INPLASY

Meta-Analysis of Cerebrospinal Fluid Heparin-Binding Protein in Diagnosing Healthcare-Associated Ventriculitis and Meningitis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202620068

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 February 2026 and was last updated on 22 February 2026.

INTRODUCTION

Review question / Objective What is the diagnostic accuracy of cerebrospinal fluid heparin-binding protein (CSF HBP) for healthcare-associated ventriculitis and meningitis (HAVM) in post-neurosurgical patients, and what is the optimal diagnostic cutoff value?

Condition being studied Healthcare-associated ventriculitis and meningitis (HAVM), a serious infectious complication occurring after neurosurgical procedures, external ventricular drain placement, or cerebrospinal fluid shunt operations. HAVM is associated with significant morbidity and mortality, and its diagnosis remains challenging because post-neurosurgical sterile inflammation can mimic infectious CSF profiles, reducing the reliability of traditional biomarkers such as CSF cell count, glucose, and protein.

METHODS

Participant or population Adult and pediatric patients with suspected healthcare-associated ventriculitis and meningitis following neurosurgical procedures (craniotomy, external ventricular drain placement, or cerebrospinal fluid shunt operations), traumatic brain injury, or other conditions requiring neurosurgical intervention.

Intervention Cerebrospinal fluid heparin-binding protein (CSF HBP) measured by enzyme-linked immunosorbent assay (ELISA), latex immunoturbidimetry, fluorescence immunoassay, or fluorescence immunochromatography.

Comparator Clinical and/or microbiological reference standards for HAVM diagnosis, including IDSA 2017 healthcare-associated ventriculitis and meningitis guidelines, CDC/NHSN surveillance definitions, composite clinical and CSF criteria based on Chinese national diagnostic standards, and microbiological confirmation with clinical criteria.

Study designs to be included Prospective and retrospective observational diagnostic accuracy studies, including cross-sectional, cohort, and case-control designs. Randomized controlled trials evaluating diagnostic accuracy were also eligible, though none were identified.

Eligibility criteria Prospective and retrospective observational diagnostic accuracy studies, including cross-sectional, cohort, and case-control designs. Randomized controlled trials evaluating diagnostic accuracy were also eligible, though none were identified.

Information sources Four electronic databases were searched from inception through February 2026: PubMed (via MEDLINE), Embase (via Elsevier), the Cochrane Library, and China National Knowledge Infrastructure (CNKI). Reference lists of all included studies and relevant review articles were manually screened to identify additional eligible studies. No language, date, or study design filters were applied.

Main outcome(s) Pooled sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR–), and diagnostic odds ratio (DOR) of cerebrospinal fluid heparin-binding protein for the diagnosis of healthcare-associated ventriculitis and meningitis.

Quality assessment / Risk of bias analysis Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, which evaluates risk of bias across four domains (patient selection, index test, reference standard, and flow and timing) and applicability concerns across three domains (patient selection, index test, and reference standard). Each domain was rated as low, high, or unclear risk of bias. Two reviewers independently assessed study quality, with disagreements resolved by consensus.

Strategy of data synthesis Diagnostic accuracy data from each study were organized into 2×2 contingency tables. Pooled estimates of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were calculated using a bivariate random-effects model. Summary receiver operating characteristic (SROC) curves with 95% confidence and prediction regions were constructed. Between-study heterogeneity was assessed using Cochran's Q statistic and I^2 index. The Spearman correlation coefficient between sensitivity and false-positive rate was calculated to evaluate threshold effects. Subgroup analyses were performed by underlying pathology, study design, assay method, and reference standard stringency, with meta-regression to identify statistically significant moderators. Optimal cutoff analysis was performed using the diagmeta method of Steinhauser et al. Clinical utility was assessed using Fagan nomograms at pretest probabilities of 25%, 50%, and 75%. Publication bias was evaluated using Deeks' funnel plot asymmetry test. All analyses were performed using R (version 4.5.0) with the mada package.

Subgroup analysis Subgroup analyses were conducted based on four pre-specified covariates: (1) underlying pathology (intracerebral hemorrhage-predominant versus brain tumor-predominant versus mixed/unspecified populations); (2) study design (prospective versus retrospective); (3) HBP assay method (ELISA versus non-ELISA); and (4) reference standard stringency (strict microbiological confirmation versus composite clinical criteria). Separate bivariate random-effects models were fitted for each subgroup, and meta-regression using likelihood ratio tests was performed to determine whether covariates were statistically significant sources of between-study heterogeneity.

Sensitivity analysis The robustness of pooled estimates was evaluated through several approaches. First, the influence of individual studies was assessed by examining whether removal of any single study substantially altered the pooled sensitivity, specificity, or diagnostic odds ratio. Second, the impact of the threshold effect on heterogeneity was evaluated using the Spearman correlation coefficient between sensitivity and false-positive rate. Third, the stability of the optimal cutoff was assessed through bootstrap resampling with 95% confidence intervals. Finally, subgroup analyses stratified by underlying pathology, study design, assay method, and reference standard stringency served as indirect sensitivity analyses to evaluate whether pooled estimates were robust across different study characteristics.

Language restriction No language restrictions were applied to the search strategy.

Country(ies) involved Taiwan.

Keywords heparin-binding protein; cerebrospinal fluid; ventriculitis; meningitis; healthcare-associated infection; diagnostic accuracy; meta-analysis; neurosurgery; biomarker.

Contributions of each author

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