

**Does TTP predict the risk of antibiotic failure? Population** Adults with documented bloodstream infection (bacteremia) confirmed by positive blood culture, including: Gram-positive organisms (with *S. aureus* as priority subgroup) Gram-negative organisms Any infection source (with stratification by source control status) Index Prognostic Factor (Exposure) Time to positivity (TTP) of blood cultures, analyzed as: Continuous variable (hours) Study-level contrasts (short vs. prolonged TTP where dichotomized) Comparator Shorter TTP vs. longer TTP Per-hour increments in TTP (for continuous modeling) Outcomes Priority Outcome Definition Primary Persistent bacteremia Positive blood cultures at 48–72 hours despite appropriate therapy Primary Relapse/recurrence Recurrent positive cultures after initial clearance (within 30–90 days) Primary Microbiological clearance Documented negative follow-up cultures Secondary All-cause mortality In-hospital or 30-day mortality Analytical Approach (for protocol) Bayesian hierarchical meta-regression Weakly informative priors informed by microbiological plausibility Heterogeneity assessed via  $\tau^2$  and prediction intervals

A shorter time to positivity (TTP) of blood cultures is a strong and independent predictor of antibiotic failure, manifested as persistent bacteremia and increased mortality, although its predictive strength is moderated by the specific pathogen and clinical context.

## Abstract

A substantial body of evidence indicates that a shorter time to positivity (TTP) of blood cultures is an independent predictor of adverse outcomes in adults with bloodstream infections. For both Gram-positive organisms like *Staphylococcus aureus* and Gram-negative organisms such as *Escherichia coli* and *Pseudomonas aeruginosa*, a shorter TTP is consistently associated with a higher risk of persistent bacteremia and increased in-hospital or 30-day mortality. Effect sizes vary, but multivariable analyses frequently confirm TTP's prognostic value after adjusting for patient severity and comorbidities. Some studies have successfully incorporated TTP into clinical prediction models with good discrimination for mortality.

However, significant heterogeneity exists across the literature, limiting the universal application of specific TTP cutoffs. The definition of a "short" TTP is inconsistent, ranging from <7 to ≤18 hours depending on the pathogen. Furthermore, a few studies report non-linear or conflicting associations, such as a U-shaped mortality risk for *S. aureus* bacteremia where both very short and very long TTPs are detrimental. In some critically ill populations, TTP was not found to be a significant predictor of mortality. The evidence linking TTP directly to relapse or recurrence is less developed. Overall, while shorter TTP is a strong indicator of a higher bacterial load and poorer prognosis, its precise clinical utility is moderated by pathogen type, infection source, and patient acuity.

## Paper search

We performed a semantic search across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We ran this query: "Does TTP predict the risk of antibiotic failure?

Population Adults with documented bloodstream infection (bacteremia) confirmed by positive blood culture, including:

Gram-positive organisms (with *S. aureus* as priority subgroup) Gram-negative organisms Any infection source (with stratification by source control status) Index Prognostic Factor (Exposure) Time to positivity (TTP) of blood cultures, analyzed as:

Continuous variable (hours) Study-level contrasts (short vs. prolonged TTP where dichotomized) Comparator

Shorter TTP vs. longer TTP Per-hour increments in TTP (for continuous modeling) Outcomes

Priority Outcome Definition Primary Persistent bacteremia Positive blood cultures at 48–72 hours despite appropriate therapy Primary Relapse/recurrence Recurrent positive cultures after initial clearance (within 30–90 days) Primary Microbiological clearance Documented negative follow-up cultures Secondary All-cause mortality In-hospital or 30-day mortality

Analytical Approach (for protocol)

Bayesian hierarchical meta-regression Weakly informative priors informed by microbiological plausibility Heterogeneity assessed via  $\tau^2$  and prediction intervals"

The search returned 500 total results from Elicit.

We retrieved 500 papers most relevant to the query for screening.

## Screening

We screened in sources based on their abstracts that met these criteria:

- **Adult Population:** Does the study include adults ( $\geq 18$  years) with documented bloodstream infection?
- **Blood Culture and TTP Data:** Does the study confirm bacteremia by positive blood culture AND report time-to-positivity (TTP) data (either quantitative measurements or clear dichotomized TTP categories)?
- **Relevant Outcomes:** Does the study report at least one of the following outcomes: persistent bacteremia, relapse/recurrence, microbiological clearance, or mortality?
- **Antibiotic Treatment Definition:** Does the study provide a clear definition of antibiotic appropriateness or treatment protocols?
- **True Bloodstream Infection:** Does the study focus on clinically significant bloodstream infections (rather than contaminated blood cultures or skin commensals without clinical significance)?
- **Study Design and Sample Size:** Is the study an observational study, randomized controlled trial, systematic review, or meta-analysis with adequate sample size ( $\geq 10$  patients for primary studies)?
- **Bacterial Infection Focus:** Does the study focus on bacterial (gram-positive and/or gram-negative) bloodstream infections rather than exclusively fungal infections?
- **Data Extractability:** Can TTP data be extracted or calculated from the study AND is antibiotic treatment status clearly documented?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

## Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **TTP Measurement:**

Extract all details about how time to positivity (TTP) was measured and categorized for predicting antibiotic failure, including:

- Exact TTP measurement method and timing
- Cutoff values used (e.g., <12h, ≤7h, >27h)
- Whether analyzed as continuous (hours) or categorical variable
- Blood culture system/methodology used
- Number of culture sets and timing of collection
- Any sequential TTP measurements or ratios

- **Antibiotic Failure Outcomes:**

Extract specific definitions and measurements of antibiotic failure outcomes relevant to TTP prediction, including:

- Persistent bacteremia (timing of follow-up cultures, definition of persistence)
- Relapse/recurrence (timeframe, definition, detection method)
- Microbiological clearance (timing, definition of clearance)
- Treatment failure (clinical or microbiological criteria)
- Mortality (timeframe: in-hospital, 30-day, 90-day)
- How each outcome was measured and at what time points
- Whether outcomes were primary or secondary endpoints

- **Study Population:**

Extract characteristics of patients with bloodstream infections relevant to TTP-antibiotic failure prediction, including:

- Organism type (Gram-positive, Gram-negative, specific species like *S. aureus*, *E. coli*)
- Infection source and whether source control was achieved
- Patient demographics and comorbidities affecting outcomes
- Severity of illness indicators (e.g., septic shock, ICU admission)
- Hospital vs. community-acquired infection
- Sample size and inclusion/exclusion criteria
- Any subgroup analyses performed

- **Predictive Association:**

Extract the statistical relationship between TTP and antibiotic failure outcomes for prediction assessment, including:

- Effect sizes (odds ratios, hazard ratios, risk ratios) with 95% confidence intervals
- Statistical significance (p-values) for TTP as predictor
- Direction of association (shorter vs. longer TTP risk)
- Predictive accuracy metrics if reported (sensitivity, specificity, AUC, positive/negative predictive values)
- Whether TTP was an independent predictor in multivariable analysis

- Comparison of different TTP cutoffs for prediction

- **Antibiotic Treatment:**

Extract antibiotic treatment details that affect interpretation of TTP-failure relationships, including:

- Definition of 'appropriate therapy' used in the study
- Timing of antibiotic initiation relative to blood culture
- Specific antibiotics used and dosing adequacy
- Duration of treatment
- Whether treatment was guided by susceptibility results
- Any treatment modifications based on TTP or clinical response
- Source control procedures and timing

- **Analysis Method:**

Extract analytical approach used to assess TTP as predictor of antibiotic failure, including:

- Type of analysis (logistic regression, Cox proportional hazards, survival analysis)
- Variables included in multivariable models
- How confounding was addressed
- Sample size calculations or power analysis
- Handling of missing data
- Subgroup or sensitivity analyses performed
- Whether prediction models were developed or validated

- **Study Design:**

Extract study design features relevant to assessing TTP as prognostic factor, including:

- Study type (prospective cohort, retrospective cohort, case-control)
- Study setting (single-center, multi-center, population-based)
- Time period and duration of study
- Follow-up duration and completeness
- Blinding of outcome assessors to TTP
- Whether TTP was measured in real-time or retrospectively
- Risk of bias considerations specific to prognostic studies

## **Study Characteristics and Design Quality**

The included studies examining time to positivity (TTP) as a predictor of antibiotic failure in bloodstream infections consist predominantly of retrospective cohort designs, with a smaller number of prospective cohort studies. Settings were varied, including single-center, multi-center, and population-based cohorts. Study durations ranged from a few months to over a decade. Sample sizes varied widely, from under 100 patients to large population-based studies with tens of thousands of participants. Follow-up durations were most commonly 30 days, although periods such as 28 days, 90 days, and in-hospital mortality were also used. No studies explicitly mentioned blinding of outcome assessors to TTP values, except for one which specified blinding of outcome assessors and data analysts. Methodological quality is subject to the inherent limitations of observational research, primarily confounding by indication and selection bias, although some studies attempted to mitigate this through multivariable adjustment and propensity score methods.

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
A. Bläckberg et al. (2022)	Yes	Retrospective observational cohort study	Population-based	2015-2018	286	At least 30 days
A. Bläckberg et al. (2023)	Yes	Retrospective cohort	Population-based	2015-2018	287	30 days
A. Marra et al. (2006)	Yes	Retrospective cohort study	Not specified	Not specified	91	Not specified
A. Nelson et al. (2017)	Yes	Retrospective cohort	Single-center	2010-2013	411	Not mentioned
A. Peri et al. (2023)	Yes	Prospective observational study	Multicenter	Not specified	102	4 days
A. Sastry et al. (2024)	Yes	Retrospective cohort	Single-center	4-year period	38,606 samples	Not mentioned
A. T. Aslan et al. (2024)	Yes	Prospective cohort	Multi-center	2021-2022	378	Not mentioned
A. Turjeman et al. (2022)	Yes	Individual participant data meta-analysis of RCTs	Multi-center	Up to May 2022	1186	At least 90 days
Achim J. Kaasch et al. (2013)	Yes	Prospective observational study	Multi-center	Not specified	256	3 months
Arianna Di Marcello et al. (2025)	Yes	Prospective, pre-post interventional study	Single-center	2022-2023	446 BSI episodes	Not mentioned
C. Cillóniz et al. (2017)	Yes	Prospective observational study	Single-center	2003-2015	278	30-40 days after discharge
C. Fang et al. (2006)	Yes	Retrospective cohort	Single-center	1997-2001	162	Up to 3 years
C. Forstner et al. (2013)	Yes	Retrospective cohort study	Single-center	2000-2011	124	At least 28 days
C. Kang et al. (2004)	Yes	Retrospective cohort	Not mentioned	Not mentioned	286	30-day mortality
C. Liao et al. (2009)	Yes	Prospective cohort study	Single-center	2007	231	At least 30 days
Chih-Cheng Lai et al. (2011)	Yes	Retrospective cohort	Single-center	2015	80	Not mentioned
Chih-Chi Lee et al. (2017)	Yes	Retrospective cohort study	Single-center	2008-2013	2349	28 days

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
Chih-Chi Lee et al. (2019)	Yes	Retrospective cohort study	Multi-center	2010-2015	1247	Not mentioned
Chih-Chi Lee et al. (2021)	Yes	Cohort study	Multicenter	4 years	2357	At least 30 days
Chih-Ping Chen et al. (2023)	Yes	Retrospective observational, case-control study	Single-center	2016-2021	101	At least 30 days
Ching-Chi Lee et al. (2021)	Yes	Cohort study	Multicenter	4 years	2357	At least 30 days
Christelle Kassis et al. (2009)	Yes	Retrospective cohort	Single-center	2005-2008	272	Not mentioned
Daniel Gao et al. (2023)	Yes	Case-control	Single-center	2014-2018	598	Not specified
Daniel N Marco et al. (2025)	Yes	Retrospective cohort study	Single-center	1991-2019	1177	30 days
David Zhang et al. (2015)	Yes	Retrospective cohort	Single-center	2008-2012	1058	Not mentioned
E. Maillart et al. (2012)	Yes	Retrospective cohort study	Single-center	2007-2010	167	Not detailed
E. Minejima et al. (2015)	Yes	Prospective observational study	Multi-center	2012-2014	196	At least 30 days
E. Minejima et al. (2019)	Yes	Prospective observational cohort	Multi-center	2012-2017	884	At least 30 days
E. von Dach et al. (2020)	Yes	Prospective cohort, randomized clinical trial	Multi-center	2017-2019	504	90 days
E. Zasowski et al. (2016)	Yes	Retrospective cohort study	Single-center	2010-2014	190	30 days
Emily Fox et al. (2022)	Yes	Retrospective case-control study	Single-center	2016-2020	108	Not explicitly mentioned
Evan J Zasowski et al. (2020)	Yes	Systematic review	Multi-study	Post-2007	145 studies	Not mentioned
F. Hamilton et al. (2021)	Yes	Prospective cohort	Multi-center	Not mentioned	3462	Not mentioned

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
Felicity Edwards et al. (2025)	Yes	Retrospective cohort	Population-based	2000-2019	84,341	Not mentioned
G. Martín-Gutiérrez et al. (2017)	Yes	Retrospective cohort study	Not specified	Not specified	361 BSI episodes	Not specified
G. Peralta et al. (2006)	Yes	Retrospective cohort	Single-center	1995-2004	105	Limited by hospital records
G. Peralta et al. (2007)	Yes	Retrospective cohort	Single-center	1997-2005	459	Not mentioned
Gavin Deas et al. (2025)	Yes	Retrospective cohort study	Multi-center	2017-2024	810	Not mentioned
H. Bae et al. (2021)	Yes	Retrospective cohort study	Single-center	2014-2018	2499	28 days
H. Le et al. (2014)	Yes	Retrospective cohort	Single-center	2008-2012	174	Not mentioned
H. Mitaka et al. (2022)	Yes	Retrospective cohort study	Multi-center	2017-2018	376	Not specified
H. Palmer et al. (2013)	Yes	Prospective cohort	Single-center	Not specified	100	Until hospital discharge or death
Hang-Cheng Chen et al. (2013)	Yes	Prospective cohort	Single-center	2008-2009	937	At least 30 days
Hea Sung Ok et al. (2013)	Yes	Prospective cohort	Single-center	2009-2010	79	Until clearance
Heather Savage et al. (2019)	Yes	Retrospective cohort	Single-center	2016-2017	164	Not mentioned
Hiroyasu Takahashi et al. (2022)	Yes	Retrospective cohort study	Single-center	1-year period	245	14 days
Hiroyoshi Iwata et al. (2025)	Yes	Retrospective cohort study	Multi-center	2018-2022	1084	Not mentioned
I. Comba et al. (2022)	Yes	Retrospective cohort	Single healthcare system, multi-site	2019	186	At least 90 days
I. Comba et al. (2024)	Yes	Observational study	Not specified	Not mentioned	186	Not mentioned

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
Ioannis Baltas et al. (2020)	Yes	Retrospective cohort study	Single-center	2017-2019	789	30 days
J. Martinez et al. (2006)	Yes	Prospective cohort	Single-center	1 year	185	Not mentioned
J. Martínez et al. (2007)	Yes	Retrospective cohort	Single-center	2 years	1872	Not mentioned
Jasanjeet Jawanda et al. (2023)	Yes	Before-and-after observational study	Single-center	2021	154	At least 30 days
Jasper Van Heuverswyn et al. (2022)	Yes	Retrospective cohort study	Single-center	2012-2019	10,628 BSI episodes	Up to 30 days
Javier López et al. (2013)	Yes	Retrospective cohort	Not explicitly mentioned	1996-2011	407	Not mentioned
Joe Pardo et al. (2014)	Yes	Retrospective cohort	Single-center	2011	626	Not mentioned
Joseph Kim et al. (2010)	Yes	Retrospective cohort	Population-based	2006-2008	684	At least 30 days
Jun Shinohara et al. (2022)	Yes	Systematic review and meta-analysis of retrospective studies	Not mentioned	Not mentioned	7778	Not mentioned
K. Buell et al. (2020)	Yes	Retrospective cohort	Multi-center	Not mentioned	15,802	Not mentioned
K. Buell et al. (2020a)	Yes	Retrospective cohort	Multi-center	Not mentioned	15,802	Not mentioned
K. Ishikawa et al. (2025)	Yes	Retrospective cohort	Single-center	Not mentioned	317	Not mentioned
K. Ishikawa et al. (2025a)	Yes	Retrospective cohort	Single-center	2015-2023	317	Not mentioned
K. Paquette et al. (2021)	Yes	Prospective cohort	Multicenter	Not specified	325	90 days
K. Seidl et al. (2010)	Yes	Prospective cohort	Multi-center	Not mentioned	36 MRSA isolates	Not mentioned
Karl Oldberg et al. (2021)	Yes	Retrospective cohort study	Population-based	2015-2018	367 episodes	Minimum of 180 days
Katharina Michelson et al. (2021)	Yes	Retrospective cohort	Single-center	2014-2016	244	Not mentioned

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
Kelly A. Cairns et al. (2016)	Yes	Prospective randomized controlled trial	Multi-center	Not mentioned	160	Not mentioned
Kevin B. Laupland et al. (2024)	Yes	Retrospective cohort	Population-based	2000-2019	88,314	At least 30 days
L. Zornitzki et al. (2023)	Yes	Prospective cohort	Single-center	2019-2023	155	Not explicitly mentioned
Lauren Cooper et al. (2024)	Yes	Retrospective cohort	Multi-center	Not mentioned	29,570	Not mentioned
Lena Gajdos et al. (2025)	Yes	Prospective cohort	Multi-center, international	Not mentioned	2600	Up to 28 days
M. Cheng et al. (2019)	Yes	Prospective cohort	Multi-center	2013-2018	325	Not explicitly mentioned
M. Falcone et al. (2020)	Yes	Retrospective cohort study	Multi-center	2015-2018	102	30 days
M. Fida et al. (2021)	Yes	Prospective cohort	Multi-center	Not specified	Not mentioned	Not detailed
M. Giannella et al. (2020)	Yes	Retrospective cohort	Single-center	2013-2016	1576	At least 30 days
M. Holubar et al. (2021)	Yes	Prospective observational study	Multicenter	Not mentioned	884	Not mentioned
M. Lambregts et al. (2019)	Yes	Retrospective cohort study	Single-center	2013-2015	801	Electronic medical records
M. Rolo et al. (2022)	Yes	Retrospective cohort	Single-center	2013-2020	328	30 days
M. Spaziante et al. (2020)	Yes	Retrospective cohort	Hospital-based	1 year	307	Not explicitly mentioned
Martin Strömdahl et al. (2024)	Yes	Retrospective cohort study	Single-center	2011-2021	1703 episodes	Not mentioned
Matthias Willmann et al. (2013)	Yes	Retrospective cohort study	Multi-center	2006-2012	74	Not mentioned
Meng-Shiuan Hsu et al. (2014)	Yes	Retrospective cohort	Single-center	5 years	87	Not mentioned
N. Deguchi et al. (2023)	Yes	Retrospective cohort	Single-center	Not mentioned	221 ( <i>S. aureus</i> )	Not mentioned

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
Nicole R. Hume et al. (2022)	Yes	Retrospective cohort study	Single-center	2014-2020	178	Excluded if discharged within 48h
O. Lesens et al. (2004)	Yes	Prospective cohort	Multi-center	Not mentioned	104	Not mentioned
Oskar Ljungquist et al. (2025)	Yes	Retrospective cohort	Population-based	2021-2023	12,585 episodes	30 days
P. Krisanapan et al. (2019)	Yes	Retrospective cohort study	Single-center	2014	181	Not mentioned
P. Moise et al. (2010)	Yes	Prospective cohort	Multi-center	1998-2002	29	Daily until clearance
P. Puerta-Alcalde et al. (2019)	Yes	Prospective cohort	Multi-center	2003-2017	850 episodes	Not mentioned
P. Simos et al. (2022)	Yes	Retrospective cohort	Single-center	Not mentioned	106	Not mentioned
P. Tsai et al. (2025)	Yes	Retrospective cohort	Not mentioned	Not mentioned	1015	30-day mortality
Paige A. Melling et al. (2020)	Yes	Prospective cohort ancillary study	Single-center	2015-2017	263	Not mentioned
Qing Zhang et al. (2016)	Yes	Retrospective cohort	Single-center	19 months	386 episodes	Not mentioned
Qing Zhang et al. (2020)	Yes	Retrospective cohort study	Single-center	2013-2018	509	Not mentioned
Qing Zhang et al. (2021)	Yes	Retrospective cohort study	Single-center	2013-2018	509	Not mentioned
R. Álvarez et al. (2012)	Yes	Retrospective observational study	Single-center	Not mentioned	226	Not mentioned
R. García Fenoll et al. (2022)	Yes	Retrospective cohort study	Single-center	2020-2021	95	At least 30 days
R. Khatib et al. (2005)	Yes	Prospective cohort	Single-center	2002-2003	357	Not mentioned
R. Khatib et al. (2006)	Yes	Retrospective cohort	Not mentioned	2002-2003	342	Not mentioned
R. Khatib et al. (2006a)	Yes	Prospective cohort	Single-center	2002	245 BSI cases	Not specified
R. Rosa et al. (2016)	Yes	Retrospective cohort	Single-center	2012-2013	250 episodes	Not mentioned

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
Rachel Perry et al. (2022)	Yes	Quasi-experimental study	Single-center	2014-2021	296	Not mentioned
Rashid Nadeem et al. (2021)	Yes	Retrospective cohort study	Single-center	2017-2018	101	Not mentioned
Riley Karpen et al. (2023)	Yes	Retrospective cohort	Single-center	2018-2020	Not specified	Not mentioned
Ritu Banerjee et al. (2023)	Yes	Secondary analysis of a randomized controlled clinical trial	Not mentioned	Not mentioned	386	Not mentioned
S. Choi et al. (2012)	Yes	Not mentioned	Not specified	Not specified	Not mentioned	Not specified
S. Siméon et al. (2019)	Yes	Prospective cohort	Multi-center	2009-2011	587	At least 30 days
S. Tong et al. (2020)	Yes	Prospective cohort	Multi-center or population-based	Not mentioned	987	Not mentioned
S. W. Ong et al. (2024)	Yes	Retrospective cohort	Population-based	2017-2021	8807	2-5 days for FUBC
S. de la Villa et al. (2023)	Yes	Retrospective times-series study	Single-center	2014-2021	109 episodes	30 days
Sandra Tingsgård et al. (2023)	Yes	Emulated trial using real-world data	Multi-center	2018-2021	1040	90 days
Sandhya Bhat K et al. (2022)	Yes	Cross-sectional study	Single-center	2018	75	Not mentioned
Santiago Grillo Perez et al. (2024)	Yes	Systematic review and meta-analysis of non-randomized studies	Not specified	Up to June 2023	1700	Not specified
Sarah Cain et al. (2014)	Yes	Retrospective cohort	Single-center	2011-2012	390	At least 28 days
Sarah Cain et al. (2015)	Yes	Retrospective cohort	Single-center	2010-2013	830	Not mentioned

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
Shang-Yu Chen et al. (2018)	Yes	Retrospective cohort	Not mentioned	30-month period	206	Not mentioned
Shi-ning Bo et al. (2010)	Yes	Retrospective cohort	Single-center	2007-2009	112	Not mentioned
Shi-ning Bo et al. (2011)	Yes	Retrospective cohort	Multi-center	2007-2009	353 episodes	Not mentioned
Siddharth Swamy et al. (2014)	Yes	Retrospective cohort	Single-center	2006-2013	178	Not mentioned
Siddharth Swamy et al. (2016)	Yes	Retrospective cohort	Single-center	2006-2013	178	Not mentioned
Suellen Gavronski et al. (2020)	Yes	Retrospective cohort	Single-center	2013-2018	5,425 blood cultures	Not mentioned
Susannah Jerwood et al. (2012)	Yes	Prospective cohort	Single-center	Not mentioned	48	Not mentioned
T. Bias et al. (2017)	Yes	Retrospective cohort	Single-center	2011-2012	111	Not mentioned
T. Dinh et al. (2015)	Yes	Retrospective cohort	Single-center	Not mentioned	793 blood samples	Not mentioned
Tae-Hoon No et al. (2025)	Yes	Retrospective cohort study	Multi-center	2018-2023	220	Up to 30 days
V. Fowler et al. (2004)	Yes	Prospective cohort	Single-center	Not mentioned	39	Not mentioned
Weiwei Hou et al. (2023)	Yes	Retrospective cohort study	Single-center	2016-2020	148	Not mentioned
Y. Chong et al. (2013)	Yes	Prospective cohort with nested case-control study	Single-center	2008-2010	483	At least 12 weeks
Ya-Chu Hsieh et al. (2022)	Yes	Systematic review and meta-analysis	Multi-study	Up to Aug 2021	24 studies	Not applicable
Yong-Ye Yang et al. (2024)	Yes	Retrospective cohort	Single-center	2016-2021	196	Not mentioned
Yong-zhong Ning et al. (2016)	Yes	Retrospective cohort	Single-center	2011-2013	886 isolates	Not mentioned
Yufang Chen et al. (2020)	Yes	Retrospective cohort study	Single-center	2014-2016	167	Not mentioned

Study	Full text retrieved?	Study Type	Setting	Time Period	Sample Size	Follow-up Duration
Yufang Chen et al. (2020a)	Yes	Retrospective cohort study	Single-center	2014-2016	167	Not specified
Yunwei Zheng et al. (2025)	Yes	Retrospective cohort	Population-based	2020-2023	610	At least 30 days
Zhanni Weber et al. (2016)	Yes	Not specified	Not specified	Not specified	71	Not specified

## Patient Populations and Bloodstream Infection Characteristics

The patient populations across studies were diverse, spanning adults with monomicrobial bloodstream infections from various pathogens. A significant portion of the research focused on specific organisms, including *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and various streptococcal species. Both Gram-positive and Gram-negative organisms were extensively represented.

Common sources of infection included catheter-related infections, urinary tract, intra-abdominal sites, and endovascular sources like infective endocarditis. Source control was noted as an important variable in several studies, with delayed source control being associated with worse outcomes, especially in *S. aureus* bacteraemia. Patient populations were frequently elderly, and common comorbidities included malignancy, diabetes, and renal disease. Severity of illness was frequently high, with many patients experiencing septic shock or requiring ICU admission. Studies included both hospital-acquired and community-acquired infections.

Study	Sample Size	Organism Distribution	Infection Source	Source Control	Severity Indicators
Meng-Shiuan Hsu et al. (2014)	87	<i>S. aureus</i>	Catheter-related (31%), Infective Endocarditis (18%)	Not mentioned	Pittsburgh score 2.7
H. Palmer et al. (2013)	100	Gram-negative bacilli	Not mentioned	Not mentioned	ICU admission
Yufang Chen et al. (2020)	167	<i>E. coli</i>	Not mentioned	Not mentioned	Septic shock (15.6%), ICU admission
Qing Zhang et al. (2020)	509	<i>E. coli</i>	Not mentioned	Not mentioned	Fever $\geq 39^{\circ}\text{C}$ , ARDS
A. Marra et al. (2006)	91	<i>S. aureus</i>	Central venous catheter	Not mentioned	Septic shock
P. Tsai et al. (2025)	1015	Monomicrobial BSIs	Not mentioned	Not mentioned	Not mentioned

Study	Sample Size	Organism Distribution	Infection Source	Source Control	Severity Indicators
Martin Strömdahl et al. (2024)	1703 episodes	<i>S. aureus</i>	Not mentioned	Not mentioned	30-day mortality (24%), Endocarditis (9%)
Matthias Willmann et al. (2013)	74	<i>P. aeruginosa</i>	Not mentioned	Not mentioned	SAPS II score
M. Rojo et al. (2022)	328	<i>P. aeruginosa</i>	Respiratory source	Not mentioned	Septic shock
R. Khatib et al. (2005)	357 patients	<i>S. aureus</i>	Endovascular source	Not mentioned	Metastatic infection (8.0%)
Chih-Ping Chen et al. (2023)	101	<i>K. pneumoniae</i>	Intra-abdominal	Not mentioned	Not mentioned
G. Peralta et al. (2007)	459	<i>E. coli</i>	Non-urinary tract or unknown	Not mentioned	Severe sepsis or shock
Daniel N Marco et al. (2025)	1177	<i>P. aeruginosa</i>	Catheter-related	Catheter removal mentioned	Not mentioned
Hea Sung Ok et al. (2013)	79	MRSA	Catheter-related, metastatic infections	Delayed catheter removal mentioned	Pitt bacteremia scores, ICU stay

## TTP Measurement Methods and Categorization

The measurement of TTP was generally defined as the time from the start of blood culture incubation to an automated alert signal. Automated blood culture systems such as BACTEC (BD) and BacT/ALERT (bioMérieux) were commonly used. Most studies required at least two sets of blood cultures.

TTP was analyzed both as a continuous variable (per-hour) and as a categorical variable based on various cutoff values. The specific cutoff values varied considerably across studies and by organism. For *E. coli*, cutoffs of  $\leq 7$ h,  $\leq 8$ h,  $\leq 11$ h, and 10h were used. For *S. aureus*, common cutoffs included  $< 12$ h,  $\leq 11.8$ h,  $\leq 12$ h,  $< 13$ h,  $\leq 13.7$ h, and  $\leq 14$ h. For *P. aeruginosa*, studies used cutoffs of  $\leq 18$ h and  $\leq 16$ h. A few studies investigated sequential TTP measurements, using a ratio of the second TTP to the first TTP, with a ratio of  $< 1.5$  indicating a poor prognosis. The rationale for selecting cutoffs was often based on receiver-operating characteristic (ROC) curve analysis to optimize sensitivity and specificity for predicting outcomes like septic shock or mortality.

Study	Blood Culture System	Number of Culture Sets	TTP Analyzed As	Cutoff Values Used	Rationale for Cutoffs
Meng-Shiuan Hsu et al. (2014)	Not mentioned	Not mentioned	Categorical (ratio)	Second TTP/first TTP ratio <1.5 ≤11 h	Not mentioned
Yufang Chen et al. (2020)	BACTEC 9120	At least two sets	Continuous & Categorical		ROC analysis for predicting septic shock
Qing Zhang et al. (2020)	Not mentioned	Not mentioned	Categorical	≤ 8h	Not mentioned
A. Marra et al. (2006)	Automated system	Not mentioned	Categorical	≤12 h	Not mentioned
Martin Strömdahl et al. (2024)	Not mentioned	Not mentioned	Continuous & Categorical	<13 h	Median TTP value
Matthias Willmann et al. (2013)	Not mentioned	Not mentioned	Categorical	≤ 18 h	Not mentioned
M. Rolo et al. (2022)	Automatically recorded	Not mentioned	Continuous & Categorical	≤16 h	ROC analysis for predicting mortality
R. Khatib et al. (2005)	Not mentioned	Not mentioned	Continuous & Categorical	≤14 h	Best sensitivity and specificity for prediction
Daniel N Marco et al. (2025)	BACTEC systems	8-10 mL per vial	Continuous & Categorical	<13h, <14h, <16h	Not mentioned
Hea Sung Ok et al. (2013)	BacT ALERT 3D	Every 2-3 days until clearance	Continuous & Categorical	<11.8 h	Not mentioned
Qing Zhang et al. (2021)	BACTEC FX400	Not mentioned	Categorical	≤ 8 h	Not mentioned
C. Cillóniz et al. (2017)	BACTEC 9240	Not specified	Continuous & Categorical	9.2 h	ROC analysis to differentiate risk groups
I. Comba et al. (2024)	Not specified	Not specified	Continuous & Categorical (ratio)	TTP ratio ≤1.5; initial TTP <12 h	Not mentioned

## Antibiotic Treatment Context

The definition of "appropriate therapy" across studies was consistently based on in vitro susceptibility of the isolated pathogen to the administered antibiotic regimen. The timing of initiation was a key variable, with "appropriate" often requiring commencement within a specific timeframe, such as 24 hours, after blood culture collection. Delays in appropriate therapy were associated with worse outcomes, though the critical time window varied. For instance, one study on KPC-producing *K. pneumoniae* bacteremia found that receiving active therapy within 24 hours was associated with lower 30-day mortality. Another study on community-onset bacteremia found the optimal timing

for non-critically ill patients was within 48 hours, but shifted to within 1 hour for critically ill patients.

Specific antibiotic regimens were mentioned, including glycopeptides like vancomycin for MRSA infections, and broad-spectrum beta-lactams or carbapenems for Gram-negative infections. Dosing adequacy was sometimes addressed, particularly for vancomycin, where maintaining target trough levels (e.g.,  $\geq 15$  mg/L) was noted as a factor in preventing persistent bacteremia. The duration of treatment was a focus of several studies comparing shorter courses (e.g., 7-10 days) with longer courses (e.g., 14 days or more) for uncomplicated Gram-negative bacteremia, with mixed findings on efficacy.

Source control procedures, such as removal of infected catheters or drainage of abscesses, were identified as critical components of management. Delays in source control were linked to persistent bacteremia and poorer outcomes. Some studies noted that treatment modifications, such as antibiotic de-escalation, could be guided by negative culture results after 48-72 hours, although the risk of delayed growth of resistant organisms was also highlighted.

Study	Definition of Appropriate Therapy	Median Time to Appropriate Antibiotics	Common Antibiotic Regimens	Source Control Timing
Yufang Chen et al. (2020)	In vitro susceptibility and initiation within 24h	within 24 hours	Not mentioned	Not mentioned
Daniel N Marco et al. (2025)	Active agent within 24h before susceptibility results	within 24 hours	Not mentioned	Catheter removal mentioned, timing not specified
Hea Sung Ok et al. (2013)	Not explicitly defined	Not mentioned	Vancomycin, teicoplanin	Catheter removal within 24h considered early
Qing Zhang et al. (2021)	Effective against causative microorganism	Not specified	Not mentioned	Not mentioned
M. Lambregts et al. (2019)	Based on local sepsis guidelines	Not specified	2nd-gen cephalosporin + aminoglycoside	Not mentioned
C. Cillóniz et al. (2017)	According to IDSA/ATS guidelines for CAP	Not mentioned	$\beta$ -lactam + macrolide, fluoroquinolone monotherapy	Not mentioned
C. Kang et al. (2004)	Susceptible agent within 24h of blood culture	within 24 hours	Not mentioned	Not mentioned
M. Falcone et al. (2020)	In vitro susceptibility by EUCAST breakpoints	8.5h (survivors) vs 48h (non-survivors)	Ceftazidime-avibactam, colistin, meropenem	Within 24 hours
E. Zasowski et al. (2016)	Susceptible to enterococci and any copathogen	Median 31.6 hours	Linezolid, daptomycin, ampicillin	Documented but timing not detailed

Study	Definition of Appropriate Therapy	Median Time to Appropriate Antibiotics	Common Antibiotic Regimens	Source Control Timing
Ching-Chi Lee et al. (2017)	Based on Sanford Guide and CLSI breakpoints	Mean 2.0 hours	Various broad-spectrum agents	Not detailed

## Outcome Definitions and Measurement

Studies predominantly defined and measured outcomes related to microbiological persistence and mortality. Persistent bacteremia was a primary outcome, commonly defined as positive follow-up blood cultures (FUBCs) despite appropriate antibiotic therapy. The timeframe for defining persistence varied, with common windows being ≥48 hours, ≥72 hours, ≥4 days, and ≥7 days.

Mortality was a key secondary or primary outcome in most studies, with specified timeframes including in-hospital, 28-day, 30-day, and 90-day mortality. Relapse or recurrence of bacteremia was less frequently assessed but was defined as recurrent positive cultures after a period of initial clearance, typically within a 30 to 90-day window. Microbiological clearance was documented via negative follow-up cultures but was not always a formal endpoint. Some studies used composite endpoints, such as clinical failure, which could include persistent bacteremia, mortality, or the need to escalate therapy.

Study	Persistent Bacteremia Definition	Relapse Definition and Timeframe	Clearance Definition	Mortality Timeframe
Meng-Shiuan Hsu et al. (2014)	>48h positive cultures	Not mentioned	Not mentioned	In-hospital
Hea Sung Ok et al. (2013)	≥ 7 days	Not mentioned	Negative FUBCs	30-day
P. Moise et al. (2010)	Not mentioned	Not mentioned	Time to first negative culture	Not mentioned
V. Fowler et al. (2004)	≥7 days of therapy	Not mentioned	Not mentioned	Not mentioned
E. Minejima et al. (2019)	≥3 days positive cultures	Not explicitly defined	Not explicitly defined	30-day
Y. Chong et al. (2013)	≥7 days despite therapy	Recurrence within 12 weeks	Implied by FUBCs	12-week & 30-day
E. Minejima et al. (2015)	≥ 4 days positive cultures	Recurrence within 30 days	Not mentioned	30-day
Emily Fox et al. (2022)	≥ 4 days positive cultures	Recurrence within 14 days	Clearance within 4 days	In-hospital
Javier López et al. (2013)	48-72h positive cultures	Not mentioned	Not mentioned	In-hospital
O. Lesens et al. (2004)	>24h positive cultures	Not mentioned	Not mentioned	Not specified

Study	Persistent Bacteremia Definition	Relapse Definition and Timeframe	Clearance Definition	Mortality Timeframe
R. Khatib et al. (2006a)	≥3 days positive cultures	Not mentioned	Not mentioned	Not mentioned
C. Forstner et al. (2013)	≥7 days	Not mentioned	Failure of microbiological eradication mentioned	28-day
M. Giannella et al. (2020)	24h-7 days positive FUBCs	Not mentioned	Not mentioned	30-day
S. W. Ong et al. (2024)	2-5 days positive FUBCs	Not mentioned	Not mentioned	30-day, 90-day
K. Paquette et al. (2021)	Persistent bacteremia mentioned, not defined	Not mentioned	Not mentioned	90-day

## TTP and Persistent Bacteremia/Microbiological Failure

A shorter TTP was frequently associated with persistent bacteremia or microbiological failure. In studies of *S. aureus* bacteremia (SAB), a TTP of <11.8 hours was associated with an increased risk of persistence. Similarly, another study found that a TTP ≤12.4 hours was significantly associated with persistent SAB. The concept of sequential TTP was also explored, where a ratio of the second TTP to the first of <1.5 was identified as an independent risk factor for poor outcomes in persistent SAB, including mortality. Furthermore, a decrease in TTP in follow-up blood cultures after primary therapeutic intervention was associated with a significantly higher frequency of 30-day mortality or secondary infections in patients with persistent SAB.

For Gram-negative bacteremia, the evidence is less extensive but points in a similar direction. One study found that for patients with *P. aeruginosa* BSI, a TTP <13 hours was independently associated with catheter-related infections, a common cause of persistence. Other studies defined persistence based on positive follow-up cultures at various time points (e.g., ≥48-72 hours, ≥3-4 days, or ≥7 days) but did not always directly link this to initial TTP values. The duration of bacteremia itself was found to be a critical predictor, with each additional day of positive blood cultures incrementally increasing the risk of metastatic complications and mortality in SAB.

| Study | Outcome Definition | TTP Exposure (Cutoff or Continuous) | Effect Size Type | Effect Estimate (95% CI) | p-value | Adjustment Variables || --- | --- | --- | --- | --- | --- | --- | --- | Hea Sung Ok et al. (2013) | Persistent MRSA bacteremia | < 11.8 hours | Not specified | Not specified | 0.029 | Univariate analysis || E. Maillart et al. (2012) | Persistent SAB | ≤12.4 hours | Not specified | Not specified | 0.010 | Not specified || Daniel N Marco et al. (2025) | Catheter-related PAE-BSI | < 13 hours | OR | 3.7 (1.7-8.2) | Not specified | Multivariable analysis || Meng-Shiuan Hsu et al. (2014) | Poor outcome in persistent SAB | Second TTP/first TTP ratio <1.5 | OR | 0.2 (0.07-0.6) | 0.004 | Higher Pittsburgh scores || S. Choi et al. (2012) | 30-day mortality or secondary foci | Decrease in TTP of FUPBC | Not specified | Not specified | 0.005 | Not specified || E. Minejima et al. (2019) | 30-day mortality | Per day of bacteremia | RR | 1.16 (1.10-1.22) | <0.0001 | Not specified || E. Minejima et al. (2019) | 30-day mortality | 3+ days of bacteremia | aOR | 1.17 (1.06-1.29) | 0.002 | Age, gender, Pitt score, source risk, source control || R. Khatib et al. (2005) | Extended bacteremia (≥3 days) | ≤14 hours | Not specified | Not specified | <0.0005 | Independent predictor in logistic regression || R. Khatib et al.

(2005) | Metastatic infection | ≤14 hours | Not specified | Not specified | <0.0005 | Independent predictor in logistic regression |

## TTP and Relapse/Recurrence

The association between TTP and the relapse or recurrence of bacteremia is not as extensively documented as other outcomes. One study defined relapse in *S. aureus* bacteremia as an episode occurring more than 8 days after the end of a previous episode, but did not directly link it to TTP. Another investigation of persistent SAB noted a higher rate of relapse within 12 weeks among patients with bacteremia lasting ≥7 days compared to those with resolving bacteremia, though a direct TTP association was not specified. In a study of vancomycin-resistant enterococcal bacteremia, recurrent bacteremia within 14 days was a secondary outcome, but no statistically significant difference was found between patients with persistent and non-persistent initial bacteremia. Overall, while persistent bacteremia (which is correlated with shorter TTP) is linked to higher relapse rates, a direct, independent predictive role of initial TTP for relapse or recurrence has not been firmly established across the included literature.

## TTP and Mortality Outcomes

A substantial body of evidence indicates an association between shorter TTP and increased mortality in patients with bloodstream infections. This relationship has been observed for various pathogens and across different mortality timeframes. For Gram-negative bacteremia, a shorter TTP has been identified as an independent predictor of in-hospital or 30-day mortality for infections caused by *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. For instance, studies on *E. coli* bacteremia reported adjusted odds ratios for mortality ranging from 3.80 to 4.89 for patients with TTP below cutoffs of 11 or 7 hours. A large population-based study found that a TTP in the first quartile (≤10 hours) was associated with a significantly increased risk of 30-day mortality across a wide range of both Gram-negative and Gram-positive organisms, with an adjusted odds ratio of 1.43.

For *S. aureus* bacteremia, the findings are more complex. Several studies have confirmed that a shorter TTP (e.g., ≤12h or ≤13.7h) is an independent predictor of increased hospital or 30-day mortality. However, other studies have reported a U-shaped or even an inverse relationship. One large study found that a very long TTP (>48h) was also associated with increased 30-day mortality, alongside a short TTP (≤12h). Another reported a U-shaped curve for the risk of infective endocarditis, a complication with high mortality. A meta-analysis concluded that short TTP was significantly associated with mortality (OR 2.98), but some individual studies found no significant association between TTP and mortality, particularly in cohorts of critically ill patients with septic shock or in specific pathogens like *Streptococcus pyogenes*.

Study	Mortality Timeframe	TTP Exposure Definition	Effect Estimate (95% CI)	Adjustment Variables
H. Palmer et al. (2013)	In-hospital	Per hour shorter	OR 1.10 (1.00-1.21)	Severity of illness, ESBL-producing GNB, ICU admission
Yufang Chen et al. (2020)	In-hospital	≤11 h	OR 3.80 (1.04-12.90)	ICU admission, Pittsburgh score, Charlson Comorbidity Index

Study	Mortality Timeframe	TTP Exposure Definition	Effect Estimate (95% CI)	Adjustment Variables
A. Marra et al. (2006)	In-hospital	≤12 h	OR 6.9 (1.07-44.66)	Charlson score, MRSA infection
Matthias Willmann et al. (2013)	In-hospital	≤ 18 h	HR 3.83 (Not specified)	SAPS II score, cardiac disease, appropriate treatment
M. Rolo et al. (2022)	30-day	≤16 h	aOR 2.27 (2.12-4.25)	Neutropenia, septic shock, respiratory source, nosocomial acquisition, MDR/XDR phenotype
Chih-Ping Chen et al. (2023)	30-day	Per hour increase	HR 0.82 (Not specified)	Pittsburg bacteremia score
G. Peralta et al. (2007)	In-hospital	Short TTP (lowest quartile)	HR 3.13 (1.28-7.64)	Haematological illness, Charlson score, non-urinary source, severe sepsis/shock
J. Martinez et al. (2006)	Fatal outcome (in-hospital)	≤7 h	OR 4.37 (1.38-13.8)	Immunocompromising condition, peritonitis, pneumonia
Kevin B. Laupland et al. (2024)	30-day	≤10 h (first quartile)	OR 1.43 (1.35-1.50)	Age, sex, onset, comorbidity, focus of infection
Joseph Kim et al. (2010)	30-day	>48 h and ≤12 h	Not specified	Age, nosocomial acquisition, MRSA, focus of infection, liver disease
Shi-ning Bo et al. (2011)	In-hospital	≤7 h	OR 4.886 (2.572-9.283)	Neutropenia, comedication of steroids/immunosuppressants
S. Siméon et al. (2019)	30-day	≤13.7 h	Not specified	Age, McCabe score, methicillin resistance, stroke, pneumonia, CRP
C. Cillóniz et al. (2017)	In-hospital & 30-day	<9.2 h	OR 5.35 (1.55-18.53) for in-hospital; OR 2.47 (0.85-7.21) for 30-day	Multiple potential confounders
C. Liao et al. (2009)	30-day	<7 h	OR 2.46 (1.20-5.05)	Pittsburg bacteraemia score, active malignancy

Study	Mortality Timeframe	TTP Exposure Definition	Effect Estimate (95% CI)	Adjustment Variables
Yong-Ye Yang et al. (2024)	30-day	Per hour increase	OR 0.79 (Not specified)	Pitt bacteraemia score, source control implementation
A. Bläckberg et al. (2023)	30-day	$\leq 7.9$ h	OR 4.4 (1.6–12.2)	Age
A. Bläckberg et al. (2022)	30-day	Shorter TTP (continuous)	OR 3.7 (1.2–11.3)	Age, Charlson Comorbidity Index, focus of infection
Weiwei Hou et al. (2023)	In-hospital	$<9.4$ h	OR 2.7 (1.0–7.4)	Age, creatinine, WBC, CRP (TTP not independent)
Hiroyasu Takahashi et al. (2022)	14-day	$\leq 11$ h	HR 19.6 (Not specified)	Pitt bacteremia score

## Subgroup Analyses: Organism Type and Source Control

Subgroup analyses consistently highlight the importance of organism type in modifying the predictive value of TTP. The association between shorter TTP and adverse outcomes appears robust for *S. aureus* and common Gram-negative Enterobacteriales such as *E. coli* and *K. pneumoniae*. A large population-based study provided specific adjusted odds ratios for 30-day mortality associated with a first-quartile TTP ( $\leq 10$  hours) for multiple organisms, including *S. aureus* (aOR 1.56), *E. coli* (aOR 1.37), and *Pseudomonas* species (aOR 2.23). Another study found differences in TTP between methicillin-susceptible and methicillin-resistant *S. aureus* (MRSA), and a study on sequential TTP noted that the correlation between initial and subsequent TTP varied by MRSA versus MSSA status. For Enterococcus species, one study found that while shorter TTP was associated with higher mortality rates in univariate analysis for *E. faecalis* and VSEfm, it was not an independent risk factor in survival analysis.

The influence of source control on the TTP-outcome relationship is less clearly defined, though it is recognized as a major prognostic factor in its own right. For *P. aeruginosa* bacteraemia, one study found that in catheter-related infections, a TTP  $<14$ h exacerbated mortality among patients where the catheter was not removed within 48h (OR 2.9). This suggests that a short TTP may identify a high-risk group where timely source control is particularly critical. In *S. aureus* bacteraemia, delayed source control was associated with prolonged bacteraemia, which in turn is linked with shorter TTPs and worse outcomes. Another study identified that a short TTP ( $\leq 12$ h) was more common in patients with a central venous catheter source.

Study	Subgroup Examined	Sample Size	Effect Estimate (95% CI)		Interaction p-value
			CI)	Interaction p-value	
Kevin B. Laupland et al. (2024)	<i>S. aureus</i>	Not specified	aOR 1.56 (1.41-1.73)	Not reported	
Kevin B. Laupland et al. (2024)	<i>S. pneumoniae</i>	Not specified	aOR 1.91 (1.49-2.46)	Not reported	
Kevin B. Laupland et al. (2024)	<i>Pseudomonas</i> species	Not specified	aOR 2.23 (1.85-2.69)	Not reported	

Study	Subgroup Examined	Sample Size	Effect Estimate (95% CI)	Interaction p-value
Kevin B. Laupland et al. (2024)	<i>E. coli</i>	Not specified	aOR 1.37 (1.23-1.53)	Not reported
Kevin B. Laupland et al. (2024)	Enterobacterales	Not specified	aOR 1.38 (1.16-1.63)	Not reported
Daniel N Marco et al. (2025)	Catheter-related <i>P. aeruginosa</i> BSI, catheter not removed	Not specified	OR 2.9 (1.04-8)	Not reported
Daniel N Marco et al. (2025)	Non-catheter-related <i>P. aeruginosa</i> BSI, inactive empiric therapy	Not specified	OR 3.8 (1.5-10)	Not reported
H. Bae et al. (2021)	<i>E. coli</i> bacteremia	328	Not specified	Not reported
H. Bae et al. (2021)	<i>Klebsiella</i> bacteremia	188	Not specified	Not reported
Katharina Michelson et al. (2021)	<i>E. faecalis</i>	Not specified	HR 2.73	p=0.17
Katharina Michelson et al. (2021)	VSEfm	Not specified	HR 1.63	p=0.15
Katharina Michelson et al. (2021)	VREFm	Not specified	HR 1.24	p=0.63
Joseph Kim et al. (2010)	MSSA vs MRSA	684	Shorter TTP for MSSA (p=0.015)	Not reported
I. Comba et al. (2024)	MRSA vs MSSA	186	Shorter STTP & lower TTP ratio for MRSA (p<0.001)	Not reported

## Analytical Approaches and Model Performance

The predominant analytical methods used to assess TTP as a prognostic factor were multivariable logistic regression and Cox proportional hazards models. These models typically included TTP (either as a continuous or dichotomized variable) along with a range of potential confounders. Key covariates frequently adjusted for included severity of illness scores (e.g., Pitt bacteremia score, APACHE II, SOFA score), patient comorbidities (e.g., Charlson Comorbidity Index), demographic factors like age, and infection characteristics such as source, pathogen type, and methicillin resistance.

A few studies reported metrics of predictive accuracy. For predicting septic shock in *E. coli* bacteremia, one study found an Area Under the Curve (AUC) of 0.71, with a sensitivity of 73.1% and specificity of 65.2% for a TTP cutoff of 11 hours. For infective endocarditis in SAB, a negative predictive value of 96% was reported for a TTP >13 hours. Some studies developed and validated formal prediction models incorporating TTP. One such study developed a scoring

model for mortality in cancer patients with *E. coli* bacteremia that included TTP ≤8h as a risk factor, demonstrating excellent discrimination (AUC 0.858 and 0.835 in development and validation cohorts, respectively). Another study developed a prognostic score for *Enterobacteriaceae* BSI combining TTP ≤11h and a Pitt score ≥4 points, which stratified patients into different 14-day survival categories.

Study	Primary Analysis Method	Key Covariates in Multivariable Models	AUC or Other Discrimination Metrics	Model Validation Approach
Qing Zhang et al. (2020)	Logistic regression	Fever ≥ 39°C, inappropriate antibiotic therapy, metastasis, ARDS, blood transfusion, TTP ≤ 8h	AUC: 0.858 (dev), 0.835 (val)	Internal validation group
Martin Strömdahl et al. (2024)	Multivariate logistic regression	TTP <13 hours	NPV of TTP >13h: 96%	Not specified
M. Rolo et al. (2022)	Multivariate logistic regression	Neutropenia, septic shock, respiratory source, nosocomial acquisition, MDR/XDR phenotype	AUC: 0.62	Not specified
Yufang Chen et al. (2020a)	Multivariate logistic regression	ICU admission, neutropenia, Pittsburgh score, Charlson Index	AUC for septic shock: 0.71	Not specified
C. Cillóniz et al. (2017)	Logistic and linear regression	Age, PSI class, severe CAP, septic shock, renal failure, complications	AUC for in-hospital mortality: 0.91; for 30-day mortality: 0.88	Internal validation with bootstrapping (implied)
Katharina Michelson et al. (2021)	Survival analysis	Not specified	AUC for cardiovascular source: 0.75	Not specified
H. Le et al. (2014)	Logistic regression	Not specified	AUC for severe sepsis/shock: 0.792; for death: 0.708	Not specified
Chih-Ping Chen et al. (2023)	Cox proportional hazards	Pittsburg bacteremia score	AUC for mortality: 0.75	Not specified
Yong-Ye Yang et al. (2024)	Logistic regression	Pitt bacteraemia score, source control	AUC for 30-day mortality: 0.73	Not specified
Weiwei Hou et al. (2023)	Multivariate logistic regression	Age, creatinine, WBC, CRP	AUC for in-hospital mortality: 0.61	Not specified
Hiroyasu Takahashi et al. (2022)	Cox proportional hazards	Pitt bacteremia score	AUC for 14-day mortality: 0.841	Not specified

## Evidence Synthesis and Meta-Analytic Considerations

The overall body of evidence suggests that a shorter TTP is generally associated with a higher risk of adverse outcomes, including persistent bacteremia and mortality, in patients with bloodstream infections. This association holds across multiple bacterial species, particularly *S. aureus* and various Gram-negative bacilli. A meta-analysis confirmed this trend, reporting a pooled odds ratio of 2.98 for mortality in patients with short TTP. The direction of this association aligns with the microbiological principle that a higher initial bacterial load in the bloodstream would lead to faster growth detection *in vitro* and reflects a more severe *in vivo* infection.

However, there is significant clinical and statistical heterogeneity across the studies. The definition of "short" TTP varies widely, with cutoffs ranging from <7 hours to ≤18 hours depending on the pathogen and study population. This lack of a standardized cutoff complicates direct comparisons and meta-analytic efforts. Furthermore, some studies report conflicting or non-linear relationships. For *S. aureus* bacteremia, at least two studies found that a very prolonged TTP (>48 hours or >27 hours) was also associated with increased mortality, suggesting a U-shaped risk curve. Additionally, some large prospective studies and analyses in critically ill populations found no significant association between TTP and mortality, challenging its universal applicability as a prognostic marker.

This heterogeneity indicates that the relationship between TTP and outcome is likely modified by several factors, including the specific pathogen, infection source, severity of illness, and host immune status. A Bayesian hierarchical meta-regression approach would be well-suited to explore these sources of heterogeneity. By incorporating study-level covariates (e.g., proportion of patients with septic shock, specific organism, TTP cutoff used), such a model could estimate the influence of these factors and provide more nuanced, context-specific predictions. The existing data supports the general direction and independence of TTP as a prognostic factor, but its magnitude and clinical utility for decision-making likely depend on a combination of these clinical and microbiological variables.

## Limitations and Research Gaps

The current body of evidence on TTP as a prognostic marker has several important limitations. A primary methodological weakness is the predominance of retrospective, single-center study designs, which are susceptible to selection bias, information bias, and limited generalizability. Confounding by indication is a significant concern, as clinicians may have ordered more follow-up cultures or initiated different treatments for patients perceived to be sicker, independent of the TTP value. While many studies used multivariable regression to adjust for confounders, residual confounding likely remains.

Measurement issues also contribute to heterogeneity. There is no standardized TTP cutoff, with values ranging widely across studies, which hinders meta-analysis and the development of universal clinical guidelines. Furthermore, factors that can influence TTP independent of bacterial load—such as blood volume drawn, prior antibiotic exposure, and time delay between blood draw and incubator loading—were not consistently controlled for or reported.

Clinically, several gaps remain. The interaction between TTP and source control is understudied; while delayed source control worsens outcomes, it is unclear if TTP can modify this risk or help identify patients who would benefit most from aggressive early intervention. There is limited data for certain pathogens, including anaerobes and less common Gram-positives and Gram-negatives. Most studies have focused on mortality or persistence, with less attention paid to relapse/recurrence. Finally, very few studies have prospectively evaluated prediction models incorporating TTP or validated them in external cohorts, limiting their clinical applicability. The planned Bayesian meta-regression will be valuable for quantifying the impact of these sources of heterogeneity, but prospective, multicenter studies with standardized protocols for TTP measurement and consistent outcome definitions are needed to

definitively establish the role of TTP in clinical decision-making.

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