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Clinical Characteristics and Predictors of Mortality of Patients with Post-Neurosurgical Meningitis-A 900-Cases Cohort Study

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Aim: To express the clinical characteristics of patients with post-neurosurgical meningitis (PNM) and launch a survival analysis to screen mortality predictors.

Methods: A cohort analysis containing more than 70000 patients was evaluated, and all of them received neurosurgical procedure. Clinical and microbial epidemiology, therapy and mortality of PNM patients were reviewed. Multi-variable Cox proportional hazard models were applied to achieve survival analysis.

Results: About 900 PNM patients from 3244 cases were selected for characteristics and survival analysis, the mean age of them was 41 (27–54) years, 516 (57.3%) were men and 384 (42.7%) were women. The 28-day mortality was 12.4% (112 of 900) in patients with PNM. Hypertension, external ventricular drainage (EVD), and lumbar drainage (LD) are mortality predictors for PNM, with a hazard ratio (HR) of 2.641 (95% C.I. 1.563–4.464, P<0.001), 2.196 (95% C.I. 1.317–3.662, P=0.003), and 1.818 (95% C.I. 1.126–2.936, P=0.014). In treatment, the outcome of patients receiving three or more antibiotic combinations is better than that of patients receiving dual-drug combinations.

Conclusion: The mortality of patients with PNM was relatively high, and the risk factors related to 28-days mortality were hypertension, EVD and LD and treatment with three or more antibiotics are much better.

Keywords: Post-neurosurgical meningitis, survival analysis, mortality, characteristics, treatment

Introduction

Post-neurosurgical meningitis (PNM) is a severe complication following neurosurgery, which, although often preventable,[1] continues to impose a significant burden on patient health and healthcare resources. The consequences of PNM include extended hospital stays, increased risk of disability, and a higher likelihood of treatment failure, potentially leading to serious outcomes and posing a threat to the lives of neurosurgical and neurological patients. The reported prevalence of PNM ranges from 0.8% to 24.0%.[2–5]

The burden of PNM has been assessed in various studies, identifying several associated risk factors, including diabetes mellitus, external ventricular drain (EVD) use, lumbar drainage (LD), a lower Glasgow Coma Score (GCS), craniotomy, and malignancy.[6–8] However, these studies often examine a limited range of patient characteristics or focus on specific types of surgical procedures. Furthermore, comprehensive, longitudinal survival analyses of PNM are relatively sparse, with few studies providing large-scale and in-depth evaluations of survival outcomes.

The primary objective of this study was to conduct an epidemiological investigation into PNM and perform a survival analysis for neurosurgical patients with PNM, with a focus on identifying 28-day all cause mortality risk factors.

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Utilizing data from the Chinese Nosocomial Meningitis Database (CNMD) for the year 2020, we examined 17 variables related to PNM patients, including factors such as operation duration, ICU admission, and the use of external ventricular drains (EVD). Additionally, this study assessed the clinical characteristics of PNM patients, microbial distribution, antimicrobial susceptibility testing (AST) patterns, and therapeutic approaches. To our knowledge, this is the largest, longitudinal study globally to comprehensively evaluate clinical characteristics and survival outcomes in patients with PNM.

Method

Setting and Study Design

We conducted a 9-year retrospective cohort analysis of patients diagnosed with PNM at Beijing Tiantan Hospital and Capital Medical University, the largest tertiary neurosurgical center in China. The study included individuals aged 14 years and older who underwent neurosurgery and were diagnosed with PNM, with data collected from the Chinese Nosocomial Meningitis Database (CNMD) starting in 2012. The neurosurgical procedure including cranial tumors, spinal tumors, functional neurosurgery, neurovascular surgery, craniocerebral trauma surgery, and so on. Since all neurosurgery patients have signed a general informed consent form, non-confidential record of all patients can be used for clinical research, therefore, the Ethics Committee of Beijing Tiantan Hospital granted a waiver for informed consent. The entire study was approved by the Ethics Committee of Beijing Tiantan Hospital and complies with the Declaration of Helsinki.

Definitions

According to the definition provided by the Infectious Diseases Society of America (IDSA) in 2017[3] and the US Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN),[4] PNM is characterized by a positive CSF culture obtained more than 48 hours post-neurosurgery, or the presence of at least two symptoms and signs (eg, body temperature >38.0°C, headache, neck stiffness, meningeal or cranial nerve signs) in conjunction with one or more abnormal CSF laboratory biomarkers (elevated CSF leukocyte count, protein, or decreased CSF glucose concentration compared to reference ranges); positive CSF Gram stain; positive blood cultures; positive non-culture diagnostic CSF tests; or a positive single antibody titer for immunoglobulin M or a four-fold increase in paired immunoglobulin G for a specific organism.

Patients with CSF cultures positive for coagulase-negative *staphylococcus*(CoNS), *Micrococcus, Bacillus*, or *Propionibacterium acnes* were excluded due to their high contamination potential. To avoid analyzing recurrences, only the initial positive CSF culture was considered for patients with multiple positive cultures. Individuals who died within 24 hours of the index CSF culture collection date were excluded, as well as those who were not treated due to palliative care.

The microbiological data on PNM patients included pathogen distribution and AST. Pathogens were classified into gram-positive (G+) bacteria, gram-negative (G-) bacteria, fungi, and Mycobacterium. Identification was performed using conventional biochemical methods or matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). AST identified four common resistance patterns: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), 3rd-generation cephalosporin-resistant, and carbapenem-resistant gram-negatives phenotypes. Resistance to 3rd-generation cephalosporins was inferred from ceftazidime and ceftriaxone resistance, carbapenem resistance from imipenem and meropenem resistance, and methicillin resistance in S. aureus from oxacillin resistance. The Clinical and Laboratory Standards Institute (CLSI) 2023 guidelines were used to classify susceptibility (resistant, intermediate, and susceptible).

Data extracted from the Chinese Nosocomial Meningitis Database (CNMD) included demographic information (sex and age), medical records, and clinical microbiological tests. We selected 17 variables associated with mortality from PNM, such as tumor presence, malignant tumor, diabetes, hypertension, operation duration, reoperation, craniotomy, surgical site, incision type, ICU admission, CSF leakage, external ventricular drainage (EVD), length of stay (LOS), assisted mechanical ventilation (AMV), body temperature, sepsis, and hospital-acquired pneumonia (HAP). Additionally,

we evaluated three timed variables: infection duration, effective treatment duration, and total costs, using the most extreme vital signs (eg, temperature, sepsis) recorded 1–3 days after PNM onset.

Therapy

Antibiotic administration was categorized into three types: 1) antibiotic prophylaxis: antibiotics were administered 0.5 hours prior to the neurosurgical procedure; 2) empirical therapy: antibiotics were given before the results of the AST were available; and 3) precise therapy: antibiotics were prescribed based on the AST results. Additionally, the use of broad-spectrum antibiotics was assessed.

Statistical Analysis

As applicable, χ^2 or Fisher's exact tests and the *t*-test or Mann–Whitney *U*-test were utilized for descriptive statistics. To elucidate the clinical attributes of PNM, we initially conducted a comparative evaluation of the clinical features between survivors and non-survivors, analyzed the distribution of microbiological agents, and examined resistance patterns.

In the subsequent phase, a multivariable survival analysis was employed to estimate the primary 28-day outcome for PNM patients, given that mortality beyond 28 days was deemed less likely to be directly associated with PNM. Initially, a univariate analysis was performed for both groups, with statistical significance assessed using the p-value. Subsequently, a Cox proportional hazards model was developed to evaluate the impact of factors with p-value on PNM mortality. From this model, we estimated the impact of PNM on 28-days all-cause mortality as the hazard ratio (HR), which is suitable for datasets with minimal administrative censoring. The HR measures the association between predictors and the risk of hospital mortality. The results are reported as p-values, HRs, and 95% confidence intervals (C. I). Statistical analyses were conducted using SPSS 20.0 software (IBM, New York, USA), and figures were created with Prism 7.0 (GraphPad, San Diego, USA).

Results

Overall, 3244 out of 71,909 (4.51%) patients were found to be positive for CSF culture during the study period. Among these, 1775 patients were positive for CoNS, 188 for *Micrococcus*, 126 for Bacillus, and 37 for *Propionibacterium acnes*. A total of 318 cases were excluded: 209 due to having only a CSF ventriculo-peritoneal shunt, 45 due to mortality from other causes, 24 due to discharge within 24 hours, and 40 due to incomplete clinical documentation. The remaining 900 PNM patients were included in the study, of which 112 were non-survivors and 788 were survivors. A flowchart illustrating the patient inclusion process is shown in Figure 1.

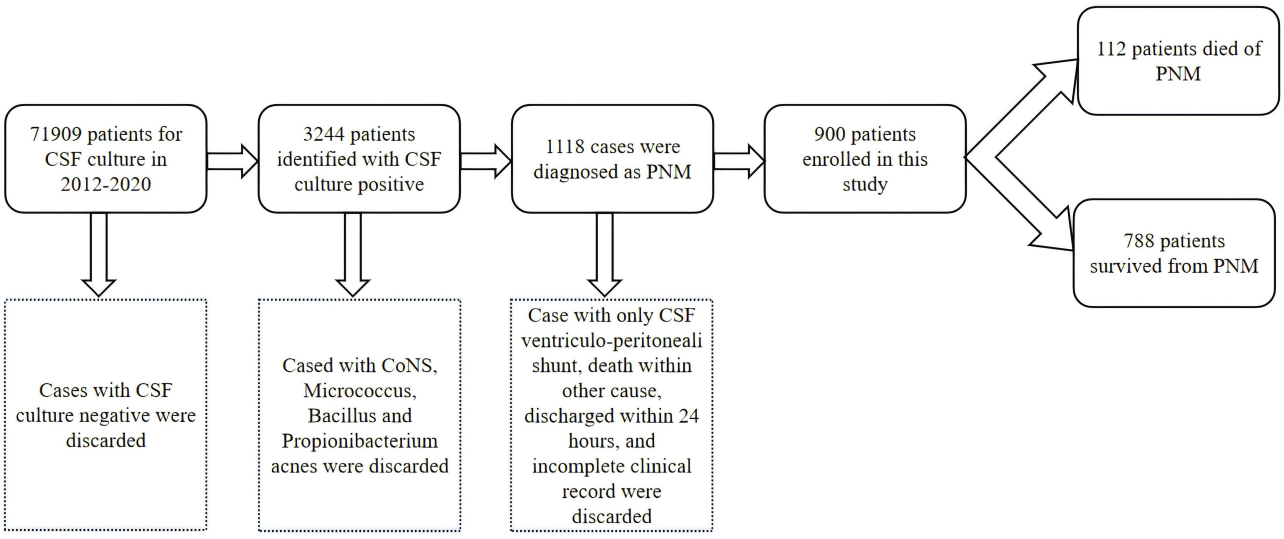

Figure 1 Flowchart of PNM patients' selection process and final sample size.

Microbiology

In the cohort of 900 cases, G+ bacteria related PNM constituted 383 out of 900 (42.6%) of all culture-positive cases. Conversely, G- bacteria related PNM cases represented 55.1% (496/900). Infections caused by fungi, Mycobacterium, and mixed-species infections were observed at rates of 1.3%, 0.2%, and 0.8%, respectively. Among non-survivors, the proportion of G+ bacteria was notably lower compared to survivors (P<0.05), while the prevalence of G- bacteria was significantly higher in the non-survivor group (P<0.05). The overall distribution of microorganisms is detailed in Tables 1 and 2 provides data on the susceptibilities of the four most critical AST types to the antibiotics tested. Notably, MRSA, third-generation cephalosporin-resistant G- bacteria, and carbapenem-resistant G- bacteria showed significant differences between the two groups.

Table 1 Distribution of Microorganisms Isolated from Cerebrospinal Fluids of PNM Patients

Microorganism	All Patients (900)	Non-Survivors (112)	Survivors (788)	P
Gram-positive bacteria	383(42.6%)	35(31.3%)	348(44.2%)	0.011
Staphylococcus aureus	103(11.4%)	18(16.1%)	85(10.8%)	0.112
Enterococcus faecalis	67(7.4%)	2(1.8%)	65(8.2%)	0.011
Enterococcus faecium	62(6.9%)	1(0.9%)	61(7.7%)	0.004
Streptococcus viridans	76(8.4%)	9(8.0%)	67(8.5%)	0.999
Streptococcus pneumoniae	14(1.6%)	1(0.9%)	13(1.6%)	0.999
Other positive bacteria	61(6.8%)	4(3.6%)	57(7.2%)	0.225
Gram-negative bacteria	496(55.1%)	74(66.1%)	422(53.6%)	0.015
Acinetobacter baumannii	101(11.2%)	19(17.0%)	82(10.4%)	0.053
Klebsiella pneumoniae	107(11.9%)	28(25.0%)	79(10.0%)	<0.001
Escherichia Coli	33(3.7%)	3(2.7%)	30(3.8%)	0.788
Klebsiella aerogenes	30(3.3%)	6(5.4%)	24(3.0%)	0.252
Acinetobacter lwoffii	20(2.2%)	0(0.0%)	20(2.5%)	0.159
Pseudomonas aeruginosa	23(2.6%)	3(2.7%)	20(2.5%)	0.999
Enterobacter cloacae	19(2.1%)	4(3.6%)	15(1.9%)	0.281
Serratia marcescens	15(1.7%)	2(1.8%)	13(1.6%)	0.999
Klebsiella oxytoca	11(1.2%)	0(0.0%)	11(1.4%)	0.377
Other negative bacteria	137(15.2%)	5(4.5%)	132(16.8%)	<0.001
Double-species infection	7(0.8%)	3(2.7%)	4(0.5%)	0.045
Fungus	12(1.3%)	0(0.0%)	12(1.5%)	0.380
Candida albicans	6(0.7%)	2(1.8%)	4(0.5%)	0.165
Candida parapsilosis	3(0.3%)	1(0.1%)	2(2.5%)	0.329
Candida tropicalis	2(0.2%)	1(0.1%)	1(0.1%)	0.234
Candida glabrata	1(0.1%)	0(0.0%)	1(0.1%)	0.999
Mycobacterium	2(0.2%)	0(0.0%)	2(0.3%)	0.999
Total	900(100.0%)	112(100.0%)	788(100.0%)	-

Table 2 4 the Most Important AST of the Microorganisms

Groups	All Patients	Non-Survivors	Survivors	P
MRSA	37(37.9%)	12(66.7%)	25(29.4%)	0.006
VRE	16(12.2%)	1(25.0%)	15(11.8%)	0.410
3-rd generation cephalosporin resistance Gram-negative bacteria	152(36.0%)	37(50.0%)	115(27.2%)	<0.001
Carbapenem resistance Gram-negative bacteria	105(24.9%)	36(48.6%)	69(16.4%)	<0.001

During the targeted 900 cases, G+ bacteria related PNM accounted for 383/900 (42.6%) of all culture-positive individuals. However, the percentage of G- bacteria related cases was 55.1% (496/900). Fungus, Mycobacterium and double-species infections accounted for 1.3%, 0.2% and 0.8%, respectively. In the non-survivor group, the percentage of G+ bacteria related PNM was significantly lower than that of survivors (P<0.05), and similarly, G- bacteria related PNM cases accounted for a higher percentage in the non-survivor group (P<0.05). Whole microorganism distribution is shown in Table 1, and the susceptibilities of the 4 utmost important AST types to the investigated antibiotics are presented in Table 2. From that, MRSA, 3rd generation cephalosporin-resistant G- bacteria, and carbapenem-resistant G- bacteria were significantly different in the two groups.

Patients

Of the 900 PNM patients included in the final analysis, the mean age was 41 (27–54) years, 516 (57.3%) were men and 384 (42.7%) were women (Table 3). A total of 621 (69.0%) patients had a cerebral or spinal tumor, and 282 (31.3%) had malignant tumors. The proportions of patients who had diabetes and hypertension were 3.7% and 15.7%, respectively. Other relevant variables are shown in Table 1.

Table 3 Demographic, Clinical Characteristics of PNM Cases and Univariate Analysis

Variable	All Patients (900)	Non-Survivors(112)	Survivors(788)	P
Basic condition				
Gender	516(57.3%)	70(62.5%)	446(56.6%)	0.262
Age	41(27,54)	41(27,53)	47(31,58)	0.157
Original disease				
Cranial tumors	603(67.0%)	73(65.2%)	530(67.3%)	0.668
Spinal tumors	18(2.0%)	1(0.9%)	17(2.2%)	0.715
Functional neurosurgery	48(5.3%)	2(1.8%)	46(5.8%)	0.111
Neurovascular surgery	58(6.4%)	8(7.1%)	50(6.3%)	0.840
Craniocerebral trauma surgery	53(5.9%)	7(6.3%)	46(5.8%)	0.830
Others	120(13.3%)	21(18.8%)	99(12.6%)	0.076
Risk factors				
Diabetes	33(3.7%)	5(4.4%)	28(3.6%)	0.592
Hypertension	141(15.7%)	33(29.5%)	108(13.7%)	<0.001
TEM(°C)	37.6±0.9	37.8±0.9	37.6±0.9	0.025

(*Continued*)

Table 3 (Continued).

Variable	All Patients (900)	Non-Survivors(112)	Survivors(788)	P
Tumor	621(69.0%)	80(71.4%)	541(68.7%)	0.587
Malignant tumor	282(31.3%)	48(42.9%)	234(29.7%)	0.007
Length of operation(hours)	4.5±3.0	5.0±3.0	4.5±3.0	0.062
Reoperation	199(22.1%)	39(34.8%)	160(20.3%))	0.001
Craniotomy	625(69.4%)	79(70.5%)	546(69.3%)	0.872
Surgical site				0.715
Head	882(98.0%)	111(99.1%)	771(97.8%)	
Spine	18(2.0%)	1(0.9%)	17(2.2%)	
Type of incision				0.481
Clean	471(52.3%)	55(49.1%)	416(52.8%)	
Contamination	429(47.7%)	57(50.9%)	372(47.2%)	
ICU admission	357(39.7%)	80(71.4%)	277(35.2%)	<0.001
CSF leakage	138(15.3%)	23(10.5%)	115(14.6%)	0.122
EVD	362(40.2%)	69(61.6%)	293(37.2%)	<0.001
LD	257(28.6%)	48(42.9%)	209(26.5%)	0.001
AMV	359(39.9%)	77(68.8%)	282(35.8%)	<0.001
Sepsis	64.0(7.1%)	12(10.7%)	52(6.6%)	0.120
HAP	124.0(13.8%)	52(46.4%)	72(9.1%)	<0.001
Time procedure				
LOS(days)	24(18, 36)	31(21, 48)	23(17.0, 34.3)	<0.001
Time of PNM occurrence (days)	8(4, 13)	10.0(6.0, 16.0)	7.0(4.0, 12.0)	<0.001
Effective treatment days (days)	5.1±7.3	6.8±10.5	4.9±6.8	0.794
Fee(Yuan)	71099.9 (50062.7, 118198.88)	137254.0 (70352.5, 230416.0)	68721.8 (48569.8, 106318.4)	<0.001

From Table 1, the distribution of sex, age and comorbidities was similar between the two groups, except hypertension, which was more common in non-survivor participants (29.5% VS 13.7%, P<0.001). Factors, including body temperature (TEM), malignant tumor, ICU admission, EVD, LD, AMV and HAP, were not evenly distributed between participants in the two groups (P<0.05). There were more patients with malignant tumors (42.9% VS 29.7%), reoperations (34.8% VS 20.3%), ICU admissions (71.4% VS 35.2%), EVD (61.6% VS 37.2%), LD (42.9% VS 26.9%), AMV (68.8% VS 35.8%) and HAP (46.4% VS 9.1%) in non-survivors than survivors. We observed no difference between the two groups in the time of PNM occurrence and effective treatment days except for the LOS (P<0.001). In total, the median fee burden of the non-survivors was much higher than that of the survivors (137254.0 vs 68721.8, P<0.001).

Survival Analysis

The 28-day all cause mortality was 12.4% (112 of 900) in patients with PNM. The results of survival analysis by the Cox proportional hazards model are summarized in Figure 2 and Table 4, including hypertension, EVD and LD. Of the

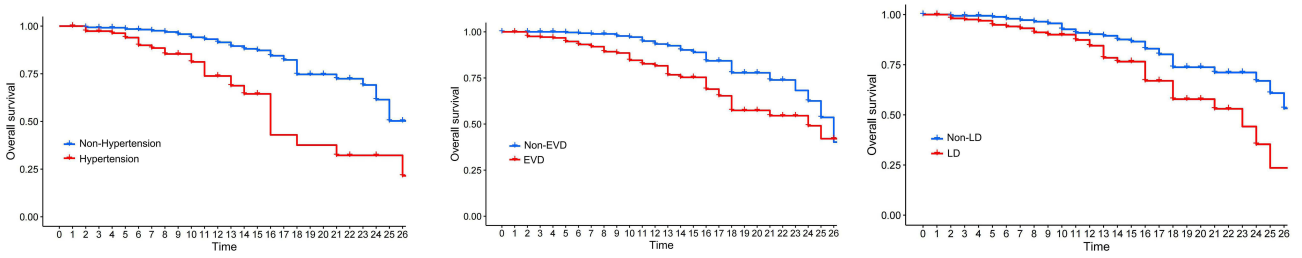

Figure 2 Independent risk factors and survival analysis of PNM associated with PNM 28-days mortality.

targeted four parameters, hypertension, EVD and LD were adverse events for PNM, with a HR of 2.641 (95% C.I. 1.563–4.464, P<0.001), 2.196 (95% C.I. 1.317–3.662, P=0.003), and 1.818 (95% C.I. 1.126–2.936, P=0.014), respectively.

Therapy

A total of 77.6% (698/900) of patients received antibiotic prophylaxis, 88.6% (797/900) acquired empirical therapy, and 85.9% (773/900) were treated with high-grade antibiotics (including: 3-rd 4-th generation cephalosporins, carbapenems, vancomycin, linezolid, etc). The percentages of mono-, dual- and triple- or more-combined antibiotics in empirical therapy were 29.4% (234/797), 48.6% (387/797) and 22.1% (176/797), respectively. Meanwhile, 85.4% (769/900) of patients underwent precise therapy, and the three antibiotic usage ratios were 18.2% (140/769), 59.9% (461/769) and 20.5% (168/769). The combination of vancomycin and meropenem is the most commonly used treatment regimen in empirical therapy (36.1%, 288/797) and precise therapy (45.9%, 353/769), and the percentages of different antibiotic therapy types are shown in Table 5.

In terms of empirical therapy, the mortality rates of patients with triple or more antibiotic combinations and dual-drug combinations were 19.9% (35/176) and 11.6% (45/387), respectively. For precise treatment, the mortality rates of patients with triple or more antibiotic combinations and dual-drug combinations were 24.4% (41/168) and 13.4% (62/461), respectively, and the difference was statistically significant (P=0.013, P=0.001). The percentages of mono-, dual-, and triple or more antibiotic therapy types are shown in Figure 3.

Table 4 Cox Proportional Hazards Analysis of Risk Factors Associated with PNM 28-Days Mortality

Variable	P	HR	95.0% C.I.
Malignant tumor	0.179	1.417	0.853–2.355
Hypertension	<0.001	2.641	1.563–4.464
Reoperation	0.158	0.685	0.406–1.157
ICU	0.166	1.514	0.842–2.720
EVD	0.003	2.196	1.317–3.662
LD	0.014	1.818	1.126–2.936
AMV	0.612	1.170	0.639–2.142
TEM(°C)	0.453	1.027	0.958–1.101
HAP	0.257	1.355	0.801–2.290

Table 5 Percentages Application of Different Antibiotic Therapy in PNM Patients

Application	Antibiotics	All Patients	Non-Survivors	Survivors	P
Antibiotic prophylaxis(698)	Cefuroxime	393(56.3%)	41(56.9%)	352(56.2%)	0.999
	Ceftriaxone	206(29.5%)	15(20.8%)	191(30.5%)	0.102
	Cefotaxime	34(4.9%)	10(13.9%)	24(3.8%)	0.001
	Others	65(9.3%)	6(8.3%)	59(9.4%)	0.999
Empirical therapy(794)	Ceftriaxone	54(6.8%)	6(5.6%)	48(7.0%)	0.685
	Cefuroxime	77(9.7%)	6(5.6%)	71(10.3%)	0.160
	Meropenem	46(5.8%)	4(3.7%)	42(6.1%)	0.383
	Vancomycin	27(3.4%)	4(3.7%)	23(3.3%)	0.777
	Vancomycin + Meropenem	288(36.1%)	29(26.9%)	259(37.6%)	0.031
	Cefuroxime + Vancomycin + Meropenem	32(4.0%)	7(6.5%)	25(3.6%)	0.184
	Others	273(34.3%)	52(48.1%)	221(32.1%)	0.002
Precise therapy(769)	Vancomycin	33(4.3%)	1(0.9%)	32(4.9%)	0.440
	Meropenem	57(7.4%)	6(5.4%)	51(7.8%)	0.440
	Vancomycin + Meropenem	353(45.9%)	41(36.6%)	312(47.5%)	0.073
	Cefotaxime + Vancomycin + Meropenem	28(3.6%)	7(6.3%)	21(3.2%)	0.165
	Cefuroxime + Vancomycin + Meropenem	32(4.2%)	7(6.3%)	25(3.8%)	0.301
	Others	266(34.6%)	50(44.6%)	216(32.9%)	0.018

Discussion

Neurosurgery always involves the opening of the central nervous and CSF circulatory systems and causes blood-brain barrier destruction, which easily leads to PNM. While reported incidence rates may vary,[5] screening for mortality risk factors is critical due to the elevated rate of poor prognosis among patients. In keeping with our findings, previous studies with a smaller number of PNM patients have also found predictors to reduce the mortality ratio. However, this cohort originated from the largest PNM database in China, with the most representative characteristics. We first summarize the clinical and microbial characteristics in patients with PNM, and the predictors for 28-day mortality account for

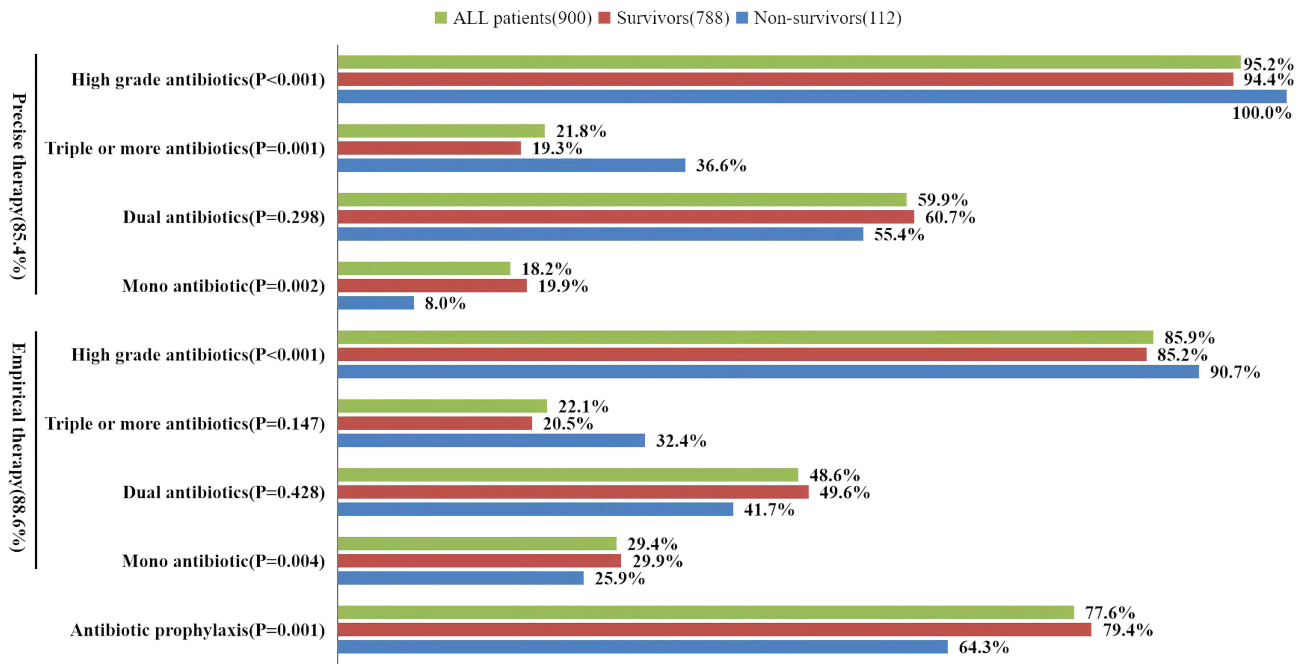

Figure 3 Percentage of different antibiotic therapy types.

confounding by indication through the use of Cox propensity score modeling. To the best of our knowledge, this is the largest and longest cohort of patients with PNM in which a survival analysis has been evaluated.

The pathogens that cause PNM are mainly bacteria. In our study, the proportion of PNM cases caused by G- bacteria was higher than that caused by G+ bacteria, and the proportion of gram-negative bacteria in the non-survivor group was significantly higher than that of the gram-positive bacteria, similar to reports in the literature.[9] The majority of multidrug-resistant bacteria, which always lead to poor outcomes in patients because of severe infection, are gram-negative bacteria, such as carbapenem-resistant *Enterobacteriaceae* (CRE), extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPE).[10] There is a high mortality rate in the treatment process due to the lack of sensitive antibiotics. A follow-up study indicated that infections caused by gram-negative bacteria do have certain sequelae effects, and better antibiotic care is urgently needed.[11] Drug resistance is a very important factor in patients with infections, and a number of studies have shown that different mechanisms of drug resistance have significant differences in the outcomes of multiple infections.[12] For example, ESBL production is a critical risk factor for sepsis caused by *Enterobacteriacea*e.[13] Another Spanish study showed that CRE infection significantly affected the mortality of sepsis patients.[14] The results of our study showed that, except for VRE, the proportion of drug-resistant bacteria in the non-survivor group was significantly higher than that in the survivor group.

We observed significant mortality in patients with PNM, and the mortality rate in our study was higher than that in previous reports.[15–17] PNM patients with adverse outcomes, had greater levels of hypertension, EVD and LD than those of surviving patients. Hypertension is one of the inducers of immune system diseases. For example, pulmonary hypertension is closely related to immune suppression.[18,19] Compared with healthy people, the immunity of hospitalized patients has a downward trend, and hypertension will aggravate the occurrence of this situation and lead to a poor outcomes.[20] Similarly, hypertension can induce some inflammation,[21] and the presence of strong inflammation in patients, such as a "cytokine storm", will increase the difficulty of clinical treatment. In addition, patients with cerebral aneurysm-related diseases, hypertension is also a risk factor for poor prognosis.[22] Therefore, hypertension, as an independent predictor for survival in PNM patients, has a certain theoretical basis. EVD and LD are common operations in neurosurgical patients, and they have similar clinical characteristics. PNM caused by both of them are catheter-related infections. Catheter-related infections are an important cause of patient death,[23] and EVD is also an independent predictor for craniotomy. Additionally, in traumatic brain injury, previous study report that early (≤24 h post-injury) insertion may result in better long-term functional outcomes.[24] Impurity eyewinker entry is one of the major causes of infection, and if antibiotics are not administered in time, bacteria will adhere to the catheter, and bacteria such as *Pseudomonas aeruginosa* that can form biofilms can have serious consequences.[25]

Previous reports have shown that antibiotic prophylaxis can effectively reduce infection occurrence.[26] and our previous research also supports this theory.[27] Up to 80% of PNM patients received antibiotic prophylaxis. The use of antibiotic prophylaxis in the survivor group was significantly higher than that in the non-survivor group (P=0.001). Nevertheless, empirical treatment and precise treatment and the choice of antibiotics are closely related to patient mortality.

In infectious patients, several retrospective studies targeting multi-resistant bacteria have recommended improved survival in patients receiving two or more combinations of active antibiotics in vitro, mostly in patients with high risk of mortality.[28,29] It has been reported that compared with single drug usage, multidrug combinations can have a better cure rate for certain infections.[30,31] However, there are also reports showing that for some special drug-resistant bacterial infections, multidrug combinations cannot achieve expected results,[32,33] as has been shown in recent clinical trials. In our study, we recommended that dual-drug combinations and triple-drug combinations are statistically significant in empirical treatment (P=0.013) and precise treatment (P=0.001) of PNM. The mortality rate of patients with triple drug combinations is lower. However, the synergistic effect of different antibiotics on PNM still needs further exploration and research.

Our study has some limitations. First, it is a retrospective study in a single center, although it is the largest PNM series from the CNMD reported thus far. Second, the molecular characteristics of the patients' infections and drug resistance genes were not analyzed, which may have certain shortcomings for precision drug therapy.

Conclusion

In our study, using a Cox proportional hazards model, 3 variables, hypertension, external ventricular drainage, and lumbar drainage were selected as mortality clinical predictors in patients with PNM. Clinically, when dealing with PNM patients presenting with these three characteristics, physicians should employ special measures such as antibiotics prophylaxis or supportive treatment to reduce the mortality rates. For treatment, the clinical significance of three or more drug combinations was higher than that of dual-drug usage, which may provide effective measures for the treatment of patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to disclose.

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