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Title:

Factors Associated with HIV Coinfection among 440 Patients with Neurosyphilis: A Single-Center Retrospective Study from 2020 to 2025

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Abstract

Background: Neurosyphilis patients with human immunodeficiency virus (HIV) coinfection present diagnostic and management challenges, yet features distinguishing HIV-coinfected from non-coinfected neurosyphilis patients remain incompletely characterized. We aimed to identify clinical and laboratory factors independently associated with HIV coinfection in this population.

Methods: This single-center retrospective study included 440 patients diagnosed with neurosyphilis between 2020 and 2025. Of these, 243 had neurosyphilis without HIV infection and 197 had HIV coinfection. We compared demographic characteristics, serum and cerebrospinal fluid (CSF) toluidine red unheated serum test (TRUST) results, CSF white blood cell counts and protein concentrations, $CD4^+$ T-cell counts, peripheral blood cell counts, and biochemical parameters between the two groups. Between-group comparisons were performed using the Mann–Whitney U test, chi-square test, or Fisher's exact test, as appropriate. We conducted univariable and multivariable logistic regression analyses to identify factors associated with HIV coinfection.

Results: The prevalence of HIV coinfection was 44.8%. Compared with patients with neurosyphilis alone, those with HIV coinfection were younger, were more likely to be male, and had higher proportions of a CSF-TRUST titer of 1:1 and higher absolute lymphocyte counts. In contrast, they had lower $CD4^+$ T-cell counts and absolute neutrophil counts (all $P < 0.001$). Multivariable logistic regression analysis showed that increasing age, higher $CD4^+$ T-cell counts, and higher absolute neutrophil counts were independently associated with lower odds of HIV coinfection. Male sex, a CSF-TRUST titer of 1:1, and a higher absolute lymphocyte count were independently associated with higher odds of HIV coinfection (all $P < 0.01$).

Conclusions: Patients with neurosyphilis and HIV coinfection were characterized by younger age, a marked male predominance, low-titer CSF-TRUST positivity, and alterations in peripheral immune cell profiles. Younger age, male sex, a CSF-TRUST titer of 1:1, lower $CD4^+$ T-cell and neutrophil counts, and a higher lymphocyte count were independently associated with HIV coinfection. These findings may facilitate the early identification and risk stratification of HIV coinfection among patients with neurosyphilis.

Keywords: neurosyphilis; HIV coinfection; $CD4^+$ T cells; CSF TRUST; associated factors.

Background

Syphilis is a multisystem sexually transmitted infection caused by Treponema pallidum that can result in serious cardiovascular, musculoskeletal, and neurological complications. Although effective prevention and treatment strategies are available, syphilis remains an important global public health concern[1]. The World Health Organization estimated that approximately 6 million new syphilis infections occurred worldwide in 2016 (World Health Organization, 2018). In China, syphilis re-emerged in the late 1990s after nearly three decades of marked decline, a resurgence that has been associated with rapid urbanization and changing sexual behaviors[2]. In 2025, 640,034 cases were reported nationwide, corresponding to an incidence of approximately 45.7 per 100,000 population and an 11.9% increase compared with 2024. Syphilis ranked fourth among Class B notifiable infectious diseases, underscoring its continued importance as a major public health concern in China.

Neurosyphilis occurs when T. pallidum invades the central nervous system (CNS) and can develop at any stage of syphilis infection. It encompasses a spectrum of clinical entities, including asymptomatic neurosyphilis, acute syphilitic meningitis, meningovascular syphilis, general paresis, and tabes dorsalis[3, 4]. The diagnosis of neurosyphilis poses significant challenges because no single laboratory test is sufficiently sensitive and specific to confirm CNS involvement. Although CSF-VDRL is highly specific, its sensitivity is limited (30% – 70%), and CSF-TRUST, though widely used in China, has comparable diagnostic constraints[5, 6]. Furthermore, CSF protein elevation and pleocytosis are nonspecific markers that may be influenced by various inflammatory and infectious conditions. This diagnostic uncertainty is clinically consequential because untreated neurosyphilis may progress to irreversible neurological damage, including dementia, paresis, and sensory deficits[4].

Syphilis and HIV share common routes of transmission, particularly sexual contact, resulting in frequent coinfection. Following infection, T. pallidum disseminates through interactions with endothelial cells, extracellular matrix components, and circulating blood cells. Treponemal adhesins, including Tp0751 and Tp0136[7, 8], facilitate tissue adhesion and invasion, while platelet activation and endothelial dysfunction may promote systemic spread and increase blood–brain barrier permeability, contributing to central nervous system involvement. Syphilitic mucosal lesions may facilitate HIV acquisition, whereas HIV-related immune dysfunction, especially $CD4^+$ T-cell depletion, may alter the clinical course of syphilis and increase the risk of neurological involvement[9]. Importantly, HIV coinfection further complicates the already challenging diagnosis of neurosyphilis: HIV-related

immunosuppression can alter serological responses, modify CSF inflammatory parameters, and broaden the spectrum of neurological manifestations, thereby blurring diagnostic boundaries. Consequently, the identification of HIV coinfection among patients with neurosyphilis is critical for optimizing treatment strategies, monitoring immune function, and preventing disease progression. Therefore, routine HIV screening and integrated management are important for patients with syphilis, particularly those with suspected or confirmed neurosyphilis.

The toluidine red unheated serum test (TRUST) is commonly used to evaluate disease activity and treatment response, whereas the T. pallidum particle agglutination assay (TPPA) is primarily used for confirmation. However, interpretation of serological results may be challenging in certain clinical settings, particularly in patients with HIV infection. Cerebrospinal fluid examination is essential for assessing neurological involvement in suspected neurosyphilis, although HIV coinfection may further complicate the interpretation of cerebrospinal fluid findings[10].

Previous studies have described the epidemiological overlap between HIV and syphilis and have investigated risk factors for neurosyphilis among HIV-infected populations[9]. However, most existing studies have approached neurosyphilis as a complication of HIV infection rather than examining HIV coinfection within a neurosyphilis cohort. Furthermore, the demographic, serological, CSF, immunological, and biochemical features that distinguish HIV-coinfected from non-coinfected neurosyphilis patients remain incompletely characterized. Recent studies in infectious diseases have increasingly integrated routine clinical characteristics with immune and other biological markers to characterize disease course, support risk assessment, and inform individualized management comments[11-13]. A comprehensive understanding of these differences is needed to facilitate early identification of HIV coinfection in neurosyphilis patients, which has important implications for treatment selection, immune monitoring, and prognostic assessment.

This single-center retrospective study included patients diagnosed with neurosyphilis between January 2020 and December 2025. We compared the demographic, clinical, cerebrospinal fluid, hematological, immunological, and biochemical characteristics of patients with and without HIV coinfection and identified factors independently associated with HIV coinfection. These findings may contribute to the early recognition, risk stratification, and individualized management of HIV coinfection in patients with neurosyphilis.

Methods

Design and setting

This retrospective study reviewed the electronic medical records of patients with syphilis who attended the Second Hospital of Nanjing between January 2020 and December 2025. Eligible patients had a confirmed outpatient diagnosis of syphilis and received standardized treatment at our institution. We documented standardized case report forms and routine physical examination findings throughout follow-up. We collected baseline demographic and clinical data, including age, sex, and other relevant clinical characteristics, at treatment initiation. Baseline laboratory evaluations included $CD4^+$ T-lymphocyte count, the toluidine red unheated serum test (TRUST), and the Treponema pallidum particle agglutination (TPPA) assay.

Patient characteristics

The study focused on NS patients who underwent initial screening at the Second Hospital of Nanjing. The inclusion criteria were as follows: (1) a confirmed diagnosis of syphilis based on simultaneously positive toluidine red unheated serum test (TRUST) and *Treponema pallidum* particle agglutination (TPPA) assay results; (2) neurosyphilis diagnosed according to the diagnostic guidelines issued by the U.S. and European Centers for Disease Control and Prevention (CDC), based on reactive cerebrospinal fluid (CSF) treponemal test results combined with either an elevated CSF white blood cell (WBC) count ($>5\times10^6$/L) or an elevated CSF protein concentration (> 45 mg/dL) in the presence of a nonreactive CSF-VDRL result; (3) availability of complete clinical records, cerebrospinal fluid (CSF) laboratory data, and HIV antibody test results. According to CSF laboratory findings, patients were classified as confirmed neurosyphilis and non-neurosyphilis. Patients with neurosyphilis were further categorized into HIV coinfection and non-coinfection groups.

The exclusion criteria were as follows: (1) severe immunodeficiency, organ transplantation, or ongoing antitumor radiotherapy/chemotherapy; (2) discontinuation of treatment or loss to regular follow-up; (3) incomplete medical records or incomplete diagnostic data for neurosyphilis; (4) concomitant central nervous system diseases; and (5) pregnancy or lactation.

Clinical data collection

Clinical data were retrospectively extracted from the electronic medical records of patients with neurosyphilis diagnosed between 2020 and 2025. Patients were categorized into the neurosyphilis-only group and the HIV coinfection group according to their HIV infection status.

The collected variables included demographic characteristics (age and sex), syphilis serological findings, cerebrospinal fluid (CSF) parameters, immunological indices, hematological measurements, and biochemical indicators. Syphilis-related variables included serum toluidine red unheated serum test (TRUST) titers, serum Treponema pallidum particle agglutination assay (TPPA) results, CSF-TRUST titers, and CSF-TPPA results. CSF white blood cell count and protein concentration were recorded to assess central nervous system inflammatory responses.

Immunological and hematological variables included $CD4^+$ T-cell count and absolute neutrophil, lymphocyte, and monocyte counts, as well as hemoglobin concentration and platelet count. Biochemical parameters included serum creatinine, urinary creatinine, urea, serum albumin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, estimated glomerular filtration rate, C-reactive protein, and high-sensitivity C-reactive protein. HIV infection status was determined according to the results of standard HIV-specific diagnostic testing documented in the medical records. All collected data were anonymized before statistical analysis.

Data completeness was assessed for all collected variables. Variables with missing data rates exceeding 5% were excluded from the analysis. For the remaining variables, missing values were minimal (< 5%) and were handled using complete-case analysis, as the proportion of missing data was considered too low to necessitate imputation. All included patients had complete records for the primary variables of interest, including HIV status, demographic characteristics, syphilis serological results, CSF parameters, and $CD4^+$ T-cell counts.

Clinical management

Treatment was administered in accordance with the Chinese Guidelines for the Diagnosis and Treatment of Syphilis, Gonorrhea, and Genital Chlamydia trachomatis Infection (2020). Patients without neurosyphilis received intramuscular benzathine penicillin G at 2.4 million units once weekly for 1–2 doses for early syphilis or 3 doses for late syphilis. Procaine penicillin for 15–20 days was used as an alternative. For patients with penicillin allergy, doxycycline was administered for 15 days for early syphilis or 30 days for late syphilis, with ceftriaxone used when appropriate. These patients were generally treated as outpatients and monitored by serial serum nontreponemal antibody titers.

Patients with neurosyphilis received intravenous aqueous crystalline penicillin G at 18–24 million units daily, administered as 3-4 million units every 4 hours for 10–14 days. Clinicians gave additional intramuscular benzathine penicillin G when clinically indicated.

Alternative regimens included doxycycline for 30 days or intravenous ceftriaxone for 10–14 days in patients with penicillin allergy. Prednisone at 30 mg/day for 3 days was administered before antimicrobial therapy to reduce the risk of a Jarisch–Herxheimer reaction, particularly in symptomatic patients. All patients with neurosyphilis were hospitalized and underwent multidisciplinary follow-up. Clinical response and laboratory findings were assessed after treatment, and cerebrospinal fluid examinations were repeated every 3–6 months until normalization of the leukocyte count.

Statistical analysis

Statistical analyses were performed using jamovi (version 2.7, The jamovi project, https://www.jamovi.org). GraphPad Prism 10.1.2 (GraphPad Software, San Diego, CA, USA) was used for data visualization and curve plotting. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed data are presented as means ± standard deviations (SDs) and were compared using Student's t-test, whereas non-normally distributed data are expressed as medians with interquartile ranges (IQRs) and analyzed using the Mann-Whitney U test. Categorical variables are summarized as frequencies (percentages) and were compared using Pearson's chi-square or Fisher's exact test, as appropriate.

Univariable binary logistic regression was performed to evaluate potential factors associated with HIV coinfection and clinical outcomes. HIV coinfection status was entered as the binary dependent variable (1 = HIV coinfection, 0 = no coinfection), and each candidate variable was entered individually as an independent variable to estimate its unadjusted odds ratio (OR) and 95% confidence interval (CI). Variables demonstrating a $P < 0.05$ in the univariatable analysis or variables considered clinically significant were subsequently included in a multivariable logistic regression model to identify factors associated with HIV coinfection. Multicollinearity was assessed by variance inflation factors (VIF); all VIF values were below 5, indicating no serious multicollinearity. Because CD4+ T-cells are a subset of total lymphocytes and are biologically correlated, a sensitivity analysis was performed by repeating the multivariable logistic regression after excluding absolute lymphocyte count from the model, to assess whether the association between CD4+ T-cell count and HIV coinfection was independent of total lymphocyte count. Both unadjusted and adjusted odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were calculated. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

Given the large number of between-group comparisons performed, the potential for type

I error due to multiple testing should be acknowledged; however, as this study was primarily exploratory and hypothesis-generating, formal multiple comparison correction (e.g., Bonferroni or Benjamini-Hochberg false discovery rate) was not applied. Accordingly, the reported P-values should be interpreted as descriptive rather than confirmatory.

Results

Clinical and diagnostic characteristics of the included patients

A total of 815 syphilis-related cases enrolled between 2020 and 2025 were systematically screened in this study **(Figure 1)**. Initially, all patients underwent serum Treponema pallidum testing, and those with reactive serological results further underwent lumbar puncture for cerebrospinal fluid (CSF) examination. Of these, 52 patients were excluded because they did not undergo lumbar puncture, while 763 patients completed lumbar puncture and provided CSF specimens, which were subsequently subjected to CSF treponemal testing. Patients with negative CSF treponemal test results (n = 323) were assigned to the non-neurosyphilis (general syphilis) group.

Patients with reactive CSF treponemal tests proceeded to CSF Venereal Disease Research Laboratory (VDRL) testing, and their diagnoses were comprehensively determined in combination with CSF protein levels. Specifically, patients with a reactive CSF-VDRL result, or a nonreactive CSF-VDRL result but an elevated CSF white blood cell (WBC) count (> 5 × 10^6/L) or an elevated CSF protein concentration (> 45 mg/dL), were diagnosed with neurosyphilis. Conversely, patients with a nonreactive CSF-VDRL result and a normal CSF protein level were categorized into the non-neurosyphilis group.

Ultimately, 440 patients were definitively diagnosed with neurosyphilis. Among them, 243 (55.2%) were categorized as non-co-infected, and 197 (44.8%) as HIV co-infected. This standardized screening workflow established a clear diagnostic classification system distinguishing between general syphilis and neurosyphilis, and successfully stratified the infection status of patients with neurosyphilis, thereby providing a robust foundation for subsequent analyses of clinical characteristics and prognostic outcomes.

Baseline demographic characteristics and serological findings

A total of 440 patients with neurosyphilis were included, of whom 369 (83.86%) were male **(Figure 2 and Table 1)**. The proportion of male patients was significantly higher in the HIV coinfection group than in the non-coinfection group (97.97% vs 72.43%, P < 0.001). The median age of the overall cohort was 46 years (interquartile range [IQR], 38–58 years). Patients with HIV coinfection were significantly younger than those without HIV coinfection (median age, 33 vs 55 years; P < 0.001), indicating a younger age distribution among patients with HIV-associated neurosyphilis.

The median serum toluidine red unheated serum test (TRUST) titer was 1:16 in the overall cohort. However, patients with HIV coinfection showed a distribution toward higher serum

TRUST titers. The proportion of patients with a serum TRUST titer ⩾1:32 was significantly higher in the HIV coinfection group than in the non-coinfection group (46.20% vs 34.16%, P=0.011). Serum Treponema pallidum particle agglutination assay results were reactive in all patients, confirming serological evidence of syphilis infection throughout the study population.

Cerebrospinal Fluid Syphilis Markers and Inflammatory Profiles

Among the 440 patients with neurosyphilis, the distribution of CSF-TRUST titers differed significantly between the two groups. Patients with HIV coinfection predominantly exhibited low-titer reactivity, with a substantially higher proportion having a CSF-TRUST titer of 1:1 than those without HIV coinfection (54.82% vs 7.82%, P<0.001), whereas titers of 1:2, 1:4, 1:8, and 1:16 predominated in the non-coinfected group (all P<0.05). The reactive rate of CSF-TRUST did not differ significantly between groups (72.08% vs 69.14%, P=0.501), indicating that HIV coinfection shifts the titer distribution toward low-titer reactivity rather than altering overall seropositivity. Extremely high titers (1:32, ≥1:128) were observed exclusively in the non-coinfected group, although cell counts were small; a titer of 1:64 did not differ between groups (P=0.712) (Figure 2 and Table 1). These findings indicate that HIV coinfection was associated with a distinct CSF-TRUST response characterized by predominantly low-titer positivity.

The median CSF white blood cell count in the overall cohort was 17.0 cells/μL (interquartile range [IQR], 7.0–45.0 cells/μL). Although the median values were identical in the HIV coinfection and non-coinfection groups (17.0 vs 17.0 cells/μL), the overall distributions differed significantly (P < 0.001). The median CSF protein concentration was 440.0 mg/L (IQR, 322.0–582.0 mg/L) in the overall cohort and was significantly lower in patients with HIV coinfection than in those without HIV coinfection (380.0 vs 460.0 mg/L, P < 0.001).

HIV-Related Immunological Characteristics

$CD4^+$ T-cell count serves as a primary marker for evaluating the immune status of patients with HIV infection. In this study, the median $CD4^+$ T-cell count among patients with neurosyphilis was 534 cells/μL (interquartile range [IQR], 315–884 cells/μL). Patients with HIV coinfection had a significantly lower median $CD4^+$ T-cell count than those without HIV coinfection (335 vs 634 cells/μL, P < 0.001; Figure 2 and Table 1).

Stratified analyses further revealed substantial immunological differences between the two groups. The patient's CD4+ T-cell count is classified into two categories according to the WHO clinical criteria: A CD4+ T-cell count ⩾ 350 cells/uL was observed in 84.36% of patients

in the non-coinfection group compared with 54.31% of those in the HIV coinfection group. Conversely, a CD4+ T-cell count < 350 cells/uL was 45.69% in the HIV coinfection group versus 15.64% in the non-coinfection group. These findings indicate more pronounced cellular immune impairment and severe immunosuppression in a subset of patients with neurosyphilis and HIV coinfection, reflecting the role of HIV-related immune deficiency in shaping clinical and laboratory profiles.

Peripheral Blood Cell Counts and Biochemical Profiles

Peripheral blood cell profiles differed between patients with and without HIV coinfection. The absolute neutrophil count was significantly lower in the HIV coinfection group than in the non-coinfection group (3.23 vs 4.94 × 10^9/L, $P < 0.001$), whereas the absolute lymphocyte count was significantly higher (1.87 vs 1.66 × 10^9/L, $P < 0.001$). No significant between-group difference was observed in the absolute monocyte count ($P = 0.771$; Figure 2 and Table 1).

Several hematological and biochemical parameters also differed between the groups. Patients with HIV coinfection had higher hemoglobin levels (143.0 vs 135.0 g/L, $P < 0.001$) but lower platelet counts (204.0 vs 215.0 × 10^9/L, $P = 0.038$) than those without HIV coinfection. Serum creatinine was higher in the HIV coinfection group (77.1 vs 66.5 μmol/L, $P < 0.001$), whereas urinary creatinine, urea, and estimated glomerular filtration rate did not differ significantly between groups. The HIV coinfection group also had a slightly higher serum albumin concentration (42.6 vs 41.4 g/L, $P < 0.001$) and a lower high-density lipoprotein cholesterol level (1.10 vs 1.29 mmol/L, $P < 0.001$). No significant differences were observed in low-density lipoprotein cholesterol, C-reactive protein, or high-sensitivity C-reactive protein levels (Figure 2 and Table 1).

Distribution of Cerebrospinal Fluid TRUST Titers

The distribution of cerebrospinal fluid (CSF) toluidine red unheated serum test (TRUST) titers was compared between patients with neurosyphilis without coinfection and those with HIV coinfection using a stacked bar chart (Figure 3). CSF-TRUST results were categorized as negative or as titers of 1:1, 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, and ≥1:128, with the proportion of patients in each category presented as a percentage (Figure 3).

Distinct CSF-TRUST titer distributions were observed between the two groups. Patients without HIV coinfection exhibited a broader range of titers, with relatively higher proportions at 1:2, 1:4, and 1:8 and a detectable proportion of high-titer results (≥1:32). In contrast, patients with HIV coinfection were predominantly concentrated in the low-titer range, particularly at 1:1, whereas titers ≥1:16 were less frequent. These findings demonstrate that HIV coinfection

was associated with a CSF-TRUST profile characterized predominantly by low-titer reactivity.

Factors Associated With HIV coinfection Among Patients With Neurosyphilis

Among the 440 patients with neurosyphilis, 197 (44.8%) had HIV coinfection and 243 (55.2%) did not. HIV coinfection status was entered as the dependent variable in the logistic regression analyses. In the univariable analysis, age, male sex, serum TRUST titer ≥1:32, CSF-TRUST titer of 1:1, CSF protein concentration, $CD4^+$ T-cell count, absolute neutrophil count, absolute lymphocyte count, hemoglobin level, platelet count, and high-density lipoprotein cholesterol level were significantly associated with HIV coinfection (all $P < 0.05$; Table 2 and Figure 4). The strongest positive associations were observed for male sex (OR, 18.368; 95% CI, 6.562–51.412; $P < 0.001$) and a CSF-TRUST titer of 1:1 (OR, 14.306; 95% CI, 8.288–24.696; $P < 0.001$).

In the multivariable analysis, age, male sex, a CSF-TRUST titer of 1:1, $CD4^+$ T-cell count, absolute neutrophil count, and absolute lymphocyte count remained independently associated with HIV coinfection. Increasing age was inversely associated with HIV coinfection (adjusted OR [aOR], 0.923; 95% CI, 0.896–0.950; $P < 0.001$), whereas male sex was associated with higher odds of coinfection (aOR, 6.980; 95% CI, 1.793–27.175; $P = 0.005$). A CSF-TRUST titer of 1:1 demonstrated the strongest independent association with HIV coinfection (aOR, 18.909; 95% CI, 7.878–45.387; $P < 0.001$). Higher $CD4^+$ T-cell counts (aOR per cell/μL, 0.998; 95% CI, 0.997–0.999; $P < 0.001$) and absolute neutrophil counts (aOR per 1×10^9/L, 0.562; 95% CI, 0.455 – 0.696; $P < 0.001$) were inversely associated with HIV coinfection, whereas a higher absolute lymphocyte count was positively associated with coinfection (aOR per 1×10^9/L, 2.445; 95% CI, 1.303 – 4.587; $P = 0.005$). In a sensitivity analysis excluding absolute lymphocyte count, CD4+ T-cell count remained independently associated with HIV coinfection (aOR per cell/μL 0.999, 95% CI, 0.998–1.000; P=0.002), consistent with the primary multivariable model (aOR per cell/μL 0.998, 95% CI, 0.997–0.999; P<0.001). The association between CD4+ T-cell depletion and HIV coinfection was therefore not materially confounded by total lymphocyte count.

A serum TRUST titer ≥1:32 showed a borderline association after multivariable adjustment (aOR, 2.016; 95% CI, 0.994–4.087; $P = 0.052$), whereas the remaining variables were no longer statistically significant. As illustrated in the forest plot (Figure 4), a CSF-TRUST titer of 1:1 had the largest effect estimate among the positively associated factors, followed by male sex and absolute lymphocyte count. Overall, younger age, male sex, a CSF-

TRUST titer of 1:1, lower $CD4^+$ T-cell and absolute neutrophil counts, and a higher absolute lymphocyte count constituted the principal independent characteristics associated with HIV coinfection among patients with neurosyphilis.

Discussion

In this retrospective study of 440 patients with neurosyphilis, 197 (44.8%) had concurrent HIV infection. Compared with patients without HIV coinfection, those with HIV coinfection were younger, predominantly male, and more likely to exhibit low-titer CSF-TRUST reactivity, lower $CD4^+$ T-cell and absolute neutrophil counts, and higher absolute lymphocyte counts. Multivariable logistic regression further identified younger age, male sex, a CSF-TRUST titer of 1:1, lower $CD4^+$ T-cell and absolute neutrophil counts, and a higher absolute lymphocyte count as characteristics independently associated with HIV coinfection. Collectively, these findings indicate that HIV coinfection is associated with a distinct demographic, serological, and immunological profile among patients with neurosyphilis.

From a demographic perspective, patients with HIV coinfection were substantially younger than those without coinfection, with median ages of 33 and 55 years, respectively. Moreover, 97.97% of patients in the HIV coinfection group were male, compared with 72.43% in the non-coinfection group. After adjustment for potential confounders, male patients had approximately sevenfold higher odds of HIV coinfection than female patients, whereas each 10-year increase in age was associated with an approximately 55% reduction in the odds of coinfection. These findings suggest that younger men constitute a prominent demographic subgroup among patients with HIV-associated neurosyphilis. Recent studies by Kömür et al. and Wu et al. have highlighted that HIV-associated neurosyphilis predominantly affects younger MSM populations and is strongly associated with high-risk sexual behaviors, suggesting that specific sexual networks and exposure patterns may contribute to the epidemiological overlap between HIV infection and neurosyphilis[14, 15]. Accordingly, clinicians should maintain a high index of suspicion for HIV and other sexually transmitted infections in younger male patients diagnosed with neurosyphilis. Nevertheless, age and sex should be regarded as clinical indicators that prompt further testing rather than diagnostic criteria.

Serological analyses revealed that although a serum TRUST titer $\geqslant$1:32 was more frequently observed in patients with HIV coinfection, this association did not remain statistically significant after multivariable adjustment, suggesting limited independent discriminatory value[16, 17]. In contrast, CSF-TRUST titers demonstrated a distinct distribution pattern between groups. A CSF-TRUST titer of 1:1 was observed in 54.82% of patients with HIV coinfection compared with 7.82% of those without coinfection and remained the strongest independent factor associated with HIV coinfection (adjusted OR, approximately 19). This

predominance of low-titer CSF-TRUST reactivity may reflect altered intrathecal antibody responses in the context of HIV-related immune dysregulation[18-20]. However, the underlying mechanisms require further investigation. Clinically, low-titer CSF-TRUST positivity in patients with suspected HIV-associated neurosyphilis should not be interpreted as mild disease or used to exclude neurosyphilis. Instead, diagnosis should rely on an integrated assessment of neurological manifestations, serum and CSF syphilis serology, CSF inflammatory parameters, and immune status. Sun et al. studies have shown that elevated serum TRUST titers are associated with an increased risk of neurosyphilis among HIV/syphilis co-infected patients, suggesting the clinical value of serological burden assessment for identifying patients requiring CSF examination[21]. Although CSF-TRUST 1:1 may serve as a supportive indicator for identifying patients at increased likelihood of HIV coinfection, it cannot replace definitive HIV-specific testing.

Although CSF inflammatory parameters differed between groups, their clinical discriminatory value appeared limited. The median CSF leukocyte count was identical in both groups (17.0 cells/μL), and the lower CSF protein concentration observed in patients with HIV coinfection was no longer independently associated after adjustment. These findings suggest that CSF leukocyte and protein levels may be influenced by multiple factors, including intrathecal inflammation, blood–CSF barrier integrity, disease duration, and host immune status, and therefore should not be interpreted in isolation for identifying HIV coinfection[18, 22, 23].

In contrast, $CD4^+$ T-cell depletion represented one of the most clinically relevant immunological features of HIV-associated neurosyphilis[24, 25]. Patients with HIV coinfection exhibited substantially reduced $CD4^+$ T-cell counts, with a higher proportion showing severe immunosuppression (<350 cells/μL). Moreover, $CD4^+$ T-cell count remained independently associated with HIV coinfection after multivariable adjustment, highlighting its value in assessing HIV-related immune dysfunction[26]. Hu et al. reported that despite comparable CD4 recovery, ART-treated PLWH with persistent CD8 T cell activation exhibited sustained CD4/CD8 ratio inversion, expansion of senescent and activated CD8 subsets, and diminished regulatory T cells, accompanied by upregulated interferon-stimulated genes and pro-inflammatory transcriptional programs[27]. Therefore, $CD4^+$ T-cell evaluation should be incorporated into the clinical assessment of neurosyphilis patients, particularly those with suspected HIV coinfection, to facilitate immune stratification and identify individuals at increased risk of opportunistic infections and other immune-related complications.

Peripheral blood cell profiles also differed between the two groups. Patients with HIV

coinfection had lower absolute neutrophil counts but higher absolute lymphocyte counts, and both remained independently associated with HIV coinfection in the multivariable analysis[28, 29]. Each increase of 1 × 10^9/L in the absolute neutrophil count was associated with an approximately 44% reduction in the odds of coinfection, whereas a higher absolute lymphocyte count was associated with increased odds of coinfection. The coexistence of a higher total lymphocyte count and a lower $CD4^+$ T-cell count is not contradictory because the absolute lymphocyte count encompasses multiple lymphocyte subsets, including $CD4^+$ and $CD8^+$ T cells, B cells, and natural killer cells. The observed pattern may therefore reflect redistribution or differential expansion of lymphocyte subsets in the context of HIV infection[27].

Patients with HIV coinfection had higher hemoglobin, serum creatinine, and albumin levels but lower platelet counts and high-density lipoprotein cholesterol levels. None of these variables remained independently associated with HIV coinfection after multivariable adjustment. The higher hemoglobin concentration may be partly explained by the greater proportion of male patients in the HIV coinfection group[30]. Although serum creatinine was higher in this group, the absence of significant differences in urea and estimated glomerular filtration rate does not support clinically evident impairment of overall renal function. Similarly, differences in platelet count, albumin, and lipid profiles may reflect demographic, nutritional, metabolic, inflammatory, or treatment-related factors rather than HIV coinfection[31, 32].

The distribution of cerebrospinal fluid (CSF) TRUST titers differed markedly between groups. A CSF-TRUST titer of 1:1 was detected in 54.82% of HIV-coinfected patients, compared to only 7.82% in those without HIV coinfection. Conversely, higher titers ranging from 1:2 to 1:32 were more prevalent in the non-coinfected group. In multivariable models, a CSF-TRUST titer of 1:1 demonstrated the strongest independent association with HIV coinfection, with an adjusted odds ratio of approximately 19. This predominance of low-titer reactivity may reflect altered intrathecal antibody responses in the context of HIV-related immune dysfunction[18, 19]. Impaired immune cell function could modify the intensity or persistence of local treponemal antibody production, resulting in persistently positive CSF-TRUST at relatively low titers rather than an enhanced overall serological response[33]. However, the underlying immunological mechanisms cannot be determined from the current observational data and warrant further investigation.

Several limitations of this study should be acknowledged. First, this was a single-center retrospective study conducted at an infectious disease specialty hospital, which inherently serves a patient population with a higher prevalence of HIV infection than general hospitals. Consequently, the HIV coinfection rate observed in this cohort (44.8%) is substantially higher

than that reported in general hospital settings. Second, the retrospective design precluded the collection of certain longitudinal data, including treatment outcomes and follow-up CSF findings. In addition, information on antiretroviral therapy and HIV viral load was not available for all patients, precluding analysis of their potential modifying effects on the observed associations.

Conclusions

In conclusion, HIV coinfection among patients with neurosyphilis was characterized by younger age, male predominance, low-titer CSF-TRUST reactivity, reduced $CD4^+$ T-cell and neutrophil counts, and an increased absolute lymphocyte count. A CSF-TRUST titer of 1:1 demonstrated the strongest independent association with HIV coinfection. These findings may facilitate early clinical recognition and targeted HIV testing but require validation in prospective, multicenter studies incorporating detailed virological, immunological, and longitudinal outcome data.

Abbreviations

BBB = Blood-Brain Barrier

$CD4^+$ T = Cluster of Differentiation 4 positive T lymphocyte

$CD8^+$ T = Cluster of Differentiation 8 positive T lymphocyte

CI = Confidence Interval

CDC = Centers for Disease Control

CRP = C-Reactive Protein

CSF = Cerebrospinal Fluid

CSF-RPR = Cerebrospinal Fluid Rapid Plasma Reagin

CSF-TPPA = Cerebrospinal Fluid Treponema Pallidum Particle Agglutination

CSF-TRUST = Cerebrospinal Fluid Toluidine Red Unheated Serum Test

CSF-VDRL = Cerebrospinal Fluid Venereal Disease Research Laboratory

HDL-C = High-Density Lipoprotein Cholesterol

HIV = Human Immunodeficiency Virus

hs-CRP = high-sensitivity C-Reactive Protein

IQR = Interquartile Range

LDL = Low-Density Lipoprotein Cholesterol

OR = Odds Ratio

PLWH = People Living with HIV

RPR = Rapid Plasma Reagin

TP = Treponema pallidum

TPPA = Treponema Pallidum Particle Agglutination

TRUST = Toluidine Red Unheated Serum Test

VDRL = Venereal Disease Research Laboratory

WBC = White Blood Cell

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the Second Hospital of Nanjing (Approval No. 2026-LS-ky154). The requirement for informed consent was waived due to the retrospective nature of the study, and all patient data were anonymized prior to analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable. This study is a retrospective analysis of anonymized clinical data and does not contain any individual person’s identifiable data, images, or videos.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. If you need the raw data, please contact chhuayi@sina.cn.

Competing interests

The authors declare that they have no competing interests.

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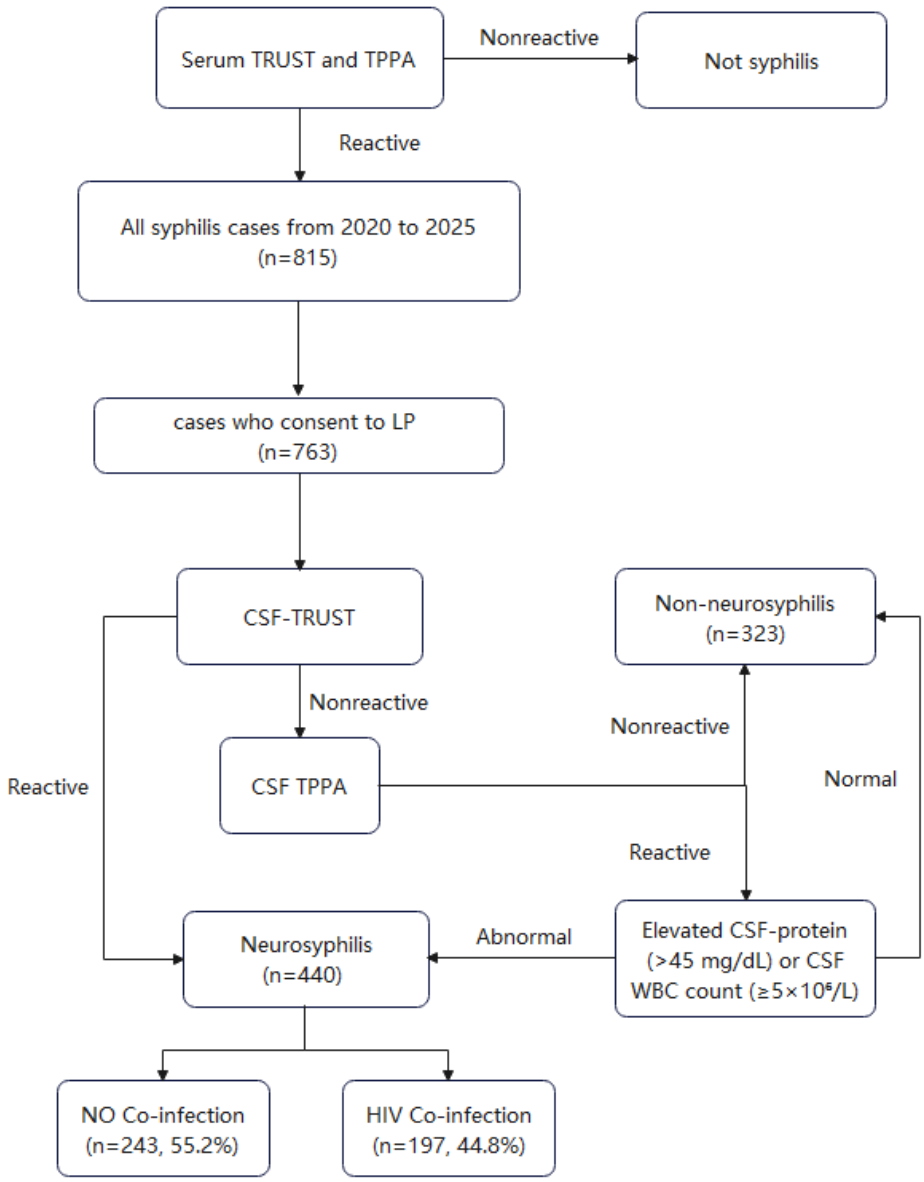
Authors' contributions

CY and YZ conceived the project. MZ and WW designed the study. SG, YJ, XM, WQ, MX, and AC collected the study data. MZ, ZW, and XL analyzed the data and wrote the draft manuscript. All authors reviewed, revised, and approved the final version of the manuscript.

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529 **Figure**



530

531 **Figure 1.** Research flowchart of neurosyphilis patients in this study.

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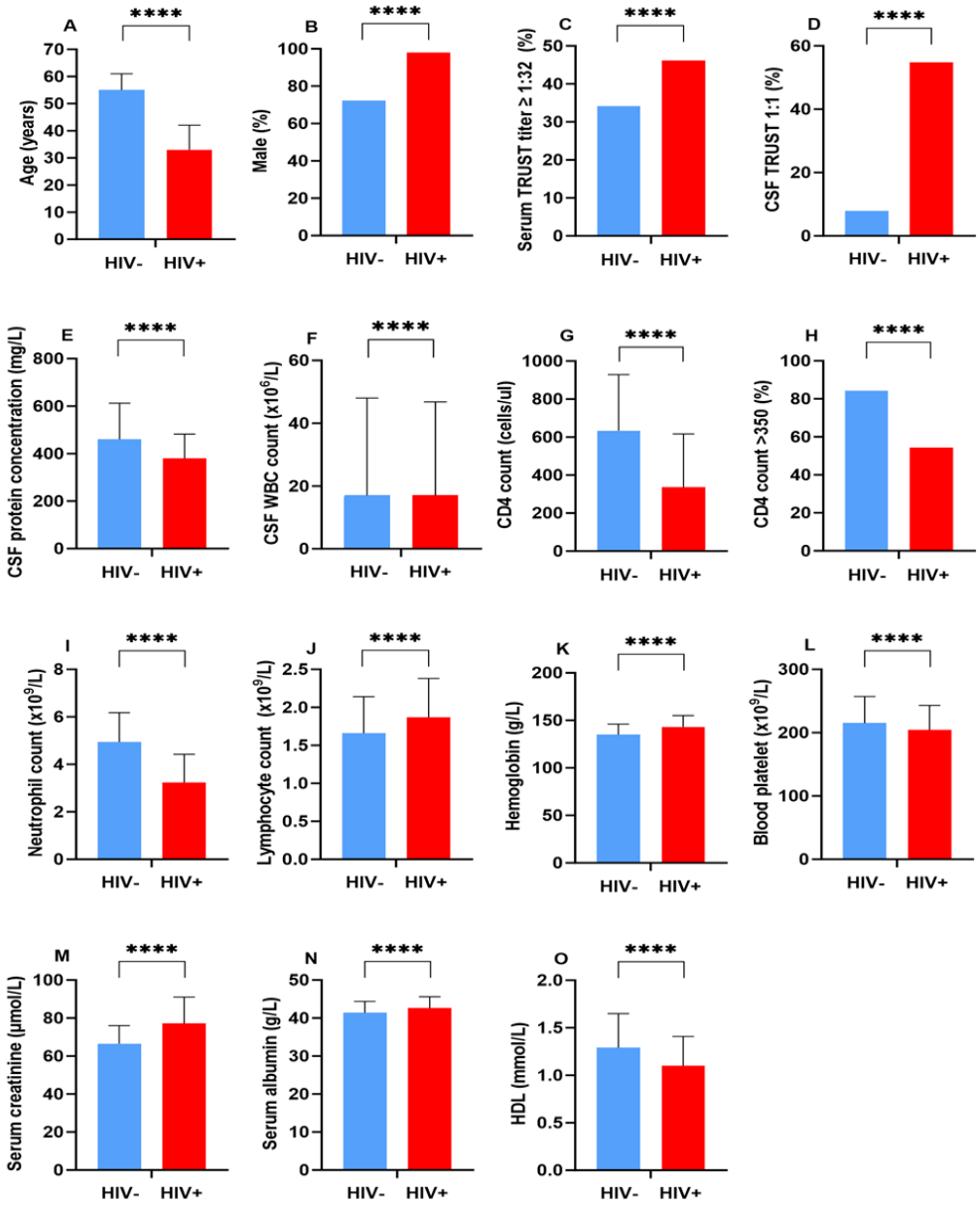
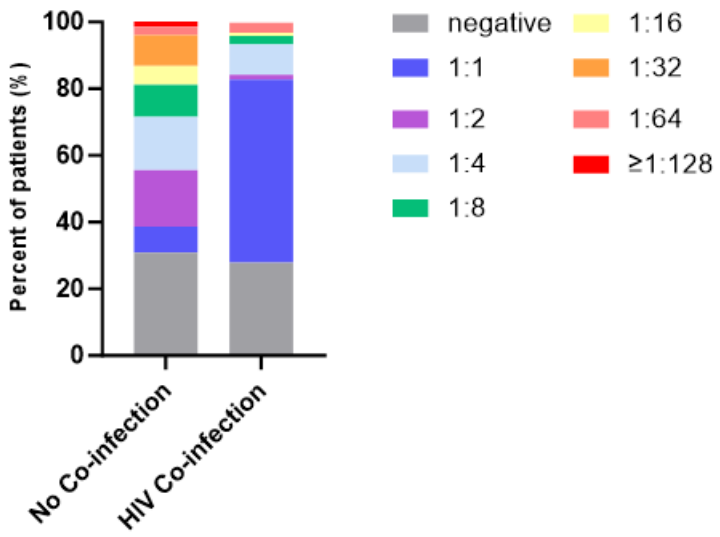


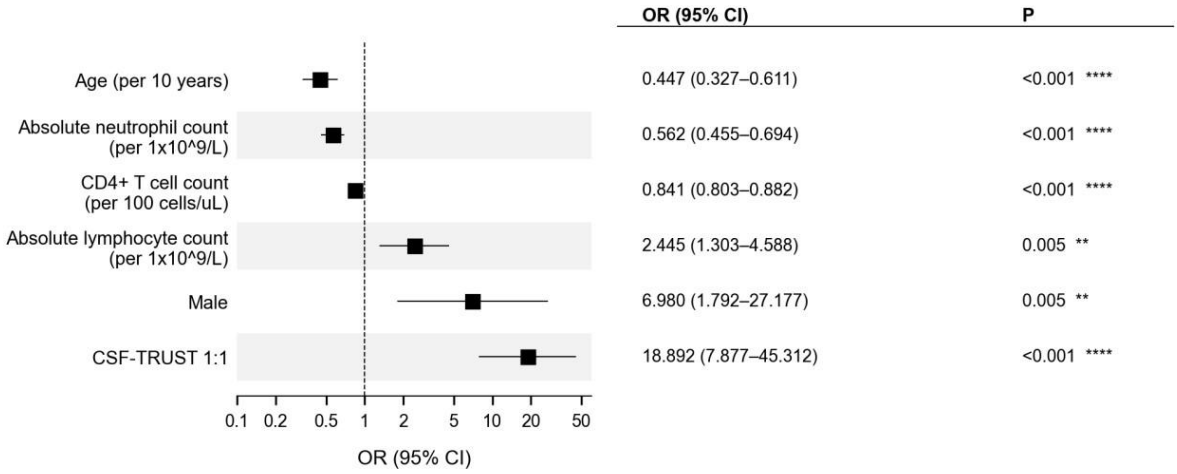
Figure 2. Distinct clinical and immunological profiles of neurosyphilis patients with and without HIV coinfection



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538 **Figure 3.** Distribution of cerebrospinal fluid TRUST titers in neurosyphilis patients with and
539 without HIV coinfection

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542 **Figure 4.** Forest plot of factors independently associated with HIV coinfection among patients
543 with neurosyphilis.

544

545 **Table 1.** Baseline characteristics of neurosyphilis patients with and without HIV coinfection

Characteristic	Overall (n=440)	No coinfection (n=243)	HIV coinfection (n=197)	P-value
Demographic characteristics				
Gender (male), n (%)	369 (83.86)	176 (72.43)	193 (97.97)	**<0.001**
Age (years), median (IQR)	46 (38-58)	55 (46-63)	33 (27-42)	**<0.001**
Serological characteristics				
Serum TRUST titer, median (IQR)	1:16 (1:4-1:32)	1:16 (1:4-1:32)	1:16 (1:8-1:64)	**<0.05**
1:1, n (%)	30 (6.81)	9 (3.70)	21 (10.66)	—
1:2, n (%)	39 (8.92)	27 (11.11)	12 (6.19)	—
1:4, n (%)	44 (10.07)	27 (11.11)	17 (8.76)	—
1:8, n (%)	66 (15.10)	47 (19.34)	19 (9.64)	—
1:16, n (%)	87 (19.91)	50 (20.58)	37 (18.78)	—
1:32, n (%)	80 (18.31)	48 (19.75)	32 (16.24)	—
1:64, n (%)	47 (10.76)	20 (8.23)	27 (13.71)	—
1:128, n (%)	29 (6.64)	9 (3.70)	20 (10.15)	—
1:256, n (%)	16 (3.66)	5 (2.06)	11 (5.58)	—
1:512, n (%)	2 (0.46)	1 (0.41)	1 (0.51)	—
Serum TRUST ≥1:32, n (%)	174 (39.55)	83 (34.16)	91 (46.20)	**0.011**
Serum TPPA positive, n (%)	440 (100)	243 (100)	197 (100)	—
Cerebrospinal fluid characteristics				
CSF TRUST positive, n (%)	310 (70.45)	168 (69.14)	142 (72.08)	**0.501**
CSF TRUST 1:1, n (%)	127 (28.86)	19 (7.82)	108 (54.82)	**<0.001**
CSF TRUST 1:2, n (%)	44 (10.00)	41 (16.87)	3 (1.52)	**<0.001**
CSF TRUST 1:4, n (%)	57 (13.95)	39 (16.05)	18 (9.14)	0.032
CSF TRUST 1:8, n (%)	28 (6.36)	23 (9.47)	5 (2.54)	0.003
CSF TRUST 1:16, n (%)	16 (3.64)	14 (5.76)	2 (1.02)	0.008
CSF TRUST 1:32, n (%)	22 (5.00)	22 (9.05)	0 (0.00)	**<0.001**
CSF TRUST 1:64, n (%)	12 (2.73)	6 (2.47)	6 (3.05)	0.712
CSF TRUST ≥1:128, n (%)	4 (0.91)	4 (1.65)	0 (0.00)	0.132
CSF WBC count, median (IQR), /μL	17.0 (7.0-45.0)	17.0 (8.0-48.0)	17.0 (5.0-46.8)	**<0.001**
CSF protein, median (IQR), mg/L	440.0 (322.0-582.0)	460.0 (358.0-612.0)	380.0 (252.8-482.0)	**<0.001**
CSF TPPA positive, n (%)	440 (100)	243 (100)	197 (100)	—
Immunological characteristics				
CD4 count, median (IQR), cells/μL	534.0 (315.0-884.0)	634.0 (385.0-929.0)	335.0 (195.0-617.0)	**<0.001**
CD4 ⩾350 cells/μL, n (%)	312 (70.9)	205 (84.4)	107 (54.3)	**<0.001**
CD4 < 350 cells/μL, n (%)	128 (29.1)	38 (15.6)	90 (45.7)	—
Hematological characteristics				
Neutrophil count, median (IQR), ×10⁹/L	3.98 (2.69-5.32)	4.94 (3.49-6.18)	3.23 (2.13-4.42)	**<0.001**
Lymphocyte count, median (IQR), ×10⁹/L	1.76 (1.31-2.24)	1.66 (1.23-2.14)	1.87 (1.42-2.38)	**<0.001**
Monocyte count, median (IQR), ×10⁹/L	0.48 (0.34-0.62)	0.48 (0.34-0.64)	0.48 (0.30-0.60)	0.771
Hemoglobin, median (IQR), g/L	138.0 (127.0-150.0)	135.0 (124.0-146.0)	143.0 (132.0-155.0)	**<0.001**
Platelet count, median (IQR), ×10⁹/L	209.5 (173.0-251.0)	215.0 (176.0-257.0)	204.0 (168.0-243.0)	**0.038**
Biochemical characteristics				
Serum creatinine, median (IQR), μmol/L	70.0 (58.0-82.0)	66.5 (56.5-76.0)	77.1 (63.0-91.0)	**<0.001**
Urinary creatinine, median (IQR), mmol/L	8.80 (5.40-13.20)	8.80 (5.50-13.00)	8.80 (5.30-13.50)	0.707
Urea, median (IQR), mmol/L	5.17 (4.0-6.6)	5.23 (4.00-6.80)	5.11 (4.00-6.30)	0.222
Serum albumin, median (IQR), g/L	41.8 (38.2-44.8)	41.4 (37.5-44.4)	42.6 (39.5-45.6)	**<0.001**
HDL, median (IQR), mmol/L	1.19 (0.93-1.57)	1.29 (0.91-1.65)	1.10 (0.84-1.41)	**<0.001**

LDL, median (IQR), mmol/L	2.70 (2.00-3.50)	2.75 (2.00-3.50)	2.60 (2.00-3.40)	0.239
eGFR, median (IQR), mL/min/1.73m²	108.0 (91.5-121.7)	107.5 (89.5-121.0)	109.6 (94.5-122.5)	0.244
CRP, median (IQR), mg/L	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	0.131
hs-CRP, median (IQR), mg/L	0.86 (0.50-2.73)	0.86 (0.50-2.95)	0.85 (0.50-2.35)	0.831

*Note: Continuous variables are expressed as median (interquartile range, IQR); categorical variables are expressed as n (%).

*P-values were calculated using the Mann-Whitney U test for continuous variables and the chi-square test (or Fisher's exact test) for categorical variables. Bold P-values indicate statistical significance ($P < 0.05$).

* CRP detection limit is 10 mg/L, and those below the detection limit are recorded as 10.0 mg/L; CRP was therefore reported descriptively only.

*All confidence intervals were rounded to 3 decimal places; a CI upper bound of 1.000 may occur due to rounding

*Abbreviations: TRUST, toluidine red unheated serum test; TPPA, Treponema pallidum particle agglutination; CSF, cerebrospinal fluid; WBC, white blood cell; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein.

Table 2. Logistic regression analysis of HIV coinfection factors in neurosyphilis

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Age (years)	0.918	0.903–0.934	<0.001	0.923	0.896–0.950	<0.001
Male sex	18.368	6.562–51.412	<0.001	6.98	1.793–27.175	0.005
Serum TRUST ≥1:32	1.655	1.125–2.434	0.010	2.016	0.994–4.087	0.052
CSF-TRUST 1:1	14.306	8.288–24.696	<0.001	18.909	7.878–45.387	<0.001
CSF WBC (u/L)	1	0.999–1.002	0.638	1	0.997–1.004	0.784
CSF protein (mg/L)	0.999	0.998–1.000	0.007	0.999	0.998–1.001	0.396
$CD4^+$ T-cell count (cells/μL)	0.998	0.998–0.999	<0.001	0.998	0.997–0.999	<0.001
Absolute neutrophil count (1×10^9/L)	0.548	0.475–0.633	<0.001	0.562	0.455–0.696	<0.001
Absolute lymphocyte count (1×10^9/L)	1.715	1.273–2.311	<0.001	2.445	1.303–4.587	0.005
Hemoglobin (g/L)	1.032	1.018–1.046	<0.001	1.009	0.984–1.035	0.473
Platelet count (1×10^9/L)	0.996	0.992–0.999	0.009	0.996	0.990–1.003	0.275
Serum creatinine (μmol/L)	1.006	0.998–1.015	0.147	1.004	1.000–1.008	0.055
Serum albumin (g/L)	1.041	0.993–1.090	0.098	0.89	0.786–1.009	0.069
HDL (mmol/L)	0.079	0.035–0.178	<0.001	0.336	0.086–1.316	0.117

*+Sensitivity analysis excluding absolute lymphocyte count yielded similar results for all retained variables; CD4 aOR 0.999 (95% CI, 0.998 – 1.000), P = 0.002.

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