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ORIGINAL RESEARCH

Prediction of the Risk of Hospital Deaths in Patients with Hospital-Acquired Pneumonia Caused by Multidrug-Resistant *Acinetobacter baumannii* Infection: A Multi-Center Study

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Purpose: To predict the risk of hospital deaths in patients with hospital-acquired pneumonia (HAP) caused by multidrug-resistant *Acinetobacter baumannii* (MDR-AB) infection.

Patients and Methods: A total of 366 patients who were diagnosed with HAP caused by MDR-AB infection were enrolled between January 2013 and December 2016. The sociological characteristics and clinical data of these cases were collected. Univariate and multivariate logistic analyses were used to explore the risk factors of hospital deaths before medication and after drug withdrawal. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were utilized to assess the predictive effectiveness of the models with or without the adjustment.

Results: Hospital deaths occurred in 142 cases (38.80%). The results showed that acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores before medication and after drug withdrawal were associated with the risk of hospital deaths. Adjusting the covariants including the age, autoimmune disease, venous cannula, transfer of patients from other hospitals, and APACHE II score at admission, then no differences were discovered in predicting the hospital deaths between adjusted APACHE II and adjusted SOFA scores before medication (AUC: 0.808 vs 0.803, P =0.614) and after drug withdrawal (AUC: 0.876 vs 0.878, P =0.789).

Conclusion: Before medication or after drug withdrawal, the adjusted APACHE II and adjusted SOFA scores all performed well in determining the predictive effectiveness of the hospital deaths in patients with HAP caused by MDR-AB infection, indicating that the appropriate infection control may reduce the occurrence of nosocomial deaths and improve the prognosis.

Keywords: multidrug-resistant *Acinetobacter baumaii*, hospital-acquired pneumonia, intensive care units, hospital deaths

Introduction

Hospital-acquired pneumonia (HAP) is the main nosocomial infection resulting in increased morbidity, mortality, and medical costs.[1] Administration of appropriate antibiotics is important to improve the prognostic outcomes of HAP.[2,3] Previous epidemiologic studies reported that the incidence of HAP with an upward trend was due to the infection of multidrug-resistant (MDR) microorganisms.[4,5] The carbapenem-resistant microbial pathogens, such as *Acinetobacter baumannii* (AB) and *Pseudomonas aeruginosa*, are major pathogens of HAP in Asia.[6] Of which, the

occurrence of HAP caused by AB infection has gradually increased ranging from 26% to 82.5% in recent years.[7] It is essential for clinicians to pay attention to AB infection in HAP to avoid the inappropriate empirical therapy and overuse of colistin.

MDR-AB, an important pathogen associated with outbreaks of nosocomial infections, mostly occurs in intensive care units (ICUs), and leads to urinary tract, blood-stream and surgical infections, as well as pneumonia which is the most common clinical symptom.[8] Early studies showed that the infection caused by MDR-AB is difficult to treat, resulting in increased mortality and longer length of stay.[9] It was estimated that 55% of elderly inpatients underwent 30-day nosocomial death due to the blood-stream infection caused by MDR-AB,[10] and 40.7–73% of critically ill patients died from MDR-AB infection.[11–13] Numerous studies have explored the risk factors of HAP caused by MDR-AB infection.[14,15] To the best of our knowledge, however, the prediction of the risk of hospital deaths in patients with HAP caused by MDR-AB has been rarely reported. In the current study, we assessed different models for predicting the risk of hospital deaths, and compared the predictive effectiveness of these models in patients with HAP caused by MDR-AB infection.

Patients and Methods

Patients

A total of 1,475 cases from two hospitals who were diagnosed with HAP were enrolled between January 2013 and December 2016, with the age ≥18 years old. After excluding antibiotic use <3 days, colonization, experiential therapy, non MDR-AB infection and age <18 years, 366 cases were finally divided into hospital deaths (n=142) and non-hospital deaths (n=224) groups. This study was approved by the Institutional Review Board (IRB) of China-Japan Friendship Hospital (No.2017–104) and Beijing Chao-Yang Hospital (No.2017–202), and all patients or their relatives provided informed consent.

Diagnostic Criteria

HAP (ICD-10) is defined as a newly developed pneumonia after 48-hours admission, which occurs when a patient has not received invasive mechanical ventilation and is not in the incubation period of pathogenic infection.

The designation of MDR was defined as the absence of susceptibility to >3 of the following antimicrobials or groups of antimicrobials: ampicillin/sulbactam, aztreonam, ceftazidime, ciprofloxacin, gentamicin, imipenem, piperacillin, trimethoprim/sulfamethoxazole, carbapenems, and amikacin.[16,17] Bacterial isolation and antimicrobial susceptibility testing were performed in accordance with the methodology of the Clinical and Laboratory Standards Institute.[18]

Diagnosis of HAP caused by MDR-AB was assessed according to the criteria of the Centers for Disease Control (CDC).[19] Tracheal aspirate and sputum specimens were sent for bacterial culture only when their Gram's stains showed at least 25 neutrophils and less than 10 epithelial cells per low-power field. Growth was assessed using the semi-quantitative method. The etiologic pathogen was determined if the tracheal aspirate or sputum culture had at least a moderate growth.

Clinical Data

The general and hospital information at admission were noted including age, gender, history of diseases, time and place of infection, venous cannula, mechanical ventilation, acute physiology and chronic health evaluation II (APACHE II) and use of drugs. The APACHE II and sequential organ failure assessment (SOFA) scores were recorded before medication and after drug withdrawal.

Statistical Analysis

All statistical analyses were performed using SAS 9.4 (IBM Corp.). Continuous data were presented as the mean ± standard deviation (SD) or [M(Q_{25}, Q_{75})] and analyzed by *t*-test or Mann–Whitney *U*-test. Categorical data were presented as frequency (n) and percentage (%) and analyzed using Chi-square (χ^2) test. Univariate and multivariate logistic analyses were used to explore the risk factors of hospital deaths before medication and after drug withdrawal. The receiver operating characteristic (ROC) curve and area under curve (AUC) were utilized to assess the predictive effectiveness of with or without the adjustment. P <0.05 was considered as statistical differences.

Results

The Characteristics of HAP Patients Caused by MDR-AB Infection at Admission

Of the total 1,475 cases, 634 and 841 were collected from the China-Japan Friendship Hospital and Beijing Chao-Yang Hospital, respectively. After excluding 360 of non-ICU and 123 emergency patients, 992 received the drug treatments. Then exclusion of the colonization (n=252), experiential

therapy (n=351), antibiotic use <3 days (n=12), age <18 years (n=1) and HAP caused by other bacterial infections (n=10), 366 subjects were finally enrolled in this study. The flow chart of the case screening is shown in Figure 1.

The baseline data of 366 patients with a mean age of 67.70±17.23 years were assessed including 243 (66.39%) males and 123 (33.61%) females. Among these cases, 142 (38.80%) occurred as hospital deaths. There were statistical differences in the age (t=−4.20, P <0.001), autoimmune disease (χ^2=11.843, P <0.001), venous cannula (χ^2=25.392, P <0.001), transfer of patients from other hospitals (χ^2=7.256, P =0.007) and APACHE II scores (t=−5.25, P <0.001) between the hospital deaths and non-hospital deaths groups. The characteristics of HAP patients caused by MDR-AB infection at admission is listed in Table 1.

The Characteristics of Patients Before Medication and After Drug Withdrawal

In this study, the APACHE II and SOFA scores were assessed as the differences between the two groups before medication and after drug withdrawal (Table 2). We found the significant differences in APACHE II (15.48 vs 31.13, t=−8.63, P <0.001) and SOFA (4 vs 7, Z=7.458, P <0.001) scores before medication between the two groups. After drug withdrawal, the differences were also shown in APACHE II (13.51 vs 24.39, t=13.62, P <0.001) and SOFA (2 vs 8, Z=10.986, P <0.001) scores.

Univariate and Multivariable Logistic Analyses for Hospital Deaths Among HAP Patients Caused by MDR-AB Before Medication and After Drug Withdrawal

The univariate and multivariable logistic analyses for hospital deaths before medication and after drug withdrawal are shown in Table 3. Before medication, there were differences in APACHE II (OR: 1.179, 95% CI: 1.129–1.231) and SOFA (OR: 1.268, 95% CI: 1.183–-1.359) scores for hospital deaths, with all P <0.001. The results of the multivariable logistic analysis (adjusting for age, autoimmune disease, venous cannula, transfer of patients from other hospitals and APACHE II score at admission) showed that the risk of hospital deaths was increased by 0.158 and 0.250 for every 1 point increase in the APACHE II and SOFA scores, respectively. After drug withdrawal, APACHE II (OR: 1.225, 95% CI: 1.172–1.280) and SOFA (OR: 1.376, 95% CI: 1.283–1.475) scores were associated with the hospital deaths among HAP cases caused by MDR-AB infection. The further analysis (adjusting for age, autoimmune disease, venous cannula, transfer of patients from other hospitals, APACHE II score at admission) found that a 0.219- and 0.398-fold increase in the risk of hospital deaths with per 1 point increase in APACHE II and SOFA scores, respectively.

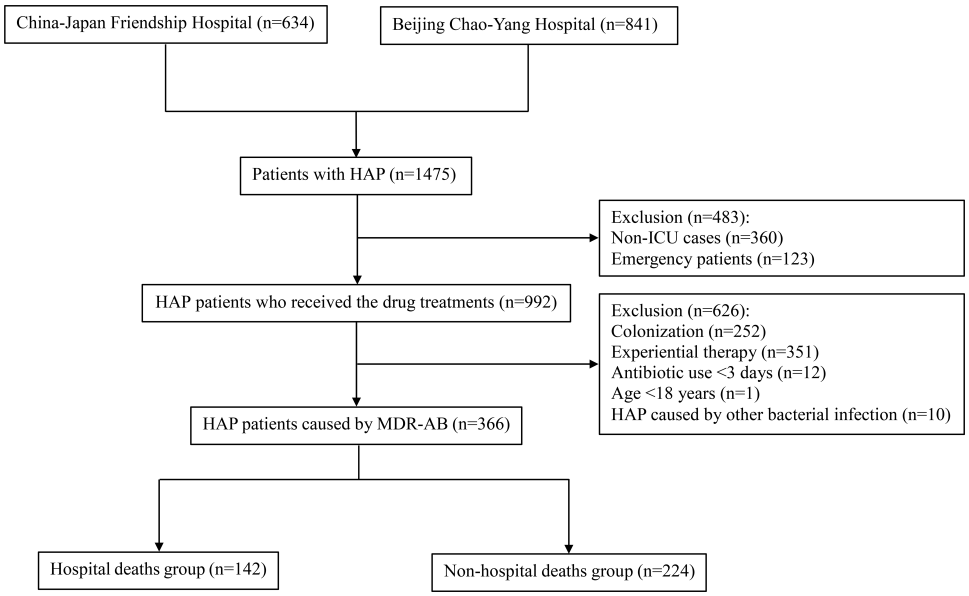

Figure 1 The flow chart of the case screening.

Table 1 The Characteristics of HAP Patients Caused by MDR-AB at Admission

Variables	Total	Hospital Deaths		Statistics	*P*
		No (n=224)	Yes (n=142)		
Age, years, $\bar{x} \pm S$	67.70±17.23	64.76±17.84	72.35±15.17	t=−4.20	<0.001
Gender, n (%)				χ^2=0.268	0.605
Male	243 (66.39)	151 (67.41)	92 (64.79)		
Female	123 (33.61)	73 (32.59)	50 (35.21)		
Diabetes, n (%)				χ^2=0.041	0.840
No	203 (65.70)	124 (65.26)	79 (66.39)		
Yes	106 (34.30)	66 (34.74)	40 (33.61)		
Autoimmune disease, n (%)				χ^2=11.843	<0.001
No	325 (89.29)	209 (93.72)	116 (82.27)		
Yes	39 (10.71)	14 (6.28)	25 (17.73)		
Medical history, n (%)					
Pulmonary diseases	100 (42.71)	57 (40.71)	43 (45.74)	χ^2=0.582	0.446
Tumors	48 (24.87)	26 (21.67)	22 (30.14)	χ^2=1.743	0.187
Liver diseases	13 (7.39)	8 (7.34)	5 (7.46)	–	1.000
Cardiac diseases	109 (49.10)	61 (45.52)	48 (54.55)	χ^2=1.730	0.188
Nervous system diseases	144 (58.06)	88 (57.14)	56 (59.57)	χ^2=0.142	0.707
Renal diseases	34 (16.83)	19 (15.08)	15 (19.74)	χ^2=0.735	0.391
Time of infection, weeks, n (%)				χ^2=2.623	0.269
≤1	201 (55.07)	125 (56.05)	76 (53.52)		
1< time ≤2	75 (20.55)	40 (17.94)	35 (24.65)		
>2	89 (24.38)	58 (26.01)	31 (21.83)		
Venous cannula, n (%)				χ^2=25.392	<0.001
No	120 (33.33)	95 (43.38)	25 (17.73)		
Yes	240 (66.67)	124 (56.62)	116 (82.27)		
Mechanical ventilation, n (%)				χ^2=3.201	0.074
No	36 (9.84)	27 (12.05)	9 (6.34)		
Yes	330 (90.16)	197 (87.95)	133 (93.66)		
Transfer of patients from other hospitals, n (%)				χ^2=7.256	0.007
No	205 (50.61)	113 (50.45)	92 (64.79)		
Yes	161 (43.99)	111(49.55)	50 (35.21)		
Place of infection, n (%)				–	0.060
ICU	356 (97.80)	220 (99.10)	136 (95.77)		
Non-ICU	8 (2.20)	2 (0.90)	6 (4.23)		
APACHE II score, $\bar{x} \pm S$	19.31±6.06	18.03±5.55	21.32±6.29	t=−5.25	<0.001
Type of antibiotic used, n (%)				Z=0.965	0.335
≤2	56 (15.30)	38 (16.96)	18 (12.68)		
3	128 (34.97)	78 (34.82)	50 (35.21)		
4	182 (49.73)	108 (48.21)	74 (52.11)		
Antifungal agents, n (%)				χ^2=1.609	0.205
No	149 (40.71)	97 (43.30)	52 (36.62)		
Yes	217 (59.29)	127 (56.70)	90 (63.38)		
Tigecycline, n (%)				χ^2=0.867	0.352
No	158 (43.17)	101 (45.09)	57 (40.14)		
Yes	208 (56.83)	123 (54.91)	85 (59.86)		

Abbreviations: HAP, hospital-acquired pneumonia; MDR-AB, multidrug-resistant *Acinetobacter baumannii*; ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation.

Table 2 The Characteristics of Patients Before Medication and After Drug Withdrawal

Variables	Total	Hospital Deaths		Statistics	P
		No (n=224)	Yes (n=142)		
Before medication					
APACHE II score, $\bar{x} \pm S$	17.67±6.40	15.48±5.18	21.13±6.63	t=−8.63	<0.001
SOFA score, M(Q_1, Q_3)	5 (3, 7)	4 (2, 6)	7 (4, 10)	Z=7.458	<0.001
After drug withdrawal					
APACHE II score, $\bar{x} \pm S$	17.73±9.00	13.51±5.77	24.39±9.19	t=13.62	<0.001
SOFA score, M(Q_1, Q_3)	4 (2, 8)	2 (1, 5)	8 (5, 13)	Z=10.986	<0.001

Abbreviations: APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Table 3 Univariate and Multivariable Logistic Analyses for Hospital Deaths Among HAP Patients Caused by MDR-AB Before Medication and After Drug Withdrawal

Variables	Univariate		Multivariable	
	OR (95% CI)	P	OR (95% CI)*	P
Before medication				
APACHE II score	1.179 (1.129–1.231)	<0.001	1.158 (1.097–1.223)	<0.001
SOFA score	1.268 (1.183–1.359)	<0.001	1.250 (1.150–1.359)	<0.001
After drug withdrawal				
APACHE II score	1.225 (1.172–1.280)	<0.001	1.219 (1.161–1.281)	<0.001
SOFA score	1.376 (1.283–1.475)	<0.001	1.398 (1.286–1.518)	<0.001

Notes: *Adjusting the age, autoimmune disease, venous cannula, transfer of patients from other hospitals and APACHE II score at admission.
Abbreviations: HAP, hospital-acquired pneumonia; MDR-AB, multidrug-resistant *Acinetobacter baumannii*; OR, odds ratio; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Prediction for the Risk of Hospital Deaths Before Medication and After Drug Withdrawal

The comparison of different scores with or without the adjustment for predicting the hospital deaths are displayed in Tables 4 and 5.

Before Medication

The predictive power of APACHE II and SOFA scores in the risk of hospital deaths were inferior to adjusted APACHE II (0.750 vs 0.808, P =0.003) and adjusted SOFA (0.731 vs 0.803, P =0.004) scores, respectively (Table 4). Then no differences were discovered in predicting the hospital deaths between adjusted APACHE II and adjusted SOFA scores (0.808 vs 0.803, P =0.614) (Table 5 and Figure 2A).

After Drug Withdrawal

In Table 4, the AUC of APACHE II score was similar with adjusted APACHE II (0.854 vs 0.876, P =0.088).

Table 4 Comparison of the AUC of the Scores with or Without the Adjustment of Predicting the Risk of Hospital Deaths

Variables	Without the Adjustment		Adjustment*		Z	P
	AUC (95% CI)	S.E	AUC (95% CI)	S.E		
Before medication						
APACHE II score	0.750 (0.702–0.794)	0.026	0.808 (0.763–0.848)	0.023	3.001	0.003
SOFA score	0.731 (0.682–0.776)	0.027	0.803 (0.757–0.843)	0.024	2.872	0.004
After drug withdrawal						
APACHE II score	0.854 (0.814–0.889)	0.020	0.876 (0.837–0.908)	0.018	1.709	0.088
SOFA score	0.840 (0.800–0.878)	0.022	0.878 (0.839–0.910)	0.019	2.443	0.015

Notes: *Adjusting for age, autoimmune disease, venous cannula, transfer of patients from other hospitals, and APACHE II score at admission.
Abbreviations: AUC, area under curve; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Table 5 Comparison of the Adjusted Scores for Predicting the Risk of Hospital Deaths Among HAP Patients Caused by MDR-AB

Variables	AUC (95% CI)	S.E	Sensitivity (95% CI)	Specificity (95% CI)	Cut-off	Z	P
Before medication							
Adjusted APACHE II score	0.808 (0.763–0.848)	0.023	73.53 (65.3–80.7)	74.31(68.0–80.0)	0.383		
Adjusted SOFA score	0.803 (0.757–0.843)	0.024	77.78 (69.8–84.5)	67.89 (61.3–74.0)	0.324	0.504	0.614
After drug withdrawal							
Adjusted APACHE II score	0.876 (0.837–0.908)	0.018	77.94 (70.0–84.6)	81.65 (75.9–86.6)	0.386		
Adjusted SOFA score	0.878 (0.839–0.910)	0.019	70.37 (61.9–77.9)	89.86 (85.1–93.5)	0.455	0.267	0.789

Abbreviations: HAP, hospital-acquired pneumonia; MDR-AB, multidrug-resistant *Acinetobacter baumannii*; AUC, area under curve; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Compared with adjusted SOFA score, the predictive effectiveness of SOFA score was lower (0.840 vs 0.878, P =0.015). We further assessed the adjusted scores for the risk of hospital deaths, and found no statistical differences between the two adjusted scores (0.876 vs 0.878, P =0.789) (Table 5 and Figure 2B).

Discussion

In this study, we analyzed the clinical characteristics of patients with HAP caused by MDR-AB infection, and conducted different models for predicting the risk of hospital deaths, and further compared the predictive effectiveness of these models among these cases. Our findings showed that the AUC of adjusted APACHE II and adjusted SOFA scores had no statistical differences before medication or after drug withdrawal, indicating the predictive values of the scores were similar, which may be effective tools for predicting the risk of hospital deaths, and then may be available for clinicians to timely implement intervention and treatment.

Nosocomial infections-associated MDR-AB have been a global health care issue, mainly occurring in low- and middle-income countries.[20–22] Previous studies reported that the incidence of MDR-AB infection were approximately 2- to 5-fold higher in ICU than other wards,[23] which may be due to long-term bed rest and weak resistance of ICU patients, invasive diagnostic, treatment procedures (endotracheal intubation, ventilator, etc.) and extensive use of antimicrobial agents.[24] Furthermore, the antimicrobial resistance of AB can lead to a high rate of treatment failure.[23] Although the resistance is closely related to deaths, numerous risk factors also contribute to

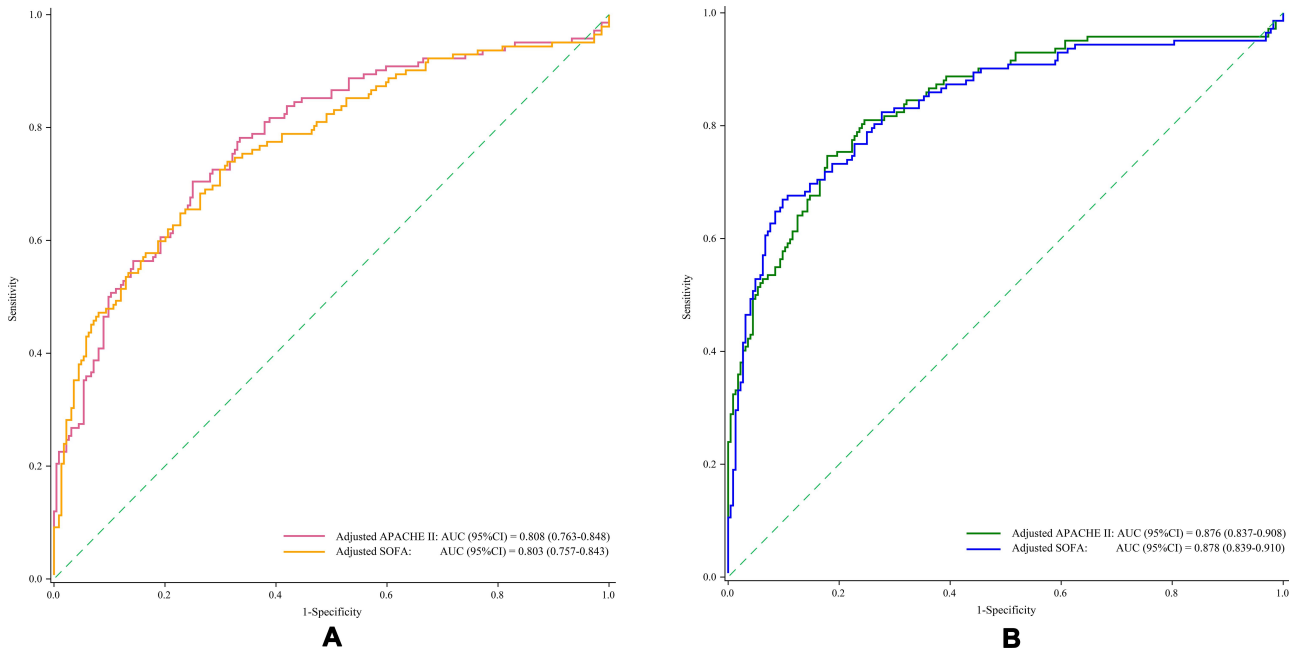

Figure 2 ROC curves of different scores for predicting the risk of hospital deaths before medication (**A**) and after drug withdrawal (**B**) among HAP patients caused by MDR-AB infection.

increasing the difficulties regarding the choice of antimicrobials used in the treatment of severe infections caused by this microorganism, resulting in a worse prognosis.[25] Therefore, it is necessary to carry out reasonable monitoring and infection control, use functional microbiology labs, as well as rational antibiotics administration, to prevent or contain an explosive growth of microorganisms.[14]

There was 38.80% of hospital mortality among HAP cases caused by MDR-AB infection in the current study, which was similar to some other studies.[26–28] Wisplinghoff et al[28] mentioned that the mortality rate in patients with MDR-AB infection was twice that in controls.[28] MDR-AB infection is a marker for increased mortality risk in patients with severe underlying illness but not an independent predictor of mortality.[29] We assessed the roles of APACHE II and SOFA scores before medication and after drug withdrawal in the hospital deaths among HAP cases caused by MDR-AB. Our results showed that all the two scores were independent risk factors for nosocomial deaths before medication or after drug withdrawal. When adjusting the age, autoimmune disease, venous cannula, transfer of patients from other hospitals and APACHE II score at admission, the risk of hospital deaths before medication was increased by 0.158 and 0.250 for every 1-point increase, and a 0.219- and 0.398-fold increase in the risk of hospital deaths after drug withdrawal per 1-point increase in APACHE II and SOFA scores, respectively. An early study proposed by Joung et al[30] supported our findings. Then we further investigated the predictive power of the two scores in the risk of hospital deaths. The results showed that the predictive effectiveness of adjusted APACHE II and adjusted SOFA scores were similar before medication or after drug withdrawal. It was indicated that these adjusted scores were useful tools for death risk prediction in patients with HAP caused by MDR-AB, which may be considered for clinical evaluation.

The strengths of our study were that various predictive models were conducted to assess the mortality risk in hospital before medication and after drug withdrawal. We found that the adjusted APACHE II and adjusted SOFA scores performed well in predictive effectiveness. In addition, there were several limitations that should invoke caution for the interpretation of our findings. First, only 366 patients were enrolled in this study overall which may reduce the statistical power. Second, some confounding variables may be missed on the basis of a retrospective investigation and limited clinical data. Further studies with better designs are needed to get more comprehensive views for predicting the risk of hospital deaths of HAP caused by MDR-AB infection.

Conclusion

We carried out various models for predicting the risk of hospital deaths in HAP patients caused by MDR-AB. Our findings showed that APACHE II and SOFA scores were independent risk factors for nosocomial deaths before medication or after drug withdrawal. Additionally, the predictive effectiveness of adjusted APACHE II and adjusted SOFA scores were similar before medication or after drug withdrawal, indicating that these scores may be available tools for clinical assessment.

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Disclosure

The authors report no conflicts of interest in this work.

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