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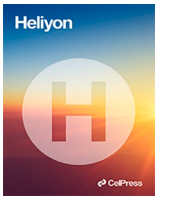

Research article

Association between blood culture turnaround time and clinical prognosis in emergency department patients with community acquired bloodstream infection: A retrospective study based on electronic medical records

Po-Hsiang Hsu [a], Renin Chang [a,*], Chun-Hao Yin [b,c], Yao-Shen Chen [d,e], Jin-Shuen Chen [d,e]

[a] *Department of Emergency, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[b] *Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[c] *Institute of Health Care Management, National Sun Yat-sen University, Taiwan*
[d] *Department of Administration, Kaohsiung Veterans General Hospital, Taiwan*
[e] *Department of Internal Medicine, Kaohsiung Veterans General Hospital, Taiwan*

A B S T R A C T

Importance: Previous investigations have found that time to positive blood culture (TTP) is a prognostic factor for clinical outcomes. In fact, what the emergency physician sees from the medical information system is TAT (turnaround time) defined as time required to post a bacterial culture report. We propose a definition of blood culture TAT that more closely aligns with clinical considerations by measuring the time from starting specimen culture to the release of an official blood culture report.

We were curious to know whether the duration of TAT is as intricately linked to the prognosis of bacteremia as TTP.

Objectives: To examine the association between TAT and outcomes of adult patients who present to the ED with community acquired bacteremia.

Design: Setting, and Participants: This retrospective study utilized electronic medical records from Kaohsiung Veterans General Hospital (KVGH), a 1000-bed tertiary medical center in Taiwan. Patients were adults aged 18 years and older who presented to ED (Emergency department) for initial diagnosis of community acquired bacteremia from January 1, 2016 to March 31, 2021. Data analysis was performed from December 2022 to January 2023.

Main outcomes and measures.

The primary outcomes included mortality in the ED, all-cause in-hospital mortality, length of hospital stay, and all-cause 30-day mortality in relation to the individual first report of positive blood culture TAT.

Results: A total of 4011 eligible patients with bacteremia were evaluated, of which 207 patients had a blood culture TAT of ≤48 h. The overall 30-day all-cause mortality rate was 13%. Contrary to expectation, no statistically significant differences were observed in clinical prognosis between the TAT groups (≤48 versus >48 h). Subgroup analyses indicated that the length of TAT did not have a significant effect on clinical prognosis in patients who underwent lactate level assessment. Furthermore, no difference in clinical outcome was noted between TAT groups (≤48 versus >48 h) in terms of Gram-negative bacilli or Gram-positive cocci bacteremia. However, in patients with delayed antibiotic treatment (>3 h), a shorter TAT was significantly associated with a fatal outcome.

Conclusion: In adults with community-acquired bacteremia, this study did not observe a significant association between blood culture TAT and clinical prognosis, except in cases of delayed antibiotic treatment.

* Corresponding author. Department of Emergency, Kaohsiung Veterans General Hospital, No. 386, Dazhong 1st Road, Zuoying District, Kaohsiung City, 813, Taiwan.

E-mail address: rhapsody1881@gmail.com (R. Chang).

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1. Introduction

Obtaining a blood culture is an important step in examining a patient with an infectious disease [1]. As we know, patients with bacterial infection make up a large proportion of emergency patients in Taiwan, in addition, the number of visits is increasing year by year due to the aging society [2]. For this reason, blood culture has become the most common and important blood test in emergency department. Because quantification of blood cultures is not routinely conducted in clinical; generally, the time between start incubation and growth detected by continuously monitored blood culture system, defined as the time to positivity (TTP), can be used as a marker for measuring the severity of bacteremia [3,4].

Previous studies have shown that a shorter TTP was associated with a poorer clinical prognosis in patients with such as *Streptococcus pneumoniae* bacteremia, *Staphylococcus aureus* bacteremia, *Escherichia coli* bacteremia and *Pseudomonas aeruginosa* bacteremia [5,6]., [7–9] In the most studies, TTP was defined as the time between starting incubation of the blood cultures and the positive signal in the continuous monitoring system. In fact, this definition of TTP is not practical for frontline medical staff because information systems do not tell physicians the exact time of TTP. Instead, what doctors know is the timing when the official report was released. Therefore, we propose a definition of blood culture turnaround time (TAT) that is closer to the clinical perspective, i.e., considers the time from the blood draw is performed to the release of the official blood culture report.

Nowadays, for the treatment of sepsis, it is recommended to start antimicrobial agents as soon as possible after confirmation, because early administration is closely related to the prognosis. The definition of sepsis-3 [10] was published in 2016 and not only recommended "sequential organ failure assessment (SOFA)" or "rapid sequential organ failure assessment (qSOFA)" also brought the concept of antibiotics administered within an hour for patient with septic shock; within 3 h for patient with possible sepsis without shock [11]. Therefore, we considered the timing of antibiotic administration and analyzed the relationship between TAT and clinical prognosis in patients with bacteremia seen after 2016.

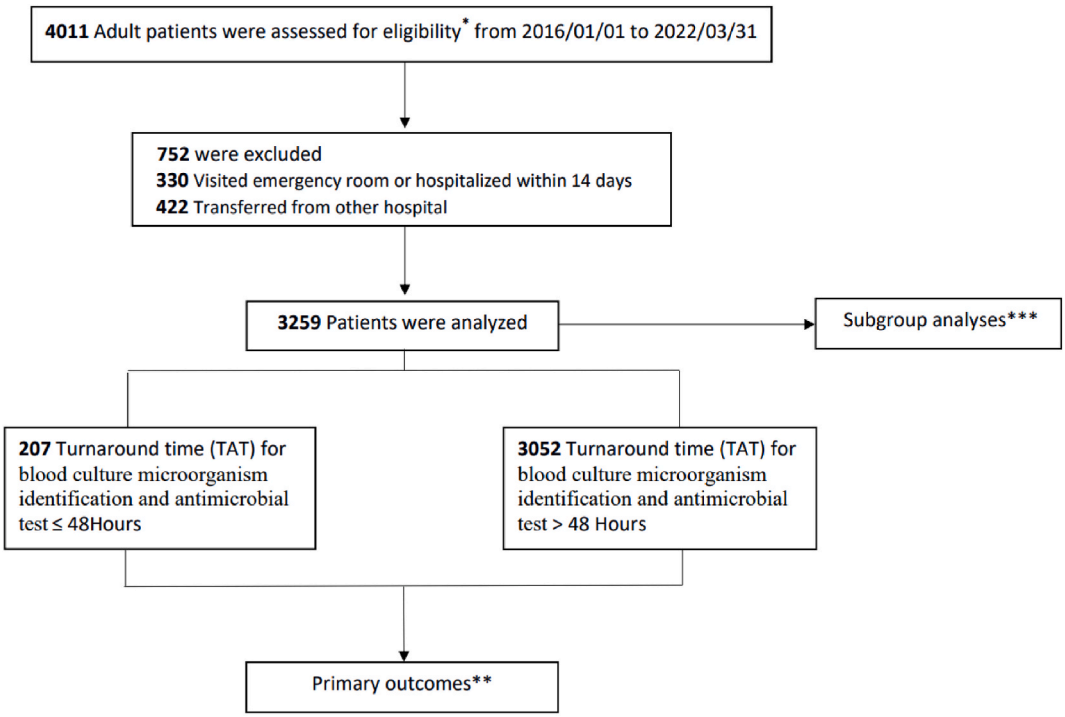

Fig. 1. Flow diagram for selecting bacteremia cases *Participants, aged 18 years and older, admitted via the emergency department (ED) for community acquired infections with positive blood culture results reporting, also met following two criteria:
(1) Blood culture was obtained within 48hrs after entering emergency room;
(2) GPC, GNB or GNC was documented in the blood culture results reporting ** Primary outcomes include: hospital length of stay; mortality in emergency department; 30-day mortality for any cause; in-hospital mortality for any cause *** 4 subgroups include:
(1) Patients of available lactate
(2) Patients with Gram Positive Cocci bacteremia
(3) Patients with Gram Negative Bacillus bacteremia
(4) Antibiotic administered > 3 h at ED.

2. Method

2.1. Setting and study participants

A retrospective cohort study was conducted in a 1000-bed tertiary care hospital in Kaohsiung Veterans General Hospital, Taiwan. Blood culture records from electronic medical records were screened and data were collected from January 2016 to March 2022. All patients aged 18 years or older admitted via the emergency department (ED) with positive result in one or more blood cultures were included. Patients younger than 18 years, with positive blood culture result with no Gram-positive cocci, Gram negative bacilli or Gram-negative cocci revealed in the final report or blood culture not obtained within 48 h after entering emergency room, were excluded. Also, patients transferred from other hospital, or had history of ED visiting or hospitalization within 14 days were excluded, concerning for nosocomial infection (Fig. 1).

2.2. Comorbidities

Comorbidity is defined as the disease or status that may affect the prognosis of septic patient, such as cancer, autoimmune disease, chronic kidney disease, chronic liver disease, coronary artery disease, diabetes mellitus, hypertension, hyperlipidemia and history of organ transplantation [12,13].、 [14–19]. The past medical history is confirmed by corresponding ICD coding ever documented in electronic medical records within the past year before hospital admission.

2.3. Data collection

Demographic data, data on past medical conditions, laboratory data at ER (Emergency room), outcomes data. and microbiological data, including microorganism identification and TAT were accessed from the electronic medical record. Among data of blood sampling, we present white blood cell count (WBC), hemoglobin (Hb), platelet (Plt), glucose (Glc), creatinine (Crea), lactate (Lac), and C-reactive protein (CRP). If multiple lab data were available, we picked highest value of WBC, Crea, Lac, and CRP; lowest value of Hb, Plt and Glc, according to the correlation of sepsis severity [20–25]. Outcome measurements included length of hospitalization, mortality in ER, In-hospital mortality and 30-day mortality for any cause.

2.4. Blood cultures

After being collected at bedside, during day-hours, blood cultures were transported to the in-hospital microbiology department by dedicated hospital transportation employees every 2 h. During evening and night hours, blood cultures were delivered to the laboratory medicine department in ER soon after obtaining (maximum time less than an hour). After overnight incubation, those blood cultures were sent to microbiology department in the coming morning. BIOMERIEUX BACT/ALERT VIRTUO Microbial Detection Systems is available in both microbiology department and laboratory medicine department in ER, providing continuous monitoring positive signal in blood specimens. Once a positive signal is detected in the continuous monitoring system, further exam by Gram staining will be performed. In the meantime, strain identification and antimicrobial were conducted using BIOMERIEUX VITEK® MS MALDI-TOF Microbial Identification System and BIOMERIEUX Vitek 2 system. The official blood culture report will be published after the species identification in the next day morning.

We excluded the cases whose final blood culture report demonstrate polymicrobial or gram-positive bacilli for higher possibility of contamination [26].

2.5. Definitions

Turnaround time (TAT) was defined as the time span between when the specimen is sent to the laboratory to begin culture and when the blood culture report containing microorganism identification was released. Community-acquired bloodstream infections were defined to be those in which the first culture-positive blood specimen was obtained within 48 h of entering the hospital [27].

2.6. Subgroup analyses

The lactate level is not a routine examination for patients in the emergency department. In our hospital, we only check the lactate level in patients who present with respiratory failure or an unstable hemodynamic status. Previous studies have shown a significant correlation between lactate and sepsis, and it has even been used as a therapeutic indicator [28,29]. We selected patients who had their lactate value checked in the emergency room as the subgroup 1 and analyzed the association between their clinical outcomes and blood culture TAT. Also, we enrolled cases with monomicrobial blood culture results, dividing into Gram-positive cocci bacteremia and Gram-negative bacilli bacteremia as subgroup 2 and subgroup 3. Lastly, patients who did not receive antibiotics within 3 h of being admitted to the emergency room were selected for subgroup 4.

2.7. Statistical analysis

Demographic and clinical characteristics were calculated for the entire study population, divided into the TAT$\leq$ 48 h and TAT$>$48

h groups, and expressed as mean ± standard deviation or number (percentage). Differences between the two groups were calculated by using the independent student *t*-test and χ2-test or Fisher's exact test for continuous and categorical variables, respectively, owing to the expected cell counts are less than 5 in a contingency table. All statistical analyses were performed using Statistical Analysis Software (SAS; version 9.4; SAS System for Windows) and SPSS (version 20; SPSS Inc., Chicago, Illinois, USA). A p value of <0.05 was considered statistically significant.

3. Results

3.1. Study population characteristics

After exclusion of polymicrobial, contaminated blood cultures, cases transferred from other hospital and patients who has history of recent admission, total of 3259 individual adult patients were included, representing 3259 episodes of bacteremia. The median (interquartile range) turnaround times for bacterial isolates from blood collection were 67.20 (60.0–76.8), 43.2 (36.0–45.6), and 67.20 (62.40–79.20) hours for overall group, TAT<48hrs group, and TAT>48hrs group, respectively. Among 3259 bacteremia cases, 207 cases had TAT≤ 48 h and 3052 cases had TAT> 48 h. The studies population demographic and clinical characteristics are shown in Table 1.

The mean age was 69.8 years and men accounted for 54%. The comorbidities included cancer (15%), autoimmune disease (1%), coronary artery disease (13%), chronic kidney disease (21%), chronic liver disease (47%), diabetes mellitus (28%), hypertension (53%), hyperlipidemia (17%) and receiver of organ transplant (1%). The mean Charlson Comorbidity Index score is 1.6 (Table 1). Among 3259 patients, about 30% had received inotropic agents and 8% used ventilator during treatment. "There were 1753 (54%) patients who were given antibiotics longer than 3 h after entering the emergency room. No significant difference was found in baseline characteristics or most underlying diseases between patients in the group with TAT≤ 48 h and those in the group with TAT> 48 h. No statistically significant differences were observed in the general laboratory data between the two groups examined in the emergency room, except for the lactate values. Patients with shorter blood culture TAT were more likely to be detected higher lactate value. (The mean lactate value in patients with TAT≤ 48 h was 8.8 mmol/L, whereas 5.5 mmol/L in patients with TAT> 48 h; $P = 0.002$). There were five cases diagnosed with bacteremia, but lacking a complete blood count, which is a basic blood examination. We believe this

Table 1
Basic characteristics among 3259 adult patients presented to the emergency department (ED) and hospitalized for community acquired bacteremia, categorized by turnaround time (TAT) for microorganism identification (≤48 h versus >48 h).

	Total	TAT≤ 48 h	TAT> 48 h	p-value
	n = 3259 (%)	n = 207 (%)	n = 3052 (%)	
Characteristics				
Age, year	69.8 ± 16.1	70.3 ± 17.8	69.8 ± 16.0	0.678
Male	1742 (54)	118 (57)	1624 (53)	0.290
Body mass index, kg/m^2	24.7 ± 4.7	25.0 ± 4.8	24.7 ± 4.6	0.505
qSOFA score	1.2 ± 1.0	1.2 ± 0.9	1.2 ± 1.0	0.956
Antibiotics administrated >3 h	1753 (54)	110 (53)	1643 (54)	0.846
Inotropic agents use	970 (30)	62 (30)	908 (30)	0.951
Ventilator use	250 (8)	23 (11)	227 (7)	0.055
Comorbidities[a]				
Charlson Comorbidity Index score	1.6 ± 2.4	1.5 ± 2.5	1.6 ± 2.4	0.435
Cancer	487 (15)	32 (16)	455 (14)	0.830
Autoimmune diseases	33 (1)	5 (2)	28 (1)	0.037
Hemodialysis or peritoneal dialysis	93 (3)	10 (5)	83 (3)	0.077
Organ transplantation	9 (1)	0 (0)	9 (1)	1.000
Coronary artery disease	428 (13)	30 (15)	398 (13)	0.549
Hypertension	1733 (53)	111 (54)	1622 (53)	0.894
Diabetes mellitus	907 (28)	53 (26)	854 (28)	0.460
Hyperlipidemia	567 (17)	26 (13)	541 (18)	0.058
Chronic kidney disease	677 (21)	44 (21)	633 (21)	0.860
Chronic liver disease	1542 (47)	96 (46)	1446 (47)	0.780
Laboratory data at ER[b]				
White blood cell count (x1000/Cumm), n = 3254	14.1 ± 8.2	13.3 ± 7.1	14.2 ± 8.2	0.137
Hemoglobin (g/dL), n = 3254	11.4 ± 2.4	11.4 ± 2.4	11.4 ± 2.4	0.820
Platelet (x1000/Cumm), n = 3254	198.2 ± 106.6	201.2 ± 111.4	198.0 ± 106.3	0.678
Glucose (mg/dL), n = 3187	158.3 ± 66.2	153.0 ± 66.1	158.7 ± 66.1	0.237
Creatinine (mg/dL), n = 3222	1.9 ± 1.9	1.9 ± 2.0	1.9 ± 1.9	0.812
Lactate(mmol/L), n = 1548	5.8 ± 10.7	8.8 ± 15.1	5.5 ± 10.3	0.002
C-reactive protein (mg/dl), n = 3216	11.8 ± 9.6	11.3 ± 10.4	11.8 ± 9.6	0.493

TAT = turnaround time (TAT) for microorganism identification; qSOFA = quick sequential organ failure assessment.
ER = emergency room.
[a] Specific ICD coding ever documented in electronic medical records within the past year before hospital admission.
[b] We present the highest value of WBC/creatining/lactate/c-reactive protein obtained at ER; present lowest value of glucose, Hemoglobin and platelet.

was related to the shorter waiting time for admission, difficulties in obtaining blood samples, or patients being referred from an outpatient clinic (where the blood examination was done before the ER admission).

4. Clinical outcomes

In Table 2, no significant difference in the length of hospital stay between two groups was observed (15.5 days vs.15.4 days; $P = 0.972$). Furthermore, among the fatal cases, there was also no difference in mortality in ED, 30-day mortality for any cause, or in-hospital mortality for any cause between the 2 groups.

4.1. Subgroup analyses

In Table S2, the length of TAT had no significant effect on the clinical prognosis of patients who checked lactate value. In addition, in the subgroup analysis of Gram Negative Bacillus (GNB) or Gram Positive Cocci (GPC) bacteremia, there were also no difference in clinical outcome between the TAT ≤48 h group and the TAT >48 h group (Tables S4 and S6). Eventually, in the group of patients receiving delay antibiotic treatment (>3 h), shorter TAT was associated with poor prognosis in 30-day mortality for any cause (20% vs.12%; $P = 0.010$) and in-hospital mortality for any cause (19% vs. 12%; $P = 0.036$) (Table S8).

5. Discussion

It is widely accepted that there is a clear association between short TTP and mortality. Previous studies have pointed to the TTP as a prognostic factor that is detrimental to clinical outcomes [5–9]. There were several definitions of TTP, with the most common being defined as the time taken from the start of incubation to a positive signal being alarmed in the continuous monitoring system. However, the relationship between TAT, defined as the time from the start of incubation to official report release, and clinical outcomes was rarely described. Obviously, the TAT is more meaningful for frontline staff in the emergency department. Because the emergency physician don't know when the positive signal being alarmed. Furthermore, the patients enrolled in our study were emphasized in patients admitted to ward via emergency department, meanwhile, patients who were transferred from other hospitals and revisited the hospital were excluded to make the enrolled population more representative of community-acquired bloodstream infections.

Based on previous studies, TTP has been reported to be approximately 12 h, a duration evidently shorter than our findings [9]. However, it is essential to note that, by definition, the TAT should exceed the TTP. Recent studies on TAT have revealed that the period from specimen collection to organism identification typically spans around 48 h, a timeframe that remains shorter than our recorded statistics [30]. We surmise that there are the following reasons: 1. Gram staining is not performed immediately after positive signal being alarmed in the continuous monitoring system. Gram staining is conducted four times during the day shift (at 8:00, 11:00, 14:00, and 16:30). However, it is performed only once during the night shift at 20:30, and not in the graveyard shift. Consequently, there is no assurance that the Gram stain can be completed promptly, particularly during the night. 2. blood culture reports containing microorganism identification are only released before 11 a.m. during the daily day shift. This implies that if the specimen undergoes Gram staining in the morning, the report will not be available until the following morning at the earliest. Unlike TTP, these delays are also likely to contribute to the lack of correlation between TAT and prognosis in patients with bacteremia.

There are some limitations regarding our research. First, the ability to detect clinical variables as significant predictors of mortality would be limited under a single hospital retrospective study design. Second, due to the technical challenges in screening the database of our hospital, coagulase-negative staphylococci (CoNS) was not excluded. It is widely acknowledged that CoNS frequently appear as isolates in blood culture samples, but are primarily considered as contaminants. Additionally, since further antimicrobial testing is not required, the official blood culture report will be released promptly if CoNS is detected, resulting in a shorter TAT. However, subgroup analyses show that there was no correlation between worse clinical outcomes and a shorter TAT in the group with GNB bacteremia, suggesting that the presence or absence of CoNS interference made no difference. Third, the TAT is defined as the time between starting of incubation (T1) and releasing the official blood culture report (T2), however, except bacteria's grow speed, T2 is also associated with specific strains of bacteria, some of which do not require further antimicrobial testing. e.g., CoNS, group B *Streptococcus*.

In the overall subgroups of our study, there was no association found between a shorter turnaround time (TAT) and a poorer clinical prognosis. Only in those patients receiving delayed antibiotic treatment, a shorter TAT of less than 48 h was associated with a higher mortality rate. In conclusion, as frontline staff in the emergency department, when we find an early-released positive blood culture report accompanied by delayed antibiotic administration, we should be cautious with these patients, as they have higher mortality

Table 2
Primary outcomes categorized by TAT for microorganism identification (≤48 h versus >48 h).

Primary outcomes	Total	TAT≤ 48hrs	TAT> 48hrs	p-value
	n = 3259 (%)	n = 207 (%)	n = 3052 (%)	
Hospital length of stay (day)	15.4 ± 15.9	15.5 ± 14.8	15.4 ± 16.0	0.972
Mortality in emergency department	30 (1)	1 (1)	29 (1)	0.496
30-day mortality for any cause	426 (13)	35 (17)	391 (12)	0.091
In-hospital mortality for any cause	437 (13)	31 (15)	406 (13)	0.494

TAT = turnaround time (TAT) for microorganism identification.

rate. Currently, we have not identified a correlation between TAT (Turnaround Time) length and the prognosis of bacteremia. Considering the limitations of our study, further exploration is needed.

Data availability statement

Study data will be made available at the reasonable request and consent of Kaohsiung Veterans General Hospital.

CRediT authorship contribution statement

Po-Hsiang Hsu: Writing – original draft, Conceptualization. **Renin Chang:** Writing – original draft, Validation, Conceptualization. **Chun-Hao Yin:** Software, Methodology, Formal analysis, Data curation. **Yao-Shen Chen:** Writing – review & editing, Supervision, Methodology. **Jin-Shuen Chen:** Writing – review & editing, Supervision.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27957.

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