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Research Article

Prognostic Value of Cerebrospinal Fluid to Determine Mortality in Meningeal Tuberculosis

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Abstract

Background and Objective: Meningeal tuberculosis is directly related to primary pulmonary infection. In HIV positive patients, it has high mortality, and there are factors identified as to be related to the forecast; others still under study. We took on the task of determining if the cerebrospinal fluid (CSF) has any prognostic value in the mortality of patients with meningeal tuberculosis hypothesizing that alterations in the concentrations of the CSF components have prognostic value.

Material and Methods: Retrospective study. Patients treated at Hospital Central of San Luis Potosí, Mexico; from 2010 to 2015, with the diagnosis of meningeal tuberculosis. Thirty patients were included.

A descriptive analysis of the variables was carried out where continuous is expressed as average or median, and categorical variables as frequencies. Bivariate analysis with student's t and Wilcox or Kruskal-Wallis for the continuous variables and the categorical chi-square and/or Fisher's exact test, the value of $p < 0.05$ was considered significant. A non-parametric analysis of variables for prediction was carried out of a dependent variable.

Results: There was no direct relationship between cerebrospinal fluid and mortality. The mortality of 46.7% was observed. Severity at admission is directly related to mortality; HIV it was not associated with the prognosis of the patients. It was possible to generate a tree of regression for decision making identifying patients with malignancy forecast with an error of 8%.

Conclusion: It is challenging to establish a relationship between fluid alterations on CSF and mortality in these patients. According to an analysis from secondary data, a direct correlation was found between the severity of the patient income and an increased risk of death and the generation of a regression tree for decision making.

Keywords: Tuberculosis; CSF (Cerebrospinal Fluid); PCR (Polymerase Chain Reaction)

Background

Tuberculosis (TB) continues to be the deadliest contagious diseases in the world (WHO declared this in its 2014 global report). It is estimated that in 2013, there were 9 million people who developed the disease, and 1.5 million died because of it; 360,000 were HIV positive [1].

The presentation of extrapulmonary TB is directly proportional to the prevalence of TB and the neurological involvement of TB infection. It constitutes approximately 5% to 15% with predominance in children. Involvement of the central nervous system (CNS) in TB is five times more frequent in positive HIV patients compared with HIV negative patients. On the other hand, the presence of TB in CNS is a definition of Acquired Immunodeficiency Syndrome (AIDS), but it also occurs in immunocompetent individuals. There have been identified several clinical-pathological presentations of TB infection in CNS: Tuberculous meningitis, tuberculoma, tuberculous abscess, vasculitis, and others. Virtually, all forms of TB infection are caused by M. tuberculosis and other non-tuberculous mycobacteria such as intracellular M avium that can cause disease, especially in immunocompromised patients [2].

Meningeal tuberculosis can occur as a result of hematogenous seeding, reactivation of metastatic foci of M tuberculosis in the cerebral parenchyma and meninges which have been asymptomatic for months or years after a primary infection, or due to a rupture of a para-meningeal tuberculous granuloma into the subarachnoid space [3-6]. As a result of this dissemination and due to the deve-

lopment of specific cellular immunity (among them the formation of anti-TNF alpha, IL-12, and interferon gamma), protective immunity created against the bacteria leads to the formation of granulomas that contain inside viable bacilli [7]. Although it can happen at any time after the primary infection, it appears most often years or decades later in the presence of alteration of the mechanisms of an immune response either during childhood or the elderly. It can also be triggered after conditions or treatments that alter cellular immunity [8].

The alteration of the immunity mechanisms that form the granuloma predisposes to the reactivation of these latent foci and development of tuberculous. Even though in recent years, there has been a constant reduction of the total number of cases of tuberculosis, the decrease in cases of extra-pulmonary TB has not been steady and has even increased. The reasons are not known although they could be secondary to several causes, including the reduced use of BCG vaccine or a change in a susceptible population, there are no prospective studies that have analyzed the reasons for this increment [5].

This infection leads to inflammation with the production of a thick exudate at the base of the brain (involving the optic nerves in the chiasm, the bridge, and the cerebellum).

Histologically and depending on the stage, an initial increase in polymorphonuclear leukocytes, macrophages, and lymphocytes is observed [9]. At a later stage, lymphocyte proliferation and formation of caseating granulomas, as well as involving the vessels that traverse the meninges, affecting mainly those of medium and small caliber, with inflammation of the adventitia and formation of granulomas which can lead to occlusion of the vessels, causing infarcts of the irrigating areas. The inflammatory response causes compression of neural tissue and compromise of fluid flow cerebrospinal fluid, leading to complications of infarction, hydrocephalus, and cerebral edema [6].

The risk factors that are related to the development of tuberculosis extrapulmonary are fundamental: Age, female gender, the existence of HIV infection and patient comorbidities such as the presence of chronic renal failure, diabetes mellitus or the presence of immunosuppression [10].

The average age of patients with extrapulmonary tuberculosis is higher than in patients with primary pulmonary infection. Among the patients who present extrapulmonary tuberculosis, those that develop pleural disease or meningeal tumors are usually younger than those with lymph node involvement, osteoarticular, genitourinary, and gastrointestinal [5].

As mentioned, meningeal tuberculosis is the most severe form of tuberculous and is a substantial cause of morbidity and mortality. The early diagnosis and initiation of the treatment are crucial for a successful result. However, the rapid and effective detection of M. tuberculosis, in the SCF of patients with MTB remains a challenge for mainly due to the lack of fast and effective methods [7,8,10].

Nowadays, the gold standard for the detection of M. tuberculosis in diagnosis is the cultivation, but it is prolonged and requires specialized procedures. The serological methods are convenient, but they lack sensitivity and specificity. Although PCR is a rapid technique, it is expensive to be used as a routine in developing countries. So various research groups have developed methods to try to make an earlier diagnosis and to influence in a positive in the outcome of these patients [11].

The conventional microscopic smear with Ziehl-Neelsen (ZN) is a practical and quick method for the identification of acid-fast alcohol bacilli. Especially useful for developing countries. However, the cons for its use is the low rate of detection in a range of around 20%; one of the main reasons is that the bacilli are hardly dyed once they enter the cells. Another reason is that a large volume of CSF is required for diagnosis [12,13]. There is a method capable of detecting the intracellular bacilli, using only 0.5 ml CSF by cytospin technique and fixation with formaldehyde with detection of 93.8% of bacilli observed intracellular, as well as an increase of 16.7% in the detection rate of extracellular bacilli [14].

As a result of most guidelines for the management of meningeal tuberculosis, the analysis of a CSF sample determining the glucose concentration, the protein levels, and the number of leukocytes is necessary to decide a plan. Also, the analysis of other biochemical markers for diagnostic support, such as the activity of Adenosine Deaminase (ADA) as determined in a study in Quito. The obtained samples were analyzed within one hour of having been achieved getting as results that ADA levels> 6U/l have a sensitivity of 55.9% and a specificity of 94.8% in this way contributing for the diagnosis of MTB, with a possibility post-test of 87% of having the infection [15].

In the diagnosis of meningeal tuberculosis, the analysis by acid amplification nucleic acids using the Polymerase Chain Reaction (PCR) has shown a sensitivity of 56% and a specificity of 98%. The new tests of amplification of several genes have increased sensitivity up to ranges between 85% to 95% [16]. As is the use of the nested-PCR technique (N PCR) where it is extracted DNA, and two subsequent amplification using two oligonucleotide primers. In

this study, the N-PCR was found positive in all patients with MTB confirmed by culture, and when comparing them with the patients in the non-MTB control group all had a negative N-PCR test [17].

The guidelines of the British Society of Infections for the management of meningeal tuberculosis, establish that the delay in TB treatment is strongly associated with death and neurological sequelae. On the other hand, due to the low sensitivity of the diagnostic test, its availability is limited in developed countries. Finally, it concludes that treatment has to be initiated in patients with suspected CNS tuberculosis, although it is often challenging to suspend it, and the response (either lack of it or quick response) must determine when to stop the treatment, so they recommend that a safe policy is to give a complete cure in all patients unless an alternative diagnosis is made [8].

In the diagnosis of meningeal tuberculosis, clinicians face substantial challenges, the pathogenesis of the disease is still poorly understood, rapid and effective diagnostic tests are not yet available and the best.

Management for these patients is not yet well defined, and the diagnosis is based on the clinical evidence, which is combined with laboratory and image findings. Standardized diagnostic criteria are not yet well established, and most studies use different definitions of cases. This absence of standardization makes the comparison in the results of the different difficult studies, as well as limits the use of the data found and progress in the driving. So, a consensus developed in Cape Town, South Africa, in 2009, where it proposed that patients with suspected tuberculosis should be classified into one of four categories according to the strength of clinical laboratory or radiological findings, proposed categories are definitive, probable and possible meningeal tuberculosis and no meningeal tuberculosis. A patient with suspected meningeal TB should be considered depending on the findings of lumbar puncture or brain image. The results of the other tests will determine the final category; if in M tuberculosis is isolated, the patient must be considered as tuberculous meningitis. Conversely, if there is evidence of alternative diagnosis, the patient is considered into the category of meningeal non-tuberculosis [18].

The clinical stage of the disease influences the result of meningeal tuberculosis at the beginning of treatment. This has been evidenced in several studies that show that the presence of cranial neuropathy was associated to a bad result; patients suspected of meningeal tuberculosis are grouped into some of the severity groups according to the British Medical Criteria Research Council. This system is reproducible at all levels of expertise and in different specialties, and that is why the graduation system is considered more reliable. In stage I the patient is alert and oriented without deficit focal neurological, in stage II the patient with the score on the scale of Glasgow from 14 to 11 with focal neurological deficit and stage III a patient with 10 points or less from the Glasgow scale, with or without focal neurological deficit [19].

Mortality in MTB is estimated between 16% to 71% [20]. Several reports show prognostic factors, which include age, level of awareness, stage of the disease, isolation of M tuberculosis in CSF biochemical studies, cerebral infarcts, and hydrocephalus, as well as early diagnosis and initiation of treatment, all these factors mentioned can affect complication rates and mortality of meningeal TB [21].

The AIDS epidemic, global overpopulation, increased migration, and the increase in the drug-resistance of M tuberculosis, have contributed substantially to the morbidity and mortality of the infection [22]. There are 15 millions of patients coinfected with HIV and M Tuberculosis and 50 million of the infected with multidrug-resistant M tuberculosis. Currently, tuberculosis is the leading infectious cause of death and represents a priority problem of Health [23,24].

Despite advances in diagnostic tools and options for treatment, it continues being a pathology whose management is very challenging. From the patients receiving treatment with anti-tuberculous medication, 20% to 50% die, and those that survive will present a significant neurological deficit. Fatal cases have a remarkable relationship with a delay in the diagnosis and treatment as well as the relationship with HIV infection [25].

In the absence of tools that allow us to make a more accurate diagnosis and early in our environment (nucleic acids in CSF, ADA, better means of culture), we need to look for prognostic factors that help us determine the risk of mortality in a patient with meningeal TB and try to modify this risk with an earlier and timely treatment.

Justification

Meningeal tuberculosis is a significant cause of serious illness, especially in developing countries, mortality for meningeal tuberculosis is around 20% and 41% [11]. More than a quarter of patients with meningeal tuberculosis die before treatment is started, and up to 50% of those that have been started, the treatment die within the first 60 days [6].

Several advances have been made regarding early diagnosis through algorithms and have also been validated [7] based on clinical data and CSF analysis. To achieve a more timely start of treatment, many factors have also reported as prognosis: Age, stage of the disease stage of consciousness, presence of disease outside the central nervous system, isolation of M tuberculosis, hydrocephalus, and infarction and CSF [6].

Even with these advances, the diagnostic approach and the relationships have demonstrated that the cerebrospinal fluid characteristically shows pleocytosis with a predominance of lymphocytes, and high levels of proteins, which have related to untreated patients, and hypoglycorrhachia. This has been correlated with more advanced stages of the disease [2] and the relationship with alterations in cerebrospinal fluid characteristics as levels of proteins, lactate, and glucose are prognostic factors for patients [15]. Other studies have not shown this direct relationship between alterations of CSF and poor prognosis for these patients. There is still not enough evidence that supports or rejects some associations (such as protein level). This study tries to identify if there is any alteration in the CSF that achieves relation for those patients who have a poor prognosis.

Hypothesis

Alterations in the initial cerebrospinal fluid of patients with meningeal TB have prognostic value for the mortality of patients with this disease.

Objectives

Determine if the alterations exist in the components of the spinal fluid are related to mortality in patients with Meningeal tuberculosis.

- Determine if the concentration of proteins in cerebrospinal fluid is related to mortality.
- Determine if the leukocyte count in cerebrospinal fluid is proportional to mortality.
- Determine if the proportion of mononuclear cells in liquid cerebrospinal fluid is associated with mortality
- Determine the glucose concentration in cerebrospinal fluid related to mortality.
- Determine if there is any other systemic factor related to the mortality.

Inclusion and exclusion criteria

- **Inclusion:** All patients diagnosed with meningeal tuberculosis and who have enough data in the file for categorization.
- **Exclusion**: Those files that do not have enough data for the study.

Statistical analysis

R cmdr package of R software version 3.2.2 (R Core Team (2014). A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. For analysis statistical and creation of tables.

The study variables were classified as categorical, which included, the outcome in improvement and death, diagnosis as definitive, probable and possible, severity as stage I, II, III, sex, HIV. The continuous variables, age, albumin serum, cells in cerebrospinal fluid, glucose, leukocytes, mononuclear, proteins the calculation and description of frequencies were generated through the program statistical. The comparison of categorical variables was carried out using tables of contingency using the chi-square test or Fisher's exact test as appropriate to determine the independence of the variables, taking a p less than 0.05 as significant. In the same way, the analysis was carried out multivariate and logistic regression to establish the attributable risk. Because in this study, the considered variables did not have statistically significant values, but some trends related to the mortality, we decided to generate a regression tree and classification to generate a model that can help in making decisions because once analyzed through logistic regression. It was not possible to establish risk factors, considering this model of statistical analysis where analysis of different variables and with possible complex interactions. This method has several useful advantages: It is easy to interpret and to estimate, inexpensive, though this type of tree can manipulate numerical and categorical variables. Each one represents a node in the tree from which the rest nodes children, thus determining which is the variable that best divides the data into two groups (making this partition at the level where the highest power is generated predictive) repeating this process until the subgroups contain a number minimum data or until no improvement can be made in the homogeneity of the subgroups leading, to terminal nodes to which it is assigned a class when the variable is categorical or is predicted the value of the variable answer in the case that it is continuous.

By making this regression tree model, it allowed to classify and discriminate those with poor prognosis and make the necessary adjustments to their management to be able to change the outcome of these patients.

Ethics

Research without risk, because it is a descriptive, observational study, no interventions, and the informed consent of the subjects was not necessarily included in the study. The personal information that was collected during the study was only used for the analysis of results.

Characteristic	Operational Definition	Possible value	Type of variable
Sex	Phenotype	Female 1 Male 2	Categoric
Ending	Type	Improved 1 Death 2	Categoric
HIV	Reactivity	Positivity1 Negativity 2	Categoric
Diagnosis	Type	Define Probable Possible	Categoric
Severity	Stadium	I II III	Categoric
Age	Years of life	Aging	Continuous
CSF proteins	CSF proteins concentration	mg/dL value	Continuous
CSF glucose	CSF proteins concentration	mg/dL value	Continuous
CSF leucocytes	Leucocytes count	Count cell/ml	Continuous
CSF MNC	Percentage of MNC cell of the Leucocytes count	% value	Continuous
Serum albumin	Albumin concentration in serum	Mg/dL value	Continuous

Table 1: General characteristics and variables of the study.

Variable	Status	Number of patients	Percentage
Ending	Improve	17	56.5
	Death	13	43.3
Diagnosis	MTB define	13	43.3
	MTB probable	11	36.7
	MTB possible	6	20.0%
Severity	I	9	30%
	II	13	43.3%
	III	8	26.7%
Gender	Male	19	63.3%
	Female	11	36.7%
VIH	Reactive	6	20%
Variable	Mean (standard deviation) Medium (IQ1-IQ3)	Minimum	Maximum
Albumin	3.36(2.85-3.19)	1.61	6.67
CSF cells	136 (64-218)	0	10,000
Age (years)	44.8 (±21.0)	16.0	84.0
Glucose (mg/dL)	41.3 ((±24.6)	4.0	101
CSF leucocytes (%)	75.0 (26-126)	0	346
CSF mononuclear cells (%)	77.5 (22.5-100)	0	100
Protein (mg/dL)	154.1(88.8-216.9)	16.4	530

Table 2. Characteristics in number and percentage of the study population.

Results

A review of the files of patients diagnosed with tuberculous meningitis allowed to classify them according to the consensus for the diagnosis of MTB in any of the following four: Definitive, probable, possible and not meningeal tuberculosis. Also, they were classified in any of the stadiums according to Medical Research Council. By severity upon admission, data were obtained on the levels of serum albumin, and concentrations of the components of CSF. The final result was dichotomized into death and improvement.

No statistically significant differences were found in the characteristics of the population studied, the average age was 44.8 years (16-84), the female sex represented 36.7% with an n = 11, and male of 63.3% with one n = 19. Regarding the primary outcome of come of mortality, it was 43.3%. Data was grouped according to the diagnosis of meningeal tuberculosis infection definitive 43.3% n = 13, possible TBM 20% n = 6, and probable TBM 36.7% n = 11. A). Yes, as to the severity of the infection with the Medical Research Council scale, in grade I 30% n = 9, grade II 43.3% n = 13, and grade III 26.7% n = 8.

There were several values of the CSF constituents as cellularity, leukocytes, percentage of mononuclear cells, proteins and glucose, as well as serum albumin concentration, the average number of days to death was of 15.2 (+10.5) (3-33), the reactivity in Elisa to HIV was 20% with n = 6. and the mortality in this subgroup was 15% of all deaths.

Variable	Death = 13	Improve = 17	Confidence intervals	p
Albumin	3.3 (±1.3)	3.7 ((±0.9)	(-1.43,051)	0.3
Cells	82 (63-166)	160 (66-240)		0.3
Age (years)	46.8 (±19.9)	43.3 (±22.3)	(-12.33,19.43)	0.7
Glucose (mg/dL)	43.6 (±20.9)	39.6(±27.6)	(-14.13,22.20)	0.7
Leucocytes	76.0 (34-114)	66 (16-132)		0.9
Mononuclear cells	70.0 (30-100)	80 (20-100)		0.9
Protein	167 (133.7-254.4)	125.4 (86.5-176.6)		0.2

Table 3: Final results.

When the severity was compared to their income, it was found that of the 13 patients with stage I had a mortality of 15.4% n = 2, stage II had a mortality of 30.7% with n = 4 and the 8 patients with stage III had a mortality of 53.9% n = 7 with a p 0.01, the mortality was more frequent in the male 76.9% n = 10, comparing it with female 23.1% n = 3.

The data were analyzed in terms of alterations in the concentration of different components of the CSF obtaining the following results, the average level of mortality among the patients with death was 82/mm3 (63-166), leukocytes of 76.0 mm3 (34-114), percentage of mononuclear cells 70% (30-100), proteins of 167 mg/dl (133.7-254.4) and glucose of 43.6 mg/dl (± 20.9) confidence interval of (-14.33, 22.20) p = 0.7. In the same way, albumin serum in patients with death was 3.3mg/dl (± 1.3). With interval confidence (-1.43, 0.51) and p = 0.3. A multivariate logistic regression analysis was performed without evidence of collinearity, curvilinear relations. In a second statistical analysis and using likelihood ratio tests with a regression tree and classification, generating a model that includes serum albumin, glucose in CSF and proteins in cerebrospinal fluid with which found an error of 8% misclassification as poor prognosis and high mortality, having glucose in CSF> 24.74 mg/dl, serum albumin> 2,965 mg/dl, and proteins in CSF> 129.53 mg/dl.

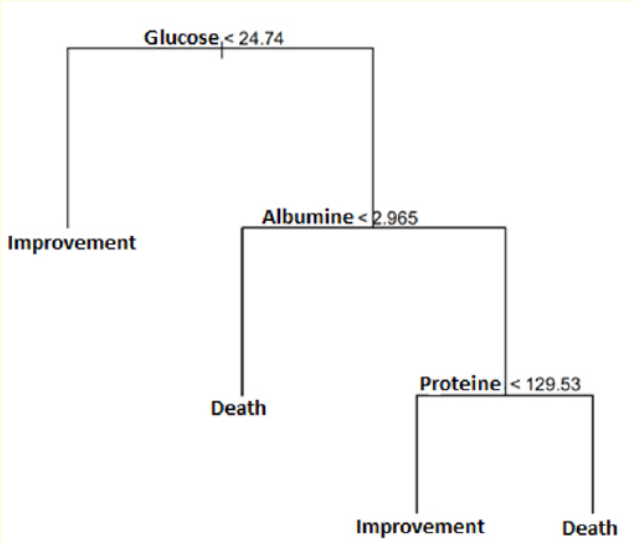

Figure 1: Algorithm according with the SCF characteristics.

Discussion

LCR is a tool that can be useful to predict the outcome of these patients, we found concentrations of glucose and CSF proteins with levels of glucose 43.6 mg/dl (± 20.9) in those who died and with levels of 39.6 mg/dl (± 27.6) in those who had improvement, and with protein levels of 167 mg/dl (133.7-254.4) in deaths and 125.4 mg/dl (86.5-176.6) in those who had improvement. This is comparable to what was found by C.-H. Lu in 2001 in his study of 36 patients, 23 men, from 21 to 83 years old, whom they grouped into good results n: 18 and bad result n: 18 which included those who died and to whom they had severe neurological sequelae. Those with poor results had levels of glucose in CSF of 32.1 ± 17.4 mg/dl, proteins 682.2 ± 806.3 mg/dl and leukocytes 203.7 ± 223.4 cel/mm3. On the other hand, in a secondary analysis and trying to identify another systemic marker value for prognosis was included serum albumin observed a tendency to be altered in patients with a poor prognosis, serum albumin concentrations were 3.3 mg/dl (± 1.3) in whom died, comparing it with patients with an improvement that was 3.7 mg/dl (± 0.9), there are no references to this behavior but something similar refers in the study of patients with pulmonary tuberculosis Alvarez-Uria 2013, in patients reactive to HIV and who started anti-tuberculous treatment, observed that it can be useful as a diagnostic marker, and also in serum albumin concentrations, it was observed that mortality in patients with tuberculosis gradually increased with lower levels of albumin [26].

Taking into consideration these few variables that showed some tendency in patients with death, they were used to perform a second analysis and develop a tree decision and see its usefulness in making decisions is with the patient, which allows us, according to our model, to classify our patients as having a poor prognosis and risk of death or with good prognosis and clinical improvement, with an error of 8%.

Classifying patients according to definite diagnostic certainty, probable, possible and not TB is very valuable since it will allow us to compare the results with other studies in a more structured way since until at the moment in most of the studies. The classification of patients does not follow this consensus, and for these differences, the findings cannot be compared adequately. We hope that the following guidelines of this consensus allow us to make an appropriate comparison.

One of the main prognostic factors that were identified as the severity of the clinical picture upon admission and has been identified in several studies one of them shows a mortality rate of 25.8 for stage I, of 40.5% for stage II and 42.9% for stage III.

Another critical factor in the frequency of the disease is HIV. In our study, we found a prevalence of 20% of patients reactive to HIV comparable to other reports in the literature such as the 2014 Pascopella study with a prevalence of 21% of patients with HIV, a mortality of 25% for HIV negative and up to 67% in HIV positive patients, we found a mortality of 15.4% in reactive patients, which indicates that it is not a factor that really influences the outcome of these patients [27].

Limitations and/or New Research Perspectives

During the review of clinical records, complete data was obtained.

As for the first lumbar puncture, it is diagnosed that it was performed, on the other hand about the follow-up of the patients, they were more challenging to obtain due to that there is no standardization regarding the time to perform subsequent lumbar punctures, another limitation of this study is the retrospective design and the number of patients. Therefore, it is proposed to standardize the time and number of control punctures to perform in these patients, to be able to analyze the evolution of the fluid cerebrospinal fluid and obtain data on changes that guide us to the type of response (towards improvement or deterioration) of the patients and in this way achieve to identify those that it is necessary to modify the therapeutic scheme. Achieve to identify more factors related to the result, and develop a scale to classify the severity of these patients.

Conclusion

The mortality rate of 43.3% concerning published reports. We found higher mortality in the male gender, the severity at admission has a relationship directly with mortality and according to the analysis by reason of likelihood with the decision tree and analyzing a simplified model (which includes albumin serum, glucose, and proteins in cerebrospinal fluid) was found as predictor mortality with an error of 8% misclassification. This is a model that can support in decision-making, especially considering that in our environment does not yet have enough technology, which allows a diagnosis, and in this way reduce complications and the unfortunate result of these patients.

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