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Westgeest, A.C.; Ruffin, F.; Kair, J.L.; Park, L.P.; Korn, R.E.; Webster, M.E.; ... ; Fowler, V.G. .J.r.

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Original article

The association of female sex with management and mortality in patients with *Staphylococcus aureus* bacteraemia

Annette C. Westgeest [1, 2, *], Felicia Ruffin [1], Jackson L. Kair [1], Lawrence P. Park [1, 3], Rachel E. Korn [1], Maren E. Webster [1], Leo G. Visser [2], Emile F. Schippers [2, 4], Mark G.J. de Boer [2, 5], Merel M.C. Lambregts [2], Vance G. Fowler Jr. [1, 6]

[1] *Division of Infectious Diseases, Duke University, Durham, NC, USA*
[2] *Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands*
[3] *Duke Global Health Institute, Duke University, Durham, NC, USA*
[4] *Department of Internal Medicine, Haga Teaching Hospital, The Hague, The Netherlands*
[5] *Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands*
[6] *Duke Clinical Research Institute, Durham, NC, USA*

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ABSTRACT

Objectives: The association of biological female sex with outcome in patients with *Staphylococcus aureus* bacteraemia remains unresolved. The aim of this study was to determine the independent association of female sex with management and mortality in patients with *S. aureus* bacteraemia.
Methods: This is a post hoc analysis of prospectively collected data from the *S. aureus* Bacteraemia Group Prospective Cohort Study. Adult patients with monomicrobial *S. aureus* bacteraemia at Duke University Medical Center were enrolled from 1994 to 2020. Univariable and multivariable Cox regression analyses were performed to assess differences in management and mortality between females and males.
Results: Among 3384 patients with *S. aureus* bacteraemia, 1431 (42%) were women. Women were, as compared with men, more often Black (581/1431 [41%] vs. 620/1953 [32%], p < 0.001), haemodialysis dependent (309/1424 [22%] vs. 334/1940 [17%], p 0.001) and more likely to be infected with methicillin-resistant *S. aureus* (MRSA) (697/1410 [49%] MRSA in women vs. 840/1925 [44%] MRSA in men, p 0.001). Women received shorter durations of antimicrobial treatment (median 24 [interquartile range 14–42] vs. 28 [interquartile range 14–45] days, p 0.005), and were less likely to undergo transesophageal echocardiography as compared with men (495/1430 [35%] vs. 802/1952 [41%], p < 0.001). Despite these differences, female sex was not associated with 90-day mortality in either univariable (388/1431 [27%] in women vs. 491/1953 [25%] in men, p 0.204) or multivariable analysis (adjusted hazard ratio for women 0.98 [95% CI, 0.85–1.13]).
Discussion: Despite significant differences in patient characteristics, disease characteristics, and management, women and men with *S. aureus* bacteraemia have a similar mortality risk. **Annette C. Westgeest, Clin Microbiol Infect 2023;29:1182**

Introduction

Staphylococcus aureus, a major cause of bloodstream infections, is associated with high morbidity and mortality [1,2]. Previous studies have reported conflicting results regarding sex-related differences in *S. aureus* bacteraemia (SAB). Some [3–7], but not all [8–10], previous studies have reported higher mortality rates in women with SAB compared with men. Sex-related differences in outcome may be because of a variety of social or biological factors. For example, in a superantigen-mediated model of toxic shock using human leukocyte antigen (HLA) class II transgenic mice, women were more susceptible to lethal toxic shock caused by *S. aureus* enterotoxin B [11]. Alternately, previous cohort studies

* Corresponding author. Annette C. Westgeest, Department of Infectious Diseases, Leiden University Medical Center, C5-P, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
E-mail address: a.c.westgeest@lumc.nl (A.C. Westgeest).

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may simply have been limited by small sample size and study design. As a result, the true interaction between sex and outcome among patients with SAB is unknown.

The primary aim of this study was to determine the independent association of female sex with mortality in patients with SAB. Next, we sought to identify differences in patient, disease and management characteristics between women and men. The large study size and detailed prospective data collection, including bacterial genotyping provided the unique possibility to address the ongoing controversy on sex differences in SAB.

Methods

Study population

This is a post hoc analysis of prospectively collected data from the *S. aureus* Bacteraemia Group Prospective Cohort Study (SABG-PCS). Adult (≥18 years), hospitalized, non-neutropenic (neutrophil count >1 × 10^9/L) patients with monomicrobial SAB at Duke University Medical Center were enrolled from 1994 to 2020. Beginning in 2001, written informed consent was obtained from patients or their legal representatives to comply with Health Insurance Portability and Accountability Act regulations. If a patient died before the notification of their blood culture results, the patient was included using an institutional review board–approved Notification of Decedent Research. From March until September 2020, because of the COVID-19 pandemic, enrolment was temporarily paused. If a patient experienced multiple SAB episodes, only the initial episode was included. Follow-up was done through participants' medical records assessment at 90 days after first positive blood culture for all patients. Both clinical and microbiological data are collected in the SABG-PCS. Enrolment and data collection methods have been published previously [2].

Definitions

Sex was defined as biological sex assigned at birth [12]. The following sources were considered primary endovascular infection: central venous catheters, arterio-venous fistulas, subcutaneous catheters, intracardiac devices and endovascular grafts [13]. The route of acquisition was classified as hospital-acquired, healthcare-associated or community-acquired as previously defined [14]. The duration of symptoms was defined as the time from the patient-reported onset of symptoms to the day of first positive blood culture. Recurrent SAB after this first episode was defined as a second episode of SAB after resolution of this first and occurring at least 14 days after the last positive blood culture associated with this episode [15]. Persistent bacteraemia was defined as ≥3 days of positive blood cultures after appropriate treatment was initiated [2]. Patients were considered to have a hematogenous metastatic infection if they exhibited any of the following conditions during their hospitalization for SAB: infective endocarditis, vertebral osteomyelitis, septic arthritis, septic emboli, septic thrombophlebitis or deep tissue abscess [2]. Main antibiotic regimen was defined as the primary antibiotic used for definitive treatment of the episode of SAB.

Bacterial genotyping

The *S. aureus* isolates from the first blood culture obtained from enrolled patients underwent *spa* genotyping and further analyses to determine USA300 clone as previously described [2,16].

Outcome measures and statistical analysis

The primary study outcome was 90-day mortality, stratified by sex. The time count started from the day of the first positive blood culture. Secondary outcomes were 30-day mortality, and differences in patient, disease and management characteristics between women and men. Data were presented as counts plus percentages or proportions for categorical variables and as medians plus interquartile ranges (IQR) for continuous variables. Fisher's exact, Chi-square and Mann-Whitney U tests were used to analyse differences in patient and disease characteristics. Survival curves were constructed using the Kaplan-Meier method. Cox regression analysis was used to assess the independent effect of female sex on mortality. Variables with $p < 0.01$ in univariable analysis and clinically relevant variables were added to the multivariable analysis. To evaluate differences in subgroups, mortality by sex was additionally analysed for methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) separately, stratified for route of acquisition and for different time periods. All statistical analyses were performed using IBM SPSS statistics version 28.0.1.1.

Ethical approval

Ethical approval was granted by the Duke University Medical Center institutional review board.

Results

A total of 3384 patients were enrolled from 1994 to 2020. Among them, 1431 (42%) were women. Median age was 60 years in both sexes (Fig. S2). Female patients with SAB were, as compared with male patients, more frequently Black (581/1431 [41%] vs. 620/1953 [32%], $p < 0.001$), more often haemodialysis dependent (309/1424 [22%] vs. 334/1940 [17%], p 0.001), more likely to have implanted foreign material (817/1422 [58%] vs. 1014/1949 [52%], p 0.002) and more likely to have used corticosteroids in the past month (315/1422 [22%] vs. 355/1933 [18%], p 0.008, Table 1). By contrast, men more frequently had a history of injection drug use (142/1933 [7%] vs. 64/1422 [5%], p 0.001) and experienced higher rates of metastatic infection (813/1952 [42%] vs. 512/1431 [36%], p 0.001).

Microbiological characteristics

Women were more likely to be infected with MRSA as opposed to MSSA, compared with males (697/1410 [49%] MRSA in female patients vs. 840/1925 [44%] MRSA in male patients, p 0.001). In the 3136 isolates that were genotyped, 516 distinct *spa* types were identified, which were equally distributed between the sexes (p 0.265, Table S1). Ninety-one per cent (2599/2843) of the isolates with an identified Clonal Complex (CC) belonged to one of the six most common CCs: CC002, CC004, CC008, CC012, CC084, and CC0189, which were also similarly distributed between sexes (p 0.080, Table S2). The percentage of patients infected with the USA300 clone was equal in women and men (respectively 130/1326 and 173/1810, both 10%, p 0.854, Table 1).

Medical management

Women were less likely to undergo transesophageal echocardiography (TEE) as compared with men (495/1430 [35%] vs. 802/1952 [41%], $p < 0.001$). There was no difference in transthoracic

Table 1
Patient and clinical characteristics stratified by sex

	All patients $N = 3384$	Female patients $N = 1431$	Male patients $N = 1953$	p[a]
Demographics				
Female sex, *n* (%)	1431 (42.3)	1431 (100)	0 (0)	
Age in years, *median (IQR)*	60 (47–70)	60 (47–71)	60 (48–70)	0.164
Race, *n* (%)				<0.001
White	2063 (61.0)	806 (56.3)	1257 (64.4)	
Black	1201 (35.5)	581 (40.6)	620 (31.7)	
Other	120 (3.5)	44 (3.1)	76 (3.9)	
Comorbidities, *n* (%)				
Diabetes mellitus	1296 (38.5)	562 (39.5)	734 (37.8)	0.316
Haemodialysis dependent	643 (19.1)	309 (21.7)	334 (17.2)	0.001
Organ transplant	218 (6.5)	78 (5.5)	140 (7.2)	0.047
Injection drug use	206 (6.1)	64 (4.5)	142 (7.3)	0.001
Corticosteroid use past 30 d	670 (20.0)	315 (22.2)	355 (18.4)	0.008
Foreign body present	1831 (54.3)	817 (57.5)	1014 (52.0)	0.002
Initial source of bacteraemia, *n* (%)				0.037
Endovascular	912 (27.0)	421 (29.4)	491 (25.1)	
Pulmonary	319 (9.4)	136 (9.5)	183 (9.4)	
Skin/soft tissue	707 (20.9)	301 (21.0)	406 (20.8)	
Other	770 (22.8)	311 (21.7)	459 (23.5)	
Unknown	676 (20.0)	262 (18.3)	414 (21.2)	
Micro-organism, *n* (%)				
Methicillin-resistance (MRSA)	1537 (46.1)	697 (49.4)	840 (43.6)	0.001
USA300[b]	303 (9.7)	130 (9.8)	173 (9.6)	0.854
Presentation, *median (IQR)*				
Days of symptoms until diagnosis[c]	2 (1–5)	2 (1–4)	2 (1–5)	0.014
APS score	8 (5–13)	9 (5–13)	8 (5–13)	0.037
Route of acquisition, *n* (%)				0.009
Hospital-acquired	920 (27.2)	405 (28.4)	515 (26.4)	
Healthcare-associated	1878 (55.6)	810 (56.8)	1068 (54.8)	
Community-acquired	579 (17.1)	212 (14.9)	367 (18.8)	
Persistence				
Persistent bacteraemia[d], *n* (%)	1269 (37.5)	517 (36.1)	752 (38.5)	0.161
No. of days positive blood cultures, *median (IQR)*	1 (1–4)	1 (1–4)	1 (1–4)	0.210
Disease management				
TTE performed, *n* (%)	2540 (75.3)	1057 (74.0)	1483 (76.2)	0.158
TEE performed, *n* (%)	1297 (38.4)	495 (34.6)	802 (41.1)	<0.001
Duration of antibiotics, *median (IQR)*	28 (14–44)	24 (14–42)	28 (14–45)	0.005
Intervention performed[e], *n* (%)	1656 (49.1)	702 (49.3)	954 (48.9)	0.834
Clinical outcomes, *n* (%)				
Metastatic infection	1325 (39.2)	512 (35.8)	813 (41.6)	0.001
Recurrent bacteraemia[f]	317 (9.4)	147 (10.3)	170 (8.7)	0.135
Mortality 30 d	682 (20.2)	301 (21.0)	381 (19.5)	0.278
Mortality 90 d	879 (26.0)	388 (27.1)	491 (25.1)	0.204

Values are counts (%) for categorical variables and medians (interquartile ranges) for continuous variables. APS assessed at time of patient's first blood culture.
APS, acute physiology score; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.
[a] Fisher's exact, Mann-Whitney U, and Pearson Chi-Square tests were used in the analyses.
[b] USA300 status was missing in 248 (7%) patients. For all other variables, missing data was <3%.
[c] More than 14 days of symptoms was set as 14 days.
[d] Defined as 3 days or more of positive blood cultures.
[e] Whether an intervention was performed to treat the bacteraemia (e.g. surgery, drainage, line or device removal).
[f] Recurrent SAB means recurrence after this first SAB episode.

echocardiography use between sexes. Women received shorter durations of antimicrobial treatment (median 24 [IQR 14–42] vs. 28 [IQR 14–45] days, p 0.005) compared with men (Table 1 and Fig. S3). The main antibiotic regimen was similar in women and men with MRSA bacteraemia but differed significantly in MSSA bacteraemia. Male patients with MSSA bacteraemia were more often treated with cefazolin or an anti-staphylococcal penicillin, whereas female patients with MSSA bacteraemia were more often treated with other non-first-choice antibiotic regimens (p < 0.006, Table 2).

Outcome

Despite differences in clinical presentation and management of SAB in women and men, no significant differences were noted in 90-day mortality in either univariable (388/1431 [27%] in women vs. 491/1953 [25%] in men, p 0.204, Table 1) or multivariable analysis (adjusted hazard ratio for women 0.98, 95% CI, 0.85–1.13, Fig. 1). Thirty-day mortality was also similar in women and men (301/1431 [21%] in women vs. 381/1953 [20%] in men, p 0.278). In the patients who died within 90 days, the median time from first positive blood culture to death was similar in both sexes (median 13 [IQR 5–27] days in women vs. 12 [IQR 4–28] days in men, p 0.346, Fig. 2). When stratified for MSSA versus MRSA, no difference in mortality between sexes was found in either group (Table S3). Furthermore, no significant differences in mortality between women and men were noted across study time periods (1994–2002; 2003–2011; 2012–2020, Table S4) or when analyses were stratified by route of acquisition (community-acquired, healthcare-associated or hospital-acquired SAB; Table S5).

Table 2
Main antibiotic regimen for patients with MRSA and MSSA bacteraemia stratified by sex

Main antibiotic regimen	All patients	Female patients	Male patients	p[a]
MRSA bacteraemia, *n* (%)	*n* = 1498	*n* = 679	*n* = 819	0.29
Vancomycin	1332 (88.9)	595 (87.6)	737 (90.0)	
Daptomycin	69 (4.6)	33 (4.9)	36 (4.4)	
Other[b]	97 (6.5)	51 (7.5)	46 (5.6)	
MSSA bacteraemia, *n* (%)	*n* = 1746	*n* = 689	*n* = 1057	0.006
Cefazolin	842 (48.2)	318 (46.2)	524 (49.6)	
Anti-staphylococcal penicillin	380 (21.8)	135 (19.6)	245 (23.2)	
Other[b]	524 (30.0)	236 (34.3)	288 (27.2)	

Values are counts (%). Data were missing in <3%.
MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.
[a] Pearson Chi-Square tests were used for the analyses.
[b] Other antibiotics used in MSSA bacteraemia were mainly vancomycin, ceftriaxone and daptomycin. Other antibiotics used in MRSA bacteraemia were mainly linezolid.

Discussion

The interaction between female sex and mortality in SAB—and bloodstream infections in general—has been controversial for decades [6,17]. The historical tendency to include fewer female patients in scientific studies may have contributed to the knowledge gap concerning sex-specific outcomes in SAB [18].

Some, but not all [19,20], studies have reported higher rates of mortality in females with hospital-acquired bloodstream infection [21], severe sepsis [22,23] and endocarditis [24]. The previous literature on sex differences in patients with SAB is similarly contradictory (Table 3). For example, although studies from Israel [7] and Denmark [3] reported higher mortality in female patients with SAB, similar publications from Finland [9] and Korea [8] found no overall mortality difference in patients with SAB. Our study adds to this ongoing discussion by reporting on a large, prospective cohort of U.S. patients with a high prevalence of recognized risk factors for poor outcome in SAB [15,25–27].

Although men and women with SAB in our study had similar outcomes, their characteristics differed significantly. For example, less than half (43%) of admitted patients with SAB were female, whereas 51% of the North Carolinian population is female [28]. This suggests a lower *a priori* risk of SAB in female than male patients and is consistent with previous reports [27]. Although different health-seeking behaviour between sexes has been suggested [5], in our study both men and women had a median of 2 days from start of symptoms until diagnosis. Female patients had higher rates of MRSA compared with males, possibly due in part to a higher prevalence of haemodialysis dependence, healthcare exposure, corticosteroid therapy and other well-described risk factors for MRSA [29–31]. Interestingly, rates of bacteraemia with the hypervirulent USA300 MRSA clone were similar among the two sexes despite the higher rates of MRSA infection in women overall.

Although transthoracic echocardiography use was similar between sexes, TEE was performed significantly less often in female than male patients, a finding that is consistent with previous reports [32,33]. Furthermore, a shorter median duration of antibiotics was prescribed in female compared with male patients. It is unclear whether these differences reflect a sex-driven bias in management or simply the fact that men in our study had higher rates of metastatic infection, and thus more often a true indication for TEE and prolonged therapy. Alternately, it is also possible that the higher rate of metastatic infection identified in male patients may reflect the higher rate of diagnostic testing with TEE and other modalities.

A limitation of our study is the setting: a single academic centre in a region with high MRSA prevalence, making the results less

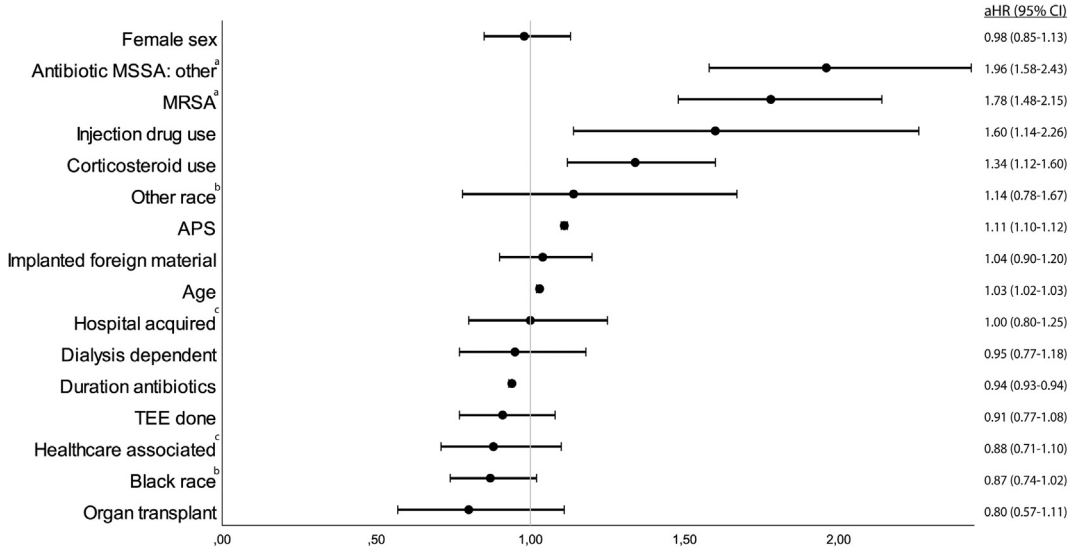

Fig. 1. Forest plot with adjusted hazard ratios for 90-day mortality in patients with *S. aureus* bacteraemia. aHR, adjusted hazard ratio; APS, acute physiology score at time of first positive blood culture; MRSA, methicillin-resistant *Staphylococcus aureus*; TEE, transesophageal echocardiography. [a]Reference: MSSA bacteraemia treated with cefazolin or anti-staphylococcal penicillin. [b]Reference: white race. [c]Reference: community-acquired.

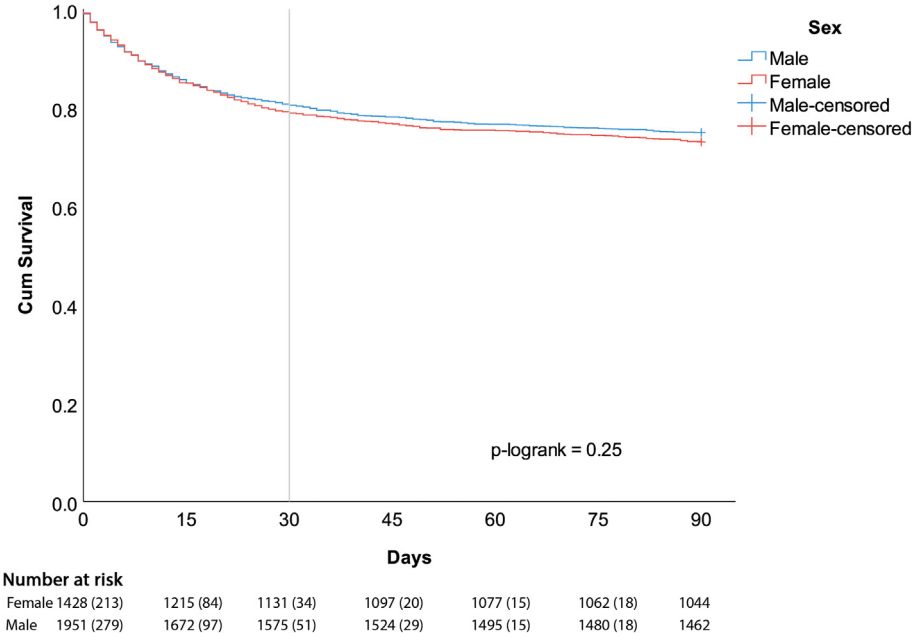

Fig. 2. Survival in female and male patients with *Staphylococcus aureus* bacteraemia. Kaplan-Meier survival curve with proportional cumulative survival of females and males with *S. aureus* bacteraemia.

Table 3
Summary of studies focused on sex differences in mortality in patients with *S. aureus* bacteraemia

Study	Years of patient inclusion	Country	Number of patients	MSSA or MRSA	Outcome
Forsblom et al. [9] Infection 2018	1999–2002 2006–2007	Finland	617	MSSA	No difference in 90-d mortality between sexes
Kang et al. [8] CMI 2018	2009–2017	South Korea	1974	MSSA and MRSA	No difference in overall mortality between sexes Higher mortality in males with CCWI ≤3 and MRSA
Smit et al. [3] CMI 2017	2000–2011	Denmark	2638	MSSA	Higher 30-d mortality in females (29% vs. 22%; aHR 1.30)
Mansur et al. [7] Gend Med 2012	1988–2007	Israel	1293	MSSA and MRSA	Higher 30-day mortality in females (45% vs. 35%; OR 1.54)

aHR, adjusted hazard ratio; CCWI, Charlson Comorbidity Weighted Index score; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

generalizable to some other settings. Our study could have been underpowered to detect a small sex difference. A large meta-analysis would be helpful to determine smaller differences. Also, only the first episode of bacteraemia was considered; therefore, a bias towards less severe SAB is possible. Another potential limitation is the long period of time during which the study was conducted, starting back in the nineties. Awareness of sex differences has increased over the years in many medical fields. However, because we found consistent results on sex differences in all time periods, this does not seem to be of important influence in our study. The increasing overall mortality over time is remarkable, and we hypothesize that the increasing tertiary care function of Duke University Hospital and the introduction of informed consent, which provides the possibility for patients to refuse participation, may be contributing factors. Finally, although sex assigned at birth was reported in the SABG-PCS, gender was not. People assigned female at birth and people identifying as women may comprise clinically distinct populations with different effects on health [12,34].

In conclusion, significant differences between females and males exist in patient, disease and management characteristics of SAB. Whereas some differences may be because of fixed biological distinctions or can be explained by different disease manifestations, others warrant further research to determine whether a sex-driven bias exists. Despite the multiple differences, women and men in this large cohort of patients with SAB have a similar mortality risk.

Author contributions

MMCL, MGJdB, EFS, LGV, ACW and VGF were responsible for study concept and design. FR, JLK, REK, and MEW were responsible for acquisition of the data. ACW and JLK wrote the first draft of the manuscript. LPP contributed to the data analysis. All authors were responsible for interpretation of the results and revision of the manuscript.

Transparency declaration

Conflicts of interest

VGF reports personal fees from Novartis, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., MedImmune, Bayer, Basilea, Affinergy, Janssen, Contrafect, Regeneron, Destiny, AmpliPhi Biosciences, Integrated Biotherapeutics; C3J, Armata, Valanbio; Akagera, Aridis, Roche, grants from NIH, MedImmune, Allergan, Pfizer, Advanced Liquid Logics, Theravance, Novartis, Merck; Medical Biosurfaces; Locus; Affinergy; Contrafect; Karius; Genentech,

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Data availability

Requests for access to the data will be considered on a case by case basis by the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.06.009.

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