CLINICAL OUTCOMES AND RISK FACTORS FOR MORTALITY IN DIABETIC PATIENTS WITH STAPHYLOCOCCUS AUREUS PNEUMONIA: A CASE-CONTROL STUDY

Vo Pham Minh Thu[1,2], Nguyen Thuy Quyen[1], Tran Cong Dang[1] and Nguyen The Bao[1,✉]

[1]Can Tho University of Medicine and Pharmacy
[2]Can Tho University of Medicine and Pharmacy Hospital

The study was conducted to investigate the clinical outcomes and mortality risk factors related to Staphylococcus aureus pneumonia in patients with and without diabetes mellitus (DM). This was a case-control study on 118 patients with S. aureus pneumonia hospitalized between April 2021 and May 2023. The results reveal that diabetic female patients were prone to acquire Staphylococcus aureus pneumonia than non DM group (66.7% vs. 36.6%, p = 0.003); DM patients have more comorbidities (4.64 ± 2.07 vs. 3.46 ± 1.85; p = 0.003) compared to non-DM patients. Clinical outcomes, including 30-day all-cause mortality and pneumonia-related complications, showed no significant difference between patients with and without DM (all p > 0.05). Two independent risk factors for mortality in DM patients with S. aureus pneumonia are age > 65 (OR = 0.09, 95%CI: 0.01-0.64, p = 0.017) and central nervous system disease (OR = 18.54, 95%CI: 1.81-190.07, p = 0.014). The relatively high mortality rate in DM patients, predominantly attributed to MRSA infection, underscores the importance of staying focus on the diagnosis and adopting an appropriate initial antibiotic treatment approach. It is crucial to particularly note individuals with multiple comorbidities, especially those with central nervous system diseases.

Keywords: Staphylococcus aureus, pneumonia, diabetic mellitus, mortality.

I. INTRODUCTION

Pneumonia is the most common lower respiratory tract infection; data in the United States indicated the incidence of patients hospitalized for pneumonia was 649 per 100,000 person-year, and the in-hospital mortality and 30-day mortality were 6.5% and 13%, respectively.[1] Among the diverse pathogens of this disease, *S. aureus* has emerged as a causative agent of severe pneumonia with many complications and high mortality. Community-acquired pneumonia caused by *S. aureus* had a 30-day mortality of four times higher, and hospital stays two times higher compared to *Streptococcus pneumoniae*.[2] In the model of nosocomial pneumonia and ventilator-associated pneumonia, *S. aureus* had a high all-cause mortality of up to 55.5%, even when treated early with appropriate antibiotic therapy.[3]

Diabetes is currently a global non-communicable epidemic with an increasing trend in the future,[4] which raises concerns about an increase in infectious diseases, especially pneumonia. Several mechanisms have explained that hyperglycemia, decreased immunity, impaired lung function, and chronic complications such as heart disease, kidney failure, and pulmonary microangiopathy increase the risk of lower respiratory tract infections.[5] However, information regarding *S.*

Corresponding author: Nguyen The Bao
Can Tho University of Medicine and Pharmacy
Email: drntbao12345@gmail.com
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aureus pneumonia is minimal. In a 2019 study, diabetic patients with poor glycemic control are more susceptible to methicillin-resistant *S. aureus* infection, higher risk of antibiotic resistance, a higher co-infection rate, and more severe pneumonia than non-DM.[6] To supplement existing data, we conducted this study "Clinical outcomes and risk factors for mortality in diabetic patients with *Staphylococcus aureus* pneumonia: a case-control study in Can Tho City, Vietnam", with two main objectives:

1. Comparison of clinical outcomes of *S. aureus* pneumonia between diabetic and non-diabetic patients.

2. Analysis of some risk factors in-hospital mortality in diabetic patients with *S. aureus* pneumonia.

II. MATERIALS AND METHODS

1. Research subjects

Patients was diagnosed with *S. aureus* pneumonia and treated at Can Tho Central General Hospital and Can Tho University of Medicine and Pharmacy Hospital from April 2021 to May 2023.

Inclusion criteria

- Patients ≥18 years old.

- Patients with a diagnosis of *S. aureus* pneumonia with all 3 of the following criteria:

+ Symptoms and signs: at least one of the signs, such as temperature > 38°C or < 36°C, have ruled out other causes; leukocytosis (≥ 12 x 10^9/L) or leukopenia (≤ 4 x 10^9/L); Consciousness disorders in elderly patients have ruled out other causes. At the same time, at least two of the following signs such as purulent sputum or change in sputum properties or increased sputum secretion or increased need for sputum aspiration; cough or increased coughing or shortness of breath or rapid breathing; crackles or wheezes sounds on lung examination, worsening of gas exchange including hypoxemia, increased need for oxygen supply, or increased need for mechanical ventilation.

+ Imaging evidence: new or progressive lesions did not disappear quickly on chest imaging tests (straight chest X-ray, chest computed tomography, chest magnetic resonance imaging) and can be infiltration, consolidation, cavitation, and air bubbles.

+ Microbiological evidence: one of the criteria is a culture of blood and/or pleural fluid or respiratory secretions isolated from *S. aureus*. The clinical specimens were stained and cultured on a selective medium (brain heart infusion, blood agar, chocolate agar, and MacConkey agar) at the Department of Microbiology, Can Tho University of Medicine and Pharmacy. After overnight incubation, microbial colonies were observed, selected for suspension culture, and subjected to identification and antibiotic susceptibility testing using the Vitek 2 Compact system (bioMérieux, France). Results were reported within 3-5 days after sample collection, with positive results indicating bacterial isolation and pathogen identification, while negative results indicated absence or failure to isolate the pathogenic bacteria.

- Patients with a diagnosis of *S. aureus* pneumonia were divided into two groups:

+ Case group: patients with DM. Diagnosis of diabetes according to the 2021 American Diabetes Association guidelines[7]: At least one of the following criteria such as a hemoglobin A1c (HbA1c) ≥ 6.5%; a fasting plasma glucose ≥ 7.0 mmol/L (≥ 16 mg/dL); a random plasma glucose ≥ 11.1 mmol/L (200 mg/dL) with classic symptoms of hyperglycemia or hyperglycemic crisis.

+ Control group: patient without DM.

Exclusion criteria

- The patient's blood culture, pleural fluid culture, and respiratory secretion culture results were of other bacteria and/or co-infection with *S. aureus*.

- Death within 48 hours of diagnosis of pneumonia.

- The patient refused to continue participating in the study.

2. Research methods

Study design

A case-control study. Data were extracted and collected from medical records.

Sample size

The sample was conveniently chosen, selecting all patients with *S. aureus* pneumonia who met the criteria for hospitalization during the study period based on the data collection form. A total of 118 eligible patients were recruited and followed until the end of the study, comprising 36 diabetic patients (study group) and 82 non-diabetic patients (control group).

Study contents

Demographic and clinical characteristics: age (years, mean, ≤ 65/> 65), gender (male/female), co-morbidities including hypertension, coronary artery disease, heart failure, chronic obstructive pulmonary disease [COPD], renal failure, liver disease, central nervous system [CNS] disease, cancer (yes/no per one), methicillin-resistant *S. aureus* [MRSA] (yes/no),[8,9] Charlson comorbidities index [CCI] (mean, < 3/≥ 3).[10,11]

Primary clinical outcome: 30-day all-cause mortality (alive/death) was defined as all-cause death in the hospital or at home from the time of diagnosis of *S. aureus* pneumonia.

Secondary clinical outcomes: respiratory failure (yes/no), acute respiratory distress syndrome [ARDS] (yes/no), septic shock (yes/no), acute kidney injury (yes/no), length of hospital stay (days, mean), duration of intensive care unit [ICU] stay (days, mean).[6,12]

Analyze the association between demographic and clinical characteristics with the 30-day all-cause mortality event of the DM group.

Statistical analysis:

The data were analyzed by Statistical Package for the Social Sciences (SPSS) software 22.0.

3. Research ethic

The board of directors of Can Tho Central General Hospital as well as the ethics committee for biomedical research at Can Tho University of Medicine and Pharmacy approved this study with decision number 421/QĐ-ĐHYD dated May 4, 2020.

III. RESULTS

A total of 118 patients with *S. aureus* pneumonia were included in the study; among them, 36 were in the DM group, and 82 were in the non-DM group. The baseline demographic and clinical characteristics of the research population are shown in Table 1.

Table 1. Baseline demographic and clinical characteristics

Characteristics	DM (n = 36)	non-DM (n = 82)	P-value
Age, mean ± SD	67.81 ± 12.91	62.91 ± 17.05	0.127†
Age > 65 (yes), n (%)	20 (55.6)	39 (47.6)	0.424*

Characteristics	DM (n = 36)	non-DM (n = 82)	P-value
Gender (female), n (%)	24 (66.7)	30 (36.6)	0.003*
Hypertension (yes), n (%)	27 (75.0)	47 (57.3)	0.067*
Coronary artery disease (yes), n (%)	10 (27.8)	12 (14.6)	0.091*
Heart failure (yes), n (%)	8 (22.2)	14 (17.1)	0.508*
COPD (yes), n (%)	2 (20)	8 (80)	0.721**
Renal failure (yes), n (%)	7 (5.6)	14 (66.7)	0.756*
Liver disease (yes), n (%)	0 (0)	5 (6.1)	0.321**
CNS disease (yes), n (%)	11 (34.4)	23 (28.0)	0.782*
Cancer (yes), n (%)	0 (0)	5 (6.1)	0.321**
CCI, mean ± SD	4.64 ± 2.07	3.46 ± 1.85	0.003†
CCI group (≥ 3), n (%)	31 (86.1)	60 (73.2)	0.123*
MRSA (yes), n (%)	31 (86.1)	69 (84,1)	0.785*

*Chi-squared test, **Fisher's Exact Test, †Independent Samples T-Test.

Compared to the non-DM patients, DM patients had a significantly higher value percentage of females (66.7% vs. 36.6%, p = 0.003) and the mean score of CCI (4.64 ± 2.07 vs. 3.46 ± 1.85; p = 0.003). There were no difference in the remaining characteristics between the two groups, although the DM group tended to have higher age and underlying diseases (p > 0.05).

Table 2. Clinical outcomes of pneumonia patients with and without diabetes

Characteristics	DM (n = 36)	non-DM (n = 82)	P-value
Primary outcome			
30-day all-cause mortality (death), n (%)	18 (50.0)	39 (47.6)	0.087*
Secondary outcomes			
Respiratory failure (yes), n (%)	26 (72.2)	71 (86.6)	0.06*
ARDS (yes), n (%)	8 (22.2)	18 (22.0)	0.974*
Septic shock (yes), n (%)	10 (17.8)	21 (25.6)	0.805*
Acute kidney injury (yes), n (%)	6 (16.7)	11 (13.4)	0.643*
Length of hospital stay, mean (SD)	13.53 ± 7.90	13.61 ± 9.08	0.963†
Duration of ICU stay, mean (SD)	11.08 ± 9.30	8.14 ± 7.42	0.284†

*Chi-squared test, †Independent Samples T-Test.

Regarding the primary outcome, the 30-day all-cause mortality of the DM group was higher than that of the non-DM group. In terms of secondary outcomes, DM patients with *S. aureus* pneumonia had longer ICU stays and higher rates of ARDS and acute kidney injury; on the contrary, the non-DM group was more dominant for the remaining outcomes. However, all differences were not statistically significant (all p > 0.05).

Table 3. Univariate and multivariate analyses of associated factors for mortality in *S. aureus* pneumonia among diabetics

Factors	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age > 65 (yes), n (%)	0.25 (0.06-0.99)	0.044**	0.09 (0.01-0.64)	0.017
Gender (female), n (%)	1.66 (0.41-6.71)	0.48*	3.86 (0.46-32.5)	0.215
Hypertension (yes), n (%)	2.5 (0.52-12.14)	0.443**	0.75 (0.08-7.57)	0.810
Coronary artery disease (yes), n (%)	0.57 (0.13-2.51)	0.457*	0.4 (0.03-4.83)	0.471
Heart failure (yes), n (%)	0.52 (0.10-2.61)	0.691**	0,94 (0,05-16,78)	0.966
COPD (yes), n (%)	1 (0.06-17.33)	1**	-	-
Renal failure (yes), n (%)	0.7 (0.13-3.7)	1**	-	-
CNS disease (yes), n (%)	8.0 (1.41-45.41)	0.011*	18.54 (1.81-190.07)	0.014
CCI, mean (SD)	-	0.175†	-	-
CCI group (≥ 3), n (%)	0.63 (0.09-4.28)	1*	-	-
MRSA (yes), n (%)	0.63 (0.09-4.28)	1*	-	-

*Chi-squared test, **Fisher's Exact Test, †Independent Samples T-Test.

Univariate analysis showed that only age > 65 and CNS disease were two factors associated with mortality in diabetic patients with *S. aureus* pneumonia (p = 0.044 and p = 0.011, respectively). In multivariate analysis, age > 65 reduced mortality risk (OR = 0.09, 95%CI: 0.01-0.64, p = 0.017), whereas CNS disease increases mortality risk (OR = 18.54,

95%CI: 1.81-190.07, p = 0.014). The remaining factors were not related to 30-day all-cause mortality.

IV. DISCUSSION

Our study was conducted on 118 patients with pneumonia caused by *S. aureus*, both with and without DM. Among them, patients with *S. aureus* pneumonia were predominantly elderly individuals with an average age > 60, with numerous comorbidities in both the diabetes and non-diabetes groups. This is also reflected in the difference in the CCI between the two groups, being higher in the DM group than in the non-DM group (4.64 vs. 3.46, p = 0.003). However, when categorizing CCI with a cutoff score of 3 or higher, no significant difference was observed. We found a higher proportion of female patients with *S. aureus* pneumonia in the DM group compared to that of the non-DM group (66.7 vs. 36.6, p = 0.003). Similar to the research findings of Shorr AF and colleagues, the authors noted that women with DM are a factor that increases the risk of pneumonia caused by MRSA.[13]Our research findings indicated that in both the DM and non-DM patient groups, the clinical outcomes of pneumonia caused by *S. aureus* are similar. Although the primary outcome of 30-day mortality was higher in in the DM group than in the non-DM group, the difference was not statistically significant (50% vs. 47.6%, p = 0.087). Further analysis of secondary outcomes, including respiratory failure, ARDS, septic shock, acute kidney injury, length of hospital stay, and ICU admission time, also yielded similar results in both groups. Study by Di Yacovo S et al. observed no significant difference in clinical characteristics and severity of pneumonia between patients with and without DM.[14] However, in a comprehensive analysis by Barmanray RD et al. on the impact of diabetes on the outcomes of hospitalized community-acquired pneumonia patients, it was noted that the DM patients had a higher 30-day mortality rate than the non-DM patients. Additionally, in-hospital mortality was higher in the DM group than in the non-DM group (35.3% vs. 31%, p = 0.009).[15] We attribute this to the inherently severe nature of *S. aureus* pneumonia, as the current study revealed that over 80% of patients had MRSA. Similarly, a previous report by Thabet N and colleagues documented 88% of patients with severe *S. aureus* pneumonia.[9] Therefore, we believe that, considering the predominantly severe nature of *S. aureus* pneumonia in our patient population, diabetes may not be a significant factor influencing treatment outcomes.

The independent factors influencing the 30-day all-cause mortality in DM patients with *S. aureus* pneumonia, including age > 65 (OR = 0.09, p = 0.017) and CNS disease (OR = 18.54, p = 0.014). In our study, among patients with DM and *S. aureus* pneumonia, the deceased group had a lower average age than the surviving group. This finding contrasts with the study by Huang D et al., and the authors observed that in severe pneumonia patients with DM, the in-hospital mortality group had a higher average age than the surviving group.[16] This difference may arise from our study focusing on patients with pneumonia caused by S. aureus, unlike the research of Huang D, which included pneumonia patients with various pathogens. This could be because, in the empiric antibiotic treatment of elderly patients with DM, more attention is given to specific bacterial pathogens like *S. aureus*. The initial antibiotic choice for treating *S. aureus* is prioritized in this older population with DM compared to other groups. The study by Shorr AF et al. indicated that DM and CNS diseases are risk factors for MRSA.[13] Therefore, in pneumonia patients with diabetes, especially those with additional comorbidities

such as cerebrovascular diseases, assessing the risk of MRSA infection and initiating appropriate antibiotic treatment early on is crucial for improving patient outcomes.

Our study has limitations, such as a restricted sample size, especially within the diabetes patient group, which results in an insufficient number of deceased patients to accurately reflect risk factors.

V. CONCLUSION

Our key findings indicate no significant difference in clinical outcomes of *Staphylococcus aureus* pneumonia between patients with and without diabetic mellitus. Overall, the relatively high mortality rate in diabetic patients (approximately 50%), mainly attributed to MRSA infection, underscores the need for attention to young individuals with multiple comorbidities, especially those with central neural system diseases. It suggests the importance of follow-up and appropriate initial treatment.

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