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Review Article

VALIDATION OF SCREENING MODEL FOR MENINGITIS: A REVIEW

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ABSTRACT

Moksha

Meningitis is a condition caused by the inflammation of the meninges. Meningitis can be caused by bacteria, viruses, fungi, parasites, and amebic. Interestingly some meningitis is infectious, while other is non-infectious. The non-infectious causes of meningitis are autoimmune illnesses, cancer/paraneoplastic syndromes, and medication responses. There are several risk factors associated with meningitis, like a defect in the dural, alcoholism, age, medical condition, some kind of exposure, and so on. Since meningitis is a serious and delicate condition, the need of several screening models is required to validate meningitis. These models depend on thematical calculations like regression models, multiple regression models, and logistic models, and some animal models are also there for meningitis. Hence, here we discussed meningitis and models briefly.

Keywords: Meningitis, Validation, Screening models

INTRODUCTION

The inflammation of the meninges is known as meningitis. The dura mater, arachnoid mater, and pia mater are the three membranes that surround the vertebral canal and skull, encapsulating the brain and spinal cord. Encephalitis, on the other hand, is a kind of brain inflammation.¹⁻²

The signs and symptoms of meningeal inflammation have been described in various historical books throughout history; nevertheless, it was not until surgeon John Abercrombie characterized it in 1828 that the term 'meningitis' became widely used. Despite advances in diagnosis, treatment, and immunization, 8.7 million cases of meningitis were recorded globally in 2015, with 379,000 fatalities.³⁻⁵

Infectious and non-infectious causes of meningitis include autoimmune illnesses, cancer/paraneoplastic syndromes, and medication responses. Bacteria, viruses, fungi, and, less typically, parasites are the infectious etiologic agents of meningitis. ⁶ However, the bacterial meningitis is most commonly seen.

Meningitis can be caused by a variety of microorganisms. The most common bacteria are Streptococcus pneumoniae, *Haemophilus influenzae*, and *Neisseria meningitidis*. The one that may cause big epidemics is N. meningitidis, which causes meningococcal meningitis. N. meningitidis has been divided into 12 serogroups, six of which (A, B, C, W, X, and Y) can produce epidemics.⁷

N. meningitidis is capable of causing a wide range of illnesses. Septicemia, arthritis, and meningitis are among the invasive disorders induced by N. meningitidis, which are referred to as invasive meningococcal disease (IMD). Other invasive illnesses caused by S. pneumoniae include otitis and pneumonia.⁷

Hence, in this article we will discuss about the risk factors, types of meningitis, and also discuss about the validation of screening model for different types of meningitis.

Risk factors

- 1. Medical conditions that last a long time (renal failure, diabetes, adrenal insufficiency, cystic fibrosis)
- 2. Age's extremes
- 3. Under vaccination
- 4. Immunosuppression is a condition in which the immune system is inhibited (iatrogenic, transplant recipients, congenital immunodeficiencies, AIDS)
- 5. Living in cramped quarters
- 6. Exposures:
 - Excursions to endemic regions (Southwestern U.S. for cocci; Northeastern U.S. for Lyme disease)
 - Vectors are a kind of data that may be (mosquitoes, ticks)
- 7. Alcoholism is a mental illness caused by excessive use of
- 8. A ventriculoperitoneal (VP) shunt is present.
- 9. Endocarditis caused by bacteria
- 10. Malignancy
- 11. Defects in the dural
- 12. IV drug administration
- 13. Sickle cell disease is a kind of anemia that affects people.
- 14. Splenectomy.6

Different types of meningitis

There are different causes and types of meningitis present worldwide. They are widely classified as follows: -



Bacterial meningitis

Bacterial meningitis, an infectious condition characterized by infection and inflammation of the meninges, has a high morbidity and fatality rate across the world.⁸ If left untreated, bacterial meningitis can be deadly in 50% of cases. The etiologic agents that cause bacterial meningitis differ depending on the age group. Most instances of bacterial meningitis in newborns are caused by group B Streptococcus agalactiae, Escherichia coli, and Listeria monocytogenes, whereas Streptococcus pneumoniae and *Neisseria meningitidis* cause the majority of cases in children and adults. ⁹⁻¹⁰ Although *Haemophilus influenzae* has been linked to bacterial meningitis in people of all ages; it is most common in children under the age of five.¹¹⁻¹² Given the wide variation in bacterial meningitis incidence and causative agents between areas, it's critical to distinguish between them while treating bacterial meningitis patients.⁹⁻¹⁰

Viral meningitis

Many cases of meningitis are caused by viruses every year, but they are generally missed since the consequences are not as severe as bacterial meningitis or viral encephalitis.¹³⁻¹⁴ However, viruses are now understood to be more significant as bacterial meningitis declines due to vaccination and molecular diagnostics usage rises.¹³⁻¹⁹ Meningitis is caused by a variety of viruses. However, the majority of infections are caused by enteroviruses, herpesviruses, or arthropod-borne viruses in specific regions of the world (arboviruses). Mumps virus is a serious disease in unprotected people.²⁰

Fungal meningitis

The increased proportion of immunocompromised individuals, such as those undergoing pharmacological immunosuppression and chemotherapies, and the high number of people living with HIV and AIDS, are all contributing to an increase in CNS fungal infections. Fungal meningitis (FM) is a challenging CNS illness to identify since it has vague symptoms and no evidence of meningeal irritation. Due to the difficulties in identifying FM, therapy is delayed, resulting in an increase in morbidity and death.²¹⁻²² Apart from the immunocompromised, even apparently immune-competent people can have FM, as seen in the cases of *Cryptococcus neoformans* and *Coccidioides immitis.*²³

Parasitic meningitis

Various parasites can induce meningitis or have various effects on the brain and nervous system. In comparison to viral and bacterial meningitis, parasite meningitis is far less prevalent. Eosinophilic meningitis, often known as eosinophilic meningoencephalitis or EM, is an uncommon type of meningitis caused by parasites.

In certain afflicted patients, the three primary parasites that cause EM are:

Angiostrongylus cantonensis (neurologic angiostrongyliasis) *Baylisascaris procyonis* (baylisascariasis; neural larva migrans) *Gnathostoma spinigerum* (neurognathostomiasis)²⁴

Amebic meningitis

Naegleria fowleri causes primary amebic meningoencephalitis (PAM), an uncommon brain infection that is typically deadly. *Naegleria fowleri* is an amoeba that lives in the wild (a single-celled living organism that is too small to be seen without a microscope.) From 1962 through 2019, the CDC received 148 reports of infections in the United States, with no more than 8 cases recorded per year.²⁴

Non-infectious meningitis

Infectious illnesses, which are caused by microorganisms that transmit from person to person, are not the sole causes of meningitis. Some causes of meningitis, however, are non-infectious and do not transmit from one person to another, such as cancer, lupus, certain drugs, head injury, and brain surgery.²⁴

Validation Models for Meningitis Prediction models

Diagnostic prediction algorithms have been created to determine the likelihood of bacterial meningitis (BM) in individuals who have a suspected CNS infection. External validation in patients with suspected meningitis, on the other hand, is required to assess the diagnostic accuracy of these models. Patients who had a lumbar puncture for a suspected CNS infection were included in this procedure. Following a thorough assessment of the literature, the author tested selected BM models on our sample. And, if feasible, evaluated the calibration of the models by calculating sensitivity, specificity, predictive values, and area under the curve (AUC). Surprisingly, the results revealed the existence of seventeen BM prediction models. These models' sensitivity varied from 37 percent to 100 percent. The specificity of these models ranged from 44% to 99%. Oostenbrink's cerebrospinal fluid model had the greatest AUC of 0.95 (95 percent CI 0.91–0.997). In all models, calibration revealed overestimation or underestimation. ²⁵

Logistic regression model

The connection of one or more independent (predictor) factors with a binary dependent (outcome) variable is estimated using logistic regression. ²⁶ A binary (or dichotomous) variable is a categorical variable with just two possible values or degrees, such as "positive versus negative hypoxemia" or "dead vs living." ²⁷

Hence, In the United States, a prediction model based on clinical and cerebrospinal fluid (CSF) analysis has been suggested to distinguish Lyme meningitis (LM) from non-Lyme aseptic meningitis (NLAM). For European patients, no such concept has yet been offered. The goal of our research was to create a model that could distinguish LM from NLAM based on clinical and CSF biologic data.

Therefore, Age, duration of symptoms, presence of cranial neuropathy, CSF WBC count, percentage of neutrophils in CSF, and CSF protein value were all included while developing the prediction model. Four predictors (duration of symptoms, presence or absence of cranial nerve palsies, proportion of neutrophils in the CSF, and CSF protein) contributed statistically to the prediction from these data. The predictive model predicts LM = 1/1 + exp(Z) with Z = 0.371 duration of symptoms (day) + 4.873 cranial neuritis (1 = yes; 0 = no) 0.151 neutrophils cells (percent) + 0.059 CSF protein (mg/dL) 5.926, with P 0.041 for all chosen variables.

Interestingly, the result suggests that the study involved a total of 93 participants (LM: 26 patients; NLAM: 67 individuals). Patients with LM had a higher percentage of neutrophil cells in the CSF (3.4 percent vs. 51 percent), had a longer duration of symptoms before admission (8.8 vs. 1.8 days), had a higher CSF protein (71 vs. 38 mg/d), and had a lower percentage of neutrophil cells in the CSF (3.4 percent vs. 51 percent) than patients with NLAM. These four factors were combined to provide a projected likelihood. The model exhibited a negative predictive value of 100% and a positive predictive value of 92.3 percent at a cutoff point of >0.432, with a sensitivity of 100% and a specificity of 97 percent. Hence, it can be concluded that first European prediction model for LM is presented. This model may help clinicians manage aseptic meningitis (AM) while waiting for serologic testing, especially in Lyme endemic areas, because of its strong negative predictive value. ²⁸

Multivariable regression model

Assume the set of p independent variables represented by the vector $X' = (X1, X2, \dots, Xp)$. P(Y = 1/X) = P(

The logit of a multiple logistic regression model is calculated as follows:

$$g(X) = \beta_0 + \beta_1 x_1 + \beta_2 X_2 + \dots + \beta_p X_p$$

Hence the logistic regression model is ²⁹ $\pi(X) = \exp(g(X))/(1 + \exp(g(X)))^{30}$

Utilization of Multivariable logistic regression

Here, in this study the objective was to utilize objective factors available at the time of patient presentation, design and verify a simple multivariable model to discriminate bacterial meningitis from aseptic meningitis in children.

The following predictors of bacterial meningitis were found in the derivation set using multivariable logistic regression and recursive partitioning analyses: Bacteria in the cerebrospinal fluid (CSF), CSF protein of 80 mg/dL, peripheral absolute neutrophil count of 10,000 cells/mm3, seizure before to or at the time of presentation, and CSF absolute neutrophil count of 1000 cells/mm3. On the basis of the derivation set, a Bacterial Meningitis Score (BMS) was created by assigning 2 points to a positive Gram stain and 1 point to each of the other factors. The result shows that A BMS of 0 correctly identified kids with aseptic meningitis in the validation set, while misclassifying no child with bacterial meningitis. A score of 0 had a 100% negative predictive value for bacterial meningitis (95 percent confidence interval: 97 percent -100 percent). With a sensitivity of 87 percent (95 percent confidence interval: 72 percent -96 percent), a BMS2 indicated bacterial meningitis. 31

Animal model for meningitis

In order to track the progression of the illness during meningococcal infection, Sjölinde et al. used in-vivo BLI to look at how the meningococci bacteria localized in CD46 transgenic mice. ³² In a different study, BLI was employed in a mouse model of Neisseria meningitides infection to investigate potential therapies for meningitis.33 In a mouse model of pneumococcal meningitis brought on by S. pneumoniae, Mook-Kanamori et al. tried the antibiotic daptomycin (a lipopeptide). Serotype 3 S. pneumoniae with an integrated lux operon was administered intracerebrally (into the brain cavity) to mice. In addition to measuring bioluminescence and the quantity of bacterial CFUs in the cerebrospinal fluid, Caspase-3 staining was utilized to identify apoptosis in brain histological sections (CSF). ³⁴ The independent monitoring of two different bioluminescence reporters, made feasible by the distinct light emission spectra and substrates needed for lux and fuc, allowed for the evaluation of illness progression and therapeutic response.35 The team was able to individually monitor the two bioluminescence reporters using a highly sensitive BLI system and assess the course of the disease as well as the response to treatment since lux and Fuc have different spectrum light emission and substrate requirements.35-36

Development of a mouse model for pneumococcal meningitis

A potentially fatal infection of the central nervous system is bacterial meningitis (CNS). *Streptococcus pneumoniae*,^{9,37} which accounts for 70% of infections, is the most prevalent pathogen after the newborn period. The death rate from pneumococcal meningitis still ranges between 16 and 37 percent, and 30-52 percent of survivors experience neurological sequelae.^{38,40} Cerebral infarction, hemorrhages, motor and sensory deficiency, seizures, memory and cognitive deficits, and hearing loss are among complications related to pneumococcal meningitis.⁴¹⁻⁴² Numerous of these clinical characteristics have been replicated in animal models, which serve as the foundation for the development of innovative drugs and pathophysiological research.⁴³⁻⁴⁴ In order to highlight many of the human pathogenic aspects, the author describes the creation of an adult mouse model of pneumococcal meningitis in this article.

It's interesting to note that the author created a pneumococcal meningitis mouse model in which the histological, inflammatory, and observed consequences reflect the clinical and pathological findings in people after bacterial meningitis.⁴⁵ The most significant characteristics of this model are its ability to combine a modest inoculum dosage with a protracted illness development, providing a repeatable environment for examining clinical symptoms as well as enough time to develop the histological abnormalities found in a human environment.

Hence, it can be concluded that this mouse model's value comes from the fact that it offers a highly reproducible experimental setting for pneumococcal meningitis and offers some of the most important outcome parameters, including bacterial titers, meningeal and parenchymal infiltration, cytokine profiles, microglial activation, neuronal apoptosis in the hippocampus, perivascular infiltration, and (micro) hemorrhages. The author believes that combining these diseased characteristics, which are typical of what is seen in human autopsy investigations into a single model, is a useful tool in the analysis of pathophysiological and therapeutic intervention studies.⁴⁶

CONCLUSION

The meningitis is a serious and delicate medical condition and if left untreated and undetected for long time can be life threating. Even, though a lot of advancement in medical science has occurred to treat the meningitis successfully. The need of screening models becomes the need of the hour, as the screening models not only predicted the possibility of the occurrence of meningitis but also give us more insight of the conditions and how the drugs and other treatment option work in that condition. In present time these screening models indeed help us and give deep knowledge about the condition but more work are still required to get more better understanding from the screening models.

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