Time to Blood Culture Positivity as a Predictor of Clinical Outcome among Septic Patients

Alrik Earle T. Escudero, MD,[1] Janice C. Caoili MD[1]

Abstract

Introduction: In the setting of Sepsis, Blood Culture is one of the important diagnostic tools in aiding a clinician to determine the offending pathogen. Following the Sepsis Bundle, Blood Culture is obtained at two sites before initiation of antibiotics. However, blood Cultures are one of the expensive tests wherein some clinicians find it unnecessary and costly. This study would provide more information regarding positive blood cultures among septic patients as a prognostic tool regarding the time to positivity. Reporting Time to Positivity would aid clinicians in the severity of the infection and could be used as a clinical predictor of mortality. This study investigated the optimal cutoff point of the time to positivity to predict mortality and the association between time to positivity of blood cultures with mortality among septic patients.

Methods: This was a single-center cross-sectional study with a retrospective chart review of septic patients with positive blood cultures. The optimal cutoff point of time to positivity was determined and associated with mortality.

Results: 405 adult in-patients with sepsis in Makati Medical Center from April 1, 2017, to April 30, 2018, were reviewed. The suggested optimal cutoff TTP is ≤19.1 hours, with sensitivity 79.78%, specificity 28.48%, accuracy 39.75%, Youden's index 8.26%. The overall mortality rate is 21.98%. The mortality rate was higher in the TTP < 19.1 group at 23.91% compared to the>19.1 hours group. Predictors associated with mortality are age, liver comorbidity, genitourinary source of infection, and short TTP.

Conclusion: A short TTP was associated with higher mortality rates. TTP can be clinically used to predict poorer outcomes. Therefore, patients with a short TTP should be monitored more closely, and appropriate antibiotics should have been initiated.

Keywords: Time to Positivity, Blood Culture, Mortality

Introduction

Sepsis is defined as a systemic inflammatory response of the body to an overwhelming microbial infection. If left untreated, it usually results in shock, multi-organ dysfunction, organ failure, and death, contributing to one leading cause of mortality and morbidity.[1] Upon recognition of sepsis as recommended by the Surviving Sepsis Campaign 2016, Two Sets of Blood Cultures are obtained before initiating antimicrobials. Blood Culture is an important diagnostic tool in detecting bacteremia

Time to Positivity (TTP) of blood cultures is defined as the time elapsed between the start of incubation and the automated alert signal indicating growth in the culture bottle. [2] Several studies have shown that shorter TTP is associated with significantly higher mortality risk in patients with bacteremia caused by several bacterial species, like *Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia,* and *Pseudomonas aeruginosa*.[3-6]

Time to positivity has been correlated as an indirect marker of bacterial load and has an inverse relationship with blood bacterial load. It could be used as an early predictor for mortality and a marker for the severity of illness. Previous studies have suggested an association between a short TTP and poor prognosis in patients with bacteremia caused by various bacterial species.[2]

TTP of blood cultures is considered a predictor of the clinical outcome for bacteremia. The rapid detection of bloodstream infections has an impact on the length of hospitalization and the mortality of bacteremic patients.[7]

This study investigated the association between time to positivity of blood cultures with mortality among septic patients. The study determined the optimal cutoff point for time to positivity to predict mortality and compared

[1] Department of Internal Medicine, Makati Medical Center
Corresponding Author: Alrik L. Escudero, MD eMail: alrikescudero@gmail.com

Table I. Baseline characteristics of patients with sepsis (n = 405)

	Frequency (%); Mean ± SD; Median (Range)
Age	63 (19 – 100)
Sex	
Male	169 (41.73)
Female	236 (58.27)
Comorbidities	
Cardiac	233 (57.53)
Endocrine	167 (41.23)
Oncologic	83 (20.49)
Renal	78 (19.26)
Neurologic	46 (11.36)
Lung	34 (8.40)
Liver	18 (4.44)
Source of infection	
Respiratory	154 (38.02)
Genitourinary	129 (31.85)
Gastrointestinal	72 (17.78)
Skin and soft tissues	50 (12.35)
Length of hospital stay	10 (1 – 391)

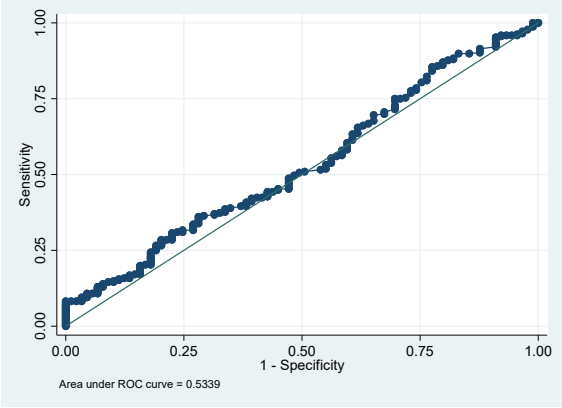

Figure 1. Receiver–operating characteristic (ROC) curve analysis plot determines the cutoff value of time to positivity in mortality prediction. AUC = 0.5339. Suggested optimal cutoff TTP is ≤19.1 hours, with sensitivity 79.78%, specificity 28.48%, accuracy 39.75%, Youden's index 8.26%.

the outcomes between those below and above the cutoff point of time to positivity in terms of mortality rate.

Methods

The study is a cross-sectional chart review of patients aged more than 18 years old with at least one positive blood culture from April 2017- to April 2018. The study was done at Makati Medical Center, a tertiary hospital in Makati, Metro Manila, Philippines, with more than 600 beds.

All patients identified with at least one positive blood culture from April 2017 – to April 2018 were reviewed**.** An automated microbial detection system was used (Biomerieux BacT/ALERT). The time the blood culture bottle was incubated was recorded, and the time the blood culture was flagged to be positive was recorded electronically. Blood culture was flagged negative if no growth was noted after five days of incubation. The Microbiology Section records all identified positive blood cultures; subsequently, the HCLAB/MRN number of the recorded positive blood cultures was retrieved, and charts from the identified patients were reviewed. The time the specimen was flagged positive was subtracted from the time the specimen was incubated, which would be recorded as the time to positivity.

Charts of patients included in the study were reviewed, followed from the time of bacteremia identification through hospital discharge or death. In addition, the following data were collected, including age, gender, site of infection, and duration of hospitalization. Patients excluded from the study include incomplete medical records, polymicrobial infection, or absence of signs or symptoms of bloodstream infection. In addition, adverse outcomes (in-hospital mortality) were recorded during hospitalization. Confounders identified in this study were co-existing comorbidities.

Each patient's clinical condition was classified as systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, or septic shock using criteria previously published by the American College of Chest Physicians/Society of Critical Care Medicine (1). SIRS was defined as two or more of the following: 1) a temperature of greater than 38°C or less than 36°C, 2) a heart rate of more than 90 beats per minute, 3) a respiratory rate of more than 20 breaths per minute or a partial arterial CO_2 pressure < 32 mm Hg, or 4) a white blood cell count > 12 x10^9/liter or < 4 x 10^9/liter or the presence of more than 10% immature neutrophils. Severe sepsis was defined as organ dysfunction, hypotension, or systemic manifestations of hypoperfusion. Septic shock was defined as sepsis associated with hypotension unresponsive to intravenous fluid challenge or the need for treatment with a vasopressor agent.[8]

A total of 232 patients were required for this study based on a level of significance of 5%, an area under the curve of 0.66, and a precision estimate of 0.05. Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median, and range for ordinal variables, and mean and standard deviation for interval/ratio variables.

Mann-Whitney U and Chi-square test were used to determine the difference of median length of hospital stay and mortality rate between those below and above the optimal cutoff point of time to positivity, respectively. Receiver operating characteristic (ROC) curves were constructed to determine the optimal cutoff value for time to positivity in predicting mortality. Since increasing values indicate higher risks of the fatal outcome in ROC

Table II. Clinical outcomes comparing time to positivity groups of blood culture (n=405)

	Total (n = 405)	TTP ≤19.1 hours (n = 297)	TTP >19.1 hours (n = 108)	p-value
	Median (Range); Frequency (%)			
Mortality	89 (21.98)	71 (23.91)	18 (16.67)	0.120*
Length of hospital stay, days	10 (1 – 391)	9 (1 – 117)	10 (2 – 391)	0.130†

Statistical Tests Used: * - Chi-square test; † - Mann Whitney U test

Table III. Factors associated with mortality via Cox's proportional hazards model (n = 405)

	Died (n = 89)	Alive (n = 316)	Crude Hazard Ratio (95% CI)	p-value
	Median (Range); Frequency (%)			
Age	63 (19 – 97)	63 (20 – 100)	**1.018 (1.01 – 1.03)**	**0.002**
Sex				
Male	48 (53.93)	121 (38.29)	1.453 (0.96 – 2.21)	0.080
Female	41 (46.07)	195 (61.71)	Reference	-
Comorbidities				
Cardiac	59 (66.29)	174 (55.05)	1.528 (0.98 – 2.40)	0.064
Endocrine	38 (42.70)	129 (40.82)	1.358 (0.88 – 2.09)	0.163
Oncologic	31 (34.83)	52 (16.46)	**1.563 (1.01 – 2.43)**	**0.047**
Renal	17 (19.10)	61 (19.30)	1.321 (0.77 – 2.62)	0.310
Neurologic	10 (11.24)	36 (11.39)	0.806 (0.42 – 1.56)	0.521
Lung	6 (6.74)	28 (8.86)	0.728 (0.32 – 1.67)	0.453
Liver	9 (10.11)	9 (2.85)	**3.237 (1.62 – 6.48)**	**0.001**
Source of infection				
Skin and soft tissues	9 (10.11)	41 (12.97)	Reference	-
Respiratory	51 (57.30)	103 (32.59)	1.672 (0.82 – 3.40)	0.156
Gastrointestinal	20 (22.47)	52 (16.46)	1.250 (0.57 – 2.75)	0.579
Genitourinary	9 (10.11)	120 (37.97)	0.491 (0.19 – 1.24)	0.132
TTP				
≤19.1 hours	71 (79.78)	226 (71.52)	1.694 (1.01 – 2.85)	**0.046**
>19.1 hours	18 (20.22)	90 (28.48)	Reference	-

analysis, the inverse function of TTP was applied. Youden's J index was defined for all points along the ROC curve, and the maximum value of the index was used as a criterion for selecting the best cut point.

Survival probabilities were estimated using the Kaplan-Meier method. A Cox proportional hazard model calculated crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI). Assumptions of Cox models were met in this analysis. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

Results

We reviewed 405 adult in-patients with sepsis (*Table I*), they had a median age of 63 years old, and 58% were female. The most common comorbidities were cardiac (57%) and endocrine (41%). Infections were primarily respiratory (38%) or genitourinary (32%). They had a median hospital stay of 10 days (*Table I*).

We performed ROC analysis to determine the optimal cutoff value of time to positivity in predicting mortality. The discriminating power of AUC (0.5339) is relatively low. Our data show that a cutoff TTP of ≤19.1 hours yield a sensitivity of 79.78% and low specificity of 28.48%, and accuracy of 39.75% (*Figure 1*).

The overall mortality rate is 21.98% (*Table II*). Using the optimal cutoff value, the mortality rate was higher in the TTP ≤ 19.1 group at 23.91% compared to >19.1 hours group, although the difference was not statistically significant ($p = 0.120$).

Factors associated with mortality included older age (cHR = 1.018, 95% CI 1.01 to 1.03, $p=0.002$), presence of cancer (cHR = 1.563, 95% CI 1.01 to 2.43, $p = 0.047$), presence of liver disease (cHR = 3.237, 95% CI 1.62 to 6.48, $p=0.001$), and a TTP of 19.1 hours or less (cHR = 1.694, 95% CI 1.01 to 2.85, $p=0.046$) (*Table III*)

Performing backward stepwise selection, predictors associated with mortality among culture-positive septic adults are age (aHR = 1.017, 95% CI 1.01 – 1.03, p = 0.003), having a liver comorbidity (aHR = 2.855, 95% CI 1.42 – 5.74, $p = 0.003$), genitourinary source of infection (aHR = 0.336, 95% CI 0.17 – 0.67, $p = 0.002$), and short TTP (aHR = 1.812, 95% CI 1.08 – 3.05, $p=0.025$). This model is significant, explaining 3.82% in the variation of mortality over time ($p < 0.001$).

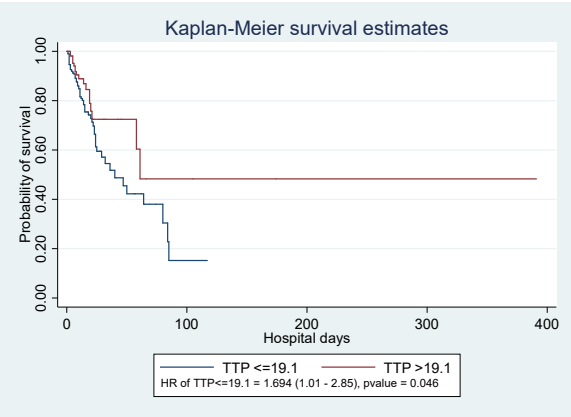

Figure 2. Kaplan-Meier survival curve among septic patients.

Table IV. Predictors associated with mortality among septic patients (n = 405)

	Adjusted Hazard Ratio (95% CI)	p-value
Age	1.017 (1.01 – 1.03)	0.003
Comorbidity, liver	2.855 (1.42 – 5.74)	0.003
Source of infection, genitourinary	0.336 (0.17 – 0.67)	0.002
TTP, ≤19.1 hours	1.812 (1.08 – 3.05)	0.025

R^2 = 3.82%, *p value < 0.001*

Using the TTP cutoff value of 19 hours or less, the probability of survival of 50% is steeper, between 37 to 40 hours. While for a TTP of longer than 19.1, survival drops to 50% between 58 to 61 hours. The hazards ratio is 1.694 (95% CI 1.01 to 2.85, p = 0.046), and the probability of survival between the two curves is statistically different (*Figure 2*).

Discussion

This study showed that the overall mortality rate of patients with positive blood cultures is at 21.98%. The optimal cutoff value associated with increased mortality is a TTP of ≤19.1 hours at 23.91% compared to >19.1 hours group at 16.6%. However, to our knowledge, there are no local studies to date investigated the value of TTP, and there is no standard value for TTP in relation to the mortality rate of patients.

Several studies have shown different cutoff points. In a study done by Maillart et al. (2012), the median TTP was 13.6 hours with a mortality rate (27.5%), while a study done by Marra et al. (2006) TTP of less than 12 hours has been associated with increased mortality. Cilloniz et al. (2017), a TTP of less than 9.2 hours was associated with a higher mortality rate. In this study, the difference between the mortality rate of patients with a TTP of less than 19.1 hours compared to TTP of more than 19.1 hours was not statistically significant. Though clinically comparing both groups, a shorter TTP was associated with a higher mortality rate. Therefore, TTP can be used as a marker of the severity of infection. Several studies have correlated it with a higher bacterial load in the blood; with this in mind, patients with shorter TTP should be monitored more closely.

Other factors associated with increased mortality in this study included older age, the presence of cancer, and liver disease. Age and the presence of cancer were attributable to increased risk of mortality in septic patients, which could be due to an immunocompromised state wherein these patients would mount a weaker immune response against bloodstream infections. The presence of liver disease among septic patients was also associated with a higher mortality rate. According to Gustot et al. (2009), bacterial infections were more common among patients with decompensated liver cirrhosis than those with compensated liver cirrhosis. However, the exact mechanism has still to be elucidated. A study by Wasmuth et al. (2006) attributed that the increased severity of infection among patients with liver disease could be linked to the downregulation of monocyte human antigen-DR expression, deficiencies in C3 and C4, and impairment of macrophage receptor-mediated clearance of antibody-coated bacteria. In addition, sepsis-induced acute liver decompensation on chronic liver disease has been associated with a poor short-term prognosis, contributing to increased mortality rates observed among patients.

The study also showed that a short TTP was associated with a decreased overall survival rate. In line with this, reporting of TTP would also aid clinicians in escalating or de-escalating antibiotics. In our institution, the attending physician is alerted by the microbiology laboratory when a blood culture is flagged positive, reporting the bacteria's initial Gram Stain and morphology. The attending physician is guided by this and can streamline from the initial antibiotic choice. The TTP is a parameter that can be easily obtained using an automated microbial system. Reporting TTP would provide clinicians with useful prognostic information to identify patients who could benefit from more aggressive management and prevent the worst outcomes.

Limitations of the present study were that it was done retrospectively and in a single-center, limiting generalization. In addition, the data gathered were limited to the information indicated in the charts. Variables not considered in this study were the time of blood sample collection, antibiotic administration before blood collection, the specific type of bacteria isolated, which may act as confounding variables regarding overall survival. For further studies, we recommend correlating TTP prospectively with outcomes of patients with respiratory and urinary infections identified as the more common sources of infection and correlate with the specific pathogen in relation to the type of bacteria.

Conclusion

In conclusion, the study determined that a short TTP < 19.1 hours is associated with an increased mortality rate; though not statistically significant, it has clinical

significance. Furthermore, a short TTP can be correlated clinically to predict and anticipate poorer outcomes. Therefore, patients with a short TTP should be monitored more closely, and appropriate antibiotics should have been initiated.

References

1. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA 2014; 311:1308.
2. G. Martín-Gutiérrez et al. / Enferm Infecc Microbiol Clin. Time to positivity of blood cultures in patients with bloodstream infections: A useful prognostic tool 2017;35(10):638–644
3. Martínez JA, Soto S, Fabrega A, Almela M, Mensa J, Soriano A, et al. Relationship of phylogenetic background, biofilm production, and time to detection of growth in blood culture vials with clinical variables and prognosis associated with Escherichia coli bacteremia. J Clin Microbiol. 2006; 44:1468–74.
4. Willmann M, Kuebart I, Vogel W, Flesch I, Markert U, Marschal M, et al. Time to positivity as prognostic tool in patients with Pseudomonas aeruginosa bloodstream infection. J Infect. 2013; 67:416–23.
5. Kim J, Gregson DB, Ross T, Laupland KB. Time to blood culture positivity in Staphylococcus aureus bacteremia: association with 30-day mortality. J Infect. 2010; 61:197–204.
6. Liao CH, Lai CC, Hsu MS, Huang YT, Chu FY, Hsu HS, et al. Correlation between time to positivity of blood cultures with clinical presentation and outcomes in patients with Klebsiella pneumoniae bacteraemia: prospective cohort study. Clin Microbiol Infect. 2009; 15:1119–25
7. Kim SH, Yoon YK, Kim MJ Et al. Clinical impact of time to positivity for Candida species on mortality in patients with candidaemia J Antimicrob Chemother 2013; 68: 2890–2897
8. Marra A., Edmond M., Forbes B. Et. Al. Time to Blood Culture Positivity as a Predictor of Clinical Outcome of *Staphylococcus aureus* Bloodstream Infection JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 2006, p. 1342–1346
9. Maillart E., Karmali R., Miendje Dey VY, Et. Al The Association between Time to Positivity and Staphylococcus Aureus Bacteremia in a Geriatric Population J Med Microb Diagn 2012, 1:4
10. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform* 2014; 48:193 – 204. Accessed from https://www.ncbi.nlm.nih.gov/pubmed/24582925.
11. [2] Cilloniz C, Ceccato A, de la Calle C, Gabarrus A, Garcia-Vidal C, Almela M, et al. (2017) Time to blood culture positivity as a predictor of clinical outcomes and severity in adults with bacteremic pneumococcal pneumonia. PLoS ONE 12(8): e0182436. https://doi.org/10.1371/journal. pone.0182436
12. Tang PC, Lee CC, Li CW, Li MC, Ko WC, Lee NY. Time-to-positivity of blood culture: An independent prognostic factor of monomicrobial Pseudomonas aeruginosa bacteremia. *J Microbiol Immunol Infect* 2017; 50(4):486-493. https://www.ncbi.nlm.nih.gov/pubmed/26455486 (accessed January 28, 2019).
13. Gustot T, Durand F, Lebrec D Et. Al (2009) Severe Sepsis in Cirrhosis, American Association for the Study of Liver Diseases.
14. Wasmuth HE, Kunz D, Yagmur E et al. (2005) Patients with acute on chronic liver failure display 'sepsis-like' immune paralysis, Journal of Hepatology Volume 42, Issue 2, February 2005, Pages 195-201