Dysfunctional accessory gene regulator (agr) as a prognostic factor in invasive Staphylococcus aureus infection: a systematic review and meta-analysis

Soon Ok Lee1, Shinwon Lee1*, Jeong Eun Lee1, Kyoung-Ho Song2, Chang Kyung Kang3, Yu Mi Wi4, Rafael San-Juan5, Luis E. López-Cortés6, Alicia Lacoma7, Cristina Prat7,8, Hee-Chang Jang9, Eu Suk Kim2, Hong Bin Kim2 & Sun Hee Lee1

The accessory gene regulator (agr) locus of Staphylococcus aureus is a quorum-sensing virulence regulator. Although there are many studies concerning the effect of dysfunctional agr on the outcomes of S. aureus infection, there is no systematic review to date. We systematically searched for clinical studies reporting outcomes of invasive S. aureus infections and the proportion of dysfunctional agr among their causative strains, and we performed a meta-analysis to obtain estimates of the odds of outcomes of invasive S. aureus infection with dysfunctional versus functional agr. Of 289 articles identified by our research strategy, 20 studies were meta-analysed for crude analysis of the impact of dysfunctional agr on outcomes of invasive S. aureus infection. Dysfunctional agr was generally associated with unfavourable outcomes (OR 1.32, 95% CI 1.05–1.66), and the impact of dysfunctional agr on outcome was more prominent in invasive methicillin-resistant S. aureus (MRSA) infections (OR 1.54, CI 1.20–1.97). Nine studies were meta-analysed for the impact of dysfunctional agr on the 30-day mortality of invasive S. aureus infection. Invasive MRSA infection with dysfunctional agr exhibited higher 30-day mortality (OR 1.40, CI 1.03–1.90) than that with functional agr. On the other hand, invasive MSSA infection with dysfunctional agr exhibited lower 30-day mortality (OR 0.51, CI 0.27–0.95). In the post hoc subgroup analysis by the site of MRSA infection, dysfunctional agr was associated with higher 30-day mortality in MRSA pneumonia (OR 2.48, CI 1.17–5.25). The effect of dysfunctional agr on the outcome of invasive S. aureus infection may vary depending on various conditions, such as oxacillin susceptibility and the site of infection. Dysfunctional agr was generally associated with unfavourable clinical outcomes and its effect was prominent in MRSA and pneumonia. Dysfunctional agr may be applicable for outcome prediction in cases of invasive MRSA infection with hardly eradicable foci such as pneumonia.

1Department of Internal Medicine, Pusan National University School of Medicine and Medical Research Institute, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea. 2Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Bundang Hospital, Seongnam, Republic of Korea. 3Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Hospital, Seoul, Republic of Korea. 4Division of Infectious Diseases, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea. 5Unit of Infectious Diseases, University Hospital 12 de Octubre, Instituto de Investigación Hospital “12 de Octubre” (i+12), Universidad Complutense, Avenida de Córdoba, s/n, Madrid, Spain. 6Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena/Departamento de Medicina, Universidad de Sevilla/Instituto de Biomedicina de Sevilla, Sevilla, Spain. 7Microbiology Department, Hospital Universitari Germans Trias i Pujol, Institut d’Investigación Germans Trias i Pujol, CIBER Enfermedades Respiratorias (CIBERES), Universitat Autònoma de Barcelona, Badalona, Spain. 8Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands. 9Department of Infectious Diseases, Chonnam National University Medical School, Gwang-ju, Republic of Korea. *email: ebnenezere.lee@gmail.com
Staphylococcus aureus is a major pathogen responsible for invasive infections such as bacteraemia, endocarditis, osteomyelitis, arthritis, and pneumonia. Invasive S. aureus infection is still associated with high mortality and morbidity, and recent studies have shown that the mortality rates of S. aureus bacteraemia (SAB) are 20–30%, even though antibiotic therapies are advanced. Many studies have shown that the persistent infection despite the use of susceptible antibiotics is associated with poor clinical outcomes. To improve the outcomes of invasive S. aureus infection, it is essential to understand how S. aureus establishes and maintains infection in the host for a long time.

Staphylococcus aureus utilizes virulence factors to establish and maintain infection, depending on its growth phase. Among the various virulence factors of S. aureus, the accessory gene regulator (agr) locus, which is a quorum-sensing virulence regulator, can play an important role in perpetuating infection. At high cell density, the agr quorum-sensing circuit leads to decreased production of cell-wall-associated factors, causing the dispersion of the biofilm, the spread of the infection, and a simultaneous increase in exoproteins, including protease, haemolysin, and super-antigen production. The agr locus also leads to increased production of many murein hydrolases that are involved in autolysis. Therefore, the dysfunction of the agr locus can cause the strain to form abundant biofilms and become deficient in autolysis even though the bacterial density is high. These changes can contribute to the persistence of the infection by hindering the host immune system.

According to recent studies, the alteration of agr function can result in decreased activity of various antibiotic agents against S. aureus. The attenuation of the bactericidal activity of vancomycin against S. aureus, the increased minimum inhibitory concentration of vancomycin and the development of vancomycin intermediate/resistant S. aureus (VISA) phenotypes are associated with dysfunctional agr. Dysfunctional agr of S. aureus can affect the incoenm effect of methicillin-sensitive S. aureus (MSSA) against beta-lactam antibiotics and reduce susceptibility to daptomycin. Many clinical studies have also reported the influence of dysfunctional agr on the courses of invasive S. aureus infection, and some studies have shown that dysfunctional agr may be related to unfavourable outcomes such as persistent bacteraemia and a high mortality rate. The information, however, is conflicting and can be affected by various conditions and situations in which the studies were performed. However, no study that systematically reviews and quantitatively analyses the studies concerning the association between agr dysfunction and clinical outcomes has been performed so far.

The aim of this study was to perform a systematic literature review and meta-analysis to measure the association between the dysfunction of the agr locus and clinical outcomes in patients with invasive S. aureus infection. We performed subgroup analysis evaluating MRSA and MSSA as well as different sites of infection.

Results
The database search identified 286 articles, and we identified three more articles. Afterwards, 53 studies were removed due to duplication and 215 studies were excluded due to a lack of relevant information regarding our redefined outcome parameters and insufficient design. Finally, 20 studies were included in our analyses (Fig. 1). Among the 20 included studies, 18 studies collected cases of bacteraemia and their blood isolates, and two studies collected cases of lower respiratory infections and their respiratory isolates. Among 18 bacteraemia studies, seven studies used the isolates that were consecutively collected, and seven studies selected the cases and isolates by specific conditions other than the site of infection; infection with persistent bacteraemia, infection by MRSA with vancomycin MIC ≥ 2 mg/L, or ICU setting. Four studies selected cases and isolates by specific sites of infection: catheter-related infection, infection with removed eradicable foci and without metastatic infection, endocarditis, or pneumonia.

Nineteen studies identified dysfunctional agr isolates by measuring delta-hemolysin production according to the method of Sakoulas G et al., and 1 study identified dysfunctional agr isolates by agr CAMP assay and the vesicle lysis test.

Four studies included all cases of invasive S. aureus infections regardless of oxacillin susceptibility, 12 studies included only MRSA cases, and four studies included only MSSA. Twelve studies reported mortality as their main outcome, five studies reported the persistent bacteraemia as their main outcome, and 12 studies reported treatment failure (composite outcomes). Detailed characteristics of the included studies are provided in Table 1.

Overall unfavourable outcomes.
For the association between dysfunctional agr and overall unfavourable outcomes of invasive S. aureus infection, data were available for 20 studies comprising 3426 patients (Fig. 2). To estimate the crude overall tendency, we conducted a meta-analysis using all included studies, although treatment failure was variably defined in each study. Pooled analysis showed that invasive S. aureus infection with dysfunctional agr was significantly associated with unfavourable outcomes (OR 1.32, 95% CI 1.05–1.66, \( I^2 = 0.27, \) Fig. 2A). The analysis of fourteen studies with MRSA demonstrated that invasive MRSA infection with dysfunctional agr exhibited an increased likelihood of unfavourable outcomes, and the effect was statistically significant (OR 1.54, 95% CI 1.20–1.97, \( I^2 = 0.10, \) Fig. 2B), while the analysis of seven MSSA studies demonstrated that invasive MSSA infection with dysfunctional agr did not increase the likelihood of unfavourable outcomes nor was it statistically significant (OR 0.71, 95% CI 0.47–1.09, \( I^2 = 0.0, \) Fig. 2C).

Mortality.
For the association between dysfunctional agr and the mortality of invasive S. aureus infection, data were available for 13 studies comprising 2659 patients, and pooled analysis showed that invasive S. aureus infection with dysfunctional agr significantly increased the likelihood of death in MRSA but decreased the likelihood of death in MSSA (Supplementary Fig. 1).
For the association between dysfunctional agr and 30-day mortality of invasive S. aureus infection, we included studies that reported or provided 30-day mortality as an outcome and that did not selectively include patients with specific sites of infection; data were available for nine studies comprising 2305 patients (Fig. 3). Pooled analysis showed that invasive S. aureus infection with dysfunctional agr was not associated with higher 30-day mortality in analyses that did not consider oxacillin susceptibility (OR 1.22, 95% CI 0.90–1.65, $I^2 = 0.32$, Fig. 3A). However, in the subgroup analysis of five studies with MRSA, invasive MRSA infection with dysfunctional agr showed significantly higher 30-day mortality than that with functional agr (OR 1.40, 95% CI 1.03–1.90, $I^2 = 0$, Fig. 3B). On the other hand, invasive MSSA infection with dysfunctional agr showed lower 30-day mortality than that with functional agr (0.51, 95% CI 0.27–0.95, $I^2 = 0$, Fig. 3C).

Mortality by the site of infection. We investigated the association between dysfunctional agr and 30-day mortality of invasive S. aureus infection by sites of infections for the five most common infection sites: central-line-associated bloodstream infection (CLABSI), pneumonia, skin and soft tissue infection (SSTI), bone and joint infection (BJI) and endocarditis (Supplementary Table 2).

Pooled analysis showed that dysfunctional agr was associated with higher 30-day mortality than functional agr in MRSA pneumonia (OR 2.48, 95% CI 1.17–5.25, $I^2 = 0$, Fig. 4A). BJI with MRSA with dysfunctional agr (OR 1.86, 95% CI 0.49–7.14, Fig. 4B) also had an increased likelihood of death within 30 days, while CLABSI with
| Study and publication year | Location | Study period | Isolate No., MR/MS (%) | No. of centres | Inclusion/study setting | No. (%) of IE | Main therapeutic agents (%) | Proportion of agr dysfunction according to outcomes (no. of agr dysfunction/total no.) | Proportion of high VM MIC (%) |
|---------------------------|----------|--------------|------------------------|---------------|-------------------------|--------------|-----------------------------|---------------------------------------------------------------------------------|--------------------------|
| Schweizer (2011) 18       | USA      | 2003–2007    | 814, MR(60)/MS(40)     | 1             | SAB, adult/retrospective| 138 (17)     | VM (86)                     | Death (30 day) 3/109 vs. Survival 149/705                                      | MIC ≥ 1.5 (76.2)         |
| Chong (2013) 13           | Korea    | 2008–2010    | 159, MR (100)          | 1             | MRSAB excluding intermediate duration, Adult/Prospective | NR           | VM (92.8), TP (3.6), LZ (3.6) | PB 44/65 vs. NPB 63/94**                                                                | NR                      |
| Jang (2013) 14            | Korea    | 2005–2008    | 307, MR (100)          | 2             | MRSAB (≥ 16 years)/retrospective | 2 (0.7)     | GP (75.2)                    | Death (30 day) 36/98 vs. Survival 72/209                                      | MIC = 2 (12.7), hVISA (6.2) |
| Wi (2015) 27              | Korea    | 2011–2012    | 146, MS (100)          | 9             | MSSAB/prospective     | 19 (13)     | BLT (69.2), BLT + GP (21.9), GP (2.1) | Death (30 day) 2/33 vs. Survival 17/113                                      | NR                      |
| Kang (2015) 31            | Korea    | 2009–2013    | 171, MR (100)          | 1             | MRSAB (≥ 15 years)/prospective | NR          | fVM (99.4), LZ (0.6)       | Death (30 day) 3/109 vs. Survival 149/705                                      | MIC ≥ 1.5 (76.2)         |
| López-Cortés (2015) 26    | Spain    | 2008–2011    | 135, MS (100)          | 1             | MSSAB/prospective     | NR          | fBTL (87.6), GP (6.2), others (6.2) | PB 14/26 vs. NPB 48/99                                                            | MIC ≥ 1.5 (21.5)         |
| Sullivan (2017) 37        | USA      | 2010–2012    | 252, MS (100)          | 1             | MSSAB (≥ 18 years)/Retrospective | NR          | fVM (66.5), BLT (27.3), others (6.2) | Death (30 day) 2/45 vs. Survival 18/207                                      | MIC ≥ 2 (33.3)           |
| Fowler (2004) 7           | USA      | 1995–2000    | 39, MR (100)           | 1             | SAB (≥ 18 years), All PB (n = 21) and randomly selected NPB (n = 18) | 9 (23.1)    | VM (97.4), [adjunctive AG (33.3), RF (10.3)] | PB 15/21 vs. NPB 7/18                                                            | NR                      |
| Moise (2007) 38,a         | USA      | 1998–2002    | 34, MR (100)           | 6             | Randomly selected agr II MRSAB and matched non-agr II MRSAB | 0 (0)       | VM**                       | PB 14/16 vs. NPB 11/18                                                           | NR                      |
| McCalla (2008) 39,b       | USA      | 2002–2005    | 89, MR (100)           | M             | MRSAB from clinical trial comparing DM (n = 45) vs. standard treatment (n = 44)/Post hoc analysis** | NR          | DM (50.6), VM + AG (49.4)   | Failure 16/55 vs. Cure 9/34                                                      | NR                      |
| Walraven (2011) 41        | USA      | 2002–2009    | 139, MR (100)          | 1             | MRSAB (≥ 18 years) and received VM/retrospective | 29 (20.9)   | VM (100)                    | Failure 13/67 vs. Cure 13/72                                                     | MIC ≥ 1.5 (92.1)         |
| Casapao (2013) 43         | USA      | 2004–2012    | 122, MR (100)          | 5             | hVISA (n = 61) and matched VSSAB (n = 61)/retrospective | 48 (39.3)   | VM (100)                    | Failure 15/70 vs. Success 7/52                                                   | hVISA (50)               |
| Hu (2015) 30              | Taiwan   | 2009–2010    | 48, MR (100)           | 1             | MRSAB & treated in ICUs (≥ 18 years)/retrospective | NR          | NR                         | Death (in hospital) 12/35 vs. Survival 1/13                                     | hVISA (27.1)            |
| Kang (2017) 32            | Korea    | 2009–2016    | 152, MR (100)          | 11            | Persistent SAB among 860 MRSAB (≥ 15 years)/retrospective | 11 (7.2)    | fVM (90.1), [adjunctive RF (10.5)] | Death (in hospital) 34/50 vs. Survival 50/102**                                   | MIC ≥ 1.5 (56.6), hVISA (7.2) |
| Yang (2018) 44            | Taiwan   | 2009–2012    | 147, MR (100)          | 1             | High VM MIC (≥ 2 mg/L) MRSAB/Retrospective | NR          | DM (37.4), GM (54.4), Others (8.2) | Failure 24/79 vs. Success 17/68                                                | hVISA (37.4)            |

**Studies that collected cases and isolates by the specific site of infection**

Sharma-Kuinkel (2012) 45       | USA      | 2005–2007    | 287, MR (60)/MS (40)   | M             | S. aureus LRTI from clinical trial comparing TV vs. VM/Post hoc analysis** | NR         | VM, TV                      | Failure 19/34**, 4/18 vs. Cure 60/138**, 13/96                                 | NR                      |

Continued
Table 1. Studies in which the association between *agr* dysfunction and treatment outcomes of invasive *Staphylococcus aureus* infections was able to be evaluated. MRSA (*B*), methicillin-resistant *Staphylococcus aureus* (bacteraemia); MSSA (*B*), methicillin-susceptible *Staphylococcus aureus* (bacteraemia); *h*VISA (*B*), heterogeneous vancomycin intermediate *Staphylococcus aureus* (bacteraemia); VSSA (*B*), vancomycin susceptible *Staphylococcus aureus* (bacteraemia); SAB, *Staphylococcus aureus* bacteraemia; PB, persistent bacteraemia; *NPB*, non-persistent bacteraemia; IE, infective endocarditis; LRT (*I*), lower respiratory tract (infection); NR, not reported; CNS, central nervous system; MIC, minimal inhibitory concentration; IQR, interquartile range; ICU, intensive care unit; GP, glycopeptide; VM, vancomycin; TP, teicoplanin; TV, telavancin; AG, aminoglycoside; RF, rifampin; DM, daptomycin; LZ, linezolid; BLT, beta-lactam. *agr* functionality was measured by *agr* score in this study, *agr* score 0–1 was considered as *agr* dysfunction and *agr* score 2–4 as *agr* function. *There is a record of the vancomycin trough level of each group, but there is no record of definite antibiotic use. †Excluded LRTI cases in our analysis because colonization cases were mixed. ‡Excluded from analysis because this study was conducted on selected cases from the study of Chong et al. §Studies reported definitive therapy. ¶Initial therapy as their main therapeutic agents; otherwise, therapies were not reported.

MRSA with dysfunctional *agr* (OR 0.79, 95% CI 0.39–1.61, Fig. 4C) and SSTI with MRSA with dysfunctional *agr* (OR 0.72, 95% CI 0.33–1.60, Fig. 4D) had a decreased likelihood of death within 30 days, and both results were not statistically significant. And infective endocarditis with MRSA with dysfunctional *agr* (OR 0.78, 95% CI 0.29–2.09, Fig. 4E) also had a decreased likelihood of death within 30 days, and the result was not statistically significant.

Pooled analysis showed that CLABSI with MSSA with dysfunctional *agr* had a decreased likelihood of death within 30 days, and BJI with MSSA with dysfunctional *agr* had an increased likelihood of death within 30 days, and both results were not statistically significant (Supplementary Fig. 2).

**Persistent bacteraemia.** Among the 18 SAB studies, five studies considered the persistent bacteraemia as an outcome, comprising 375 patients. Pooled analysis showed that SAB with dysfunctional *agr* was generally not associated with persistent bacteraemia (OR 1.54, 95% CI 0.78–3.04, *P* = 0.39, Fig. 5A). In the subgroup analysis of three studies of MRSA SAB, we observed an increased likelihood of persistent bacteraemia, but the increase was not statistically significant (OR 2.15, 95% CI 0.74–6.19, *P* = 0.57, Fig. 5B). In the subgroup analysis of 2 studies of MSSA, we observed no difference in the rates of persistent bacteraemia between the dysfunctional *agr* group and the functional *agr* group (OR 0.91, 95% CI 0.40–2.08, *P* = 0, Fig. 5C).

**Discussion**

To date, many studies have analysed the association between *agr* dysfunction and poor clinical outcomes of invasive *S. aureus* infection in various clinical settings. Since Schweizer et al. reported that SAB with dysfunctional *agr* was associated with excessive mortality among severely ill patients, subsequent studies have demonstrated that *agr* dysfunction was associated with higher mortality, and the persistence of bacteraemia...
Figure 2. The results for the association of agr dysfunction with overall outcome in patients with invasive S. aureus infection: (A) total, (B) MRSA, and (C) MSSA.
in patients with SAB, especially in MRSA bacteraemia. However, some studies reported that agr dysfunction of MRSA bacteraemia was not associated with treatment failure or mortality. Despite the fact that various studies have addressed the association between agr dysfunction and the outcome of invasive S. aureus infection, data on its role in different infections and populations remained scattered. Despite the necessity for the integration of the information, this subject has never been systematically reviewed. Therefore, we systematically reviewed and performed a meta-analysis of 20 studies focusing on the association between clinical outcomes and dysfunctional agr in invasive S. aureus infections to investigate whether agr dysfunction can be a marker of poor clinical outcome. We performed data analysis using three different outcomes, namely 30-day mortality, antibiotic treatment failure, and all-cause mortality. The results of our meta-analysis are shown in Figures 3A-C.

Figure 3. The results for the association of agr dysfunction with 30-day mortality in patients with invasive S. aureus infection: (A) total, (B) MRSA, and (C) MSSA.

### Table 1

| Study                        | agr dysfunction Events | agr function Events | Odds Ratio | OR   | 95% CI | Weight |
|------------------------------|------------------------|---------------------|------------|------|--------|--------|
| Schweizer ML et al 2011      | 33 182                 | 76 632              | 1.62       | 1.04 | 2.53   | 20.3%  |
| Jang HC et al 2013           | 36 108                 | 62 199              | 1.10       | 0.67 | 1.82   | 18.3%  |
| Wi YM et al 2015             | 2 19                   | 31 127              | 0.36       | 0.08 | 1.67   | 3.6%   |
| Kang CK et al 2015           | 35 123                 | 14 72               | 1.65       | 0.82 | 3.33   | 12.3%  |
| López-Cortés LE et al 2015   | 14 65                  | 23 70               | 0.56       | 0.26 | 1.22   | 10.8%  |
| Kang CK et al 2017           | 25 84                  | 14 66               | 1.57       | 0.74 | 3.34   | 11.2%  |
| Sullivan SB et al 2017       | 2 20                   | 43 232              | 0.49       | 0.11 | 2.18   | 3.7%   |
| Yang CC et al 2018           | 18 41                  | 31 106              | 1.89       | 0.90 | 3.99   | 11.3%  |
| Chong YP 2013                | 20 107                 | 8 52                | 1.26       | 0.52 | 3.10   | 8.7%   |

**Random effects model**: 749 events, 1556 total events. Heterogeneity: $I^2 = 32\%$, $\chi^2 = 0.0649$, $p = 0.16$.

**P = 0.202**

### Table 2

| Study                        | agr dysfunction Events | agr function Events | Odds Ratio | OR   | 95% CI | Weight |
|------------------------------|------------------------|---------------------|------------|------|--------|--------|
| Jang HC et al 2013           | 36 108                 | 62 199              | 1.10       | 0.67 | 1.82   | 36.9%  |
| Kang CK et al 2015           | 35 123                 | 14 72               | 1.65       | 0.82 | 3.33   | 18.7%  |
| Kang CK et al 2017           | 25 84                  | 14 66               | 1.57       | 0.74 | 3.34   | 16.3%  |
| Yang CC et al 2018           | 18 41                  | 31 106              | 1.89       | 0.90 | 3.99   | 16.6%  |
| Chong YP 2013                | 20 107                 | 8 52                | 1.26       | 0.52 | 3.10   | 11.5%  |

**Random effects model**: 463 events, 495 total events. Heterogeneity: $I^2 = 0\%$, $\chi^2 = 0$, $p = 0.77$.

**P = 0.030**

### Table 3

| Study                        | agr dysfunction Events | agr function Events | Odds Ratio | OR   | 95% CI | Weight |
|------------------------------|------------------------|---------------------|------------|------|--------|--------|
| Wi YM et al 2015             | 2 19                   | 31 127              | 0.36       | 0.08 | 1.67   | 17.0%  |
| López-Cortés LE et al 2015   | 14 65                  | 23 70               | 0.56       | 0.26 | 1.22   | 65.5%  |
| Sullivan SB et al 2017       | 2 20                   | 43 232              | 0.49       | 0.11 | 2.18   | 17.5%  |

**Random effects model**: 104 events, 429 total events. Heterogeneity: $I^2 = 0\%$, $\chi^2 = 0$, $p = 0.88$.

**P = 0.035**

---

Scientific Reports | (2020) 10:20697 | https://doi.org/10.1038/s41598-020-77729-0
Figure 4. The association of agr dysfunction with mortality in patients with invasive MRSA infection according to the site of infection.
Overall unfavourable outcomes, 30-day mortality and persistent bacteraemia. To reduce the complexity due to variably defined outcomes, we performed subgroup analysis by the site of infection using 30-day mortality. This meta-analysis demonstrated that invasive *S. aureus* infection with dysfunctional *agr* significantly increased the likelihood of unfavourable outcomes. However, the implication of *agr* dysfunction on the outcomes of invasive *S. aureus* infections was not prominent. The reason for the modest implication of dysfunctional *agr* on outcomes of invasive *S. aureus* infection could be that the studies dealt with various end points such as mortality, treatment failure (composite outcomes) and the persistence of bacteraemia. Oxacillin susceptibility, one of most important confounding factors, can affect the outcomes of invasive *S. aureus* infection. Therefore, we performed a meta-analysis with the studies that reported or provided information on 30-day mortality according to the functionality of the *agr* locus of causative strains to minimize the effect of variances of end points of studies. The analysis demonstrated that invasive *S. aureus* infection with dysfunctional *agr* showed an increased likelihood of 30-day mortality in MRSA and a decreased likelihood of 30-day mortality in MSSA. It was interesting that dysfunctional *agr* could affect outcomes of invasive *S. aureus* infection differently according to the oxacillin susceptibility of isolated strains.

The difference in the impacts of dysfunctional *agr* on MRSA and MSSA infections can be speculated as follows. First, various experimental and clinical studies suggested that *S. aureus* acquires the ability to maintain persistent infection due to dysfunctional *agr* but loses virulence at the cost of dysfunctional *agr* and vancomycin in invasive *S. aureus* infections.

---

**Figure 5.** The results for the association of *agr* dysfunction with persistent bacteraemia in patients with *S. aureus* bacteraemia: (A) total, (B) MRSA, and (C) MSSA.
other powerful confounding factors, such as a high proportion of community-acquired MRSA and high vancomycin MIC, hVISA phenotype, different sites of infections (endocarditis or pneumonia), and the removal (or not) of foreign bodies.

First, reduced vancomycin susceptibility (RVS) needs to be considered an important factor when we evaluate factors affecting unfavourable outcomes of invasive MRSA infections because intravenous administration of vancomycin is recommended as the standard treatment of patients with invasive MRSA infection, as a matter of fact, most of the included studies administered vancomycin as the main therapeutic agent for MRSA infections. A previous study reported that a high MIC of vancomycin is associated with high mortality and treatment failure in MRSA bacteraemia and agr dysfunction is associated with the attenuation of the bactericidal activity of vancomycin and the development of vancomycin intermediate/resistant S. aureus (VISA). This suggests that there is a possible intrinsic survival advantage of dysfunctional agr under vancomycin selective pressure. However, most studies that used vancomycin as the main therapeutic agent showed a significant association between agr dysfunction and unfavourable outcomes regardless of vancomycin MIC. Therefore, dysfunctional agr might be a marker of poor clinical outcomes of MRSA bacteraemia regardless of vancomycin MICs of causative organisms when patients were treated with vancomycin.

Second, the implication of agr dysfunction on unfavourable outcomes can be affected by specific conditions other than vancomycin MICs, such as the severity of infections and the proper removal of sources. Schweizer ML et al. demonstrated that agr dysfunction in SAB isolates was independently associated with high mortality among severely ill patients. Hu HC et al. reported that S. aureus infection possessing dysfunctional agr, which was associated with the hVISA phenotype, exhibited markedly higher in-hospital mortality (12/13, 92.3%) than functional agr infection (23/35, 65.7%) in an ICU-setting study. The study that limited the subjects to patients with adequate source control, which was another important factor for the outcome of invasive S. aureus infection, demonstrated that agr dysfunction is an independent risk factor for MRSA bacteraemia that persists despite the source control. These findings suggested that dysfunctional agr can be a microbiological predictor of unfavourable outcomes in severe MRSA infection despite proper source control.

Third, the site of infection is one of most important factors in the outcomes of invasive S. aureus infection, and the implication of agr dysfunction on unfavourable outcomes can be affected by the site of infection. Therefore, we performed a subgroup analysis considering the site of infection. In the subgroup analysis by the site of infection, lower respiratory infection caused by MRSA with dysfunctional agr showed significantly higher mortality than MRSA with functional agr. BJI with MRSA with dysfunctional agr had an increased likelihood of mortality, although this result was not statistically significant. On the other hand, CLABSI and SSTI were not significantly affected by agr dysfunction. It is interesting that dysfunctional agr can affect the outcomes of invasive S. aureus infection differently according to the site of infection, although the reason for this difference is unclear. One probable explanation is as follows. First, patients with eradicable foci of infections, such as CLABSI and SSTI, might be more easily treated, and the magnitude of the effect of agr dysfunction on outcomes would be minimal. On the other hand, patients with foci that are difficult to eradicate, such as pneumonia and BJI, might be more difficult to treat, and the magnitude of the effect of dysfunctional foci would be more prominent. Second, the vancomycin molecule is relatively large and penetrates poorly into the alveolar lining fluid and alveolar macrophages and into the bone and joints, further exacerbating the effect of RVS due to dysfunctional agr.

The results of this meta-analysis should be interpreted with caution. First, the enrolled studies of our meta-analysis used different patient populations, different definitions of treatment failure, different definitions of the persistence of bacteraemia, and different time points of mortality. Except for seven studies that used consecutively collected isolates, the other enrolled studies used isolates from selected cases, such as specific sites of infection, persistent bacteraemia, and higher vancomycin MICs in treatment in ICUs. The studies that used isolates from selected cases may have selected more virulent strains or those causing more difficult-to-treat infection, making it hard to compare the data with those of the studies that collected all consecutive isolates. To compensate for this heterogeneity of studies, we conducted subgroup analysis according to the sites of infection. We could extrapolate the effect of agr dysfunction on severity of disease based on the subgroup analysis by the site of infection. Moreover, the analysis was not adjusted for important factors that might affect clinical outcomes, such as source control, antibiotics used, time elapsed from infection onset to adequate therapy, incomplete vancomycin dosing, hVISA or strains with higher vancomycin MICs, severity of illness scoring, etc. Most of the included studies were retrospective, observational studies; therefore, publication bias is likely.

Second, most studies that investigated the association between agr dysfunction of MRSA bacteraemia and 30-day mortality were performed in Korea. In Korea, more than 70% of MRSA is SCCmec type II (mainly ST5),
and 20–30% is SCCmec type IV/IVa (mainly ST72)\textsuperscript{71}. Several molecular epidemiology studies reported that 41–90% of SCCmec type II–MRSA was associated with agr dysfunction, but 3–12% of SCCmec type IV/IVa-MRSA was associated with agr dysfunction in Korea\textsuperscript{24,31,72,73}. Therefore, our results should be interpreted with caution because it is not clear whether the poor outcomes of invasive MRSA infection with dysfunctional agr in our results might be affected by the predominance of a specific clone, SCCmec type II (mainly ST5), which was associated with dysfunctional agr. Third, except for 1 study\textsuperscript{24}, all included studies evaluated the activity of agr by the delta-haemolysin test. The interpretation of the delta-haemolysin test can be subject to low sensitivity\textsuperscript{74}. However, Shopsin et al. performed a delta-haemolysin test and Northern blotting test for RNA III production and found that the delta-haemolysin test was a fair specific marker for dysfunctional agr\textsuperscript{29,75}.

### Conclusion

Invasive S. aureus infection with dysfunctional agr was associated with unfavourable clinical outcomes. However, dysfunctional agr is not universally applicable to clinical decision making because dysfunctional agr can affect the clinical outcome of invasive S. aureus infection differently according to the oxacillin susceptibility profile. The implication of dysfunctional agr was also different according to the sites of infection. However, dysfunctional agr may be used as a predictor of outcomes of invasive S. aureus infection if the patients have pneumonia caused by MRSA. Further study is warranted to determine how dysfunctional agr affects oxacillin susceptibility differently and according to sites of infection in invasive S. aureus infection.

### Methods

#### Search strategy and selection criteria.

We searched for clinical studies reporting the proportion of dysfunctional agr and its association with outcomes of invasive S. aureus infections from database inception to 26th September 2018 in Medline and ISI Web of Science (Science Citation Index Expanded). The combination of the following keywords were used to search the studies: "Staphylococcus aureus", "bacteremia", "pneumonia", "endocarditis", "osteomyelitis", "arthritis", "Quorum sensing", "agr (accessory gene regulator)", and "delta-hemolysin". We excluded review articles, case reports and experimental studies. We also excluded colonization studies or epidemiological studies that did not report outcomes associated with agr functionality. Two authors (Shinwon Lee, Soon Ok Lee) independently performed the literature search and identified all studies potentially relevant for this review (Fig. 1).

#### Data analysis.

To analyse the association between the dysfunction of agr and outcomes of invasive S. aureus infections, we calculated odds ratios (ORs) comparing the odds of outcomes of S. aureus infection with dysfunctional agr and the odds of that with functional agr.

We used meta-analysis to obtain estimates of the odds of outcomes of invasive S. aureus infection with dysfunctional agr and presented ORs and their 95% confidence intervals (CIs) in random-effects model analysis. Meta-analysis results are presented as forest plots, and funnel plots were inspected to judge potential evidence for publication bias. We applied a two-sided significance level of 0.05. R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and R package 'meta' were used for all statistical analyses\textsuperscript{76,77}.

The number of patients and events for the dysfunctional versus functional agr group were extracted by one author (Shinwon Lee). The results were independently validated by another author (Soon Ok Lee). We extracted information on study designs, settings, patient characteristics, method for isolate collection (or selection) and the year of data collection to assess potential heterogeneity in the study populations. A formal risk assessment of the individual studies was judged according to the Newcastle–Ottawa Scale (NOS)\textsuperscript{78}. To investigate whether dysfunctional agr is associated with poor outcome among cases of invasive disease, we compared outcomes, mainly 30-day mortality and the persistent bacteraemia. The included studies reported various end points as their outcomes, such as 30-day mortality, in-hospital mortality, S. aureus bacteraemia-attributable mortality, persistent bacteraemia, treatment failure, and development of complications (Table 1). We analysed data using three different outcomes, namely overall unfavourable outcomes, 30-day mortality and persistent bacteraemia. We defined overall unfavourable outcomes as comprehensive negative results from each study. Additionally, we performed post hoc analysis to determine the association between dysfunctional agr and mortality according to the site of infection. Information that was not mentioned in the original article was requested by contacting the authors directly. The study protocol is registered on PROSPERO with reference number ID: CRD42019134966.

**Received:** 11 August 2020; **Accepted:** 17 November 2020

**Published online:** 26 November 2020

### References

1. van Hal, S. J. et al. Predictors of mortality in Staphylococcus aureus Bacteremia. Clin. Microbiol. Rev. 25, 362–386. \textsuperscript{https://doi.org/10.1128/CMR.05022-11} (2012).
2. Turnidge, J. D. et al. Staphylococcus aureus bacteremia: A major cause of mortality in Australia and New Zealand. Med. J. Aust. 191, 368–373 (2009).
3. Kaasch, A. J. et al. Staphylococcus aureus bloodstream infection: A pooled analysis of five prospective, observational studies. J. Infect. 68, 242–251. \textsuperscript{https://doi.org/10.1016/j.jinf.2013.10.015} (2014).
4. Benfield, T. et al. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. Clin. Microbiol. Infect. 13, 257–263. \textsuperscript{https://doi.org/10.1111/j.1469-0691.2006.01589.x} (2007).
5. Song, K. H. et al. Characteristics of invasive Staphylococcus aureus infections in three regions of Korea, 2009–2011: A multi-center cohort study. BMC Infect. Dis. 13, 581. \textsuperscript{https://doi.org/10.1186/1471-2334-13-581} (2013).
6. Lee, S. O. et al. Predictors of death in community acquired Staphylococcus aureus bacteraemia: A major cause of mortality in Australia and New Zealand. Med. J. Aust. 191, 368–373 (2009).
7. Kaasch, A. J. et al. Staphylococcus aureus bloodstream infection: A pooled analysis of five prospective, observational studies. J. Infect. 68, 242–251. \textsuperscript{https://doi.org/10.1016/j.jinf.2013.10.015} (2014).
8. Benfield, T. et al. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. Clin. Microbiol. Infect. 13, 257–263. \textsuperscript{https://doi.org/10.1111/j.1469-0691.2006.01589.x} (2007).
9. Song, K. H. et al. Characteristics of invasive Staphylococcus aureus infections in three regions of Korea, 2009–2011: A multi-center cohort study. BMC Infect. Dis. 13, 581. \textsuperscript{https://doi.org/10.1186/1471-2334-13-581} (2013).
6. Chang, F. Y. et al. A prospective multicenter study of Staphylococcus aureus bacteremia: Incidence of endocarditis, risk factors for mortality, and clinical impact of methillin resistance. Medicine (Baltimore) 82, 322–332. https://doi.org/10.1097/md.000000000000091185.03122.40 (2003).

7. Fowler, V. G Jr. et al. Persistent bacteremia due to methillin-resistant Staphylococcus aureus infection is associated with agr dysfunction and low-level in vitro resistance to thrombin-induced platelet microbicidal protein. J. Infect. Dis. 190, 1140–1149. https://doi.org/10.1086/423145 (2004).

8. Hawkins, C. et al. Persistent Staphylococcus aureus bacteremia: An analysis of risk factors and outcomes. Arch. Intern. Med. 167, 1861–1867. https://doi.org/10.1001/archinte.167.17.1861 (2007).

9. Khatri, R. et al. Persistence in Staphylococcus aureus bacteremia: Incidence, characteristics of patients and outcome. Scand. J. Infect. Dis. 38, 7–14. https://doi.org/10.3109/00315550300072384 (2006).

10. Khatri, R. et al. Persistent Staphylococcus aureus bacteremia: Incidence and outcome trends over time. Scand. J. Infect. Dis. 41, 1–9. https://doi.org/10.1080/00315550701417711 (2009).

11. Yoon, Y. K., Kim, J. Y., Park, D. W., Sohn, J. W. & Kim, M. J. Predictors of persistent methillin-resistant Staphylococcus aureus bacteremia in patients treated with vancomycin. J. Antimicrob. Chemother. 65, 1015–1018. https://doi.org/10.1093/jac/dkq050 (2010).

12. Boles, B. R. & Horswill, A. R. Agr-mediated dispersal of Staphylococcus aureus biofilms. PLoS Pathog. 4, e1000052. https://doi.org/10.1371/journal.ppat.1000052 (2008).

13. Coelho, L. R. et al. agr RNAsII divergently regulates glucose-induced biofilm formation in clinical isolates of Staphylococcus aureus. Microbiology 154, 3480–3490. https://doi.org/10.1099/mic.0.016104-0 (2008).

14. Hodile, E. et al. The role of antibiotics in modulating virulence in Staphylococcus aureus. Clin. Microbiol. Rev. 30, 887–917. https://doi.org/10.1128/cmrr.00129-16 (2017).

15. Oregi, Y. et al. Expression of virulence factors by Staphylococcus aureus grown in serum. Appl. Environ. Microbiol. 77, 8097–8105. https://doi.org/10.1128/aem.05316-11 (2011).

16. Painter, K. L., Krishna, A., Wigneshwararaj, S. & Edwards, A. M. What role does the quorum-sensing accessory gene regulator system play during Staphylococcus aureus bacteremia? Trends Microbiol. 22, 676–685. https://doi.org/10.1016/j.tim.2014.09.002 (2014).

17. Singh, R. & Ray, P. Quorum sensing-mediated regulation of staphylococcal virulence and antibiotic resistance. Future Microbiol. 9, 669–681. https://doi.org/10.2217/fmb.14.31 (2014).

18. Wang, B. & Muir, T. W. Regulation of virulence in Staphylococcus aureus: Molecular mechanisms and remaining puzzles. Cell Chem. Biol. 23, 214–224. https://doi.org/10.1016/j.chembiol.2016.01.004 (2016).

19. Fujimoto, D. F. & Bayles, K. W. Opposing roles of the Staphylococcus aureus virulence regulators, Agr and Sar, in triton X-100- and penicillin-induced autolysis. J. Bacteriol. 180, 3724–3726 (1998).

20. Tsuji, B. T., Harigaya, Y., Lesse, A. J., Sakoulas, G. & Mylon, J. M. Loss of vancomycin bactericidal activity against accessory gene regulator (agr) dysfunctional Staphylococcus aureus under conditions of high bacterial density. Diagn. Microbiol. Infect. Dis. 64, 220–224. https://doi.org/10.1016/j.diagmicrobio.2009.01.028 (2009).

21. Sakoulas, G. et al. Accessory gene regulator (agr) locus in geographically diverse Staphylococcus aureus isolates with reduced susceptibility to vancomycin. Antimicrob. Agents Chemother. 46, 1492–1502. https://doi.org/10.1128/aac.46.5.1492-1502.2002 (2002).

22. Harigaya, Y., Ngo, D., Lesse, A. J., Huang, V. & Tsuji, B. T. Characterization of heterogeneous vancomycin-intermediate resistance, MIC and accessory gene regulator (agr) dysfunction among clinical bloodstream isolates of Staphylococcus aureus. BMC Infect. Dis. 11, 287. https://doi.org/10.1186/1471-2334-11-287 (2011).

23. Holmes, N. E. et al. Genetic and molecular predictors of high vancomycin MIC in Staphylococcus aureus bacteremia isolates. J. Clin. Microbiol. 52, 3384–3393. https://doi.org/10.1128/JCM.01320-14 (2014).

24. Jang, H. C. et al. Difference in agr dysfunction and reduced vancomycin susceptibility between MRSA bacteremia involving SCCmec types IV/IVa and I-III. PLoS ONE 7, e49136. https://doi.org/10.1371/journal.pone.0049136 (2012).

25. Tsuji, B. T., MacLean, R. D., Dresser, L. D., McGavin, M. J. & Simor, A. E. Impact of accessory gene regulator (agr) dysfunction on vancomycin pharmacodynamics among Canadian community and health-care associated methillin-resistant Staphylococcus aureus. Antm. Clin. Microbiol. Antimicrob. 10, 20. https://doi.org/10.1128/acidomicrobiol.00010-17 (2020).

26. Viedma, E. et al. Relationship between agr dysfunction and reduced vancomycin susceptibility in methillin-susceptible Staphylococcus aureus causing bacteremia. J. Antimicrob. Chemother. 69, 51–58. https://doi.org/10.1093/jac/dkt337 (2014).

27. Oregi, Y. et al. Expression of virulence factors by Staphylococcus aureus inactivates daptomycin by releasing membrane phospholipids. Nat. Microbiol. 2, 16194. https://doi.org/10.1038/s41564-019-0164 (2019).

28. Schweitzer, M. L. et al. Increased mortality with accessory gene regulator (agr) dysfunction in Staphylococcus aureus among bacteremic patients. Antimicrob. Agents Chemother. 55, 1082–1087. https://doi.org/10.1128/AAC.00918-10 (2011).

29. Park, S. Y. et al. agr Dysfunction and persistent methillin-resistant Staphylococcus aureus bacteremia in patients with removed iradicable foci. Infection 41, 111–119. https://doi.org/10.1159/000150102-012-0348-0 (2013).

30. Kang, C. K. et al. agr dysfunction affects staphylococcal cassette chromosome mec type-dependent clinical outcomes in methillin-resistant Staphylococcus aureus bacteremia. Antimicrob. Agents Chemother. 59, 3125–3132. https://doi.org/10.1128/AAC.04962-14 (2015).

31. Kang, C. K. et al. agr function affects clinical outcomes in patients with persistent methillin-resistant Staphylococcus aureus bacteremia. Eur. J. Clin. Microbiol. Infect. Dis. 36, 2187–2191. https://doi.org/10.1007/s10096-017-3044-2 (2017).

32. Moise, P. A., Sakoulas, G., Forrest, A. & Schentag, J. J. Vancomycin in vitro bactericidal activity and its relationship to efficacy in clearance of methillin-resistant Staphylococcus aureus bacteremia. Antimicrob. Agents Chemother. 51, 2582–2586. https://doi.org/10.1128/AAC.00939-06 (2007).

33. McCalla, C. et al. Microbiological and genotypic analysis of methillin-resistant Staphylococcus aureus bacteremia. Antimicrob. Agents Chemother. 52, 3441–3443. https://doi.org/10.1128/AAC.00357-08 (2008).
40. Fowler, V. G. J. et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N. Engl. J. Med. 355, 653–665. https://doi.org/10.1056/NEJMoa053783 (2006).

41. Walraven, C. J. et al. Site of infection rather than vancomycin MIC predicts vancomycin treatment failure in methicillin-resistant Staphylococcus aureus bacteremia. J. Antimicrob. Chemother. 66, 2386–2392. https://doi.org/10.1093/jac/dkr301 (2011).

42. Casapao, A. M. et al. Clinical outcomes in patients with heterogeneous vancomycin-intermediate Staphylococcus aureus bloodstream infection. Antimicrob. Agents Chemother. 57, 4252–4259. https://doi.org/10.1128/AAC.00830-13 (2013).

43. Hu, H. C. et al. Clinical outcomes and molecular typing of heterogeneous Staphylococcus aureus bacteremia in patients in intensive care units. BMC Infect. Dis. 15, 444. https://doi.org/10.1186/s12879-015-1215-2 (2015).

44. Yang, C. C. et al. Risk factors of treatment failure and 30 day mortality in patients with bacteremia due to MRSA with reduced vancomycin susceptibility. Sci. Rep. 8, 7868. https://doi.org/10.1038/s41598-018-26277-9 (2018).

45. Sharma-Kuinkel, B. K. et al. Presence of genes encoding panton-valentine leukocidin is not the primary determinant of outcome in patients with hospital-acquired pneumonia due to Staphylococcus aureus. J. Clin. Microbiol. 50, 848–856. https://doi.org/10.1128/JCM.02191-12 (2012).

46. Rubinstein, E. et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. Clin. Infect. Dis. 52, 31–40. https://doi.org/10.1093/cid/ciq031 (2011).

47. Velasco, C. et al. Clinical and molecular epidemiology of meticillin-resistant Staphylococcus aureus causing bacteraemia in Southern Spain. J. Hosp. Infect. 81, 257–263. https://doi.org/10.1016/j.jhin.2012.09.017 (2012).

48. McDanel, J. S. et al. Association between microbial characteristics and poor outcomes among patients with methicillin-resistant Staphylococcus aureus pneumonia: A retrospective cohort study. Antimicrob. Resist. Infect. Control 4, 51. https://doi.org/10.1186/s13756-015-0092-1 (2015).

49. San-Juan, R. et al. Pathogen-related factors affecting outcome of catheter-related bacteremia due to methicillin-susceptible Staphylococcus aureus in a Spanish multicenter study. Eur. J. Clin. Microbiol. Infect. Dis. 36, 1757–1765. https://doi.org/10.1007/s10096-017-2989-5 (2017).

50. Fernandez-Hidalgo, N. et al. Impact of Staphylococcus aureus phenotype and genotype on the clinical characteristics and outcome of infective endocarditis. A multicentre, longitudinal, prospective, observational study. Clin. Microbiol. Infect. 24, 985–991. https://doi.org/10.1016/j.cmi.2017.12.002 (2018).

51. Park, S. Y. et al. Impact of reduced vancomycin MIC on clinical outcomes of methicillin-resistant Staphylococcus aureus bacteremia. Antimicrob. Agents Chemother. 57, 5536–5542. https://doi.org/10.1128/AAC.01137-13 (2013).

52. Abdelnour, A., Arvidson, S., Bremell, T., Ryden, C. & Tarkowski, A. The accessory gene regulator (agr) group and function in the proclivity of Staphylococcus aureus to cause sepsis. J. Infect. Dis. 200, 2386–2392. https://doi.org/10.1093/infdis/ji00218 (2009).

53. Shopsin, B. et al. Mutations in agr do not persist in natural populations of methicillin-resistant Staphylococcus aureus. J. Infect. Dis. 202, 1593–1599. https://doi.org/10.1093/infdis/jit015 (2010).

54. Thompson, T. A. & Brown, P. D. Association between the agr locus and the presence of virulence genes and pathogenesis in Staphylococcus aureus using a Caenorhabditis elegans model. Int. J. Infect. Dis. 54, 72–76. https://doi.org/10.1016/j.ijid.2016.11.011 (2017).

55. Gillassy, A. F. et al. Role of the accessory gene regulator (agr) in pathogenesis of staphylococcal osteomyelitis. Infect. Immun. 63, 3373–3380 (1995).

56. Small, P. M. & Chambers, H. F. Vancomycin for Staphylococcus aureus endocarditis in intravenous drug users. Antimicrob. Agents Chemother. 34, 1227–1231. https://doi.org/10.1128/AAC.34.6.1227 (1990).

57. Caston, J. J. et al. Vancomycin minimum inhibitory concentration is associated with poor outcome in patients with methicillin-susceptible Staphylococcus aureus bacteremia regardless of treatment. Scand. J. Infect. Dis. 46, 783–786. https://doi.org/10.1080/03639484.2014.931596 (2014).

58. Falcon, R. et al. Vancomycin MICs and risk of complicated bacteremia by glycopeptide-susceptible Staphylococcus aureus. Eur. J. Clin. Microbiol. Infect. Dis. 38, 1061–1066. https://doi.org/10.1007/s10096-019-05050-7 (2019).

59. Kok, E. Y. et al. Association of vancomycin MIC and molecular characteristics with clinical outcomes in methicillin-susceptible Staphylococcus aureus. Clin. Infect. Dis. 55, 755–771. https://doi.org/10.1093/cid/cir935 (2012).

60. Sakoulas, G., Moelling, J. R. C. & Eliopoulos, G. M. Adaptation of methicillin-resistant Staphylococcus aureus in the face of vancomycin therapy. Clin. Infect. Dis. 42, 340–350. https://doi.org/10.1086/491713 (2006).

61. Moise-Broder, P. A. et al. Accessory gene regulator group II polymorphism in methicillin-resistant Staphylococcus aureus is predictive of failure of vancomycin therapy. Clin. Infect. Dis. 37, 1708–1707. https://doi.org/10.1086/421092 (2004).

62. Tsuji, B. T., Rybak, M. J., Lau, K. L. & Sakoulas, G. Evaluation of accessory gene regulator (agr) group and function in the proclivity towards vancomycin intermediate resistance in Staphylococcus aureus. Antimicrob. Agents Chemother. 51, 1089–1091. https://doi.org/10.1128/AAC.00071-06 (2007).

63. Graziani, A. L., Lawson, L. A., Gibson, G. A., Steinberg, M. A. & MacGregor, R. R. Vancomycin concentrations in infected and noninfected human bone. Antimicrob. Agents Chemother. 32, 1320–1322. https://doi.org/10.1128/AAC.32.9.1320 (1988).

64. Lamer, C. et al. Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. Antimicrob. Agents Chemother. 37, 281–286. https://doi.org/10.1128/AAC.37.2.281 (1993).

65. Rubinstein, E., Kolle, M. H. & Nathwani, D. Pneumonia caused by methicillin-resistant Staphylococcus aureus. Clin. Infect. Dis. 39(6 Suppl 3), S378–S385. https://doi.org/10.1086/533594 (2004).

66. Chen, C. J. & Huang, Y. C. New epidemiology of Staphylococcus aureus infection in Asia. Clin. Microbiol. Rev. 20, 605–623. https://doi.org/10.1128/9609.12075 (2014).

67. Bae, E. et al. Impact of community-onset methicillin-resistant Staphylococcus aureus on Staphylococcus aureus bacteremia in a Central Korea Veterans Health Service Hospital. Ann. Lab. Med. 39, 158–166. https://doi.org/10.3343/alm.2019.39.2.158 (2019).

68. Chong, Y. P. et al. Accessory gene regulator (agr) dysfunction in Staphylococcus aureus bloodstream isolates from South Korean patients. Antimicrob. Agents Chemother. 57, 1509–1512. https://doi.org/10.1128/AAC.01260-12 (2013).

69. Traber, K. E. et al. agr function in clinical Staphylococcus aureus isolates. Microbiology 154, 2265–2274. https://doi.org/10.1099/mic.0.2007/011874-0 (2008).
75. Shopsin, B. et al. Prevalence of agr dysfunction among colonizing Staphylococcus aureus strains. J. Infect. Dis. 198, 1171–1174. https://doi.org/10.1086/592051 (2008).
76. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. https://www.R-project.org/ (2019).
77. Schwarzer, G. Meta: An R package for meta-analysis. R News 7, 40–45 (2007).
78. Wells, G. et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. (2000).

Acknowledgements
This work was summarized in an abstract (Abstract No. 2716) for the 29th European Congress of Clinical Microbiology and Infectious Diseases, Amsterdam, Netherlands, 2019. This work was funded by the National Research Foundation of Korea (NRF-2018R1A1A1A05079369). We thank Yong Pil Chong (Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea), I. García Luque (Department of Microbiology, School of Medicine, University of Sevilla, Sevilla, Spain) and all other authors of the primary studies.

Author contributions
S.W.L. formulated the hypothesis, performed the systematic analysis and data extraction and drafted the manuscript. S.O.L. independently performed the systematic analysis and data extraction and wrote the manuscript. S.W.L. and S.O.L. performed the statistical analysis and reviewed the manuscript. J.E.L., K.H.S., C.K.K., Y.M.W., R.S.J., L.L.C., A.L., C.P., H.C.J., E.S.K., H.B.K., and S.H.L. reviewed the manuscript and provided the scientific background. All authors reviewed and approved the manuscript prior to submission.

Funding
This work was supported by a National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) (NRF-2018R1A1A1A05079369).

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41598-020-77729-0.

Correspondence and requests for materials should be addressed to S.L.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2020