

MINI-REVIEW

Relationship between characteristics and clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis: A systematic review and meta-analysis

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Abstract

Neurological complications of human immunodeficiency virus (HIV) infection are a global health concern; cerebral toxoplasmosis, caused by *Toxoplasma gondii*, is one such complication. This condition is one of the causes of mortality in HIV patients. However, evidence on the relationship between patient characteristics and clinical outcomes remains limited; therefore, we conducted this systematic review and meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Literature searches were conducted on PubMed, ScienceDirect, and the Cochrane Library. Data from studies that met the inclusion criteria were extracted, presented descriptively, and analyzed using Review Manager 5.4. Our study included 6 research articles involving 778 patients. Based on the data analysis, it was found that decreased consciousness and low CD4⁺ cell counts significantly played a role in the worsening of the clinical condition of HIV/AIDS patients with cerebral toxoplasmosis, with odds ratios of 4.29 (95% CI: 2.74–6.73; $p < 0.001$) and 7.52 (95% CI: 2.45–23.10; $p < 0.001$), respectively. Meanwhile, the variables of male sex, old age, anemia, and highly active antiretroviral therapy were not significantly associated with clinical outcomes. This study indicates that decreased consciousness and low CD4⁺ cell counts are factors significantly associated with the clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis.

Keywords: Cerebral toxoplasmosis; Clinical characteristics; Clinical outcomes; Human immunodeficiency virus/Acquired immunodeficiency syndrome; Neuro-infection

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1. Introduction

Human immunodeficiency virus (HIV) is a virus that attacks the human immune system, especially cluster of differentiation (CD)4⁺ cells, which play an important role in maintaining the body's resistance to various infections. If HIV infection is not treated adequately, it will develop into acquired immunodeficiency syndrome (AIDS), a condition in which the body becomes highly susceptible to various infections and other

lethal diseases due to a severely damaged immune system.¹ In 2024, an estimated 543,000 people are living with HIV in Indonesia. As many as 40,000 new cases of infection occur each year, with 28,000 deaths due to AIDS.²

Cerebral toxoplasmosis is the most common opportunistic infection in HIV/AIDS patients, caused by infection with the protozoan *Toxoplasma gondii*. This parasite can live in the human body in a latent state. However, in individuals with a weak immune system, such as HIV/AIDS patients with low CD4⁺ cell counts (<100 cells/ μ L), this parasite can reactivate and cause serious infections in the brain. As many as 30–50% of advanced HIV patients experience cerebral toxoplasmosis, with the highest incidence found in Africa, Latin America, and Southeast Asia.³ In Indonesia, 20–40% of HIV/AIDS patients experience cerebral toxoplasmosis each year. The main symptoms include headache, fever, seizures, impaired consciousness, and focal neurological deficits such as limb weakness and speech disorders. Diagnosis of this disease often requires ancillary investigations, such as brain magnetic resonance imaging and computed tomography scans, as well as serology and polymerase chain reaction tests to detect *T. gondii* DNA. Treatment options for HIV/AIDS patients with cerebral toxoplasmosis include antiprotozoal agents, such as pyrimethamine and sulfadiazine, accompanied by other supportive therapies to control symptoms and improve the patient's immune status. However, the success of therapy depends heavily on factors such as disease severity, the patient's immune response, and access to adequate treatment. Therefore, understanding the clinical characteristics of HIV/AIDS patients with cerebral toxoplasmosis is critical in determining the optimal therapeutic strategy and improving patient prognosis.³

To understand the relationship between the characteristics of HIV/AIDS patients and the clinical outcomes of cerebral toxoplasmosis, meta-analysis and systematic review-based research have a significant role. Based on this background, we aim to analyze the relationship between the characteristics of HIV/AIDS and clinical outcomes in cerebral toxoplasmosis patients. This study further aims to identify risk factors, clinical manifestation patterns, and the effectiveness of therapies applied in various previous studies.

2. Materials and methods

2.1. Study design

We conducted a systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with the overall study screening process shown in [Figure 1](#). We registered

the meta-analysis protocol in the PROSPERO database under ID CRD420251272936.

Article searches were conducted across reputable databases, including PubMed, ScienceDirect, and the Cochrane Library, from January 1, 2000, to December 1, 2025. Boolean operators were used. The keywords used included (“Toxoplasmosis cerebral” OR “Toxoplasmosis encephalitis”) AND (“Clinical characteristic” OR “Factor related”) AND (“Clinical outcome” OR Death” OR “Clinical response”) AND (“HIV/AIDS” OR “Human Immunodeficiency Virus” OR “Acquired Immunodeficiency Syndrome”).

2.2. Study eligibility

The inclusion criteria were: (i) English-language clinical studies; (ii) studies evaluating factors related to clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis; and (iii) studies reporting sufficient data for statistical analysis. Meanwhile, the exclusion criteria were non-English articles, articles with unavailable full text, articles that were not research articles, and gray literature (articles that had not undergone peer review). Study quality analysis was conducted on included studies using the Newcastle-Ottawa Scale (NOS) according to the research design (cohort and case-control), with scoring classifications: low (0–3), moderate (4–6), and high (7–9).

2.3. Data extraction, analysis, and interpretation

Data analysis was conducted by integrating and describing all data systematically to enable conclusions to be drawn. The data were in the form of study characteristics information (name of main author, year of publication, research location, and research design), factors that potentially affect patient clinical outcomes (sex, age, cognitive decline, low CD4⁺ cell counts, anemia, and use of highly active antiretroviral therapy [HAART]), and patient clinical outcomes (death and response to therapy). The collected data were analyzed using Review Manager 5.4 (The Cochrane Collaboration, United Kingdom). The results of the data analysis are displayed as odds ratios (ORs) with confidence intervals (CIs), homogeneity (I^2), and significance values (p) in forest plots. Publication bias analysis was performed qualitatively using Begg's funnel plot, with low bias indicated by the symmetry of the resulting graph.

3. Result

3.1. The characteristics of included studies

This systematic review and meta-analysis included 6 research articles involving 778 patients. Demographically, there were 2 studies from Asian and African populations

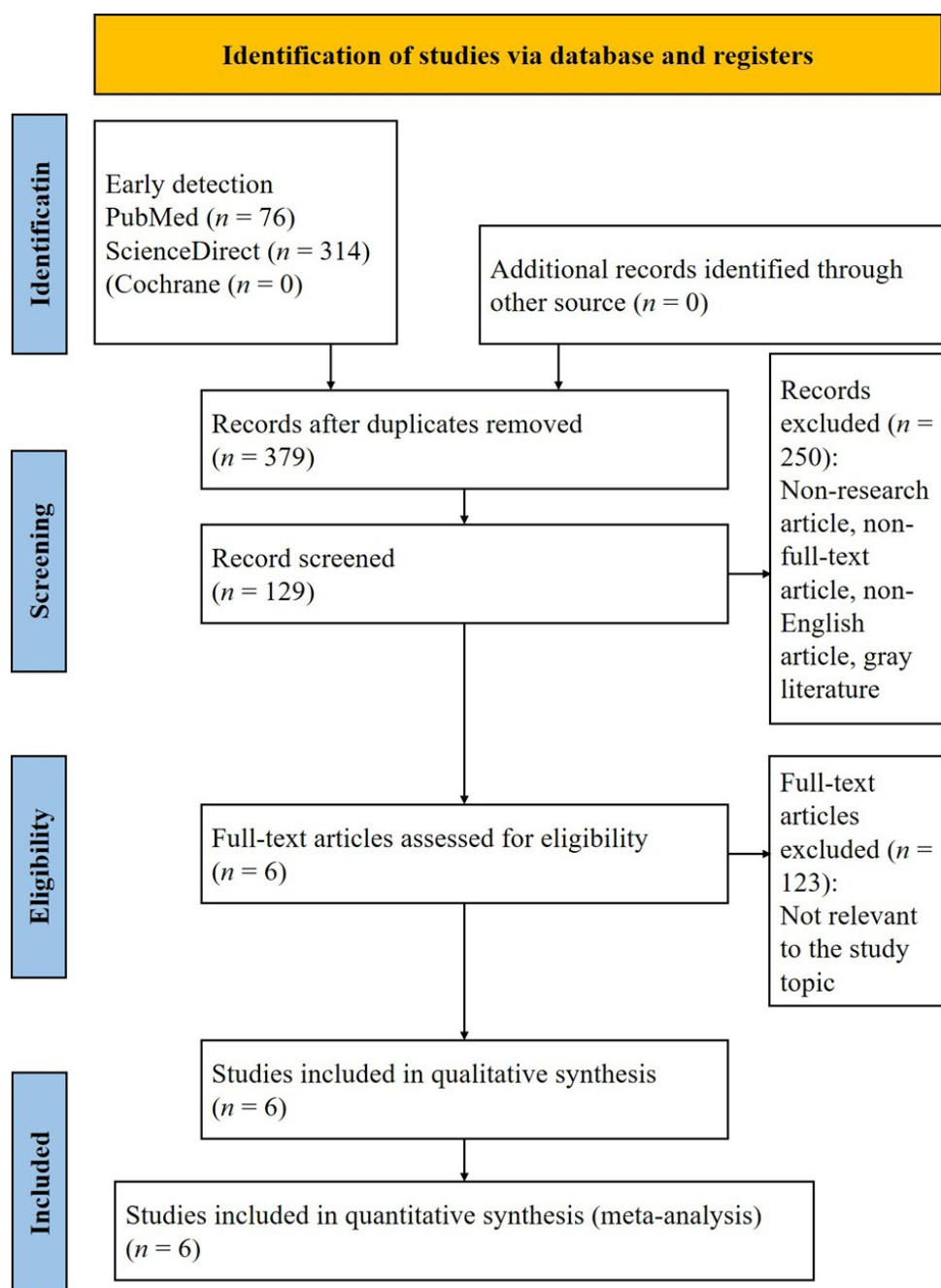


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart

and 1 study each from Europe and South America. There were 3 cohort studies and 3 case-control studies. The clinical outcomes analyzed included the association between clinical characteristics and both mortality and patient response to therapy. The results are shown in Table 1, which describes variables from clinical characteristics that have the potential to affect the clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis. Cognitive decline, decreased consciousness, use of

HAART, fever symptoms, low CD4⁺ cell counts, sexual partners, hematological markers (hemoglobin, leukocytes, and neutrophil-to-lymphocyte ratio), low Karnofsky score, psychomotor slowing, frequency of neurological deficits, and seizures were factors considered for further analysis. Study quality was assessed using the Newcastle–Ottawa Scale (NOS), with 5 good-quality studies (points 7–9) and 1 moderate-quality study (points 6). Specific assessments of study quality are shown in Table 2.

Table 1. Characteristics of included studies

Study	Nation	Design	Sample	Clinical outcome	Research outcome	NOS
Antinori <i>et al.</i> ⁴	Italy	Prospective cohort	205	Mortality within six months	Patient mortality was significantly associated with cognitive decline (OR 2.18; $p = 0.03$), decreased consciousness (OR 2.65; $p = 0.005$), and HAART administration after TE diagnosis (OR 0.19; $p < 0.001$)	8
Li <i>et al.</i> ⁵	China	Case-control	94	Patient mortality	Patient mortality was significantly associated with symptoms of fever (OR 7.76; $p = 0.031$), decreased consciousness (OR 5.06; $p = 0.033$), onset >15 days (OR 3.34; $p = 0.048$), and low CD4 ⁺ cell counts (OR = 5.43; $p = 0.011$)	9
Saavedra <i>et al.</i> ⁶	Ghana	Retrospective cohort	222	Mortality seven days after treatment	Gender, duration of illness, and HAART administration did not significantly affect mortality seven days after treatment	6
Sow <i>et al.</i> ⁷	Guinea	Case-control	87	Patient mortality	Patient mortality was significantly associated with partner status (OR 9.93; $p = 0.007$), low CD4 ⁺ cell counts (OR 19.04; $p = 0.009$), and decreased consciousness (OR 5.18; $p = 0.02$)	9
Suryaprabha <i>et al.</i> ¹	Indonesia	Case-control	122	Patient mortality	Patient mortality was significantly associated with decreased consciousness ($p < 0.001$), WBC levels ($p = 0.04$), and NLR ($p < 0.001$)	7
Vidal <i>et al.</i> ⁸	Brazil	Prospective cohort	48	Mortality and therapeutic response within one year	Clinical outcomes such as patient mortality were significantly associated with decreased consciousness (OR 22.3; $p < 0.001$), low Karnofsky score (OR 16.8; $p < 0.001$), psychomotor slowing (OR 14.9; $p = 0.001$), decreased Hb (OR 8.9; $p = 0.010$), duration of neurological symptoms (OR 1.1; $p = 0.030$), and seizures (OR 5.9; $p = 0.037$)	8

Abbreviations: HAART: Highly active antiretroviral therapy; Hb: Hemoglobin; NLR: Neutrophil-to-lymphocyte ratio; NOS: Newcastle-Ottawa Scale; OR: Odds ratio; TE: Toxoplasmic encephalitis; WBC: White blood cell.

Table 2. Newcastle–Ottawa Scale scores of included studies

Study	Selection	Comparability	Exposure/Outcome	Total
Antinori <i>et al.</i> ⁴	☆☆☆☆	☆	☆☆☆	8
Li <i>et al.</i> ⁵	☆☆☆☆	☆☆	☆☆☆	9
Saavedra <i>et al.</i> ⁶	☆☆☆	☆	☆☆	6
Sow <i>et al.</i> ⁷	☆☆☆☆	☆☆	☆☆☆	9
Suryaprabha <i>et al.</i> ¹	☆☆☆	☆	☆☆☆	7
Vidal <i>et al.</i> ⁸	☆☆☆	☆☆	☆☆☆	8

Notes: Newcastle–Ottawa Scale domain scores are presented as stars; total score ranges from 0 to 9 (Selection: 0–4; Comparability: 0–2; Exposure/Outcome: 0–3).

3.2. Clinical characteristics with clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis

The results of the analysis in this study are presented quantitatively in Figure 2. It was found that decreased consciousness and low CD4⁺ cell counts significantly played a role in worsening the clinical condition of HIV/AIDS patients with cerebral toxoplasmosis, with ORs of 4.29 (95% CI: 2.74–6.73; $p < 0.001$) and 7.52 (95% CI: 2.45–23.10; $p < 0.001$), respectively. Meanwhile, the variables of male sex (total OR: 1.22; $p = 0.52$; in Asia, OR: 1.08; $p = 0.84$; in Africa, OR: 1.51; $p = 0.52$), old age (OR: 0.80; $p = 0.47$), anemia (OR: 2.70; $p = 0.35$), and HAART use (OR: 0.59; $p = 0.37$) were not significantly associated with clinical outcomes.

3.3. Publication bias

This study conducted a qualitative test for publication bias using Begg's funnel plot. The results are shown in Figure 3, which demonstrates that the male sex analysis showed low publication bias, with a graph that is symmetrical and even. In contrast, other variables showed strong publication bias. This may be due to the limited number of studies conducted to date. These findings are reinforced by quantitative results showing that the variables male sex, decreased consciousness, and HAART use did not exhibit publication bias, whereas the variables old age, low CD4⁺ cell counts, and anemia did, as listed in Table 3.

4. Discussion

Our analysis showed that the male sex was not significantly associated with the risk of experiencing worsening clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis. Within the included studies, Sow *et al.*⁷ reported insignificant correlation between male sex and worsening clinical outcomes in patients (OR: 1.64; 95% CI: 0.46–5.85). This condition can be caused by several factors.

Cerebral edema functions not merely as a radiological finding but also as an intermediate pathophysiological mechanism through which baseline factors, such as level of consciousness, immune status, anemia, and advanced age, may directly influence mortality and neurological prognosis in HIV/AIDS patients with cerebral toxoplasmosis. Expanding the manuscript to address corticosteroid use, as highlighted by recent evidence from Goldman *et al.*⁹, is therefore highly pertinent, given that steroid administration is often prompted by clinical deterioration due to edema and mass effect rather than toxoplasmosis itself. Furthermore, insights from the stroke literature by Tan *et al.*¹⁰ provided a valuable conceptual framework for interpreting heterogeneity in outcomes identified in the meta-analysis, emphasizing that edema-directed

interventions can modify short-term survival without necessarily improving long-term neurological recovery. Integrating these perspectives strengthens the causal narrative of the meta-analysis by situating cerebral edema and its management as key effect modifiers that bridge patient characteristics and outcomes, thereby enhancing the clinical relevance and mechanistic coherence of the study's conclusions.

First, the pathogenesis of cerebral toxoplasmosis in HIV/AIDS patients mainly depends on the level of immunosuppression, characterized by low CD4⁺ cell counts. This factor plays a greater role in determining prognosis than demographic factors such as sex and age. Decreased immunity due to HIV causes reactivation of latent *T. gondii*, which is a major factor in the severity of infection and clinical outcomes in patients. Second, sex does not directly affect the course of cerebral toxoplasmosis, as *T. gondii* infection and reactivation are driven primarily by immune status rather than biological differences between men and women. Although some studies have shown sex differences in immunological responses, in cerebral toxoplasmosis, these differences are insufficient to affect overall clinical outcomes.¹¹

Our data analysis showed that older age was not significantly associated with worsening clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis. Similarly, within the included studies, Li *et al.*¹ reported an insignificant correlation between older age and worsening clinical outcomes, with an OR of 1.510 (95% CI: 0.364–6.256). Exposure to HIV generally occurs at a younger age, coinciding with the onset of sexual activity—one of the transmission pathways of HIV/AIDS—and the latent period before symptom development may extend up to eight years. Opportunistic infections, including cerebral toxoplasmosis, tend to manifest during advanced stages of HIV infection when CD4⁺ cell counts drop below 200 cells/mm³, a process that may occur within 2 to 10 years without antiretroviral treatment and is mostly found in individuals aged ≤ 35 years. Research has indicated a higher susceptibility to cerebral toxoplasmosis among individuals in their 30s, potentially due to declining CD4⁺ cell counts, poor adherence to antiretroviral therapy, and exposure to *T. gondii* through the consumption of raw or undercooked meat and vegetables. In Indonesia, satay—a widely consumed meat dish—has been identified as a potential source of infection.¹²

Our data analysis showed that decreased consciousness significantly increased the worsening of clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis. Within the included studies, Vidal *et al.*⁸ showed a significant correlation between decreased consciousness and worsening clinical outcomes, with an OR of 22.3

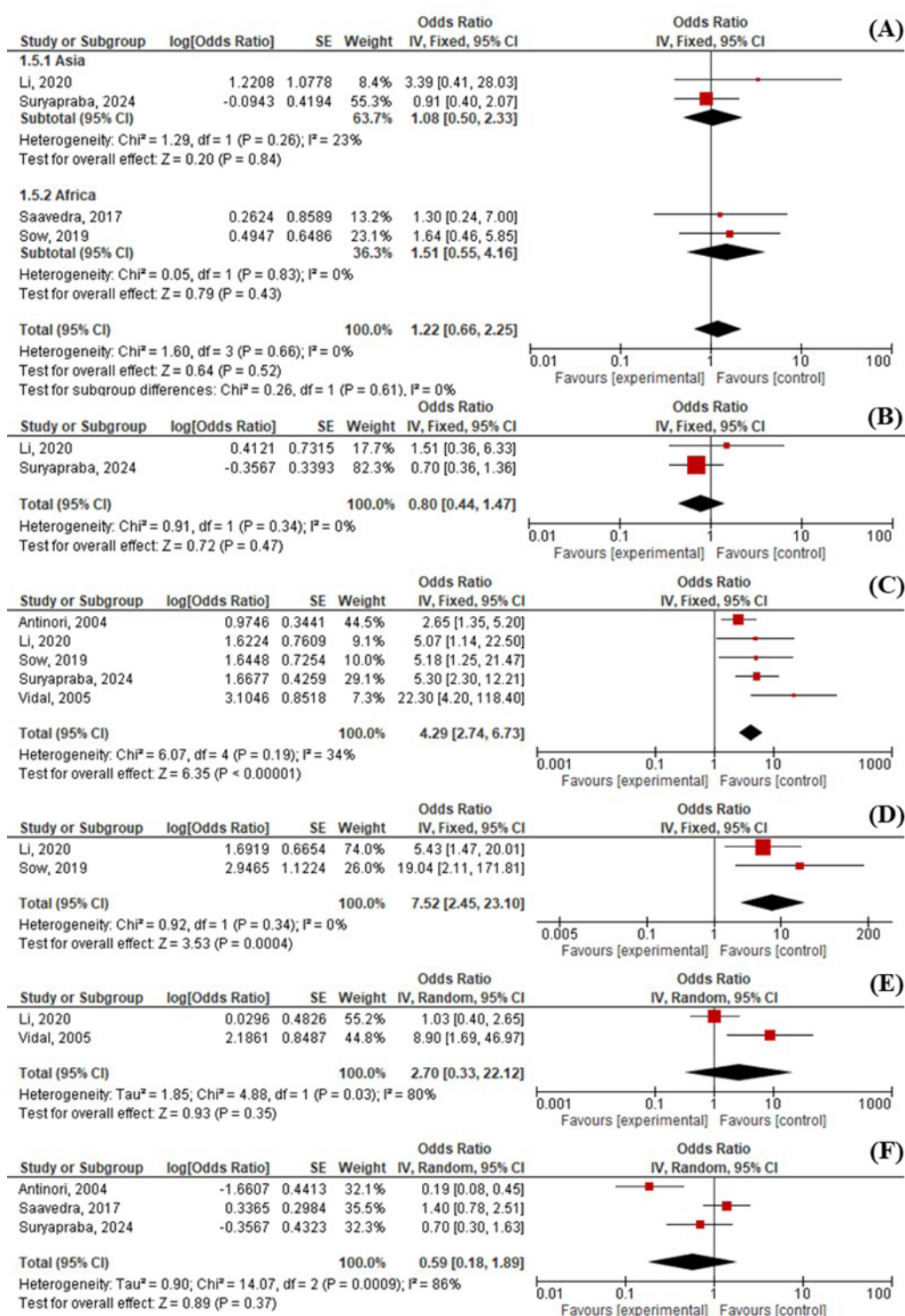


Figure 2. Forest plots of the analysis results of factors related to clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis: Male sex, old age, decreased consciousness, low CD4⁺ cell counts, anemia, and use of HAART.

Abbreviations: CI: Confidence interval; HAART: Highly active antiretroviral therapy; IV: Inverse-variance; OR: Odds ratio; SE: Standard error.

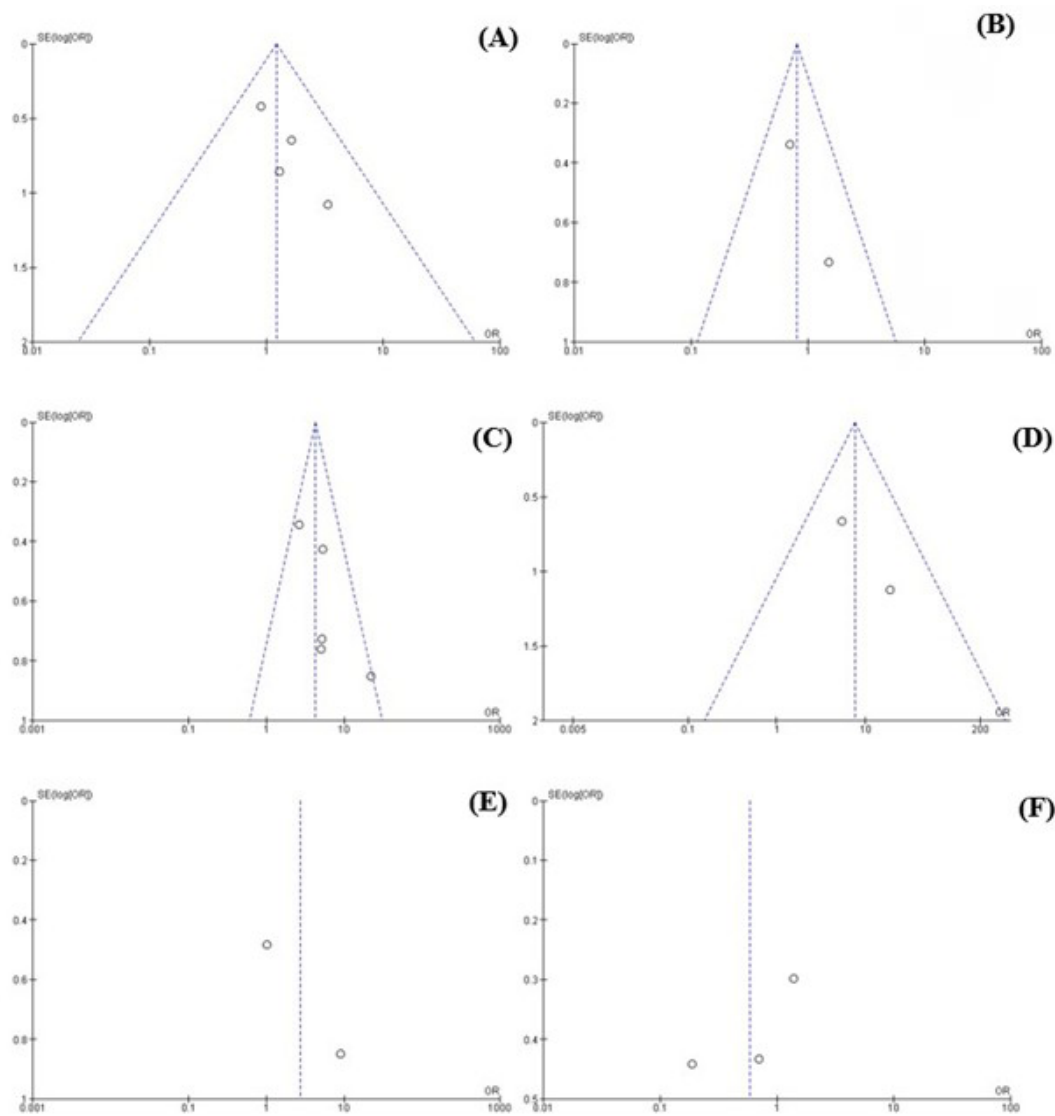


Figure 3. The funnel plots of the risk of bias results from factors related to clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis. (A) Male sex. (B) Old age. (C) Decreased consciousness. (D) Low CD4⁺ cell counts. (E) Anemia. (F) Use of highly active antiretroviral therapy (HAART). Abbreviations: OR: Odds ratio; SE: Standard error.

Table 3. Analysis of publication bias

Variables	No. of studies	Meta-analysis model	I ² (%)	Egger intercept	p-value
Male sex	4	Fixed effect	0	0.88	0.59
Old age	2	Fixed effect	0	1.96	<0.001
Decreased consciousness	5	Fixed effect	34	2.45	0.67
Low CD4 ⁺ cell counts	2	Fixed effect	0	2.75	<0.001
Anemia	2	Random effects	80	5.89	<0.001
HAART use	3	Random effects	86	−9.91	0.38

Abbreviation: HAART: Highly active antiretroviral therapy.

(95% CI: 4.2–119.3; $p < 0.001$). Impaired consciousness may be caused by disorders of the ascending reticular activating system, which covers the thalamus and bilateral hemispheres extensively. The prognosis of patients with cerebral hemorrhage in the hemispheres and thalamus is worse than that of patients with hemorrhage in the basal ganglia because the prognosis of cerebral toxoplasmosis is related to the degree of consciousness in the pre-treatment phase.¹³

The meta-analysis results showed that low CD4⁺ cell counts were significantly associated with worse clinical outcomes in patients with cerebral toxoplasmosis. Similarly, previous studies have confirmed that *T. gondii* infection often occurs in individuals with weakened immune systems, especially when CD4⁺ cell counts are < 100 cells/mm³.¹⁴ More specifically, patients with CD4⁺ cell counts < 50 cells/mm³ have the highest risk. Low CD4⁺ cell counts are a significant risk factor for the development of toxoplasmic encephalitis (TE). A study by Ananda and Maisara¹⁴ reported that TE generally develops in patients with CD4⁺ cell counts below 100 cells/ μ L, and that further decreases in CD4⁺ cell counts increase the risk of more severe neurological complications. Another study by Li *et al.*⁵ also found a strong association between low CD4⁺ cell counts and both faster disease progression and higher mortality rates in patients with TE. Therefore, the results of this meta-analysis further strengthen the understanding that monitoring and maintaining higher CD4⁺ cell counts are essential in reducing the risk of complications and mortality in HIV/AIDS patients with cerebral toxoplasmosis.

Our analysis showed that anemia has an insignificant correlation with worse clinical outcomes. Several previous studies have explored the association between anemia and TE in HIV/AIDS patients. A study by Obeagu *et al.*¹⁵ showed the potential for increased metabolic derangements and systemic inflammation in HIV patients with anemia, which may worsen immune responses to opportunistic infections, including *T. gondii*. Similarly, Ying *et al.*¹⁶ found that anemia in patients with TE is often associated with nutritional deficiencies and more severe immunosuppression, factors that can indirectly exacerbate disease progression. However, as the present meta-analysis found an insignificant relationship between anemia and clinical outcomes, further large-scale studies are needed to confirm whether anemia independently contributes to a worse prognosis in patients with TE.

The meta-analysis showed an insignificant correlation between HAART use and clinical outcomes in TE patients, suggesting that although HAART has the potential to improve clinical outcomes, its effect in the analyzed population may not be strong enough to reach statistical significance. Previous studies have widely supported the

benefits of HAART in reducing the incidence of TE, as well as improving the overall clinical outcomes in HIV/AIDS patients. Prasitsuebsai *et al.*¹⁷ reported that the risk of opportunistic infections, including TE, can be reduced through the use of HAART by increasing CD4⁺ cell counts and suppressing HIV replication. In addition, Hassana *et al.*¹² stated that TE patients who received HAART showed better neurological recovery than those who did not. However, our findings showed that the relationship was not significant. This lack of significance may be attributable to factors such as delays in HAART initiation, low therapy adherence, or other clinical factors that were not fully controlled in the included studies.

This research has several limitations, including the small number of included studies. Although only six studies were eligible, they comprised populations from Asia, South America, Europe, and Africa, which may enhance the generalizability of the findings. In addition, all available variables have been analyzed in detail, and subgroup analyses were carried out to provide a more specific picture while minimizing potential bias.

5. Conclusion

This systematic review and meta-analysis concluded that decreased consciousness and low CD4⁺ cell counts are significantly associated with clinical outcomes in HIV/AIDS patients with cerebral toxoplasmosis.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

We registered the meta-analysis protocol in the PROSPERO database under ID CRD420251272936.

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