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Risk Factors and Clinical Outcomes of Mixed Acinetobacter Baumannii Bloodstream Infection

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Abstract

Background: Although the clinical features of *Acinetobacter baumannii* bloodstream infection are well described, the specific clinical characteristics of mixed *Acinetobacter baumannii* bloodstream

infection are rarely reported. The objective of this study was to examine the risk factors and clinical outcomes of mixed *Acinetobacter baumannii* bloodstream infection.

Methods: A retrospectively observational study was performed from January 2013 to December 2018 in a tertiary hospital. All patients with *Acinetobacter baumannii* bloodstream infection were enrolled,the data were collected from electronic medical records.

Results: A total of 594 episodes were enrolled, 21% (126/594) of which were mixed *Acinetobacter baumannii* bloodstream infection.The most common co-pathogens were *Klebsiella pneumoniae* (20.81%), followed by *Pseudomonas aeruginosa* (16.78%) and *Enterococcus faecium* (12.08%). Compared with monomicrobial *Acinetobacter baumannii* bloodstream infection, the main source of mixed *Acinetobacter baumannii* bloodstream infection was from skin and soft tissue(28.6% vs.10.5%, P<0.001). A multivariate analysis revealed burn injury was independently associated with mixed *Acinetobacter baumannii* bloodstream infection(adjusted odds ratio,3.569; 95% confidence interval, 1.954-6.516). Patients with mixed *Acinetobacter baumannii* bloodstream infection were more likely to have longer hospitalization length of stay [40(21,68) vs. 27(16,45), P<0.001]and hospitalization days after BSI [22(8,50) vs. 13(4,28), P<0.001]. However, no significant difference in mortality was observed between the two groups.

Conclusions: Mixed *Acinetobacter baumannii* bloodstream infection is not a rare event, which accounts for one fifth of all *Acinetobacter baumannii* bloodstream infection. The main source is from skin and soft tissue, and burn injury is an independent risk factor. Although the mortality is not different, patients with mixed *Acinetobacter baumannii* bloodstream infection might have poor outcomes, which merits more attention by physicians in the future.

Keywords: *Acinetobacter baumannii*; Bloodstream infection; Mixed *Acinetobacter baumannii* bloodstream infection; Monomicrobial *Acinetobacter baumannii* bloodstream infection; Risk factors;

Background

Bloodstream infection (BSI) is a major cause of hospital-acquired sepsis, leading to approximately 157,000 deaths per year in Europe and more than 79,000 deaths per year in North America[1]. As an important gram-negative bacterium, *Acinetobacter baumannii* (AB) accounts for 9% ～ 35%of all episodes of BSI and displays a rising tendency[2, 3].Due to increases in antibiotics exposure, invasive operations and carbapenem resistance, *Acinetobacter baumannii* bloodstream infection (AB-BSI) becomes most frequent in critically ill patients[4-6]. The overall mortality in patients with AB-BSI

ranges widely from 29% to 63%[7-9].Therefore, AB-BSI has become a major challenge in clinic, concerning its rapid spread of multidrug-resistant, high morbidity and mortality[9, 10].

Most of BSI is monomicrobial, but the trend of polymicrobial BSI (pBSI) is rising, which accounts for 6%-34% of BSI in previous studies[11-14]. Compared with monomicrobial BSI (mBSI), pBSI always presents a higher APACHE II score, more frequency of severe sepsis/septic shock and a higher mortality[14-16]. But there are some limitations in these previous studies as follows:(1) Although the clinical characteristics of AB-BSI were often described, pBSI was always excluded in these studies[7, 9, 17].(2)The outcomes were poor in patients with pBSI than those with mBSI in some studies[14, 15], while no differences of their prognosis were observed in other studies concerning a specific microorganism, such as *Pseudomonas aeruginosa, Klebsiella pneumoniae*or, *Enterococcus*[18-20]. (3)The clinical significance and outcomes of pBSI versus mBSI were indeed investigated[14, 15], but as an important nosocomial infectionstrain, specific mixed *Acinetobacter baumannii* bloodstream infection(Mixed-AB-BSI) had never been described. Whether there are some differences in high multidrug resistance rate of AB, more severity of illness or high mortality between groups of Mixed-AB-BSI and monomicrobial *Acinetobacter baumannii* bloodstream infection(Mono-AB-BSI), and which factors are associated with Mixed-AB-BSI are still not well known.Herein, we designed this retrospective study to determine the incidence, risk factors and outcomes of Mixed-AB-BSI in comparison with Mono-AB-BSI.

Materials And Methods

Patients and study design

We reviewed the medical records of patients who were admitted between January 2013 and December 2018 at the Second Affiliated Hospital, Zhejiang University School of Medicine, a 3200-bed tertiary healthcare facility in Hangzhou, China. The present study received human research ethics approval (No.2019-116) from the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine. Due to the retrospective nature of the study, the Ethics Committee determined that no patient consent was required.

All patients with AB-BSI episodes who had symptoms and signs of infection were included. Only the first episode was included from patients with more than one episodes of BSI. Exclusion criteria were as follows: a) Age <18 years old; b) AB was considered as nonpathogenic bacterium; c) Case data were incomplete or missing. Common skin contaminant organisms (e.g. *Bacillus spp.,*

Corynebacterium spp., Micrococcus spp., Streptococci, Lactobacillus spp. and *Coagulase-negative Staphylococci*) were considered as pathogens, only when they were present in two or more consecutive blood cultures from separate blood draws[21].

Data collection

Documented patient demographics and other clinical and laboratory data were collected including sequential organ failure assessment (SOFA) score, Pitt bacteremia score and the Charlson Comorbidity Index (CCI) score, the Acute Physiology and Chronic Health Evaluation(APACHE) II score in the first 24 h following the onset of BSI, major surgery, mechanical ventilation, hemodialysis, liver and kidney functions, inflammatory markers like white blood cell count, procalcitonin and C reactive protein, duration of hospital stay, length of intensive care unit (ICU) stay before BSI onset, invasive devices (such as central venous catheter, urinary catheters, and drainage catheters). The microbiological data like species in the Mixed-AB-BSI, likely source of BSI, and sensitivity to antibiotics were gathered. Outcomes (length of hospital stay, length of ICU stay, septic shock and 28-day mortality) were also collected.

Species identification and antibiotic sensitivity test

Blood culture was performed by using a BacT/ALERT 3D system (Becton-Dickinson, Sparks, MD, USA) in the microbiology laboratory. Species identification was completed using Bruker Daltonics Data Analysis.Antibiotic susceptibility was determined by the VITEK 2 system (Card number: AST-GN16; AST-GP67) or the Kirby-Bauer Disk Diffusion method (Oxoid, UK) according to the recommendations by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing. During the study period, there were no changes in microbiological laboratory technique.

Definitions

Diagnosis of AB-BSI was based on the Centers for Disease Control (CDC) definition for Bloodstream Infection Event[22].Contaminants were defined as one single positive blood culture in the absence of clinical manifestations[22].The onset of AB-BSI was defined at the time when the blood culture that eventually grew AB was obtained. Nosocomial BSI was defined as the first positive blood culture obtained ≥48 h after hospital admission and with no evidence of infection at admission[7, 12]. Prior exposure to antimicrobial agents was defined as treatment for at least 72 hours within 30 days prior to the positive blood culture[23]. Appropriate antimicrobial treatment was defined that at least one

antibiotic that was active to pathogenic microorganism confirmed by in vitro sensitivity test within 24 hours of BSI onset[9]. Source of BSI was recorded according to the definitions of CDC[22].Multidrug resistance to AB was defined as resistance to ≥3 classes of antibiotics (quinolones, extended-spectrum cephalosporins, β-lactam/β-lactamase inhibitor combinations,aminoglycosides and carbapenems)[24].Sepsis and Septic shock were defined according to the definition of International Sepsis Definitions Conference[21].

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software (IBM Corp, Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation if normally distributed, and as median and interquartile range (IQRs) if nonnormally distributed. Categorical variables were compared by Pearson $\chi 2$ test or Fisher exact test. Variables with $P<0.05$ in the univariate logistic regression analysis were entered into a multivariate logistic regression model to determine the independent variables. In addition, clinical scores like APACHE II score, SOFA score, Pitt Bacteremia Score, and CCI were also examined in the multivariate logistic regression model. All tests were 2-tailed, and $P<0.05$ was considered significant.

Results

Demographic characteristics

From January 2013 to December 2018, a total of 958 positive blood culture samples with AB were initially included, and 594 cases AB-BSI were finally recruited in the analysis.126(21%) cases were Mixed-AB-BSI, and 468(79%) cases were Mono-AB-BSI(Figure1).The median age was 61 years (IQR,48-71),and 70.5% of them were male. The patients with Mono-AB-BSI had more seniors than those with Mixed-AB-BSI (age≧60 years, 54.5% vs 44.4%, p=0.046). 96.1% patients (571/594)had at least one comorbidity, and a significant high percentage of burn injury was observed in Mixed-AB-BSI compared with Mono-AB-BSI (23.0% vs. 8.3%, $p<0.05$). The detailed demographic characteristics of these patients were shown in Table 1.

Biological indicators

The comparison of biological indicators between Mixed-AB-BSI and Mono-AB-BSI is shown in Table 2. Got (Glutamic-oxaloacetic transaminase) was higher in the patients with Mixed-AB-BSI, but there was no significant difference in other liver function indicators and biochemical indicators between these two groups.

Independent risk factors for Mixed-AB-BSI

Table 3 shows the results of multivariate logistic regression analysis. The burn injury was an independent risk factor for Mixed-AB-BSI (adjusted odds ratio [aOR], 3.569; 95% confidence interval [CI], 1.954-6.516).

Etiologic agents of BSI

149 other microorganisms besides AB were isolated from 126 patients with Mixed-AB-BSI, with two microorganisms accounting for 84.1% (106/126) and three microorganisms for 15.87% (20/126). Gram-negative bacteria, gram-positive bacteria and fungi accounted for 67.1%, 30.2%, and 2.7% respectively. The most accompanying bacteria in the Mixed-AB-BSI was *Klebsiella pneumoniae*(31/149,20.8%), followed by *Pseudomonas aeruginosa*(25/149,16.8%) and *Enterococcus faecium*(18/149,12.1%). The detailed description of isolated microorganisms is shown in Figure2.

The source of AB-BSI was mainly from respiratory tract (25.9%, 154/594) , followed by primary BSI (22.4%, 133/594) and central venous catheter (15%, 89/451). Compared with Mono-AB-BSI, Mixed-AB-BSI was more often from skin and soft tissue(28.6% vs. 10.5%, p<0.001), but less from respiratory tract (15.1% vs. 28.8%, p=0.002) and intracranial (2.4% vs. 8.5%, p=0.018)(Table 4).

Antibiotic resistance and appropriate therapy

All samples were treated with antibiotics. Antibiotic sensitivity test showed that there was no difference between the two groups of Mono-AB-BSI and Mixed-AB-BSI. The resistances of AB to ciprofloxacin, ceftazidime, nitrofurantoin, and carbapenems were very high in both groups(more than 90%). On the contrary, the ratio of resistance of AB to amikacin, tigecycline, or colistin was relatively low in the two groups(less than 30%).Nine strains of AB resistant to colistin were found in the Mono-AB-BSI group, but none in the Mixed-AB-BSI group(Table 4).

A total of 28.5% (169/594) patients received appropriate empiric antibiotic therapy. Of note, the appropriate rate of empirical antimicrobial therapy among the patients with Mixed-AB-BSI was substantially higher than that with Mono-AB-BSI (38.9% vs. 25.6%, p = 0.003).

Outcomes

The incidence of septic shock was similar (25.4% vs. 28.8%, p=0.445) between the two groups. Compared with the Mono-AB-BSI, the Mixed-AB-BSI had longer total hospitalization days[40(21,68) vs. 27(16,45), P<0.001] and hospitalization days after BSI onset [22(8,50) vs. 13(4,28), P<0.001].These were no significant differences in the 14-day, 28-day, and in-hospital mortality

between the two groups(Table 5).

Discussion

In our study, some meaningful results were observed. First, Mixed-AB-BSI occupied a high ratio in AB-BSI. Second, gram-negative bacteria was the most common co-pathogen, followed by gram-positive bacteria and fungi. Compared with Mono-AB-BSI, the main source of Mixed-AB-BSI was skin and soft tissue. Third, in the univariate analysis, patients with Mixed-AB-BSI were younger, accompanied with more burn injury and fewer tumors. Burn injury was the only independent risk factor for Mixed-AB-BSI after multivariate logistic regression analysis. Last, patients with Mixed-AB-BSI might have poor outcomes including longer total hospitalization days and prolonged hospitalization days after BSI onset.

In the current study, the incidence of Mixed-AB-BSI was 21%, which was comparable with previous studies ranging from 19% to 35%[25, 26].Gram-negative bacteria was the most common co-pathogens among Mixed-AB-BSI, which was consistent with the condition of BSI induced by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*[18, 20]. Similarly, the most common co-pathogen was also gram-negative bacteria (57.1%), followed by gram-positive bacteria (38.3%) and fungi (4.6%) in mixed-enterococcal bloodstream infection reported in our previous study[19].These studies suggest that gram-negative bacteria be most prevalent in bloodstream infection or mixed bloodstream infection.

In this study, patients with Mono-AB-BSI were older and accompanied with more tumors compared with the Mixed-AB-BSI group. However, the CCI, APACHE II score and SOFA score, reflecting the severity of underlying disease, did not show any difference in both groups, which was similar to a recent study[27].The only independent risk factor for Mixed-AB-BSI was burn injury after the multivariate analysis.43% (29/68) of burn patients suffered from Mixed-AB-BSI, which was consistent with Tang et al.'s study showing that more than 20% of burn patients suffered from pBSI[28]. As an independent risk factor for Mixed-AB-BSI in the current study, burn injury itself might partially reflect the fact that a significantly increased source from skin and soft tissue was observed in Mixed-AB-BSI compared with Mono-AB-BSI (28.6% vs. 10.5%, $p<0.001$). As described in previous studies that burn injury could cause down-regulation of cellular and humoral immune responses, extensive disruption of skin barrier, gastrointestinal bacterial translocation, prolonged hospitalization and invasive diagnostic/therapeutic management[29-31], thus burn patients are at a high risk of BSI. As many

pathogens are colonized in the skin, thus these bacteria are more likely to invade the blood through the skin of burn patients and cause pBSI like Mixed-AB-BSI in the current study.

The overall in-hospital mortality rate of AB-BSI was high (47.6%)in our study, which was equivalent to the range of 29%～63% reported by others[7, 11]. We couldn't find any difference in mortality including 14-day, 28-day, or in-hospital mortality between groups of Mixed-AB-BSI and Mono-AB-BSI, this fact had also been demonstrated by a recent research showing that no internal correlation was exist between Mixed-AB-BSI and a higher mortality[27].This might be due to the following factors: (1)The CCI, APACHE II score and SOFA score, reflecting the severity of underlying diseases, did not show any difference in both groups. As aging and tumor are predictors for immunosuppressive state[1], patients with Mixed-AB-BSI were younger and accompanied with fewer solid tumors in comparison with Mono-AB-BSI(Table 1), which might partially contribute a protective role in the mortality in the current study. (2) Biological indicators between Mixed-AB-BSI and Mono-AB-BSI were basically the same (Table 2), meaning that there were no obvious differences in liver and kidney functions between these two groups. (3)Appropriate empirical antibiotic treatment could improve the prognosis and reduce the mortality of BSI[11, 32]. The appropriate ratio of empirical antibiotic treatment in patients with Mixed-AB-BSI was significantly higher than that with Mono-AB-BSI (38.9% vs. 25.6%, p=0.003), which might partially explain a similar mortality between groups of Mixed-AB-BSI and Mono-AB-BSI in the current study.

This study had several limitations. First, this was a retrospective, observational single-center study and the sample size of AB-BSI patients was still small, though we included the relatively largest number of patients with Mixed-AB-BSI up to now.Thus, it might limit the general applicability of our findings in some degree. Second, overall mortality, but not attributable mortality was used to evaluate the outcome. Overall mortality might be affected by many factors other than infection, thus the exactly attributable mortality of Mixed-AB-BSI is still unknown. Third, we only concerned AB-BSI in the current study and did not evaluate the overall occurrence of BSI in the hospital, so it was impossible to assess the overall incidence of Mixed-AB-BSI or Mono-AB-BSI. Taken together, our findings in the current study might be not applicable in some other conditions,thus future multi-center prospective studies are needed to investigate.

Conclusion

Mixed-AB-BSI is relatively common among AB-BSI, which accounts for more than one fifth. The main source of Mixed-AB-BSI is from skin and soft tissue, and burn injury is the only independent risk factors for Mixed-AB-BSI. Although mortality is similar, patients with Mixed-AB-BSI exhibit substantially worse outcomes than those with Mono-AB-BSI including prolonged total hospitalization days and hospitalization days after BSI, which merits more attention by physician.

Abbreviations

BSI:bloodstream infection;AB:*Acinetobacter baumannii;*AB-BSI:*Acinetobacter baumannii* bloodstream infection;mBSI:monomicrobial bloodstream infection;pBSI:polymicrobial bloodstream infection;Mixed-AB-BSI:mixed *Acinetobacter baumannii* bloodstream infection;Mono-AB-BSI:monomicrobial *Acinetobacter baumannii* bloodstream infection;SOFA:sequential organ failure assessment;APACHE:Acute Physiology and Chronic Health Evaluation;CCI:Charlson Comorbidity Index;CLSI: Clinical and Laboratory Standards Institute;COPD:chronic obstructive pulmonary disorder;WBC: White blood count;ANC:absolute neutrophil count;GPT: glutamic-pyruvic transaminase;GOT: glutamic oxaloacetic transaminase;ALP:alkaline phosphatase;γ-GT:gamma glutamyl transpeptidase;LDH:lactic dehydrogenase;TBil: total bilirubin;SCr:serum creatinine;PCT: procalcitonin;ICU：intensive care unit;IQR: inter quartile range;CDC：Centers for Disease Control;aOR: adjusted odds ratio;CI: confidence interval.

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Not applicable.

Ethical approval and consent to participate

The study data comprised anonymized data recorded in the medical record as part of routine patient care and the study received human research ethics approval (No.2019-116) from the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine.Due to the retrospective nature of the study, the Ethics Committee determined that no patient consent was required.

Consent for publish

Not applicable.

Authors contributions

Zhenhua Qian and Shufang Zhang conceived the idea, performed the analysis, and drafted the manuscript. Na Li and Weixing Ma interpreted the results and helped to revise the manuscript. Kai Zhang, Feizhen Song, Cheng Zheng, Li Zhong helped to collect data. Yesong Wang, Jiachang Cai, Hongwei Zhou, Wei Cui helped to analyze the data. Gensheng Zhang helped to frame the idea of the study and helped to analyze the data. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have competing interests.

Availability of data and materials

Data can be obtained from the corresponding author.

References

1. M G, microbiology A-HMJC, Microbiology itopotESoC, Diseases I: **Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe**. 2013, **19**(6):501-509.
2. S F, X D, H Q, Z H, xue YDJZwzbjjy: **[Microbial characteristics in culture-positive sepsis and risk factors of polymicrobial infection in ICU]**. 2015, **27**(9):718-723.
3. X W, C Z, H L, H C, L J, Z W, K L, J Z, X X, Y J *et al*: **[Microbiological profiles of pathogens causing nosocomial bacteremia in 2011, 2013 and 2016]**. 2018, **34**(8):1205-1217.
4. Gales AC, Castanheira M, Jones RN, Sader HSJDMID: **Antimicrobial resistance among Gram-negative bacilli isolated from Latin America: results from SENTRY Antimicrobial Surveillance Program (Latin America, 2008–2010)**. 2012, **73**(4):354-360.
5. Pattarachai K, Anan C, Thean Yen T, Evelina L, Sally R, Jemelyn G, Todd DJIJoAA: **Comparative in vitro activity of carbapenems against major Gram-negative pathogens: results of Asia-Pacific surveillance from the COMPACT II study**. 2012, **39**(4):311-316.
6. **Nosocomial bacteremia due to Acinetobacter baumannii_ epidemiology, clinical features and treatment**. *Clinical Microbiology and Infection* 2002.
7. Metan G, Sariguzel F, Sumerkan B: **Factors influencing survival in patients with multi-drug-resistant Acinetobacter bacteraemia**. *Eur J Intern Med* 2009, **20**(5):540-544.
8. Nutman A, Glick R, Temkin E, Hoshen M, Edgar R, Braun T, Carmeli YJCM, Infection: **A case-control study to identify predictors of 14-day mortality following carbapenem-resistant Acinetobacter baumannii bacteraemia**. 2015, **20**(12):O1028-O1034.
9. Gu Z, Han Y, Meng T, Zhao S, Zhao X, Gao C, Huang W: **Risk Factors and Clinical Outcomes for Patients With Acinetobacter baumannii Bacteremia**. *Medicine (Baltimore)* 2016,

95(9):e2943.

10. **Risk Factors for Nosocomial Bloodstream Infections Due to Acinetobacter baumannii_ A Case-Control Study of Adult Burn Patients**. 1999.
11. Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, Reller LB: **The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults**. *Clin Infect Dis* 1997, **24**(4):584-602.
12. Hilmar W, Tammy B, Tallent SM, Harald S, Wenzel RP, Edmond MB, %J Clinical Infectious Diseases: **Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study**. 2004, **39**(3):309-317.
13. Tabah A, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, Paiva JA, Cakar N, Ma X, Eggimann P *et al*: **Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study**. *Intensive Care Med* 2012, **38**(12):1930-1945.
14. D K, EL Q, KH B, T M, LD S, JAMA NTJ: **The increasing importance of polymicrobial bacteremia**. 1979, **242**(10):1044-1047.
15. M P, G P, P D, G A, E A, NK G, I K, A M, V M, A P *et al*: **Polymicrobial bloodstream infections: Epidemiology and impact on mortality**. 2013, **1**(4):207-212.
16. McKenzie FE: **Case mortality in polymicrobial bloodstream infections**. *J Clin Epidemiol* 2006, **59**(7):760-761.
17. Blot S, Vandewoude K, Colardyn F: **Nosocomial bacteremia involving Acinetobacter baumannii in critically ill patients: a matched cohort study**. *Intensive Care Med* 2003, **29**(3):471-475.
18. Aliaga L, Mediavilla JD, Llosa J, Miranda C, Rosa-Fraile M: **Clinical significance of polymicrobial versus monomicrobial bacteremia involving Pseudomonas aeruginosa**. *Eur J Clin Microbiol Infect Dis* 2000, **19**(11):871-874.
19. Zheng C, Cai J, Liu H, Zhang S, Zhong L, Xuan N, Zhou H, Zhang K, Wang Y, Zhang X *et al*: **Clinical Characteristics And Risk Factors In Mixed-Enterococcal Bloodstream Infections**. *Infect Drug Resist* 2019, **12**:3397-3407.
20. Liu Q, Wu J, Wang Z, Wu X, Wang G, Ren J: **Polymicrobial Bacteremia Involving Klebsiella pneumoniae in Patients with Complicated Intra-Abdominal Infections: Frequency, Co-Pathogens, Risk Factors, and Clinical Outcomes**. *Surg Infect (Larchmt)* 2019, **20**(4):317-325.
21. Levy MM, Fink MPMarshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay GJCCM: **2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference**. 2003, **31**(4):1250.
22. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM: **CDC definitions for nosocomial infections, 1988**. *Am J Infect Control* 1988, **16**(3):128-140.
23. Sun JD, Huang SF, Yang SS, Pu SL, Zhang CM, Zhang LPJCMI: **Impact of carbapenem heteroresistance among clinical isolates of invasive Escherichia coli in Chongqing, southwestern China**. 2015, **21**(5):469.e461-469.e410.
24. Halachev MR, Chan JZ, Constantinidou CI, Cumley N, Bradley C, Smith-Banks M, Oppenheim B, Pallen MJ: **Genomic epidemiology of a protracted hospital outbreak caused by multidrug-resistant Acinetobacter baumannii in Birmingham, England**. *Genome Med* 2014,

6(11):70.
25. JM C, MJ R, J P, B B, FJ C, JL G-G, C O, America CAJCidaopotIDSo: **Bacteremia due to Acinetobacter baumannii: epidemiology, clinical findings, and prognostic features**. 1996, **22**(6):1026-1032.
26. Wisplinghoff H, Edmond MB, Pfaller MA, Jones RN, Wenzel RP, Seifert H: **Nosocomial bloodstream infections caused by Acinetobacter species in United States hospitals: clinical features, molecular epidemiology, and antimicrobial susceptibility**. *Clin Infect Dis* 2000, **31**(3):690-697.
27. Wang YC, Ku WW, Yang YS, Kao CC, Kang FY, Kuo SC, Chiu CH, Chen TL, Wang FD, Lee AY: **Is Polymicrobial Bacteremia an Independent Risk Factor for Mortality in Acinetobacter baumannii Bacteremia?** *J Clin Med* 2020, **9**(1).
28. Tang CQ, Li JQ, Shou BM, Pan BH, Chen TS, Xiao YQ, Zheng XP, Xiao SC, Tan Q, Xia ZF: **Epidemiology and outcomes of bloodstream infections in 177 severe burn patients from an industrial disaster: a multicentre retrospective study**. *Clin Microbiol Infect* 2018, **24**(2):199 e191-199 e197.
29. Church D, Elsayed S, Reid O, Winston B, Lindsay R: **Burn wound infections**. *Clin Microbiol Rev* 2006, **19**(2):403-434.
30. Santucci SG, Gobara S, Santos CR, Fontana C, Levin AS: **Infections in a burn intensive care unit: experience of seven years**. *J Hosp Infect* 2003, **53**(1):6-13.
31. Fitzwater J, Purdue GF, Hunt JL, O'Keefe GE: **The risk factors and time course of sepsis and organ dysfunction after burn trauma**. *J Trauma* 2003, **54**(5):959-966.
32. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH: **The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting**. *Chest* 2000, **118**(1):146-155.

Figure captions:

Figure 1: Flowchart of study participant enrollment. Abbreviations: Mono-AB-BSI, monomicrobial *Acinetobacter baumannii* bloodstream infection;Mixed-AB-BSI, mixed *Acinetobacter baumannii* bloodstream infection.

Figure 2: Distribution of the additional organisms in Mixed *Acinetobacter baumannii* bloodstream infection.

Table 1 Demographic and clinical characteristics of the patients with Mono-AB-BSI or Mixed-AB-BSI

Characteristics	Total (n=594)	Mono-AB-BSI (n = 468)	Mixed-AB-BSI (n =126)	P-value
Age≧60 years	311(52.4%)	255(54.5%)	56(44.4%)	0.046
Male sex	419(70.5%)	330(70.5%)	89(70.6%)	0.979
Co-morbidities				
Diabetes mellitus	82(13.8%)	62(13.2%)	20(15.9%)	0.448
Chronic kidney disease	67(11.3%)	51(10.9%)	16(12.7%)	0.571
Chronic liver disease	45(7.6%)	34(7.3%)	11(8.7%)	0.581
COPD[a] or Severe asthma	77(13%)	59(12.6%)	18(14.3%)	0.618
Chronic cardiac insufficiency	130(21.9%)	98(20.9%)	32(25.4%)	0.283
Solid tumour	77(13%)	68(14.5%)	9(7.1%)	0.028
Trauma	146(24.6%)	119(25.4%)	27(21.4%)	0.355
Burn injury	68(11.4%)	39(8.3%)	29(23.0%)	<0.001
Hypertension	190(32%)	145(31%)	45(35.7%)	0.312
Cerebrovascular accident	166(27.9%)	131(28%)	35(27.8%)	0.962
CCI[b], median (IQR)	2(1,3)	2(1,3)	2(0,3)	0.507
APACHE II score, median	18(13,22)	18(14,22)	17(13,22)	0.375
SOFA score, median	6(4,9)	6(4,9)	6(3,9)	0.442
Pitt Bacteremia Score, median	4(3,6)	4(3,6)	4.5(3,6)	0.704
Hospitalization ward				
Medical	8(1.3%)	5(1.1%)	3(2.4%)	0.257
Surgical	63(10.6%)	47(10%)	16(12.7%)	0.390
ICU	523(88%)	416(88.9%)	107(84.9%)	0.223
Previous treatment				
Hyperalimentation	227(38.2%)	176(37.6%)	51(40.5%)	0.556
Mechanical ventilation(n)	550(92.6%)	434(92.7%)	116(92.1%)	0.798
Surgery	369(62.1%)	295(63%)	74(58.7%)	0.377
Blood transfusion	247(41.6%)	189(40.4%)	58(46.0%)	0.254
Renal replacement therapy	109(18.4%)	84(17.9%)	25(19.8%)	0.626
Carbapenems exposure	237(39.9%)	182(38.9%)	55(43.7%)	0.333
Invasive devices				
Central line	558(93.9%)	441(94.2%)	117(92.9%)	0.566
Indwelling urinary catheter	541(91.1%)	424(90.6%)	117(92.9%)	0.430
Drainage (any site)	253(42.6%)	197(42.1%)	56(44.4%)	0.636
Prior hospital stay, median days (IQR)	11(7,18)	11(6,18)	11.5(7,20)	0.367
Nosocomial infection	559(94.1%)	438(93.6%)	121(96%)	0.301

a:chronic obstructive pulmonary disorder;b:Charlson Comorbidity Index;

Table2 Comparison of biological indicators between Mono-AB-BSI and Mixed-AB-BSI

Biochemical Indicators	Total (n=594)	Mono-AB-BSI (n = 468)	Mixed-AB-BSI (n =126)	P-value
Temperature(˚C)(IQR)	38.6(38.0,39.1)	38.6(38.1,39.1)	38.5(38.0,39.03)	0.139
WBC[a](×10^9/L) (IQR)	10.2(6.9,14.3)	10.6(7.03,14.4)	9.65(6.65,13.68)	0.354
Hematocrit(%)(IQR)	25.15(21.7,29.93)	25.3(22.0,30.48)	24.2(21.0,28.33)	0.031
Platelet(×10^9/L)(IQR)	144(77.75,228.25)	147.5(79,234.75)	128.5(69.75,217.5)	0.340
ANC[b] (IQR)	8.71(5.76,12.77)	9.02(5.87,12.93)	8.35(5.27,12.10)	0.276
Albumin(g/L)(mean ± S.D)	30.65 ± 5.82	30.85±5.82	30.4±5.79	0.201
GPT[c](U/L)(IQR)	37(23,68)	37(23,70)	39(27.5,63.25)	0.330
GOT[d](U/L)(IQR)	41(26,67)	39(26,66)	48.5(28,75.5)	0.021
TBil[e](umol/L)(IQR)	19.6(12.18,34.23)	19.6(12.13,35.78)	19.65(12.18,31.95)	0.787
SCrf(umol/L)(IQR)	62(46,99)	63(46,100.75)	57(44.75,95.25)	0.673
lactic acid(IQR)	2.1(1.3,3.1)	2.1(1.3,3.2)	2(1.28,2.83)	0.461
CRP[g] (IQR)	119.85(67.05,195.5)	120.25(67.90,199.75)	119.35(63.98,180.0)	0.431
PCT[h] (IQR)	1.74(0.45,6.53)	1.72(0.44,6.71)	1.91(0.50,6.31)	0.979

a:White blood count;b:Absolute neutrophil count;c:Glutamic-pyruvic transaminase;d:Glutamic-oxaloacetic transaminase;e:Total bilirubin; f: Serum creatinine;g::C reactive protein;h: Procalcitonin.

Table 3 Logistic regression analysis of factors associated with Mixed-AB-BSI

Characteristics	Univariable Analysis		Multivariable Analysis	
	Unadjusted OR（95%CI）	p-value	Adjusted OR（95%CI）	p-value
Age ⩾60 years	0.668(0.450,0.993)	0.046	0.855(0.546,1.338)	0.493
Male sex	0.994(0.646,1.531)	0.979		
Diabetes mellitus	1.236(0.715,2.136)	0.449		
Chronic kidney disease	1.189(0.653,2.166)	0.571		
Chronic liver disease	1.211(0.600,2.484)	0.582		
COPD[a] or Severe asthma	0.866(0.490,1.529)	0.619		
Chronic cardiac insufficiency	0.779(0.492,1.231)	0.284		
Solid tumour	1.936(1.027,3.651)	0.028	2.120(0.973,4.620)	0.059
Trauma	1.250(0.779,2.008)	0.355		
Burn injury	2.313(1.664,3.214)	<0.001	3.569(1.954,6.516)	*0.000*
Hypertension	0.808(0.534,1.222)	0.313		
Cerebrovascular accident	1.011(0.652,1.568)	0.962		
CCI[b]	0.965(0.869,1.071)	0.500	1.119(0.984,1.274)	0.087
APACHE II score	0.986(0.956,1.016)	0.352	0.980(0.934,1.029)	0.423
SOFA score	0.991(0.942,1.042)	0.721	0.986(0.925,1.052)	0.671
Pitt Bacteremia Score	1.017(0.936,1.104)	0.696	1.083(0.969,1.212)	0.162
Medical	0.443(0.104,1.878)	0.269		
Surgical	0.768(0.419,1.405)	0.391		
ICU	1.421(0.806,2.504)	0.225		
Hyperalimentation	0.886(0.593,1.325)	0.556		
Mechanical ventilation(n)	1.100(0.528,2.293)	0.798		
Surgery	1.198(0.802,1.790)	0.377		
Blood transfusion	0.794(0.535,1.180)	0.254		
Renal replacement therapy	0.884(0.537,1.453)	0.626		
Carbapenems exposure	0.821(0.552,1.223)	0.333		
Central line	1.256(0.575,2.745)	0.567		
Indwelling urinary catheter	0.741(0.352,1.562)	0.431		
Drainage (any site)	0.909(0.611,1.351)	0.636		
Prior hospital stay	1.005(0.996,1.015)	0.293		
Nosocomial infection	0.603(0.229,1.588)	0.306		

a:chronic obstructive pulmonary disorder; b: Charlson Comorbidity Index;

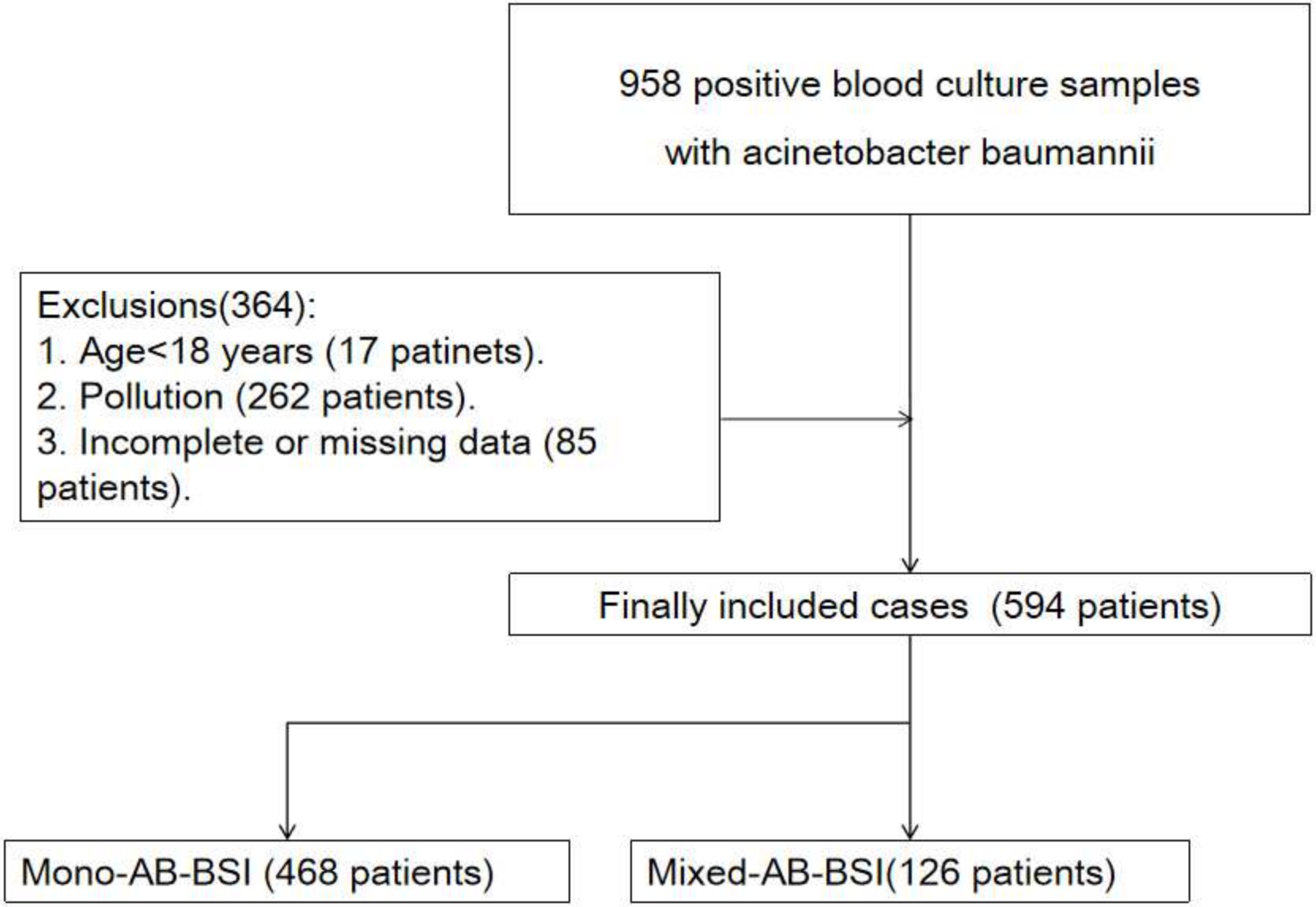
Table 4 Comparison of the microbiological characteristics with Mono-AB-BSI and Mixed-AB-BSI

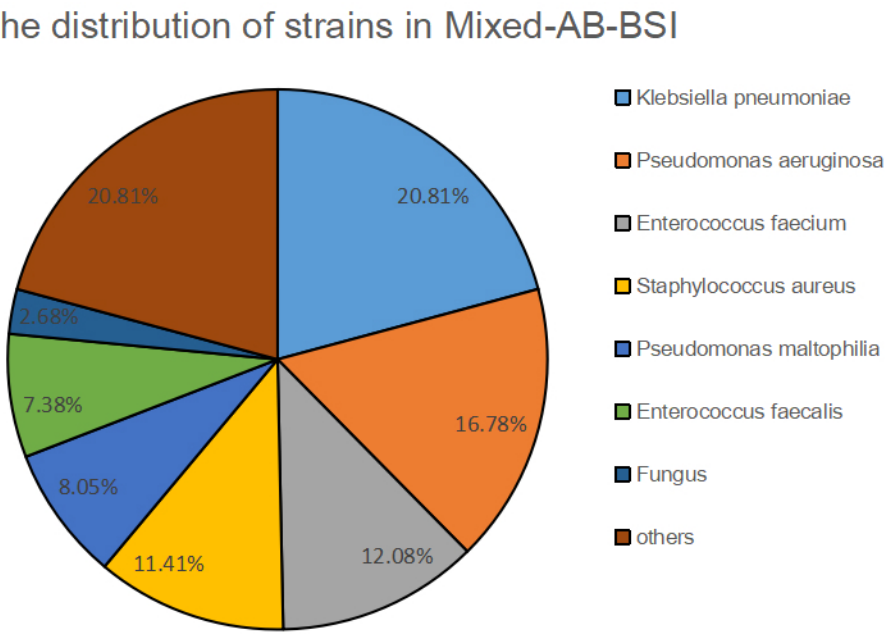
Antibiotic resistance	Total (n=594)	Mono-AB-BSI (n =468)	Mixed-AB-BSI (n =126)	P-value
Source of BSI				
Respiratory tract	154(25.9%)	135(28.8%)	19(15.1%)	0.002
Central venous catheter	89(15%)	64(13.7%)	25(19.8%)	0.085
Skin and Soft tissue	85(14.3%)	49(10.5%)	36(28.6%)	<0.001
Intracranial	43(7.2%)	40(8.5%)	3(2.4%)	0.018
Primary	133(22.4%)	107(22.9%)	26(20.6%)	0.594
others[a]	90(15.2%)	73(15.6%)	17(13.5%)	0.552
Antibiotic resistance of AB[b]				
Amikacin (330 vs 81)[c]	145(24.4%)	115(24.6%)	30(23.8%)	0.380
Ciprofloxacin(467 vs 126)[c]	545(91.8%)	431(92.1%)	114(90.5%)	0.701
Ceftazidime(463 vs 125)[c]	556(93.6%)	440(94%)	116(92.1%)	0.598
Tobramycin(460 vs 121)[c]	409(68.9%)	316(67.5%)	93(73.8%)	0.068
Levofloxacin(467 vs 126)[c]	519(87.4%)	412(88%)	107(84.9%)	0.532
Nitrofurantoin(431 vs 117)[c]	541(91.1%)	425(90.8%)	116(92.1%)	0.864
Cefoperazone/Sulbactam(460 vs 125)[c]	520(87.5%)	409(87.4%)	111(88.1%)	0.756
Gentamicin(455 vs 121)[c]	461(77.6%)	358(76.5%)	103(81.7%)	0.229
Piperacillin/Tazobactam(241 vs 61)[c]	273(46%)	217(46.4%)	56(44.4%)	0.761
Carbapenems(467 vs 126)[c]	550(92.6%)	435(92.9%)	115(91.3%)	0.673
Tigecycline(391 vs 106)[c]	165(27.8%)	135(28.8%)	30(23.8%)	0.475
Colistin(253 vs 57)[c]	9(1.5%)	9(1.9%)	0(0%)	0.083
Treatment after the onset of BSIs				
Appropriate empiric antibiotic treatment	169(28.5%)	120(25.6%)	49(38.9%)	*0.003*

a:biliary tract,Heart surgery,Urinary tract,Intraabdominal;b:AB:Acinetobacter baumannii and not all agents listed tested in all isolates;c:The numbers in parentheses represent the total numbers of AB isolates performed susceptibility test.

Table 5 Comparison of outcomes between Mono-AB-BSI and Mixed-AB-BSI

Prognostic indicators	Total (n=594)	Mono-AB-BSI (n =468)	Mixed-AB-BSI (n =126)	P-value
Total Hospitalization days(M) (IQR)	29(18,50)	27(16,45)	40(21,68)	<0.001
Hospitalization days(M) after BSI (IQR)	14(5,32)	13(4,28)	22(8,50)	<0.001
Total ICU residence days(M)(IQR)	18(10,32)	17(10,29)	20(10,45)	0.080
ICU residence days after BSI(M)(IQR)	7(2,18)	7(2,17)	10(1,30)	0.151
Cause sepsis (n,%)	573(96.5%)	454(97%)	119(94.4%)	0.167
Cause Septic shock (n,%)	167(28.1%)	135(28.8%)	32(25.4%)	0.445
14-day mortality (n,%)	211(35.5%)	175(37.4%)	36(28.6%)	0.066
28-day mortality (n,%)	252(42.4%)	206(44%)	46(36.5%)	0.130
In-hospital mortality (n,%)	283(47.6%)	228(48.7%)	55(43.7%)	0.312


958 positive blood culture samples with acinetobacter baumannii
Exclusions(364):
1. Age<18 years (17 patinets).
2. Pollution (262 patients).
3. Incomplete or missing data (85 patients).
Finally included cases (594 patients)
Mono-AB-BSI (468 patients)
Mixed-AB-BSI(126 patients)


The distribution of strains in Mixed-AB-BSI
20.81%
16.78%
12.08%
11.41%
8.05%
7.38%
2.68%
20.81%
Klebsiella pneumoniae
Pseudomonas aeruginosa
Enterococcus faecium
Staphylococcus aureus
Pseudomonas maltophilia
Enterococcus faecalis
Fungus
others

Figures

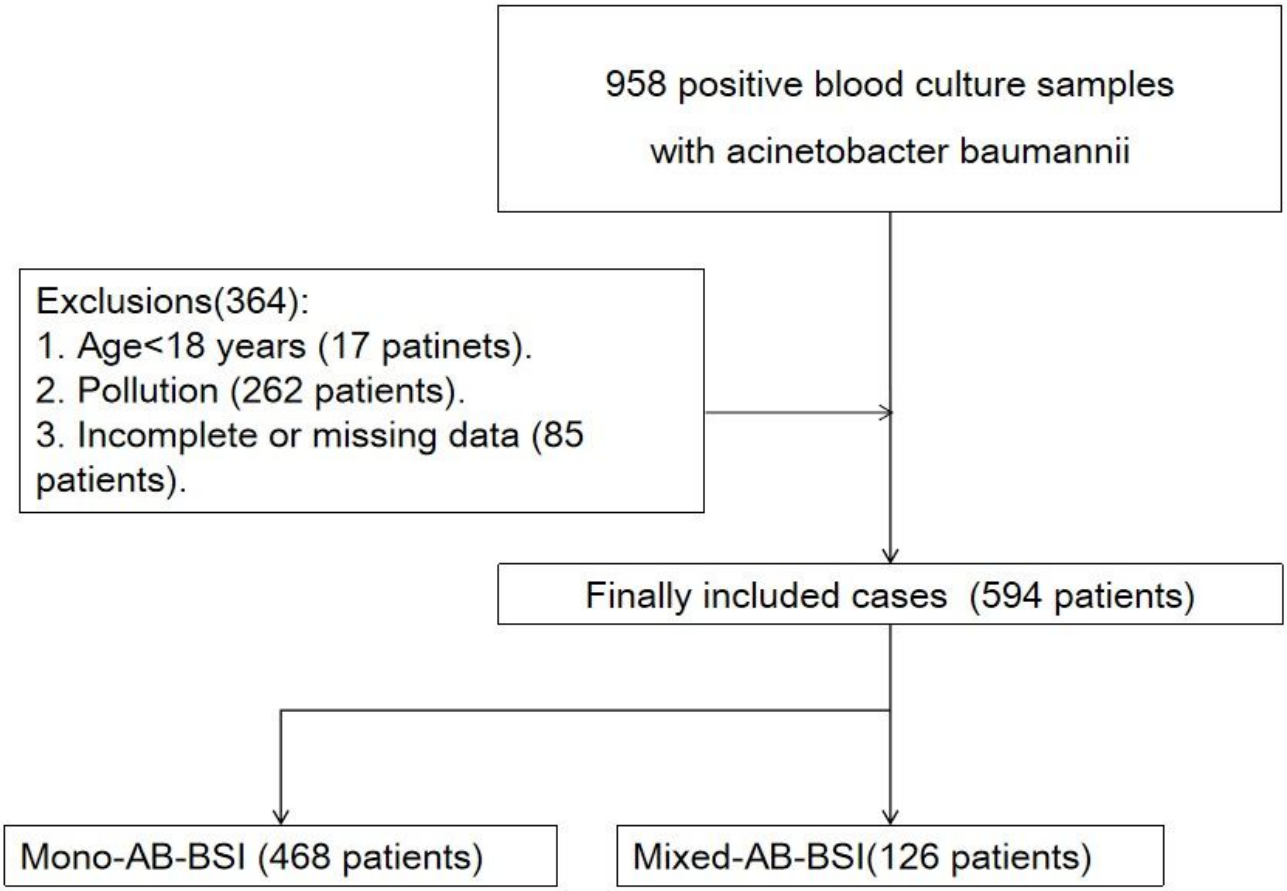


Figure 1

Flowchart of study participant enrollment. Abbreviations: Mono-AB-BSI, monomicrobial Acinetobacter baumannii bloodstream infection;Mixed-AB-BSI, mixed Acinetobacter baumannii bloodstream infection.

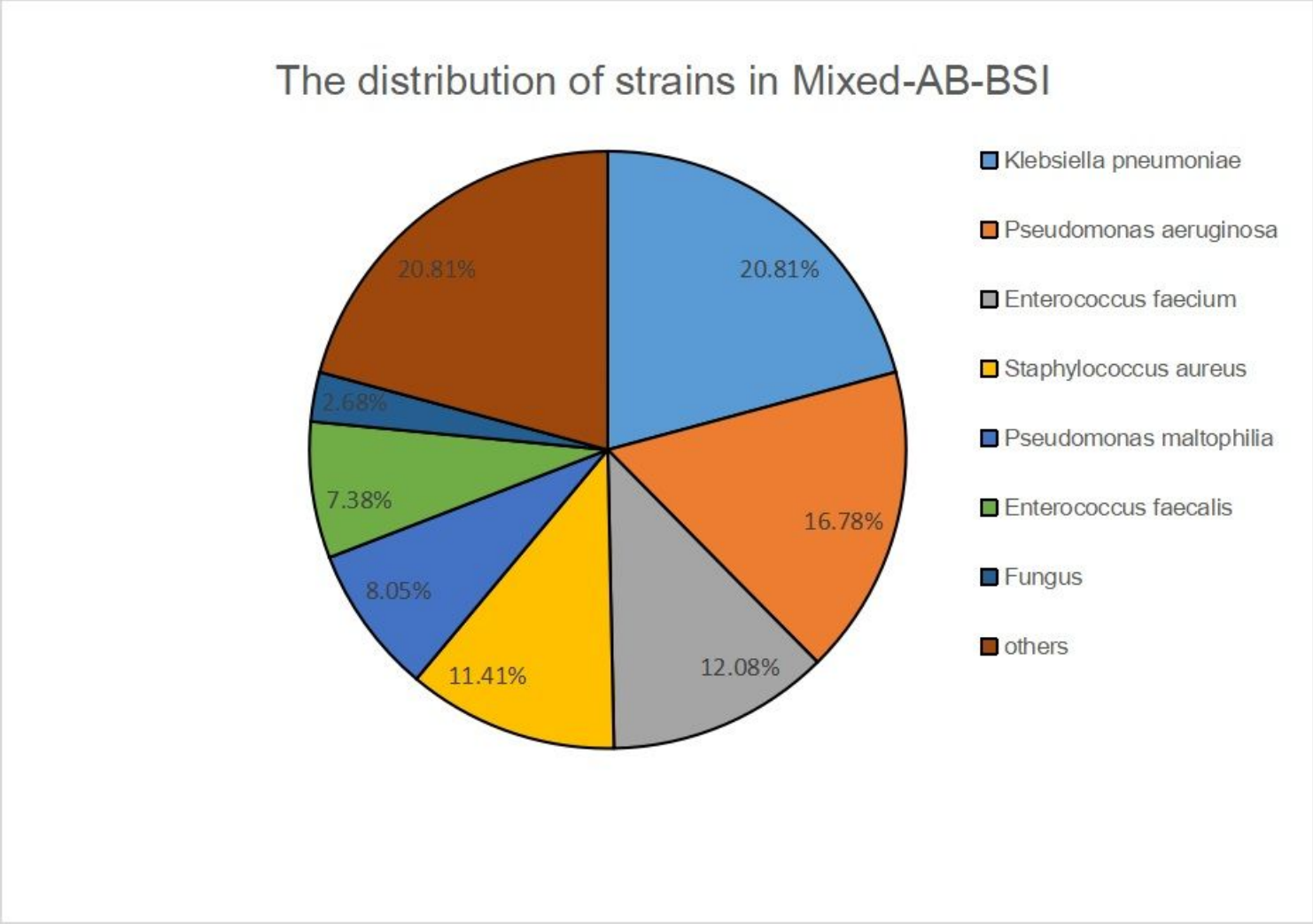


Figure 2

Distribution of the additional organisms in Mixed Acinetobacter baumannii bloodstream infection.