

The Effect of HIV/AIDS Infection on the Clinical Outcomes of COVID-19: A Meta-Analysis

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ABSTRACT -- Purpose: Patients with HIV may be more likely to become severely ill from COVID-19. The present meta-analysis aims to determine the impact of HIV/AIDS infection on the clinical outcomes of COVID-19. **Methods:** A comprehensive literature search was performed to identify relevant cohort studies to evaluate the association of HIV/AIDS infection with clinical outcomes of COVID-19. International databases, including PubMed (Medline), Web of Sciences, Scopus, and Embase, were searched from the emergence of the COVID-19 pandemic until January 2022. We utilized the risk ratio (RR) with its 95% confidence interval (95% CI) to quantify the effect of cohort studies. **Results:** Twelve cohort studies were included in this meta-analysis, which examined a total number of 17,786,384 patients. Among them, 40,386 were identified to be HIV positive, and 17,745,998 were HIV negative. The pooled analyses showed HIV positive patients who were co-infected with SARS-CoV-2 were 58% more likely to develop a fever (RR=1.58; 95% CI: 1.42, 1.75), 24% more likely to have dyspnea (RR=1.24; 95% CI: 1.08, 1.41), 45% more likely to be admitted to ICU (RR=1.45; 95% CI: 1.26, 1.67), and 37% more likely to die from COVID-19 (RR=1.37; 95% CI: 1.30, 1.45) than HIV negative patients. **Conclusion:** HIV/AIDS coinfection with COVID 19 increased the risk of fever, dyspnea, ICU admission, and mortality.

INTRODUCTION

On March 11, 2020, World Health Organization (WHO) announced a new β -coronavirus pandemic called coronavirus disease 2019 (COVID-19). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, non-segmented positive-sense RNA virus that causes severe acute respiratory illness (1-5). In most cases, patients who develop acute respiratory distress syndrome have underlying factors such as age over 65, pregnancy, obesity or being overweight, weakened immune system (e.g., HIV/AIDS infection), long-term administration of immunosuppressive drugs, or other underlying disorders. Various studies have confirmed these factors as the major factors

influencing the clinical manifestations of the disease and its exacerbation (6-9).

Among these factors, HIV/AIDS infection is of particular importance due to the immunosuppressing nature of the disease, WHO special attention to the disease, the comorbidity effects of HIV infection with other sexually transmitted and blood-borne infections, the occurrence of possible side effects due to the use of antiretroviral therapy (ART), and the risk factor for developing cardiovascular disease and other non-communicable diseases. Therefore, the study of its presence in patients with COVID-19 infection is clinically relevant (10-12). People living with HIV (PLWH) are assumed to be at higher risk of contracting SARS-CoV-2, especially when they have low CD4 T cell counts or are not on ART (13). A recently published paper indicated that PLWH are

not protected from COVID-19 or the severity of the disease, and HIV-related immunosuppressive condition may increase their risk for developing severe COVID-19 disease. However, the study did not conclude excess morbidity and mortality among PLWH (14). Another study claimed that higher mortality among PLWH occurs when results are adjusted for other risk factors. Thus, the conflicting results are due to differences between studies in their power to account for confounding variables (15).

Although up to now, significant findings have been published regarding HIV and SARS-CoV-2 coinfection, the results of the studies are inconclusive. Given the small number of studies, the inconsistency of the report is understandable. Performing a meta-analysis to combine the results of these studies might shed light on the contradictory information. Thus, this study aims to investigate the pooled association between the presence of HIV/AIDS coinfection and clinical outcomes of COVID-19.

ABBREVIATION. HIV/AIDS: The Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; COVID-19: Coronavirus Disease of 2019; PLWH: People living with HIV; ICU: Intensive Care Units; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: The protocol has been registered in the International Prospective Register of Systematic Reviews; WHO: World Health Organization; UNAIDS: United Nations Programme on HIV/AIDS; UNDP: United Nations Development Programme

METHODS

The present study is a systematic review and meta-analysis based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16) criteria. The protocol had been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42021277864.

Search terms and search strategy

To identify related studies, a comprehensive search was conducted at four international databases: PubMed (Medline), Scopus, Embase, and Web of Science. The search period was from the emergence of the COVID-19 pandemic until January 2022. The keywords for searching the databases include: "Acquired Immune Deficiency Syndrome Virus", "AIDS", "HIV Infections", "Human Immunodeficiency Virus", "COVID-19 Virus Disease", "2019 nCoV Infection", "Coronavirus Disease-19", "2019-nCoV Disease", "Coronavirus Disease 2019", "SARS-CoV-2 Infection", and

"COVID 19 Pandemic". Two authors (MS and MZ) independently conducted the literature search. After determining the keywords, the search strategy was designed and performed on the databases. Furthermore, google scholar and other relevant reports/databases such as the World Health Organization (WHO) report, UNAIDS, and UNDP were searched to find eligible articles. In addition, a manual search was performed by reviewing the references of the selected studies.

Eligibility Criteria

The primary purpose of this study was to determine the effect of HIV/AIDS infection on clinical outcomes of COVID-19, including ICU admission and mortality. Primarily, cohort studies were included in this meta-analysis. Additionally, studies that had compared the frequency of symptoms of COVID-19 (such as fever and dyspnea/shortness of breath) in HIV/AIDS versus healthy individuals were included. Review articles, case-control, case reports or series, systematic reviews, meta-analyses, cross-sectional studies, books, clinical trials, and letters to the editors were excluded from the study.

Screening and Selection

After completing the search, all articles were entered into the EndNote software version 8. In the next step, similar studies were deleted by finding the duplicates, and then the studies were reviewed. The title of the studies was first screened. Next, the screening was performed based on the abstract and full text of the articles. Two authors (MS and MZ) performed this step independently, and a third person (YM) resolved the disputes.

Quality Assessment

The Joanna Briggs Institute (JBI) checklist for cohort studies was used to perform a "quality assessment" on preliminary selected articles for the meta-analysis. This scale has 11 questions. These questions include: how to select the exposed and non-exposed groups, the ability to compare study groups in terms of measurable variables and confounders, how to control them, how to measure the outcome in both exposed and non-exposed groups, and ultimately how to analyze the data. All questions were categorized as "Yes", "No", "Not Applicable", and "Not Reported".

Data Extraction

First, a checklist of several questions, including the authors' name, design, sample size, country,

outcomes (death, admission to ICU, fever, and dyspnea), and effect size (the risk ratio), was designed to extract information. Then, information extraction based on the checklist was independently conducted by two authors (MZ and MS), and disputes were resolved by a third person (YM).

Statistical Analysis

The effect size in this study was the risk ratio (RR). To perform the meta-analysis, the log RR and log standard error (SE) of RR was calculated and analyzed. Metan command was used for the analysis by considering the model of combining random effects model in STATA software version 16. A L'Abbé plot was constructed by plotting the Log risks of the HIV group versus the Log risks of the healthy group. The L'Abbé plot and tau index were used to assess the heterogeneity between the studies. To measure the percentage of heterogeneity, I square and Q Cochran tests were used. Eggers's test and funnel plot diagram were also utilized to evaluate publication bias.

RESULTS

Search Results

Eighty-six studies in PubMed, Scopus, Web of Science, and Embase databases were found using the keywords. After screening the title, abstract, and full text, twelve cohort studies (17-21) were finally selected for meta-analysis, which fully met the inclusion criteria of the present study (Figure 1).

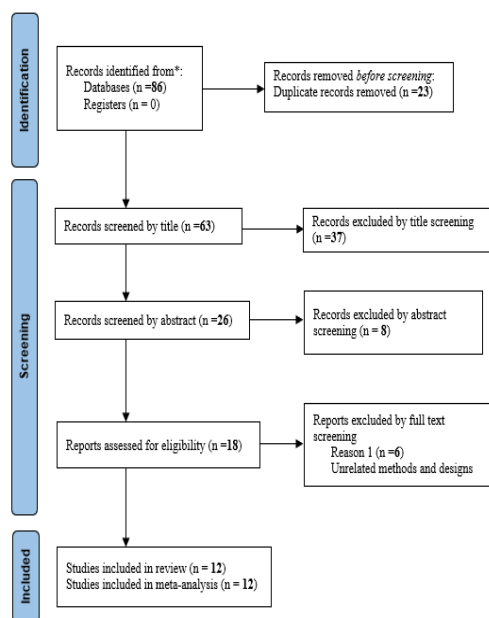


Figure 1. The search results and PRISMA diagram

Study Characteristics

The selected studies investigated a total number of 17,786,384 people, of whom 40,386 were HIV-positive, and 17,745,998 were HIV negative. The sample size of studies ranged from 63 to 17,282,905 participants, with 21 to 27,480 patients for HIV positive and 42 to 17,255,425 for HIV negative patients. The mean age of the patients in these studies was 55 years old. 51.64% of participants were male. The most common diseases in HIV-positive people were high blood pressure, diabetes, and kidney disease. Seven studies were conducted in the United States (22-28), two studies were in South Africa (29, 30), and the remainders were conducted in the United Kingdom (31), Israel (32), and Chile (33). (Table 1).

Meta-Analysis Results

Three cohort studies (27, 32, 33) evaluated the association between HIV/AIDS infection and fever incidents due to COVID-19. The lowest and highest determined effect was attributed to the study of D'Souza G *et al.* (18) and Ceballos ME *et al.* (17), respectively. The pooled analysis of the included studies showed HIV/AIDS patients infected with COVID-19 were 58% more likely to develop fever than non-HIV/AIDS patients with COVID-19 (RR= 1.58; 95% CI: 1.42, 1.75) (Figure 2a). However, the L'Abbé Plot and Q statistics indicated substantial heterogeneity between the studies ($I^2 = 89.78\%$, p -value < 0.01) (Figure 2b). Regarding the association between HIV/AIDS infection and dyspnea due to COVID-19, the lowest and highest determined effects were attributed to the study of D'Souza G *et al.* [18] and Karmen-Tuohy S *et al.* (19), respectively. After combining the four selected studies (26-28, 33), COVID-19 patients with HIV/AIDS were 24% more likely to develop dyspnea as compared to non-HIV/AIDS patients with COVID-19 (RR= 1.24; 95% CI: 1.08, 1.41) (Figure 3a). The L'Abbé Plot and I-square index show low heterogeneity between studies ($I^2 = 49.64\%$, p -value = 0.11) (Figure 3b). The lowest and highest determined RR of HIV/AIDS infection and ICU admission were attributed to the study of Nagarakanti SR *et al.* (20) and Ceballos ME *et al.* (17), respectively. The pooled analysis of five studies (23, 26, 28, 32, 33) showed that HIV/AIDS patients infected with COVID-19 were 45% more likely to be admitted to ICU than non-HIV/AIDS patients with COVID-19 (RR= 1.45; 95% CI: 1.26, 1.67) (Figure 4a). The L'Abbé Plot and Q statistics showed substantial heterogeneity

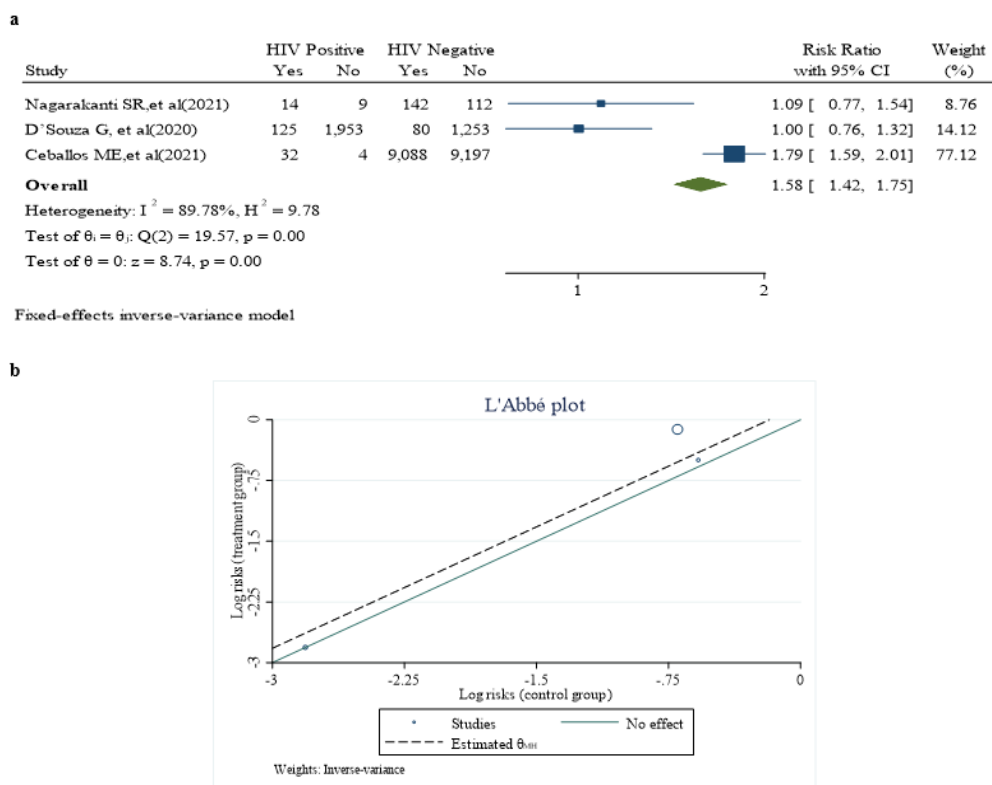


Figure 2. The forest plot of pooled risk ratio between fever due to COVID-19 and HIV infection (a), and the L'Abbé plot regarding interstudy heterogeneity on the association between fever and HIV infection (b).

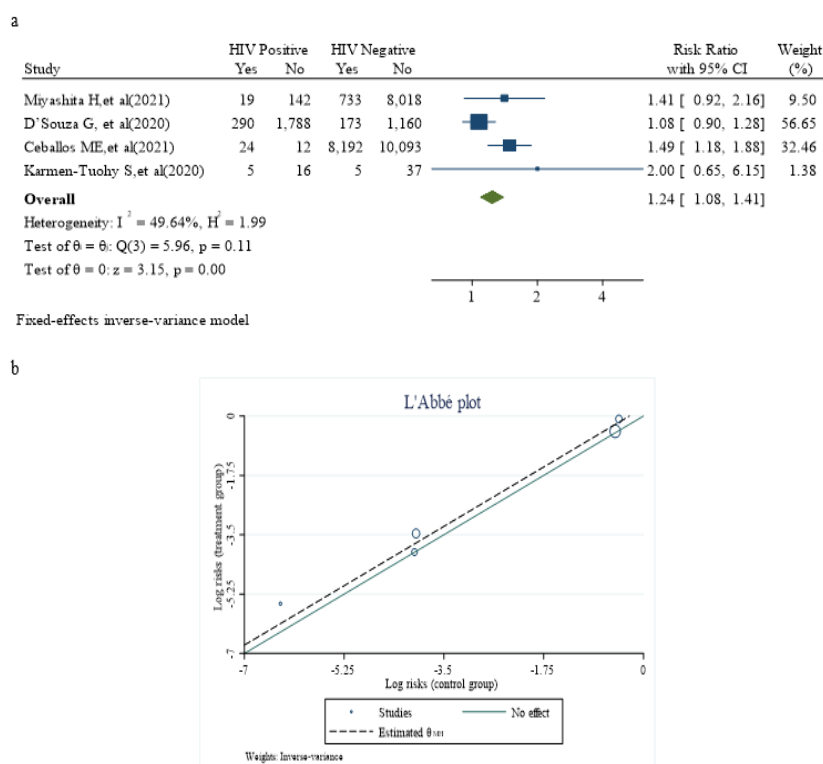


Figure 3. The forest plot of pooled risk ratio between dyspnea due to COVID-19 and HIV infection (a) and the L'Abbé plot regarding interstudy heterogeneity on the association between dyspnea and HIV infection (b).

between studies ($I^2 = 77.05\%$, p -value < 0.01) (Figure 4b).

Eleven cohort studies (22-26, 28-33) investigated the association between HIV/AIDS infection and the mortality rate due to COVID-19. The lowest and highest determined effects were attributed to the study of Nagarakanti SR *et al.* (20) and Harrison SL *et al.* (25), respectively. The pooled

analysis of these studies showed that the patients with HIV/AIDS infection were 37 % more likely to die from COVID-19 than non-HIV/AIDS patients (RR= 1.37; 95% CI: 1.30, 1.45) (Figure 5a). The L'Abbé Plot and Q statistics shows substantial heterogeneity between studies ($I^2 = 76.64\%$, p -value < 0.01) (Figure 5b). The Funnel Plot indicated no publication bias (Figure 5c).

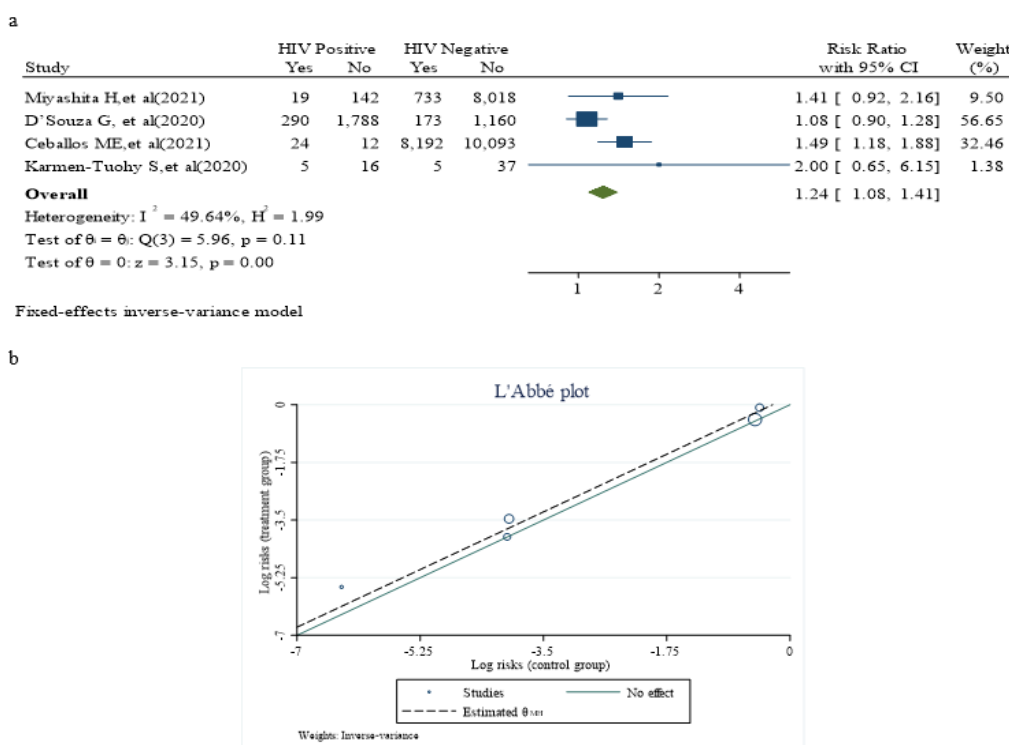


Figure 4. The forest plot of pooled risk ratio between ICU admission due to COVID-19 and HIV infection (a) and the L'Abbé plot regarding interstudy heterogeneity on the association between ICU admission and HIV infection (b).

DISCUSSION

This meta-analysis aimed to determine the association between the presence of HIV/AIDS infection and the clinical outcomes of COVID-19. The pooled analysis of twelve cohort studies (17-21) revealed that concurrent HIV/AIDS and COVID-19 infections put the patients at higher risk for fever, dyspnea, ICU admission, and mortality.

Two hypotheses have been suggested for the clinical characteristics of PLWH who are COVID-19 infected. Firstly, although PLWH are more susceptible to COVID-19 infection, having lymphopenia may protect them against severe signs and symptoms of COVID-19 due to the inability to present an overactive Tcell response (34). On the

other hand, PLWH have a chronic elevated inflammatory condition, which may lead to cytokine

storms in severe cases of COVID-19 (35). Hence, future study is required to clarify the underlying biological conditions which could explain the clinical manifestations of COVID-19 in HIV-infected patients.

HIV and SARS-CoV-2 coinfection have been reported in different countries. The first case of the coinfection was reported from Wuhan, China. Subsequently, other cases of coinfection have been reported in the UK, USA, Spain, Italy, Germany, and other countries, with the United States and the United Kingdom having the highest cases (11). In a univariate analysis, the severity of COVID-19 was significantly correlated with an age of 50 years or

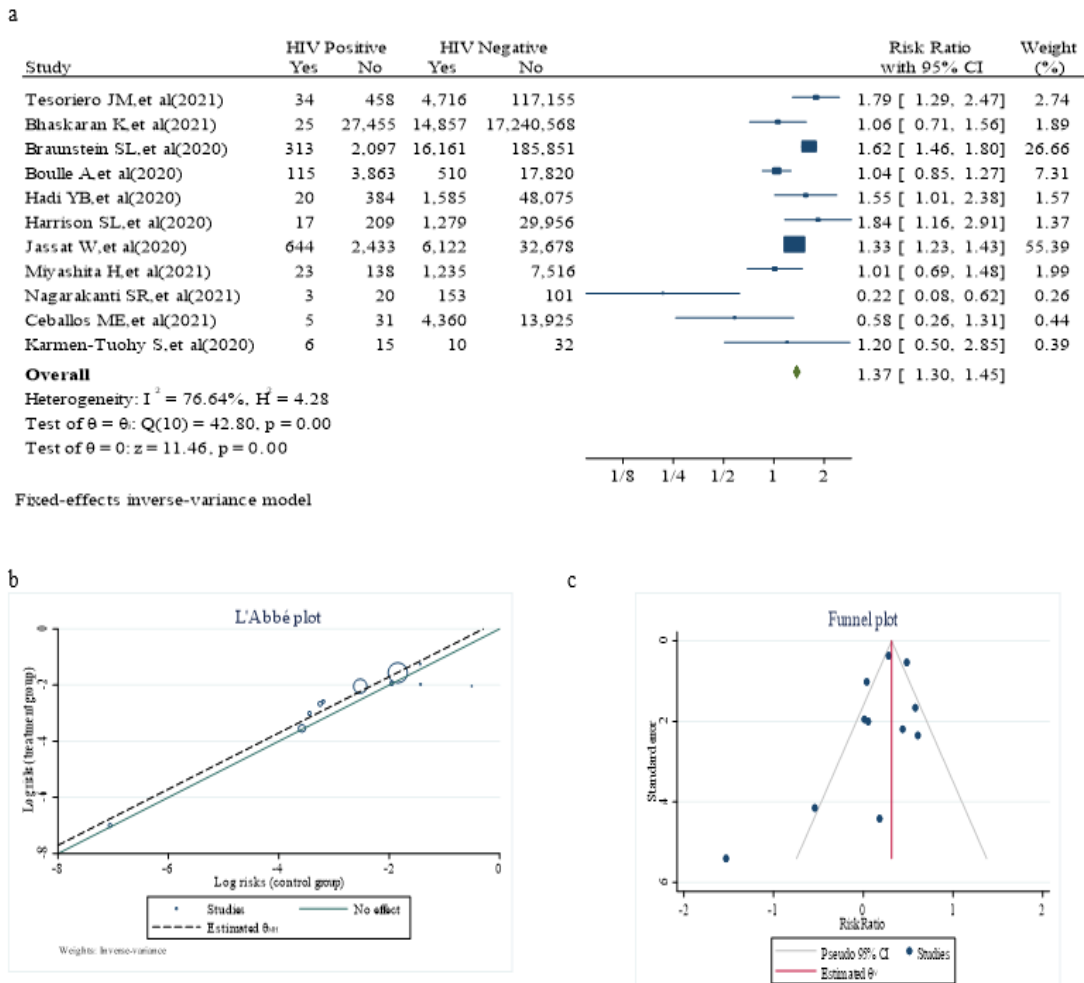


Figure 5. The forest plot of pooled risk ratio between mortality due to COVID-19 and HIV infection (a), the L'Abbé plot regarding interstudy heterogeneity on the association between mortality and HIV infection (b), and the funnel plot regarding publication bias for the association between mortality and HIV infection (c).

older, a CD4+ T cell nadir of $< 200/\mu\text{l}$, current CD4+ T cells $< 350/\mu\text{l}$, and the presence of at least one comorbidity [36]. Besides, the mortality rates were higher in HIV-positive people with low CD4 counts.

Multiple studies have presented the correlation between COVID-19 mortality rate and HIV/AIDS coinfection. The most significant finding of this study was to show a higher mortality rate and ICU admission in PLWH co-infected with SARS-CoV-2 compared to HIV-negative patients. In the present study, we tried to update the previous meta-analyses done by Ssentongo P et al. [37] and Dong Y et al. [38]. Vizcarra P *et al.* showed a higher prevalence of mortality in PLWH suffering from COVID-19 than in patients without HIV (21). However, several other studies have indicated no differences in mortality, hospitalization, ICU admission, and intubation rate between HIV-positive and negative patients infected with COVID-19 (36, 37). Mirzaei H *et al.* have found

that older age and multi-morbidity risks seem to be crucial factors for the increased rate of death (38). In another study, the authors stated that there is no higher risk associated with severe COVID-19 infection in HIV/AIDS patients if HIV infection is well-controlled (39). Also, it has been reported that the rate of mechanical ventilation or death and discharge among hospitalized patients did not vary between those living with HIV and HIV-negative patients (40).

Additionally, we evaluated fever and dyspnea incidence in PLWH and the general population. A meta-analysis conducted by Lee KW *et al.* reported that the most common symptoms among PLWH were fever, dry cough, and dyspnea, respectively(41). This study found that HIV-positive patients infected with COVID 19 are more likely to develop a fever and dyspnea and have a higher mortality rate and ICU admission than

Table 1. The characteristics of included studies¹

Authors	Sample Size	Country	HIV positive and covid19	HIV negative and covid19	HIV(P) Died	HIV(n) Died	HIV(P) Dyspnea	HIV(n) Dyspnea	HIV(P) ICU	HIV(n) ICU	HIV(P) fever	HIV(n) fever
Tesoriero, et al (22)	122363	USA	492(0.40%)	121871(99.6%)	34(6.91%)	4716(3.86%)	NR	NR	NR	NR	NR	NR
Bhaskaran, et al (31)	1728290	UK	27480(0.15%)	17255425(99.9%)	25(0.09)	14857(0.086)	NR	NR	NR	NR	NR	NR
Braunstein, et al (23)	204422	USA	2410(1.18%)	202012(98.8%)	313(13%)	16161(8%)	NR	NR	120(5%)	6060(3%)	NR	NR
Boulle, et al (29)	22308	South Africa	3978(17.83%)	18330(82.2%)	115(2.90%)	510(2.78%)	NR	NR	NR	NR	NR	NR
Hadi, et al (24)	50064	USA	404(0.80%)	49660(99.2%)	20(4.95%)	1585(3.19%)	NR	NR	NR	NR	NR	NR
Harrison, et al (25)	31461	USA	226(0.7%)	31235(99.3%)	17(7.5%)	1279(4.09%)	NR	NR	NR	NR	NR	NR
Jassat, et al (30)	41877	South Africa	3077(7.3%)	38800(92.7%)	644(20.92%)	6122(15.77%)	NR	NR	NR	NR	NR	NR
Miyashita, et al (26)	8912	USA	161(1.80%)	8751(98.2%)	23(14.28)	1235(14.11%)	19(11.80%)	733(8.37%)	36(22.36%)	1946(22.23%)	NR	NR
Nagarakanti, et al (32)	277	ISRAEL	23(8.30%)	254(91.7%)	3(13.04%)	153(60.23%)	NR	NR	2(8.7%)	102(40.15%)	14(60.86%)	142(55.90%)
D'Souza, et al (27)	3411	USA	2078(60.9%)	1333(39.1%)	NR	NR	290(13.95%)	173(12.97%)	NR	NR	125(6.01%)	80(6%)
Ceballos, et al (33)	18321	CHILE	36(20%)	18285(99.8%)	5(13.88%)	4360(23.84%)	24(66.66%)	8192(44.80%)	8(22.2%)	2011(10.99%)	32(88.88%)	9088(49.70%)
Karmen-Tuohy, et al (28)	63	USA	21(33.33%)	42(66.7%)	6(28.57%)	10(23.80%)	5(23.80%)	5(11.90%)	6(28.6%)	7(16.66%)	NR	NR

All cohrt; NR, notrecorde; n, numbers; p, positive.

non-HIV/AIDS patients. To the best of our knowledge, up to this time, no other meta-analysis has investigated these correlations. We believe the manuscript represents valid and novel work.

Limitations

Although the COVID-19 pandemic has traveled globally, the vast majority of the countries have not reported their COVID-19 related research results, including the data regarding HIV/AIDS patients. A larger sample size that includes the data from more regions and countries is required to have more conclusive results. Additionally, other important variables such as virus load, the number of CD4 cells, and the differences in access to the medical care system also need to be considered in future evaluations.

In this meta-analysis, the heterogeneity percent in all calculated outcomes was lower than 80 % but significant. This showed that primary studies (cohort studies) are different in methodology, sample sizes, and sample methods, measuring the outcomes and type of patients. The primary limitations are the small number of studies included in the analysis and the lack of subgroup analyses based on these variables. Thus, we require further large-scale cohort studies on the population with COVID-19, HIV, and healthy controls matching these variables to confirm our results.

CONCLUSIONS

This meta-analysis showed that the HIV/AIDS positive patients infected with COVID 19 were more likely to develop a fever and dyspnea and had a higher mortality rate and ICU admission than non-HIV/AIDS patients. This study may help establish health policies to manage COVID-19 infection in high-risk populations, especially HIV/AIDS patients.

CONFLICTS OF INTEREST. The authors declare there are no competing interests.

CONTRIBUTORSHIP STATEMENT. Study concept and design: Yousef Moradi. Acquisition, analysis, and interpretation of data: Yousef Moradi, Mostafa Zareie, Hojat Dehghanbanadaki, Hamed Gilzad Kohan, Ghobad Moradi, Farhad Moradpour, Seyede Maryam Mahdavi Mortazavi, and Marzieh Soheili. Drafting of the manuscript: Yousef Moradi, Hamed Gilzad Kohan, and Marzieh Soheili. Critical revision of the manuscript for important intellectual content: Yousef Moradi, Hojat Dehghanbanadaki, Hamed Gilzad Kohan, and Marzieh Soheili. Project

administration: Yousef Moradi. All authors have approved the final draft of the manuscript.

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