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Early antibiotics administration reduces mortality in sepsis patients in tertiary care hospital

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Abstract

Introduction Early antibiotic administration is one of the core treatments of sepsis which associated with reduced mortality rate. However, the appropriate timing of antibiotics remains a controversial issue, especially in patients without septic shock. Here, we reported the outcomes of early antibiotic administration within one hour from the time of infection suspicion in a tertiary care hospital.

Methods We reviewed the medical records and sepsis protocols in Chulabhorn Hospital, Bangkok, Thailand, from January 2021 to December 2023 for patients presenting with sepsis. We had our own sepsis protocol which we used for early detection and treatment of sepsis patients. We compared the 28-day mortality, 90-day mortality, and the length of stay between patients with time-to-antibiotics (TTA) within one hour and patients with TTA more than one hour.

Results We recruited 1,506 patients into our study. The mean age is 68 years and 49.40% of patients is female. 90.97% of the patients have comorbidities. The most common comorbidities were cancer (68.66%), and hypertension (33.40%). The 28-day mortality rate and the 90-day mortality rate were significantly lower in the patients with TTA within one hour compared to those with TTA more than one hour ($P=0.009$ and $P=0.042$, respectively). Nonetheless, adjusted mortality rate was significantly lower in only 28-day mortality rate but not 90-day mortality rate. Subgroup analysis showed that the mortality rate was significantly lower in patients with ICD-10 diagnosis of infections (15.35% vs. 21.51%, $P=0.029$), patients with cancer (17.29% vs. 24.11%, $P=0.016$), and patients with solid cancer (20.86% vs. 28.18%, $P=0.036$). However, subgroup analysis for the mortality rate at 90 days were not statistically significant.

Conclusion Antibiotic administration within one hour from the time of infection suspicion is associated with lower mortality rates at 28 days but not at 90 days after adjusted analysis. Cancer patients, especially patients with solid cancer, will benefit more with time-to-antibiotics less than one hour.

Keywords Sepsis, Antibiotics, Infection, Time-to-antibiotics, Mortality rate

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Introduction

Sepsis is one of the many emergencies in medicine. It is a syndrome of physiological and pathological dysfunctions in the host caused by severe infection [1]. Sepsis and septic shock are one of the major health care problems in Thailand and in the world [2, 3]. Even with advanced health care, mortality rate in sepsis patient can be as high as 30%. Septic shock patients have even higher mortality rate, reaching 50% in some studies [4]. Early antibiotic administration is one of the core treatments of sepsis which can reduced many poor outcomes such as mortality and length of stay in the hospital. Data supporting early antibiotic treatment are strong in septic shock. Ideally antibiotics should be given to a septic shock patient within one hour [5]. However, in sepsis patients without shock, the data supporting early antibiotic treatment are still controversial [6]. Nonetheless, delayed antibiotic treatment after interval exceeding 3–6 h may lead to increase mortality in some studies [7, 8]. Both early identification of sepsis patients and good hospital support system will lead to success of early antibiotic administration. Each hospital might need to develop their own protocol which will suit the hospital setting and patient characteristics in that hospital.

In hospitals where the patient population is largely immunocompromised, such as our hospital Chulabhorn Hospital, sepsis remains a critical concern in clinical settings. Recognizing the heightened vulnerability of infection among cancer patients, especially those experiencing chemotherapy-induced neutropenia, we developed and implemented a specialized protocol aimed at the early screening and management of sepsis, particularly the first hour of antibiotics treatment. This protocol specifically addresses the unique needs of this at-risk group. Early identification and timely intervention are crucial for improving outcomes in sepsis cases, which are predominantly seen among cancer patients. In this study, we presented the outcomes observed over the past three years since implementing early antibiotic administration, highlighting its effectiveness and impact on patient care.

Methods

We retrospectively reviewed the medical records and sepsis protocols in Chulabhorn Hospital, Bangkok, Thailand, from January 2021 to December 2023 for patients presenting with sepsis. The inclusion criteria were patients age at least 18 years old who suspected of sepsis at the emergency department or the outpatient clinics. We excluded patients who did not have the record of time of sepsis suspicion or time of antibiotic administration. According to our sepsis protocol, the screening criteria were aimed to be simplified for registered nurse and nurse assistants to easily identified at risk patients and to triage patients for rapid evaluation and treatment at emergency department and outpatient clinics. The main goal of this protocol is to identify patients who are suspected of infection that need prompt evaluation and treatment. In practice, when a patient arrived at the screening point of emergency department and outpatient clinics, the screening staff will immediately implement this protocol to ensure no lag time between hospital arrival to sepsis detection and management. Specific goals are that the eligible patients should be given antibiotics within one hour from the screening point. This protocol is shown in supplementary figure S1 and S2. The study adhered to the principles of the Declaration of Helsinki and followed Good Clinical Practice guidelines. The Ethics Committee of Human Research at the Chulabhorn Royal Academy granted approval for the study (no. EC 064/2567).

Screening protocol

We established specifically targeting both post-chemotherapy cancer patients and general populations who presenting with fever or symptoms suggestive of infection. These criteria are divided into two parts: suspicion of sepsis and suspicion of febrile neutropenia (FN). In our protocol, FN refers to cancer patients who develop fever or suspicion of bacterial infection within two weeks after receiving chemotherapy. For the sepsis part, the patients need to meet at least two of the following criteria: (1) body temperature > 38.0 °C or < 36.0 °C, (2) heart rate more than 90 beats per minute, and (3) respiratory rate more than 20 breaths per minutes. Patients meeting at least two of these sepsis criteria, along with clinical suspicion of bacterial infection, are directed to the sepsis/FN fast track.

Management protocol

All patients who met the sepsis or FN criteria were eligible to proceed to the sepsis/FN fast-track protocol. The investigations included plasma glucose, complete blood count, renal and liver function test, serum lactate, and the other microbiologic tests as the attending staffs considered appropriate for each individual. The two sets of blood cultures were collected before antibiotics were administered. We also listed the important initial management including antibiotics, intravenous fluid resuscitation, volume assessment, infectious specialist consultation, and consideration for intensive care unit (ICU) admission.

Data collection

Basic data were collected from the sepsis/FN protocol including sex, age, time-to-antibiotics (TTA), the reasons if the TTA was not within one hour after screening,

and whether the patients was included via suspicion of sepsis or suspicion of FN. We also collected other data from electronic health records (EHR) and from hospital information systems (HIS), including the final diagnosis and comorbidities of the patient as coded in by using the 10th revision of the International Classification of Diseases (ICD-10), and complete blood count to identify the neutropenia. The ICD-10 codes that we used to identify the diagnosis of infectious diseases that lead to sepsis involved in code A00-B99 and infectious diseases affecting specific organ systems are shown in supplementary table S1. The ICD-10 codes that we used to identify comorbidities of interest are presented in supplementary table S2. Since we did not have enough data and laboratory investigations to calculate the sequential organ failure assessment (SOFA) score that usually be used to classify the severity of sepsis patients, we extracted other data that might be associated with severe infection or need for organ support instead. We looked through the ICD-9 coding for procedures that might associated with severe infection including ICU admission, administration of vasopressor, use of central line or arterial line, use of mechanical ventilation, and use of dialysis.

Outcomes

The primary outcome was mortality rate at 28 days. The secondary outcome was mortality rate at 90 days and length of stay. We compared every outcome between patients with TTA less than one hour and patients with TTA more than one hour. We also did the subgroup analysis for the following groups: (1) patients suspected of sepsis, (2) post-chemotherapy cancer patients suspected of febrile neutropenia, (3) post-chemotherapy cancer patients with fever and laboratory-confirmed diagnosis of neutropenia (absolute neutrophil count of less than 500/mm^3), (4) patients with the diagnosis of infections according to ICD-10 coding in the EHR and HIS, (5) patients with evidence of severe infection or need for organ support, (6) patients without evidence of severe infection or need for organ support, (7) patients with cancer, (8) patients with solid cancer, (9) patients with hematologic malignancy, and (10) patients with age > 60 years. The subgroup analyses were done for both mortality rates at 28 days and 90 days.

Statistical analysis

Statistical analyses were conducted using Stata MP, version 18.0 (StataCorp LP, College Station, TX, USA). The Shapiro–Wilk test was used to assess data normality. Continuous variables were compared using the Mann–Whitney U test, while categorical variables were analyzed using Pearson's Chi-squared test or Fisher's exact test, as appropriate. Survival analysis was performed using the Kaplan–Meier estimator, and comparisons between Kaplan–Meier curves were conducted using the Log-Rank test. Exploratory multivariable Cox regression analysis was conducted to adjust for baseline variables that showed statistically significant differences between the two groups. We used the *P*-value of 0.05 as the cut-point for statistical significance.

Results

We recruited 1,506 patients into our study as shown in Fig. 1. The baseline characteristics were shown in Table 1. The baseline characteristics of patients with TTA within one hour and after one hour including age, sex, and comorbid conditions were not statistically different. The median age is 68 years and 49.40% of patients is female. 1,379 patients (91.57%) have comorbidities. The most common comorbidities of our patients were cancer (68.66%), hypertension (33.40%), dyslipidemia (22.58%), diabetes mellitus (17.26%), chronic kidney disease (10.96%), and chronic lung disease (8.57%). Of those patients with cancer, 781 patients (75.53%) have solid cancers, 253 patients (24.47%) have hematologic malignancies, and 29 patients (2.80%) have both solid cancers and hematologic cancers. 482 patients (32.01%) have some factors that associated with severe infection or need for organ support. The most common factors were ICU admission (20.72%), vasopressor administration (12.55%), use of invasive mechanical ventilation (5.91%), use of non-invasive mechanical ventilation (4.71%), and use of arterial line (4.71%).

Based on ICD-10 diagnostic data, 975 patients (64.74%) were identified as having confirmed infections. The most common ICD-10 category included patients with documented infections and/or infectious agents identified (39.18%). When categorized by organ system, the most common infection sites were pneumonia and/or empyema thoracis (15.47%), urosepsis (14.14%), and hepatobiliary infections (11.42%), as detailed in supplementary table S3.

The median time to antibiotics in our whole study is 50 min (IQR 35–67). 1,085 patients (72.05%) received antibiotics within one hour, and the median TTA was 40 min (IQR 30–50). 421 patients (27.95%) received antibiotics after one hour, and the median TTA in this group is 95 min (IQR 75–136). However, patients with a TTA > 1 h had higher rates of ICU admission (18.80% vs. 25.65%, $P=0.004$), vasopressor administration (11.06% vs. 16.39%, $P=0.07$), use of non-invasive mechanical ventilator (3.87% vs. 6.89%, $P=0.019$), arterial line placement (3.87% vs. 6.89%, $P=0.019$), and central line placement (2.86% vs. 5.23%, $P=0.037$). Patients in the TTA > 1 h group were more likely to have at least one factor associated with severe infection or the need for organ support

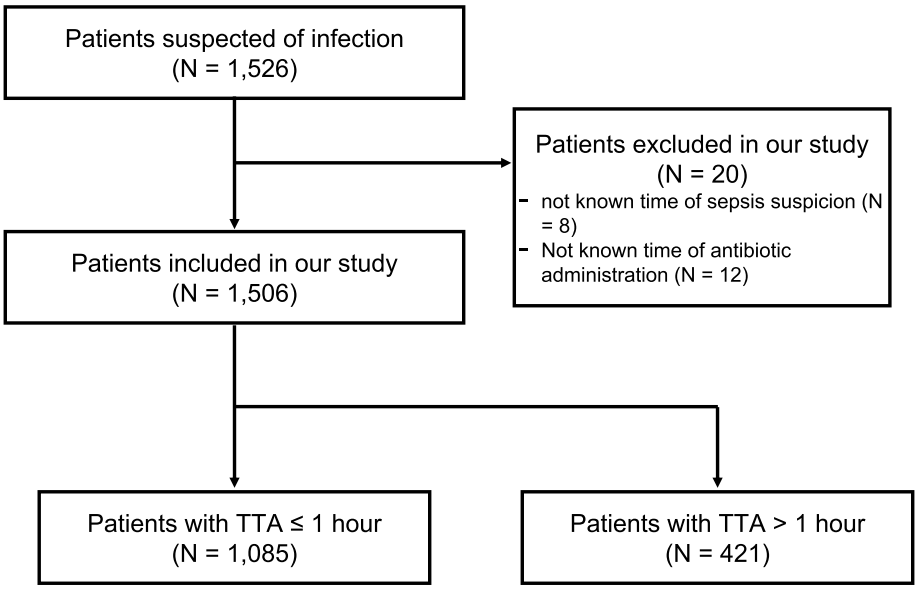

Fig. 1 Study flow. We recruited 1,526 patients who we suspected of infection by our sepsis protocol. We excluded 20 patients (8 patients due to unknown time of sepsis suspicion and 12 patients due to unknown time of antibiotic administration.) We included 1,506 patients into our study. We can further divide these patients into two groups, those who received antibiotics within 1 h (TTA ≤ 1 h, *N* = 1,085 patients) and those who received antibiotics later than one hour (TTA > 1 h, *N* = 421 patients). Abbreviation: TTA = time-to-antibiotics

compared to those in the TTA ≤ 1 h group (29.68% vs. 38.00%, $P=0.002$). In our study, 721 patients (47.88%) received an infectious disease specialist consultation at the time of suspected sepsis or FN.

The outcomes

The 28-day mortality rate was significantly lower in the patients with TTA within one hour compared to those with TTA more than one hour ($P=0.009$), as shown in Fig. 2A. Moreover, the 90-day mortality rate was significantly different in the group with TTA within one hour compared with a group with TTA more than one hour ($P=0.042$), as also shown in Fig. 2B. However, the lengths of stay in both groups were also not significantly different (median length of stay 8 days vs. 7 days, $P=0.116$). After adjusting the survival analysis for factors associated with severe infection or the need for organ support, the 28-day mortality rate remained significantly lower in patients with a TTA ≤ 1 h compared to those with a TTA > 1 h ($P=0.049$). However, the 90-day mortality rate did not differ significantly between the TTA ≤ 1 h group and the TTA > 1 h group ($P=0.151$). The most common reasons for delayed antibiotic administration, as detailed in supplementary table S4, were the doctor's decision to wait for further investigations (43.64%), followed by initial parameters not meeting protocol criteria but worsening over time (16.36%), and delays caused by a crowded emergency department (14.55%).

Subgroup analysis

For the mortality rate at 28 days, we found that the mortality rate was significantly lower in patients with ICD-10 diagnosis of infections (15.35% vs. 21.51%, $P=0.029$), patients with cancer (17.29% vs. 24.11%, $P=0.016$), and patients with solid cancer (20.86% vs. 28.18%, $P=0.036$). The subgroup analysis for the mortality rate at 28 days were shown in Table 2. The other subgroups the mortality rates were lower in every subgroup who received antibiotics within one hour; nonetheless, the lower mortality rates were not statistically significant. For the mortality rate at 90 days, the mortality rate in the subgroup analysis were not statistically significant. All subgroup analysis were shown in supplementary table S5.

Discussion

Early antibiotic administration remains a cornerstone in sepsis management, yet the optimal timing continues to be a subject of critical debate [9–13]. The timing of antibiotic therapy was a bit controversial whether the antibiotic should be given within one hour from the suspicion of infection or not. Our study underscores the significance of initiating antibiotics within one hour in sepsis patients, the majority of whom were cancer patients, demonstrating substantial reductions in both 28-day and 90-day mortality rates. However, only the 28-day mortality rate in the TTA ≤ 1 h group was reduced after adjustment for factors associated with severe infection or

Table 1 Baseline characteristics of the study participants

Characteristics	Overall (*N* = 1,506)	TTA ≤ 1 h (*N* = 1,085)	TTA > 1 h (*N* = 421)	*P*-value
Median age (IQR)	68.00 (57, 78)	68.00 (57, 79)	68.00 (57, 78)	0.950
Female (%)	744 (49.40%)	528 (48.66%)	216 (51.31%)	0.388
Thai nationality (%)	1,439 (95.55%)	1,037 (95.58%)	402 (95.40%)	0.618
Median TTA (minutes) (IQR)	50.00 (35.00, 67.00)	40.00 (30.00, 50.00)	95.00 (75.00, 136.00)	< 0.001
Comorbidities				
- All cancer	1,034 (68.66%)	752 (69.31%)	282 (66.98%)	0.417
- Solid cancer	781 (51.86%)	561 (51.71%)	220 (52.26%)	0.893
- Hematologic malignancy	253 (16.80%)	211 (19.45%)	71 (16.86%)	0.280
- Hypertension	503 (33.40%)	358 (33.00%)	145 (34.44%)	0.636
- Dyslipidemia	340 (22.58%)	239 (22.03%)	101 (23.99%)	0.453
- Cardiovascular disease	260 (17.26%)	171 (15.76%)	89 (21.14%)	0.016
- Diabetes	259 (17.20%)	181 (16.68%)	78 (18.53%)	0.438
- CKD	165 (10.96%)	119 (10.97%)	46 (10.93%)	1.000
- Chronic lung disease	129 (8.57%)	91 (8.39%)	38 (9.03%)	0.768
- Cerebrovascular disease	69 (4.58%)	46 (4.24%)	23 (5.46%)	0.378
- Valvular heart disease	21 (1.39%)	12 (1.11%)	9 (2.14%)	0.197
- Cirrhosis	16 (1.06%)	10 (0.92%)	6 (1.43%)	0.406
- HIV infection	2 (0.13%)	2 (0.18%)	0 (0.00%)	1.000
Factors associated with severe infection or need for organ support				
- ICU admission	312 (20.72%)	204 (18.80%)	108 (25.65%)	0.004
- Vasopressor administration	189 (12.55%)	120 (11.06%)	69 (16.39%)	0.007
- Invasive mechanical ventilation	89 (5.91%)	62 (5.71%)	27 (6.41%)	0.693
- Non-invasive mechanical ventilation	71(4.71%)	42 (3.87%)	29 (6.89%)	0.019
- Use of arterial line	71(4.71%)	42 (3.87%)	29 (6.89%)	0.019
- Use of central line	53 (3.52%)	31 (2.86%)	22 (5.23%)	0.037
- Dialysis	49 (3.25%)	36 (3.32%)	13 (3.09%)	0.948
- At least one of the above factors	482 (32.01%)	322 (29.68%)	160 (38.00%)	0.002

Abbreviations: *CKD* Chronic kidney disease, *ICU* Intensive care unit, *IQR* Interquartile range, *HIV* Human immunodeficiency virus, *TTA* Time-to-antibiotics

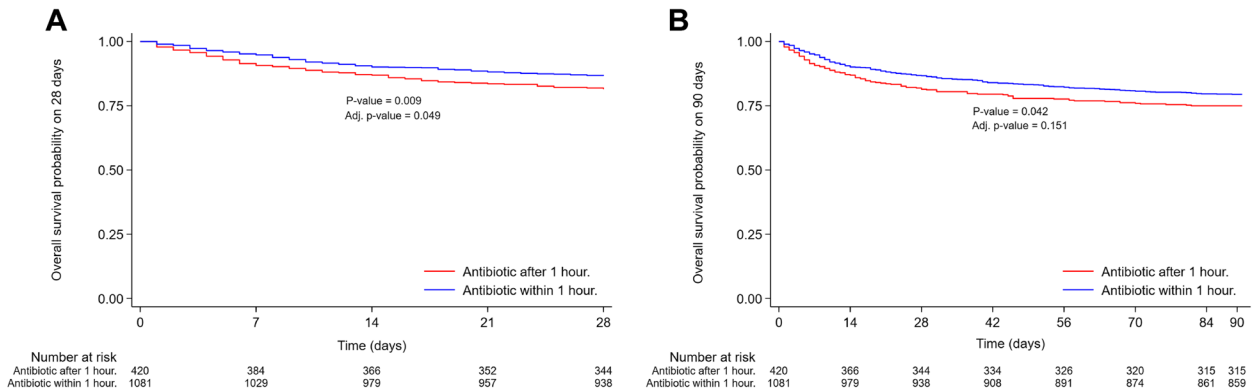

Fig. 2 Kaplan–Meier survival curve of the mortality rate of the patients at 28 days and 90 days. Survival curve of patients compared between patients with TTA ≤ 1 h and patients with TTA > 1 h before and after adjusting the survival analysis for factors associated with severe infection or the need for organ support. **A** Survival curve at 28 days showed statistically significant mortality reduction in group with TTA ≤ 1 h. (*P* = 0.009 before and *P* = 0.049 after adjusted). **B** Survival curve at 90 days also showed statistically significant mortality reduction in group with TTA ≤ 1 h. (*P* = 0.042 before and *P* = 0.151 after adjusted). Abbreviation: TTA = time-to-antibiotics. Abbreviation: TTA = time-to-antibiotics

Table 2 Outcome and subgroup analysis

Characteristics	Overall	TTA ≤ 1 hour	TTA > 1 hour	P-value
Outcome				
Mortality rate at 28 days	230 / 1506 (15.27%)	150 / 1085 (13.82%)	80 / 421 (19.00%)	0.015
Subgroup analysis for mortality rate at 28 days				
1. Patients suspected of sepsis	225 / 1317 (17.08%)	148 / 940 (15.75%)	77 / 377 (20.42%)	0.050
2. Patients suspected of febrile neutropenia	12 / 376 (3.19%)	7 / 291 (2.41%)	5 / 85 (5.88%)	0.152
3. Patients with confirmed diagnosis of febrile neutropenia	4 / 149 (2.68%)	2 / 117 (1.71%)	2 / 32 (6.25%)	0.202
4. Patients with the ICD-10 diagnosis of infections	166 / 975 (17.03%)	109 / 710 (15.35%)	57 / 265 (21.51%)	0.029
5. Patients with evidence of severe infection/need for organ support	123 / 482 (25.52%)	77 / 322 (23.91%)	46 / 160 (28.75%)	0.300
6. Patients without evidence of severe infection/need for organ support	107 / 1024 (10.45%)	73 / 763 (9.57%)	34 / 261 (13.03%)	0.144
7. Patients with cancer	198 / 1034 (19.15%)	130 / 752 (17.29%)	68 / 282 (24.11%)	0.016
8. Patients with solid cancer	179 / 781 (22.92%)	117 / 561 (20.86%)	62 / 220 (28.18%)	0.036
9. Patients with hematologic malignancies	23 / 282 (8.16%)	15 / 211 (7.11%)	8 / 71 (11.27%)	0.315
10. Patients age > 60 years	174 / 1037 (16.78%)	117 / 749 (15.62%)	57 / 288 (19.79%)	0.129

Abbreviations: *ICD-10* the 10th revision of the international classification of diseases, *TTA* Time-to-antibiotics

the need for organ support. Importantly, these benefits were observed across key subgroups, including patients with ICD-10-defined infections, those with cancer, and specifically those with solid malignancy. These findings emphasize the critical role of timely intervention in improving outcomes for high-risk populations in tertiary care settings.

Many of the patients in our study had cancer, some of which also received chemotherapy within two weeks before the episode of infection. This subgroup of cancer patients, particularly those with solid tumors, demonstrated a significantly lower 28-day mortality rate, decreasing from 24.11% to 17.29%. Cancer patients often exhibit a state of immunosuppression due to chemotherapy and radiotherapy, which impair phagocytic activity in addition to causing cytodepletion. The use of cytostatics and corticosteroids further exacerbates immunosuppression. Additionally, many tumor cells evade cytotoxic immune responses and display functional defects that impair antigen presentation and alter the function of dendritic cells, macrophages, natural killer (NK) cells, and CD8 T cells. These combined factors contribute to more severe sepsis, a condition that is often underexplored in recent literature and clinical practice despite septic shock rates in this group ranging from 6 to 57% [14, 15]. Thus, solid cancer patients may be considered at higher risk of severe outcomes compared to general sepsis patients, even in the absence of septic shock or procedures indicative of severe infection.

There are some strengths of this study. First, our study was conducted in a tertiary care hospital with large proportion of cancer patients, specifically solid cancer cases, differentiates this study from other studies that primarily focused on hematologic malignancies which could fill the knowledge gaps [16, 17]. Over 90% of patients in our study had comorbidities, and almost 70% of patients in our study had cancer. Therefore, early antibiotic therapy within 1-h should be considered in these groups of patients. Second, using sepsis protocol is also very important in sepsis treatment. Our study used the protocol that developed for our own hospital, a tertiary care hospital specialized in cancer care, which might contribute to the lower mortality rate. We already knew that good outcomes of sepsis treatment also resulted from other supportive treatment such as adequate fluid resuscitation, fluid assessment, infectious diseases specialist consultation and multidisciplinary care. Using sepsis protocol not only will alert the team in caring of sepsis patients, but also reminds the team to consider every aspect of sepsis treatment, which will result in better outcomes. Thus, we suggested that a tertiary care hospital should develop their own sepsis protocol that suitable for their own circumstances. Third, our study also had comparable mortality rate with the previous study even though we had a lot of cancer and post-chemotherapy patients, which again demonstrated that our sepsis care is comparable with sepsis care in other countries.

There were also a few weaknesses in our study. First, our study is a retrospective observational study. As a result, we lacked sufficient clinical and laboratory

data, as well as biomarkers, to describe disease severity or calculate severity scores, such as the SOFA score or Charlson Comorbidity Index. Furthermore, we did not use the standard criteria for the diagnosis of sepsis based on Sepsis-3. However, we used the ICD-9 for procedure coding that associated with intensive care setting to classify the patients with severe features. Second, the indicators of severe infection are higher in groups with TTA more than one hour. Nonetheless, we adjusted the mortality rate with multivariable cox regression analysis, which shown that the 28-day mortality rate was still significantly lower in patients with TTA within one hour, but the 90-days mortality rate was not statistically different. Third, the type and duration of empirical antibiotics, the bacterial culture results, as well as the antibiotic resistance patterns of each pathogen, were not described. However, 47.88% of patients in our study had an infectious disease specialist consultation since the time of suspicion of sepsis or FN, which can ensure the appropriateness of antibiotic utilization in our study. And lastly, immunosuppression associated with cancer, advanced-stage cancer, or metastatic disease was not evaluated. Since the issued about TTA is still controversy, and our study had limitations as discussed above, we strongly recommend that further prospective study should be done with extensive data collection to clarify the issue of TTA in the management of patients with sepsis.

Conclusion

This study showed that if a patient was suspected of infection, if the antibiotic was given to the patient within one hour from the time of infection suspicion, the patient will have lower mortality rate at both 28 days and 90 days compared with if the was given to the patient later than one hour, especially if the patient had solid cancer or was later confirmed the diagnosis of infection. This lower 28-day mortality rate could still be observed after adjusted with confounding factors, but not in 90-day mortality rate.

Abbreviations

CD	Cluster of differentiation
EHR	Electronic health records
FN	Febrile neutropenia
HIS	Health information systems
ICD-9	The 9th revision of the International Classification of Diseases
ICD-10	The 10th revision of the International Classification of Diseases
ICU	Intensive care unit
IQR	Interquartile range
NK	Natural killer
SOFA	The sequential organ failure assessment
TTA	Time-to-antibiotics
TX	Texas
USA	United States of America

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10532-2.

Supplementary Material 1.

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Clinical trial number

Not applicable.

Consent to Participate declaration

The need for consent to participate was waived by an Institutional Review Board (IRB) named Ethics Committee of Human Research, Chulabhorn Royal Academy.

Authors' contributions

Conceptualization: S.I., and T.S.; methodology and formal analysis: S.I., T.T., and K.T.; investigation: S.I., J.B. and M.H.; data curation: T.T., and K.T.; writing – original draft preparation: S.I.; writing – review and editing: S.I., and T.S.; supervision: T.S.; project administration: S.I., and T.S. All authors have read and agreed to the published version of the manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The study adhered to the principles of the Declaration of Helsinki and followed Good Clinical Practice guidelines. The Ethics Committee of Human Research at the Chulabhorn Royal Academy granted approval for the study (no. EC 064/2567).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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