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Original Article

Predictors of mortality in post-neurosurgical Gram-negative bacterial meningitis: a five-year retrospective study

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Abstract

Introduction: The incidence of Gram-negative bacterial meningitis (GNBM) has increased with the growing number of neurosurgical procedures. Concurrently, global antimicrobial resistance, particularly among Gram-negative pathogens causing healthcare-associated infections, has contributed to high morbidity and mortality. This study aimed to identify clinical and laboratory parameters associated with mortality in post-neurosurgical GNBM (PN-GNBM).

Methodology: This retrospective study included adult patients who developed GNBM at least 48 hours after a neurosurgical procedure in the intensive care unit of a tertiary hospital between January 2019 and March 2024. Clinical findings and laboratory results before and at the time of diagnosis were obtained from the hospital information system. The factors associated with all-cause 28-day mortality were evaluated. Statistical analyses were performed using SPSS version 19, with $p < 0.05$ considered statistically significant.

Results: A total of 21 PN-GNBM patients were included. The 28-day mortality rate was 60%. Evaluation of peripheral blood leukocyte ratios at the time of diagnosis revealed that a low lymphocyte-to-platelet ratio (LPR) significantly predicted mortality on days 7, 14, and 21 (p = 0.046, 0.003, and 0.005, respectively), whereas a high neutrophil-to-lymphocyte ratio (NLR) predicted 14-day mortality (p = 0.035). *Acinetobacter baumannii* was the most frequently isolated pathogen with 81.81% carbapenem resistance rate.

Conclusions: NLR and LPR are inexpensive and readily accessible biomarkers that may support early mortality prediction and risk stratification in PN-GNBM. These preliminary findings should be validated in larger multicenter studies.

Key words: post-neurosurgical meningitis; Gram-negative bacteria; mortality; neutrophil-to-lymphocyte ratio (NLR); lymphocyte-to-platelet ratio (LPR), lymphocyte-to-monocyte ratio (LMR).

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Introduction

The mortality rate in healthcare-associated meningitis (HCAM) or ventriculitis ranges between 9.3 and 40.3%, and the condition is associated with prolonged hospital stay and increased treatment costs [1]. In recent years, Gram-negative bacteria (GNB)—particularly carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant Enterobacterales (CRE), and multidrug-resistant (MDR) or difficult-to-treat-resistant (DTR) *Pseudomonas aeruginosa*—have increasingly emerged as the predominant causative agents of post-neurosurgical meningitis (PNM) [2–7]. These pathogens were prioritized in the 2024 Infectious Diseases Society of America (IDSA) Antimicrobial Resistance Guideline because of their limited therapeutic options and high associated mortality [8]. In PNM, the shift toward GNB etiology is clinically significant, as treatment is more complex, antibiotic penetration into the cerebrospinal fluid (CSF) is variable, and management of surgical devices often becomes necessary [1,8]. However, the number of studies conducted on this topic in our country in recent years remains considerably limited [9–11].

Only a limited number of studies have explored the association between the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), and mortality in sepsis cases [12,13]. Evidence regarding the prognostic value of NLR in pediatric bacterial meningitis and adult tuberculous meningitis is likewise scarce [14,15]. However, to date, no published study has comprehensively evaluated the impact of NLR, LPR, or the lymphocyte-to-monocyte ratio (LMR) on mortality in post-neurosurgical Gram-negative bacterial meningitis (PN-GNBM).

Given the high morbidity and mortality associated with PN-GNBM and the urgent need for accessible and reliable early prognostic indicators, elucidating the role of peripheral blood leucocyte ratios may provide clinically meaningful insights.

Therefore, this study aimed to identify clinical and laboratory predictors of mortality in PN-GNBM, with a particular emphasis on assessing NLR, LPR, and LMR as potential early biomarkers to support risk

stratification and timely clinical decision-making in this vulnerable patient population.

Methodology

Study design

The study design was retrospective, single-center, and observational. The records of patients followed in the neurosurgery intensive care unit (ICU) of a 1,045 bed tertiary care hospital between 1 January 2019 and 31 March 2024 were reviewed. The diagnosis of HCAM was made according to the Centers for Disease Control and Prevention healthcare-associated infection diagnosis guidelines [16].

Patient selection criteria

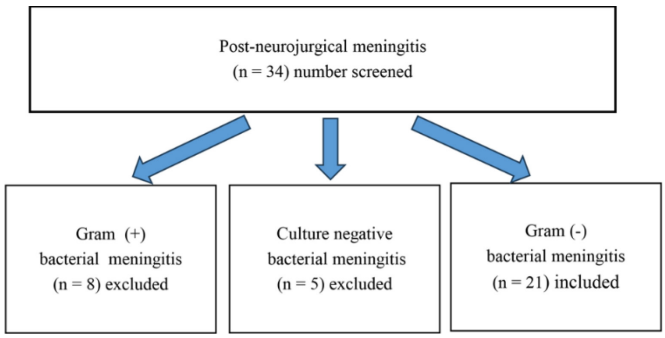
The inclusion criteria were: age ≥ 18 years, history of neurosurgical intervention (e.g., lumbar drainage (LD), ventriculoperitoneal shunt (VPS), external ventricular drainage (EVD), craniotomy, spinal surgery), onset of clinical signs of meningitis ≥ 48 hours after the procedure, microbiological confirmation of GNB from CSF, and accompanied by CSF findings consistent with bacterial meningitis (elevated leukocytes, low glucose, high protein).

The exclusion criteria were: age <18 years, pregnant patients, patients of PNM caused by non–GNB (e.g., Gram-positive cocci, *Mycobacterium tuberculosis*, fungi), culture negative PNM, meningitis occurring within 48 hours post-surgery (to exclude community-acquired or perioperative contamination), and patients without confirmed diagnostic data (e.g., incomplete microbiology or missing CSF results).

Sample analysis

The cerebrospinal fluid samples were incubated using the automated BACTEC FX system (BACTEC FX; Becton Dickinson and Company, Sparks, MD, USA). Upon detection of a positive signal during incubation, subcultures were performed onto eosin methylene blue agar, 5% sheep blood agar and chocolate agar (Becton Dickinson and Company, Sparks, MD, USA). These media were then incubated at 37 °C in 5–10% CO_2 for 24–48 hours. In parallel, Gram-stained smears were prepared and evaluated.

Figure 1. Flowchart of patient selection.



Identification of the isolates was carried out using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibility testing was performed using an automated system (Phoenix; Becton Dickinson and Company, Sparks, MD, USA), and the results were interpreted according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [17].

MDR was defined as resistance to ≥ 1 drug in more than 3 antimicrobial categories (third-generation cephalosporins, carbapenems, aminoglycosides, quinolones, tetracyclines, polymyxins, trimethoprim-sulfamethoxazole, and chloramphenicol antibiotics) [18]. Carbapenem resistance was defined as resistance to at least 1 of the following agents: imipenem, meropenem, or ertapenem. Carbapenem resistance results obtained from the automated system were confirmed by disk diffusion and E-test methods [8].

Clinical findings and laboratory test results before and at the time of diagnosis were obtained from the hospital information system, and factors affecting all-cause 28-day mortality were evaluated.

The independent variables recorded were: demographic characteristics (gender, age), surgery indications (hemorrhage, intracranial mass, and others), comorbidities (malignancy, hypertension, diabetes mellitus, and others), intervention types (craniotomy, spinal surgery, LD, VPS, EVD), presence of EVD prior to meningitis, presence of CSF leakage, presence of infection prior to meningitis, mechanical ventilation (MV), central venous catheter (CVC), Glasgow coma scale (GCS) score, cerebrospinal fluid parameters (leukocyte count, glucose concentration, protein level, and lactate dehydrogenase (LDH) activity), complete blood count (peripheral blood leukocyte count, neutrophil count, lymphocyte count, monocyte count, platelet count), concurrent blood glucose levels at the time of lumbar puncture, cerebrospinal fluid/blood glucose ratio, C-reactive protein (CRP), antibiotic susceptibility test results of the strains isolated from CSF (*Acinetobacter baumannii* and others), empirical and pathogen-targeted antibiotic therapies and their initiation times, and intrathecal/intraventricular (IT/IVT) antibiotic therapies.

The dependent variables were all-cause mortality rates at 7, 14, 21, and 28 days after the diagnosis of

meningitis.

Statistical analysis

Statistical tests were performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA). Descriptive analyses were used for examining the demographic data. Chi-square or Fischer's exact test was used to compare nominally measured independent variables with the nominal dependent variables. Shapiro-Wilk test was used to find out if the the continuous variables distributed normally. Independent sample t-tests compared normally distributed continuous independent variables with dependent variables. Mann-Whitney U tests were used when the continuous independent variables did not show a normal distribution. *p* values below 0.05 were considered statistically significant.

Ethical approval

Ethical approval was obtained from the local ethics committee on 18 July 2024 with approval number 0021.

Results

Twenty one patients with PN-GNBM were examined. Figure 1 shows a flowchart explaining the patient selection process. Most (71.42%) of the patients were males. The mean age of the population was 54.62 ± 18.50 (range 18–90) years. The comorbidities of the patients are summarized in Table 1.

Of the total 21 patients, GCS was available for 13 (61.90%) patients. There were 7 patients with a GCS score of 14–15, 1 patient with a score between 8–13, and 5 patients with a score below 8. The most common reasons for surgery were intracranial hemorrhage (38.09%) and mass lesions (33.33%). Shunt dysfunction (4.76%), brain abscess (4.76%), and CSF leakage (4.76%) were also noted. The most frequent interventions were craniotomy (n = 19, 90.47%) and EVD (n = 18, 85.71%). Six (28.57%) patients had VPS. Spinal surgery and LD were performed in 2 (9.52%) patients. EVD was inserted in 6 patients prior to meningitis, and 8 of the total EVDs were replaced. The shunt was either removed or replaced in all patients with VPS.

Table 1. Comorbidities of 21 patients with post-neurosurgical Gram-negative bacterial meningitis.

Comorbidities	n (%)
Hypertension	6 (28.57)
***Malignancy**	5 (23.80)
Diabetes mellitus	2 (9.52)
COPD	1 (4.77)
Cerebrovascular disease	1 (4.77)
Coronary artery disease	1 (4.77)
Multiple Comorbidities	5 (23.80)

*Excluding primary brain tumors (stomach, testicular, lung, or rectum cancer). COPD: chronic obstructive pulmonary disease.

Mortality analysis was performed on 20 patients because 1 patient was transferred to another medical center before day 28. The 28-day all-cause mortality rate was 60% (n = 12). Although CSF leakage was significantly lower in patients who died on day 28, this result was not considered clinically significant due to the small number of cases. No significant effect on mortality was observed for the other independent factors listed in Supplementary Table 1.

The blood and CSF laboratory test results at the time of the diagnosis of meningitis are summarized in Table 2. When CSF values (leukocyte count, protein, glucose, and LDH levels, along with the simultaneous CSF-to-blood glucose ratio) of mortal patients are compared with patients who survived, no significant effect on the 28-day mortality was found (*p*: 0.416, 0.184, 0.186, 0.148 and 0.715 respectively). Similarly, blood values (leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, as well as CRP levels) at the time of the diagnosis of meningitis did not have a statistically significant effect on the 28-day mortality (*p*: 0.640, 0.635, 0.542, 0.336, 0.810, 0.176 respectively).

At the time of meningitis diagnosis, patients with fatal outcomes exhibited substantially higher blood NLR and significantly lower LPR compared to survivors; but, the LMR did not demonstrate a predictive effect on mortality. Importantly, NLR independently predicted 14-day mortality, while LPR showed a robust association with 7-, 14-, and 21-day mortality. In this study, NLR and LPR were identified as potential new biomarkers for the early prediction of mortality in patients with PN-GNBM (Table 3).

Table 2. Blood and CSF values at the time of post-neurosurgical gram-negative bacterial meningitis diagnosis.

Blood	n	Mean ± SD	CSF	n	Median (min–max)
Leukocyte count (/mm³)	21	15725.71 ± 8.831.05	Leukocyte count (/mm³)	21	460 (0–25000)
Neutrophil count (/mm³)	21	14340.95 ± 8264.64	Protein (g/L)	20	266.5 (57–2770)
Lymphocyte count (/mm³)	21	744.24 ± 510.33	LDH (U/L)	20	338 (32–13626)
Monocyte count (/mm³)	21	592.86 ± 458.94	Glucose (mg/dL)	19	7 (1–134)
Platelet count (/mm³)	21	221000.00 ± 103359.567	CSF glucose/ blood glucose	12	0.60 (0.016–0.456)
CRP (mg/L)	21	140.1 ± 100.1	N/A	N/A	N/A

CSF: cerebrospinal fluid; LDH: lactate dehydrogenase; **CRP: C-reactive protein;** N/A: not available.

Table 3. Relationship of neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and lymphocyte-to-platelet ratio (LPR) with mortality of patient with post-neurosurgical Gram-negative bacterial meningitis.

	[+]Laboratory test results											
	Day 7			Day 14			Day 21			Day 28		
	NS (n = 4)	S (n = 17)	*p*	NS (n = 6)	S (n = 15)	*p*	NS (n = 9)	S (n = 12)	*p*	NS (n = 12)	S (n = 8)	*p*
NLR	32.3 ± 16.5	10.3 ± 2.5	0.06	32.4 ± 13.6	20.4 ± 9.8	0.035	29.6 ± 13.4	19.5 ± 9.1	0.54	25.9 ± 14.1	22.4 ± 7.7	0.526
LMR	1.77 ± 0.7	1.5 ± 0.36	0.746	1.49 ± 0.72	2.07 ± 1.53	0.251	1.5 ± 0.7	2.2 ± 1.6	0.222	1.9 ± 1	1.7 ± 0.002	0.815
LPR	0.0023 ± 0.0009	0.0039 ± 0.0020	0.046	0.0021 ± 0.0008	0.0042 ± 0.001	0.003	0.0023 ± 0.0010	0.0046 ± 0.0019	0.005	0.002 ± 0.001	0.004 ± 0.002	0.055

S: survivors; NS: non-survivors. [+] Laboratory test results: mean ± SD (n) in non-survivors / mean ± SD (n) in survivors; *p* value (*t*-test).

The distribution of the 21 GNB is shown in Figure 2. The most frequently isolated GNB from CSF was *A. baumannii* (n = 11, 52.38%). Polymicrobial growth in CSF was not detected. There was no significant difference in 28-day mortality between *Acinetobacter meningitis* and other GNBM ($p = 1$).

Among the 21 isolates, 57.14% (n = 12) were resistant to meropenem. The rates of CRAB and carbapenem resistant *Klebsiella pneumoniae* were 81.81% (n = 9) and 66.66% (n = 2), respectively. Resistance to colistin was not detected in any of the 21 isolates. One strain of *Pseudomonas* had a DTR pattern (Figure 3).

Empirical antibiotic therapy was administered to 95.23% of the patients, including meropenem (n = 19), ceftazidime (n = 1) , vancomycin (n = 13), linezolid (n = 1), and colistin (n = 2). The antibiotic therapy was revised in 14 patients due to treatment failure or based on drug susceptibility test results, and IV therapy was augmented with IT/IVT antibiotics (colistin (n = 9), amikacin (n = 2), colistin with amikacin (n = 3)). The 28-day mortality rates were similar when IV treatment alone was compared with IV combined with IT/IVT treatment ($p = 1$).

Figure 2. Distribution of bacteria isolated from cerebrospinal fluid.

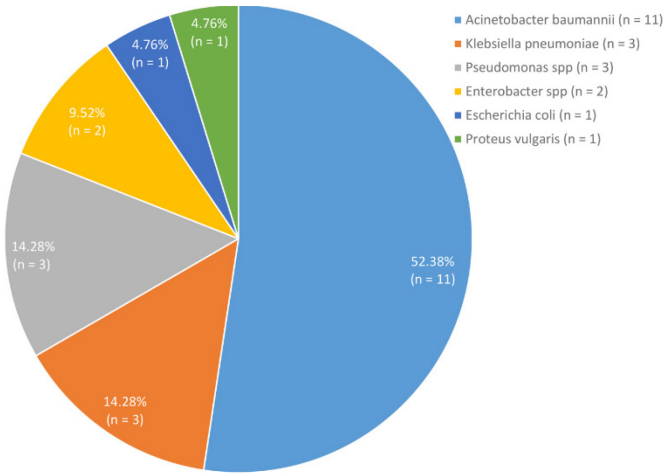
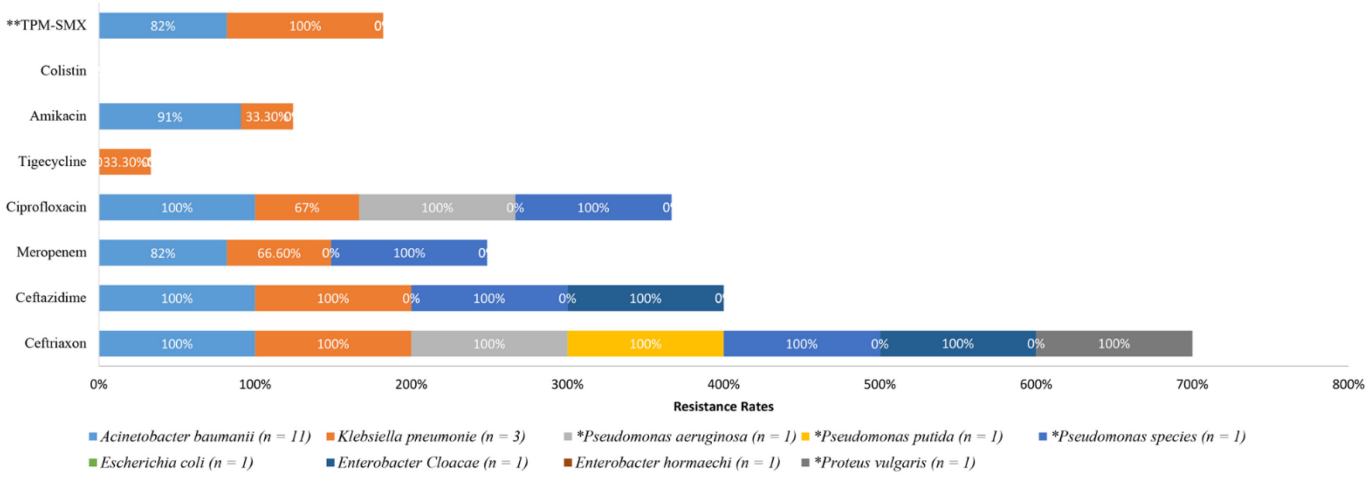


Figure 3. Antibiotic resistance rates of bacteria isolated from cerebrospinal fluid cultures.



* Due to intrinsic resistance, tigecycline susceptibility of *Pseudomonas aeruginosa*; and tigecycline, polymyxins susceptibility of *Proteus vulgaris* were not tested. ** TMP-SMX: trimethoprim-sulfamethoxazole.

The average time of starting pathogen-targeted antibiotic therapy was 2.35 ± 1.81 days (range 0–6 days). The average time to CSF sterilization after treatment was 9.40 ± 8.60 days (n = 15). The average time between meningitis diagnosis and mortality was 13.50 ± 9.73 days. Despite CSF sterilization being achieved in 15 patients, the survival rate at 28 days was low in these patients (n = 5, 33.33%).

Discussion

A notable rise in mortality associated with PNM has emerged with the increasing number of neurosurgical procedures performed worldwide. This trend underscores the critical need for early identification of high-risk patients to improve clinical outcomes. In this study, two readily obtainable hematological indices—NLR and LPR—calculated from routine complete blood count parameters were identified that serve as significant predictors of early mortality in PN-GNBM. These findings highlight the prognostic utility of simple, low-cost biomarkers, particularly in settings where access to advanced diagnostic tools may be limited.

Several clinical and epidemiological predictors of mortality in PN-GNBM have been described in the literature [19,20]. While some studies have associated comorbidities with increased mortality, others—including this study—found no significant relationship [2,7,19–21]. Prior studies have identified factors such as low GCS, EVD presence, sepsis, mechanical ventilation, intensive care unit stay, pathogen type, antimicrobial resistance, and low CSF glucose as potential contributors to poor outcomes [2,6,7] However, a meta-analysis of 80 PNM studies reported that age and GCS scores did not predict mortality, whereas low CSF glucose was associated with increased risk [21]. In line with these findings, age and GCS score were not associated with mortality in the present cohort. This may reflect the fact that nearly all patients were critically ill—frequently requiring mechanical ventilation, craniotomy, and EVD—thereby diminishing the discriminative impact of these parameters.

Consistent with the literature, hemorrhage and intracranial mass were the most frequent neurosurgical indications in this cohort [2,3,5,6,9–11].

Recently, it has been shown that systemic inflammation and infection processes affect not only leukocyte and platelet counts, but also NLR, LMR, and PLR [22,23]. NLR is a reliable parameter that describes immune response to various stimuli and stress factors. In a recent multi-center cohort study, blood NLR was associated with all-cause mortality with Gram negative bacteremia [24]. In a study conducted in children with meningitis, CSF NLR was reported to be significantly higher in patients with bacterial meningitis compared to those with viral meningitis, and higher in GNBM compared to Gram-positive bacterial meningitis [25]. In the present study, high blood NLR was significantly associated with 14-day mortality, suggesting that this parameter could be a prognostic indicator in PN-GNBM, as tuberculosis and community-acquired bacterial meningitis [12,14,15]. On the other hand, the apoptosis of B and T cells during systemic infections leads to the depletion of lymphocytes. Lymphopenia in peripheral blood is associated with mortality and hospital-acquired infections and may be a better predictor than neutrophil and total white blood cell counts [23]. Increased number of activated immature platelets in peripheral circulation can worsen coagulation disorders and systemic inflammatory reactions causing increased disease severity and mortality in patients with sepsis [26]. In this study, the significant association of a low LPR with 7-, 14-, and 21-day mortality indicated that lymphopenia could predict poor prognosis and mortality earlier than NLR. Recent limited studies conducted on adult patients with sepsis and on pediatric populations with varicella zoster meningitis have demonstrated that high PLR was associated with poor prognosis and increased mortality, supporting the findings of the present study [13,27].

Previous studies have reported that the most frequent GNB isolated from the CSF in HCAM were *A. baumannii*, *E. coli*, and *K. pneumoniae* [2–4,19,28–30]. Similarly, in our country, GNB were predominantly isolated in HCAM, with *A. baumannii* being the most frequent pathogen [9–11,31]. In this study, similar to previous studies, the most frequent isolated bacteria was *A. baumannii*, followed by *Klebsiella* spp. and *Pseudomonas* spp.

Globally, CRAB isolated from CSF remains alarmingly high, with reported rates ranging from 62% to 100% [2–4]. In Turkey, these rates have risen dramatically from 37.5% to 90% between 2017 and 2023 [9,11,31]. In the present cohort, the CRAB rate was 81.81%, consistent with global data and underscoring that CRAB meningitis has become a critical clinical challenge both worldwide and nationally. Similarly, two studies from China have reported CRE rates of 15% and 44% in CSF isolates, predominantly *K. pneumoniae* [6,7]. In this study, carbapenem resistance among *K. pneumoniae* strains reached 66.66%, a notably high level. This concerning resistance pattern is likely influenced by prior antibiotic

exposure, present in 65% of the patients. These findings highlight the urgent need for robust infection control strategies and the global reinforcement of rational antibiotic stewardship.

Zhang *et al.* reported a mortality rate of 66% in GNB meningitis [19], and previous studies have consistently shown that *Acinetobacter* spp. meningitis carries a particularly high mortality burden, ranging from 40% to 55% [2,5,11,31]. In the present study, the 28-day mortality rate was 60%, aligning with these findings. Mortality attributable to *Acinetobacter* spp. reached 63%, which is likely related to the predominance of *Acinetobacter* strains among the isolates. These results further emphasize the significant clinical impact of *Acinetobacter*-associated meningitis and its contribution to poor outcomes in PN-GNBM.

Previous studies have suggested that adding IT/IVT colistin to systemic colistin may reduce intensive care unit stay and mortality in CRAB meningitis or ventriculitis [32,33], although Ceylan *et al*. reported higher mortality with IT colistin in *A. baumannii* meningitis, particularly among older patients and those without CSF sterilization, and noted a possible association with meropenem use [34]. Combined IT and IV polymyxin therapy demonstrated clinical benefit in a small pediatric cohort [35]. In contrast, the findings in this study did not show a survival advantage with adjunctive IT/IVT colistin or amikacin, which may reflect the limited sample size and reduced power to detect a therapeutic effect. Despite achieving CSF sterilization in most cases, mortality remained high, likely due to severe disease presentation, delays in switching from empirical to targeted therapy, comorbidities, and the severity of the underlying neurosurgical conditions. These observations highlight the ongoing uncertainty regarding IT/IVT therapy in PN-GNBM and underscore the need for larger, methodologically robust studies.

This study has several limitations. It is a retrospective, single-center study with a relatively small sample size. Multivariate analysis could not be performed, as the number of variables allowed in the logistic model was limited to approximately 10% of the total sample, and the analysis would not have added significant explanatory value. All patients were critically ill and managed in the intensive care unit, and GCS were not available for all participants. The study was also conducted during the coronavirus disease 2019 (COVID-19) pandemic, which may have affected case management. Despite these limitations, the study provides significant insights, encompassing 63 months of real-world data on PN-GNBM. Its relevance and generalizability are further strengthened by being conducted in a 1,045-bed high-volume tertiary-care hospital, reflecting complex clinical practice and reinforcing its applicability to similar healthcare settings.

Conclusions

This study demonstrates that readily available and cost-effective hematological biomarkers—NLR and LPR—can accurately predict early mortality in PN-GNBM, underscoring their potential for timely risk stratification and evidence-based clinical decision-making; however, larger multicenter studies are warranted to validate these findings.

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Conflict of interest

No conflict of interest is declared.

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Annex – Supplementary Items

Supplementary Table 1. Evaluation of factors affecting 28-day all-cause mortality in post-neurosurgical Gram-negative bacterial meningitis.

Characteristics	Total n (%)	Nonsurvivor n (%)	Survivor n (%)	*p* value
*Age (mean ± SD)	20 (100)	12 (60) (58.83 ± 19.10)	8 (40) (46.63 ± 16.59)	0.158
Male	15 (75)	8 (%53.33)	7 (46.67)	0.603
Female	5 (25)	4 (80)	1 (20)*	
GCS	13 (65)			
3–13	5 (41.66)	4 (80)	1 (20)	0.242
14–15	7 (58.33)	2 (28.57)	5 (71.43)	
Comobidities	10 (50)	6 (60)	4 (40)	1
Infection prior to meningitis	13 (65)	8 (61.53)	5 (38.47)	1
Hemorrhage	9 (45)	7 (77.77)	2 (22.23)	0.596
İntracranial mass	7 (35)	4 (57.14)	3 (42.86)	1
Craniotomy	18 (90)	10 (55.56)	8 (44.44)	0.495
EVD	17 (85)	11 (64.70)	6 (35.30)	0.537
Before meningitis EVD	6 (30)	5 (83.33)	1 (16.67)	0.325
VPS	5 (25)	2 (40)	3 (60)	0.347
CSF leakage	5 (25)	0 (0)	5 (100)	0.004
LD	2 (10)	0 (0)	2 (100)	0.670
Spinal surgery	2 (10)	0 (0)	2 (100)	0.670
CVC	17 (85)	10 (58.82)	7 (41.18)	1
MV	17 (85)	10 (58.82)	7 (41.18)	1

Since one patient was lost to follow-up before 28 days, the 28-day mortality calculations in the table were performed based on 20 patients. *Age; presented as mean ± SD; it was not statistically significant due to the small sample size (type II error). **GCS: Glasgow coma scale; EVD: external ventricular drainage; VPS: ventriculoperitoneal shunt;** CSF: cerebrospinal fluid; **LD: lumbar drainage; CVC: central venous catheter; MV: mechanical ventilation.**