

1 **Title:** Modalities and accuracy of diagnosis of external ventricular drainage—related
2 infections: a prospective multicentre observational cohort study

3
4
5
6 **Authors:** Berger-Estilita J¹, Passer M², Giles M², Wiegand J³, Merz TM⁴.

7
8
9 1. Department of Anaesthesiology and Pain Therapy, Inselspital, Bern University
10 Hospital, University of Bern, Switzerland

11 6
12 7 2. Department of Intensive Care Medicine, Royal North Shore Hospital, University of
13 Sydney, Sydney, NSW, Australia

14 8
15 8 3. Intensive Care Unit, Lindenhofspital, Bern, Switzerland

16 9
17 9
18 10 4. Department of Intensive Care Medicine, Inselspital, Bern University Hospital,
19 University of Bern, Switzerland

20 11
21 12
22 13
23 14
24 15
25 16
26 14 Corresponding author:

27 15 Tobias M Merz

28 16 Department of Intensive Care Medicine,

29 17 Bern University Hospital,

30 18 3010 Bern, Switzerland

31 19 tobias.merz@insel.ch

32 20
33 21
34 22 We would like to disclosure that partial results of this study were presented as conference
35 23 poster entitled "Does antibiotic prophylaxis influence the incidence of EVD-related
36 24 infections? A prospective multicentre study" at the 30th Annual Congress of the European
37 25 Society of Intensive Care Medicine (ESICM), held in Vienna on the 23 - 27 September 2017.

1 **Abbreviations and acronyms:**

2 AB: Antibiotic; AUC: Area under the curve; AUROC: AUC area under the ROC curve; CD-ERI:
3 clinically diagnosed EVD related infection, CP-ERI: culture-proven EVD related infection, CSF
4 WBCC: CSF white blood cell count; CNS: central nervous system; CoNS: Coagulase-Negative
5 Staphylococci; CRP: C-reactive protein; CSF: cerebrospinal fluid; ERI: EVD-related infection;
6 EVD: external ventricular drain; GCS: Glasgow Coma Score; GOS: Glasgow Outcome Score;
7 ICH: intracerebral haemorrhage; ICP: intracerebral pressure; ICU: intensive care unit; LOS:
8 length of hospital stay; PMN: Polymorphonuclear Neutrophils; RBC: red blood cell; RBCC: red
9 blood cell count; ROC: Receiver operating characteristic; S-CRP: serum C-reactive protein; S-
10 WBCC: Serum white blood cell count; SAH: subarachnoid haemorrhage; SIRS: systemic
11 inflammatory response syndrome; TBI: Traumatic brain injury; WBC: White Blood Cell

1 **Abstract:**

2
3
4 3 **Background:** Device infection is a major complication of placement external ventricular drains
5 4 (EVD). Diagnostic features are often masked by underlying disease or cerebrospinal fluid (CSF)
6 5 contamination by blood. We aim to assess which diagnostic modalities are applied for EVD-
7 6 related infection (ERI) diagnosis and evaluate their accuracy.

8 7 **Methods:** This observational prospective study included 187 adult patients with an EVD.
9 8 Modalities of clinical diagnosis of ERI diagnosed by treating physicians on clinical grounds and
10 9 blood and CSF analysis (CD-ERI) were assessed prospectively. Additionally, the diagnostic
11 10 accuracy of clinical and laboratory parameters for the diagnosis of culture proven ERI (CP-ERI)
12 11 was evaluated, using data of the study patients and including a retrospective cohort of 39
13 12 patients with culture-proven ERI (CP-ERI).

14 13 **Results:** Thirty-one CD-ERIs were diagnosed in the prospective cohort. Most physicians used
15 14 CSF analysis to establish the diagnosis. ROC analysis revealed an AUC of 0.575 ($p=0.0047$) for
16 15 the number of positive SIRS criteria and AUC of 0.5420 ($p= 0.11$) for the number of
17 16 pathological neurological signs for diagnosis of CP-ERI. Diagnostic accuracy of laboratory
18 17 values was AUC 0.596 ($p=0.0006$) for serum white blood cell count (WBCC), AUC 0.550
19 18 ($p=0.2489$) for serum CRP, AUC 0.644 ($p< 0.0001$) for CSF WBCC and AUC 0.690 for CSF
20 19 WBC/red blood cell count ratio (both $p< 0.0001$). Neither a temporal trend in potential
21 20 predictors of CP-ERI nor a correlation between clinical diagnosis and proven CSF infection was
22 21 found.

23 22 **Conclusions:** Clinicians base their diagnosis of ERI mostly on CSF analysis and occurrence of
24 23 fever, leading to over-diagnosis. The accuracy of the clinical diagnosis is low. Commonly used
25 24 clinical and laboratory diagnostic criteria have a low sensitivity and specificity for ERI.

26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48 26 Key words: External Ventricular Device, EVD-related infection, diagnosis, CSF changes
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 **Introduction:**

2 The insertion of an external ventricular drain (EVD) is a common and potentially lifesaving
3 procedure in neurocritical care[9]. EVDs are often used for monitoring of intracerebral
4 pressure (ICP) and drainage of cerebrospinal fluid (CSF) in the context of intracerebral
5 haemorrhage (ICH), subarachnoid haemorrhage (SAH) and traumatic brain injury (TBI)[2,37].
6 EVD-related Infection (ERI) is one of the major complications of EVD placement, representing
7 a serious hospital-acquired infection. Reported incidences of EVD-related infections range
8 from 5% to more than 20% of EVD-placements [1,4,8,18,38,2,10,15,23,25,27] and are
9 associated with poorer neurological outcomes, increased healthcare costs and prolonged
10 hospital stays [16,10,15,23-25,27].

11 Rapidly available parameters for the diagnosis of ERI include clinical signs such as fever,
12 nuchal rigidity and a change in mental status, blood tests including elevated white blood cell
13 (WBC) count, neutrophilia with a shift towards immature band forms or elevated serum C -
14 reactive protein (CRP)[3] and altered CSF parameters – such as increases in CSF white blood
15 cell count (CSF WBCC). However, clinical features of EVD-related central nervous system
16 infection are often masked by an altered level of consciousness due to the patient’s
17 underlying condition or because of the frequent use of sedation in neuro-critical care
18 patients. Blood tests are non-specific, in that they may indicate infections of sites other than
19 the CNS or be elevated due to causes not related to an infection. Finally, changes in CSF
20 parameters can be concealed by the presence of blood in the CSF space common in ICH, SAH
21 and TBI patients, making the diagnosis of ERI difficult[34,7].

22 Positive CSF Gram stains and/or cultures in the context of new clinical signs of CNS infection
23 plus changes in CSF parameters represent the gold standard for the diagnosis of an EVD-
24 related infection.[35,19] However, Gram stains often are negative even in culture-positive
25 CSF[31] and CSF cultures take several days until bacterial growth can safely be excluded and
26 do not allow early diagnosis of infection. Therefore only in a minority of patients a certain
27 diagnosis of culture proven ERI (CP-ERI) can be made based on evidence for the presence of
28 bacteria in the cerebrospinal space. Most often clinicians have to base diagnosis and
29 treatment on clinical features in correlation with changes in blood and CSF parameters
30 (clinically diagnosed ERI [CD-ERI]).

31 Recommendations for diagnosis and treatment of ERI represent expert opinion and are
32 deducted from established criteria for the diagnosis of non-EVD-related central nervous

1 system (CNS) infections [34,2,28,35,6,12]. Information on which parameters clinicians base
2 the diagnosis of EVD-infections is not reported in the literature.
3
4
5
6 4 In this study, we aim to prospectively assess which diagnostic modalities to detect ERI are
7 most commonly applied by clinicians in the neurocritical care setting. Additionally, we
8
9
10 6 evaluate the diagnostic accuracy of these parameters in a large cohort of patients.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 **Methods and Materials:**

2
3
4 3 *Study design:* Prospective observational multicentre study with a *post hoc* analysis that
5
6 4 includes a retrospective cohort for comparison.

7 5 *Setting:* Patients were enrolled in the intensive care units (ICU) of the University Hospital of
8
9 6 Bern, Switzerland (centre 1), Royal North Shore Hospital of Sydney (centre 2) and the Alfred
10
11 7 Hospital in Melbourne (centre 3), Australia.

12
13 8
14
15 9 *Participants:*

16
17 10 • *Prospective Cohort*

18
19 11 Consecutive patients over 16 years of age suffering from ICH, SAH or TBI in whom an EVD was
20
21 12 inserted during the study period of 24 months were enrolled in the study (prospective
22
23 13 period). Patients with diagnosed or suspected primary CNS or systemic infection [34] and
24
25 14 patients receiving systemic antibiotic treatment in the 72 hours before EVD placement were
26
27 15 excluded.

28
29 16
30
31 17 • *Retrospective cohort*

32
33 18 Because of a very low number of positive CSF cultures and Gram stains in the prospective
34
35 19 cohort, we included a second, retrospective cohort of patients from centre 1 and 2 with
36
37 20 proven ERI. Records of all adult patients older than 16 years of age suffering from ICH, SAH or
38
39 21 TBI in whom an EVD was inserted over a period of five years prior to study commencement
40
41 22 were reviewed. Patients with diagnosed or suspected primary CNS or systemic infection [34]
42
43 23 and patients receiving systemic antibiotic treatment in the 72 hours before EVD placement
44
45 24 were not included in the retrospective cohort.

46 25
47
48 26 *Data sources:* Collected baseline characteristics in both cohorts included patient
49
50 27 demographics, main diagnosis, Glasgow Coma Score (GCS), Hunt & Hess[21]and Fisher[11]
51
52 28 grading systems for SAH and ICH score[17] for ICH at ICU admission, length of hospital stay
53
54 29 (LOS), survival at hospital discharge and Glasgow Outcome Score (GOS). Clinical data included
55
56 30 clinical signs of a systemic inflammatory response syndrome (SIRS) (temperature >38.3 °C or
57
58 31 <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min or PaCO₂ < 32 mmHg),
59
60 32 and of CNS infection (nuchal rigidity, headache, and changes in mental status). In the case of

1 sedated patients where conclusive assessment of neurological status was not possible, signs
2 of CNS infection were rated as absent. Laboratory data included all available measurements
3 of red blood count (RBCC), serum WBCC count, serum C-reactive protein (CRP) level, CSF
4 RBCC, CSF WBCC, CSF Gram stain and CSF cultures. Blood tests were performed on a daily or
5 alternate-day basis and CSF samples were regularly (every 24 to 72h) collected from the day
6 of EVD placement as per routine care. For data collection and statistical analysis, the day of
7 EVD insertion was defined as day 0. Patient records were matched with the microbiology
8 database of all cultured microorganisms in CSF and all positive Gram stains of CSF to identify
9 patients with proven EVD-related infections during the course of the hospital stay. In the
10 prospective cohort, the experience level of the person placing the EVD and aspects of surgical
11 technique, the type of antibiotic strategy used, and the duration of catheter use were also
12 collected.

13
14 *Diagnosis of ERI:* In the prospective cohort, the treating clinicians had to fill out a
15 questionnaire to report occurrence of CD-ERI or non-EVD related infections and subsequent
16 antibiotic treatment. Physicians were required to indicate on which of the following
17 parameters the diagnosis suspicion had been based: serum WBCC, percentage of blood WBC
18 band forms, serum CRP levels, CSF cell count, CSF RBCC/WBCC ratio, presence of positive SIRS
19 criteria and/or clinical signs of CNS infection.

20
21 In both cohorts, CP-ERI was defined as occurrence of a positive CSF culture or Gram stain and
22 concomitant occurrence of at least two SIRS criteria (temperature >38.3 °C or <36 °C, heart
23 rate >90 beats/min, respiratory rate >20 breaths/min or PaCO₂ < 32 mmHg) or occurrence of
24 one of any neurological sign of CNS infection (nuchal rigidity, headache, or changes in mental
25 status) plus increased CSF WBCC[34].

26
27 *Statistical analysis:* Data is presented as mean and standard deviation or median and quartiles
28 as indicated. Normal distribution was established using D'Agostino & Pearson omnibus
29 normality test.

30 Fisher's Test, Chi-square, student's *t*-test and Mann-Whitney *U* test were used to compare
31 variables of patients with and without CD-ERI in the prospective cohort of study patients. Chi
32 Square test was used to detect a significant correlation between the clinical diagnosis of ERI

1 and CP-ERI in the prospective group.

2 The correlation between clinical signs, blood results or CSF parameters and occurrence of CP-
3 ERI was assessed using data from both, the prospective and retrospective cohort combined.
4 Patient-days were classified according to their temporal relation to the time point of diagnosis
5 of CP-ERI as pre-infection, peri-infection (within 48h before and after diagnosis of CP-ERI) and
6 post-infection (>48h after diagnosis of CP-ERI). Data from pre-infection patient days versus
7 peri-infection patient days were used to evaluate the predictive value of clinical and
8 laboratory indicators in predicting CP-ERI. Receiver operating characteristic (ROC) curves
9 were constructed plotting sensitivity vs. 1-specificity to evaluate the predictive value of
10 clinical and laboratory indicators in predicting occurrence of culture positive ERI; the results
11 are reported as area under the ROC curve (AUROC) and significance value.

12 Additionally, linear mixed-effect models were used to assess temporal changes of parameters
13 potentially indicating ERI and differences between patients with and without CP-ERI. Results
14 are reported as F value and significance p. Potential temporal curve changes based on a 7-day
15 time period before the development of diagnosed infection were assessed by fitting growth
16 curves up to a third order polynomial as a covariate and occurrence of infection as fixed
17 effect. In patients in which no CP-ERI occurred, the first 7 days after EVD insertion was used
18 as comparison period. Statistical significance was determined when $p < 0,05$ (two-sided). All
19 statistical analyses were performed using IBM SPSS Statistics 24 (SPSS Inc. Chicago, Illinois).

20
21 *Ethics approval:* The study protocol was reviewed and approved by the relevant institutional
22 review boards (Ethics Committee Bern, Switzerland; the Alfred Health Ethics Committee,
23 Melbourne, Australia; and the Hawkesbury Human Research Ethics Committee, Northern
24 Sydney Central Coast Health, Australia). All procedures were in accordance with the
25 institutional and national research committees and with the 1964 Helsinki declaration and its
26 later amendments or comparable ethical standards.

1 **Results:**

2 The baseline characteristics of both cohorts, the number of culture or gram stain positive ERIs
3 and causal organisms are presented in Table 1.
4

5 *Clinical diagnosis of EVD-related infection in the prospective cohort:*

6 Thirty-one CD-ERIs occurred. The main diagnostic parameters on which ERI was based and
7 technical aspects of EVD placement and are presented in Table 2, in groups stratified by
8 presence/absence of clinical EVD infection. There was no significant difference in age and LOS
9 for the presence of CD-ERI. There was no significant correlation of age and LOS and
10 occurrence of CD-ERI. One hundred and forty-two non-EVD related infections were
11 diagnosed. Pneumonia was the main other form of infection (78 patients, 54.9%), followed
12 by bloodstream infection (7 patients, 4.7%). Infections not related to EVD placement had an
13 onset time of 5.3±4.8 days, while CD-ERIs developed later, although without significant
14 difference ($p=0.134$). In 25.4% of EVD-days systemic antibiotics were used, either for
15 prophylaxis or treatment of CD-ERI or for treatment of other infections. Most patients
16 received antimicrobial treatment with 3rd or 4th generation cephalosporins, according to local
17 protocol.
18

19 Most physicians used CSF analysis to establish presence of CD-ERI, with CSF WBCC the most
20 relevant criterion. A combination of more than one criterion was used in 16 cases (45,7%).
21 Neurological signs of nuchal rigidity and altered consciousness, as well as positive CSF cultures
22 and CSF changes (elevated CSF protein, elevated CSF lactate and reduced CSF to blood glucose
23 ratio) were not used as a diagnostic criteria by any physicians. Single-shot antibiotic
24 prophylaxis for EVD placement was used in 125 patients (66.8%), whereas 62 patients (33.2%)
25 received continuous prophylactic antibiotics for the duration of EVD drainage. Antimicrobial
26 empirical treatment choices are summarized in Table 2. There were 414 antibiotic-exposure
27 days. All patients but one received systemic antimicrobial treatment; none of them were
28 treated with intraventricular antibiotics and none of the EVDs was antibiotic-coated.
29 Monotherapy was only used in 7 patients (20%). Most frequently, antimicrobial combinations
30 included dual therapy with glycopeptide plus carbapenem (20%) and triple therapy with
31 cephalosporin plus metronidazol plus glycopeptide (20%).
32

33 One hundred and sixteen EVD days were counted in the prospective cohort. Episodes of

1 *abnormal temperature* occurred 503 times (31.1% of EVD days), increased *heart rate* and
2 *respiratory rate* were present in 690 (42.7%) and 624 (38.6%) episodes, respectively.
3 Incidence for signs and symptoms of central nervous system infection was: 21 episodes (1.3%)
4 of *nuchal rigidity*; 150 episodes (9.3%) of *decreased mental status*; and 187 episodes (11.6%)
5 of *headache*. A total of 553 episodes (34.2%) of two or more positive SIRS criteria occurred.
6 The range and incidence of pathological results of potential indicators of ERI are summarized
7 in Table 3. Finally, the Chi Square test did not reveal a significant correlation between the
8 clinical diagnosis of ERI and proven CSF infection in the prospective cohort (p=0.0580).

9
10 *Prediction of CP-ERI using clinical features and blood and CSF parameters using both cohorts:*

11 A total of 46 CP-ERI occurred in the two study cohorts (7 in the prospective and 39 in the
12 retrospective cohort). The CP-ERI rate was 4.33 cases per 1000 catheter-days in the
13 prospective cohort. The ROC analysis of potential clinical indicators of EVD infection revealed
14 an AUROC of 0.575 (95%-CI 0.5194 - 0.6307, p= 0.0047) for the number of positive SIRS
15 criteria, and an AUROC 0.5420 (95%-CI 0.4880 - 0.5960, p= 0.11) for the number of
16 pathological neurological signs. Figure 1 shows the results of the ROC analysis of laboratory
17 data potentially indicating EVD-related infections. S-WBCC, CSF WBCC and CSF RBCC/WBCC
18 ratio revealed an AUC of significantly >0.5. Table 4 reports the temporal trends of single
19 potential predictors of ERI in groups stratified by the presence/absence of proven ERI. No
20 significant temporal trend in potential predictors of CP-ERI was found during the 7 days prior
21 to culture or gram stain proven ERI, indicating that no significant increase in number of SIRS
22 criteria and neurological signs of CNS infection occurred nor higher levels of S-CRP or
23 increases in S-WBCC, CSF WBCC and CSF WBCC/RBCC ratio were measured in the lead up to
24 CP_ERI Patients *without* CP-ERI showed significant changes of SIRS criteria and S-CRP over
25 time during the first 7 days after EVD placement.

1 **Discussion:**

2 In our multicentre observational study, clinicians based their diagnosis of ERI mostly on CSF
3 analysis and the occurrence of fever. The frequency of CD-ERI was considerably higher than
4 the incidence of CP-ERI and the two were not correlated. Our analysis indicates that
5 commonly used diagnostic parameters have a low sensitivity and specificity for detection of
6 ERI.

7
8 There are several limitations to our study. Because of the low number of CP-ERI in our
9 prospective sample, we needed to use a retrospective cohort. This may introduce
10 heterogeneity in the study population and entails the use of a more complex methodology
11 and statistical analysis. In order to minimize this bias, we identified the retrospective cohort
12 using the same inclusion and exclusion criteria and baseline characteristics as for our
13 prospective group. Additionally, the parameters used in the study analysis consist of
14 laboratory values, defined measurements of vital signs included in the SIRS criteria and signs
15 of CNS infection which are all routinely and prospectively assessed in all neuro-critical care
16 patients. It can be assumed that these parameters are measured with the same precision in
17 the prospective and retrospective cohort. Another important limitation was that data were
18 restricted to parameters collected in the clinical context. This resulted in missing values and
19 did not include more recently established infection markers, such as sTREM-1[13], for
20 determining ERI. We used positive CSF culture or gram stain results as the gold standard
21 diagnosis of ERI, but this might be associated with a bias caused by the suboptimal sensitivity
22 and specificity of CSF gram stains and cultures for diagnosing EVD-related infection. Culture
23 results can be impaired by concomitant antibiotic treatment, that was present in our patient
24 cohort, during 25% of EVD-days (either for prophylaxis of ERI, treatment of ERI or treatment
25 of concomitant infection). Nevertheless, we believe that our analysis is valuable and has
26 several strengths: on the one hand, the trial included a large cohort of patients with EVDs; on
27 the other hand, the focus of the study was on evaluating how the diagnosis of ERIs established
28 in the context of current guidelines [34,19,12], which are mostly based on expert opinion,
29 therefore justifying the need for a further analysis.

30
31 Timely diagnosis and the commencement of adequate antimicrobial therapy is key in
32 improving patients' outcomes in ERIs and prompts clinicians to start empiric antibiotic

1 therapy in patients in whom ERI is suspected. Several authors [19,8,29] argue that only
2 positive CSF cultures, in conjunction with CSF pleocytosis, low glucose level, or high protein
3 level, reliably indicate EVD-related infection. In the absence of positive cultures, some
4 researchers accept CSF pleocytosis alone as sufficient evidence of CSF infections [32,22].
5 However, other authors report that determining ERI based on CSF direct examination has
6 been shown to have low sensitivity[35,36] and that CSF culture results are not readily
7 available and not reliable. Our results indicate that clinicians base their diagnosis of EVD
8 infection mainly on the presence of fever and increased CSF WBC counts. But such a diagnosis
9 based on clinical and CSF criteria may be misleading: firstly, in the neurocritical population,
10 SIRS criteria and pathological neurological findings can be a manifestation of the underlying
11 disease or be influenced by concomitant treatment, such as sedation. Secondly, any type of
12 systemic infection induces systemic inflammation and can lead to increased levels of CRP and
13 serum WBCC and concurrent infections occur frequently. Finally, the presence of
14 intraventricular blood can distort the typical CSF WBC/RBC ratio and be a non-infectious
15 source of fever.

16
17 In our data, the number of positive SIRS criteria was significantly higher after the occurrence
18 of proven infection, whereas the number of pathological neurological signs did not differ. The
19 perceived lack of specificity for CD-ERI might explain why these clinical and laboratory
20 indicators of infection were used less frequently for diagnosis of ERI.

21
22 Although retrospective data[13,14,37,30,5] have suggested that CSF WBCC and CSF
23 WBCC/RBCC ratio are useful in the diagnosis of EVD-related infection, our analysis suggests
24 that commonly used bedside clinical and laboratory parameters are not a reliable basis to
25 diagnose or exclude ERIs. Occurrence of positive SIRS criteria and of neurological signs of
26 infection did not sufficiently discriminate between states of confirmed or absent culture-
27 proven EVD infection. We were not able to identify any cut-offs for serum or CSF parameters
28 that were associated with acceptable sensitivity and specificity to be of value in the clinical
29 context. Analysing serum or CSF levels of potential indicators of ERI over time – as opposed
30 to using specific cut-off values – revealed a high inter-individual variability between
31 measurements; and occurrence of CP-ERI was not associated with any significant temporal
32 changes of diagnostic markers. Remarkably, only a third of the patients with proven ERI had

1 an elevated temperature. Typical neurological symptoms of ERI - such as headache, neck
2 stiffness or decreased were only reported in 10% of patients. This might reflect the nature of
3 device-associated infections, which are frequently caused by slow-replicating microorganisms
4 of low virulence growing in biofilms, such as CoNS (Coagulase-Negative Staphylococci) and
5 Propionibacterium acnes.

6
7 In accordance with other studies [7,26,37,8,28,2], the most common pathogens were CoNS.
8 The spectrum of these microorganisms suggests that the patient's skin flora is an important
9 source of EVD infection. The type of antibiotic prophylaxis (periprocedural vs continuous) did
10 not influence the incidence of EVD-related infections. In most patients receiving antimicrobial
11 prophylaxis before EVD placement, the chosen regimes did not cover the cultured pathogen
12 spectrum. The use of broad-spectrum penicillins and 2nd generation cephalosporins does not
13 show adequate coverage of *Staphylococcus epidermidis*[33], the main pathogenic agent of
14 this group. Another important aspect is that the isolation of *S. epidermidis* and other CoNS in
15 the CSF needs to be interpreted with caution, as this may represent contamination [20]. An
16 analysis to explore if antibiotic treatment previous to EVD insertion protects against infection
17 would be interesting and may have clinical consequences, but our data is very small for this
18 exploratory analysis and we suggest it to be investigated with other studies.

19
20 Our study therefore raises the discussion that routine CSF analysis on a daily basis or at two
21 day intervals is questionable, although it is the standard practice in most neuro-critical care
22 units. CSF culture is the only diagnostic parameter with a high specificity, but its sensitivity
23 impaired by antibiotic use so a restrictive antibiotic strategy for ERI and other infection could
24 become a trend. We agree that if CSF infection is suspected, CSF cultures should be performed
25 and empirical antibiotic treatment should be commenced, but treatment should be stopped
26 immediately once cultures come back negative.

27
28 Because CSF parameters are difficult to interpret, others sources for laboratorial diagnosis
29 should be sought. Promising other biomarkers of CSF infection already exist[13], but he
30 specificity/sensitivity of these has not been assessed yet in patients treated with an EVD.

31
32 In conclusion, clinicians base their diagnosis of ERI mostly on CSF analysis and occurrence of

1 fever. The frequency of clinically diagnosed ERI is considerably higher than the incidence of
2 proven ERI and the accuracy of the clinical diagnosis is low. This might lead to frequent use of
3 antibiotic treatment, causing an increase in risk of inducing growth of antibiotic-resistant
4 pathogens and impair the sensitivity of CSF cultures. Our analysis indicates that commonly
5 used clinical and laboratory diagnostic criteria have a low sensitivity and specificity for
6 detection of EVD-related infection, therefore routine analysis of CSF samples to screen
7 patients for ERI does not seem to be justified.
8

9 **Compliance with ethical standards**

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
No funding was received for this research.

All authors certify that they have no affiliations with or involvement in any organization or
entity with any financial interest (such as honoraria; educational grants; participation in
speakers' bureaus; membership, employment, consultancies, stock ownership, or other
equity interest; and expert testimony or patent-licensing arrangements), or non-financial
interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in
the subject matter or materials discussed in this manuscript.

Due to the observational nature of the study, which only used data obtained during routine
care, formal consent is not required.

This article does not contain any studies with animals performed by any of the authors.

1 **References:**

- 2 1. Arabi Y, Memish ZA, Balkhy HH, Francis C, Ferayan A, Al Shimemeri A, Almuneef MA (2005)
3
4 3 Ventriculostomy-associated infections: incidence and risk factors. *Am J Infect Control*
5
6 4 33:137-143
- 7 5 2. Beer R, Lackner P, Pfausler B, Schmutzhard E (2008) Nosocomial ventriculitis and meningitis
8
9 6 in neurocritical care patients. *J Neurol* 255:1617-1624. doi:10.1007/s00415-008-0059-
10
11 7 8
- 12 8 3. Berger C, Schwarz S, Schaebitz WR, Aschoff A, Schwab S (2002) Serum procalcitonin in
13
14 9 cerebral ventriculitis. *Crit Care Med* 30:1778-1781
- 15 10 4. Bogdahn U, Lau W, Hassel W, Gunreben G, Mertens HG, Brawanski A (1992) Continuous-
16
17 11 pressure controlled, external ventricular drainage for treatment of acute
18
19 12 hydrocephalus--evaluation of risk factors. *Neurosurgery* 31:898-903; discussion 903-
20
21 13 894
- 22 14 5. Bota DP, Lefranc F, Vilallobos HR, Brimiouille S, Vincent JL (2005) Ventriculostomy-related
23
24 15 infections in critically ill patients: a 6-year experience. *J Neurosurg* 103:468-472
- 25 16 6. Cinibulak Z, Aschoff A, Apedjinou A, Kaminsky J, Trost HA, Krauss JK (2016) Current practice
26
27 17 of external ventricular drainage: a survey among neurosurgical departments in
28
29 18 Germany. *Acta Neurochir (Wien)* 158:847-853. doi:10.1007/s00701-016-2747-y
- 30 19 7. Conen A, Walti LN, Merlo A, Fluckiger U, Battegay M, Trampuz A (2008) Characteristics and
31
32 20 treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a
33
34 21 retrospective analysis over an 11-year period. *Clin Infect Dis* 47:73-82.
35
36 22 doi:10.1086/588298
- 37 23 8. Dettenkofer M, Ebner W, Els T, Babikir R, Lucking C, Pelz K, Ruden H, Daschner F (2001)
38
39 24 Surveillance of nosocomial infections in a neurology intensive care unit. *J Neurol*
40
41 25 248:959-964
- 42 26 9. Dey M, Jaffe J, Stadnik A, Awad IA (2012) External ventricular drainage for intraventricular
43
44 27 hemorrhage. *Curr Neurol Neurosci Rep* 12:24-33. doi:10.1007/s11910-011-0231-x
- 45 28 10. Edwards NC, Engelhart L, Casamento EM, McGirt MJ (2015) Cost-consequence analysis of
46
47 29 antibiotic-impregnated shunts and external ventricular drains in hydrocephalus. *J*
48
49 30 *Neurosurg* 122:139-147. doi:10.3171/2014.9.JNS131277
- 50 31 11. Fisher CM, Kistler JP, Davis JM (1980) Relation of cerebral vasospasm to subarachnoid
51
52 32 hemorrhage visualized by computerized tomographic scanning. *Neurosurgery* 6:1-9

- 1 12. Fried HI, Nathan BR, Rowe AS, Zabramski JM, Andaluz N, Bhimraj A, Guanci MM, Seder
2 DB, Singh JM (2016) The Insertion and Management of External Ventricular Drains: An
3 Evidence-Based Consensus Statement : A Statement for Healthcare Professionals from
4 the Neurocritical Care Society. *Neurocrit Care* 24:61-81. doi:10.1007/s12028-015-
5 0224-8
- 6 13. Gordon M, Ramirez P, Soriano A, Palomo M, Lopez-Ferraz C, Villarreal E, Meseguer S,
7 Gomez MD, Folgado C, Bonastre J (2014) Diagnosing external ventricular drain-related
8 ventriculitis by means of local inflammatory response: soluble triggering receptor
9 expressed on myeloid cells-1. *Crit Care* 18:567. doi:10.1186/s13054-014-0567-0
- 10 14. Grille P, Verga F, Biestro A (2017) Diagnosis of ventriculostomy-related infection: Is
11 cerebrospinal fluid lactate measurement a useful tool? *J Clin Neurosci* 45:243-247.
12 doi:10.1016/j.jocn.2017.07.031
- 13 15. Gutierrez-Gonzalez R, Boto GR, Perez-Zamarron A (2012) Cerebrospinal fluid diversion
14 devices and infection. A comprehensive review. *Eur J Clin Microbiol Infect Dis* 31:889-
15 897. doi:10.1007/s10096-011-1420-x
- 16 16. Hagel S, Bruns T, Pletz MW, Engel C, Kalff R, Ewald C (2014) External ventricular drain
17 infections: risk factors and outcome. *Interdiscip Perspect Infect Dis* 2014:708531.
18 doi:10.1155/2014/708531
- 19 17. Hemphill JC, 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC (2001) The ICH score:
20 a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 32:891-897
- 21 18. Hoefnagel D, Dammers R, Ter Laak-Poort MP, Avezaat CJ (2008) Risk factors for infections
22 related to external ventricular drainage. *Acta Neurochir (Wien)* 150:209-214;
23 discussion 214. doi:10.1007/s00701-007-1458-9
- 24 19. Horan TC, Andrus M, Dudeck MA (2008) CDC/NHSN surveillance definition of health care-
25 associated infection and criteria for specific types of infections in the acute care
26 setting. *Am J Infect Control* 36:309-332. doi:10.1016/j.ajic.2008.03.002
- 27 20. Humphreys H, Jenks PJ (2015) Surveillance and management of ventriculitis following
28 neurosurgery. *J Hosp Infect* 89:281-286. doi:10.1016/j.jhin.2014.12.019
- 29 21. Hunt WE, Hess RM (1968) Surgical risk as related to time of intervention in the repair of
30 intracranial aneurysms. *J Neurosurg* 28:14-20. doi:10.3171/jns.1968.28.1.0014

- 1 22. Kirmani AR, Sarmast AH, Bhat AR (2015) Role of external ventricular drainage in the
2 management of intraventricular hemorrhage; its complications and management.
3 Surg Neurol Int 6:188. doi:10.4103/2152-7806.172533
4
- 5 23. Kitchen WJ, Singh N, Hulme S, Galea J, Patel HC, King AT (2011) External ventricular drain
6 infection: improved technique can reduce infection rates. Br J Neurosurg 25:632-635.
7 doi:10.3109/02688697.2011.578770
8
- 9 24. Konstantelias AA, Vardakas KZ, Polyzos KA, Tansarli GS, Falagas ME (2015) Antimicrobial-
10 impregnated and -coated shunt catheters for prevention of infections in patients with
11 hydrocephalus: a systematic review and meta-analysis. J Neurosurg 122:1096-1112.
12 doi:10.3171/2014.12.JNS14908
13
- 14 25. Kubilay Z, Amini S, Fauerbach LL, Archibald L, Friedman WA, Layon AJ (2013) Decreasing
15 ventricular infections through the use of a ventriculostomy placement bundle:
16 experience at a single institution. J Neurosurg 118:514-520.
17 doi:10.3171/2012.11.JNS121336
18
- 19 26. Kulkarni AV, Drake JM, Lamberti-Pasculli M (2001) Cerebrospinal fluid shunt infection: a
20 prospective study of risk factors. J Neurosurg 94:195-201.
21 doi:10.3171/jns.2001.94.2.0195
22
- 23 27. Leverstein-van Hall MA, Hopmans TE, van der Sprenkel JW, Blok HE, van der Mark WA,
24 Hanlo PW, Bonten MJ (2010) A bundle approach to reduce the incidence of external
25 ventricular and lumbar drain-related infections. J Neurosurg 112:345-353.
26 doi:10.3171/2009.6.JNS09223
27
- 28 28. Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES, Jr. (2002) Ventriculostomy-related
29 infections: a critical review of the literature. Neurosurgery 51:170-181; discussion
30 181-172
31
- 32 29. Mayhall CG, Archer NH, Lamb VA, Spadora AC, Baggett JW, Ward JD, Narayan RK (1984)
33 Ventriculostomy-related infections. A prospective epidemiologic study. N Engl J Med
34 310:553-559. doi:10.1056/NEJM198403013100903
35
- 36 30. Mounier R, Lobo D, Cook F, Fratani A, Attias A, Martin M, Chedeveigne K, Bardon J, Tazi
37 S, Nebbad B, Bloc S, Plaud B, Dhonneur G (2015) Clinical, biological, and
38 microbiological pattern associated with ventriculostomy-related infection: a
39 retrospective longitudinal study. Acta Neurochir (Wien) 157:2209-2217; discussion
40 2217. doi:10.1007/s00701-015-2574-6
41

- 1 31. Neuman MI, Tolford S, Harper MB (2008) Test characteristics and interpretation of
2 cerebrospinal fluid gram stain in children. *The Pediatric infectious disease journal*
3 27:309-313. doi:10.1097/INF.0b013e31815f53ba
4
5 32. Pfisterer W, Muhlbauer M, Czech T, Reinprecht A (2003) Early diagnosis of external
6 ventricular drainage infection: results of a prospective study. *J Neurol Neurosurg*
7 *Psychiatry* 74:929-932
8
9 33. *The Sanford Guide to Antimicrobial Therapy 2017* (2017). 41st. edn. Antimicrobial
10 *Therapy, Inc., Dallas, TX*
11
12 34. Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Michael Scheld W, van de Beek D,
13 Bleck TP, Garton HJ, Zunt JR (2017) 2017 Infectious Diseases Society of America's
14 Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. *Clin*
15 *Infect Dis.* doi:10.1093/cid/ciw861
16
17 35. van de Beek D, Drake JM, Tunkel AR (2010) Nosocomial bacterial meningitis. *N Engl J Med*
18 362:146-154. doi:10.1056/NEJMra0804573
19
20 36. Viallon A, Desseigne N, Marjollet O, Birynczyk A, Belin M, Guyomarch S, Borg J, Pozetto B,
21 Bertrand JC, Zeni F (2011) Meningitis in adult patients with a negative direct
22 cerebrospinal fluid examination: value of cytochemical markers for differential
23 diagnosis. *Crit Care* 15:R136. doi:10.1186/cc10254
24
25 37. Wiegand J, Hickson L, Merz TM (2016) Indicators of external ventricular drainage-related
26 infections--a retrospective observational study. *Acta Neurochir (Wien)* 158:595-601;
27 discussion 601. doi:10.1007/s00701-016-2709-4
28
29 38. Wyler AR, Kelly WA (1972) Use of antibiotics with external ventriculostomies. *J Neurosurg*
30 37:185-187. doi:10.3171/jns.1972.37.2.0185
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 Tables:

2 Table 1. Patient demographics, clinical characteristics and types of organisms grown in study
3 subjects.

Variable	Patients enrolled in the Prospective Cohort n=187	Patients enrolled in the Retrospective Cohort n=39
Male, n (%)	102(54,5)	17(43,6)
Mean age (years)	53,65±17,99	48,4±16,9
Reason for EVD placement, n (%)		
ICH	48(25,7)	5(12,8)
SAH	85(45,5)	20(51,3)
TBI	54(28,9)	9(23,1)
Neurological findings at time of admission		
GCS (mean score ±SD)	8,83±4,15	9,4±4,7
Hunt & Hess Score (median)	3	3
Fisher Scale (median)	3	4
LOS (days)	24,8±25,7 (hospital)	16,6±11,9 (ICU)
Survival (at discharge)	141(75,4)	32(82,0)
Outcome (GOS) (median)	3	3
Number of positive CSF cultures	6	38
Number of positive CSF gram stains	1	18
Cultured Organism		
<i>Staphylococcus aureus</i>		4
Coagulase-negative staphylococci (CoNS)	3	14
<i>Enterococcus faecalis</i>		4
<i>Enterobacteriaceae</i>	2	8
<i>Propionibacterium acnes</i>	1	--
<i>Pseudomonas aeruginosa</i>		3
Acinetobacter spp		7
Sphingomonas paucimobilis		1
Bacillus		1

4
5 (CSF: Cerebrospinal Fluid, EVD: External Ventricular Drain, GCS: Glasgow Coma Score, GOS:
6 Glasgow Outcome Score, ICH: Intracranial Haemorrhage, SAH: Subarachnoid Haemorrhage,
7 TBI: Traumatic Brain Injury)

Table 2: EVD-placement characteristics and parameters for CD-ERI (prospective cohort)

Variable	Patients with occurrence of CD-ERI n=31	Patients without occurrence of CD-ERI n=156	P Value
Experience of doctor placing EVD			0,704
1 to 10 years	3(9,7%)	11(7,1%)	
11 to 25 years	11(35,5%)	67(42,9%)	
Over 25 years	17(54,8%)	78(50,0%)	
Location of EVD placement			0,242
Emergency Department	12(38,7%)	85(54,5%)	
ICU	1(3,2%)	6(3,8%)	
Operating Theatre	18(58,1%)	65(41,7%)	
Surgical Technique for EVD insertion			0,757
Long-tunnel	25(80,6%)	116(74,4%)	
Short-tunnel	4(12,9%)	26(16,7%)	
Straight	2(6,5%)	14(9,0%)	
Type of Site Shaving (Large Shaving/Small Shaving)	15(48,4%)/16(52,6%)	84(53,8%)/72(46,2%)	0.719
Number of attempts for placement (one/more than one)	24(77,4%)/7(22,6%)	133(85,3%)/23(14,7%)	0,413
Type of AB prophylaxis used (continuous/periprocedural)	13(41,9%)/18(58,1%)	49(31,4%)/107(68,6%)	0,353
Choice of diagnostic Parameters	0,7%		
Positive CSF Stain	22,5%		
Elevated CSF WBC	9,2%		
Elevated CSF PMN	2,8%		
Elevated Serum CRP	7,0%		
Elevated Serum WBC	10,6%		
Fever			
Choice of AB treatment			
Penicillin	7 (20%)		
Cephalosporin	17 (48,6%)		
Carbapenem	12 (34,2%)		
Glycopeptide	27 (77,1%)		
Metronidazol	10 (28,6%)		

(AB: Antibiotic, CD-ERI: clinically diagnosed EVD related infection, CSF: Cerebrospinal Fluid, CRP: C-Reactive Protein, EVD: External Ventricular Drain, ICU: Intensive Care Unit, PMN: Polymorphonuclear Neutrophils, WBC: White Blood Cells)

Table 3: Characteristics of different markers used in the diagnosis of CD-ERI (prospective cohort)

	Number of episodes	Min.	Max.	Mean	Std. Deviation	Pathological findings Number of episodes
Serum CRP (mg/L)	687	2	542	79.95	85.021	> 10 mg/L: 571 (83,1%)
Serum WBC (cells/ml)	1486	3	3810 0	5249. 53	6317.624	>12,000/mL: 245 (16,5%)
Serum WBC immature bands (%)	198	0	62	18.56	14.443	
CSF RBC (cells/μL)	944	0	1590 750	61738 .21	150651.10 4	
CSF WBC (cells/μL)	915	1	4750	113.9 1	336.063	≥5 cells/μL: 643 (70,3%)
CSF PMN (cells/μL)	689	1	4350	102.2 2	303.873	
CSF Protein (mg/dL)	146	1	893	47.06	112.307	>45 μg/dL: 35 (24,0%)
CSF Lactate (mmol/L)	505	0	13	2.80	1.258	>4 mmol/L: 74 (4,6%)
CSF pH	199	7	9	8.01	.290	
CSF Glucose (mmol/L)	441	1	8	4.13	.961	
Serum Glucose (mmol/L)	1438	3	22	8.19	2.171	
CSF/Serum Glucose Ratio	398	.20	1.67	.5437	.15998	<0.5: 130 (32,7%)
CSF WBC/RBC Ratio	898	.00	1.00	.0181	.07046	>0,01: 229 (25,5%)

CD-ERI: clinically diagnosed EVD related infection, CSF: Cerebrospinal Fluid, CRP: C-Reactive Protein, PMN: Polymorphonuclear Neutrophils, RBC: Red Blood Cells, WBC: White Blood Cells)

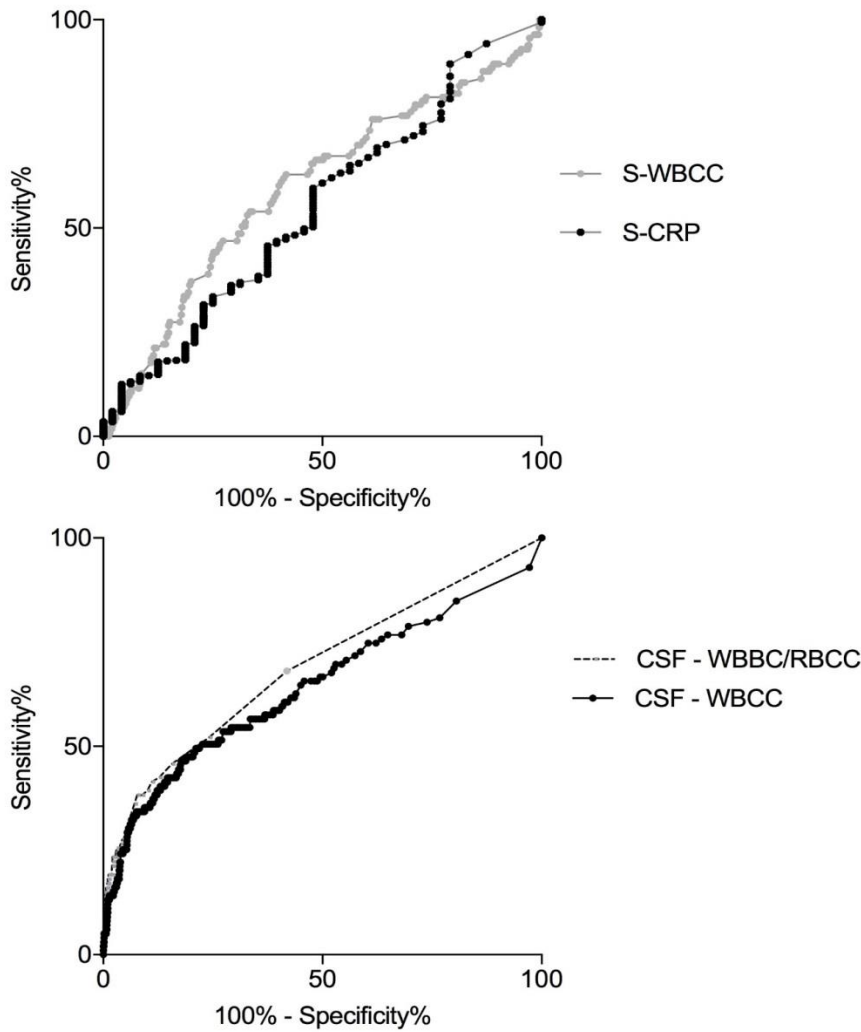
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 4: Analysis for temporal trends of single potential predictors of ERI in groups stratified by presence/absence of CP-ERI (*combined data from both cohorts*). The table describes if a linear, square and cubic increase in number or levels of parameters occurs in the lead up of CP-ERI or during the first 7 days after EVD placement (patients without occurrence of CP-ERI), model parameters are reported as weighing factor F and respective significance level.

		SIRS criteria		Neurological signs		S-CRP		S-WBCC		CSF WBCC		CSF WBCC/RBCC ratio	
		F	<i>p</i>	F	<i>p</i>	F	<i>p</i>	F	<i>p</i>	F	<i>p</i>	F	<i>p</i>
CP-ERI (n=180)	Time	3.112	0.079	0.237	0.627	0.227	0.634	0.061	0.805	0.002	0.960	0.113	0.737
	Time ²	3.767	0.053	0.000	0.995	0.085	0.772	0.049	0.825	0.038	0.846	0.200	0.655
	Time ³	2.783	0.096	0.004	0.952	0.178	0.674	0.002	0.967	0.220	0.639	0.016	0.901
No CP- ERI (n=46)	Time	5.205	0.023	0.082	0.775	21.355	0.000	0.459	0.498	0.459	0.498	1.444	0.230
	Time ²	2.219	0.137	0.949	0.330	5.724	0.017	0.299	0.584	0.299	0.584	1.454	0.228
	Time ³	1.475	0.225	1.460	0.227	1.407	0.236	0.162	0.688	0.162	0.688	1.531	0.216

(CP-ERI: culture-proven EVD related infection) CSF: Cerebrospinal Fluid, EVD: External Ventricular Drain, PMN: Polymorphonuclear Neutrophils, RBCC: Red Blood Cell Count, S-CRP: Serum C-Reactive Protein, SIRS: Systemic Inflammatory Response Syndrome, S-WBCC: Serum White Blood Cell Count)

1 Figure 1. ROC Curves for serum and CSF parameters used for diagnosis of ERI (combined
 2 data from both cohorts).



3
 4
 5 Legend 1: Illustration of the ROC curves for serum parameters [white blood cell count (S-
 6 WBCC) and serum C-reactive Protein (S-CRP)] (upper plot) and CSF parameters [CSF
 7 WBCC/RBCC Ratio and CSF white blood cell count (CSF WBCC)] (lower plot). S-WBCC: AUC
 8 0.596 (95% CI 0.538 - 0.654); $p=0.0006$, S-CRP: AUC 0.550 (95% CI 0.465 - 0.634), $p=0.2489$;
 9 CSF WBCC/RBCC ratio: AUC 0.690 (95% CI 0.626 - 0.753), $p< 0.0001$; CSF WBCC: AUC 0.644
 10 (95% CI 0.576 to 0.711), $p< 0.0001$.