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The Predictor Factors of Mortality in Adult with Bacterial Meningitis

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ABSTRACT

Meningitis is one of the infectious diseases of the central nervous system with high mortality and morbidity rates worldwide. One of the causes of meningitis is bacterial infection. Data from the Global Burden of Disease Study in 2019, there were 236,000 cases of death and 2.51 million cases of meningitis globally. Due to the high mortality from bacterial meningitis in adult, recognizing predictive factors is needed to improve monitoring and education related to the disease for sufferers. This study discusses several predictive factors of mortality in patients with bacterial meningitis, especially clinically.

Keywords: adult, bacterial meningitis, mortality, predictors,

INTRODUCTION

Meningitis is an inflammation of the meninges and subarachnoid space that can be life-threatening. (1) Bacterial meningitis is an infection of the meninges caused by bacteria. The incidence of bacterial meningitis is around 2-6 per 100,000 people per year, peaking in young adults and in old age. The prevalence of bacterial meningitis in developing countries is higher, where the average incidence is around 50 cases per 100,000 cases compared to the incidence of viral meningitis of 10-15 per 100,000 per year. (2-3) Patients over the age of 65 years showed 51% of cases and 67% died. (4) Meningitis caused by *Neisseria meningitidis* can be found worldwide, but the highest incidence in the "meningitis belt" occurs in sub-Saharan Africa. Meningococcal meningitis is hyperendemic in the African region and the epidemic period during the dry season (December - June), reported more than 1000 cases per 100,000 population. Bacteria that cause meningitis are generally *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus), and *Haemophylus influenzae*, and *Streptococcus suis* (S.suis) is most commonly found in Asia. *Streptococcus suis* bacteria are identified as the most common pathogen and rank third cause of bacterial meningitis in adults in Vietnam and Hong Kong. (5) The epidemiology of S. suis infection differs between Western and Asian countries, and the high risk of eating raw or undercooked pork, such as pork blood, organs and pork, is common in Asian countries. In 2009, there were about 700 cases of *S. suis* infection worldwide, and most came from China and Vietnam. (5) One study, bacterial meningitis caused by *S. suis* in Indonesia, especially in Bali, showed 44 cases spread across several areas on the island of Bali in 2014 – 2017. (6) Therefore, this paper aims to identify predictive factors for death in patients with bacterial meningitis, especially clinically.

LITERATURE REVIEW

Factors associated with death in meningitis are determined by several variables such as

age over 60 years, male gender, presence of impaired consciousness, seizures, fever, causative germs (S. Pneumonia or S. Aureus), prolonged fever (>10 days) other infections, administration of corticosteroids, leukocyte count and cerebrospinal fluid (CSS) <100/mm3 and time of antibiotic administration. In addition to these factors, in Arismunandar's study, it was stated that CSS glucose levels <40 mg/dL were a mortality factor in adult patients with bacterial meningitis. [7] Factors associated with death in meningitis vary, depending on the age group and the type of meningitis. Several studies have identified risk factors for death in adults with bacterial meningitis.

AGE

In bacterial meningitis, it is said to have a high risk of mortality with increasing age. In a study by Akaishi et al., the mortality rate of meningitis caused by bacteria, fungi, tuberculosis, and carcinomatosus increased with age, with a peak age at 70 to 79 years. [8] In elderly people, complex changes and changes in the function of the innate and adaptive immune systems will occur, which can cause immunodeficiency. Several studies have shown that elderly patients have an increased incidence of severe infections and sepsis with increasing age accompanied by a high risk of mortality. [6]

GENDER

Male gender is said to be associated with higher mortality rates in bacterial meningitis (Odd Ratio = 1.18; p = 0.0188), viral (Odd Ratio = 1.38; p = 0.0398) and carcinomatous meningitis (Odd ratio 1.39; p < 0.0001). In another study of 621 patients with bacterial meningitis, 396 male patients and 225 female patients were reported. The overall mortality rate was 30.4%. [9] In the Klein and Flanagan article, adult women showed a stronger innate immune response compared to men, so that the immune system in women tends to be faster in eliminating bacteria from the body. The hormones progesterone and estrogen in women have anti-inflammatory effects. In addition, women show a greater antibody response, higher basal immunoglobulin levels and B cell counts. [10]

UNDERLYING PATHOGENS

Pathogenic organisms that cause meningitis such as bacteria, viruses, fungi, and parasites, are said to be one of the risk factors for mortality. In bacterial meningitis, the pathogenic organisms are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Streptococcus aureus*, *Escherichia coli*, and *Neisseria meningitidis*, but *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria show a higher risk of death. While in meningitis caused by viruses, namely herpes simplex virus, the mortality rate is high. Around 2047 patients with herpetic meningitis, 28 patients died during hospitalization. [8] In addition to the herpes simplex virus, some viruses that cause meningitis are Enterovirus, varicella zoster virus, Mumps virus, and coxsackie virus. One study showed that the most common bacteria causing meningitis were meningococcal, followed by pneumococcal, *Listeria monocytogenes*, Bacillus cereus, gram-positive bacteria, gram-negative bacteria, *Haemophilus influenzae*, but pneumococcal bacteria caused the highest mortality. [8]

CLINICAL MANIFESTATION: SEIZURE

Bacterial meningitis can also cause seizures. Seizures can be associated with central nervous system infection, sepsis, hypoxic, traumatic brain injury, malignancy, stroke, systemic inflammation, toxic effects of drugs, and electrolyte disturbances. In a study conducted by Zoons et al., it was found that 41% of deaths occurred in patients with seizures and 16% in patients without seizures. [11] Pathophysiological mechanisms by which seizures contribute to increased mortality in bacterial meningitis include [12]:

- Increased Intracranial Pressure: Seizures can worsen intracranial pressure, leading to further brain injury and potential herniation.

- Neuronal Damage: The inflammatory response associated with bacterial meningitis can cause excitotoxicity, were excessive neuronal stimulation results in cell death.
- Systemic Effects: Seizures can also trigger systemic complications such as respiratory failure or metabolic disorders, further complicating the clinical manifestation.

CLINICAL MANIFESTATION: UNCONSCIOUS

Altered consciousness in bacterial meningitis is often characterized by confusion, lethargy, or unresponsiveness. This is a clinical manifestation that indicates severe disease progression and can be associated with increased intracranial pressure, brain edema, or systemic infection. The presence of altered consciousness is a significant predictor of poor outcomes, including higher mortality rates. Several studies have documented an association between altered consciousness and mortality in bacterial meningitis. A study examining 43 cases of bacterial meningitis reported that 92% of patients showed altered consciousness. The overall mortality rate in this group was very high, at 53%. [13] These findings underscore the critical nature of altered mental status as a warning sign of impending death. A systematic review identified altered consciousness as a significant risk factor for death in children with bacterial meningitis, with an odds ratio (OR) of 4.85. This suggests that patients presenting with altered mental status are almost five times more likely to die compared to those without such symptoms. [14]

LOW GLUCOSE PROFILE IN CSF

In Arismunandar's study, it was found that low CSF glucose levels of less than 40 mg/dL had a 3.76 times greater chance of mortality compared to meningitis patients with CSF glucose levels ≥ 40 mg/dL. [7] Low glucose levels in CSF are also an indicator of poor prognosis. A meta-analysis noted that patients who died had average CSF glucose levels of less than 30 mg/dL. [15] These findings underscore the importance of monitoring CSF glucose levels as a potential prognostic marker.

INFLAMMATION PROCESS

In bacterial meningitis, there will be a release of Tumor Necrosis Factor-α (TNF-α), Interleukin (IL)-1β, and IL-6 which will trigger a cascade of inflammatory mediators, including cytokines, chemokines, Platelet - Activating Factor (PAF), antimicrobial peptides, prostaglandins, Matrix Metalloproteinases (MMP), and Nitric Oxide (NO). Patients with bacterial meningitis have significantly increased levels of IL-6, IL-8, IL-10, and TNF-α in the CSF compared to serum. Serum IL-8 increases significantly in patients with neurological complications, poor clinical outcomes, and death. [16] Research conducted by Hardiman et al. at Dr. Hospital. Sardjito Yogyakarta, it is said that the neutrophil-lymphocyte ratio value of more than 5,225 statistically ($p = 0.004$ and risk ratio (RR) = 10.78) can be a predictor of mortality in pediatric patients with bacterial meningitis, and can be used as a parameter to predict the outcome of patients with bacterial meningitis.[17] Other studies have shown that patients with RNL values above the cut-off (10.5) died compared to below the cut-off value.[18]

ROLE OF NEURTOPHIL

Neutrophils are a type of phagocytic white blood cell and are part of the innate immune system. Specifically, neutrophils belong to the category of granulocytes, which form the most abundant cell type in human blood, comprising 40% to 70% of all white blood cells. An important role of neutrophils is in detecting and eliminating extracellular pathogens, such as bacteria and fungi. [19] Neutrophils are characterized by a multilobed nucleus and cytoplasmic granules containing enzymes such as myeloperoxidase and lysozyme, which help degrade bacterial cell walls. [20] The main function of these cells is to phagocytose foreign particles and microorganisms,

thereby preventing tissue damage. When exposed to proinflammatory cytokines, chemokines, mitochondria, and products derived from bacteria and viruses, neutrophils undergo priming - a condition in which they become more responsive to activating stimuli. [21] In this healthy state, neutrophils exhibit increased formation of reactive oxygen species, increased exocytosis activity, and increased chemotaxis toward sites of inflammation.

Systemic inflammation will affect the number of leukocytes, especially neutrophils, monocytes, and lymphocytes so that the number of leukocytes will increase. High leukocyte counts indicate the degree of disease and are associated with mortality. Neutrophils released from the bone marrow are induced by endotoxin, cytokines, complement, and granulocyte colony-stimulating factor (G-CSF). In the early phase of bacterial meningitis, Tumor Necrosis Factor-α (TNF-α), Interleukin (IL)-1β, and IL-6 will be released which will trigger a cascade of inflammatory mediators, including cytokines, chemokines, Platelet - Activating Factor (PAF), antimicrobial peptides, prostaglandins, Matrix Metalloproteinases (MMP), and Nitric Oxide (NO). Neutrophil migration to the CSF contributes to the inflammatory process in the brain. In response to cytokines, chemokines, and other chemotactic stimuli, neutrophils penetrate the microvascular basement membrane, leaving the bloodstream to accumulate in the CSF, demonstrating a pleocytosis pattern in the CSF. These inflammatory mediators increase capillary permeability, allowing more immune cells to enter the area of infection and trigger a more extensive inflammatory reaction. This results in an increase in the number of neutrophils at the site of infection, often seen as leukocytosis on blood tests. During severe infections such as sepsis, neutrophils can die through a variety of pathways including apoptosis, necrosis, necroptosis, pyroptosis, netosis, and autophagy. Neutrophils are responsible for the host immune response to pathogens through several defense mechanisms, including chemotaxis, phagocytosis, release of reactive oxygen species, granular proteins, and cytokine production. Increased numbers of isolated neutrophils and resulting in increased RNL can be observed in several conditions such as bacterial or fungal infections, acute stroke, myocardial infarction, atherosclerosis, severe trauma, cancer, complications after surgery. [22] This is due to the early phase of infection characterized by a proinflammatory state mediated by neutrophils and other inflammatory cells. The systemic inflammatory response is associated with suppression of neutrophil apoptosis, which is mediated by neutrophils as part of the innate response.

ROLE OF LYMPHOCYTE

Lymphocytes are an essential component of the adaptive immune system, providing targeted and long-lasting defense against pathogens. This system is characterized by its ability to recognize specific antigens, develop immunological memory, and mount a tailored response to eliminate infection. The two main types of lymphocytes involved in adaptive immunity are B cells and T cells. Adaptive immunity is activated when pathogens evade the innate immune system, prompting a more complex response. This response is initiated through recognition of antigens presented by antigen-presenting cells (APCs) such as dendritic cells. These cells capture pathogens, process them into smaller peptide fragments, and display them on their surface using major histocompatibility complex molecules, which are essential for T cell activation.

- B-cell lymphocytes: responsible for humoral immunity, which involves the production of antibodies. When activated by a specific antigen, B cells differentiate into plasma cells that secrete antibodies (immunoglobulins). These antibodies circulate in the bloodstream and bind to antigens, neutralizing the pathogen or marking it for destruction by other immune cells. Some B cells become

memory B cells after the initial infection, allowing for a faster and stronger response on subsequent exposure to the same pathogen. [23]

- T-cell lymphocytes: activated T cells proliferate and differentiate into effector T cells or memory T cells. Effector T cells directly kill infected cells or produce cytokines that coordinate the immune response, while memory T cells remember the previous infection to mount a rapid defense upon re-exposure. [19]

ROLE OF NEURTOPHIL LYMPHOCYTE RATIO

Neutrophil-lymphocyte ratio (NLR) is a simple test to determine a person's inflammatory status. NLR is calculated as a simple ratio between the number of neutrophils and lymphocytes measured in peripheral blood and is a biomarker that combines two aspects of the immune system. Where the innate immune response is derived from neutrophils, and adaptive immunity is supported by lymphocytes. [24] NLR has become a widely accepted biomarker because of its ability to predict prognosis and monitor disease activity. In the 1990s and early 2000s, NLR began to gain traction as a biomarker that could potentially be useful beyond basic diagnostics. Researchers noted that NLR can provide insight into the body's overall inflammatory state, which may correlate with disease severity and outcome. [25]

Several mechanisms contribute to elevated RNL values indicating systemic inflammations:

- Acute Infection: Neutrophilia occurs due to bacterial infection or other acute inflammatory processes.
- Chronic Disease: Conditions such as cancer can cause sustained neutrophil activation and lymphopenia through a variety of mechanisms, including cytokine-mediated effects on bone marrow lymphopoiesis suppression.
- Immune Dysregulation: Autoimmune diseases are often the result of a dysregulated immune response that causes an imbalance favoring a pro-inflammatory state characterized by increased neutrophilia relative to lymphopenia.
- Cytokines and Chemokines: Pro-inflammatory cytokines such as IL-6 can stimulate neutrophilia while suppressing lymphopoiesis indirectly through feedback loops involving glucocorticoids or direct effects on lymphoid tissues.

Research conducted by Hardiman et al., at Dr. Sardjito Hospital, Yogyakarta, stated that the neutrophil-lymphocyte ratio value of more than 5,225 can statistically be a predictor of mortality in pediatric patients with bacterial meningitis, and can be used as a parameter to predict the outcome of patients with bacterial meningitis [17]. Another study conducted by Matteo et al., at two hospitals in Italy in 2020-2021, showed that the neutrophil-lymphocyte ratio (RNL) value is an independent predictor of mortality and poor outcomes in COVID-19 patients and can identify someone with a high-risk COVID-19 infection.[26] In the study by Paulus et al., at Dr. Soetomo Hospital, Yogyakarta, the RNL cut-off value of 10.5 was statistically significant as a predictor of mortality in patients with bacterial meningitis.[18]

CONCLUSION

Several predictive factors for mortality in bacterial meningitis are determined by old age, male gender, underlying pathogen, poor initial clinical manifestations such as seizures or decreased consciousness, low glucose in CSF, and high levels of inflammatory markers such as RNL. Further studies with larger populations are needed to determine the extent of the relationship between inflammation and high mortality in bacterial meningitis and the possibility of other underlying causes.

Declaration by Authors

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