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ORIGINAL RESEARCH

Longitudinal Analysis of Risk Factors for Clinical Outcomes of *Enterobacteriaceae* Meningitis/ Encephalitis in Post-Neurosurgical Patients: A Comparative Cohort Study During 2014–2019

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Purpose: Our study is a retrospective observational study conducted in one of the largest clinical centers of neurosurgery in China. We aimed to investigate the antimicrobial susceptibility patterns of the *Enterobacteriaceae* isolates responsible for nosocomial meningitis/ encephalitis in post-neurosurgical patients. Meanwhile, we tried to evaluate the risk factors for mortality following *Enterobacteriaceae* meningitis/encephalitis.

Patients and Methods: Medical data on clinical characteristics, antibiotic susceptibilities, and mortality were reviewed until patients' discharge or death in the hospital. Data for a total of 164 cerebrospinal fluid (CSF) infection cases due to *Enterobacteriaceae* after neurosurgery were collected between January 2014 and November 2019 in order to identify risk factors affecting the outcome. Kaplan–Meier survival analysis and multivariable Cox proportional hazard models were applied.

Results: In this study, a total of 2416 neurosurgical meningitis/encephalitis cases were reported between 2014 and 2019. *Enterobacteriaceae* accounted for 7.3% (176/2416) of all the bacterial infections. Of them, 164 *Enterobacteriaceae* isolates were available to divide into two groups according to the final outcome of whether the patient died or survived. In total, 38 patients died (23.2%) and 126 patients survived (76.8%). The most frequent infecting species was *Klebsiella pneumoniae* (47.0%, 77/164). Fourteen-day and 30-day mortality rates were 7.9% (13/164) and 15.2% (25/164). Kaplan–Meier survival analysis revealed that the risk factors of *Enterobacteriaceae* meningitis/encephalitis that resulted in poor outcomes included comorbidities, Glasgow Coma Scale (GCS) score, sepsis, intensive care unit (ICU) admission, extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, and ventilation. A GCS score of less than or equal to 8 (P=0.04, HR 2.562) was identified to be a significant risk factor for mortality according to the multivariable Cox proportional hazards model.

Conclusion: In-hospital mortality caused by *Enterobacteriaceae* meningitis/encephalitis in neurosurgery was high. A GCS score of ≤8 was an independent risk factor for mortality following *Enterobacteriaceae* meningitis/encephalitis in post-neurosurgical patients.

Keywords: *Enterobacteriaceae*, post-neurosurgical meningitis/encephalitis, antibiotic susceptibility, antibiotic resistance, in-hospital mortality

Introduction

Meningitis is one of the main complications occurring in post-neurosurgical patients, and poses a high mortality with prolonged hospital stays and costs.[1,2] It has been reported that the incidence of post-neurosurgical bacterial meningitis/encephalitis is

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0.3–8.6% and it is particularly high in developing countries.[3,4] The etiology of post-neurosurgical meningitis/encephalitis includes a wide spectrum of microorganisms from gram-positive cocci to gram-negative bacilli. During the last decades, gram-negative organisms have seemed to be increasing as causative agents of post-neurosurgical meningitis/encephalitis.[5] Among the gram-negative bacteria, *Enterobacteriaceae* is a large group of etiology resulting in post-neurosurgical meningitis/encephalitis with high morbidity and mortality rates.[6]

However, related research on the clinical risk factors of post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis is limited. We retrospectively analyzed the epidemiology of post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis patients in 2014–2019 from Beijing Tiantan hospital to evaluate the risk factors for predicting the survival of post-neurosurgical patients with *Enterobacteriaceae* meningitis/encephalitis. The results may be able to identify the factors that significantly affect post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis and provide evidence for the prevention and early clinical treatment of post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis.

To our knowledge, this is the largest case series on post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis and is the first study of such crucial risk factors in predicting survival in China. We believe the data in this paper is of great clinical significance.

Patients and Methods

Study Setting

This study was performed at the Beijing Tiantan Hospital & Capital Medical University, a tertiary hospital with 1850 beds and more than 15,000 annual surgeries, between January 2014 to November 2019. The protocol for this study was approved by the clinical diagnosis department of the Beijing Tiantan Hospital & Capital Medical University. Neurosurgery operations included craniotomy, transsphenoidal and spinal surgeries. Patients with incomplete medical records were excluded from the study.

Clinical and Epidemiological Data

Post-neurosurgical patients' medical records were reviewed to determine whether infections were nosocomial *Enterobacteriaceae* using cerebral spinal fluid (CSF) bacteria culture reports and antimicrobial susceptibility test results. All of the patients' eligible daily progress notes were extracted from the standard database. We reviewed several factors including the patients' routine information (age, gender), comorbidities (hypertension, diabetes mellitus), primary pathology, Glasgow Coma Scale (GCS) score, time from procedure to infection, length of hospital stay (LOS), sepsis, Intensive Care Unit (ICU) admission, producing Extended-Spectrum Beta-Lactamase (ESBLs), surgical wound classification, extra ventricular drainage (EVD), lumbar drainage (LD), ventilation and cerebrospinal fluid (CSF) leakage.[7,9] The antibiotic susceptibility of *Enterobacteriaceae* isolations was determined by CLSI (Clinical and Laboratory Standards Institute) guidelines.[10] Post-neurosurgical meningitis/encephalitis patients were followed up until discharge or death in the hospital to assess the clinical outcome.

Microbiologic Methods

Identification and antimicrobial susceptibility were performed in the clinical diagnosis department of the Beijing Tiantan Hospital testing according to a standardized procedure. CSF culture positive specimens were placed onto Columbia blood agar and incubated in an incubator containing 5% CO2 for 18–24 hours. All of the isolates were identified by the Vitek-2 Compact or Vitek MS automated system (bioMerieux, Marcy 1 'etoile, France). Vitek AST-GN and AST-GP cards were used on the Vitek-2 instrument for broth microdilution to obtain the minimum inhibitory concentration (MIC) of all the isolates. Breakpoint values were used according to the 2019 guidelines as described in the CLSI document M100-S23.

Treatment Protocol and Outcomes

All of the patients were given antibiotic prophylaxis 0.5 hours before neurosurgery according to the department's antibiotic policy. When meningitis/encephalitis was clinically suspected, the patients initially received empirical antibiotics until the culture sensitivity reports were awaited. Once the antimicrobial susceptibility results were available, the patients received definitive antibiotics.

The clinical outcomes of this study were defined as follows: (1) In-hospital mortality: Death in the hospital with clinical evidence of post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis infection. (2) 30-day mortality: Death within 30 days after the first CSF bacteria culture was positive; mortality not attributable to infection: Patients who died after post-neurosurgical meningitis/encephalitis but as a result of causes independent of the infectious process were excluded from this study.

Statistical Analysis

Student's *t*-test and Mann–Whitney *U*-test were used to compare the two groups for continuous variables depending on whether the data was of normal distribution. Categorical variables were performed using the χ2 test in mortality risk factor analysis. A value of $P<0.05$ was considered to have statistical significance. The number of days from the first CSF bacteria positive culture to death in the hospital within 30 days was displayed on Kaplan–Meier curves, and the rates of survival were compared using Log rank testing. In addition, values of $P<0.10$ were considered to be probable predictor variables for the multivariable Cox proportional hazards regression analysis and hazard ratios based on multivariate analysis were calculated. All tests were two-tailed. The data were analyzed by SPSS 21.0 software (IBM New York, US) and WHONET 5.5. The graph of antimicrobial susceptibility was performed using Prism 8.0 (Graphpad, San Diego, USA).

Results

Microbiology

In total, 176 *Enterobacteriaceae* isolates from 2416 isolates collected from CSF bacteria positive cultures between January 2014 and November 2019 were collected in one of the largest centers for neurosurgery in China. The respective microorganisms are presented in Figure 1. No multiple organism infections were found and antimicrobial susceptibility test results are illustrated in Figure 2.

Clinical Characteristics

Between January 2014 and November 2019, 176 patients with post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis were included in this study. There were seven patients missing key data and five patients who died due from other causes all of whom were excluded from this study (death occurred after an episode of meningitis/encephalitis but as a result of causes independent of the infectious process). Two of the five patients died from multiple organ failure (MOF), while another patient died from an alimentary tract hemorrhage. In addition, intracranial hematoma and acute respiratory distress syndrome (ARDS) resulted in another two patients' death respectively. A flow chart is shown in Figure 3. All of the patients were divided into two groups according to the final outcomes. One was a survivor group containing 126 patients and the other was the non-survivor group containing 38 patients. The median age was 40.1±15.4 years. Among these patients, 94 of 164 patients (57.3%) were male. There were no significant differences in age and sex distributions between the two groups. During hospitalization the average GCS score was 7.7±3.8. The GCS scores in the non-survivor group (5.8±3.8) were significantly lower than those in the survivor group (8.6±3.5) (P=0.021). Patients LOS was 26.4 days (IQR 20.0–40.0 days) and the median time for a CSF positive culture was 6 days (IQR 2.5–13.5 days). In total, 72 of the 164 patients (43.9%) suffered from a tumor and three of the patients' primary pathology was trauma. Other primary pathologies included tuberculosis 1.2% (2/164) and hepatitis B 2.4% (4/164). There were 68 patients with a clean surgical wound operation while the rest had a clean-contaminated surgical

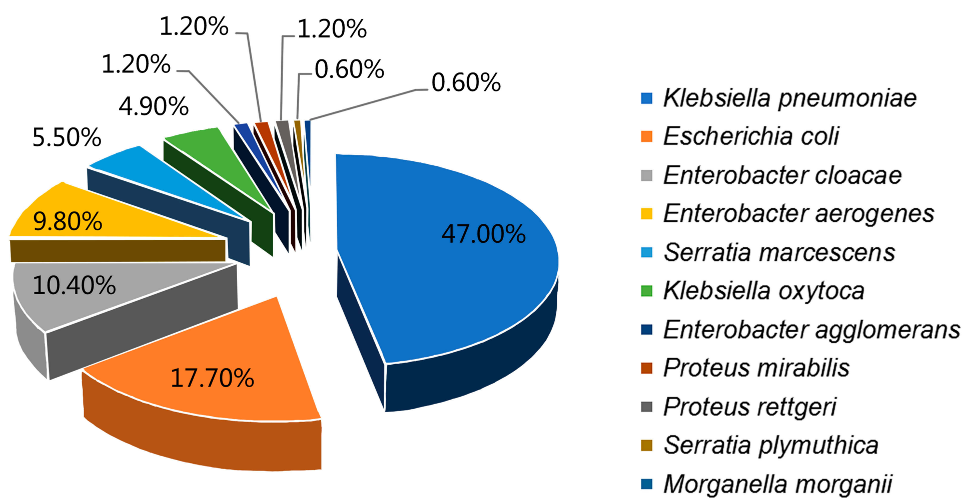

Figure 1 Species found in *Enterobacteriaceae* related meningitis/encephalitis during 2014–2019.

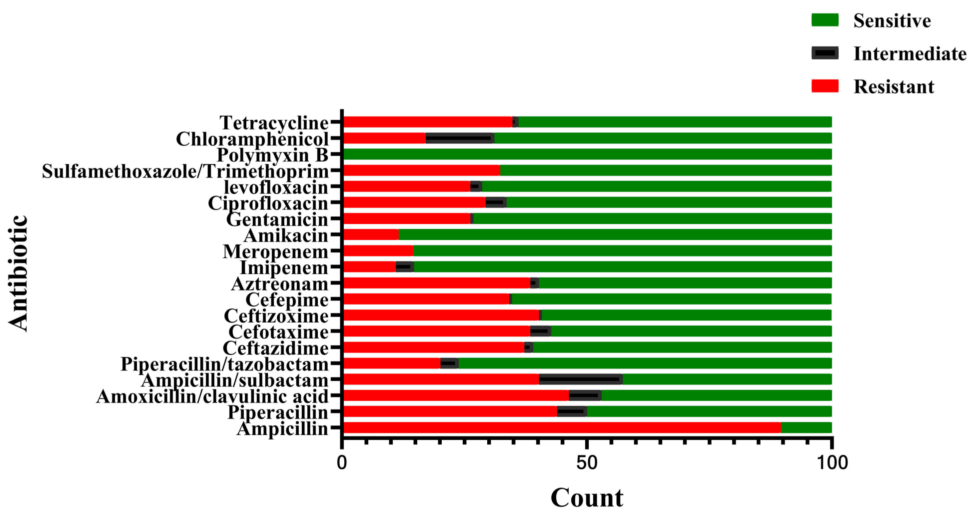

Figure 2 Antimicrobial susceptibility tests of species found in *Enterobacteriaceae* related meningitis/encephalitis during 2014–2019.

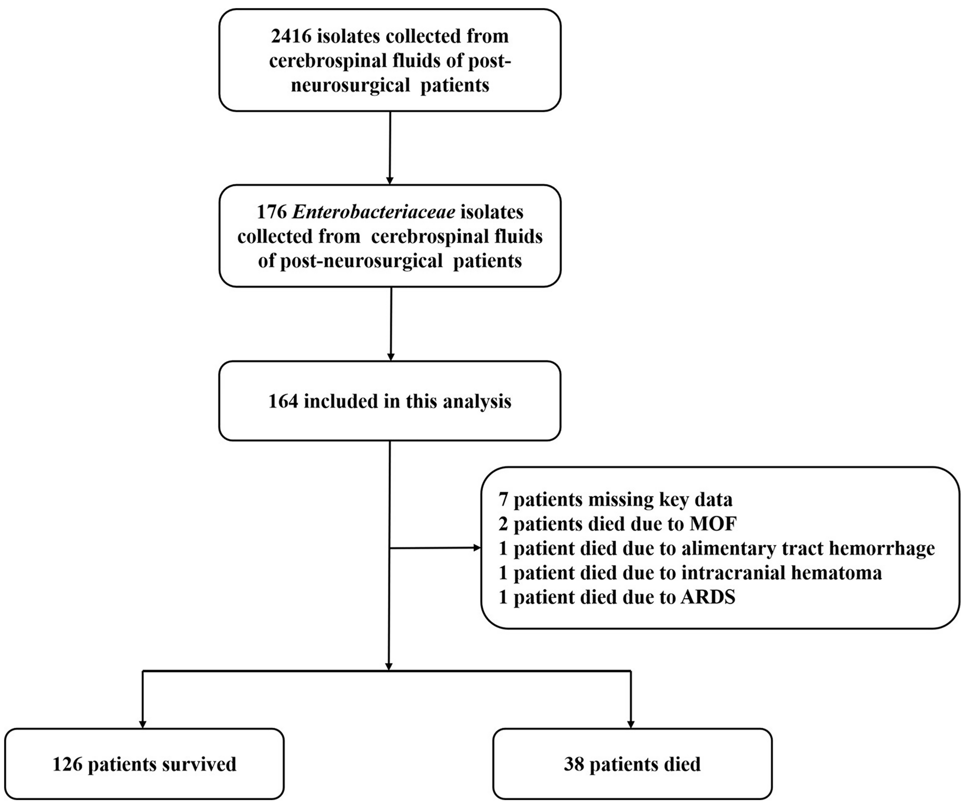

Figure 3 Flowchart of the included patients with post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis.
Abbreviations: MOF, multiple organ failure; ARDS, acute respiratory distress syndrome.

wound operation. Sixty-seven (40.9%) cases had extra ventricular drainage (EVD) and 92 (56.1%) had lumbar drainage (LD). Overall, 61 patients (37.2%) were admitted into the ICU, and there were statistically more patients admitted into ICU from the non-survivor group (71.1%) than the survivor group (27.0%) (P<0.001). The ESBL-producing *Enterobacteriaceae* isolates identified from the non-survivor group (52.6%) were significantly more than those of the survivor group (33.3%) (P=0.032). The rate of the non-survivor group (55.3%) for using ventilation was significantly higher than that in the survivor group (16.7%) (P<0.001). There were 89 patients who underwent

Table 1 Comparison of the Factors of the Non-Survivor Group versus the Survivor Group. (Data are Presented as Number (%) of Patients, Mean ± SD, or Median [IQR] Unless Indicated Otherwise)

Factors	Total (n=164)	Non-Survivor (n=38)	Survivor (n=126)	P
Age (years)	40.1±15.4	42.0±16.9	39.5±15.0	0.518
Male (%)	94 (57.3%)	20 (52.7%)	74 (58.7%)	0.505
Comorbidities				
Diabetes mellitus	4 (2.4%)	3 (7.9%)	1 (0.8%)	0.013
Hypertension	16 (9.8%)	8 (2.1%)	8 (6.3%)	0.007
Primary pathology				
Tumor	72 (43.9%)	12 (31.6%)	60 (47.6%)	0.081
Trauma	3 (1.8%)	0 (0.0%)	3 (2.4%)	0.337
Tuberculosis	2 (1.2%)	0 (0.0%)	2 (1.2%)	0.435
Hepatitis B	4 (2.4%)	1 (2.6%)	3 (2.4%)	0.93
GCS Score	7.7±3.8	5.8±3.8	8.6±3.5	0.021
Time from procedure to infection, days	6 [2.5–13.5]	13.5 [8–16.8]	6 [2.0–12.0]	0.084
LOS, days	26.5 [20.0–40.0]	29.5 [19.3–42.0]	26 [20.0–39.8]	0.665
Sepsis	31 (18.9%)	17 (44.7%)	14 (11.1%)	*P*<0.001
ICU admission	61 (37.2%)	27 (71.1%)	34 (27%)	*P*<0.001
Producing ESBLs	62 (37.8%)	20 (52.6%)	42 (33.3%)	0.032
Surgical wound classification				
Clean	68 (41.5%)	17 (44.7%)	51 (40.5%)	0.640
Clean-contaminated	96 (58.5%)	21 (55.3%)	75 (59.5%)	0.640
EVD	67 (40.9%)	19 (50.0%)	48 (38.1%)	0.191
LD	92 (56.1%)	23 (60.5%)	69 (42.1%)	0.530
Ventilator	42 (25.6%)	21 (55.3%)	21(16.7%)	*P*<0.001
CSF leakage	36 (22.0%)	8 (21.1%)	28 (22.2%)	0.879
Craniotomy	89 (54.3%)	25 (65.8%)	64 (50.8%)	0.104

Abbreviations: GCS, Glasgow Coma Scale; LOS, length of hospital stay; ICU, intensive care unit; ESBLs, extended-spectrum beta-lactamase; EVD, extra ventricular drainage; LD, lumbar drainage; CSF, cerebrospinal fluid.

a craniotomy. The incidence of CSF leakage was 22.0% (36/164). All of the factors are shown in Table 1.

Treatments and Mortality

Antibiotic therapies and outcomes of the *Enterobacteriaceae* infections are illustrated in Table 2. In total, 90.2% of the patients were treated with antibiotic prophylaxis medication. Cefuroxime sodium and ceftriaxone were found to be the two most commonly used prophylactic antibiotics among post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis patients. Vancomycin plus meropenem were the most commonly used empirical antibiotics. There were no significant differences in antibiotic therapy between the two groups. Total in-hospital mortality due to *Enterobacteriaceae* meningitis/encephalitis was 23.2% (38/164). The LOS in the patients of the non-survivor group was 29.5 days (IQR 19.3–42.0 days). Overall, the 126 patients who survived (76.8%) had a median length of hospital stay of 26.0 days (IQR 20.0–39.8 days).

Factors Affecting Survival

Seventy-one of the 164 cases were in hospital for more than 30 days after their first positive CSF bacteria culture. Finally, in this study, the overall 30-day mortality that was attributable to infection rate was 35.2% (25/71). On univariate analysis, comorbidities (diabetes mellitus and hypertension),

Table 2 Antibiotic Therapy and Clinical Outcomes of Patients with Post-Neurosurgical *Enterobacteriaceae* Meningitis/Encephalitis

Factors	Total (n=164)	Non-Survivor (n=38)	Survivor (n=126)	P
Antibiotic prophylaxis	148 (90.2%)	32 (84.2%)	116 (92.1%)	0.153
Ceftriaxone	39 (23.8%)	8 (21.1%)	31 (24.6%)	0.652
Ceftazidime	15 (9.1%)	3 (7.9%)	12 (9.5%)	0.76
Cefuroxime	51 (31.1%)	7 (18.4%)	44 (34.9%)	0.054
Meropenem	28 (17.1%)	8 (21.1%)	20 (15.9%)	0.457
Vancomycin	15 (9.1%)	6 (15.8%)	9 (7.1%)	0.105
Cefoperazone/Sulbactam	2 (1.2%)	0 (0.0%)	2 (1.6%)	0.435
Received empirical antibiotics	131 (79.9%)	32 (84.2%)	99 (78.6%)	0.447
Single antibiotics	26 (15.9%)	5 (13.2%)	21 (16.7%)	0.689
Ceftazidime	3 (1.8%)	0 (0.0%)	3 (2.4%)	0.337
Meropenem	17 (10.4%)	3 (7.9%)	14 (11.1%)	0.569
Cefuroxime	2 (1.2%)	0 (0.0%)	2 (1.6%)	0.435
Vancomycin	3 (1.8%)	1 (2.6%)	2 (1.6%)	0.674
Polymyxin	1 (0.6%)	1 (2.6%)	0 (0.0%)	0.068
Combination two antibiotics	90 (54.9%)	20 (12.2%)	60 (47.6%)	0.588
Vancomycin+Meropenem	75 (45.7%)	14 (8.5%)	61 (48.4%)	0.209
Meropenem+Ceftazidime	3 (1.8%)	1 (2.6%)	2 (1.6%)	0.674
Others	12 (7.3%)	5 (13.2%)	7 (5.6%)	0.115
Combination three antibiotics	15 (9.1%)	5 (13.2%)	10 (7.9%)	0.328
Vancomycin+Meropenem+Ceftazidime	12 (7.3%)	3 (7.9%)	9 (7.1%)	0.876
Others	3 (1.8%)	2 (5.3%)	1 (0.8%)	0.072
Received definitive therapy	137 (83.5%)	31 (81.6%)	106 (84.1%)	0.710
Single antibiotics	21 (12.8%)	2 (5.3%)	19 (15.1%)	0.112
Meropenem	19 (11.6%)	2 (5.3%)	17 (13.5%)	0.165
Vancomycin	2 (1.2%)	0 (0.0%)	2 (1.6%)	0.435
Combination two antibiotics	88 (53.7%)	15 (39.5%)	73 (57.9%)	0.673
Vancomycin+Meropenem	77 (47.0%)	14 (8.5%)	63 (50.0%)	0.154
Vancomycin+Ceftazidime	8 (4.9%)	1 (2.6%)	7 (5.6%)	0.463
Meropenem+Cefoperazone/Sulbactam	3 (1.8%)	0 (0.0%)	3 (2.4%)	0.337
Others	28 (17.1%)	8 (21.1%)	20 (15.9%)	0.457
Combination three antibiotics	14 (8.5%)	4 (10.5%)	10 (7.9%)	0.617
Meropenem+Vancomycin+Ceftazidime	6 (3.7%)	3 (7.9%)	3 (2.4%)	0.113
Meropenem+Ceftazidime+Tigecycline	5 (3.0%)	1 (2.6%)	4 (2.4%)	0.864
Others	3 (1.8%)	0 (0.0%)	3 (2.4%)	0.337

GCS score ≤8, sepsis, ICU admission, producing ESBLs, and ventilation were related to poorer outcomes ($P<0.05$). Kaplan-Meier survival analysis for the above mentioned six risk factors can be seen in Figure 4. We included all factors with a $P<0.10$ on univariate analysis to make further evaluation using a Cox proportional hazards model, and hazard ratios were calculated. As shown in Table 3, on multivariate analysis, GCS scores ≤8 were found to be an independent risk factor for mortality.

Discussion

Meningitis/encephalitis after neurosurgical procedures is gradually increasing and has caused a formidable challenge, resulting in high mortality rates.[11] In this study, we retrospectively analyzed 2416 isolates of neurosurgery in one of the largest neurosurgical centers of China. Among these isolates, there were 176 cases that resulted in neurosurgical bacterial meningitis/encephalitis. The incidence of meningitis/encephalitis infection was 7.3%, which is roughly the same as that reported in current literature.[12]

Enterobacteriaceae is the most important pathogenic bacteria in clinical bacterial infectious diseases. In some previous reports, staphylococcus aureus, coagulase negative staphylococcus, and enterococcus gram-positive bacteria were common pathogenic bacteria of post-neurosurgical

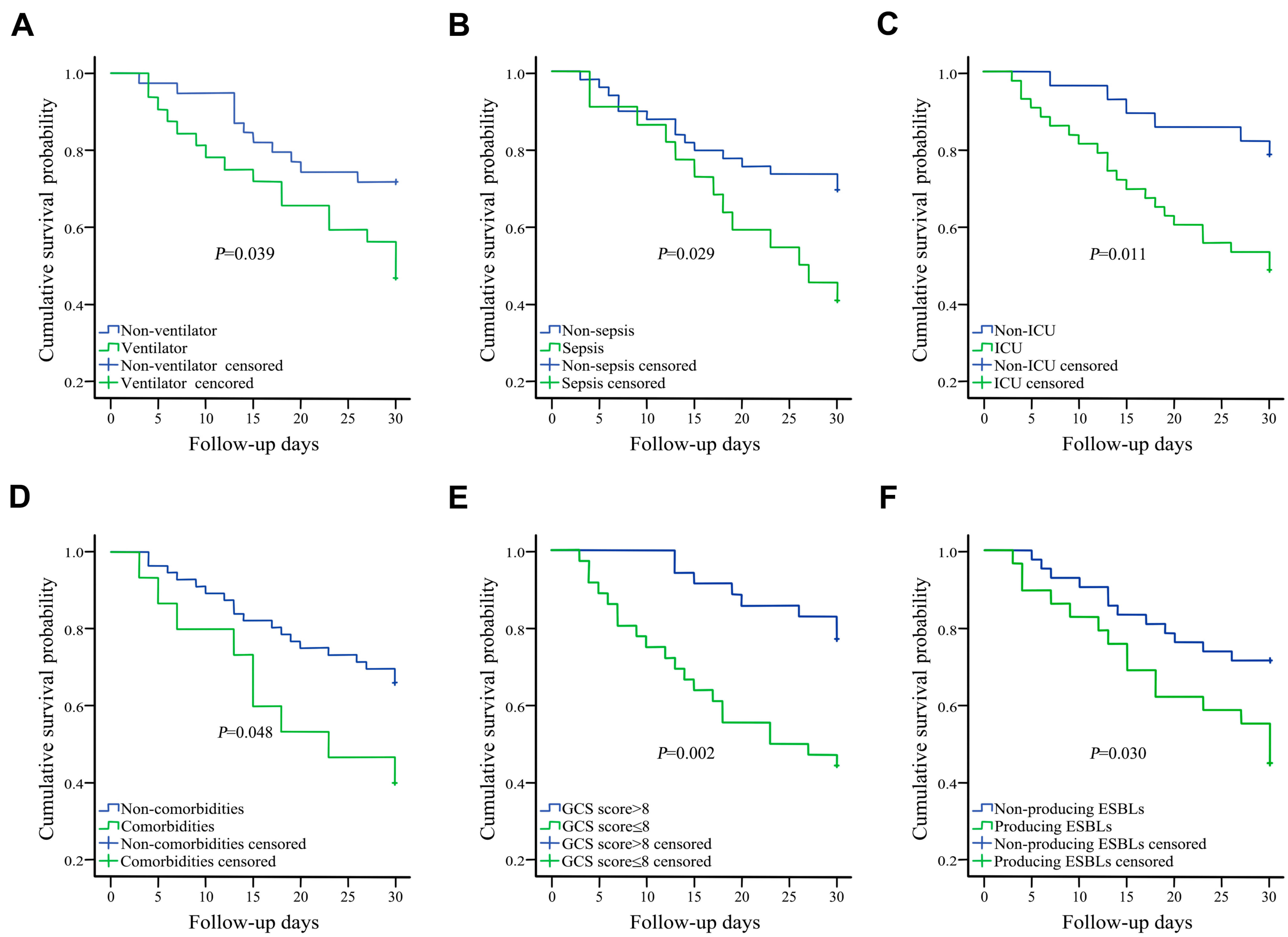

Figure 4 Kaplan–Meier survival analyses for ventilation (**A**), sepsis (**B**), ICU (**C**), comorbidities (**D**), GCS score (≤8) (**E**), and producing ESBLs (**F**).
Abbreviations: ICU, intensive care unit; GCS, Glasgow Coma Scale; ESBL, extended-spectrum beta-lactamase.

meningitis/encephalitis. However, during the last decades, gram-negative bacilli, especially *Enterobacteriaceae* has become the most common pathogenic bacteria in post-neurosurgical meningitis/encephalitis patients.[13,14] Carbapenem-resistant *Enterobacteriaceae* and ESBL-producing *Enterobacteriaceae* were one of the most urgent antibiotic-resistant bacteria assigned by the World Health Organization (WHO) in 2017.[15] Haifa analyzed 185 cases of adult post-neurosurgical meningitis/encephalitis cases, of which, 117 (63.2%) were infected by gram-negative bacilli, with *Enterobacteriaceae* accounting for 55.[16] Diagnosis and early treatment of infections caused by ESBL-producing *Enterobacteriaceae* bacteria has become an important problem that needs to be solved urgently due to its resistance to a variety of biological drugs, including three generations of cephalosporins. ESBL, which is common in *Enterobacteriaceae*, hydrolyzes super broad-spectrum cephalosporins and clavulanic acid inhibits their hydrolysis.[17] In this study, the top three species of *Enterobacteriaceae* were *K. pneumoniae* (77, 47%), *E. coli* (29, 17.7%), and *E. cloacae* (17, 10.4%) (Figure 1), which is consistent with the results of our previous study.[18]

From this study, 37.8% of *Enterobacteriaceae* were found to produce ESBLs. Overall, 89.6% of *Enterobacteriaceae* were found to be resistant to

Table 3 Prognostic Risk Factors of Post-Neurosurgical *Enterobacteriaceae* Meningitis/Encephalitis Screened by Multivariate Cox Proportional Hazards Model

Factors	HR (95% CI)	P
Ventilation	1.209 (0.519–2.816)	0.660
Sepsis	1.281 (0.560–2.931)	0.557
Producing ESBLs	1.119 (0.483–2.592)	0.793
ICU admission	2.274 (0.832–6.215)	0.109
Comorbidities	1.594 (0.679–3.739)	0.284
GCS score≤8	2.588 (1.056–6.346)	0.038

Abbreviations: HR, hazard ratio; CI, confidence interval; ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit; GCS, Glasgow Coma Scale.

ampicillin. It has been reported that the most effective and reliable antibiotics to treat infections caused by ESBL-producing *Enterobacteriaceae* are Carbapenems.[19] Similarly, in our study, more than 80% of the isolates were sensitive to imipenem and meropenem indicating that this combination of antibiotics can be used for antibiotic prophylaxis of suspected meningitis after neurosurgery. All of the isolates were sensitive to polymyxin B.

According to the present study, preoperative antibiotic prophylaxis and intraoperative antibiotic administration are routine procedures currently used in neurosurgery. In our study, the combination of two antibiotics was more common in definitive therapy. In total, 77 of the 164 patients were given vancomycin plus meropenem. Although our results were not statistically significant, antibiotic combinations seemed to be more effective than single therapy antibiotics for *Enterobacteriaceae* meningitis/encephalitis in post-neurosurgical patients.

As previously reported, the mortality rate of meningitis/encephalitis in post-neurosurgical patients ranges from 15% to 35%,[20,21] and consistent with these prior studies, the total in-hospital mortality rate for the diagnosis of *Enterobacteriaceae* meningitis/encephalitis in our study was 23.2%. Many previous studies have only shown the risk factors of neurosurgical infection, which include percentage of males, CSF leakage, surgical diagnosis, surgeon, early reoperation, surgical duration, EVD, LD, diabetes, and so on.[3,22] However, few reports have focused on risk factors for predicting survival in post-neurosurgical patients. As we know, our study is the first to analyze death risk factors associated with *Enterobacteriaceae* meningitis/encephalitis in post-neurosurgical patients. Ravi Sharma's recent study predicted survival following Acinetobacter meningitis/ventriculitis and suggested that an age >40 years, GCS score ≤8, presence of EVD, CSF WBC count >200 cells/mm3, and the presence of comorbidities were risk factors for mortality.[23] While the impact of the surgical wound, ICU admission, ventilation, producing ESBLs, CSF leakage, and craniotomy were not evaluated in his report. In univariate analysis of the risk factors for predicting *Enterobacteriaceae* meningitis/encephalitis survival, we found that ICU admission, ventilation, producing ESBLs, sepsis, GCS score ≤8, and comorbidities were significant risk factors for mortality. GCS scores greater than 8 and without comorbidities (diabetes mellitus or hypertension) predicted better outcomes, which was in line with the Ravi Sharma's study. In addition, patients with ventilation, sepsis, ICU admission, and producing ESBLs were found to have lower survival rates during the follow-up days.

GCS scores are widely used as a useful predictor for investigating patients with head injuries due to its ease of application, simplicity, and quickness.[24,26] GCS scores for all of the patients were recorded on admission. There was a significant difference in the GCS scores between the dead (5.8±3.8) and alive (8.6±3.5) patients (P=0.021). According to our study, in multivariate Cox regression analysis it was also associated with 30-day mortality. A GCS score ≤8 was an independent risk factor for in-hospital death (HR=3.144, P=0.006). This finding highlights that patients with a low GCS score are more likely to have a poor outcome and antibiotic prophylaxis strategies could be developed in advance.

Several limitations exist in this study. Firstly, this is a single center, with a single source of patients, which may restrict the general applicability of the findings worldwide. In addition, the sample size of the survival analysis group was relatively small, because many patients stayed in the hospital less than 30 days. Therefore, the power of the outcome studies was limited. Secondly, post-neurosurgical aseptic meningitis was not concerned in this study. Among post-neurosurgical patients, aseptic meningitis accounts for a large proportion. Post-neurosurgical aseptic meningitis is induced by exfoliated tumor cells, hemolysis products, bone dust and implants, which are usually produced during surgery.[27] Both aseptic meningitis and bacterial meningitis patients have similar clinical symptoms whereas patients with aseptic meningitis have milder clinical symptoms and require no antibiotic treatment. However, the main task of this study is to evaluate the clinical outcome of *Enterobacteriaceae* meningitis/encephalitis, so aseptic meningitis was not embedded in this article. Thirdly, the patients' surgical exposure time is not fully recorded in our database, and the complexity of surgery is difficult to quantify, so we have not included these two indicators in our study. As previously reported, the surgery duration, major craniotomy and transsphenoidal surgery as associated with the development of meningitis after neurosurgical procedures. Patients undergoing long and complicated operations always mean an increased incidence of meningitis. Lastly, laboratory indicators were not involved in our study, we will assess the impact of laboratory indicators on post-neurosurgical meningitis outcome in the future. Considering all of these limitations, we intend to confirm the present results using a larger observational study or even a prospective cohort study.

Conclusion

In the current study, we classified the largest database of post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis. More than 85% of the isolates were sensitive to imipenem and meropenem, and all of the isolates were sensitive to polymyxin B. We obtained a high mortality rate in the post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis. GCS scores ≤8 were found to be an independent predictor for in-hospital mortality in post-neurosurgical *Enterobacteriaceae* meningitis/encephalitis. Appropriate definitive treatment for *Enterobacteriaceae* meningitis/encephalitis is essential.

Ethics and Consent Statement

Our study has been conducted in accordance with the Declaration of Helsinki and been approved by the Beijing Tiantan Hospital of Capital Medical University. We performed a retrospective analysis of patient clinical information and did not conduct experiments on patient specimens. The data of the patients were maintained with confidentiality. In this study, only the medical records obtained from previous clinical treatment were used for retrospective analysis, and there was almost no risk to the patients. Considering of these reasons, after consultation with the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University, written patient consent was not required.

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Disclosure

The authors report no conflicts of interest in this work.

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