Heparin-Binding Protein in Cerebrospinal Fluid as a Biomarker for Bacterial Meningitis: A Study of Diagnostic Accuracy

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Objective: We aimed to evaluate the diagnostic accuracy of heparin-binding protein (HBP) in cerebrospinal fluid for the diagnosis of bacterial meningitis in patients with a suspected central nervous system infection.
Methods: This prospective multicenter cohort study determined the diagnostic accuracy of HBP in cerebrospinal fluid (CSF) for bacterial meningitis among a cohort of consecutive patients with a suspected central nervous infection. The final clinical diagnosis was considered the reference standard. The results were validated in a separate cohort.
Results: A total of 631 Dutch patients were evaluated for the current study, of which 73 (12%) had a final diagnosis of bacterial meningitis. For the differentiation of bacterial meningitis from all other disorders, diagnostic accuracy was high with an area under the curve (AUC) of 0.98 (95% confidence interval [CI] 0.96–1.00). With the proposed cutoff of 5.2 ng/ml, sensitivity was 97% with a specificity of 96%. In the population of patients with a CSF leukocyte count of 5-1,000/mm^3, the AUC was 0.96 (95% CI 0.87–1.00), outperforming CSF leukocytes (AUC 0.88 [95% CI 0.79–0.97]). Combining HBP with CSF C-reactive protein (CRP) significantly increased accuracy in this population and reached a 100% sensitivity (AUC 1.00 [95% CI 0.99–1.00], cutoff 0.07, sensitivity 100%, specificity 96%). These results remained robust in an external validation cohort of 120 Danish patients (AUC 0.97 [95% CI 0.93–1.00]).
Interpretation: HBP can correctly distinguish bacterial meningitis from other disorders. It can be of additional value to current diagnostics in cases where CSF leukocyte count is relatively low, particularly when combined with CSF CRP.

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Bacterial meningitis is a life-threatening disease and rapid diagnosis and treatment are essential for a good prognosis.[1] Cerebrospinal fluid (CSF) examination is the cornerstone of the diagnostic work-up in bacterial meningitis and is typically characterized by an elevated CSF leukocyte count, elevated CSF protein, and a decreased CSF to blood glucose ratio.[2] Yet, these CSF abnormalities can also be present in other central nervous system (CNS) infections such as viral meningitis or encephalitis and even in non-infectious CNS disorders, where an elevated CSF leukocyte count can be present in up to 50% of cases.[3] Additionally, not all patients with bacterial meningitis present with the typical CSF changes, and approximately 2% have completely normal CSF parameters at presentation.[2,4,5] A definite

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diagnosis of bacterial meningitis can be made through microbiological examination such as CSF culture or molecular-based diagnostics. However, the turnaround time for such investigations may be prolonged and the yield impaired by delayed lumbar puncture and administration of antibiotics. Hence, there is a continued need for novel ways to diagnose bacterial meningitis in a timely and accurate manner.

Heparin-binding protein (HBP), also known as azurocidin, is a protein that resides in the secretory vesicles of neutrophils from which it is released after neutrophil activation. Since it is a prefabricated protein, release occurs promptly after the activation of neutrophils and causes a rapid increase in HBP concentration. HBP has several functions in the inflammatory response after release into the bloodstream where it acts an attractant for more leukocytes and stimulates cytokine release.[6] Previous studies have investigated HBP as a potential biomarker for sepsis in plasma and found it to be correlated with the development of severe sepsis and septic shock in patients with fever and to outperform traditional biomarkers such as C-reactive protein (CRP), white blood cell count, procalcitonin and lactate.[7–9] This has demonstrated the potential of HBP as a marker in bacterial infections.

In this study, we evaluated the diagnostic accuracy of HBP in the CSF for the diagnosis of bacterial meningitis in patients with a suspected central nervous system infection.

Methods

Patient Inclusion and Reference Standard

For the derivation cohort, we used data and CSF from the I-PACE study (Improving Prognosis by using innovative methods to diAgnose Causes of Encephalitis). This study is an ongoing multicenter prospective cohort study in the Netherlands with the primary aim of enhancing diagnostic methods in central nervous system infections. The methods have been previously described elsewhere in detail.[10,11] In short, all adult patients (≥16 years of age) who were suspected of having a CNS infection and underwent CSF examination were eligible for inclusion. Exclusion criteria consisted of recent head trauma or neurosurgery within the past 3 months, as well as patients with a neurosurgical device in situ and patients who underwent a lumbar puncture at the outpatient clinic. Patients suitable for enrollment were identified during morning rounds or reported to the research team by their attending physicians. Written informed consent was obtained from all participants or their representatives. Information on clinical characteristics, laboratory and microbiological examination, final diagnosis, and outcome was collected in online case record form. The study adhered to Dutch privacy legislation and was approved by the biobank ethics committee of the Amsterdam UMC, location AMC, Amsterdam, The Netherlands (number BTC AMC2014_290). The final diagnosis for all recorded episodes was independently determined by 2 physicians (S.O., S.S.) and any discrepancies were addressed through consultation of a third physician (M.B.) specialized in neuroinfectious and inflammatory diseases. Diagnosis was based on all available data and included clinical characteristics, laboratory features, CSF parameters, imaging, and microbiological results. This categorization was considered the reference standard to reflect clinical practice. The procedures and reasoning of this categorization have been previously described.[3]

We performed external validation of our results using patients included in the Danish Study Group of Infections of the Brain (DASGIB) cohort. Methods of this study have been previously described in detail.[12] In short, the DASGIB is a nationwide, prospective study of all adults (≥18 years of age) with a community-acquired CNS infection managed by departments of infectious diseases in Denmark. The reference standard is based on results of the lumbar puncture, clinical presentation, microbiological investigations, and cranial imaging.

Sample Collection and Index Test

When available, leftover CSF obtained during the diagnostic lumbar puncture was stored in the I-PACE biobank at −80 °C until further analysis. Patients were included in the current study if there was sufficient CSF (30 µl) present for HBP measurements. The index test consisted of the HBP concentration measured in CSF. Concentrations were measured according to manufacturer's instructions using the Human Azurocidin/CAP37/HBP ELISA kit (ThermoFisher Scientific). When HBP was not detectable above the lower limit of detection, the concentration of the lower limit of detection was appointed for further analyses. For samples where HBP was over the upper limit of detection, the highest extrapolated concentration in the cohort was appointed. For a previous study on biomarkers in CSF, we measured 12 cytokines, chemokines, and acute phase reactants (CRP, procalcitonin, CXCL-10, macrophage-derived chemokine [MDC], interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor alpha [TNF-α], migration inhibitory factor [MIF], IL-1RA, CXCL-13, IL-1β) in patients from the I-PACE cohort. Methods of these measurements were previously described in detail.[13]

Statistical Analysis

Statistical analyses were performed using SPSS statistical software, version 28 (SPSS, Inc), and R, version 4.2.1. Baseline characteristics were summarized using descriptive statistics, presenting medians and interquartile ranges (IQR). Diagnostic accuracy was evaluated by the calculation of sensitivity, specificity, as well as the area under the curve (AUC) of the receiver operator characteristics (ROC) curve. An AUC value of above 0.90 was considered as excellent discrimination, between 0.80 and 0.90 as good discrimination, 0.70–0.80 as fair discrimination,

0.60–0.70 as poor discrimination, and <0.60 signified no discrimination. We compared the diagnostic accuracy of HBP for the diagnosis of bacterial meningitis versus all other diagnoses, as well as versus viral CNS infections specifically. We performed these analyses in the whole cohort, and in the population of patients with a CSF leukocyte count of 5–1,000/mm^3, where diagnostic uncertainty is highest. We conducted multivariable LASSO regression analyses to assess the predictive value of HBP in addition to CSF leukocytes and previously measured inflammatory markers. Due to the explorative nature of the current study, no power calculation could be performed. This study was reported according to the Standards for Reporting Diagnostic accuracy studies (STARD) checklist.

Results

From 2017 to 2023, we included 974 episodes in the I-PACE study (Fig 1). Sufficient residual CSF was available in 755 of 974 episodes (76%) and HBP concentration was technically successfully measured in 631 of 755 samples (84%). The median age in the total cohort was 55 years (IQR 38–68) and 319 of 631 (51%) episodes occurred in females (Table 1, Table S1). Headache was the most common symptom upon presentation and was observed in 311 out of 517 (60%) episodes, followed by an altered mental status (defined as a Glasgow Coma Scale score ≤ 14) in 292 out of 625 (47%) episodes.[14] A fever of >38.0 °C was documented in 207 out of 610 (34%) episodes and neck stiffness was observed in 95 of 418 (23%). The classic bacterial meningitis triad, consisting of an altered mental status, fever, and neck stiffness, was present in 38 out of 406 episodes (9%). Median blood leukocyte count and CRP were 9.2 × 10^9/L (IQR 6.4–13.9) and 18 mg/L (IQR 3–75), respectively. A lumbar puncture was performed in all episodes. Median CSF leukocyte count in the whole cohort was 3/mm^3 (1–35) and 276 of 630 (44%) episodes showed an elevated CSF leukocyte count of ≥5/mm^3.

A final diagnosis of a CNS infection was made in 165 of 631 episodes (26%) of which 73 (12%) were diagnosed with bacterial meningitis (Fig 1). Of all bacterial meningitis episodes, in 47 of 73 (64%), the diagnosis was confirmed by detection of the pathogen in the CSF through CSF culture, polymerase chain reaction (PCR), or Gram-staining. The most common causative pathogen was *Streptococcus pneumoniae* (n = 36), followed by *Neisseria meningitidis* (n = 5), *Streptococcus pyogenes* (n = 3), *Listeria monocytogenes* (n = 2), and *Haemophilus influenzae* (n = 1). Furthermore, 70 of 631 (11%) episodes were diagnosed with a viral CNS infection, 22 (4%) with another CNS infection, 66 (10%) with CNS inflammatory disease, 243 (39%) with other neurological disease, 134 (21%) with systemic infection, and 23 (4%) with a noninfectious, non-neurological disorder. Mortality in all episodes was 8% (53 of 631 episodes), and 46% (288 of 631) had a unfavorable outcome, defined as scores 1–4 on the Glasgow Outcome Scale score (Table 1, Table S1).[15]

HBP Measurements

Of all HBP measurements performed, in 525 out of 631 (83%) HBP was not detectable above the lower limit of detection of 0.4 ng/ml and in 2 out of 631 (0.3%) episodes the concentration was above the upper limit of detection. HBP was detectable above 0.4 ng/ml in 106 out of 631 (17%) episodes, of which 71 were episodes of bacterial meningitis. Of all bacterial meningitis episodes, HBP was detectable in 71 of 73 (97%; Fig 2). In the 2 bacterial meningitis patients where HBP could not be detected, CSF

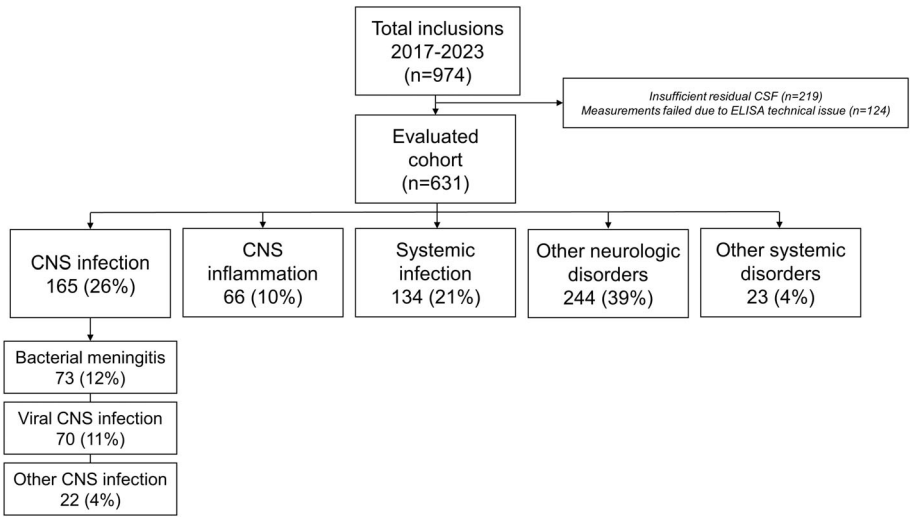

FIGURE 1: Flowchart of diagnostic categories. CNS = central nervous system; ELISA = enzyme-linked immunosorbent assay.

TABLE 1. Baseline Characteristics of 631 Adults with Suspected Central Nervous System Infection

Parameter	All (n = 631)	Bacterial meningitis (n = 73)	All other diagnosis (n = 558)
Age (years)	55 (38–68)	55 (43–68)	56 (37–68)
Female sex	319/631 (51%)	37/73 (51%)	282/558 (51%)
Clinical presentation			
Headache	311/517 (60%)	50/55 (91%)	261/462 (56%)
Altered mental status (GCS ≤ 14)	292/625 (47%)	57/73 (78%)	235/552 (43%)
Fever (>38.0 °C)	207/610 (34%)	47/73 (64%)	160/537 (30%)
Neck stiffness	95/418 (23%)	42/61 (69%)	53/357 (15%)
Seizures	94/586 (16%)	6/67 (9%)	88/519 (17%)
Bacterial meningitis triad	38/406 (9%)	25/70 (36%)	13/345 (4%)
Blood chemistry			
CRP (mg/L)	18 (3–75)	157 (78–261)	11 (2–52)
Leukocytes (10^9/L)	9.2 (6.4–13.9)	19.9 (13.3–24.7)	8.5 (6.1–12.1)
CSF examination			
CSF leukocytes (per mm^3)	3 (1–35)	3,122 (1,233-7,157)	2 (1–10)
CSF leukocytes ≥5/mm^3	276/630 (44%)	73/73 (100%)	203/557 (36%)
CSF leukocytes ≥100/mm^3	121/630 (19%)	71/73 (97%)	50/557 (9%)
CSF protein (g/L)	0.47 (0.32–0.90)	3.35 (1.47–5.71)	0.42 (0.31–0.68)
Outcome			
Death	53/631 (8%)	8/73 (11%)	45/558 (8%)
Unfavorable outcome (GOS 1–4)	288/631 (46%)	24/73 (33%)	264/589 (47%)

Note: Data are presented as n/N (%) or median (interquartile ranges). CRP was known for 570 episodes, Blood leukocytes was known for 613 episodes, CSF leukocytes was known for 630 episodes, CSF protein was known for 624 episodes.
Abbreviations: CRP = C-reactive protein; CSF = cerebrospinal fluid; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale.

cultures were negative in both cases. In 35 non-bacterial meningitis episodes, HBP was detectable. These episodes consisted of 17 CNS infections (13 viral CNS infections, 4 other CNS infections), 3 CNS inflammatory disorders, 6 systemic infections, and 9 other neurological disorders. For bacterial meningitis, the median HBP concentration was 84.3 ng/ml (44.6–152.1; Fig 2). For all other diagnosis the median concentration was 0.4 ng/ml (IQR 0.4–0.4). HBP concentration was strongly correlated with CSF leukocyte count (ρ = 0.74 [95% CI 0.70–0.78], $p < 0.001$, Fig S1).

In 52 of 73 (71%) bacterial meningitis cases, time between treatment initiation and the lumber puncture was reported. In 32 of 52 (62%), antibiotic treatment was started prior to the lumbar puncture, with a median time of 1.6 hours (IQR 1.3–4.9). Timing of the treatment initiation in relation to the lumbar puncture was not associated with a lower HBP concentration in CSF (r = 0.00 [95% CI −0.27–0.27, $p = 0.99$], Fig S2).

HBP Diagnostic Accuracy

The AUC of HBP for differentiating bacterial meningitis from all other diagnosis was 0.98 (95% CI 0.96–1.00), which was similar to CSF leukocyte count with an AUC of 0.99 (95% CI 0.98–1.00) (Table 2, Fig 3A). The Youden's index was calculated at a cutoff of 5.2 ng/ml, which resulted in a sensitivity of 97% (95% CI 90–100) and specificity of 96% (95% CI 94–98; Table 2). There were 2 bacterial meningitis cases with a leukocyte count below 100/mm^3. In both cases, HBP concentration was above the Youden's index cutoff of 5.2 ng/ml. For distinguishing

bacterial meningitis from viral CNS infections, the AUC of HBP was 0.97 (95% CI 0.95–1.00, Fig 3B).

In patients with a CSF leukocyte count between 5 to 1,000/mm^3, including 14 bacterial meningitis cases (of which 10 [71%] had a positive CSF culture), the AUC for discriminating bacterial meningitis from all other diagnosis was 0.96 (95% CI 0.87–1.00). HBP outperformed CSF leukocyte count in this population, which showed an AUC of 0.88 (95% CI 0.79–0.97; Table 3, Fig 3C). With the cutoff of 5.2 ng/ml, sensitivity was 93% (95% CI 66–100) with a specificity of 94% (95% CI 90–97; Table 3). For the differentiation of bacterial meningitis from viral CNS infections, the AUC value was 0.95 (0.86–1.00; Fig 3D). Diagnostic accuracy of HBP was slightly better when calculated in the population of strictly CSF microbiologically confirmed bacterial meningitis cases (47 of 73 cases, Table S2).

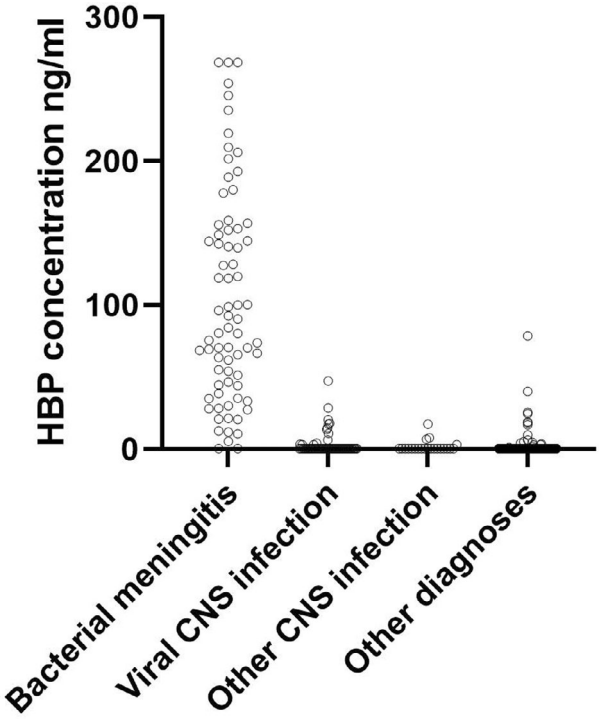

FIGURE 2: Heparin-binding protein (HBP) concentrations. CNS = central nervous system.

Regression Analysis

Additional data on concentrations of additional inflammatory biomarkers (CRP, procalcitonin, CXCL-10, MDC, IL-6, IL-8, IL-10, TNF-α, MIF, IL-1RA, CXCL-13, IL-1β) were available in 554 of 631 episodes (88%). We performed LASSO regression to assess whether combining HBP, CSF leukocytes, and other inflammatory markers would increase diagnostic accuracy. For differentiating bacterial meningitis from all other diseases in the whole cohort, a combination of HBP, CSF leukocytes, and CRP was selected and yielded an AUC of 1.00 (95% CI 0.99–1.00, Fig S3). The Youden's index of the combined model was determined at 0.14, resulting in a sensitivity of 100% and a specificity of 98%. For distinguishing bacterial meningitis from viral CNS infection in the whole cohort, selecting HBP, CSF leukocytes, and CRP resulted in an AUC of 0.98 (95% CI 0.97–1.00, Fig S3). In the population of patients with 5-1,000/mm^3 CSF leukocytes, the variables CRP and HBP were selected with an AUC of 1.00 (95% CI 0.99–1.00, Fig S3). The Youden's index in this subpopulation of the combined model was determined at 0.07, resulting in a sensitivity of 100% and a specificity of 96%. In the subpopulation of patients with 5–1,000/mm^3 CSF leukocytes, the combination of HBP and CRP performed the best for the differentiation between bacterial and viral CNS infections (AUC 0.99 [95% CI 0.98–1.99], Fig S3). In all regression models, the combined model outperformed individual variables in diagnosing bacterial meningitis.

Validation Cohort

We validated our results in 120 patients from the DASGIB study, which included 34 bacterial meningitis patients,

TABLE 2. Test Characteristics of HBP and CSF Leukocyte Count for Differentiating Bacterial Meningitis from Other Diseases Among 631 Adults with Suspected Central Nervous System Infections

Parameter		Cutoff value	Sensitivity	Specificity
HBP AUC = 0.98 (0.96–1.00)	Youden's index	5.2 ng/mL	97%	96%
	100% sensitivity	0 ng/mL	100%	0%
	100% specificity	79.5 ng/mL	53%	100%
CSF leukocyte count AUC = 0.99 (0.98–1.00)	100% sensitivity	11.5 cells/mm^3	100%	77%
	100% specificity	2,960 cells/mm^3	52%	100%

Abbreviations: AUC = area under the curve; CSF = cerebrospinal fluid; HBP = heparin-binding protein.

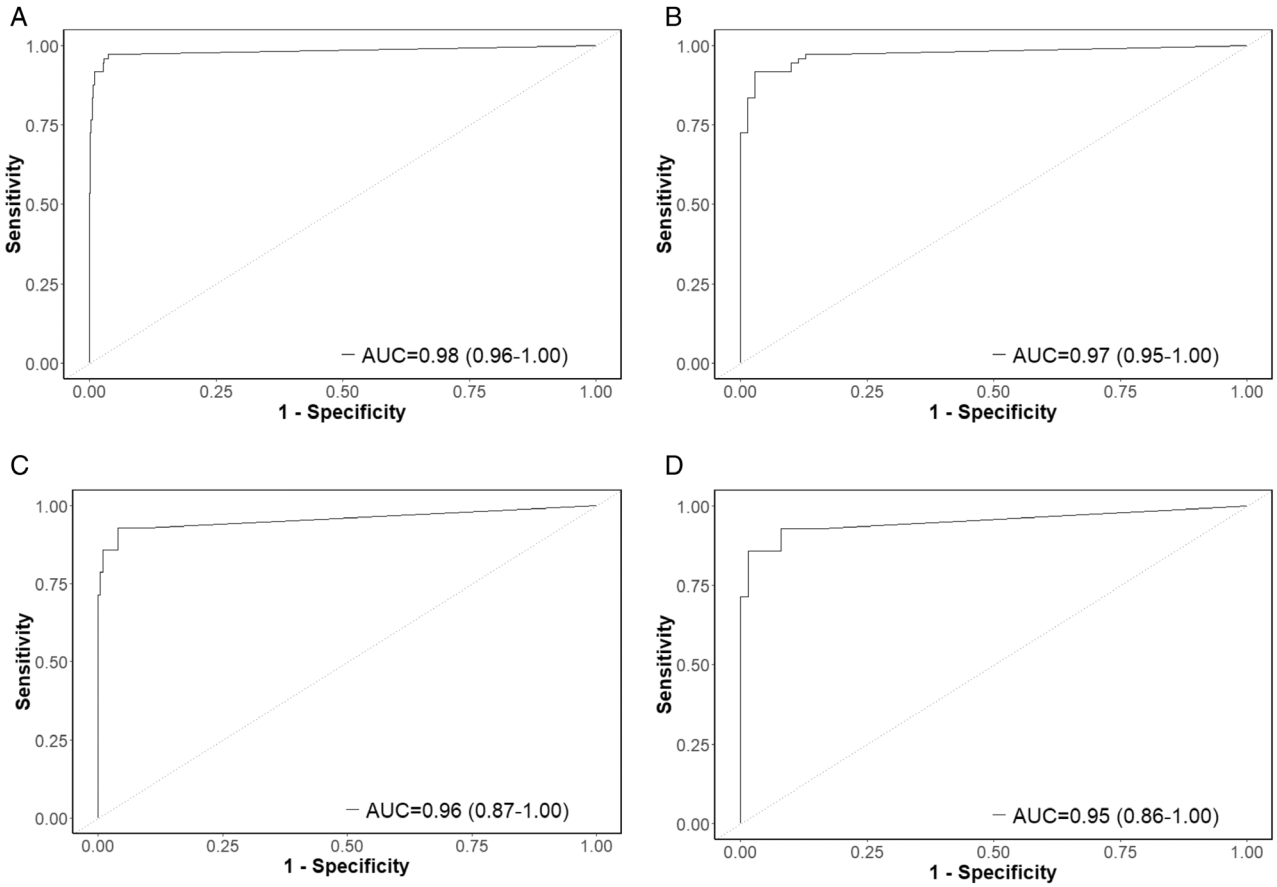

FIGURE 3: Receiver operating curves (ROC) of heparin-binding protein (HBP) for differentiating bacterial meningitis from other conditions overall and in subgroups of patients with suspected central nervous system infection. (A) ROC curve of HBP for differentiating bacterial meningitis from all other diseases in the whole population. (B) ROC curve of HBP for differentiating bacterial meningitis from all other diseases in patients with a cerebrospinal fluid (CSF) leukocyte count 5–1,000/mm^3. (C) ROC curve of HBP for differentiating bacterial meningitis from viral central nervous system (CNS) infections in the whole population. (D) ROC curve of HBP for differentiating bacterial meningitis from viral CNS infections in patients with a CSF leukocyte count 5–1,000/mm^3. AUC = area under the curve.

TABLE 3. Test Characteristics of HBP and CSF Leukocyte Count for Differentiating Bacterial Meningitis from Other Diseases in 212 Patients with a CSF Leukocyte Count 5–1,000/mm^3

Parameter		Cutoff value	Sensitivity	Specificity
HBP AUC = 0.96 (0.87–1.00)	Youden's index	5.2 ng/mL	93%	94%
	100% sensitivity	0 ng/mL	100%	0%
	100% specificity	31.0 ng/mL	71%	100%
CSF leukocyte count AUC = 0.88 (0.79–0.97)	100% sensitivity	11.5 cells/mm^3	100%	38%
	100% specificity	939.5 cells/mm^3	7%	100%

Abbreviations: AUC = area under the curve; CSF = cerebrospinal fluid; HBP = heparin-binding protein.

69 patients with a viral CNS infection, and 17 patients initially suspected of having a CNS infection who received final diagnosis of a headache syndrome. The clinical characteristics of the bacterial meningitis cases were comparable to those in the derivation cohort (Table S3) For differentiating bacterial meningitis from both viral CNS infections and controls, the AUC of HBP alone was 0.97 (95% CI 0.93–1.00). Using the proposed cutoff of 5.2 ng/ml, the corresponding sensitivity and specificity were 97% and 78%, respectively. The combined model of HBP, CRP,

and CSF leukocytes yielded an AUC of 0.99 (95% CI 0.98–1.00) in the validation cohort.

Discussion

HBP has a high diagnostic accuracy for predicting bacterial meningitis. In the whole population of patients suspected of a central nervous system infection, HBP showed similar performance to CSF leukocyte count (AUC 0.98 and AUC 0.99, respectively), limiting the additional value to current diagnostics. However, when CSF leukocyte count is relatively low, between 5 and 1,000 cells per mm^3, differentiation between bacterial meningitis and other diagnosis may be particularly challenging. In this subgroup of patients, we found that HBP concentration outperformed CSF leukocyte count, especially for distinguishing bacterial meningitis from viral CNS infection (AUC 0.96 and 0.95 for HBP, and AUC 0.88 and 0.79 for CSF leukocyte count) and can therefore be of incremental value when CSF leukocyte count is inconclusive. Additionally, HBP concentrations were not significantly influenced by antibiotic treatment prior to the lumbar puncture. Lastly, combining HBP with CRP increased accuracy significantly. These results remained robust after external validation.

A 2024 meta-analysis on the utility of HBP in diagnosing bacterial infections included 7 studies on HBP in CSF.[16] Cutoff values differed per study, ranging from 2.47 to 56.7 ng/ml. A pooled sensitivity of 96% (95% CI 0.85–0.99) with a specificity of 95% (95% CI 0.89–0.97) was reported, which is in line to our results. These previous studies have only included confirmed cases of bacterial or viral meningitis and controls, which may reduce the generalizability for clinical practice. An important strength of our study is that we measured HBP in a clinically relevant cohort, in which the whole spectrum of patients with a suspected CNS infection is included.

In our previous study on biomarkers in CSF for the diagnosis of CNS infections and bacterial meningitis, we found a high diagnostic accuracy of CRP, IL-6, and IL-1β. These parameters combined provided excellent discrimination between bacterial meningitis and other disorders, as well as viral CNS infections. This prompted validation of CRP in CSF as a marker for bacterial meningitis, utilizing local equipment already used for routine blood CRP measurements. We demonstrated that CRP in CSF measured using this assay can correctly identify bacterial meningitis, and we now routinely measure CRP in CSF as a marker for bacterial meningitis in our local clinical practice. The current study indicates that combining HBP with CRP increases accuracy even further. While HBP alone cannot achieve 100% sensitivity in diagnosing bacterial meningitis, combining it with CRP allows for 100% sensitivity while maintaining high specificity, especially in cases where CSF leukocyte count is inconclusive.

Our study has several limitations. First, we only included patients from the European population in the current study. Additional validation in other populations with different epidemiology is needed to ascertain global generalizability. Second, due to the exploratory nature of this study, we were unable to conduct a power calculation. Although we performed external validation of our results, a predefined samples size might have contributed to greater statistical robustness, especially in the subgroup analyses.

Furthermore, we did not measure HBP in blood and could therefore not compare concentrations in blood to those in CSF. Since a lumbar puncture is an invasive procedure, a blood test for diagnosing bacterial meningitis would be of great value. However, since previous research has shown that inflammatory markers in blood cannot differentiate bacterial meningitis from other disorders, we expect that HBP concentration in blood will not be of additional value in diagnosing bacterial meningitis.[13] While it has been found that 2% of bacterial meningitis patients present with a normal CSF leukocyte count, in our cohort there were no cases with a CSF leukocyte count below 5/mm^3.[4,5] There were 2 bacterial meningitis patients with a CSF leukocyte count below 100/mm^3, which both had an elevated HBP concentration. This indicates that HBP is of value in cases where CSF leukocyte count is relatively low. Last, our samples underwent at least 1 freeze–thaw cycle for this experiment, and it is uncertain whether this may have affected results. One study on HBP measurements in serum found that HBP concentrations remained stable across multiple freeze–thaw cycles.[17] Although not directly applicable to CSF, this suggests that the potential influence on our results is likely low.

In conclusion, measurement of HBP in CSF may be a helpful marker for the diagnosis of bacterial meningitis in adults. In the whole population of patients with a suspected CNS infection, the diagnostic accuracy of HBP concentration is similar to CSF leukocytes and incremental value is therefore limited. However, in cases where CSF leukocyte count is relatively low, HBP can aid in distinguishing bacterial meningitis from other disorders, especially when combined with CSF CRP.

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Author Contributions

S.O., Dvd.B., and M.B. contributed to the conception and design of the study; S.O., S.S., A.C., J.B., and H.N. contributed to the acquisition and analysis of data; S.O. contributed to drafting the text and preparing the figures. All authors read and approved the final manuscript.

Potential Conflict of interest

All authors declare no competing interests.

Data Availability

Data protection regulations in the Netherlands do not allow for sharing of individual participant data. Datasets with selected aggregated data will be shared upon request. Proposals can be directed to ipace@amsterdamumc.nl.

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