariate analysis showed that a qSOFA score of 3 was associated with a 2.5-fold increase in OMM (OR = 2.5, 95 % CI = 1.1–5.4, $p = 0.02$). It is possible that the relatively higher OMM rate in our study, compared to the literature, is due to the inclusion of only SS patients diagnosed with Sepsis-3 criteria and the relatively lower proportion of patients with a qSOFA score of 2.

The sepsis guideline, updated in October 2021, recommends using SIRS score instead of qSOFA as a single screening tool for patients with sepsis or septic shock (strong, moderate-quality evidence) [37]. However, in our study sample, there was no statistically significant difference between a SIRS score of 2, 3, or 4, nor between scores of 2 and 3 or 4, and OMM. On the other hand, a qSOFA score of 3 was associated with significantly higher OMM rate than a score of 2.

The SOFA score is another major factor associated with OMM in sepsis and SS. In a study by Wu et al., the average SOFA score at the time of SS diagnosis was found to be 15 (with a range of 13–17) in 206 cases diagnosed using Sepsis-3 criteria. Another study by Chen et al. analyzed critically ill patients with sepsis and SS according to both Sepsis-3 and Sepsis 1 criteria. The mean SOFA score in the overall Sepsis-3 SS subgroup ($n = 483$), in the group with 30-day survival, and in the group with day-30 mortality were 4.7 ± 1.8, 4.0 ± 3.7, and 9.7 ± 4.3, respectively ($p < 0.001$) [38]. In a multicenter sepsis point prevalence study conducted by Baykara et al. in Turkey in 2018, the mean SOFA score was 11 (min = 8–max = 14). This study also found that a SOFA score greater than 11 increased the risk of 30-day mortality (OR = 1.1, 95 % CI, 1.06–1.16, $p < 0.001$). Our study produced similar results, with a mean SOFA score of 11.4 ± 2.8 at the onset of SS attack for the entire

Table 4
Univariate analysis of independent significant variables on one-month survival.

Risk factors			Number of patients	One month mortality n (%)	p value
Diagnosed unit	Emergency Service		64	56 (87.5)	0.001
	Hospital wards		140	93 (66.4)	
SIRS score	SIRS 2		62	44 (70.9)	0.546
	SIRS 3		83	64 (77.1)	
	SIRS 4		59	41 (69.4)	
	SIRS 2		62	44 (70.9)	0.659
	SIRS 3–4		142	105 (73.9)	
SOFA score	SOFA < 11		70	37 (52.8)	0.000002
	SOFA ≥11		134	112 (83.5)	
qSOFA score	qSOFA 2		58	31 (53.4)	0.00007
	qSOFA 3		146	118 (80.8)	
Lactate value in arterial blood gas	Lactate 2–4 mmol/L		100	62 (62)	0.000049
	Lactate > 4 mmol/L		104	87 (83.6)	
Starting antimicrobial therapy after vasopressor	≤1 h		54	33 (61.1)	0.021
	>1 h		150	116 (77.3)	
Underlying disease	Comorbidity	Absent	11	8 (72.7)	0.980
		One	61	44 (72.1)	
		>1	132	97 (73.4)	
	Chronic renal failure	Absent	176	125 (71)	0.103
		Present	78	74 (94.8)	
	Hypertension	Absent	133	94 (70.6)	0.324
		Present	71	55 (77.4)	
	Congestive heart failure	Absent	158	120 (75.9)	0.082
		Present	46	29 (63)	
Type of infection	Community-acquired SS		78	62 (79.4)	0.102
	Nosocomial-acquired SS		126	87 (69)	
Laboratory values	Leukocytosis	Absent	42	28 (66.6)	0.296
		Present	162	121 (74.6)	
	Procalcitonin	<0.5 μg/l	1	1 (100)	0.481
		≥0.5 μg/l	66	44 (66.6)	
Timing of Infectious Diseases consultation	≤30 min		75	51 (68)	0.252
	>30 min		92	61 (66.3)	
Microbiological agent	Etiological agent	Absent	102	74 (72.5)	0.874
		Present	102	75 (73.5)	
	Empirical therapy	Non coverage	24	18 (75)	0.851
		Coverage	78	57 (73)	
	Antifungal therapy	Absent	102	67 (65.6)	0.0607
		Present	102	82 (80.3)	
	Only Gram-positive agent		20	13 (65)	0.558
	Only Gram-negative agent		51	38 (74.5)	
	CS agent		39	32 (82)	0.272
	CR agent		31	22 (70.9)	
	MSS/PSE agent		12	8 (66.6)	0.549
	MRS/PRE agent		25	19 (76)	
	Fungal agent	Absent	187	137 (73.2)	0.811
		Present	17	12 (70.5)	
COVID-19	SARS-CoV-2 PCR	Positive	8	7 (87.5)	0.553
		Negative	89	70 (78.6)	
Supportive therapy	Vitamin C and corticosteroid	Absent	147	104 (70.7)	0.236
		Present	57	45 (78.9)	

(SS=septic shock, SOFA=Sepsis related Organ Failure Assessment, SIRS=systemic inflammatory response syndrome, qSOFA=Sepsis related Organ Failure Assessment, CS=carbapenem sensitive, CR=carbapenem resistant, MSS=methicillin susceptible staphylococci, MRS=methicillin resistant staphylococci, PSE=penicillin susceptible enterococci, PRE=penicillin resistant enterococci, SARS-CoV-2=severe acute respiratory syndrome-Coronavirus 2, COVID-19=Coronavirus Disease 2019)

Table 5
Logistic regression analysis of the independent variables on one-month mortality.

Covariate	Odds ratio	95 % CI	p
Diagnosis of SS in the Emergency Service	3.8	1.4–9.6	0.005
SOFA score ≥11	3.1	1.4–6.5	0.003
qSOFA score of 3	2.5	1.1–5.4	0.02
Arterial lactate level > 4 mmol/L	2.2	1–4.6	0.027
Starting antibiotics after first hour of vasopressor	1.7	0.8–3.7	0.133

(SS=septic shock, SOFA=sepsis related organ failure assessment, qSOFA=quick sepsis related organ failure assessment, CI=confidence interval)

cohort. In the multivariate analysis, we found that a SOFA score greater than 11 increased the risk of OMM with a relatively higher odds ratio than was found in the study by Baykara et al. (OR = 3.1, 95 % CI, 1.4–6.5, $p = 0.003$ vs. OR = 1.1, 95 % CI, 1.06–1.16, $p < 0.001$).

Lactate level is another commonly reported independent prognostic factor in sepsis and SS [5]. In a cohort of 1865 sepsis cases, compared to those with levels <2 mmol/L, OMM was found to be significantly higher in patients with lactate levels >4.9 mmol/L ($p = 0.002$) [39]. In a 2018 study in Lebanon that investigated the relationship between in-hospital mortality and lactate levels in critically ill patients in the Emergency Service, patients with lactate levels between 2 and 4 mmol/L (OR = 7.1, 95 % CI 2.22–22.87, $p = 0.001$) and >4 mmol/L (OR = 29.4, 95 % CI 9.75–89.07, $p < 0.001$) had a significantly higher risk of OMM compared to the group with <2 mmol/L [40]. Similarly, our study found that the OMM rate was higher in the group with lactate levels >4 mmol/L in both univariate and multivariate analyses ($p = 0.027$, OR = 2.2, 95 % CI = 1–4.6).

In our study, we found that the rate of septic shock (SS) diagnosed in the Emergency Service was consistent with the literature. However, the OMM rate was higher than previous reports [27,32]. Furthermore, the OMM rate in the Emergency Service was lower than those who were

transferred to the In-Hospital Units and those diagnosed with SS in In-Hospital Units. This could be due to a few factors. Firstly, patients may have experienced prolonged stays in the Emergency Service caused by a temporary lack of ICU beds in the hospital. Secondly, a smaller proportion of patients received antibiotic therapy within the <1 h period after vasopressors in the Emergency Service. Finally, the mean SOFA ($p = 0.847$) and lactate levels ($p = 0.03$) in the Emergency Service cohort were higher compared to those in the In-Hospital Units cohort, which could have contributed to the relatively high OMM rate.

While numerous studies in the literature concentrate on units where sepsis is diagnosed, there is a necessity for more research on mortality rates in different units, particularly for those diagnosed in the Emergency Service compared to In-Hospital Units. Additionally, it is crucial to develop training programs to enhance awareness of the diagnosis and treatment of sepsis in the Emergency Service and all hospital units. Speedy transfer of sepsis patients from the Emergency Service to ICUs may improve survival rates.

The evidence supporting the claim that delayed antimicrobial therapy increases mortality is limited, with most studies being retrospective analyses. At the same time, the favorable outcomes of early administration of antibiotics in sepsis, especially considering the latest sepsis guidelines, lack strong support from randomized clinical trials. As expected, the number of patients who received antimicrobial therapy within the first hour was relatively low in our study, in line with the existing literature. However, the rate of 26.4 % in the presented study was higher than those reported by Castano et al. (8 %) [41], Hwang et al. (9.9 %) [42], Whiles et al. (11.4 %) [43], Kumar et al. (14.5 %) [6], and Ko et al. (14.8 %) [44], and similar to the rates reported in studies by Li et al. (27.3 %) [26] and De Groot et al. (28.3 %) [45].

There are several factors that may cause delays in the initiation of antimicrobial therapy. These include: i) difficulty and delays in the diagnosis of sepsis/SS ii) mandatory approval processes for expanded spectrum antibiotics due to regulations of reimbursement institutions [46], that requires an Infectious Diseases consultation/approval as was the fact in the presented study iii) mandatory complicated online drug reports for some antimicrobials, such as those required for expanded spectrum antifungals in Turkey (such as needed for echinocandins commonly used in septic shock) iv) problems or obstacles due to temporary problems in the performance of the local and national internet system v) short or long term inadequate doctor, nurse, and healthcare staff as well as inadequate hand hygiene [47–52]. Therefore, to our knowledge, no study has reported a rate of starting antibiotics in the first hour greater than 30 % [6,26,41–45,53]. Despite these challenges, our rate is one of the highest reported in the literature.

Our study has certain limitations that need to be addressed. Firstly, we could not evaluate antimicrobial therapy on a minute-by-minute basis after vasopressor initiation due to the unavailability of electronic records during that period. Instead, we had to rely on 15-min intervals on hardcopy records for antibiotic administration. Secondly, in order to avoid time loss while waiting for treatment from the hospital pharmacy, we administered treatment more quickly by bringing antibiotics to the consultation with the consultant. However, we could not ensure the continuity of this approach. Thirdly, our analysis focused solely on antimicrobial therapy, culture compatibility, and laboratory values at the time of SS diagnosis and did not examine antimicrobial modifications during follow-up. Fourthly, we excluded cases of SS with intra-abdominal infection due to insufficient data on source control, and we excluded neutropenic cases due to their special host considerations. Fifthly, the literature contains studies that demonstrate superior outcomes when a β-lactam agent is administered before vancomycin [54]. It is possible that initiating vancomycin therapy before β-lactam antibiotics may result in delays in β-lactam administration to cover the most common organisms. Nevertheless, in our study, the sequence of drug administration could not be taken into account. Lastly, we did not evaluate other factors that could impact survival, such as vasoactive medications, blood products, immunoglobulins, anticoagulant agents, mechanical ventilation, sedation and analgesics, plasma glucose control, renal replacement therapy, venous thromboembolism/stress ulcer prophylaxis, and nutrition. Additionally, we did not evaluate compliance with the Survival Sepsis Campaign in the first hour of treatment package as it was defined after the start of the study. Although we used Sepsis-3 criteria for sepsis screening, all the cases also fulfilled the Sepsis-1 criteria. Finally, we only included patients who were consulted by the thesis student and supervisor to maintain a more consistent treatment approach.

In conclusion, considering the increasing incidence of sepsis/septic shock and their high mortality rates, more publications are needed on this issue. To our knowledge, this is the first homogeneous study conducted in Turkey and on the SS subgroup defined according to both Sepsis-3 and Sepsis-1 criteria, and also one of the very limited number of studies in the world that investigated the factors affecting OMM and the relationship between the duration of antimicrobial therapy after starting vasopressor and OMM using both Sepsis-1 and Sepsis-3 criteria. Our findings revealed that early antibiotic treatment was associated with increased survival in univariate analysis, but not in multivariate analysis. We also found that the diagnosis of SS in the Emergency Service, SOFA score ≥11, qSOFA score of three (but not SIRS score), and lactate value in arterial blood gas ≥4 mmol/L were independent predictors of OMM in SS. Therefore, it is important to make more efforts to start antibiotics within 1 h of diagnosing SS in order to improve patient outcomes.

CRediT authorship contribution statement

Deniz Akyol: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **İlkin Çankayalı:** Data curation. **Murat Ersel:** Data curation. **Kubilay Demirağ:** Data curation. **Mehmet Uyar:** Data curation. **Özge Can:** Data curation. **Enver Özçete:** Data curation. **Funda Karbek-Akarca:** Data curation. **Tahir Yağdı:** Data curation. **Çağatay Engin:** Data curation. **Erkin Özgiray:** Data curation. **Taşkın Yurtseven:** Data curation. **Burcu Yağmur:** Data curation. **Sanem Nalbantgil:** Data curation. **Pervin Ekren:** Data curation. **Devrim Bozkurt:** Data curation. **Hadiye Şirin:** Data curation. **Feriha Çilli:** Data curation. **Ebru Demirel Sezer:** Data curation. **Meltem Taşbakan:** Methodology, Data curation. **Tansu Yamazhan:** Methodology, Data curation. **Hüsnü Pullukçu:** Methodology, Data curation. **Hilal Sipahi:** Data curation, Formal analysis, Investigation. **Bilgin Arda:** Methodology, Data curation, Writing – review & editing. **Sercan Ulusoy:** Conceptualization, Data curation, Writing – review & editing. **Oğuz Reşat Sipahi:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

A part of this study has been presented as a poster presentation European Conference for Clinical Microbiology and Infectious Diseases, Lisbon, 2022, poster 0240, and Türkiye-Ekmud Annual Congress 2022 as an oral presentation. Authors thank Israa Sinan from King Hamad University Hospital for English proofreading.

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