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Risk factors for 90-day all-cause mortality in post-operative central nervous system infections (PCNSIs)

A retrospective study of 99 patients in China

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Abstract

Post-operative central nervous system infections (PCNSIs) are serious complications of craniotomy. Many factors, including patient-related, surgical, and postoperative factors, affect the survival of patients with PCNSIs. Timely and effective implementation of antibiotics targeting pathogenic bacteria is crucial to reduce mortality. Metagenomic next-generation sequencing (mNGS) has been used successfully to detect pathogens associated with infectious diseases. This study was designed to evaluate the factors influencing mortality and to explore the application value of mNGS in patients with PCNSIs. We conducted a retrospective study of patients with PCNSIs in our unit from 1/12/2019 to 28/2/2021. Clinical data, cerebrospinal fluid (CSF) parameters, surgical information, and mNGS results were collected. Follow-up telephone calls were made in June 2021 for 90 days survival after discharge. 99 patients were enrolled, and the overall mortality rate was 36.4% (36/99). Kaplan–Meier survival analysis suggested that the risk factors for poor prognosis included age ≥ 53 years, Glasgow Coma scale (GCS) score ≤ 8, CSF/blood glucose ratio (C/B-Glu) ≤ 0.23, 2 or more operations, mechanical ventilation (MV), and non-mNGS test. MV and poor wound healing were independent risk factors for 90 day mortality according to the multivariate Cox proportional hazards model (OR = 6.136, $P = .017$, OR = 2.260, $P = .035$, respectively). Among the enrolled patients, causative pathogens were identified in 37. Gram-negative pathogens were found in 22 (59.5%) patients, and the remaining 15 (40.5%) were Gram-positive pathogens. Univariate analysis showed that white cell count and protein and lactate levels in the CSF of the Gram-negative group were higher than those of the Gram-positive group ($P < .05$). mNGS and conventional microbiological culture were tested in 34 patients, and the positive detection rate of mNGS was 52.9%, which was significantly higher than that of microbiological culture (52.9% vs 26.5%, $\chi^2 = 4.54$, $P = .033$). The mortality rate of PCNSIs is high, and patients with MV and poor wound healing have a higher mortality risk. Gram-negative pathogens were the predominant pathogens in the patients with PCNSIs. mNGS testing has higher sensitivity and has the potential to reduce the risk of mortality in patients with PCNSIs.

Abbreviations: C/B-Glu = CSF/blood glucose ratio, CNS = central nervous system, CSF = cerebrospinal fluid, EVD = external ventricular drainage, GCS = Glasgow Coma scale, ICU = intensive care unit, mNGS = metagenomic next-generation sequencing, MV = mechanical ventilation, PCNSIs = post-operative central nervous system infections.

Keywords: clinical outcome, metagenomic next-generation sequencing (mNGS), pathogens, post-operative central nervous system infections (PCNSIs), risk factors

1. Introduction

Post-operative central nervous system infections (PCNSIs) are common and serve as complications secondary to craniotomy, resulting in serious neurological dysfunction or even death. The incidence of PCNSIs varies from 0.5% to 21.4%.[1–3] Many previous studies have only shown the risk factors for PCNSIs, including diabetes, trauma surgery, time of operation, surgical duration, intraoperative bleeding, external ventricular drainage (EVD), and cerebrospinal fluid (CSF) leakage.[4,5] However, few studies have focused on risk factors for predicting survival in patients with PCNSIs.

The pathogen distribution of PCNSIs includes a spectrum of microorganisms, from Gram-positive bacteria to Gram-negative

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bacteria, and is highly variable. Previous studies have shown that the primary pathogens are Gram-positive bacteria, while a shift towards Gram-negative bacteria has been observed, and Gram-negative organisms seem to be increasing as primary causative agents of PCNSIs.[6–8] The most commonly used gold standard for pathogenic microorganism detection is microbiological culture of CSF. However, it is time-consuming and has a low positive rate with a sensitivity range of 7.56% to 41%.[9,10] Metagenomic next-generation sequencing (mNGS) is an emerging application capable of detecting thousands of fragments in a laboratory test and reducing the number of tests and period of detection. Recent studies that compared the diagnostic performance of mNGS with traditional microbiological culture demonstrated that the sensitivity of mNGS for the detection of microorganisms ranged from 34.45% to 85.7%, which exceeded that of culture and was rarely affected by prior antibiotic use.[9–11] Therefore, mNGS has greatly advanced infection diagnosis and has the potential to be used as a front-line diagnostic tool to identify causative pathogens in patients with suspected intracranial infection. However, studies focusing on the influence of mNGS testing on PCNSIs patients were scarce.

To explore the factors influencing mortality, compare the clinical features of Gram-positive and Gram-negative pathogens, and explore the value of mNGS in PCNSIs patients, we retrospectively reviewed PCNSIs patients admitted to The First Affiliated Hospital of Zhengzhou University from December 1, 2019 to February 28, 2021.

2. Materials and Methods

2.1. Participants

In neurological intensive care unit (ICU), patients met the clinical diagnostic criteria of central nervous infection after craniotomies which adjudicated by their clinicians from December 1, 2019 to February 28, 2021 were included in this study.

2.2. Data collection

Clinical data, including age, sex, trauma, Glasgow Coma scale (GCS) score, hypoalbuminemia, hormonotherapy, and mechanical ventilation (MV), and surgical data, including time of operation, intraoperative blood loss, surgery to infection time, drainage devices, wound healing, and treatment, were collected. CSF samples were collected under aseptic condition by the following ways: lumbar puncture, lumbar cistern drainage or ventricular drainage. The most typical changes in CSF analysis reports were recorded, including the white cell count, neutrophil percentage, protein, glucose, chloride, lactate, and microbial cultures. Patients' CSF samples were sent for mNGS only consent was obtained from their families, and the results were interpreted by clinicians. Finally, follow-up telephone calls were made in June 2021 for 90 days survival after discharge.

2.3. Ethics statement

The study was approved by the local research ethics committee of the First Affiliated Hospital of Zhengzhou University in China (approval number: 2020-KY-507). Written or oral informed consent was obtained from legal representatives of patients.

2.4. Statistical analysis

SPSS 26.0 software and GraphPad Prism software packages were used for statistical analysis. Descriptive statistics for continuous and categorical variables were summarized as means (SDs) or medians (25th and 75th percentiles) and numbers (percentages), respectively. The mean and median were used as the cutoff values for age, GCS score, and CSF/blood glucose ratio (C/B-Glu). In univariate analysis, quantitative variables were analyzed using the independent *t* test and Mann–Whitney test, and categorical variables were analyzed using the Chi-square test, Fisher's exact test, and continuity-adjusted Chi-square test. Univariate survival analysis was performed using Kaplan–Meier (K-M) plots. Factors with a *P* value of less than .1 on the univariate analysis were entered into the multivariate Cox proportional hazards model. Fisher's exact test was used to compare the detection rates of mNGS and microbiological culture. A *P* significance was set at $P < .05$.

3. Results

3.1. Basic data and clinical features

A total of 99 PCNSIs patients (65 men, 34 women; mean age: 52.89 ± 15.17years) were enrolled in this study. 36(36.4%) patients died between the diagnosis of PCNSIs and 90d after discharge. There was significant difference in age distributions between the death group and survival group (57.97 ± 13.92 vs 49.98 ± 15.19, $P = .011$). 34(34.3%) patients were sent for CSF mNGS test, and the submission rate of the survivor group was higher than that of the death group (22.2%), with the difference close to statistical significance ($P = .055$). The GCS scores in the non-survivor group (5.5(3.25–8.75)) were significantly lower than those in the survivor group (9(6–14)) ($P = .001$). CSF glucose and C/B-Glu levels were lower in the non-survival group than in the survival group and the number of patients with C/B-Glu ≤ 0.23 in the death group was higher than that in the survival group. Patients who had 2 or more craniotomies in the non-survivor group were significantly more than the survivor group (69.4% vs 39.7%, $P = .004$). 26(27.1%) patients experienced poor wound healing. There were 59 (63.4%) patients with extra ventricular drainage (EVD) and 27(44.3%) patients with 2 or more EVDs. 33(91.7%) patients in the non-survivor group required MV, which was significantly higher than that in the survivor group ($P = .001$). All of these factors are shown in Table 1.

3.2. Factors influencing survival

On univariate analysis, age, GCS score, C/B-Glu, 2 or more operations, and MV were associated with poorer outcomes ($P < .05$). Kaplan–Meier survival analysis was performed for these risk factors. To evaluate the impact of mNGS testing on survival, an additional Kaplan–Meier survival analysis was performed. The results are shown in Figure 1. We included all factors with a $P < .10$ on univariate analysis to perform further survival analysis using a Cox proportional hazards model, and hazard ratios were calculated. As shown in Table 2, MV and poor wound healing were the independent risk factors for mortality.

3.3. Comparison of PCNSIs caused by Gram-negative and Gram-positive pathogens

Causative pathogens were found in 37 patients with PCNSIs using CSF microbiological culture or CSF mNGS tests. Of these, 22(59.5%) were Gram-negative and 15(40.5%) were Gram-positive. The CSF white cell count and protein and lactate levels of the Gram-negative group were significantly higher than those of the Gram-positive group ($P < .05$). The overall mean time from surgery to infection time was 9.67 days and the Gram-negative group was higher than that of the Gram-positive group ($P = .05$). There were no significant differences in the rate of MV use, duration of MV, ICU length of stay, or mortality between the 2 groups. The results were shown in Table 3.

Table 1

Demographic and clinical characteristics of 99 patients with post-operative central nervous system infections.

Characteristics	Total(n = 99)	Mortality(n = 36)	Non-mortality (n = 63)	*P* value
Male, gender	65(65.7)	26(72.2)	39(61.9)	.325
Age, yrs	52.89 ± 15.17	57.97 ± 13.92	49.98 ± 15.19	.011
mNGS test	34(34.3)	8(22.2)	26(41.3)	.055
Disease evaluation				
Trauma	17(17.2)	9(25)	8(12.7)	.118
GCS score	8(5–13)	5.5(3.25–8.75)	9(6–14)	.001
Diabetes mellitus	8(8.1)	3(8.3)	5(7.9)	1.000
Hypoalbuminemia	74(74.7)	28(77.8)	46(73)	.600
Hormonotherapy	3(3.0)	2(5.6)	1(1.6)	.618
CSF parameters				
Glucose, mmol/L	1.85(0.74–3.02)	1.23(0.20–2.22)	2.23(1.32–3.76)	.001
C/B-Glu	0.23(0.08–0.38)	0.12(0.02–0.30)	0.27(0.19–0.43)	.002
C/B-Glu ≤ 0.23	49(50.5)	24(66.7)	25(41)	.015
Surgical data				
Twice or more operations	50(50.5)	25(69.4)	25(39.7)	.004
From surgery to infection, d	5(4–10)	6.5(4–12.25)	5(4–10)	.237
Duration of surgery, min	210(120–270)	210(185–240)	200(97.5–300)	.845
IBL, mL	200(100–400)	200(100–300)	250(112.5–400)	.640
EVD	59(63.4)	23(63.9)	36(63.2)	.943
Two or more EVDs	27(44.3)	11(445.8)	16(43.2)	.842
Lumbar drainage	20(22.7)	8(22.9)	12(22.6)	.981
Brain parenchyma drainage	2(2.2)	0(0)	2(3.6)	.521
Subdural or subcutaneous drainage	43(51.2)	18(54.5)	25(49)	.621
Poor wound healing	26(27.1)	13(37.1)	13(21.3)	.093
Treatment				
Preoperative antibiotics	36(67.9)	12(66.7)	24(68.6)	.888
High-grade antibiotics	96(97)	35(97.2)	61(96.8)	1.000
MV	69(69.7)	33(91.7)	36(57.1)	.001
Duration of MV, days	9(3–14.75)	9(2.25–15.5)	10(3.25–14.74)	.716
Hospital length of stay, days	28 (17–45)	16.5(10–27.75)	36(25–49)	.000
ICU length of stay, days	22(14–32)	15.5(9.25–27.25)	26(17–40)	.001

C/B-Glu = CSF/blood glucose ratio, CSF = cerebrospinal fluid, EVD = external ventricular drainage, GCS = Glasgow Coma Scale, IBL = intraoperative blood loss, ICU = intensive care unit, mNGS = metagenomic next-generation sequencing, MV = mechanical ventilation.

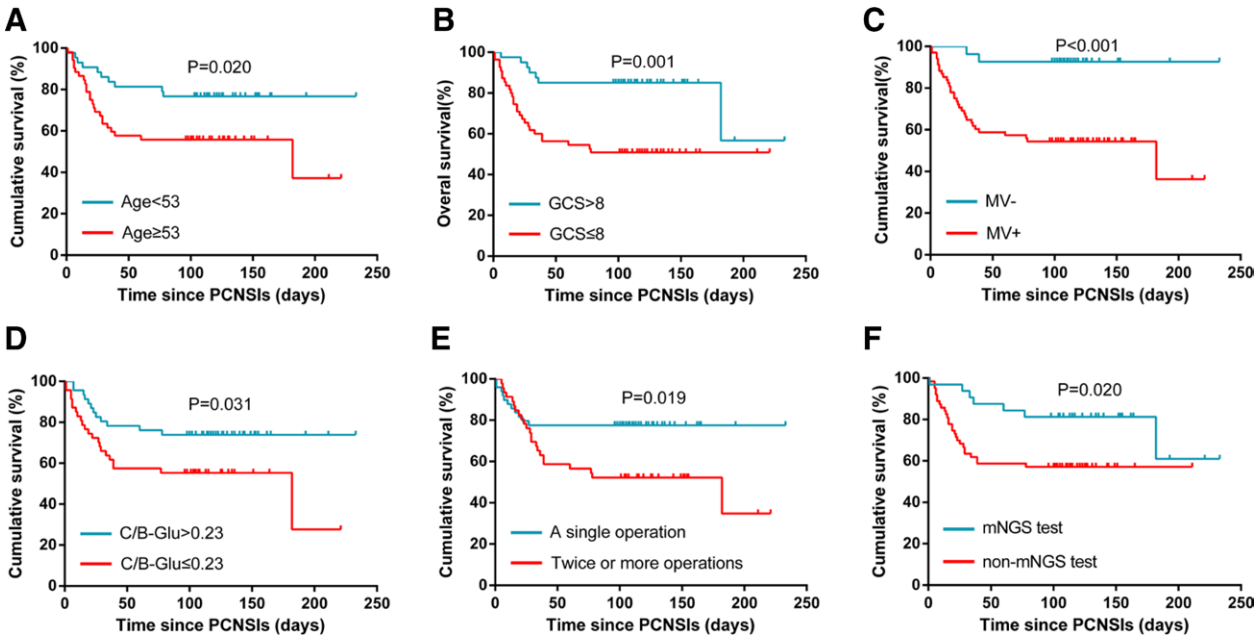

Figure 1. Kaplan–Meier survival analyses for Age ≥ 53(A), GCS ≤ 8 (B), MV (C), C/B-Glu ≤ 0.23 (D), Twice or more operations (E), mNGS test (F). C/B-Glu = CSF/blood glucose ratio, GCS = Glasgow Coma Scale, mNGS = metagenomic next-generation sequencing, MV = mechanical ventilation.

3.4. Comparison of diagnostic values between mNGS and microbial cultures

Among 99 PCNSIs, 34 were tested for CSF mNGS as well as conventional CSF microbial culture. Eighteen (52.9%) patients had positive mNGS results, and 9 (26.5%) had positive culture findings. The detection rate of mNGS was significantly higher than that of microbial culture ($P = .019$) (Table 4). Pathogenic bacteria were detected in 10 culture-negative patients using mNGS testing.

Table 2

Prognostic risk factors for post-operative central nervous system infections screened by multivariate cox proportional hazards model.

Variables	HR	95%CI	*P* value
Age ≥ 53	2.139	0.957–4.785	.064
GCS ≤ 8	1.568	0.616–3.993	.346
MV	6.136	1.378–27.329	.017
C/B-Glu ≤ 0.23	1.708	0.809–3.604	.160
Twice or more operations	1.203	0.545–2.658	.647
Poor wound healing	2.260	1.061–4.818	.035
mNGS test	0.501	0.196–1.281	.149

C/B-Glu = CSF/blood glucose ratio, CI = confidence interval, GCS = Glasgow Coma Scale, HR = hazard ratio, mNGS = metagenomic next-generation sequencing, MV = mechanical ventilation.

4. Discussion

The mortality rate of intracranial infection post-neurosurgery ranges from 23.2% to 40.3%.[8,12,13] In our study, the overall mortality rate of PCNSIs was 36.4%, which is consistent with the results of previous studies. Many previous studies have only shown the risk factors for PCNSIs, while literature regarding factors affecting survival is uncommon. Shi et al and Zhang et al reported that age > 50 years, MV, ICU admission, pulmonary infections, and GCS score ≤ 8 were risk factors for increased mortality, whereas CSF information, operative data, and mNGS testing were not evaluated in their studies.[13,14] Our study revealed that in addition to GCS score, MV, and age, C/B-Glu ≤ 0.23, a total number of operations larger than 2 and non-mNGS test were also risk factors for mortality. In the Cox proportional hazards analysis, we found that MV and poor wound healing were significant risk factors for mortality.

Poor wound healing includes exudates, CSF leakage, surgical site infection, dehiscence, and so on. Previous studies have shown that poor wound healing is linked to the risk of postoperative intracranial infection and increases the rates of re-operation and re-admission.[3,15] Factors such as surgery for tumors, glucocorticoids, diabetes, radiation, chemotherapy, poor nutrition, and EVD can all contribute to poor wound healing.[16,17] Our study confirmed that poor wound healing is a significant risk factor for death, and clinicians should pay more attention to wound healing after craniotomy.

As an emerging diagnostic technology that can quickly detect all nucleic acids in the CSF in 1 test, mNGS has been successfully used clinically for rapid identification of pathogens in patients with central nervous system (CNS) infection. Our study compared the effectiveness of mNGS with that of traditional microbiological testing methods and found that the sensitivity of mNGS (52.9%) was higher than that of culture (26.5%). This result is consistent with previous studies.[9,11,18] However, previous studies on mNGS have mostly focused on its diagnostic efficacy, and the influences of mNGS on outcomes in patients with PCNSIs have been rarely studied. In the respiratory domain, Zhang et al found that the 28-day mortality rate of acute respiratory distress syndrome in the mNGS group was significantly lower than that in the non-mNGS group.[19] Kaplan–Meier survival analyses revealed that mNGS testing could reduce 90d mortality in patients with PCNSIs. The difference was not statistically significant in the multivariate Cox proportional hazards model, potentially due to the small sample size, and further studies are planned.

One patient in our study, with positive CSF culture findings, showed a negative mNGS test. A possible reason for this unexpected outcome could be that the CSF specimen submitted for the mNGS test was collected after 4 days of antimicrobial

Table 3

Characteristics of patients with Gram-negative bacteria and Gram-positive bacteria.

Characteristics	Total n = 37	Gram-Negative n = 22(%)	Gram-Positive n = 15(%)	*P* value
Basic characteristics				
Male, gender	27(73)	16(72.7)	11(73.3)	1.000
Age, yrs	50.62(13.35)	49.55(13.89)	52.2(12.82)	.56
Trauma	7(18.9)	5(22.7)	2(13.3)	.677
Diabetes mellitus	5(13.5)	3(20.0)	2(9.1)	.377
GCS score	8(5–14)	6.5(4.75–10.25)	10(5–15)	.161
Hypoalbuminemia	28(75.7)	17(77.3)	11(73.3)	1.000
Hormonotherapy	2(5.4)	2(9.1)	0(0.0)	.505
CSF parameters				
White cells count, mm^3	6224.54(10166.13)	8913.86(12283.13)	2280.20(3377.95)	.024*
PMN neutrophils, %	90(80.1–95.1)	90.25(79.75–96.98)	89.8(83.2–92.8)	.448
Protein, mg/L	5155.81(6044.22)	6392.1(6519.53)	3342.6(4925.45)	.007*
Glucose, mmol/L	1.26(0.15–3.94)	0.42(0.06–2.35)	1.49(0.74–4.74)	.105
C/B-Glu	0.10(0.01–0.31)	0.03(0.01–0.20)	0.22(0.05–0.39)	.096
C/B-Glu ≤ 0.23	25(71.4)	17(81.0)	8(57.1)	.252
Chloride, mmol/L	118.57(12.31)	115.79(9.72)	122.65(14.76)	.096
Lactate, mmol/L	11.35(5.46)	13.58(4.38)	8.83(5.57)	.011
Surgical data				
Twice or more operations	20(54.1)	14(63.6)	6(40.0)	.193
From surgery to infection time, days	9.67(6.22)	11.15(7.35)	7.38(2.9)	.05
EVD	20(70.6)	17(81)	7(53.8)	.130
Poor wound healing	18(51.4)	12(60)	6(40)	.315
Treatment and outcome				
High-grade antibiotics	36(97.3)	22(100)	14(93.3)	.405
MV	25(67.6)	17(77.3)	8(53.3)	.164
Duration of MV, days	9(4–18.5)	9(4.5–23.5)	9(2.5–14.5)	.628
Hospital length of stay, days	29(18–43)	28.5(15.5–50.75)	29(19–39)	.891
ICU length of stay	25.0 (16.5–32.0)	28.0(15.5–37.25)	22.0(17.0–31.0)	.366
Mortality	17(43.2)	12(54.5)	5(26.7)	.176

C/B-Glu = CSF/blood glucose ratio, CSF = cerebrospinal fluid, EVD = external ventricular drainage, GCS = Glasgow Coma Scale, ICU = intensive care unit, MV = mechanical ventilation, PMN = polymorphonuclear leukocytes.

*Variables were taken the natural logarithm in the analysis, because of its non-normally distribution.

Table 4

Comparison between metagenomic next-generation sequencing testing and microbial cultures.

	Culture(+)	Culture(–)	Total
mNGS(+)	8	10	18(52.9)
mNGS(–)	1	15	16(74.1)
Total	9(26.5)	25(73.5)	34(100)

mNGS = metagenomic next-generation sequencing.

therapy with the combination of meropenem and vancomycin. According to the conclusion of Yi Zhang et al, after more than 4 days of effective antimicrobial therapy, the mNGS detection rate would be significantly decreased.[9] The improved body temperature and CSF parameters proved that the treatment conducted in this patient was effective, and the contemporaneous culture results were negative. Five days later, the patient presented with hyperpyrexia and heavy exudation in the surgical wound, indicating that the infection was aggravated. The CSF specimens collected at this point developed positive culture findings; however, regrettably, mNGS was not submitted again.

Gram-negative organisms were the dominant pathogen in our cohort, accounting for 59.5% of PCNSIs pathogens, which is in line with prior studies.[8,20–22] Our study provides references and bases for empirical antibiotic treatment in patients suspected of having intracranial infections after craniotomy. CSF white cell count and protein and lactate levels were higher in the Gram-negative group, suggesting that Gram-negative organisms change CSF analysis reports more prominently. Behice et al found that the fatality rate of nosocomial meningitis caused by Gram-negative microorganisms is higher than that of Gram-positive bacteria.[8] Similarly, our study found that the fatality rate of PCNSIs caused by Gram-negative pathogens was 54.5%, which was higher than that of Gram-positive pathogens (26.7%), although this trend was not statistically significant due to the small sample size.

Limitations: First, the small sample size and single center data may have limited the generalizability of our findings. Second, the economic situation and extent to which patients were concerned by their family may influence the submission rate of mNGS and patient outcomes. In addition, the predominant causative pathogen of PCNSIs was bacteria, so the diagnostic value of mNGS in viral, fungal, and parasitic CNS infections was not discussed in our study. These issues will be discussed in future studies. Considering these limitations, we intend to conduct a larger observational study or prospective cohort study in the future.

5. Conclusion

In this study, we observed a high mortality rate among patients with PCNSIs. MV and poor wound healing were independent risk factors for 90d mortality. CSF mNGS testing has a higher sensitivity than microbial culture and has the potential to reduce the risk of mortality in patients with PCNSIs. Gram-negative pathogens were the predominant pathogens in patients with PCNSIs, and CSF inflammatory findings were more pronounced than those of Gram-positive pathogens.

Author contributions

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Software: Yanan Zhao, Yafei Xu.
Supervision: Wenjing Deng, Junfang Teng.
Visualization: Yanan Zhao, Pengwei Pan.
Writing – original draft: Yanan Zhao.
Writing – review & editing: Yanan Zhao, Wenjing Deng.

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