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Meta-Analysis

Mortality of TB-HIV Co-Infection Patients Based on CD4 Level: Meta-Analysis

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ABSTRACT

Background: Tuberculosis (TB) is the most common cause of death in the world in patients with the Human Immunodeficiency Virus (HIV). Understanding CD4 as a predictor of mortality from TB-HIV co-infection is critical to improving disease management and minimizing mortality. This study aims to examine the mortality risk of TB-HIV co-infected patients based on CD4 values.
Subjects and Method: Meta-analysis was performed according to the PRISMA flow chart and the PICO model (Population: TB-HIV co-infected patients, Intervention: CD4 value <200 cells/µL, Comparison: CD4≥200 cells/µL, Outcome: mortality). The databases used are Google Scholar, PubMed, Scopus, Proquest, and Science Direct. Keywords used (coinfection OR "mixed infection") AND (HIV OR "Human Immunodeficiency Virus") AND (TB OR "tuberculosis") AND ("CD4 count" OR "T4 lymphocyte") AND "mortality". The inclusion criteria were full-text articles with cohort studies published in 2012-2022, articles in English, and multivariate analysis in the form of adjusted hazard ratio. Analysis was performed with Revman 5.3.
Results: There are 17 articles with cohort design originating from Ethiopia, Khayelitsha, Kenya, Cape Town, Uganda, Brazil, Suriname, Sao Paulo, Guinea Bissau, Myanmar, Durban, Ireland, China, and multi-country studies between Europe and Latin America totaling 24,514 research sample. A meta-analysis of 10 study cohorts concluded that CD4<200 cells/µL had a 2.00 times risk of mortality compared with CD4 values ≥200 cells/µL (aHR=2.00; 95% CI 1.44 to 2.78; p<0.001). A meta-analysis of 7 study cohorts concluded that CD4<100 cells/µL had a 2.40-time risk of mortality compared with CD4 values≥200 cells/µL (aHR=2.40; 95% CI 1.61 to 3.57; p<0.001). A meta-analysis of 7 study cohorts concluded that CD4<50 cells/µL had a 3.12 times risk of mortality compared with CD4 values≥200 cells/µL (aHR=3.12; 95% CI 1.51 to 6.46; p<0.001).
Conclusion: Decreased CD4 values increase the risk of mortality.

Keywords: tuberculosis, HIV, CD4, mortality, meta-analysis

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BACKGROUND

Tuberculosis (TB) is the most common cause of death in the world in Human Immunodeficiency Virus (HIV) patients (García et al., 2020). In HIV-infected persons, the risk of developing TB severity is between 10%-20% compared to patients without HIV coinfection (Kiros et al., 2020). HIV is known to cause dysfunction of the immune system. In particular, untreated progressive HIV infection is associated with decreased

Mycobacterium tuberculosis-specific CD4 counts (Kisuya et al., 2018).

People with HIV/Acquired Immunodeficiency Syndrome (AIDS) are more susceptible to TB infection. The presence of several opportunistic microbial infections can lead to poor treatment outcomes (Peetluk et al., 2022). This can occur due to TB-HIV co-infection using antiretroviral therapy (ARV) and intensive phase TB treatment simultaneously. On the other hand, HIV not only increases the prevalence of TB but also has a negative effect on complications (Peetluk et al., 2022). HIV promotes the development of latent or acute infection of Mycobacterium tuberculosis (Muyaya et al., 2019).

Delays in diagnosis and delay in therapy in TB-HIV co-infected patients indirectly affect mortality in HIV-TB co-infection (Odume et al., 2017). Delay in starting ARVs can result in AIDS-related illness and even death, 63% of deaths occur within the first 6 months of therapy (Yende-Zuma et al., 2016). Unfortunately, an observational study at Sanglah Hospital showed that out of 60 TB-HIV co-infected patients, only 20 patients (33.3%) started ARVs within 2 months of TB therapy (Naidoo et al., 2013).

Understanding CD4 is critical to improving disease management and minimizing early mortality. Peripheral blood CD4 cell values have been shown to be a strong predictor of TB events (Assefa et al., 2014). Previous research stated that the risk of death was affected by CD4<200 cells/µL (aHR=2.47; 95% CI= 1.49 to 4.09; p<0.001) (Wejse et al., 2015). Another study showed that the CD4 category <200 cells/µL affectted the survival rates of TB/HIV co-infected patients (aHR=6.05; 95% CI 2.83 to 12.95; p<0.001) (Wondimu et al., 2020).

These conditions prompted the authors to conduct a study on the mortality of TB-HIV coinfected patients based on CD4 values by meta-analysis.

SUBJECTS AND METHOD

1. Study Design

The meta-analysis was carried out using the PRISMA flowchart using the Google Scholar, PubMed, Scopus, Proquest, and Science Direct databases. Keywords used (coinfecttion OR "mixed infection") AND (HIV OR "Human Immunodeficiency Virus") AND (TB OR tuberculosis) AND ("CD4 count" OR "T4 lymphocyte") AND mortality. There were 17 studies with cohort research designs published in 2012-2022 that met the inclusion criteria. Analysis was performed with Revman 5.3.)

2. Steps of Meta-Analysis

Meta analysis was carried out in 5 steps as follows:

1) Formulate research questions in PICO format (Population, Intervention, Comparison, Outcome).
2) Look for primary study articles from various electronic and non-electronic databases such as PubMed, ScienceDirect, Google Scholar, Scopus.
3) Perform screening to determine inclusion and exclusion criteria and carry out a critical assessment
4) Extract primary study data and synthesize effect estimates using the RevMan 5.3 application.
5) Interpret the results and draw conclusions.

3. Inclusion Criteria

Full-text paper articles using cohort studies. Relationship measure used by HR. The analysis used was multivariate with adjusted Hazard Ratio (aHR). The research subjects were patients diagnosed with tuberculosis and HIV co-infection. One of the interventions was a CD4 value <200 cells/µL. English articles. Outcome is mortality.

4. Exclusion Criteria

Articles with research subjects <15 years and no CD4 data.

5. Operational Definition of Variables

Article search was carried out according to the criteria according to the PICO model. There was a PICO in this study, the population was TB-HIV co-infected patients, the intervention was CD4 <200 cells/µL, and mortality was the outcome.

TB-HIV co-infected patients are patients who have been diagnosed with tuberculosis and HIV.

CD4 value is a marker of Th lymphocytes which play an important role in HIV and Mycobacterium tuberculosis infection. CD4 value categories are <50 cells/µL, <100 cells/µL, and <200 cells/µL

Mortality is the cessation the process of activity in an individual's biological body which is characterized by loss of brain function, cessation of heartbeat, cessation of blood pressure and cessation of breathing processes.

6. Study Instruments

The quality assessment in this study used the list of critical assessments for cohort studies published by the Joanna Briggs Institute.

7. Data Analysis

The articles in this study were collected according to the PRISMA flowchart and analyzed using the Review Manager 5.3 application. The analysis was carried out by calculating the effect size and heterogeneity consistency value (I^2) of the selected research results. The results of data analysis are in the form of forest plots and funnel plots.

RESULTS

The results of the article search were obtainned from the meta-analysis process using the PRISMA flowchart, which can be seen in Figure 1. The total number of articles obtained was 17 articles. The distribution of articles comes from four continents namely Asia, Africa, Europe and South America. There were 10 studies originating from the African continent (4 from South Africa, 5 East Africa, and 1 West Africa), 2 studies from the Asian continent (1 from Myanmar and 1 from China), 2 studies from Europe (1 from Ireland). and 1 cross-country study of Western Europe and Eastern Europe), and 3 studies from the South American continent (1 from Suriname and 2 from Brazil) in Figure 2 with details in Table 1.

Assessment of study quality was carried out quantitatively and qualitatively, this study used a critical appraisal checklist for cohort studies (Moola et al., 2017). Critical appraisal which consists of 11 questions. Each “yes” answer was given a score of 2, “unclear” answer was given a score of 1 and “no” answer was given a score of 0. The assessment of the quality of the study is shown in Table 2. Based on the answers from the quality assessment, the total score of the answers ranged from 15 to 16 scores, it shows that the quality of the article is feasible for meta-analysis. The study description in Table 3 shows the mortality of TB-HIV co-infected patients based on CD4 values <200 cells/µL. There are 13 articles with a total sample of 57,715 research subjects.

The study description in Table 4 shows the mortality of TB-HIV co-infected patients based on CD4 values <100 cells/µL. There are 7 articles with a total sample of 49,257 research subjects.

The study description in Table 5 shows the mortality of TB-HIV co-infected patients based on CD4 values <50 cells/µL. There are 7 articles with a total sample of 47,170 research subjects.

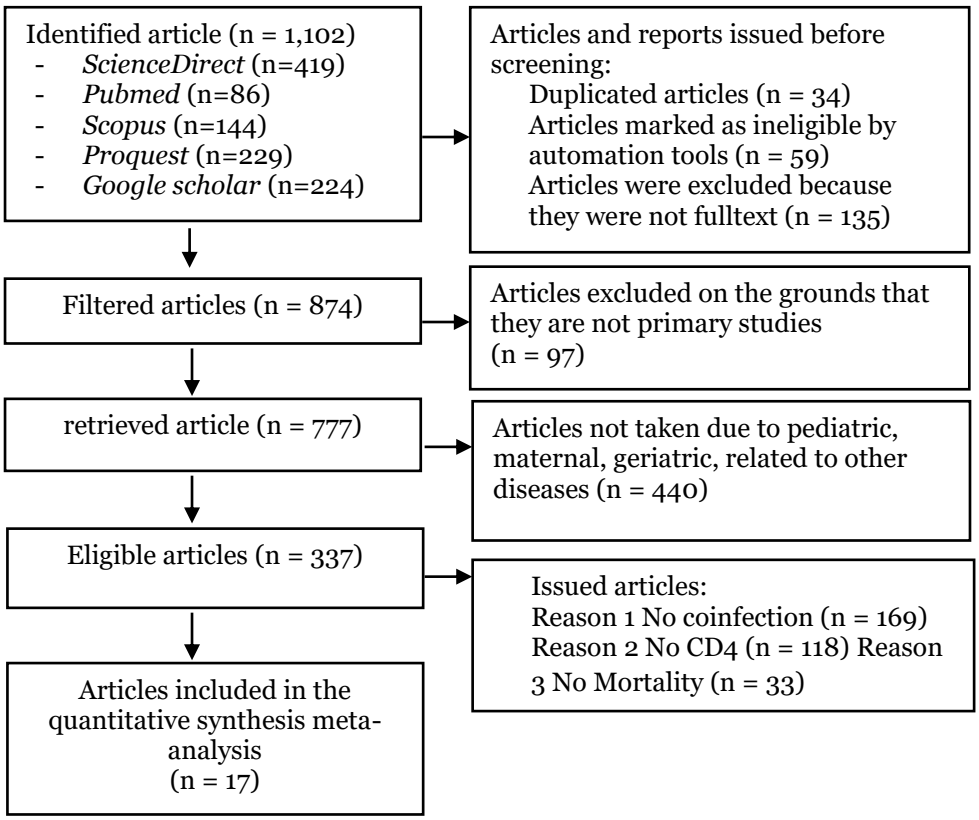

Figure 1. PRISMA Diagram Search for Mortality Articles in TB-HIV Coinfected Patients based on CD4 Value

Figure 2. Resarch Distribution Map

Table 1. Assessment of article quality by cohort study design

Primary Study	Criteria											Total
	1	2	3	4	5	6	7	8	9	10	11	
Aung et al. (2019)	2	2	2	2	1	2	2	2	2	2	2	21
Azeez et al. (2022)	2	2	2	2	1	2	2	1	1	0	2	17
Bassett et al. (2012)	2	2	2	2	1	2	2	2	1	0	2	18
Daniels et al. (2015)	2	2	2	2	1	2	2	2	1	0	2	19
Huerga et al (2019)	2	2	2	2	2	2	2	2	0	0	2	18
Ji et al. (2018)	2	2	2	2	2	2	2	1	1	1	2	19
Kaplan et al. (2014)	2	2	2	2	0	2	2	2	0	0	2	16
Kassa et al. (2012)	2	2	2	2	1	2	2	2	1	0	2	18
Nansera et al. (2012)	2	2	2	1	0	2	2	0	2	2	2	17
Podlekareva et al. (2016)	2	2	2	2	0	2	2	2	2	2	2	20
Sileshi et al. (2013)	2	2	2	2	0	2	2	2	2	0	2	18
Silva et al. (2018)	2	2	2	2	2	2	2	2	0	0	2	18
Stijnberg et al. (2019)	2	2	2	2	2	2	2	2	1	0	2	19
Tancredi et al. (2022)	2	2	2	2	1	2	2	2	2	2	2	21
Tesfayohannes et al. (2022)	2	2	2	2	1	2	2	2	2	2	2	21
Wejse et al. (2014)	2	2	2	2	1	2	2	2	2	0	2	19
Zenner et al. (2015)	2	2	2	2	2	2	2	2	2	1	2	21

Description of the question criteria:

1 = Were the two groups equivalent and recruited from the same population?
2 = Was exposure measured in subjects in the exposed and unexposed groups?
3 = Is exposure measured validly and reliably?
4 = Is there any identification of confounding factors?
5 = What are the strategies for dealing with confounding factors?
6 = Were the participants or group free of disease which was the outcome since study entry (or at the time of exposure)?
7 = Are the outcomes measured validly and reliably?
8 = Was the follow-up time reported and long enough for an outcome to occur?
9 = Was follow up complete, or if not, was there a reason for loss to follow up explained?
10 = Are strategies for dealing with incomplete follow-up implemented?
11 = Is data analysis appropriate?

Answer score description:

0 = No
1 = Can't tell
2 = Yes

1. Mortality of HIV-TB Coinfected Patients based on CD4 Value <200 cells/Ml

Table 2. Description of primary mortality studies based on CD4 values <200 cells/µL

Author (Year)	Country	Sample	P	I	C	O
Azeez *et al.* (2022)	Ethiopia	1,525	TB/HIV co-infected patients aged ≥15 years	CD4<200	CD4≥200	Died (database)
Daniels *et al.* (2015)	Khayelitsha	696	Patients coinfected with RR-TB and HIV ≥15-59 years	CD4≤200	CD4>200	Died (database)
Huerga *et al.* (2019)	Kenya	594	HIV-positive TB patients aged ≥15 years	CD4<200	CD4≥200	Died (tracing)

Author (Year)	Country	Sample	P	I	C	O
Kaplan *et al.* (2014)	Cape Town	38,996	HIV-positive TB patients aged ≥15 years	CD4≤200	CD4>200	Died (database)
Kassa et al. (2012)	Ethiopia	4,210	HIV patients with TB ≥15 years	CD4<200	CD4≥200	Died (database)
Nansera et al. (2012)	Uganda	386	TB-HIV co-infected patients ≥15 years	CD4<200	CD4≥200	Died (phone family)
Sileshi et al. (2013)	Ethiopia	422	TB-HIV co-infected patients ≥15-59 years	CD4≤200	CD4≥200	Died (database)
Silva et al. (2018)	Brazil	924	Individuals with concomitant TB and HIV/AIDS, who received hospital care during the study period.	CD4≤200	CD4>200	Records data and clinical notifications
Stijnberg et al. (2019)	Suriname	252	TB/HIV co-infected patients aged ≥15-59 years	CD4≤200	CD4>200	Died (database)
Tancredi et al. (2022)	Sao Paulo	4,581	TB-HIV co-infected patients ≥13-59 years	CD4≤200	CD4>200	Die
Tesfayohannes et al. (2022)	Ethiopia	665	HIV patients on antiretroviral therapy with TB coinfection ≥17-59 years	CD4<200	CD4≥200	(database) (surveillance database)
Wejse et al. (2014)	Guinea Bissau	1,312	HIV-positive TB patients aged ≥15 years	CD4<200	CD4≥200	Died (database)
Zenner et al. (2015)	Ireland	3,188	HIV patients with TB ≥15 years	CD4<200	CD4≥200	Died (result of home visit)

Table 3. Adjusted Hazard Ratio (aHR) Mortality of TB-HIV Coinfected Patients based on CD4 Value <200 cells/µL

Author (Year)	aHR	CI 95%	
		Lower Limit	Upper Limit
Azeez et al. 2022	0.95	0.75	1.21
Daniels et al. 2015	1.21	0.50	3.10
Huerga et al. 2019	3.21	1.42	7.28
Kaplan et al. 2014	3.04	2.38	3.89
Kassa et al. 2012	1.28	0.85	1.94
Nansera et al. 2012	0.75	0.58	0.96
Sileshi et al. 2013	3.07	1.33	7.07
Silva et al. 2018	1.40	0.86	2.27
Stijnberg et al.2019	5.49	3.28	9.20
Tancredi et al. 2022	2.32	1.97	2.72
Tesfayohannes et al. 2022	2.77	1.30	5.94
Wejse et al. 2014	2.47	1.49	4.09
Zenner et al. 2015	2.79	2.32	3.36

a. Forest Plot

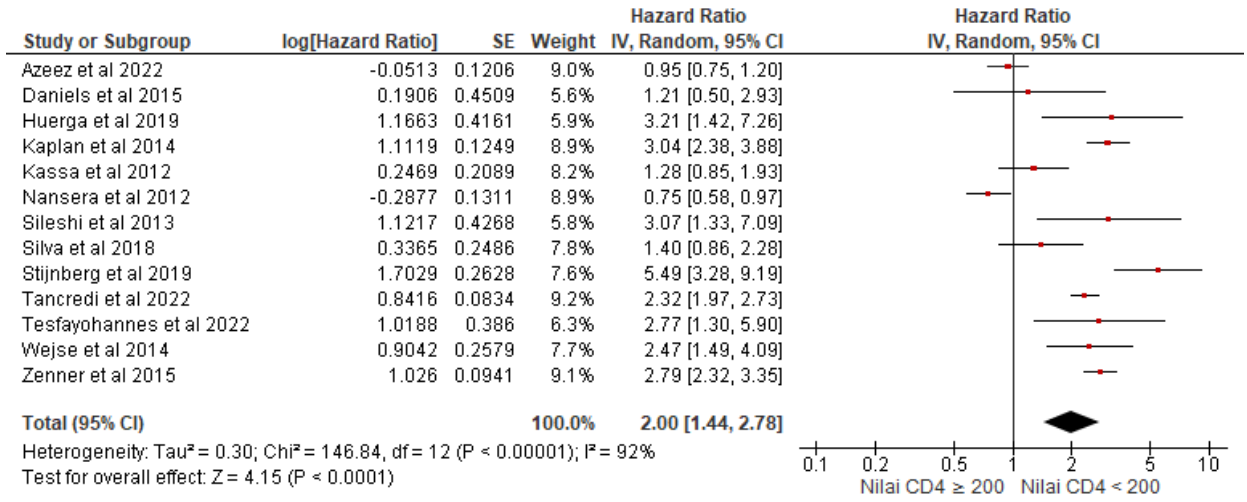

Figure 3. Forest Plot Mortality of HIV-TB Coinfected Patients based on CD4 Value <200 cells/µL

Interpretation of the results of the meta-analysis process can be seen through the Forest plot. The forest plot in Figure 3 shows that there is a relationship between CD4 values and the risk of death in TB-HIV co-infected patients. TB-HIV co-infected patients with CD4 <200 cells/µL had a 2.00 times risk of death compared to CD4 ≥200 cells/µL and the relationship was statistically significant (aHR=2.00; 95% CI 1.44 to 2.78; p<0.001). The forest plots also show the estimated effect between primary studies that were investigated in the meta-analysis assessing large or heterogeneous variation with I2 = 92% (p<0.001). Thus, the calculation of the estimated effect is carried out using the random effect model approach.

Funnel Plot

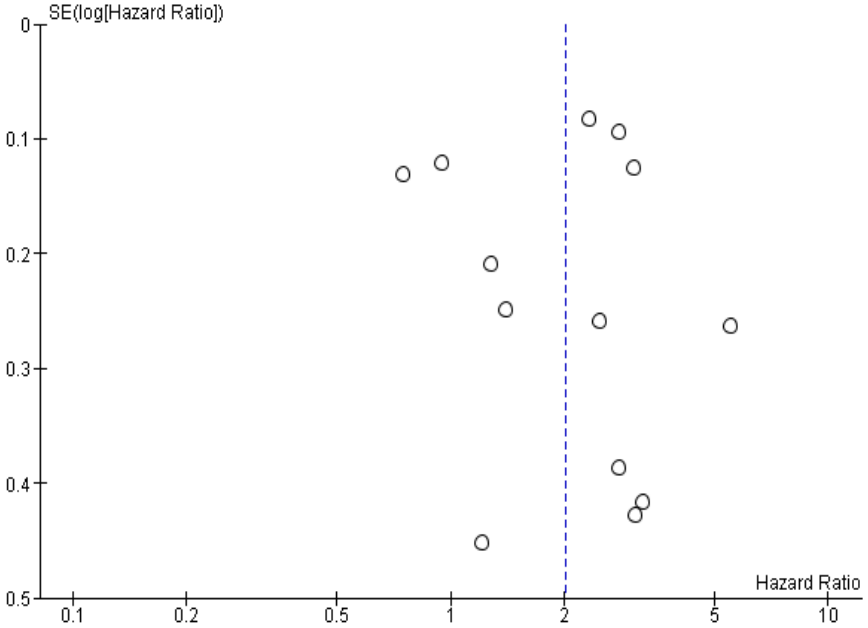

Figure 4. Funnel Plot Mortality of HIV-TB Coinfected Patients based on CD4 Value <200 cells/µL

The funnel plot in Figure 4 shows that the distribution of effects is more to the right of the estimated average vertical line than to the left, indicating publication bias. The location of the distribution of effect estimates is more to the right of the estimated average vertical line, while the location of the estimated average in the forest plot also shows results to the right of the vertical hypothesis 0, so the publication bias exaggerates the effect of the actual CD4 value (over estimate).

2. Mortality of HIV-TB Coinfected Patients based on CD4 Value <100 cells/µL

Table 4. Description of primary mortality studies based on CD4 values <100 cells/µL

Author (Year)	Country	Sample	P	I	C	O
Aung et al. (2019)	Myanmar	3,598	TB-HIV co-infected patients aged ≥15 years	CD4<100	CD4≥200	Died (family data/
Bassett et al. (2012)	Durban	951	HIV patients on antiretroviral therapy with TB coinfection aged ≥18 years	CD4≤100	CD4>200	electronic medical record)
Daniels et al. (2015)	Khayelitsha	696	Patients coinfected with RR-TB and HIV ≥15-59 years	CD4≤100	CD4>200	Died (phone family/
Kaplan et al. (2014)	Cape Town	38,996	HIV-positive TB patients aged ≥15 years	CD4≤100	CD4>200	electronic medical record)
Sileshi et al. (2013)	Ethiopia	422	TB-HIV co-infected patients ≥15-59 years	CD4≤100	CD4>200	Died (database)
Podlekareva et al. (2016)	Europe, Latin America	1,406	HIV-positive patient aged ≥16 years with TB	CD4≤100	CD4>200	Died (database)
Zenner et al. (2015)	Ireland	3,188	HIV patients with TB ≥15 years	CD4<100	CD4≥200	Died (database)

Table 5. Adjusted Hazard Ratio (aHR) M Mortality of TB-HIV Coinfected Patients based on CD4 Value <100 cells/µL

Author (Year)	aHR	CI 95%	
		Lower Limit	Upper Limit
Aung et al. 2019	1.53	1.25	1.87
Bassett et al. 2019	2.00	1.41	2.84
Daniels et al. 2015	2.10	1.00	4.41
Kaplan et al. 2014	4.38	3.41	5.63
Sileshi et al. 2013	3.57	1.48	8.61
Podlekareva et al. 2016	1.33	0.83	2.13
Zenner et al. 2015	3.53	2.98	4.18

a. Forest Plot

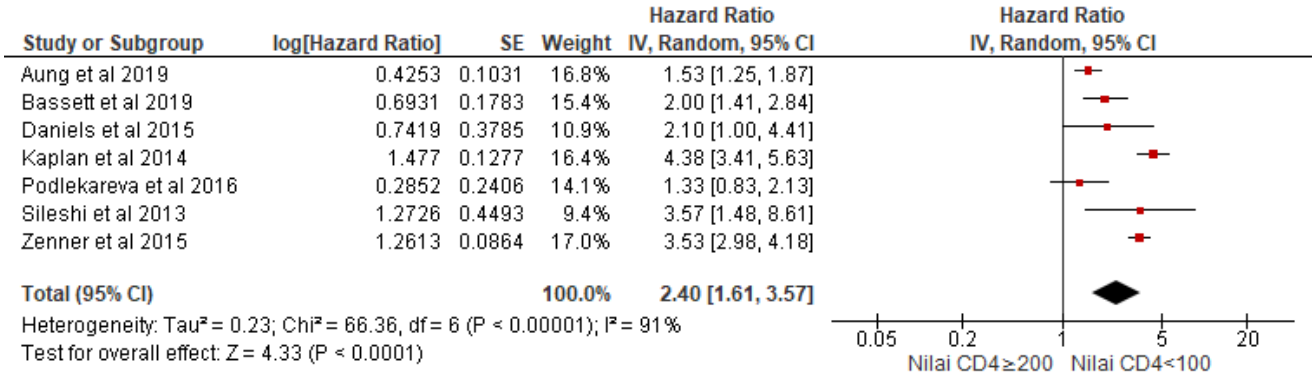

Figure 5. Forest Plot Mortality of HIV-TB Coinfected Patients based on CD4 Value <100 cells/µL

The forest plot in Figure 5 shows that there is a relationship between the CD4 score and the risk of death in TB-HIV co-infected patients. TB-HIV co-infected patients with CD4 <100 cells/µL had a 2.40 times risk of death compared to CD4≥200 cells/µL and the it was statistically significant (aHR= 2.40; 95% CI 1.61 to 3.57; p<0.001). The forest plots also show the estimated effect between primary studies that were investigated in the meta-analysis assessing large or heterogeneous variation with I^2= 91% (p<0.001). Thus, the calculation of the estimated effect is carried out using the random effect model approach.

b. Funnel Plot

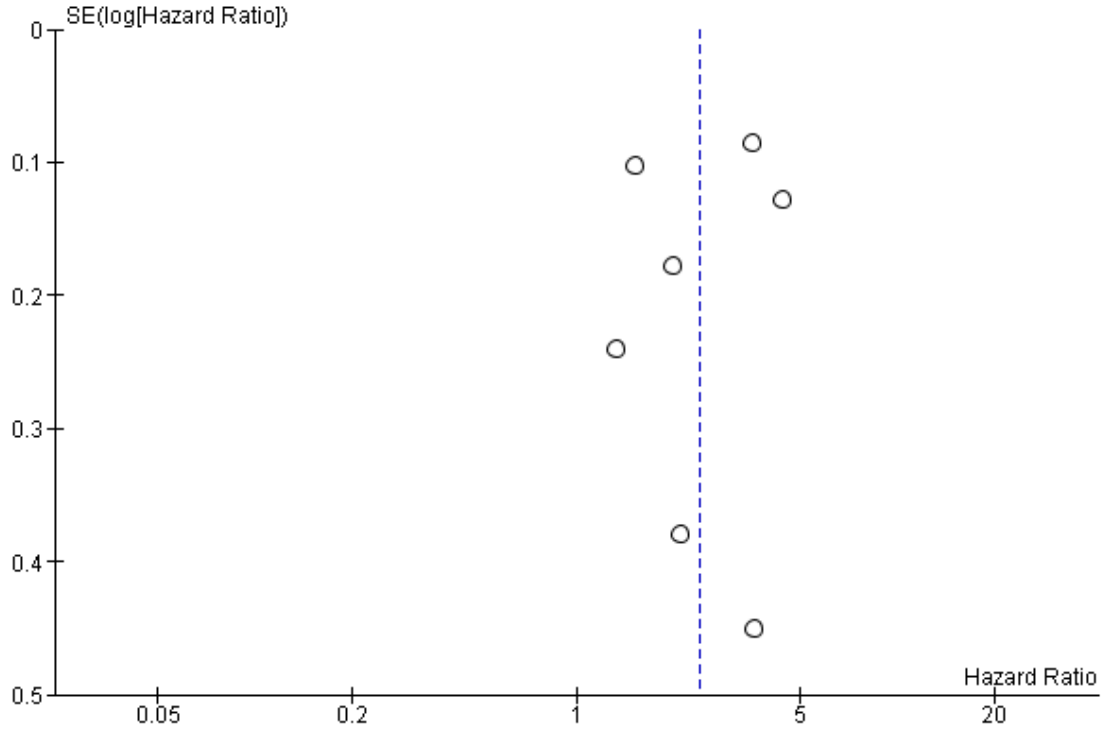

Figure 6. Funnel Plot Mortality of HIV-TB Coinfected Patients based on CD4 Value <100 cells/µL

Table 7. Description of primary mortality studies based on CD4 values <50 cells/µL

Author (Year)	Country	Sample	P	I	C	O
Azeez et al. (2022)	Ethiopia	1,525	TB/HIV co-infected patients aged ≥15 years	CD4≤50	CD4>200	Died (database)
Ji et al (2018)	China	359	HIV patients with TB ≥15 years	CD4≤50	CD4>200	Died (database)
Kaplan et al. (2014)	Cape Town	38,996	HIV-positive TB patients aged ≥15 years	CD4≤50	CD4>200	Died (database)
Kassa et al. (2012)	Ethiopia	4,210	HIV patients with TB ≥15 years	CD4≤50	CD4>200	Died during treatment (database)
Sileshi et al. (2013)	Ethiopia	422	TB-HIV co-infected patients ≥15-59 years	CD4≤50	CD4>200	Died during treatment (database)
Podlekareva et al. (2016)	Europe, Latin America	1,406	HIV-positive patients aged ≥16 years with a consecutive diagnosis of TB between 1 January 2011 and 31 December 2013	CD4≤50	CD4>200	Died (database)
Stijnberg et al. (2019)	Suriname	252	TB/HIV co-infected patients aged ≥15-59 years	CD4≤50	CD4>200	Died during treatment

Table 8. Adjusted Hazard Ratio (aHR) Mortality of TB-HIV Coinfected Patients based on CD4 Value <50 cells/µL

Author (Year)	aHR	CI 95%	
		Lower Limit	Upper Limit
Azeez et al. 2022	1.16	0.99	1.36
Ji et al. 2018	2.38	1.27	4.46
Kaplan et al. 2014	6.71	5.26	8.56
Kassa et al. 2012	1.80	1.17	2.78
Sileshi et al. 2013	4.83	1.98	11.77
Podlekareva et al. 2016	3.46	2.02	5.93
Stijnberg et al. 2019	5.83	3.02	11.25

a. Fores Plot

The forest plot in Figure 7 shows that there is a relationship between CD4 values and the risk of death in TB-HIV co-infected patients. TB-HIV co-infected patients with CD4 <50 cells/µL had a 3.12 times risk of dying compared to CD4≥200 and the relationship was statistically significant (aHR=3.12; 95% CI 1.51 to 6.46; p=0.002). The forest plot also shows the estimated effect between primary studies that were investigated in the meta-analysis assessing large or heterogeneous variation with I^2= 96% (p = 0.002). Thus, the calculation of the estimated effect is carried out using the random effect model approach.

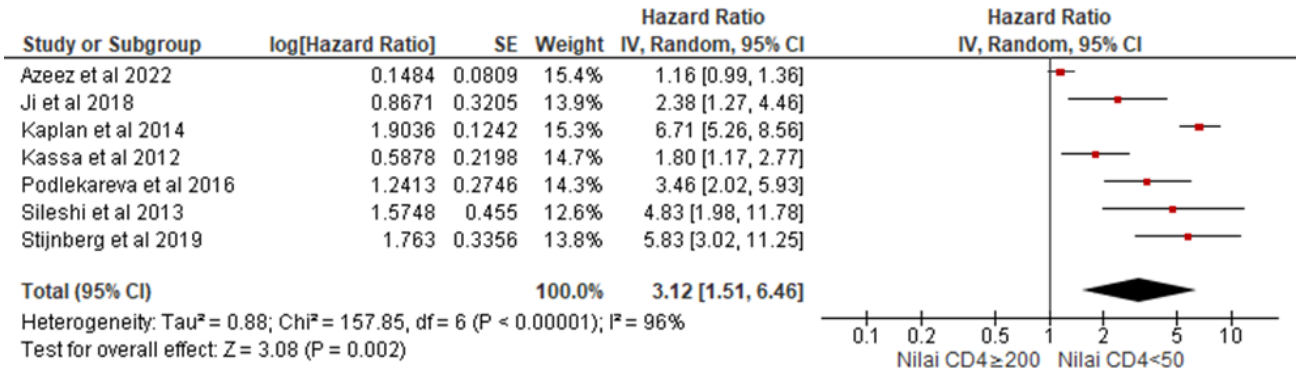

Figure 7. Forest Plot Mortality of HIV-TB Coinfected Patients based on CD4 Value <50 cells/µL

b. Funnel Plot

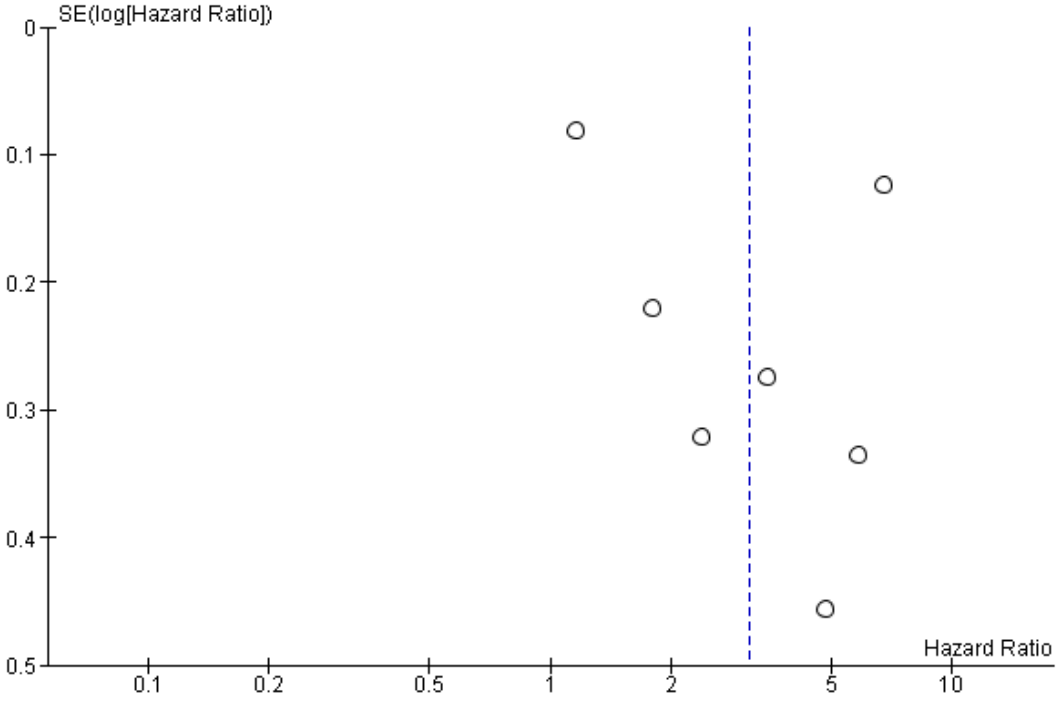

Figure 8. Funnel Plot Mortality of HIV-TB Coinfected Patients based on CD4 Value <50 cells/µL

The funnel plot in Figure 8 shows that the distribution of effects is more to the right of the estimated average vertical line than to the left, indicating publication bias. The location of the distribution of effect estimates is more to the right of the estimated average vertical line, while the location of the estimated average in the forest plot image also shows results to the right of the vertical hypothesis 0, so the publication bias exaggerates the effect of the actual CD4 value on risk of mortality in TB-HIV co-infected patients (over estimate).

DISCUSSION

TB-HIV coinfection makes a significant contribution to death (World Health Organization, 2020). This is in accordance with

previous research. A study conducted in Uganda showed that the majority of TB-HIV co-infected patients on anti-tuberculosis treatment tended to experience severe immunodeficiency, malnutrition, anemia and a number of co-morbidities. This is the reason TB-HIV co-infected patients are at high risk of death (Nansera et al., 2012).

A similar study was reported in a 12-year cohort study in the state of São Paulo that was followed up to 12 years. The main findings of this study are to show that mortality is higher in the first year after AIDS diagnosis and survival rates are lower (Tancredi et al., 2022).

Another study identified important predictors of mortality in TB-HIV co-infected patients, including CD4 score, duration of HIV infection, duration of HIV exposure, injecting drug use, HCV coinfection and smoking history. Some of these factors can be modified significantly for individuals and populations, including immune status and behavioral factors (Brothers et al., 2017). In addition, a study revealed other factors related to contextual factors, poor emotional health and lack of social support that have important effects on patient care and survival (Layer et al., 2014).

The high mortality of TB-HIV co-infected patients can be explained by delays in coming to health services due to a number of barriers, such as socio-economic reasons, poor access to care, delays in TB diagnosis or delays in HIV testing, as well as a lack of resources in the health system. already overwhelmed by high patient loads, shortages of staff, expertise and supplies (Nansera et al., 2012).

This study aims to discuss the CD4 score as an important predictor of TB-HIV mortality. Understanding the predictors of TB-HIV co-infection is very important to improve the management of TB-HIV co-infection and minimize mortality (Gomes et al., 2015). Other studies state that low CD4 counts and higher levels of drug resistance are major risk factors for death in both MDR-TB and XDR-TB patients with HIV (Gandhi et al., 2012).

HIV is known to cause dysfunction of the immune system. In particular, untreated progressive HIV infection is associated with decreased *Mycobacterium tuberculosis*-specific CD4 counts (Kisuya et al., 2018). Despite the fact that HIV treatment guidelines recommend initiation of ARVs regardless of CD4 cell count, individuals usually experience reduced CD4 cells at the time of diagnosis and initiation of HIV treatment (Tweya et al., 2014). This is caused by the presence of immune reconstruction inflammatory syndrome (IRIS), namely an increase in CD4 values and an immune response that usually occurs in the first 3 to 6 months of initiation of ARV therapy (Thapa et al., 2022).

This study states that the lower the CD4 count, the higher the risk of mortality in TB-HIV co-infected patients. This is consistent with previous systematic studies and meta-analyses which stated that decreased CD4 values in HIV positive patients who were not on ARV treatment were a strong predictor of TB (Ellis et al., 2017) TB itself is an opportunistic disease and a major cause of death that is often found in PLHIV (Pullar et al., 2014).

Decreased CD4 count causes the body's defense mechanism to be overwhelmed by various opportunistic infections. The results showed that patients with CD4 values of less than 200 cells/µl were 2 times more likely to develop TB than those with CD4 values of more than 200 cells/µl (Mitku et al., 2016). This is what health workers need to pay attention to when a patient has a lower CD4 value.

In contrast to the results of a study conducted by Kantipong et al, (2012) which

gave the result that a CD4 count above 200 cells/μL at the diagnosis of TB (aOR=5.23; 95% CI 1.05 to 26.10; p=0.04) was a significant predictor of death associated with TB. These results explained that there is a link with immune restoration syndrome (Kantipong et al., 2012). There is still a knowledge gap regarding the appropriate timing for antiretroviral treatment and TB therapy, weighing the benefits of survival against the risk of developing immune reconstitution syndrome (Yuengling et al., 2018).

The limitation of this study is the existence of publication bias shown in the funnel plot and language bias because in this study only articles published in English were used, thus ignoring articles published in other languages. In this study there are limitations in the search for articles. Not a large number of articles were analyzed for the variable mortality of TB-HIV co-infected patients based on CD4 values, because there are still few studies on mortality using multivariate analysis. The retrospective study used in this systematic review and meta-analysis has several limitations including the availability, quality, and completeness of data in the records of patients included in the primary study.

AUTHOR CONTRIBUTION

Victoria Husadani Permata Sari as a researcher who selects topics, searches for and collects research data. Setyo Sri Rahardjo and Bhisma Murti analyzed the data and reviewed research documents.

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CONFLICT OF INTEREST

There was no conflict of interest.

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