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Diagnostic accuracy of cerebrospinal fluid 14-3-3 protein for the diagnosis of human prion disease: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 May 2026 and was last updated on 9 May 2026.

INTRODUCTION

Review question / Objective This systematic review and meta-analysis aims to evaluate the diagnostic accuracy of cerebrospinal fluid 14-3-3 protein for the diagnosis of human prion diseases.
The review question was structured according to the PICOS framework:
Population (P): Patients with suspected human prion disease, including sporadic, genetic and acquired forms of prion disease.
Index test (I): Detection or measurement of 14-3-3 protein in cerebrospinal fluid.
Comparator/Reference standard (C): Neuropathological confirmation by brain biopsy or autopsy, RT-QuIC, or accepted diagnostic criteria for prion disease.
Outcomes (O): Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio and other measures of diagnostic accuracy.
Study design (S): Observational diagnostic accuracy studies, including cohort, case-control and cross-sectional studies.
The objective of this review is to synthesize the available scientific evidence regarding the diagnostic performance of cerebrospinal fluid 14-3-3 protein in patients with suspected prion disease and to investigate differences in diagnostic accuracy among prion disease subtypes and laboratory detection methods.

Condition being studied Human prion diseases are rare, progressive and fatal neurodegenerative disorders caused by the abnormal misfolding of the cellular prion protein (PrPC) into a pathogenic isoform (PrPSc). These diseases are characterized by rapid neuronal degeneration, spongiform changes in the central nervous system and severe neurological impairment. Human prion diseases include sporadic, genetic and acquired forms, such as sporadic Creutzfeldt-Jakob disease, genetic Creutzfeldt-Jakob disease, variant

Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome and fatal familial insomnia.
The clinical presentation commonly includes rapidly progressive dementia, myoclonus, cerebellar dysfunction, extrapyramidal symptoms and behavioral or psychiatric manifestations. Due to the absence of curative treatment and the rapid progression of the disease, early and accurate diagnosis is essential for appropriate clinical management and palliative care.
The definitive diagnosis of prion disease usually depends on neuropathological confirmation obtained through brain biopsy or autopsy. However, less invasive biomarkers have become increasingly important in clinical practice. Among these biomarkers, cerebrospinal fluid 14-3-3 protein has been widely investigated as an indicator of neuronal injury and neurodegeneration. Elevated levels of 14-3-3 protein have been associated with prion diseases, especially sporadic Creutzfeldt-Jakob disease, although increased concentrations may also occur in other neurological disorders, potentially affecting diagnostic specificity.
Therefore, evaluating the diagnostic accuracy of cerebrospinal fluid 14-3-3 protein may contribute to improving diagnostic strategies for human prion diseases.

METHODS

Search strategy The literature search will be performed in the following electronic databases: PubMed/MEDLINE, Embase, Cochrane Library and LILACS. No restrictions regarding publication date or language will be applied. In addition, manual searches of the reference lists of included studies and relevant reviews will be conducted to identify potentially eligible articles.
The search strategy will combine controlled vocabulary terms, including Medical Subject Headings (MeSH) and Emtree terms, with free-text keywords related to prion diseases and cerebrospinal fluid 14-3-3 protein. Boolean operators “AND” and “OR” will be used to combine search terms appropriately.
The main search terms will include:
“Prion Diseases”
“Creutzfeldt-Jakob Disease”
“Prion Disease”
“14-3-3 Protein”
“Protein 14-3-3”
“Cerebrospinal Fluid”
“CSF”
“Diagnosis”
“Diagnostic Accuracy”
“Sensitivity and Specificity”
“Biomarkers”

A preliminary PubMed search strategy will be structured as follows:
(“Prion Diseases”[Mesh] OR “Creutzfeldt-Jakob Disease”[Mesh] OR “prion disease” OR “Creutzfeldt-Jakob disease”) AND (“14-3-3 Proteins”[Mesh] OR “14-3-3 protein” OR “protein 14-3-3”) AND (“Cerebrospinal Fluid”[Mesh] OR “CSF” OR “cerebrospinal fluid”) AND (“Sensitivity and Specificity”[Mesh] OR “diagnostic accuracy” OR “diagnosis”).
The search strategy may be adapted according to the specific indexing systems and requirements of each database.

Participant or population The review will include studies involving human participants with suspected or confirmed prion disease. Eligible populations may include patients with sporadic, genetic or acquired forms of human prion disease, such as sporadic Creutzfeldt-Jakob disease, genetic Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, fatal familial insomnia and Gerstmann-Sträussler-Scheinker syndrome.
Studies including adult or pediatric participants of any sex and ethnicity will be considered. Participants must have undergone cerebrospinal fluid analysis for detection or quantification of 14-3-3 protein as part of the diagnostic investigation.
Control groups may include healthy individuals or patients with other neurological disorders used for differential diagnosis.

Intervention The index test evaluated in this review will be the detection or quantification of cerebrospinal fluid 14-3-3 protein in patients with suspected human prion disease. Different laboratory methods used for 14-3-3 protein analysis, including Western blotting and enzyme-linked immunosorbent assay (ELISA), will be considered. Studies evaluating the diagnostic performance of this biomarker alone or in combination with other diagnostic tests will be eligible if separate data for 14-3-3 protein are available.

Comparator The comparator or reference standard will include definitive or accepted diagnostic methods for human prion diseases, such as neuropathological confirmation obtained through brain biopsy or autopsy, positive RT-QuIC results, or established clinical diagnostic criteria for prion disease. Studies comparing cerebrospinal fluid 14-3-3 protein results with healthy controls or patients with other neurological disorders will also be considered when appropriate for diagnostic accuracy analysis.

Study designs to be included Observational diagnostic accuracy studies will be included, such as cohort, case-control and cross-sectional studies evaluating the diagnostic performance of cerebrospinal fluid 14-3-3 protein in human prion diseases. Studies must provide sensitivity, specificity, or sufficient data to construct 2 × 2 contingency tables. Reviews, editorials, letters, conference abstracts without sufficient data, animal studies and experimental laboratory studies will be excluded.

Eligibility criteria Studies will be eligible if they evaluate cerebrospinal fluid 14-3-3 protein as a diagnostic biomarker for human prion diseases and provide sufficient methodological and diagnostic data for analysis. Only original studies conducted in humans will be included.
Studies will be excluded if they:
do not evaluate 14-3-3 protein in cerebrospinal fluid;
do not use an accepted reference standard for diagnosis;
present duplicated data or overlapping populations;
lack sufficient data to calculate diagnostic accuracy measures;
are reviews, editorials, case reports, letters, conference abstracts without full data, animal studies or in vitro studies.
When multiple publications report data from the same population, the study with the most complete dataset will be included.

Information sources The electronic databases PubMed/MEDLINE, Embase, Cochrane Library and LILACS will be systematically searched to identify eligible studies. No restrictions regarding publication year or language will be applied.
Additional studies may be identified through manual screening of the reference lists of included articles and relevant reviews. Grey literature sources, when accessible, may also be consulted to minimize publication bias.
When necessary, corresponding authors of eligible studies may be contacted by email to obtain missing or unclear data related to diagnostic accuracy outcomes or methodological details.

Main outcome(s) The primary outcomes of this systematic review and meta-analysis will be the diagnostic accuracy measures of cerebrospinal fluid 14-3-3 protein for the diagnosis of human prion diseases. The main effect measures will include sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR–) and diagnostic odds ratio (DOR), all reported with 95% confidence intervals.

For each included study, true positive, false positive, true negative and false negative values will be extracted or calculated to construct 2 × 2 contingency tables. These data will allow pooled analyses of diagnostic performance.
When available, additional outcomes such as area under the receiver operating characteristic curve (AUC), cut-off values and subgroup-specific diagnostic performance according to prion disease subtype or laboratory detection method will also be evaluated.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included studies will be independently assessed by two reviewers using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. Disagreements between reviewers will be resolved through discussion or consultation with a third reviewer.
The QUADAS-2 tool evaluates four domains: patient selection, index test, reference standard, and flow and timing. Each domain will be assessed regarding risk of bias, and the first three domains will also be evaluated for concerns regarding applicability.
Studies will be classified as having low, high or unclear risk of bias according to the signaling questions proposed by QUADAS-2. The results of the quality assessment will be summarized in tables and figures to support interpretation of the findings and to evaluate the reliability of the pooled diagnostic accuracy estimates.

Strategy of data synthesis Data from the included studies will be synthesized qualitatively and quantitatively. Initially, the characteristics of the eligible studies will be summarized in standardized tables, including study design, population characteristics, type of prion disease, laboratory method used for 14-3-3 protein detection, reference standard and diagnostic accuracy measures.
For quantitative synthesis, 2 × 2 contingency tables will be constructed using the numbers of true positives, false positives, true negatives and false negatives extracted from each study. Pooled estimates of sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR–) and diagnostic odds ratio (DOR) will be calculated with 95% confidence intervals.
A bivariate random-effects model will be applied to account for potential heterogeneity between studies. Summary receiver operating characteristic (SROC) curves and area under the curve (AUC) values may also be generated to evaluate overall diagnostic performance.

Heterogeneity will be investigated through visual inspection of forest plots and SROC curves, in addition to subgroup analyses and sensitivity analyses when appropriate. Publication bias will be assessed using Deeks' funnel plot asymmetry test when sufficient studies are available.
The meta-analysis will be performed using Statistical Software for Data Science (STATA® 17) and MetaDisc 2.0 software.

Subgroup analysis Subgroup analyses will be performed when sufficient data are available to investigate potential sources of heterogeneity in the diagnostic accuracy of cerebrospinal fluid 14-3-3 protein.
The analyses may include comparisons according to:
subtype of prion disease, including sporadic Creutzfeldt-Jakob disease, genetic prion disease and variant Creutzfeldt-Jakob disease;
laboratory detection method used for 14-3-3 protein analysis, such as Western blotting or ELISA;
type of reference standard applied for diagnosis;
geographic region or country of study; and
study design characteristics or risk of bias classification.
These subgroup analyses aim to evaluate whether diagnostic performance varies according to clinical, methodological or laboratory factors.

Sensitivity analysis Sensitivity analyses will be conducted to evaluate the robustness and consistency of the pooled diagnostic accuracy estimates. These analyses may include the exclusion of studies classified as having high risk of bias according to the QUADAS-2 assessment, studies with incomplete diagnostic data, studies with small sample sizes, and studies using less rigorous reference standards.
Additional sensitivity analyses may be performed according to the laboratory method used for cerebrospinal fluid 14-3-3 protein detection and according to the subtype of prion disease evaluated.
The impact of each individual study on the pooled estimates will also be assessed by sequentially removing studies from the meta-analysis when appropriate. Differences between the primary analysis and sensitivity analyses will be considered when interpreting the reliability and stability of the results.

Country(ies) involved Brazil – Universidade do Extremo Sul Catarinense (UNESC), Criciúma, Santa Catarina.

Keywords Prion disease; Creutzfeldt-Jakob disease; 14-3-3 protein; cerebrospinal fluid; diagnostic accuracy.

Contributions of each author
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