REVIEW ARTICLE

Significant association between HIV infection and increased risk of COVID-19 mortality: a meta-analysis based on adjusted effect estimates

Xueya Han[1] · Hongjie Hou[1] · Jie Xu[1] · Jiahao Ren[1] · Shuwen Li[1] · Ying Wang[1] · Haiyan Yang[1] · Yadong Wang[2]

Abstract

To investigate the relationship between human immunodeficiency virus (HIV) infection and the risk of mortality among coronavirus disease 2019 (COVID-19) patients based on adjusted effect estimate by a quantitative meta-analysis. A random-effects model was used to estimate the pooled effect size (ES) with corresponding 95% confidence interval (CI). I^2 statistic, sensitivity analysis, Begg's test, meta-regression and subgroup analyses were also conducted. This meta-analysis presented that HIV infection was associated with a significantly higher risk of COVID-19 mortality based on 40 studies reporting risk factors-adjusted effects with 131,907,981 cases (pooled ES 1.43, 95% CI 1.25–1.63). Subgroup analyses by male proportion and setting yielded consistent results on the significant association between HIV infection and the increased risk of COVID-19 mortality. Allowing for the existence of heterogeneity, further meta-regression and subgroup analyses were conducted to seek the possible source of heterogeneity. None of factors might be possible reasons for heterogeneity in the further analyses. Sensitivity analysis indicated the robustness of this meta-analysis. The Begg's test manifested that there was no publication bias ($P = 0.2734$). Our findings demonstrated that HIV infection was independently associated with a significantly increased risk of mortality in COVID-19 patients. Further well-designed studies based on prospective study estimates are warranted to confirm our findings.

Keywords COVID-19 · HIV · Mortality · Meta-analysis

Introduction

Evidence has suggested that increasing age and comorbidities were interrelated with worse outcomes in coronavirus disease 2019 (COVID-19) [1–5]. Due to the immunocompromised status, people living with human immunodeficiency virus (HIV) were assumed more likely to suffer from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related mortality [6–8]. Several previous meta-analyses have addressed the association between HIV infection and the risk of COVID-19 mortality with conflicting conclusions, moreover they were stuck in failing to consider the influence of certain confounding factors on the pooled effects owing to that un-adjusted effect estimates extracted from individual original literature were used to calculate the pooled effects in the previous meta-analyses [9–14]. In fact, the influence of certain confounding factors on the association between HIV infection and the risk of mortality in COVID-19 patients may bear on the output of results. For instance, Zimmermann et al. reported HIV infection status was associated with a significantly lower risk of mortality of COVID-19 patients (hazard ratio (HR): 0.757, 95% confidence interval (CI): 0.632–0.906) in the univariate model, while the significant association reversed in the multiple regression analysis (HR: 1.360, 95% CI (1.13–1.63) [15]. It is not the only study that dramatic change came up after adjusting age and sex (un-adjusted HR: 0.77. 95% CI 0.54–1.11; adjusted HR: 1.45, 95% CI 1.00–2.12) during assessing the association between HIV status and mortality in COVID-19 patients [16]. With the emergence of researches focusing

✉ Haiyan Yang
   yhy@zzu.edu.cn

1 Department of Epidemiology, School of Public Health, Zhengzhou University, No. 100 of Science Avenue, Zhengzhou 450001, Henan Province, China

2 Department of Toxicology, Henan Center for Disease Control and Prevention, Zhengzhou 450016, Henan Province, China

on the confounding factors-adjusted association between HIV infection and COVID-19 mortality, an update meta-analysis based on adjusted effect estimates is necessary to assess whether there exists a relationship between HIV infection and COVID-19 mortality or not.

Methods

Search strategy

A comprehensive search of the literature was performed in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17] based on the central databases of PubMed, Springer Link, Web of Science, Wiley Library, Elsevier ScienceDirect, Scopus and Cochrane Library, which retrieved all potential articles published from inception to November 25, 2021. Pertinent keywords and terms were used to magnify the output from the literature search containing three parts: (1) "COVID-19," "coronavirus disease 2019," "2019-nCoV," "2019 novel coronavirus," "SARS-CoV-2," "severe acute respiratory syndrome coronavirus 2"; (2) "HIV," "AIDS," "human immunodeficiency virus," "acquired immunodeficiency syndrome"; and (3) "mortality," "fatality," "death," "non-survivor," "deceased." (Detailed search strategy is shown in Table S1.) Additional articles, originating from references of the included studies and relevant reviews, were also included in the campaign of research.

Eligibility criteria and data extraction

Only in these ways were studies included in this meta-analysis: (1) studies reporting adult confirmed cases of COVID-19 regardless of country or antiretroviral therapy (ART); (2) peer-reviewed articles in English; (3) the endpoint contained death of the participants in COVID-19; and (4) studies with available data on the adjusted effect size with 95% CI regarding the association between HIV infection and COVID-19 mortality. Case reports, review papers, preprints, duplications, and errata must cast away accordingly. Searching for literature, study selection and data extraction were performed by two investigators independently. In case of disagreement, the third person would be brought in to resolve the disputes on a negotiating basis. The extracted information is at list: first author, study design, country, number of participants, the mean (standard deviation) or median (interquartile range) age, proportion of males, frequency of HIV infection (percentage of patients), the adjusted effect size (HR, OR (odds ratio) and RR (risk ratio)) with 95% CI and setting.

Statistical analysis

The pooled ES with corresponding 95% CI evaluating the association between HIV infection and COVID-19 mortality was conducted by a random-effects meta-analysis model [2] providing a visual depiction of the meta-analysis findings through forest plots. I^2 statistic was used to test for heterogeneity across the included studies. Sensitivity analysis by removing single study at a time was carried out to assure the robustness of the findings. Begg's test was applied to evaluate the potential publication bias. The analysis was performed using the package "meta" on R software (version 4.1.1). Statistical significance of testing standard was set as $P < 0.05$.

Results

Characteristics of the included studies

There existed 16,575 records from electronic databases and 30 records by cross-referencing from the identified studies. Forty and three records were identified after screening abstracts/titles (16,605) and full texts (4,222) with discarding duplicated articles, reviews, case reports, expert consensus, corrections, protocols, comments or data not related to HIV infection and data deficiencies. There were 40 eligible articles [6–8, 15, 16, 18–52] that included more than 13 million individuals after three studies were excluded allowing for less sample sizes from the same sources. The detail of selection process is shown by a flow chart (Fig. 1). A total of 131,907,981 sample sizes ranging from 270 to 66,050,590 were ultimately included in this meta-analysis. The included studies originated from 17 countries spread on four regions—Americas (n = 19 studies), Europe (n = 11 studies), Asia (n = 5 studies) and Africa (n = 5 studies). Across most studies (28/40), the number of HIV infection and percentage in all COVID-19 infection was relatively low (< 3%). The summary information of included studies is presented in Table 1.

Estimated risk of HIV infection on COVID-19 mortality

This meta-analysis based on risk factors-adjusted effects presented that HIV infection was associated with a significantly higher risk of COVID-19 mortality (pooled ES 1.43, 95% CI 1.25–1.63) (Fig. 2), although between-study variation was high ($I^2 = 89\%$, $P < 0.01$). There is nearly a 45% excess risk of death among HIV patients as compared to the individuals without HIV infection. Subsequently
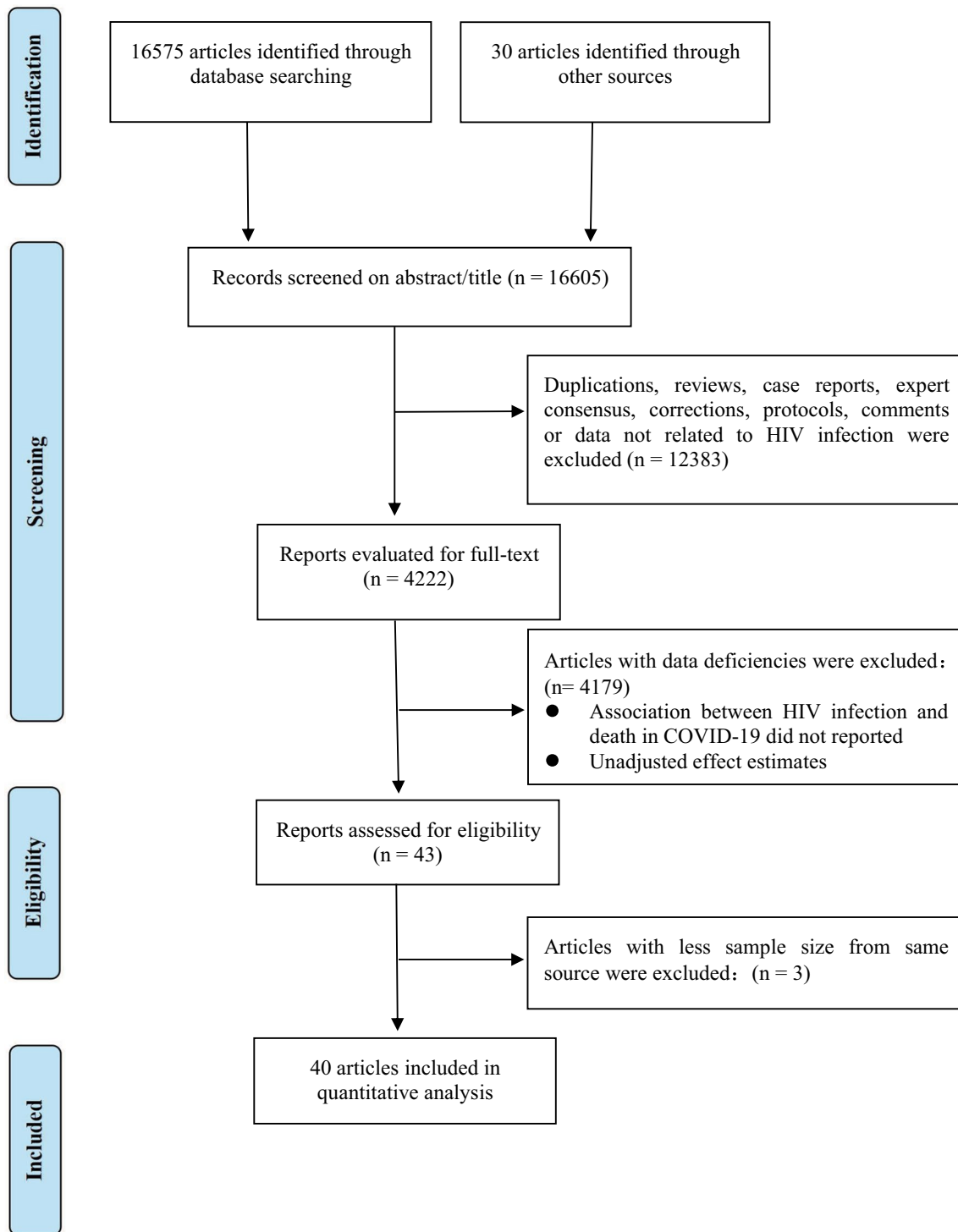
Fig. 1 Flow chart of the process of study selection of PRISMA

stratified analyses based on the type of effects showed that HIV infection was a risk factor for death in COVID-19 patients compared with those without HIV infection for the subgroups with OR and HR (pooled OR 1.20, 95% CI 1.01–1.44 and pooled HR 1.67, 95% CI 1.30–2.15,

separately), but not for RR (pooled RR 1.64, 95% CI 0.91–1.44) (Table 2 and Figure S1). Subgroup analyses by male proportion and setting of participants yielded consistent results on significantly positive association between HIV infection and COVID-19 mortality (pooled ES 1.50,

Table 1 The general information of the eligible studies in the meta-analysis

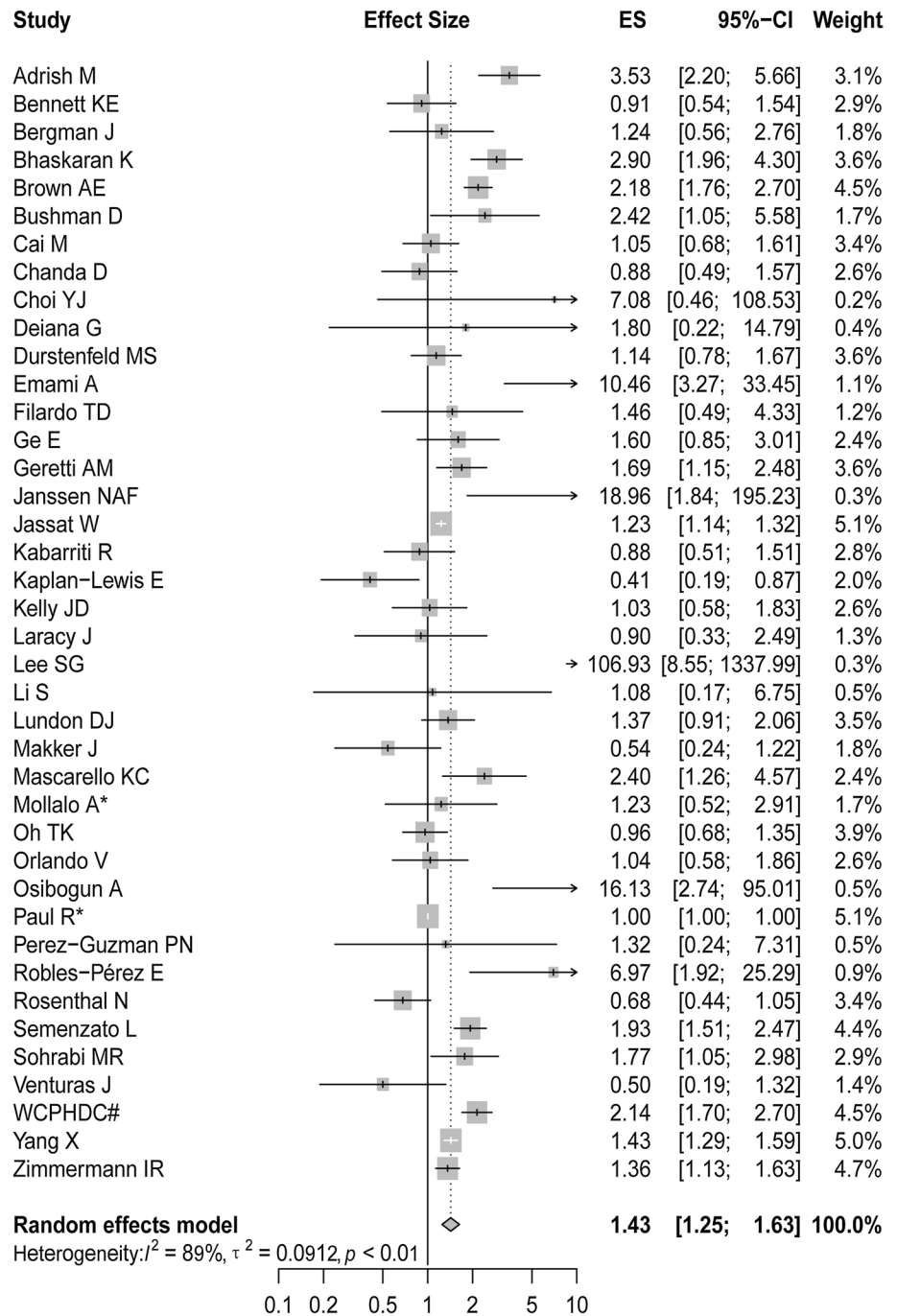| Author	Location	Study design	Sample size	Age	Male (%)	HIV (n/%)	Adjusted effect (95% CI)	Outcome	Setting
Adrish M	USA	Retrospective study	469	54.49 ± 16.19	59.5	37 (7.89)	HR: 3.53 (1.57–4.03)	In-hospital mortality	Hospitalized
Bennett KE	Ireland	Retrospective study	19,789	NR	NR	364 (1.84)	OR: 1.24 (0.77–2.00)	In-hospital mortality	Hospitalized
Bergman J	Swedish	Retrospective study	68,575	46 ± 21	39.1	84 (0.12)	HR: 1.24 (0.56–2.77)	Death	Hospitalized
Bhaskaran K	UK	Retrospective study	17,282,905	50.0 ± 22.2	50.0	27,840 (0.16)	HR: 2.90 (1.96–4.30)	Mortality	All patients
Brown AE	UK	Retrospective study	45,657,664	NR	68.63	92,643 (0.20)	RR: 2.18 (1.76–2.70)	Death	All patients
Bushman D	USA	Case–control study	1029	56 (23–64)	65.5	28 (2.72)	OR: 2.42 (1.05–5.59)	Death	Hospitalized
Cai M	USA	Retrospective study	49,238	63.3 (49.8–73.1)	88.50	504 (1.02)	OR: 1.05 (0.67–1.58)	30-day mortality	All patients
Chanda D	Zambia	Prospective study	443	NR	57.3	122 (27.54)	HR: 0.88 (0.49–1.56)	Death	Hospitalized
Choi YJ	South Korea	Retrospective study	7590	47.3	40.8	7 (0.09)	OR: 7.080 (0.462–108.575)	Mortality	All patients
Deiana G	Italy	Matched case–control study	1223	58.47 (45.3–78.3)	40.8	NR	OR: 1.8 (0.2–13.5)	Deceased	All patients
Durstenfeld MS	USA	Retrospective study	21,528	62.24 ± 17.87	54.09	220 (1.02)	OR: 1.14 (0.78–1.68)	In-hospital mortality	Hospitalized
Emami A	Iran	Retrospective study	1239	51.48 ± 19.54	55.9	5 (0.40)	HR: 10.46 (3.27–33.45)	Death	Hospitalized
Filardo TD	USA	Retrospective study	270	58 (50–67)	67.4	5 (1.85)	RR: 1.46 (0.49–4.31)	Mortality	Hospitalized
Ge E	Canada	Retrospective study	167,500	42.7 (21.9)	48.00	332 (0.20)	HR: 1.60(0.85–3.00)	30-day all-cause mortality	All patients
Geretti AM	UK	Prospective study	47,592	72.7 ± 17.8	56.9	122 (0.26)	HR: 1.69 (1.15–2.48)	28-day mortality	Hospitalized
Janssen NAF	Netherland, Belgium	Retrospective study	519	64 (55–72)	72.80	6 (1.16)	OR: 18.96 (1.84–195.11)	Death	Hospitalized
Jassat W	South Africa	Retrospective study	151,779	53.4	44.9	13,793 (9.09)	OR: 1.23 (1.15–1.33)	In-hospital mortality	Hospitalized
Kabarriti R	USA	Retrospective study	5902	57.5 (mean)	46.9	92 (1.56)	HR: 0.88 (0.51–1.51)	Death	Hospitalized
Kaplan-Lewis E	USA	Retrospective study	304	55.33 ± 13.4	70.07	110 (36.18)	OR: 0.41 (0.19–0.86)	Mortality	All patients
Kelly JD	USA	Prospective study	27,640	56.03	88.6	332 (1.20)	OR: 1.03 (0.58–1.83)	30-day Mortality	All patients
Laracy J	USA	Retrospective study	340	58.4 ± 12.7	71	68 (20)	HR: 0.9 (0.3–2.3)	In-hospital mortality	Hospitalized
Lee SG	Korea	Retrospective study	7339	47.1 ± 19.0	40.1	4 (0.05)	OR: 106.93 (6.38->999)	Death	All patients
Li S	USA	Retrospective study	6218	59.0 ± 19.1	47.60	35 (0.56)	OR: 1.077 (0.172–6.753)	In-hospital mortality	Hospitalized
Lundon DJ	USA	Cross-sectional analysis	8928	58.0 ± 18.8	46.2	140 (1.57)	OR: 1.37 (0.91–2.05)	Mortality	Hospitalized

Table 1 (continued)

Author	Location	Study design	Sample size	Age	Male (%)	HIV (n/%)	Adjusted effect (95% CI)	Outcome	Setting
Makker J	USA	Retrospective study	1206	62.0 ± 12.0	60.70	79 (6.55)	OR: 0.54 (0.24–1.23)	In-hospital mortality	Hospitalized
Mascarello KC	Brazil	Cross-sectional analysis	104,359	42.2	46.9	NR	RR: 2.40 (1.26–4.57)	Death	All patients
Mollalo A[a]	USA	Retrospective study	NR	NR	NR	NR	OR: 1.23 (0.52–2.91)	Mortality	All patients
Oh TK	South Korea	Retrospective study	8070	49.34	39.5	9 (0.11)	HR: 0.96 (0.68–1.35)	In-hospital mortality	Hospitalized
Orlando V	Italy	Retrospective study	3497	NR	55.6	68 (1.94)	OR: 1.04 (0.58–1.86)	Death	All patients
Osibogun A	Nigeria	Retrospective study	2184	43 (33–55)	65.8	7 (0.32)	OR: 16.13 (2.74–95.07)	Death	Hospitalized
Paul R[a]	USA	Retrospective study	3104	NR	NR	301 (9.70)	RR: 1.002 (1.000–1.004)	Mortality	All patients
Perez-Guzman PN	UK	Retrospective study	614	69 (56.5–81.5)	62.21	9 (1.47)	OR: 1.32 (0.24–7.36)	In-hospital mortality	Hospitalized
Robles-Pérez E	USA	Retrospective study	70,531	NR	43.2	70 (0.10)	OR: 6.97 (1.92–25.28)	Death	All patients
Rosenthal N	USA	Prospective study	64,781	56.1 ± 19.9	49.3	252 (0.39)	OR: 0.68 (0.44–1.04)	In-hospital mortality	Hospitalized
Semenzato L	France	Retrospective study	66,050,590	43 ± 24	48	146,204 (0.22)	HR: 1.93 (1.51- 2.47)	In-hospital mortality	Hospitalized
Sohrabi MR	Iran	Prospective study	205,645	52.8 ± 21.1	54.5	154 (0.07)	OR: 1.77 (1.053–2.973)	Mortality	Hospitalized
Venturas J	South Africa	Prospective study	384	50 (39–60)	53	108 (28.13)	OR: 0.50 (0.20–1.40)	In-hospital mortality	Hospitalized
WCPHDC[b]	the Western Cape	Cohort study	22,308	NR	31.6	3978 (17.83)	HR: 2.14 (1.70–2.70)	Death	All patients
Yang X	USA	Cohort study	1,436,622	47 (32–61)	44.96	13,170 (0.92)	OR: 1.43 (1.29–1.59)	Death	All patients
Zimmermann IR	Brazil	Retrospective study	398,063	61.5	55.5	467 (0.12)	HR: 1.360 (1.13–1.63)	In-hospital mortality	Hospitalized

The age (years) was presented as mean ± standard deviation or median (interquartile range, IQR); CI, confidence interval; NR, not clearly reported; USA, The United states of America; UK, The United Kingdom; [a] indicates combined effects based on subgroups; [b] indicates Western Cape Department of Health in collaboration with the National Institute

95% CI 1.16–1.94 for male proportion ≥ 50% and pooled ES 1.45, 95% CI 1.20–1.74 for male proportion < 50%; and pooled ES 1.58, 95% CI 1.23–2.03 for all patients and pooled ES 1.34, 95% CI 1.12–1.61 for hospitalization, Table 2, Fig. S2 and Fig. S3). Following subgroup analyses with age, sample size and study design demonstrated that this significant association between HIV infection and the increased risk of COVID-19 mortality did exist among studies with separated subgroups: age < 60 (pooled ES 1.50, 95% CI 1.25–1.81); sample sizes ≥ 8000 (pooled ES 1.47, 95% CI 1.28–1.70); sample sizes < 8000 (pooled ES 1.52, 95% CI 1.04–2.22); retrospective study (pooled ES 1.45, 95% CI 1.23–1.71); except with separated subgroup: prospective study (pooled ES 1.05, 95% CI 0.71–1.55)

(Table 2, Fig. S4, Fig. S5 and Fig. S6). As for subgroup analysis for region manifested that HIV infection could increase the risk of COVID-19 mortality in Asia (pooled ES 3.99, 95% CI 1.37–11.60), Europe (pooled ES 1.74, 95% CI 1.37–2.20) and Americas (pooled ES 1.23, 95% CI 1.03–1.47), but did not exist in Africa (pooled ES 1.38, 95% CI 0.87–2.20) (Table 2 and Fig. S7). Coming through further meta-regression to pursue the source of heterogeneity, none of factors mentioned above might be possible reasons of heterogeneity (age: P value = 0.6579; male proportion: P value = 0.2859; sample size: P value = 0.7892; setting: P value = 0.3483; study design: P value = 0.0826; region: P value = 0.1033) (Table 2).

Fig. 2 Forest plot presents the relationship between HIV infection and COVID-19 mortality with pooled effect and its 95% confidence intervals (CI). * indicates combined effects based on subgroups; ** indicates Western Cape Department of Health in collaboration with the National Institute

Study	Effect Size	ES	95%−CI	Weight
Adrish M		3.53	[2.20; 5.66]	3.1%
Bennett KE		0.91	[0.54; 1.54]	2.9%
Bergman J		1.24	[0.56; 2.76]	1.8%
Bhaskaran K		2.90	[1.96; 4.30]	3.6%
Brown AE		2.18	[1.76; 2.70]	4.5%
Bushman D		2.42	[1.05; 5.58]	1.7%
Cai M		1.05	[0.68; 1.61]	3.4%
Chanda D		0.88	[0.49; 1.57]	2.6%
Choi YJ		7.08	[0.46; 108.53]	0.2%
Deiana G		1.80	[0.22; 14.79]	0.4%
Durstenfeld MS		1.14	[0.78; 1.67]	3.6%
Emami A		10.46	[3.27; 33.45]	1.1%
Filardo TD		1.46	[0.49; 4.33]	1.2%
Ge E		1.60	[0.85; 3.01]	2.4%
Geretti AM		1.69	[1.15; 2.48]	3.6%
Janssen NAF		18.96	[1.84; 195.23]	0.3%
Jassat W		1.23	[1.14; 1.32]	5.1%
Kabarriti R		0.88	[0.51; 1.51]	2.8%
Kaplan−Lewis E		0.41	[0.19; 0.87]	2.0%
Kelly JD		1.03	[0.58; 1.83]	2.6%
Laracy J		0.90	[0.33; 2.49]	1.3%
Lee SG		106.93	[8.55; 1337.99]	0.3%
Li S		1.08	[0.17; 6.75]	0.5%
Lundon DJ		1.37	[0.91; 2.06]	3.5%
Makker J		0.54	[0.24; 1.22]	1.8%
Mascarello KC		2.40	[1.26; 4.57]	2.4%
Mollalo A*		1.23	[0.52; 2.91]	1.7%
Oh TK		0.96	[0.68; 1.35]	3.9%
Orlando V		1.04	[0.58; 1.86]	2.6%
Osibogun A		16.13	[2.74; 95.01]	0.5%
Paul R*		1.00	[1.00; 1.00]	5.1%
Perez−Guzman PN		1.32	[0.24; 7.31]	0.5%
Robles−Pérez E		6.97	[1.92; 25.29]	0.9%
Rosenthal N		0.68	[0.44; 1.05]	3.4%
Semenzato L		1.93	[1.51; 2.47]	4.4%
Sohrabi MR		1.77	[1.05; 2.98]	2.9%
Venturas J		0.50	[0.19; 1.32]	1.4%
WCPHDC#		2.14	[1.70; 2.70]	4.5%
Yang X		1.43	[1.29; 1.59]	5.0%
Zimmermann IR		1.36	[1.13; 1.63]	4.7%
Random effects model		**1.43**	**[1.25; 1.63]**	**100.0%**

Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.0912$, $p < 0.01$

0.1 0.2 0.5 1 2 5 10

Sensitivity analysis and publication bias

After removing single study at a time, the forest plot still indicated that the pooled effect did not drastically alter, which indicated the robustness of this meta-analysis (Fig. 3). Graphically, the funnel plot analysis intuitively presented symmetry among the included studies (Fig. 4). Statistically, the Begg's test manifested that there was no publication bias for the publications ($P = 0.2734$).

Discussion

Although several meta-analyses have investigated the association between HIV infection and COVID-19 mortality, they obtained contradictory findings and the influence of certain confounding factors on the pooled effect was not taken into account [9–14]. This meta-analysis investigated the relationship between HIV infection and COVID-19 mortality on the basis of risk factors-adjusted effects. Our findings

Table 2 Subgroup analysis and meta-regression

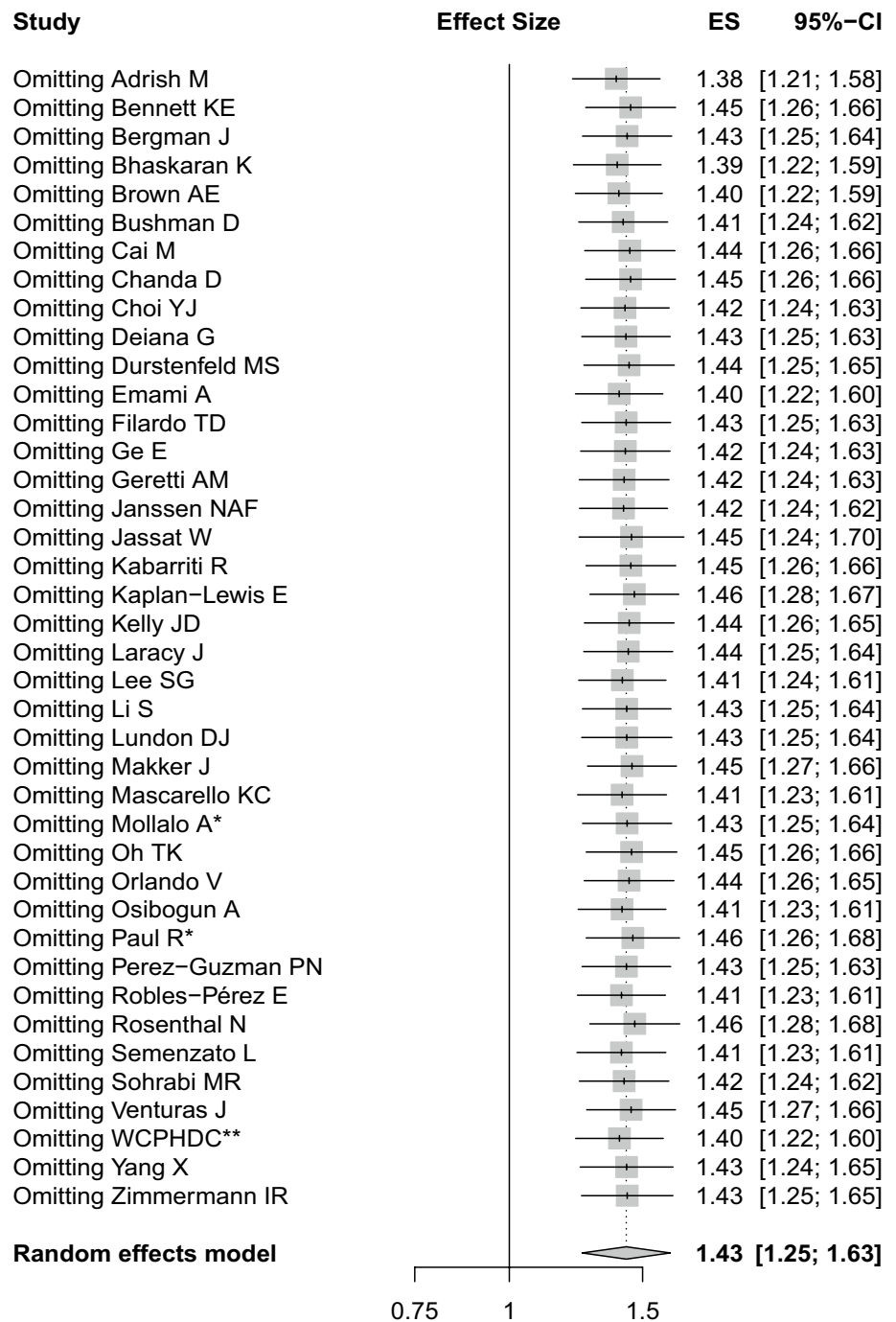| Variables	No. of studies	Meta-regression			Subgroup analysis	Heterogeneity		
		Tau^2	Z-Value	P value	Pooled Effect (95% CI)	I^2	τ^2	P value
Age (years)		0.1392	–	0.6579				
≥ 60	7	–	-0.9049	0.3655	1.25 (0.95 − 1.65)	54%	0.0584	0.04
< 60	25	–	–	–	1.50 (1.25 − 1.81)	79%	0.1058	< 0.01
NR	8	–	-0.3686	0.7124	1.42 (0.97 − 2.10)	93%	0.2360	< 0.01
Male (%)		0.1044	–	0.2859				
≥ 50	21	–	0.1127	0.9103	1.50 (1.16 − 1.94)	79%	0.2186	< 0.01
< 50	16	–	–	–	1.45 (1.20 − 1.74)	78%	0.0650	< 0.01
NR	3	–	-1.4583	0.8802	1.002 (1.000 − 1.004)	0%	0	0.84
Sample size		0.1026	–	0.7892				
≥ 8000	20	–	0.6288	0.5295	1.47 (1.28 − 1.70)	80%	0.0606	< 0.01
< 8000	19	–	–	–	1.52 (1.04 − 2.22)	80%	0.3879	< 0.01
NR	1	-0.1521		0.8791	1.23 (0.52 − 2.91)	–	–	–
Setting		0.1341	-0.9378	0.3483				
All patients	16	–	–	–	1.58 (1.23 − 2.03)	93%	0.1543	< 0.01
Hospitalized	24	–	–	–	1.34 (1.12 − 1.61)	73%	0.0964	< 0.01
Study design		0.0880	–	0.0826				
Retrospective study	28	–	-2.2147	0.0268	1.45 (1.23 − 1.71)	89%	0.0894	< 0.01
Prospective study	6	–	-1.1487	0.2507	1.05 (0.71 − 1.55)	69%	0.1516	< 0.01
Other	6	–	–	–	1.75 (1.36 − 2.24)	62%	0.0438	0.02
Region		0.1007	–	0.1033				
Asia	5	–	1.2369	0.2161	3.99 (1.37 − 11.60)	87%	0.9965	< 0.01
Europe	11	–	0.9406	0.3469	1.74 (1.37 − 2.20)	57%	0.0704	< 0.01
Americas	19	–	-0.5381	0.5905	1.23 (1.03 − 1.47)	85%	0.0771	< 0.01
Africa	5	–	–	–	1.38 (0.87 − 2.20)	88%	0.1811	< 0.01
Effect		0.1202	–	0.1361				
OR	23	–	-1.9172	0.0552	1.20 (1.01 − 1.44)	69%	0.0667	< 0.01
RR	4	–	-0.1810	0.8564	1.64 (0.91 − 2.96)	95%	0.2864	< 0.01
HR	13	–	–	–	1.67 (1.30 − 2.15)	80%	0.1423	< 0.01

NR, not clearly reported; CI, confidence interval; OR, odds ratio; RR, risk ratio; HR, hazard ratio

demonstrated that HIV infection was significantly associated with an increased risk of COVID-19 mortality based on 40 eligible articles with 131,907,981 COVID-19 patients reporting risk factors-adjusted effects, which suggests that HIV infection might be an independent risk factor for predicting fatal COVID-19. Subgroup analyses by setting and male proportion yielded consistent results on the significant association between HIV infection and the increased risk of COVID-19 mortality. Allowing for the existence of heterogeneity, further meta-regression and subgroup analyses were conducted to seek the possible source of heterogeneity. None of factors for subgroups might be possible reasons for heterogeneity in the further analyses that can be utilized to interpret the source of heterogeneity.

Clinical features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection varied from asymptomatic outcome to the dead endpoint. Evidence exists that elevated levels of infectious biomarkers and inflammatory cytokines may result in the significant decrease of the number of T cells in COVID-19 patients and both helper T cells and suppressor T cells in patients with COVID-19 were below normal levels [53]. This indicated the novel coronavirus might impact T lymphocytes. Moreover, the distinctive characteristic of HIV infection was persistent immune dysfunction manifested as low counts of $CD4^+$ T cells, which was subject to death than the HIV-negative patients [48]. This can be attributed to that immune activation, inflammation and coagulopathy are more common in HIV infection despite mitigation with drug-induced control of HIV virus replication [54–56]. Then, in regard to the individual co-infected with HIV and SARS-CoV-2, it is prone to interfering with immune homeostasis, promoting tissue damage and resulting in severe outcome of patients in a double whammy to consume $CD4^+$ T cells. Mentioned above statements, to some extent, explained the relationship between HIV infection and COVID-19 death. It is worth pursuing

Fig. 3 Sensitivity analysis for pooled effect and 95% CI by deleting single study at a time. * indicates combined effects based on subgroups; ** indicates Western Cape Department of Health in collaboration with the National Institute

Study	Effect Size	ES	95%–CI
Omitting Adrish M		1.38	[1.21; 1.58]
Omitting Bennett KE		1.45	[1.26; 1.66]
Omitting Bergman J		1.43	[1.25; 1.64]
Omitting Bhaskaran K		1.39	[1.22; 1.59]
Omitting Brown AE		1.40	[1.22; 1.59]
Omitting Bushman D		1.41	[1.24; 1.62]
Omitting Cai M		1.44	[1.26; 1.66]
Omitting Chanda D		1.45	[1.26; 1.66]
Omitting Choi YJ		1.42	[1.24; 1.63]
Omitting Deiana G		1.43	[1.25; 1.63]
Omitting Durstenfeld MS		1.44	[1.25; 1.65]
Omitting Emami A		1.40	[1.22; 1.60]
Omitting Filardo TD		1.43	[1.25; 1.63]
Omitting Ge E		1.42	[1.24; 1.63]
Omitting Geretti AM		1.42	[1.24; 1.63]
Omitting Janssen NAF		1.42	[1.24; 1.62]
Omitting Jassat W		1.45	[1.24; 1.70]
Omitting Kabarriti R		1.45	[1.26; 1.66]
Omitting Kaplan–Lewis E		1.46	[1.28; 1.67]
Omitting Kelly JD		1.44	[1.26; 1.65]
Omitting Laracy J		1.44	[1.25; 1.64]
Omitting Lee SG		1.41	[1.24; 1.61]
Omitting Li S		1.43	[1.25; 1.64]
Omitting Lundon DJ		1.43	[1.25; 1.64]
Omitting Makker J		1.45	[1.27; 1.66]
Omitting Mascarello KC		1.41	[1.23; 1.61]
Omitting Mollalo A*		1.43	[1.25; 1.64]
Omitting Oh TK		1.45	[1.26; 1.66]
Omitting Orlando V		1.44	[1.26; 1.65]
Omitting Osibogun A		1.41	[1.23; 1.61]
Omitting Paul R*		1.46	[1.26; 1.68]
Omitting Perez–Guzman PN		1.43	[1.25; 1.63]
Omitting Robles–Pérez E		1.41	[1.23; 1.61]
Omitting Rosenthal N		1.46	[1.28; 1.68]
Omitting Semenzato L		1.41	[1.23; 1.61]
Omitting Sohrabi MR		1.42	[1.24; 1.62]
Omitting Venturas J		1.45	[1.27; 1.66]
Omitting WCPHDC**		1.40	[1.22; 1.60]
Omitting Yang X		1.43	[1.24; 1.65]
Omitting Zimmermann IR		1.43	[1.25; 1.65]
Random effects model		**1.43**	**[1.25; 1.63]**

0.75   1   1.5

the mechanisms in detail under the further investigations on which pathway might have increased lethality for the HIV-positive compared with the rest among people with a diagnosis of COVID-19.

After an in-depth subgroup analysis with age, we found a higher estimate for mortality in the <60 years of age group compared with the ≥ 60 years of age group (1.50 vs 1.25). Younger persons living with diagnosed HIV may also be at higher risk of mortality due to COVID-19 complications [57]. This is an interesting phenomenon. Persons living with diagnosed HIV hospitalized and dying from COVID-19 were younger than persons living without diagnosed HIV [58–60]. This finding may lend support to the hypothesis that HIV infection can accelerate biological aging [61, 62]. Subgroup with male proportion $\geq 50\%$ in HIV and the novel coronavirus co-infection had a slightly higher risk of death than those $<50\%$ (1.50 vs 1.45). Meanwhile, as reported in Yang et al.'s study, male patients had higher risk of COVID-19 death compared with females whether or not with HIV infection [49]. With a large burden of other comorbidities
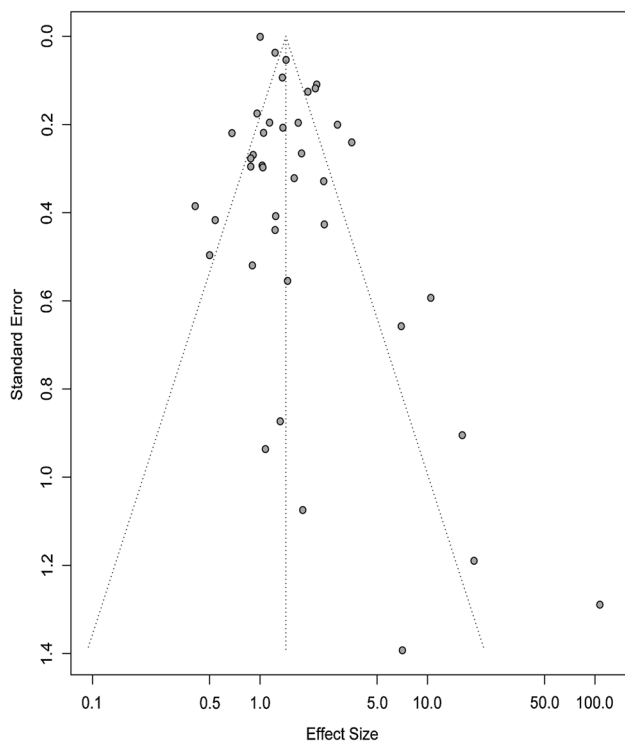
Fig. 4 Publication bias in Begg's test based on funnel plot

may also influence the association between HIV infection and death of the novel coronavirus. As mentioned in the background, comorbidities were interrelated with worse outcomes in COVID-19. When stratifying for existence of comorbidities, the association between HIV and COVID-19 mortality was significantly higher in those with comorbidities [21, 51]. Region is also an influencing factor. When performing subgroup by continents, we found different risk effects among regions, which may be related to the prevalence of HIV infection and different measures for COVID-19. CD4$^+$ T cells counts, viral load, and type of antiretroviral therapy that associated HIV status can influence the progression of the physical condition in turn to affect the severity of COVID-19 [51, 63].

We acknowledged several limitations in the review, which were mainly distributed in the following areas. First, prospective studies are more capable of proving the cause declared in this study and are more likely to delivery conservative results and conclusions, but most of the included studies were retrospective, only six prospective studies were included and failed to deliver to the significant association between HIV infection and COVID-19 mortality on our pooled effect, which might result from the relatively small number of included prospective studies. Therefore, further meta-analyses based on a large number of prospective studies are warranted to verify our findings

in future, while the more relevant articles by study design in prospective study are available. Second, across most studies (28/40), the numbers of HIV infection and percentage in all COVID-19 patients were relatively low (< 3%). In another aspect, there were also several articles with high prevalence rates in HIV infection, which may result from selection bias despite the robust results of the sensitivity analysis. Third, most of the included studies originated from Americas and Europe. Finally, HIV/acquired immunodeficiency syndrome (AIDS) as a long-lasting disease, dosage use of drugs in convention was not reported clearly so that the meta-analysis did not address the influence of AIDS therapy on the association between HIV infection and COVID-19 mortality presently.

This study suggested that effective measures to mitigate COVID-19 risk among the HIV-positive should be included in HIV programs in order to reduce the mortality in COVID-19. Under the management of HIV patients without COVID-19, beyond the routine disease treatment, prevention and control for HIV patients, precautionary measures for COVID-19 should be more targeted and conventional. Patients with HIV infection need priority consideration for the SARS-CoV-2 vaccine through a combination of prevention and treatment, especially in countries with severe HIV burdens and higher numbers of vulnerable populations. In addition, patients in COVID-19 with HIV infection need to pay attention to deal with possibly poor progression and death in view of physicians.

In conclusion, our findings demonstrated that HIV infection was independently associated with a significantly increased risk of mortality in COVID-19 patients, which suggests that HIV infection might be a predictor for fatal COVID-19. Further well-designed studies based on prospective study estimates are warranted to confirm our findings. This study suggested that routine interventions and treatment for HIV patients with COVID-19 should be given rise to wider attention.

Code Availability Not applicable.

Declarations

Conflicts of interest All authors report that they have no potential conflicts of interest.

Human and animal rights Not applicable.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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