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Meta-Analysis

Mortality Risk in COVID-19 Patients with HIV-Comorbidity: Meta-Analysis

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ABSTRACT

Background: Coronavirus disease 2019 or known as COVID-19 is a disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2). Comorbidities that are risk factors for COVID-19 death include hypertension, diabetes, heart disease, COPD, HIV (Human Immunodeficiency Virus), kidney failure, and cancer. This study aims to estimate the magnitude of the risk of death in COVID-19 patients with comorbid HIV, with a meta-analysis of the primary studies conducted by the previous authors.
Subjects and Method: This study is a systematic review and meta-analysis with the following PICO, population: COVID-19 patients. Intervention: HIV comorbidity. Comparison: without co-morbid HIV. Outcome: Mortality. The articles used in this study were obtained from four data-bases, namely PubMed, Google Scholar, Springerlink, and Science direct, using the search keys "HIV/AIDS" AND "Mortality" OR "death" AND "COVID-19 OR SARS-CoV-2. The included article is a full-text English language with a cohort study design from 2020 to 2021 and reports the adjusted Odds Ratio (aOR) in a multivariate analysis. Article selection is done by using PRISMA flow diagram. Articles were analyzed using the Review Manager 5.3 application.
Results: A total of 9 cohort studies involving 3,397,186 COVID-19 patients from America, Europe, and Africa were selected for a systematic review and meta-analysis. The data collected showed that COVID-19 patients with HIV comorbidities had a mortality risk of 3.30 times compared to COVID-19 patients without HIV comorbidities (aOR = 3.30; 95% CI = 2.87 to 3.81; p<0.001).
Conclusion: HIV increases mortality risk in COVID-19 patients.

Keywords: HIV, COVID-19, SARS-CoV-2, mortality

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BACKGROUND

COVID-19 is an infectious disease caused by the Coronavirus, and first appeared in Wuhan, China at the end of 2019. Globally, the number of COVID-19 cases as of March 16, 2022 was 460,280,168 confirmed cases, including 6,050,018 deaths. On March 16, 2022, the highest to lowest number of confirmed cases of COVID-19, according to WHO, was in Europe as many as 189,964,699 cases, in the Americas as many as 149,185,071, in Southeast Asia as many as 56,586,444 cases, in the West Pacific Continent as many as 21,466,737 cases, in the Continent In the Eastern Mediterranean there were 21,466,737 cases and on

the African continent there were 8,501208 cases (WHO, 2022).

COVID-19 is an infectious disease that spreads throughout the world causing a global pandemic. Common symptoms of COVID-19 infection that are felt include fever 83%, cough 82%, shortness of breath 31%, muscle pain 11%, confusion 9%, headache 8%, sore throat 5%, rhinorrhea 4%, chest pain 2%, diarrhea 2%, and nausea and vomiting 1%. Some patients experience only mild symptoms such as low-grade fever, mild fatigue or even no symptoms at all (Chen et al., 2020).

Severely ill patients can experience coagulation dysfunction, septic shock, multi-organ dysfunction, and even an increased risk of death. Risk factors for COVID-19 death include age, gender, geographic location, and comorbidities (Albitar et al., 2020). Comorbidities that are risk factors for COVID-19 death include hypertension, diabetes, heart disease, COPD, HIV, kidney failure, and cancer (Jassat et al., 2021).

Individuals with comorbid HIV experience different body conditions from other individuals, including: a decrease in the number of CD4 cells in the body. CD4 cells are white blood cells that are used to fight viruses. When CD4 cells decrease, it can trigger the viral load in the blood. In addition, it can also trigger lymphadeno-pathy, which is an enlargement or swelling of the glands of the immune system due to a viral infection (located in the lymph nodes). If this happens continuously, it can trigger tissue damage (CDC, 2018; WHO, 2022).

Based on the existing literature, summary statistics are needed to calculate the estimated effect of HIV comorbidity on the risk of death of COVID-19 patients. A meta-analysis is a statistical combination of results from two or more separate studies, with the objectives of: (1) increasing precision; (2) Answering questions that were not addressed by the previous primary study; and (3) Resolve controversies arising from studies that appear to contradict or generate new hypotheses (Deeks et al., 2021).

This study aims to analyze previous primary studies in assessing the effect of HIV comorbidity on mortality in COVID-19 patients. The authors will use a systematic review and meta-analysis approach to analyze the effect of HIV comorbidities on mortality in COVID-19 patients. The findings of this study can assist health care providers in taking preventive action and implementing early treatment strategies for at-risk groups with comorbid HIV.

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and meta-analysis. The articles used in this study were obtained from several databases namely PubMed, Google Scholar, Springer-link, and Science Direct from 2020 to 2021, using the search keys "HIV/AIDS" AND "Mortality" OR "death" AND "COVID-19 OR SARS-CoV-2.

2. Inclusion Criteria

The inclusion criteria in this research article were: Full-paper article with a cohort observational study (retrospective or prospective). The research subjects were patients with confirmed COVID-19. The measure of the relationship used is the adjusted Odds Ratio. The study outcome was mortality of COVID-19 patients.

3. Exclusion Criteria

The exclusion criteria in this research article were: Statistical results reported in the form of bivariate analysis. Articles published in languages other than English. Patients with other comorbidities.

4. Operational Definition of Variables

The article search was carried out by considering the eligibility criteria determined using the PICO model. Population: COVID-19 patients. Intervention: HIV comorbidity. Comparison: without comorbid HIV. Outcome: Mortality.

HIV: A disease caused by the Human Immunodeficiency Virus (HIV) which causes a decrease in the human immune system. The HIV population in question is HIV positive patients of various stages, both male and female, and are patients with all age categories. HIV is categorized into HIV-positive and HIV-negative. Instruments: Rapid-test. Measurement Scale: categorical

COVID-19 Patient Mortality: Mortality due to comorbid HIV is determined by mortality status in patients diagnosed with COVID-19, and is a patient with all age categories. Mortality was categorized as dead and alive. Instrument: document confirming death related to COVID-19. Measurement Scale: categorical.

5. Study Instruments

The research is guided by the PRISMA flow diagram and quality assessment using the Critical Appraisal Skills Program (CASP, 2018).

6. Data Analysis

The data in the study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots were used to determine the size of the relationship and heterogeneity of the data. A fixed effect model was used for homogeneous data, while a random effect model was used for heterogeneous data across studies.

RESULTS

The article search process was carried out through several journal databases including PubMed, Google Scholar, SpringerLink, and Science direct from 2020 to 2021. The review process for related articles can be seen in the PRISMA flow diagram in figure 1. Research related to mortality risk of COVID-19 patients with comorbidities HIV consists of 9 articles from the initial search process yielding 1,506 articles, after the deletion process of published articles obtained 1,056 articles with 62 of them meeting the requirements for further full-text review. A total of 9 articles that met the quality assessment were included in the quantitative synthesis using meta-analysis.

Figure 2 shows that the research articles come from three continents, namely America, Europe, and Africa. Table 1, the researchers conducted an assessment of the quality of the study. Table 2 shows 9 articles from the cohort study as evidence of the association of the influence of HIV comorbidities on the mortality risk of COVID-19 patients.

The Forest Plot in Figure 3 shows that COVID-19 patients with comorbid HIV had a 3.30 times mortality risk compared to COVID-19 patients without comorbid HIV, and the results were statistically significant (aOR= 3.30; 95% CI= 2.87 to 3.81; p <0.001). The Forest Plot also provides high heterogeneity information. The estimated effect of all primary studies in this meta-analysis (I^2= 86%), thus the mean estimation was calculated using the Random Effect Model.

The funnel plot in Figure 4 shows that the distribution of the estimated effect is more on the right than on the left of the average vertical line of the estimated effect which is in the same direction as the average diamond image, which is also to the right of the vertical line of the null hypothesis of effect estimation. Thus, publication bias tends to overestimate the true effect (overestimate).

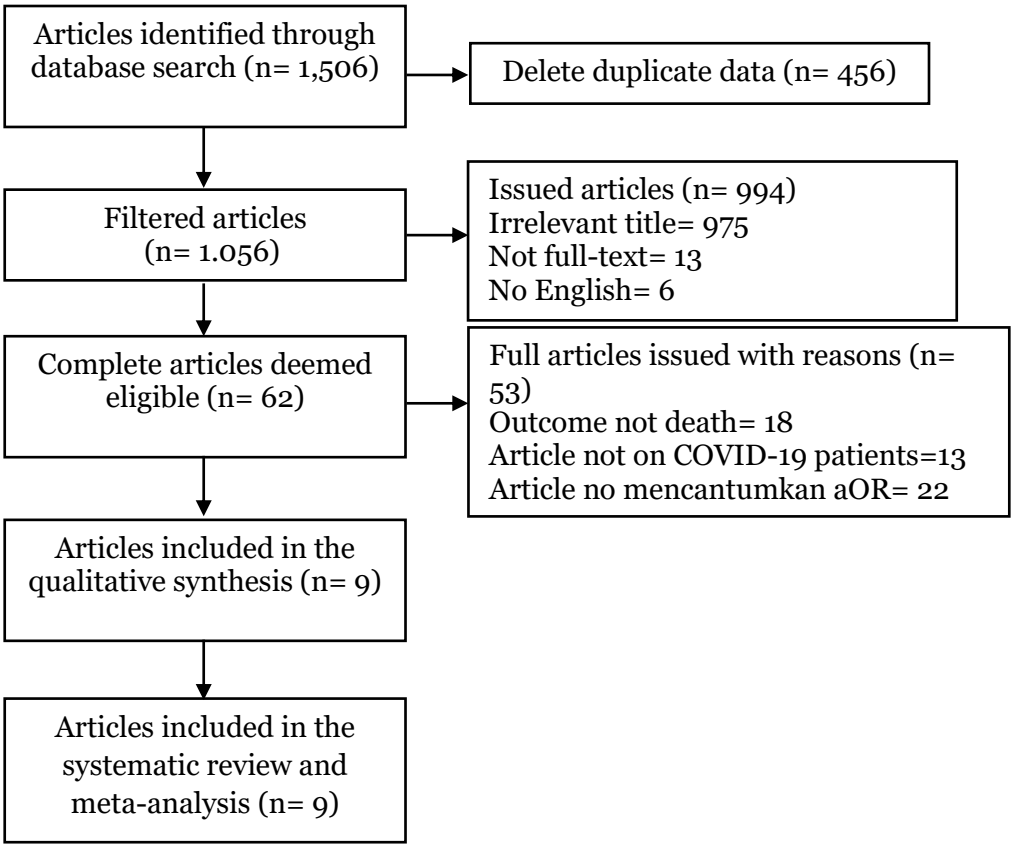

Figure 1. PRISMA Flowchart

Figure 2. Map of study area

Table 1. Assessment of study quality published by the Critical Appraisal Skills Program (CASP)

No	Indicators	Author and Year								
		Del et al. (2020)	Bennetta et al. (2021)	Ge et al. (2021)	Jassat et al. (2021)	Sun et al. (2020)	Perez-Guzman et al. (2020)	Sierra et al. (2019)	Venturas et al. (2021)	Yang et al. (2021)
1.	Does the cohort study clearly address the clinical problem?	2	2	2	2	2	2	2	2	2
2	Was the cohort of research subjects in the exposed and unexposed groups selected in the right way?	2	1	2	2	2	2	2	2	2
3	Is exposure to COVID-19 accurately measured to minimize bias?	1	2	2	2	2	2	2	1	1
4	Was the outcome (death status) measured accurately to minimize bias?	2	2	2	2	2	2	2	2	2
5	Did the researcher identify all the important confounding factors? Did the researcher take confounding factors into account in the design and/or analysis?	2	2	2	2	1	2	2	2	1
6	Did the research subject complete the full time of the study? Were the research subjects followed (follow-up) for a long time?	2	1	2	2	1	2	2	1	1
7	Are the results of this study reported in aOR?	2	2	2	2	2	2	2	2	2
8	How precise are the results?	2	2	2	2	2	2	2	2	2
9	Are the results reliable?	2	2	2	2	2	2	2	2	2
10	Are the results applicable to the local (local) population?	2	1	2	2	2	2	2	2	2
11	Are the results of this study compatible with the available evidence?	2	2	2	2	2	2	2	2	2
12	What are the implications of this research for practice?	1	2	2	2	2	2	2	2	2
	Total	**22**	**21**	**24**	**24**	**22**	**24**	**24**	**22**	**21**

Note:
2: Yes; 1= Can't tell; 0= No

Table 2. Description of the primary studies included in the meta-analysis primary studies

Author	Country	Study Design	Sample		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aOR (CI 95%)
			COVID-19	HIV					
Venturas et al. 2021	South Africa	Retrospective study	384	108	all adult patients with known HIV status	People Live with HIV	People live without HIV	Mortality	1.14 (0.50 to 2.60)
Bennetta et al. 2021	Ireland	Retrospective cohort study	19,789	364	those who were confirmed cases of COVID-19	People with HIV Risk factor	People live without HIV	Death	0.87 (0.56 to 1.35)
Sun et al. 2021	United States	Retrospective cohort study	1,446,913	3660	Positive COVID-19	People with HIV	People without HIV	Mortality	1.28 (1.27 to 1.29)
Jassat et al. 2021	South Africa	Cohort study	219,265	13 793	individuals admitted to hospital with COVID-19	People with HIV	People without HIV	Death	1.25 (1.18 to 1.33)
Perez-Guzman et al. 2020	United Kingdom (UK)	Retrospective cohort	559	-	(RT-PCR)–positive SARS-CoV-2 infection	positive SARS-CoV-2	People without HIV	Hospital Death	1.32 (0.24 to 7.36)
et al. 2020	Spanish	Cohort Study	236	77 590	HIV-positive persons	patients with COVID-19	People without HIV	Death	2.6 (1.6 to 4.0)
Yang et al. 2021	USA	Cohort Study	1,436,622	13170	COVID-19 case	People with HIV	People without HIV	Mortality	1.43 (1.29 to 1.59)
Ge et al. 2021	Washington United States	Cohort study	256,855	332	Positive test result of the novel corona virus (SARS-CoV-2)	HIV	No HIV	Death	1.67 (1.15 to 2.42)
Sierra et al. 2020	Spain	retrospective analysis	16563	98	COVID-19 admissions	People with HIV	People without HIV	Death	0.53 (0.29 to 0.96)

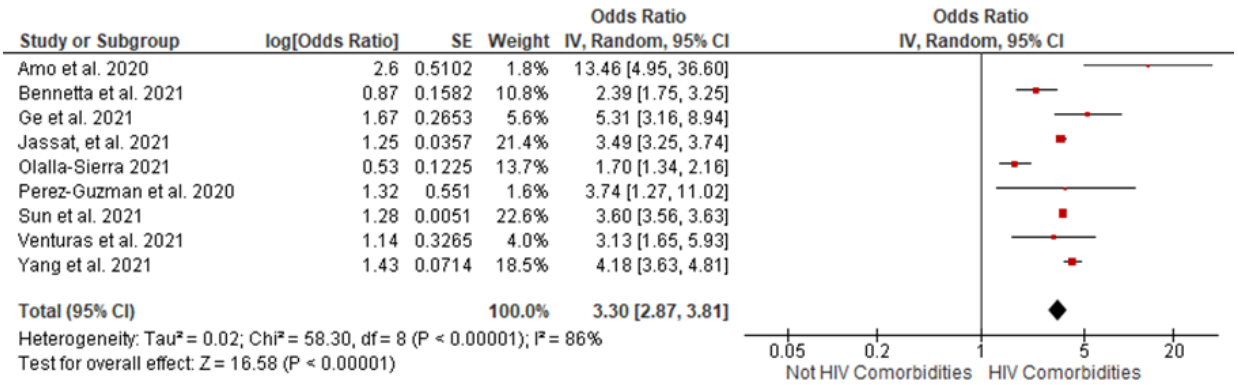

Figure 3. Forest Plot of Mortality Risk in COVID-19 Patients with Comorbid HIV

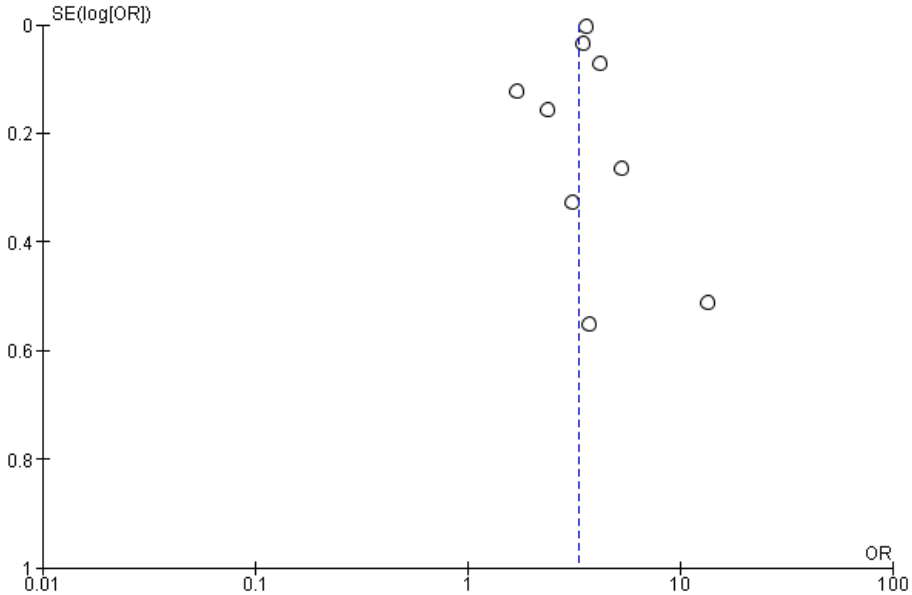

Figure 4. Funnel Plot of Death Risk in COVID-19 Patients with Comorbid HIV

DISCUSSION

This systematic review and meta-analysis research raised the theme of the effect of HIV comorbidities on mortality in COVID-19 patients. The dependent variable analyzed was COVID-19 mortality. The independent variable analyzed was HIV comorbidity. This study discusses HIV comorbidities, this is considered important because it is considered a high risk group for the severity and even mortality of COVID-19 patients (CDC, 2020; Kouhpayeh, 2021; Danwang, 2022).

The combined estimate of the effect of HIV comorbidities on the mortality of COVID-19 patients was processed using RevMan 5.3 with the generic inverse variance method. This method is used to analyze data in the form of rate, time to event, hazard ratio, ordinal scale, adjusted estimate, difference of average mean), or the ratio of the mean (ratio of mean).

A total of 9 cohort observational research articles were used as a source of meta-analysis of the effect of HIV comorbidities on mortality in COVID-19 patients. This study shows that HIV comorbidity is statistically significant in influencing mortality of COVID-19 patients. The forest plot results showed that COVID-19 patients with comorbid asthma had a mortality risk of 3.30 times compared to COVID-19 patients without HIV comorbidities, and the results were statistically significant (aOR= 3.30; 95% CI= 2.87 to 3.81; p <0.001).

HIV comorbidity can increase the risk of mortality in COVID-19 patients, the results of this study are in line with the study of Davies et al. (2020) which stated that COVID-19 patients with HIV were more at risk for death with (aHR = 2.14; 95% CI = 1.70 to 2.70). WHO (2019) also stated that HIV infection was associated with an increased risk of death in the African region with (aHR= 1.29; 95% CI= 1.23 to 1.34).

Bhaskaran et al. (2021) shows that people living with HIV are a high risk group for COVID-19 death in the UK. The research of Bhaskaran et al 2021 suggests that people living with HIV need to be given priority on the SARS-CoV2 vaccine. The results of the study of Yang et al 2021 stated that individuals who have immune dysfunction due to HIV have a greater risk of dying from COVID-19. Appropriate prevention strategies with drug administration should be given to reduce mortality in COVID-19 patients with comorbid HIV. Other similar studies are Garreti et al 2020 in the UK, Osibogun et al 2021 research in Nigeria.

Individuals with comorbid HIV experience different body conditions from other individuals, including: a decrease in the number of CD4 cells in the body. CD4 cells are white blood cells that are used to fight viruses. When CD4 cells decrease, it can trigger the viral load in the blood. In addition, it can also trigger lymphadenopathy, where there is enlargement or swelling of the glands of the immune system due to viral infection (located in the lymph nodes). If this happens continuously, it can trigger tissue damage (CDC, 2018; WHO, 2022).

The individual's condition will be exacerbated if infected with COVID-19. This is because, individuals infected with COVID-19 generally experience complications such as an increase in cytokine storms (this will be exacerbated if the individual has comorbid HIV, due to viral load, lymphadenopathy) will be even more severe if experiencing cytokine storms. Another complication is experiencing thromboembolism, where blood clots occur in the blood), if this situation occurs, it is likely that individuals with comorbid HIV will have a greater chance of experiencing severity and even death from COVID-19 (CDC, 2018; WHO, 2022) .

As a result, the above-mentioned mechanisms can contribute to the worsening of the patient's condition due to SARS-CoV-2 infection, even leading to death. The limitations of this study are that there is a language bias because it only uses English articles, a publication bias shown in the funnel plot results, and a search bias because it only uses four databases..

AUTHOR CONTRIBUTION

Nindita Arum Veibiani is the main researcher who selects the topic, searches for and collects research data. Bhisma

Murti and Argyo Demartoto analyzed the data and reviewed research documents.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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