Antimicrobial Resistance and Molecular Epidemiology of *Staphylococcus aureus* Causing Bloodstream Infections at Ruijin Hospital in Shanghai from 2013 to 2018

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*Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* (MRSA) is an important issue associated with significant morbidity and mortality and well known as a predominant pathogen causing bloodstream infection (BSIs) globally. To estimate the antibiotic resistance and molecular characteristics of *S. aureus* causing BSIs in Shanghai, 120 *S. aureus* isolates (20 isolates each year) from the patients with *S. aureus* BSIs from 2013 to 2018 were randomly selected and enrolled in this study. Fifty-three (44.2%) MRSA isolates were determined, and no isolate was found resistant to vancomycin, daptomycin, synercid, linezolid and ceftaroline. The toxin genes *tst*, *sec*, *seg* and *sei* were found more frequently among MRSA isolates compared with MSSA isolates (all *P* < 0.0001). Twenty-nine sequence types (STs) were identified, and ST5 (23.3%) was the most common ST, followed by ST398 (11.7%) and ST764 (10.0%). SCC* mec* II (73.6%) was the most frequent SCC* mec* type among MRSA isolates. The dominant clonal complexes (CCs) were CC5 (ST5, ST764, ST765 and ST3066; 36.7%) and the livestock-associated clone CC398 (ST398, 11.7%). MRSA-CC5 was the predominant CC among MRSA isolates. The dominant clonal complexes (CCs) were CC5 (ST5, ST764, ST765 and ST3066; 36.7%) and the livestock-associated clone CC398 (ST398, 11.7%). SCC* mec* II MRSA was found in 34 isolates accounting for 91.9% (34/37) among CC5 MRSA isolates. In addition, all 29 *tst*-positive MRSA isolates were CC5-MRSA as well. Our study provided the properties and genotypes of *S. aureus* causing BSIs at Ruijin Hospital in Shanghai from 2013 to 2018, and might suggest of value clues for the further study insights into pathogenic mechanisms intrinsically referring to the development of human-adapted *S. aureus* clones and their diffusions.

Bloodstream infections (BSIs) is a severe infection with high incidence and lethality all over the world, and it always prolonged hospital stay for a long period¹. It has been reported to be one of the seven leading causes of death in North America and Europe². *Staphylococcus aureus* is well known as one of the most important human pathogens across the world and is capable of causing a variety of infections in healthcare facilities and communities. Furthermore, *S. aureus* is one of the major and most fatal causes of bacteremia with an estimated mortality of 20%, and at least 50% of patients with *S. aureus* bacteremia (SAB) will develop complicated bacteremia³. *S. aureus* is one of the most common causes of severe BSIs with high morbidity and mortality. Early mortality associated with SAB appears to have plateaued at approximately 20–30%¹, and imposes a substantial burden on patients and healthcare systems. In the United States, the annual incidence of SAB is 4.3 to 38.2 per 100,000 person-years, and the 30-day all-cause mortality of SAB is 20% and has not changed since the 1990s⁴. In Ireland,
were referred to MicroScan Pos Combo Panel Type 44 (Beckman Coulter, Inc. USA). ATCC29213 strain S. aureus tam(8/4–16/8 ciprofloxacin(1–2 μg/ml), levofloxacin(1–4 μg/ml), ampicillin(2–8 μg/ml), ampicillin/sulbac-tam(8/4–16/8 μg/ml), cefoxitin screen(4 μg/ml), oxacillin(0.25, 1–2 μg/ml), erythromycin(0.5–4 μg/ml), clindamycin(0.25–0.5 μg/ml), azithromycin(2–4 μg/ml), gentamicin(4–8 μg/ml), levofloxacin(1–4 μg/ml), moxifloxacin(0.5–1.4 μg/ml), ciprofloxacin(1–2 μg/ml), cefazolin(8–16 μg/ml), rifampin(1–2 μg/ml), ampicillin(2–8 μg/ml), ampicillin/sulbac-tam(8/4–16/8 μg/ml), amoxicillin/K Clavulanate(4/2 μg/ml), tetracycline(4–8 μg/ml), chloramphenicol(8–16 μg/ml), trimethoprim/sulfamethoxazole(0.5/9.5–2/38 μg/ml), vancomycin(0.5–16 μg/ml), daptomycin(1.4 μg/ml), synercid(0.5–2 μg/ml), linezolid(2–4 μg/ml), cefepime(0.5–2 μg/ml). The antibiotics selected and their ranges were referred to MicroScan Pos Combo Panel Type 44 (Beckman Coulter, Inc. USA). S. aureus ATCC29213 strain was used as the quality control for the antimicrobial susceptibility testing.

Toxin genes detection. A total of 13 significant toxin genes clinically including lukS/F-PV, tst, eta, etb, sea-sec and seg-sej were detected on all 120 S. aureus isolates in this study by polymerase chain reaction (PCR) as described previously. lukS/F-PV encodes Panton-Valentine leukocidin; tst encodes toxic shock syndrome toxin 1; eta and etb encode exfoliative toxin A and B; sea-sec and seg-sej encodes staphylococcal enterotoxins SEA-SEE and SEG-SEJ.

Molecular typing. Multilocus sequence typing (MLST), spa typing and agr typing were performed on all 120 S. aureus isolates according to the guidelines on the websites (https://pubmlst.org/, http://spa.ridom.de/index.shtml) and other published documents and researches. mecA detection was performed on all 120 S. aureus isolates as well to confirm the existence of MRSA. SCCmec types of MRSA were determined by the previous method as described. The gene blaZ, which produces beta-lactamase and inactivates penicillin by hydrolyzing the beta-lactam ring, was detected on all 120 S. aureus isolates.

Statistical analysis. The chi-square or Fisher’s exact test was used for statistical analysis as appropriate, and a two-sided P value of < 0.05 was considered for statistical significance. All statistical analysis in this study was conducted by the software package SAS 8.2 (SAS Institute Inc., Cary, NC, USA).

Results. From January 2013 to December 2018, the median age of patients with SAB in this study was 59 years (range: 7 months-97 years; interquartile range: 44–69 years), and the sex distribution (male/female) was 67.5%/32.5%. The mortality of patients with SAB was 25.8%, while 15 (12.5%) patients were transferred with unknown outcomes.

The incidence of S. aureus accounting for BSIs was 7.4% at Ruijin Hospital in Shanghai from August 2015 to December 2018, for the system transferring in 2015 and data missing as described in materials and methods.

Antimicrobial resistance. Fifty-three (44.2%) S. aureus isolates were confirmed as MRSA in this study, and all 53 MRSA isolates were mecA-positive. We did not discover any isolate resistant to vancomycin, daptomycin, synergic, linezolid and ceftriazone. No isolate was found showing a reduced vancomycin susceptibility or intermediate to vancomycin among the 120 S. aureus isolates in this study (supplementary information). The resistance...
isolates including 17 MRSA and 51 MSSA isolates were detected ant to penicillin. Sixty-eight (56.7%) S. aureus MRSA isolates detected in the study were resistant to penicillin, and 51 (51/67, 76.1%) MSSA isolates were resist-

MRSA isolates were observed showing multi-drug resistance in this study.

spa mec isolates, SCC t034 (7/120, 5.8%). One ST2959 MSSA isolate could not be spa typed (negative for certain PCR). Among 53 MRSA isolates, SCCmec II (39/53, 73.6%) was the most frequent SCCmec type as presented in Table 4, followed by SCCmec V (8/53, 15.1%), SCCmec IV (4/53, 7.5%) and SCCmec I (2/53, 3.8%). As shown in Fig. 1, produced by eBURST based on the ST data in this study, CC5 (ST5, ST764, ST965 and ST3066; 44/120, 36.7%) was the most common clonal complex (CC), followed by the livestock-associated (LA) clone CC298 (ST398, 14/120, 11.7%). Furthermore, based on the ST data in this study, CC5 (ST5, ST764, ST965 and ST3066; 44/120, 36.7%) was the most common clonal complex (CC), followed by the livestock-associated (LA) clone CC298 (ST398, 14/120, 11.7%). Furthermore, MRSA-CC5 has been the dominant CC among MRSA isolates in this study and the percentage was as high as 69.8% (37/53), and all tst-positive MRSA isolates (n = 29) were CC5-MRSA as well. The agrI (66/120, 55%) was the most frequent agr group, followed by agrII (50/120, 41.7%), agrIII (2/120, 1.7%), and agrIV (2/120, 1.7%).

In 2013, the most common ST was ST5 (20.0%), followed by ST1801 (15.0%), ST764 (15.0%), ST199 (10.0%); in 2014, the most common ST was ST5 (20.0%), followed by ST188 (15.0%), ST7 (15.0%) and ST764 (10.0%); in 2015, the most common ST was ST764 (25.0%), followed by ST1821 (15.0%), ST398 (10.0%), ST5 (10.0%) and ST199 (10.0%); in 2016, the most common ST was ST5 (40.0%), followed by ST398 (15.0%), ST59 (10.0%) and ST1921 (10.0%); in 2017, the most common ST was ST5 (20.0%), followed by ST1921 (10.0%); in 2018, the most common ST was ST398 (25.0%), followed by ST5 (20.0%). To sum up, ST5 (or CC5) has been highly prevalent among S. aureus isolates causing BSIs from 2013 to 2018 in Shanghai.

rates of antibiotics tested for overall 120 S. aureus isolates from 2013 to 2018 were presented in Table 1. All 53 MRSA isolates detected in the study were resistant to penicillin, and 51 (51/67, 76.1%) MSSA isolates were resistant to penicillin. Sixty-eight (56.7%) S. aureus isolates including 17 MRSA and 51 MSSA isolates were detected blaZ-positive, and all 51 MSSA isolates resistant to penicillin were blaZ-positive as well. Forty-six (46/53, 86.8%) MRSA isolates were observed showing multi-drug resistance in this study.

Virulence factors. The toxin genes etb and see were not discovered among all S. aureus isolates in this study. The seg was found most frequently among the toxin genes screened, occurring in 60 isolates (50.0%) as presented in Table 2. The tst, sec, seg and sei were found more frequently among MRSA isolates compared with MSSA isolates (all P < 0.0001). However, sed was observed more frequently among MSSA isolates (P = 0.0254), and sed was detected only among eight MSSA isolates as shown in Table 2. Besides, sei was found only among four MSSA isolates, but there was no significant difference statistically between MSSA and MRSA isolates (P = 0.1946).

Molecular types. Twenty-nine sequence types (STs) were identified among all 120 S. aureus isolates as presented in Table 3. ST5 (28/120, 23.3%) was the most common ST, followed by ST398 (14/120, 11.7%) and ST764 (12/120, 10.0%); and 1002 (12/120, 10.0%) was the most common spa type followed by t2460 (10/120, 8.3%) and t034 (7/120, 5.8%). One ST2959 MSSA isolate could not be spa typed (negative for certain PCR). Among 53 MRSA isolates, SCCmec II (39/53, 73.6%) was the most frequent SCCmec type as presented in Table 4, followed by SCCmec V (8/53, 15.1%), SCCmec IV (4/53, 7.5%) and SCCmec I (2/53, 3.8%). As shown in Fig. 1, produced by eBURST based on the ST data in this study, CC5 (ST5, ST764, ST965 and ST3066; 44/120, 36.7%) was the most common clonal complex (CC), followed by the livestock-associated (LA) clone CC98 (ST398, 14/120, 11.7%). Furthermore, MRSA-CC5 has been the dominant CC among MRSA isolates in this study and the percentage was as high as 69.8% (37/53), and all tst-positive MRSA isolates (n = 29) were CC5-MRSA as well. The agrI (66/120, 55%) was the most frequent agr group, followed by agrII (50/120, 41.7%), agrIII (2/120, 1.7%), and agrIV (2/120, 1.7%).

In 2013, the most common ST was ST5 (20.0%), followed by ST1801 (15.0%), ST7 (15.0%), ST764 (15.0%) and ST398 (10.0%); in 2014, the most common ST was ST5 (30.0%), followed by ST188 (15.0%), ST7 (15.0%) and ST764 (10.0%); in 2015, the most common ST was ST764 (25.0%), followed by ST1821 (15.0%), ST398 (10.0%), ST5 (10.0%) and ST199 (10.0%); in 2016, the most common ST was ST5 (40.0%), followed by ST398 (15.0%), ST59 (10.0%) and ST1921 (10.0%); in 2017, the most common ST was ST5 (20.0%), followed by ST1921 (10.0%); in 2018, the most common ST was ST398 (25.0%), followed by ST5 (20.0%). To sum up, ST5 (or CC5) has been highly prevalent among S. aureus isolates causing BSIs from 2013 to 2018 in Shanghai.

Table 1. The antibiotic resistance rates of Staphylococcus aureus isolates causing bloodstream infections from 2013 to 2018.
Eighty-one (67.5%) patients developed SAB 48 hours or more after admission to hospital that were considered as healthcare-associated (HA) infections, and 43 (53.1%) patients were infected with MRSA. ST5 (24/81, 29.6%) was the most common ST among HA-S. aureus isolates, and CC5 (36/81, 44.4%) was the most common CC as well. In addition, CC5-II MRSA (28/43, 65.1%) was the most frequent clone among HA-MRSA isolates.

**Discussion**

*S. aureus* or MRSA is an important pathogen and frequent cause of invasive infections as well as bloodstream infections around the world. In this study, SAB accounted for 7.4% of BSIs cases in Shanghai from 2013 to 2018, much lower than that in a regional burn center in Jiangxi province in China, which is 25.9% from 2012 to 2016. Coincidentally, in the United States, the incidence of MRSA BSIs in hospitals and communities dropped off 74% and 40% respectively from 2005 to 2016. According to the latest data provided by the European Antimicrobial Resistance Surveillance Network (EARSNet) (2013–2016), more than a third of countries with low and high MRSA prevalence have reported significantly decreasing trends among bloodstream infections, and the population-weighted average MRSA BSIs percentage has dropped from 18.1% in 2013 to 13.7% in 2016. The exact reasons for this specific decline among MRSA BSIs are not fully understood. However, in spite of these positive developments, *S. aureus* or MRSA still remains a priority for public health in Europe, with 10 of 30 countries reporting prevalence rates of MRSA > 25%, including Greece.

The mortality rate of *S. aureus* BSIs in Shanghai was 25.8% from 2013 to 2018 in this study, similar to that reported in other published researches of adult patient with *S. aureus* BSIs (around 20–30%) in other countries. However, it was much higher than that among infants with *S. aureus* BSIs in both Europe and USA which have shown overall mortality of 6.4–16%. The prevalence of methicillin resistance among *S. aureus* isolates in Hong Kong has risen to >50% while the mortality rates of MRSA bloodstream infections are close to one-third as reported. The proportion of MRSA among *S. aureus* BSIs in Shanghai was 44.2% in this study. Nevertheless, methicillin resistance is always significantly associated with higher mortality as well as comorbid conditions, intensive care unit admission, and prior exposure to antibiotics. In addition, chronic lung disease, previous hospitalization and older patients (>79 years) are related with increased mortality as well. The mortality in MSSA infections significantly declined and the average time to anti-staphylococcal therapy in MSSA infections decreased even though the mortality in MRSA infections was unchanged. The declining mortality in MSSA infections might be related to the reduction in the duration of targeted therapy. These results emphasize the potential for rapid diagnostics and early optimization of treatment to impact outcomes in MSSA bacteremia. Nevertheless, it was revealed that the treatment failure rate of complicated MRSA bloodstream infections was as high as 40%. MRSA might still need more attention when the patient was determined with MRSA bloodstream infections.

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| Toxin genes | Positive rate (%) | MSSA (n = 67) n (%) | MRSA (n = 53) n (%) | P value |
|-------------|------------------|---------------------|---------------------|---------|
| lukS/F-PV   | 1 (0.8)          | 0                   | 1 (1.9)             | 0.4417  |
| tst         | 32 (26.7)        | 3 (4.5)             | 29 (54.7)           | <0.0001 |
| eta         | 1 (0.8)          | 1 (1.5)             | 0                   | 1.0000  |
|etz          | 0                | 0                   | 0                   | —       |
| sea         | 18 (15.0)        | 7 (10.4)            | 11 (20.8)           | 0.1164  |
| seb         | 5 (4.2)          | 1 (1.5)             | 4 (7.5)             | 0.2345  |
| sec         | 33 (27.5)        | 4 (6.0)             | 29 (54.7)           | <0.0001 |
| sed         | 8 (6.7)          | 8 (11.9)            | 0                   | 0.0254  |
| see         | 0                | 0                   | 0                   | —       |
| seg         | 60 (50)          | 22 (32.8)           | 38 (71.7)           | <0.0001 |
| seh         | 55 (45.8)        | 26 (38.8)           | 29 (54.7)           | 0.0824  |
| sei         | 57 (47.5)        | 20 (29.9)           | 37 (69.8)           | <0.0001 |
| sej         | 4 (3.3)          | 4 (6.0)             | 0                   | 0.1946  |

Table 2. Prevalence of toxin genes among *Staphylococcus aureus* isolates causing bloodstream infections from 2013 to 2018.
Spain over 15 years (2002–2017) revealed that CC5 was the most prevalent CC and the proportion of CC5 among healthcare-associated S. aureus isolates was higher than that among community-associated S. aureus isolates, and CC5 was much more associated with methicillin resistance. Simultaneously, CC5 MRSA was also prevalent in Spain over 15 years (2002–2017) revealed that CC5 was the most prevalent CC and the proportion of CC5 among healthcare-associated S. aureus isolates was higher than that among community-associated S. aureus isolates, and CC5 was much more associated with methicillin resistance. Simultaneously, CC5 MRSA was also prevalent in Spain.

### Table 3. Molecular characteristics of Staphylococcus aureus isolates causing bloodstream infections from 2013 to 2018.

| ST | Isolates, n | MSSA, n | MRSA SCCmec Type(n) | spa type(n) | Virulence factors(n) |
|----|-------------|---------|---------------------|-------------|----------------------|
| 5  | 28          | 3       | II (24) IV (1)      | t1818 (1),t2460 (9),t2664 (2),t311 (3),t4450 (1),t458 (1),t601 (1),t9353 (2),t9563 (4),t2460 (1) | t3 (21),sea(4),seb(1),sec(21),seg(24),set(15),set(22) |
| 764| 12          | 2       | II (8) IV (2)       | t002 (8) t002 (2) t002 (2) | t3 (21),sea(2),set(3),seg(8),seb(8),set(8) |
| 965| 2           | 2       |                     | t062 (2) | t3 (21),sea(2),set(2),set(2) |
| 3066| 2          | 0       | II (2)              | t5076 (2) | t3 (21),sea(2),set(2),set(2) |
| 398| 14          | 10      | I (1) V (3)         | t034 (1) t034 (3) t051 (4),t053 (3),t1451 (1),t118 (1),t118609 (1) | None |
| 7  | 8           | 8       |                     | t179 (4) t091 (3),t605 (1) | seh(5) |
| 199| 6           | 6       |                     | t084 (2),t2325 (1),t277 (1),t546 (1),t803 (1) | seh(2) |
| 1801 | 6       | 0   | II (1) V (1)       | t037 (1) t030 (1),t037 (2),t421 (1) | set(1),set(4),set(2) |
| 1921 | 6       | 6   |                     | t164 (6) | seh(6),set(3),set(6) |
| 6  | 5           | 5       |                     | t9121 (1),t18586 (1),t1131 (1),t304 (1),t701 (1) | seh(5),set(1),set(1),set(1),set(1) |
| 188 | 5           | 5       |                     | t184 (9),t2421 (1),t2279 (1),t346 (1),t803 (1) | seh(2) |
| 59  | 4           | 2       | II (1) IV (1)       | t437 (1) t437 (1) t437 (1),t441 (1) | seh(1),set(1),set(1) |
| 1821 | 3       | 2   | V (1)              | t4549 (1) t4549 (2) | None |
| 2959 | 2       | 2   |                     | t9353 (1),t1131 (1) | seh(1),set(1) |
| 1  | 2           | 2       |                     | t127 (2) | seh(1),set(1),set(1) |
| 217 | 2           | 0       | V (2)              | t309 (2) | pvl(1),set(2),set(2) |
| 630 | 1           | 0       | V (1)              | t2196 (1) | None |
| 946 | 1           | 1       |                     | t437 (1) | seh(1),set(1) |
| 2315 | 1       | 1   |                     | t11687 (1) | seh(1),set(1),set(1) |
| 2872 | 1       | 1   |                     | t4608 (1) | seh(1),set(1),set(1) |
| 1181 | 1       | 1   |                     | t3277 (1) | seh(1),set(1),set(1) |
| 72  | 1           | 1       |                     | t148 (1) | seh(1),set(1) |
| 683 | 1           | 1       |                     | t148 (1) | seh(1),set(1) |
| 45  | 1           | 1       |                     | t094 (1) | seh(1),set(1) |
| 1659 | 1       | 1   |                     | t774 (1) | seh(1),set(1) |
| 25  | 1           | 1       |                     | t081 (1) | seh(1),set(1),set(1) |
| 182 | 1           | 1   |                     | t616 (1) | seh(1),set(1),set(1) |
| 2867 | 1       | 1   |                     | t18585 (1) | None |
| 858 | 1           | 1       |                     | t118607 (1) | None |

Table 3. Molecular characteristics of Staphylococcus aureus isolates causing bloodstream infections from 2013 to 2018. ST, sequence type by multi-locus sequence typing; SCCmec, Staphylococcal cassette chromosome mec; spa, Staphylococcus protein A gene; NT, not-typeable; None, no virulence gene detected.
in a French hospital between 2010 and 2017 as well; the prevalence rate of CC398 isolates among *S. aureus* BSIs increased from 3.6% in 2010 to 20.2% in 2017 (*P* < 0.05)33. CC398 MRSA emerged but remains very sparse and CC398 MSSA disseminates in the community as suggested. In this study in Shanghai, 4 CC398 MRSA and 10 CC398 MSSA isolates were discovered. More recently, CC398 MSSA have been increasingly being reported as the cause of invasive infections among patients who have no contact with livestock, and CC398 MSSA bloodstream infections were always associated with high mortality34. It has been hypothesized that lysogeny may play an important role in increasing the ability of ST398 clone to cause human infections, and the significant risk calling for urgent attention is that ST398 clone family will still increase its threat to public health by continuing to obtain virulence and/or multidrug resistance genes from healthcare-associated *S. aureus* clones35. Therefore, it is deeply needed to monitor the extraordinary cloning of human adaptive *S. aureus* like CC398 and genomic studies might can figure out the determinants of its diffusion.

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Table 4. SCC*mec* types of 53 MRSA isolates causing bloodstream infections from 2013 to 2018. SCC*mec*, Staphylococcal cassette chromosome *mec*; ST, sequence type by multi-locus sequence typing; *spa*, Staphylococcus protein A gene; None, no virulence gene detected.

| SCC*mec* type(n) | ST(n) | *spa* type(n) | virulence factors(n) |
|------------------|-------|---------------|----------------------|
| I (2)            | ST398 (1) | t034 (1) | None |
|                  | ST1801 (1) | t037 (1) | seb(1) |
| II (39)          | ST5 (24) | t1818 (1), t2460 (9), t264 (2), t311 (3), t450 (1), t458 (1), t9353 (2), t9363 (4) | tst(21), seh(1), seb(1), seg(24), seh(15), sei(22) |
|                  | ST764 (8) | t002 (8) | tst(3), seh(2), seb(3), seg(8), seh(8), sei(8) |
|                  | ST1801 (4) | t030 (1), t037 (2), t421 (1) | seb(1), seh(2) |
|                  | ST3066 (2) | t5076 (2) | tst(2), seh(2), seg(2), sei(2) |
|                  | ST59 (1) | t437 (1) | seh(1) |
| IV (4)           | ST764 (2) | t002 (2) | tst(2), seh(2), seg(2), seh(2), sei(2) |
|                  | ST5 (1) | t2460 (1) | tst(1), seh(1), seg(1), sei(1) |
|                  | ST59 (1) | t437 (1) | seh(1), seh(1) |
| V (8)            | ST398 (3) | t034 (3) | seh(1) |
|                  | ST217 (2) | t309 (2) | pvl(1), seg(1), sei(2) |
|                  | ST630 (1) | t1296 (1) | None |
|                  | ST1801 (1) | t459 (1) | seh(1) |
|                  | ST1821 (1) | t14549 (1) | None |
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**Author contributions**

Conceived and designed the experiments: L.H. and Y.N. Performed the experiments: F.G. and W.H. Analyzed the data F.G., W.H. and S.W. Contributed reagents/materials/analysis tools: S.X., X.L. and Q.Z. Wrote the paper: F.G., W.H. and L.H. Final approval of the submitted manuscript: All.

**Competing interests**

The authors declare no competing interests.

**Additional information**

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