Original Article

Unlocking the mysteries of bacterial meningitis in Bosnia and Herzegovina: Predicting outcomes in developing country settings

Izeta Hamza[1], Rusmir Baljić[2 #], Amila Muratspahić[2 #], Meliha Šehić[3 #], Nejra Selak[4 #]

[1] Health Center of Canton Sarajevo, Sarajevo, Bosnia and Herzegovina
[2] Clinic of Infectious Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[3] Department of Infectious Diseases, Cantonal Hospital Zenica, Zenica, Bosnia and Herzegovina
[4] Department of Pathology, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

# Authors contributed equally to this work.

Abstract

Introduction: Acute bacterial meningitis (ABM) is a serious infectious disease and medical emergency. Given the fact of its high mortality and morbidity, detecting prognostic factors is potentially useful in improving treatment strategies. This paper aims to determine prognostic factors of short-term outcomes of patients with ABM in a developing country - Bosnia and Herzegovina, measured by the Modified Rankin Scale (MRS) at discharge.

Methodology: In this retrospective cohort study, 56 patients treated at the Clinic of Infectious Diseases, Clinical Center University of Sarajevo, for 11 years (2012-2022) were included. Statistical analysis was performed using IBM SPSS Statistics version 29.0.1.0.

Results: The subjects' average age was 31.6 ± 27.7 years, with the youngest patient being 4 months and the oldest 75 years old. Among those, 31 were male and 25 were female. Unfavorable outcomes had 16 (28.6%) patients, including fatal outcomes in four patients and severe disabilities in 12 patients (MRS: 2-6), while 40 (71.4%) patients had favorable outcomes (MRS: 0-1). In the multivariate analysis, predictors of unfavorable outcomes included age older than 60 years, duration of symptoms longer than 24 hours, presence of neurological defects at admission, impaired consciousness, respiratory distress, and no corticosteroid use during treatment.

Conclusions: There is certainly a window of opportunity for patients with ABM: The shorter the time between disease onset and treatment initiation, the better the disease outcome.

Key words: Acute bacterial meningitis; prognostic factors; corticosteroids; outcome prediction.

Introduction

Acute bacterial meningitis (ABM) is a serious infection of the central nervous system (CNS) and medical emergency that requires immediate diagnostic tests and lumbar puncture in the first place to establish the specific cause and initiate effective therapy. In developing countries, ABM has a mortality rate of up to 54%, while 24% of those who survive develop chronic neurological sequelae [1]. These consequences can persist throughout life, significantly reducing its overall quality. Increased morbidity in these patients also affects the length of hospital stay and resource utilization. Universal vaccination against *Haemophilus influenzae type B* is crucial in preventing the incidence of bacterial meningitis, significantly reducing the risk of infection and its severe consequences. Vaccination against *Streptococcus pneumoniae* (*S. pneumoniae*) and *Neisseria meningitidis* (*N. meningitidis*) could also prevent the incidence of ABM. In our conditions, only a vaccine for *Haemophilus influenzae* type B is a part of the mandatory vaccination calendar. Furthermore, the availability of more antibiotics and good care facilities can reduce the negative consequences of ABM. Early identification of patients with poor prognosis contributes to individualized treatment and a more aggressive therapeutic approach. Numerous clinical features, biochemical, and microbiological factors have been identified as prognostic factors in ABM, such as abnormal neurologic examination on admission, cerebrospinal fluid (CSF) glucose < 45 mg/dL [2], leukopenia and CSF/serum glucose ratio < 0.25 [3], history of chronic renal failure, purpura fulminans, disseminated intravascular coagulation, *S. pneumoniae* as the causative agent [4], older age, neurological complications, and initial Glasgow Coma Scale (GCS) ≤ 8 [5]. Prognosis plays a vital role in patient management and decision-making. Given the fact of high mortality and morbidity of this disease, it is

necessary to make efforts to reduce the devastating statistics. One of the tools for achieving this goal is the determination of reliable prognostic factors. Detecting them, especially modifiable factors, is potentially useful in improving treatment strategies for this potentially fatal infection.

However, to date, studies are mainly performed elsewhere in Europe, so the present study aimed to determine which parameters in our conditions can serve as reliable prognostic factors to improve the diagnostic approach and therapeutic strategies in the treatment of ABM.

Methodology

A retrospective observational cohort study was conducted at the Clinic of Infectious Disease, University Clinical Center in Sarajevo, from January 1st, 2012, to December 31st, 2021. It included 56 patients, regardless of age, diagnosed with ABM. If patients were transferred between institutions, data from their initial hospitalization were used. Parameters relevant to ABM were collected, including demographic characteristics, duration of hospital treatment, clinical manifestations at admission (focusing on neurological status), laboratory parameters, CSF analysis, microbiological tests, and disease course follow-up. To date, none of the patient's family members were previously identified as individuals possibly to have some of the major inborn errors of immunity. Clinical manifestations included fever, headache, vomiting, neck stiffness, meningeal signs, and focal neurological symptoms. The time from symptom onset to hospital admission, presence of comorbidities, and predisposing conditions like trauma, ear infections, sinusitis, and pneumonia were noted. Blood laboratory parameters related to bacterial meningitis diagnosis were analyzed, including white and red blood cell counts (WBC, RBC), hemoglobin (Hb), hematocrit (Hct), neutrophil and lymphocyte percentages, platelet count, lactate dehydrogenase (LDH), C-reactive protein (CRP), sodium, potassium, calcium and chloride levels. Immediately after excluding contraindications, an examination of CSF obtained by lumbar puncture including its macroscopic

appearance, cell count, glucose, and protein levels, was performed. Microbiological analysis included blood and urine cultures, throat, and nose swabs.

Data were gathered from various medical institutions, including urgent care, pediatric, and other clinics within the University Clinical Center Sarajevo, and regional hospitals in East Sarajevo, Travnik, and Bihać.

Inclusion criteria were patients diagnosed with community-acquired ABM during the study period. Exclusion criteria were life-threatening comorbidities, incomplete documentation, and patients with neurosurgical implants.

Patients were divided into two groups based on short-term outcomes at discharge, defined using the Modified Rankin Scale (MRS) (Table 1). Those with scores of 2-6 (outcomes with disability and death) were classified as having an unfavorable, while those with scores of 0-1 (no or low disability) were considered to have a favorable outcome.

Statistical analysis

Data are summarized in tables, including case numbers, percentages, mean values (SD), and interquartile range (Q1-Q3). Univariate analysis compared two outcome-based groups using the Mann-Whitney U test for numerical variables and Fisher's exact or chi-square test for categorical variables. Significant variables from this analysis were used in multivariate analysis. A logistic regression model was developed to predict unfavorable outcomes (MRS 2-6). Results included Omnibus test values, Nagelkerke R squared, and Hosmer and Lemeshow test to assess model adequacy. A $p < 0.05$ was considered significant. IBM SPSS Statistics 29.0.1.0 was used for all analyses.

Ethical statement

The principles of the 2008 Helsinki Declaration for patient rights in biomedical research were followed in this study. Approval was obtained from the Ethical Committees of the University Clinical Center Sarajevo and the Faculty of Medicine, University of Sarajevo.

Table 1. Modified Rankin Scale explained.

Modified Rankin Scale (MRS)	n
No symptoms	0
No significant disability. Able to carry out all usual activities, despite some symptoms	1
Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities	2
Moderate disability. Requires some help, but able to walk unassisted.	3
Moderately severe disability. Unable to attend to own bodily needs without assistance, or unable to walk unassisted.	4
Severe disability. Requires constant nursing care and attention, bedridden, incontinent.	5
Dead	6

Results

Patient characteristics and clinical data

Fifty-six patients were enrolled in this study. Thirty-one (55.8%) were male and the mean age was 31.6 ± 27.7 years (range 4 months - 75 years). Comorbidities were present in 18 patients (32.1%) including diabetes mellitus type 1 or 2, renal and liver diseases, epilepsy, psychiatric disorders, and cardiovascular diseases of an ischemic nature: Conditions such as status post-acute myocardial infarction., arterial hypertension, and arrhythmias. Concurrent infections were present in 23 patients (41.1%), and 5 patients (8.9%) had a history of head injury or cerebrospinal fluid (CSF) leak. No significant correlation was observed between these risk factors and the outcome. Detailed characteristics are given in Table 2. The most frequent clinical presentation was fever (54/56; 96,4%), vomiting (46/56; 80,4%), and neck stiffness (40/56; 71.4%). Thirty-two patients presented had altered mental status (57.1%).

CSF examination

In our study, 96.4% of patients had cloudy CSF, one had clear CSF, and data were missing for one individual. The mean CSF cell count was 3517 (range 532-4294). A significant difference in CSF protein content was identified between patients with favorable and unfavorable outcomes ($p = 0.027$), however, no significant difference in the median CSF glucose concentration ($p = 0.208$) and CSF-to-plasma glucose ($p = 0.785$) was observed between outcome groups (Table 3).

Causative microorganisms

In this cohort, positive cerebrospinal fluid (CSF) cultures were observed in 23 patients (41.1%). The most frequently isolated pathogen was *S. pneumoniae*, identified in 17 (30.4%) patients. *N. meningitidis* was detected in 4 patients (7.1%). Other isolated bacteria included *E. coli*, *L. monocytogenes*, and *Pseudomonas spp.* (Table 2).

Blood cultures were positive in 18 patients (32.1%), with *S. pneumoniae* being the most frequently isolated, followed by *N. meningitidis*. Additional isolated bacteria were *E. faecalis*, methicillin-resistant *Staphylococcus epidermidis* (MRSE), methicillin-sensitive *Staphylococcus epidermidis* (MSSE), *E. coli*, and *Pseudomonas spp.* In three instances, multiple pathogens were identified, including both Gram-positive (G + and Gram-negative (G -) bacteria.

Specifically, one case involved *S. epidermidis*, *S. alpha haemolyticus* (serotyping was not performed),

and *Pseudomonas aeruginosa.* In another case, the bacteria isolated were *E. coli* and MRSE, while the third case showed *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and MRSE.

As *S. pneumoniae* was the most common isolated causative agent, an analysis was conducted to determine whether it was associated with an unfavorable outcome. Univariate analysis showed that *S. pneumoniae* was not statistically significantly associated with an

Table 2. Characteristics of the study population.

Characteristics	
Male sex, n (%)	31 (55.8)
Age, years (mean ± SD)	31.6 ± 27.7
Risk factors, n (%)	
Comorbidities	18 (32)
Concurrent infection	23 (41.1)
History of head injury or CSF leak	5 (8.9)
Initial presentation, n (%)	
Febrile	54 (96.4)
Vomiting	46 (80.4)
Headache	33 (58.9)
Petechiae	8 (14.3)
Neck stiffness	40 (71.4)
Altered mental status	32 (57.1)
Convulsion	7 (12.5)
Neurologic symptoms	20 (35.7)
Positive meningeal signs	43 (73.2)
Laboratory data	
CRP (mg/dL), median (IQR)	177.47 (72.5-268.3)
WBC (× 10^9/L), median (IQR)	18.4 (12.1-24.9)
LDH (U/L), median (IQR)	284.4 (223-322)
CSF glucose (mmol/L), median (IQR)	1.9 (0.3-2.8)
CSF/Plasma glucose ratio, median (IQR)	0.239 (0.05-0.367)
CSF culture positive	**23 (41.1)**
S. pneumoniae	17 (30.4)
N. meningitidis	4 (7.1)
E. coli	1 (1.8)
L. monocytogenes	1 (1.8)
Pseudomonas spp	1 (1.8)
Blood cultures positive	**18 (32.1)**
S. pneumoniae	5 (9.0)
N. meningitidis	1 (1.8)
MRSE	1 (1.8)
MSSE	1 (1.8)
E. faecalis	1 (1.8)
Pseudomonas spp.	1 (1.8)
S. alpha haemolyticus	1 (1.8)
Course	3 (5.5)
ICU stay	38 (67.9)
Respiratory failure	8 (14.3)
Convulsions	7 (12.5)
MRS	
Death (6)	4
Major disability (5)	2
Moderately severe disability (4)	3
Moderate disability (3)	2
Mild disability (2)	5
Low disability (1)	4
No disability (0)	36
Unfavorable outcome (MRS 2-6)	16 (28)

SD: Standard deviation; CSF: Cerebrospinal fluid; CRP: C-reactive protein; IQR: Interquartile range; WBC: White blood cells; RBC: Red blood cells; LDH: Lactate dehydrogenase; *S. pneumoniae*: Streptococcus pneumoniae; *N. meningitidis*: Neisseria meningitidis; *E. coli*: Escherichia coli; *E. faecalis*: Enterococcus faecalis; *S. alpha haemolyticus*: Staphylococcus alpha haemolyticus; ICU: Intensive Care Unit; MRS: Modified Rankin Scale.

Table 3. Univariate analysis of predictors of favorable and unfavorable outcome.

Clinical presentation	Favorable outcome (MRS 0-1) (N = 40)	Unfavorable outcome (MRS 24-6) (N = 16)	OR (95% CI)	*p*
Age > 60 years, n	10 (25%)	6 (37.5%)	5.7 (1.5-20.1)	**0.014**
Gender, male	22 (55%)	9 (56.3%)	1.05 (0.3-3.4)	**0.007**
Duration of symptoms before admission > 24 hours, n	11 (27.5%)	11 (68.75%)	5.8 (1.64-20.5)	**0.004**
Elevated body temperature, n	40 (100%)	14 (87.5%)	3.9 (2.5-6.1)	0.078
Headache, n	22 (55%)	11 (68.8%)	2.8 (0.7-11.8)	0.142
Vomiting, n	34 (85%)	11 (68.8%)	0.6 (0.5-1.4)	0.681
Abdominal pain, n	3 (7.5%)	1 (6.3%)	0.8 (0.08-8.6)	1
Petechiae/ecchymoses, n	7 (17.5%)	1 (6.3%)	0.3 (0.03-2.8)	0.416
Neck stiffness, n	26 (65%)	14 (87.5%)	3.8 (0.7-19)	0.114
Altered state of consciousness, n	18 (45%)	14 (87.5%)	8.6 (1.7-42.7)	**0.004**
Convulsions, n	3 (7.5%)	4 (25%)	4.1 (0.8-21)	0.094
Neurological symptoms, n	11 (27.5%)	9 (56.3%)	3.4 (1-11.3)	**0.043**
Positive meningeal signs, n	29 (72.5%)	12 (75%)	1 (0.3-3.4)	1
CRP (mg/dL), median (IQR)	162.8 (64.3-246)	214.1 (113.3-317.5)		0.11
WBC (× 109/L), median (IQR)	18.5 (12-25.4)	18 (12.1-19.9)		0.624
LDH (U/L), median (IQR)	274 (221-312)	310.7 (231-417)		0.336
CSF-cell count, median (IQR)	2850 (390-3704)	5184 (706-6941)		0.384
Proteinorachia (g/L), median (IQR)	3.1 (1.2-4.1)	5.3 (2.2-7.4)		**0.027**
Glycorachia (mmol/L), median (IQR)	1.7 (0.3-2.8)	2.5 (1-3.2)		0.208
Plasma/CSF glucose ratio, median (IQR)	0.25 (0.05-0.4)	0.22 (0.08-0.33)		0.785
Respiratory failure, n			51.8 (5.2-513.5)	**< 0.001**
Not having corticosteroid therapy, n			5.6 (1.5-20.5)	**0.007**

unfavorable outcome (*p* = 0.304, 95% CI [0.389-5.358]).

Hospitalization and outcomes

Notably, the majority of patients (73.2%) received antibiotics for upper and lower respiratory tract infections at home before hospital admission. The average hospital stay was 26.6 ± 15.1 days (range 8-66 days), with no statistically significant differences between the outcome groups (*p* = 0.394). On average, the time from symptom onset to hospitalization was 1.54 ± 1.95 days (range 6 hours-10 days), and the difference in this duration between the groups was significant. (*p* = 0.027).

Thirty-eight (67.9%) were admitted to the ICU, eight patients (14.3%) experienced respiratory insufficiency, and 7 (12.5%) had seizures during hospitalization.

Unfavorable outcomes were observed in 28% (16 patients). Among subjects who died (MRS = 6), the median age was 57.5 years (IQR 49.5-66 years). Among them, two patients had no comorbidities, one had a psychiatric disorder, and another had hypertension and arrhythmias. Among the patients who survived, two remained independently immobile, with one of these patients not verbalizing. Three patients

experienced gait instability and scant spontaneous motor activity. Two developed psychogenic syndrome and plegia of the upper extremities, while five were left with mixed or complete hearing loss and sensorimotor dysphasia.

The univariate analysis identified the following significant variables: Age over 60, altered consciousness on admission, neurological symptoms, symptom duration over 24 hours before admission, respiratory insufficiency, and absence of corticosteroid treatment. positive blood cultures, and elevated CSF proteins (Table 3).

The final multiple logistic regression model comprised five variables: Age over 60, symptom duration over 24 hours before admission, altered consciousness, neurological symptoms, and absence of corticosteroid treatment (Table 4). Age and absence of corticosteroid therapy were significant predictors of unfavorable outcome.

Subgroup analysis

As 81.3% of patients with unfavorable outcomes were over 18 years old, separate univariate and multivariate analyses were conducted for this age group. No statistically significant difference in

Table 4. Multiple logistic regression analysis for unfavorable outcome for significant factors in univariate analysis.

	OR (95% CI)	*p*
Age (> 60 vs <60 years old)	**7.243 (1.2-43.9)**	**0.031**
Duration of symptoms before admission (> 24 vs < 24 hours)	**10.12 (1.75-58.5)**	**0.010**
Altered state of consciousness (yes vs no)	7.337 (0.785-68.56)	0.08
Neurological symptoms (yes vs no)	0.934 (0.16-5.40)	0.939
Corticosteroid therapy (no vs yes)	**7.55 (1.32-43.34)**	**0.023**

hospitalization duration was found between patients younger than 18 and those older than 18.

In the univariate analysis of admission clinical presentations, symptom duration before admission ($p =$ 0.016) and LDH levels exceeding 300 U/L ($p = 0.044$) emerged as independent prognostic factors for unfavorable outcomes.

The multiple logistic regression model included two variables: Symptom duration longer than 24 hours prior to admission and LDH levels greater than 300 U/L. The results of the logistic regression indicate that patients older than 18 years whose duration of symptoms before admission exceeded 24 hours was associated with a 15.7-fold increased likelihood of experiencing an unfavorable outcome.

ICU stays

Of the patients, 38 (67.8%) were admitted to the ICU. The presence of petechiae/ecchymoses was identified as the only independent prognostic factor associated with ICU transfer ($p = 0.44$), while other examined parameters were not statistically significant.

Discussion

This study identified that age above 60 years, altered mental status at admission, presence of neurological symptoms, duration of symptoms before admission, presence of respiratory insufficiency, and absence of corticosteroids in treatment were identified as independent prognostic factors of unfavorable outcome.

After developing the multiple binary logistic regression model, the analysis indicated that age above 60 years, duration of symptoms before admission, and absence of corticosteroids in treatment were prognostic factors for an unfavorable outcome. The model included five independent predictors, which satisfied the validity requirement of at least 10 patients per predictor.

Based on our analyses, it was evident that the majority of patients initially presented with a fever (96.4%), while 80.4% reported vomiting, 73.2% exhibited positive meningeal signs, 71.4% presented with neck stiffness, and 58.9% experienced headaches. Additionally, the presence of neurological symptoms was identified in 35.7% of patients. Seizures were observed in 12.5% of patients, primarily affecting younger individuals. The high proportion of these clinical manifestations emphasizes the need for a thorough evaluation during the initial examination of every patient suspected of having a CNS infection.

It is important to also consider less common clinical manifestations, since approximately half of the patients with meningitis may not show typical meningeal signs upon physical examination. Using a combination of several tests to detect meningeal signs can reduce the risk of misdiagnosis [6].

The initial clinical presentations of patients diagnosed with ABM were comparable to those reported in other industrialized countries. In a retrospective study of 161 patients averaging 55.9 ± 15.5 years diagnosed with ABM, Sang *et al.* reported the presence of elevated temperature in 88.2% of patients, while neck stiffness was observed in 62.5%.

Changes in mental status were noted in 52.2% of patients, while the presence of headache and vomiting was not evaluated [5]. However, there was a difference in the clinical manifestations of pediatric ABM. Yi *et al.*, in their 15-year retrospective study, reported that only 54% of patients exhibited fever. On the other hand, this study did not show changes in consciousness and meningeal signs [3]. Namani *et al.,* in a prospective study involving 77 children aged one month to 16 years, reported that 57.1% of patients experienced changes in mental status, and 18.8% had convulsions before admission [7]. The limitation of our study is the fact that a precise numerous scale such as the Glasgow coma scale couldn't be used because it hadn't been determined upon the hospital admission. Lower values of GCS are well known as a factor for a poor outcome in patients with ABM [5].

Regarding the causative agents of ABM, based on the results of this study, *S. pneumoniae* was isolated in the cerebrospinal fluid (CSF) in 30.4% of patients, and *N. meningitidis* in 7.1%. Other isolated bacteria included *E. coli*, *L. monocytogenes*, and *Pseudomonas spp*. In 32 (57.1%) patients, no bacteria were isolated from the CSF, and data were unavailable for one patient. At the given moment, additional microbiology tests such as PCR and serological tests for bacterial pathogens were not available. The causative agents should be interpreted according to the age of the patients involved. Specifically, *S. pneumoniae* was isolated in five patients under 18 years of age, while the remaining cases occurred in patients older than 18 years. *N. meningitidis* was isolated more frequently in younger patients, as expected.

In more than half of the patients, cerebrospinal fluid cultures were negative. A possible reason might be the antibiotic treatment administered before the lumbar puncture sample collection. Blood cultures were positive in 18 (32.1%) patients. *S. pneumoniae* was most commonly isolated, followed by *N. meningitidis*.

Other isolated bacteria included *E. faecalis*, MRSE, MSSE, *E. coli*, and *Pseudomonas spp*. In three patients, more than one pathogen was isolated, including both Gram-positive and Gram-negative bacteria. These cases were predominantly observed in patients with positive CSF cultures. The importance of vaccination against Pneumococci, Meningococci, and *Hemophilus influenzae* type b in preventing or reducing the risk of bacterial meningitis critical, particularly in children and adults with risk factors such as immunodeficiency, asplenia, or those who have had a cochlear implant installed. Unfortunately, the application of these vaccinations remains insufficient in daily practice in our country, underscoring a critical area for public health improvement.

According to our study, the male gender was at higher risk for an unfavorable outcome ($p = 0.007$). This finding aligns with certain previous studies. Koomen *et al.* [8] and Oostenbrink *et al.* [9] identified male gender as a prognostic factor for unfavorable outcomes, whereas Wang *et al.* [2] reported female gender as a significant predictor.

Age, as a prognostic factor identified in both univariate and multivariate analyses, represents a non-modifiable factor. This association likely stems from the higher prevalence of comorbidities with advancing age, as well as age-related immunosenescence. Notably, 32% of patients had no documented comorbidities. Consistent results were also reported by Bijlsma *et al.* [10] and Sunwoo *et al.* [5].

Predisposing factors such as the presence of otitis, sinusitis, and pneumonia were not statistically significant in relation to the outcome, which may be considered encouraging for the affected patients. However, Cabellos *et al.* [11] reported, and Bijlsma *et al.* [10] identified the absence of these predisposing conditions as a prognostic factor.

Symptom duration prior to admission represents a modifiable factor, particularly in the context of timely detection of CNS infections at the primary healthcare level. A multicenter retrospective study by Tubiana *et al.* identified the time interval between hospitalization and performing a LP as a prognostic factor for unfavorable outcomes, as measured by the Modified Rankin Scale (MRS). The critical threshold for an unfavorable prognosis was one day. This underscores the need to minimize the time interval between admission and LP by adhering to specific CT scan guidelines thereby avoiding delays caused by unnecessary CT scans [4]. In cases where head CT is warranted for patients with suspected ABM, initiating empiric antimicrobial therapy prior to imaging is recommended to prevent delays in treatment [12]. Atypical clinical presentations, including the absence of headache, neck stiffness, or fever, could also contribute to delayed diagnosis and treatment. Although intentional delays in therapy are never justified, diagnosis can be quite challenging in cases with atypical characteristics [13]. In this study, due to the lack of precise data, we were unable to examine this prognostic factor, but we did demonstrate that symptom duration longer than 24 hours before admission was a prognostic factor for an unfavorable outcome. This prognostic factor was also identified by Koomen *et al.* [8], Roine *et al.* [14], and Kaaresen *et al.* [15] with a cut-off value of 48 hours, and Pelkonen et al., with a cut-off value of 72 hours [16].

Altered mental status as an independent prognostic factor was identified by Roine *et al.* [14] and Pelkonen *et al.* [16], but most studies have shown that an initial presentation with a GCS < 8 is a prognostic factor for an unfavorable outcome [17–22].

Neurological symptoms as a prognostic factor for an unfavorable outcome were also noted by Bijlsma *et al.* [10], Tubiana *et al.* [4], Pelkonen *et al.* [16], and Namani *et al.* [7].

Our study found that none of the laboratory parameters was of prognostic importance when analyzing all participants (N = 56), while an LDH level higher than 300 U/L (due to increased permeability of neuronal cell membranes) was determined as an independent prognostic factor in the group of patients older than 18 years. Sonwoo *et al.* [5], Bijlsma *et al.* [10], and Kirimi *et al.* [23] identified high CRP as a prognostic factor of unfavorable outcome. Wee *et al.* [3] and Lovera *et al.* [17] found that the presence of leukopenia is a prognostic factor of unfavorable outcome in their studies.

Our study did not identify any significant prognostic factors in CSF analysis, with the exception of elevated CSF protein levels, possibly due to small sample size and heterogeneous patient population, which included both children and adults. Previous research identified CSF glucose levels of 45 mg/dL as an unfavorable outcome prognostic factor [2–4].

Our study did not find any of the pathogens, whether isolated from CSF or blood cultures, to be significant prognostic factors. However, Wee *et al.* [3] and Lin *et al.* [24] indicated that *S. pneumoniae* as a causative agent is a prognostic factor for an unfavorable outcome. The potential cause of inconsistent results may be the small sample size and the inability to confirm *S. pneumoniae* as a causative agent due to

antibiotic therapy administered prior to sample collection.

Early use of corticosteroids in settings of ABM caused by *S. pneumoniae*, is well known useful adjunctive treatment to antibiotics. Dexamethasone easily passes blood-brain barrier. According to our study, patients who were not treated with corticosteroid therapy during hospitalization had a sevenfold higher likelihood of an unfavorable outcome, suggesting that the use of dexamethasone may act as a protective factor in our subjects, for whom *S. pneumoniae* was the most common causative agent. The absence of corticosteroids in treatment as a prognostic factor was also proven by Cabellos *et al.* [11], while Koomen *et al.* identified the use of dexamethasone for less than 48 hours as a prognostic factor for an unfavorable outcome [8].

The limitations of our study include its small, age-diverse sample, which, although beneficial for identifying age-related prognostic factors, may affect the generalizability of the results. Retrospective design hinders complete data analysis, suggesting a need for prospective studies. Follow-up assessments to detect post-discharge sequelae would enhance prognostic accuracy. The study contributes to the overview of clinical manifestations and prognostic factors of bacterial meningitis in Bosnia and Herzegovina, as it includes patients from the entire Federation of Bosnia and Herzegovina, all of whom were hospitalized at the Department of Infectious Diseases at the University Clinical Center in Sarajevo.

CIs provided in our study vary, with some being relatively narrow and others quite wide. Some quite broad CIs indicate a high level of uncertainty or variability in this estimate. This could be due to a small sample size or high variability within the sample. Further research with larger or more homogeneous samples to obtain more precise estimates is needed.

In this retrospective cohort study, we confirm the profound influence of ABM on both mortality and quality of life, casting a shadow over affected individuals. One pivotal prognostic factor that demands attention is the duration of symptoms before hospitalization. The good news is that this factor is within our power to modify, and by enhancing education in academic and primary healthcare settings, we have the potential to substantially improve the alarming statistics linked to this disease.

Yet, to combat ABM effectively, a comprehensive grasp of its intricate pathophysiological processes is imperative. Furthermore, our quest should not stop there; we must continue to explore uncharted territory in the search for new prognostic factors that may hold the key to better outcomes.

Conclusions

In our analysis, we've uncovered compelling insights. Age, specifically over 60, emerges as a powerful predictor of unfavorable outcomes in our study, while gender shows no influence. When examining clinical signs, we found that patients with acute bacterial meningitis typically exhibit at least two key symptoms linked to CNS infection – fever, altered consciousness, headache, or neck stiffness.

Digging deeper, our univariate analysis isolates altered consciousness upon admission and the presence of neurological symptoms as independent prognostic factors. In the realm of laboratory parameters, except for proteinorachia, none hold prognostic significance.

However, a ray of hope shines through – the use of dexamethasone in treatment can be seen as a protective factor. Yet, perhaps the most impactful revelation is that the duration of symptoms before admission is a modifiable prognostic factor that demands our attention.

Intensive vaccination of both children and adults against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b is crucial in effectively reducing the incidence and severity of bacterial meningitis. This proactive approach not only safeguards individual health but also significantly contributes to public health by diminishing the spread and impact of these potentially life-threatening infections.

To address this ongoing challenge, continuous and rigorous training for healthcare professionals, particularly in primary care settings, is vital. Acute bacterial meningitis remains a significant threat, and our findings emphasize the need for further research to mitigate its devastating consequences.

Corresponding author
Ms Izeta Hamza, MD
Trg solidarnosti 27
71 000 Sarajevo
Bosnia and Herzegovina.
Tel: +38762851528
Email: hamza.izeta1@gmail.com

Conflict of interests
No conflict of interests is declared.

References

1. Hasbun R (2022) Progress and challenges in bacterial meningitis: a review. JAMA 328: 2147–2154. doi: 10.1001/jama.2022.20521.
2. Wang AY, Machicado JD, Khoury NT, Wootton SH, Salazar L, Hasbun R (2014) Community-acquired meningitis in older adults: clinical features, etiology, and prognostic factors. J Am Geriatr Soc 62: 2064–2070. doi: 10.1111/jgs.13110.
3. Wee LYJ, Tanugroho RR, Thoon KC, Chong CY, Choong CT, Krishnamoorthy S, Maiwald M, Tee NWS, Tan NWH (2016) A 15-year retrospective analysis of prognostic factors in childhood bacterial meningitis. Acta Paediatr 105: e22-29. doi: 10.1111/apa.13228.
4. Tubiana S, Varon E, Biron C, Ploy M-C, Mourvillier B, Taha M-K, Revest M, Poyart C, Martin-Blondel G, Lecuit M, Cua E, Pasquet B, Preau M, Hoen B, Duval X, Duval X, Hoen B, Mourvillier B, Ploy M-C, Tubiana S, Varon E, Caron F, Bollaert P-E, Gaillot O, Taha M-K, Poyart C, Bonacorsi S, Vandenesch F, Cambau E, Lecuit M, Gravet A, Frachet B, Broucker TD, Levy Bruhl D, Raffi F, Anguel N, Argaud L, Arista S, Armand-Lefevre L, Balavoine S, Baraduc R, Barnaud G, Beraud G, Bernard L, Bernars G, Bertei D, Bessede E, Billard Pomares T, Biron C, Bland S, Boileau J, Boubeau P, Bourdon S, Bousquet A, Boyer S, Bozorg-Grayeli A, Bret L, Bretonniere C, Bricaire F, Brocas E, Brun M, Buret J, Burucoa C, Cabalion J, Cabon M, Cambau E, Camuset G, Canevet C, Caron F, Carricajo A, Castan B, Caumes E, Cazanave C, Chabrol A, Challan-Belval T, Chanteperdrix-Marillier V, Chaplain C, Charlier-Woerther C, Chaussade H, Chirouze C, Clair B, Colot J, Conil J-M, Cordel H, Cormier P, Cousson J, Cronier P, Cua E, Dao-Dubremetz A, Dargere S, Degand N, Dekeyser S, Delaune D, Denes E, Dequin P-F, Descamps D, Descloux E, Desmaretz J-L, Diehl J-L, Dimet J, Dinh A, Duval X, Escaut L, Fabe C, Faibis F, Flateau C, Fonsale N, Forestier E, Fortineau N, Gagneux-Brunon A, Garandeau C, Garcia M, Garot D, Gaudry S, Goehringer F, Gravet A, Gregoire-Faucher V, Grosset M, Gubavu C, Gueit I, Guelon D, Guimard T, Guinard J, Hadou T, Helene J-P, Henard S, Henry B, Hochart A-C, Hoen B, Illes G, Jaffuel S, Jarrin I, Jaureguy F, Joseph C, Juvin M-E, Kayal S, Lacassin F, Lamaury I, Lanotte P, Laurens E, Laurichesse H, Le Brun C, Le Moing V, Le Turnier P, Lecuyer H, Ledru S, Legrix C, Lemaignen A, Lemble C, Lemee L, Lesens O, Levast M, Lhommet C, Males S, Malpote E, Martin-Blondel G, Marx M, Masson R, Matray O, Mbadi A, Mechai F, Mellon G, Merens A, Meyohas MC, Michon A, Mootien Yoganaden J, Morquin D, Mouly S, Mrozek N, Nguyen S, Nguyen Y, Ogielska M, Oziol E, Page B, Patrat-Delon S, Patry I, Pechinot A, Picot S, Pierrejean, Piroth L, Plassart C, Plessis P, Ploy M-C, Portel L, Poubeau P, Poupard M, Poyart C, Prazuck T, Quaesaet L, Raffi F, Ramanantsoa A, Rapp C, Raskine L, Raymond J, Revest M, Riche A, Robaday-Voisin S, Robin F, Romaszko J-P, Rousseau F, Roux A-L, Royer C, Saada M, Salmon D, Saroufim C, Schmit J-L, Sebire M, Segonds C, Sivadon-Tardy V, Soismier N, Kerneis S, Son O, Sunder S, Suy F, Tande D, Tankovic J, Valin N, Van Grunderbeeck N, Vandenesch F, Varon E, Verdon R, Vergnaud M, Vernet-Garnier V, Vidal M, Vitrat V, Vittecoq D, Vuotto F, Coordination and statistical analyses, Gorenne I, Laouenan C, Marcault E, Mentre F, Pasquet B, Roy C, Tubiana S (2020) Community-acquired bacterial meningitis in adults: in-hospital prognosis, long-term disability and determinants of outcome in a multicentre prospective cohort. Clin Microbiol Infect 26: 1192–1200. doi: 10.1016/j.cmi.2019.12.020.
5. Sunwoo J-S, Shin H-R, Lee HS, Moon J, Lee S-T, Jung K-H, Park K-I, Jung K-Y, Kim M, Lee SK, Chu K (2021) A hospital-based study on etiology and prognosis of bacterial meningitis in adults. Sci Rep 11: 6028. doi: 10.1038/s41598-021-85382-4.
6. Akaishi T, Kobayashi J, Abe M, Ishizawa K, Nakashima I, Aoki M, Ishii T (2019) Sensitivity and specificity of meningeal signs in patients with meningitis. J Gen Fam Med 20: 193–198. doi: 10.1002/jgf2.268.
7. Namani S, Milenković Z, Koci B (2013) A prospective study of risk factors for neurological complications in childhood bacterial meningitis. J Pediatr 89: 256–262. doi: 10.1016/j.jped.2012.10.001.
8. Koomen I, Grobbee DE, Roord JJ, Donders R, Jennekens-Schinkel A, van Furth AM (2003) Hearing loss at school age in survivors of bacterial meningitis: assessment, incidence, and prediction. Pediatrics 112: 1049–1053. doi: 10.1542/peds.112.5.1049.
9. Oostenbrink R, Moons KGM, Derksen-Lubsen G, Grobbee DE, Moll HA (2002) Early prediction of neurological sequelae or death after bacterial meningitis. Acta Paediatr 91: 391–398. doi: 10.1080/080352502317371616.
10. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, van der Ende A, van de Beek D (2016) Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study. Lancet Infect Dis 16: 339–347. doi: 10.1016/S1473-3099(15)00430-2.
11. Cabellos C, Verdaguer R, Olmo M, Fernández-Sabé N, Cisnal M, Ariza J, Gudiol F, Viladrich PF (2009) Community-acquired bacterial meningitis in elderly patients: experience over 30 years. Medicine 88: 115–119. doi: 10.1097/MD.0b013e31819d50ef.
12. Jellema K (2019) CT in patients suspected of bacterial meningitis? First antibiotics!. Ned Tijdschr Geneeskd 163: D3601. [Article in Dutch].
13. UpToDate (2023) Initial therapy and prognosis of bacterial meningitis in adults. Available: https://www.uptodate.com/contents/initial-therapy-and-prognosis-of-bacterial-meningitis-in-adults. Accessed: 21 May 2023.
14. Roine I, Peltola H, Fernández J, Zavala I, González Mata A, González Ayala S, Arbo A, Bologna R, Miño G, Goyo J, López E, Dourado de Andrade S, Sarna S (2008) Influence of admission findings on death and neurological outcome from childhood bacterial meningitis. Clin Infect Dis 46: 1248–1252. doi: 10.1086/533448.
15. Kaaresen PI, Flaegstad T (1995) Prognostic factors in childhood bacterial meningitis. Acta Paediatr 84: 873–878. doi: 10.1111/j.1651-2227.1995.tb13783.x.
16. Pelkonen T, Roine I, Monteiro L, Correia M, Pitkäranta A, Bernardino L, Peltola H (2009) Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in sub-Saharan Africa. Clin Infect Dis 48: 1107–1110. doi: 10.1086/597463.
17. Lovera D, Arbo A (2005) Risk factors for mortality in Paraguayan children with pneumococcal bacterial meningitis. Trop Med Int Health 10: 1235–1241. doi: 10.1111/j.1365-3156.2005.01513.x.
18. Kornelisse RF, Westerbeek CM, Spoor AB, van der Heijde B, Spanjaard L, Neijens HJ, de Groot R (1995) Pneumococcal

meningitis in children: prognostic indicators and outcome. Clin Infect Dis 21: 1390–1397. doi: 10.1093/clinids/21.6.1390.

19. Fakhir S, Ahmad SH, Ahmad P (1992) Prognostic factors influencing mortality in meningococcal meningitis. Ann Trop Paediatr 12: 149–154. doi: 10.1080/02724936.1992.11747560.

20. Akpede GO, Akuhwa RT, Ogiji EO, Ambe JP (1999) Risk factors for an adverse outcome in bacterial meningitis in the tropics: a reappraisal with focus on the significance and risk of seizures. Ann Trop Paediatr 19: 151–159. doi: 10.1080/02724939992473.

21. Pikis A, Kavaliotis J, Tsikoulas J, Andrianopoulos P, Venzon D, Manios S (1996) Long-term sequelae of pneumococcal meningitis in children. Clin Pediatr 35: 72–78. doi: 10.1177/000992289603500204.

22. Klinger G, Chin CN, Beyene J, Perlman M (2000) Predicting the outcome of neonatal bacterial meningitis. Pediatrics 106: 477–482. doi: 10.1542/peds.106.3.477.

23. Kirimi E, Tuncer O, Arslan S, Ataş B, Caksen H, Uner A, Oner AF, Odabaş D (2003) Prognostic factors in children with purulent meningitis in Turkey. Acta Med 57: 39–44. doi: 10.18926/AMO/32839.

24. Lin M-C, Chiu N-C, Chi H, Ho C-S, Huang F-Y (2015) Evolving trends of neonatal and childhood bacterial meningitis in northern Taiwan. J Microbiol Immunol Infect 48: 296–301. doi: 10.1016/j.jmii.2013.08.012.