Research Article

Ability of Procalcitonin and C-Reactive Protein for Discriminating between Bacterial and Enteroviral Meningitis in Children Using Decision Tree

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Bacterial meningitis (BM) is a public health burden in developing countries, including Central Asia. This disease is characterized by a high mortality rate and serious neurological complications. Delay with the start of adequate therapy is associated with an increase in mortality for patients with acute bacterial meningitis. Cerebrospinal fluid culture, as a gold standard in bacterial meningitis diagnosis, is time-consuming with modest sensitivity, and this is unsuitable for timely decision-making. It has been shown that bacterial meningitis differentiation from viral meningitis could be done through different parameters such as clinical signs and symptoms, laboratory values, such as PCR, including blood and cerebrospinal fluid (CSF) analysis. In this study, we proposed the method for distinguishing the bacterial form of meningitis from enteroviral one. The method is based on the machine learning process deriving making decision rules. The proposed fast-and-frugal trees (FFTree) decision tree approach showed an ability to determine procalcitonin and C-reactive protein (CRP) with cut-off values for distinguishing between bacterial and enteroviral meningitis (EVM) in children. Such a method demonstrated 100% sensitivity, 96% specificity, and 98% accuracy in the differentiation of all cases of bacterial meningitis in this study. These findings and proposed method may be useful for clinicians to facilitate the decision-making process and optimize the diagnostics of meningitis.

1. Introduction

Meningitis is a life-threatening inflammatory disease of the brain and spinal cord, mostly caused by bacterial, viral, and fungal infection [1–3]. Meningococcal infection has been a big threat to the globe and exists as a sporadic, hypervirulent, and epidemic disease. In 2012, an estimated 1.2 million cases of meningococcal infection per year were reported, with ~135,000 deaths worldwide [4]. The average annual incidence of meningococcal infection in Kazakhstan for the last decade is 0.83/100 000 with a peak in 2015 (2.42/100 000) [5].

Bacterial meningitis as a more serious form of meningitis is caused by pyogenic bacteria, such as S. pneumoniae, N. meningitidis, and H. influenzae [6]. Viruses are the most common cause of aseptic meningitis, primarily enteroviruses, together with numerous nonviral and noninfectious disorders [7, 8].

Although bacterial meningitis has a lower incidence rate than viral/aseptic meningitis [9, 10], prompt correct diagnosis
forms of meningitis, bacteremia (meningococcemia). Ples with meningitis of nonenteroviral etiology and combined and children over 17 years old. The study did not include sam-
tuberculous meningitis, benign and malignant brain tumors,
the presence of clinical signs of meningitis. Serum, results of a positive culture study for pathogens, and
bacterial or viral nucleic acids identi-
to 17 years old, both sexes, presence of bacterial antigen,
culture is highly speci-
clinical symptoms (fever, headache, and neck stiffness). CSF
fluid (or detecting etiological agent
PCR), along with typical
culture medium for cultivation and identi-
Chinese). CSF
and adequate treatment are necessary due to its hazardous
nature [11]. Delay in the start of proper therapy introduces
the potential for increased morbidity and mortality if
the patient does indeed have acute bacterial meningitis [12].
Diagnosis of bacterial meningitis is based on a positive
culture of cerebrospinal fluid (or detecting etiological agent
by polymerase chain reaction—PCR), along with typical
clinical symptoms (fever, headache, and neck stiffness). CSF
culture is highly specific but lacks sensitivity, especially when
antimicrobials have been given as well as the time needed
until results appear [13]. In this case, PCR analysis can play
a diagnostic role, but as the direct culture of cerebrospinal
fluid, it takes some time. It should also be noted that not
every clinic has the appropriate equipment and capabilities
for conducting PCR analysis in CSF, especially in developing
countries [14].
Distinguishing bacterial meningitis is often difficult [15]
and therefore highly accurate decision support tools are
necessary to guide decision making and limit unnecessary
hospital admissions and prolonged antibiotic use.
Our study is aimed at assessing the role of clinical presen-
tations, serum, and CSF profiles to distinguish BM and EVM
in children.

2. Materials and Methods

2.1. Subjects. Recruiting patients for the study was carried out
in the Department of Reanimation and Intensive Care, Infec-
tion Department No. 1, Multidisciplinary City Children’s
Hospital No. 3, Nur-Sultan City (Kazakhstan). The study
covers the period between 2017 and 2019.
Inclusion criteria were as follows: children from 1 month
to 17 years old, both sexes, presence of bacterial antigen,
bacterial or viral nucleic acids identified in CSF in blood
serum, results of a positive culture study for pathogens, and
the presence of clinical signs of meningitis.
Exclusion criteria were as follows: children diagnosed with
tuberculous meningitis, benign and malignant brain tumors,
and children over 17 years old. The study did not include sam-
with meningitis of nonenteroviral etiology and combined
forms of meningitis, bacteremia (meningococcemia).

The study has been approved by the Local Ethics Commit-
tee of the National Laboratory Astana (NLA) at Nazarbayev
University (by 22nd of September 2017. Approval No. 20).
A total of 269 patients were recruited and divided into 6
groups from 1 month to 10 years and more (Table 1).

2.2. Physical Examination. Clinical symptoms such as tem-
perature, vomiting, impaired consciousness, headache, pallor
of the skin, rash, tension, and bulging of the fontanel in
children under one-year-old, stiff neck muscles, Lesage,
Brudzinski, and Kernig symptoms were determined.

2.3. Laboratory Examination. The number of white blood
cells (WBC), neutrophils, and level of protein in the CSF were
determined using the Cobas Integra 400 plus analyzer
(Roche, EU). The level of glucose in CSF was determined
using the Cobas Integra 400 plus analyzer (Roche, EU). The level of glucose in CSF was determined
using the ABL800 Flex Analyzer (Radiometer Medical ApS,
Denmark). The levels of haemoglobin, erythrocyte sedimen-
tation rate (ESR), white blood cells, count, neutrophils, and
platelets in blood were determined using the hematologic
analyzer Sysmex XP-300 (Sysmex). The levels of CRP and
procalcitonin were analysed using fluorescence immuno-
chromatographic system Finecare FIA Meter (Guangzhou
Wondfo Biotech Co. Ltd., China.).
Samples of CSF or blood were placed on the surface of the
culture medium for cultivation and identification on the
“chocolate” agar (based on trypticase soy agar with the addition
of defibrinated ram blood). Then, the samples were incu-
bated at a temperature of 37.0°C in an atmosphere of 5.0%
CO2 for 24-48 hours. The presence of etiological agents
of viral meningitis was determined by commercial PCR kits
according to the manufacturer’s protocol.

2.4. Statistical Analysis. Statistical analysis was carried out
using SigmaPlot 11.0 software (Systat Software Inc., USA)
with the following conditions:

1) Quantitative Data with a Normal Distribution. Stu-
dent t-test for two groups or analysis of variance
(ANOVA), when the number of groups is more than two

| Table 1: Demographic data of the studied population with meningitis. |
|---|---|---|---|---|
| Age (in months) | [ALL] N=269 | EVM N=146 | BM N=123 | p,overall |
| Age group: | | | | |
| ≤1 y | 48.0 [17.0; 96.0] | 82.5 [40.0; 124] | 23.0 [9.00; 50.0] | <0.001 |
| >1-3 y | 52 (19.3%) | 11 (7.53%) | 41 (33.3%) | <0.001 |
| >3-5 y | 61 (22.7%) | 23 (15.8%) | 38 (30.9%) | |
| >5-7 y | 46 (17.1%) | 27 (18.5%) | 19 (15.4%) | |
| >7-10 y | 33 (12.3%) | 17 (11.6%) | 16 (13.0%) | |
| >10 y | 36 (13.4%) | 30 (20.5%) | 6 (4.88%) | |
| Gender: | | | | 0.622 |
| Male | 152 (56.5%) | 80 (54.8%) | 72 (58.5%) | |
| Female | 117 (43.5%) | 66 (45.2%) | 51 (41.5%) | |
Table 2: Underlying and associated conditions in bacterial and enteroviral meningitis groups in the studied population.

|                         | [ALL] N = 269 | EVM N = 146 | BM N = 123 | \(p\) overall |
|-------------------------|---------------|-------------|------------|--------------|
| Temperature (°C):       | 38.5 [37.8; 39.0] | 37.9 [37.4; 38.5] | 39.0 [38.6; 39.5] | <0.001 |
| Vomiting:              | 262 (97.4%) | 144 (98.6%) | 118 (95.9%) | 0.252 |
| Headache:              | 146 (54.3%) | 44 (30.1%) | 102 (82.9%) | <0.001 |
| Bulging fontanelle (for ≤18 months olds): | 71 out 72 (98.6%) | 19 out 20 (95%) | 52 out 52 (100%) | 0.278 |
| Neck rigidity:         | 266 (98.9%) | 146 (100%) | 120 (97.6%) | 0.094 |
| Kernig’s sign:         | 168 (62.5%) | 67 (45.9%) | 101 (82.1%) | <0.001 |
| Brudzinski’s sign:     | 61 (22.7%) | 6 (4.11%) | 55 (44.7%) | <0.001 |
| Loss of consciousness: | 15 (5.58%) | 0 (0.00%) | 15 (12.2%) | <0.001 |
| Drowsiness:            | 36 (13.4%) | 5 (3.42%) | 31 (25.2%) | <0.001 |
| Spasms:                | 27 (10.0%) | 0 (0.00%) | 27 (22.0%) | <0.001 |

Table 3: Laboratory findings of blood and cerebrospinal fluid in the studied population.

|                         | [ALL] N = 269 | EVM N = 146 | BM N = 123 | \(p\) overall |
|-------------------------|---------------|-------------|------------|--------------|
| Glucose in CSF: [2.3-3.9] mmol/L | 2.80 [1.60; 3.80] | 3.70 [3.10; 4.80] | 1.50 [0.57; 1.90] | <0.001 |
| Haemoglobin in blood: [110-140] g/L | 119 (16.7) | 125 (15.4) | 111 (15.2) | <0.001 |
| Protein in CSF: [0.12-0.45] g/L | 0.50 [0.20; 1.30] | 0.20 [0.10; 0.40] | 1.50 [0.60; 2.10] | <0.001 |
| CRP in blood: [≤10] mg/L | 22.8 [4.80; 110] | 5.00 [2.12; 12.0] | 118 [43.5; 196] | <0.001 |
| ESR in blood: [0-10] mm/H | 15.0 [10.0; 22.0] | 12.0 [7.00; 17.0] | 18.0 [14.5; 30.0] | <0.001 |
| Procalcitonin in blood: [≤0.05] ng/mL | 0.05 [0.02; 0.30] | 0.02 [0.01; 0.03] | 3.30 [2.15; 5.15] | <0.001 |
| WBC in CSF: [≤30] × 10^9/L | 380 [110; 1300] | 126 [78.2; 233] | 1455 [815; 4250] | <0.001 |
| WBC in blood: [4.5 – 10.5] × 10^9/L | 13.1 [8.80; 18.0] | 9.25 [7.60; 12.2] | 18.0 [15.0; 23.2] | <0.001 |
| Neutrophils in CSF: [≤10] × 10^9/L | 72.0 [19.0; 90.0] | 21.5 [10.0; 61.5] | 88.0 [75.0; 90.0] | <0.001 |
| Neutrophils in blood: [42-72%] | 79.8 [69.9; 87.1] | 74.0 [58.2; 84.0] | 85.0 [76.3; 90.0] | <0.001 |
| Platelets in blood: [180 – 320] × 10^9/L | 233 [195; 314] | 228 [190; 288] | 256 [209; 321] | 0.020 |

(2) Quantitative Data with Abnormal Distribution. Non-parametric Kruskal-Wallis test and Mann–Whitney test for independent groups; and Wilcoxon Matched Pairs Test for dependent groups.

(3) Categorical Data. Chi-square or Fisher’s tests if necessary (when the expected frequency is less than 5 in one of the cells).

Shapiro-Wilk test was employed for the evaluation of the distribution of data (normality test). \(p < 0.05\) was considered statistically significant for all analyses.

2.5. Modelling. Fast-and-frugal trees (FFTs) as a supervised learning algorithm described in Phillips, Neth, Woike, and Gaismaier [16] and implemented in FFTrees R package was used to predict a binary criterion BM and EVM. Before the machine training, we split the entire dataset into training (80%) and testing (20%) subsets. An optimal cut-off point was calculated according to the highest accuracy (minimal false-negative and false-positive results). The area (AUC, area under curve) under the receiver operating characteristic curve (ROC) was used to check the prognostic value of a particular parameter. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for the given cut-off values for predicting bacterial meningitis.

3. Results

A total of 269 children (117 females and 152 males) were included in this study. The median and IQR age of the participants were 48.0 [17.0-96.0] months old. Children with EVM, that had a median age of 82.5 [40.0; 124] months old, were older compared with the BM group (median age 23.0 [9.00; 124] months old, \(p < 0.001\) (Table 1). The highest rate of meningitis was found out among children aged up to 1-year old in a group with BM. In contrast, the rate of EVM was relatively low (7.53%) in a group up to 1-year children, while in groups > 1 year, EVM incidences were higher (on average18.48%) and reached 26% in the group > 10 years.

Among the studied patients, bacterial meningitis represented 45.7% (123 patients) compared to 54.3% (146 patients) nonbacterial (enteroviral) meningitis. Among bacterial meningitis, 95 were due to \(N. meningitidis\), 25 cases \(S. pneumoniae\),
Among 146 viral/septic cases, all 146 cases were caused by enterovirus. The most common presenting symptom in children with BM was the high temperature (39°C vs. 37.9°C, \(p < 0.001\)) followed by headache (82.9%) and Kernig’s sign (82.1%). The occurrence of Brudzinski’s sign (44.7%), drowsiness (25.2%), spasms (22%), and loss of consciousness (12.2%) was significantly higher in the BM group compared with the EVM group (\(p < 0.001\)). Vomiting, bulging fontanelle, and neck rigidity had no difference among these groups. The clinical features of BM and EVM groups are presented in Table 2.

Table 3 represents the comparison of the laboratory results of blood and CSF between the two groups. Blood and CSF laboratory testing data showed significantly increased levels of proteins, CRP, procalcitonin, WBC, neutrophils, and platelets in the blood of children with BM (\(p < 0.001\)). WBC and neutrophils in CFS were also significantly higher in the BM group (\(p < 0.001\)). The blood glucose level was 1.50 [0.57; 1.90] mmol/L in the BM group, which is significantly lower than that for the EVM group (3.70 [3.10; 4.80] mmol/L; \(p < 0.001\)). Haemoglobin was also significantly lower in the BM group in comparison with the EVM group (\(p < 0.001\)).

Fast-and-frugal trees (FFTs) algorithm was performed for providing efficient and accurate decisions in the prediction of bacterial meningitis. All data, such as demographic variables (gender and age), clinical data, and laboratory results, were included in training FFTs to get the best-trained algorithm based on the highest sensitivity. The results
4.6 times by 2018 compared to 2015 [5]. Towards a decrease in 3.6 times by 2016, 7 times by 2017, and 2015 (2.4 per 100 000). In subsequent years, there was a trend.

The early diagnostics of meningitis and differentiation between bacterial and viral meningitis is based on the assessment of clinical signs and symptoms and laboratory tests (blood and CSF analysis) [11, 22, 23].

In contrast to the standard method, our study is focused on searching a novel method of meningitis diagnostics and differentiation. The proposed method is based on the validation of the factors such as demographic variables, clinical, and routine diagnostic tests, with the most discriminating power and sensitivity in differentiating bacterial meningitis from nonbacterial (enteroviral) meningitis.

Our trained FFTree model determined two parameters, procalcitonin and C-reactive protein, based on which the differentiation of BM from EVM is effective. Definition of the decision tree is “if procalcitonin > 0.16 ng/mL, decide BM, If CRP < 31.2 mg/L, decide EVM, otherwise, decide BM”. This trained FFT model demonstrated an extremely high sensitivity (98.6%, 95.8%, and 90.3%, respectively) in discriminating between bacterial and enteroviral meningitis. Previous studies also showed the same results with variation in cut-off values to distinguish bacterial and viral meningitis [24–31]. At the same time, the authors emphasized the importance of the heterogeneity of populations, techniques, and approaches of decision-making threshold for BM diagnosis markers.

### Table 4: Validation of clinical and laboratory parameters in bacterial meningitis prediction.

| Parameters                      | Threshold | Direction | N   | Sens  | Spec  | PPV  | NPV  | Acc  |
|---------------------------------|-----------|-----------|-----|-------|-------|------|------|------|
| Procalcitonin in blood (ng/mL)  | 0.16      | >         | 216 | 0.990 | 0.983 | 0.980| 0.991| 0.986|
| CRP in blood (mg/L)             | 31.2      | >         | 216 | 0.939 | 0.974 | 0.969| 0.950| 0.958|
| Glucose in CSF (mmol/L)         | 2.2       | ≤         | 216 | 0.848 | 0.949 | 0.933| 0.881| 0.903|
| Neutrophils in CSF (×10⁶/L)     | 64        | >         | 216 | 0.980 | 0.726 | 0.752| 0.977| 0.843|
| WBC in CSF (×10⁶/L)             | 513       | >         | 216 | 0.818 | 0.872 | 0.844| 0.850| 0.847|
| Temperature (°C)                | 38.4      | >         | 216 | 0.909 | 0.752 | 0.756| 0.907| 0.824|
| Protein in CSF (g/L)            | 0.3       | >         | 216 | 0.949 | 0.709 | 0.734| 0.943| 0.819|
| WBC in blood (×10⁹/L)           | 12.5      | >         | 216 | 0.879 | 0.769 | 0.763| 0.882| 0.819|
| Headache                        | Yes       | =         | 216 | 0.838 | 0.701 | 0.703| 0.837| 0.764|
| Age (months)                    | 85        | ≤         | 216 | 0.949 | 0.470 | 0.603| 0.917| 0.690|
| Kernig’s sign                   | Positive  | =         | 216 | 0.838 | 0.538 | 0.606| 0.797| 0.676|
| Brudzinski’s sign               | Positive  | =         | 216 | 0.424 | 0.949 | 0.875| 0.661| 0.708|
| Neutrophils in blood (%)        | 73        | >         | 216 | 0.879 | 0.453 | 0.576| 0.815| 0.648|
| ESR in blood (mm/H)             | 11        | >         | 216 | 0.859 | 0.462 | 0.574| 0.794| 0.644|
| Haemoglobin in blood (g/L)      | 113       | ≤         | 216 | 0.576 | 0.744 | 0.655| 0.674| 0.667|
| Spasms                          | Single    | =         | 216 | 0.212 | 1.000 | 1.000| 0.600| 0.639|
| Drowsiness                      | Yes       | =         | 216 | 0.232 | 0.957 | 0.821| 0.596| 0.625|
| Platelets in blood (×10⁶/L)     | 252       | >         | 216 | 0.545 | 0.607 | 0.540| 0.612| 0.579|
| Consciousness                   | Nonnormal | =         | 216 | 0.111 | 1.000 | 1.000| 0.571| 0.593|
| Gender                          | M         = | 216 | 0.566 | 0.444 | 0.463| 0.547| 0.500|

Abbreviations: sens: sensitivity; spec: specificity; ppv: positive predictive value; npv: negative predictive value; acc: accuracy.

The early diagnostics of meningitis and differentiation of bacterial forms from aseptic (viral) ones plays a crucial role in the effective treatment of children. The analysis of CSF culture, as a gold standard in bacterial meningitis diagnostics, is a time-consuming process with modest sensitivity (70–85%). Moreover, in the case of antibiotic pretreatment, the sensitivity of CSF culture decreases by 20% [21]. In this regard, the CFS culture test is unsuitable for timely decision-making and effective diagnostics. The classic approach for the differentiation between bacterial and viral meningitis is based on the assessment of clinical signs and symptoms and laboratory tests (blood and CSF analysis) [11, 22, 23].
In this paper, we addressed the task of distinguishing bacterial from viral meningitis in children through a machine learning-based approach deriving making decision rules. The proposed FFTree decision tree approach showed an ability to determine procalcitonin and CRP in blood with cut-off values for distinguishing between bacterial and enteroviral meningitis in children. It should be noted that the proposed method uses a minimally invasive procedure for taking material for diagnosis. Also, the method demonstrated 100% sensitivity, 96% specificity, and 98% accuracy in differentiation of all cases of bacterial meningitis in this study. These findings and proposed method may be useful for clinicians to facilitate the decision-making process and optimize the diagnostics of meningitis.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

Each author declares that he/she has no commercial associations (e.g., consultancies, stock ownership, equity interest, and patent/licensing arrangement) that might pose a conflict of interest in connection with the submitted article.

Authors’ Contributions

Dmitriy Babenko and Samat Kozhakhmetov conceived and designed the experiments. Samat Kozhakhmetov, Aliya Seidullayeva, Dinagul Bayesheva, Bayan Turdalina, and Baurzhan Omarkulov performed the experiments. Dmitriy Babenko, Samat Kozhakhmetov, and Almagul Kushugulova analysed the data. Aigul Almabayeva and Marina Zhaneliyeva contributed reagents/materials/analysis tools. Dmitriy Babenko, Almagul Kushugulova, and Samat Kozhakhmetov wrote the paper.

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