Clinical Neurology and Neurosurgery 178 (2019) 36–41

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Corrected white blood cell count, cell index, and validation of a clinical model for the diagnosis of health care-associated ventriculitis and meningitis in adults with intracranial hemorrhage

Kevin Montes[a], Helena Jenkinson[a], Onaizah B. Habib[a], Yoshua Esquenazi[b], Rodrigo Hasbun[a,*]

[a] Department of Internal Medicine, UT Health McGovern Medical School, Houston, TX, United States
[b] Department of Neurosurgery, UT Health McGovern Medical School, Houston, TX, United States

ARTICLE INFO

Keywords:
Healthcare-associated meningitis
Intracranial hemorrhage
Diagnosis
Clinical model

ABSTRACT

Objectives: To evaluate the utility of the corrected CSF white blood cell (WBC) count, cell index, CSF lactate, CSF glucose and a newly developed diagnostic model for the diagnosis of healthcare-associated ventriculitis or meningitis (HCAVM) in the setting of intracranial hemorrhage (ICH).

Patients and methods: A case-control study of 111 adult patients with ICH with HCAVM (cases) or without HCAVM (controls) matched 1:2 by age, Glasgow Coma Scale (GCS), and Acute Physiology and Chronic Health Evaluation II (APACHE II) score enrolled in a large tertiary care center from 2003 to 2016.

Results: Subjects were appropriately matched by age, GCS, and APACHE II score ($P > 0.2$). Cases had significantly higher CSF WBC count (uncorrected and corrected), cell index, and CSF lactate, but lower CSF glucose levels than controls ($P < 0.05$). There were no differences between CSF protein, CSF neutrophilic pleocytosis, and serum C-reactive protein between cases and controls ($P > 0.1$). The diagnostic accuracy as analyzed by the area under the receiver operating characteristic curve (AUC of ROC) was found to be good for the cell index (0.825), fair for the corrected CSF WBC count (0.770), and poor for the diagnostic model and uncorrected CSF WBC count (0.652 and 0.653, respectively).

Conclusion: The diagnosis of HCAVM in patients with ICH remains challenging and although no single parameter is sufficient for diagnosis the cell index proved to be an important indicator of infection in our study.

1. Introduction

Intracranial hemorrhage (ICH) can be a life-threatening condition and frequently requires neurosurgical intervention, such as external ventricular drain (EVD) placement or craniotomy, which carry a 2–27% risk of developing a nosocomial infection [1]. Early recognition of infection is critical as health care-associated ventriculitis and meningitis (HCAVM) is associated with a worse prognosis [2]. However, the diagnosis of HCAVM in the setting of ICH can be challenging. Clinical signs of HCAVM (fever, nuchal rigidity, headache, or altered mental status) can be frequently seen in the postoperative period after neurosurgery or can be obfuscated by sedation or infection elsewhere in the body [1,3]. The utility of standard cerebrospinal fluid (CSF) and blood parameters, such as peripheral white blood cell (WBC) counts, CSF protein, and CSF glucose can be unreliable for the diagnosis of HCAVM [4,5]. The use of CSF cell count to guide clinical management is also limited as bleeding into the CSF causes an invasion of leukocytes to phagocytose the blood, causing chemical meningitis [6,7]. Diagnosis typically depends on the presence of a positive CSF culture, which is highly specific, but lacks sensitivity, especially in the setting of previous antibiotic exposure [8–11]. Furthermore, CSF cultures may take several days to become positive potentially delaying therapy [1,8]. The objective of the present study was to evaluate different laboratory variables and to validate a novel clinical model for the diagnosis of nosocomial meningitis [12].

2. Materials and methods

2.1. Study design

A case-control study at a tertiary care university hospital in which cases were matched 1:2 with controls according to age (± 5 years), Glasgow Coma Scale (GCS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (± 1). Subjects were matched by age

* Corresponding author at: UT Health McGovern Medical School, 6431 Fannin St. 2.112 MSB, Houston, TX 77030, United States.
E-mail address: Rodrigo.Hasbun@uth.tmc.edu (R. Hasbun).

https://doi.org/10.1016/j.clineuro.2019.01.012
Received 20 November 2018; Received in revised form 11 January 2019; Accepted 20 January 2019
Available online 21 January 2019
0303-8467/

and altered mental status because both are independently associated with CSF abnormalities and worse clinical outcomes [9,10]. The Committee for the Protection of Human Subjects approved the study and because of the retrospective nature of the study, the informed consent was waived.

2.2. Definition

A case was defined as an adult patient (> 16 years old) with ICH complicated by ventriculitis or meningitis as defined by the 2015 Centers of Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) definition [11]. All cases with HCAVM had a positive CSF culture. Controls were those with ICH in the absence of HCAVM as diagnosed by the CDC/NHSN definition with negative CSF cultures and no antibiotic exposure to reduce the risk of misclassification bias.

2.3. Data collection

Patient electronic medical records from 2003 to 2016 at a large tertiary care center were retrospectively analyzed. Data collected include demographic data, comorbidities, immune status, neurologic exam, GCS score, APACHE II score, neurosurgical history, type of ICH, and history of antibiotic and steroid use. The Glasgow Coma Scale is a standardized assessment of the level of consciousness in patients with brain injury by assessing motor, verbal, and eye-opening responses with results ranging from 3 to 15 (with 3 being the worst and 15 the best) [2]. The APACHE II score classifies disease severity by assessing 12 physiologic measurements with a higher score indicating an increased risk for mortality [2]. The following laboratory parameters were collected: peripheral WBC count, peripheral red blood cell (RBC) count, blood glucose, serum C-reactive protein (CRP), CSF lactate, CSF WBC count, CSF RBC count, and CSF glucose. An adverse clinical outcome was defined as a Glasgow outcome scale 1–4. [9]. All external ventricular devices used during the study period were antibiotic-coated. CSF was obtained at the time of placement of the external ventricular device and only repeated in those with suspected infection. In the absence of an EVD, a lumbar puncture was performed.

2.4. Evaluated parameters for diagnosis of HCAVM

A new model for the diagnosis of postoperative nosocomial meningitis (NM) has been proposed which assesses the following clinical and laboratory variables: aneurysmal subarachnoid hemorrhage diagnosis (1 point), CRP ≥ 6 mg/dl (1 point), CSF/blood glucose ratio ≤ 0.4 (1 point), CSF leak (1.5 points), CSF granulocytes ≥ 50% (1.5 points), and CSF lactate ≥ 4 mmol/L (4 points). A score of 6 or greater was associated with a high probability of HCAVM [12].

Cell index is a ratio of the WBC and RBC in the CSF divided by the WBC and RBC in the peripheral blood, shown below [13].

$$\text{Cell index} = \frac{(WBC_{CSF}/RBC_{CSF})}{(WBC_{Blood}/RBC_{Blood})}$$

In the setting of ICH, because CSF is contaminated with blood, the ratio of WBC to RBC in the CSF should be roughly proportional to the ratio of WBC to RBC in peripheral. A deviation in this proportion, which can occur during infection or inflammation, may be noted by calculating the cell index [13].

A corrected CSF WBC count has been used in pediatrics to account for blood in the CSF after a traumatic lumbar puncture. A study using a correction factor of 1000:1 (i.e., subtract 1 from the CSF WBC count for every 1000 RBC in the CSF) reduced the number of infants with false-positive elevation in CSF WBC [14]. In this study, we analyzed 3 separate correction factors (500:1, 750:1, and 1000:1).

Table 1
Demographics, clinical status, and hospital course of 111 patients with intracranial hemorrhage with and without health care-associated meningitis.

Characteristic	ICH + meningitis (n = 37)	ICH alone (n = 74)	P value
Demographics			
Male sex	20/37 (54)	28/74 (38)	0.104
Age, mean (SD)	50.5 (13.3)	50.8 (12.3)	0.912
Caucasian race	17/37 (46)	31/74 (41)	0.684
Clinical status			
Charlson Comorbidity Index Score ≥ 2	23/37 (62)	12/74 (16)	< 0.001
Immunocompromised*	1/37 (3)	3/74 (4)	1
Clinical Examination			
Fever (> 38 °C)	16/37 (43)	21/74 (28)	0.117
Abnormal neurologic examination**	27/37 (75)	74/74 (100)	< 0.001
APACHE II score, mean (SD)	11.38 (5.1)	11.23 (5.1)	0.886
GCS score, mean (SD)	10.8 (4.1)	10.8 (4.0)	0.973
Hospital Course			
Mechanical ventilation days, mean (SD)	11.9 (8.0)	7.4 (8.5)	0.048
Required EVD	32/37 (86)	69/74 (93)	0.241
ICU admission	31/37 (83)	74/74 (100)	0.001
Antibiotics prior to LP	14/34 (41)	0/74 (0)	< 0.001
Adverse clinical outcome†	31/37 (83)	22/74 (30)	< 0.001

Values are shown as number (%) unless otherwise stated.
ICH, intracranial hemorrhage; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; CSF, cerebrospinal fluid; EVD, external ventricular drain; SD, standard deviation; ICU, intensive care unit; LP, lumbar puncture.
* Steroids, cirrhosis.
** Abnormal neurologic examination defined as a GCS score of < 15 or focal neurologic deficit.
† Adverse clinical outcome defined as a Glasgow Outcome Scale of score ≤ 4, where 1 indicates death, 2 indicates persistent vegetative state, 3 indicates severe disability, and 4 indicates moderate disability.

2.5. Statistical analysis

Bivariate analyses were done with Pearson χ^2 or Fisher exact tests to identify variables which were significantly different between cases and controls. The diagnostic accuracy of the different clinical and laboratory parameters was assessed by calculating the area under the receiver operating curve (ROC) and categorized as excellent (0.9–1.0), good (0.80-0.90); fair (0.70-0.80), poor (0.60-0.70), and fail (0.50-0.60). All statistical analyses were conducted with IBM (International Business Machines Corporation) SPSS® (Statistical Package for the Social Sciences, Armonk, New York, USA, version 25).

3. Results

3.1. Patient demographics, clinical status, and hospital course

Our study consisted of 111 patients, 37 cases and 74 controls, which were matched 1:2 appropriately by age, APACHE II score, and GCS score (P > 0.2). Patient demographics, baseline clinical status, and hospital course are shown in Table 1. There was no significant difference in gender, race, immunocompromised status, the presence of fever, or incidence of placement of an EVD between cases and controls (P > 0.1). Cases were significantly more likely to have a Charlson Comorbidity Index Score of greater than 2, to require more days of mechanical ventilation, and to have an adverse clinical outcome (P < 0.05). Controls were significantly more likely to have an abnormal neurologic examination (defined as a GCS score of < 15 or any focal neurologic deficit), and require admission to the intensive care unit (P < 0.05). A total of 14 of 34 (41%) of the patients with ICH and

Table 2
Microbiologic studies, laboratory data, and analysis of the nosocomial meningitis model in patients with intracranial hemorrhage with and without meningitis.

Characteristic	ICH and meningitis	ICH alone	*P* value
Microbiology			
Positive CSF culture*	37/37 (100)	0/74 (0)	< 0.001
CSF gram stain	15/37 (41)	0/74 (0)	< 0.001
Laboratory Data, mean (SD)			
CSF protein	146.1 (120.8)	145.6 (187.0)	0.988
CSF glucose	57.4 (31.3)	79.1 (23.3)	< 0.001
CSF granulocyte percentage	52.9 (33.6)	61.2 (27.4)	0.239
CSF RBC count	31454.2 (67,842.1)	117,660.1 (39,184.3)	0.235
CSF WBC count	2213.3 (6135.4)	192.3 (427.9)	0.005
Corrected WBC count by 500	1897.4 (5804.0)	−43.0 (732.5)	0.005
Corrected WBC count by 750	1915.9 (5801.3)	35.4 (531.2)	0.006
Corrected WBC count by 1000	1870.1 (5723.3)	74.6 (454.1)	0.008
Cell index	4.299 (17.779)	0.007 (0.043)	0.039
CSF lactate	5.7 (4.8)	3.6 (1.3)	0.036
CSF/serum glucose ratio	0.409 (0.227)	0.595 (0.172)	< 0.001
Serum CRP	109.3 (99.6)	30.5 (34.5)	0.144
Nosocomial meningitis model			
CRP ≥ 6 mg/dl	3/3 (100)	4/5 (80)	1
CSF/blood glucose ratio ≤ 0.4	13/36 (36)	6/73 (8)	< 0.001
Aneurysmal SAH	12/37 (32)	32/73 (43)	0.249
CSF leak	7/37 (19)	4/72 (6)	0.042
CSF granulocytes ≥ 50%	19/31 (61)	39/56 (70)	0.429
CSF lactate ≥ 4 mmol/L	13/24 (54)	4/26 (15)	0.007
NM model score, median (range)	4.5 (1-8.5)	2.5 (1-7.5)	< 0.001
NM model score ≥ 6	12/37 (32)	4/74 (5)	< 0.001

Values are shown as number (%) unless otherwise stated.
ICH, intracranial hemorrhage; CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell; CRP, C-reactive protein; SAH, subarachnoid hemorrhage; NM, nosocomial meningitis.

* Gram-positive organisms (26/37): coagulase negative *Staphylococcus* (14/37), *Staphylococcus aureus* (5/37), *Streptococcus* species (4/37), *Enterococcus* species (1/37), *Propionibacterium acnes* (1/37), *Micrococcus* (1/37); gram-negative organisms (9/37): *Serratia marcescens* (3/37), *Pseudomonas* species (2/37), *Klebsiella pneumoniae* (2/37), *Stenotrophomonas maltophilia* (1/37), *Escherichia coli* (1/37); fungal organisms (2/37): *Candida rugosa* (1/37), *Acremonium* (1/37).

meningitis received antibiotics prior to lumbar puncture.

3.2. Microbiology, laboratory data, and the nosocomial meningitis model

As demonstrated in Table 2 and discussed previously, all cases and no controls had a positive CSF culture. Only 15 patients (41%) with culture-proven meningitis had a positive Gram stain. Patients with ICH and meningitis had significantly higher average CSF WBC counts, corrected CSF WBC counts, CSF cell index, and CSF lactate. The average serum CRP was higher in those with meningitis, but the difference was not significant. Additionally, the mean CSF glucose and CSF/serum glucose ratio were significantly lower in cases ($P < 0.05$). The differences in these variables can be visualized in Fig. 1.

We compared the results for each criterion from the nosocomial meningitis model among cases and controls. Cases were significantly more likely to fulfill the following criteria: CSF/blood glucose ratio of ≤ 0.4, the presence of a CSF leak, CSF lactate of ≥ 4 mmol/L, and a score NM model score of ≥ 6. There were no significant differences between cases and controls in having ≥ 50% granulocytes in the CSF, presence of an aneurysmal SAH, or having a serum CRP ≥ 6 mg/dl. Only 8 of our 111 patients (7%) had a CRP collected and only 24 of the cases (65%) and 26 of the controls (35%) had a CSF lactate measured.

Table 3 presents the distribution of scores of the NM model in patients with ICH with and without meningitis. In our study, only one-third of cases would have been appropriately identified as having a high likelihood of having nosocomial meningitis when using the diagnostic model. Fig. 2 demonstrates the receiver operating characteristic (ROC) curves for several continuous and dichotomized variables. The cell index had the best discrimination (area under the ROC [AUROC] of 0.825) of the different variables we assessed. The CSF WBC correction factors of 500:1, 750:1, and 1000:1 had AUROCs of 0.770, 0.769, and 0.757, respectively, and the uncorrected CSF WBC count had an AUROC 0.653. Using the proposed threshold of a score of greater than 6, the NM model had an AUROC of 0.652.

4. Discussion

Positive CSF cultures are the principal tool for the diagnosis of HCAVM. However, one large study of 215 patients found that half of all patients with HCAVM received antibiotics prior to CSF analysis with subsequent CSF cultures positive in only about half of the cases [9]. Furthermore, the diagnosis may be delayed as only 20% of patients with HCAVM have a positive CSF Gram stain with cultures taking up 48–72 hours to become positive [9]. Due to all these reasons, there is an urgent necessity to identify other means to reliably make the diagnosis. This study sought to assess the utility of a variety of clinical factors – including the corrected CSF WBC count, cell index, and a diagnostic model – for the diagnosis of HCAVM.

The limits of using an uncorrected CSF WBC count to diagnose HCAVM have been discussed extensively in the literature and current guidelines indicate it may not be useful to assess the presence of infection [1,8,15]. Furthermore, studies have found that bleeding into the brain, even in the absence of infection, can provoke the invasion of leukocytes to phagocytose the extravasated blood, leading to sterile inflammation and pleocytosis [3,13].

The use of a correction factor to interpret CSF WBC counts following traumatic lumbar puncture has been studied in pediatrics [14]. However, data on its use in adults is limited. Our study found that the use of all the correction factors (500:1, 750:1, and 1000:1) performed similarly and had greater discriminatory function than the uncorrected CSF WBC count. However, given the overall low AUROC of the corrected CSF WBC counts, its use as the sole determinant of infection is not recommended.

The cell index assesses changes in the ratio between the CSF WBCs and RBCs in comparison to the same ratio in the blood, which should be approximately 1:1. An increase in the CSF WBC count out of proportion to the increase in blood WBC is suggestive of infection. The first study to propose the cell index found that after following the cell index daily an increase in the cell index was highly indicative of ventriculitis and permitted more rapid diagnosis compared to CSF cultures. However, this study was limited by its small sample size (N = 13) [13]. Studies aiming to validate the use of the cell index have had mixed results. One study of 39 patients with culture-proven EVD-related infections evaluated the cell index at the time of EVD placement, 2 days before the occurrence of infection, and at the day of the positive CSF culture. There was about a 2.5-fold increase in the cell index between the time of the EVD placement and the time of the positive CSF culture, but the increase was not statistically significant [1]. Another study of 34 patients found that using an absolute cell index of 2.9 had a sensitivity of 95% and specificity of 92.9% with an AUROC of 0.982. When evaluating the relative change in cell index, it was found that a 4.33-fold increase from baseline to when HCAVM was first suspected had a sensitivity of 82.4% and a specificity of 87.5% with an AUROC of 0.882 [16]. In our study, the cell index was the best predictor of HCAVM of the variables we assessed. The average absolute cell index for patients with ICH and HCAVM was 4.3, compared to 0.007 for those with only ICH.

The model we validated in this study developed a score using

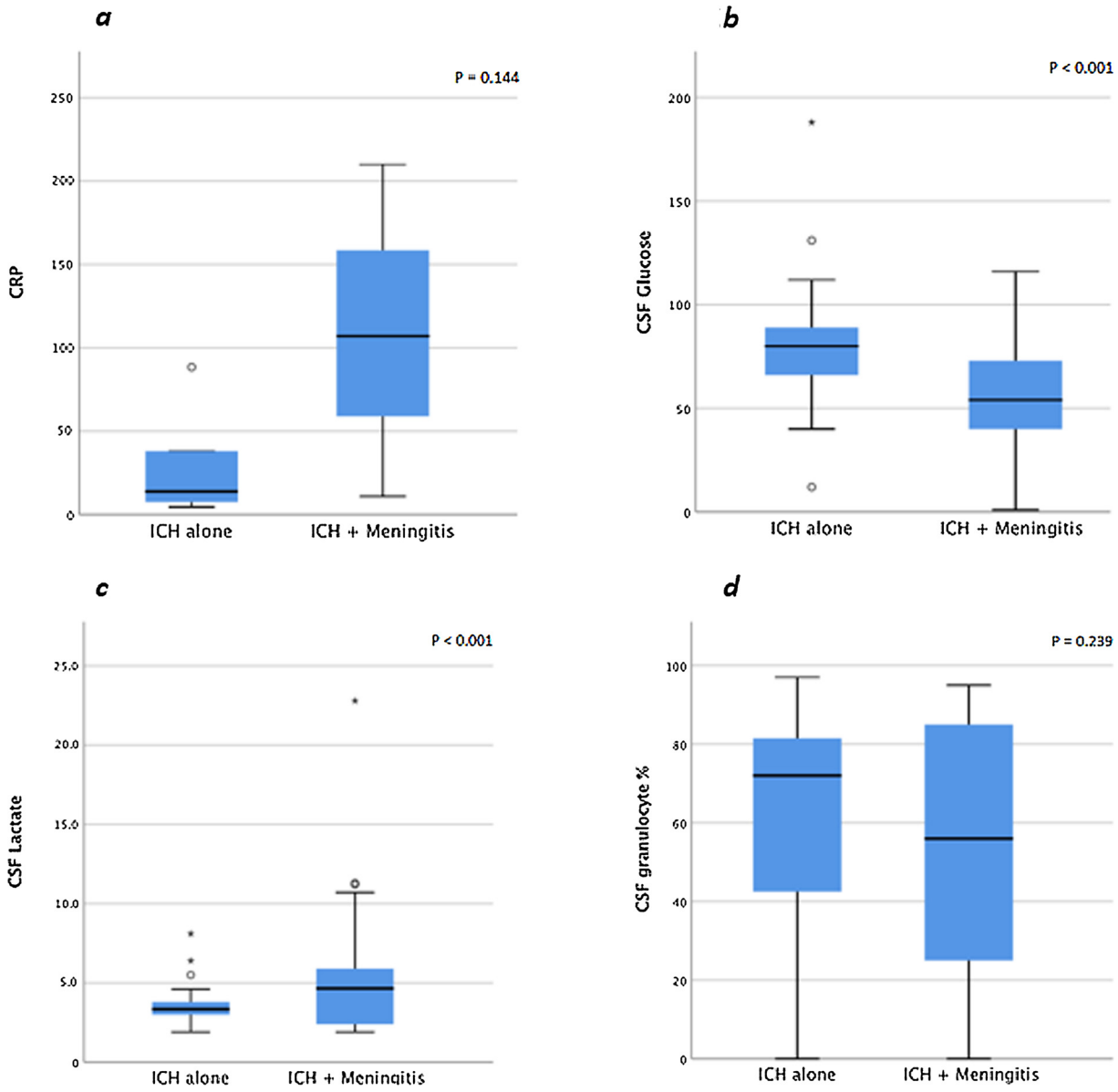

Fig. 1. Box-and-whisker plots comparing the means and distribution of a variety of clinical parameters and of the nosocomial meningitis (NM) model in patients with intracranial hemorrhage (ICH) with and without meningitis. Fig. 1a CRP, C-reactive protein; Fig. 1b CSF (Cerebrospinal fluid) glucose; Fig. 1c CSF lactate levels; Fig. 1d CSF granulocyte percentage; Fig. 1e CSF to serum glucose ration; Fig. 1 f. NM (nosocomial meningitis) prediction score.

Table 3
Scoring of the nosocomial meningitis diagnostic model in patients with intracranial hemorrhage with and without meningitis.

NM model score	ICH and meningitis	ICH alone	Total
0-1.5	9 (31)	20 (69)	29
2-3.5	8 (15)	45 (85)	53
4-5.5	8 (62)	5 (38)	13
6-7.5	9 (69)	4 (31)	13
8-9.5	3 (100)	0 (0)	3
10	0 (0)	0 (0)	0

Values are presented as number (%).
NM, nosocomial meningitis; ICH, intracranial hemorrhage.

certain dichotomized clinical and laboratory variables, which if 6 or greater, suggests a high likelihood of HCAVM. In the original article, the clinical model had an AUROC of 0.94 when comparing patients with confirmed or probable infection to patients without HCAVM (negative CSF culture and CSF WBC count < 250 cells/L) [12]. In our study population, the clinical model had a sensitivity of 32.4%, a specificity of 94.6%, and an AUROC of 0.65. Overall, the model had a poor discriminate function when applied at our institution. This could be partially explained as serum CRP and CSF lactates (two variables in the model) were done infrequently in our hospital (7% and 45%, respectively).

The strengths of this study included that the cases and controls were well matched by age, GCS, and severity of illness (APACHE 2). Additionally, as controls did not receive antibiotics either before or after the CSF and cases only included patients with positive CSF cultures, misclassification bias was minimized. Furthermore, to the knowledge of the authors, this is the first study to compare the corrected and uncorrected CSF WBC counts in adults patients with ICH and HCAVM and the first to validate the newly published clinical model. However, our study is limited by the low rates of collection of serum CRP and CSF lactate, which could have contributed to the poor performance of the model.

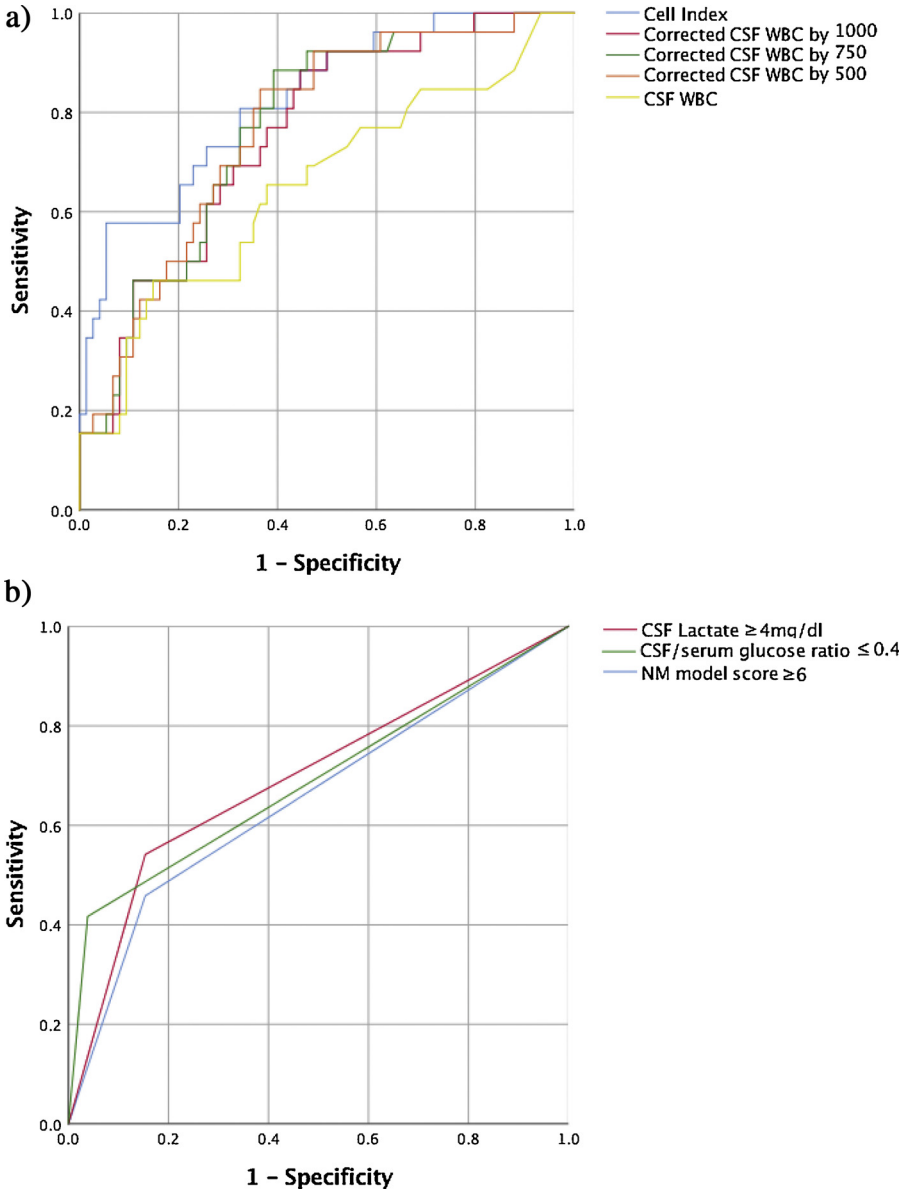

Fig. 2. Receiver operating characteristic (ROC) curves. (a) Diagnostic accuracy of cell index, corrected CSF WBC count, and uncorrected CSF WBC count with area under the ROC curves with confidence intervals (CI): cell index 0.825 (CI 0.733-0.916); corrected CSF WBC by 1000 0.757 (CI 0.655-0.858), corrected CSF WBC by 750 0.769 (CI 0.669-0.869); corrected CSF WBC by 500 0.770 (CI 0.670-0.870); uncorrected CSF WBC 0.653 (CI 0.523-0.783).
(b) Diagnostic accuracy of CSF lactate ≥ 4 mmol/L, CSF/serum glucose ≤ 0.4, and NM model score ≥ 6 with area under the curves with confidence intervals (CI): CSF lactate ≥ 4 mmol/L: 0.694 (CI 0.544-0.844); CSF/serum glucose ≤ 0.4: 0.689 (CI 0.538-0.840); NM (nosocomial meningitis) model score ≥ 6: 0.652 (CI 0.497-0.807). CSF, cerebrospinal fluid; WBC, white blood cell; NM, nosocomial meningitis

5. Conclusions

The diagnosis of HCAVM in adults with ICH remains challenging. In the absence of a positive CSF culture, laboratory markers and clinical models may aid clinicians in the diagnosis of HCAVM but further research should evaluate novel and more sensitive tools such as molecular diagnostics in the future.

Funding

Grant A Starr Foundation.

Conflicts of interest

RH is a speaker for Merck and Biofire and a consultant to Biomeriaux and Gilead Sciences. All other authors have no conflicts of interest.

References

[1] J. Wiegand, L. Hickson, T.M. Merz, Indicators of external ventricular drainage-related infections—a retrospective observational study, Acta Neurochir. (Wien) 158 (2016) 595–601.
[2] O.B. Habib, C. Srihawan, L. Salazar, R. Hasbun, Prognostic impact of health care–associated meningitis in adults with intracranial hemorrhage, World Neurosurg. 107 (2017) 2–5.
[3] D. Ross, H. Rosegay, V. Pons, Differentiation of aseptic and bacterial meningitis in postoperative neurosurgical patients, J. Neurosurg. 69 (1988) 669–674.
[4] W. Pfisterer, M. Mühlbauer, T. Czech, A. Reinprecht, Early diagnosis of external ventricular drainage infection: results of a prospective study, J. Neurol. Neurosurg. Psychiatry 74 (2003) 929–932.
[5] S. Muttaiyah, S. Ritchie, A. Upton, S. Roberts, Clinical parameters do not predict infection in patients with external ventricular drains: a retrospective observational study of daily cerebrospinal fluid analysis, J. Med. Microbiol. 57 (2008) 207–209.
[6] R. Beer, P. Lackner, B. Pfausler, E. Schmutzhard, Nosocomial ventriculitis and meningitis in neurocritical care patients, J. Neurol. 255 (2008) 1617–1624.
[7] J. Hoogmoed, D. van de Beek, B.A. Coert, et al., Clinical and laboratory characteristics for the diagnosis of bacterial ventriculitis after aneurysmal subarachnoid hemorrhage, Neurocrit. Care 26 (2017) 362–370.
[8] A. Conen, L.N. Walti, A. Merlo, et al., Characteristics and treatment outcome of cerebrospinal fluid shunt–associated infections in adults: a retrospective analysis over an 11-year period, Clin. Infect. Dis. 47 (2008) 73–82.
[9] C. Srihawan, R.L. Castelblanco, L. Salazar, et al., Clinical characteristics and predictors of adverse outcome in adult and pediatric patients with healthcare-associated ventriculitis and meningitis, Open Forum Infect. Dis. 3 (2016) 1–6.
[10] C. Srihawan, O. Habib, L. Salazar, R. Hasbun, Healthcare-associated meningitis or ventriculitis in older adults, J. Am. Geriatr. Soc. 65 (2017) 2646–2650.
[11] CDC, NHSN, CDC / NHSN surveillance definitions for specific types of infections, Surveill. Defin. 2015 (2014) 1–24.

[12] O.H. Hernández Ortiz, H.I. García García, F. Muñoz Ramírez, et al., Development of a prediction rule for diagnosing postoperative meningitis: a cross-sectional study, J. Neurosurg. (2017) 1–10.
[13] B. Pfausler, R. Beer, K. Engelhardt, et al., Cell index - a new parameter for the early diagnosis of ventriculostomy (external ventricular drainage)-related ventriculitis in patients with intraventricular hemorrhage? Acta Neurochir. (Wien) 146 (2004) 477–481.
[14] T.W. Lyons, A.T. Cruz, S.B. Freedman, et al., Interpretation of cerebrospinal fluid white blood cell counts in young infants with a traumatic lumbar puncture, Ann. Emerg. Med. 69 (2017) 622–631.
[15] A.R. Tunkel, R. Hasbun, A. Bhimraj, et al., Infectious diseases society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis, Clin. Infect. Dis. 2017 (64) (2017) 701–706.
[16] L.W. Lunardi, E.R. Zimmer, S.C. dos Santos, et al., A. Cell index in the diagnosis of external ventricular drain-related infections, World Neurosurg. 106 (2017) 504–508.