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Risk factors and mortality outcomes of COVID-19 in people living with HIV: a systematic review and meta-analysis

Mahmoud Kandeel

Department of Biomedical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa, Saudi Arabia; Department of Pharmacology, Faculty of Veterinary Medicine, Kafrelsheikh University, Kafrelsheikh, Egypt

Abstract

This study was performed to reveal the risk factors associated with mortality in people living with HIV (PLHIV) who were diagnosed with COVID-19. Studies reporting deaths among PLHIV and infected with SARS-CoV-2 were investigated. After protocol setup and registration, the extracted sources were categorized and assessed for quality. This study examined ten articles with a total of 46,136 patients. Patients aged ≥ 60 years (hazard ratio [HR] = 2.22; 95% CI: 1.617, 3.050; p < 0.001), male (HR = 1.668; 95% CI: 1.179, 2.361; p = 0.004), and people with diabetes (risk ratio [RR] = 3.34; 95% CI: 1.45, 7.68; p = 0.005) were at higher risk of death. Adherence to antiretroviral therapy (ART) reduced mortality risk (RR = 0.90; 95% CI: 0.83, 0.98; p = 0.02). Patients in the survival groups showed a statistically significant lower mean of C-reactive protein (mean difference = 114.08; 95% –74.05, 154.10; p < 0.001). Deceased patients showed higher mean levels of interleukin-6 (IL-6). Chronic respiratory disorders, hypertension, oxygen requirement, admission to an intensive care unit, D-dimer levels, and HIV viral load < 50 copies RNA/mL before admission did not show statistically significant differences between the deceased and survival groups. ART therapy reduced mortality risk (RR = 0.90; 95% 0.83, 0.98; p = 0.02). Identifying PLHIV at higher mortality risk could improve the outcomes of COVID-19 by stratifying these patients to the most effective treatment in a timely fashion.

Keywords

COVID-19. People living with HIV. Risk factors. Meta-analysis.

Introduction

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus of a new strain of the β-coronavirus family. Since the beginning of the infection in December 2019, COVID-19 has emerged as a leading cause of morbidity and mortality worldwide. By March 2020, the WHO declared the disease a pandemic[1]. By December 2022, more than 600 million people had been infected with SARS-CoV-2. This contagiousness resulted in approximately 6.5 million deaths worldwide, the most consequential health crisis since the influenza pandemic. The global case-fatality rate of COVID-19 was estimated to be 3.4%, which is higher than seasonal influenza[2]. Whereas most cases of the pandemic are mild, the elderly population and patients with underlying illnesses are at higher risk of severe COVID-19 disease and death[3].

Correspondence to:
Mahmoud Kandeel
E-mail: mkandeel@kfu.edu.sa

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HIV is a global deliberating infectious disease. Of note, more than 36 million people are living with HIV (PLHIV), with approximately 1.5 million new cases annually[4]. Despite the advances in the treatment of HIV, a significant number of HIV-related deaths continue to occur, estimated at more than 650,000 cases annually[5]. The presence of comorbidities has drastically impacted the outcomes of COVID-19. The worldwide prevalence of HIV infection among COVID-19 patients was nearly 2%, being more prevalent in sub-Saharan Africa. Furthermore, the mortality risk is more than two-fold among PLHIV who are diagnosed with COVID-19[6]. In PLHIV, a weakened immune system may exacerbate the SARS-CoV-2 infection and increase their vulnerability to adverse outcomes. Depleting CD4 cells reduces the ability of the human body to defend against the SARS-CoV-2 infection[7]. Most HIV-related deaths are attributable to secondary opportunistic infections and abnormal inflammatory responses. Low CD4 counts, indicative of a compromised immune system, predominantly drive the risk of such infections. In addition, high viral loads and uncontrolled viral replication can further exacerbate the risk, particularly in patients with already low CD4 counts. Therefore, an increased risk of SARS-CoV-2 infection, severe disease, and death might be expected in PLHIV. The repercussions of SARS-CoV-2 infection among PLHIV could be challenging as more aggressive preventive and therapeutic measures could be needed. In addition, the majority of PLHIV reside in areas with poor access to proper care for managing COVID-19 and HIV[8].

There is a critical need to understand the risk of mortality in PLHIV during the COVID-19 pandemic. Conflicting results regarding the association between HIV infection and COVID-19-related death resulted in controversial findings, making it difficult to draw firm conclusions from the available literature. Predicting if patients with HIV are more vulnerable to death is pivotal for the patients and the health-care providers. This study was performed to gather the scattered evidence related to the potential prognostic factors associated with mortality in PLHIV who are diagnosed with COVID-19. Recognizing such evidence will help health-care providers precisely assort and timely employ the appropriate management of patients at high risk of developing poor outcomes.

Methods

Protocol development and registration

This review was performed in accordance with PRISMA and the Cochrane collaboration guidelines (Supplementary Table 1). The methodology of the present work was documented in a PROSPERO protocol (registration number: CRD42022364110).

Data source

A systematic literature search was executed on September 29, 2022, using these databases: Google Scholar, PubMed, ISI, SIGLE, Scopus, Clinical trials, VHL, mRCT, NYAM, EMBASE, ICTRP, and Cochrane Collaboration. The search strategy used vocabulary terms specific to each searched database. A manual search screened the references of the included studies to reveal all extra articles that were not indexed. The following keywords were used; “COVID-19”, “SARS-CoV-2”, “2019-nCoV”, “coronavirus”, “human immunodeficiency virus”, “HIV”, “AIDS”, “acquired immunodeficiency syndrome”, “mortality”, “death”, “fatal”, and “fatality”.

Study selection, inclusion, and exclusion criteria

Studies were included that reported risk factors of death among PLHIV who were diagnosed with COVID-19 infection. Non-comparative studies or articles that did not report the possible risk factors of death in PLHIV who were diagnosed with COVID-19 were rejected. Furthermore, studies with inaccessible data, review articles, animal studies, guidelines, comments, case reports, letters, posters, editorials, and book chapters were excluded from the study. The screening processes were performed independently to reveal the articles that met the eligibility criteria. The screening processes were summarized using a PRISMA flowchart.

Data extraction

The following data characteristics were extracted from the ten included articles: the study ID, year of publication, study region, study design, and study period. Baseline characteristics of the included articles were extracted, including sample size, patients’ age, race, and comorbidities. The data related to HIV infection were extracted, consisting of viral load, CD4 count (per mm^3), history of AIDS diagnosis, duration of infection, and treatment regimen. The data related to the COVID-19 pandemic were extracted, including the laboratory parameters, radiological parameters, medications used, and duration of hospitalization. Two authors recorded the data using Microsoft Excel. The data were extracted from figures using WebPlotDigitizer.

Quality assessment and categorization

The quality of the included observational articles was evaluated using the National Institute of Health (NIH) quality assessment tool. The studies were categorized into good (> 65%), fair (30-65%), and bad (< 30%).

Data analysis

Standardized mean difference or weighted mean difference was used for pooling the continuous data. Mean and standard deviation were calculated from the reported data as mean and range or median and range. The risk ratio (RR) was used for pooling the binary variables. Hazard ratios (HR) were pooled from the relevant articles to calculate the pooled summary of HR. The random-effects model was implemented. Statistical heterogeneity was appreciated using the Higgins I^2 statistic and the Cochrane Q (χ^2 test). Data analysis was performed using Comprehensive Meta-Analysis v3 software and RevMan version 5.4. The significance was revealed at the value of $p < 0.05$.

Results

Search strategy and outcomes

The literature search yielded 171 articles eligible for screening. Fifty-seven studies were excluded as duplicates, resulting in 114 studies being included for screening. Of these, 101 articles were excluded, making 13 eligible for full-text screening. Five articles were ousted, yielding eight articles suitable for data extraction. Two studies were identified through manual searching. Eventually, ten articles were included for systematic review and meta-analysis. The search strategy is shown in supplementary table 2. The screening processes and exclusion categories are shown in the PRISMA flowchart (Fig. 1).

Characteristics of patients and their demographic aspects

The present study included ten studies of 46,136 patients[9-18]. There were six articles of retrospective design and four articles of prospective design. The mean age of the eligible patients ranged from 42 to 62 years. There were 5893 patients with diabetes mellitus, 9985 patients with hypertension, and 285 patients with chronic respiratory disorders (Table 1).

Ninety patients among the deceased group had complained of cough. Whereas 87 deceased patients had complained of dyspnea, 180 surviving patients had dyspnea. Furthermore, 96 and 57 patients had been admitted to the intensive care unit among the deceased and the survival groups, respectively. The mean C-reactive protein ranged from 187.6 to 201.75 mg/dl among the deceased group. All the included retrospective and prospective studies were of good quality based on the NIH quality assessment tool (Table 2).

Risk factors of mortality

Patients-related risk factors

Age ≥ 60 years

Three studies[10,12,17], including 27,813 PLHIV who were diagnosed with COVID-19, revealed the impact of age ≥ 60 years on the mortality risk. Patients aged ≥ 60 years were 2.22 times more likely to die (HR = 2.22; 95% 1.617, 3.050; $p < 0.001$) in the random-effects model ($I^2 = 0\%$, $p = 0.936$) (Fig. 2A).

Male gender

Four articles[10,12,13,17], including 27935 PLHIV who were diagnosed with COVID-19, assessed the impact of the male gender on the risk of mortality. In the random-effects model ($I^2 = 27.2\%$, $p = 0.24$), male patients were 1.66 times at higher risk of death (HR = 1.668; 95% 1.179, 2.361; $p = 0.004$) (Fig. 2B).

Two or more medical conditions

Three studies reported the risk of mortality among PLHIV who were diagnosed with COVID-19 and living with two or more medical comorbidities[10,12,17]. In the random-effects model ($I^2 = 86.68\%$, $p = 0.001$), there was no significant association with the risk of death (HR = 1.642; 95% 0.908, 2.972; $p = 0.101$) (Fig. 2C).

Chronic respiratory disorders

Five articles[9,11,13,16,18] evaluated the association between chronic respiratory disorders and death among PLHIV who were diagnosed with COVID-19. There was no difference between the deceased and survival groups (RR = 1.41; 95% 0.90, 2.21; $p = 0.14$) in the random-effects model ($I^2 = 0\%$, $p = 0.52$) (Fig. 2D).

Hypertension

The impact of hypertension on mortality risk in PLHIV who were diagnosed with COVID-19 was assessed in five articles[9-11,16,18] that included 33,895 patients. There

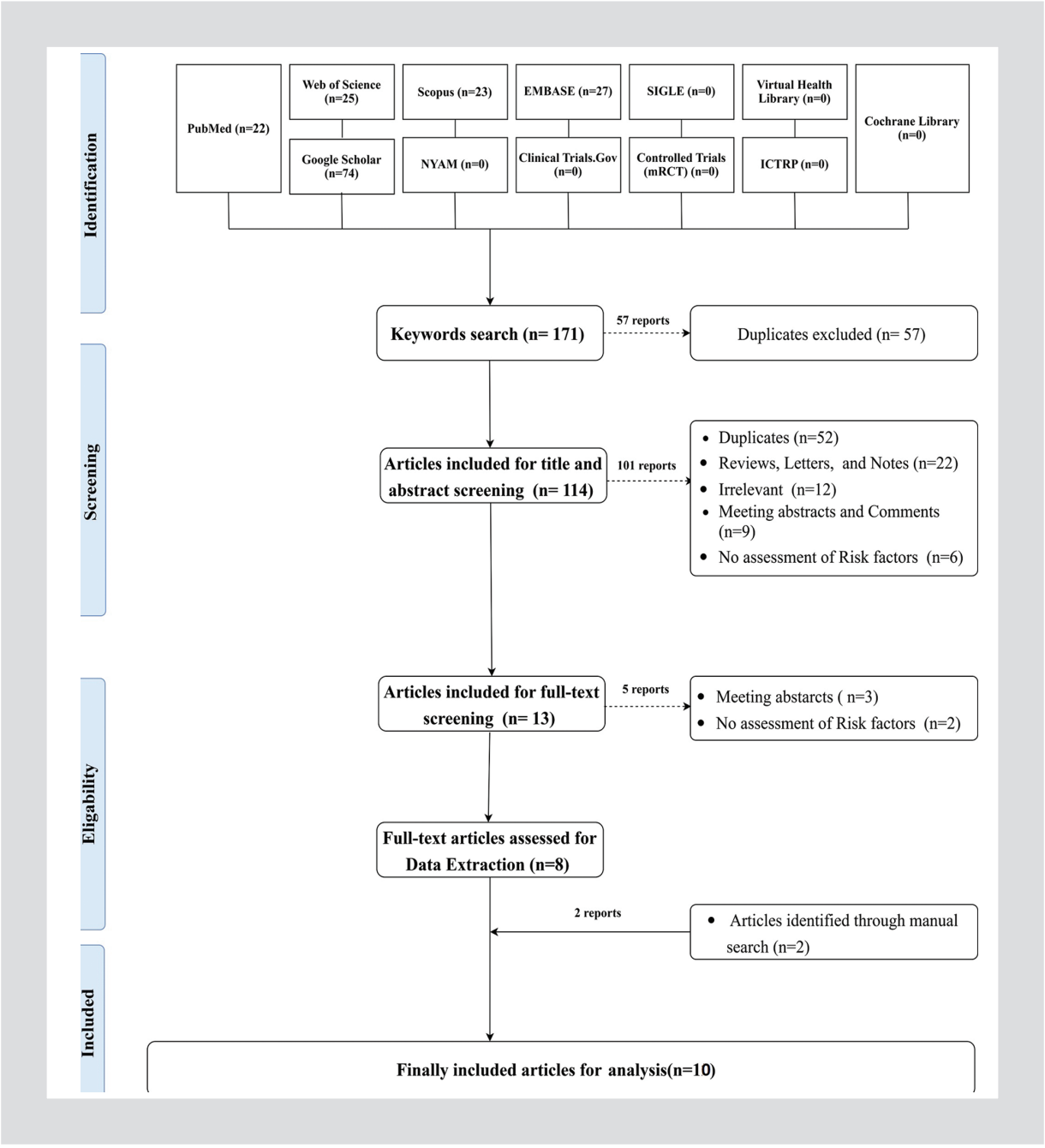

Figure 1. *PRISMA flow chart showing the process of the literature search, title, abstract, and full-text screening, systematic review, and meta-analysis.*

was no significant difference between the deceased and survival groups (RR = 1.63; 95% 0.43, 6.19; p = 0.48) in the random-effects model (I^2 = 96%, p < 0.001) (Fig. 2E).

Diabetes mellitus

The association between diabetes mellitus and mortality risk in PLHIV who were diagnosed with COVID-19 was reported in six articles, including 34,608 patients[9-11,13,16,18]. In the random-effects model (I^2 = 89%, p < 0.001), patients with diabetes were 3.34 times more likely to die (RR = 3.34; 95% 1.45, 7.68; p = 0.005) (Fig. 2F).

COVID-19-related risk factors

Oxygen requirement

Three studies[11,13,14], including 230 PLHIV who were diagnosed with COVID-19, assessed the difference between the deceased and survival groups regarding

Table 1. Demographic characteristics of the included studies

S. No.	Study ID	Study region	Study design	Study period	Sample size		Gender				Age				Comorbidities	
							Females		Males		All		60-69 years		DM	
					Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived
					Number	Number	Number	Number	Number	Number	Mean ± SD	Mean ± SD	Number	Number	Number	Number
1	Boulle et al., 2020[27]	South Africa	Prospective cohort study	1 March 9 June 2020	115	3863	62	3039	53	824	NR	NR	21	98	58	372
2	Bhaskaran et al., 2021[28]	UK	Retrospective cohort study	1 Feb-22 June 2020	25	27455	9693	7	17762	18	48 (40-55)†		3130		2695	14
3	Ceballos et al., 2021[29]	Chile	Prospective, observational cohort study	16 April and 23 June 2020	5	31	1	2	4	29	57 (39-71)*	41 (32-48)*	NR	NR	2	2
4	Chanda et al., 2021[30]	Zambia	Prospective cohort study	March-December 2020	87		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5	Geretti et al., 2021[31]	UK	Prospective cohort study	17 January 4 June 2020	30	92	9	33	21	59	55 (49, 61)†	58 (53, 70)†	6	20	10	15
6	Ho et al., 2021[32]	USA	Retrospective cohort study	2 March 2020 and 15 April 2020	19	53	6	12	13	39	62 (55-68)*	59 (54-67)*	NR	NR	NR	NR
7	Jassat et al., 2020[33]	South Africa	Retrospective study	March 2020 to 27 March 2021	3,407	10,386	8884		4893		NR	NR	1574		2669	
8	Moreno-Torres et al., 2022[34]	Spain	Retrospective study	1 January to 31 December 2020	22	212	7	52	15	160	58.9 (15.7)	52.6 (10.4)	NR	NR	4	28

(Continues)

Table 1. Demographic characteristics of the included studies *(continued)*

S. No.	Study ID	Study region	Study design	Study period	Sample size		Gender				Age				Comorbidities	
							Females		Males		All		60-69 years		DM	
					Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived
					Number	Number	Number	Number	Number	Number	Mean ± SD	Mean ± SD	Number	Number	Number	Number
9	Rocha et al., 2021[35]	Brazil	Retrospective study	March to August 2020	83	163	NR	NR	60	112	57 (47-65)*	49 (39-58)*	34	35	NR	NR
10	Sigel et al., 2020[36]	USA	Retrospective study	12 March and 23 April 2020	18	70	5	17	NR	NR	62 (57-67)*	58.5 (53-67)*	NR	NR	4	20

S. No.	Study ID	Study region	Study design	Study period	Comorbidities									
					Hypertension		CKD		Chronic respiratory disorder		Current smokers		Liver disease	
					Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived
					Number	Number	Number	Number	Number	Number	Number	Number	Number	Number
1	Boulle et al., 2020[27]	South Africa	Prospective cohort study	1 March 9 June 2020	48	692	21	82	10	218	NR	NR	NR	NR
2	Bhaskaran et al., 2021[28]	UK	Retrospective cohort study	1 Feb-June 22 2020	5275	15	1552	9	1095		NR	NR	NR	NR
3	Ceballos et al., 2021[29]	Chile	Prospective, observational cohort study	16 April and 23 June 2020	3	3	2	2	0	1	0	10	0	1
4	Chanda et al., 2021[30]	Zambia	Prospective cohort study	March-December 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
6	Ho et al., 2021[32]	USA	Retrospective cohort study	2 March and 15 April 2020	NR	NR	NR	NR	NR	NR	2	9	NR	NR

(Continues)

Table 1. Demographic characteristics of the included studies *(continued)*

S. No.	Study ID	Study region	Study design	Study period	Comorbidities									
					Hypertension		CKD		Chronic respiratory disorder		Current smokers		Liver disease	
					Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived
					Number		Number		Number		Number	Number	Number	Number
7	Jassat et al., 2020[33]	South Africa	Retrospective study	March 2020 to 27 March 2021	3,857		9,982		975		NR	NR	NR	NR
8	Moreno-Torres et al., 2022[34]	Spain	Retrospective study	1 January to 31 December 2020	4	55	3	16	5	30	NR	NR	7	63
9	Rocha et al., 2021[35]	Brazil	Retrospective study	March to August 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10	Sigel et al., 2020[36]	USA	Retrospective study	12 March and 23 April 2020	6	27	NR	NR	2	6	11	37	1	4

*Data reported in the form of median and range.

†Data reported in the form of median and interquartile range.

DM: diabetes mellitus; CKD: chronic kidney disease; NR: non-reported.

Table 2. COVID-19 related manifestations, laboratory findings, and quality assessment

S. No.	Study ID	COVID-related manifestations											
		Respiratory symptoms						Gastrointestinal manifestations				Fever	
		Cough		Sore throat		Dyspnea		Diarrhea		Vomiting			
		Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived	Deceased	Survived
		Number	Number	Number	Number	Number	Number	Number	Number	Number	Number	Number	Number
1	Boulle et al., 2020[27]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2	Bhaskaran et al., 2021[28]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
3	Ceballos et al., 2021[29]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
4	Chanda et al., 2021[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5	Geretti et al., 2021[31]	26	70	1	13	21	67	8	20	4	19	24	75
6	Ho et al., 2021[32]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
7	Jassat et al., 2020[33]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
8	Moreno-Torres et al., 2022[34]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
9	Rocha et al., 2021[35]	64	135	7	28	66	113	12	36	6	13	52	123
10	Sigel et al., 2020[36]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

(Continues)

Table 2. COVID-19 related manifestations, laboratory findings, and quality assessment *(continued)*

		Admitted to ICU		Laboratory findings				HIV related data				Quality assessment	
		Deceased	Survived	White-cell count, cells/L		C-reactive protein, mg/dL		Baseline CD4 count before admission cells/mm^3		HIV viral load < 50 copies RNA/mL before admission			
		Number	Number	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Number	Number	%	Decision
1	Boulle et al., 2020[27]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	75%	Good
2	Bhaskaran et al., 2021[28]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	75%	Good
3	Ceballos et al., 2021[29]	NR	NR	NR	NR	NR	NR	543	564 (389-691)*	4	15	66.66%	Good
4	Chanda et al., 2021[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	75%	Good
5	Geretti et al., 2021[31]	20	19	8.4 ± 4.98	6.3 ± 3.08	187.6 ± 120.6	96.3 ± 88.1	NR	NR	NR	NR	75%	Good
6	Ho et al., 2021[32]	13	6			272 ± 35.1	122.8 ± 31.8	686 (466-800)*	503 (325-786)*	NR	NR	66.66%	Good
7	Jassat et al., 2020[33]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	75%	Good
8	Moreno-Torres et al., 2022[34]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	75%	Good
9	Rocha et al., 2021[35]	63	32	NR	NR	NR	NR	NR	NR	51	109	75%	Good
10	Sigel et al., 2020[36]	NR	NR	7.55 ± 1.55	7.3 ± 0.9	201.75 ± 27.25	101 ± 25	NR	NR	12	37	75%	Good

*Data reported in the form of median and range.

ICU: intensive care unit; NR: non-reported.

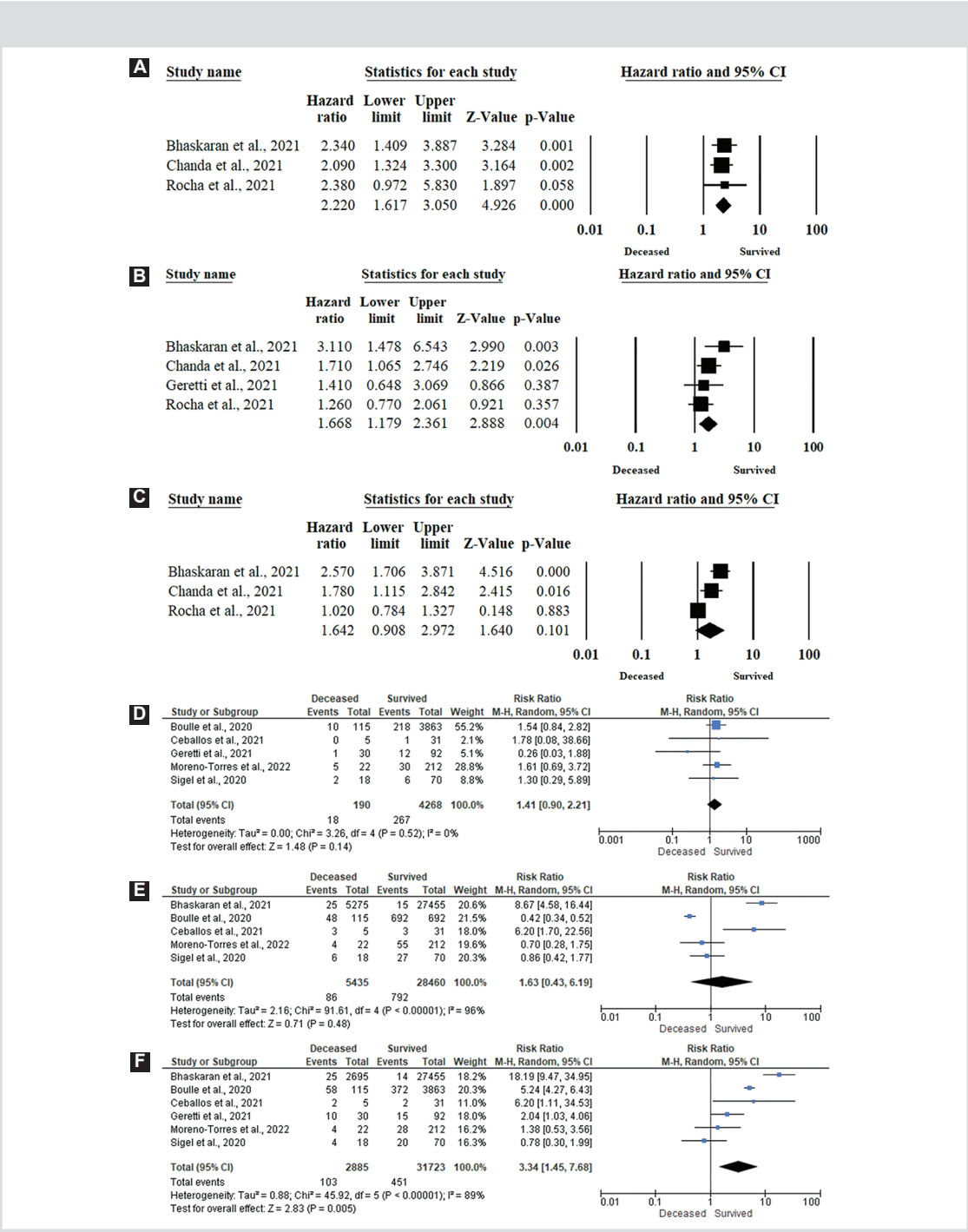

Figure 2. *Forest plot of summary analysis of the* **A:** *hazard ratio (HR) and 95% CI of the impact of age ≥ 60 years on the mortality risk among PLHIV and diagnosed with COVID-19.* **B:** *HR and 95% CI of the impact of male gender on the mortality risk among PLHIV and diagnosed with COVID-19.* **C:** *HR and 95% CI of the impact of two or more medical comorbidities on the mortality risk among PLHIV and diagnosed with COVID-19.* **D:** *risk ratio (RR) and 95% CI of the impact of chronic respiratory disorders on the mortality risk among PLHIV and diagnosed with COVID-19.* **E:** *RR and 95% CI of the impact of hypertension on the mortality risk among PLHIV and diagnosed with COVID-19.* **F:** *RR and 95% CI of the impact of diabetes mellitus on the mortality risk among PLHIV and diagnosed with COVID-19. The size of the blue and black squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome. IV: inverse variance.*

the oxygen requirement. There was no statistically significant difference between the groups (RR = 0.93; 95% 0.37, 2.30; p = 0.87) (Fig. 3A).

Admission to the intensive care unit (ICU)

The impact of admission to ICU on the mortality risk in PLHIV who were diagnosed with COVID-19 was assessed in three articles that included 440 patients. In the random-effects model (I^2 = 0%, p = 0.42), patients admitted to the ICU were 3.83 times more at risk of dying (RR = 3.83; 95% 2.96, 4.96; p < 0.001) (Fig. 3B).

Laboratory parameters

White-cell count

Two articles[13,18], including 210 patients, assessed the difference in white cell count between the deceased and the survival groups. There was no statistically significant difference between the groups (mean difference [MD] = 0.96; 95% −0.80, 2.73; p = 0.28) (Fig. 3C).

D-dimer

The difference in mean D-dimer levels between the deceased and survival groups was reported in two articles, including 160 patients[14,18]. In the random-effects model (I^2 = 94%, p < 0.001), there was no statistically significant difference between the groups (MD = 1.85; 95% −0.90, 4.59; p = 0.19) (Fig. 3D).

C-reactive protein

Three studies[13,14,18] that included 282 PLHIV who were diagnosed with COVID-19 assessed the difference between the deceased and the survival groups regarding the mean C-reactive protein. Patients in the survival groups showed a statistically significant lower mean of C-reactive protein (MD = 114.08; 95% −74.05, 154.10; p < 0.001) in the random-effects model (I^2 = 94%, p < 0.001) (Fig. 3E).

IL-6

Two studies, including 160 patients, reported the difference in mean IL-6 levels between the deceased and survival groups[14,18]. Patients in the deceased group showed a statistically significant higher mean level of IL-6 (MD = 78.74; 95% 41.13, 116.35; p < 0.001) in the random-effects model (I^2 = 84%, p = 0.01) (Fig. 3F).

HIV-related risk factors

HIV viral load < 50 copies RNA/mL before admission

Three studies[11,17,18] included 248 PLHIV who were diagnosed with COVID-19 and assessed the difference in HIV viral load < 50 copies RNA/mL before admission between the deceased and the survival groups. There was no statistically significant difference between the groups (MD = 1.15; 95% 0.82, 1.61; p = 0.41) (Fig. 3G).

On antiretroviral therapy (ART) therapy

Five articles[11,13,14,17,18], including 564 PLHIV who were diagnosed with COVID-19, evaluated the impact of ART therapy on the risk of death. In the random-effects model (I^2 = 47%, p = 0.11), ART therapy reduced the risk of mortality (RR = 0.90; 95% 0.83, 0.98; p = 0.02) (Fig. 3H).

Discussion

HIV is a considerable, worldwide health challenge. In the COVID-19 era, PLHIV is particularly vulnerable to substantial morbidity and mortality, with compromised immune response. However, the available data have offered limited insight regarding factors predicting mortality in patients with COVID-19 and HIV[19]. Furthermore, there is a demanding concern regarding identifying the prognostic factors associated with mortality in PLHIV diagnosed with COVID-19. Therefore, this study was executed to reveal the significant predictors of death among 46,136 PLHIV from seven different nations.

The present study revealed that PLHIV aged ≥ 60 years, male patients, and those with diabetes mellitus were at higher risk of mortality. Whereas PLHIV admitted to the ICU were at higher risk of death, patients on ART therapy were at lower risk. PLHIV who had higher mean levels of C-reactive protein or IL-6 were more susceptible to death. Parallel with these findings, Varshney et al's., 2022 scoping review revealed a higher risk of death among PLHIV over 50 years old[20]. Furthermore, the risk of death among males living with HIV was approximately double that of females. Varshney et al., 2022 reported twice the risk of mortality among male patients relative to females living with HIV[20]. This finding reflects the gender inequities during the pandemic and highlights the need to allocate the available resources to improve the outcomes among male patients. Adequate allocation of health resources in the COVID-19 era is mandatory to

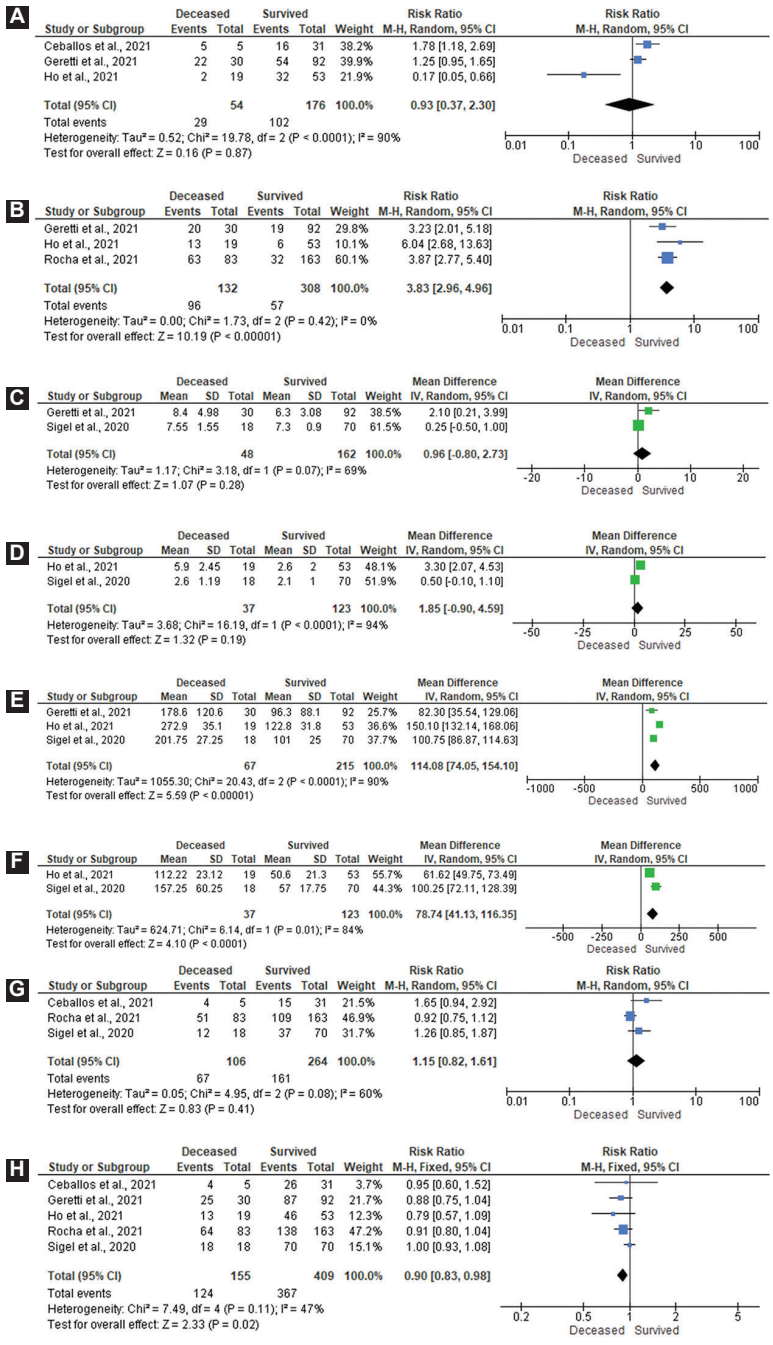

Figure 3. *Forest plot of summary analysis of the* **A:** *risk ratio (RR) and 95% CI of the impact of oxygen requirement on the mortality risk among PLHIV and diagnosed with COVID-19.* **B:** *RR and 95% CI of the impact of admission to ICU on the mortality risk among PLHIV and diagnosed with COVID-19.* **C:** *mean difference (MD) and 95% CI of the difference in white cell count between the deceased and the survived groups among PLHIV and diagnosed with COVID-19.* **D:** *MD and 95% CI of the difference in D-dimer levels between the deceased and the survived groups among PLHIV and diagnosed with COVID-19.* **E:** *MD and 95% CI of the difference in C-reactive protein level between the deceased and the survived groups among PLHIV and diagnosed with COVID-19.* **F:** *MD and 95% CI of the difference in interleukin-6 between the deceased and the survived groups among PLHIV and diagnosed with COVID-19.* **G:** *MD and 95% CI of the difference in HIV viral load < 50 copies RNA/mL before admission between the deceased and the survived groups among PLHIV and diagnosed with COVID-19.* **H:** *RR and 95% CI of the impact of ART therapy on the mortality risk among PLHIV and diagnosed with COVID-19. The size of the blue, green, and black squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome. IV: inverse variance.*

implement the appropriate management of PLHIV accurately. The presence of two or more medical comorbidities did not influence the mortality risk among PLHIV. This contradicts the findings of Varshney et al., 2022 who stated a higher risk of mortality among PLHIV with multiple comorbidities[20]. The discrepancy between our results and Varshney et al's., 2022 study might be attributed to the lack of quantitative data synthesis in the later study. Furthermore, there were no case-control studies in the Varshney et al., 2022 scoping review.

In our study, the absence of significant associations between certain comorbidities and mortality in PLHIV with COVID-19 may be attributed to limitations in statistical power, particularly as more than half of the included articles were of retrospective design, which carries a risk of selection bias. The heterogeneity observed in our findings could also stem from variations in demographic characteristics, study regions, study designs, duration of HIV infection, and follow-up periods across the included studies. Furthermore, our analysis was constrained by the limited and inconsistent reporting of CD4 count data, with only three values providing this information in a format not suitable for quantitative synthesis, thus precluding a comprehensive assessment of its impact on mortality.

In the present study, PLHIV who were admitted to ICU were at higher risk of death. Notably, HIV infection prolongs hospital stays, increases the risk of ICU admission, and escalates mortality risk from viral pneumonia. HIV infection induces structural and mechanical changes in the respiratory system, altering the immune response and increasing the risk of COVID-19-related deaths[21]. Adherence to ART therapy reduces the risk of death among PLHIV. The interruption of adherence to ART therapy due to social distancing during the pandemic may worsen the COVID-19-related outcomes among PLHIV. There is a need to increase the commitment to HIV treatment programs besides the increasing efforts to control the COVID-19 pandemic[22].

There were higher levels of inflammatory markers among PLHIV who were at higher risk of dying. This included a high mean level of C-reactive protein or IL-6. It was noteworthy that PLHIV can mount inflammatory reactions in response to SARS-CoV-2 infection, despite the immune dysregulation associated with HI. In contrast, Tesoriero et al., 2022 proposed a protective role of immunodeficiency and low CD4 count against severe inflammatory response to SARS-CoV-2 infection[23]. Further studies are needed to understand the pathological cascades of the inflammatory events in PLHIV diagnosed with COVID-19.

Despite the evidence obtained in the current study, certain limitations are inevitable. More than half of the eligible articles were of the retrospective design, carrying a high risk of selection bias. Subsequently, there was heterogeneity between the included articles. The difference in demographic characteristics, study regions, study designs, duration of HIV infection, and follow-up periods might contribute to this heterogeneity. Despite the inclusion of multivariate models, some predictors are not adjusted by confounding variables that may influence the risk of death among PLHIV. The evaluation of the impact of CD4 counts on mortality was constrained by the limited availability and inconsistent reporting of these data across the included studies. Only three values provided CD4 count information, and that in the form of median values and ranges, which are not amenable to quantitative synthesis required for a meta-analysis. Consequently, our analysis does not encompass the potential influence of CD4 counts on mortality, acknowledging this as a significant limitation in the scope of our findings.

Conclusions

This study revealed the potential predictors of mortality among PLHIV diagnosed with COVID-19. Males PLHIV, those aged ≥ 60 years, or those who had diabetes mellitus were at higher risk of mortality. Adherence to ART therapy could improve the outcomes of COVID-19, decreasing the risk of mortality. Furthermore, high levels of C-reactive protein or IL-6 were associated with a higher risk of death among PLHIV. Integrating these findings into healthcare protocols could help health-care providers identify PLHIV at higher mortality risk and improve the outcomes of COVID-19 by stratifying the patients to the most effective treatment in a timely fashion.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.23000017. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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