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Reevaluation of the impact of methicillin-resistance on outcomes in patients with *Staphylococcus aureus* bacteremia and endocarditis

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Background/Aims: Methicillin-resistant *Staphylococcus aureus* (MRSA) is highly prevalent in hospitals, and has recently emerged in the community. The impact of methicillin-resistance on mortality and medical costs for patients with *S. aureus* bacteremia (SAB) requires reevaluation.
Methods: We searched studies with SAB or endocarditis using electronic databases including Ovid-Medline, Embase-Medline, and Cochrane Library, as well as five local databases for published studies during the period January 2000 to September 2011.
Results: A total of 2,841 studies were identified, 62 of which involved 17,563 adult subjects and were selected as eligible. A significant increase in overall mortality associated with MRSA, compared to that with methicillin-susceptible *S. aureus* (MSSA), was evidenced by an odds ratio (OR) of 1.95 (95% confidence interval [CI], 1.73 to 2.21; $p < 0.01$). In 13 endocarditis studies, MRSA increased the risk of mortality, with an OR of 2.65 (95% CI, 1.46 to 4.80). When three studies, which compared mortality rates between CA-MRSA and CA-MSSA, were combined, the risk of methicillin-resistance increased 3.23-fold compared to MSSA (95% CI, 1.25 to 8.34). The length of hospital stay in the MRSA group was 10 days longer than that in the MSSA group (95% CI, 3.36 to 16.70). Of six studies that reported medical costs, two were included in the analysis, which estimated medical costs to be $9,954.58 (95% CI, 8,951.99 to 10,957.17).
Conclusions: MRSA is still associated with increased mortality, longer hospital stays and medical costs, compared with MSSA in SAB in studies published since the year 2000.

Keywords: Methicillin resistance; Staphylococcus aureus; Bacteremia; Endocarditis; Mortality

INTRODUCTION

Hospital-acquired (HA) methicillin-resistant *Staphylococcus aureus* (MRSA) infections are a major cause of illness and death and impose serious economic costs on patients and hospitals. The estimated number of *S. aureus*-related hospitalizations increased by 62% from 294,570 to 477,927, and the estimated number of MRSA-related hospitalizations more than doubled, from 127,036 to 278,203, from 1999 through 2005 in the Unit-

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ed States [1]. Published studies on mortality for patients with *S. aureus* bacteremia (SAB) indicated an increased risk of mortality for patients with MRSA compared to those with methicillin-susceptible *S. aureus* (MSSA) bacteremia [2]. Thus bacteremia due to HA-MRSA results in increased direct medical costs and hospital stays, compared with that due to MSSA [3].

Cases of MRSA have been documented among healthy community-dwelling persons without established risk factors for MRSA acquisition, lately defined as community-associated (CA)-MRSA [4]. Community-genotype strains carrying SCC*mec* type IV have now emerged as a significant cause of healthcare-associated (HCA) and hospital associated (HA) infections in the USA and European countries [5-9]. Despite the epidemiologic changes in hospital MRSA strains with the encroachment of CA-MRSA into healthcare settings [9,10], whether methicillin resistance adversely affects outcomes in patients with community-associated *S. aureus* bacteremia is unclear [11,12]. After the year 2000, newer antimicrobial agents active against MRSA have become available to treat MRSA and are in use as alternatives for treating serious MRSA infections. The efficacy of new antibiotics in terms of reducing mortality in patients infected with *S. aureus,* especially MRSA, has not been verified. Furthermore, progress in high-quality clinical management has been made in the last few years as evidenced by the fact that case fatality can be reduced by hospital infection control systems [13]. These factors, including the emergence of MRSA strains with reduced vancomycin susceptibility, enhanced the controversy regarding the clinical impact of methicillin resistance on outcomes in SAB [14].

Meta-analyses by Cosgrove et al. [2] and Whitby et al. [15] comparing the mortality rate of MRSA and MSSA bacteremia found that methicillin resistance was associated with an increased mortality. In a recent meta-analysis, a significant increase in mortality associated with MRSA bacteremia was evident in the odds ratio (OR) of 1.93 (95% confidence interval [CI], 1.54 to 2.42), when 31 articles were combined with data regarding mortality associated with both MSSA and MRSA bacteremia [2]. There were also worse outcomes in studies that involve nosocomial SAB, compared to those involving a significant proportion of CA-SAB [2]. However, in the era of the emergence of CA-MRSA and the advent of newer antimicrobial agents active against MRSA, the impact of methicillin-resistance on mortality and medical costs for patients with SAB needs to be reevaluated. Therefore, we performed a systematic review and meta-analysis to investigate the effect of methicillin-resistance on mortality, length of hospital stay and medical costs of patients with SAB based on reports published after the year 2000.

METHODS

Literature search and selection of eligible studies

We searched studies of SAB or endocarditis using electronic databases including Ovid-Medline, Embase-Medline, and the Cochrane Library, as well as five local databases providing information on Korean medical research, published from January 1, 2000 to September 15, 2011. We used the search filter recommended by the Scottish Intercollegiate Guidelines Network to efficiently identify cohort studies. We also reviewed the bibliographies of relevant articles to identify additional publications. A full-text search of eight databases in English or Korean were reviewed using the terms "*Staphylococcus aureus*" AND "bacteremia" OR "endocarditis." Two reviewers (D.A.P. and S.M.L.) independently evaluated titles, abstracts and citations to assess relevance for full review. We applied no language restriction in the electronic database search, which was limited to studies involving humans.

The inclusion criteria were as follows: studies (1) targeting SAB or *S. aureus* endocarditis (SAE); (2) comparison of outcomes of MRSA and MSSA; (3) evaluating any type of mortality, the length of hospital stay (LOS) or medical costs; and (4) involving adults 18 years older. The exclusion criteria were as follows: (1) not original research; (2) animal or pre-clinical studies; (3) not cohort studies; (4) only an abstract; (5) studies not published in Korean or English; and (6) duplicate reports. Therefore, all cohort studies in adults with SAB or endocarditis were included if they compared outcomes of MRSA to those of MSSA. Outcomes of methicillin-resistance were analyzed in terms of all-cause mortality, in-hospital mortality, SAB-related mortality, and 30-day mortality. The LOS and medical costs were also compared between the MRSA and MSSA groups. Studies involving children

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or neonates and those of a case-control design were excluded. We also excluded studies involving the same population during an overlapping 1-year study period.

Since this study had evaluated the published data of applicable studies, it was not required to obtain approval by the Institutional Review Board. Obtaining written informed consent was not applicable in the performance of a meta-analysis where no foreseeable harm is expected to result from the study.

Data extraction

Using a standardized form developed in advance, two independent reviewers extracted the following pre-specified data: first author, publication year, country, study period, study setting, study design, total number of study participants, the number and proportion of individuals in the MRSA and MSSA groups, age, proportion of males, cases with nosocomial- and community-acquired bacteremia, SAE, and results of predetermined outcomes during the follow-up period. We also collected the adjusted estimates of mortality in SAB and endocarditis and confounding variables considered in the statistical models of each study. Agreement was obtained after discussion between the two reviewers. We did not assess the methodological quality of included studies because most did not differ in design or in the methods used for recruiting participants.

Data synthesis and analysis

We employed a random-effects model using the method described by DerSimonian and Laird [16] to synthesize data from included studies. For the outcome data on mortality, we calculated the OR and 95% CI as summary statistics. For continuous outcomes, such as the length of hospital stay and medical costs, weighted mean differences (WMDs) and 95% CIs were calculated.

We assessed statistical heterogeneity using the Cochrane Q-test ($p < 0.10$) and I^2 statistic, with $I^2 > 50\%$ indicating at least moderate heterogeneity [17]. To assess the potential explanations for heterogeneity, we performed subgroup analyses using pre-specified criteria including disease characteristics (bacteremia including mixed populations and endocarditis) and the type of infection (community-acquired infections and ≥ 70% vs. < 70% nosocomial infection). We also performed sensitivity analyses using summary estimates in studies adjusted for confounding variables. First, we used a funnel plot asymmetry approach to assess publication bias qualitatively, and then we confirmed the symmetry of the funnel plot using Begg and Mazumdar's rank correlation test (Supplementary Fig. 1) [18,19]. If publication bias was suspected, we performed the Trim and Fill method to obtain symmetry in the funnel plot and to determine the effect of hypothetical studies on the pooled estimate [20]. Statistical analysis was performed using Review Manager version 5.0 (RevMan, The Cochrane Collaboration, Oxford, UK) and Stata software version 10.0 (SE, Stata Corp., College Station, TX, USA). A p value of 0.05 was regarded as statistically significant.

RESULTS

Study populations

A total of 2,841 studies were searched from January 2000 through September 2011. Of 2,075 studies from which duplicated reports were eliminated, 92 (eight studies in Korea and 84 in other countries) were selected after the first and second literature review. A flow diagram of

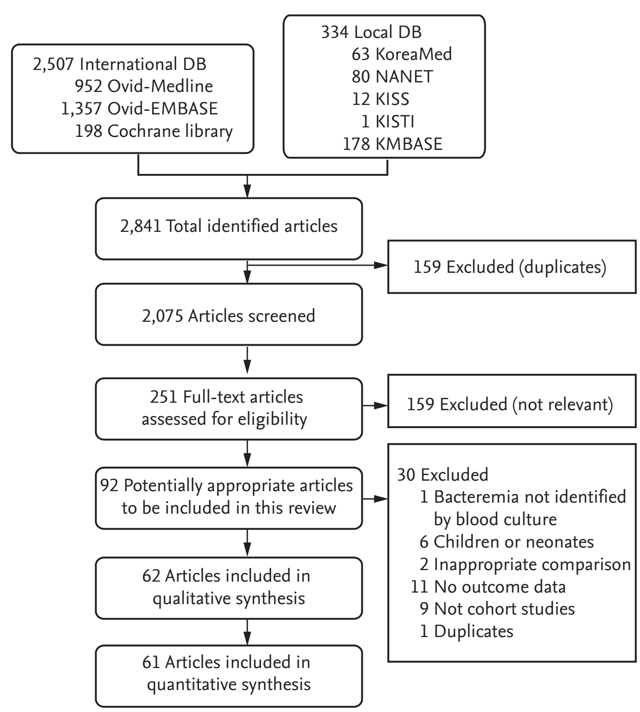

Figure 1. Flow diagram detailing reviewed articles and exclusion. DB, database.

Table 1. Characteristics of the studies of *Staphylococcus aureus* bacteremia or endocarditis included in the systematic review

No.	Author	Year	Study period	Country	Total no. of cases	Proportion of HA-MRSA/CA-MRSA/MSSA[a,b,c]	Population	IE (% of cases)	Types of outcomes	Mortality rate, %		Crude OR (95% CI)
										MRSA	MSSA	
1	Holmes [21]	2011	2007.1–2008.11	Australia New Zealand	532	22.2/15.8/62.0[b]	SAB		30-Day mortality	22.1	14.2	1.72 (1.09–2.71)
2	Kao [22]	2011	2004.1–2004.12	Taiwan	137	42.3/5.8/51.8[a]	SAB		Hospital mortality	43.9	21.1	2.93 (1.38–6.19)
3	Lubart [23]	2011	2004.1–2005.12	Israel	68	66.2/33.8[c]	SAB		14-Day mortality	40.0	13.0	4.44 (1.15–17.18)
4	Park [24]	2011	2003.1–2008.12	Korea	266	46.6/7.9/45.5[a]	SAB		30-Day mortality	21.4	28.9	0.67 (0.38–1.17)
5	Big [25]	2010	2004.1–2008.7	USA	76	60.5/39.5[c]	SAB		Hospital mortality	34.8	20.0	2.13 (0.72–6.29)
6	Kang [26]	2010	2004.9–2006.8	Korea	709	46.4/53.6[c]	SAB/SAE	31 (4.4)	30-Day mortality	33.1	17.1	2.40 (1.69–3.41)
7	Khan [27]	2010	2007.7–2008.6	Qatar	53	13.2/86.8[c]	SAB		Hospital mortality	28.6	28.3	1.02 (0.17–5.91)
8	Kim [28]	2010	2006.7–2008.12	Canada	684	27.9/72.1[c]	SAB		30-Day mortality	25.1	15.4	1.84 (1.22–2.77)
9	Ponce-de-Leon [29]	2010	2003.1–2007.12	Mexico	172	45.9/0/54.1[b]	SAB		30-Day mortality, hospital mortality, 7-day mortality, LOS	21.5	21.5	1.0 (0.48–2.08)
10	Takayama [30]	2010	1990.1–2006.12	Japan	33	30.3/0/69.7[b]	SAE	33 (100)	Hospital mortality	70.0	34.8	4.38 (0.88–21.71)
11	Wehrhahn [31]	2010	2-Year period	Australia	81	0/22.2/77.8[b]	SAB/SAE	15 (18.5)	30-Day mortality	22.2	11.1	2.29 (0.59–8.91)
12	Ammerlaan [32]	2009	2007.1–2007.12	Europe	334	23.1/76.9[c]	SAB		30-Day mortality	26.0	23.3	1.15 (0.64–2.07)
13	Ben-David [33]	2009	2000.1–2003.8	Israel	182	52.2/0/47.8[b]	SAB		Hospital mortality, LOS, total medical cost	25.3	18.4	1.5 (0.74–3.06)
14	Khatib [34]	2009	2002.1–2003.6	USA	78	78.2/21.8[c]	SAB		Hospital mortality	34.4	5.9	8.4 (1.04–67.79)
15	Kim [35]	2009	1995.1.–2006.12	Korea	73	16.4/26.0/57.5[b]	SAE	73 (100)	Hospital mortality,	35.5	2.4	22.55 (2.72–187.07)
16	Rieg [36]	2009	2002–2007	Germany	521	12.9/0/87.1[a]	SAB		Hospital mortality	41.8	18.7	3.12 (1.82–5.35)
17	Rubio-Terres [37]	2009	2005.1–2005.12	Spain	366	26.8/6.3/66.9[b]	SAB		Hospital mortality, LOS (in wards), ICU stay, cost per episode bacteremia	39.7	25.3	1.94 (1.22–3.09)
18	Turnidge [38]	2009	2007.6–2008.5	Australia New Zealand	1865	24.1/75.9[c]	SAB		30-Day mortality	30.0	17.7	2.0 (1.57–2.55)
19	Allard [39]	2008	1991–2005	Canada	815	8.3/0.1/91.5[a]	SAB		30-Day mortality	33.3	23.1	1.67 (0.98–2.83)
20	Baroudi [40]	2008	1990.1–2006.1	USA	27	55.6/44.4[c]	SAE	27 (100)	Hospital mortality	40.0	50.0	0.67 (0.14–3.09)
21	Libert [41]	2008	2002.1–2004.12	Belgium	140	31.4/12.9/55.7[b]	SAB		Hospital mortality	54.8	35.9	1.90 (0.97–3.76)
22	Malani [42]	2008	2004–2005	USA	68	52.9/47.1[c]	SAB		Hospital mortality	25.0	12.5	3.88 (1.29–11.68)
23	Bader [43]	2007	2003.1–2004.12	USA	135	23.0/31.8/45.2[b]	SAB		Hospital mortality	33.8	18.0	2.32 (1.03–5.22)

Table 1. Continued

No.	Author	Year	Study period	Country	Total no. of cases	Proportion of HA-MRSA/CA-MRSA/MSSA[a,b,c]	Population	IE (% of cases)	Types of outcomes	Mortality rate, % MRSA	Mortality rate, % MSSA	Crude OR (95% CI)
24	Cagatay [44]	2007	2001.10–2002.12	Turkey	57	80.7/19.3[c]	SAB		SAB-related mortality (30-day)	54.3	63.6	0.68 (0.17–2.65)
25	Das [45]	2007	2001–11–2002–12	UK	140	49.3/10.7/40.0[b]	SAB		SAB-related mortality (within 10-day), LOS	33.3	16.1	2.61 (1.12–6.08)
26	Greiner [46]	2007	1999.12–2005.5	Germany	109	18.3/7.4/74.3[b]	SAB		Total hospital cost	NR	NR	NR
27	Hsu [47]	2007	1995–2005	Taiwan	123	39.0/61.0[c]	SAE	123 (100)	Hospital mortality	41.7	16.0	3.75 (1.61–8.71)
28	Wang [48]	2007	1990–2004	Taiwan	1148	74.1/25.9[c]	SAB		30-Day mortality	49.8	27.6	2.60 (1.95–3.47)
29	Depuydt [49]	2006	1992–2002	Belgium	32	59.4/40.6[c]	Bacteremic SAP		Hospital mortality	72.2	NR	NR
30	Guilarde [50]	2006	2000.1–2001.12	Brazil	111	55.0/45.0[c]	SAB		SAB-related mortality	47.5	20.0	3.63 (1.54–8.53)
31	Heo [51]	2006	2000.1–2005.8	Korea	231	0/27.3/72.7[b]	SAB		Hospital mortality	30.2	19.6	1.77 (0.91–3.41)
32	Kim [52]	2006	1999.1–2003.5	Korea	96	64.6/3.1/32.3[a]	SAB		Hospital mortality	26.2	0.0	22.73 (1.32–391.68)
33	Lesse [53]	2006	1997.1–2003.12	USA	38	63.2/36.8[c]	SAB		Hospital mortality	33.3	21.4	1.83 (0.4–8.49)
34	Marra [54]	2006	2003.12.15–2004.12.31	USA	91	46.2/53.8[c]	SAB		Hospital mortality	26.2	4.1	8.69 (1.80–41.88)
35	Nori [55]	2006	1999.1–2004.2	USA	22	50.0/50.0[c]	SAE	22 (100)	Hospital mortality	54.5	45.5	1.44 (0.27–7.71)
36	Perovic [56]	2006	1999.11–2002.10	South Africa	449	18.7/4.7/76.6[b]	SAB		SAB-related mortality(14-day)	33.3	20.1	1.99 (1.23–3.23)
37	Shorr [57]	2006	2002–2003	USA	1540	21.2/6.2/72.6[a]	SAB		Hospital mortality	23.5	16.4	1.57 (1.19–2.06)
38	Wyllie [58]	2006	1997.4–2004.3	UK	441	51.5/0/48.5[b]	SAB		30-Day mortality	33.5	27.1	1.35 (0.90–2.04)
39	Cassettari [59]	2005	1999.5–1999.8	Brazil	163	58.9/0/41.1[b]	SAB		Hospital mortality, SAB-related mortality (15-day)	44.8	29.9	1.91 (0.99–3.69)
40	DeRyke [60]	2005	1999.1–2004.4	USA	60	70.0/0/30.0[b]	Bacteremic SAP		Hospital mortality, SAB-related mortality, infection-related LOS	54.8	55.6	0.97 (0.32–2.94)
41	Fowler [61]	2005	2000.6–2003.12	USA Multicontinent	424	26.7/6.7/66.7[a]	SAE	424 (100)	Hospital mortality	29.8	23.3	1.39 (0.89–2.20)
42	Lodise [62]	2005	1999.1–2001.1	USA	353	39.9/8.2/51.8[b]	SAB		SAB-related mortality, 30-day mortality, SAB-related LOS and hospital cost	30.6	15.3	2.44 (1.45–4.10)

Table 1. Continued

No.	Author	Year	Study period	Country	Total no. of cases	Proportion of HA-MRSA/CA-MRSA/MSSA[a,b,c]	Population	IE (% of cases)	Types of outcomes	Mortality rate, %		Crude OR (95% CI)
										MRSA	MSSA	
43	Reed [63]	2005	1996.7.–2001.8	USA	143	37.8/62.2	SAB		Hospital-mortality, LOS, ICU stay, total hospital cost	14.8	9.0	1.76 (0.62–5.01)
44	Yoon [64]	2005	1986.3–2004.3	Korea	32	18.8/12.5/68.8[b]	SAE	32 (100)	Hospital mortality	50.0	9.1	10.0 (1.48–67.55)
45	Chang [65]	2004	1988.1–2002.12	Taiwan	12	66.7/33.3[c]	SAE	12 (100)	Hospital mortality	100	0	153.0 (2.58–9,077.05)
46	Cordova [66]	2004	1997.7–1999.6	Australia	501	7.8/3.2/89.0[a]	SAB		Hospital mortality (within 16-day), 7-day mortality, LOS	27.3	16.8	1.86 (0.98–3.53)
47	Osmon [67]	2004	2001.12–2002.9	USA	265	36.2/19.6/44.2[a]	SAB		Hospital mortality, LOS, ICU stay	13.5	16.2	0.81 (0.41–1.59)
48	Chang [68]	2003	1994.8–1996.3	USA	64	15.6/15.6/68.8[a]	SAE	64 (100)	30-Day mortality, 14-Day mortality	50.0	22.7	3.40 (1.10–10.47)
49	Kim [69]	2003	1998.1–2002.3	Korea	29	48.3/51.7[c]	SAB		SAB-related mortality	57.1	20.0	5.33 (1.02–27.76)
50	Melzer [70]	2003	1995.1–2000.12	UK	815	46.9/0/53.1[b]	SAB		SAB-related mortality, overall mortality	29.6	13.6	2.66 (1.87–3.79)
51	Na [71]	2003	1990.1–2000.5	Korea	10	20.0/80.0[c]	SAE	10 (100)	Hospital mortality	100	25	13.00 (0.45–377.47)
52	Blot [72]	2002	1992.1.–1998.12	Belgium	85	55.3/0/44.7[b]	SAB		Hospital mortality, 15-day mortality, 30-day mortality, ICU stay	53.2	18.4	5.03 (1.85–13.69)
53	Campillo [73]	2002	1996.1–2001.3	France	83	90.4/0/9.6[b]	SAB/peritonitis		Hospital mortality	60.0	75.0	0.5 (0.09–2.64)
54	Talon [74]	2002	1997.1–1998.12	France	99	11.1/19.2/69.7[b]	SAB	51.7	SAB-related mortality (14-day)	43.3	20.3	3.00 (1.18–7.62)
55	Tumbarello [75]	2002	1991.1–2000.12	Italy	129	24.8/7.0/68.2[b]	SAB		Hospital mortality, LOS	34.1	11.4	4.04 (1.61–10.17)
56	Cosgrove [76]	2001	1997.7–2000.6	USA	348	27.6/72.4[c]	SAB		Hospital mortality, SAB-related mortality, SAB-related LOS and hospital charge	22.9	19.8	1.20 (0.68–2.12)
57	Morin [77]	2001	1998.1–1998.12	USA	192	9.9/5.2/84.9[a]	SAB		Hospital mortality	13.8	10.4	1.37 (0.43–4.42)
58	Wisplinghoff [78]	2001	1995.12–1997.5	USA	82	48.8/0/51.2[b]	SAB		Hospital mortality	25.0	23.8	1.07 (0.39–2.92)
59	Ibrahim [79]	2000	1997.6–1999.7	USA	94	48.9/51.1[c]	SAB		Hospital mortality	37.0	25.0	1.76 (0.73–4.27)

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Table 1. Continued

No.	Author	Year	Study period	Country	Total no. of cases	Proportion of HA-MRSA/CA-MRSA/MSSA[a,b,c]	Population	IE (% of cases)	Types of outcomes	Mortality rate, %		Crude OR (95% CI)
										MRSA	MSSA	
60	Roghmann [80]	2000	1995.10–1998.1	USA	125	22.7/7.0/70.3[b]	SAB		30-Day mortality	32.4	23.9	1.53 (0.66–3.57)
61	Selvey [81]	2000	1992–1997	Australia	504	37.3/0/62.7[b]	SAB		Hospital mortality, SAB-related mortality	18.6	13.0	1.53 (0.94–2.51)
62	Soriano [82]	2000	1991.1–1998.12	Spain	908	19.9/4.8/75.2[b]	SAB/SAE	31 (3.4)	SAB-related mortality (30-day), LOS	21.8	8.9	2.84 (1.88–4.28)

HA, hospital-acquired; MRSA, methicillin-resistant *S. aurues*; CA, community-acquired; MSSA, methicillin-susceptible *S. aureus*; IE, infective endocarditis; OR, odds ratio; CI, confidence interval; SAB, *S. aureus* bacteremia; SAE, *S. aureus*-associated infective endocarditis; LOS, length of hospital stay; ICU, intensive care unit; SAP, *S. aureus*-associated pneumonia.

[a]Represents the proportion of cases which were epidemiologically defined according to CA- and HA-MRSA.

[b]Represents the proportion of cases which were classified into community-onset and hospital-onset MRSA without definition of CA-MRSA.

[c]Indicates the proportion of cases with MRSA, when onset of bacteremia was not defined according to the epidemiologic definition.

identification of eligible studies is shown in Fig. 1. Of these, 62 cohort studies were selected as eligible that reported any outcome regarding mortality, LOS and medical costs after review of the full-text of articles (Table 1) [21-82]. Pooled data for 17,563 patients (6,390 MRSA and 11,173 MSSA) were included in the analysis. All were cohort studies, comprising 41 retrospective, 20 prospective and one both retro- and prospective study. The characteristics of the selected studies are shown in Table 1 according to year of publication.

Mortality in patients with methicillin-resistant and methicillin-susceptible SAB and endocarditis

Of the 62 studies, 60 reported all-cause mortality including in-hospital mortality, 14- and 30-day mortality and SAB-related mortality. The clinical characteristics of all patients with MRSA and MSSA in the 62 studies are summarized in Table 1. A significant increase in all-cause mortality associated with MRSA was evident with a pooled OR of 1.95 (95% CI, 1.73 to 2.21; I^2 = 44%) compared to that of MSSA (Fig. 2) [21-82]. The pooled OR for 40 studies that reported in-hospital mortality was 1.90 (95% CI, 1.57 to 2.28; I^2 = 51%). In 13 studies that compared 30-day mortality rates in SAB, MRSA increased the odds of death 1.89-fold compared to MSSA (95% CI, 1.58 to 2.26; I^2 = 40%). In the 16 studies that documented SAB or infection-related mortality, generic inverse variance methods were used. The pooled OR was 2.04 (95% CI, 1 63 to 2.55; I^2 = 40%).

Of the 62 selected studies, 13 reported the outcomes of SAE, among which 10 involved a population with SAE [30,35,40,47,55,61,64,65,68,71], and the remaining three reported outcomes of SAE as part of SAB episodes [26,31,82]. Methicillin-resistance increased the risk of mortality by 2.65-fold in those patients (95% CI, 1.46 to 4.80; I^2 = 50%). There was no significant heterogeneity among the results of these studies. Further analysis primarily involving the SAE population showed a pooled OR of 3.32 (95% CI, 1.68 to 6.59).

Mortality in patients with methicillin-resistant and methicillin-susceptible SAB and endocarditis in the Korean population

In a meta-analysis of eight studies which reported all-cause mortality in SAB and endocarditis in the Korean population, methicillin-resistance was associated with

Study or Subgroup	MRSA Events	MRSA Total	MSSA Events	MSSA Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Selvey 2000	35	188	41	316	2.7%	1.53 [0.94, 2.51]	2000
Ibrahim 2000	17	46	12	48	1.4%	1.76 [0.72, 4.27]	2000
Soriano 2000	49	225	61	683	3.2%	2.84 [1.88, 4.28]	2000
Roghmann 2000	12	37	21	88	1.5%	1.53 [0.66, 3.57]	2000
Wisplinghoff 2001	10	40	10	42	1.1%	1.07 [0.39, 2.92]	2001
Morin 2001	4	29	17	163	0.9%	1.37 [0.43, 4.42]	2001
Cosgrove 2001	22	96	50	252	2.4%	1.20 [0.68, 2.12]	2001
Blot 2002	25	47	7	38	1.1%	5.03 [1.85, 13.69]	2002
Talon 2002	13	30	14	69	1.3%	3.00 [1.18, 7.62]	2002
Campillo 2002	45	75	6	8	0.5%	0.50 [0.09, 2.64]	2002
Tumbarello 2002	14	41	10	88	1.3%	4.04 [1.61, 10.17]	2002
Melzer 2003	113	382	59	433	3.5%	2.66 [1.87, 3.78]	2003
Chang 2003	10	20	10	44	1.0%	3.40 [1.10, 10.47]	2003
Kim 2003	8	14	3	15	0.5%	5.33 [1.02, 27.76]	2003
Na 2003	2	2	2	8	0.1%	13.00 [0.45, 377.47]	2003
Chang 2004	8	8	0	4	0.1%	153.00 [2.58, 9077.05]	2004
Cordova 2004	15	55	75	446	2.1%	1.85 [0.98, 3.53]	2004
Osmon 2004	20	148	19	117	2.0%	0.81 [0.41, 1.59]	2004
Yoon 2005	5	10	2	22	0.4%	10.00 [1.48, 67.55]	2005
DeRyke 2005	23	42	10	18	1.0%	0.97 [0.32, 2.94]	2005
Lodise 2005	52	170	28	183	2.6%	2.44 [1.45, 4.10]	2005
Cassettari 2005	43	96	20	67	2.0%	1.91 [0.99, 3.69]	2005
Fowler 2005	42	141	66	283	2.9%	1.39 [0.89, 2.20]	2005
Reed 2005	8	54	8	89	1.1%	1.76 [0.62, 5.01]	2005
Lesse 2006	8	24	3	14	0.6%	1.83 [0.40, 8.49]	2006
Guilarde 2006	29	61	10	50	1.4%	3.63 [1.54, 8.53]	2006
Nori 2006	6	11	5	11	0.5%	1.44 [0.27, 7.71]	2006
Marra 2006	11	42	2	49	0.5%	8.34 [1.73, 40.22]	2006
Shorr 2006	99	422	183	1118	3.9%	1.57 [1.19, 2.06]	2006
Perovic 2006	35	105	69	344	2.8%	1.99 [1.23, 3.23]	2006
Kim 2006	17	65	0	31	0.2%	22.73 [1.32, 391.68]	2006
Wyllie 2006	76	227	58	214	3.2%	1.35 [0.90, 2.04]	2006
Heo 2006	19	63	33	168	2.0%	1.77 [0.91, 3.41]	2006
Hsu 2007	20	48	12	75	1.5%	3.75 [1.61, 8.71]	2007
Wang 2007	424	851	82	297	3.9%	2.60 [1.95, 3.47]	2007
Bader 2007	25	74	11	61	1.6%	2.32 [1.03, 5.22]	2007
Cagatay 2007	25	46	7	11	0.7%	0.68 [0.17, 2.65]	2007
Das 2007	28	84	9	56	1.5%	2.61 [1.12, 6.08]	2007
Baroudi 2008	6	15	6	12	0.6%	0.67 [0.14, 3.09]	2008
Allard 2008	23	69	172	746	2.6%	1.67 [0.98, 2.83]	2008
Malani 2008	9	36	4	32	0.8%	2.33 [0.64, 8.48]	2008
Libert 2008	34	62	28	78	2.0%	2.17 [1.10, 4.29]	2008
Rieg 2009	28	67	85	454	2.5%	3.12 [1.82, 5.35]	2009
Ammerlaan 2009	20	77	60	257	2.3%	1.15 [0.64, 2.07]	2009
Rubio-Terres 2009	48	121	62	245	2.9%	1.94 [1.22, 3.09]	2009
Ben David 2009	24	95	16	87	1.8%	1.50 [0.74, 3.06]	2009
Kim 2009	11	31	1	42	0.3%	22.55 [2.72, 187.07]	2009
Khatib 2009	21	61	1	17	0.3%	8.40 [1.04, 67.79]	2009
Turnidge 2009	135	450	250	1415	4.1%	2.00 [1.57, 2.55]	2009
Khan 2010	2	7	13	46	0.4%	1.02 [0.17, 5.91]	2010
Takayama 2010	7	10	8	23	0.5%	4.38 [0.88, 21.71]	2010
Wehrhahn 2010	4	18	7	63	0.7%	2.29 [0.59, 8.91]	2010
Big 2010	16	46	6	30	1.0%	2.13 [0.72, 6.29]	2010
Ponce-de-Leon 2010	17	79	20	93	1.8%	1.00 [0.48, 2.08]	2010
Kang 2010	109	329	65	380	3.5%	2.40 [1.69, 3.41]	2010
Kim 2010	48	191	76	493	3.2%	1.84 [1.22, 2.77]	2010
Kao 2011	29	66	15	71	1.7%	2.93 [1.38, 6.19]	2011
Holmes 2011	44	199	46	324	2.9%	1.72 [1.09, 2.71]	2011
Park 2011	31	145	35	121	2.4%	0.67 [0.38, 1.17]	2011
Lubart 2011	18	45	3	23	0.7%	4.44 [1.15, 17.18]	2011
Total (95% CI)		**6338**		**11075**	**100.0%**	**1.95 [1.73, 2.21]**	
Total events	2101		2014				

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 105.17$, df = 59 (P = 0.0002); $I^2 = 44\%$
Test for overall effect: Z = 10.70 (P < 0.00001)

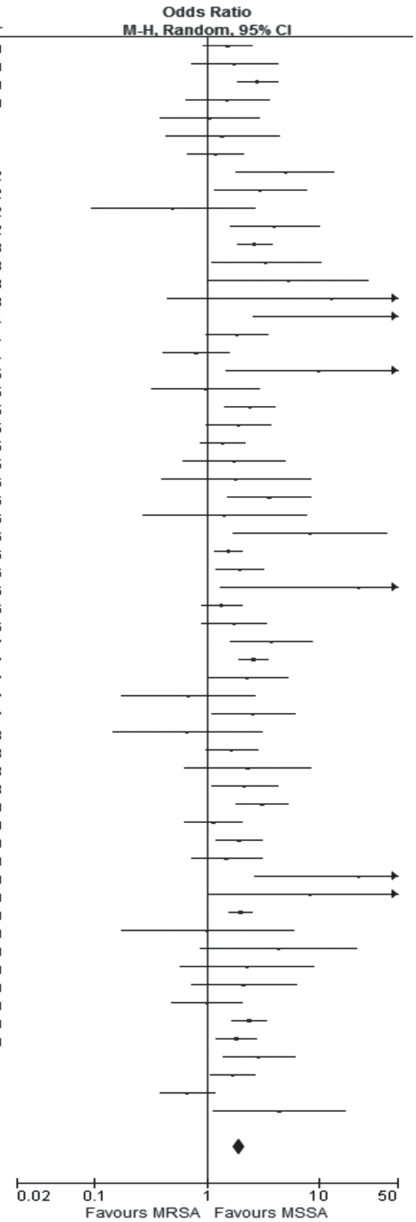

Figure 2. Forest plot summary of the results of 60 studies which reported all-cause mortality. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; CI, confidence interval.

increases in mortality with a pooled OR of 3.14 (95% CI, 1.48 to 6.67) (Fig. 3) [24,26,35,51,52,64,69,71]. There was significant heterogeneity among the results of these studies (I^2 = 76%). Of eight studies, three studies analyzed the outcomes of SAE in Korean populations [35,64,71]; in these, the mortality risk of MRSA increased 14.19-fold compared to that of MSSA (95% CI, 3.84 to 52.41).

Community- and hospital-acquired SAB

Twenty-two studies reported outcomes of CA-SAB; of these, only three studies compared mortality rates between CA-MRSA and CA-MSSA. MRSA increased the odds 3.23-fold, compared to MSSA (95% CI, 1.25 to 8.34) when the three studies were combined (Fig. 4) [31,39,74]. Forty-one studies reported the outcomes in patients of nosocomial SAB. In the 13 selected studies in which ≥ 70% of the cases of SAB were hospital-acquired, the

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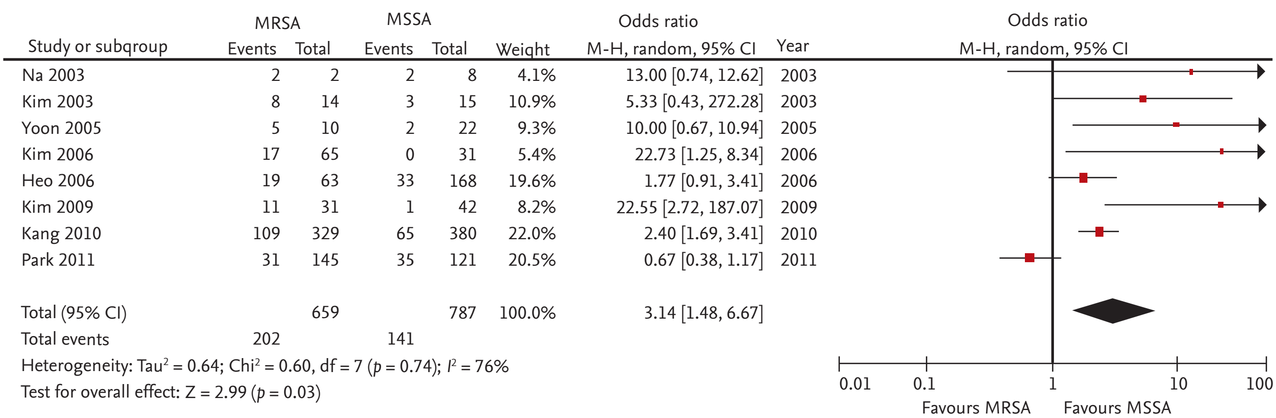

Figure 3. Forest plot summary of results of eight which reported all-cause mortality in *Staphylococcus aureus* bacteremia and endocarditis in the Korean population. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; CI, confidence interval.

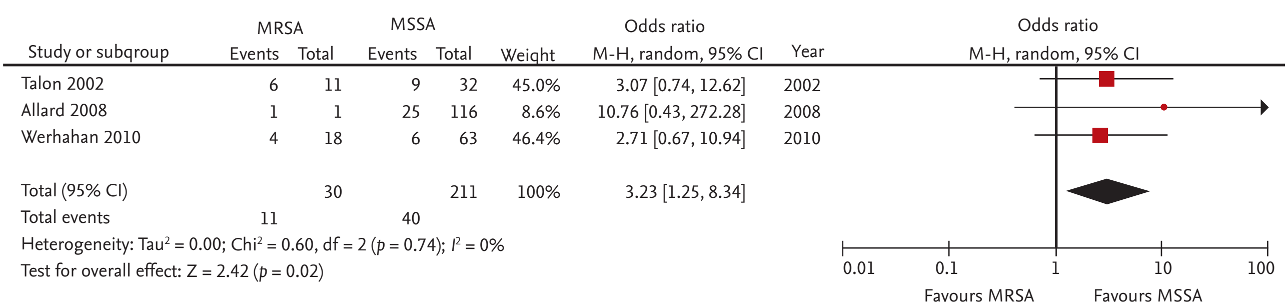

Figure 4. Forest plot summary of results of three studies which reported mortality rates between community-associated (CA)-methicillin-resistant *Staphylococcus aureus* (MRSA) and CA-methicillin-susceptible *S. aureus* (MSSA). CI, confidence interval.

pooled OR was 1.70 (95% CI, 1.29 to 2.25). In contrast, in 28 studies in which less than 70% were nosocomial, the OR was 1.95 (95% CI, 1.66 to 2.29).

LOS, ICU stay, and medical costs

LOS was divided into two categories for analysis—the total LOS and the length of stay after the onset of bacteremia. Eight studies reported total LOS (Table 2) [29,37,45,63,66,67,75,82]. Of them, four studies were combined for the meta-analysis of total LOS [37,63,67,75]. The average total LOS in the MRSA group was 10.03 days longer than that in the MSSA group; this difference was significant (WMD, 10.03; 95% CI, 3.36 to 16.70; I^2 = 83%). The result of a sensitivity analysis, excluding the heterogeneous studies, indicated that patients with MRSA bacteremia stayed 6.72 days longer (WMD, 6.72; 95% CI, 3.38 to 10.0) than those with MSSA bacteremia without heterogeneity (I^2 = 31%). Among six studies that reported length of stay after the onset of bacteremia, data from two studies [62,63] were included in the analysis and showed that the average stay was 5.02 days longer in the MRSA group than the MSSA group (WMD, 5.02; 95% CI, 2.66 to 7.38), with homogeneity (I^2 = 0%). Four studies described the length of intensive care unit (ICU) stay. Patients with MRSA bacteremia stayed in the ICU 6.46 days longer (WMD, 6.46; 95% CI, 0.87 to 12.04), with heterogeneity among combined studies (I^2 = 86%) than those with MSSA. Of six studies that reported medical costs (Table 3) [33,37,46,62,63,76], two were included in the analysis, and the estimated medical costs were $9,954.58 (WMD, 9,954.58; 95% CI, 8,951.99 to 10,957.17) with a statistically significant difference between groups and homogeneity between the two studies (I^2 = 0%) [62,63].

Table 2. Length of hospital stay

No.	Author	Year	Populations	LOS, day		p value
				MRSA	MSSA	
1	Ponce-de-Leon [29]	2010	SAB	31 (1–585)[a]	21 (0–140)[a]	0.003
2	Rubio-Terres [37]	2009	SAB	24.8 (19.9–29.9)[b]	22.66 (18.8–26.5)[b]	NR
3	Das [45]	2007	SAB	14[c]	8[c]	0.004
4	Reed [63]	2005	SAB	16.6 ± 12.7[d]	9.3 ± 8.5[d]	< 0.0001
5	Cordova [66]	2004	SAB	16 (6–25, 1–211)[e]	14 (7–30, 1–273)[e]	NR
6	Osmon [67]	2004	SAB	22.1 ± 24.9[d]	13.2 ± 13.5[d]	0.001
7	Tumbarello [75]	2002	SAB	49 ± 27[d]	24 ± 16[d]	< 0.001
8	Soriano [82]	2000	SAB	18[f]	8[f]	< 0.00001

LOS, length of hospital stay; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; SAB, *S. aureus* bacteremia; NR, not recorded.
[a]Mean (range).
[b]Mean (95% confidence interval).
[c]Median.
[d]Mean ± SD.
[e]Median (interquartile range, range),
[f]Mean.

Table 3. Medical costs

No	Author	Year	Medical costs		p value
			MRSA	MSSA	
1	Rubio-Terres [37]	2009	€11,044.59/episode[a]	€9839.25/episode[a]	-
2	Ben-David [33]	2009	ICU origin: $113,852 (48,961–55,001)[b] General origin: $53,409 (32,945–84,053)[b]	ICU origin: $42,137 (32,388–74,781)[b] General origin: $35,131 (18,340–50,896)[b]	ICU origin: < 0.001 General origin: 0.005
3	Greiner [46]	2006	€24,931[a]	€10,573[a]	< 0.05
4	Lodise [62]	2005	$21,577 (17,061–27,290)[c]	$11,668 (9,550–14,223)[c]	0.001
5	Reed [63]	2005	$28,297 ± 23,619[d]	$16,066 ± 16,337[d]	< 0.0001
6	Cosgrove [76]	2001	$26,424 (14,006–50,484)[b]	$19,212 (9,999–36,548)[b]	0.008

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; ICU, intensive care unit.
[a]Mean.
[b]Median (interquartile range).
[c]Mean (95% confidence interval).
[d]Mean ± SD.

Publication bias

We generated contour-enhanced funnel plots to evaluate the presence of potential publication bias for the meta-analyses performed in our review (Supplementary Fig. 1). No evidence of publication bias was noted in the funnel plots and the adjusted rank correlation tests in the meta-analyses for all-cause mortality (p = 0.10), in-hospital mortality (p = 0.056), 30-day mortality (p = 0.714), or SAB-related mortality (p = 0.557).

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DISCUSSION

This systematic review of 62 relevant reports published since 2000 that evaluated the outcomes of SAB and endocarditis in adults, suggested that methicillin-resistant isolates is associated with increased mortality, hospital stay and medical costs, compared with susceptible isolates. A significant increase in all-cause mortality associated with MRSA, compared to that with MSSA compromised of 17,565 patients from 62 combined studies was evident with a pooled OR of 1.95. This is consistent with the report in 2003 by Cosgrove et al. [2] which had combined 31 studies with a total of 3,962 patients of an OR of mortality associated with MRSA of 1.93, compared with MSSA. In 60 studies that reported mortality outcomes, the relative risk (RR) was estimated to be 1.59 based on the mean mortality rate of 33.1% (2,101/6,338) in the MRSA group and 18.2% (2,014/11,075) in the MSSA group. In studies of in-hospital mortality, the RR was estimated at 1.54. This is also similar to the RR of 1.42 reported by Cosgrove et al. [2]. In the analysis involving SAB-related mortality, the pooled OR was 2.04 (95% CI, 1.63 to 2.55; I^2 = 40%). This was compatible with the OR of 2.2 (95% CI, 1.2 to 3.8) reported by Cosgrove et al. [2]. In this analysis reevaluating the impact of methicillin-resistance on mortality in the era of the changing epidemiology and treatment of MRSA infections, a similar trend for a strong association between methicillin-resistance and a significantly increased mortality risk was identified through a review of the literature. Through a systematic review using a database published since the year 2000, two studies reported length of stay after the onset of bacteremia; patients in the MRSA group stayed 5.02 days longer than those in the MSSA group (95% CI, 2.66 to 7.38).

We also intended to evaluate the risk of mortality in endocarditis by comparing the groups with MRSA and MSSA. Interestingly, methicillin resistance increased the risk of mortality in SAE by 2.65 (95% CI, 1.46 to 4.80). Further analysis, involving primarily the SAE population, showed a pooled OR of 3.32 (95% CI, 1.68 to 6.59), which is higher than that reported by Cosgrove et al. [2] 1.79 (95% CI, 0.84 to 3.81). This is different than our expectation that mortality would be lower among patients with MRSA endocarditis as a consequence of better management with new antibiotics. Although glycopeptides were the only treatment option for MRSA infections before 2000, new treatment agents, including daptomycin and linezolid, for MRSA have been introduced since that time. Hence, the outcomes in the MRSA group were expected to be better than those in the past, especially in SAE, which is a severe form of SAB. The increased risk of mortality in the SAE group is attributable in part to the delay between data collection and publication. More than half of the study population was collected before 2000. Besides, only fifteen studies specified the treatment regimens for SAB; the mainstay of therapy for these was limited to glycopeptides. There was no study evaluating the clinical outcomes of SAB according to the treatment regimens between glycopeptides and the new anti-MRSA agents among the 62 relevant studies. Thus, the estimated risk in our analysis does not fully reflect changes in treatment of MRSA infections using new antibiotics as alternatives to glycopeptides. Further studies are required to evaluate the risk of methicillin-resistance for mortality in the SAE population under treatments with antibiotics other than glycopeptides.

Traditionally, bacteremia and endocarditis are classified as either CA or HA (nosocomial). CA-MRSA infections have emerged in the past few years as an important medical problem, especially in children without traditional risk factors for healthcare-associated MRSA. To evaluate the risk for emergence of methicillin-resistance in the community, we examined the outcomes of 22 studies reporting outcomes for CA-SAB as part of SAB; of these, three studies reported outcomes by comparing CA-MRSA and CA-MSSA. Interestingly, methicillin-resistance increased the risk of death by 3.23 (95% CI, 1.25 to 8.34). Furthermore, in nosocomial SAB, methicillin-resistance had a relatively low risk of morality in adults with ≥ 70% HA-SAB, compared to those with < 70% HA-SAB. These findings are opposed to previous reports in adults, which have described non-severe outcomes in CA-SAB compared to those in HA-SAB with a few notable exceptions. Given the different distribution pattern of CA- and HA-SAB, empiric antimicrobial therapy for CA-SAB could be less appropriate than for patients with HA-SAB. Since clinical practice guidelines for the treatment of MRSA often do not recommend coverage for CA-MRSA, the association between the presence of CA-MRSA and mortality in SAB suggests that patients with CA-MRSA were more likely to have received antibiotics not effective against methicillin-resistant strains [83]. Heterogeneity among study results, however, was detected in subgroup analyses; thus, further studies are required to determine the impact of methicillin-resistance on outcomes in adults with CA-SAB.

This study had several limitations. First, we included all adult subjects irrespective of disease patterns and severity of illness in this meta-analysis; this wide distribution of subject characteristics may result in heterogeneity between the combined studies. In this study, however, the heterogeneity test results were considerably lower than those in the general meta-analysis by Cosgrove et al. [2]. When we assessed the statistical heterogeneity with I^2 > 50% as the indication of at least moderate heterogeneity, between-study statistical heterogeneity was not found in this meta-analysis (I^2 statistic, 44%). Twenty-two studies were selected as high-quality in the assessment of bias risk of 62 relevant papers; with these, the sensitivity analysis showed a pooled OR of 2.12 (95% CI, 1.76 to 2.55), a significantly increased risk of mortality of methicillin-resistance in SAB. Heterogeneity in the combined studies was not identified (I^2 = 46%). Thus heterogeneity did not have a major impact on the results. Therefore, a wide distribution of subject characteristics between studies in this meta-analysis is not considered to have had a huge impact on the results. Second, this analysis included data in part collected before the year 2000. Given that our data were collected around 2000, the mainstay of therapy for MRSA in this analysis was confined to glycopeptides; this may not fully reflect current medical treatment, in which newer antimicrobial agents active against MRSA have become available. Further study of the effect of new antimicrobial agents on mortality of patients with SAB is required.

Despite these limitations, the present systematic review of studies published since 20 suggests that methicillin-resistance is associated with increased mortality and hospital stay compared with susceptible isolates in SAB and endocarditis. In the SAE and CA-SAB infection subgroups, methicillin-resistance was associated with increased mortality.

KEY MESSAGE

1. Methicillin-resistance is still associated with increased mortality and hospital stay, compared with susceptible isolates in *Staphylococcus aureus* bacteremia.
2. In comparison of outcome between community-acquired methicillin-resistant and methicillin-susceptible *S. aureus* bacteremia, methicillin-resistance increased the risk for mortality.

Conflict of interest
No potential conflict of interest relevant to this article was reported.

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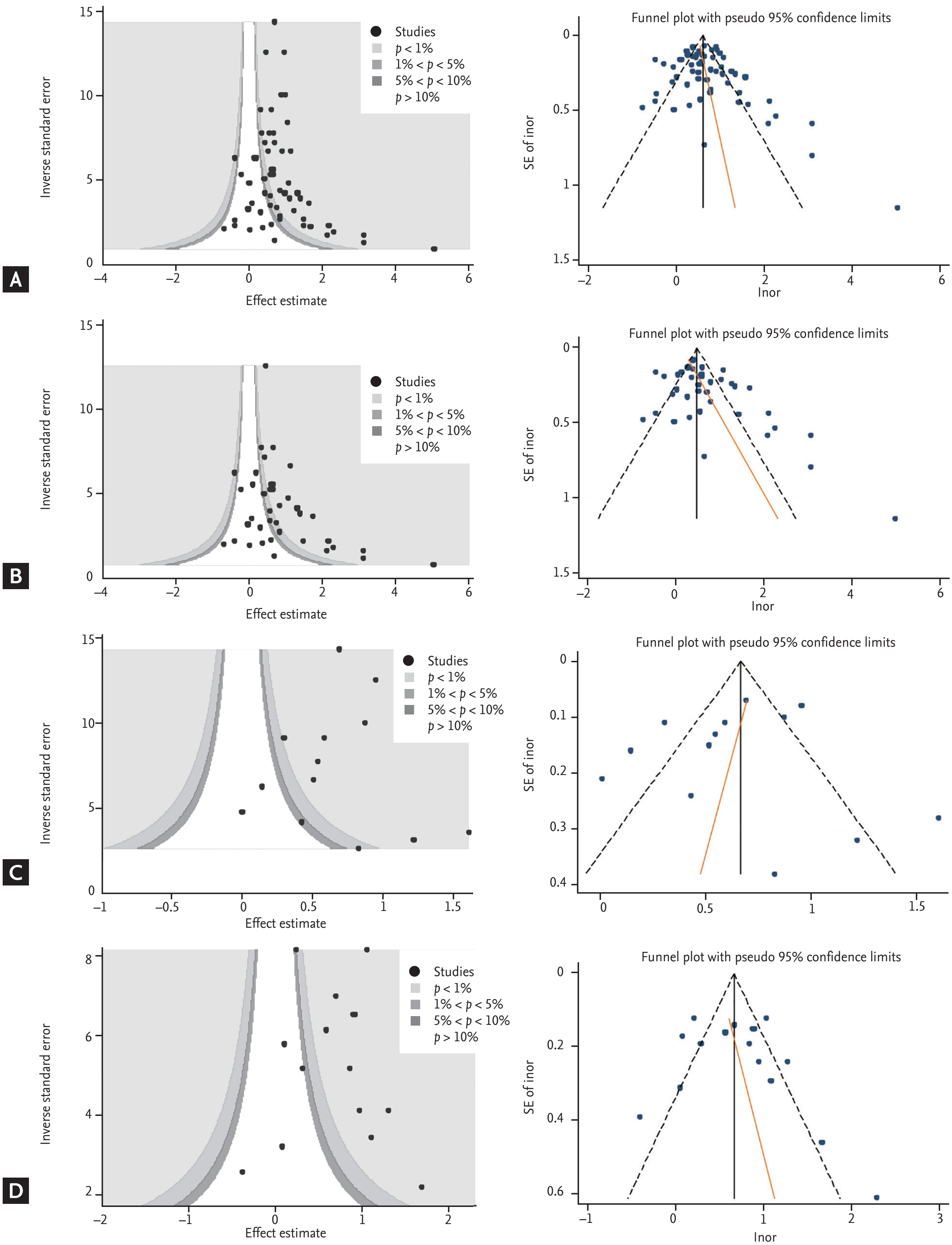

Supplementary Figure 1. Contour-enhanced funnel plot and Begg & Mazumdar's rank correlation test for exploring publication bias for all-cause mortality (A), in-hospital mortality (B), 30-day mortality (C), and *Staphylococcus aureus* bacteremia-related mortality (D).