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Original Article

A risk score for identifying patients at a low risk of bacterial meningitis amongst adults with cerebrospinal fluid leucocytosis and a negative gram stain result: a derivation and validation study

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ABSTRACT

Objectives: We aimed to derive and validate a risk score to differentiate patients with bacterial meningitis from those with viral meningitis or encephalitis amongst patients presenting with cerebrospinal fluid (CSF) leucocytosis and a negative Gram staining result.

Methods: We included adults with bacterial and viral meningitis or encephalitis presenting with CSF leukocyte counts of >10 per mm^3 and a negative Gram staining result from cohorts in Houston, Texas (2004–2019), and the Netherlands (2012–2021). Derivation and the first validation were performed in the American patients and further validation in the Dutch patients.

Results: Derivation was performed in 109 American patients with bacterial meningitis (median age, 56 years; interquartile range [IQR], 46–66 years; 46% women) and 194 with viral meningitis or encephalitis (median age, 46 years; IQR, 33–60 years; 53% women). Serum leukocyte counts of >10.0 × 10^9/L, CSF leukocyte counts of >2000 per mm^3, granulocyte counts of >1180 per mm^3, protein levels of >2.2 g/L, glucose levels of <1.9 mmol/L and fever on admission were included in the risk score, which was dichotomized into 'low risk' (0 present) and 'high risk' (>0 present). The first validation showed a sensitivity of 100% (95% CI, 96.6–100) and specificity of 34.0% (95% CI, 27.4–41.2). Further validation in 262 Dutch patients with bacterial meningitis (median age, 57 years; IQR 44–70 years; 45% women) and 68 with viral meningitis (median age, 34 years; IQR, 28–45 years; 60% women) showed a sensitivity of 99.6% (95% CI, 97.9–100) and specificity of 41.2% (95% CI, 29.4–53.7).

Conclusions: Our risk score may be able to rule out bacterial meningitis amongst patients presenting with CSF leucocytosis and a negative Gram staining result. However, it needs prospective testing prior to clinical implementation. **Thijs M. van Soest, Clin Microbiol Infect 2022;▪:1**

Introduction

In most patients with suspected central nervous system (CNS) infections, cerebrospinal fluid (CSF) examination is indicated because clinical characteristics fail to differentiate between neurologic infections and other diagnoses. In a prospective, single-centre study, including 363 episodes of suspected CNS infection, CSF leucocytosis differentiated best between bacterial meningitis and other diagnoses (area under the curve [AUC], 0.95) [1]. Gram staining of the CSF can rapidly identify bacterial meningitis with high specificity [2,3]. However, when the Gram stain does not show bacteria, the majority of patients with a suspected CNS infection and CSF leucocytosis are admitted to the hospital to be treated empirically, leading to overtreatment [4,5]. A risk score that could accurately exclude bacterial meningitis would be helpful in

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deciding who can be safely discharged for home without further intravenous antibiotics and dexamethasone treatment.

Clinical risk scores have assessed the likelihood of bacterial meningitis in patients presenting with suspected CNS infections. However, in a systematic review, validation of 17 of these scores in adults showed that none performed well enough to recommend routine use in patient care [6]. We derived and validated a new risk score to differentiate patients with bacterial meningitis from patients with viral meningitis or encephalitis amongst those with leucocytosis and a negative Gram staining result.

Methods

We assembled a derivation cohort and a validation cohort. The derivation cohort consisted of episodes of bacterial meningitis, viral meningitis, or viral encephalitis in the United States. The validation cohort consisted of episodes of bacterial meningitis or viral meningitis in the Netherlands. In both the derivation and validation cohorts, only episodes with >10 CSF leukocytes per cubic millimetre and a negative Gram staining result were included. We excluded episodes of health-care-associated ventriculitis and meningitis, as defined by the Infectious Diseases Society of America guidelines [7].

Derivation cohort (United States)

For the derivation cohort, patients were retrospectively identified from the Memorial Hermann Health System and Lyndon B. Johnson hospital in Houston, Texas, all secondary and tertiary care facilities. Consecutive adult patients (aged >17 years) with bacterial meningitis, viral meningitis, or encephalitis were retrospectively identified from two electronic medical record systems, one covering December 2004 to May 2019 for bacterial meningitis cases and the other covering December 2015 and May 2019 for cases of viral meningitis or encephalitis. The requirement to obtain informed consent was waived by the institutional review boards because of the retrospective nature of the study.

Bacterial meningitis episodes were included based on positive CSF bacterial culture results, a positive Gram stain result, or positive blood culture results with a common causative pathogen of community-acquired bacterial meningitis, combined with >10 leukocytes in the CSF [8]. The case definition of viral meningitis or encephalitis was a patient presenting with a clinical syndrome meeting the diagnosis of encephalitis [9] or aseptic meningitis [10] with an attributable microbiologic aetiology, defined as detectable genetic material in the CSF by specified PCR using commercially available platforms at each institution for cytomegalovirus, herpes simplex virus (HSV), enterovirus, and varicella zoster virus or detectable West Nile virus IgM antibody in the CSF or serum for West Nile virus. Multiplex or universal PCRs were not used during the study period.

Validation cohort (the Netherlands)

Three prospective clinical cohorts, MeninGene, PACEM and I-PACE, were used to assemble the validation cohort. The MeninGene study is a nationwide study that prospectively included patients aged ≥16 years with community-acquired bacterial meningitis at 88 secondary and tertiary care facilities in the Netherlands. Patients were included following a daily update, including the name of the hospital and treating physician, by the Netherlands Reference Laboratory for Bacterial Meningitis, which receives approximately 85% of all CSF isolates of patients with bacterial meningitis [11]. Detailed inclusion procedures have been discussed previously [12]. In the present study, patients consecutively included between January 2012 and July 2021 were evaluated. PACEM was a single-centre study that included patients between September 2012 and February 2015 [1]. The I-PACE study is an on-going, multi-centre, prospective study at 11 secondary and tertiary care facilities. For both the studies, patients aged ≥16 years were included if they had undergone a lumbar puncture following suspicion of a CNS infection. Patients were identified during morning rounds or reported to the investigators by the treating physician. Final diagnoses were reported by the treating physician. If there was no consensus on the final diagnosis, two investigators independently classified the diagnoses based on available clinical, laboratory and follow-up data. In the present study, patients included in the I-PACE study between September 2017 and December 2020 were analysed.

For the validation cohort, bacterial meningitis was defined based on a bacterial pathogen identified in the CSF, a positive blood culture result combined with >10 leukocytes per cubic millimetre in the CSF or CSF results indicative of bacterial meningitis according to the criteria defined by Spanos et al. [8,13]. The episodes were classified as viral meningitis if there was microbiologic evidence based on PCR or other microbiologic tests in the CSF [1] or when the treating physician or the two investigators classified the diagnosis as viral meningitis. For all the studies, written informed consent was obtained from all included patients or legal representatives after receiving written information. Local medical ethics committees approved all the involved studies.

Procedures and definitions

Neurologic, blood, and CSF examinations were routinely performed on admission according to the hospital protocols. Microbiologic testing was required to be included in the cohorts, and the exact tests were performed at the discretion of the treating physician.

Analysis

The outcome predicted by our risk score was the diagnosis of bacterial meningitis, which was defined as previously described. The risk score was derived using a bivariate analysis of possible predictors of the diagnosis of bacterial meningitis available on admission, which consisted of age, medical history, including infection with the human immunodeficiency virus, headache, nausea, neck stiffness, fever, seizures, Glasgow Coma Scale scores of <15, serum leukocyte counts of >10.0 × 10^9/L and the criteria defined by Spanos et al. [13], including CSF leukocyte counts of >2000 per mm^3, CSF granulocyte counts of >1180 per mm^3, CSF glucose levels of <1.9 mmol/L and CSF protein levels of >2.20 g/L. Variables that were clinically plausible and significantly associated with the diagnosis of bacterial meningitis were included in the risk score. One point could be scored for every variable. Subsequently, the risk score was dichotomized into 'low risk' (0 points) and 'high risk' (>0 points) for bacterial meningitis. The first validation was performed in the U.S. cohort, and subsequently, a broad geographic validation study was performed in the Dutch cohort. Patients were excluded when data regarding one or more of the risk score items were missing and no points were scored for the other risk score items for which data were available.

The AUC of the receiver operating characteristic (ROC) curve was calculated to evaluate the diagnostic accuracy of the risk score, with 95% CIs. The sensitivities and specificities were calculated for the dichotomized risk score for bacterial meningitis. All analyses were performed using R, version 4.0.3. The positive and negative likelihood ratios and 95% CIs were calculated using the 'bootLR' package

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[14]. The values are displayed as median with interquartile range (IQR) or absolute number with percentage. Continuous variables were compared using the Mann-Whitney *U* test, and categorical data were compared using the Fisher exact test. A p value of <0.05 was considered statistically significant. No formal power calculation was performed; however, a convenience sample was used from available cohorts.

Results

Derivation cohort (United States)

A total of 202 episodes of bacterial meningitis were identified using the medical records from 2004 to 2019, of which 109 (54%) had a negative CSF Gram staining result and >10 CSF leukocytes per cubic millimetre. In these 109 episodes, the median age of the patients was 56 years (IQR, 46–66 years), and 50 (46%) were women (Table 1). The most common causative pathogens were *Streptococcus pneumoniae* in 75 episodes (69%), *Staphylococcus aureus* in 11 (10%) and *Haemophilus influenzae* in 6 (6%; Table S1). CSF cultures yielded positive results in 46 out of the 109 episodes (42%).

In total, 214 cases of viral meningitis or encephalitis were identified between 2015 and 2019 amongst 214 episodes, of which 194 (91%) had >10 CSF leukocytes per cubic millimetre. The median age of the patients was 46 years (IQR, 33–60 years), and 53% were women (Table 1). The most common viral aetiology was HSV (45%). All the viral and bacterial pathogens are listed in Table S1.

In the bivariate analysis, age, headache, nausea, neck stiffness, fever, altered mental status (defined as a Glasgow Coma Scale score of <15), serum leukocyte counts of >10.0 × 10^9/L and CSF results indicative of bacterial meningitis according to the criteria defined by Spanos et al. [13], consisting of CSF leukocyte counts of >2000 per mm^3, CSF granulocyte counts of >1180 per mm^3, CSF glucose levels of <1.9 mmol/L and CSF protein levels of >2.20 g/L, showed significant differences between bacterial and viral meningitis (Table 1). Fever, serum leukocyte counts of >10.0 × 10^9/L and the CSF results according to the criteria defined by Spanos et al. [13] were selected to be included in the risk score (maximum 6 points; Table 2). Fig. S1 shows the added value of each variable by selecting the most common variable in patients with bacterial meningitis consecutively.

The ROC curve for the risk score (Fig. 1(a)) showed an AUC of 0.92 (95% CI, 0.89–0.95). None of the bacterial meningitis episodes had a 'low-risk' score (sensitivity, 100%; 95% CI, 96.67–100), and the negative likelihood ratio was 0.00 (95% CI, 0.00–0.076). Out of 237 patients with a 'high-risk' score, 109 (46%) had bacterial meningitis (specificity, 34.02%; 95% CI, 27.39–41.15). The positive likelihood ratio was 1.52 (95% CI, 1.37–1.68).

Validation cohort (the Netherlands)

In the Netherlands, 269 individual bacterial meningitis episodes with CSF leucocytosis and a negative Gram staining result were identified. Three episodes of listerial meningitis were excluded because of missing data necessary for risk categorization. In one episode, data regarding only fever were missing; in another, data regarding fever, CSF protein level and CSF glucose level were missing; and in the third episode, data regarding CSF protein and glucose levels were missing. This resulted in 266 episodes: 230 from the MeninGene cohort and 36 from the PACEM and I-PACE cohorts (Fig. S2). The median age of the patients was 57 years (IQR, 44–70 years), and 45% of the episodes occurred in female patients (Table 3). The most common pathogens were *S. pneumoniae*, *N. meningitidis* and *L. monocytogenes* in 77 episodes (29%), 35 (13%)

Table 2
Risk score

Variable	Number of points (total = 6)
Fever (≥38.0°C)	1
Serum leukocyte count > 10 × 10^9/L	1
CSF leukocyte count > 2000/mm^3	1
CSF granulocyte count > 1180/mm^3	1
CSF glucose level < 1.9 mmol/L	1
CSF protein concentration > 2.20 g/L	1

A risk score of >0 point indicated a high risk. CSF, cerebrospinal fluid.

Table 1
Characteristics of the U.S. derivation cohort

Characteristic	Bacterial meningitis *N* = 109	Viral meningitis *N* = 194	p value
Age (y)	56 (46–66)	46 (33–60)	<0.001
Female sex	50/109 (46%)	103/194 (53%)	0.23
Ethnic group			<0.001
White	38/99 (38%)	98/188 (52%)	
African American	34/99 (34%)	89/188 (47%)	
Hispanic	25/99 (25%)	1/188 (1%)	
Asian	2/99 (2%)	0/188 (0%)	
HIV	9/109 (8%)	15/194 (8%)	>0.99
Headache	63/109 (58%)	142/187 (76%)	0.002
Nausea	40/109 (37%)	112/189 (59%)	<0.001
Neck stiffness	31/109 (28%)	76/183 (42%)	0.033
Fever (≥38.0°C)	78/109 (72%)	101/194 (52%)	0.001
Seizures	13/109 (12%)	21/194 (11%)	0.85
GCS score < 15	63/109 (58%)	46/194 (24%)	<0.001
Serum leukocytes (× 109/L)	15.1 (10.4–21.9)	8.4 (6.5–11.0)	<0.001
>10.0	86/109 (79%)	60/194 (31%)	<0.001
CSF leukocytes (cells/mm3)	1580 (352–4900)	161 (65–324)	<0.001
>2000	45/109 (41%)	2/194 (1%)	<0.001
CSF granulocytes (cells/mm3)	1254 (253–4500)	6 (0–31)	<0.001
>1180	57/109 (53%)	1/194 (1%)	<0.001
CSF glucose (mmol/L)	1.7 (0.3–3.0)	3.2 (2.8–3.6)	<0.001
<1.9	59/109 (54%)	2/194 (1%)	<0.001
CSF protein (g/L)	2.81 (1.36–4.60)	0.88 (0.58–1.20)	<0.001
>2.2	69/107 (64%)	7/194 (4%)	<0.001

CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; GCS, Glasgow Coma Scale.

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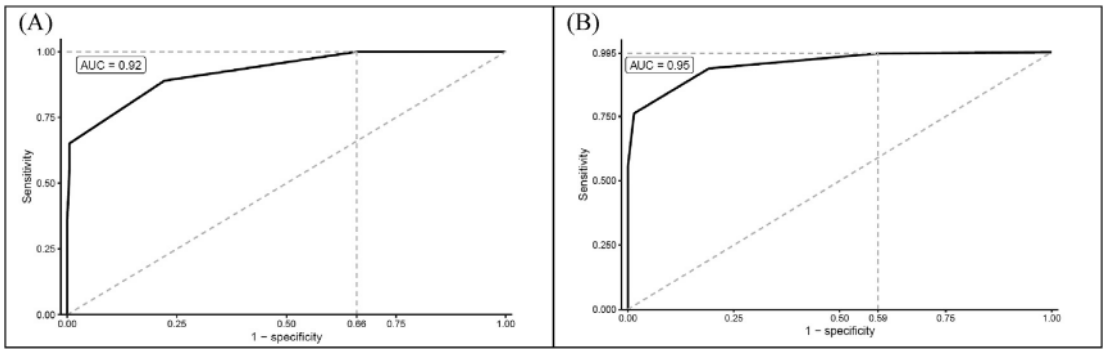

Fig. 1. Receiver operating characteristic (ROC) curves of the risk score. (a) ROC curve for the diagnosis of bacterial meningitis in the U.S. cohort. The horizontal and vertical lines represent a sensitivity of 100% and its corresponding specificity (34%). (b) ROC curve for the diagnosis of bacterial meningitis in the Dutch cohort based on 246 episodes for which all variables were non-missing. The horizontal and vertical lines represent a sensitivity of 99.5% and its corresponding specificity (41%).

Table 3
Characteristics of the Dutch validation cohort

Characteristic	Bacterial meningitis $N = 266$	Viral meningitis $N = 68$	p value
Age (y)	57 (44–70)	34 (28–45)	<0.001
Female sex	119/266 (45%)	41/68 (60%)	0.029
Ethnic group			<0.001
White	176/196 (90%)	18/35 (51%)	
African American	15/196 (8%)	14/35 (40%)	
Hispanic	1/196 (1%)	0/35 (0%)	
Asian	4/196 (2%)	3/35 (9%)	
HIV	2/263 (1%)	3/68 (4%)	0.061
Headache	186/239 (78%)	66/68 (97%)	<0.001
Nausea	122/228 (54%)	41/68 (60%)	0.33
Neck stiffness	159/239 (67%)	22/62 (35%)	<0.001
Fever (≥38.0°C)	174/259 (67%)	28/68 (41%)	<0.001
Seizures	22/257 (9%)	1/68 (1%)	0.058
GCS score < 15	21/36 (58%)	9/68 (13%)	<0.001
Serum leukocytes ($\times 10^9$/L)	15.2 (12.0–21.7)	8.6 (7.0–10.7)	<0.001
>10	220/262 (84%)	22/68 (32%)	<0.001
CSF leukocytes (cells/mm^3)	2615 (923–6078)	152 (42–337)	<0.001
>2000	155/266 (58%)	0/68 (0%)	<0.001
CSF granulocytes (cells/mm^3)	1563 (428–5160)	7 (5–9)	<0.001
>1180	120/197 (61%)	0/68 (0%)	<0.001
CSF glucose (mmol/L)	1.8 (0.4–3.3)	3.2 (3.0–3.7)	<0.001
<1.9	134/262 (51%)	1/68 (1%)	<0.001
CSF protein (g/L)	2.88 (1.50–5.62)	0.61 (0.46–0.92)	<0.001
>2.20	159/259 (61%)	3/68 (4%)	<0.001

GCS, Glasgow Coma Scale; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

and 30 (11%), respectively (Table S2). In 139 of 245 episodes (57%), the pathogen was identified using CSF cultures. The differences in demographics, presenting features, and pathogens between the derivation and validation cohorts are shown in Table S3.

Viral meningitis was diagnosed in 69 episodes, of which one was excluded because of missing data necessary for risk categorization (serum leukocytes). In all these episodes, there were no signs of encephalitis. In the remaining 68 episodes, the median age of the patients was 34 years (IQR, 28–45 years), and 41 episodes (60%) occurred in female patients (Table 3). PCR identified a pathogen in 55% of the cases, most commonly HSV (22%) or an enterovirus (18%; Table S2). The differences in demographics, presenting features, and pathogens between the derivation and validation cohorts are shown in Table S4.

The ROC curve of the risk score for the diagnosis of bacterial meningitis, based on 257 episodes for which all variables were non-missing, showed an AUC of 0.95 (95% CI, 0.93–0.98; Fig. 1(b)). The sensitivity of a 'high-risk' score for bacterial meningitis was 99.62% (95% CI, 97.92–100; 265/266 episodes). The negative likelihood ratio was 0.01 (95% CI, 0.00–0.04). The specificity was 41.17% (95% CI, 29.37–53.77), and the positive likelihood ratio of a 'low-risk' score was 1.69 (95% CI, 1.40–2.10). Fig. S3 shows the added value of each variable by selecting the most common variable in the bacterial meningitis episodes in the Dutch cohort consecutively.

The patient with bacterial meningitis who scored no points on our risk score was a 28-year-old woman with *S. aureus* endocarditis and meningitis. She presented with stomach pain, headache, and a score of 14 on the Glasgow Coma Scale. She was shivering but had no fever. Her vital signs showed a respiratory rate of 22 breaths/min, heart rate of 110 beats/min, and blood pressure of 98/77 mm Hg, indicating sepsis. A blood examination showed a C-reactive protein level of 371 mg/L and a leukocyte count of 7.5 $\times$ 10^9/L. A CSF examination showed a leukocyte count of 240 per mm^3, protein level of 0.63 g/L and glucose concentration of 3.7 mmol/L.

Discussion

Our study showed that our risk score may be able to rule out bacterial meningitis amongst patients with bacterial or viral meningitis, CSF leucocytosis and a negative Gram staining result.

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Naturally, as with any test, the score should only be used in conjunction with individual patient characteristics and further diagnostic testing. This is demonstrated by the patient with endocarditis and meningitis who had a false-negative result using our risk score but would have been treated with antibiotics because of sepsis. Furthermore, the test includes only variables that are routinely tested and is available on hospital admission, making it easy to use.

A previous Dutch validation study of 17 diagnostic prediction models for bacterial meningitis concluded that no model performed well enough to recommend routine use in clinical practice for the diagnosis of bacterial meningitis [6]. Only half of the models and just two prediction models were restricted to the adult population [15,16]. These two studies reported a high sensitivity (99%–100%) and specificity (89%–98%) in the derivation data; however, subsequent validation of these models by the aforementioned Dutch study resulted in a substantially lower sensitivity (74%–85%) and specificity (50%–70%). Its results are difficult to compare because our score considered a different population: those with a negative CSF Gram staining result and >10 CSF leukocytes per cubic millimetre. However, it is promising that our risk score showed a sensitivity of 99.6%–100% in both the derivation and validation cohorts in different countries.

Our study has limitations. First, a substantial number of patients in the Dutch cohort, classified as having viral or bacterial meningitis, lacked identification of the causative pathogen. This is consistent with other cohort studies of patients with viral meningitis; for those in whom a clinical diagnosis of a viral CNS infection was made, no causative virus could be identified in 35% to 42% of cases [1,17–19]. There were no signs of encephalitis in the episodes of viral meningitis of unknown cause. Out of all patients with bacterial meningitis, 11%–22% had negative CSF culture results [2]. Furthermore, it is a strength of our study that the definitions of viral and bacterial meningitis were broader in our validation cohort, indicating that the risk score works in patients with and without microbiologically or virologically confirmed disease. Although false diagnoses cannot be ruled out, we believe that the vast majority had viral or bacterial meningitis. Second, the patients in the United States were retrospectively included. However, a selection bias was unlikely because all the episodes were consecutively included.

In conclusion, the easy-to-use risk score may be able to rule out bacterial meningitis amongst those with bacterial or viral meningitis, presenting with CSF leucocytosis and a negative Gram staining result, and, thus, may have the potential to reduce unnecessary treatment and admissions. However, it needs prospective testing prior to clinical implementation. Furthermore, studies that investigate how risk scores improve clinical practice are lacking and should be performed to determine their value in addition to clinical judgement.

Author contributions

TMvS: methodology, software, validation, formal analysis, investigation, data curation, writing – original draft and visualization; LtH: methodology, software, validation, formal analysis, investigation, data curation, writing – original draft and visualization; NC: data curation, resources and investigation; MWB: methodology, writing – review and editing and supervision; MCB: methodology, writing – review and editing, supervision and funding acquisition; DUP: methodology, software, formal analysis and investigation; DvdB: methodology, writing – review and editing, supervision and funding acquisition; RH: conceptualization, methodology, investigation and writing – review and editing.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.10.001.

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