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Original Article

Epidemiological characteristics of ventilator-associated pneumonia in neurosurgery: A 10-year surveillance study in a Chinese tertiary hospital

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP) is a significant and common health concern. The epidemiological landscape of VAP is poorly understood in neurosurgery patients. This study aimed to explore the epidemiology of VAP in this population and devise targeted surveillance, treatment, and control efforts.

Methods: A 10-year retrospective study spanning 2011 to 2020 was performed in a large Chinese tertiary hospital. Surveillance data was collected from neurosurgical patients and analyzed to map the demographic and clinical characteristics of VAP and describe the distribution and antimicrobial resistance profile of leading pathogens. Risk factors associated with the presence of VAP were explored using boosted regression tree (BRT) models.

Results: Three hundred ten VAP patients were identified. The 10-year incidence of VAP was 16.21 per 1000 ventilation days. All-cause mortality was 6.1%. The prevalence of gram-negative bacteria, fungi, and gram-positive bacteria among the 357 organisms isolated from VAP patients was 86.0%, 7.6%, and 6.4%, respectively; most were multidrug-resistant organisms. *Acinetobacter baumannii, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were the most common pathogens. The prevalence of carbapenem-resistant *A. baumannii, P. aeruginosa,* and *K. pneumoniae* was high and increased over time in the study period. The BRT models revealed that VAP was associated with number of days of ventilator use (relative contribution, 47.84 ± 7.25), Glasgow Coma Scale score (relative contribution, 24.72 ± 5.67), and tracheotomy (relative contribution, 21.50 ± 2.69).

Conclusions: Our findings provide a better understanding of the epidemiology of VAP and its risk factors in neurosurgery patients.

1. Introduction

Neurosurgical patients are at higher risk of developing healthcare-associated infections (HAIs) because of their underlying illnesses such as brain injury and the associated nervous system interventions that they have undergone; moreover, many require clinical monitoring using invasive devices [1]. Ventilator-associated pneumonia (VAP), which is defined as pneumonia in a patient who has been mechanically ventilated for at

Abbreviation: BMI, body mass index; CR, carbapenem resistant; CRPA, carbapenem resistant *Pseudomonas aeruginosa*; CRKP, carbapenem resistant *Klebsiella pneumoniae*; CRAB, carbapenem resistant *Acinetobacter baumannii*; GCS, Glasgow Coma Scale; HAIs, healthcare-associated infections; ICU, intensive care unit; MDRPA, multiple drug-resistant *Pseudomonas aeruginosa*; MDRKP, multiple drug-resistant *Klebsiella pneumoniae*; MDRAB, multiple drug-resistant *Acinetobacter baumannii*; PSM, Propensity score matching; RT-NISS, real-time nosocomial infection surveillance system; VAP, ventilator-associated pneumonia.

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least 48 hours, has increasingly became a frequent and significant HAI in the neurosurgery intensive care unit (ICU) [2,3]. VAP is associated with a longer hospital stay, worse functional outcome, increased mortality, higher cost of health care, increased use of medical resources, and increased risk of readmission [4-6].

There is extensive literature and guidelines on preventing VAP and these measures have gradually decreased the incidence of VAP over the past decade [7,8]. However, the incidence of VAP remains high, so does the rate of mortality in patients with VAP. Moreover, these rates differ according to region and socioeconomic status [3,9]. Generally, the incidence of VAP is much higher in developing countries than developed ones [10]. Furthermore, neurosurgery ICU patients may have distinct characteristics that predispose them to infection [11].

In China, the epidemiology of VAP is not well-studied; however, a recent study conducted in 14 general ICUs reported a VAP incidence of 4.5 cases per 1000 ventilation days and a 28-day mortality rate of 45% [3]. To effectively target and mitigate VAP, it is imperative to gain a profound understanding of its epidemiological characteristics and risk factors. Knowing the distribution and antimicrobial resistance patterns of the primary VAP pathogens is also important. Therefore, this study aimed to explore the epidemiology of VAP across a 10-year period in neurosurgery patients in a tertiary-care hospital. Our goal was to develop focused surveillance, treatment, and control strategies for the future.

2. Methods

2.1. Setting and study design

This retrospective study was carried out in a tertiary hospital with approximately 3,800 beds in Beijing, China. The hospital employs a hospital-wide real-time nosocomial infection surveillance system (RT-NISS) [12]. The neurosurgery department serves as a pivotal specialty within this hospital, encompassing 172 beds across four general wards and one ICU. Annually, it averages 3,970 hospitalizations, with approximately 1,890 patients requiring mechanical ventilation in the neurosurgery department. The neurosurgery department primarily treats patients with intracerebral hemorrhage, brain tumors, and other neurosurgical diseases. The yearly total number of hospitalized neurosurgical patients and their clinical data were obtained from January 1, 2011 to December 31, 2020. With the help of the RT-NISS, neurosurgical patients were grouped according to VAP diagnosis (VAP and no VAP groups). To protect patient privacy, the study excluded sensitive patient identifiers (e.g., name and identification numbers). Hospital ethics committee approval (S2019-142-02) was obtained. The flowchart was shown in Fig. 1.

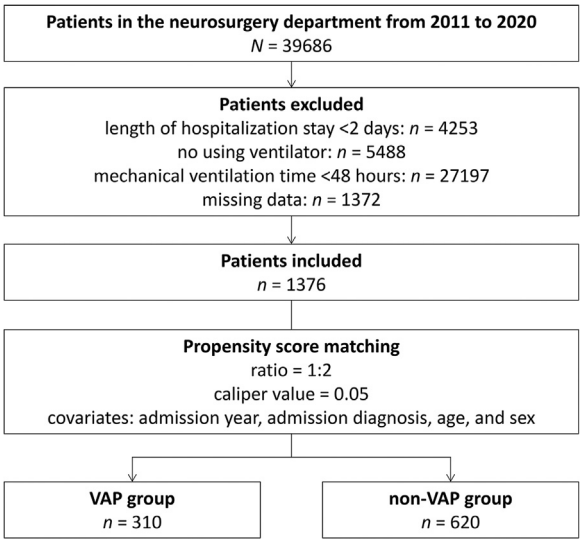

Fig. 1. The flowchat of study.
VAP: ventilator-associated pneumonia.

2.2. Data collection

The following data were collected: (1) demographic characteristics including age, sex, body mass index, smoking habit, alcohol habit, admission diagnosis, Glasgow Coma Scale (GCS) score [13,14], and pre-existing comorbidities; (2) VAP pathogens (duplicate isolates from the same patient were excluded) and their antimicrobial susceptibilities; and (3) clinical characteristics including tracheotomy, days of ventilator use, length of hospital stay, and clinical outcome (discharge or death).

2.3. Definitions

VAP was defined as the presence of new or/and progressive pulmonary infiltrates on chest radiography in a patient ventilated for more than 48 hours plus at least two of the following clinical findings [2]: body temperature >38°C; white blood cell count $>12\times10^9$/L or $<4\times10^9$/L; and (3) presence of purulent tracheal aspirate. Patients in the no VAP group were selected from neurosurgical patients who had been placed on mechanical ventilation for at least 48 hours but did not develop VAP. Propensity score matching (PSM) was performed to reduce confounding bias by balancing characteristics and risk factors between groups in a 1:2 ratio (VAP: no VAP) using the logit of the propensity score from the logistic regression model, and the caliper value was 0.05. Covariates included in the model were admission year, admission diagnosis, age, and sex. GCS score was determined based on clinical data available from the first 24 hours of admission. Patients were then divided into three categories based on GCS score: one, GCS score 3 to 8; two, GCS score 9 to 12; and three, GCS score 13 to 15 [13,14]. A lower GCS score/category indicates a more severe coma

and worse neurological condition. The number of days of ventilator use in the VAP group was calculated as the number of days of ventilator use before the occurrence of VAP; the same number in the no VAP group was calculated as the total number of days of mechanical ventilation. Bacterial isolates resistant to at least three different antimicrobial drug classes were considered multiple drug-resistant (MDR); those resistant to imipenem or meropenem or ertapenem were classified as carbapenem resistant (CR).

2.4. Microbiology and antimicrobial susceptibility testing

Microbiological samples in VAP patients were collected from tracheal aspirates, sputum, or bronchial aspiration. Pathogens were identified according to National Clinical Inspection Operation specifications and cultured using the Vitek 2 automated system (bioMérieux, Marcy-l'Étoile, France). Antibiotic susceptibility testing was performed using the Vitek 2 system or the Kirby-Bauer Disk Diffusion method (Oxford, UK) following the 2010 and 2018 Clinical and Laboratory Standards Institute guidelines [15].

2.5. Statistical analyses

Categorical variables are expressed as numbers with percentage and were compared using the chi-square test or Fisher's exact test. Continuous variables are expressed as means with standard deviation (SD) or median with interquartile range (IQR) and were compared using the Student's t test or Mann–Whitney U test. A two-tailed p value <0.05 was considered significant. To explore the risk factors associated with VAP, a case-control design was constructed using VAP group patients as cases and no VAP group patients as controls. Machine learning was used to investigate the risk factors associated with VAP at the individual level with the boosted regression tree (BRT) algorithm, which has been widely used for disease risk assessment [16,17]. In this study, a tree complexity of 5, learning rate of 0.005 and bag fraction of 75% were used to identify the optimal tree for each bootstrap data. The relative contribution of each variable was estimated from the identified trees and served as an indicator of each variable's importance. The variables whose mean of relative contribution in the BRT models more than 5 were considered to be significantly contribute to the occurrence of VAP[16]. To ensure robust inference, cross validation was performed using 240 randomly selected cases (77% of the total number of VAP patients) and 480 controls to train the model; a random selection of 70 cases and 140 controls were used to test the final model. The relative contributions (mean and standard deviation) were reported using 100 replications. The response curves for variables (with a mean relative contribution >5) were mapped with an overlapped of frequency of the variable. Area under the receiver operating characteristic curve was used to evaluate model performance. We also performed a sensitivity analysis using a random selection of 70 cases and 210 controls to test the model. The analysis was performed using R version 4.1.3 with the gbm package. Statistical analyses were performed using SPSS software version 26.0 (IBM, Armonk, NY, USA) and R version 4.1.3 (www.r-project.org).

3. Results

3.1. Demographic and clinical characteristics of patients with VAP

The number of hospitalized neurosurgery patients from 2011 to 2020 was 39686 and 310 developed VAP (Table 1). The 10-year incidence of VAP was 16.21 per 1000 ventilation days (range, 13.57 to 19.79). The annual incidence increased by 14.58% between 2011 and 2015; from 2016 to 2020, the increase was greater (17.77%); this difference was significant ($p = 0.08$). Patient characteristics befofe PSM are shown in Supplementary table 1. After PSM, patient characteristics according to group are shown in Table 2. In the VAP group, 197 patients (63.5%) were male, mean age was 53.8 ± 17.5 years (range, 5–92), and mean body mass index was 24.9 ± 4.0 kg/m^2 (range,

Table 1
The incidence of ventilator-associated pneumonia in neurosurgery patients from 2011 to 2020.

Year	No. of hospitalization *(n)*	No. of ventilator days	No. of patient with VAP *(n)*	Incidence (‰)
2011	4411	1029	16	15.55
2012	4403	2022	30	14.84
2013	3534	2141	31	14.48
2014	3797	2122	31	14.61
2015	3877	2080	29	13.94
2016	4066	1850	33	17.84
2017	4065	2240	44	19.64
2018	4175	2211	30	13.57
2019	4336	1918	36	18.77
2020	3022	1516	30	19.79
Total	39686	19129	310	16.21

No., number; VAP, ventilator-associated pneumonia

Table 2
Patient characteristics according to group.

Characteristics	VAP $n = 310$ (%)	Non - VAP $n = 620$ (%)	p
Age (years)	53.8±17.5	54.4±16.2	0.644[a]
BMI (kg/m^2)	24.9±4.0	24.9±3.4	0.782[a]
Sex			
Male	197(63.5)	383(61.8)	0.599[b]
Female	113(36.5)	237(38.2)	
Comorbidity			
Diabetes			
Yes	34(11.0)	59(9.5)	0.487[b]
No	276(89.0)	561(90.5)	
Hypertension			
Yes	100(32.3)	155(25.0)	0.019[b]
No	210(67.7)	465(75.0)	
Heart disease			
Yes	19(6.1)	29(4.7)	0.346[b]
No	291(93.9)	591(95.3)	
Smoking (current or former)			
Yes	49(15.8)	100(16.1)	0.899[b]
No	261(84.2)	520(83.9)	
Drink (current or former)			
Yes	45(14.5)	78(12.6)	0.411[b]
No	265(85.5)	542(87.4)	
liver abnormality			
Yes	33(10.6)	58(9.4)	0.532[b]
No	277(89.4)	562(90.6)	
kidney abnormality			
Yes	14(4.5)	19(3.1)	0.259[b]
No	296(95.5)	601(96.9)	
Admission diagnosis			0.139[b]
Brain tumor	124(40.0)	274(44.2)	
Intracerebral hemorrhage	105(33.9)	204(32.9)	
Brain injury	31(10.0)	33(5.3)	
Spinal cord disease	20(6.5)	49(7.9)	
Hydrocephalus	7(2.3)	17(2.7)	
Others	23(7.4)	43(6.9)	
GCS score			<0.001[b]
1 (scores:3-8)	150(48.4)	43(6.9)	
2 (scores:9-12)	16(5.2)	37(6.0)	
3 (scores:13-15)	144(46.5)	540(87.1)	
Days of ventilator use	6.4±5.0	2.8±2.7	<0.001[c]
Tracheotomy			
Yes	123(39.7)	39(6.3)	<0.001[b]
No	187(60.3)	581(93.7)	
Length of hospital stay (Median)	24(17,36)	14(9,19)	<0.001[c]
Outcome			0.001[b]
Discharge	291(93.9)	607(97.9)	
Death	19(6.1)	13(2.1)	

VAP, ventilator-associated pneumonia; BMI, body mass index; GCS, Glasgow Coma Scale.
[a] Student's t test.
[b] Chi-square test.
[c] Mann-Whitney U test.

13.5–45.6). The prevalence of smoking and alcohol use, diabetes, heart disease, liver abnormality, and kidney abnormality did not significantly differ between the VAP and no VAP groups. However, the prevalence of hypertension (32.3% vs. 25.0%; $p = 0.019$) and tracheotomy (39.7% vs. 6.3%; $p < 0.001$) was significantly higher in the VAP group. Brain tumor (40.0%, 124 patients), intracerebral hemorrhage (33.9%, 105 patients), and brain injury (10.0%, 31 patients) accounted for 83.9% of the admission diagnoses in the VAP group. VAP onset occurred in the first 2 weeks of mechanical ventilation in 256 patients (82.6%). All-cause mortality was significantly higher in the VAP group (6.1% vs. 2.1%; $p = 0.001$). The median length of hospitalization was significantly higher in the VAP group (24 days [IQR, 17–36] vs. 14 days [IQR, 9–19]; $p < 0.001$).

Table 3
Factors associated with ventilator-associated pneumonia in the boosted regression tree model.

Variables*	Relative contribution (Mean ± SD, %)
Days of ventilator use	47.84 ± 7.25
GCS score	24.72 ± 5.67
Tracheotomy	21.50 ± 2.69
Hypertension	3.98 ± 0.85
Smoking	0.69 ± 0.35
Kidney abnormality	0.65 ± 0.33
Sex	0.61 ± 0.21

GCS: Glasgow Coma Scale. SD: standard deviation.
* The variables whose mean of relative contribution in the BRT models more than 5 were considered to be significantly contribute to the occurrence of VAP.

3.2. Distribution and antimicrobial resistance of causative pathogens

Three hundred fifty-seven isolates were isolated from the 310 patients of the VAP group; multiple isolates were obtained from 131 patients (42.0%). The distribution of the 357 isolates (Fig. 2A) was as follows: gram-negative bacteria, 307 (86.0%); fungi, 27 (7.6%); and gram-positive bacteria, 23 (6.4%). The predominant bacteria was *Acinetobacter baumannii* (26.6%), followed by *Klebsiella pneumoniae* (21.3%), *Pseudomonas aeruginosa* (19.3%), *Stenotrophomonas maltophilia,* and *Staphylococcus aureus* (5.9%). *Candida albicans* (2.8%) and *C. tropicalis* (2.8%) were the most frequent fungal pathogens.

Among the *A. baumannii* isolates, 96.3% were MDR and 86.4% were carbapenem resistant. Among the *K. pneumoniae* isolates, 61.5% were MDR and 27.7% were carbapenem resistant. MDR and carbapenem-resistant strains comprised 36.7% and 20.0% of the *P. aeruginosa* isolates, respectively. Fig. 2B shows the prevalence of MDR and carbapenem resistance among these gram negative organisms over the entire study period as well as changes in isolate distribution from 2011–2015 to 2016–2020. The prevalence of resistance was higher in the second half of the study period, significantly so for MDR *P. aeruginosa* and MDR *K. pneumoniae*.

3.3. Risk factors for VAP

Risk factors for VAP are shown in Table 3. Our BRT model demonstrated that days of ventilator use, tracheotomy, and GCS score were significantly associated with VAP with relative contributions of 47.84 (SD 7.25), 24.72 (SD 5.67), and 21.50 (SD 2.69), respectively. The response curves (Fig. 3A) showed the risk of VAP rapidly increased with days of ventilator use and stayed steady after 4 days of ventilator use. Tracheotomy at the individual level was a risk factor for VAP. Lower GCS score also posed a higher risk for VAP. The average discriminatory ability of the BRT models over 100 resamples was 90.3% (95% confidence interval, 87.9–92.7) for the train dataset (Fig. S1) and 85.8% (95% confidence interval, 82.9–88.7) for the test dataset (Fig. 3B), indicating decent predictive power. The area under the receiver operating characteristic curve for the sensitivity analyisis was 0.868 (95% confidence interval, 84.0–89.7), which indicates good robustness for the model (Fig. S2). The sensitivity was 80.0% and the specificity was 85.5% for the all dataset, which indicating a good for the predictive power for the final BRT model.

4. Discussion

VAP, which is associated with significant morbidity and mortality, has emerged as a prevalent complication among patients receiving mechanical ventilation, particularly those critically ill in ICUs. It is critical to understand the clinical and microbiological characteristics of VAP as well as its associated risk factors in order to prevent it [18,19]. Therefore, our study attempted to demonstrate an updated epidemiological picture of mechanically ventilated neurosurgery patients and explore the main risk factors for VAP. Our aim was to help prioritize strategies for VAP prevention.

Among 310 neurosurgery patients who developed VAP, the estimated overall incidence of VAP from 2011 to 2020 was 16.21 per 1000 ventilation days. This incidence increased over the study period and all-cause mortality was 6.1%. The incidence of VAP in our study was much higher than that reported by an ICU study conducted in China (4.5%) [3] and a study of neurological patients in acute care hospitals in the United States (2.1%) [20]. However, it was lower than that reported by the EU-VAP/CAP study (18.3‰) and a study from lower–middle-income countries (18.5%) [21,22]. Differences in VAP incidence between various regions and hospital settings may be related to interstudy differences in definitions of VAP, surveillance methods, study populations, and socioeconomic status [3,10]. Our study investigated neurosurgery patients in a large tertiary hospital in China. Most patients had complicated conditions and were critically ill, so were vulnerable to developing VAP [23]; thus, the incidence of VAP was relatively high. While compared with another study that reported a mortality rate of 10% [24], we reported a lower all-cause mortality rate, possibly because our study included all neurosurgery patients, not just ones who were admitted to the neurosurgery ICU from beginning to end.

The mechanical ventilation utilization ratio and days of hospitalization have a strong relationship with VAP development; namely, higher utilization ratio and longer hospitalization stay increase the risk of VAP [25,26]. We also found that VAP onset occurred in the first 2 weeks of ventilation in 82.6% of patients and that hospitalization was longer in patients who developed VAP. These findings are consistent with those in other reports [27].

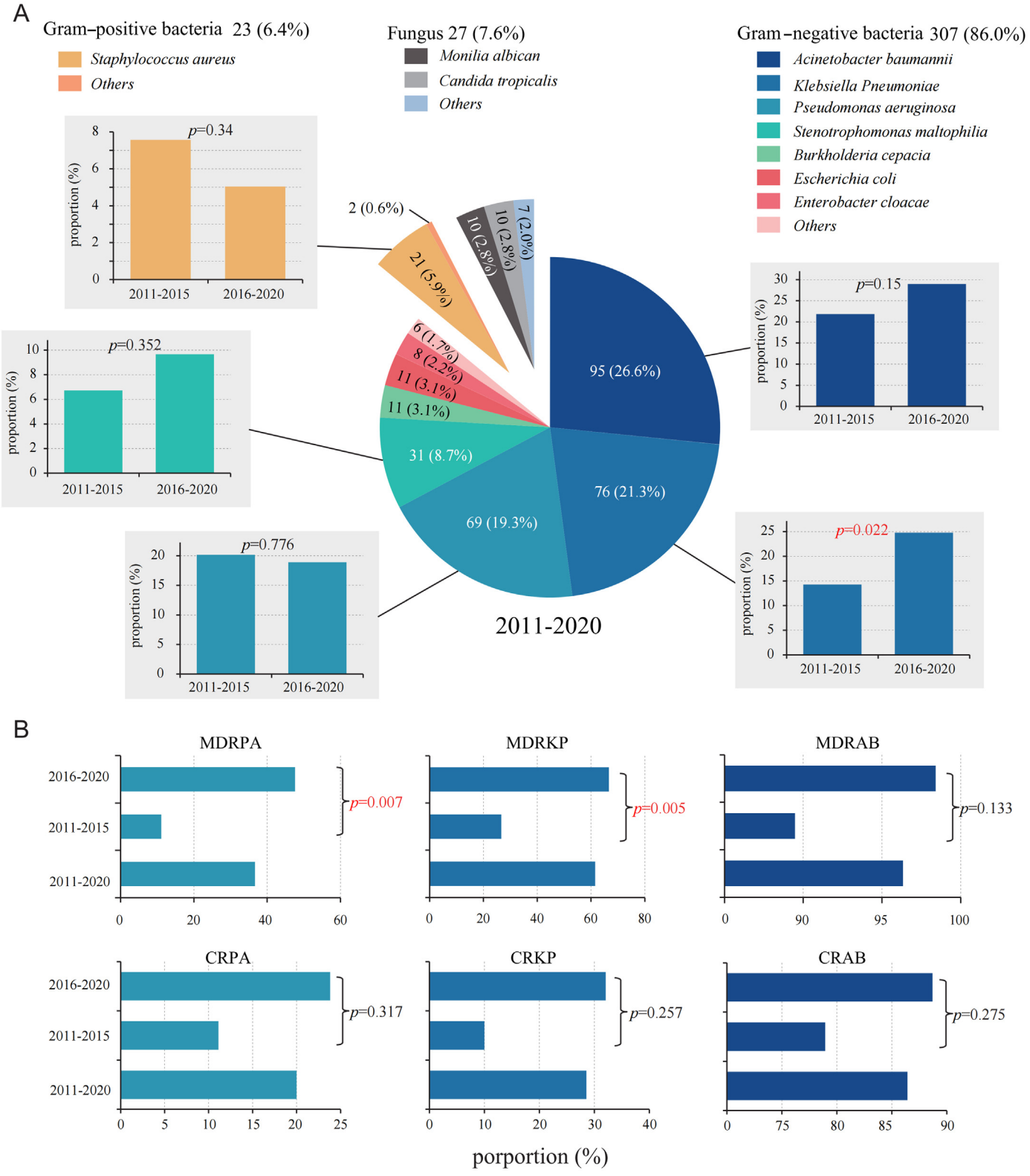

Fig. 2. (A) Distribution of causative pathogens. (B) Distribution of major multiple drug-resistant organisms.
MDRPA: multiple drug-resistant *Pseudomonas aeruginosa*; MDRKP: multiple drug-resistant *Klebsiella pneumoniae*; MDRAB: multiple drug-resistant *Acinetobacter baumannii*; CRPA: carbapenem resistant *Pseudomonas aeruginosa*; CRKP: carbapenem resistant *Klebsiella pneumoniae*; CRAB: carbapenem resistant *Acinetobacter baumannii*.

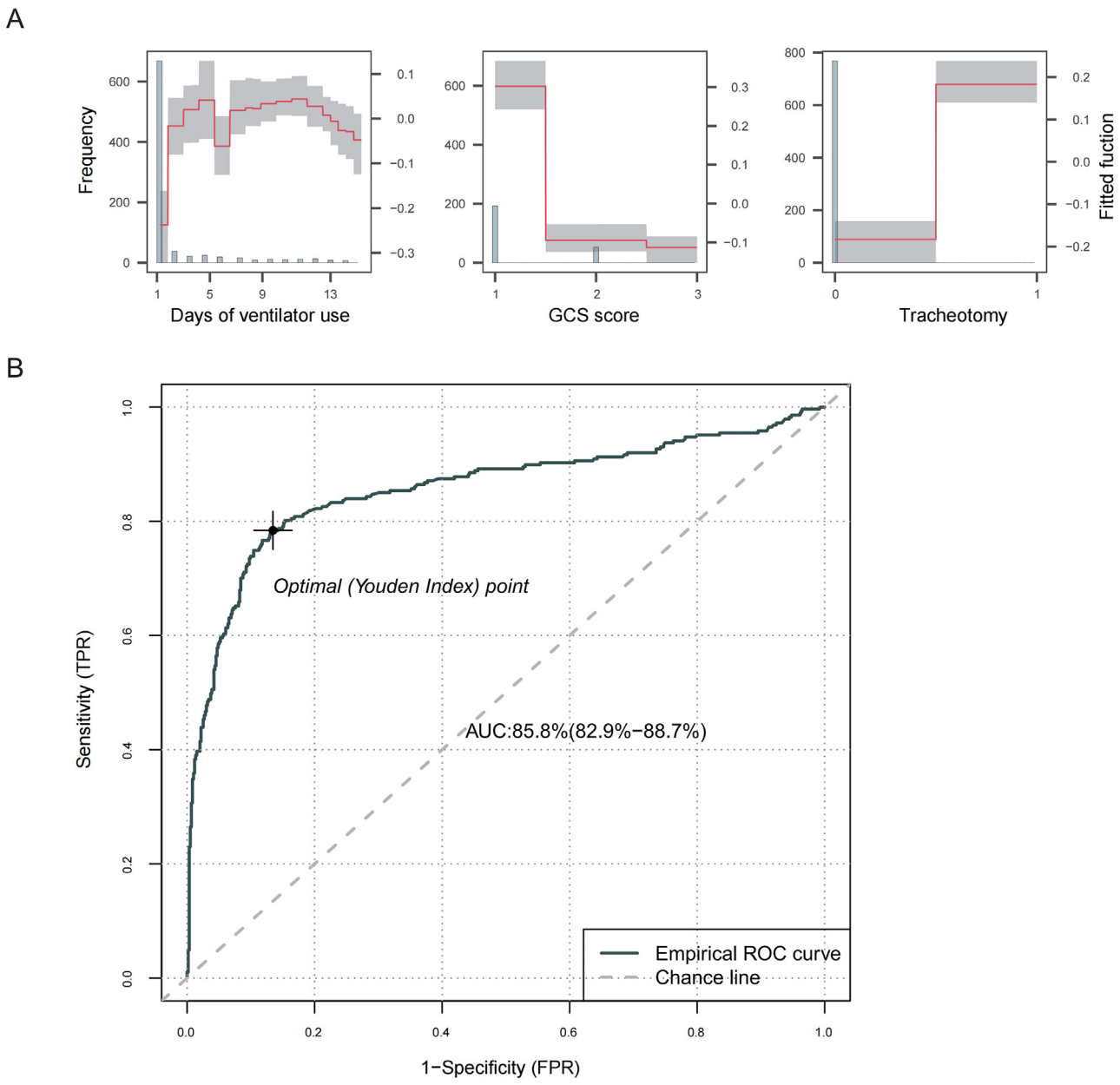

Fig. 3. Risk factor analysis results from the boosted regression tree models. (A) Response curves of factors associated with the presence of ventilator-associated pneumonia based on the boosted regression model. The red curves and gray bands show the average and range, respectively. Frequency distributions of the variables are shown by histograms based on all 100 resamples. (B) The receiver operating characteristic curve and area under the curve values of the models after averaging 100 resamples.

Understanding the distribution of VAP pathogens can facilitate empiric antimicrobial selection . In China, gram-negative bacteria such as *A. baumannii, K. pneumoniae*, and *P. aeruginosa* cause most cases of VAP and other HAIs. The observed increase in MDR gram-negative bacteria (especially carbapenem-resistant ones) in China poses a significant threat to public health and has been caused by irrational use of antimicrobials in clinical treatment [28]. Similar to other studies [29], we also found that *A. baumannii, K. pneumoniae,* and *P. aeruginosa* were the most frequent causative pathogens of VAP, and most were MDR. Moreover, we observed a high prevalence of carbapenem-resistant *A. baumannii, K. pneumoniae,* and *P. aeruginosa*, which appears to also be increasing over time. However, a study conducted in the United States reported that *S. aureus* was the dominant pathogen (33%); this organism only accounted for 5.9% of VAP cases in our study. Nonetheless, our results provide a local distribution and antibiotic resistance profile of pathogens causing VAP and suggest that MDR organisms should be strongly considered when selecting empiric antimicrobials.

In our study, days of ventilator use, tracheotomy, and GSC score were risk factors associated with VAP in neurosurgery inpatients. In addition, the longer the ventilator was used, the higher the risk of VAP. Previous studies

have shown that the incidence of VAP is related to the number of days of ventilator use [30,31]. The shell and pipeline of the ventilator need to be regularly and properly disinfected with sterile water, and condensed water should be disposed of promptly. Doctors must understand the indications for weaning and extubation and withdraw the ventilator as soon as appropriate to reduce the time patients are on the ventilator, which reduces the risk of VAP. Our results indicated that tracheotomy was an independent risk factor for VAP. This is consistent with reporting from previous studies [32,33]. Tracheotomy produces irritation of the respiratory mucosa, and consequently an increase in mucus secretion [34]. In addition, tracheotomy can directly damage the patient's throat, allowing the lower airway to communicate directly with the outside world. This provides a pathway for pathogenic bacteria to enter the respiratory tract. The impaired defense barrier of the respiratory tract weakens the function of the airway cilia in clearing pathogenic bacteria, inhibits the cough mechanism, and increases the risk of aspiration, which causes an inflammatory response in the respiratory tract [34,35].

The GCS is used to objectively evaluate the severity of brain dysfunction and coma. The lower the GCS score, the more severe the disturbance of consciousness. Our study showed that the lower the GCS score, the higher the risk of VAP, especially in patients with GCS score between 3 and 8, which is consistent with previous reports [33,36]. The patient's level of consciousness greatly influences their ability to swallow, cough, and expectorate, making it particularly challenging for those in a coma. In such patients, the protective reflexes of swallowing and coughing are either weakened or nonexistent, leading to a heightened risk of aspiration. Additionally, the inability to effectively eliminate respiratory system secretions creates favorable conditions for bacterial growth, thus predisposing patients to VAP.

In this study, we attempted to explore the risk factors of VAP using machine learning, which is efficient in dealing with non-linear relationships and interactions between covariates [37]. Receiver operating characteristic analysis showed the average discriminatory ability of the BRT models over 100 resamples was 85.8%, suggesting high performance. The BRT algorithm was derived from an ensemble machine learning method, which has been widely used for explaining and predicting disease risk for avian influenza [38], Middle East respiratory syndrome coronavirus [17], and scrub typhus [39]. Machine learning has been increasingly integrated into clinical practice and applied in pre-clinical data processing, bedside diagnosis assistance, patient stratification, treatment decision making, and early warning as part of primary and secondary prevention. It is also widely used for investigation of risk factors and prognostication [40], including diagnosis and prediction of VAP [41,42].

This study has several limitations. First, it was a single center study, so our results may not be applicable to other regions or hospitals. Second, not all patients without VAP were included in the no VAP group; therefore, bias may have been present. Finally, compared with other studies, other important risk factors such as gene polymorphisms and the use and appropriateness of antimicrobial treatments were not evaluated in our study.

5. Conclusions

Although essential in certain critically ill patients, mechanical ventilation can result in VAP if preventive measures are not employed. By mapping a 10-year epidemiological landscape of VAP in neurosurgery patients in a large Chinese tertiary hospital, we found that an upward trend of VAP incidence was accompanied by an increasing prevalence of carbapenem-resistant organisms, indicating that the burden of VAP in neurosurgical patients needs to be highlighted for its significant impact in terms of mortality, excess costs, and other complications. Moreover, we also identified that the number of days of ventilator use, GCS score, and tracheotomy play an important role in VAP. We believe that our findings will fill crucial gaps in the epidemiology of VAP in neurosurgery patients and provide valuable information regarding VAP control and prevention.

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Author contributions

M-MD, H-WY, and Y-XL conceived, designed and supervised the study. Z-HY, X-LL, C-LL, YT, J-JS, Z-QY, Y-LB, B-WL, and L-QF collected, cleaned, and analyzed the data. Z-HY, X-LL, C-LL, YT, M-MD, H-WY, and Y-XL wrote the draft of the manuscript and interpreted the findings. All authors read and approved the final report.

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Declaration of competing interest

All authors declare that they have no conflict of interest, and the study has not been published previously or submitted for publication elsewhere, either completely or in part, or in another form or language. The publication

of this study is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. We hope that you will find our paper acceptable.

Data available statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics statement

Not applicable.

Informed consent

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.imj.2024.100128.

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