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Utility of cell index in the diagnosis of healthcare-associated ventriculitis and meningitis: an analytical cross-sectional study

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Abstract

Background The diagnosis of healthcare-associated ventriculitis and meningitis (HCAVM) can be complex because multiple factors confound the interpretation of cerebrospinal fluid (CSF) tests. The cell index (CI) may help in the diagnosis of HCAVM. It does not incur additional medical cost and it avoids delays from the turnaround time of CSF cultures. It is derived by calculating the ratio of CSF white blood cell (WBC) and red blood cell (RBC) divided by the ratio of peripheral WBC and RBC. This study aimed to evaluate the diagnostic utility of this parameter.

Methods An analytic, observational, cross-sectional study was conducted at the University of the Philippines – Philippine General Hospital. All admitted pediatric and adult patients from 2015 to 2022 who underwent external ventricular drain (EVD) insertion for hydrocephalus secondary to intracranial hemorrhage (ICH), acute ischemic stroke, intracranial neoplasms, traumatic brain injury, or congenital hydrocephalus were screened. Records of patients fulfilling the inclusion criteria were then reviewed.

Results A total of 363 patients underwent EVD insertion from 2015 to 2022. Of these, 161 were included in the study. Two-thirds (66.5%) were adults ≥ 19 years old whereas the remaining were pediatric patients 1 to < 19 years old. There were no patients < 12 months old as they fulfilled at least one exclusion criteria. Forty-nine of them were later confirmed to have HCAVM based on the CDC/NHSN criteria. A CI cut-off of ≥ 1.21 gave a maximum sensitivity of 30.6% and specificity of 86.4%. Receiver operating characteristic area under the curve (AUC-ROC) analysis was 0.585. Subgroup analysis by age showed sensitivity of 52.9% in the pediatric age group and 3.13% in adults. Subgroup analysis by neurologic indication showed sensitivity of 27.6% for ICH and 35.0% for neoplasms. Subsequent AUC-ROC analyses, however, showed that CI failed to adequately diagnose HCAVM in these subgroups.

Conclusions In our population of neurologic patients who underwent EVD insertion, the cell index is not a reliable parameter in the diagnosis of HCAVM.

Keywords Cell index, Ventriculitis, Meningitis, Healthcare-associated

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Introduction

An external ventricular drain (EVD) is a device inserted to divert cerebrospinal fluid (CSF) to control hydrocephalus and/or to monitor intracranial pressure (ICP) [1, 2]. Although standard measures to ensure asepsis is followed during the procedure, the development of healthcare-associated ventriculitis and meningitis (HCAVM) remains one recognized complication [1].

Currently, the gold standard for the diagnosis of HCAVM is a positive CSF culture and sensitivity (CS) result [3]. However, considering the delay before the final result is released, clinical parameters raising the suspicion for HCAVM are used to empirically diagnose the condition [3, 4]. Traditional diagnostic parameters such as CSF pleocytosis, hyperproteinorrachia, hypoglycorrhachia, and the presence of microorganisms on preliminary Gram stain (GS) are sought to further support the suspicion of HCAVM [5]. However, changes brought about by chemical meningitis from the intraventricular extension of hemorrhage, EVD-related changes, or prior antimicrobial exposure may confound these diagnostic parameters [4, 6].

The cell index (CI) was first introduced in 2004 but it was only in recent years that studies had been undertaken to further investigate its utility in diagnosing HCAVM [7]. It is calculated as the ratio of the CSF white blood cell (WBC) and red blood cell (RBC) divided by the ratio of peripheral WBC and RBC. The assumption is that after contamination, the leukocytes and erythrocytes in the CSF should be in the same proportion as the peripheral blood [7]. A more than fivefold increase in the CI had been originally used by the proponents to significantly indicate the presence of an EVD-associated infection [8, 9]. Its sensitivity and specificity, however, was not yet explored at that time.

This study aims to evaluate the utility of CI in diagnosing HCAVM by determining its sensitivity, specificity, and receiver operating characteristic area under the curve (AUC-ROC). It also aims to review its optimal cut-off as a measure of diagnostic accuracy.

Methods

Study design and setting

An analytic, observational, cross-sectional study was conducted at the University of the Philippines – Philippine General Hospital (UP-PGH) following the guidelines set forth by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative [10]. UP-PGH is the largest government hospital and the sole national referral center for tertiary care in the Philippines [11].

Case identification and sampling

All admitted patients from 2015 to 2022 who underwent EVD insertion were identified using the operation logs of the Neurosurgery service. Pediatric patients < 19 years old and adults ≥ 19 years who warranted CSF diversion due to intracranial hemorrhage (ICH) [e.g. intraparenchymal hemorrhage, intraventricular hemorrhage (IVH), subarachnoid hemorrhage (SAH)], acute ischemic stroke (AIS), intracranial neoplasm, traumatic brain injury (TBI), or congenital hydrocephalus were included. For patients who underwent multiple EVD insertions, only data from their first EVD were included. Patients were excluded if they had been diagnosed with a central nervous system infection (CNSI), had undergone ventricular taps during their admission, or had previously existing devices such as ventriculoperitoneal shunts or Ommaya reservoir prior to the EVD insertion.

Data collection

Records review of the identified patients was done in the Medical Records Division. The following demographic and clinical data were collected and tabulated: age, sex, Glasgow Coma Scale (GCS) on admission, diagnosis warranting EVD insertion, and if applicable, intracerebral hemorrhage score, Hunt & Hess grade, Fisher scale, and National Institutes of Health Stroke Scale (NIHSS). Suspicion of HCAVM arose in patients with an EVD who developed new-onset fever with no other identified foci of infection. At the time of suspicion, data collected were peripheral RBC and WBC count, CSF RBC and WBC count, CSF total protein and glucose, CSF gram stain and culture results, active systemic infections, and ongoing antibiotic therapy. The final diagnosis for each patient upon discharge was also recorded.

Definitions

The Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC/NHSN) definition for HCAVM was followed in this study (see Fig. 1) [3]. In brief, HCAVM is diagnosed either using CSF culture or a combination of clinical and diagnostic parameters not attributable to other infectious causes.

The cell index was calculated as the ratio of the CSF WBC and RBC divided by the ratio of the peripheral WBC and RBC [7]. Any fivefold increase in the CI was related to an EVD-associated infection [8, 9].

CSF pleocytosis in the adult population was defined by the presence of > 5 WBC per cubic millimeter of CSF [12]. On the other hand, in the pediatric population, age group-specific cut-offs were followed [13].

Should there be RBC contamination of the CSF, corrected WBC was computed in this study by subtracting 1 WBC for every 750 RBC in a given CSF sample. This practice had been studied extensively in Pediatrics owing

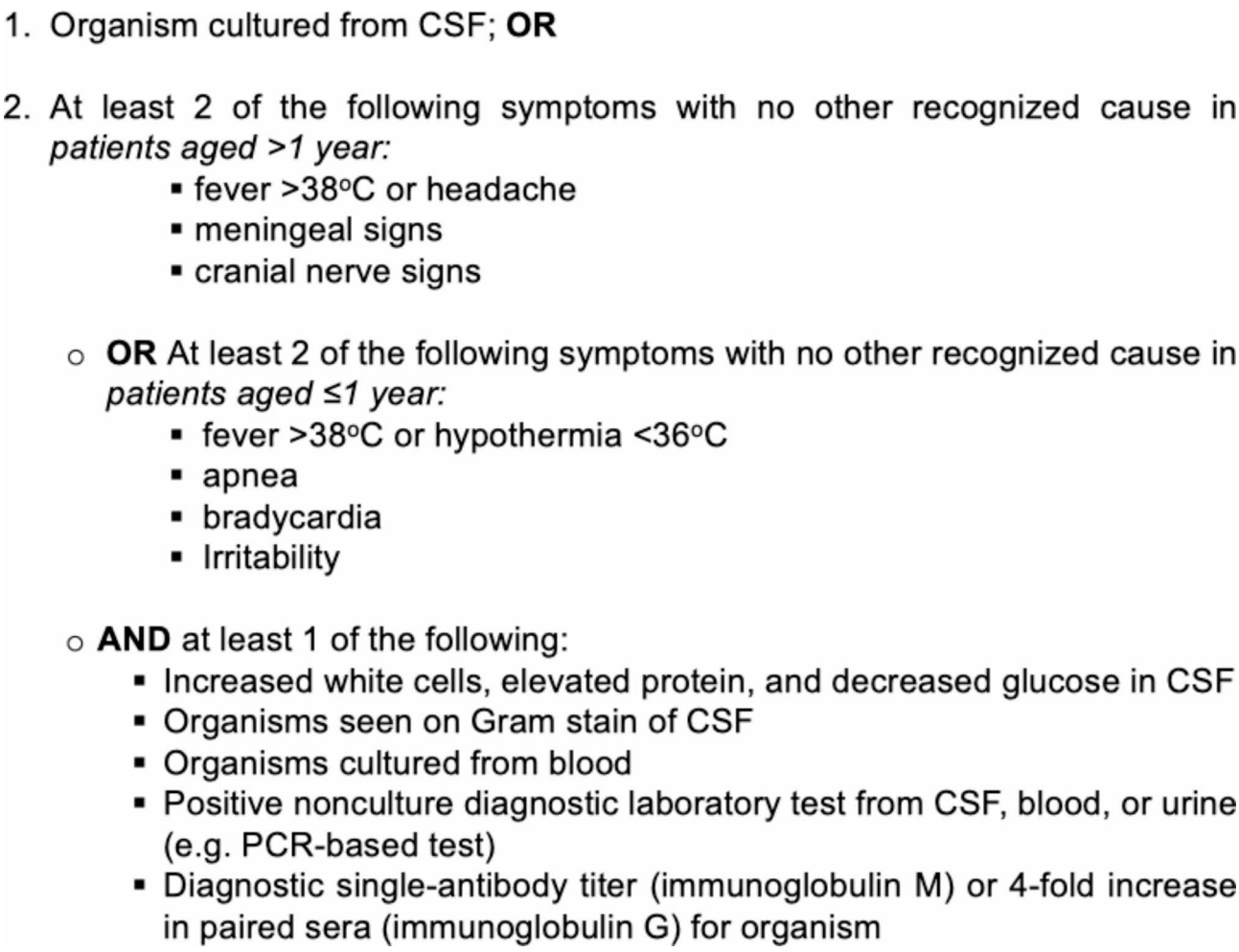

Fig. 1 CDC/NHSN diagnostic criteria for HCAVM

to the need to account for alterations in the true CSF WBC count after a traumatic lumbar tap [14]. Although data regarding the practice in the adult population is limited, a recent study showed that the correction factors of 500 RBC:1 WBC, 750 RBC:1 WBC, and 1,000 RBC:1 WBC performed similarly [4]. Although further studies are needed to investigate the accuracy of the practice for CSF samples derived from EVDs, in principle, correcting WBC can help discriminate pleocytosis secondary to an infection versus pleocytosis from inadvertent blood contamination.

On the other hand, CSF hyperproteinorrachia in the adult population was defined as having a CSF protein of >50 mg/dL [15]. In the pediatric population, acceptable cut-offs were again followed depending on the age group [13]. As bleeding into the CSF also lead to spillage of serum proteins, corrected CSF protein was derived by subtracting 1 mg/dL of protein for every 1,000 RBCs in the CSF.

Lastly, CSF hypoglycorrhachia was defined as a CSF glucose of <40 mg/dL for both adult and pediatric population [5, 13]. The CSF to serum glucose ratio was not available in the majority of patients due to lacking simultaneous serum glucose result.

Statistical analysis

Data analysis was performed using Stata version 17. Missing values were neither replaced nor imputed. Normality of distribution of numerical variables was assessed by Shapiro-Wilk test and significance level was set at α=0.05.

The demographic and clinical profile of the study participants were summarized by descriptive statistics. Categorical variables were described as frequency and percentages.

The prevalence of HCAVM among admitted patients who underwent EVD insertion was determined and presented as a point estimate with 95% confidence interval. ROC curve analysis was performed to determine the diagnostic accuracy of CI at a cut-off of ≥5. Cut-off analysis was then performed by balancing the clinically

important sensitivity and specificity levels in diagnosing HCAVM.

Ethical considerations

The study ensured adherence to the 2017 National Ethical Guidelines of Health and Health-related Research [16]. The protocol was also approved by the UP Manila Research Ethics Board (UPMREB 2023-0150-01).

Results

Population

A total of 363 patients underwent EVD insertion from the period of 2015 to 2022 in our institution. Of these, 184 patients were excluded based on the previously mentioned exclusion criteria while 18 patients were excluded due to missing data. One hundred and sixty one patients were then included for full chart review. Among them, 71 were suspected to have developed HCAVM. The diagnosis was ultimately ruled out in 22 patients but confirmed in 49 patients following the CDC/NHSN definition. Please refer to Fig. 2 for the flow diagram during sample selection. The prevalence of HCAVM in our sample was 30.4%, 95% CI [23.4, 38.2].

Baseline characteristics

Table 1 shows the baseline characteristics of all 161 patients. More than half (54.7%) of the sample were males. Two-thirds (66.5%) were adults whereas the remaining were pediatric patients. There were no patients < 12 months old as they fulfilled at least one exclusion criteria. The most common neurologic indications for EVD insertion were ICH and intracranial neoplasms at 47.2% each. Parenchymal hemorrhages were the most common (71.1%) type of ICH whereas infratentorial tumors most commonly (52.6%) warranted EVD insertion. Twenty-six percent (26%) of those who required EVD insertion had a GCS of ≤ 8 on admission. For those with ICH or AIS, more than half (53.9%) had severe stroke based on their NIHSS.

The period from EVD insertion to the development of HCAVM suspicion ranged from zero to 26 days, with its mean at six days. With regards to the timing of HCAVM suspicion and CSF collection, among the 71 patients suspected of HCAVM, 14.0% (10) were suspected of the condition only after the abnormal CSF results were noted. In these cases, the time from CSF collection to suspicion ranged from one to five days, with a mean of 2.5 days. On the other hand, in 86.0% (61) of the cases, HCAVM suspicion arose first. CSF samples were then sent for analysis

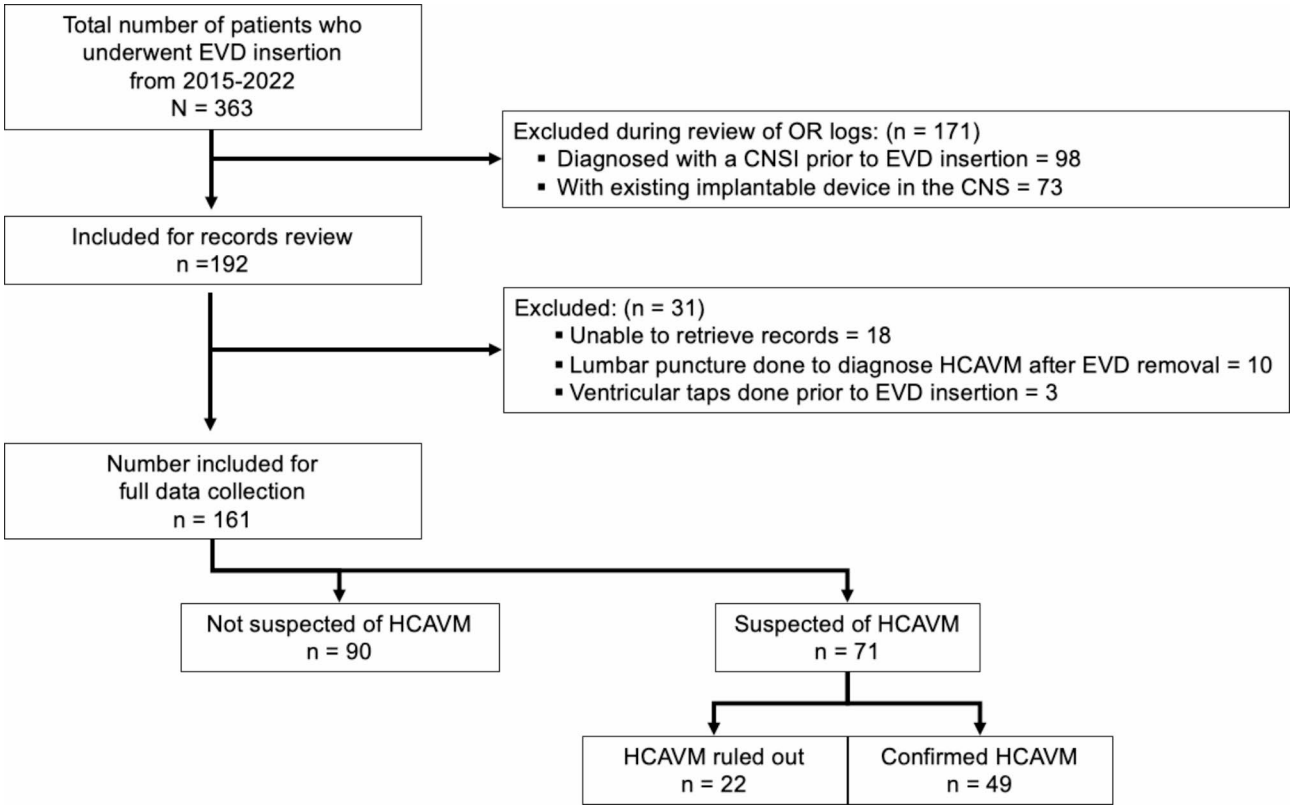

Fig. 2 Flow diagram during sample selection

Table 1 Baseline demographic and clinical data of 161 patients who underwent EVD insertion

PARAMETER[a]	FREQUENCY (%)
Age	
1 to < 19 years old	54 (33.5%)
≥ 19 years old	107 (66.5%)
Sex	
Male	88 (54.7%)
Female	73 (45.3%)
Diagnosis Warranting EVD Insertion	
a. Intracranial hemorrhage	76 (47.2%)
Parenchymal hemorrhage	54 (71.1%)
Supratentorial	39 (72.2%)
Infratentorial	15 (27.8%)
Subarachnoid hemorrhage	12 (15.8%)
Intraventricular hemorrhage	10 (13.1%)
b. Acute Ischemic Stroke	7 (4.35%)
Supratentorial	0 (0%)
Infratentorial	7 (100%)
c. Intracranial neoplasms	76 (47.2%)
Supratentorial	26 (34.2%)
Infratentorial	40 (52.6%)
Intraventricular	9 (11.8%)
Multifocal	1 (1.32%)
d. Traumatic Brain Injury	2 (1.24%)
Glasgow Coma Scale [n = 157]	
13–15	88 (56.1%)
9–12	28 (17.8%)
8 and below	41 (26.1%)
Intracerebral Hemorrhage Score [n = 33]	
0	0 (0.00%)
1	4 (12.1%)
2	14 (42.4%)
3	13 (39.4%)
4	2 (6.06%)
5	0 (0.00%)
6	0 (0.00%)
Hunt & Hess Grade [n = 10]	
1	2 (20.0%)
2	3 (30.0%)
3	1 (10.0%)
4	3 (30.0%)
5	1 (10.0%)
Fisher Scale [n = 6]	
1	0 (0.00%)
2	0 (0.00%)
3	1 (16.7%)
4	5 (83.3%)
NIH Stroke Scale [n = 39]	
0–4 (Minor)	6 (15.4%)
5–15 (Moderate)	7 (17.9%)
16–20 (Moderate-Severe)	5 (12.8%)
> 21 (Severe)	21 (53.9%)
HCAVM suspicion	
a. Not suspected	90 (55.9%)
b. Suspected	71 (44.1%)
Ruled out	22 (31.0%)
Confirmed	49 (69.0%)

[a]Unless otherwise specified, "n" is 161

on the same day of suspicion to up to 10 days after the suspicion, with the mean being 0.8 days.

Among those who were suspected with HCAVM but who had the diagnosis eventually ruled out, 27.3% displayed pleocytosis, none had hypoglycorrhachia, and 85.7% had hyperproteinorrachia. Gram stain was negative in all (100%) whereas only one (4.76%) had a growth on CSF culture. This, however, was deemed only as a contaminant. CI was negative for 95.4% of the sample. All (100%) had ongoing intravenous antibiotics at the time of suspicion with 90.9% of them receiving the medications for a pre-existing systemic infection. Table 2 displays the clinical and diagnostic data of these patients.

Among those suspected and eventually confirmed to have HCAVM, 69.4% displayed pleocytosis, 17.4% had hypoglycorrhachia, and 87.0% had hyperproteinorrachia. Gram stain only showed organisms in 13.6% of the cases whereas less than half (42.6%) had growth on CSF culture. Among those with culture positive results, Gram negative pathogens predominated at 85.7% with *Burkholderia cepacia* being the most common (33.3%) pathogen. CI was positive for only 18.4% of the sample. Almost all (93.9%) had been on intravenous antibiotics at the time of suspicion with 76.1% of them receiving the medications for a pre-existing systemic infection. Table 2 displays the clinical and diagnostic data of these patients.

Cell index

Using data from the 71 patients whom HCAVM was suspected, a CI of ≥5.00 had a sensitivity of 18.4%, 95% CI [8.76, 32.0] and a specificity of 95.5%, 95% CI [77.2, 99.9]. Figure 3 demonstrates the ROC curve drawn to determine its diagnostic accuracy. An AUC-ROC of 0.599, 95% CI [0.4673, 0.7322] was derived.

Following this, analysis to determine the sensitivity and specificity of CI at varying cut-offs was performed as shown in Table 3. Three mathematical models were then used to identify the optimal combination of sensitivity and specificity as shown in Table 4 [17, 18]. All three models pointed to a cut-off of ≥0.27. However, as this cut-off did not provide clinical utility and was against the principle of CI as a diagnostic parameter wherein a value of 1 is considered normal, cut-off values which were >1.00 were reviewed instead. A cut-off value of ≥1.21 was deemed the optimal clinical cut-off point as it offered the highest sensitivity of 30.6% while offering a specificity of 86.4%. Sensitivity was prioritized over specificity in

selecting the cut-off because CI deals with the diagnosis of an infectious condition whose complications can be severe or fatal if missed [17, 19].

The over-all sensitivity, specificity, and AUC-ROC of CI and its sensitivity, specificity, and AUC-ROC after performing subgroup analyses (i) for age and (ii) for neurologic indication for EVD insertion were then determined using the optimal cut-off of ≥1.21 (refer to Table 5). Over-all, the AUC-ROC of CI following this cut-off was 0.585. Stratifying the sample by age, the sensitivity of CI was higher in the pediatric population at 52.9% whereas it was only 3.13% among the adult population. In terms of the neurologic indication, CI had a sensitivity of 27.6% for those with ICH and a sensitivity of 35.0% for those with intracranial neoplasms. AUC-ROC was 0.598 in the pediatric age group and 0.516 in the adults. In addition, AUC-ROC was 0.571 in those with ICH whereas it was 0.592 among those with intracranial neoplasms. Subgroup analysis for patients with AIS and TBI could not be performed because of insufficient sample with these indications.

Discussion

Reports of HCAVM from multiple studies range from 0.3 to 23.2% of all patients who underwent EVD insertion [20]. This is in contrast to our institution's experience of a prevalence of 30.4% among those who underwent the said procedure. The wide range had been attributed to factors such as differences by which the devices had been handled, the presence of IVH during placement, and the frequency of EVD manipulation [3, 8, 12]. The risk also increases if catheterization duration reaches more than five days with the risk reaching its peak at days nine to 11 post-insertion [3, 8, 12]. In our study, the range of EVD placement prior to the suspicion of HCAVM was zero to 26 days, with its mean at six days. However, analysis of potential risk factors contributing to the higher prevalence of HCAVM in our institution was beyond the scope of this study.

The CSF qualitative and quantitative results may also be influenced by factors such as (1) the primary neurologic indication for EVD insertion, (2) the presence of foreign devices in the CNS, and (3) one's prior exposure to antibiotics.

CSF pleocytosis had been documented in 2 to 13% of cases of AIS but this was often self-limited and bore no diagnostic significance [21, 22]. This abnormality had also been documented in approximately 3% of cases of intraparenchymal hemorrhage [22]. Cases of SAH can also cause elevated CSF RBC count, hyperproteinorrachia, and hypoglycorrhachia [23]. On the other hand, IVH may result to a picture of chemical or aseptic meningitis as activated leukocytes enter the CSF to phagocytose the RBCs [7]. CSF evaluation of patients with primary CNS tumors such as gliomas, lymphomas, and meningiomas had also been shown to display pleocytosis in 16 to 30% of cases on top of hyperproteinorrachia and hypoglycorrhachia. Pleocytosis was more frequently observed among tumors localized near the ventricular system as this facilitated shedding of cells to the CSF [22, 24].

There may also be leukocyte infiltration as a response to foreign bodies within the CNS such as the EVD [6]. The yield of CSF cultures may also be lowered by active antimicrobials which patients receive for other ongoing systemic infections. In one study, almost half of patients which eventually developed HCAVM had been on antibiotics even prior to the suspicion for the said nosocomial CNSI [4]. In this study, the proportion was higher with 93.9% of those suspected and eventually diagnosed with HCAVM receiving intravenous antibiotics. More than three-fourths (76.1%) of this subset were receiving the medications because of a pre-existing systemic infection. Because of prior antimicrobial exposure, CS studies can be negative in 23% up to 78% of patients with HCAVM despite it being the reference standard [12]. In our sample, 57.4% had culture negative results. Among those with CSF positive results, Gram negative pathogens were the predominant growth at 85.7%.

The interpretation of a prior antibiotic exposure and a negative CSF CS result becomes more complex in the subgroup whom HCAVM was suspected but eventually ruled out. In this study, all (100%) of those under this subset had been receiving intravenous antibiotics. Almost all (90.2%) were on antimicrobials because of a pre-existing systemic infection. The diagnosis of HCAVM was ultimately ruled out after careful consideration of their overall CSF picture and after a different focus of infection was detected.

Given the effect of antibiotic exposure on CSF CS yield, one may intuitively think that the same intervention may also affect other CSF parameters. However, recent studies showed that in pediatric and adult patients with HCAVM who received antibiotics, serum and CSF WBC did not significantly differ from those who did not receive treatment prior to CSF sampling [25]. The same results regarding CSF WBC were also observed among children with community-acquired bacterial meningitis [26]. In addition, there were no significant differences in CSF WBC count regardless of the duration of prior antibiotic exposure [26]. It is however, beyond the scope of this study to characterize the effects of the duration of antibiotic exposure in the CSF parameters and CI of the included patients.

Currently, there are no defined guidelines on how to factor in the various CSF changes brought about by the pre-existing CNS pathology, the post-operative state, and one's prior antimicrobial exposure. CI had been proposed as a measure to take into account changes in the CSF

Table 2 Clinical and diagnostic data of patients suspected to have HCAVM

	FREQUENCY (%)	
PARAMETER	**SUSPECTED BUT RULED OUT [*N* = 22]**	**SUSPECTED AND CONFIRMED [*N* = 49]**
Cerebrospinal fluid studies		
a. Pleocytosis	[*n* = 22]	[*n* = 49]
Present	6 (27.3%)	34 (69.4%)
Absent	16 (72.7%)	15 (30.6%)
b. Cell Index	[*n* = 22]	[*n* = 49]
Positive	1 (4.54%)	9 (18.4%)
Negative	21 (95.4%)	40 (81.6%)
c. Hypoglycorrhachia	[*n* = 21]*	[*n* = 46]*
Present	0 (0.00%)	8 (17.4%)
Absent	21 (100%)	38 (82.6%)
d. Hyperproteinorrachia	[*n* = 21]*	[*n* = 46]*
Present	18 (85.7%)	40 (87.0.%)
Absent	3 (14.3%)	6 (13.0%)
e. Gram stain	[*n* = 21]*	[*n* = 44]*
Gram positive organism seen	0 (0.00%)	0 (0.00%)
Gram negative organism seen	0 (0.00%)	6 (13.6%)
No organisms seen	21 (100%)	38 (86.4%)
f. Culture	[*n* = 21]*	[*n* = 47]*
Culture positive	1 (4.76%)	20 (42.6%)
Number of growth		
Single organism	1 (100%)	19 (95.0%)
Dual organisms	0 (0.00%)	1 (5.00%)
Isolated organism		
Gram positive pathogen	0 (0.00%)	3 (14.3%)
Staphylococcus haemolyticus	0 (0.00%)	1 (33.3%)
Staphylococcus capitis	0 (0.00%)	1 (33.3%)
Streptococcus viridans	0 (0.00%)	1 (33.3%)
Gram negative pathogen	1 (100%)	18 (85.7%)
Acinetobacter baumanii+	1 (100%)	2 (11.1%)
Acinetobacter lwoffii	0 (0.00%)	2 (11.1%)
Acinetobacter nosocomialis	0 (0.00%)	1 (5.55%)
Burkholderia cepacia	0 (0.00%)	6 (33.3%)
Klebsiella pneumoniae	0 (0.00%)	4 (22.2%)
Serratia marcescens	0 (0.00%)	1 (5.55%)
Sphingomonas paucimobilis	0 (0.00%)	1 (5.55%)
Stenotrophomonas maltophilia	0 (0.00%)	1 (5.55%)
Culture negative	20 (95.2%)	27 (57.4%)
Antibiotic Exposure		
a. With ongoing intravenous antibiotics	22 (100%)	46 (93.9%)
For a pre-existing systemic infection	20 (90.9%)	35 (76.1%)
Prophylactic antibiotics[a]	2 (9.09%)	8 (17.4%)
Empiric antibiotics[b]	0 (0.00%)	3 (6.52%)
b. Without ongoing intravenous antibiotics	0 (0.00%)	3 (6.12%)
Pre-existing Systemic Infection/s		
a. No pre-existing infection	2 (9.09%)	14 (28.6%)
b. With pre-existing infection	20 (90.9%)	35 (71.4%)
Number of infections		
One	19 (95.0%)	33 (94.7%)
Two	1 (5.00%)	2 (5.26%)
Type of infection		
Bacteremia	0 (0.00%)	2 (5.40%)
Nosocomial sepsis	2 (9.52%)	6 (16.2%)

Table 2 (continued)

	FREQUENCY (%)	
PARAMETER	**SUSPECTED BUT RULED OUT [*N* = 22]**	**SUSPECTED AND CONFIRMED [*N* = 49]**
Pneumonia	17 (80.9%)	25 (67.6%)
Urinary tract infection	2 (9.52%)	4 (10.8%)

*"n" differs because of missing data during chart review

+Growth was deemed as only a contaminant

[a]Prophylactic antibiotics refer to those started prior to the EVD insertion and maintained during the duration of catheterization until the suspicion of HCAVM. The medication consistently used was Ceftriaxone

[b]Empiric antibiotics refer to those started to cover for the suspicion of HCAVM even prior to sending CSF studies for evaluation

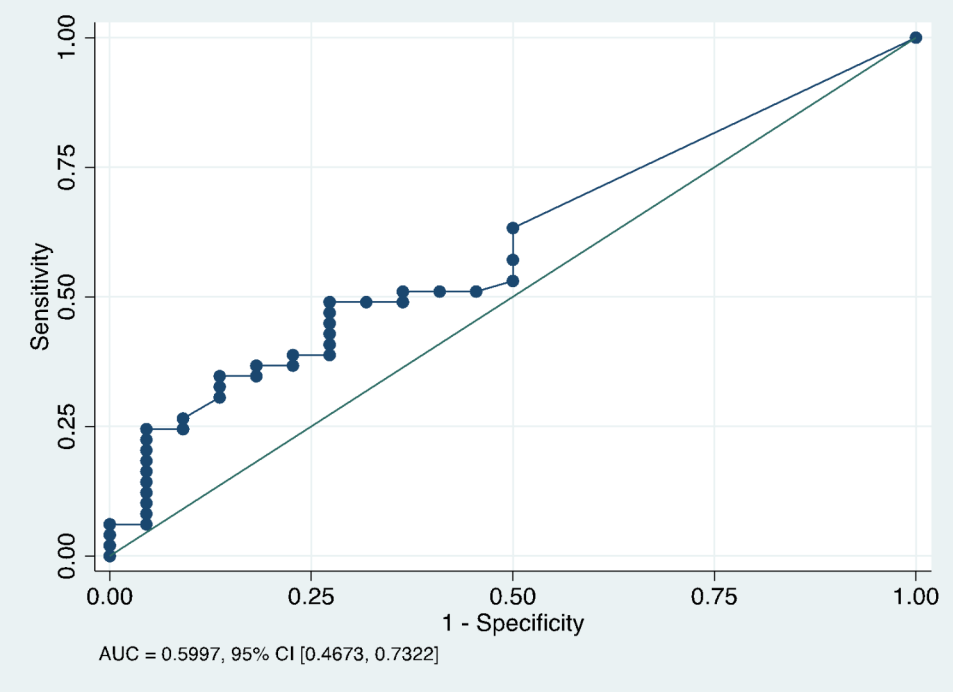

Fig. 3 AUC-ROC analysis for CI at a cut-off of 5

composition from RBC contamination secondary to the existing CNS pathology or the operative procedure. The hypothesis is that ventricular blood simply dilutes the CSF with peripheral blood; hence, CSF WBC and RBC should exist in similar proportion as that of the peripheral blood.

The utility of CI was first documented in 2004 after patients who developed HCAVM showed a significant increase in the said parameter at least 3 days prior to conventional diagnosis. A limitation, however, was the study's limited sample size of only 13 [7]. A follow-up study with 39 patients evaluated its utility but results did not attain statistical significance [2]. Subsequent studies showed positive results although they identified various cut-off points as compared to the 5-fold increase cut-off as originally proposed [9]. One study with 34 samples showed that a cut-off of 2.9 had a sensitivity of 95.0%, specificity of 92.9%, and AUC-ROC of 0.982 [1]. Another study with a sample size of 111 utilized a cut-off of 4.3 which showed an AUC-ROC of 0.825 [4]. The latest study included a sample size of 95 patients and utilized a cut-off of 10.4 revealing a sensitivity of 80.0%, specificity of 70.5%, and AUC-ROC of 0.727 [6]. An important observation, however, is that these previous studies only included patients ≥ 16 years old. The patients included also predominantly had ICH as the main neurologic indication for EVD insertion. Hence, the utility of the said parameter has not yet been previously studied in the pediatric age group and in other neurologic indications.

In our study, using the originally proposed cut-off value of 5, a sensitivity of 18.4%, specificity of 95.5%, and AUC-ROC of 0.599 were acquired. Following the optimal cut-off value of ≥ 1.21 improved the sensitivity to 30.6% but decreased specificity to 86.4% as an effect. However, AUC-ROC did not differ significantly at 0.585. As compared to previous studies which revealed higher sensitivity-specificity and fair to excellent diagnostic accuracy for CI following AUC-ROC analysis [27], our study showed

Table 3 Cut-off analysis of CI in predicting HCAVM ($n=71$)

CUT-OFF	SENSITIVITY	SPECIFICITY	CORRECTLY CLASSIFIED
≥ 0	100.0%	0.0%	69.0%
≥ 0.01	63.3%	50.0%	59.2%
≥ 0.02	57.1%	50.0%	54.9%
≥ 0.04	53.1%	50.0%	52.1%
≥ 0.06	51.0%	54.6%	52.1%
≥ 0.08	51.0%	59.1%	53.5%
≥ 0.11	51.0%	63.6%	54.9%
≥ 0.12	49.0%	63.6%	53.5%
≥ 0.26	49.0%	68.2%	54.9%
≥ 0.27	49.0%	72.7%	56.3%
≥ 0.28	46.9%	72.7%	54.9%
≥ 0.33	44.9%	72.7%	53.5%
≥ 0.42	42.9%	72.7%	52.1%
≥ 0.43	40.8%	72.7%	50.7%
≥ 0.52	38.8%	72.7%	49.3%
≥ 0.54	38.8%	77.3%	50.7%
≥ 0.59	36.7%	77.3%	49.3%
≥ 0.68	36.7%	81.8%	50.7%
≥ 0.7	34.7%	81.8%	49.3%
≥ 0.87	34.7%	86.4%	50.7%
≥ 0.93	32.7%	86.4%	49.3%
≥ 1.21	30.6%	86.4%	47.9%
≥ 1.31	26.5%	90.9%	46.5%
≥ 1.61	24.5%	90.9%	45.1%
≥ 2.05	24.5%	95.5%	46.5%
≥ 2.86	22.5%	95.5%	45.1%
≥ 3.24	20.4%	95.5%	43.7%
≥ 6.26	18.4%	95.5%	42.3%
≥ 6.28	16.3%	95.5%	40.9%
≥ 11.03	14.3%	95.5%	39.4%
≥ 13.01	12.2%	95.5%	38.0%
≥ 16.7	10.2%	95.5%	36.6%
≥ 18.56	8.2%	95.5%	35.2%
≥ 24.18	6.1%	95.5%	33.8%
≥ 95.75	6.1%	100.0%	35.2%
≥ 527.39	4.1%	100.0%	33.8%
≥ 3175.03	2.0%	100.0%	32.4%
> 3175.03	0.0%	100.0%	31.0%

Cut-off of ≥ 5.0: Sensitivity = 18.4%, 95% CI [8.76, 32.0]; Specificity = 95.5%, 95% CI [77.2, 99.9]

Table 4 Results of mathematical models to guide the selection of the optimal cut-off value for CI

MODEL	CUT-OFF VALUE	SENSITIVITY	SPECIFICTY
Youden	0.265	49.0%	72.7%
Euclidean	0.265	49.0%	72.7%
Liu	0.265	49.0%	72.7%

lower sensitivity and AUC-ROC with the latter indicating that CI failed to adequately diagnose HCAVM.

Subgroup analysis done for age showed that CI offers a higher sensitivity at 52.9% although with a lower specificity at 66.7% in the pediatric population. However, its AUC-ROC of 0.598 indicates that the parameter is also unable to adequately diagnose HCAVM in this age group. This is also true for the adult population wherein AUC-ROC was only 0.516. Analyzing the utility of the parameter in terms of the neurologic indication for EVD insertion, for cases of ICH and intracranial neoplasms, their sensitivity and specificity lie close to the sensitivity and specificity of CI over-all. However, both their AUC-ROC also fail to adequately diagnose HCAVM.

In addition to a single CI determination, changes in its trend during subsequent CSF sampling may also potentially help diagnose HCAVM. Available studies looking into serial CI showed trends of slowly increasing CI values until the time of conventional diagnosis of HCAVM. To further analyze these trends, the CI escalation ratio was a parameter proposed by dividing the highest CI derived by the baseline CI at the time of EVD insertion [6, 12]. However, because of the inconsistent CSF sampling schedules in our sample, this study only focused on the utility of CI at the point of initial HCAVM suspicion. The significance of looking into the trend and/or the CI escalation ratio may be better studied in a prospective study which will ensure a predefined CSF sampling schedule from EVD insertion until its removal.

As of writing, this had been the largest study evaluating the diagnostic utility of CI as it reviewed the records of a total of 161 patients who underwent EVD insertion and analyzed the parameter's utility in 71 patients who were suspected with HCAVM. This is also the first study to include the pediatric population. In addition, as compared to previous studies which predominantly included patients with various forms of ICH, our sample included a significant proportion with intracranial neoplasms.

Additional limitations of the study, however, must also be acknowledged. First, its retrospective design may have posed unrecognized confounders. Second, among those with intracranial neoplasms, the interpretation of CI may be confounded by potential CSF alterations owing to leptomeningeal spread or prior treatments received. The utility of CI in this particular subgroup may be further explored in another study.

Table 5 Sensitivity, specificity, and AUC-ROC of CI using a cut-off of ≥ 1.21

	SENSITIVITY	SPECIFICITY	AUC-ROC
Over-all	30.6% [18.3, 45.4]	86.4% [65.1, 97.1]	0.585 [0.487, 0.683]
By age			
<19 years old	52.9% [27.8, 77]	66.7% [22.3, 95.7]	0.598 [0.358, 0.838]
≥ 19 years old	3.13% [0.10, 16.2]	100% [79.4, 100]	0.516 [0.485, 0.546]
By neurologic indication			
Intracranial hemorrhage	27.6% [12.7, 47.2]	86.7% [59.5, 98.3]	0.571 [0.450, 0.693]
Acute ischemic stroke	Insufficient data	Insufficient data	Insufficient data
Intracranial neoplasm	35.0% [15.4, 59.2]	83.3% [35.9, 99.6]	0.592 [0.396, 0.787]
Traumatic brain injury	Insufficient data	Insufficient data	Insufficient data

Conclusion

In neurologic patients who underwent EVD insertion, our data revealed no sufficient evidence that a CI cut-off of 5 is a good predictor of the diagnosis of HCAVM. Adjusting the cut-off to ≥1.21 improved its sensitivity although it still failed in its diagnostic accuracy. Subgroup analysis by age and by neurologic indication for EVD insertion showed varying sensitivity and specificity but all still did poorly in diagnostic accuracy.

Abbreviations

AIS	Acute ischemic stroke
AUC-ROC	Receiver operating characteristic area under the curve
CDC/NHSN	Centers for Disease Control and Prevention's National Healthcare Safety Network
CI	Cell index
CNS	Central nervous system
CNSI	Central nervous system infection
CS	Culture and sensitivity
CSF	Cerebrospinal fluid
EVD	External ventricular drain
GCS	Glasgow Coma Scale
GS	Gram stain
HCAVM	Healthcare-associated ventriculitis and meningitis
ICH	Intracranial hemorrhage
ICP	Intracranial pressure
IVH	Intraventricular hemorrhage
NIHSS	National Institutes of Health Stroke Scale
RBC	Red blood cell
SAH	Subarachnoid hemorrhage
TBI	Traumatic brain injury
UP-PGH	University of the Philippines – Philippine General Hospital
WBC	White blood cell

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Author contributions

JJBG - conceptualization, investigation, writing – original draft; DJS - conceptualization, investigation; KTDJS - conceptualization, investigation; MAT – conceptualization, writing – review & editing, supervision; KJOK – conceptualization, writing – review & editing, supervision; PMDP – conceptualization, writing – review & editing, supervision.

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Data availability

All data generated and analyzed during this study are included in this published article. The dataset is available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare no known or potential conflicts of interest.

Ethics approval

The protocol was approved by the UP Manila Research Ethics Board (UPMREB 2023-0150-01).

Consent to participate

The UP Manila Research Ethics Board waived the need for consent given the nature of the study.

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