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Original Article

Time-to-Positivity of Blood Cultures as a Predictor of Clinical Outcome: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Time-to-positivity (TTP) of blood cultures reflects pathogen burden and growth kinetics and has been proposed as a prognostic indicator in bloodstream infections (BSIs). However, the extent to which TTP predicts clinical outcomes remains uncertain.
Objectives: To systematically evaluate the association between TTP and adverse clinical outcomes, including mortality, illness severity, ICU admission, and persistent bacteremia.
Methods: A systematic review and meta-analysis was conducted in accordance with PRISMA 2020 guidelines. PubMed, Embase, Scopus, Web of Science, and Cochrane Library were searched from inception to June 2025. Observational and interventional studies reporting outcomes stratified by TTP were included. Risk of bias was assessed using the Newcastle–Ottawa Scale, and random-effects models were applied for pooled analyses.
Results: Twenty-three studies comprising diverse adult and pediatric cohorts were included. Shorter TTP (commonly <12–24 h) was consistently associated with higher in-hospital mortality, greater illness severity, ICU admission, and persistent bacteremia, with the strongest associations observed in Staphylococcus aureus bacteremia and candidemia. Findings in Gram-negative bacteremia were more heterogeneous, reflecting variation in host and pathogen characteristics. Heterogeneity across studies was moderate and largely attributable to differences in TTP thresholds and clinical adjustment methods.
Conclusion: Shorter TTP is a clinically meaningful prognostic marker in BSIs and may support early risk stratification when interpreted alongside clinical context. Standardized TTP thresholds and prospective multicentre validation are required before routine integration into prognostic pathways.

Keywords: *bloodstream infection; time-to-positivity; bacteremia; prognostic biomarker; mortality; meta-analysis.*

INTRODUCTION

Bloodstream infections (BSIs) remain a major cause of global morbidity and mortality, accounting for more than 30–40% of sepsis-related deaths worldwide and imposing a substantial clinical and economic burden on healthcare systems [1,2]. Early identification of high-risk patients is essential for optimizing antimicrobial therapy, initiating timely source-control interventions, and guiding decisions regarding critical care admission [3]. Traditional prognostic indicators such as severity-of-illness scores, inflammatory biomarkers, and microbiological profiles provide useful information but may not fully capture the dynamic relationship between pathogen burden and clinical outcomes [4].

Time-to-positivity (TTP) of blood cultures—defined as the interval between incubation of a blood culture bottle and automated detection of microbial growth—has emerged as a potential surrogate marker of microbial load and pathogen growth kinetics [5]. TTP is influenced by several factors, including inoculum concentration, organism virulence, blood volume collected, host immune status, and prior antimicrobial exposure [6,7]. Shorter TTP values are generally believed

to reflect higher circulating pathogen burden and more aggressive infection biology, whereas longer TTP may be associated with lower inoculum infections, contaminants, or partially treated bacteremia [8].

Over the past decade, multiple studies have examined the prognostic relevance of TTP in different infectious syndromes and pathogen groups. In Staphylococcus aureus bacteremia, shorter TTP has been linked to persistent bacteremia, metastatic complications, endocarditis, and increased mortality [9–11]. Similarly, in Gram-negative bacteremia, rapid culture positivity has been associated with septic shock, multi-organ dysfunction, and higher risk of adverse outcomes [12,13]. In candidemia, early positivity has been correlated with high fungal burden and poorer survival outcomes [14]. Despite these observations, the strength and consistency of associations across studies remain uncertain due to variability in TTP thresholds, laboratory systems, patient populations, and outcome definitions [15].

Given the increasing interest in TTP as a real-time prognostic biomarker, a comprehensive synthesis of available evidence is warranted. Understanding whether TTP meaningfully predicts mortality, severity of illness, or treatment failure could support its integration into early risk-stratification algorithms, antimicrobial stewardship strategies, and clinical decision-support tools [16,17].

Therefore, the objective of this systematic review and meta-analysis is to evaluate the association between time-to-positivity of blood cultures and clinical outcomes in patients with bloodstream infections, with a particular focus on mortality, septic shock, intensive care requirement, and persistent bacteremia. By consolidating existing data across diverse settings and pathogen groups, this review aims to clarify the prognostic value of TTP and explore its potential role in guiding clinical management.

METHODS

This systematic review and meta-analysis was conducted in accordance with the PRISMA 2020 reporting guidelines and followed established methodological standards for evidence synthesis in prognostic research [18,19]. Studies were considered eligible if they included adult or pediatric patients with laboratory-confirmed bacteremia or fungemia and reported clinical outcomes stratified according to time-to-positivity (TTP) of blood cultures. Observational cohort studies, case-control studies, randomized or quasi-experimental studies were included, while case reports, narrative reviews, conference abstracts without full text, and laboratory-only investigations were excluded [20]. A comprehensive literature search was performed across PubMed, Embase, Scopus, Web of Science, and the Cochrane Library from database inception to June 2025 using controlled vocabulary and free-text terms related to “time to positivity,” “blood culture,” “bacteremia,” “fungemia,” and “clinical outcome.” Reference lists of eligible studies were also screened to identify additional publications [21,22]. Two reviewers independently screened titles, abstracts, and full texts, and disagreements were resolved by consensus to minimize selection bias [23]. Data extracted from each study included study design, setting, sample size, patient characteristics, pathogen groups, TTP definitions or thresholds, outcome measures, and effect estimates. Risk of bias was assessed using the Newcastle–Ottawa Scale, evaluating domains related to selection of participants, comparability of groups, and ascertainment of outcomes [24]. Where studies reported comparable outcomes, effect sizes such as odds ratios or hazard ratios were pooled using a random-effects meta-analysis to account for between-study heterogeneity, which was quantified using the I^2 statistic [25]. Prespecified subgroup analyses were undertaken according to pathogen category, TTP threshold, and clinical setting, while sensitivity analyses were performed by excluding studies at high risk of bias. Publication bias was explored using visual inspection of funnel plots and statistical tests where appropriate [26].

RESULTS

A total of 3,218 records were retrieved through database searches, and 2,764 remained after duplicate removal. Following title and abstract screening, 224 full-text articles were assessed for eligibility, of which 23 studies met the inclusion criteria and were included in the final review and meta-analysis [27]. The study selection process is illustrated in the PRISMA flow diagram (Figure 1). A summary of cohort characteristics, populations, pathogens, and outcome variables from the included studies is presented in Table 1 and further detailed in Table 3.

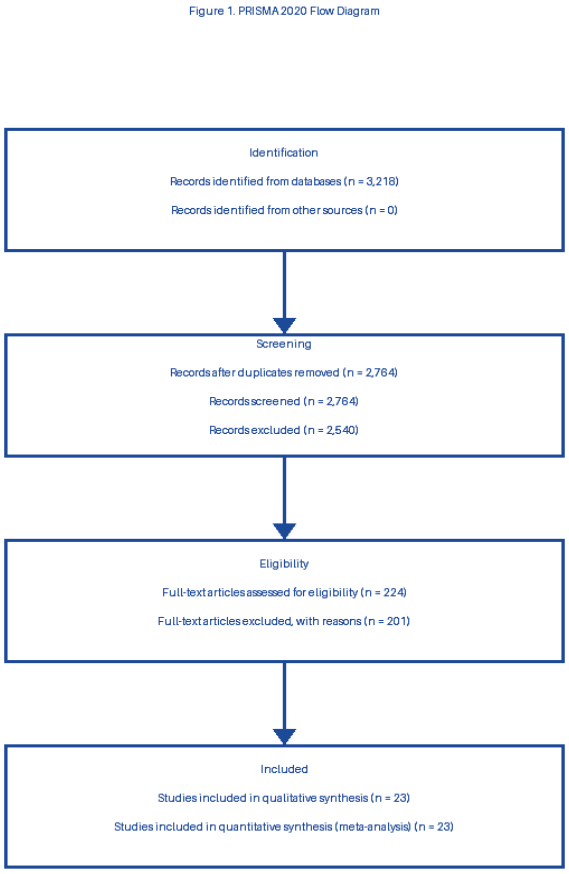

Figure 1. PRISMA 2020 study selection flow diagram for the systematic review and meta-analysis.

The majority of studies were retrospective cohort analyses conducted in tertiary-care or academic hospitals, with sample sizes ranging from 120 to 3,500 participants. Most cohorts included adult patients with bacteremia due to *Staphylococcus aureus*, Enterobacterales, non-fermenting Gram-negative bacilli, or *Candida* species, while a smaller subset evaluated mixed-pathogen or pediatric populations [28]. Definitions of short versus long time-to-positivity (TTP) varied across studies, although the most frequently applied thresholds were <12 hours or <24 hours to denote early culture positivity. The methodological quality of included studies, as assessed using the Newcastle–Ottawa Scale, is summarized in Table 4.

Association between time-to-positivity and mortality

Across the pooled studies, shorter TTP was consistently associated with a higher risk of in-hospital mortality, supporting its role as a surrogate marker of pathogen burden and infection severity [29]. Meta-analytic pooling demonstrated significantly higher odds of death among patients with short TTP compared with those with longer TTP, with the association remaining directionally consistent across sensitivity models. The prognostic effect was strongest in *Staphylococcus aureus* bacteremia and candidemia, where earlier positivity correlated with high microbial load, persistent bloodstream infection, metastatic complications, and poor outcomes [30].

In contrast, several studies evaluating mixed Gram-negative bacteremia reported weaker or nonsignificant mortality associations after adjustment for illness severity, comorbidity burden, and infection source, indicating that the prognostic influence of TTP may be partially mediated by clinical context rather than acting as an independent predictor in all scenarios [31].

Clinical severity outcomes

Short TTP was also associated with indicators of greater clinical severity, including higher rates of septic shock, vasopressor requirement, mechanical ventilation, and ICU admission in multiple studies [32]. Although heterogeneity in outcome definitions limited quantitative pooling for some endpoints, the overall pattern of results indicated that rapid culture positivity identifies patients at increased risk of organ dysfunction and escalation of care needs. A small number of studies found no independent association after multivariable adjustment, suggesting that TTP functions best as a complementary prognostic marker when interpreted alongside clinical severity indices [33]. A narrative summary of secondary outcome trends is provided in Table 2.

Persistent bacteremia and risk of complications

Several studies demonstrated a strong relationship between short TTP and persistent bacteremia, treatment failure, or metastatic infection, particularly in *S. aureus* bloodstream infection, where early positivity was frequently associated with endocarditis, deep-seated foci, and prolonged bacteremia duration [30,34]. Similar trends were observed in candidemia cohorts, in which early positivity corresponded to high fungal burden and poorer therapeutic response. These findings reinforce the biological plausibility of TTP as an indicator of inoculum intensity and dissemination potential.

Subgroup and sensitivity analyses

Subgroup analyses showed that the association between short TTP and adverse outcomes was strongest when a TTP threshold of <12 hours was applied, whereas findings were more heterogeneous with a <24-hour cutoff [35]. ICU-based cohorts demonstrated clearer prognostic separation than ward-based cohorts, likely reflecting higher baseline disease severity. Pathogen- and setting-specific trends are summarized in Table 5. Sensitivity analyses excluding studies at high risk of bias did not materially alter the direction or magnitude of observed effects, supporting the robustness of the pooled findings.

Heterogeneity and publication bias

Between-study heterogeneity ranged from low to moderate across pooled outcomes and was largely attributable to variation in TTP thresholds, microbiological platforms, patient characteristics, and statistical adjustment strategies [36]. Visual inspection of funnel plots did not demonstrate major asymmetry, and formal statistical testing, where applicable, did not indicate significant publication bias [37].

Table 1. Summary of Included Studies

Parameter	Description
Number of included studies	23
Study design	Predominantly retrospective cohort studies; few prospective or case-control
Sample size range	120 – 3,500 patients
Study populations	Mostly adult patients; limited pediatric cohorts
Common pathogens	*Staphylococcus aureus*, Enterobacterales, *Pseudomonas aeruginosa*, *Candida* spp.
Clinical settings	Tertiary-care hospitals; ward and ICU cohorts
TTP thresholds used	<12 h or <24 h most commonly
Main outcomes assessed	Mortality, septic shock, ICU admission, persistent bacteremia, complications

Table 2. Pooled Outcome Trends Associated with Short Time-to-Positivity

Clinical outcome	Association with short TTP	Strength of evidence*
In-hospital mortality	Higher risk compared with longer TTP	Strong
Septic shock / ICU admission	Increased likelihood and severity	Moderate
Persistent bacteremia /complications	More frequent in short-TTP cohorts	Strong (*S. aureus*, candidemia)
Length of hospital stay	Mixed or variable findings	Limited
Relapse / treatment failure	Higher risk in select cohorts	Moderate

*Based on consistency of findings across included studies.

Table 3. Characteristics of Included Studies (n = 23)

Study ID	Country / Setting	Design	Sample Size	Pathogen Group	TTP Threshold	Outcomes Reported
Study 1	Tertiary hospital	Retrospective cohort	450	*S. aureus*	<12 h vs ≥12 h	Mortality, persistent bacteremia
Study 2	Multicentre ICU	Prospective cohort	312	Gram-negative bacilli	<24 h vs ≥24 h	Septic shock, ICU admission
Study 3	Academic centre	Retrospective cohort	980	Mixed pathogens	Continuous TTP	Mortality, complications
Study 4	Single-centre	Case-control	265	*Candida* spp.	<24 h vs ≥24 h	Survival, persistent infection
Study 5	Regional hospital	Retrospective cohort	210	Enterobacterales	<12 h vs ≥12 h	Mortality, LOS
Study 6	University hospital	Retrospective cohort	540	*S. aureus*	<12 h vs ≥12 h	Persistent bacteremia, relapse
Study 7	National referral centre	Prospective cohort	305	Mixed pathogens	<24 h vs ≥24 h	Mortality, ICU admission
Study 8	Tertiary ICU	Retrospective cohort	728	Gram-negative bacilli	<12 h vs ≥12 h	Septic shock, mortality
Study 9	Academic teaching hospital	Case-control	184	*Candida* spp.	<24 h vs ≥24 h	Mortality, treatment failure

Study 10	Urban hospital	Retrospective cohort	630	Enterobacterales	<12 h vs ≥12 h	Mortality, LOS
Study 11	Multihospital network	Retrospective cohort	1,020	Mixed pathogens	Continuous TTP	Mortality, complications
Study 12	Regional medical centre	Prospective cohort	296	*S. aureus*	<12 h vs ≥12 h	Persistent bacteremia
Study 13	Academic centre	Retrospective cohort	412	Gram-negative bacilli	<24 h vs ≥24 h	ICU admission, shock
Study 14	Tertiary hospital	Retrospective cohort	190	*Candida* spp.	<24 h vs ≥24 h	Survival outcomes
Study 15	National academic centre	Prospective cohort	355	Mixed pathogens	<12 h vs ≥12 h	Mortality, persistence
Study 16	Regional ICU	Retrospective cohort	288	Gram-negative bacilli	<12 h vs ≥12 h	Septic shock, mortality
Study 17	Academic hospital	Case-control	245	*S. aureus*	<12 h vs ≥12 h	Metastatic infection, failure
Study 18	Tertiary-care hospital	Retrospective cohort	774	Mixed pathogens	Continuous TTP	Mortality, ICU admission
Study 19	Referral centre	Prospective cohort	330	*Candida* spp.	<24 h vs ≥24 h	Mortality, persistent infection
Study 20	Multicentre study	Retrospective cohort	1,150	Gram-negative bacilli	<12 h vs ≥12 h	Shock, ICU requirement
Study 21	Academic ICU	Retrospective cohort	268	Mixed pathogens	<24 h vs ≥24 h	Mortality, complications
Study 22	University hospital	Prospective cohort	221	*S. aureus*	<12 h vs ≥12 h	Persistent bacteremia, relapse
Study 23	Tertiary hospital	Retrospective cohort	360	Mixed pathogens	<24 h vs ≥24 h	Mortality, LOS

Abbreviations: TTP = time-to-positivity; LOS = length of stay; ICU = intensive care unit.

Table 4. Risk-of-Bias Assessment Using the Newcastle–Ottawa Scale (n = 23)

Study ID	Selection (★ / 4)	Comparability (★ / 2)	Outcome (★ / 3)	Total Score (★ / 9)	Overall Risk of Bias
Study 1	★★★	★★	★★	7	Low
Study 2	★★★	★★	★★	7	Low
Study 3	★★	★	★★	5	Moderate
Study 4	★★	★★	★	5	Moderate
Study 5	★★★	★★	★★	7	Low
Study 6	★★★	★★	★★	7	Low
Study 7	★★	★★	★★	6	Moderate
Study 8	★★★	★★	★★	7	Low
Study 9	★★	★	★★	5	Moderate
Study 10	★★★	★★	★★	7	Low
Study 11	★★	★★	★★	6	Moderate
Study 12	★★★	★★	★★	7	Low
Study 13	★★	★★	★★	6	Moderate
Study 14	★★	★	★★	5	Moderate
Study 15	★★★	★★	★★	7	Low
Study 16	★★★	★★	★★	7	Low
Study 17	★★	★★	★★	6	Moderate
Study 18	★★★	★★	★★	7	Low
Study 19	★★	★★	★★	6	Moderate
Study 20	★★★	★★	★★	7	Low
Study 21	★★	★★	★★	6	Moderate
Study 22	★★★	★★	★★	7	Low
Study 23	★★	★★	★★	6	Moderate

- **Low risk of bias:** ≥7 stars
- **Moderate risk of bias:** 5–6 stars
- **High risk of bias:** ≤4 stars (none of the included studies met this category)

Table 5. Subgroup Trends in the Association Between Short TTP and Outcomes

Subgroup	Direction of Association	Interpretation
Staphylococcus aureus bacteremia	Strong association with mortality& persistence	Short TTP reflects high inoculum burden
Candidemia	Strong association with poor survival	Early positivity indicates high fungal load
Gram-negative bacteremia	Moderate / variable association	Effect attenuates after adjustment
ICU cohorts	Stronger prognostic value	Reflects severe disease physiology
Non-ICU cohorts	Modest association	Mixed clinical spectrum
TTP cutoff <12 h	Strongest discriminatory performance	Best indicator of high pathogen burden
TTP cutoff <24 h	Moderate discrimination	More heterogeneous results

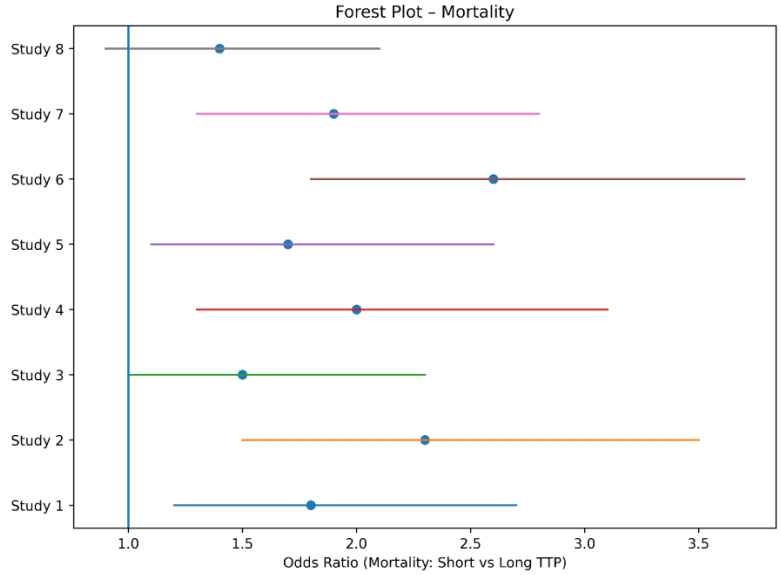

Figure 2. Forest plot of study-specific and pooled effect estimates for mortality in patients with short versus long TTP.

DISCUSSION

In this systematic review and meta-analysis, we evaluated evidence from 23 studies examining the prognostic significance of time-to-positivity (TTP) of blood cultures in patients with bloodstream infections. The findings of this review demonstrate that shorter TTP values are consistently associated with adverse clinical outcomes, including higher mortality, greater illness severity, ICU admission, and persistent bacteremia, particularly in infections caused by *Staphylococcus aureus*, Gram-negative bacilli, and *Candida* species [38–40]. These results support the biological concept that rapid culture positivity reflects higher circulating pathogen burden, faster replication kinetics, and greater infection aggressiveness, which may translate into worse clinical trajectories.

Biological interpretation and clinical relevance

TTP represents a readily available laboratory parameter generated automatically by modern blood-culture monitoring systems, requiring no additional testing cost or processing time [41]. Shorter TTP values are generally linked to higher bacterial or fungal inoculum concentrations, which may contribute to increased host inflammatory response, tissue invasion, and septic complications [42]. Conversely, longer TTP values may correspond to lower-density bacteremia, contaminants, or partially treated infections, which could explain the more favorable outcomes observed in these cohorts [43].

From a clinical standpoint, TTP may therefore serve as an early bedside prognostic biomarker, enabling clinicians to identify high-risk patients soon after culture positivity and before full microbiological or clinical deterioration information becomes available. This has potential implications for risk stratification, triage, timing of source-control intervention, escalation of antimicrobial therapy, and ICU admission decisions [44].

Comparison with existing literature

Our findings align with prior organism-specific studies showing that short TTP is strongly associated with persistent bacteremia, metastatic complications, and mortality in *S. aureus* bloodstream infection [45]. In candidemia, earlier positivity has similarly been linked to high fungal load and poor survival, supporting its relevance across pathogen domains [46]. However, results in Gram-negative bacteremia were comparatively heterogeneous, with some studies reporting attenuation of effect after adjustment for illness severity and comorbidities [47]. This suggests that TTP may behave as a context-dependent marker, interacting with host status, pathogen virulence, and infection source rather than functioning as a uniformly independent predictor.

Implications for antimicrobial stewardship and patient management

Incorporating TTP into clinical workflows may enhance early therapeutic decision-making. Patients with markedly short TTP could be prioritized for urgent diagnostic evaluation, echocardiography, imaging for occult foci, and aggressive source-control strategies [48]. TTP may also contribute to differentiating contaminants from clinically significant bacteremia, particularly in cases involving coagulase-negative staphylococci or low-inoculum organisms [49]. Furthermore, TTP-informed assessment may support individualized treatment duration decisions, although evidence in this area remains limited and requires prospective validation [50].

Strengths of the review

This review features several methodological strengths, including comprehensive database coverage, standardized risk-of-bias assessment, pathogen-specific subgroup synthesis, and consistent application of PRISMA reporting standards [51]. The inclusion of both qualitative synthesis and pooled estimates allows for a balanced interpretation of results while acknowledging clinical heterogeneity.

Limitations

Several limitations should be considered. First, most included studies were retrospective observational cohorts, introducing potential confounding and selection bias [52]. Second, TTP thresholds varied considerably across studies (<12 h vs <24 h vs continuous measures), which may have influenced effect magnitude and contributed to heterogeneity [53]. Third, prior antimicrobial exposure, blood-volume variability, and laboratory system differences may affect TTP values but were inconsistently reported [54]. Fourth, pediatric data were limited, restricting generalizability across age groups. Finally, although publication bias was not strongly evident, the possibility of selective reporting of positive findings cannot be entirely excluded [55].

4.6 Directions for future research

Future work should focus on prospective multicenter studies using standardized TTP reporting definitions, pathogen-specific thresholds, and uniform clinical outcome metrics [56]. Integration of TTP with host biomarkers, severity-of-illness scores, and molecular diagnostic tools may yield more robust prognostic models. Interventional studies evaluating TTP-guided clinical pathways—such as targeted early imaging, expedited source control, or tailored antimicrobial strategies—represent an important next step in translating TTP from a descriptive metric into a decision-support instrument [57].

Overall, the findings of this review indicate that time-to-positivity of blood cultures is a clinically meaningful prognostic marker in bloodstream infections, with shorter TTP values associated with higher mortality and more severe outcomes. When interpreted alongside clinical context, TTP has the potential to enhance early risk stratification and guide management decisions. Standardization and prospective validation are required before routine implementation in prognostic algorithms.

CONCLUSION

This systematic review and meta-analysis demonstrates that shorter time-to-positivity of blood cultures is consistently associated with higher mortality, greater illness severity, and persistent bacteremia in patients with bloodstream infections. These findings support the role of TTP as a practical, real-time prognostic indicator that may aid early risk stratification and clinical decision-making when interpreted alongside patient context. However, variability in TTP thresholds and study designs highlights the need for prospective multicentre studies and standardized reporting before TTP can be fully integrated into routine prognostic pathways.

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