

Impact of Diabetes Mellitus on Bacterial Resistance in Septic Patients with Staphylococcus aureus Pulmonary Infection

Zhiye Zou

Shenzhen Second People's Hospital & First Affiliated hospital of Shenzhen University

Shuiqing Gui

Shenzhen Second People's Hospital & First Affiliated hospital of Shenzhen University

Xisi He

hexisi441845068@126.com

Shenzhen Second People's Hospital & First Affiliated hospital of Shenzhen University

Article

Keywords: Diabetes Mellitus, Staphylococcus aureus, Antimicrobial Resistance, Sepsis, Pulmonary Infection

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-7731031/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Objective

To investigate the association between diabetes mellitus (DM) as a comorbidity and antimicrobial resistance in septic patients with *Staphylococcus aureus* (*S. aureus*) pulmonary infection, with the aim of guiding early clinical antimicrobial therapy.

Methods

A retrospective cohort study was conducted using data from the MIMIC-IV database, analyzing 2072 adult septic patients with *S. aureus* pulmonary infection. Logistic regression, stepwise model building, and subgroup analyses were performed to assess the relationship between diabetes status and multidrug-resistant *Staphylococcus aureus* (MDRSA) infection in these septic patients.

Results

Septic patients with *S. aureus* pulmonary infection and DM exhibited a significantly higher incidence of MDRSA infection compared to those without DM (55.4 vs. 45.3%, $p < 0.001$). Multivariate analysis within subgroups revealed that the association remained significant ($p < 0.05$) in patients > 65 years old, males, non-emergency admissions, those without chronic pulmonary disease, those requiring mechanical ventilation, and those with a maximum SOFA score < 6 . In subgroups where the p-value was non-significant ($p > 0.05$), the odds ratio (OR) consistently remained above 1.

Conclusion

Diabetes mellitus may be associated with increased antimicrobial resistance in septic patients with *S. aureus* pulmonary infection. Close monitoring of antimicrobial effectiveness and timely adjustment of antimicrobial regimens are warranted in these patients.

Introduction

Diabetes mellitus (DM) represents a global public health crisis, affecting over 530 million individuals worldwide as of 2021, with projections anticipating this number will rise to 1.3 billion by 2050 ^{1,2}. Chronic hyperglycemia associated with DM contributes to immune dysfunction and systemic inflammation, significantly increasing susceptibility to severe bacterial infections, particularly those caused by *Staphylococcus aureus* (*S. aureus*) within the respiratory tract ^{3,4}. Such infections can escalate to sepsis, a life-threatening condition characterized by high mortality rates and substantial healthcare costs ⁵.

Emerging evidence indicates that patients with DM face an elevated risk of multidrug-resistant organism (MDRO) infections, potentially due to prolonged hyperglycemia-induced oxidative stress, immunosuppression, and frequent antibiotic exposure from recurrent hospitalizations^{6–8}. However, the association between DM and multidrug-resistant *S. aureus* (MDRSA) remains controversial. While some studies indicate that DM is an independent risk factor for MDRSA^{9,10}, others argue that confounding variables, such as age and comorbidities, may obscure this relationship^{11–13}. Furthermore, limited data exist on how DM interacts with MDRSA in critically ill septic patients with pulmonary infections, particularly across diverse clinical subgroups.

This retrospective cohort study utilizes data from the MIMIC-IV database to evaluate the impact of DM on antimicrobial resistance in septic patients with *S. aureus* pulmonary infections. By adjusting for confounders and conducting stratified analyses, we aim to clarify the role of DM in promoting MDRSA and to inform evidence-based antimicrobial stewardship practices.

Materials and Methods

1.1 Data Source:

Data for this study were obtained from the publicly available MIMIC-IV database, a comprehensive repository of de-identified clinical data from patients admitted to the Beth Israel Deaconess Medical Center (Boston, MA, USA) emergency department or intensive care units (ICUs) between 2008 and 2022. The database includes demographics, diagnoses, procedures, laboratory results, and other clinical information from over 364,000 unique individuals. Access to the database was granted after completion of the Collaborative Training Initiative (CITI) program and approval by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology (certification number: 35951237).

1.2 Participants:

A total of 2072 adult septic patients meeting the inclusion and exclusion criteria were included in the study. Inclusion criteria were: (1) Sepsis defined according to Sepsis 3.0 criteria (infection + SOFA score); (2) *Staphylococcus aureus* isolated from a pulmonary source; (3) Diagnosis of pneumonia. Exclusion criteria were: (1) Age < 18 or ≥ 95 years; (2) ICU stay < 24 hours (N = 51); (3) Death in the ICU < 24 hours; (4) Multiple admissions (only the first admission was included).

1.3 Data Processing:

MIMIC-IV data are derived from hospital electronic health records and ICU clinical information systems, and are processed through collection, organization, and de-identification steps. Patient identifiers were removed and dates adjusted to ensure data privacy and security.

1.4 Definitions:

- Staphylococcus aureus was defined based on microbiological culture results.
- Multidrug-resistant (MDR) was defined as resistance to three or more classes of antimicrobial agents.
- Pulmonary infection was defined based on ICD-9 or ICD-10 diagnosis codes.

1.5 Ethical Considerations:

All patient data in the database were de-identified to protect privacy, and informed consent was therefore not required.

1.6 Statistical Analysis:

Statistical analyses were performed using STATA version 18 (StataCorp, College Station, TX, USA). Continuous variables that did not conform to a normal distribution were expressed as median and interquartile range [M (QL, QU)], and compared using the Mann-Whitney U test. Categorical variables were expressed as counts or percentages, and compared using the Chi-square test. Missing values for body weight were imputed using multiple imputation. Logistic regression was used with stepwise model building to test the sensitivity of the outcome. Subgroup analyses were performed on the MDR outcome using both univariate and multivariate logistic regression. The multivariate model adjusted for all variables listed in Table 1. A p-value < 0.05 was considered statistically significant.

Table 1
Baseline Characteristics of Septic Patients with and without Diabetes Mellitus
Complicated by Staphylococcus aureus Pulmonary Infection

Variables*	Non-diabetes (N = 1424)	Diabetes (N = 648)	P-Value
Age	61.5(47.3,74.8)	66.2(56.8,76.5)	< 0.001
Gender(male)	882(61.9)	421(65.0)	0.19
Weight	78.0(65.7,94.7)	85.0(71.0,105.0)	< 0.001
Admission(emergency)	711(49.9)	298(46.0)	0.096
Race(white)	844(59.3)	364(56.2)	0.19
Insurance(medicare)	646(45.4)	381(58.8)	< 0.001
History of disease			
Hypertension	818(57.4)	510(78.7)	< 0.001
Coronary heart disease	183(12.9)	150(23.1)	< 0.001
Chronic pulmonary disease	402(28.2)	208(32.1)	0.073
Chronic renal insufficiency	177(12.4)	220(34.0)	< 0.001
Malignant cancer	159(11.2)	49(7.6)	0.011
Maximum SOFA score	6.0(3.5,9.0)	7.0(4.0,9.5)	< 0.001
Mechanical ventilation in ICU	1319(92.6)	593(91.5)	0.38
Renal replacement therapy in ICU	45(3.2)	34(5.2)	0.021

Complicated by Staphylococcus aureus Pulmonary Infection

Abbreviation: SOFA sequential organ failure assessment; ICU intensive care unit.

* Because all continuous variables were not normally distributed, the continuous variables were expressed as median (IQR). Categorical variables were expressed as n (%).

Results

2.1 Baseline Characteristics

Data from 2369 septic patients were initially screened, and 2072 patients met the inclusion criteria for the study (Fig. 1). All patients had Staphylococcus aureus isolated during their ICU stay. 648 patients had a history of DM, while 1424 patients did not have DM.

Compared to patients without DM, patients with DM were older (66.2 vs. 61.5 years, $p < 0.001$), had a higher body weight, and had a higher prevalence of hypertension (78.7 vs. 57.4%, $p < 0.001$) and coronary heart disease (23.1 vs. 12.9%, $p < 0.001$). Patients with DM also had more severe illness (Maximum SOFA score, 7.0 vs. 6.0, $p < 0.001$) and a higher proportion requiring renal replacement therapy in the ICU (5.2 vs. 3.2%, $p = 0.021$). In contrast, patients without DM had a higher prevalence of malignant cancer (11.2 vs. 7.6%, $p = 0.011$) compared to patients with DM (Table 1).

2.2 Primary Outcome

Patients with DM had a significantly higher incidence of MDRSA infection (55.4 vs. 45.3%, $p < 0.001$). In stepwise logistic regression models, the association remained stable, with ORs fluctuating between 1.347 and 1.500 and p -values < 0.05 (Fig. 2 and Table 2).

Table 2
Association between diabetes and Multi-drug resistant Staphylococcus aureus using an extended model approach

Variables	Odd ratio	95% confidence interval	P value
Model 1	1.500	1.245–1.808	< 0.001
Model 2	1.393	1.146–1.693	0.001
Model 3	1.396	1.146-1.700	0.001
Model 4	1.358	1.105–1.671	0.004
Model 5	1.356	1.102–1.667	0.004
Model 6	1.347	1.094–1.658	0.005
Adjusted covariates:			
Model 1 = diabetes mellitus.			
Model 2 = Model 1 + Age, Gender, Weight.			
Model 3 = Model 2 + Admission(emergency), Race(white), Insurance(medicare).			
Model 4 = Model 3 + history of disease including Hypertension, Coronary heart disease, Chronic pulmonary disease, Chronic renal insufficiency, Malignant cancer.			
Model 5 = Model 4 + Maximum SOFA score.			
Model 6 = All the variables in Table 1.			

2.3 Subgroup Analysis

Univariate analysis revealed significant differences ($p < 0.05$) in the association between DM and MDRSA infection across subgroups defined by age, gender, admission type, maximum SOFA score, presence or absence of chronic pulmonary disease, and use or non-use of mechanical ventilation. The exceptions were chronic pulmonary disease and non-mechanical ventilation, where $p > 0.05$. After adjusting for all

variables listed in Table 1 in multivariate analysis, all subgroups had ORs greater than 1. The association between DM and MDRSA infection remained statistically significant ($p < 0.05$) in subgroups of patients who were > 65 years old (OR, 1.69 [95%CI, 1.25–2.28]), male, non-emergency admissions, without chronic pulmonary disease, with mechanical ventilation (OR, 1.37 [95%CI, 1.10–1.70]), and had a maximum SOFA score < 6 (OR, 1.41 [95%CI, 1.02–1.96]).

We adjusted all the variables in Table 1. The p-value for interaction in the last column ($p = 0.213$) indicates that there was no statistically significant difference in the association between diabetes status and MDRSA infection in septic patients with *S. aureus* pulmonary infection when comparing the subgroup aged < 65 years with the subgroup aged > 65 years. This suggests that the observed hazard ratios (HR) of 1.14 and 1.69 in these two age groups were not significantly different, and the effect of diabetes on MDRSA infection was similar across these age strata. The interpretation for other subgroups, such as gender, admission type, and maximum SOFA score, follows a similar logic.

Conversely, a p-value for interaction < 0.05 suggests that the association between diabetes status and MDRSA infection in septic patients with *S. aureus* pulmonary infection differed significantly between the compared subgroups.(Fig. 3)

Discussion

This study demonstrates a significant association between DM and MDRSA infections in critically ill septic patients with pulmonary involvement. Patients with DM exhibited a 10.1% absolute increase in MDRSA incidence compared to non-DM patients (55.4% vs. 45.3%, $p < 0.001$), with adjusted odds ratios consistently exceeding 1 across key clinical subgroups. These findings align with emerging evidence suggesting that DM exacerbates antimicrobial resistance (AMR) risks, particularly in critically ill populations, and underscore the need for tailored antimicrobial stewardship in this vulnerable cohort.

The observed association aligns with emerging evidence linking DM to heightened risks of MDRO infections^{14,15}. Chronic hyperglycemia, a hallmark of DM, promotes immune dysfunction through impaired neutrophil activity, diminished phagocytic capacity, and dysregulated cytokine responses, which may facilitate persistent bacterial colonization and the development of resistance^{3,16,17}. Recent animal studies have demonstrated that hyperglycemia can enhance the progression of bacterial infections, with bacterial virulence genes being up-regulated in mouse models of hyperglycemia^{18,19}. Additionally, frequent healthcare exposures and antibiotic use in diabetic patients likely contribute to selective pressure favoring resistant strains^{20,21}. Our findings extend prior studies by demonstrating that this relationship persists even after rigorous adjustment for confounders such as age, comorbidities, and illness severity (e.g., SOFA scores), reinforcing DM as a clinically relevant risk factor for MDRSA in critically ill populations.

Stratified analyses revealed heterogeneous effects of diabetes on the risk of MDRSA. Older diabetic patients (> 65 years) exhibited the highest risk (OR = 1.69), likely due to the synergistic effects of age-

related immunosenescence and diabetes-induced immunosuppression^{22,23}. Similarly, the association remained significant among males, non-emergency admissions, and mechanically ventilated patients, suggesting that clinical context modulates resistance dynamics. For instance, mechanical ventilation may exacerbate mucosal damage and biofilm formation, amplifying opportunities for resistant strains to thrive in diabetic hosts^{24,25}. Conversely, the non-significant interaction between DM and chronic pulmonary disease ($p > 0.05$) implies that pre-existing lung pathology may overshadow diabetes-specific effects on resistance in these patients^{26–28}. These subgroup-specific insights highlight the importance of individualized risk assessment and antimicrobial selection.

Despite these robust findings, several limitations warrant consideration. First, the retrospective design introduces potential biases, such as unmeasured confounders (e.g., glycemic control metrics and antibiotic exposure history) and reliance on the accuracy of diagnostic coding. Second, the single-center data from MIMIC-IV may limit the generalizability of the findings to other populations or healthcare settings. Third, while MDRSA was defined as resistance to three or more antibiotic classes, granular data on specific resistance mechanisms (e.g., *mecA* gene presence) were unavailable, which precludes deeper mechanistic insights. Finally, the study design limits causal inference; prospective cohort studies or translational experiments are needed to elucidate temporal relationships and molecular pathways.

Conclusion

In conclusion, this study provides substantial evidence linking diabetes to MDRSA pulmonary infections in septic patients, offering critical insights for clinical risk stratification and optimization of antimicrobial strategies. The interplay between diabetes and antimicrobial resistance remains complex, necessitating interdisciplinary efforts to unravel the molecular mechanisms and translate findings into actionable interventions. As AMR threats escalate, integrating metabolic profiles with microbial resistance signatures will be pivotal for advancing precision anti-infective therapies.

Declarations

Ethics approval and consent to participate

The dataset in this study was obtained from MIMIC-IV database. We had completed the CITI Program and approval by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology (certification number: 35951237). The individual information of the patients included in this database was anonymous, and ethical review and informed consent were waived. All methods were performed in accordance with the relevant guidelines and regulations. The research was conducted in accordance with the Declaration of Helsinki.

Clinical Trial

Clinical trial number: Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed during the current study are publicly available in the MIMIC-IV repository (<https://mimic-iv.mit.edu/>).

Competing interests

The authors declare that they have no competing interests.

Funding

The study was supported by grants from the Sanming Project of Medicine in Shenzhen (NO. SZSM202211016), Shenzhen Fund for Guangdong Provincial High-level Clinical Key Specialties (NO. SZGSP006), Shenzhen Second People's Hospital Clinical Research Fund of Guangdong Province High-level Hospital Construction Projects (NO. 2023yjlcjy010) and Research Project of Shenzhen Health Economics Association (No. 202546).

Authors' contributions

ZYZ and SQG designed the experiments. ZYZ collected and analyzed the data. ZYZ and XSH drafted manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Lancet, J. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. **402**(10397):203–234. (2023).
2. Sun, H. et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract.* **183**, 109119 (2022).
3. Casqueiro, J., Casqueiro, J. & Alves, C. Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian J. Endocrinol. Metabol.* **16** (Suppl 1(Suppl1), S27–36 (2012).
4. Wooten, D. A. & Winston, L. G. Risk factors for methicillin-resistant *Staphylococcus aureus* in patients with community-onset and hospital-onset pneumonia. *Respir. Med.* **107** (8), 1266–1270 (2013).

5. Singer, M. et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* **315** (8), 801–810 (2016).
6. Falcone, M. et al. Diabetes and acute bacterial skin and skin structure infections. *Diabetes Res. Clin. Pract.* **174**, 108732 (2021).
7. Critchley, J. A. et al. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. *Diabetes care.* **41** (10), 2127–2135 (2018).
8. Berbudi, A., Rahmadika, N., Tjahjadi, A. I. & Ruslami, R. Type 2 Diabetes and its Impact on the Immune System. *Curr. Diabetes. Rev.* **16** (5), 442–449 (2020).
9. Liu, C. et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin. Infect. diseases: official publication Infect. Dis. Soc. Am.* **52** (3), e18–55 (2011).
10. Zhang, Q. R., Chen, H., Liu, B. & Zhou, M. Methicillin-resistant Staphylococcus aureus pneumonia in diabetics: a single-center, retrospective analysis. *Chin. Med. J.* **132** (12), 1429–1434 (2019).
11. Pearson-Stuttard, J., Blundell, S., Harris, T., Cook, D. G. & Critchley, J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. *Lancet Diabetes Endocrinol.* **4** (2), 148–158 (2016).
12. Erben, N. et al. Healthcare-associated infections and the distribution of causative pathogens in patients with diabetes mellitus. *Eur. J. Clin. Microbiol. Infect. diseases: official publication Eur. Soc. Clin. Microbiol.* **32** (6), 821–825 (2013).
13. Vinken, J. E. M. et al. Antimicrobial resistance in women with urinary tract infection in primary care: No relation with type 2 diabetes mellitus. *Prim. Care Diabetes.* **12** (1), 80–86 (2018).
14. Akash, M. S. H., Rehman, K., Fiayyaz, F., Sabir, S. & Khurshid, M. Diabetes-associated infections: development of antimicrobial resistance and possible treatment strategies. *Arch. Microbiol.* **202** (5), 953–965 (2020).
15. Yi, H. et al. Increased Antimicrobial Resistance among Sputum Pathogens from Patients with Hyperglycemia. *Infect. drug Resist.* **13**, 1723–1733 (2020).
16. Restrepo, B. I., Twahirwa, M., Rahbar, M. H. & Schlesinger, L. S. Phagocytosis via complement or Fc-gamma receptors is compromised in monocytes from type 2 diabetes patients with chronic hyperglycemia. *PLoS one.* **9** (3), e92977 (2014).
17. Macdonald, K. E., Boeckh, S., Stacey, H. J. & Jones, J. D. The microbiology of diabetic foot infections: a meta-analysis. *BMC Infect. Dis.* **21** (1), 770 (2021).
18. Shook, J. C. et al. Diabetes potentiates the emergence and expansion of antibiotic resistance. *Sci. Adv.* **11** (7), eads1591 (2025).
19. Keogh, R. A. et al. Group B Streptococcus adaptation promotes survival in a hyperinflammatory diabetic wound environment. *Sci. Adv.* **8** (45), eadd3221 (2022).
20. Stacey, H. J., Clements, C. S., Welburn, S. C. & Jones, J. D. The prevalence of methicillin-resistant Staphylococcus aureus among diabetic patients: a meta-analysis. *Acta Diabetol.* **56** (8), 907–921

- (2019).
21. Zhou, J., Lin, Y., Liu, Y. & Chen, K. Antibiotic exposure and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. *Environ. Sci. Pollut. Res. Int.* **28** (46), 65052–65061 (2021).
 22. Frydrych, L. M., Bian, G., O'Lone, D. E., Ward, P. A. & Delano, M. J. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. *J. Leukoc. Biol.* **104** (3), 525–534 (2018).
 23. Wang, F. et al. Novel Subgroups and Chronic Complications of Diabetes in Middle-Aged and Elderly Chinese: A Prospective Cohort Study. *Front. Endocrinol.* **12**, 802114 (2021).
 24. Alsayed, S., Marzouk, S., Mousa, E. & Ragab, A. Bronchial aspirates glucose level as indicator for methicillin-resistant *Staphylococcus aureus* (MRSA) in intubated mechanically ventilated patients. *J. Egypt. Soc. Parasitol.* **44** (2), 381–388 (2014).
 25. Rhodes, N. J. et al. Machine Learning To Stratify Methicillin-Resistant *Staphylococcus aureus* Risk among Hospitalized Patients with Community-Acquired Pneumonia. *Antimicrob. Agents Chemother.* **67** (1), e0102322 (2023).
 26. Kabitz, H. J. et al. Diabetic polyneuropathy is associated with respiratory muscle impairment in type 2 diabetes. *Diabetologia* **51** (1), 191–197 (2008).
 27. Frizzelli, A., Aiello, M., Calzetta, L., Bertorelli, G. & Chetta, A. The interplay between diabetes mellitus and chronic obstructive pulmonary disease. *Minerva Med.* **114** (1), 68–73 (2023).
 28. van den Borst, B., Gosker, H. R., Zeegers, M. P. & Schols, A. M. Pulmonary function in diabetes: a metaanalysis. *Chest* **138** (2), 393–406 (2010).

Figures

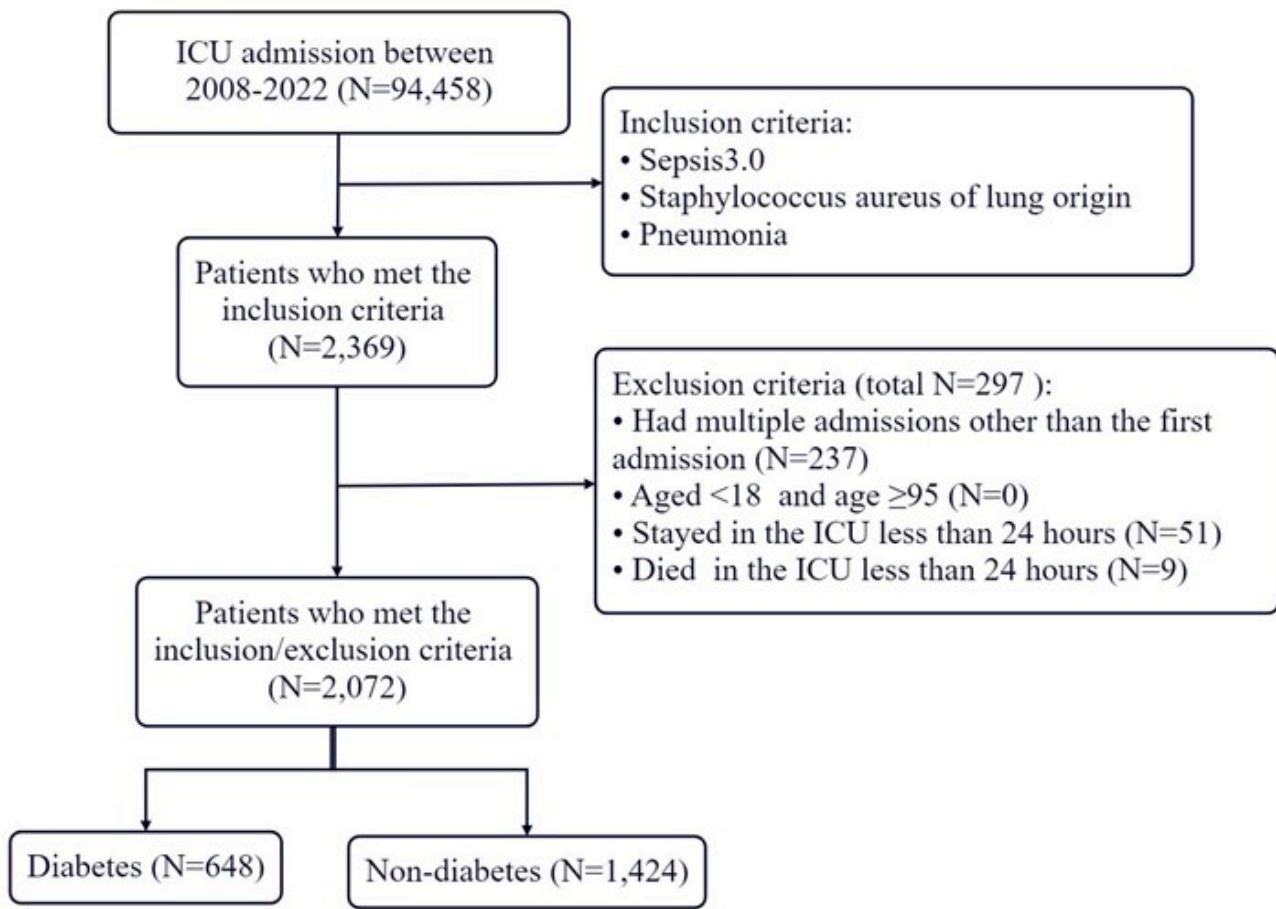


Figure 1

Study Flowchart.

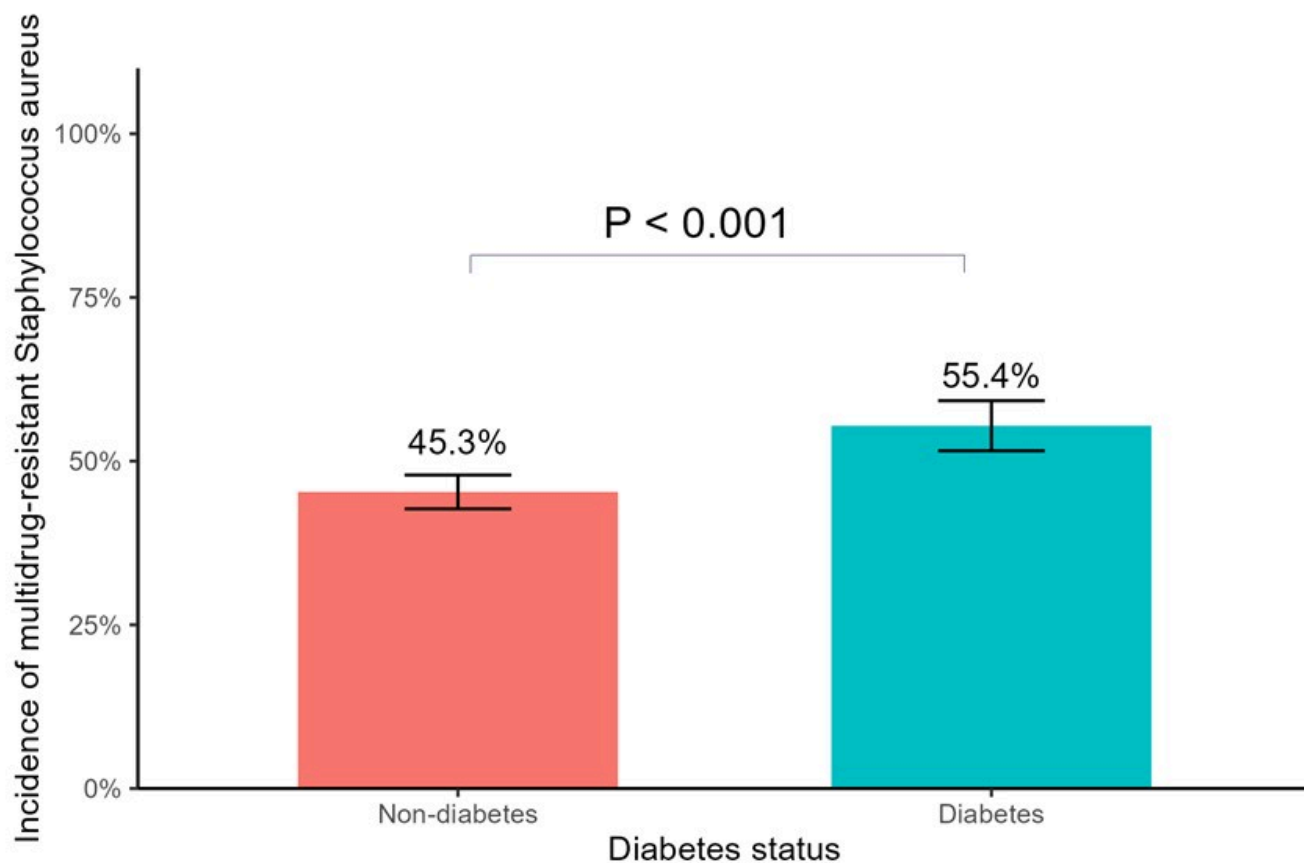


Figure 2

Incidence of Multidrug-Resistant Staphylococcus aureus Infection in Septic Patients with Different Diabetic Statuses.

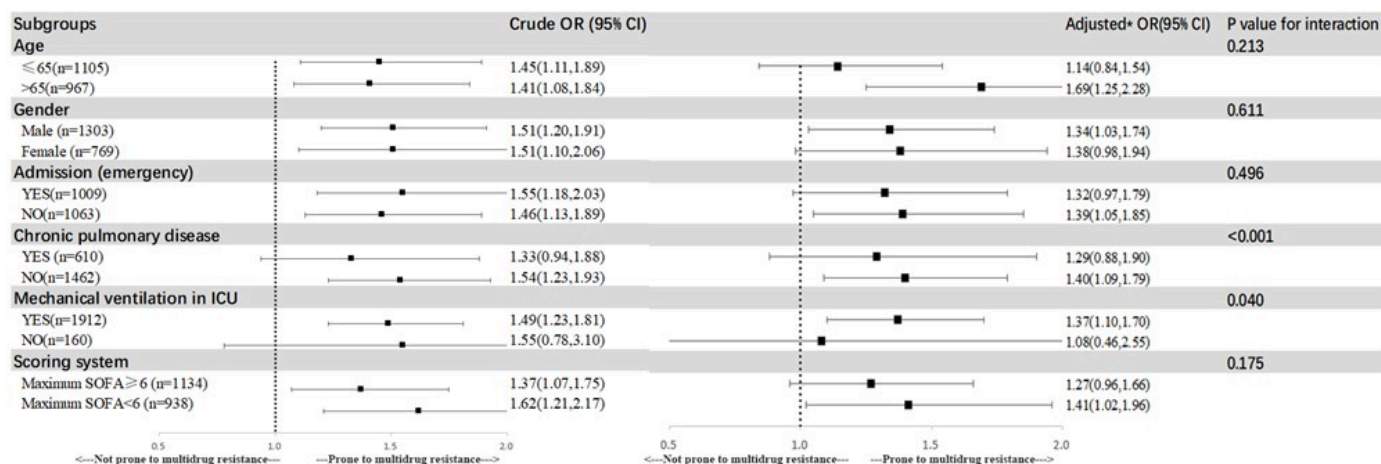


Figure 3

Impact of Different Diabetic Statuses on Subgroups of Septic Patients with Staphylococcus aureus Pulmonary Infection.