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Original article

Time to positivity in bloodstream infection is not a prognostic marker for mortality: analysis of a prospective multicentre randomized control trial

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ABSTRACT

Objectives: Time to positivity (TTP), calculated automatically in modern blood culture systems, is considered a proxy for microbial load and has been suggested as a potential prognostic marker in bloodstream infections. In this large, multicentre, prospectively collected cohort, our primary analysis aimed to quantify the relationship between the TTP of monomicrobial blood cultures and mortality.
Methods: Data from a multicentre randomized controlled trial (RAPIDO) in bloodstream infection were analysed. Bloodstream infections were classified into 13 groups/subgroups. The relationship between mortality and TTP was assessed by logistic regression, adjusted for site, organism, and clinical variables, and linear regression was applied to examine the association between clinical variables and TTP. Robustness was assessed by sensitivity analysis.
Results: In total 4468 participants were included in the RAPIDO. After exclusions, 3462 were analysed, with the most common organisms being coagulase-negative staphylococci (1072 patients) and *Escherichia coli* (861 patients); 785 patients (22.7%) died within 28 days. We found no relationship between TTP and mortality for any groups except for streptococci (odds ratio (OR) with each hour 0.98, 95%CI 0.96−1.00) and *Candida* (OR 1.03, 95%CI 1.00−1.05). There was large variability between organisms and sites in TTP. Fever (geometric mean ratio (GMR) 0.95, 95%CI 0.92−0.99), age (GMR per 10 years 1.01, 95%CI 1.00−1.02), and neutrophilia were associated with TTP (GMR 1.03, 95%CI 1.02−1.04).
Conclusions: Time to positivity is not associated with mortality, except in the case of *Candida* spp. (longer times associated with worse outcomes) and possibly streptococci (shorter times associated with worse outcomes). There was a large variation between median times across centres, limiting external validity.
Fergus Hamilton, Clin Microbiol Infect 2021;▪:1

Introduction

Modern blood culture systems record detailed timing information about how long blood culture bottles are incubated for. This information, often known as time to positivity (TTP), has been used for a wide variety of clinical indications [1–4]. The most clinically utilized use of TTP data is to identify central-line-associated bloodstream infections (CLABSIs) and to differentiate them from other sources of bloodstream infection (BSI); this diagnostic technique is included in the Infectious Disease Society of America (IDSA) guidance on management of CLABSIs [5–7].

Given that TTP is associated with bacterial load and is easily measured, there is significant clinical and scientific interest in understanding the relationship between TTP and patient outcome. Multiple prior studies have reported on the association between TTP and clinical outcome across multiple bacteria and fungi, with conflicting results [1–4,8–11].

The many reasons cited for these conflicting results include: retrospectively recorded outcome data, heterogeneity of infective organisms, different blood-culture systems across hospitals,

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and—most importantly—a focus only on the time on the blood culture machine, ignoring the crucial information regarding how long the blood culture bottles were left before being placed in the incubating blood culture system.

In this study, we report clinical outcomes associated with time to positivity of blood cultures from a prospectively collected cohort of BSIs from the multicentre RAPIDO trial.

Methods

For brevity, the methods are largely reported in the Supplementary Material, with an overview here.

This study aimed to (a) quantify the association between TTP and clinical outcomes, and (b) identify clinical factors associated with TTP. All participants included were part of a large pragmatic randomized controlled trial (RAPIDO) of direct matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) identification of adult blood cultures that ran across seven National Health Service (NHS) laboratories in the UK, and was recently published in CMI [12].

For this analysis, all participants in RAPIDO who had monomicrobial blood cultures with clinically relevant and/or common pathogens were included (flow chart in Fig. 1, included organisms in Supplementary Material Table S1, excluded ones in Supplementary Material Table S2). Microbial data (identification, timings) and clinical data (demographics, comorbidities, outcome) were extracted from the trial database.

For our primary analysis we estimated the association between 28-day mortality (our primary outcome) and time to positivity using logistic regression as a univariate analysis. Recruiting site and infecting organism were included as fixed effects. For sensitivity analyses, we (a) replicated the analysis using time measure on the machine, rather than total time from taking blood culture, (b) included relevant clinical comorbidities in a multivariable analysis, and (c) limited our analysis to those patients not on appropriate antimicrobial therapy at the time of blood-culture collection. For our secondary analysis we estimated the association between time to positivity and clinical variables with linear regression.

Results

Flow chart and baseline characteristics of included participants

The RAPIDO trial included 4468 participants. Of those, 4104 had monomicrobial cultures in both bottle sets, and 4037 had the same organism in each bottle; 384 cultures were excluded with rare organisms or known contaminants (list in Supplementary Material

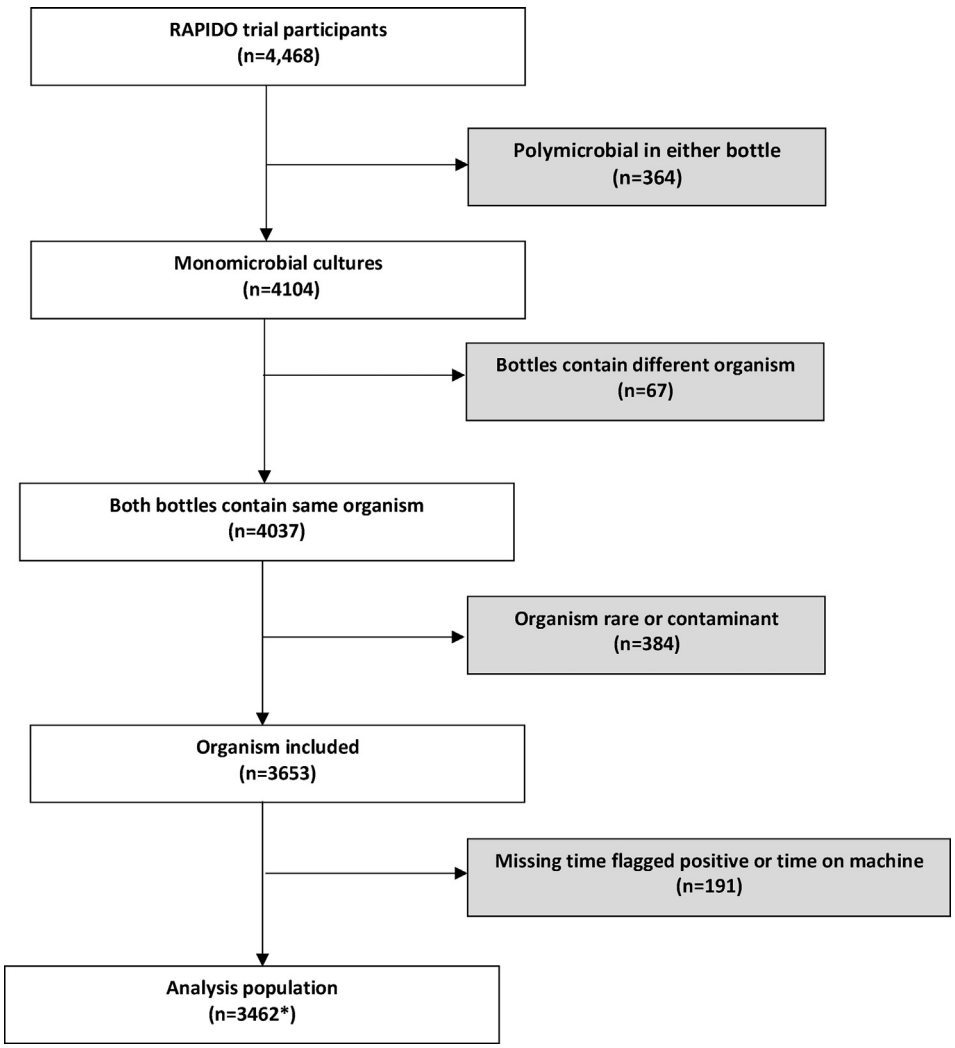

Fig. 1. Flowchart of participants.

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Table 1
Number of deaths, by organism

Organism	Died	
	n	%
Anaerobes	7/30	23.3%
Candida spp.	25/53	47.2%
CoNS	225/1072	21.0%
Escherchia coli	181/861	21.0%
Enterobacter spp.	10/55	18.2%
Enterobacterales (other)	17/81	21.0%
Enterococci	29/123	23.6%
Group A streptococci	12/46	26.1%
Group B streptococci	4/45	8.9%
Group C/G streptococci	12/40	30.0%
Klebsiella spp.	51/207	24.6%
Proteus spp.	11/65	16.9%
Pseudomonas spp.	43/125	34.4%
Staphylococcus aureus	106/365	29.0%
Streptococci (other)	24/162	14.8%
Streptococcus pneumoniae	28/132	21.2%
Overall	**785/3462**	**22.7%**

CoNS, coagulase-negative staphylococci.

Table S1). Finally, 191 participants were excluded with missing time-to-positivity data, leaving a final analysis population of 3462 patients.

Figure 1 describes the flow throughout the study.

Supplementary Material Table S2 describes the baseline clinical characteristics for each subgroup of included bacteria, with Table 1 displaying the mortality for each subgroup, and Table 2 describing the time to positivity of each organism stratified by mortality. Supplementary Material Table S3 describes the time to positivity of each organism broken down by time on machine and time before machine. Importantly, this cohort was quite sick at baseline, with an overall mortality of 22.7%, and with a large number of patients who were frail (median Charlson's Comorbidity Score 3; IQR 2–4) and sick (8.8% ventilated on day of blood culture sampling).

The most common included group were coagulase-negative staphylococci (CoNS) isolates, with 1072 included patients, followed by *Escherichia coli*, with 861 included patients. Mortality was highest with *Candida* spp. (25/53, 47.2%) and *Pseudomonas* spp. (43/125, 34.4%). It was lowest in Group B streptococci (4/45, 8.9%), other streptococci (24/162, 14.8%) and *Proteus* spp. (11/65, 16.9%).

Global relationship between TTP and mortality

Supplementary Material Table S4 describes the baseline demographics between cultures that were positive before and after 24 h. There were limited differences between groups, although fever was slightly more common in the TTP <24 h group, as was organ transplantation and use of immunosuppressive drugs. Supplementary Material Fig. S1 shows the raw mortality across the whole cohort by time to positivity, which shows no clear relationship, although mortality in the very few (47/3462) samples that grew in under 10 h was higher (18/47, 38.3%) than any other time period. Additionally, Fig. 2 shows the total distribution of time to positivity within the whole cohort.

Relationship between time to positivity and mortality in individual organism/group

Table 2 shows the median time to positivity for survivors and non-survivors for each organism/group. Time to positivity also varied greatly between organisms, as would be expected by microbial growth kinetics. The longest time to positivity was in *Candida* spp., with a median total time of 45.3 h (IQR 34.2, 69.9) and anaerobes (total time 36.8 h, IQR 31.7, 54.2). In contrast, the shortest time to positivity was in Group C/G streptococci (total time 15.7 h, IQR 13.7, 21.0).

There was no clear relationship between median time to positivity and mortality. This is visualized in Fig. 3, which displays the time to positivity against mortality for each group.

Logistic regression model

In the logistic regression model, which adjusted for centre and organism alone, there was no relationship between time to positivity and mortality in any organism except *Candida* spp., where there was a slight increase in mortality with increasing time to positivity (OR 1.03, 95%CI 1.00–1.05). This was in the opposite direction to what would be expected, and should be interpreted with

Table 2
Time to positivity by 28-day mortality status and organism

	Survived			Died			Overall		
		TTP (h)			TTP (h)			TTP (h)	
	n	Median	(IQR)	*n*	Median	(IQR)	*n*	Median	(IQR)
Anaerobes ($n = 30$)	23	36.3	(31.7, 51.5)	7	46.1	(30.7, 64.7)	30	36.8	(31.7, 54.2)
Candida spp. ($n = 53$)	28	38.8	(28.4, 52.7)	25	52.5	(36.1, 86.4)	53	45.3	(34.2, 69.9)
CoNS ($n = 1072$)	847	30.2	(23.7, 37.6)	225	30.6	(24.7, 38.4)	1072	30.3	(23.8, 37.9)
Escherichia coli ($n = 861$)	680	17.3	(14.4, 23.8)	181	16.4	(13.6, 22.4)	861	17.1	(14.2, 23.4)
Enterobacter spp. ($n = 55$)	45	19.9	(14.4, 24.4)	10	17.6	(16.0, 19.0)	55	18.8	(14.4, 24.4)
Enterobacterales (other) ($n = 81$)	64	18.0	(14.5, 22.8)	17	19.5	(16.7, 30.4)	81	18.1	(15.0, 24.9)
Enterococci ($n = 123$)	94	20.1	(16.3, 24.8)	29	19.8	(18.0, 25.5)	123	19.9	(17.1, 25.0)
Group A streptococci ($n = 46$)	34	17.7	(14.7, 23.3)	12	16.6	(15.4, 20.8)	46	17.1	(14.8, 22.0)
Group B streptococci ($n = 45$)	41	16.4	(12.8, 22.8)	4	11.1	(10.0, 13.2)	45	16.2	(12.0, 21.5)
Group C/G streptococci ($n = 40$)	28	16.0	(14.1, 20.5)	12	15.0	(11.8, 23.5)	40	15.7	(13.7, 21.0)
Klebsiella spp. ($n = 207$)	156	18.4	(14.0, 26.7)	51	17.9	(14.3, 25.6)	207	18.2	(14.1, 26.2)
Proteus spp. ($n = 65$)	54	20.1	(16.4, 33.1)	11	24.9	(16.2, 81.5)	65	20.3	(16.4, 34.9)
Pseudomonas spp. ($n = 125$)	82	22.2	(19.5, 28.6)	43	24.9	(19.6, 29.5)	125	23.0	(19.6, 28.9)
Staphylococcus aureus ($n = 365$)	259	20.7	(16.4, 28.6)	106	21.0	(16.2, 32.4)	365	20.7	(16.3, 29.7)
Streptococci (other) ($n = 162$)	138	25.9	(20.3, 37.4)	24	27.4	(21.1, 33.9)	162	25.9	(20.4, 36.8)
Streptococcus pneumoniae ($n = 132$)	104	16.4	(14.6, 20.4)	28	18.6	(15.2, 22.7)	132	17.1	(14.6, 20.8)
Overall ($n = 3462$)	**2677**	**22.5**	**(16.5, 32.3)**	**785**	**23.1**	**(16.8, 33.0)**	**3462**	**22.7**	**(16.5, 32.5)**

CoNS, coagulase-negative staphylococci.

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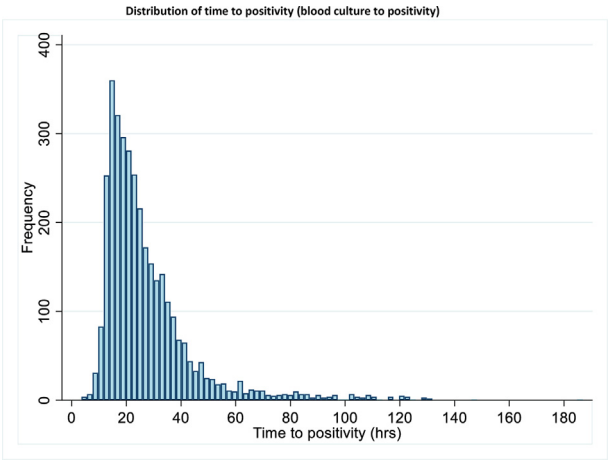

Fig. 2. Distribution of time to positivity (blood culture to positivity).

some caution given the low numbers ($n = 53$). All streptococci except pneumococci were combined for this model due to the low numbers of events in Group B streptococci. There was no evidence of an interaction between time to positivity and organism (p 0.159). These estimates are shown in Fig. 4.

Sensitivity analyses

In the subsequent model we also included relevant clinical features as described in the Methods. Again, this showed no clear evidence of a relationship between time to positivity and mortality in any organism group except *Candida* spp. (Supplementary Material Fig. S2). We also performed a sensitivity analysis adjusting for receipt of appropriate therapy on date of blood culture sampling, and results were consistent with the primary analysis (Supplementary Material Fig. S3). Unsurprisingly, the rate of appropriate therapy differed by organism and by centre, but addition of this to the model made no difference to the primary outcome (Supplementary Material Tables S5 and S6). Lowest rates of appropriate therapy were in *Candida* spp. (51/53 (96.2%) not appropriate), with the highest rates in Group A streptococci (88/132 (71.7%) on appropriate therapy).

As a final sensitivity analysis, we analysed time to positivity calculated from the time on the machine, rather than from time taken. In this model, time to positivity in both *Streptococcus pneumoniae* (OR 0.85, 95%CI 0.74–0.97) and other streptococci (OR 0.96, 95%CI 0.92–0.99) was statistically significant, although in the opposite direction to that in *Candida* spp., suggesting that increasing time to positivity is associated with increased survival in streptococci but worsening mortality in *Candida* spp. (Supplementary Material Fig. S4).

Additional analyses on Candida spp.

Given the inverse relationship between mortality and TTP identified in *Candida* spp., we focused on this pathogen in more detail. Due to low numbers, we report a descriptive analysis only. Thirty-five of these blood cultures were identified as *Candida albicans*, with patient death in 46% (16/35). Ten were identified as

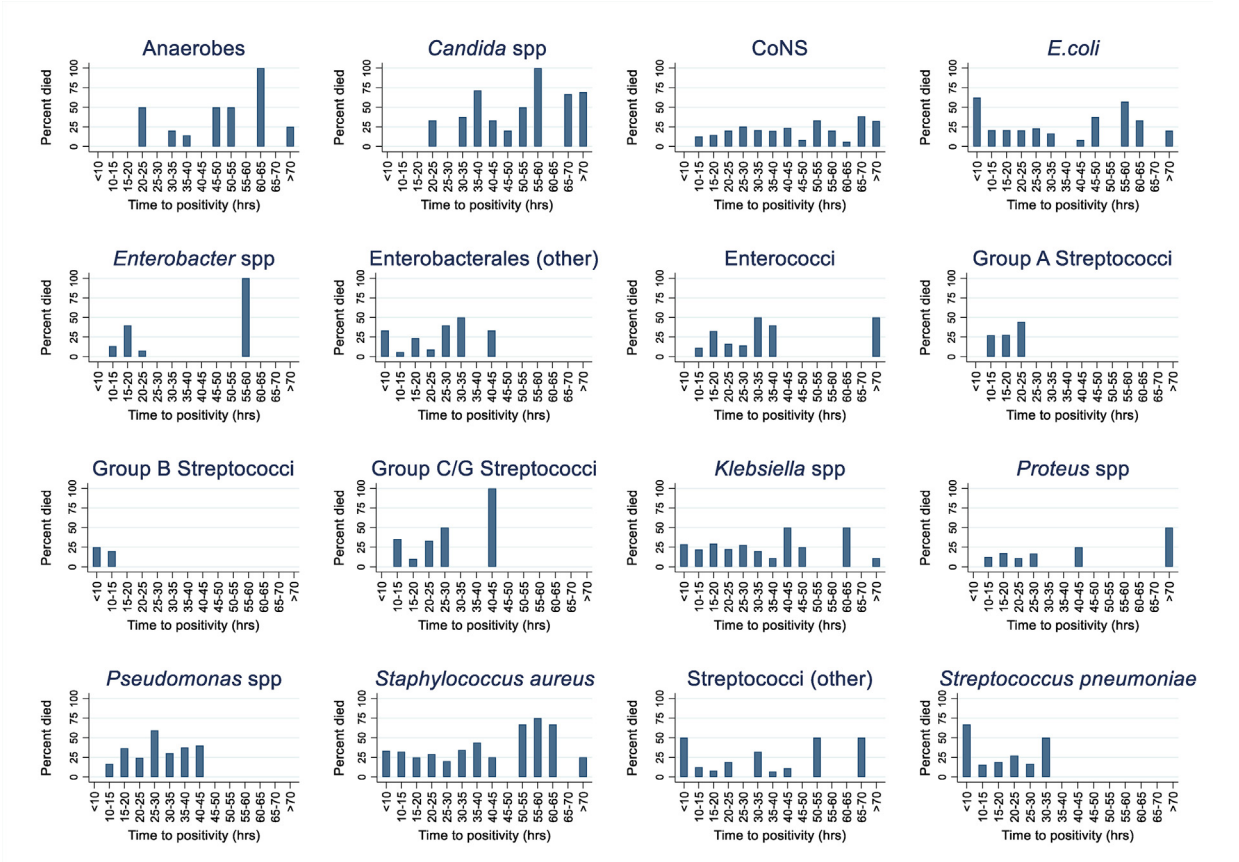

Fig. 3. Twenty-eight-day mortality rates, by organism group and category of time to positivity.

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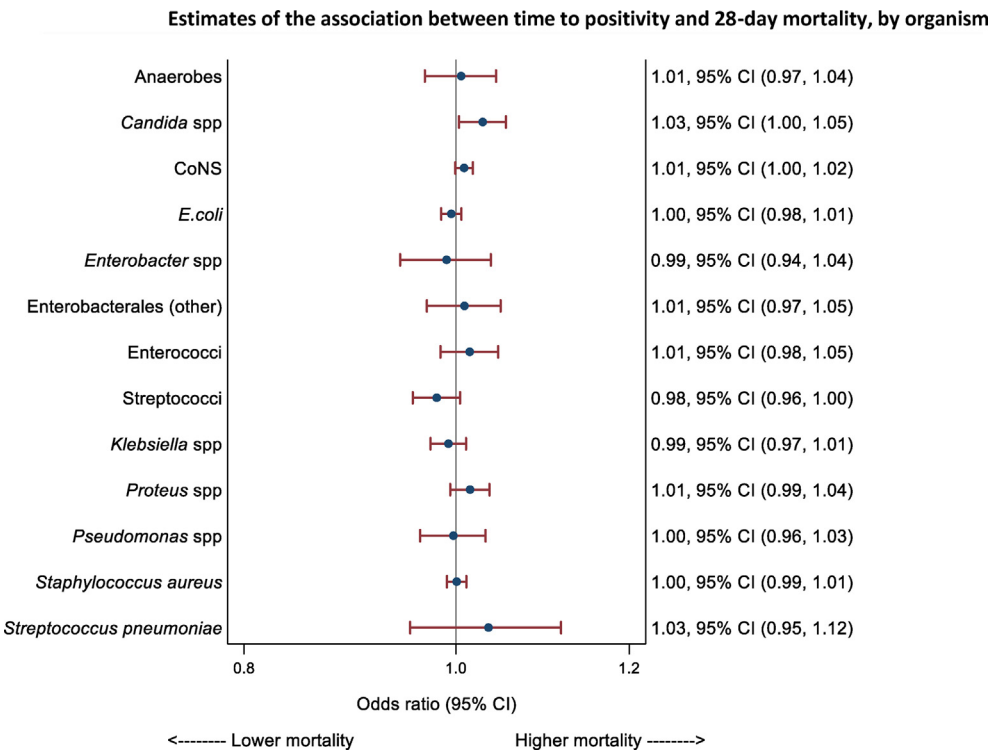

Fig. 4. Estimates of the association between time to positivity and 28-day mortality, by organism. Effect estimates are from a logistic regression model of 28-day mortality, adjusted for centre and organism with an interaction between organism and time to positivity (p for interaction 0.1592). Group A streptococci, Group B streptococci, Group C/G streptococci and other streptococci are combined due to the small number of events in Group B.

Candida glabrata, with patient death in 40% (4/10). No other species was identified more than twice. Time to positivity was much greater in *Candida glabrata* (mean 87.9 h in patients who died, 51.1 h in patients who survived) than in *Candida albicans* (mean 46.8 h in patients who died, 41.8 h in patients who survived). Susceptibility data (where available) showed that 38/42 (90.4%) were susceptible to fluconazole.

Clinical and microbial features that are associated with time to positivity

As a secondary outcome, we aimed to identify whether any clinical features are associated with time to positivity. We performed linear regression with time to positivity as the outcome variable, which was logged to improve model fit, with centre, organism, and clinical features as predictor variables. As such, the effect estimates should be interpreted as geometric mean ratios (GMRs) rather than odds ratios. GMRs should be interpreted on the multiplicative scale, not the additive scale, but the directions of association remain the same as for odds ratios.

Table 3 shows the output of this model. Unsurprisingly, organism group was strongly associated with time to positivity, with all organisms having a significant relationship with time to positivity compared to the reference group (coagulase-negative staphylococci). Centre also had a significant impact on time to positivity, with all centres except one showing a different time to positivity to the reference centre (Centre 3). In terms of clinical features, increasing age was associated with increasing time to positivity, as was increasing neutrophilia. However, the presence of fever had an opposite relationship, with fever associated with lower time to positivity.

Discussion

In this large, multicentre, prospectively collected cohort of bloodstream infections with detailed timing information, we found no robust evidence of a relationship between mortality and time to positivity in staphylococci (both coagulase-negative and *S. aureus*), *Pseudomonas*, enterococci, *Bacteroides*, and all members of the Enterobacterales. For *Candida* spp., we identified a relationship between increasing time to positivity and mortality, contrary to our expectations, although numbers were small. Conversely, in streptococci, we found a more expected association between decreased time to positivity and mortality, although this was only identified in a sensitivity analysis, and not in the main results.

We did not find a clear relationship between time to positivity and any clinical variables except age, fever, and neutrophilia, suggesting in the case of fever and neutrophils the anticipated role of the organism load in driving the initial inflammatory response.

Strengths and limitations

This paper has the strength of the scale of prospective data collection from a large randomized control trial, and was largely complete. Notably, detailed information on timing both from sample collection and from time on machine were available, allowing us to take account of this potential source of heterogeneity. However, as this was a pragmatic trial, we do not have detailed information on the clinical and laboratory processes at each site, although all sites are laboratories accredited by the United Kingdom Accreditation Service (UKAS). Study centre had a significant impact on time to positivity, which was accounted for in our models, but has significance for external validity of previous single-centre studies. We were unable to include time to effective

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Table 3
Estimates of the association between clinical features and time to positivity

	GMR	95%CI
Organism		
CoNS	*Ref*	
Anaerobes	1.34	(1.14, 1.58)
Candida spp.	1.53	(1.34, 1.75)
Escherichia coli	0.64	(0.62, 0.67)
Enterobacter spp.	0.71	(0.62, 0.80)
Enterobacterales (other)	0.65	(0.59, 0.73)
Enterococci	0.69	(0.63, 0.75)
Group A streptococci	0.61	(0.53, 0.70)
Group B streptococci	0.53	(0.46, 0.62)
Group C/G streptococci	0.56	(0.48, 0.65)
Klebsiella spp.	0.69	(0.64, 0.74)
Proteus spp.	0.8	(0.72, 0.90)
Pseudomonas spp.	0.82	(0.75, 0.90)
Staphylococcus aureus	0.75	(0.71, 0.80)
Streptococci (other)	0.92	(0.86, 1.00)
Streptococcus pneumoniae	0.58	(0.54, 0.64)
Centre		
3	*Ref*	
1	0.98	(0.94, 1.02)
2	1.2	(1.14, 1.26)
4	1.09	(1.01, 1.17)
5	1.06	(1.01, 1.12)
6	0.87	(0.82, 0.94)
7	1.14	(1.07, 1.21)
Age (per 10 years)	1.01	(1.00, 1.02)
Male	1.02	(0.99, 1.06)
On immunosuppressive drugs	0.96	(0.91, 1.02)
Any prior transplant	1.01	(0.93, 1.10)
Systemic corticosteroids	0.94	(0.88, 1.01)
Suspected hospital-acquired infection	0.98	(0.95, 1.01)
Neutrophil count (per 5×10^9/L)	1.03	(1.02, 1.04)
Fever on day 0	0.95	(0.92, 0.99)

CoNS, coagulase-negative staphylococci; GMR, geometric mean ratio.
Analysis of time to positivity was performed on the log scale to improve model fit, therefore effect estimates are reported as geometric mean ratios.
Note: Day 0 is date of blood culture sampling.

treatment as a variable in our models, as this will strongly correlate (and is a collider with) time to positivity. However, 44% of the cohort were already on effective therapy at the time of the blood culture, and the evidence that delay in effective therapy is strongly associated with outcomes is weak, as shown by RAPIDO and other trials [12,14,15]. Although we controlled for time to appropriate therapy in our analyses, more detailed information on timings would allow a more nuanced understanding of the potential impact, and should be a focus of future research.

Finally, we are confident about findings in bacterial groups with a large number of patients such as in *E. coli*, coagulase-negative staphylococci, and *S. aureus*. For other groups (e.g. *Proteus* spp., anaerobes, and Group B streptococci), the numbers were relatively small, and interpretation of these results should be more cautious.

Comparisons with previous literature

These results are surprising, and largely inconsistent with the previous literature that has identified time to positivity as a potential independent biomarker of severity in multiple prior cohorts (reviewed in [4]); however, our cohort is an order of magnitude larger in both scale and comprehensive data collection.

It is valuable to explore the reasons underlying our main finding of a lack of association between TTP and outcome. First, it is important to note that time to positivity is a function of at least four factors—pathogen load in the bottle, pathogen growth kinetics, host factors, and laboratory/processing factors—although it is often simply thought of as a measure of microbial load. Most explanations for the association between mortality and time to positivity equate the increased mortality with an increased pathogen load, as is seen in evolutionary and ecological studies of infection, as the other factors are fixed (growth kinetics), random (laboratory processing), or small (host factors).

There are therefore two broad explanations for our conflicting results. First, pathogen load is simply not associated with outcome in clinical human infection, or time to positivity is not reliable enough an indicator of pathogen load to be clinically useful. The first argument is plausible, although there is a wealth of data from non-culture-based techniques (largely PCR) that has consistently associated higher microbial loads with worse outcomes in infection [16–25] (reviewed in [26]).

Despite this evidence, there is increasing recognition that survival from pathogens requires both resistance (host approaches that reduce pathogen loads) and tolerance (host approaches that improve survival independently of pathogens) [27,28]. This is supported by the epidemiological evidence that patients with weakened immune systems (e.g. transplant patients) do not generally have greatly increased mortality from severe infections [29–31], and the evidence of the benefit of steroids in infections like coronavirus disease 2019 (COVID-19) [32]. It is therefore possible that microbial load is not that relevant to outcomes in a relatively elderly cohort with bloodstream infection.

The second explanation—that host and laboratory factors overpower the relevance of microbial load—is perhaps more likely. Most previous studies focused on single-centre cohorts with a single pathogen, using a single laboratory. However, we found large differences in both time to the machine and time on the machine between centres for the same organisms, suggesting that most variation was unrelated to the microbial load of the organism. Also, host factors appear to have some impact on time to positivity, suggesting that the case mix within a hospital might also alter time to positivity. This has significant implications for the external validity of time to positivity, suggesting that, even if time to positivity is associated with outcome, thresholds at one centre are very unlikely to be relevant at another centre.

Implications for research

Future studies should focus on non-culture-based techniques using an approach minimizing external validation, and should aim to identify whether the impact of pathogen load varies by organism.

Implications for clinical practice

Time to positivity is not strongly associated with mortality and has limited external validity. Clinicians should be cautious in interpreting time-to-positivity data as a marker of severity. Studies should look at the impact of prior antimicrobial therapy on time to positivity and other microbial load markers.

Conclusions

Time to positivity was not associated with mortality in a large, prospectively collected, multicentre cohort, except in *Candida* spp. (longer times associated with worse outcomes, caveated by small numbers), and possibly in streptococci (slower times associated with worse outcomes). There was a large variation between median times across centres, limiting external validity.

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Author contributions

FH conceived of the idea, and performed some analyses. RE performed most of the analyses, and produced figures and graphs. PG provided writing assistance, drafting, and editing. AM provided the data, and assisted with writing and editing of the manuscript.

Transparency declaration

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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.2021.05.043.

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