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Evaluation of the diagnostic accuracy and prognostic value of CXCL10 and CXCL8 biomarkers in neurosyphilis: a systematic review and meta-analysis

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Prestes, GS; Valgas, JC; Daniel, HR.

Corresponding author:
Gabriele Prestes

gsp@unesc.net

Author Affiliation:
Universidade do Extremo Sul Catarinense (UNESC), School of Medicine, Translational Biomedicine Laboratory, Criciúma, Santa Catarina, Brazil.

ADMINISTRATIVE INFORMATION

Support - This study has no external financial support or specific funding source.

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 8 May 2026 and was last updated on 8 May 2026.

INTRODUCTION

Review question / Objective The objective of this systematic review and meta-analysis is to evaluate the diagnostic accuracy and prognostic value of the biomarkers CXCL10 and CXCL8 in patients with neurosyphilis.
The review question was structured according to the PICOS framework:
P (Population): Adult patients (≥18 years) diagnosed with syphilis and evaluated for neurosyphilis;
I (Index test/Intervention): Measurement of CXCL10 and CXCL8 levels in cerebrospinal fluid (CSF);
C (Comparator): Conventional diagnostic methods for neurosyphilis, especially CSF-VDRL and other treponemal and non-treponemal tests;
O (Outcomes): Diagnostic accuracy measures, including sensitivity, specificity, diagnostic odds ratio (DOR), area under the curve (AUC), and prognostic associations related to disease severity, progression, and therapeutic response;
S (Study design): Original observational studies, including cohort, cross-sectional, and case-control studies.
The main review question is: “Are CXCL10 and CXCL8 effective biomarkers for the diagnosis and prognosis of neurosyphilis?”.

Condition being studied Neurosyphilis is a severe manifestation of infection caused by Treponema pallidum, in which the bacterium invades the central nervous system (CNS). It may occur at any stage of syphilis and can present with a wide spectrum of neurological and psychiatric manifestations, including meningitis, stroke, cognitive impairment, dementia, tabes dorsalis, visual disturbances, hearing loss, and psychiatric symptoms. In some cases, neurosyphilis may remain asymptomatic, making diagnosis particularly challenging.
The diagnosis of neurosyphilis currently relies on the interpretation of cerebrospinal fluid (CSF) findings and serological tests, especially CSF-

VDRL, treponemal tests, cell count, and protein concentration. However, these methods have important limitations due to variable sensitivity and specificity, which may delay diagnosis and treatment.

Recently, inflammatory chemokines such as CXCL10 and CXCL8 have emerged as promising biomarkers for neurosyphilis. CXCL10 is associated with T-cell recruitment and inflammatory responses mediated by interferon-gamma, while CXCL8 is involved in neutrophil activation and blood-brain barrier disruption. Elevated levels of these biomarkers in CSF have been associated with neurosyphilis and may provide improved diagnostic and prognostic performance compared with conventional laboratory methods.

Therefore, this systematic review aims to evaluate the diagnostic accuracy and prognostic relevance of CXCL10 and CXCL8 in neurosyphilis.

METHODS

Search strategy A systematic literature search will be conducted in the following electronic databases: MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, and Web of Science. These databases were selected due to their broad coverage of biomedical and clinical literature relevant to infectious diseases, neurology, and diagnostic biomarkers.

The search strategy will be developed using controlled vocabulary terms from Medical Subject Headings (MeSH) and DeCS, as well as free-text terms and synonyms related to CXCL10, CXCL8, and neurosyphilis. Boolean operators “AND” and “OR” will be applied to combine the search terms appropriately.

The core search strategy will include the following terms:

(“CXCL10” OR “C-X-C motif chemokine 10” OR “IP-10” OR “Interferon gamma-induced protein 10”)

AND

(“CXCL8” OR “C-X-C motif chemokine 8” OR “IL-8” OR “Interleukin-8”)

AND

(“Neurosyphilis” OR “Syphilitic Meningoencephalitis” OR “Treponema pallidum and central nervous system”)

Search strategies will be adapted according to the indexing system and syntax requirements of each database. No restrictions regarding publication year or language will be applied. Only studies involving human participants will be considered.

In addition to the electronic search, the reference lists of all included studies and relevant reviews will be manually screened to identify additional eligible publications not captured during the initial database search.

Participant or population The review will include adult patients (≥18 years old) diagnosed with syphilis who were evaluated for neurosyphilis. Studies involving patients with confirmed, suspected, symptomatic, or asymptomatic neurosyphilis will be considered. Participants may include individuals with or without HIV coinfection. Only studies involving human subjects will be included. Animal studies, in vitro studies, pediatric populations, and studies without sufficient diagnostic data related to neurosyphilis will be excluded.

Intervention The interventions evaluated in this review are the measurement and analysis of the inflammatory biomarkers CXCL10 and CXCL8 in cerebrospinal fluid (CSF) for the diagnosis and prognostic assessment of neurosyphilis. Studies assessing the diagnostic performance of these biomarkers through laboratory techniques such as enzyme-linked immunosorbent assay (ELISA), multiplex immunoassays, or other validated analytical methods will be included. The review will investigate whether CXCL10 and CXCL8 levels are associated with the presence, severity, progression, or therapeutic response of neurosyphilis.

Comparator The comparators in this review will include conventional diagnostic methods currently used for neurosyphilis diagnosis, especially cerebrospinal fluid Venereal Disease Research Laboratory test (CSF-VDRL), rapid plasma reagin (RPR), treponemal tests, cerebrospinal fluid protein concentration, leukocyte count, and polymerase chain reaction (PCR) assays when available. Studies comparing the diagnostic performance of CXCL10 and CXCL8 with these established laboratory methods will be considered.

Study designs to be included Original observational studies evaluating the diagnostic accuracy or prognostic value of CXCL10 and/or CXCL8 in neurosyphilis will be included. Eligible study designs will comprise cohort studies, cross-sectional studies, and case-control studies. Only studies involving human adult participants and providing sufficient diagnostic data, such as sensitivity, specificity, true positives, false positives, true negatives, or false negatives, will be considered.

Eligibility criteria Inclusion criteria will comprise: (1) original observational studies, including cohort,

cross-sectional, and case-control studies; (2) adult participants (≥18 years) with confirmed or suspected neurosyphilis; (3) studies evaluating CXCL10 and/or CXCL8 levels in cerebrospinal fluid; and (4) studies reporting diagnostic accuracy or prognostic outcomes related to neurosyphilis.
Exclusion criteria will include: (1) animal or in vitro studies; (2) pediatric populations; (3) reviews, editorials, conference abstracts, letters, case reports, or studies without primary data; (4) studies not related to neurosyphilis diagnosis or prognosis; and (5) studies without sufficient data for extraction or analysis.

Information sources The following electronic databases will be searched: MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, and Web of Science. These databases were selected due to their extensive coverage of biomedical and clinical research literature.
Additionally, the reference lists of all included studies and relevant review articles will be manually screened to identify potentially eligible studies not retrieved during the electronic database search. When necessary, corresponding authors of selected studies may be contacted to obtain missing or additional data relevant to the review.
Grey literature sources, conference proceedings, editorials, dissertations, and unpublished studies will not be systematically included due to the focus on peer-reviewed original studies with sufficient methodological and diagnostic data.

Main outcome(s) The primary outcomes of this systematic review and meta-analysis will be the diagnostic accuracy measures of CXCL10 and CXCL8 for neurosyphilis. The evaluated outcomes will include sensitivity, specificity, positive predictive value, negative predictive value, diagnostic odds ratio (DOR), area under the receiver operating characteristic curve (AUC), and likelihood ratios when available.
For each included study, true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) will be extracted to construct 2 × 2 contingency tables. These measures will be used to estimate pooled diagnostic performance with 95% confidence intervals.
Additionally, when available, the review will assess prognostic outcomes associated with CXCL10 and CXCL8 levels, including disease severity, clinical progression, neurological impairment, and therapeutic response in patients with neurosyphilis.

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 QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool. This instrument evaluates four key domains: patient selection, index test, reference standard, and flow and timing.
Each domain will be assessed for risk of bias, while the first three domains will also be evaluated regarding concerns about applicability. Studies will be classified as having low, high, or unclear risk of bias according to the QUADAS-2 guidance criteria.
Any disagreements between reviewers will be resolved through discussion and, when necessary, by consultation with a third reviewer. The results of the quality assessment will be presented descriptively and summarized using tables and graphical representations to facilitate interpretation of the methodological quality of the included studies.

Strategy of data synthesis A qualitative synthesis of all included studies will initially be performed, summarizing study characteristics, population data, biomarker measurement methods, diagnostic criteria, and main findings related to CXCL10 and CXCL8 in neurosyphilis.
Whenever sufficient homogeneous data are available, a diagnostic meta-analysis will be conducted. For each study, 2 × 2 contingency tables will be constructed using true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN). Pooled estimates of sensitivity, specificity, and diagnostic odds ratio (DOR), with corresponding 95% confidence intervals, will be calculated using a bivariate random-effects model.
Summary receiver operating characteristic (SROC) curves will be generated to evaluate the overall diagnostic performance of CXCL10 and CXCL8. Heterogeneity among studies will be assessed visually and statistically, considering differences in study design, biomarker assessment techniques, HIV coinfection, and diagnostic criteria for neurosyphilis.
If meta-analysis is not feasible due to insufficient or highly heterogeneous data, a structured narrative synthesis will be presented. Publication bias will be investigated using Deeks' funnel plot asymmetry test when applicable. Statistical analyses will be performed using STATA® 17 and MetaDisc 2.0 software.

Subgroup analysis Subgroup analyses will be performed whenever sufficient data are available to investigate potential sources of heterogeneity and variations in diagnostic performance. The planned subgroup analyses will include:
Type of biomarker evaluated (CXCL10 versus CXCL8);

Presence or absence of HIV coinfection;
Symptomatic versus asymptomatic neurosyphilis;
Different laboratory methods used for biomarker measurement (e.g., ELISA, multiplex assays);
Different reference standards used for neurosyphilis diagnosis;
Study design characteristics;
Severity or clinical stage of neurosyphilis.
These analyses aim to determine whether the diagnostic accuracy and prognostic value of CXCL10 and CXCL8 vary according to clinical, methodological, or laboratory factors.

Sensitivity analysis Sensitivity analyses will be conducted to evaluate the robustness and stability of the pooled diagnostic accuracy estimates. The analyses will be performed by sequentially excluding studies considered to have a high risk of bias according to the QUADAS-2 assessment, as well as studies with incomplete diagnostic data or extreme effect estimates.
Additional sensitivity analyses may include the exclusion of studies with small sample sizes, studies involving HIV-coinfected populations only, or studies using different diagnostic reference standards for neurosyphilis.
Furthermore, alternative statistical models, including random-effects approaches, will be applied to verify the consistency of the pooled sensitivity, specificity, and diagnostic odds ratio (DOR) estimates. The impact of each study on the overall results will also be assessed to identify possible influential studies contributing disproportionately to heterogeneity.

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

Keywords Neurosyphilis; CXCL10; CXCL8; biomarkers; diagnostic accuracy; systematic review.

Contributions of each author
Author 1 - Gabriele Prestes - Author 1 conceptualized the study, supervised the review design, contributed to the methodology, critically revised the protocol, and approved the final version of the protocol.
Email: gsp@unesc.net
Author 2 - Júlia Valgas - Author 2 contributed to the literature search strategy, study selection planning, data extraction design, and manuscript drafting.
Email: juliacominvalgas@unesc.net
Author 3 - Henrique Daniel - Author 3 contributed to the methodological planning, eligibility criteria definition, study screening planning, and manuscript drafting.
Email: henriquerdaniel@unesc.net