Eur J Clin Microbiol Infect Dis (2017) 36:887–896
DOI 10.1007/s10096-016-2877-4

ORIGINAL ARTICLE

Thrombocytopaenia during methicillin-sensitive *Staphylococcus aureus* bacteraemia

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Received: 2 November 2016 / Accepted: 12 December 2016 / Published online: 23 December 2016

Abstract The prognostic impact of thrombocytopaenia in *Staphylococcus aureus* bacteraemia (SAB) has previously been determined at bacteraemia onset only and relevant pre-bacteraemic thrombocytopaenia predisposing parameters have not been accounted for. We evaluated the prognostic impact of low thrombocyte count in SAB excluding pre-bacteraemic factors potentially causing thrombocytopaenia. This was a multicentre retrospective analysis of methicillin-sensitive SAB (MS-SAB) patients. Thrombocyte count was determined at blood culture collection and at days 3 and 7. Thrombocytopaenia was defined as a thrombocyte count less than 150 $\times 10^9$/L. Patients with chronic alcoholism, liver diseases and haematologic malignancies were excluded. Altogether, 495 patients were identified. Thrombocytopaenia at blood culture and at day 3 associated to endocarditis ($p < 0.05$ and $p < 0.01$) and defervescence ($p < 0.001$ and $p < 0.01$). Mortality at 90 days was higher for patients with thrombocytopaenia at blood culture collection (26 vs. 16%, $p < 0.05$), at day 3 (32 vs. 13%, $p < 0.01$) and at day 7 (50 vs. 14%, $p < 0.001$). In receiver operating characteristic analyses, thrombocytopaenia predicted a poor outcome at blood culture collection ($p < 0.05$), at day 3 ($p < 0.001$) and at day 7 ($p < 0.001$). When accounting for all prognostic parameters, thrombocytopaenia at day 3 [hazard ratio (HR), 1.83; $p = 0.05$] demonstrated a trend towards poor outcome, whereas thrombocytopaenia at day 7 (HR, 3.64; $p < 0.001$) associated to poor outcome. Thrombocytopaenia at blood culture collection was not a prognostic parameter when all prognostic factors were taken into account. However, thrombocytopaenia at day 3 indicated a poor outcome and thrombocytopaenia at day 7 was a significant independent negative prognostic marker that has not been previously reported in SAB.

Introduction

Staphylococcus aureus causes severe bacteraemic community- and hospital-acquired infections [1, 2]. Despite potent anti-staphylococcal antibiotics and new antimicrobial agents [3], the prevalence of complications related to *S. aureus* bacteraemia (SAB), such as endocarditis and recurrent bacteraemia, remain high [4, 5]. Prognosis of SAB is impaired by delayed onset of antibiotic therapy, inadequate antibiotic therapy and methicillin-resistant *S. aureus* (MRSA) [6–8]. Vancomycin therapy, as compared to beta-lactam antibiotics, is linked also to impaired prognosis [9, 10]. Recently, infectious disease specialist consultation has received much attention, as it has been observed to improve treatment, enhance deep infection focus identification and better outcome [1, 11]. Reports have presented deep infection foci in up to 53–80% of SAB patients [2, 4, 11, 12]. Despite infectious disease specialist consultations guided management and effective antimicrobial agents, SAB still carries a high mortality rate of 12–32% [1, 2, 4, 13].

Thrombocytopaenia is frequently encountered in severe infections and it has been observed to predict complications and outcome in sepsis [14, 15]. *Staphylococcus aureus* is known to interact with platelets. Bacterial surface-expressed proteins such as fibronectin binding protein or clumping factor

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A (ClfA) or structures like cell-wall peptidoglycan mediate local platelet activation [16, 17], which may result in systemic haemostasis disorder, coagulation cascade activation and disseminated intravascular coagulation (DIC) [18]. In vitro studies have demonstrated that *S. aureus* may connect to adhered platelet formations and enhance platelet activation, which may open the path to bacterial colonisation of endovascular epithelium and formation of endovascular infections and endocarditis [19, 20]. Furthermore, infective endocarditis may induce thrombocytopaenia through breakdown of platelets by the damaged heart valve [21] or entrapment in thromboembolic complications such as stroke [22].

Several clinical studies have presented thrombocytopaenia in SAB as an independent parameter for poor outcome [15, 23–28]. These studies, however, have included high (14–100%) occurrence of MRSA bacteraemia and have evaluated the prognostic impact of low thrombocyte count at SAB onset only, i.e. at a single time-point. Furthermore, to the best of our knowledge, pre-bacteraemic thrombocytopaenia predisposing parameters have been accounted for in only one report [15] and the prognostic impact of thrombocytopaenia among patients managed without intensive care unit (ICU) treatment has not previously been investigated.

The objective of the present study was to evaluate the prognostic impact of thrombocytopaenia at three time-points within the first seven days of methicillin-sensitive SAB (MS-SAB). Patients with pre-bacteraemic risk factors for thrombocytopaenia were excluded. The vast majority of patients were provided with formal bedside infectious disease specialist consultation guaranteeing otherwise proper SAB management. The study setting included only methicillin-sensitive *S. aureus* strains. Hence, each patient received proper antibiotic therapy from the first day of SAB, including low use of vancomycin, i.e. minimal impact of differences in empirical antibiotic therapy.

Materials and methods

Settings and study population

This was a retrospective multicentre study recruiting every adult patient with at least one blood culture positive for *S. aureus* at five university and seven central hospitals in Finland during January 1999 to May 1999 and January 2000 to August 2002. The patient cohort was further extended by including all adult patients with at least one positive blood culture for *S. aureus* from Helsinki University Central Hospital in Finland in 2006–2007. *Staphylococcus aureus* isolates and corresponding patient data were matched by using the unique personal number given to all residents of Finland. There was a 3 days median time period between blood culture sampling and clinical awareness of *S. aureus* being the causative pathogen. Data were retrieved from written (1999–2002) and electronic (2006–2007) patient archives. Data documentation included: sex, age, acquisition of bacteraemia, underlying diseases, severity of illness at bacteraemia onset, length and administration route of any antibiotic therapy. Radiological, bacteriological and pathological investigations were applied to verify infection foci. In a few cases, clinical suspicion solely was accepted for infection focus diagnosis. Time to defervescence (axillary temperature below 37.5 °C) and duration of hospitalisation were recorded. The primary end-point was mortality at 28 and 90 days. Patients were followed for 90 days.

Exclusion criteria

Patients with known pre-bacteraemic risk factors predisposing to thrombocytopaenia were excluded: chronic alcoholism, acute or chronic liver diseases and haematological malignancies. These exclusion criteria are accounted for in Tables 2, 3 and 4 and Fig. 1a, b. Further exclusion criteria were: age < 18 years, pregnancy, breastfeeding, imprisonment, epilepsy, bacteraemia 28 days prior to the study and polymicrobial bacteraemia. No cases of MRSA bacteraemia were accepted.

Antibiotic therapy

Semi-synthetic penicillin was regarded as the standard antibiotic therapy, whereas patients with contradictions for penicillin were provided with cefuroxime, ceftriaxone, clindamycin or vancomycin. Fluoroquinolone and/or rifampicin served as additional antibiotic therapy. Patients with deep infection foci diagnosed received intravenous antibiotic therapy for at least 28 days, whereas in the absence of any deep infection, 14 days was regarded as a proper length. Previous reports provide detailed information on antimicrobial therapy indications, dosages and administration routes [29, 30].

Definitions

Bacteraemia with the first positive blood culture for *S. aureus* obtained ≥48 h after hospital admission was defined as healthcare-associated (HA) SAB. The same applied when the patient had undergone haemodialysis within the preceding two months or remained in a long-term care facility. McCabe's criteria were used to classify underlying diseases [31]. Sepsis, in combination with hypotension, hypoperfusion or organ failure, was viewed as severe sepsis [32]. Endocarditis was defined according to the modified Duke criteria [33]. Consultations by infectious disease specialists within seven days of the first positive blood cultures for *S. aureus* were documented and categorised into: (i) formal (bedside) consultation, (ii) informal (telephone) consultation and (iii)

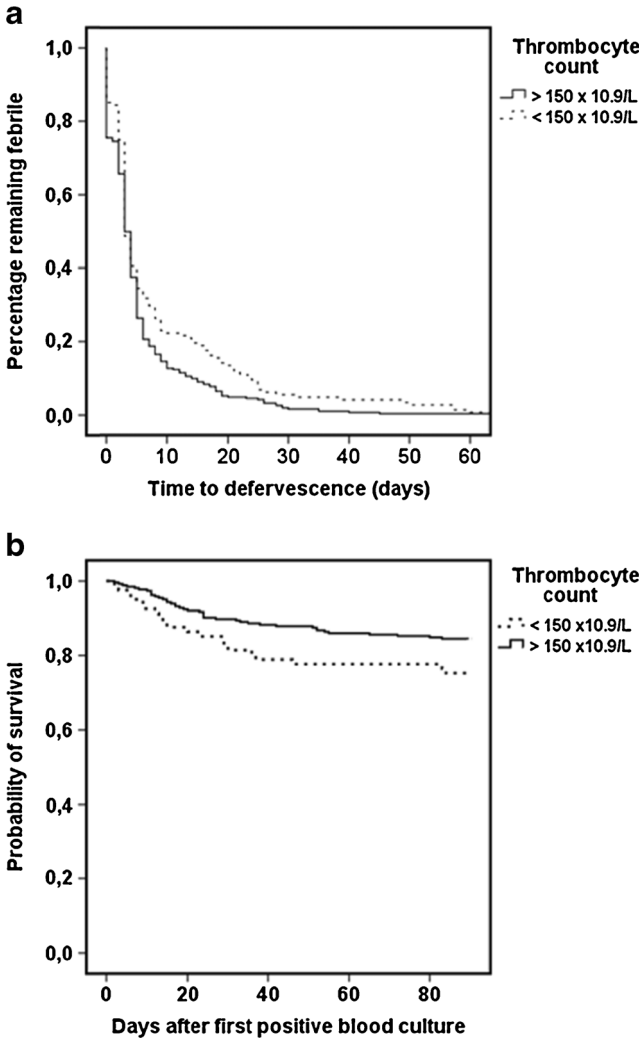

Fig. 1 Kaplan–Meier analysis for time to defervescence (days) (**a**) and 90-day survival (**b**) in 347 patients with methicillin-sensitive *Staphylococcus aureus* bacteraemia (MS-SAB) categorised according to the blood culture collection time-point thrombocyte cut-off value of 150×10^9/L. Patients with pre-bacteraemic conditions predisposing to thrombocytopaenia (i.e. haematological malignancies, chronic alcoholism and acute or chronic liver diseases, $n = 148$) have been excluded. For Fig. **a**, the log-rank analysis was <0.01 and similar graphical presentation was observed at days 3 and 7 (log-rank non-significant). For **b**, the log-rank was non-significant and similar graphical presentation was observed at days 3 and 7 (log-rank < 0.001)

no consultation [11]. Deep infection foci were defined as pneumonia, endocarditis, osteomyelitis, deep-seated abscess or foreign-body infections. Thrombocytes (platelet count) were measured at the blood culture collection time-point and at days 3 and 7, and thrombocytopaenia was defined as a platelet count of less than 150×10^9/L. The present study did not monitor fibrin marker laboratory values (D-dimer or fibrinogen) and, hence, exact DIC criteria could not be determined [34]. However, we applied a simplified DIC score system categorising patients into a DIC-like condition (thrombocytes < 100 and thromboplastin time < 70%) and severe DIC-like condition (thrombocytes < 50 and thromboplastin time < 40%).

Statistical analysis

Pearson's χ^2 test was applied for categorical variable comparison and the Mann–Whitney *U*-test was used for analysing non-parametric data. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Univariate factors with $p < 0.05$ were accepted for Cox proportional hazards regression model analysis of factors predicting mortality and hazard ratios (HRs) with 95% CIs were calculated. Survival estimates were performed with the Kaplan–Meier method. Receiver operating characteristic (ROC) analyses were applied to evaluate the discriminative power of thrombocytopaenia in predicting 90-day mortality. The area under the curve (AUC) was calculated for each ROC analysis. All tests were two-tailed and $p < 0.05$ was considered as significant. All analyses were performed with SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

The patient cohort

Altogether, 617 SAB patients were identified. However, thrombocyte values at blood culture collection were retrieved from only 495 patients. Among these 495 patients, the exclusion criteria were met for 148 patients and constituted pre-bacteraemic risk factors for thrombocytopaenia, i.e. haematologic malignancy ($n = 33$) and acute or chronic liver disease, chronic alcoholism or both ($n = 115$). For analysis, 347 patients with thrombocyte count documented at blood culture collection were included, whereas at day 3 and at day 7, the corresponding patient numbers were 272 and 317, respectively.

From the day of positive blood culture, each patient was provided with an intravenous antibiotic agent effective in vitro against the *S. aureus* blood isolate; 250 (51%) patients received anti-staphylococcal penicillin (cloxacillin), 196 (39%) received cefuroxime or ceftriaxone and 9 (2%) received vancomycin and the rest, 40 (8%), received clindamycin, a carbapenem or other antibiotics. Rifampicin and a fluoroquinolone as an additional antibiotic was provided to 298 (60%) and 247 (50%) patients, respectively. Most patients (91%) received an infectious disease specialist consultation within seven days of positive blood cultures. The vast majority of patients were provided with formal bedside consultation 405 (82%), whereas a minority received informal telephone consultation, 58 (12%), and 32 (6%) were managed without any infectious disease specialist guidance.

Demographics and thrombocytopaenia predisposing factors

Patient demographics, underlying conditions, foreign devices, severity of illness and outcome were categorised according to thrombocytopaenia at the blood culture collection time-point without excluding patients with pre-bacteraemic risks for thrombocytopaenia (Table 1). In total, 32% of all patients had thrombocytes below the reference range at the time of blood culture collection (Table 1). One-third (148, 30%) of patients had pre-bacteraemic risk factors for thrombocytopaenia. Male gender was associated to thrombocytopaenia (72% vs. 59%, $p < 0.01$), whereas no difference in thrombocytopaenia was observed regarding age or place of bacteraemia acquisition. Patients with McCabe's healthy—nonfatal classification had less often thrombocytopaenia (57 vs. 76%, $p < 0.001$), whereas acute or chronic liver disease (27 vs. 13%, $p < 0.001$), chronic alcoholism (22 vs. 11%, $p < 0.01$) and haematological malignancies (16 vs. 2%, $p < 0.001$) were more often associated to thrombocytopaenia at the time of blood culture collection (Table 1). The association of thrombocytopaenia to male gender was due to the high degree of male chronic alcoholics and, after excluding patients with chronic alcoholism, the connection between thrombocytopaenia and male gender disappeared. Severe sepsis and ICU treatment, as well as endocarditis and pneumonia, were all significantly associated to low thrombocyte count (Table 1). A deep infection focus was diagnosed in, altogether, 373 (75%) patients (Table 1).

Thrombocytopaenia in patients without pre-bacteraemic risk factors

Severe sepsis and ICU treatment were strongly associated to thrombocytopaenia at blood culture collection and at days 3 and 7 also when patients with pre-bacteraemic risks for thrombocytopaenia were excluded (Table 2). Patients with endocarditis had more often thrombocytopaenia at blood culture collection and at day 3 (Table 2). Patients with pneumonia had also a tendency to low thrombocytes, but a significant difference was seen only at day 3 (Table 2). Patients with thrombocytopaenia had longer time to defervescence at blood culture collection ($p < 0.001$) and at day 3 ($p < 0.01$), whereas no difference was observed at day 7 (Table 2, Fig. 1a). DIC was approximated by applying a simplified DIC scoring system (and named DIC-like and severe DIC-like conditions), according to thrombocyte count and thromboplastin time results at blood culture collection. However, documentation of thromboplastin time was retrieved for only 84 (24%) patients at blood culture collection. Among patients with recorded thromboplastin time, altogether, 15 (18%) had a DIC-like condition, whereas 2 (2%) had a severe DIC-like condition.

Mortality

The total case fatality in all 495 patients at 28 days was 14% and at 90 days it was 20% (Table 1). When accounting for exclusion criteria, the mortality of patients with thrombocytopaenia at blood culture collection did not differ at days 3, 7 or 28 as compared to patients with normal platelet count, whereas the 90-day mortality was significantly higher among thrombocytopaenic patients (26 vs. 16%, $p < 0.05$) (Table 2). Thrombocytopaenia at days 3 or day 7, as compared to patients with normal platelet count, were associated to higher 28-day and 90-day mortality (Table 2, Fig. 1b).

ROC analyses were performed to evaluate the discriminative power of thrombocytopaenia in predicting 90-day mortality. In ROC analyses, thrombocytopaenia predicted a poor outcome at blood cultures (AUC 0.59, 95% CI 0.52–0.67, $p < 0.05$), at day 3 (AUC 0.68, 95% CI 0.59–0.76, $p < 0.001$) and at day 7 (AUC 0.70, 95% CI 0.60–0.79, $p < 0.001$).

Univariate analysis and Cox proportional hazards regression model analysis of factors predicting 90-day mortality were performed according to thrombocytopaenia at blood culture collection, at day 3 and at day 7 separately (Table 3). In these analysis, the factors previously associated to better prognosis, i.e. lack of fatal underlying diseases, rifampicin therapy and bedside infectious disease specialist consultation, were significantly related to lower mortality (Table 3). Factors related to higher mortality were age over 60 years, endocarditis, pneumonia and telephone infectious disease specialist consultation (Table 3). Thrombocytopaenia ($<150 \times 10^9$/L) at blood culture collection and at days 3 and 7 was significantly related to higher mortality in the univariate analysis (Table 3). Thrombocytopaenia at day 3 indicated a poor outcome ($p = 0.05$) and thrombocytopaenia at day 7 remained a significant denominator ($p < 0.001$) of 90-day mortality in the Cox proportional hazards regression model analysis (Table 3).

ICU treatment was, in the univariate analysis, significantly related to both thrombocytopaenia (Table 1) and higher mortality (Table 3), and these patients formed a significant proportion of all deceased patients. Therefore, we wanted to analyse the prognostic impact of thrombocytopaenia in patients treated outside the ICU. Thrombocytopaenia within 7 days of positive blood cultures for *S. aureus* was a significant denominator of mortality in the Cox proportional hazards regression analysis among patients treated outside the ICU as well (Table 4).

Discussion

The main finding of the present study was that a significant proportion (30%) of cases with thrombocytopaenia in MSSAB were due to pre-bacteraemic thrombocytopaenia risk factors. When these patients were excluded and the known

Table 1 Thrombocytopaenia (thrombocytes < 150 × 10^9/L) at blood culture collection in 495 patients with methicillin-sensitive *Staphylococcus aureus* bacteraemia (MS-SAB) stratified according to patient demographics, underlying conditions, bacteraemia predisposing foreign-body devices and outcome

At blood culture collection					
Variables	*N* = 495	<150[a], *n* = 160 (32)	>150[a], *n* = 335 (68)	OR (95% CI)	*p*-Value
Demographics					
Male gender	312 (63)	115 (72)	197 (59)	1.79 (1.19–2.69)	<0.01
Age > 60 years	234 (47)	69 (43)	165 (49)	0.78 (0.56–1.14)	NS
Nosocomial SAB	246 (50)	79 (49)	167 (50)	0.98 (0.67–1.43)	NS
Underlying conditions					
Healthy—nonfatal disease[b]	346 (70)	91 (57)	255 (76)	0.41 (0.28–0.62)	<0.001
Diabetes mellitus	81 (16)	19 (12)	62 (19)	0.59 (0.34–1.03)	NS
Coronary disease	114 (23)	30 (19)	84 (25)	0.69 (0.43–1.10)	NS
Chronic lung disease	86 (17)	21 (13)	65 (19)	0.63 (0.37–1.07)	NS
Chronic renal failure[c]	64 (13)	20 (13)	44 (13)	0.95 (0.54–1.66)	NS
Acute or chronic liver disease	86 (17)	43 (27)	43 (13)	2.50 (1.55–4.01)	<0.001
Malignancy (non-haematological)	50 (10)	17 (11)	33 (10)	1.09 (0.59–2.02)	NS
Malignancy (haematological)	33 (7)	26 (16)	7 (2)	9.09 (3.85–21.5)	<0.001
Chronic alcoholism	73 (15)	35 (22)	38 (11)	2.19 (1.32–3.62)	<0.01
Injection drug use[d]	58 (12)	22 (14)	36 (11)	1.32 (0.75–2.34)	NS
HIV infection	11 (2)	6 (4)	5 (1)	2.57 (0.77–8.56)	NS
Previous hospitalisation[e]	259 (52)	93 (58)	166 (50)	1.41 (0.97–2.07)	NS
Previous facility care[e]	12 (2)	5 (3)	7 (2)	1.51 (0.47–4.84)	NS
Severity of illness					
Severe sepsis	50 (10)	27 (17)	23 (7)	2.75 (1.52–4.98)	<0.01
ICU treatment at blood culture	111 (22)	49 (31)	62 (19)	1.94 (1.26–3.00)	<0.01
ICU treatment within 7 days	147 (30)	64 (40)	83 (25)	2.02 (1.35–3.01)	<0.01
Deep infection focus	373 (75)	117 (73)	256 (76)	0.84 (0.55–1.29)	NS
Endocarditis	77 (16)	35 (22)	42 (13)	1.95 (1.19–3.21)	<0.01
Pneumonia	189 (38)	74 (46)	115 (34)	1.65 (1.12–2.42)	<0.05
Foreign-body devices					
Central venous catheter	75 (15)	28 (18)	47 (14)	1.30 (0.78–2.17)	NS
Prosthetic heart valve[f]	19 (4)	8 (5)	11 (3)	1.55 (0.61–3.93)	NS
Cardiac pacemaker	14 (3)	6 (4)	8 (2)	1.59 (0.54–4.67)	NS
Mortality					
At 3 days	9 (2)	5 (3)	4 (1)	2.67 (0.71–10.1)	NS
At 7 days	22 (4)	13 (8)	9 (3)	3.20 (1.34–7.66)	<0.01
At 28 days	68 (14)	34 (21)	34 (10)	2.39 (1.42–4.01)	<0.01
At 90 days	98 (20)	47 (29)	51 (15)	2.32 (1.47–3.64)	<0.001

All patients with thrombocyte levels assessed at blood culture collection were included. Values are expressed as *n* (%) and odds ratios (ORs) with 95% confidence intervals (CIs)

NS non-significant

[a] 150 × 10^9/L

[b] According to McCabe's classification [31]

[c] Serum creatinine > 180 mmol/L

[d] Within 6 months prior to SAB

[e] Within 2 months prior to SAB

[f] Mechanical or biological valve

Table 2 Thrombocyte count at blood culture collection and at days 3 and 7 in patients with methicillin-sensitive *Staphylococcus aureus* bacteraemia (MS-SAB) categorised according to the cut-off value 150 $\times 10^9$/L

Variables	Thrombocytes at blood culture ($n = 347$)			Thrombocytes at day 3 ($n = 272$)			Thrombocytes at day 7 ($n = 317$)		
	<150[a], $n = 82$ (24)	>150[a], $n = 265$ (76)	*p*-Value	<150[a], $n = 63$ (23)	>150[a], $n = 209$ (77)	*p*-Value	<150[a], $n = 24$ (8)	>150[a], $n = 293$ (92)	*p*-Value
Severity of illness									
Severe sepsis[b]	13 (16)	13 (5)	<0.01	9 (14)	10 (5)	<0.05	5 (21)	15 (5)	<0.01
ICU treatment[b]	23 (28)	45 (17)	<0.05	–	–	–	–	–	–
ICU treatment[c]	31 (38)	61 (23)	<0.01	25 (40)	51 (24)	<0.05	13 (54)	71 (24)	<0.01
Infection foci									
Deep infection focus	61 (74)	205 (77)	NS	49 (78)	159 (76)	NS	20 (83)	228 (78)	NS
Pneumonia	34 (41)	87 (33)	NS	31 (49)	72 (34)	<0.05	9 (38)	108 (37)	NS
Endocarditis	18 (22)	32 (12)	<0.05	17 (27)	21 (10)	<0.01	6 (25)	40 (14)	NS
Osteomyelitis	18 (22)	86 (32)	NS	15 (24)	63 (30)	NS	6 (25)	88 (30)	NS
Foreign body	14 (17)	48 (18)	NS	9 (14)	43 (21)	NS	6 (25)	48 (16)	NS
Deep abscesses	30 (37)	107 (40)	NS	25 (40)	83 (40)	NS	8 (33)	119 (41)	NS
Defervescence[d] (days, mean ± SD)	8.60 (±12.1)	5.40 (±6.7)	<0.001	7.30 (±12.4)	5.40 (±6.2)	<0.01	7.80 (±14.7)	6.30 (±8.1)	NS
Mortality									
Within 3 days	2 (2)	3 (1)	NS	0	1 (<0.5)	–	–	–	–
Within 7 days	5 (6)	7 (3)	NS	3 (5)	5 (2)	NS	2 (8)	2 (1)	<0.01
Within 28 days	15 (18)	28 (11)	NS	16 (25)	17 (8)	<0.001	10 (42)	23 (8)	<0.001
Within 90 days	21 (26)	42 (16)	<0.05	20 (32)	27 (13)	<0.01	12 (50)	42 (14)	<0.001

Patients with pre-bacteraemic conditions predisposing to thrombocytopaenia (haematological malignancies, chronic alcoholism and acute or chronic liver diseases, $n = 148$) have been excluded. Values are expressed as *n* (%), unless otherwise stated

NS non-significant

[a] 150×10^9 /L

[b] At blood culture collection time-point

[c] Within 7 days

[d] Student's *t*-test

risk factors for fatal outcome in SAB were taken into account, thrombocytopaenia at blood culture collection was no longer an independent predictor of fatal outcome as suggested by many previous studies. When excluding pre-bacteraemic risk factors for thrombocytopaenia, low platelet count at day 3 indicated a poor outcome ($p = 0.05$) and thrombocytopaenia at day 7 was observed to be an independent predictor of fatal outcome ($p < 0.001$), with a hazard ratio at the same magnitude as previously recognised risk factors.

Thrombocytopaenia is commonly observed in severe infections, including SAB [14, 15, 23–28], and the prognostic value of thrombocytopaenia is acknowledged by severity of illness score estimators commonly applied in sepsis, e.g. the MODS estimator (Multiple Organ Dysfunction Score) [35] and the SOFA estimator (Sequential Organ Failure Assessment score) [36]. However, in addition to severe illnesses, thrombocytopaenia may be associated to background illnesses such as chronic alcoholism [37]. Hence, a reliable evaluation of the independent prognostic impact of thrombocytopaenia in SAB requires the exclusion of all pre-bacteraemic conditions that may cause thrombocytopaenia. The present study observed a significant connection of low thrombocyte count to chronic alcoholism, acute and chronic liver disease and haematological malignancies, and all these parameters were excluded from the final analyses. Among previous studies on the prognostic impact of thrombocytopaenia in SAB, only one has accounted for pre-bacteraemic thrombocytopaenic parameters and excluded patients with haematologic and other actively treated malignancies, cirrhosis and human immunodeficiency virus [15]. However, chronic alcoholism as an aetiology for thrombocytopaenia was not used as an exclusion criterion in this report [15]. Therefore, it has not been clarified what prognostic role thrombocytopaenia in SAB would have in patients without pre-bacteraemic risk factors.

Thrombocytopaenia in patients with severe sepsis and ICU treatment may result from various mechanisms such as systemic haemostasis disorder, coagulation cascade activation resulting in DIC or through colonisation of thrombocytes on endovascular epithelium in endocarditis or thromboembolic

Table 3 Cox proportional hazards regression model for prognostic factors for 90-day mortality in methicillin-sensitive *Staphylococcus aureus* bacteremia (MS-SAB) patients

	Univariate analysis				Cox regression analysis	
At blood culture collection, $n = 347$	Died, $n = 63$ (18)	Survived, $n = 284$ (82)	OR (95% CI)	p-Value	HR (95% CI)	p-Value
Age > 60 years	47 (69)	142 (50)	2.94 (1.59–5.42)	<0.001	1.87 (1.04–3.38)	<0.05
Healthy—nonfatal disease[a]	30 (48)	227 (80)	0.23 (0.13–0.41)	<0.001	0.35 (0.21–0.59)	<0.001
Intensive care unit[b]	20 (32)	48 (17)	2.29 (1.24–4.23)	<0.05	–	–
Endocarditis	16 (25)	34 (12)	2.50 (1.28–4.90)	<0.05	3.68 (1.92–7.03)	<0.001
Pneumonia	40 (63)	81 (29)	4.36 (2.46–7.74)	<0.001	3.62 (2.08–6.28)	<0.001
Rifampicin therapy ≥ 14 days[c]	22 (35)	160 (56)	0.42 (0.24–0.73)	<0.01	0.31 (0.18–0.56)	<0.001
Bedside IDS consultation[d]	44 (70)	249 (88)	0.33 (0.17–0.62)	<0.001	0.30 (0.17–0.53)	<0.001
Telephone IDS consultation[d]	11 (17)	24 (8)	2.30 (1.06–4.97)	<0.05	–	–
Thrombocytes < 150 $\times 10^9$/L	21 (33)	61 (21)	1.83 (1.01–3.32)	<0.05	–	–
Thrombocytes < 100 $\times 10^9$/L	10 (16)	23 (8)	2.14 (0.96–4.76)	NS		
At day 3, $n = 272$	Died, $n = 47$ (17)	Survived, $n = 225$ (83)	OR (95% CI)	p-Value	HR (95% CI)	p-Value
Age > 60 years	28 (60)	132 (59)	4.80 (2.27–10.12)	<0.001	3.14 (1.55–6.39)	<0.01
Healthy—nonfatal disease[a]	37 (78)	98 (44)	0.15 (0.08–0.30)	<0.001	0.28 (0.16–0.51)	<0.001
Intensive care unit[b]	18 (38)	181 (80)	1.90 (0.94–3.88)	NS		
Endocarditis	14 (30)	41 (18)	3.06 (1.43–6.56)	<0.01	3.01 (1.48–6.11)	<0.01
Pneumonia	28 (60)	75 (33)	2.95 (1.55–5.62)	<0.01	2.60 (1.39–4.84)	<0.01
Rifampicin therapy ≥ 14 days[c]	28 (60)	75 (33)	0.52 (0.27–0.98)	<0.05	0.36 (0.19–0.66	<0.01
Bedside IDS consultation[d]	34 (72)	198 (88)	0.36 (0.17–0.76)	<0.05	0.43 (0.22–0.83)	<0.05
Telephone IDS consultation[d]	10 (21)	20 (9)	2.77 (1.20–6.39)	<0.05	–	–
Thrombocytes < 150 $\times 10^9$/L	20 (43)	43 (19)	3.14 (1.61–6.11)	<0.01	1.83 (1.00	=0.05
Thrombocytes < 100 $\times 10^9$/L	9 (19)	20 (9)	2.43 (1.03–5.73)	<0.05	–	–
At day 7, $n = 317$	Died, $n = 54$ (17)	Survived, $n = 263$ (83)	OR (95% CI)	p-Value	HR (95% CI)	p-Value
Age > 60 years	42 (78)	126 (48)	3.81 (1.92–7.55)	<0.001	2.68 (1.40–5.16)	<0.01
Healthy—nonfatal disease[a]	23 (43)	204 (78)	0.22 (0.12–0.40)	<0.001	0.36 (0.20–0.64)	<0.01
Intensive care unit[b]	15 (28)	45 (17)	1.86 (0.95–3.67)	NS		
Endocarditis	14 (26)	32 (12)	2.53 (1.24–5.15)	<0.05	2.58 (1.31–5.06)	<0.01
Pneumonia	32 (59)	85 (32)	3.05 (1.67–5.56)	<0.001	2.86 (1.60–5.11)	<0.001
Rifampicin therapy ≥ 14 days[c]	22 (41)	149 (57)	0.53 (0.29–0.95)	<0.05	0.32 (0.17–0.58)	<0.001
Bedside IDS consultation[d]	41 (76)	235 (89)	0.38 (0.18–0.79)	<0.05	–	
Telephone IDS consultation[d]	10 (19)	20 (8)	2.76 (1.21–6.30)	<0.05	2.53 (1.26–5.08)	<0.01
Thrombocytes < 150 $\times 10^9$/L	12 (22)	12 (5)	5.98 (2.52–14.18)	<0.001	3.64 (1.79–7.43)	<0.001
Thrombocytes < 100 $\times 10^9$/L	6 (11)	4 (2)	8.09 (2.20–29.8)	<0.001	–	

Analyses have been performed at blood culture collection, at day 3 and at day 7. Patients with pre-bacteraemic parameters strongly predisposing to thrombocytopaenia (haematological malignancy, chronic alcoholism or acute or chronic liver disease, $n = 148$) have been excluded. Data are no. (%) of patients. Hazards ratio (HRs) and 95% confidence intervals (CIs) are presented

NS non-significant

[a] McCabe and Jackson [31]

[b] At blood culture collection time-point

[c] Additional antibiotic therapy

[d] *IDS* infectious disease specialist

complications such as stroke [18–20, 22]. Hence, the prognostic impact of thrombocytopaenia in SAB should be performed separately for non-ICU patients. However, only one previous report has adjusted the mortality analysis for septic shock and DIC [15], whereas separate evaluations of the prognostic impact of thrombocytopaenia for non-ICU patients have not been performed [23–28]. The present study did not document fibrin marker laboratory values (D-dimer or fibrinogen) and,

Table 4 Cox proportional hazards regression model for prognostic factors for 90-day mortality in 233 methicillin-sensitive *Staphylococcus aureus* bacteremia (MS-SAB) patients managed without intensive care unit (ICU) treatment during the initial seven days of positive blood culture

	Died, $n = 35$ (15)	Survived, $n = 198$ (85)	OR (95% CI)	p-Value	HR (95% CI)	p-Value
Age > 60 years	28 (80)	92 (46)	4.61 (1.92–11.05)	<0.001	3.61 (1.55–8.45)	<0.01
Healthy—nonfatal disease[a]	11 (31)	156 (79)	0.12 (0.06–0.27)	<0.001	0.25 (0.12–0.54)	<0.001
Endocarditis	6 (17)	18 (9)	2.07 (0.76–5.65)	NS		
Pneumonia	20 (57)	54 (27)	3.56 (1.70–7.44)	<0.001	3.15 (1.58–6.30)	<0.01
Rifampicin therapy ≥ 14 days[b]	14 (40)	106 (54)	0.58 (0.28–1.20)	NS		
Bedside IDS consultation[c]	26 (74)	181 (91)	0.27 (0.11–0.67)	<0.01	0.36 (0.16–0.79)	<0.05
Telephone IDS consultation[c]	6 (17)	12 (6)	3.21 (1.12–9.21)	<0.05	–	
Thrombocytes < 150 $\times 10^9$/L[d]	5 (14)	6 (3)	5.33 (1.53–18.57)	<0.01	3.36 (1.25–9.05)	<0.05

Patients with pre-bacteraemic parameters predisposing to thrombocytopaenia (haematological malignancy, chronic alcoholism or acute or chronic liver disease, $n = 148$) have been excluded. Data are no. (%) of patients. Hazards ratio (HRs) and 95% confidence intervals (CIs) are presented

NS non-significant

[a] McCabe and Jackson [31]

[b] Additional antibiotic therapy

[c] *IDS* infectious disease specialist

[d] Thrombocytopaenia within 7 days

therefore, did not manage to identify the exact number of DIC cases. However, applying a simplified DIC score system demonstrated that the possible DIC occurrence was very low [15]. After excluding all patients with ICU treatment within the first week, thrombocytopaenia within the first 7 days remained a strong negative prognostic parameter.

Previous studies on thrombocytopaenia and SAB have measured the thrombocyte count at onset of SAB [15, 23–28]. Thrombocytopaenia has been defined as thrombocyte count less than 100×10^9/L [23] or less than 150×10^9/L [15, 24, 25], whereas two reports have compared median thrombocyte values [26, 28]. Most studies present thrombocytopaenia as a negative prognostic parameter for 14-day [24] or 30-day mortality in multivariate analysis [15, 23–28]. The present study deviates from previous reports on thrombocytopaenia and SAB in many aspects. We present a strong connection between 90-day mortality and thrombocytopaenia at three different time-points during the initial week of SAB. In the Cox regression analysis, thrombocytopaenia at day 3 indicated a poor outcome and thrombocytopaenia at day 7 past positive blood cultures was an independent negative prognostic parameter for 90-day outcome. The negative prognostic impact of thrombocytopaenia accentuated from blood culture collection to day 3 and, further, to day 7. Moreover, the ROC analysis, evaluating the discriminative power of thrombocytopaenia in predicting 90-day mortality, was statistically significant at blood culture and at days 3 and 7. However, the AUC varied from 0.59 to 0.70, which is much lower than previously reported [15]. Hence, in contrast to previous reports, the main impact on outcome due to thrombocytopaenia is not until 3 to 7 days past blood culture collection.

However, although previous reports on thrombocytopaenia and SAB have determined thrombocytes at SAB onset only [15, 23–28], there are other reports available on the prognostic impact of low thrombocyte count in severely ill patients as well as infectious diseases patients, in which thrombocytes have been determined at several time-points [38–40]. Akca et al. studied thrombocytopaenia in ICU patients and concluded that, among severely ill patients, late thrombocytopaenia, as compared to early thrombocytopaenia, is more predictive of death [38]. Sy et al. documented thrombocyte count at days 1, 4, 8 and 12 in patients with infective endocarditis with *S. aureus* as the most common pathogen and concluded that thrombocytopaenia at presentation of infective endocarditis increases the risk for 6-month mortality by 2.5-fold, whereas thrombocytopaenia at day 8 increases the risk by 5.1-fold [39]. Nijsten et al. observed that, among non-surviving ICU patients, the thrombocyte count decreases several days after ICU admission and the lack of increase in thrombocyte count during the first 10 days is a strong negative prognostic parameter in the ICU [40]. Hence, the results of the present study are in line with the observations made by Akca et al. and Sy et al. and expand the findings of Sy et al. to all SAB cases [38–40].

The 30- and 90-day mortality rates in previous studies on thrombocytopaenia and SAB have been high (13–44% and 49–50%, respectively) [15, 23–28]. This is much higher than in the present study, with overall mortality rates of 14% at 28 days and 20% at 90 days. Most previous reports on thrombocytopaenia and SAB have included a high degree of MRSA bacteraemia (14–100%) and the total amount of various deep infection foci diagnosed have been low (7–24%), including endocarditis (3–27%). Furthermore, there is no mention of any infectious diseases specialist consultation guided SAB management [15, 23–28]. MRSA bacteraemia is

known to delay effective antibiotic therapy onset and has been connected to poorer outcome [7, 8], whereas vancomycin therapy, as compared to beta-lactam antibiotics, has been shown to weaken prognosis in SAB [9, 10]. Thorough deep infection foci localisation improves outcome [2, 11] and infectious diseases specialist consultation improves clinical practice, enhances deep infection focus identification and betters outcome [1, 11]. The present study included only MS-SAB cases and only 2% received vancomycin therapy. Hence, each patient received proper antibiotic therapy from the first day of SAB and few patients received vancomycin, thus minimising the impact of differences in empirical and definitive antibiotic therapy. The presence of only MS-SAB and proper antibiotic therapy from the first day of SAB in connection with a vast amount of diagnosed deep infection foci and infectious diseases specialist consultation guided SAB management have contributed to the low mortality in the present study.

The present study includes weaknesses that have to be taken into account when interpreting the results. First, the present study monitored thrombocyte count at blood culture collection and at days 3 and 7. These time-points were, however, arbitrarily chosen, and it is recommendable that further studies document thrombocyte count daily for more reliable and robust statistical analyses. Second, due to the retrospective nature of the study, the use of pre-bacteraemic medication was only partially documented and, thus, the influence on thrombocyte count by anti-thrombotic or anti-coagulant medication may not have been properly established. Third, thorough prognostic analyses of thrombocytopaenia in SAB require taking into account the possibility of any DIC phenomenon [15]. The present study did not document or monitor fibrin marker laboratory values (D-dimer or fibrinogen) and, hence, exact DIC criteria could not be determined [34]. However, we applied a simplified DIC scoring system according to thrombocyte count and thromboplastin time, and only 2% of patients fulfilled part of the criteria for severe DIC. Thus, most probably, the low occurrence of any potential DIC phenomenon has not influenced the results.

In conclusion, our data suggest that thrombocytopaenia in SAB is an independent prognostic parameter. In contrast to previous studies, thrombocytopaenia at the time of blood culture collection was not a prognostic parameter when other factors affecting risk for fatal outcome were taken into account. However, thrombocytopaenia on day 3 indicated a poor outcome and thrombocytopaenia at day 7 was a significant independent negative prognostic marker that has not been previously reported. Corresponding results have been achieved earlier for severely ill ICU patients and patients with endocarditis. The authors encourage clinicians managing SAB patients to observe trends in thrombocyte count, as these may reflect outcome.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement The trial was approved by the institutional review board of Helsinki University Central Hospital and the ethical committee of Helsinki University Central Hospital. A written informed consent was provided by each patient.

Funding The study has been supported by grants from the Medical Society of Finland and the foundations Dorothea Olivia, Karl Walter och Jarl Walter Perkléns minne and Svenska Kulturfonden. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

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