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ORIGINAL ARTICLE

# Time-to-positivity of blood culture: An independent prognostic factor of monomicrobial *Pseudomonas aeruginosa* bacteremia

**Poh-Chang Tang [a,b], Ching-Chi Lee [a,c], Chia-Wen Li [a,c], Ming-Chi Li [a,c], Wen-Chien Ko [a,c,*], Nan-Yao Lee [a,c,*]**

[a] *Division of Infectious Diseases, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan*
[b] *Division of Infectious Diseases, Department of Internal Medicine, Tainan Municipal Hospital, Tainan, Taiwan*
[c] *Center for Infection Control, National Cheng Kung University Hospital, Tainan, Taiwan*

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**KEYWORDS**
bacteremia;
*Pseudomonas aeruginosa*;
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**Abstract** *Background/Purpose: Pseudomonas aeruginosa* bacteremia is an important cause of nosocomial infections with high morbidity and mortality. Time-to-positivity (TTP) of blood cultures is considered to be a predictor of the clinical outcome for bacteremia. The aim of the study is to investigate the relationship between TTP and clinical outcomes in patients with monomicrobial *P. aeruginosa* bacteremia.
*Methods:* From January 2013 to June 2014, a retrospective cohort study was conducted in a 1200-bed tertiary care hospital. The cases of monomicrobial *P. aeruginosa* bacteremia were studied. TTP and clinical parameters were determined and analyzed.
*Results:* In 139 cases of *P. aeruginosa* bacteremia, TTP $\leq$ 13 hours was associated with higher Pitt bacteremia scores ($5.3 \pm 4.2$ vs. $2.3 \pm 2.8$, $p < 0.001$), severe sepsis (66.1% vs. 35.0%, $p < 0.001$), higher 30-day mortality rate (54.2% vs. 15.0%, $p < 0.001$), longer hospitalization in the survivors ($25.6 \pm 48.5$ days vs. $16.3 \pm 15.3$ days, $p = 0.16$), and more admission to intensive care unit (27.2% vs. 16.3%, $p = 0.14$). Risk factors for 30-day mortality in the univariate analysis included corticosteroid exposure, primary bacteremia, concurrent pneumonia, a high Pitt bacteremia score, severe sepsis, and TTP $\leq$ 13 hours. In the multivariate analysis, primary bacteremia, a pulmonary origin of bacteremia, severe sepsis, and TTP $\leq$ 13 hours were independent risk factors for 30-day mortality.

* Corresponding authors. Department of Internal Medicine, National Cheng Kung University Hospital, Number 138, Sheng Li Road, 704, Tainan, Taiwan.
*E-mail addresses:* winston3415@gmail.com (W.-C. Ko), nanyao@mail.ncku.edu.tw (N.-Y. Lee).

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*Conclusion:* In cases of monomicrobial *P. aeruginosa* bacteremia, a short TTP (≤ 13 hours) provides prognostic information, in addition to clinical parameters.
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## Introduction

Gram-negative bacilli (GNB) bacteremia is a clinical entity commonly complicated by severe systemic inflammatory response syndrome and increased mortality. It is a significant problem in both hospitalized and community-dwelling patients. Patients with GNB sepsis and shock have a mortality rate of 12—38%.[1,2] *Pseudomonas aeruginosa* bacteremia usually occurs in patients with serious underlying diseases, and may be monomicrobial or polymicrobial in nature. The organism is frequently acquired in health care facilities, and can cause urinary tract infection, pneumonia, and intra-abdominal infection.[3] Patients with *P. aeruginosa* have been associated with increased lengths of stay, cost of hospitalization, and mortality. Risk factors for a fatal prognosis in patients with *P. aeruginosa bacteremia* are underlying disease, the severity of systemic inflammatory response syndrome, inadequate antibiotic treatment, nosocomial infections, aged older than 65 years, and multidrug resistant strains.[3—6]

Time-to-positivity (TTP), defined as the length of time from the beginning of culture incubation to the detection of bacterial growth by an automated system, has been proposed as a diagnostic and prognostic tool, and is an independent predictor of fatal outcome. A short TTP reflects greater pathogen burden in blood culture samples. Previous studies have shown that shorter TTP is associated with a significantly higher risk of mortality among patients with bacteremia due to *Staphylococcus aureus*, *Escherichia coli*, or *Streptococcus pneumoniae*.[7—11]

*P. aeruginosa* bacteremia remains one of the most feared infections, but the relationship between TTP and *P. aeruginosa* bacteremia is rarely reported. The aim of this study is to evaluate the relationship between TTP and prognosis, clinical presentations, and risk factors of 30-day mortality in patients with *P. aeruginosa* bacteremia.

## Methods

### Setting

A retrospective cohort study was conducted in a single 1200-bed tertiary care hospital at the National Cheng Kung University Hospital, Tainan, Taiwan. Blood culture records in the Clinical Microbiology Laboratory were screened, and data were collected from January 2013 to June 2014. All patients aged 18 years or older with the growth of *P. aeruginosa* in one or more blood cultures were included. When the bacteria grew in multiple blood cultures, the shortest TTP of blood cultures was recorded. Patients younger than 18 years, with polymicrobial bacteremia or incomplete medical records, and without admission to the hospital, were excluded. Blood cultures were placed in an automated blood culture system (BACTEC FX system; Becton-Dickinson DIS, Sparks, MD, USA). The automated microbiology growth and detection system detected microbial growth from blood specimens. TTP was routinely measured and automatically recorded by the machine.

The following demographic and clinical information, including age, gender, pre-existing comorbidities, site of infections, place of bacteremia acquisition, location of care in the hospital, prior surgery/procedure, length of stay, and severity of bacteremia assessed using Pitt bacteremia score,[12,13] were collected in a predetermined case record form. The primary outcome was the 30-day mortality, and the secondary outcomes were lengths of hospital stay and sepsis-related end-organ damage. Furthermore, we evaluated the risk factors of a fatal outcome for *P. aeruginosa* bacteremia.

### Definitions

Comorbidity is defined as the disease or status that may affect the patient's immune system, such as hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, chronic hepatic or renal impairment, active malignancies, neutropenia, or receipt of corticosteroids or immunosuppressive agents. Community-onset infections were defined as those for which the first positive blood sample for culture was collected within 48 hours after admission, and the others were classified as hospital-onset infections.

Primary sites of infection were judged by primary-care physicians or the clinical information in medical records. The sources of bacteremia were determined clinically based on the presence of an active infection site coincident with bacteremia or the isolation of a microorganism from other clinical specimens prior to or on the same date as the onset of bacteremia. If the source of bacteremia could not be assigned to a specific site, it was classified as primary bacteremia.

Corticosteroid use was defined as the receipt of prednisolone ≥ 10 mg daily or equivalent dose for at least 2 weeks. Neutropenia was defined as an absolute neutrophil count ≤ 500 cells/μL. Prior surgery/procedure referred to the performance of surgical intervention or invasive procedure within 7 days before bacteremia onset. The severity of the bloodstream infection (BSI) at the time of onset was assessed using Pittsburgh bacteremia score, which is a validated scoring system based on vital signs, mental status, mechanical ventilation, and the presence of cardiac arrest. End organ damage was defined as any organ failure

at the onset of bacteremia, such as acute renal failure, respiratory failure, or hepatitis. Severe sepsis was defined as organ dysfunction, hypotension, or systemic manifestations of hypoperfusion. Multidrug-resistant phenotype[14] was defined as an isolate resistant to three or more of the following classes of antimicrobials: aminoglycosides, antipseudomonal carbapenems, antipseudomonal penicillins plus beta-lactamase inhibitors, antipseudomonal fluoroquinolones, extended-spectrum cephalosporins, or polymyxins.

Appropriate antimicrobial therapy was defined as systemic administration of at least one *in vitro* active antimicrobial agent. Empirical antimicrobial therapy was antimicrobial agent administered within 48 hours after blood culture sampling, and definitive antimicrobial therapy was the drug given after the species identification and drug susceptibility result were available.

### Statistical analysis

Data analysis was conducted using SPSS for Windows (version 21.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviations and were compared with the Student *t* test. Categorical variables, expressed as numbers and percentages, were compared by the Chi-square or Fisher's exact test. Odds ratio (OR) and corresponding 95% confidence interval (CI) was calculated in the unadjusted and multivariable-adjusted models. Briefly, the variables with $p < 0.1$ in the univariate analysis were included in the multivariate models. The possible application of TTP as a predictive laboratory marker was assessed by the receiver-operating characteristic (ROC) analysis. The area under the ROC curve (AUC) was computed for the continuous variable of TTP and different TTP cutoffs. Since increasing values indicate higher risks of the fatal outcome in ROC analysis, the inverse function of TTP was applied. A Cox regression survival model was used to compare the mortality rate between those affected by the bacteremic episodes with TTP $\leq$ 13 hours and TTP $>$ 13 hours, adjusted for confounding variables.

## Results

### Study population and patient characteristics

During the study period, *P. aeruginosa* bacteremia was found in 246 patients. Excluded from the study were 104 patients with polymicrobial bloodstream infections and three patients younger than 18 years. A total of 139 patients with *P. aeruginosa* bacteremia were included for the analysis.

The demographical and clinical characteristics of the study population are shown in Table 1. The mean age was 65.7 years with an age range of 23 years to 94 years and 57.6% were older than 65 years. Men accounted for 53.2%. The common comorbidities included solid tumor (49.6%), chronic kidney disease (28.1%), and diabetes mellitus (28.1%). Major infectious foci included lower respiratory tract infection (33.1%), vascular catheter-related infection (20.9%), and urinary tract infection (18.0%). The source of bacteremia was not identified in 32 (23.0%) episodes. Among five patients with soft-tissue infection, all had solid tumor (lower limb cellulitis in 3 patients with cervical cancer and 1 patient with thigh liposarcoma, and neck cellulitis in 1 patient with oral cancer).

Among 139 patients, only one developed metastatic infections with intra-abdominal abscess and osteomyelitis (diagnosed by computed tomography), and was cured by surgical intervention and intra-abdominal abscess drainage in combination with adequate antimicrobial therapy.

### TTP of *P. aeruginosa bacteremia*

The median TTP was 15.0 hours (range, 5.0—120.0 hours; mean ± standard deviation: 20.6 ± 19.7 hours). A ROC analysis was performed to determine the optimal cut-off point of TTP to predict the 30-day mortality (Table 2). TTP $\leq$ 13 hours has the highest AUC and OR, and therefore the cases were categorized into two groups: TTP $\leq$ 13 hours and TTP $>$ 13 hours. Approximately a half (32 cases, 54.2%) of 59 cases died in the TTP $\leq$ 13 hours group. Associated risk factors and clinical outcomes of the cases in two groups are summarized in Table 3. There were no differences between the two groups in terms of age, sex, and underlying disease. A stratified univariate analysis showed that a short TTP ($\leq$ 13 hours) was associated with a critical illness (Pitt bacteremia score $\geq$ 4), severe sepsis, end organ damage, and 14- or 30-day mortality. Among the survivors, those with TTP $\leq$ 13 hours tended to have a longer hospital stay (25.6 days vs. 16.3 days; $p = 0.16$) and more admission to intensive care units (27.2% vs. 16.3%; $p = 0.14$) than those with TTP $>$ 13 hours, though there was no statistical difference. Among the fatal cases, there was no difference in the duration between bacteremia onset and the death among two groups (7.4 days vs. 9.8 days; $p = 0.34$).

Of note, 21 patients developed *P. aeruginosa* bacteremia within 1 week after surgical interventions (7 patients with gastrointestinal surgery, 4 patients with hip/knee replacement, three urological surgery, 2 patients with spine laminectomy, 1 patient with port-A implantation, 1 patient with a ventriculoperitoneal shunt, and 1 patient with pseudoaneurysm excision) or endoscopic procedures (1 endoscopic retrograde cholangiopancreatography and 1 gastroduodenoscopy). All these patients, including eight cases without appropriate antimicrobial therapy during hospitalization, survived and in contrast 37.3% (44) of 118 cases of *P. aeruginosa* bacteremia not related to surgical intervention or procedure, died ($p = 0.001$). There were lower Pitt bacteremia scores (1.3 ± 1.5 vs. 4.0 ± 3.9; $p = 0.02$) and less episodes of severe sepsis (7.5% vs. 22.2%; $p = 0.02$) in the cases of *P. aeruginosa* bacteremia following surgical interventions or invasive procedures. However, TTP was similar in the postsurgery/procedure group and other patients (19.8 ± 15.2 hours vs. 20.7 ± 20.5 hours, $p = 0.8$).

### Clinical outcomes

The crude mortality rate was 31.7%. Patients with a short TTP ($\leq$ 13 hours) had a higher 30-day mortality rate than

**Table 1** Demographical, clinical, and microbiological characteristics of 139 adults with monomicrobial *Pseudomonas aeruginosa* bacteremia.

| Characteristics | All ($n$ = 139) | Fatal ($n$ = 44) | Surviving ($n$ = 95) | $p$ |
|---|---|---|---|---|
| Age (y) | 65.7 ± 15.4 | 64.2 ± 14.5 | 66.4 ± 15.8 | 0.455 |
| Old age (>65 y) | 80 (57.6) | 21 (26.3) | 59 (73.7) | 0.098 |
| Gender, male | 74 (53.2) | 26 (59.1) | 48 (50.5) | 0.367 |
| Underlying disease | | | | |
| Solid tumor | 69 (49.6) | 26 (59.1) | 43 (45.3) | 0.147 |
| Chronic kidney disease | 39 (28.1) | 15 (34.1) | 24 (25.3) | 0.313 |
| Diabetes mellitus | 39 (28.1) | 8 (18.2) | 30 (31.6) | 0.107 |
| Neutropenia | 22 (15.8) | 7 (15.9) | 15 (15.8) | 1.000 |
| Congestive heart failure | 19 (13.7) | 6 (13.6) | 13 (13.7) | 1.000 |
| Hematological cancer | 18 (12.9) | 7 (15.9) | 11 (11.6) | 0.588 |
| Recent steroid therapy | 12 (8.6) | 7 (15.9) | 5 (5.3) | 0.037 |
| Liver cirrhosis | 7 (5.0) | 1 (2.3) | 6 (6.3) | 0.432 |
| Source of infection | | | | |
| Pneumonia | 46 (33.1) | 25 (56.8) | 21 (22.1) | <0.001 |
| Primary bacteremia | 32 (23) | 15 (34.1) | 17 (17.9) | 0.050 |
| Vascular-catheter related infection | 29 (20.9) | 3 (6.8) | 26 (27.4) | 0.006 |
| Urinary tract infection | 25 (18) | 3 (6.8) | 22 (23.2) | 0.019 |
| Intra-abdominal infection | 6 (4.5) | 2 (4.5) | 4 (4.2) | 1.000 |
| Soft tissue infection | 5 (3.6) | 2 (4.5) | 3 (3.2) | 0.652 |
| Others | 2 (1.4) | 0 (0.0) | 2 (2.1) | 1.000 |
| Postsurgery or -procedure bacteremia | 21 (15.1) | 0 (0.0) | 21 (22.1) | <0.001 |
| Hospital-acquired bacteremia | 68 (48.9) | 22 (50.0) | 46 (48.4) | 1.000 |
| Multidrug-resistant phenotype | 22 (15.8) | 11 (25.0) | 11 (11.6) | 0.078 |
| Appropriate empirical antimicrobial therapy | 88 (63.3) | 32 (72.7) | 56 (58.9) | 0.133 |
| Appropriate definitive antimicrobial therapy | 124 (89.2) | 37 (84.1) | 87 (91.6) | 0.240 |
| Pitts bacteremia score | 3.59 ± 3.76 | 7.84 ± 3.25 | 1.55 ± 1.75 | <0.001 |
| Pitts bacteremia score ≥4 | 49 (35.3) | 38 (86.4) | 11 (11.6) | <0.001 |
| Severe sepsis | 67 (48.2) | 40 (90.9) | 27 (28.4) | <0.001 |
| End-organ damage | 52 (37.4) | 39 (88.6) | 13 (13.7) | <0.001 |

Data are presented as $n$ (%) or mean ± standard deviation.

those with TTP > 13 hours (54.2% vs. 15.0%, $p < 0.001$). Univariate analysis revealed that corticosteroid exposure, primary bacteremia, bacteremic pneumonia, severe sepsis, end-organ damage, critical illness with Pitt bacteremia score ≥ 4, and a TTP ≤ 13 hours, were associated with death. By contrast, urosepsis was related to a survival outcome (Table 1). Multivariate regression analysis revealed that primary bacteremia (OR 13.14, 95% CI 2.81—61.47), bacteremic pneumonia (OR 10.63, 95% CI 3.55—56.65), severe sepsis (OR 15.40, 95% CI 4.45—53.31), and TTP ≤ 13 hours (OR 6.1, 95% CI 2.06—18.13), were independent predictors of death (Table 4). In the Cox regression survival analysis with adjustment in confounding variables, including primary bacteremia, pneumonia and severe sepsis, the survival rate of *P. aeruginosa* bacteremia with TTP ≤ 13 hours was higher than that of TTP >13 hours ($p < 0.001$), as shown in Figure 1.

Among different infection sources, TTP of *P. aeruginosa* bacteremia varied significantly. TTP in those with urinary tract infections was longer than that in nonurinary tract infection group (34.0 hours vs. 17.6 hours, $p < 0.001$), but vascular catheter-related infections (14.6 hours in 16 patients vs. 22.1 hours in 123 patients without vascular catheter-related infections, $p = 0.038$) and primary bacteremia (15.7 hours in 32 patients vs. 22.1 hours in 107 patients with secondary bacteremia, $p = 0.008$) were linked to a shorter TTP (Figure 2).

**Table 2** Comparisons of the estimates of area under the receiver operating characteristic curves using different cutoffs of time-to-positivity in the prediction of in-hospital mortality.

| TTP cutoff (h) | Area under ROC curves | 95% CI | OR | 95% CI |
|---|---|---|---|---|
| ≤10 | 0.55 | 0.43—0.64 | 1.45 | 0.82—2.55 |
| ≤11 | 0.60 | 0.50—0.71 | 2.05 | 1.29—3.27 |
| ≤12 | 0.67 | 0.57—0.77 | 2.59 | 1.61—4.16 |
| ≤13 | 0.72 | 0.61—0.81 | 3.62 | 2.04—6.41 |
| ≤14 | 0.69 | 0.59—0.78 | 2.84 | 1.71—4.73 |
| ≤15 | 0.65 | 0.56—0.75 | 2.48 | 1.40—4.41 |
| ≤16 | 0.61 | 0.51—0.71 | 1.97 | 1.11—3.48 |

CI = confidence interval; OR = odds ratio; ROC = receiver operating characteristic; TTP = time-to-positivity.

**Table 3** Demographical and clinical characteristics of adults with monomicrobial *Pseudomonas aeruginosa* bacteremia, categorized by time-to-positivity value.

| Characteristics | TTP $\leq$ 13 h ($n$ = 59) | TTP >13 h ($n$ = 80) | $p$ |
|---|---|---|---|
| Age (y) | 64.8 ± 14.5 | 66.3 ± 16.0 | 0.72 |
| Underlying illness | | | |
| Solid tumor | 34 (57.6) | 35 (43.8) | 0.11 |
| Chronic kidney disease | 20 (33.9) | 19 (23.8) | 0.19 |
| Diabetes mellitus | 17 (28.8) | 22 (27.5) | 0.87 |
| Congestive heart failure | 11 (18.6) | 9 (11.3) | 0.22 |
| Neutropenia | 11 (18.6) | 11 (13.8) | 0.44 |
| Hematological cancer | 9 (15.3) | 9 (11.3) | 0.49 |
| Steroid | 6 (10.2) | 5 (6.3) | 0.39 |
| Lung | 6 (10.2) | 11 (13.8) | 0.52 |
| Liver cirrhosis | 2 (3.4) | 7 (8.8) | 0.20 |
| Sources of bacteremia | | | |
| Pneumonia | 23 (39.0) | 23 (28.8) | 0.21 |
| Vascular-related catheter infection | 16 (27.1) | 13 (16.3) | 0.12 |
| Primary bacteremia | 14 (23.7) | 18 (22.5) | 0.87 |
| Postsurgery or -procedure bacteremia | 12 (20.3) | 9 (11.3) | 0.97 |
| Urinary tract infection | 5 (8.5) | 20 (25.0) | 0.01 |
| Intra-abdominal infection | 4 (6.8) | 2 (2.5) | 0.22 |
| Soft tissue infection | 1 (1.7) | 4 (5.0) | 0.30 |
| Postsurgery or -procedure bacteremia | 12 (15.0) | 9 (15.3) | 1.0 |
| Hospital-acquired bacteremia | 32 (54.2) | 36 (45.0) | 0.28 |
| Appropriate empirical antimicrobial therapy | 40 (67.8) | 49 (61.3) | 0.43 |
| Appropriate definite antimicrobial therapy | 51 (86.4) | 72 (90.0) | 0.52 |
| Disease severity | | | |
| Severe sepsis | 39 (66.1) | 28 (35.0) | <0.001 |
| Pitts bacteremia score $\geq$4 | 33 (55.9) | 16 (20.0) | <0.001 |
| Outcome | | | |
| Admission to intensive care unit | 16 (27.2) | 13 (16.3) | 0.14 |
| Length of hospital stay (d) | | | |
| Fatal cases | 7.4 ± 7.7 | 9.8 ± 7.2 | 0.34 |
| Surviving cases | 25.6 ± 48.5 | 16.3 ± 15.3 | 0.16 |
| 14-d mortality | 27 (45.8) | 11 (13.8) | <0.001 |
| 30-d mortality | 32 (54.2) | 12 (15.0) | <0.001 |

Data are presented as $n$ (%) or mean ± standard deviation.
TTP = time-to-positivity.

**Table 4** Logistic regression analysis of risk factors for 30-day mortality among patients with monomicrobial *Pseudomonas aeruginosa* bacteremia.

| Variables | No. of cases (%) | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | Fatal ($n$ = 44) | Surviving ($n$ = 95) | OR | 95% CI | $P$ | OR | 95% CI | $p$ |
| Age (y) | 64.2 ± 14.5 | 66.4 ± 15.8 | — | — | 0.46 | | | |
| Gender (male) | 26 (59.1) | 48 (50.5) | 1.31 | 0.64–2.69 | 0.47 | | | |
| Prior steroid therapy | 7 (15.9) | 5 (5.3) | 4.30 | 1.1–15.58 | 0.04 | | | |
| Primary bacteremia | 15 (34.1) | 17 (17.9) | 2.37 | 1.05–5.36 | 0.05 | 13.14 | 2.81–61.47 | 0.001 |
| Pneumonia | 25 (56.8) | 21 (22.1) | 4.64 | 2.15–10.00 | <0.001 | 10.63 | 3.55–56.65 | <0.001 |
| Catheter-related infection | 3 (6.8) | 26 (27.4) | 0.19 | 0.06–0.68 | 0.006 | 0.85 | 0.08–8.95 | 0.89 |
| Urinary tract infection | 3 (6.8) | 22 (23.2) | 0.24 | 0.07–0.86 | 0.02 | 0.29 | 0.04–2.39 | 0.25 |
| Post-surgery/procedure bacteremia | 0 (0) | 22 (23.2) | 0.62 | 0.54–0.072 | <0.001 | | | 0.99 |
| Multidrug-resistant phenotype | 11 (25) | 11 (11.6) | 2.54 | 1.01–6.44 | 0.08 | 0.44 | 0.11–1.77 | 0.25 |
| Severe sepsis | 40 (90.9) | 27 (28.4) | 25.19 | 8.22–77.22 | <0.001 | 15.40 | 4.45–53.31 | <0.001 |
| Time-to-positivity $\leq$13 h | 32 (72.7) | 12 (12.6) | 3.62 | 1.59–4.32 | <0.001 | 6.10 | 2.06–18.13 | <0.001 |

Data are presented as $n$ (%) or mean ± standard deviation.
CI = confidence interval; OR = odds ratio.

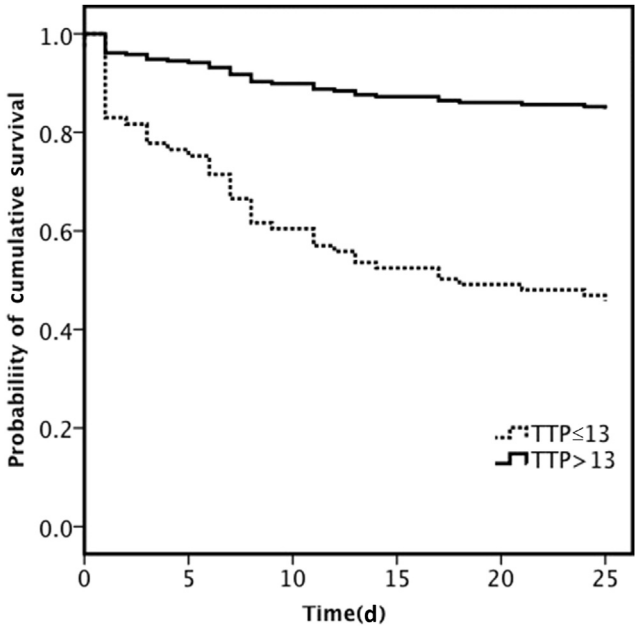


**Figure 1.** Cox regression survival curves of 139 patients with monomicrobial *Pseudomonas aeruginosa* bacteremia, according to a cutoff, 13 hours, of time-to-positivity (TTP) by adjustment of confounding variables, including primary bacteremia, pneumonia, and severe sepsis. Bacteremic episodes with TTP $\leq$ 13 hours fared worse than those with TTP >13 hours ($p < 0.001$). TTP = time-to-positivity.

## Discussion

*P. aeruginosa* BSI is a serious life-threatening condition and can lead to severe morbidity and mortality. Previous studies showed that TTP of blood cultures is a prognostic factor in the cases of bacteremia caused by *S. aureus*,[8,9] *S. pneumoniae*,[11] *E. coli*,[6,15] *Klebsiella pneumoniae*,[5] and *Burkholderia pseudomallaei*.[16] Moreover, the concept of differential TTP had been used for the diagnosis of intravenous catheter-related bloodstream infections.[17,18] The relationship of TTP and clinical outcomes in *P. aeruginosa* bacteremia was rarely described. We identified in medical literature only one study that analyzed the correlation of TTP and clinical outcome in *P. aeruginosa* bacteremia.[7] The present study with a larger sample size further supports the association of TTP of blood cultures and the prognosis in the adults with monomicrobial *P. aeruginosa* bacteremia.

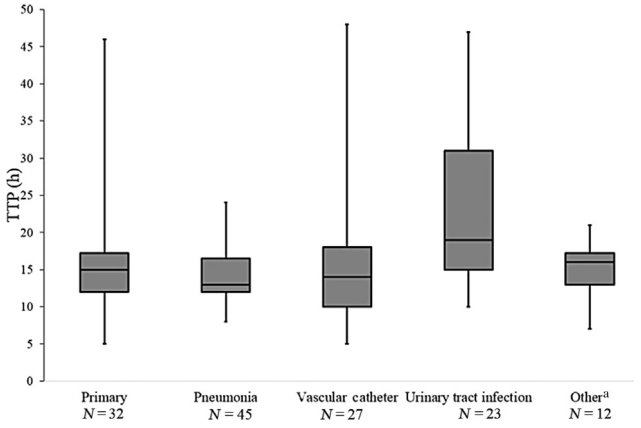


**Figure 2.** Time-to-positivity (TTP) values of different sources of 139 episodes of monomicrobial *Pseudomonas aeruginosa* bacteremia. The central rectangles span the first quartile to the third quartile of TTP, the segments inside the rectangle show the medians, and the "whiskers" above and below the boxes mean the locations of the minimum and maximum TTP values. The mean of TTP values between different sources of bacteremia show significant differences by one-way analysis of variance ($p = 0.009$). [a] Include intra-abdominal infection and soft-tissue infection. TTP = time-to-positivity.

The median TTP of our cohort was 15 hours, which is similar to the median TTP of two published reports, 14.6 hours and 15.3 hours.[7,16] We found that a TTP of $\leq$ 13 hours had a moderate predictive capability when predicting death (AUC 0.722), indicated by a line running in proximity to the 0.5 reference in the ROC analysis. Moreover, TTP was found to be an acceptable prognostic parameter in a multivariate Cox regression model with a four-fold higher risk of death in the group with a TTP of $\leq$ 13 hours. Such a microbiological variable can provide valuable prognostic information, in addition to traditional clinical variables, such as disease severity and underlying illness of affected hosts.

Several previous studies have reported the connection between different cutoffs of TTP and the outcome in GNB BSI, such as 7 hours in *K. pneumoniae* bacteremia[5]; 7 hours, 7 hours, or 10.3 hours in *E. coli* bacteremia.[6,10,15] However, for *P. aeruginosa* bacteremia we found a different cutoff, 13 hours, longer than those for *Enterobacteriaceae* bacteremia. However, the TTP in blood cultures can be influenced by bacterial burden, microorganism species, blood volume poured in the culture bottles, infection source, prior antimicrobial agents, and patient's clinical characteristics.[19] Microorganism species is an important factor in influencing the length of time for bacterial growth. Bacteremia due to lactose-fermenting GNB had a shorter TTP than those due to nonlactose fermenters (11.4 hours vs. 17.9 hours, $p = 0.001$).[4] Martinez et al[20] reported TTP did not differ significantly among *Enterobacteriaceae* (including *E. coli*, *Klebsiella*, *Enterobacter*, and *Citrobacter*) bacteremia, or among *P. aeruginosa* and other nonfermenters. They also found that the *Enterobacteriaceae* group had a shorter TTP than the nonfermenters group (< 10 hours vs. > 15 hours). In a recent article discussing TTP of bacteremia caused by GNB,[21] median TTP was 11 hours (9—16 hours) for *Enterobacteriaceae* isolates, 17 hours (14—20 hours) for *P. aeruginosa*, and 21 hours (15—67 hours) for other GNB in aerobic vials, and it supports the concept that bacterial species is an important factor influencing TTP.

It is commonly accepted that there is a significant association between a short TTP and mortality. One of the hypotheses for this observation has been the correlation between a higher bacterial load and a short TTP,[22,23] and has been extrapolated that a short TTP, reflecting a surrogate marker of bacterial concentration in blood and more severe bacteremia, would translate into adverse clinical outcomes, including high mortality rates, increased length of stays, and hospitalization cost.

TTP has been correlated with infection sources. For *E. coli* bacteremia, urinary tract and vascular catheter-related infections were correlated with a long TTP ($>$ 7 hours), and a short TTP in patients with pneumonia ($\leq$ 7 hours).[10] For *K. pneumoniae* bacteremia, primary bacteremia was more common in the TTP of the $<$ 7 hours group than in the TTP of the $\geq$ 7 hours group (45.7% vs. 22.2%; $p = 0.002$).[5] For *S. aureus* bacteremia, intravascular catheter infections and endocarditis led to a short TTP ($\leq$ 12 hours).[9,24] For pneumococcal infections, meningitis was correlated with a shorter TTP.[11] A previous study evaluating TTP as a mortality predictor in *P. aeruginosa* bacteremia applied 18 hours as the cut-off point and showed that TTP $\leq$ 18 hours was related to a fatal outcome, but there was no correlation between TTP with infection sources.[7] However, due to limited data of bacteremia caused by different species and variable patient population in published reports, the implication of these TTP cut-offs into clinical practice should be prudent.

There are some limitations regarding our study. Firstly, with the retrospective study design and the small sample size, the ability to detect clinical variables as significant predictors of mortality will be limited. Secondly, TTP is influenced by several factors, including incubation condition, blood volume in culture bottles, and initial inoculums. The volume of blood inoculated and the time before loading the vials was not recorded, but substantial variations of blood volume influencing TTP can be expected. Thirdly, some episodes could be misclassified as primary bacteremia, because microbiological or clinical assessment of potential infection sources was incomplete.

In conclusion, in the cases of monomicrobial *P. aeruginosa* bacteremia, a short TTP ($\leq$ 13 hours) can predict the disease severity. In addition to clinical parameters, TTP can provide additional prognostic information.

## Conflicts of interest

The authors have no conflicts of interest.

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