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Time to blood culture positivity an independent predictor of infective endocarditis and mortality in patients with *Staphylococcus aureus* bacteraemia

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1 **Original article**

2 **Time to blood culture positivity: an independent predictor of infective**
3 **endocarditis and mortality in patients with *Staphylococcus aureus***
4 **bacteraemia**

5
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31

32 **ABSTRACT**

33 *Objectives:* Time to blood culture positivity (TTP), a routinely available parameter in
34 automated blood culture systems, may be a proxy for infectious burden in patients with
35 bloodstream infections. We aimed to study the association between TTP and infective
36 endocarditis (IE), or death, in patients with *Staphylococcus aureus* bacteraemia.

37 *Methods:* VIRSTA is a multicenter prospective cohort study that included all adult patients
38 with *S. aureus* bacteraemia in eight university hospitals in France (2009-2011). We analyzed
39 data from four centers which collected data on TTP. Regression models were used to study
40 the association between TTP and definite IE (Duke-Li criteria), and 30 day-mortality.

41 *Results:* We included 587 patients with *S. aureus* bacteraemia: mean age was 65.3±16.3 years,
42 420/587 patients (71.6%) were male, 121/587 (20.6%) died, and 42/587 (7.2%) had definite
43 IE. Median TTP of first positive blood culture was 13.7 h (interquartile range, 9.9-18). On
44 multivariate analysis, 30-day mortality was associated with TTP≤13.7 h (74/295 (25.1%) vs
45 47/292 (16.1%), $P=0.02$), as well as old age, McCabe score, methicillin resistance, stroke,
46 pneumonia, and C-Reactive Protein. TTP was also independently associated with IE, but with
47 a U-shape curve: IE was more common in the first (TTP<10 h, 17/148, 11.5%), and the last
48 (TTP≥18 h, 8/146, 5.5%) quartiles of TTP, $P=0.002$.

49 *Conclusions:* TTP provides reliable information in patients with *S. aureus* bacteraemia, on the
50 risk of IE, and prognosis, with short TTP being an independent predictor of death. This data
51 readily available at no cost may be used to identify patients who require specific attention.

52

53 **KEY WORDS:** time to blood culture positivity; *Staphylococcus aureus*; bacteraemia; mortality;
54 infective endocarditis

55

56 **Introduction**

57 *Staphylococcus aureus* bacteraemia (SAB) is a public health issue, with an incidence
58 estimated at 15-40 per 100 000 person-years (1,2), and in-hospital mortality rates of 15-25%
59 (3–5). Age, sepsis, comorbidities, methicillin-resistant *S. aureus* (MRSA), and inadequate
60 antibiotic therapy are the main prognostic factors (3,6,7). In addition, *S. aureus* is the most
61 prevalent microorganism causing infective endocarditis (IE) (8,9), a major complication of
62 SAB (10,11).

63 Time to positivity of blood cultures (TTP) is defined as the time from the start of
64 incubation to alert signal, in automated blood culture systems. TTP may provide useful
65 information, since a short TTP may reflect high blood bacterial load, and/or enhanced
66 virulence. This property has already been harnessed to diagnose catheter-related bloodstream
67 infections based on differential TTP of paired blood cultures sampled from venipuncture and
68 the catheter (12–14). However, this parameter, available at no cost with most automated blood
69 culture systems, is rarely mentioned as a tool to adjust the management of patients with
70 positive blood cultures.

71 A few studies evaluated the association between TTP and mortality in SAB (15–17),
72 or IE (18), but they were limited by small sample size, retrospective and/or monocentre
73 design, and found discordant results. We aimed to evaluate the association between TTP and
74 i) IE, ii) mortality, in a prospective cohort of adult patients with SAB.

76 **Methods**

77 *Population*

78 The VIRSTA prospective cohort study included all consecutive adult patients with
79 SAB between April 2009 and October 2011 in 8 tertiary-care university hospitals in France

80 (19,20). Trained research assistants collected clinical, biological, therapeutic data, and
81 outcome. All patients, their relatives, or physicians, were contacted 12 weeks after the
82 beginning of SAB to check if patients were alive, and the date of death in patients who died.
83 The diagnosis of definite IE according to modified Duke criteria (21) was verified by a local
84 adjudication committee including at least one cardiologist, one infectious diseases physician,
85 and one bacteriologist. This ancillary study was restricted to the four VIRSTA sites where
86 blood culture bottles were placed in automated blood culture instruments upon receipt in
87 laboratory, 24/24 hours, 7/7 days, and TTP was routinely collected during the study period.

88

89 *Definitions*

90 SAB was defined as the isolation of *S. aureus* from at least one blood culture bottle
91 sampled by venipuncture. For each patient, only TTP of the first set of positive blood cultures
92 was retained for analysis. When both aerobic and anaerobic bottles were positive, we used the
93 shortest TTP. SAB was classified as nosocomial, healthcare-associated, or community-onset
94 using validated criteria (22). McCabe score classified patients in 4 categories (23): 1, no
95 underlying disease; 2, non-fatal underlying disease; 3, ultimately fatal underlying disease
96 (within 5 years); and 4, rapidly fatal underlying disease (within one year).

97

98 *Microbiological methods*

99 In each center, approximately 10 mL of blood was inoculated into aerobic and
100 anaerobic bottles by nurses using a standardized sterile technique (24). The BACTEC®
101 system (Becton Dickinson) was used in three sites, and BacT/Alert® (bioMérieux) in one.
102 TTP was defined as the time from the start of incubation to alert signal, as previously (12–14).
103 Antimicrobial susceptibility testing was performed per guidelines of the CASFM-EUCAST

104 (www.sfm-microbiologie.org). Strains isolated from patients with IE were centralized at the
105 French National Reference Center for Staphylococci.

106 To study the mechanisms behind short, and long TTP, we performed in-depth analysis
107 of a subset of 13 isolates from IE patients with the shortest, and the longest quartiles of TTP.
108 Firstly, we estimated the crude doubling time: each strain was adjusted to an OD_{600nm} = 0.5,
109 and 100 µL of a 1/100 dilution in BHI was inoculated in triplicate into 96-wells plates that
110 were incubated for 24 hours at 37°C with continuous OD_{600nm} monitoring (Tecan Infinite®
111 200 PRO). Doubling times were calculated from the exponential growth phase data by
112 Growthrate® 2.1. Secondly, to mimic the conditions encountered in blood culture bottles and
113 measure the TTP of a standardized inoculum, each strain was adjusted to an OD_{600nm} = 2 in
114 0.9% NaCl solution, and this suspension was diluted to achieve a concentration of 60
115 CFU/mL of *S. aureus*. One mL of this suspension was added to aerobic and anaerobic blood
116 culture bottles (bioMérieux, 3 pairs per strain), previously inoculated with 5 mL of whole
117 human blood. Blood cultures bottles were then incubated in an automated blood culture
118 instrument (Virtuo®, bioMérieux) in which TTP was recorded as in routine clinical laboratory
119 conditions. Once detected positive, a Gram stain and a Maldi-Tof identification (Vitek MS,
120 bioMérieux) were performed. Lastly, genotyping of isolates was performed with diagnostic
121 DNA microarrays, *S. aureus* Genotyping kit 2.0 (Alere, Jena, Germany) (25). The assignment
122 of isolates to clonal complexes (CCs) was performed by comparing hybridization profiles to
123 multi-locus sequence typing (MLST) reference strains.

124

125 *Statistical analysis*

126 Non-normally distributed continuous variables were reported as median with
127 interquartile range (IQR). Normally distributed continuous variables were reported as mean
128 with standard deviation. Qualitative variables were expressed as number and proportions.

129 Continuous variables were compared using Student's *t*-test for normally distributed and the
130 Wilcoxon-Mann-Whitney nonparametric test for non-normally distributed variables.
131 Differences in proportions were compared by a chi-square or a Fisher's exact test, when
132 appropriate. We performed a bivariate analysis to compare SAB with short (<median), and
133 long (>median) TTP. A logistic regression model was developed to study factors associated
134 with IE, excluding major Duke criteria in the final model. A Poisson regression model was
135 used to assess factors associated with 30-day mortality. In regression models, continuous
136 variables were modeled using fractional polynomial if relationship was nonlinear (26) . Risk
137 was expressed as relative risk (RR) for Poisson regression, and odds ratio (OR) for logistic
138 regression with 95% confidence intervals (CI).

139 First, regression analyses adjusted to age, sex and centre were undertaken to quantify
140 the relationships between the explanatory covariates and the response variables 'IE' or 'dead
141 at day 30'. Time to positivity, sex, age, centre and covariates with $P < 0.2$ level in previous
142 analyses were entered into logistic and Poisson multivariate regression models. Manual
143 backward stepwise variable elimination was then performed to determine final multivariate
144 models. We found no interaction between TTP and sex, and between TTP and methicillin-
145 resistance in models. Goodness-of-fit was checked for each model by the Pearson, Hosmer-
146 Lemeshow, and receiver operating characteristic curve tests. $P < 0.05$ was considered as
147 statistically significant in two-tailed. Analyses were performed using Stata software (version
148 12.0, Stata Corporation).

149

150 *Ethics*

151 VIRSTA study was approved by Sud-Méditerranée IV Protection to Persons
152 Committee, and registered in the European Clinical Trials Database (EUDRACT) under the
153 number 2008-A00680-55.

154

155 **Results**156 *Patient characteristics*

157 Of the 2,008 patients enrolled in the VIRSTA cohort, data on TTP was prospectively
158 collected in 587 (i.e., those admitted in the four sites where TTP was routinely collected
159 during the study period, with immediate transfer of blood cultures samples to the laboratory
160 for incubation, 24/24 hours, 7/7 days, see flowchart, web-only Supplementary Figure 1).
161 Patients characteristics are summarized in Table 1. As compared to the rest of the VIRSTA
162 cohort, these patients had a lower rate of IE: 42/587 (7.2%), vs 179/1421 (12.6%), $P < 0.0001$,
163 web-only Supplementary Table 1. Blood cultures were positive in both aerobic and anaerobic
164 bottles for 423/587 patients (72.1%), only in aerobic bottles for 97/587 (16.5%), and only in
165 anaerobic bottles for 67/587 (11.4%).

166

167 *Factors associated with short TTP (Figure 1A)*

168 The median TTP was 13.7 (IQR, 9.9-18) hours, with no significant difference in TTP
169 distribution between the two automated blood culture systems. In univariate analyses, factors
170 associated with short TTP (< 13.7 h) were renal failure, immunodepression, McCabe score of
171 4, central venous catheter, IE, stroke, emboli, and MSSA (web-only, Supplementary Table 2).
172 The median TTP was 13 (IQR, 9.5-18) hours for MSSA, and 15 (IQR, 10.6-18) hours for
173 MRSA ($P = 0.14$).

174

175 *Association between TTP and IE (Figure 1B)*

176 The relationship between TTP and IE was not linear, with a U-shape curve (Figure 2).
177 Hence, we used fractional polynomials to describe the relationship between TTP, and IE. In
178 univariate analysis, centre, community-acquired SAB, prosthetic valve, emboli, stroke,

179 osteitis, C reactive protein, and extreme quartiles of TTP (i.e. quartile 1, and 4), were
180 associated with IE (Table 2). In multivariate analysis, centre, stroke, prosthetic valve, C
181 reactive protein, TTP <10 h (quartile 1, OR 2.84 [1.33-6.10]), and TTP >18 h (quartile 4, OR
182 3.07 [0.99-9.45]) were independently associated with IE (Table 2). When we restricted the
183 analyzes to the 393 patients who underwent echocardiography (either TTE, or TEE), we
184 found similar findings, with a U-shape curve.

185

186 *Factors associated with 30-day mortality*

187 Old age, a McCabe score of 4, underlying liver disease, stroke, pneumonia, mitral
188 vegetation, MRSA, and TTP <13.7 h were associated with mortality, whereas surgical site
189 infection was associated with survival (Table 3). In multivariate analysis, TTP <13.7 h (RR
190 1.69, 95%CI 1.11-2.57), old age, McCabe score of 4, MRSA, stroke, pneumonia, and high C
191 reactive protein were independently associated with 30-day mortality.

192

193 *Microbiological study of selected strains originating from patients with IE and extreme TTP* 194 *(quartiles 1, and 4)*

195 Crude doubling time of *S. aureus* strains with short (<10 h, n=8) and long (>18 h, n=5)
196 TTP were not different (Figure 3A). The two groups of isolates (short, and long TTP during
197 the clinical study), had similar TTP in blood culture bottles inoculated with standardized
198 inocula ($P=0.9433$, Figure 3B). All strains tested were methicillin susceptible, and no specific
199 clonal complex was associated with either short or long TTP (Supplementary Table 2).

200

201 **Discussion**

202 In this prospective cohort of 587 patients with SAB, TTP of first positive blood culture
203 was independently associated with IE, and 30-day mortality. Indeed, the prevalence of IE was

204 higher both in patients with short (quartile 1, <10 h), and long (quartile 4, >18 h) TTP, with a
205 U-shape curve. Thirty-day mortality was 74/294 (25.2%) in patients with TTP <13.7 h
206 (median), versus 47/292 (16.0%) in patients with TTP \geq 13.7 h ($P=0.03$), and this association
207 persisted after adjustment for other risk factors.

208 Significant differences were observed between patients enrolled in this ancillary
209 study, and the rest of the VIRSTA cohort. However, our population was in line with most
210 recent studies of SAB in adult patients, in terms of age (mean, 60-70 years), sex ratio (65-75%
211 of males), major comorbidities (predominantly diabetes, cancer, and renal disease, >25%
212 each), and outcome (30 day-mortality, 15-25%) (4,27). In addition, predictors of mortality
213 were similar to those previously described: age, McCabe score, MRSA, pneumonia or C
214 reactive protein (28,29). Of note, the automated blood culture systems in use during the study
215 period, BACTEC®, and BacT/Alert®, are by far the most commonly used worldwide, and
216 TTP distribution (median, 13.7 hours; IQR, 9.9-18) is in line with previous studies of TTP in
217 SAB (15,16). This suggests that our findings may apply to most settings where automated
218 blood culture systems are in use.

219 The relationship between TTP and IE is poorly documented. In a cohort of 312
220 patients with SAB (18), TTP was shorter for IE (12.1 ± 4.0 h, $P=0.002$), and catheter-related
221 infections (15.1 ± 5.3 h, $P=0.004$), and longer for bone (20.6 ± 9.5 h, $P=0.04$), and respiratory
222 tract infections (24.8 ± 15.3 h, $P=0.001$). In our study, extreme quartiles (TTP \leq 10 h, and TTP
223 >18 h), were independently associated with higher risk of IE. We speculated that this biphasic
224 behavior could reflect two unrelated biological phenomenon: i) SAB with high inoculum
225 (hence, short TTP), could be at higher risk of IE; ii) once IE has developed, bacteria enter in a
226 slow metabolic state within vegetations (30,31), which may be responsible for longer TTP
227 when these bacteria seed the circulation and are inoculated in blood culture bottles. However,
228 doubling time of isolates from IE patients with shortest, or longest TTP, were not different *in*

229 *vitro*, and blood culture bottles inoculated with a standardized quantity of *S. aureus* from
230 these two groups had similar TTP. This suggests that differences in TTP reflect differences in
231 the quantity of bacteria inoculated in blood culture bottles – and thus differences in bacterial
232 concentration in circulating patient blood, rather than intrinsic characteristics of the isolates.
233 This U-shape curve may also have reflected two pathophysiological models for IE: cases with
234 shorter TTP, and thus high bacterial load, corresponding to rapidly progressive IE caused by
235 virulent strains, whilst extended TTP could result from less virulent bacteria and/or better
236 control by the host. However, IE cases with shortest (quartile 1), and longest (quartile 4) TTP
237 were similar in terms of duration of symptoms before diagnosis, clinical presentation, and
238 immunosuppression (data not shown). To our knowledge, increased risk of IE in patients with
239 long TTP has never been reported. Hence, confirmatory studies on the association between
240 TTP and IE are required.

241 We conducted a medline search to identify studies that investigated TTP in patients
242 with SAB. We found 6 studies (15–18,32,33). TTP ≤ 12 h has been associated with increased
243 in-hospital mortality (25.0%, versus 4.3% if TTP > 12 h, $P=0.006$) (32), and increased 30-day
244 mortality (OR 5.91, CI95% 1.80-19.44; $P=0.003$) (15), in two distinct cohorts of SAB. TTP
245 ≤ 14 h was an independent predictor of SAB-related mortality in another study (18). Two
246 recent studies did not confirm this association: a retrospective analysis of 684 adult and
247 pediatric SAB (MSSA and MRSA), found that TTP > 48 h was associated with higher 30-day
248 mortality as compared to TTP < 12 h (33). However, children and adults have different
249 bacterial load during bacteremia (34), so that the merging of pediatric and adult population
250 may not be appropriate. TTP was not associated with mortality in another cohort of 87 SAB
251 (17). Interestingly, this latter study and another found that a TTP ratio of < 1.5 between the
252 first and the second positive blood culture in patients on appropriate antibacterial treatment
253 was an independent risk factor for new infectious focus, and death (17,34). Accordingly,

254 failure to increase TTP by at least 50% in sequential blood cultures should prompt
255 reinforcement of anti-staphylococcal regimen, and/or extraction of foreign devices or surgical
256 intervention when appropriate.

257 Our study has limitations: only 587 patients of the VIRSTA cohort could be enrolled,
258 with significant differences with the rest of the cohort. Among them, only 393 (67.0%)
259 underwent echocardiography, of whom 42 fulfilled criteria for definite IE. Hence, analyses of
260 risk factors for IE were limited by small sample size. Secondly, two different blood culture
261 instruments were used during the study period. Finally, we did not monitor the volume of
262 blood inoculated into blood culture bottles, although this parameter has a strong impact on
263 pathogen detection, and TTP (24). Of note, short TTP implies that physicians in charge were
264 informed earlier that their patients had SAB. Theoretically, this opportunity for earlier
265 appropriate treatment may underestimate the prognostic value of short TTP. Strengths of our
266 study include its design (prospective, multicenter, observational, with consecutive enrolment
267 of all adult patients with SAB), which reduces the risk of selection bias. Many variables were
268 prospectively collected, with a low rate of missing data, which enabled to consider a large
269 range of potential confounding factors. To our knowledge, this is the largest study on TTP in
270 SAB to date. Lastly, echocardiography was performed in 393/587 (67.0%) of SAB cases.
271 Although a 100% rate would be preferable, 67.0% is, to our knowledge, the highest rate of
272 echocardiography across all observational SAB studies currently available.

273 In conclusion, results of our study advocate for the development of clinical use of TTP
274 in the management of patients with SAB. Those with short TTP should be monitored more
275 closely, and treated more aggressively, as they belong to a group at higher risk of early death.
276 Echocardiography has a higher yield in this group.

277

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281 the Institut National de la Santé et de la Recherche Médicale (Inserm).

282

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304

ACCEPTED MANUSCRIPT

305 **Table 1. Study population (n=587)**

Variables	
Demographic characteristics	
Age (y)	65.3 ± 16.3
Male	420 (71.6)
Centre	
Besançon	106 (18.1)
Lyon	301 (51.3)
Nîmes	40 (6.8)
Paris-Bichat	140 (23.8)
Co-morbid conditions	
Renal failure	153 (26.1)
Diabetes mellitus	184 (31.4)
Heart failure	120 (20.4)
Intravenous drug use	17 (2.9)
Solid cancer	174 (29.6)
Immunocompromised status	123 (21.0)
Chronic liver disease	107 (18.2)
McCabe score (n=584)	
1	58 (9.9)
2	232 (39.7)
3	200 (34.2)
4	94 (16.1)
Presumed place of acquisition (n=563)	
Community-acquired	166 (29.5)
Healthcare-associated	93 (16.5)
Nosocomial	304 (54.0)
Site of infection	
Infective endocarditis	42 (7.2)
Osteitis (n=555)	62 (11.2)
Arthritis (n=554)	63 (11.4)
Pneumonia (n=540)	73 (13.5)
Skin and skin structure infection (n=555)	186 (33.5)
Urinary tract infection (n=554)	80 (14.4)
Catheter related-infection (n=565)	173 (30.6)
Devices	
Pacemaker	39 (6.6)
Prosthetic valve	38 (6.5)
Vascular grafts	43 (7.3)

Variables	
Prosthetic joint	73 (12.4)
Clinical features	
Fever	484 (82.4)
Heart valve disease (n=525)	125 (23.8)
Stroke (n=554)	18 (3.2)
Embolus	15 (2.6)
Intensive care unit	165 (28.1)
All-cause death	156 (26.6)
All-cause death at day 30	121 (20.6)
Biological parameters	
C reactive protein (mg/L) (n=534)	182 (104-284)
Time to positivity (hours)	13.7 (9.9-18)
MRSA (n=585)	112 (19.2)
Antibiotic therapy before first blood culture (n=577)	38 (6.5)
Echocardiographic data	
TTE	364 (62.0)
TEE	154 (26.2)
TTE and/or TEE	393 (67.0)
Vegetation (n=393)	31 (7.9)

Categorical variables are presented as numbers (%). Non-normally distributed quantitative variables are reported as median (quartile 1 - quartile 3). Normally distributed quantitative variables are presented as mean \pm standard deviation. MRSA: Methicillin-resistant *Staphylococcus aureus*; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; Immunocompromised status: HIV, hematologic malignancy, immunosuppressive drugs

307 **Table 2. Risk factors for infective endocarditis in patients with *S. aureus* bacteraemia**

Variables	Definite IE (n=42)	Others (n=545)	Univariate analysis		Multivariate analysis (n=477)	
			OR (95% CI)	P	OR (95% CI)	P
Demographic characteristics						
Age, per year	64 (55-74)	67 (56-78)	0.98 (0.96–1.01)	0.10	0.99 (0.96–1.01)	0.26
Female	11 (26.2)	156 (28.6)	1.22 (0.82–1.84)	0.61	0.49 (0.18–1.29)	0.15
Centre				0.003		0.17
Lyon	14 (4.7)	287 (95.3)	1		1	
Besançon	4 (3.8)	102 (96.2)	0.81 (0.26–2.52)		0.54 (0.12–2.27)	
Nîmes	6 (15.0)	34 (85.0)	4.13 (1.46–11.68)		3.27 (0.81–13.23)	
Paris-Bichat	18 (12.9)	122 (87.1)	2.96 (1.42 – 6.15)		1.97 (0.69–5.67)	
Co-morbid conditions						
Diabete mellitus	11 (26.2)	173 (31.7)	0.84 (0.40–1.75)	0.64		
Renal failure	8 (19.0)	145 (26.6)	0.67 (0.30–1.51)	0.33		
Solid cancer	7 (16.7)	167 (30.6)	0.48 (0.20–1.12)	0.09		
Intravenous drug use	4 (9.5)	13 (2.4)	2.48 (0.72–8.52)	0.15		
Presumed place of acquisition (n=563)				0.01		0.02
Nosocomial	16 (38.1)	288 (52.8)	1		1	
Healthcare-associated	4 (9.5)	89 (16.3)	0.71 (0.23–2.21)		0.99 (0.26–3.77)	
Community	22 (52.4)	144 (26.4)	2.50 (1.24–5.04)		3.33 (1.31–8.48)	
Device						
Pacemaker	4 (6.4)	35 (9.5)	1.61 (0.50–5.14)	0.42		
Prosthetic valve	10 (23.8)	28 (5.1)	5.3 (2.25–12.49)	0.0001	7.39 (2.28–23.96)	0.001
Clinical features						
Fever	89 (73.6)	395 (84.8)	1.84 (0.62–5.46)	0.27		
Heart valve disease (n=525)	18 (43.9)	107 (22.1)	5.17 (2.43–11.03)	0.0001	4.24 (1.69–10.64)	0.002
Embolus	8 (19.0)	7 (1.3)	12.4 (3.77–40.9)	0.0001	5.50 (1.16–26.22)	0.03
Stroke (n=554)	9 (22.0)	9 (1.8)	11 (3.87–31.28)	0.0001	6.51 (1.56–27.09)	0.01
Osteitis	9 (22.0)	53 (10.3)	2.44 [1.06–5.60]	0.04		
All-cause death (n=586)	14 (33.3)	142 (26.1)	1.62 (0.80–3.27)	0.18		
Biological parameters						
TTP of first positive blood culture (h)				0.003		0.003
1.28–9.9	17 (40.5)	131 (24.0)	2.28 (1.23–3.97)		2.53 (1.22–5.25)	
10.0–13.7	11 (26.2)	136 (25.0)	1.23 (1.04–1.45)		1.22 (1.01–1.46)	
13.8–18.0	6 (14.3)	140 (25.7)	1		1	

Variables	Definite IE (n=42)	Others (n=545)	Univariate analysis		Multivariate analysis (n=477)	
			OR (95% CI)	P	OR (95% CI)	P
18.1–131.0	8 (19.0)	138 (25.3)	2.16 (0.81–5.74)		3.91 (1.26–12.11)	
MRSA (n=585)	3 (7.1)	109 (20.1)	0.30 (0.09–1.02)	0.05		
CRP (mg/L), per unit (n=534)	256 (150-302)	180 (102-282)	1.003 (1.00–1.01)	0.02		
Morphological data						
Echocardiography (TTE and/or TEE)	41 (97.6)	352 (64.6)	17.4 (2.32– 130.34)	0.005	11.07 (1.28– 95.28)	0.03

Categorical variables are presented as numbers (%). Non-normally distributed quantitative variables are reported as median (quartile 1 - quartile 3). Normally distributed quantitative variables are presented as mean \pm standard deviation.

IE: infective endocarditis; OR: odds ratio; CI: confidence interval; TTP: time to positivity; MRSA: Methicillin resistant *Staphylococcus aureus*; CRP: C reactive protein.

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309

310 **Table 3. Risk factors for 30-day mortality in patients with *S. aureus* bacteraemia**

Variables	30-day mortality (n=121)	Survived (n=466)	Univariate analysis		Multivariate analysis (n=529)	
			RR (95% CI)	P	RR (95% CI)	P
Demographic characteristics						
Age (y) per year	70.2 ± 14.8	63.6 ± 16.5	1.02 (1.01–1.04)	0.0001	1.02 (1.01–1.03)	0.02
Female	37 (36.3)	111 (29.3)	1.22 (0.82–1.84)	0.36	1.11 (0.72–2.68)	0.64
Centre				0.45		0.53
Lyon	61 (20.3)	240 (79.7)	1		1	
Besançon	19 (17.9)	87 (82.1)	0.89 (0.53–1.49)		0.92 (0.52–1.63)	
Nîmes	7 (17.5)	33 (82.5)	0.74 (0.34–1.62)		0.73 (0.33–1.65)	
Paris-Bichat	34 (24.3)	106 (75.7)	1.26 (0.83–1.92)		1.29 (0.79–2.11)	
Co-morbid conditions						
Diabete mellitus	41 (33.9)	143 (30.7)	0.99 (0.67–1.44)	0.94		
Renal failure	38 (31.4)	115 (24.7)	1.15 (0.78–1.70)	0.48		
Chronic liver disease	29 (24.0)	78 (16.7)	1.68 (1.09–2.60)	0.02		
Solid cancer	37 (30.6)	137 (29.4)	1.02 (0.69–1.50)	0.93		
McCabe score (n=584)						
1	8 (6.7)	50 (10.8)	1	0.0009		0.0009
2	36 (30.0)	196 (42.2)	0.69 (0.31–1.52)		0.83 (0.37–1.88)	
3	40 (33.3)	160 (34.5)	0.94 (0.43–2.08)		1.15 (0.52–2.54)	
4	36 (30.0)	58 (12.5)	1.93 (0.88–4.22)		2.34 (1.04–5.28)	
Clinical features						
Fever	89 (73.6)	395 (84.8)	0.67 (0.44–1.01)	0.06		
Stroke (n=554)	10 (9.1)	8 (1.8)	3.13 (1.60–6.14)	0.001	2.85 (1.36–5.96)	0.005
Embolus	3 (2.5)	12 (2.6)	0.98 (0.30–3.20)	0.97		
Mitral vegetation	4 (6.6)	6 (1.8)	2.77 [0.99-7.75]	0.05		
Source of infection						

Variables	30-day mortality (n=121)	Survived (n=466)	Univariate analysis		Multivariate analysis (n=529)	
			RR (95% CI)	P	RR (95% CI)	P
Endocarditis	12 (9.9)	30 (6.4)	1.52 (0.83–2.78)	0.18		
Osteitis (n=555)	10 (9.0)	52 (11.7)	0.83 (0.43–1.60)	0.58		
Arthritis (n=554)	7 (6.4)	56 (12.6)	0.53 (0.25–1.15)	0.11		
SSSI (n=555)	30 (27.0)	156 (35.1)	0.73 (0.48–1.11)	0.14		
Pneumonia (n=540)	26 (23.6)	47 (10.9)	2.05 (1.31–3.2)	0.002	1.69 (1.01–2.85)	0.04
Surgical site	5 (4.1)	66 (14.2)	0.32 [0.13–0.78]	0.01		
Biological parameters						
TTP of first positive blood culture (h)				0.03		0.02
> 13.7	47 (38.8)	245 (52.6)	1		1	
≤ 13.7	74 (61.2)	221 (47.4)	1.51 (1.05–2.18)		1.69 (1.11–2.57)	
MRSA (n=585)	36 (30.0)	76 (16.3)	1.25 (1.02–1.53)	0.03	1.92 (1.20–3.07)	0.006
CRP (mg/L)				0.004		0.02
3 – 104	16 (12.1)	116 (87.9)	1		1	
105 – 182	21 (15.4)	115 (84.6)	1.18 (0.61–2.27)		1.20 (0.60–2.39)	
183 – 284	34 (25.6)	99 (74.4)	2.02 (1.11–3.68)		1.93 (1.02–3.65)	
285 – 927	31 (23.3)	102 (76.7)	1.87 (1.01–3.44)		1.92 (1.00–3.71)	
No data (n=53)	19 (35.8)	34 (64.2)	3.21 (1.63–6.32)		2.99 (1.42–6.30)	
Therapeutic parameters						
Antibiotic before blood culture (n=577)	8 (6.9)	30 (6.5)	1.03 (0.50–2.13)	0.94		
Appropriate empirical antibiotic	96 (79.3)	359 (77.0)	1.08 (0.69–1.69)	0.73		

Variables	30-day mortality	Survived	Univariate analysis		Multivariate analysis	
	(n=121)	(n=466)	RR (95% CI)	P	RR (95% CI)	P

Categorical variables are presented as numbers (%). Non-normally distributed quantitative variables are reported as median (quartile 1 - quartile 3). Normally distributed quantitative variables are presented as mean \pm standard deviation.

RR: relative risk; CI: confidence interval; SSSI: Skin and skin structure infection; TTP: time to positivity; MRSA:

Methicillin resistant *Staphylococcus aureus*; CRP: C reactive protein

311

312

313 **Figure Legends**

314 **Figure 1. Association between time to blood culture positivity, and i) infective**
315 **endocarditis (Figure 1A), and ii) 30 day-mortality (Figure 1B), in patients with**
316 ***Staphylococcus aureus* bacteraemia.**

317

318 **Figure 2. Association between time to blood culture positivity and infective endocarditis**
319 **in patients with *Staphylococcus aureus* bacteraemia: Second-degree fractional**
320 **polynomial adjusted for covariates.**

321 X axis : Time to blood culture positivity in hours adjusted for covariates

322 Y axis : Partial predictor + residual of infective endocarditis

323

324 **Figure 3. *In vitro* study of *Staphylococcus aureus* isolates originating from patients with**
325 **infective endocarditis.**

326 Strains originating from patients with short (first quartile), and long (fourth quartile) time-to-
327 positivity (TTP), referred to as 'early', and 'late' strains, were tested.

328 **Figure 3A.** Doubling time calculated from the exponential growth phase data of triplicate
329 cultures in BHI

330 **Figure 3B.** TTP in artificially inoculated aerobic and anaerobic blood cultures filled with
331 human blood, with standardized inoculum.

332

333 **Supplementary Figure 1: flow chart**

334 **Supplementary Table 1. Comparison of patients enrolled in this study, and the rest of**
 335 **the VIRSTA cohort**

Variables	Study population (n=587)	Non-included patients (n=1421)	P-value
Demographic characteristics			
Age (years)	65.3 ± 16,3	65.0 ± 17.5	0.76
Male	420 (71.6)	875 (61.6)	0.0001
Co-morbid conditions			
Renal failure	153 (26.1)	408 (28.7)	0.23
Diabetes mellitus	184 (31.4)	383 (27.0)	0.05
Heart failure	120 (20.4)	400 (28.2)	0.0001
Intravenous drug use	17 (2.9)	46 (3.2)	0.69
Solid cancer	174 (29.6)	419 (29.5)	0.95
Immunocompromised status	123 (21.0)	229 (21.1)	0.50
Chronic liver disease	107 (18.2)	171 (12.0)	<0.0001
McCabe score			0.02
1	58 (9.9)	113 (8.0)	
2	232 (39.7)	483 (34.0)	
3	200 (34.2)	550 (38.7)	
4	94 (16.1)	274 (19.3)	
Presumed place of acquisition			
Community-acquired	166 (28.3)	355 (25.0)	0.13
Healthcare-associated	93 (15.8)	260 (18.3)	0.19
Nosocomial	304 (51.8)	771 (54.3)	0.31
Site of infection			
Infective endocarditis	42 (7.2)	179 (12.6)	<0.0001
Osteitis	62 (11.2)	149 (10.5)	0.67
Arthritis	63 (11.4)	104 (7.3)	4.10 ⁻³
Pneumonia	73 (13.5)	141 (10.0)	0.02
Skin and skin structure infection	186 (33.5)	394 (27.8)	0.01

Variables	Study population (n=587)	Non-included patients (n=1421)	P-value
Urinary tract infection	80 (14.4)	132 (9.4)	0.001
Catheter related-infection	173 (30.6)	315 (22.3)	<0.0001
Device			
Pacemaker	39 (6.8)	105 (7.3)	0.71
Prosthetic valve	19 (3.2)	53 (3.7)	0.59
Vascular grafts	42 (7.4)	114 (7.9)	0.66
Prosthetic joint	70 (12.3)	214 (14.9)	0.69
Clinical features			
Fever	472 (82.7)	1302 (90.7)	<0.0001
Heart valve disease	125 (21.3)	240 (16.9)	0.02
Stroke	18 (3.2)	57 (4.0)	0.42
Embolus	15 (2.6)	48 (3.4)	0.34
Intensive care unit	165 (28.1)	449 (31.6)	0.25
All-cause death at day 30	121 (20.6)	291 (20.5)	0.95
Biological parameters			
C reactive protein (mg/L)	182 (104-284)	192 (115-280)	0.29
Time to positivity (hours)	13.7 (9.9 - 18)	-	-
MRSA	112 (19.2)	268 (18.9)	0.90

Categorical variables are presented as numbers (%). Non-normally distributed quantitative variables are reported as median (quartile 1 - quartile 3). Normally distributed quantitative variables are presented as mean \pm standard deviation.

336 MRSA: Methicillin-resistant *Staphylococcus aureus*. Immunocompromised status: HIV, hematologic
 337 malignancy, immunosuppressive drugs

338

339 **Supplementary Table 2. Factors associated with time to blood cultures positivity (TTP) in**
 340 ***Staphylococcus aureus* bacteraemia in univariate analysis**

Variables	TTP ≤ 13.7 h (n=295)	TTP > 13.7 h (n=292)	P-value
Demographic characteristics			
Age (years)	66.0 ± 15.7	64.6 ± 16.9	0.29
Male	205 (69.5)	215 (73.6)	0.27
Centre			0.70
Besançon	58 (19.7)	48 (16.4)	
Lyon	146 (49.5)	155 (53.1)	
Nîmes	19 (6.4)	21 (7.2)	
Paris-Bichat	72 (24.4)	68 (23.3)	
Co-morbid conditions			
Chronic liver disease	57 (19.3)	50 (17.1)	0.49
Diabetes mellitus	92 (31.2)	92 (31.5)	0.93
Renal failure	89 (30.5)	64 (22.4)	0.02
Intravenous drug use	11 (3.7)	6 (2.0)	0.23
Solid cancer	95 (32.2)	79 (27.0)	0.17
Immunodepression	78 (26.4)	45 (15.4)	0.001
McCabe score (n=584)			0.009
1	23 (7.8)	35 (12.1)	
2	104 (35.4)	128 (44.1)	
3	118 (40.1)	82 (28.3)	
4	49 (16.7)	45 (15.5)	
Device			
Central venous catheter (n=547)	30 (10.9)	8 (2.9)	0.0001
Vascular grafts	22 (7.4)	21 (7.2)	0.90
Prosthetic joint	44 (14.9)	29 (9.9)	0.07

Clinical features

Fever	255 (86.4)	229 (78.4)	0.01
Heart valve disease (n=525)	63 (24.7)	62 (23.0)	0.64
Stroke (n=554)	17 (6.0)	1 (0.4)	0.0001
Emboli (n=551)	17 (6.1)	6 (0.7)	0.02

Site of infection

Infective endocarditis	28 (9.5)	14 (4.8)	0.03
Osteitis (n=555)	31 (11.0)	31 (11.4)	0.87
Pneumonia (n=540)	30 (10.9)	43 (16.2)	0.08
Catheter related-infection (n=565)	109 (37.8)	64 (23.1)	0.0001

Biological parameters

CRP (mg/L) (n=534)	187 (110-283)	179 (101-288)	0.66
MRSA (n=585)	42 (14.3)	70 (24.0)	0.003

Treatment data

Antibiotics before first blood culture (n=577)	17 (5.9)	21 (7.3)	0.48
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Morphological parameters

Vegetations (n=393)	18 (9.1)	13 (6.7)	0.37
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341 Categorical variables are presented as numbers (%). Non-normally distributed quantitative variables
 342 are reported as median (quartile 1 - quartile 3). Normally distributed quantitative variables are
 343 presented as mean \pm standard deviation. CRP, C Reactive Protein.

344

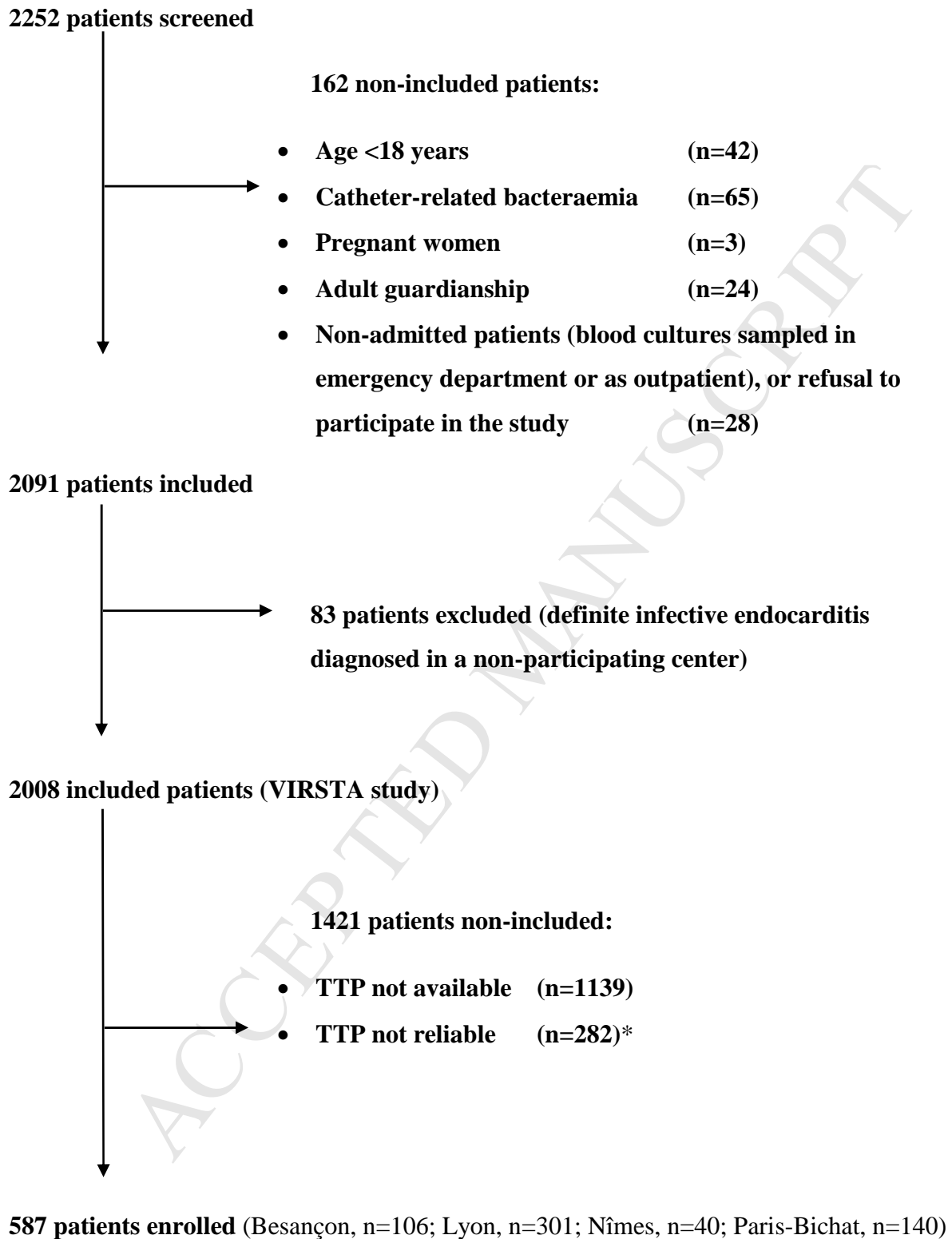
345 **Supplementary Table 3. Clonal complex of the 13 isolates sampled from patients with**
 346 **infective endocarditis, and short (<10 h), or long (>18 h) time-to-positivity (TTP) of first**
 347 **blood culture**

CC-MLST	TTP <10 h	TTP > 18 h
CC5	2	3
CC88	1	0
CC45	3	1
CC15	1	0
CC101	1	0
CC121	0	1
TOTAL	8	5

348 Note. All isolates were meticillin-susceptible *Staphylococcus aureus*

349

Supplementary Figure 1. Flow chart



* Time of incubation start not reliably collected

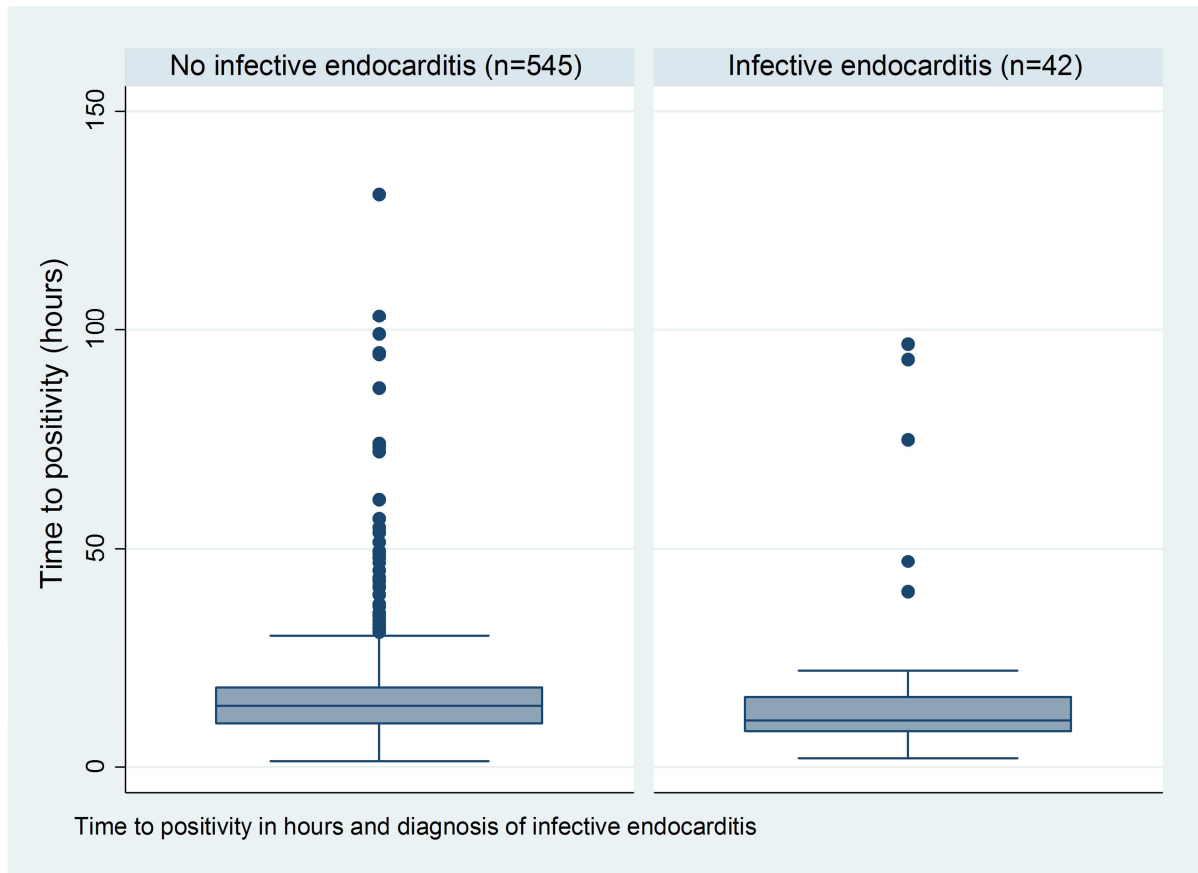
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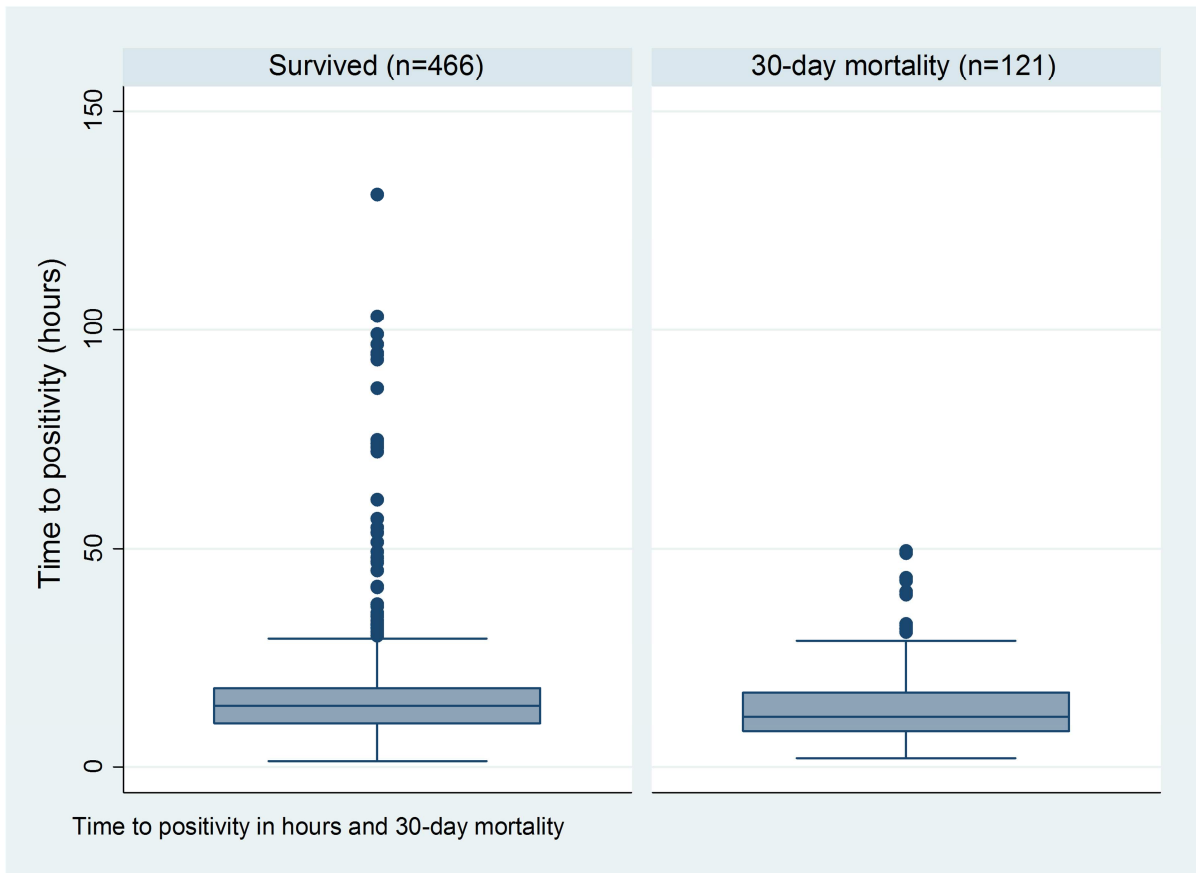
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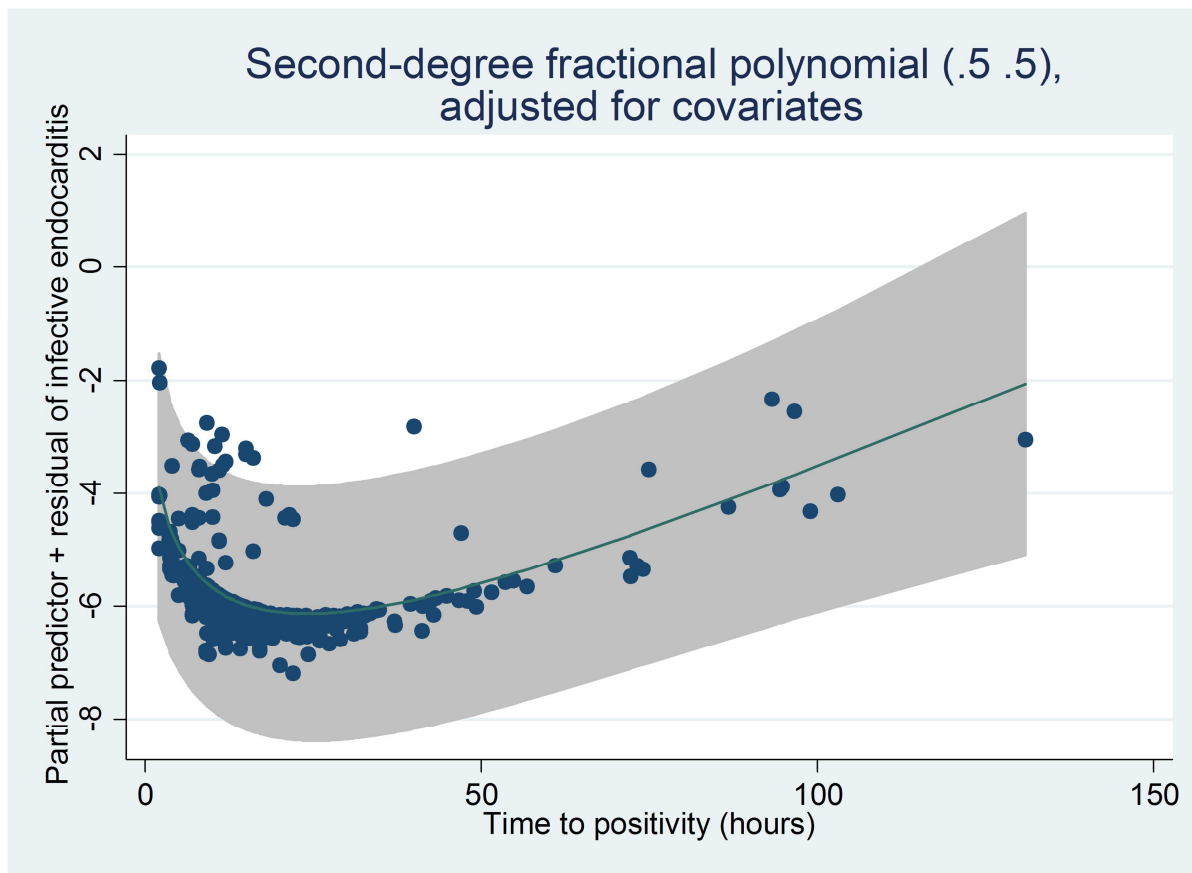
450



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