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Original article

Association of time to positivity with disease severity in bloodstream infections—a population-based cohort study

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ABSTRACT

Objectives: Short time to positivity (TTP) has been proposed as a prognostic indicator in bloodstream infection (BSI) but results have been conflicting. The aim of this study was to explore the association between TTP and disease severity, using non-linear models.

Methods: This population-based retrospective study included all blood cultures in southern Sweden from 2021 to 2023. Using healthcare databases, BSI episodes were linked to information regarding prespecified disease severity markers at the time of culture (laboratory values and vital signs) as well as patient outcomes (intensive care admission and all-cause mortality at 30 days). The associations between TTP vs. disease severity were explored using non-linear regression models.

Results: The study included 12 585 unique BSI episodes, with a median (interquartile range) TTP of 12.1 (9.7–17.7) hours, and an overall 30-day mortality rate of 14.4%. Non-linear regression models indicated a higher mortality rate with shorter TTP, with a mortality rate of 20% at a TTP of 6 hours, and 30% at a TTP of 3 hours. In Enterobacterales, beta-haemolytic streptococci, *Streptococcus pneumoniae*, *Staphylococcus aureus*, as well as in polymicrobial findings, regression models indicated that shorter TTP was associated with a risk of >30% of intensive care admission or mortality, as compared with an overall rate of 18.2%. Shorter TTP was also associated with laboratory values and vital signs. For lactate, with an overall median value of 1.9 mmol/L, the model indicated a value of 3 mmol/L at a TTP of 8 hours, and at 4 mmol/L at a TTP of 4 hours. All associations with disease severity markers and outcomes were non-linear.

Discussion: TTP is an indicator of disease severity and prognosis in BSIs. The exponential association provides a biologically plausible explanation for previously conflicting results. Future studies should focus on determining the clinical utility of TTP. **Oskar Ljungquist, Clin Microbiol Infect 2025;▪:1**

Introduction

Bloodstream infections (BSIs) have a case-fatality rate of 10–15% and have seen an increase in incidence in the last decades, especially in those aged 80 years and over [1–4]. The mainstay of BSI diagnostics is blood culture in fluid culture medium in bottles [5]. Time to positivity (TTP), the time elapsed between blood culture incubation and detection of pathogen growth, is an indirect measure of the original inoculum in blood [6]. Several studies have evaluated whether shorter TTP is associated with poor patient outcomes [7–16]. However, results have been conflicting, as demonstrated by two recent studies having reached opposite conclusions [10,16]. No conclusive explanation for the conflicting results has been presented [6,10,16]. The clinical utility of TTP has been debated, and as of today, TTP is primarily recommended to identify catheter-related BSIs [6,17].

We hypothesized that statistical methodology has contributed to previously conflicting results. Bacterial growth is an exponential

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phenomenon, where bacteria may double every 20 minutes in optimal conditions [18]. In this hypothetical scenario, 1- and 2-hour differences in TTP would represent an 8- and 64-fold difference in the original inoculum. Consequentially, if the bacterial load in blood is related to disease severity, the association between TTP and outcome is likely to be exponential. However, no previous study has modelled the association this way [9,10,12–16,19–22]. In addition, previous studies use 30-day mortality as the only outcome, which could be susceptible to confounding or factors occurring during follow-up.

We aimed to estimate the association between TTP and disease severity, using non-linear models and multiple outcomes, including 30-day all-cause mortality and 13 prespecified disease severity markers at the time of blood sampling. The overall purpose was to determine whether TTP is an indicator of disease severity and prognosis in BSI.

Methods

Study design and setting

This population-based retrospective study analysed blood cultures obtained in the Skåne region in southern Sweden, a region with 1.4 million inhabitants, served by ten hospitals. Case-finding was achieved by querying the microbiology database covering the entire region, for all blood culture bottles obtained from January 1, 2021, to December 31, 2023. Microbiology data were matched with regional healthcare databases, using Swedish unique personal identification numbers. Because 30-day mortality was the primary outcome, we employed a 30-day deduplication period to separate multiple BSI episodes in the same individual. The study was approved by the Swedish Ethical Review Authority (2023-02169 and 2024-05828-02).

According to local routines, BD Bactec Plus aerobic medium and BD Bactec Lytic anaerobic medium blood culture bottles are incubated in blood culturing cabinets (BACTEC FX, Becton Dickinson, Franklin Lakes, USA), for a standard incubation time of 5 days. The general recommendation is to obtain two aerobic + two anaerobic bottles upon suspicion of BSI. The five largest hospitals in the region have on-site cabinets, whereas samples from the other five hospitals are transported to the nearest cabinet. After detection, positive bottles are transported to the Department of Clinical Microbiology in Lund, for species identification and susceptibility testing.

Microbiology data

A blood culture set was defined as one aerobic plus one anaerobic bottle. If at least one bottle of the set was positive, the result was labelled positive. Skin commensals were considered contaminants if they were positive in only one blood culture set. The date of the first non-contaminant finding was considered the baseline date. Any results from repeated cultures within 1–30 days from the baseline date were discarded. The finding was labelled polymicrobial if several different relevant findings were identified on the baseline date. In the case of multiple bottles with identical findings on the baseline date, the bottle with the shortest non-missing TTP was prioritized, so that there was only one TTP per BSI episode. Pathogens were further classified into major categories, see Supplementary Appendix.

Clinical data

Diagnostic codes (using international classification of diseases, 10th edition, ICD-10) from the current hospitalisation and the year preceding the baseline date were retrieved, from primary and hospital care. Charlson comorbidity index was determined according to a methodology adapted for Swedish healthcare registries [23]. Concurrent antibiotics were defined as the prescription or administration of an antimicrobial for systemic use (Anatomical Therapeutical Classification [ATC] group J01) during 1–14 days preceding the baseline date. Immunosuppression was defined as the prescription or administration of an antineoplastic agent (ATC group L01) or an immunosuppressant (ATC group L04) within 2 months preceding the baseline date. A nosocomial culture was defined as a culture taken ≥48 hours after hospitalization. We also recorded whether the patient had been hospitalized in the preceding 3 months.

Outcomes

The primary outcome was 30-day all-cause mortality, using complete case analysis if vital status was missing. We also recorded a composite outcome of intensive care unit (ICU) admission or mortality, whichever came first, within 30 days. Thirteen disease severity markers at the time of culture were defined a priori, including laboratory values as well as vital signs, which had been collected according to the National Early Warning Scale 2, as per local protocol [24]. Disease severity markers within ±24 hours from the time of culture were considered baseline values and, if several, the one closest in time to culture was prioritized.

Analysis

Cultures from hospitals without on-site cabinets were excluded, because of the risk of bias associated with transportation time. Restricted cubic splines of TTP were used to estimate the non-linear association between TTP and outcomes using logistic regression models, with likelihood ratio tests to test the overall association. To estimate the influence of confounders, the association of TTP vs. mortality was adjusted for all baseline characteristics. To display the timing of the composite outcome, we used a cumulative event plot. We also performed a stratified analysis within pathogen categories of TTP vs. the composite outcome. The association of TTP vs. disease severity markers was estimated using mixed effects models with TTP, modelled non-linearly as a restricted cubic spline, as a fixed effect, and patient as a random effect. The overall association between TTP and disease severity markers was tested with an analysis of variance vs. the null model, and non-linearity was tested with analysis of variance vs. a linear model.

We performed the following sensitivity analyses:

(a) TTP vs. mortality where one random BSI episode was chosen for each individual, to overcome any bias related to repeated episodes; (b) TTP vs. mortality in patients having received antibiotics before culture; (c) TTP vs. mortality in hospitals without on-site cabinets; (d) TTP vs. mortality in paediatric patients; and (e) TTP vs. composite outcome, using a stricter definition, where both ICU and mortality had to be non-missing for a valid result.

Results

From 2021 to 2023, a total of 260 012 blood culture sets were collected in the Skåne region. The final sample consisted of 12 585 episodes obtained in hospitals with on-site cabinets, and for which TTP was available (Fig. 1). The 12 585 episodes occurred in 11 227 unique individuals, of whom 10 149 (90.4%) had 1, 880 (7.8%) 2, and 198 (1.8%) had 3 or more separate BSI episodes during the study period (Fig. 1). Baseline characteristics of the population are shown in Table 1.

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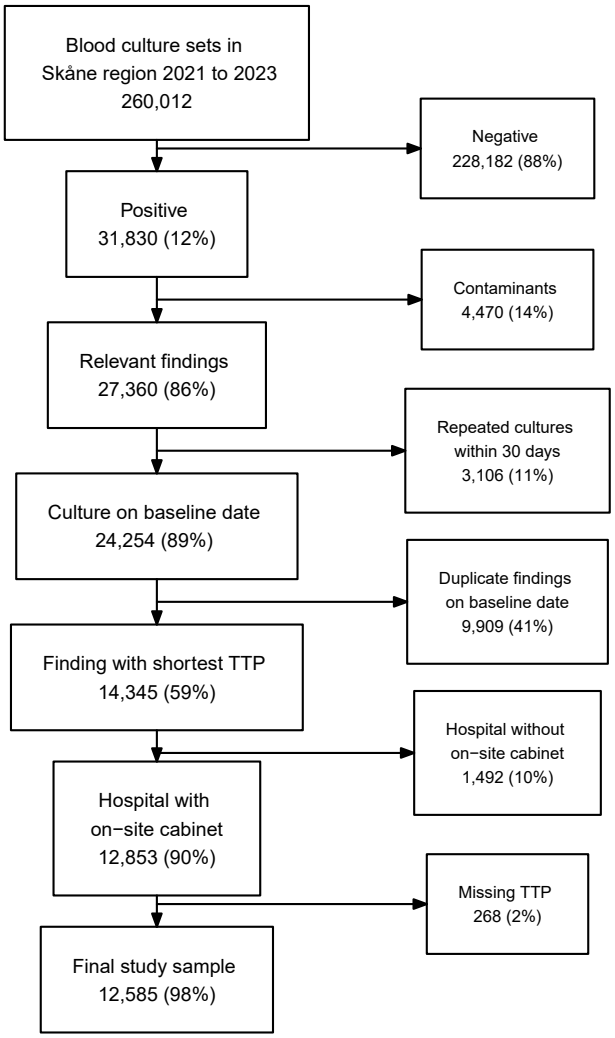

Fig. 1. Flowchart describing the process to identify and deduplicate BSI episodes from all blood cultures in the Skåne region from 2021 to 2023. BSI, bloodstream infection; TTP, time to positivity.

The overall median TTP (interquartile range) was 12.1 (9.7–17.7) hours. Vital status could be established in 12 424 (99%) of cases. The 30-day all-cause mortality rate was 1787/12 424 (14.4%). Shorter TTP was associated with mortality and the association was clearly non-linear, with a pivoting point at approximately 10 hours (see Fig. 2.) The non-linear model had a significantly better fit than linear or categorical models used in previous studies ($p < 0.001$, see Supplementary Appendix for details). The association between TTP and mortality remained highly significant after adjusting for all factors in Table 1, as seen in the marginal effect plot in Supplementary Appendix. In total, 2289 patients (18.2%) fulfilled the composite outcome of ICU admission or mortality, with 1070 (47%) events occurring in the first 3 days. The timing of TTP vs. the composite outcome is shown in the cumulative risk plot in Fig. 3.

The most common pathogen categories were Enterobacterales, *Staphylococcus aureus*, and polymicrobial findings, occurring in 38%, 13%, and 12% of BSI episodes, respectively. For these three categories, as well as for beta-haemolytic streptococci and *Streptococcus pneumoniae*, there was a non-linear association between TTP and the composite outcome, with a similar non-linear pattern. For the categories alpha-haemolytic streptococci, *Staphylococcus* species (CoNS not considered contaminants), *Enterococcus* species, and 'Other', there was no association between TTP and outcome (see Fig. 4).

Table 1
Baseline characteristics for BSI episodes.

Characteristic	$N = 12\,585$
Age (y)	74.0 (62.0–82.0)
Male sex	7141 (57%)
Comorbidities	
Cardiac disease	5298 (42%)
Pulmonary disease	2391 (19%)
Hypertension	5821 (46%)
Anaemia	2311 (18%)
Genitourinary disease	3976 (32%)
Dialysis	231 (1.8%)
Malignancy	3634 (29%)
Musculoskeletal disease	4152 (33%)
Neurological disease	3017 (24%)
Psychiatric disease	3249 (26%)
Immunodeficiency	701 (5.6%)
Peripheral vascular disease	1864 (15%)
Diabetes mellitus	3554 (28%)
Skin disease	2950 (23%)
Hepatic disease	633 (5.0%)
Charlson comorbidity index	
0 points	3497 (28%)
1–2 points	4181 (33%)
3–4 points	2338 (19%)
5+ points	2569 (20%)
Antibiotics before	2004 (16%)
Immunosuppression	990 (7.9%)
Nosocomial infection	1964 (16%)
Recent hospitalization	4072 (32%)

All values are *n* (percent of column total), except where indicated. BSI, bloodstream infection; IQR, interquartile range.

The different disease severity markers had been obtained within ±24 hours from baseline to various degrees, ranging from procalcitonin, obtained in 11% of episodes, to C-reactive protein, obtained in 91% of episodes. There was a non-linear association between shorter TTP and higher disease severity across all 13 markers, again with a suggested pivoting point at 10–12 hours (Fig. 5). The association was statistically significant for all disease severity markers.

Results from sensitivity analyses revealed similar results for TTP vs. mortality when deduplicating any multiple episodes per individual. The association of TTP vs. mortality was weaker in patients having received antibiotics before culture, but these were a select group of patients with a high degree of nosocomial infections (Supplementary Appendix). There was no association between TTP and mortality in hospitals without on-site cabinets. In paediatric patients, TTP vs. mortality results were similar to those obtained in adults. The different definitions of the composite outcome did not affect results (Supplementary Appendix).

Discussion

This study indicates that TTP is a valid prognostic indicator in BSI. Shorter TTP was associated with disease severity at the time of culturing as well as with 30-d outcomes in BSIs, consolidating results in previous studies. The hypothesis of a non-linear relationship was verified and congruent across multiple markers of disease severity and outcomes for several major BSI pathogens.

This is the first study to model the association between TTP and mortality non-linearly and disease severity increased exponentially with shorter TTP. This is important for several reasons. First, this model has biological plausibility given the exponential growth of bacteria. Second, this non-linearity provides an explanation for

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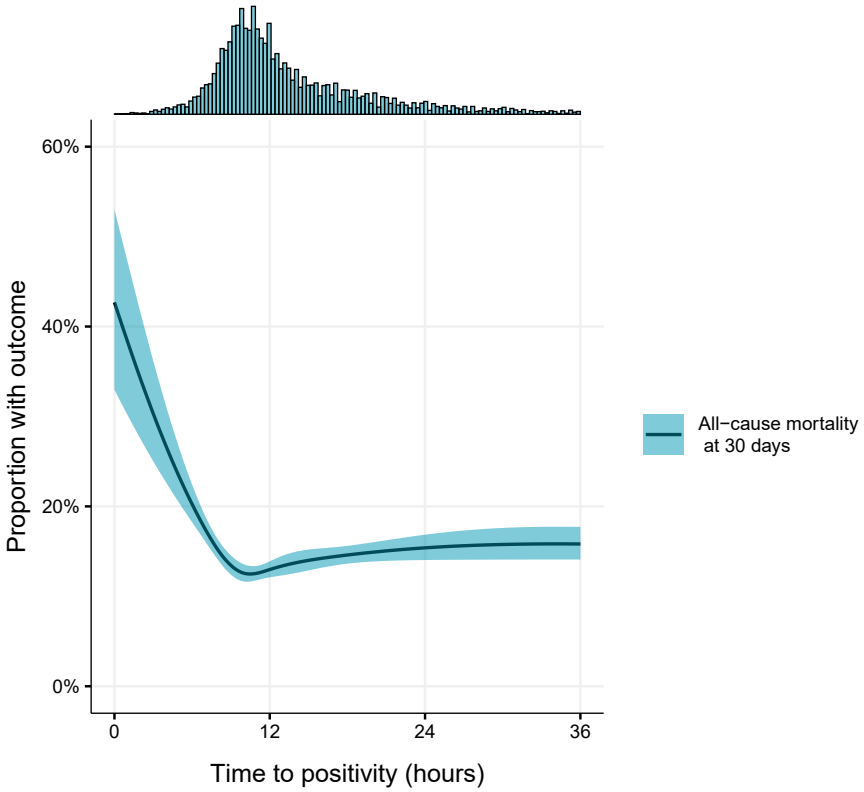

Fig. 2. Association between time to positivity (TTP) and 30-day all-cause mortality, modelled using logistic regression with restricted cubic spline models, with 95% CI (shaded area). The marginal histogram (top) shows the distribution of TTP.

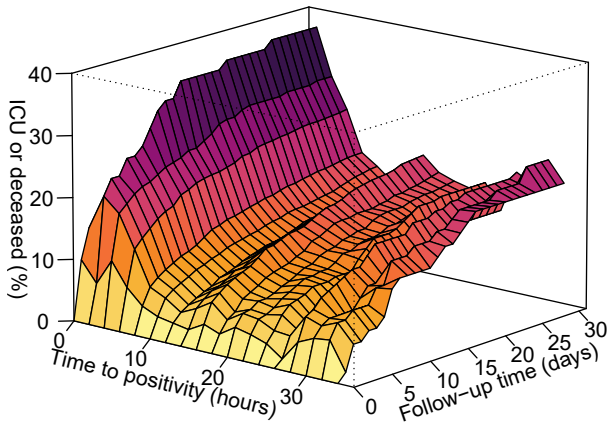

Fig. 3. Cumulative incidence plot describing the timing of outcome by time to positivity. ICU or deceased = the cumulative proportion of patients with admission to an intensive care unit or death within 30 days, by time to positivity and follow-up time. ICU, intensive care unit.

conflicting results in previous studies, using linear or categorized models [9,10,12,13,15,16,19,20,25]. To further emphasize this, we provide a linear and a categorized model in Supplementary Appendix replicating the conflicting results from two recent studies using our dataset [10,16]. The non-linear model had a substantially better fit than the linear and categorized models, indicating a better representation of the association. Third, the association seemed to reach a plateau with TTP longer than 10–12 hours, which could theoretically motivate a categorization/dichotomization at around a 10-hour cutoff. Nevertheless, as seen in Supplementary Appendix, a TTP cutoff at < 8 or <7 hours was associated with a much worse outcome than <10 hours, indicating that categorization of TTP results in a significant loss of precision.

TTP varied significantly between different species. Generally, fast-growing pathogens, such as Enterobacterales and *Streptococcus pneumoniae* had short TTPs, in line with previous studies [10,13,16]. When stratified, we found that TTP was an indicator of poor outcome in the most common pathogens, both Gram-negative and Gram-positive, and also in pathogens normally found in different foci (e.g. *S. pneumoniae* in the lungs, Enterobacterales in the urinary tract, and *S. aureus* in soft-tissue infections), suggesting that short TTP is an indicator of severity across different clinical phenotypes. However, as in previous studies, the association with poor outcomes was not seen in pathogens with lower virulence, such as alpha-haemolytic streptococci or coagulase-negative staphylococci. For *Enterococcus* species, the graph suggested an inverse relationship, with shorter TTP being associated with lower mortality, which has also been described before [10]. Further analyses of species-specific characteristics regarding TTP and its association with disease severity are desirable but were beyond the scope of this article.

This study included multiple disease severity markers at the time of culturing. Previous studies have focused on outcome, primarily all-cause mortality within 30 days [9,12–14,16,20,21]. We considered it mechanistically relevant to study disease severity at the time of culture, as BSI is an acute event and other factors may influence outcomes within 30 days. The baseline values unanimously suggested that shorter TTP was associated with disease severity at that point, again in an exponential way. The congruent association across multiple disease severity markers strengthens the hypothesis that TTP—as a proxy for pathogen concentration in blood—may have a causative effect on disease severity in BSI. We also describe a strong association with ICU admission or mortality

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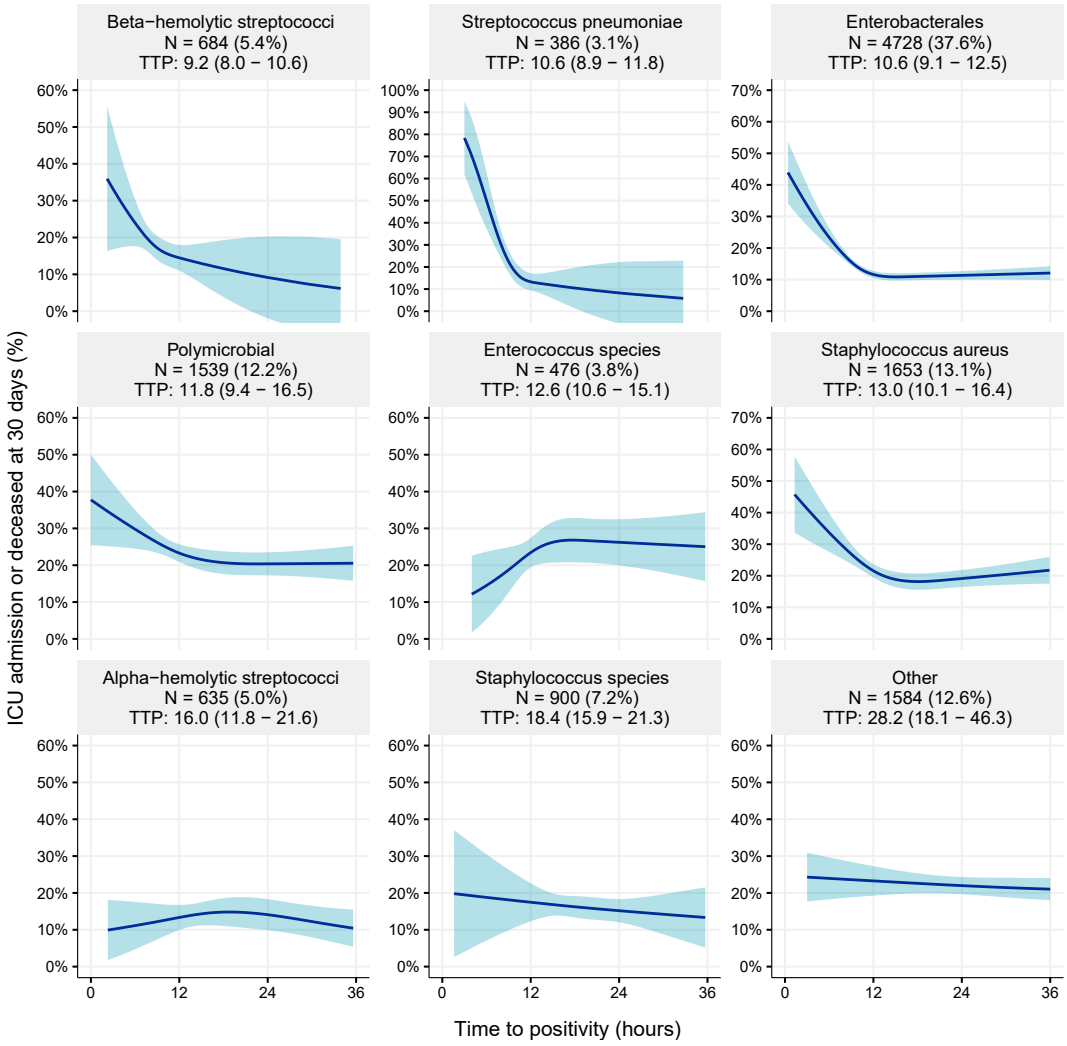

Fig. 4. Association of time to positivity vs. 30-day ICU admission or all-cause mortality by pathogen category, the pathogens are sorted from top left by increasing median TTP. *N* = number of BSI episodes with finding within that pathogen category and percentage of all (12 585) BSI episodes. TTP = time to positivity, presented as median (IQR). The line represents a logistic regression estimate using restricted cubic splines, with a 95% CI (shading). BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range.

within 30 days, which was consistent after adjustment for age, sex, comorbidities, previous antibiotics, and nosocomial infection.

Methodological strengths include a population-based large study sample, where the linkage to clinical databases provided detailed information on underlying conditions and disease severity. Weaknesses are related to the study's retrospective nature, with various degrees of missing data in disease severity markers. These were not missing at random; some disease markers are obtained primarily in patients with high disease severity, leading to a selection of patients, affecting representativity. This could also have led to bias, as the associations may be weaker in patients with less severe disease, which were not included. Furthermore, the missing data in disease severity markers made a multivariable analysis of the added predictive value of TTP vs. regular biomarkers difficult. Our definition of contaminants, although often employed, is imprecise and most likely led to incorrect inclusion of some cases of contamination. The study period included the latter part of the COVID-19 pandemic, which may have affected results in terms of representativity. Differences in blood volumes added to bottles may have affected our results, as this data was unavailable. Our finding that prolonged transportation time before incubation invalidates TTP measurements affects generalizability. Although this has been described before, our results indicate that TTP may not be a valid marker if the transportation time between venepuncture and incubation is prolonged [26].

Even if this study adds information regarding TTP as an indicator of disease severity in BSIs, its clinical utility is yet to be established. Future studies are needed to determine if TTP has any added clinical value as a biomarker. In our opinion, such studies should include commonly used biomarkers and model TTP non-linearly to fully make use of the information that TTP provides. If TTP is shown to have added value in predicting deterioration, real-time reporting of TTP could assist clinical decision-making. Our results could also motivate trials aiming to improve BSI management, e.g. by administering additional antimicrobial treatment, or by employing stricter monitoring protocols, in patients with shorter TTP.

To conclude, this study indicates that TTP is a valid prognostic indicator in BSIs and provides a potential and biologically plausible explanation for previously conflicting results. However, the added value of TTP needs to be determined and future studies should focus on the clinical utility of TTP in BSIs.

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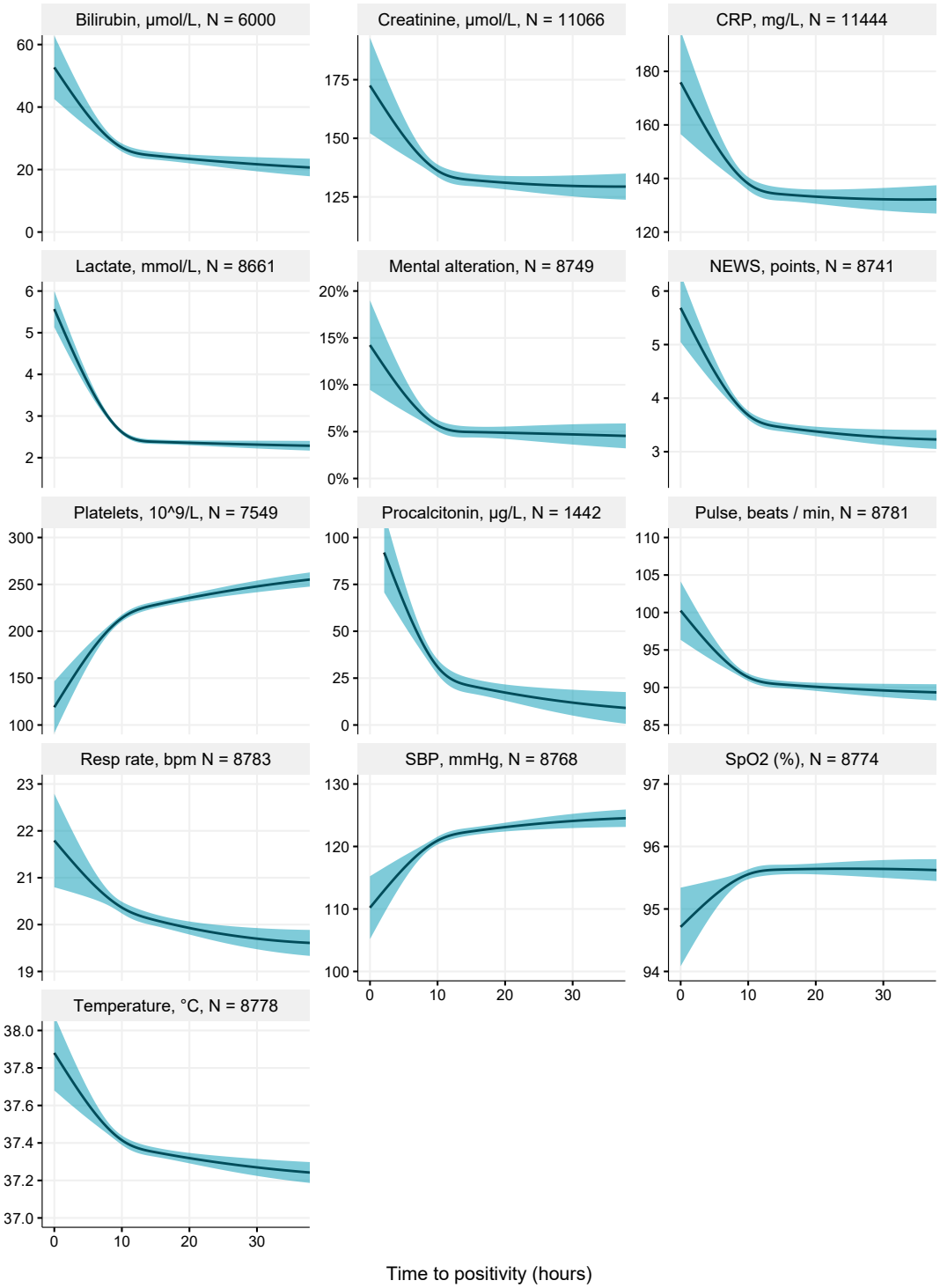

Fig. 5. Association between time to positivity and baseline disease severity markers. The associations are fitted using restricted cubic splines, with a shaded area representing a 95% CI. CRP, C-reactive protein; NEWS, National Early Warning Score; bpm, breaths per minute; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation.

Author contributions

G.T. and O.L. were responsible for conceiving the study. O. L. was responsible for performing project management and data retrieval. K.O. and T.S. were responsible for providing data analysis, retrieving microbiology data, and assisting the classification of pathogens. G.T. was responsible for performing data management, software development, and statistical analysis, with the assistance of J.T. O.L. was responsible for writing the first draft, and J.T., K.O., T.S., and G.T. were responsible for revising the first draft. All authors had full access to the data and approved the decision to submit the manuscript. O.L. and G.T. were responsible for accessing and verifying the data.

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Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

Financial report

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Data availability

The underlying dataset cannot be shared publicly because of privacy concerns related to the risk of indirect identification. Researchers with requests for data must obtain approval by the Swedish Ethical Review Authority as well as the Data Protection Officer at Region Skåne.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.05.027.

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