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Risk factors and cerebrospinal fluid indexes analysis of intracranial infection by Acinetobacter baumannii after neurosurgery

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ABSTRACT

Background: Intracranial infection by Acinetobacter baumannii (*A. baumannii*) after neurosurgery has always been a difficult problem for neurosurgeons. This study analyzed risk factors that discriminated *A. baumannii* from other bacteria causing intracranial infection after neurosurgery. It also examined the differences in the cerebrospinal fluid (CSF) indexes to explore their value in the early diagnosis of intracranial infection by *A. baumannii.*

Methods: We retrospectively reviewed ten years (January 2011 to May 2021) of postoperative central nervous system (CNS) infections in the First Hospital of China Medical University. According to the pathogen, CNS infections were divided into *A. baumannii* group and other species of bacteria group. We collected clinical and laboratory information of patients, and statistical analysis was performed with SPSS 26.0. Risk factors were screened by univariate analysis, and independent risk factors were screened by multiple logistic regression analysis. Finally, CSF-Pro, CSF-Glu, CSF-Cl, CSF-monocytes (%), CSF-multinucleated cells (%) levels, and CSF multinucleated cells%/monocytes% in the different groups were analyzed.

Results: A total of 155 patients were included, 62 cases (40%) of intracranial infection by *A. baumannii* and 93 cases (60%) by other species of bacteria. The analysis showed that indwelling nasogastric tubes ($P < 0.001$, OR = 4.231), indwelling peripherally inserted central catheters (PICCs) ($P = 0.041$, OR = 2.765), and CSF drainage obstruction ($P = 0.003$, OR = 3.765) were independent risk factors for intracranial infection by *A. baumannii* after neurosurgery. Indwelling ventriculoperitoneal shunt (VPS) was a protective factor ($P = 0.033$, OR = 0.22). In addition, compared with other bacterial groups, the *A. baumannii* group had higher CSF-pro and CSF- multinucleated cells (%) levels and lower CSF-Glu and CSF- monocytes (%) levels, and the difference was statistically significant ($P < 0.01$).

Conclusions: Our results elucidate risk factors and differences in CSF indexes for intracranial infection by *A. baumannii* after neurosurgery that could be detected and prevented early to reduce mortality.

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1. Introduction

Neurosurgical central nervous system infections (NCNSIs) is one of the common complications of neurosurgery, including subdural or epidural empyema, meningitis, ventriculitis, and brain abscess. Bacterial infection is the primary type of CNSIs [1]. With the complexity of neurosurgery, the increase in operation frequency, the longer length of hospital stays, and the early use of broad-spectrum antimicrobials, neurosurgical patients have become one of the high-risk groups for *A. baumannii* infection [2–6]. Compared with other bacteria, *A. baumannii* has strong capabilities of acquired resistance to antibiotics and cloning transmission, making treatment much more difficult [7]. Due to the long time required to confirm the diagnosis and the lack of effective antibiotics for therapy, the mortality rate has been reported to be high as 72.7% in patients with nosocomial Acinetobacter meningitis [8]. Complications with cerebral edema or cerebral ischemia may lead to severe sequelae in the nervous system, compromising the patient's quality of life [9,10]. *A. baumannii* is prone to cause outbreaks of nosocomial infection and imposes a severe economic burden on health care systems [11,12]. Studies have found that ineffective antimicrobial treatment is more common for Acinetobacter than most other pathogens, dramatically increasing mortality [13]. Because early diagnosis of intracranial infection is difficult, it is essential to analyze the risk factors of intracranial infection by *A. baumannii*.

There are many studies on risk factors for intracranial infection. However, most are divided into intracranial and non-intracranial infection groups for comparative research [14,15]. Few authors have studied which factors are more likely to cause intracranial infection of *A. baumannii* after neurosurgery and which clinical indicators have better discriminatory effects. For the early identification of risk factors of postoperative intracranial infection by *A. baumannii*, and at the same time to prevent and control it aggressively to reduce the mortality rate of patients, this article reviewed cases in the last ten years and added risk factors based on previous studies. The independent risk factors and the difference in CSF indexes for intracranial infection by *A. baumannii* were assessed in detail, which may provide data to support the early detection of intracranial infection by *A. baumannii*.

2. Materials and methods

2.1. Study population

We retrospectively reviewed patients' information on intracranial infection after neurosurgery at the First Hospital of China Medical University between January 2011 and May 2021.

2.2. Inclusion criteria

(1) Had cranial surgery at least once in our hospital; (2) fulfilled the diagnostic criteria for the etiology of CNS infections* [16]; (3) age$\geq$18 years; (4) the patient's relevant clinical data was complete.

* Diagnostic criteria for the etiology of CNS infections: (1) CSF cultures were positive. (2) The patient had clinical features and signs of intracranial infections such as postoperative fever, new headache, nausea, lethargy, change in mental status, neck stiffness, signs of peritonitis or abdominal tenderness in patients with VPS, or signs of pleuritis in patients with ventriculopleural shunts. (3) The peripheral blood WBC **>** 10.0×10^9/L, Neutrophil ratio $>$0.8. (4) The patient's CSF test showed inflammatory index changes, which met one of the following: a. Lumbar puncture pressure$>$200 mmH2O. b. the CSF is turbid. c. CSF white blood cell count $>100 \times 10^6$/L. d. CSF-pro$>$0.45 g/L, CSF-glu$<$2.2 mmol/L (5) Imaging: Brain CT or MRI showed extensive brain edema, ventricular dilation, or fluid level formation.

2.3. Exclusion criteria

(1) Patients with inflammation and abscess of meninges, ventricles, or intracranial before surgery; (2) patients with CSF infections with non-bacterial cultures; (3) age $<$18 years; (4) spinal surgery, skull plastic surgery, and ear surgery do not belong to the scope of neurosurgery. (5) patients with incomplete information and unable to do valid evaluations.

2.4. Study groups

The patients were divided into the *A. baumannii* intracranial infection group and the other species of bacteria group according to the pathogens isolated from CSF.

2.5. Data collection

Comprehensive data on each patient were collected, including information about the patient's gender, age, days of hospitalization, whether stay in the intensive care unit, basic diseases, surgical history within half a year, surgical information after admission, antibiotics usage, CSF drainage types, times of CSF collection before infection, whether presence of CSF drainage obstruction or CSF leakage, indwelling nasogastric tubes, urethral catheters or PICCs before infection, using mechanical ventilation before infection, presence of pulmonary infection, serum albumin levels, CSF routine indexes (the sample which CSF culture was positive), condition of glucocorticoids or intralipid usage, whether had intrathecal drug injection, CSF pathogen types and temporal distribution, and antibiotic susceptibility of the strains.

2.5.1. Statistical analysis

In this study, statistical analysis was performed with SPSS 26.0 statistical software. Continuous variables with a normal distribution were expressed as the mean ± standard deviation and analyzed by two sample *t-test*. Continuous variables with abnormal distribution were expressed as median (Quartiles)[*M(QL, QU)*] and analyzed by Mann-Whitney *U* test. Categorical variables were expressed as counts (percentages) and analyzed by Pearson X^2 test or Fisher exact test. The included factors were analyzed by univariate analysis. Factors with $P < 0.1$ and no multicollinearity were included in the multivariate logistic regression analysis (multicollinearity was proven to be weak when the variance inflation factor (VIF) was <10 or tolerance >0.1). Backwards stepwise multivariate regression was performed to create the final model whereby the least nonsignificant variables were removed from the model one at a time until all remaining variables had $P < 0.05$, and odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Finally, the difference in CSF indexes between *A. baumannii* and other species of bacterial groups was evaluated by pairwise comparison, and ROC curves were drawn to analyze the area under the curve (AUC), sensitivity, and specificity.

3. Results

3.1. Characteristics of pathogen in intracranial infection

155 patients were included in this study and categorized into intracranial infection by *A. baumannii* group (n = 62) and the other species of bacteria group (n = 93). A total of 176 strains were isolated, among which Gram-negative bacteria were 67.05% (118/176), Gram-positive bacteria were 32.95% (58/176), and the predominant was *A. baumannii* 35.23% (62/176), followed by *Staphylococcus epidermidis* 13.07% (23/176), *Klebsiella pneumoniae* 9.09% (16/176), *Enterococcus faecium* 6.25% (11/176), *Pseudomonas aeruginosa* 4.55% (8/176), *Staphylococcus hominis* 2.84% (5/176), *Enterococcus faecalis* 2.84% (5/176), *Staphylococcus haemolyticus* 2.27% (4/176), *Staphylococcus* 2.27% (4/176), *Acinetobacter lwoffi* 2.27% (4/176) and so on. (Details in Fig. 1). Analysis of *A. baumannii* strains from CSF were highly resistant to imipenem and meropenem with resistance rates of 91.8% and 75.0%, respectively. The susceptibility rate of *A. baumannii* to tigecycline and colistin antibiotics remained at a high level, with 94.7% and 93.3%, respectively (Fig. 2). Temporal distribution analysis of data revealed that *A. baumannii* intracranial infections after neurosurgery were mainly concentrated from July to September each year (Fig. 3). There were no significant differences in demographic characteristics or basic disease between the two groups ($P > 0.05$) and the baseline data of the two groups were stable and comparable (Table 1).

3.2. Risk factors for intracranial infection with A. baumannii

3.2.1. Univariate analysis

We included open wound or not, operative duration, numbers of operations, had implants or not during surgery, CSF drainage types, times of CSF collection before infection, CSF drainage obstruction, CSF leakage, indwelling nasogastric tubes, urethral catheters

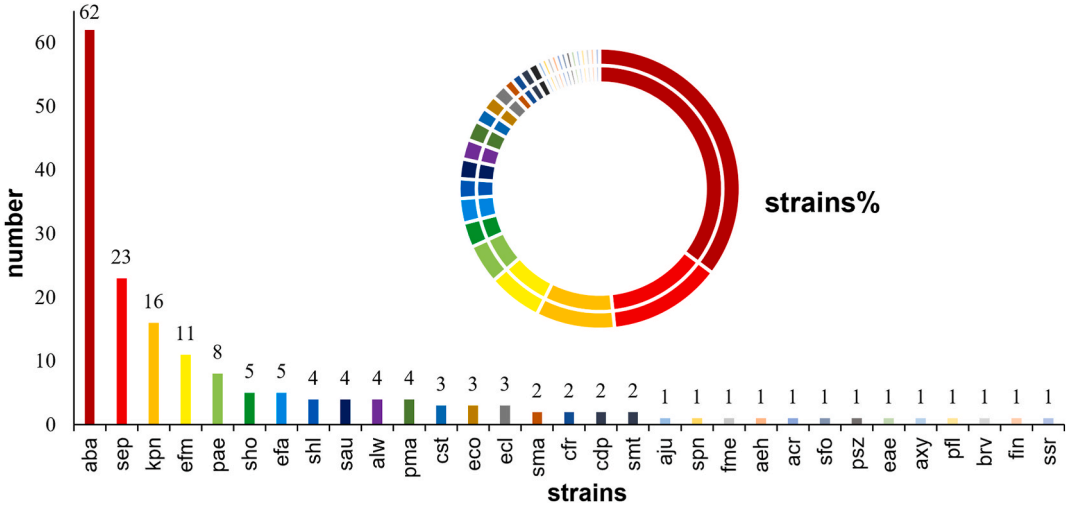

Fig. 1. Histogram of the number of strains isolated from CSF after neurosurgery from 2011 to 2021. The bar chart indicates the number of pathogens. The circle chart indicates the percentage of pathogens. Abbreviations: "aba: *Acinetobacter baumannii*; sep: *Staphylococcus epidermidis*; kpn: *Klebsiella pneumoniae*; efm: *Enterococcus faecium*; pae: *Pseudomonas aeruginosa*; sho: *Staphylococcus hominis*; efa: *Enterococcus faecalis*; shl: *Staphylococcus haemolyticus*; sau: *Staphylococcus*; alw: *Acinetobacter lwoffi*; pma: *Stenotrophomonas maltophilia*; cst: *Corynebacterium striatum*; eco: *Escherichia coli*; ecl: *Enterobacter cloacae*; sma: *Serratia marcescens*; cfr: *Citrobacter freundii*; cdp: *Diphtheroid*; smt: *Streptococcus mitis*; aju: *Acinetobacter junii*; spn: *Streptococcus penumoniae*; fme: *Chryseobacterium meningosepticum*; aeh: *Aeromonas hydrophila*; acr: *Aeromonas caviae*; sfo: *Serratia fonticola*; psz: *Pseudomonas stutzeri*; eae: *Enterobacter aerogen*; axy: *Alcaligenes xylosoxidans*; pfl: *Pseudomonas fluorescens*; brv: *Brevundimonas*; fin: *Chryseobacterium indologenes*; ssr: *Staphylococcus sciuri*".

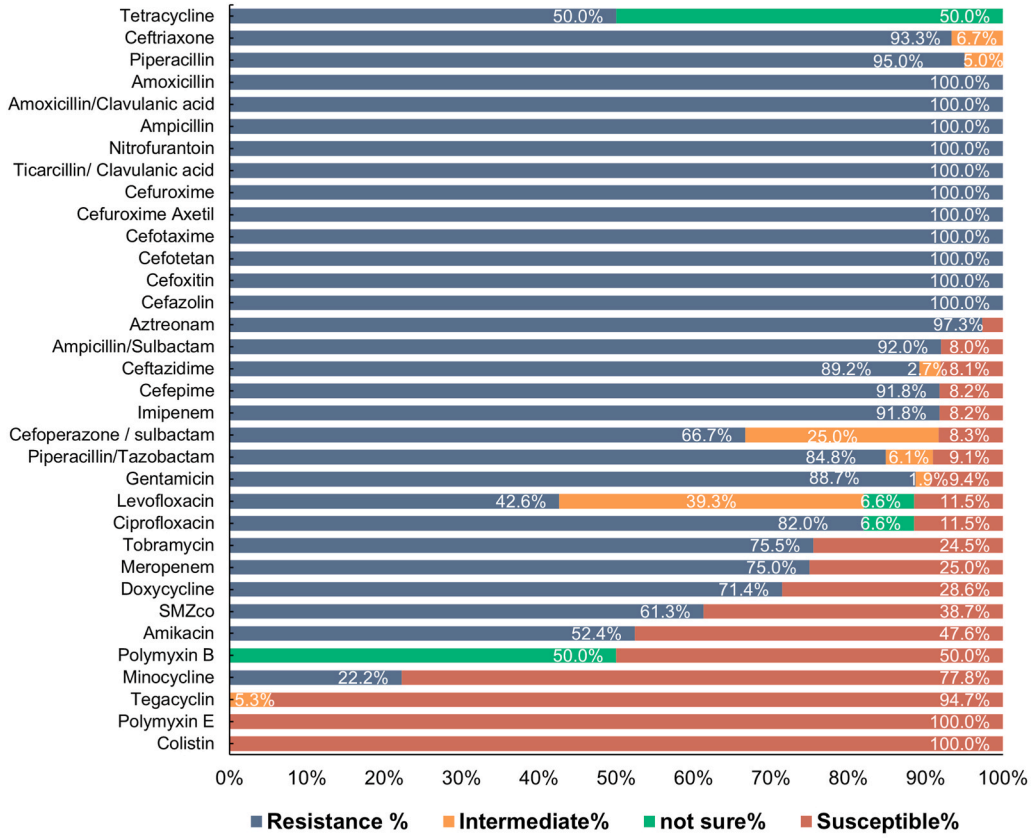

Fig. 2. Resistance rates and susceptibility rates of *A. baumannii* to various antibiotics. Gray: resistance rate; Yellow: intermediate rates; Green: not sure rates; Brown: susceptibility rates. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

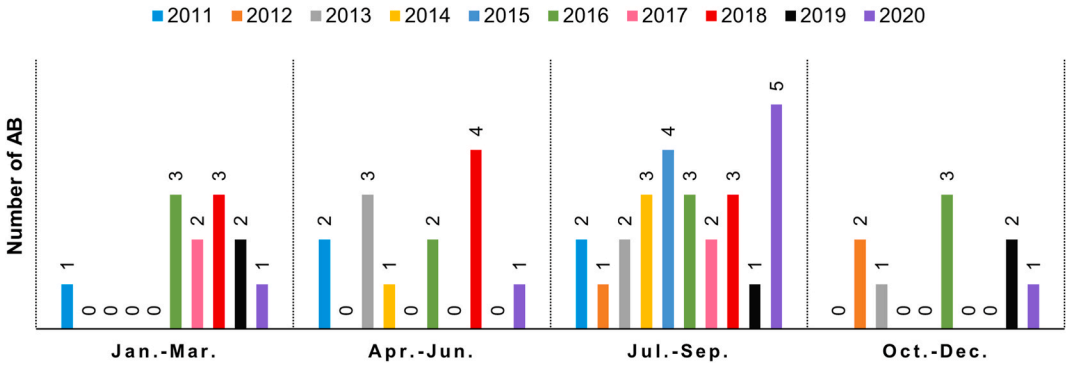

Fig. 3. Temporal distribution of intracranial infection by *A. baumannii* after neurosurgery from January 2011 to December 2020. The horizontal axis indicates the four quarters of each year, the vertical axis indicates the number of patients infected with *A. baumannii* after neurosurgery, and the years 2011–2020 are represented in different colors. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

or PICCs before infection, mechanical ventilation was used or not before infection, CSF routine indexes on the day of positive bacterial culture, antibiotics usage, whether susceptibility glucocorticoids were used before infection, intrathecal drug injection, intensive care unit stay, pulmonary infection, etc., a total of 20 factors for univariate analysis. Ten factors had statistical significance by univariate analysis ($P < 0.1$): including CSF drainage obstruction, CSF leakage, mechanical ventilation, External Ventricular/Lumbar Drains (EVD/LD), VPS, open wounds, indwelling nasogastric tubes, indwelling PICCs, admission to intensive care unit, and pulmonary infection (Table 2). The above factors were included in the multicollinearity test and multivariate analysis.

Table 1
Comparison of baseline characteristics.

	Intracranial infection by *A. baumannii* (n = 62)	Intracranial infection by other bacteria (n = 93)	Total (n = 155)	*P*-value
Age (years , $\bar{x}$ ±s)	50.5 ± 12.4	49.7 ± 13.7	50 ± 13.1	0.734
Gender (man , n, %)	40 (64.5)	52 (55.9)	92 (59.4)	0.285
Hypertension (n, %)	19 (30.6)	21 (22.6)	40 (25.8)	0.261
Diabetes mellitus (n, %)	11 (17.7)	9 (9.7)	20 (12.9)	0.142
Coronary disease (n, %)	5 (8.1)	7 (7.5)	12 (7.7)	0.902
Cerebral infarction/cerebral hemorrhage history (n, %)	3 (4.8)	2 (2.2)	5 (3.2)	0.353
Smoke history (n, %)	21 (33.9)	27 (29)	48 (31)	0.523
Neurosurgical history within half a year (n, %)	13 (21)	30 (32.3)	43 (27.7)	0.124
Days of hospitalization (median (IQR))	41 (22–66)	39 (26.3–58)	37.5 (26–58.3)	0.352
Severe hypoproteinemia (n, %)	12 (19.4)	12 (12.9)	24 (15.5)	0.277

Note: Data are presented as mean ± SD, n (%), or median (IQR).

Table 2
Univariate analysis of factors contributing to intracranial infection by *A.baumannii* after neurosurgery.

	Intracranial infection by *A. baumannii* (n = 62)	Intracranial infection by other bacteria (n = 93)	$X^2/t/Z$ value	*P*-value	*OR*	95%*CI* (lower-upper)
Invasive procedures						
Times of CSF collection*(median (IQR))	6 (2.8–10.3)	5 (3–11)	−0.720	0.471		
EVD/LD (n, %) *	45 (72.6)	54 (58.1)	3.397	**0.065**	1.912	0.956–3.825
VPS (n, %) *	3 (4.8)	15 (16.1)	4.620	**0.032**	0.264	0.073–0.956
Mechanical ventilation (n,%) *	35 (56.5)	31 (33.3)	8.132	**0.004**	2.593	1.338–5.025
Nasogastric tubes (n, %) *	42 (67.7)	29 (31.2)	20.029	**< 0.001**	4.634	2.325–9.239
Urethral catheters (n, %) *	58 (93.5)	83 (89.2)	0.838	0.360		
PICCs (n, %) *	19 (30.6)	10 (10.8)	9.679	**0.002**	3.667	1.568–8.578
Medication use						
Prophylactic use of antibiotics after operation (n, %)	57 (91.9)	82 (88.2)	0.569	0.451		
Use carbapenem before infection (n, %) *	31 (50.0)	36 (38.7)	0.569	0.165		
Use glucocorticoids after the operation (n, %)	44 (71.0)	76 (81.7)	1.932	0.117		
Use Intralipid after the operation (n, %) *	6 (9.7)	7 (7.5)	2.460	0.636		
Intrathecal drug injection (n, %) *	4 (6.5)	3 (3.2)	0.898	0.343		
Surgical information						
Open wounds (n, %)	16 (25.8)	11 (11.8)	5.053	**0.025**	2.593	1.110–6.056
Numbers of operation (n, %)						
≤2	54 (87.1)	76 (81.7)	1.108	0.268		
>2	8 (12.9)	17 (18.3)				
Operative duration (longest > 4 h (n, %)	31 (50.0)	35 (37.6)	2.326	0.127		
Implants (n, %)	40 (64.5)	60 (64.5)	< 0.001	0.999		
CSF leakage (n, %)	18 (29.0)	15 (16.1)	3.696	**0.055**	2.127	0.977–4.634
CSF drainage obstruction (n, %)	24 (38.7)	13 (14.0)	12.520	**< 0.001**	3.887	1.786–8.458
Others						
Into intensive care unit (n, %)	44 (71.0)	35 (37.6)	16.540	**< 0.001**	4.051	2.031–8.080
Pulmonary infection (n, %)	41 (66.1)	35 (37.6)	12.086	**0.001**	3.235	1.651–6.340

Notes: Data are presented as median (IQR) or n (%). EVD/LD: external ventricular/lumbar drains, VPS: ventriculoperitoneal shunt, PICCs: peripherally inserted central catheters, CSF: cerebrospinal fluid. Statistically significant *P*-values (P < 0.1) have been depicted in bold font. *: These factors are situations about patients' drugs usage or invasive procedures before positive CSF culture.

3.2.2. Multicollinearity test

Ten factors were included in the multivariate analysis, VIF in the range of 1.048–2.011 (<10) and tolerances in the range of 0.497–0.954 (>0.1), which was weakly considered multicollinearity (Table 3).

Table 3
Results of the multicollinearity test for 10 risk factors with P < 0.1 in univariate analysis.

Factors	Tolerance	VIF
EVD/LD	0.815	1.226
VPS	0.896	1.117
Mechanical ventilation	0.606	1.650
Nasogastric tubes	0.497	2.011
PICCs	0.870	1.150
Open wounds	0.904	1.106
CSF leakage	0.902	1.108
CSF drainage obstruction	0.954	1.048
Into intensive care unit	0.522	1.914
Pulmonary infection	0.614	1.627

Notes: VIF: variance inflation factors, EVD/LD: external ventricular/lumbar drains, VPS: ventriculoperitoneal shunt, PICCs: peripherally inserted central catheters, CSF: cerebrospinal fluid. VIF<10 or tolerance>0.1 means weak multicollinearity.

3.2.3. Multivariate analysis

Our results showed that indwelling nasogastric tubes, indwelling PICCs, and CSF drainage obstruction were independent risk factors (P < 0.05), VPS was a protective factor (P < 0.05, 0 < OR < 1) of intracranial infection by *A. baumannii* after neurosurgery (Table 4).

3.3. CSF index comparison and variance analysis

The other bacterial group was subdivided into three subgroups: Gram-negative isolates group, Gram-positive cocci group, and Coagulase-negative staphylococci group for comparative analysis of CSF indexes with *A. baumannii* group. (Since the number of strains in Coagulase-positive staphylococcus group was small, this article will not make a comparison.) The CSF indexes analysis of *A. baumannii* and the three subgroups showed that CSF-Pro, CSF-Glu, CSF- monocytes (%), CSF- multinucleated cells (%) and CSF multinucleated cells%/monocytes% were statistically significant (P < 0.05), None of the CSF-Cl levels were statistically significant (P > 0.05) (Table 5).

In *A. baumannii* group, the CSF protein level was higher, the glucose level was lower than those in the other three subgroups, and the difference was statistically significant. ROC curve analysis showed that (1) *A. baumannii* group compared with Gram-negative isolates group, the AUC of CSF-Pro≥3000 mg/L was 0.635 (95% CI = 0.519–0.751), and the sensitivity and specificity were 80% and 47%, respectively; the AUC of CSF-Glu≤1.1 mmol/L was 0.667 (95% CI = 0.554–0.780), and the sensitivity and specificity were 73% and 61%, respectively (Table 6, Fig. 4A). (2) In *A. baumannii* group compared with Gram-positive cocci group, the AUC of CSF-Pro≥3000 mg/L was 0.773 (95%CI = 0.679–0.867), and the sensitivity and specificity were 79% and 76%, respectively; the AUC of CSF-Glu≤1.1 mmol/L was 0.744 (95% CI = 0.647–0.840), and the sensitivity and specificity were 71% and 78%, respectively (Table 6, Fig. 4B). (3) In *A. baumannii* group compared with Coagulase-negative staphylococci group, the AUC of CSF-Pro≥3000 mg/L was 0.827 (95%CI = 0.724–0.930), and the sensitivity and specificity were 79% and 86%, respectively; the AUC of CSF-Glu≤1.1 mmol/L was 0.832 (95%CI = 0.742–0.922), and the sensitivity and specificity were 71% and 96%, respectively; and the combined AUC of the two was 0.872 (95% CI = 0.790–0.955), the sensitivity was 82%, and the specificity was 86% (Table 6, Fig. 4C).

Compared with the other three subgroups, in *A. baumannii* group, the CSF- multinucleated cells (%) was higher, and the CSF- monocytes (%) was lower. The median of multinucleated cells%/monocytes% was 6.7, the other groups were between 2 and 3, and the difference was statistically significant (P < 0.005) (Table 5). Then, the ROC analysis showed that the AUCs of multinucleated cells %/monocytes% between *A. baumannii* and Gram-negative isolates group (Fig. 5A), Gram-positive cocci group (Fig. 5B), and Coagulase-negative staphylococci group (Fig. 5C) were 0.684, 0.755, 0.761, respectively. The corresponding cut-off values, sensitivity, and specificity were 1.75 (92%, 42%), 3.65 (70%, 71%), and 3.65 (70%, 73%), respectively (Table 7).

It can be seen from the above analysis that there were significant differences in CSF indexes between *A. baumannii* and the Coagulase-negative staphylococci group. The CSF-Pro level of *A. baumannii* was higher, and the CSF-Glu level was lower. The discriminatory accuracy of multinucleated cells%/monocytes% was well, and it had a good identification value when the ratio was 3.65.

Table 4
Independent risk factors for intracranial infection by *A.baumannii* after neurosurgery.

Risk factors	*P*-value	OR	95%CI (lower limit-upper limit)	
Nasogastric tubes	< 0.001	4.231	1.973	9.072
CSF drainage obstruction	0.003	3.765	1.590	8.914
PICCs	0.041	2.765	1.044	7.322
VPS	0.033	0.220	0.054	0.888

Notes: CSF: cerebrospinal fluid, PICCs: peripherally inserted central catheters, VPS: ventriculoperitoneal shunt. P < 0.05 was considered statistically significant.

Table 5
Characteristics and differential analysis of CSF indexes between *A.baumannii* group and the three subgroups.

		Total	*A. baumannii* group (62)	Other bacteria groups	*P*-value
CSF-Pro≥3000 mg/L (n, %)	A	70 (69)	49 (79)	21 (54)	0.008
	B	60 (56.1)	49 (79)	11 (24.4)	< 0.001
	C	52 (61.9)	49 (79)	3 (13.6)	< 0.001
CSF-Glu≤1.1 mmol/L (n, %)	A	59 (58)	44 (71)	15 (39)	0.001
	B	54 (50.5)	44 (71)	10 (22.2)	< 0.001
	C	45 (53.6)	44 (71)	1 (4.5)	< 0.001
CSF-Cl (median (IQR))	A	111 (106.5–117)	111 (106–116)	112 (106.8–117.3)	0.56
	B	112 (107–116)	111 (106–116)	113.5 (109.8–116)	0.388
	C	112 (107–116)	111 (106–116)	113 (110.5–116.3)	0.292
CSF cell counts (median (IQR))	A	2355 (379–8284)	4197 (640–13944)	903.5 (188–3973.3)	0.002
	B	1120 (170–6172)	4197 (640–13944)	259.5 (76–975)	< 0.001
	C	1200 (261–9697.5)	4197 (640–13944)	127.5 (54.3–589.5)	< 0.001
CSF-multinucleated cells % (median (IQR))	A	84 (69–92)	87 (75–92)	75 (42–88)	0.002
	B	82 (62.5–90.5)	87 (75–92)	69 (37.5–85.3)	< 0.001
	C	84 (69.5–91.5)	87 (75–92)	69 (34–85.6)	< 0.001
CSF-monocytes % (median (IQR))	A	16 (9–32)	13 (8–25)	25 (12–60)	0.002
	B	19 (9.5–37.5)	13 (8–25)	31 (14.8–63.3)	< 0.001
	C	16 (8.5–30.5)	13 (8–25)	31 (14.5–66)	< 0.001
CSF multinucleated cells%/monocytes% (median (IQR))	A	5.3 (2.2–10.8)	6.7 (3–11.5)	3 (0.7–7.5)	0.002
	B	4.3 (1.7–9.6)	6.7 (3–11.5)	2.2 (0.6–5.8)	< 0.001
	C	5.3 (2.3–10.8)	6.7 (3–11.5)	2.2 (0.5–5.9)	< 0.001

Notes: Data are presented as median (IQR) or n (%). A: (*A.baumannii* with Gram-negative isolates group) 39 cases, B: (*A.baumannii* with Gram-positive cocci group) 45 cases, C: (*A.baumannii* with Coagulase-negative staphylococci group) 22 cases. CSF: cerebrospinal fluid. $P < 0.05$ was considered statistically significant.

Table 6
Discriminatory accuracy of CSF-Pro and CSF-Glu between *A.baumannii* group and Gram-negative isolates group, Gram-positive cocci group, Coagulase-negative staphylococci group.

Group	Variables	AUC	*95%CI*	Sensitivity	Specificity
A. baumannii with Gram-negative isolates	CSF-Pro≥3000 mg/L	0.635	0.519–0.751	80%	47%
	CSF-Glu≤1.1 mmol/L	0.667	0.554–0.780	73%	61%
A. baumannii with Gram-positive cocci	CSF-Pro≥3000 mg/L	0.773	0.679–0.867	79%	76%
	CSF-Glu≤1.1 mmol/L	0.744	0.647–0.840	71%	78%
A. baumannii with Coagulase-negative staphylococci	CSF-Pro≥3000 mg/L	0.827	0.724–0.930	79%	86%
	CSF-Glu≤1.1 mmol/L	0.832	0.742–0.922	71%	96%
	Combination index	0.872	0.790–0.955	82%	86%

Notes: AUC: area under the curve, CSF: cerebrospinal fluid.

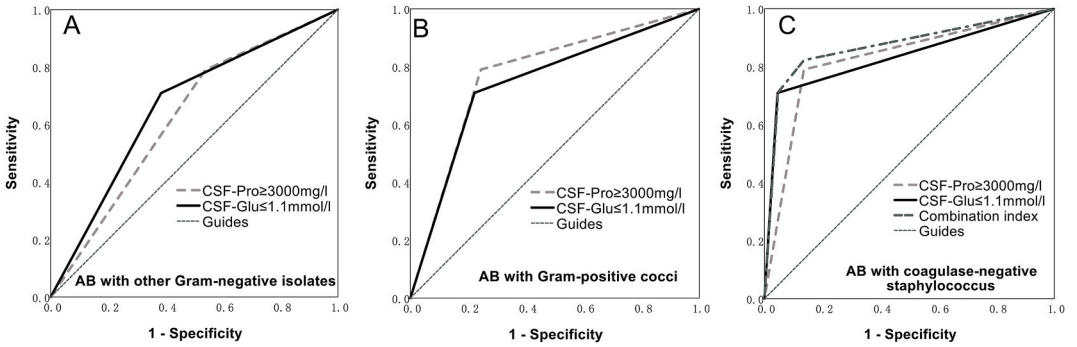

Fig. 4. ROC curves of CSF-Pro and CSF-Glu. (A: *A. baumannii* with Gram-negative isolates. B: *A. baumannii* with Gram-positive cocci. C: *A. baumannii* with Coagulase-negative staphylococci).

4. Discussion

Intracranial infection by *A. baumannii* after neurosurgery has always been an intricate problem that plagues neurosurgeons. The cranial cavity is vulnerable affected by the external environment because of the lack of protection of the bone, dura mater, and blood-brain barrier (BBB) after surgery. This confers a higher risk of intracranial infection by *A. baumannii*. The incidence of multidrug-

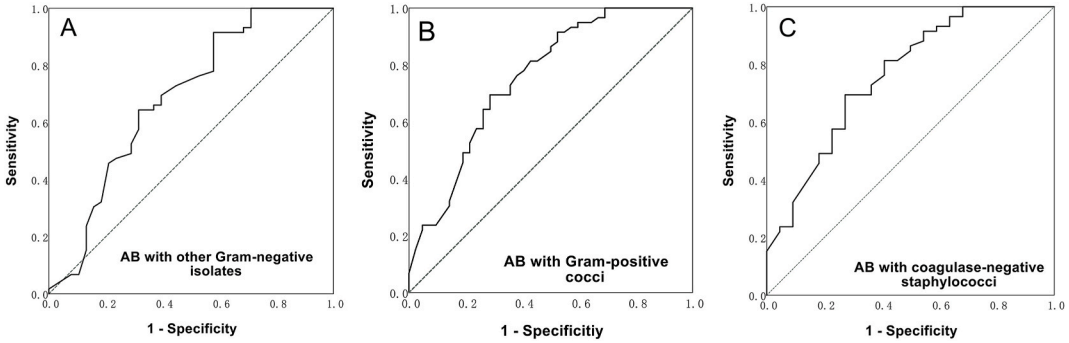

Fig. 5. ROC curves of CSF multinucleated cells%/monocytes%. (A: *A. baumannii* with Gram-negative isolates. B: *A. baumannii* with Gram-positive cocci. C: *A. baumannii* with Coagulase-negative staphylococci).

Table 7
Discriminatory accuracy of CSF multinucleated cells%/monocytes% between *A.baumannii* group and Gram-negative isolates group, Gram-positive cocci group, Coagulase-negative staphylococci group.

Variables	Group	AUC	*95%CI*	Cutoff value	Sensitivity	Specificity
CSF multinucleated cells%/monocytes %	*A.baumannii* with Gram-negative isolates	0.684	0.570–0.799	1.75	92%	42%
	A.baumannii with Gram-positive cocci	0.755	0.657–0.853	3.65	70%	71%
	A.baumannii with Coagulase-negative staphylococci	0.761	0.639–0.883	3.65	70%	73%

Notes: AUC: area under the curve, CSF: cerebrospinal fluid.

resistant Acinetobacter baumannii (MDR-Ab) infection is rising every year and has been placed on the priority list of WHO [17]. CNS infection caused by *A. baumannii* accounts for 3.6–11.2% of nosocomial intracranial infections caused by multidrug-resistant strains [18]. Intracranial infection by *A. baumannii* will affect the operation result. Many antibiotics cannot reach an effective concentration in the CSF because of the BBB [19], which leads to a difficult treatment, poor prognosis, and high mortality.

The study of Lee HY et al. found that ineffective initial therapy may be the primary driver of outcome differences of patients, rather than any other virulence differences between carbapenem susceptible and resistant strains of *A. baumannii* [20]. Therefore, early initiation of effective antimicrobial therapy is critical to patient survivability from Acinetobacter infections. Unfortunately, initiating effective therapy is a particular problem in clinic [13,21] because early diagnosis of NCNSIs is challenging. The clinical gold standard for the etiological diagnosis of intracranial infection is the traditional isolating culture method and biochemical identification, which has an extended culture cycle and low positive rates [22]. In developing countries, the isolation rate of pathogens by CSF culture of meningitis is just 5.4–24.3% [23]. The metagenomic next-generation sequencing (mNGS), a novel detection technique, is developing dramatically and has shown great potential in identifying pathogens in meningitis due to its rapid detection rate, high accuracy, and wide coverage, but it is also expensive, the sample preparation and data analysis are more complicated, and the sample is susceptible to contamination, generating false-positive results. Therefore, an analysis of risk factors is essential for the early recognition of intracranial infection by *A. baumannii*.

Several risk factors associated with neurosurgical infection have been identified in previous studies. Different literature reported vary widely due to different data inclusion criteria. "Diagnosis and treatment of CNS infection in neurosurgery 2021 Chinese expert consensus" proposed that among the patient's factors, diabetes mellitus and open brain injury are risk factors for intracranial infection after neurosurgery; Among the operation related factors, operation duration>4 h, number of craniotomies≥2 and having implants placed during operation increase the odds of intracranial infection; Among the postoperative factors, indwelling drainage tubes, frequent collection of CSF samples and complicated CSF leakage are independent risk factors for intracranial infection. Among other factors, severe hypoalbuminemia, using mechanical ventilation, parenteral nutrition, or high-dose glucocorticoids long-term after surgery all increased the incidence of CNSIs. Xiao Jinping et al. found that long hospital stays, CSF drainage obstruction, and antibiotic usage before infection are independent risk factors for developing resistance during intracranial infections by MDR-Ab [24]. Concerning the results of previous studies and the latest expert guidelines, our study found that diabetes mellitus, severe hypoalbuminemia, days of hospitalization, operation duration, times of operation, having implants placed during the operation, times of CSF collection, antibiotic usage before infection, and the use of glucocorticoids and parenteral nutrition after the operation were not risk factors for discriminating *A. baumannii* from other bacterial intracranial infections after neurosurgery (all $P > 0.1$).

Studies have shown that the predominant predispositions to Acinetobacter spp. Infection is colonization pressure, selection by exposure to broad-spectrum antibiotics, and disruption of anatomical barriers (e.g., placement of catheters or surgical injury to skin and integument) [25,26]. Our study found that indwelling nasogastric tubes and PICCs were independent risk factors for *A. baumannii* intracranial infection. Indwelling nasogastric tubes had a 4-fold risk of intracranial infection with *A. baumannii* compared with other bacteria, and indwelling PICCs had a 2-fold risk. As an opportunistic pathogen in medical settings, *A. baumannii* mainly infects the

immunocompromised population [27]. Patients with indwelling gastric tubes always have poor oral feeding, suggesting patients with poor nutritional status and low immunity [28]. The results of a study by Fu peishu et al. on neurosurgical infection by *A. baumannii* showed significance in univariate analysis with indwelling nasogastric tubes ($P < 0.001$) [29], consistent with our study. PICC is an essential route of administration for antibiotic use, fluid resuscitation, and parenteral nutrition of patients in the ICU, and its placement requires an invasive procedure in the clinic. Catheter-related bloodstream infections (CRBSIs) caused by PICCs is an important reason for increased mortality in critical patients [30]. *A. baumannii* bloodstream infections typically occur in the presence of a central venous catheter or secondarily due to extensive pneumonia, facilitating dissemination [31]. Indwelling nasogastric tubes and PICCs are the medium of *A. baumannii* infection, and *A. baumannii* avidly adheres to plastic and can establish biofilms on the tube and spread by contact [32]. Furthermore, disruption of the BBB after cranial surgery increases the probability of infection by *A. baumannii*, which enters the CNS from blood [33]. Therefore, after neurosurgery, the status of the patients should be assessed, parenteral nutrition should be changed to enteral nutrition early, and the nasogastric tubes and PICCs should be pulled out as early as possible to reduce the infection rate.

Neurosurgery is prone to various complications, of which hydrocephalus is the most common and is often treated by CSF drainage. This study divided the CSF drainage types into two categories: indwelling EVD/LD and VPS. Indwelling EVD/LD was a risk factor for *A. baumannii* intracranial infection (OR = 1.192), and indwelling VPS was a protective factor (OR = 0.264) in univariate analysis. The possible reason is that Lenie dijkshoorn mentioned in their research that *A. baumannii* widely exists in the surrounding environment of patients and can be transmitted through the contaminated environment, medical devices, and the hands of medical staff [27]. Compared with other bacteria, *A. baumannii* has a strong capacity for acquiring drug resistance. Its clinical isolates can survive for a long time on extremely dry abiotic surfaces (a characteristic rarely found in other Gram-negative pathogens) [34,35]. In the Neurosurgery Department, broad-spectrum antibiotics are prophylactically administered after placing indwelling CSF drainage tubes, which makes *A. baumannii* easier to screen out under antimicrobial selection pressure [36]. EVD/LD connects the cranial cavity with the external environment, and *A. baumannii* can travel retrograde to the intracranial space to cause infection. The VPS tube penetrates the subcutaneous tunnel behind the ear, neck, chest, and the terminal end opens in the abdominal cavity to drain CSF from the ventricle to the peritoneum for absorption, which is not connected with the outside environment, thus reducing the chance of *A. baumannii* infection. In the clinic, we can evaluate high-risk patients for intracranial infection by *A. baumannii* and using closed CSF drainage as an alternative to external drainage may reduce the risk of its infection. The incidence of EVD-related infection after neurosurgery ranges from 8% to 22%. Therefore, attention should be given to the clinical application of drainage tubes, and the removal indication should be evaluated as early as possible [37–40].

This study classified bacterial isolates into different species to analyze their CSF index differences and found that patients with intracranial infection by *A. baumannii* had higher CSF protein levels and lower CSF glucose levels. Fluctuations in CSF protein and glucose mainly reflect the metabolism and destruction status of the CNS. The general genotypic and phenotypic responses of *A. baumannii* are not identical when exposed to different human body fluids. Its genetic flexibility confers metabolic diversity, allowing *A. baumannii* to adapt to harsh conditions such as CSF and survive long-term [35]. Jasmine Martinez et al. assessed in their experiments how gene expression changes of *A. baumannii* when in contact with CSF. They found that CSF enhances its expression of genes involved in the transcription and translation machinery, FoF1-ATP synthase (the main ATP generator in the bacterial cell), and specific metabolic pathways. The effect of these alterations is that in resource-limited body fluid such as CSF, *A. baumannii* might allocate all possible resources towards metabolism using an uncoupled metabolism to optimize its survival. In addition, CSF increases the expression of a set of genes in *A. baumannii,* such as type IV pili, iron uptake systems, and poly-*N*-acetylglucosamine (PNAG), and induces the release of cytotoxic substances. These factors increase *A. baumannii* adhesion, motility, and virulence, eventually remarkably impairing the CNS [41]. CNS destroyed by *A. baumannii* stimulates the excessive release of inflammatory factors, resulting in cellular edema to reduce CSF reflux, leading to a higher CSF protein level; at the same time, the decline in brain blood flow could enhance glycolysis, leading to a lower glucose level. It may also be due to the poor treatment effect of multi-drug resistant strains on antibiotics, resulting in slow bacterial clearance. Y. Siegman-Igra et al. included 238 patients with a total of 320 CSF samples. Among them, 23 patients were positive for *A. baumannii,* and routine CSF tests showed increased protein levels (mean value 1850 mg/L) [42]. Xiao Jinping et al. analyzed the CSF indexes of MDR-Ab and found that the CSF protein level was 3126.72 ± 1257.53 mg/L and the glucose level was 0.66 ± 0.83 mmol/L, consistent with our results [24].

We also found by retrospective analysis that intracranial infection by *A. baumannii* after neurosurgery mainly concentrated from July to September. Effective prevention and control measures may be implemented in the clinic during this period to prevent cross-infection. Li Yi Wang et al. studied the seasonal factors of intracranial infection. They found that patients operated in autumn were more likely to experience intracranial infection than those operated in spring (OR = 2.866, 95%CI:1.592–5.159) [1]. The National Nosocomial Infection Surveillance (NNIS) system found that between 1987 and 1996, the prevalence of Acinetobacter infections increased by 54% between July to October in the United States compared to November through June, possibly because high humidity facilitates bacterial growth [43].

5. Limitations

This is a retrospective study. The bacterial culture results of gastric tubes or PICCs were unavailable, and the data of the operator, interoperative, or infected patient's surroundings were also inaccessible. We suggest that bacterial cultures for gastric tubes or PICC catheters should be done for high-risk patients in the clinic. Because of the small number of patients infected with other gram-negative bacilli, the comparison was not fully discussed in the study. Although our study provides evidence for the early identification of intracranial infection by *A. baumannii*, future studies are still needed because of the limited number of cases.

6. Conclusion

This study revealed that *A. baumannii* had become the area's primary pathogen of neurosurgery infection. After the operation, more attention should be paid to patients with indwelling gastric tubes, PICCs, or CSF obstructions. If patients exhibit clinical symptoms of intracranial infection and with notable changes in CSF protein and glucose, the possibility of *A. baumannii* infection should be considered in time. Among the *A. baumannii* strains isolated from CSF, the sensitivity to tigecycline and polymyxin is still high, while the sensitivity to carbapenems is poor. This study found that compared with EVD/LD, indwelling VPS had a lower incidence of *A. baumannii* infection, but the relationship between them needs further proof. We hope the results of this study will encourage doctors to pay more attention to risk factors and CSF indexes to assist in diagnosing and treating the postsurgical infection as early as possible to improve patient's quality of life.

Ethical approval

The study was approved by the Institution Ethic Committee of The First Hospital of China Medical University (AF-SOP-07-1.1-01).

Author contribution statement

Shige Li: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Pan Wang: Conceived and designed the experiments; Performed the experiments.
Sufei Tian: Contributed reagents, materials, analysis tools or data.
Jingping Zhang: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18525.

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