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AUTHOR'S AFFILIATIONS
Faculty of Medicine, Universitas Hang Tuah Surabaya, Indonesia[1]
Faculty of Medicine, Universitas Widya Mandala Surabaya, Indonesia[2]

CORRESPONDING AUTHOR
Fransiska Christela, Faculty of Medicine, Universitas Hang Tuah Surabaya, Indonesia
E-mail:
fransiskachristelaa@gmail.com

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Threshold Value of Blood Procalcitonin for the Diagnosis of Bacterial Meningitis in Children: A Systematic Review

Fransiska Christela[1], Benedicta[1], Christopher[2]

Abstract

Introduction: Bacterial meningitis is a high mortality rate in children. The diagnosis of bacterial meningitis through the medical history, physical and laboratory examinations, mainly cerebrospinal fluid analysis through lumbar puncture (LP). Procedure on children might be challenging due to the multiple adverse-effects, not all children comply with the procedure. **Objective:** This review focused on the blood Procalcitonin (PCT) threshold value as a promising blood biomarker that might be useful for diagnosing bacterial meningitis in children. **Methods**: Literature search across 3 databases, Scopus, PubMed, and ScienceDirect, used PICO framework to structure the search, following the PRISMA standards. Of 759 articles, 11 articles meet the criteria inclusion: children with meningitis under 18 years old, shows procalcitonin cut-off value and have lumbar puncture performed, sensitivity and specificity reported, in English. Exclusion criteria: studies of systematic reviews, meta-analyses, and literature reviews, value of blood procalcitonin as part of scoring system or machine learning model. **Results**: The analysis of 11 articles reveals a blood PCT cut-off value of 0.2 to 10 ng/ml, with sensitivity ranging from 24% to 100% and specificity ranging from 63% to 94%. **Conclusions**: Blood PCT helps diagnose bacterial meningitis, especially for children who are not eligible for LP procedure. The blood PCT levels between 0.2 and 5 ng/mL showed a sensitivity of over 85%. The cut-off value with 100% sensitivity was found to be 2 ng/mL. A cut-off value exceeding 5 ng/mL demonstrated a specificity of over 90%.

Keywords: bacterial meningitis, children, PCT

Review Article

INTRODUCTION

Bacterial meningitis is a disorder characterised by the invasion of bacteria into the mucosal lining, which triggers an immunological response and leads to inflammation of the meninges. Meninges are membranes that layered and secured the brain and spinal cord, which consisting of pia, subarachnoid, and subarachnoid spaces (Wall et al., 2021; Yang et al., 2023)

In 2019, the Global Burden of Disease study documented around 2.51 million instances of meningitis, resulting in 236,000 deaths worldwide. Children below the age of five face an increased chance of mortality, resulting in approximately 112,000 fatalities and 1.28 million new cases of illness. (Wulandari et al., 2023; Wunrow et al., 2023) Based on 3 years study in Indonesia, the number of suspected meningitis cases in 2015 was 339 cases, 279 cases in 2016, and estimated 353 cases in 2017

(Indonesia, 2019). The primary aetiologies of bacterial meningitis include *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* (Glimaker, 2018).

Newborns and young children are at a higher risk of developing meningitis. Symptoms of this condition include severe headaches, seizures, high body temperature, nausea, and altered states of consciousness. (Bedetti et al., 2021; Setiaji et al., 2019; Young & Thomas, 2018). Meningitis diagnosis is established through clinical examination and lumbar puncture, which examines cerebrospinal fluid (CSF) and opening pressure. The diagnosis is confirmed using Gram staining, agglutination tests, PCR, and immunohistochemistry analysis (Hrishi & Sethuraman, 2019; Setiaji et al., 2019).

Although lumbar puncture (LP) is recommended in all cases where meningitis is suspected, there are several contraindications that may prevent its execution. These include signs of increasing cranial pressures (such as altered consciousness, Cushing triad, focal neurological signs, etc.), shock, coagulation disorders, local infections at the LP site, respiratory insufficiency, and convulsions (Schulga et al., 2015). There is also a study that shows a correlation between newborn positioning and desaturation likelihood. (Bedetti et al., 2021).

Emerging studies have identified new diagnostic tests as a solution to these problems. Blood-based biomarker detection is commonly employed to differentiate between various pathological conditions. One of those biomarkers is procalcitonin (PCT). Procalcitonin level has been proven to rise in the event of bacterial meningitis (Aloisio et al., 2019; Babenko et al., 2021; Lee et al., 2020; Paudel et al., 2020; Tujula et al., 2020).

Given the significant number of cases and elevated death rate among children with meningitis, it is crucial to prioritize the confirmation of a meningitis diagnosis. Because of the contraindications and risks associated with performing lumbar puncture in children, using blood PCT as a diagnostic technique can prove beneficial. As a result, our goal is to evaluate current research in order to determine the most feasible threshold value for blood PCT as an alternative diagnostic tool for children with bacterial meningitis.

We utilized journals that specified an age range of 0-18 years and reviewed blood PCT. Recent research indicates that no single parameter can effectively differentiate or diagnose meningitis. A systematic review conducted by Chaudray et al. examines serum procalcitonin levels in bacterial and non-bacterial meningitis, focusing on a narrower age range of 0-3 years. In contrast, our study encompasses a broader age range of 0-18 years. (Chaudhary et al., 2018)

METHODS

Database Searching and Screening

A systematic review was performed across three databases: Scopus, PubMed, and ScienceDirect. The keywords we utilize are "bacterial meningitis," "procalcitonin," and "children." We employed the PICOS framework to structure our search. The primary question driving the investigation can be observed in the table provided below.

Table 1. PICO framework

Population	Patients with age < 18 years who has meningitis diagnosis
Intervention / exposure	Serum Procalcitonin
Comparison	Lumbar Puncture
Outcome	Treshold value

Study Selection

After eliminating duplicate entries, the literature search from databases generated 759 articles, leaving a total of 669 results. After reviewing the titles and abstracts, 645 studies were excluded. The inclusion criteria for this review were as follows: (1) studies involving children under the age of 18 who have been diagnosed with meningitis. (2) studies that have reported the procalcitonin cut-off value and have undergone lumbar puncture. (3) studies were identified that presented diagnostic indices, including sensitivity and specificity; (4) studies were in English. The study exclusion criteria are as follows: (1)

studies in the form of systematic reviews, meta-analyses, and literature reviews; and (2) studies that focus on diseases other than meningitis. (3) Value of blood procalcitonin as part of scoring system or machine learning model. Each author separately analyzed all of the research and compared the results only after all writers had finished screening each study. Conflicts were handled through an agreement reached via discussion. The PRISMA flowchart was utilized to demonstrate the systematic procedure employed in this review.

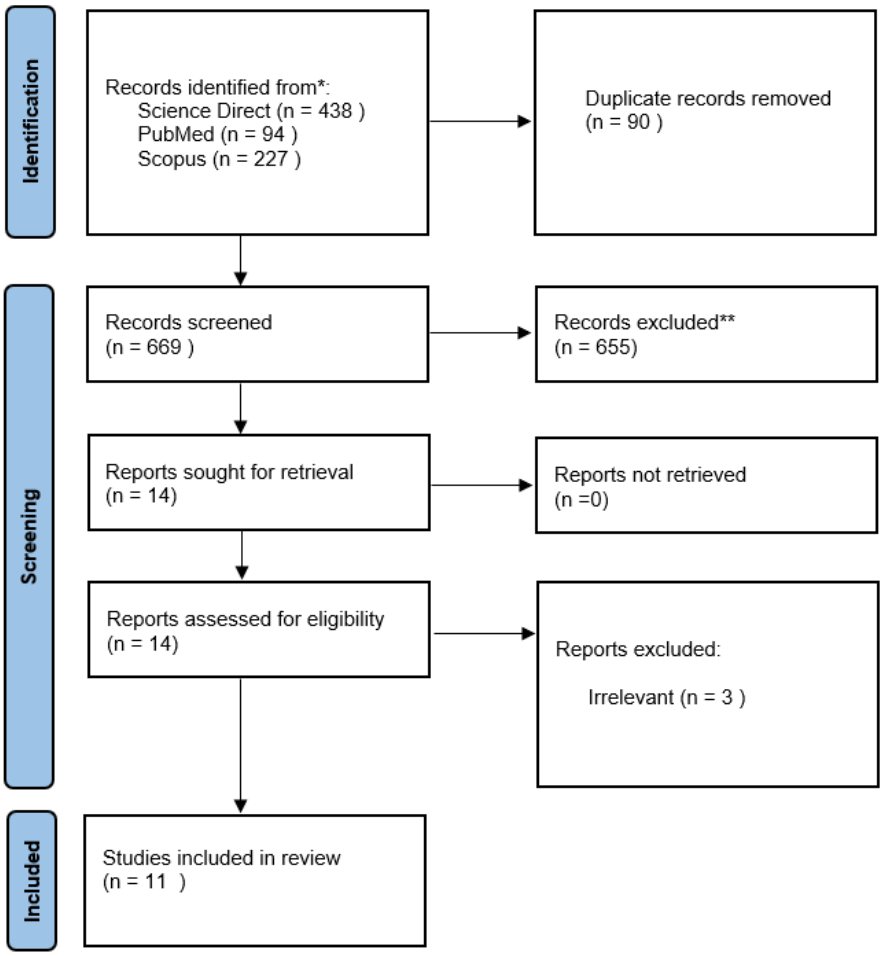

Figure 1. PRISMA Flowchart

Quality assessment and Data Extraction

This systematic review employs a critical appraisal method to analyze journals. The acquired publications were examined using the Newcastle Ottawa Scale (NOS). The articles featured had to achieve a minimum score of 6 on the checklist questions. A comprehensive analysis was conducted by assessing the title, abstract, and whole contents of the document. The data synthesis method entailed a comprehensive deliberation among each author concerning the procalcitonin cut-off value, as well as the sensitivity and specificity.

NOS Table

Nama	Selection	Comparability	Outcome/ Exposure	Total	Kesimpulan
Rajial et al.	3	1	3	7	Good
Babayeva et al.	3	1	2	6	Good
Emiroglu et al.	3	1	2	6	Good
Zhang et al.	4	2	2	7	Good
Chaudhary et al.	4	1	3	8	Good
Prasad et al.	4	1	3	8	Good
Dashti et al.	3	2	3	8	Good
Shorbagy et al.	3	1	3	6	Good
Dubos et al.	3	2	2	7	Good

RESULTS

Name	Country	Population	Cut-off Value (ng/mL)	Sensitivity (%)	Specificity (%)	Meningitis
Rajial et al., 2022	India	67 neonates	1.38	92.9	76	Culture positive Bacterial Meningitis compared to negative cultured meningitis
Babayeva et al., 2023	Turkey	48 children aged between 0 and 20 years old	0.2	82.4	80	Bacterial meningitis compared with enteroviral meningitis
Emiroglu et al., 2020	Turkey	199 children aged between 1 month and 18 years old	6.795	60	86	Bacterial Meningitis compared with aseptic meningitis (viral meningitis or unspecified meningitis)
Zhang et al., 2019	China	101 children aged < 18 years old	5.91	24.14	94.44	Bacterial Meningitis compared to all suspected meningitis patients
Chaudhary et al., 2018	Nepal	50 children ages between 3 months and 15 years	0.5	95.45	84.6	Bacterial meningitis compared to all suspected meningitis patients
Prasad et al., 2013	India	40 children aged <14 years old	5	98.5	93.5	Aseptic Meningitis compared to Septic Meningitis
Sanaei Dashti et al., 2017	Iran	50 children aged between 28 days and 14 years	0.6	66.7	59.3	Bacterial Meningitis compared to Viral Meningitis
(El shorbagy et al., 2018)	Saudi Arabia	65 children aged between 4 months and 14 years	2	100	63	Bacterial Meningitis compared to Aseptic meningitis
			10	86	82	
(Dubos et al., 2006)	France	167 children aged between 28 days and 16 years	0.5	89	86	Bacterial Meningitis compared to all suspected meningitis patients

DISCUSSION

Neonates and premature newborns are the most vulnerable populations for bacterial meningitis in children. This could be caused by a compromised phagocytosis ability due to an underdeveloped immune system or a deficiency of maternal immunoglobulins that pass through the placenta after 32 weeks of gestation. Children who have been vaccinated against common meningococcal pathogens are less likely to develop meningitis (Alamarat & Hasbun, 2020).

When children are suspected to have meningitis, prompt diagnosis is the key to deciding which treatment should be taken. Differentiating between bacterial and aseptic/viral meningitis would mean a different treatment regimen. Aseptic meningitis generally has a better prognosis compared to bacterial meningitis. (Liechti et al., 2015)

The pathogen infiltrates the central nervous system by entering the bloodstream. This triggers the immune system to respond, causing the destruction of bacteria and an inflammatory reaction, which leads to reduced blood flow to the brain, swelling, and damage to neurons (Velissaris et al., 2018). Procalcitonin, which is a precursor to calcitonin, is synthesised by the C-cells of the thyroid and released into the bloodstream by white blood cells. Chromosome 11 contains the CALC-1 gene, which is in charge of creating procalcitonin. Procalcitonin (PCT) levels in bacterial meningitis are influenced by the overexpression of the CALC-1 gene, which is typically suppressed in non-neuroendocrine tissue. Microbial infections increase CALC-1 gene expression, leading to PCT production. In bacterial infections, different cytokines like TNF-alpha, IL-1, and IL-6 increase PCT secretion, while viral infections down-regulate it, likely due to increased interferon gamma production (Paudel et al., 2020; Saeed et al., 2019)

In healthy people, the concentration of procalcitonin is well below the detectable limit. Both preterm and term neonates experience physiological increases in PCT levels throughout the first 72 hours of life. Therefore, it is advised against interpreting PCT concentrations for bacterial infections during this period. (Aloisio et al., 2019)

During bacterial infections, the levels of PCT begin to increase 4 hours after the infection starts and reach their highest point between 12 and 24 hours. If the treatment is sufficient, the levels begin to decrease at a rate of roughly fifty percent per day. However, if the treatment is insufficient, the levels of PCT stay high or increase even more. (Aloisio et al., 2019; Paudel et al., 2020)

There are multiple challenges associated with the utilization of PCT to diagnose bacterial meningitis, such as: The PCT levels can increase in many bacterial infections in children, including pneumonia, acute otitis media, and sepsis. Another example would be the decrease in PCT levels caused by antibiotic use prior to performing a lumbar puncture (LP), which might potentially result in incorrect findings during the initial assessment of bacterial meningitis in children in a point-of-care scenario. (Kim et al., 2021)

Zhang, et al. (Zhang et al., 2019) observed a sensitivity that was only 24%, which differs with the findings of Emiroglu, et al (Emiroglu et al., 2020), despite both studies employing a cut-off value of >5 ng/mL. This discrepancy may be attributed to variations in the experimental design. Emiroglu, et al (Emiroglu et al., 2020) conducted a study with two groups, one consisting of individuals with meningitis and the other consisting of individuals without meningitis. On the other hand, Zhang, et al. (Zhang et al., 2019) conducted a study with three groups for comparison: bacterial meningitis, viral meningitis, and those without meningitis.

When treating patients who are suspected of having meningitis, the main consideration is determining whether or not to administer antibiotics. It is advisable to administer antibiotic treatment to all individuals suspected of having bacterial meningitis. However, in cases of aseptic meningitis, it is recommended to discontinue antibiotic medication (Mount & Boyle, 2017). To exclude the possibility of bacterial meningitis, it is preferable to use a test with a high negative predictive value. Increased sensitivity results in a greater negative predictive value Shorbagy, et al. (El shorbagy et al., 2018) utilized a cut-off value of 2 ng/mL and reported a sensitivity of 100%.

There are other limitations associated with this study. Population bias is due to the limited number of populations. Additionally, the majority of these studies originate from a single institution, which may not accurately represent the prevalence across the entire country. This review is unable to determine whether antibiotics were used before going to the hospital. It is known that the use of

antibiotics might reduce PCT levels, which can introduce a confounding bias that may affect the results. There is a possibility of language bias in the study, as it exclusively focuses on English.

Our findings support the use of PCT as a screening tool for the diagnosis of bacterial meningitis in children, particularly in emergency department settings where obtaining a blood-based test is quicker and simpler than obtaining a spinal tap-based test. When deciding whether or not to administer antibiotics, focussing on a certain cutoff value would establish the basis for the recommended diagnosis of bacterial meningitis, hence reducing the amount of time required. Accessibility is facilitated by the fact that procalcitonin is a test that can be administered in most hospitals, as opposed to spinal tap-based tests that would need to be performed by specialists. Furthermore, there are many studies with varying results of procalcitonin value in children with bacterial meningitis, our study is made to help narrow the cut off value of blood procalcitonin.

CONCLUSION

Bacterial meningitis is a global occurrence that affects individuals of all ages, with children experiencing a higher mortality rate compared to adults. Timely and expeditious intervention is necessary to decrease the mortality rate. The distinction between bacterial and non-bacterial meningitis was also needed to determine an appropriate treatment. Accurate identification of bacterial and non-bacterial meningitis relies primarily on a thorough diagnostic examination. The recommended diagnostic approach is CSF analysis performed through an LP, but not every child is eligible for this procedure. Serum biomarkers such as PCT can be acquired and analyzed from blood samples. This can aid in the diagnosis of bacterial meningitis. The blood procalcitonin levels between 0.2 and 5 ng/mL showed a sensitivity of over 85%. The cut-off value with 100% sensitivity was found to be 2 ng/ml. A cut-off value exceeding 5 ng/mL demonstrated a specificity of over 90%. The limitations of this research include the varying age groups among individuals, a restricted population size due to the rarity of the disease, and Confounding bias resulting from specific studies failing to disclose the use of antibiotics prior to the evaluation of PCT. We recommend that future studies classify the age range into shorter segments to enable more precise cut-off values for each age group.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this study

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