Ro J Pediatr. 2023;72(3)
DOI: 10.37897/RJP.2023.3.6

Risk factors of death in children with bacterial meningitis: a systematic review and meta-analysis

Ni Made Maya Purnama Wulandari[1], Citrawati Dyah Kencono Wungu[2], Prastiya Indra Gunawan[1]

[1]Department of Child Health, Faculty of Medicine, Airlangga University, "Dr. Soetomo" General Academic Hospital, Surabaya, Easy Java, Indonesia
[2]Department of Biochemistry, Faculty of Medicine, Airlangga University, "Dr. Soetomo" General Academic Hospital, Surabaya, East Java, Indonesia

ABSTRACT

Background and objectives. To identify the risk factors that cause death in children with bacterial meningitis.

Materials and methods. Articles were obtained through a journal literature search of observational studies using electronic databases: PubMed, Scopus, ProQuest, Science Direct, and Web of Science. The articles were systematically selected using international guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols.

Results. A literature search identified 8746 articles. After screening, 19 studies were found that met the requirements for meta-analysis. There was a total of 6997 patients aged 1 month to 18 years who were included in the study. Factors that significantly influence the risk of death in children with bacterial meningitis in this meta-analysis are: age less than five years (pooled OR = 3,19; 95% CI, 1,03-9,89; p = 0.04), age less than three years (pooled OR = 18,77; 95% CI, 2,10-167,83; p = 0.009), decreased of consciousness (pooled OR = 4,85; 95% CI, 1,25-18,86; p = 0.02), seizure (pooled OR = 2,97; 95% CI, 1,09-8,07; p = 0,03), and bacteria *Streptococcus pneumoniae* compared to *Haemophilus influenzae* from culture of cerebrospinal fluid (pooled OR = 12,52; 95% CI, 8,95-17,52; p <0,00001).

Conclusions. Risk factors for death in children with bacterial meningitis were age less than five years old, age less than three years, decrease of consciousness, seizure, and cerebrospinal fluid culture result of bacteria *Streptococcus pneumoniae* compared to bacteria *Haemophilus influenzae.*

Keywords: bacterial meningitis, children, risk factors, death, systematic review, meta-analysis

Abbreviations

BBB - Blood Brain Barrier
BMI - Body Mass Index
CDC - Centers for Disease Control
CFR - Case Fatality Ratio
CI - Confidence Interval
CRP - C Reactive Protein
CSF - Cerebrospinal Fluid
CT Scan - Computed Tomography Scan
DNA - Deoxyribonucleic Acid
FEAST - Fluid Expansion as Supportive Therapy
GBS - Group B Streptococcus
GCS - Glascow Coma Scale
Hb - Hemoglobin
Hib - Haemophilus influenzae type B
HIV - Human Immunodeficiency Virus
LCS - Liquor Cerebrospinal
LDH - Lactate Dehydrogenase
NOS - Newcastle - Ottawa Scale
NOQS - Newcastle-Ottawa Quality Scale
PAF - Platelet Activating Factor
PCV - Pneumococcal Conjugate Vaccine
PCR - Polymerase Chain Reaction
PICO - Population, Intervention, Comparison, Outcome
PMN - Polymorphonuclear
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta Analyses
RE - Random Effects
SD - Standard Deviation
SIADH - Syndrome Inappropriate Antidiuretic Hormone
SLR - Systematic Literature Review
WHO - World Health Organization

Corresponding author:
Prastiya Indra Gunawan
E-mail: prastiya-i-g@fk.unair.ac.id

Article History:
Received: 25 September 2023
Accepted: 30 September 2023

INTRODUCTION

Bacterial meningitis is an inflammatory condition in the lining of the brain, which affects the pia, arachnoid and subarachnoid spaces, which occurs in response to bacteria and bacterial products [1]. This is a global public health problem and most cases and deaths occur mainly in children under five years due to various factors [2]. Children are especially susceptible because their immune systems are not yet perfect. It is estimated that more than 75% of cases occur in children under five years [3]. Mortality rates are very high, ranging from 5% to 30% of cases [4].

Several studies have been conducted to identify risk factors associated with death in children with bacterial meningitis. Previously known risk factors for death include age of disease onset [5], duration of symptoms before admission [6], etiological agent of Streptococcus pneumoniae [7], and comorbidities [8]. Identification of risk factors for death is very important to help determine which patients require more intensive treatment and longer monitoring, as well as helping clinicians to rationally counsel parents of patients regarding their child's disease prognosis in the early phase of the disease [3].

MATERIALS AND METHODS

Literature search strategy

This meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The International Prospective Register of Systematic Reviews (PROSPERO) was registered under the following identification number: CRD42022329040.

The literatures were selected by electronic search from Pubmed, Scopus, Science Direct, Web of Science, and ProQuest. Searches were conducted in February 2023 until April 2023. We developed a comprehensive search strategy based on PICO (population, issue, comparison, and outcome). Keywords that were used for searching strategy were "Bacterial meningitis" OR "bacterial meningitides" OR "pyogenic meningitis" AND child* OR pediatr* OR paediatr* OR infant* OR baby OR babies OR toddler* OR adolescen* OR teenager* AND death OR mortality OR outcome*. We systematically searched for observational studies published in English as full report articles in international journals from 2000 to 2022.

Eligibility Criteria

The literatures included in the study had to meet the following inclusion criteria: research subjects were pediatric patients aged 1 month to 18 years old; observational research in the form of prospective or retrospective cohorts, case controls, and cross-sectional studies with cases of bacterial meningitis deaths, and identifying the risk factors that cause these deaths; journal with full text; journal with publication year 2000-2022; and published in English.

The exclusion criteria were as follows: journals that cannot be accessed in full text; duplicate journal; studies involving adult and geriatric subjects; studies that evaluate risk factors associated with bacterial meningitis outcomes but do not link these factors to death; studies evaluating meningitis caused by nonbacterial agents; studies evaluating meningitis caused by the bacteria *Mycobacterium tuberculosis;* review studies; experimental studies with animals; and research with themes that do not match the objectives of this research.

Data Extraction

Articles that met the inclusion criteria were read comprehensively in full text form, and decisions regarding the final articles selected were made through a joint meeting. The extracted data is in the form of article title and author's name, year of publication, results of study quality assessment, type of study, country of origin, number of samples, population, age of subjects, study period, and research results, which are presented in tabular form.

Quality Assessment

The quality assessment of the articles selected was performed using New-Castle Ottawa Scale. Good quality if: 3 or 4 stars on item selection and 1 or 2 stars on item comparability and 2 or 3 stars on outcome/exposure. Adequate quality: 2 stars on item selection and 1 or 2 stars on item comparability and 2 or 3 stars on outcome/exposure. Poor quality if 0 or 1 star on item or 0 star on item comparability or 0 or 1 star on item outcome/exposure.

Statistical Analysis

The process of calculating data analysis and outcomes was carried out using Review Manager (Revman) 5.4 software. The meta-analysis process includes:

1. Calculate the number of patients who died for each risk factor studied.
2. Calculating heterogeneity. If p heterogeneity is >0.05 and I2 <70% then use fixed effect models, if p heterogeneity <0.05 and I2 >70% then use random effect models.
3. Calculate the pooled effect measure (using the pooled odds ratio), confidence interval (95%), and overall p value for the entire study (p is significant if p <0.05).
4. Perform subgroup analysis for each risk factor.
5. The results of the meta-analysis are described in the form of forest plots.

The technique used to identify the presence of publication bias in this research is to use a funnel

plot. If the distribution of articles is not symmetrical, there will be publication bias in the relationship between the variables being studied. If the number of studies is limited, publication bias cannot be determined.

Eligible studies

There were 19 articles selected from 8746 articles related to risk factors for death in children with bacterial meningitis. These studies were from Pubmed (15 studies), Scopus (13 studies), Web of Science (13 studies), (ProQuest with 5 studies), and 1 study from grey literature. Figure 1 describes the inclusion and exclusion steps of the articles. There was a total of 6997 patients aged 1 month to 18 years in the included studies.

All studies were assessed for quality using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (Table 1) and Newcastle-Ottawa Quality Assessment Form for Case Control Studies (Table 2).

Characteristics of the included studies

Eighteen studies were performed in developing countries, and only one study was from developed country. Those studies consisted of nine cohort studies and 10 case-control studies. The studies characteristics are presented in Table 3.

RESULTS

Age under 5 years were reported in 9 studies. Analysis of the researches shows that age <5 years increases the risk of death significantly by 3.19 times in children suffering from bacterial meningitis compared to age ≥5 years (OR = 3.19; 95% CI, 1.03-9.89; I2 93%; P = 0.04). Age <3 years were reported in 3 studies (Figure 2). A meta-analysis of those 3 studies revealed that age <3 years increases the risk of death significantly by 18.77 times in children suffering from bacterial meningitis compared to age ≥3 years (OR =18.77; 95% CI, 2.10-167.83; I2 70 %; P = 0.009).

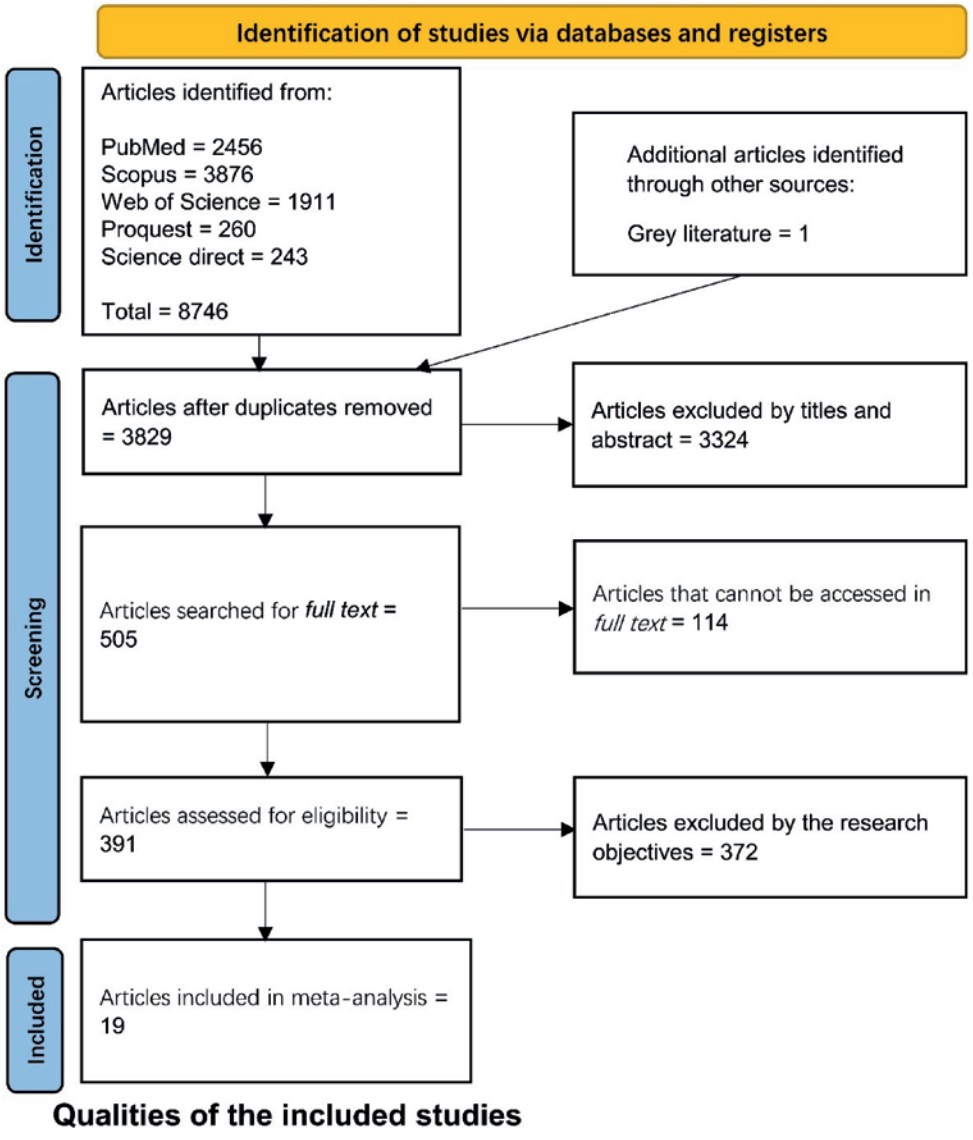

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram

TABLE 1. Newcastle-Ottawa Quality Assessment for Cohort Studies

Study	Selection				Comparability		Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	The most important factor	Any additional factor	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Rahimi et al., 2022	□	□	□	0	0	□	□	□	□	7
Widjaja et al., 2021	□	□	□	0	0	□	□	□	□	7
Maniruzzaman et al., 2019	□	□	□	0	0	□	□	□	□	7
Bari et al., 2016	□	□	□	0	0	□	□	□	□	7
Pelkonen et al., 2022	□	□	□	0	0	□	□	□	□	7
Kirimi et al., 2003	□	□	□	□	□	0	□	□	□	8
Nguyen Huu et al., 2022	□	□	□	0	0	□	□	□	□	7
Bari et al., 2017	□	□	□	0	0	□	□	□	□	7
Teixeira et al., 2021	□	□	□	0	0	□	□	□	□	7

TABLE 2. Newcastle-Ottawa Quality Assessment for Case Control Studies

Study	Selection				Comparability		Exposure			Total
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	The most important factor	Any additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Basri et al., 2015	□	□	□	0	0	□	□	□	□	7
Tadesse et al., 2017	□	□	□	0	0	□	□	□	□	7
Kuti et al., 2015	□	□	□	0	0	□	□	□	□	7
McCormick et al., 2013	□	□	□	0	0	□	□	□	□	7
Chamkhaleh et al., 2021	□	□	□	0	□	0	□	□	□	7
Johnson et al., 2007	□	□	□	0	0	□	□	□	□	7
Okike et al., 2018	□	□	□	0	0	□	□	□	□	7
Correa-Lima et al., 2014	□	□	□	0	0	□	□	□	□	7
Madoshi et al., 2022	□	0	□	0	0	□	□	□	□	6

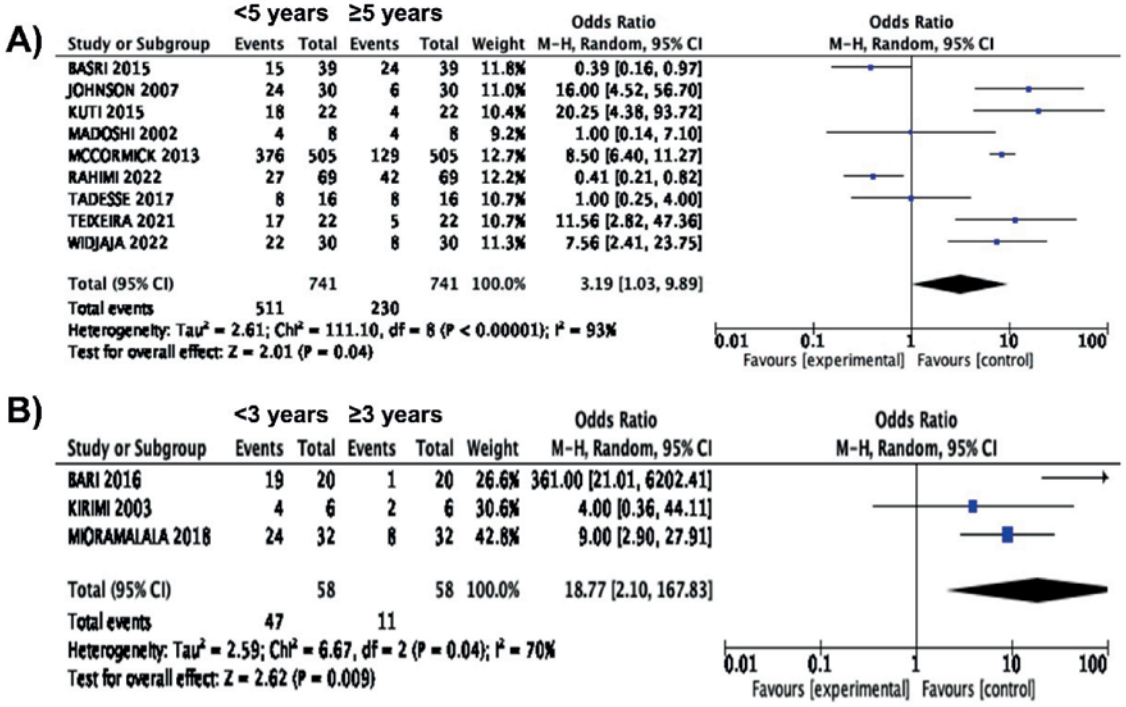

FIGURE 2. Forest plot for age. (A) Age <5 years compared to ≥5 years; (B) Age <3 years compared to ≥3 years

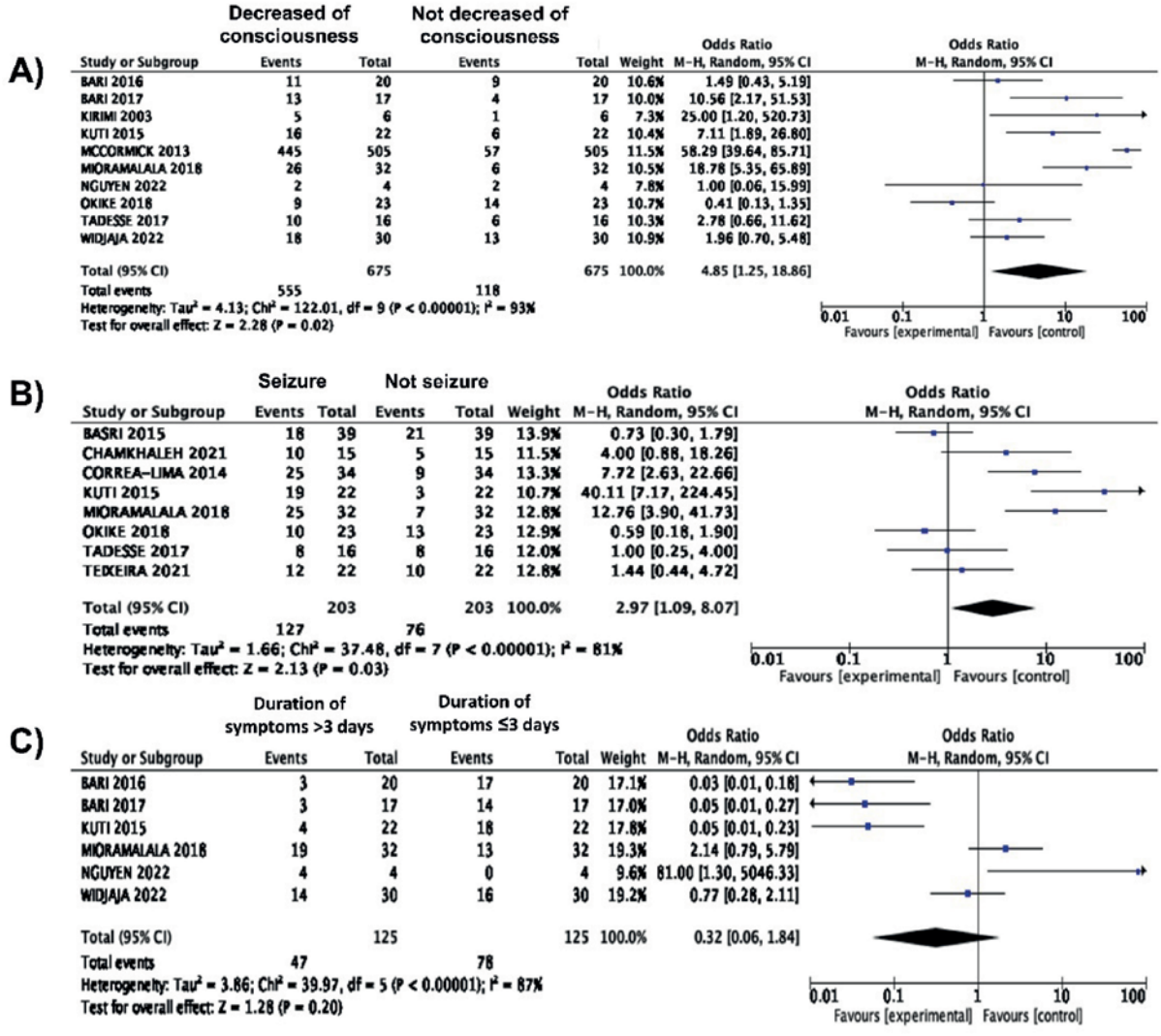

FIGURE 3. Forest plot for consciousness, seizure, and duration of symptoms. (A) Decreased of consciousness compared to not decreased of consciousness; (B) Seizure compared to not seizure; (C) Duration of symptoms >3 days compared to ≤3 days

TABLE 3. Characteristics of the included studies

Study	Total Score (New Castle Ottawa Scale)	Study design	Country	Sample (n)	Age	Study period	Outcomes of study (Risk factors for death in children with bacterial meningitis)
Rahimi BA et al., 2022	7 (high quality)	Cohort	Afghanistan	393	<18 years	February 2020-January 2021	• Coma on admission • Not getting dexamethasone therapy • Not getting PCV vaccination • Male gender • Purpura/petechiae
Basri et al., 2015	7 (high quality)	Case control	Malaysia	125	<19 years	January 2004-December 2011	• Age and decreased of consciousness (GCS<10)
Mioramalala et al., 2018	6 (moderate quality)	Case control	Madagascar	446	3-59 months	January 2012-December 2015	• Age • Dense living environment • Symptoms >5 days before admission • Decreased of consciousness • Meningococcal meningitis • Number of siblings more than 3
Tadesse et al., 2017	7 (high quality)	Case control	Ethiopia	99	≤18 years	January 2013-February 2014	• Malnutrition • Duration of symptoms before admission • Decreased of consciousness
Kuti et al., 2019	7 (high quality)	Case control	Nigeria	81	1 month - 15 years	January 2011-December 2013	• Recurrent seizure • Coma • Neck stiffness • Hyponatremia • Hyperglycemia • Low glucose level of CSF • Positive bacteria on gram staining of CSF
McCormick DW et al., 2013	7 (high quality)	Case control	Malawi	1784	<15 years	July 1997-June 2010	• HIV seropositivity • Nutritional status wasted and severely wasted • Moderate-severe anemia (Hb <8 gram/dL) • Young age (< 24 months) • Infection of *Streptococcus pneumoniae* and *Salmonella spp* • Decreased of consciousness
Chamkhaleh MA et al., 2020	7 (high quality)	Case control	Iran	202	1 months-18 years	23 December 2007-16 December 2017	• Increase LDH level of CSF • Increase protein level of CSF • Age under 1 year old
Widjaja H et al., 2022	7 (high quality)	Cohort	Indonesia	94	≤5 years dan >5 years	January 2016-December 2020	• Ratio of neutrophil-lymphocyte >5,225 • Pediatric Coma Scale 8 • Positive blood culture • Positive CSF culture
Maniruzzaman et al., 2019	7 (high quality)	Cohort	Bangladesh	60	1-12 years	February 2012-February 2013	• Malnutrition
Bari A et al, 2016	7 (high quality)	Cohort	Pakistan	199	1 months - 5 years	January-December 2012	• Low intake • Decreased of consciousness • Pathogen *Streptococcus pneumoniae*
Pelkonen et al., 2022	7 (high quality)	Cohort	Finland, Latin America, Angola	341, 597, 1085	2 months -15 years	1984-2017	• Moderate to severe anemia
Johnson et al., 2007	9 (high quality)	Case control	Nigeria	71	<16 years	5 years	• Abnormal respiratory rhythm on admission • purulent / turbid CSF • CSF protein level >150mg/dl • glucose CSF level <1mg/dl

Study	Total Score (New Castle Ottawa Scale)	Study design	Country	Sample (n)	Age	Study period	Outcomes of study (Risk factors for death in children with bacterial meningitis)
Kirimi E et al., 2003	8 (high quality)	Cohort	Turkey	48	2 months-13 years	February 1999 - December 2000	• not anemia, • low leukocyte count (<1000) on CSF • high CRP level on admission • Fever 36-48 hours after admission, • decreased of consciousness • high leukocyte count (>1000) on CSF • low CRP level
Okike IO et al., 2018	7 (high quality)	Case control	United Kingdom and Irland	298	<90 days	July 2010-July 2011	• Coma on admission, • Meningococcal meningitis • Prematurity
Correa-Lima AR, et al., 2014	7 (high quality)	Case control	Brazil	289	1 months-14 years	January 2004-December 2008	• Seizures
Nguyen-Huu CD et al., 2022	7 (high quality)	Cohort	Vietnam	33	1 months-15 years	January 2019-July 2021	• diarrhea • low appetite • seizure • local paralysis • decreased of consciousness • leucocyte >500 cells/mm^3 • higher level of neutrophil on CSF
Bari A et al., 2017	7 (high quality)	Cohort	Pakistan	503	1 months-5 years	not stated	• low appetite • sensors disturbance • severe malnutrition • prolonged duration of symptoms • incomplete vaccination status
Teixeira DC et al., 2021	7 (high quality)	Cohort	Brazil	178	0-18 years	not stated	• age less than 1 years • low CSF cellularity with median 198 cells/mm^3 • seizures • gastrointestinal symptoms • clinical severity signs on admission
Madoshi PB et al., 2022	6 (moderate quality)	Case control	Tanzania	71	neonatus and children <10 years	not stated	• patient's location • mother's parity • patients with neurological signs

Decreased of consciousness were reported in 10 studies. Analysis revealed that patient with decreased of consciousness was significantly more likely to die than patient without decreased of consciousness (OR =4.85; 95% CI, 1.25-18.86; I2 93%; P = 0.02) (Figure 3). Eight studies reported seizure. Meta-analysis revealed that seizure increases the risk of death significantly by 2.97 times in children with bacterial meningitis (OR =2.97; 95% CI, 1.09-8.07; I2 81%; P = 0.03). Duration of symptoms before admission were reported in 10 studies. Analysis of those studies showed that there was no significant association between symptom duration more than 3 days before admission and the risk of death in children with bacterial meningitis (OR=0.32; 95% CI, 0.06-1.84; I2 87%; P = 0.20) (Figure 3).

There were two studies analyzed regarding anemia with hematocrit criteria <30%. Meta-analysis revealed that anemia with hematocrit criteria <30% was not a risk factor for death in children with bacterial meningitis (OR = 0.13; 95% CI, 0.00-3.63; I2 92%; P = 0.23). Two studies reported anemia with hemoglobin criteria <11 mg/dl. Analysis showed that there was no significant association between anemia with hemoglobin criteria < 11 mg/dl and the risk of death in children with bacterial meningitis (OR=0.42; 95% CI, 0.00-1991.44; I2 94%; P = 0.84) (Figure 4 A&B). Nine studies were analyzed for malnutrition. Meta-analysis showed that malnutrition was not a risk factor for death in children with bacterial meningitis (OR = 0.69; 95% CI, 0.08-6.29; I2 97%; P = 0.74).

Streptococcus pneumoniae compared to *Haemophilus influenzae* from CSF culture result was reported in four studies. Analysis showed that patient with CSF culture result of *Streptococcus pneumoniae* was

significantly more likely to die than patient with CSF culture result of *Haemophilus influenzae* (OR =12.52; 95% CI, 8.95-17.52; I2 39%; P <0.00001) (Figure 5). Three studies reported *Streptococcus pneumoniae* compared to *Neisseria meningitidis* from CSF culture result. Analysis of those studies revealed that there was no significant increase in risk of death between CSF culture result of *Streptococcus pneumoniae* and CSF culture result of *Neisseria meningitidis* (OR=153.34; 95% CI, 0.19-124819.55; I2 97%; P = 0.14). There were two studies analyzed regarding *Streptococcus pneumoniae* compared to *Escherichia coli* from CSF culture result. Meta-analysis revealed that there was no significant association between CSF culture result of *Streptococcus pneumoniae* and CSF culture result of *Escherichia coli* (OR=15.40; 95% CI, 0.71-336.24; I2 0%; P = 0.08). Lastly, there were five studies reported *Streptococcus pneumoniae* compared to other bacteria from CSF culture result. Meta-analysis of those studies revealed that there was no significant increase in risk of death between CSF culture result of *Streptococcus pneumoniae* and CSF culture result of other bacteria (OR=0.95; 95% CI, 0.21-4.23; I2 86%; P = 0.95). Other bacteria studied in the 5 journals were Coagulase negative staphylococci, *Haemophilus influenzae, Staphylococcus aureus, Gram-negative rods, Escherichia coli, Klebsiella,* and *Streptococcus pyogenes* [9]; *Haemophilus influenzae, Neisseria meningitidis, Klebsiella, Staphylococcus aureus,* Acinetobacter, and Gram-positive bacilli [10]; *Haemophilus influenzae type B, Neisseria meningitidis, Salmonella spp, Escherichia coli, Staphylococcus aureus,* Gram-positive diplococci, and Gram-negative rods [11]; *Escherichia coli* and *Pseudomonas aeruginosa* [12]; as well as *Neisseria meningitidis* and *Haemophilus influenzae* type B [13].

DISCUSSION

Acute bacterial meningitis remains a global health challenge with high rates of mortality and morbidity despite the development of modern antibiotic therapy and vaccination strategies. Identifying risk factors for death in children with bacterial meningitis can help determine which patients may benefit from aggressive therapeutic intervention to prevent a poor prognosis.

Young age is one of the factors that has a significant influence on death in children with bacterial meningitis in the results of our meta-analysis, in our study namely age less than five years and less than three years. This is in accordance with research conducted by Basri et al in Kelantan, Malaysia that young age is a significant factor related to mortality [14]. This can be explained by the immature status of cellular and humoral immunity which causes more severe infections and affects the brain development of young children [15].

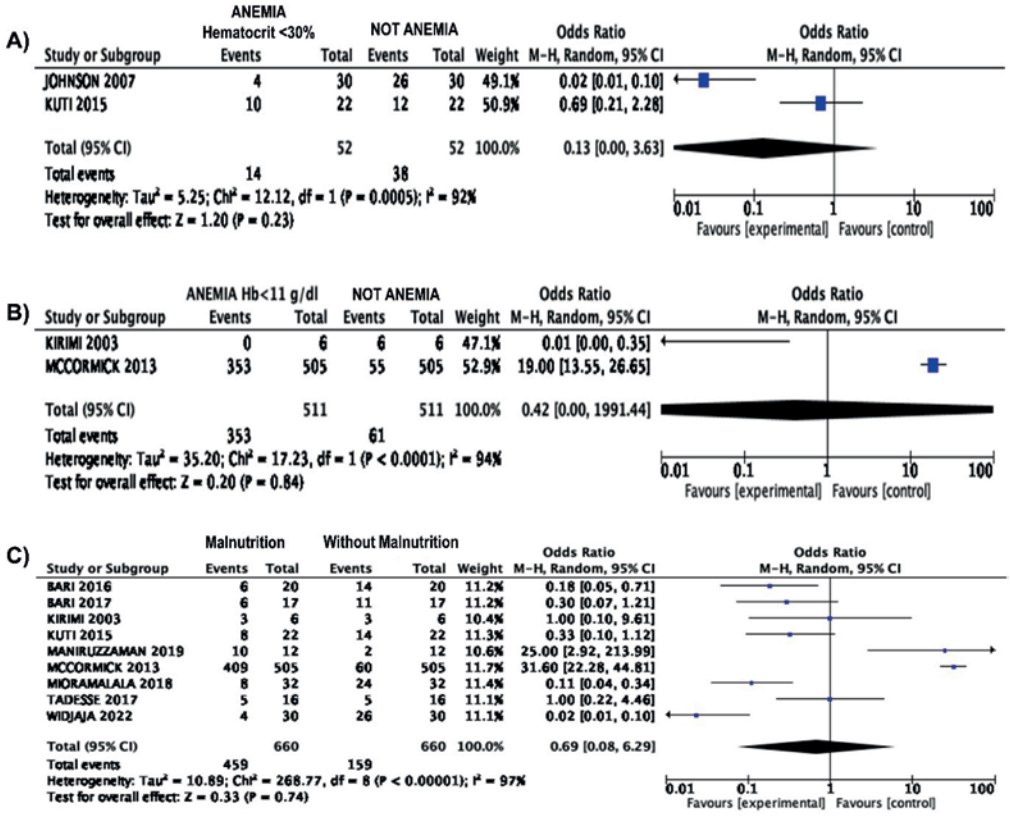

FIGURE 4. Forest plot for anemia and malnutrition. (A) Anemia with criteria of hematocrit <30% compared to without anemia; (B) Anemia with criteria of hemoglobin <11 mg/dl compared to without anemia; (C) Malnutrition compared to without malnutrition

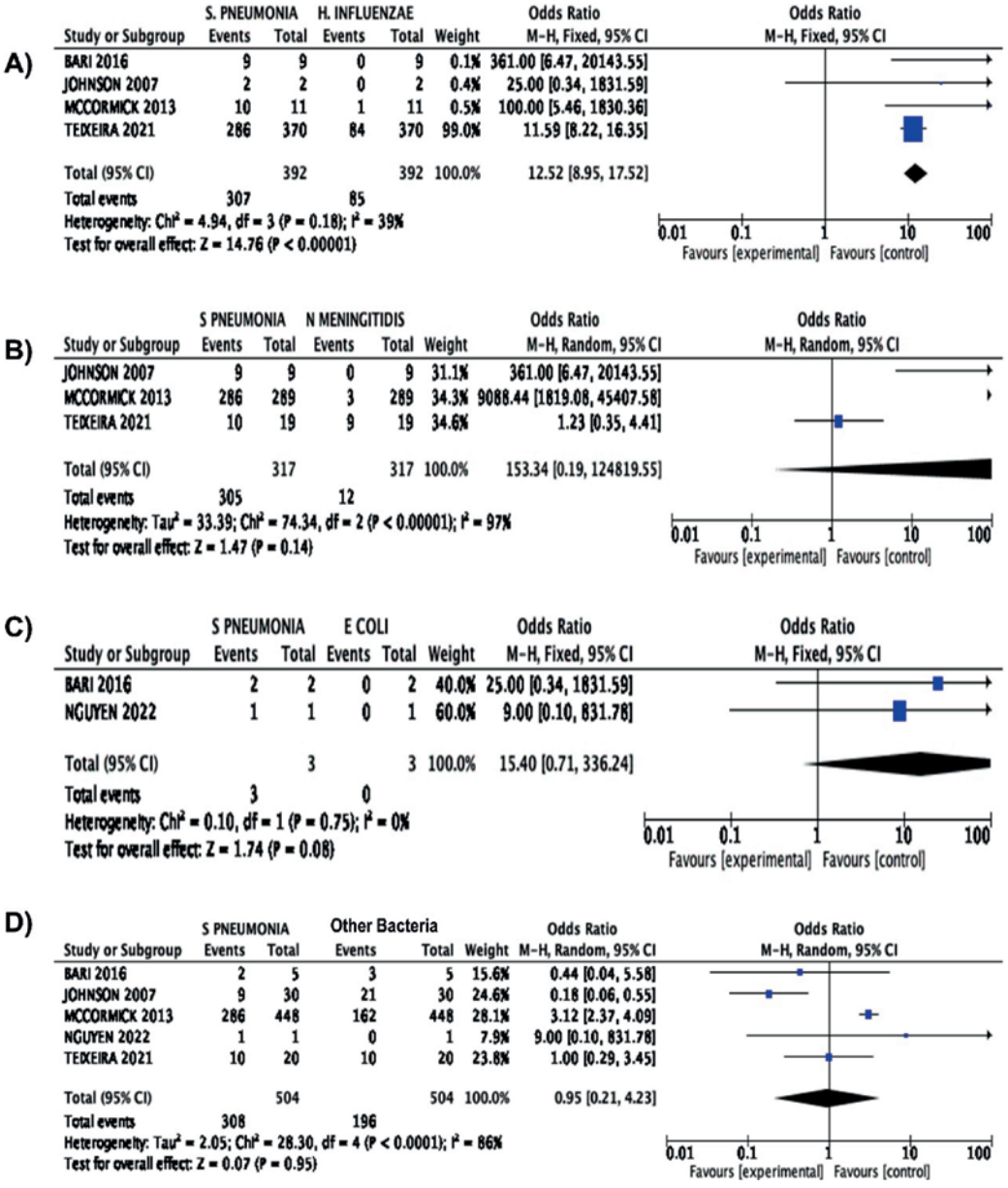

FIGURE 5. Forest plot of CSF culture results. (A) *Streptococcus pneumoniae* compared to *Haemophilus influenzae;* (B) *Streptococcus pneumoniae* compared to *Neisseria meningitidis;* (C) *Streptococcus pneumoniae* compared to *Escherichia coli;* (D) *Streptococcus pneumoniae* compared to other bacteria

Impaired consciousness is an indicator of severe neuronal injury that contributes to high mortality in bacterial meningitis [11]. Coma in children with meningitis can result from brain hemorrhage or thrombosis, hypoglycemia, or even brain edema [16,17]. In our meta-analysis, decreased consciousness was a significant risk factor for death in children with bacterial meningitis. This is in accordance with research conducted by Basri et al in Kelantan, Malaysia, Pelkonen in Angola, and McCormick in Malawi that decreased consciousness is a significant factor associated with death [11,14,18].

The results of our meta-analysis indicate that seizures are a risk factor for death in children with bacterial meningitis. This is in accordance with research by Roine which states that in several Latin American countries children with bacterial meningitis who experience seizures have a four times greater risk of death [19]. Seizures may occur due to irritation of brain tissue caused by the inflammatory process; brain edema; and subdural effusion [16]. Seizures may be directly associated with mortality, either through an increased risk of bronchial aspiration, or by progression of seizures to status epilepticus. According to a study by Correa-Lima, one of three children with bacterial meningitis who experienced acute seizures in hospital died [20].

Based on a study by Olson in Guatemala, children with symptoms that lasted more than three days before admission to hospital had a 3.7 times greater risk of dying [21]. According to Kirimi, late admission to the hospital is a poor prognostic factor [22]. Symptom duration >3 days was not a risk factor for death in children with bacterial meningitis in our

meta-analysis. This may be due to faster progression of the disease due to more pathogenic bacteria causing the patient's immune system being weaker. Faster disease progression causes a shorter duration of symptoms before admission to hospital, resulting in more deaths in children with bacterial meningitis than patient with longer duration of symptoms.

Anemia can make children more likely to suffer from infections, although on the other hand, infections can also cause anemia [23,24]. Moderate to severe anemia increases the risk of poor outcomes such as death [25]. The results of our meta-analysis show that both anemia with a hematocrit criterion of <30% and anemia with a hemoglobin criterion of <11 mg/dl is not a risk factor for death in children with bacterial meningitis. This is not in accordance with research by Roine in 2008 which stated that anemia was a risk factor for death in children with bacterial meningitis [19]. This may be due to the small number of subjects in the majority of included studies. In addition, the heterogeneity of anemia criteria between studies may also contribute to the non-significant results of the meta-analysis of our study.

Protein energy malnutrition significantly increases morbidity and mortality in children with bacterial meningitis although the mechanism is still unclear [26]. In the results of our meta-analysis, we did not find a significant relationship between malnutrition and death in children with bacterial meningitis. This is not in accordance with research from McCormick which stated that there was an association between malnutrition and death in children with bacterial meningitis [11]. This may occur due to variations in the malnutrition criteria used in each study, namely in defining and assessing malnutrition as a risk factor for death in children with bacterial meningitis.

Another factor from our meta-analysis which also has a significant effect on mortality in children with bacterial meningitis is the results of cerebrospinal fluid culture of Streptococcus pneumoniae when compared with the results of *Haemophilus influenzae.* These results are in accordance with a study by de Jonge which stated that Streptococcus pneumoniae has more pathogenic potential than other types of bacteria [15]. The high mortality is thought to be due to the cell wall component of pneumococcal bacteria, namely platelet activating factor [PAF), which can cause increased permeability of the blood brain barrier and ultimately cause brain edema [27].

On the other hand, the results of subgroup analysis calculations in our meta-analysis show that the results of cerebrospinal fluid culture of *Streptococcus pneumoniae* are not a risk factor for death in children with bacterial meningitis when compared to *Neisseria meningitidis, Escherichia coli,* and the sum of bacteria other than *Streptococcus pneumoniae.* This is may be due to the high coverage of PCV immunization in the countries where the study was conducted.

Limitation of the study

Our study has several limitations: 1) the search strategy was limited to full report articles published in English, from journals available in electronic databases. This can lead to publication bias and language bias because it can miss relevant studies; 2) The majority of studies were conducted in developing countries, so the results cannot be generalized to developed countries; 3) This meta-analysis does not explore studies that are not in journal form and studies that are not published, so there is the potential for publication bias; and 4) This meta-analysis has not examined other risk factors that often cause death in children with bacterial meningitis, namely management factors and complication factors such as cerebral edema, brain herniation, and hydrocephalus.

CONCLUSION

Age less than three years, age less than five years, decreased of consciousness, seizures, and CSF culture results of *Streptococcus pneumoniae* compared to *Haemophilus influenzae* were risk factors for death in children with bacterial meningitis, while duration of symptoms more than three days before admission, anemia with criteria for hematocrit <30% or hemoglobin <11 mg/dl, malnutrition, and CSF culture results of *Streptococcus pneumoniae* compared to *Neisseria meningitidis, Escherichia coli* and bacteria other than *Streptococcus pneumoniae* were not risk factors for death in children with bacterial meningitis.

Acknowledgements

We would like to thank our Head of Department of Child Health, Muhammad Faizi, MD, PhD. We also would like to appreciate the help of all staff in Department of Child Health for supporting and giving warm motivation for authors to complete this study.

Author's contributions

Conceptualization, N.M.M.P.W. and P.I.G.; methodology, P.I.G.; software, C.D.K.W.; validation N.M.M.P.W., P.I.G., and C.D.K.W.; formal analysis, N.M.M.P.W.; investigation, N.M.M.P.W.; resources, P.I.G; data curation, C.D.K.W.; writing—original draft preparation, N.M.M.P.W.; writing—review and editing, P.I.G.; visualization, C.D.K.W.; supervision, P.I.G.; project administration, N.M.M.P.W.; funding acquisition, P.I.G. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: The authors have no conflict of interest to disclose

REFERENCES

1. Kim KS. Acute bacterial meningitis in infants and children. Lancet Infect Dis. 2010;10(1):32-42. doi: 10.1016/s1473-3099(09)70306-8.
2. Mioramalala SA, Ramasy Razafindratovo RM, Rakotozanany A, Miarimbola R, Weldegebriel G, Mwenda JM et al. Analysis of Death and Survival Factors Associated with Childhood Bacterial Meningitis at a Reference Pediatric Hospital in Antananarivo, Madagascar. *J Immunol Sci.* 2018;Suppl(2):8-14. doi: 10.29245/2578-3009/2018/si.1102
3. Agrawal S, Nadel S. Acute bacterial meningitis in infants and children: epidemiology and management. *Paediatr Drugs.* 2011;13(6):385-400. doi: 10.2165/11593340-000000000-00000
4. Teixeira DC, Diniz LMO, Guimarães NS, Moreira H, Teixeira CC, Romanelli RMC. Risk factors associated with the outcomes of pediatric bacterial meningitis: a systematic review. *J Pediatr (Rio J).* 2020;96(2):159-67. doi: 10.1016/j.jped.2019.07.003
5. Maniruzzaman, Mohsin F, Nesa M, Chakroborty A, Zaman S, El Hadidy SHS et al. Effect of malnutrition on immediate outcome of childhood bacterial meningitis: a hospital based prospective cohort study in Bangladesh. *J Nutr Health Food Eng.* 2019;9(2):42-7. doi: 10.15406/jnhfe.2019.09.00323
6. Bargui F, D'Agostino I, Mariani-Kurkdjian P, Alberti C, Doit C, Bellier N et al. Factors influencing neurological outcome of children with bacterial meningitis at the emergency department. *Eur J Pediatr.* 2012;171(9):1365-71. doi: 10.1007/s00431-012-1733-5
7. Okike IO, Ladhani SN, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B et al. Clinical Characteristics and Risk Factors for Poor Outcome in Infants Less Than 90 Days of Age With Bacterial Meningitis in the United Kingdom and Ireland. *Pediatr Infect Dis J.* 2018;37(9):837-43. doi: 10.1097/inf.0000000000001917
8. Kirkpatrick B, Reeves DS, MacGowan AP. A review of the clinical presentation, laboratory features, antimicrobial therapy and outcome of 77 episodes of pneumococcal meningitis occurring in children and adults. *J Infect.* 1994;29(2):171-82. doi: 10.1016/s0163-4453(94)90698-x
9. Bari A, Zeeshan F, Zafar A, Ejaz H, Iftikhar A, Rathore AW. Childhood Acute Bacterial Meningitis: Clinical Spectrum, Bacteriological Profile and Outcome. *J Coll Physicians Surg Pak.* 2016;26(10):822-6
10. Johnson AW, Adedoyin OT, Abdul-Karim AA, Olanrewaju AW. Childhood pyogenic meningitis: clinical and investigative indicators of etiology and outcome. *J Natl Med Assoc.* 2007;99(8):937-47.
11. McCormick DW, Wilson ML, Mankhambo L, Phiri A, Chimalizeni Y, Kawaza K et al. Risk factors for death and severe sequelae in Malawian children with bacterial meningitis, 1997-2010. *Pediatr Infect Dis J.* 2013;32(2):e54-61. doi: 10.1097/INF.0b013e31826faf5a
12. Nguyen-Huu CD, Bui-Binh-Bao S, Tran KH, Mai VT, Nguyen-Thi DC, Tran-Thi HC et al. Main Clinical and Laboratory Features of Children with Bacterial Meningitis: Experience from a Tertiary Paediatric Centre in Central Vietnam. *Pediatric Health Med Ther.* 2022;13:289-95. doi: 10.2147/phmt.S371914
13. Teixeira DC, Diniz LMO, Moreira HMDAS, Maia MMM, Dornellas LH, Soares MLC et al. Risk Factors for Severe Outcomes in Bacterial Meningitis. *Arch Clin Infect Dis.* 2021;16(6):e110134. doi: 10.5812/archcid-110134
14. Basri R, Zueter AR, Mohamed Z, Alam MK, Norsa'adah B, Hasan SA et al. Burden of bacterial meningitis: a retrospective review on laboratory parameters and factors associated with death in meningitis, kelantan malaysia. *Nagoya J Med Sci.* 2015;77(1-2):59-68.
15. de Jonge RC, van Furth AM, Wassenaar M, Gemke RJ, Terwee CB. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. *BMC Infect Dis.* 2010;10:232. doi: 10.1186/1471-2334-10-232
16. Prober CG. Central nervous system infections. In Nelson's Textbook of Pediatrics: Eighteen Edition. WB Saunders Company. 2007. p. 2038-44.
17. Sáez-Llorens X, McCracken GH. Acute Bacterial Meningitis Beyond the Neonatal Period. In Principles and Practice of Pediatric Infectious Disease: Third Edition. *Elsevier.* 2009. p. 284-291 doi: 10.1016/B978-0-7020-3468-8.50048-1
18. Pelkonen T, Roine I, Monteiro L, Correia M, Pitkäranta A, Bernardino L et al. Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in sub-Saharan Africa. *Clin Infect Dis.* 2009;48(8):1107-10. doi: 10.1086/597463
19. Roine I, Peltola H, Fernández J, Zavala I, Mata AG, Ayala SG et al. Influence of admission findings on death and neurological outcome from childhood bacterial meningitis. *Clin Infect Dis.* 2008;46(8):1248-52. doi: 10.1086/533448
20. Corrêa-Lima ARM, Miranda-Filho DDB, Valença MM, Andrade-Valença L. Risk Factors for Acute Symptomatic Seizure in Bacterial Meningitis in Children. *J Child Neurol.* 2015;30(9):1182-5. doi: 10.1177/0883073814555907
21. Olson D, Lamb MM, Gaensbauer JT, Todd JK, Halsey NA, Asturias EJ. Risk Factors for Death and Major Morbidity in Guatemalan Children with Acute Bacterial Meningitis. *Pediatr Infect Dis J.* 2015;34(7):724-8. doi: 10.1097/inf.0000000000000720
22. Kirimi E, Tuncer O, Arslan S, Ataş B, Caksen H, Uner A et al. Prognostic factors in children with purulent meningitis in Turkey. *Acta Med Okayama.* 2003;57(1):39-44. doi: 10.18926/AMO/32839
23. Kassebaum NJ. The Global Burden of Anemia. *Hematol Oncol Clin North Am.* 2016;30(2):247-308. doi: 10.1016/j.hoc.2015.11.002
24. Abuga KM, Muriuki JM, Williams TN, Atkinson SH. How Severe Anaemia Might Influence the Risk of Invasive Bacterial Infections in African Children. *Int J Mol Sci.* 2020;21(18). doi: 10.3390/ijms21186976
25. Pelkonen T, Roine I, Kallio M, Jahnukainen K, Peltola H. Prevalence and significance of anaemia in childhood bacterial meningitis: a secondary analysis of prospectively collected data from clinical trials in Finland, Latin America and Angola. *BMJ Open.* 2022;12(3):e057285. doi: 10.1136/bmjopen-2021-057285
26. Hailemeskel H, Tafari N. Bacterial meningitis in childhood in an African city. Factors influencing aetiology and outcome. *Acta Paediatr Scand.* 1978;67(6):725-30. doi: 10.1111/j.1651-2227.1978.tb16250.x
27. Lutsar I, Friedland IR, McCracken GHJ. Pathogenesis of bacterial meningitis. *Annales Nestle.* 1997;55(3):92-102.