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Predictive value of C-reactive protein for the diagnosis of meningitis in febrile infants under 3 months of age in the emergency department

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Background: Fever is a common cause of pediatric consultation in the emergency department. However, identifying the source of infection in many febrile infants is challenging because of insufficient presentation of signs and symptoms. Meningitis is a critical cause of fever in infants, and its diagnosis is confirmed invasively by lumbar puncture. This study aimed to evaluate potential laboratory markers for meningitis in febrile infants.

Methods: We retrospectively analyzed infants aged <3 months who visited the emergency department of our hospital between May 2012 and May 2017 because of fever of unknown etiology. Clinical information and laboratory data were evaluated. Receiver operating characteristic (ROC) curves were constructed.

Results: In total, 145 febrile infants aged <3 months who underwent lumbar punctures were evaluated retrospectively. The mean C-reactive protein (CRP) level was significantly higher in the meningitis group than in the non-meningitis group, whereas the mean white blood cell count or absolute neutrophil count (ANC) did not significantly differ between groups. The area under the ROC curve (AUC) for CRP was 0.779 (95% confidence interval [CI], 0.701–0.858). The AUC for the leukocyte count was 0.455 (95% CI, 0.360–0.550) and that for ANC was 0.453 (95% CI, 0.359–0.547). The CRP cut-off value of 10 mg/L was optimal for identifying possible meningitis.

Conclusion: CRP has an intrinsic predictive value for meningitis in febrile infants aged <3 months. Despite its invasiveness, a lumbar puncture may be recommended to diagnose meningitis in young, febrile infants with a CRP level >10 mg/L.

Keywords: C-reactive protein; Fever; Infants; Meningitis; Spinal puncture

Introduction

Fever is a common cause of patient visits in pediatric practice [1]. In many patients, the main cause of infection cannot be identified based solely on the clinician's physical examination, especially in pediatric patients [2]. When infants who visit the emergency department exhibit fever without a clear source of infection, doctors must differentially diagnose various diseases from a simple viral infection to a serious bacterial infection [3]. The management of febrile infants aged < 3 months is especially challenging because of the relatively high prevalence of serious bacterial infections such as bacteremia, meningitis, and urinary tract infection, and the lack of specific signs or symptoms to differentiate these infections from a simple viral infection [4,5]. A combination of medical history and physical and laboratory findings has been widely accepted as an approach to identify the source of infection in fe-

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brile patients [6].

Meningitis is one of the causes of fever, and lumbar puncture (LP) is required to determine the presence of meningitis by obtaining a cerebrospinal fluid (CSF) sample. Making a decision of when to perform an LP to differentiate meningitis from other diseases can be difficult [7]. In early-onset sepsis in the neonatal period, the American Academy of Pediatrics (AAP) recommends performing an LP in the case of positive blood culture results, if the "clinical course or laboratory data strongly suspect bacterial sepsis," or if the infant does not respond to antimicrobial therapy [8]. However, even with meningitis, young infant patients often do not present symptoms such as fever, vomiting, or headache, and blood culture examinations normally take a couple of days. Therefore, many clinicians rely on laboratory findings, including the level of C-reactive protein (CRP), an acute-phase reactant synthesized by the liver in response to tissue injury or inflammation, which is a sensitive marker for infection [9,10]. The National Institute for Health and Care Excellence (NICE) published clinical guideline 149 (CG149) that suggests considering LP if the blood culture result is positive, the patient does not respond to antimicrobial therapy, or if the patient has a CRP level > 10 mg/L [11]. Many studies have analyzed the diagnostic markers for serious bacterial infections in febrile infants, but markers indicating meningitis and the cut-off values for the diagnosis of meningitis have rarely been evaluated.

Therefore, the aim of this study was to retrospectively assess several laboratory markers, such as CRP, white blood cell (WBC) and absolute neutrophil count (ANC), as markers of meningitis in febrile infants in the emergency department and to identify predictive values using receiver operating characteristic (ROC) curves for meningitis.

Materials and methods

1. Ethics statement

Ethical approval for this study was obtained from the Institutional Review Board of Wonkwang University Hospital (IRB No: WKUH 2019-04-045). The requirement to obtain informed consent was waived given the retrospective nature of the study.

2. Data collection, study setting, and definitions

This retrospective study included all infants aged < 3 months who visited the emergency department of our hospital from May 2012 to May 2017 for fever with no clear source of infection. Electronic medical records of 610 infant patients whose history and physical examination could not reveal the source of infection and who underwent a blood test were analyzed. The exclusion criteria were lack of blood test results and antibiotic therapy prior to the visit.

All patients underwent a full physical examination to localize the source of the fever, including the evaluation of their overall physical appearance as well as assessment of the heart, lungs, pharynges, fontanel, and ears. We collected the following clinical data from the electronic medical records: patient's age, sex, duration of fever before the hospital visit, final diagnosis, CRP level, WBC count, ANC, platelet (PLT) count, and results of the CSF analysis when LP was performed according to the ward's policy. Meningitis was defined as meningism without altered consciousness, with CSF WBC count ≥ 5/μL in infants older than 28 days and ≥ 30/μL in neonates [12]. Bacterial meningitis was confirmed based on the culture results of the CSF, Wellcogen (Remel Europe Ltd., Dartford, Kent, UK) bacterial antigen rapid latex agglutination test, or polymerase chain reaction (PCR) using dual priming oligonucleotide, Seeplex (MT Promedt Consulting GmbH, St. Ingbert, Germany). Viral meningitis was confirmed based on positive viral multiplex PCR results in the CSF. Aseptic meningitis was confirmed by negative bacterial growth in the CSF. For comparative analysis, we distinguished aseptic meningitis from viral meningitis. We confirmed that no bacterial pathogens were found in all investigated specimens from the aseptic or the viral meningitis groups. Undetermined fever was defined when the cause of fever was not revealed after 7 days of hospitalization. Urinary tract infection was diagnosed with pyuria (WBC > 5/high power field) and the isolation of > 100,000 colony-forming units per milliliter of a single pathogen from the urine collected in a urine bag. Cultures with more than one isolate were considered contaminated. Fever was defined as a tympanic membrane temperature of 38°C or higher.

3. Statistical analysis

Continuous variables were presented as mean ± standard deviation. Categorical variables were expressed as a number (%) using the cross analysis. The independent t-test was used when comparing the meningitis and non-meningitis group. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curves (AUCs) for laboratory biomarkers with respect to the diagnosis of meningitis were calculated and compared. Data were analyzed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Results

During the study period, 610 febrile infants aged < 3 months were evaluated at the emergency department or outpatient pedi-

atric department of our hospital due to fever with no clear source of infection. Of these, three patients did not undergo laboratory tests, and 36 patients were treated with antibiotic therapy prior to the visit. Thus, a total of 571 infants who met the inclusion criteria were enrolled in the study. Among the 571 patients, LP was performed in 145 patients and 57 patients were definitively diagnosed with meningitis. The meningitis group was comprised three patients with bacterial meningitis and 54 patients with aseptic or viral meningitis. Among the viral meningitis group, 50 patients were diagnosed with enteroviral meningitis, and 4 patients were diagnosed with herpes simplex virus type 2 meningitis. Moreover, 88 patients comprised the non-meningitis group (Fig. 1). Febrile illness without a source of infection was the most common final diagnosis in all studied infants, accounting for 54.3% of all diagnoses (Table 1). Urinary tract infection was the next most common diagnosis, accounting for 157 patients (27.5%). Respiratory tract infection accounted for 33 patients (5.8%). Human rhinovirus was the most common pathogen accounting for 14 patients (2.5%). Respiratory syncytial virus, parainfluenza virus, enterovirus, coronavirus, human bocavirus, and influenza virus were the pathogens detected in the respiratory tract. Gastrointestinal tract infection accounted for 14 patients (2.5%). Rotavirus was the most commonly identified pathogen and astrovirus was also detected in the stool multiplex PCR.

The demographic characteristics and laboratory findings of infants with and without meningitis were evaluated. A total of 61.4% of the non-meningitis group were male infants (n=54), and 64.9% of the meningitis group were also male infants (n=37). The mean age was 40.9±23.7 days in the non-meningitis group and 40.6±25.3 days in the meningitis group. The mean duration of fever at the time of visit was 1.9±1.9 and 1.8±1.3 days in the non-meningitis group and meningitis group, respectively. Moreover, no significant difference in sex, age, fever duration, and mean time required for improvement of fever was found. A statistically significant difference was found in terms of CRP level between the meningitis and non-meningitis groups ($p<0.05$). The mean CRP level was 24.32±33.66 mg/L in the meningitis group and 7.44±6.50 mg/L in the non-meningitis group. Other laboratory variables showed no statistically significant differences (Table 2).

For predicting meningitis, the AUC was 0.779 for CRP (95% confidence interval [CI], 0.701–0.858), 0.455 for WBC (95% CI, 0.360–0.550), and 0.453 for ANC (95% CI, 0.359–0.547) (Fig. 2). The AUC for CRP was significantly higher than that for WBC and ANC. The ROC curve was used to select optimal cut-off values of laboratory factors for predicting whether LP is needed to detect meningitis. CRP was the only laboratory parameter found to be associated with meningitis. According to the data in this study, a CRP cut-off of 10 mg/L showed both relatively high sensitivity and specificity. At that threshold, a sensitivity of 73.7%, specificity of 77.3%, and NPV of 81.9% for possible meningitis were noted in febrile infants (Table 3).

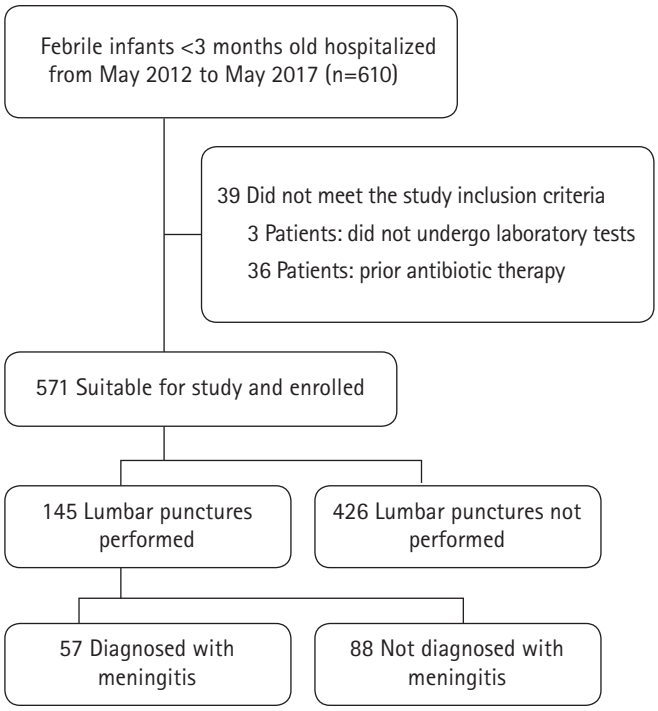

Fig. 1. Subject enrollment flow chart shows the number of patients in each classified group.

Table 1. Final diagnosis of febrile infants aged <3 months (n=571)

Final diagnosis	No. (%)
Undetermined fever	310 (54.3)
Urinary tract infection	157 (27.5)
Respiratory tract infection	33 (5.8)
Viral meningitis	28 (4.9)
Aseptic meningitis	26 (4.6)
Gastrointestinal tract infection	14 (2.5)
Bacterial meningitis	3 (0.5)

Discussion

In this study, we analyzed febrile infants with an unknown source of infection who met the inclusion criteria in the study period and compared the predictive values of commonly used laboratory data to establish effective markers for predicting meningitis.

When febrile infants without a clear source of infection seek treatment in a hospital, deciding the management approach is

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Table 2. Comparison of clinical and laboratory characteristics between the meningitis group and non-meningitis group

Variable	Meningitis (n = 57)	Non-meningitis (n = 88)	*p*-value
Male sex	37 (64.91)	54 (61.36)	0.699
Age (day)	40.6 ± 25.3	40.9 ± 23.7	0.944
Fever duration (day)	1.8 ± 1.3	1.9 ± 1.9	0.511
Fever improvement (day)	3.0 ± 1.4	2.6 ± 2.0	0.201
Hemoglobin (g/dL)	11.27 ± 2.43	11.14 ± 2.18	0.739
White blood cell count × 10^3 (/μL)	9.58 ± 5.12	10.39 ± 5.40	0.370
Absolute neutrophil count × 10^3 (/μL)	5.04 ± 3.74	5.63 ± 3.69	0.350
Neutrophil (%)	51.76 ± 15.73	52.58 ± 15.19	0.757
Lymphocyte (%)	37.80 ± 15.22	35.39 ± 13.87	0.329
Platelet count × 10^3 (/μL)	364.47 ± 126.49	344.89 ± 114.62	0.337
C-reactive protein (mg/L)	24.32 ± 33.66	7.44 ± 6.50	0.001

Values are presented as number (%) or mean±standard deviation.

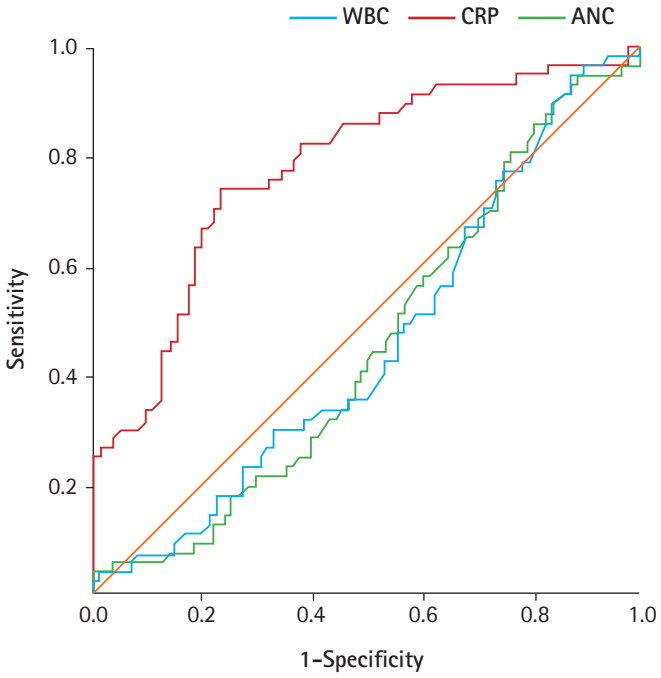

Fig. 2. Receiver operating characteristic curves for CRP (p<0.05), WBC (p=0.36), and ANC (p=0.34) for predicting meningitis shows that CRP has the most valuable predictive value indicating meningitis compared to WBC and ANC. CRP, C-reactive protein; WBC, white blood cell count; ANC, absolute neutrophil count.

Table 3. C-reactive protein decision thresholds as an indicating marker of meningitis

Threshold (mg/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
5	86.0	47.7	51.6	84.0
10	73.7	77.3	67.7	81.9
15	50.9	84.1	67.4	72.5
20	31.6	90.9	69.2	67.2

PPV, positive predictive value; NPV, negative predictive value.

quite challenging for clinicians. Particularly, febrile infants aged < 3 months are frequently evaluated for the risk of invasive bacterial infections such as bacteremia or bacterial meningitis in the pediatric department [13,14]. The probability of serious bacterial infection without a definitive etiology is reported to be approximately 12% in the neonatal period and up to 9% between 1 and 3 months of age [15]. Diagnostic tests for differentiating severe bacterial infections from viral infections have long been the focus of several investigations [16]. Chest radiography has been used for diagnosing pneumonia. Urine and CSF samples have been used for the diagnosis of urinary tract infection and meningitis, respectively [17]. However, deciding the timing of LP for CSF sampling has been challenging [7]. For neonates with early-onset sepsis, the AAP recommends performing LP if the blood culture result is positive with clinical or laboratory findings strongly indicating bacterial sepsis or if the patients do not respond to antibiotic therapy [8]. Gajdos et al. [18] analyzed predictive factors of bacterial infection in febrile infants aged < 3 months and found that only an elevation in WBC with > 50% of neutrophils and an elevation in CRP levels > 20 mg/L could predict serious bacterial infection, with a negative predictive value of 93%. Pulliam et al. [1] demonstrated that CRP level was a better diagnostic tool than WBC and ANC for predicting serious bacterial infection in a group of febrile children aged between 1 and 36 months.

During infection or inflammation, the plasma pro-calcitonin (PCT) concentration is known to both increase and return to normal concentration more rapidly than the CRP level [19]. The PCT level was also observed to increase faster than the CRP level 6 hours after the onset of severe infection or inflammation [20]. Therefore, the PCT test has been considered a useful tool for early diagnosis of infection [21]. In other studies, PCT was found to be

a useful biomarker to distinguish between bacterial and viral meningitis [22]. Moreover, in Korea, several published studies have focused on the value of laboratory markers in discriminating serious bacterial infections, and Hur et al. [23] studied the diagnostic value of PCT and CRP simultaneously using blood samples from 1,270 patients with blood culture-positive sepsis. According to their report, the diagnostic utility of the PCT was better than that of CRP. However, in the case of diagnosing neonatal bacterial infection, the PCT test was found to be more expensive, with similar or better sensitivity than CRP and acceptable specificity [24]. Kim et al. [25] also reported that in febrile infants aged ≤6 months, there is no diagnostic value of measuring serum PCT concentration for determining bacterial infection. Since a PCT assay is more expensive than CRP level analysis and is not readily available in all facilities, only a few infants are analyzed for changes in the PCT level. In contrast, CRP can be determined in less than an hour using a small amount of blood and the CRP level test is not cost intensive. Hence, we determined a cut-off level for CRP for better diagnostic accuracy and ease of access to all patients.

Sturgeon et al. [7] suggested that it does not appear prudent to assign CRP cut-off values for consideration in LP for neonates because of its low sensitivity and specificity. They emphasized the importance of a multi-faceted decision-making process based on clinical assessment, microbiology results, as well as any blood test findings such as CRP level [7].

In this study, sex and age at diagnosis in the meningitis group did not significantly differ from those in the non-meningitis group. The main finding of this retrospective study was that CRP is a relatively valuable laboratory factor in the assessment of meningitis in febrile infants aged <3 months. As shown in Fig. 2, various cut-off levels of CRP had better sensitivity, specificity, PPV, and NPV than those of WBC or ANC. Our data also showed that different cut-off values of CRP levels had different diagnostic values (Table 3). We found that with assuming a cut-off CRP level of 10 mg/L, the sensitivity and specificity for predicting meningitis were both >70%, with a relatively high NPV >80%.

This study has some limitations that need to be considered while interpreting the results. First, this study was conducted using medical records from a single hospital; thus, our study population does not represent the whole population of infants in Korea. Second, we collected urine samples using urine bags rather than catheterization or bladder puncture, which could have increased the likelihood of contamination. Finally, a comparison between the bacterial meningitis group and the aseptic meningitis group could not be performed because there were only 3 cases of bacterial meningitis in this study cohort. Even with these limitations, this comparative analysis of laboratory markers for predicting meningitis in infants is significant in terms of its contribution to the literature.

In summary, this study showed that in the evaluation of young, febrile infants in the emergency department, CRP was a stronger independent predictor for meningitis than WBC or ANC. We suggest the use of CRP levels as a part of the evaluation for every febrile infant aged <3 months. CRP levels >10 mg/L suggest the presence of meningitis in febrile infants with greater accuracy. However, clinicians should keep in mind that a single laboratory marker indicates only the probability but never the certainty of the presence or absence of meningitis.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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