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Effect of HIV infection on COVID-19 Cytokine Release Syndrome and Mortality

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Abstract

Introduction

Established predictors for COVID-19 related mortalities are diverse, with cytokine release syndrome (CRS), a key intermediator to the case fatalities being dominant and multi-faceted. The impact of these several risk factors on coronavirus mortality have been previously reported in several meta-analyses limited by small sample sizes and premature data, and CRS not fully being accounted for. The objective of this systematic review and meta-analysis was to evaluate the evidence on the risk of COVID-19 related CRS and mortality with HIV serostatus using published data, and a meta-regression to account for possible covariates

Method

Electronic databases including Google Scholar, Cochrane Library, Web of Sciences (WOS), EMBASE, Medline/PubMed, COVID-19 Research Database, and Scopus, were systematically searched till 30th February, 2022. All human studies were included irrespective of publication date or region. Twenty-two studies with a total of 19,783,097 patients detailing COVID-related mortality and eleven with a total of 2,005,274 were included. To pool the estimate, a random-effects model with risk ration as the effect measure was used. Moreover, publication bias and sensitivity analysis were evaluated followed by meta-regression. The trial was registered (CRD42021264761) on the PROSPERO register.

Results

The findings were consistent in stating the contribution of HIV infection for COVID-19 related CRS and mortality. The cumulative COVID-19 related mortality and CRS was 110270 (0.6%) and 48863 (2.4%) with total events of 2010 (3.6%), 108260 (0.5%) and 837(4.6%), 48026 (2.4%) among HIV-positive and negative persons respectively. HIV infection showed an increased risk of COVID-19 related CRS and mortality [RR= 1.48, 95% CI (1.16, 1.88) (P=0.002)] and [RR =1.19, 95% CI (1.02 -1.39) (P=0.00001)] respectively, both with substantial heterogeneity (I^2 > 80%). The true effects size in 95% of all the comparable populations fell between 0.64 to 2.22 and 0.67 to 3.29 for mortality and CRS respectively. MC studies and COVID-19 mortality with HIV infection showed a significant association [RR = 1.305, 95% CI (1.092 -1.559) (P = 0.003)], similar to studies conducted in America (RR=1.422, 95% CI 1.233–1.639) and South Africa (RR=1.123, 95% CI 1.052–1.198). HIV infection showed a risk for ICU admission [(P=0.00001) (I^2 = 0%)] and mechanical ventilation [(P=0.04) (I^2 = 0%)] as parameters of CRS. Furthermore, risk of COVID-19 related CRS is influenced by the year a study was conducted (R^2 = 0.55) and the region (R^2 = 0.11) same for mortality (R^2 = 0.60). The variance proportion explained by covariates was significant for CRS (I^2 = 86.5%, Q = 73.99, df = 10, P = 0.0000) (R^2 = 0.78) and mortality (I^2 = 87.5%, Q = 168.02, df = 21, p = 0.0000) (R^2 = 0.67).

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Conclusion

Our updated meta-analysis indicated that HIV infection was significantly associated with an increased risk for both COVID-19 – CRS and mortality, which might be modulated by regions, study setting and year. Risk for ICU admission and mechanical ventilation are the key indicators of CRS. We believe the updated data further anchoring CRS will contribute to more substantiation of the findings reported by similar earlier studies (Dong et al., 2021; K. W. Lee et al., 2021; Massarvva, 2021; Mellor et al., 2021; Ssentongo et al., 2021).

Introduction

By March 2022, there have been a cumulative 435,626,514 confirmed cases of COVID-19, including about 6 million deaths reported to WHO. SARS-CoV-2 infection may present asymptomatically or culminate to mild symptoms with a proportion of people developing severe coronavirus disease 2019 (COVID-19), which lead to hospitalization, acute respiratory distress syndrome (ARDS) or death. Established predictors for mortality are increasing age, male gender, dyspnea, hypertension and diabetes while severe COVID-19 is associated with hilar lymphadenopathy, bilateral lung and reticular pattern (Chidambaram et al., 2020).

About 38 million people globally living with HIV (PLWH), (including 1.7 million children), with a global HIV prevalence of 0.7% among adults (Vardell, 2020), may have an increased risk of adverse outcomes from COVID-19 infection as a result of HIV-associated immune dysfunction due to associated cells' alterations and depletion (Korencak et al., 2019). There may also be a higher prevalence of co-morbidities among PLWH that predispose them to adverse COVID-19 outcomes (Mirzaei et al., 2021). Conversely, PLWH may have more favorable outcomes due to increased health awareness or close medical follow-up and constant reviews with some specific antiretroviral agents under consideration as potential treatments for COVID-19(Pio Conti Ronconi G2, Caraffa A3, Gallenga CE4, Ross R5, 2020).

Severe COVID-19 disease manifested by fever and pneumonia, leading to acute respiratory distress syndrome (ARDS), has been described in up to 20% of COVID-19 cases. This is reminiscent of cytokine release syndrome (CRS)–induced ARDS and secondary hemophagocytic lymph histiocytosis (sHLH) observed in patients with SARS-CoV-2 (Moore & June, 2020), characteristics of CRS, including pulmonary inflammation, fever, and dysfunction of non-pulmonary organs. An increase in interleukin-6 in peripheral blood is a key risk factor and an early indicator of CRS in COVID-19. Both antibody and T cell responses are critical for effective control and clearance of SARS-CoV-2. More severe COVID-19 disease correlates with lymphopenia and low T cell concentrations(Chen et al., 2020; Lucas et al., 2020; Sekine et al., 2020).

COVID-19 associated mortality by HIV serostatus is not explicitly researched and most meta-analysis have focused on studies lacking comparator groups or they used a general population as controls unlike in the current study which restricts the comparator as HIV negative in the same included study. Further, cytokine release syndrome (CRS) defined by clinical, Immunological and pathologic features of COVID-19, as well as events such as mechanical ventilation, ICU

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admissions and intubations (Hong et al., 2020; Wang et al., 2020) as a known predictor of COVID-19 mortality is assessed relative to HIV sero-status. We aimed to evaluate the evidence regarding the risk of COVID-19 mortality and CRS in people with HIV (PWH) using both earlier and recently published data, and a meta-regression to ascertain the extent to which this risk is modified by other possible covariates.

Methods

We utilized a systematic review to identify studies between 1st April 2020 and 30th February 2022 that described cytokine release syndrome and COVID -19 mortality in people with HIV (PLWH) and compared them with HIV-negative people, and, meta-analysis approach followed by a meta-regression, to ascertain the covariates associated with COVID-19 cytokine release syndrome (characterized by specific parameters) and mortality. A standard search strategy was used in PubMed, and then modified according to each specific database to get the best relevant results. These included MEDLINE indexed journals; PubMed Central; NCBI Bookshelf, medRxiv, LitCovid, Trip, Google, Google Scholar and publishers' Web sites. The basic search strategy was built based on the research question formulation (i.e., PICO or PICOS). They were constructed to include free-text terms (e.g., in the title and abstract) and any appropriate subject indexing (e.g., MeSH) expected to retrieve eligible studies, with the help of an expert in the review topic field or an information specialist. The summary of search terms was; COVID-19 severity; Corona Virus Severity; Cytokine Storm, Cytokines; HIV; Inflammation; Chemokine; Interleukins and immune reactions, COVID-19 mortality, etc. After some rounds of trial, refinement and formulation of the search term for PubMed as follows: (COVID-19 OR corona-virus virus OR coronavirus disease) AND (“the study” [Publication Type] OR “study as the topic” [MeSH Terms] OR “study” AND HIV serostatus AND [All Fields]). One author with extensive literature search experience and expertise performed the preliminary screening to exclude duplicates and studies not related to HIV infection. For remaining articles, another author performed title/topic and abstract screening, with subsequent full text review by two authors using a standardized data extraction form. Where of disagreement was feasible, inclusion decisions were made by a third author. We also included preprints to capture the most recent and emerging evidence. Studies with 15 or less participants were excluded as they were less likely to have the power to detect meaningful relationships. The quality of the studies was evaluated using the Newcastle-Ottawa Scale for observational studies (Sidweli, 1993; Wells et al., 2000).

Observation studies reporting COVID-19-related cytokine release syndrome and death in people with and without HIV included in a meta-analysis. Specific relative risks (RRs) and hazard ratios were combined with random effects model to account for variability of the true effect between studies. To explore possible effect modifications, subgroup and meta-regression analyses were conducted for both COVID-19 related CRS and mortality. Meta-analysis was performed in Review Manager version 5.4 and Comprehensive Meta-Analysis (CMA) (version 3), (dichotomous data, random effects model), calculated the effect estimates as Risk Ratios (with 95% CI).

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Summary of included studies

We identified 2285 records and included a total of 33 studies (twenty-two detailing mortality and eleven detailing cytokine release syndromes as outcomes in our final analysis (Fig. 1). The included studies were peer-reviewed with some, as preprints since the research quest sought to capture even the latest data and information.

We identified twenty-one cohort studies (six prospective, fifteen retrospective) and, one case-control study comparing COVID-19-associated mortality between HIV Seropositive and HIV-sero-negative people, which we pooled in a meta-analysis (Bhaskaran et al., 2021; Braunstein et al., 2021; Chang et al., 2021; Díez et al., 2021; Durstenfeld et al., 2021; Geretti et al., 2021; Hadi et al., 2020; Karim et al., 2021; Karmen-Tuohy et al., 2020; M. J. Lee et al., 2022; Miyashita & Kuno, 2021; Nagarakanti et al., 2021; Patel et al., 2021; "Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa," 2021; Sigel et al., 2020; Spinelli et al., 2021; Tesoriero et al., 2021; Venturas et al., 2021; Yang et al., 2021; Yendewa et al., 2021). Eleven of these (Braunstein et al., 2021; Chang et al., 2021; Díez et al., 2021; Durstenfeld et al., 2021; Hadi et al., 2020; Karmen-Tuohy et al., 2020; M. J. Lee et al., 2022; Nagarakanti et al., 2021; Patel et al., 2021; Yang et al., 2021; Yendewa et al., 2021) prior to mortality also, reported and compared cytokine release syndrome, defined by a specific parameter (such as intensive care unit admission) between HIV seropositive and seronegative.

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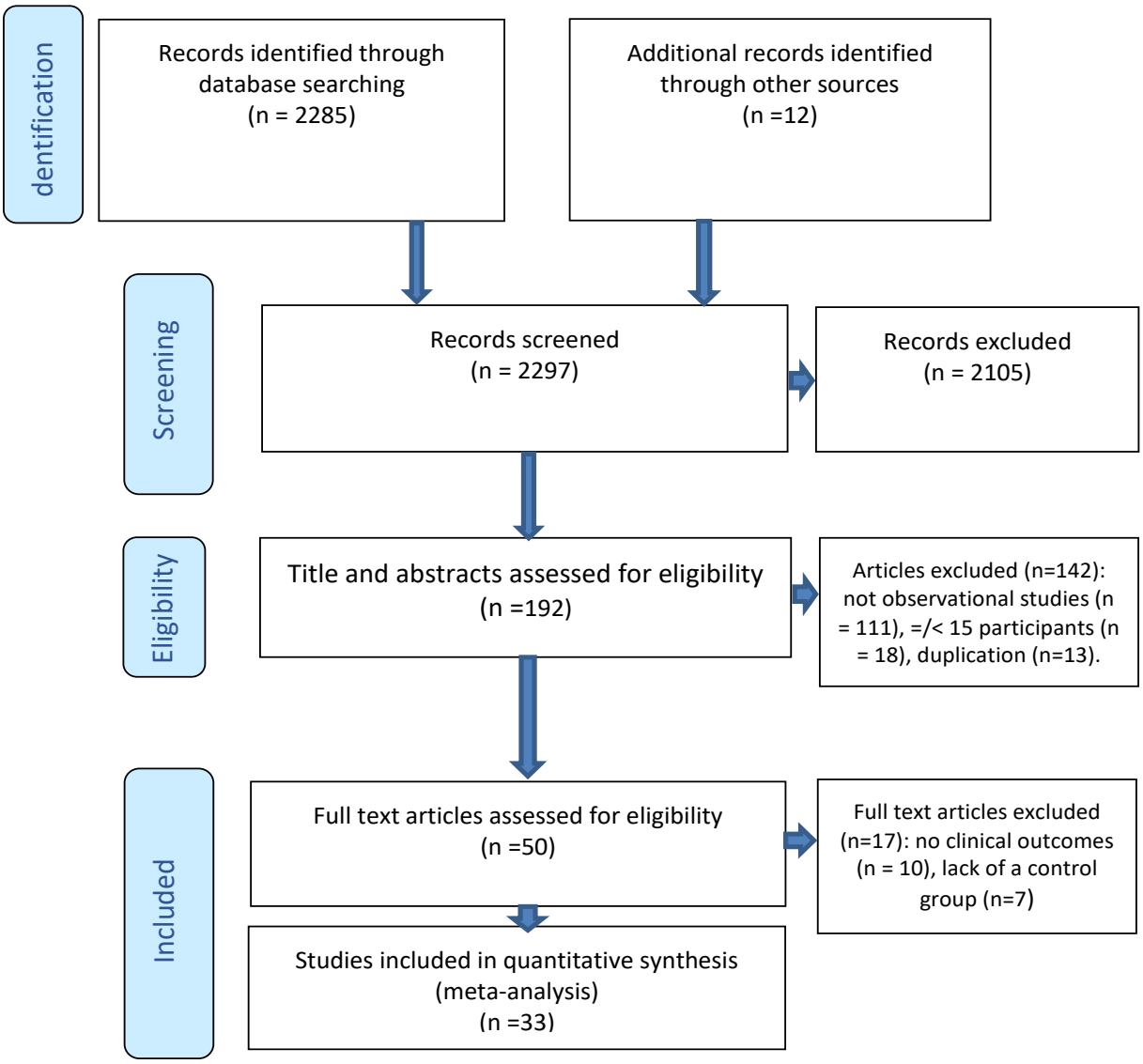
Fig. 1: PRISMA flow diagram showing studies identified and included in a systematic meta-analysis of coronavirus disease 2019 Cytokine storm and mortality



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In this meta-analysis pool, 19,783,097 from the 22 studies with mortality outcome (Bhaskaran et al., 2021; Braunstein et al., 2021; Chang et al., 2021; Díez et al., 2021; Durstenfeld et al., 2021; Geretti et al., 2021; Hadi et al., 2020; Harrison et al., 2020; Jassat et al., 2021; Karim et al., 2021; Karmen-Tuohy et al., 2020; M. J. Lee et al., 2022; Miyashita & Kuno, 2021; Nagarakanti et al., 2021; Patel et al., 2021; "Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa," 2021; Sigel et al., 2020; Spinelli et al., 2021; Tesoriero et al., 2021; Venturas et al., 2021; Yang et al., 2021; Yendewa et al., 2021) and 2,005,274 from the 11 studies (Braunstein et al., 2021; Chang et al., 2021; Díez et al., 2021; Durstenfeld et al., 2021; Hadi et al., 2020; Karmen-Tuohy et al., 2020; M. J. Lee et al., 2022; Nagarakanti et al., 2021; Patel et al., 2021; Yang et al., 2021; Yendewa et al., 2021) with cytokine release syndrome diagnosed with COVID-19 were included. This inclusion utilized the predefined given CDC reporting guidelines on COVID-19 diagnosis (Chow et al., 2020), The cumulative COVID-19 mortality was 110270 (0.6%) and that of COVID-19 cytokine release syndrome defining parameter 48863 (2.4%). The total COVID-19 mortality and cytokine release syndrome events were 2010 (3.6%), 108260 (0.5%) and 837(4.6%), 48026 (2.4%) among the HIV sero-positive and HIV-seronegative persons respectively. The cumulative incidence of COVID-19 related mortality from all studies ranged from 0.09 % to 56 % (average: 14.4%) while that of COVID-19 related cytokine release syndrome ranged from 1.5% to 40 % (average: 19 %). A summary of the studies included in this meta-analysis is available in Table 1.

Table 1: Summery of studies included in meta-analysis

First author	Location of patients	Study design and settingi	Outcome (CRS or Mortality)	Events in HIV Seropositive/ total in Cohort	Events in HIV Sero-negative/total in cohort	Cumulative incidence of Mortality and CRS (*defined by a specific parameter*) (%)
(Yang et al., 2021)	United States of America	Prospective Cohort, Cohort Collaborative (N3C) data Multiple sites	Mortality	445 / 13170	25685 / 1423452	1.81885
(Bhaskaran et al., 2021)	United Kingdom	RetrospectiveCohort, Multiple sites	Mortality	25685 / 1423452	14857 / 17255425	0.086108
(Spinelli et al., 2021)	United States of America	Matched-Case-Control, Single site	Mortality	5 / 1000	2 / 1000	0.35
(Chang et al., 2021)	United States of America	Retrospective Cohort, Single site	Mortality	1 / 10	223 / 1973	11.29602
(Patel et al., 2021)	United States of America	Retrospective Cohort, Single site	Mortality	22 / 100	1104 / 4513	24.40928

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(Durstenfeld et al., 2021)	United States of America	Prospective Cohort, Multiple sites	Mortality	36 / 220	3290 / 21308	15.44965
(Venturas et al., 2021)	South Africa	A retrospective analysis of prospectively collected data Cohort, Single	Mortality	16 / 106	64 / 276	20.94241
(Yendewa et al., 2021)	United States of America	Retrospective Cohort, Multiple sites	Mortality	49 / 1638	6798 / 295556	2.303882
(Braunstein et al., 2021)	United States of America	Retrospective Cohort, Multiple sites	Mortality	313 / 2410	16160 / 202012	8.05833
(Hadi et al., 2020)	United States of America	Prospective a propensity-matched cohort of patients without HIV Cohort, Multiple sites	Mortality	20 / 404	1585 / 48178	3.303693
(Harrison et al., 2020)	United States of America	Retrospective Cohort, Multiple	Mortality	17 / 209	1279 / 29956	4.29637
(Jassat et al., 2021)	South Africa	Retrospective Cohort, Multiple sites	Mortality	644 / 2433	6122 / 26351	23.50611
(Tesoriero et al., 2021)	United States of America	Retrospective Cohort, Multiple sites	Mortality	207 / 2781	14522 / 360738	4.051783
(Geretti et al., 2021)	United Kingdom	Prospective Cohort, Multiple sites	Mortality	30 / 81	14555 / 28460	51.10192
("Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa," 2021)	South Africa	Retrospective Cohort, Single site	Mortality	115 / 3863	510 / 17820	2.882442
(Díez et al., 2021)	Spain	Retrospective Cohort, Multiple sites	Mortality	2 / 21	12 / 105	11.11111
(Karmen-Tuohy et al., 2020)	United States of America	Retrospective Cohort, Multiple sites	Mortality	6 / 21	10 / 42	25.39683

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(Karim et al., 2021)	South Africa	longitudinal observational cohort study	Mortality	13/93	8 / 143	8.898305
(Sigel et al., 2020)	United States of America	Prospective Cohort Study, Single	Mortality	18/88	81/405	20.08114
(Miyashita & Kuno, 2021)	United States of America	Retrospective Cohort, Multiple sites	Mortality	23/161	1235/8751	24.40928
(M. J. Lee et al., 2022)	United Kingdom	Prospective Cohort Study, Multiple sites	Mortality	0/17	5/50	7.462687
(Nagarakanti et al., 2021)	ISRAEL	Retrospective Cohort, Single Site	Mortality	3/23	153/254	56.31769
Cumulative COVID-19 Mortality, all studies (%)						110270 / 19783097 (0.557395 %)
(Braunstein et al., 2021)	United States of America	Retrospective Cohort, Multiple	CRS	124 / 2419	6060 / 202012	3.024982
(Hadi et al., 2020)	United States of America	Prospective Cohort, Multiple	CRS	78 / 404	5264 / 49763	10.64843
(Díez et al., 2021)	Spain	Retrospective Cohort, Multiple	CRS	2 / 21	24 / 105	20.63492
(Karmen-Tuohy et al., 2020)	United States of America	Retrospective Cohort, Multiple	CRS	6 / 21	10 / 42	25.39683
(Yang et al., 2021)	United States of America	Cohort, Multiple	CRS	475 / 13158	24579 / 1420751	1.747252
(Chang et al., 2021)	United States of America	Retrospective Cohort, Single	CRS	5 / 10	494 / 1976	25.12588
(Durstenfeld et al., 2021)	United States of America	Prospective Cohort, Multiple	CRS	59 / 220	6545 / 21319	30.66066

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(Yendewa et al., 2021)	United States of America	Retrospective Cohort, Multiple	CRS	57 / 1629	4297 / 286467	1.511302
(Patel et al., 2021)	United States of America	Retrospective Cohort, Single	CRS	21 / 100	631 / 4513	14.13397
(Nagarakanti et al., 2021)	ISRAEL	Retrospective Cohort, Single	CRS	2 / 23	103 / 254	37.90614
(M. J. Lee et al., 2022)	United Kingdom	A matched retrospective multi-Centre analysis	CRS	8 / 17	19 / 50	40.29851
Cumulative % of studies reporting COVID-19 CRS						48863 / 2005274 (2.4367%)

Quality of evidence and risk of bias assessment

Included in Table 2 is the Newcastle-Ottawa scale for quality assessment and risk of bias. We assessed the quality of the included studies based on a modified version of the Newcastle-Ottawa Scale (NoS) which consists of 8 items with 3 subscales, and the total maximum score of these 3 subsets is 9. We considered a study which scored ≥7 a high-quality since a standard criterion for what constitutes a high-quality study has not yet been universally established. The twenty-two studies (with eleven of them having both CRS and mortality measurements making a total of thirty-three) assessed by us generated a mean value of 6.59 and as a result, overall quality was found to be moderate (NOS score min: 5, max: 8).

There were common limitations among the included studies. Most were retrospective analyses of routinely collected clinical data, meaning identification of COVID-19 cases was not systematic and depended on the local approach to screening and diagnosis with only five prospective cohort studies. This may have varied over time and between settings, and may also differ between PLWH and the general population but in the case of this study though, the studies included both HIV-seropositive and seronegative populations' data. Across all studies, the numbers of HIV-seropositive and COVID-19 infection were relatively low.

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Table 2: Newcastle-Ottawa scale for quality assessment and risk of bias.

Study Author	Case selection (max. 4)	Comparability (max. 2)	Exposure/outcome (max. 3)	Total score
(Yang et al., 2021)	***	**	**	7
(Bhaskaran et al., 2021)	***	**	*	6
(Spinelli et al., 2021)	****	**	**	8
(Chang et al., 2021)	***	*	**	6
(Patel et al., 2021)	****	**	**	8
(Durstenfeld et al., 2021)	***	**	***	7
(Venturas et al., 2021)	***	*	**	6
(Yendewa et al., 2021)	***	**	**	7
(Braunstein et al., 2021)	***	**	**	7
(Hadi et al., 2020)	***	**	*	6
(Harrison et al., 2020)	**	*	*	4
(Jassat et al., 2021)	***	**	**	7
(Tesoriero et al., 2021)	***	**	**	7
(Geretti et al., 2021)	**	**	***	7

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("Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa," 2021)	**	*	**	5
(Díez et al., 2021)	***	**	**	6
(Karmen-Tuohy et al., 2020)	***	*	***	7
(Karim et al., 2021)	***	*	***	7
(Sigel et al., 2020)	***	**	***	8
(Miyashita & Kuno, 2021)	***	*	**	6
(M. J. Lee et al., 2022)	***	*	***	7
(Nagarakanti et al., 2021)	***	*	**	6

Cumulative analyses of HIV-serostatus and the risk of COVID-19 related mortality

In this meta-analysis of the twenty-two studies (Bhaskaran et al., 2021; Braunstein et al., 2021; Chang et al., 2021; Díez et al., 2021; Durstenfeld et al., 2021; Geretti et al., 2021; Hadi et al., 2020; Harrison et al., 2020; Jassat et al., 2021; Karim et al., 2021; Karmen-Tuohy et al., 2020; M. J. Lee et al., 2022; Miyashita & Kuno, 2021; Nagarakanti et al., 2021; Patel et al., 2021; "Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa," 2021; Sigel et al., 2020; Spinelli et al., 2021; Tesoriero et al., 2021; Venturas et al., 2021; Yang et al., 2021; Yendewa et al., 2021) that accounted for COVID-19 mortality as the outcome, the risk for HIV-seropositive persons was at an excess of about 20% with a significant difference between the studies [Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 168.59$, df = 21 ($P < 0.00001$); $I^2 = 88\%$] [Risk ratio = 1.19, 95% confidence interval (CI) 1.02 -1.39] (Fig. 2). The prediction interval (Fig 3) demonstrates the true effects size in 95% of all the comparable

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populations falling between 0.64 to 2.22 demonstrating that, in some populations, the risk of COVID-19 mortality due to HIV infection is at one extreme of effect as low as 0.64 and as high as 2.22. This diversity informed the need to account for possible moderators. Thirteen of these studies were conducted in the united states of America (Braunstein et al., 2021; Chang et al., 2021; Durstenfeld et al., 2021; Hadi et al., 2020; Harrison et al., 2020; Karmen-Tuohy et al., 2020; Miyashita & Kuno, 2021; Patel et al., 2021; Sigel et al., 2020; Spinelli et al., 2021; Tesoriero et al., 2021; Yang et al., 2021; Yendewa et al., 2021)and the rest from other parts of the globe especially the United Kingdom and South Africa. A precision funnel plot for publication bias revealed considerable true heterogeneity between all the pooled studies (I^2 = 88 %; P < 0.00001) (Fig 4). The egger's regression test indicated no publication bias (intercept = -1.10498, 95% confidence interval (-2.85566, 0.64570), with t=1.31660, df=20 and 1-tailed P = 0.10143). A sensitivity analysis was performed to explore the impact of excluding or including studies in meta-analysis based on sample size, methodological quality and variance on the heterogeneity obtained (I^2 = 88 %). Elimination of six studies (Braunstein et al., 2021; Geretti et al., 2021; Harrison et al., 2020; Nagarakanti et al., 2021; Tesoriero et al., 2021; Yang et al., 2021) which were the major contributors of heterogeneity significantly reduced it [Heterogeneity: Tau^2 = 0.00; Chi^2 = 15.90, df = 15 (P = 0.39); I^2 = 6%] (Fig 5). A funnel plot of precision (Fig 6), with egger's test (intercept (= -0.16647, 95% confidence interval (-0.92034, 0.58740), with t=0.47361, df=14 and 1-tailed P = 0.32154) further indicating no publication bias.

Figure 2: A forest plot of HIV-serostatus and the risk of COVID-19 related mortality

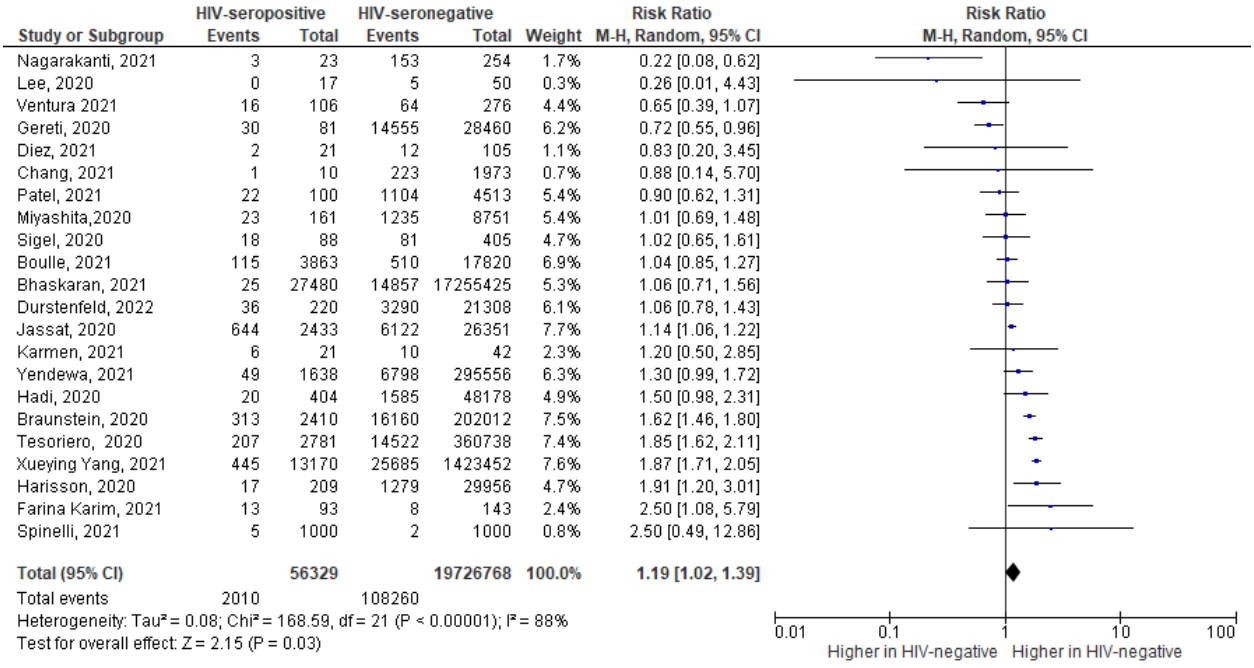

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Figure 3: The prediction interval for the true effect size in 95% comparable population

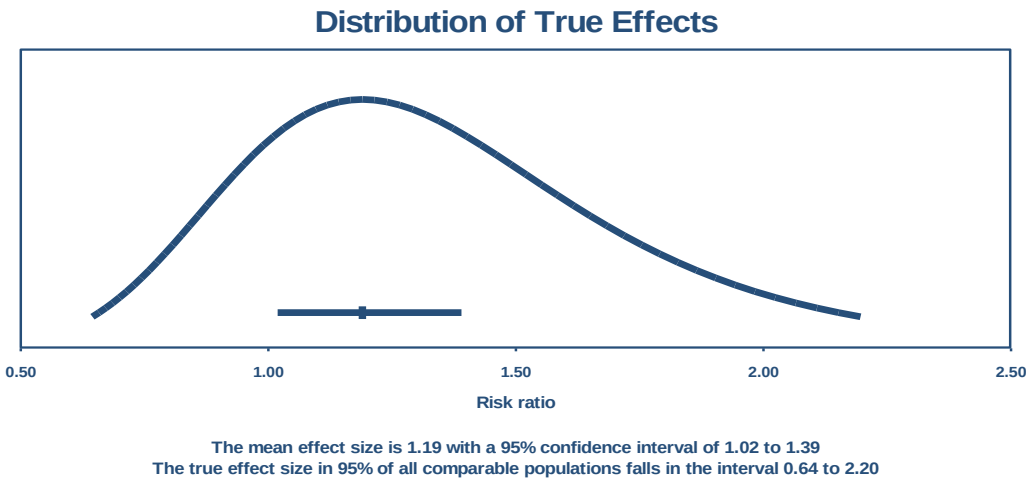

Figure 4: A precision funnel plot for publication bias

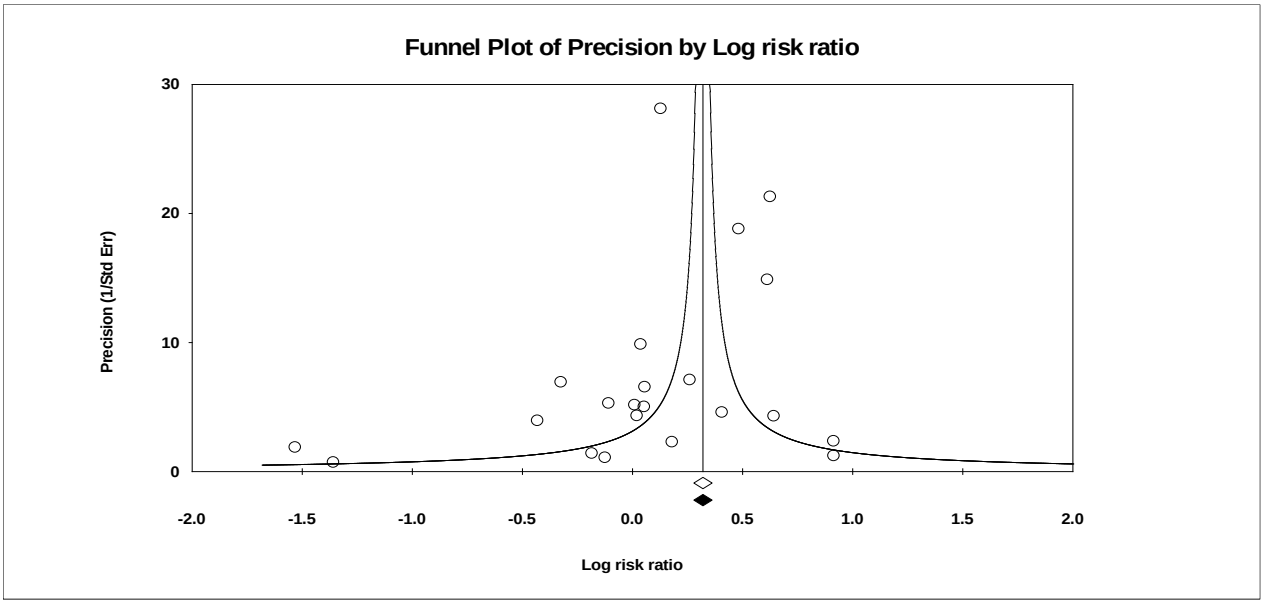

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Figure 5: A sensitivity analysis to account for the heterogeneity

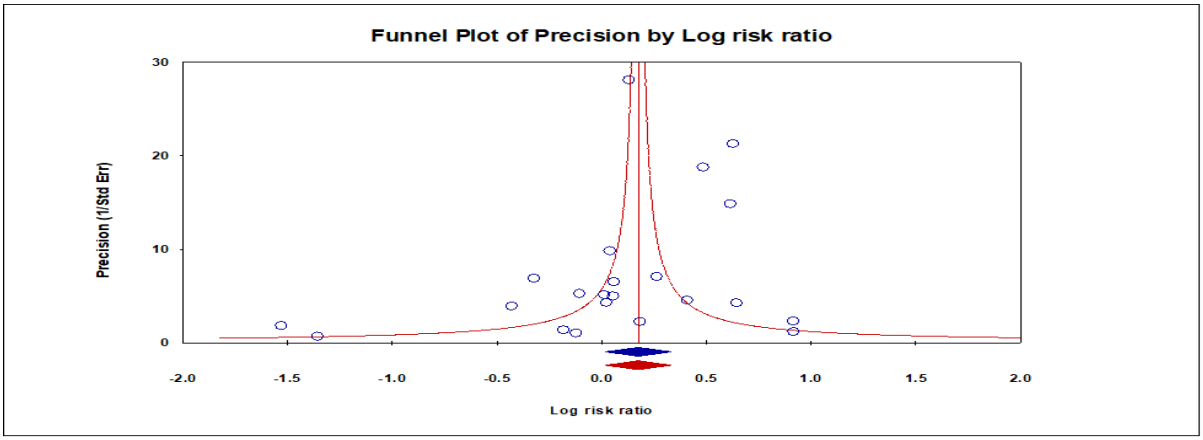
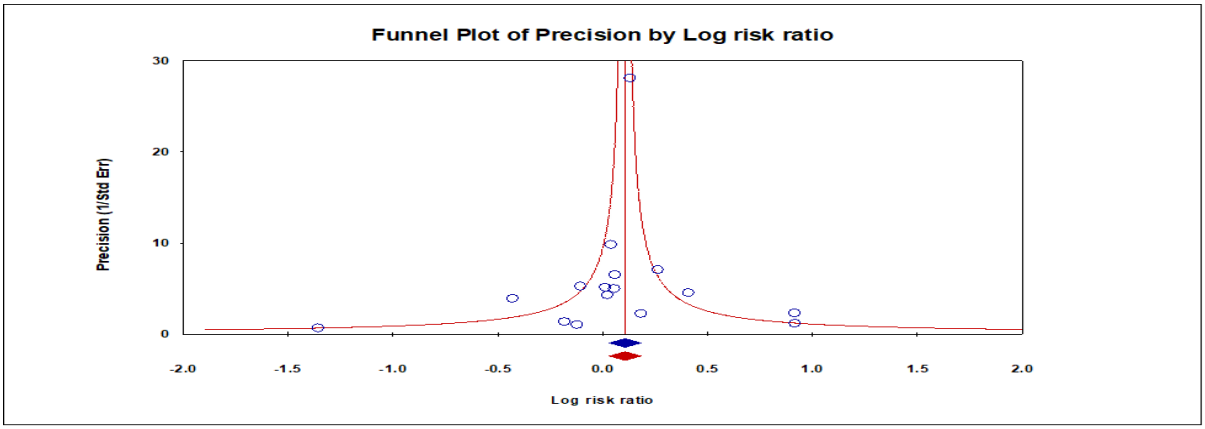


Figure 6: A funnel plot of precision with egger's test for publication bias



Heterogeneity Investigation on HIV-serostatus and the risk of COVID-19 related mortality

We conducted a subgroup analysis on the nature of a study setting or number of sites which showed that, multiple Centre studies had a higher risk for COVID-19 mortality with HIV seropositive status [Risk ratio = 1.31, 95% confidence interval (CI) 1.09 -1.56] (P = 0.003), compared to single Centre studies (P = 0.67) (Fig 7). Independent sensitivity analysis clearly revealed, single Centre studies majorly contributed to the heterogeneity after the only four studies conducted in multiple sites (Braunstein et al., 2021; Geretti et al., 2021; Tesoriero et al., 2021; Yang et al., 2021) were removed from the analysis with non in single Centre studies reducing total heterogeneity (I^2= 40.5%) Heterogeneity: Tau^2 = 0.00; Chi^2 = 9.13, df = 9 (P = 0.43); I^2 = 1% and Heterogeneity: Tau^2 = 0.09; Chi^2 = 17.09, df = 7 (P = 0.02); I^2 = 59% respectively (Fig 9).Analysis by study design grouping did not show any statistical significance with HIV seropositive status with all the three clusters (prospective, retrospective cohorts and case control) (P < 0.05) (Fig 10). By region, HIV

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infection had a higher risk of COVID-19 mortality than those without HIV infection in America (RR=1.422, 95% CI 1.233–1.639), South Africa from 4 studies (RR=1.123, 95% CI 1.052–1.198) but not in the United Kingdom (RR=0.819, 95% CI 0.651–1.1030), Spain and Israel (Fig 7).

Figure 7: Subgroup analysis on the nature of a study setting or number of sites for heterogeneity investigation

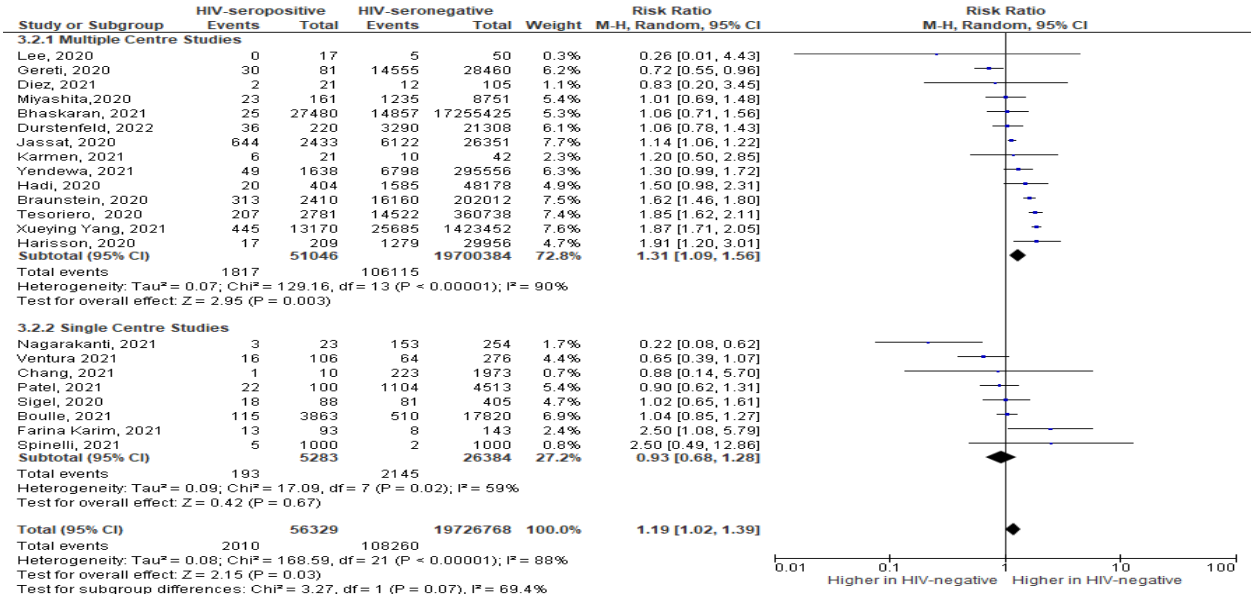

Figure 8: Independent sensitivity analysis on study setting

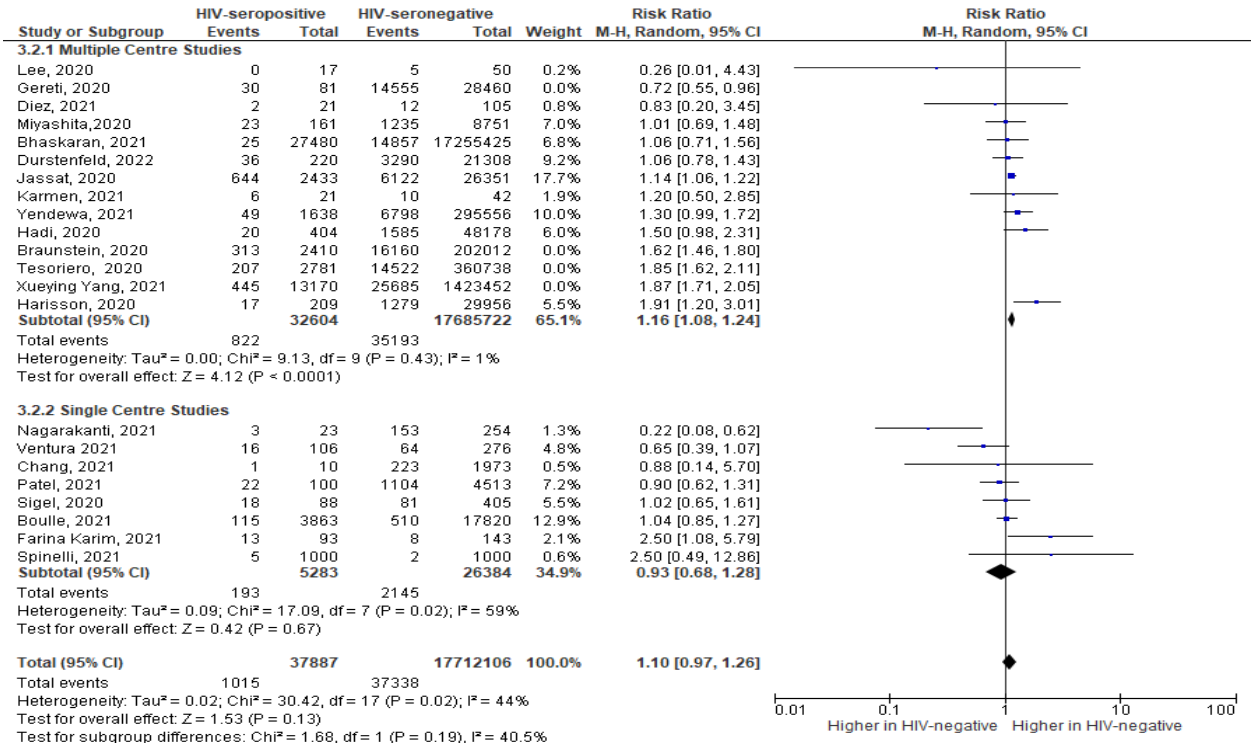

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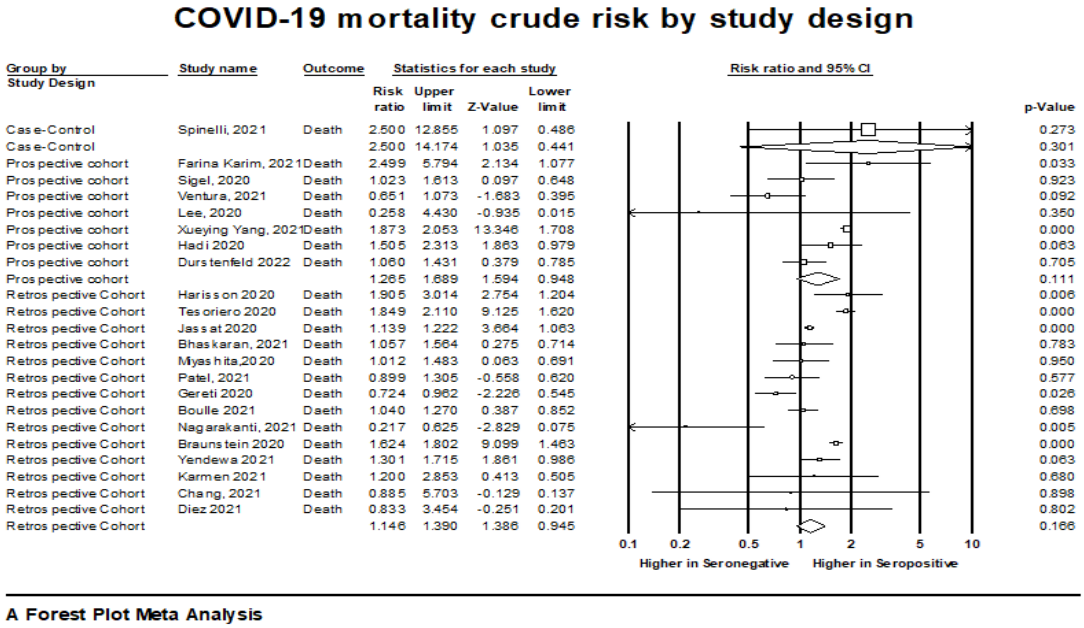
Figure 9: Analysis by study design grouping for heterogeneity investigation



A Forest Plot Meta Analysis

Figure 10: Heterogeneity Investigation by Study region

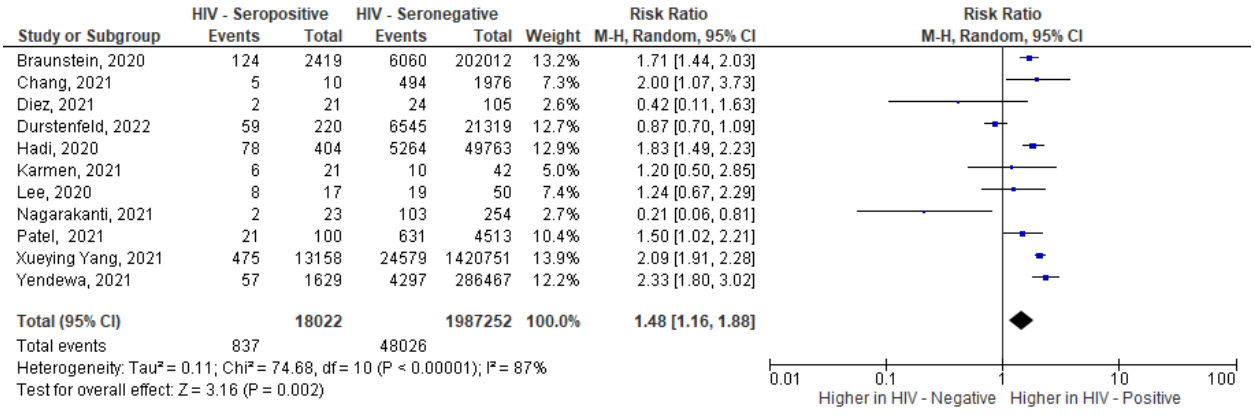


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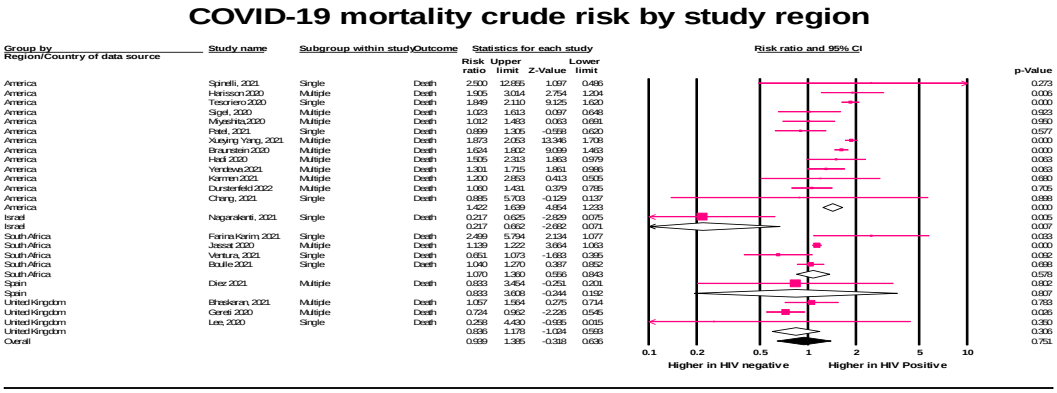
Figure 11: Risk of CRS with HIV Infection



Risk of Cytokine Release Syndrome with HIV Infection

In eleven of the twenty-two studies (Braunstein et al., 2021; Chang et al., 2021; Díez et al., 2021; Durstenfeld et al., 2021; Hadi et al., 2020; Karmen-Tuohy et al., 2020; M. J. Lee et al., 2022; Nagarakanti et al., 2021; Patel et al., 2021; Yang et al., 2021; Yendewa et al., 2021), a total of 48,863 (2.4%) patients experienced cytokine release syndrome (CRS). The analysis demonstrated about 50% increased risk of CRS with HIV sero-positive status [Risk ratio = 1.48, 95% confidence interval (CI) [1.16, 1.88) (P=0.002), with a high heterogeneity (I^2 = 87%) (Fig 11). The prediction interval (Fig 12) demonstrates the true effects size in 95% of all the comparable populations falling between 0.67 to 3.29 demonstrating that, in some populations, the risk of COVID-19 cytokine release syndrome due to HIV infection is at one extreme of effect as low as 0.67 and as high as 3.29, thus necessitated accounting for any possible covariates. A precision funnel plot for publication bias revealed considerable true heterogeneity between all the pooled studies (I^2 = 87 %; P < 0.00001) (X). The egger's regression test indicated a publication bias (intercept = -2.23097, 95% confidence interval (-4.76459, 0.30266), with t=1.99193, df=9. The 1-tailed P = 0.03878). Sensitivity analysis by removing five studies (Díez et al., 2021; Durstenfeld et al., 2021; Nagarakanti et al., 2021; Yang et al., 2021; Yendewa et al., 2021) which caused major heterogeneity, explicitly showed a risk of CRS with HIV seropositive [Risk ratio = 1.71, 95% confidence interval (CI) [1.51, 1.92) (P=0.00001) (I^2 = 0%)] (Fig 13), with no-publication bias as revealed by funnel precision plot in a total of 12720 (4.9%).

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Figure 12: The prediction interval for the true effect size in 95% comparable population

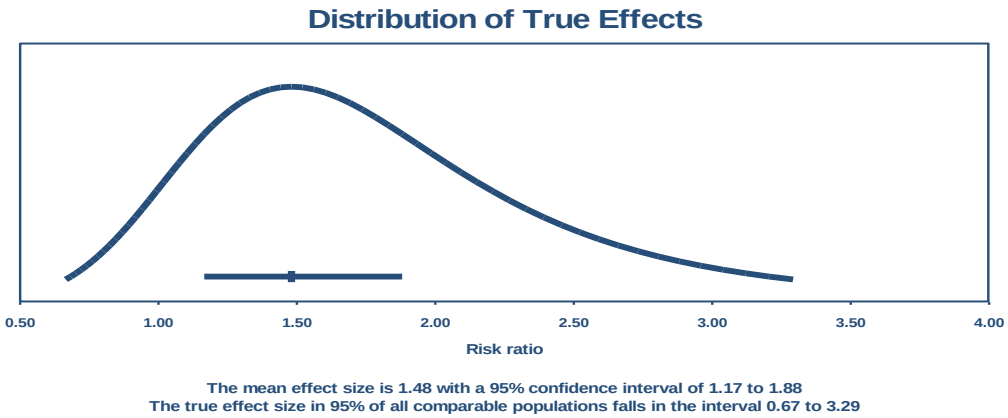
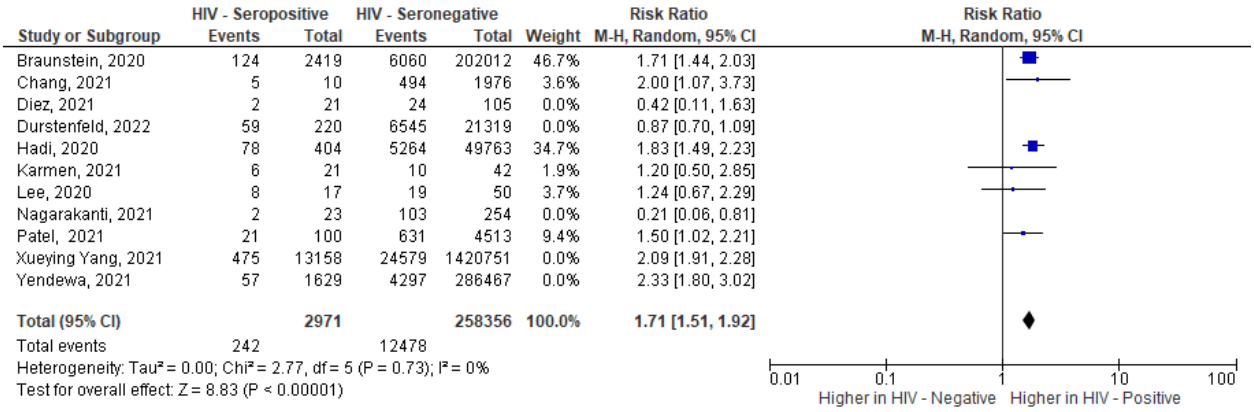


Figure 13: Sensitivity analysis on the risk of CRS with HIV seropositive



Sub-group and sensitivity analysis on CRS parameter by HIV- serostatus

Cytokine release syndrome, known as a cytokine storm – is one of the major hallmarks of severe COVID-19 illness that leads to lung, other organs damage and is also directly related to the severity of COVID-19 ARDS (Huang et al., 2020), a major life-threatening complication leading to respiratory failure and the need for mechanical ventilation (Wang et al., 2020).In the context of this study, CRS was implicated by critical care services (ICU) admission in four studies (Braunstein et al., 2021; Chang et al., 2021; Karmen-Tuohy et al., 2020; Yendewa et al., 2021), mechanical ventilation in three studies (Díez et al., 2021; M. J. Lee et al., 2022; Nagarakanti et al., 2021), increased intubation rates in one study (Patel et al., 2021), elevated interleukin - 6 in one study (Durstenfeld et al., 2021), clinical severity of COVID-19 in one study (Yang et al., 2021), needed inpatient services (Hadi et al., 2020). On subgroup analysis, HIV seropositive status had a

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risk on ICU/critical care service [Risk ratio = 1.90, 95% confidence interval (CI) (1.52, 2.37) (P=0.00001) (I^2 = 40%)] and general inpatient services [Risk ratio = 1.83, 95% confidence interval (CI) (1.49, 2.23) (P=0.00001) but not with elevated interleukin-6 (IL-6) (P=0.23) and mechanical ventilation [Risk ratio = 1.14, 95% confidence interval (CI) (0.68, 1.94) (P=0.62) (I^2 = 81%)]. Test for subgroup differences showed a high heterogeneity (I^2 = 90.6%) (Fig 15). A sensitivity analysis on subgroups clearly demonstrated that, HIV infection has a risk on CRS indicated by ICU admission (P=0.00001) (I^2 = 0%)] after removing one study (Yendewa et al., 2021) and mechanical ventilation (P=0.04) (I^2 = 0%)] after removing three studies causing major between study differences (Díez et al., 2021; Nagarakanti et al., 2021; Yang et al., 2021) (Fig 16).

Figure 14: Sub-group analysis on CRS parameter by HIV- serostatus

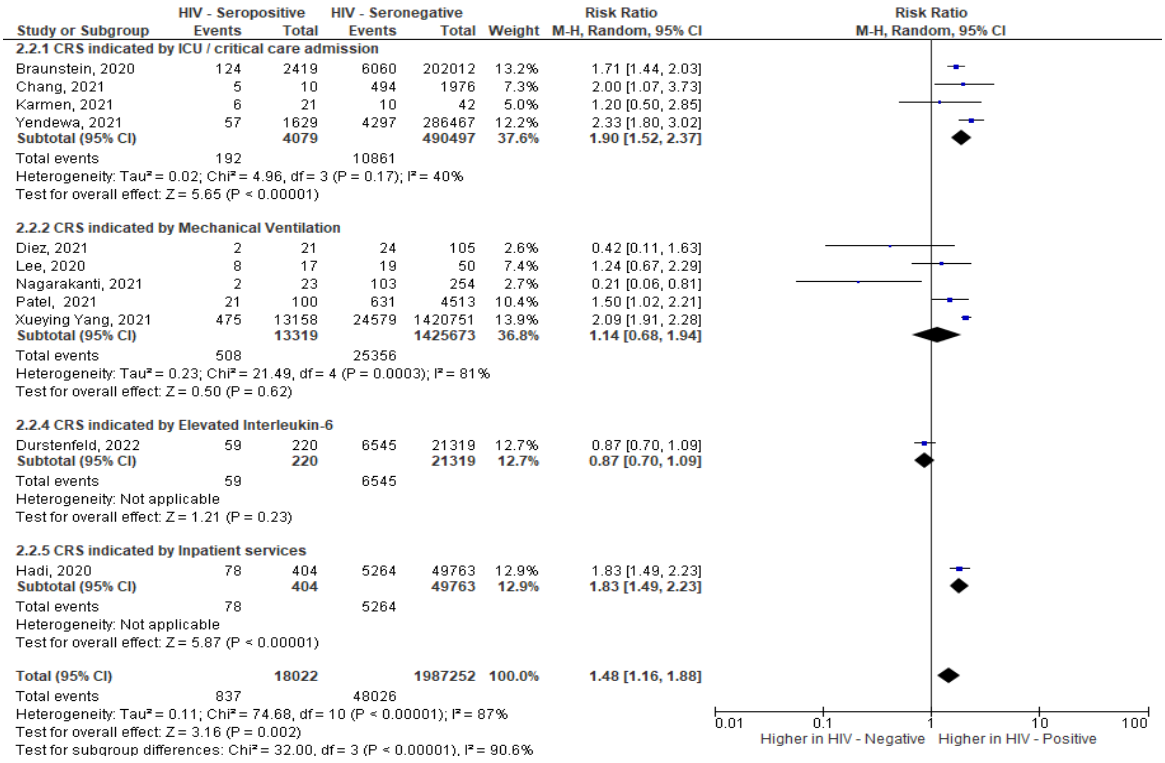

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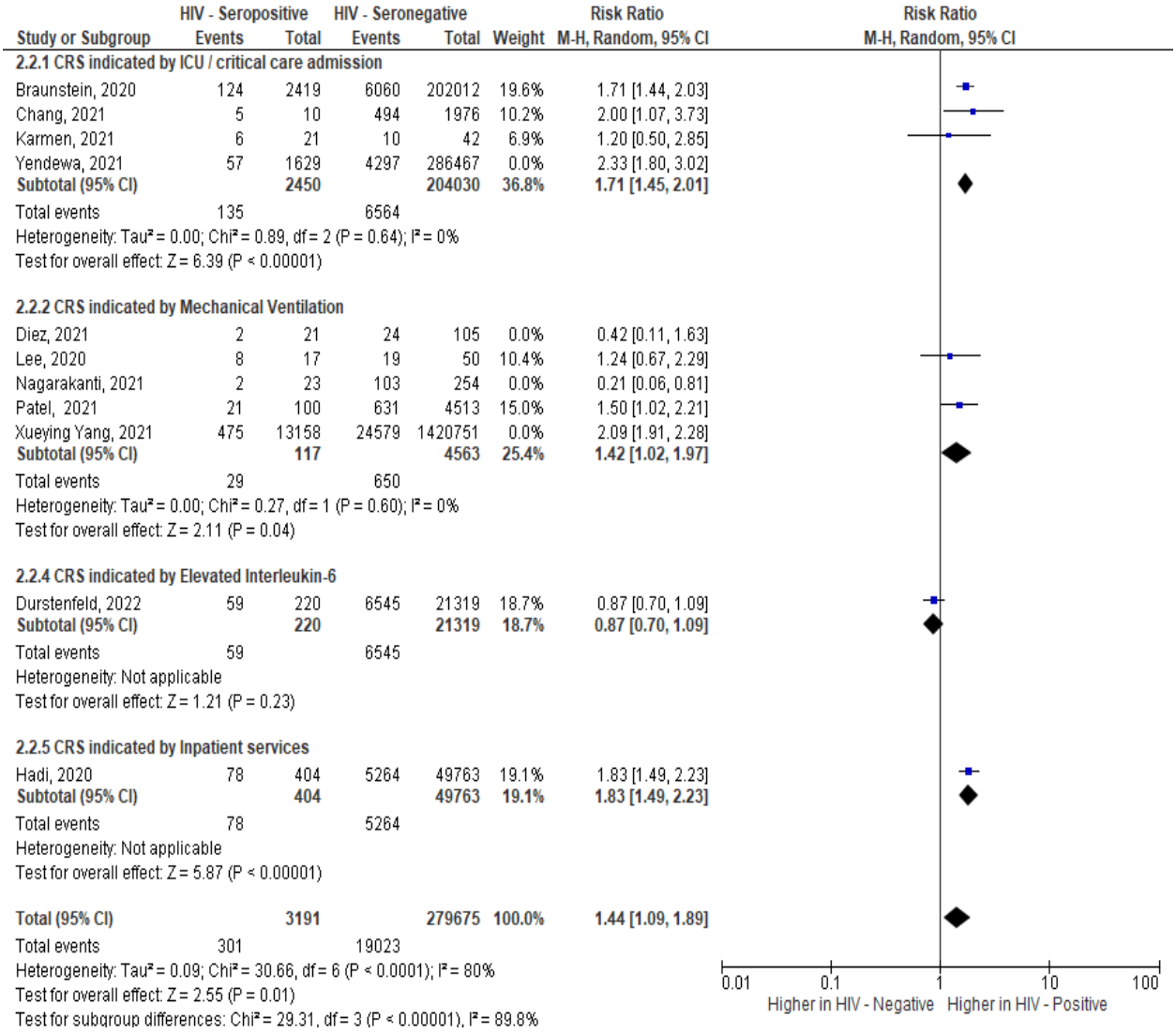
Figure 15: Sensitivity analysis on CRS parameter by HIV- serostatus



Meta-regression for possible moderators of coronavirus disease 2019 CRS and mortality with HIV-serostatus

The values of I^2 in studies accounting for COVID-19-CRS and COVID-19 related mortality was 87 and 88 respectively, which means that in both, over 80% of the observed variance came from real differences between studies and, as such, can potentially be explained by study-level covariates. To ascertain this, the analysis assessed the possible influence of pre-determined moderators. On the test of the individual covariate, the year a study was conducted predicted CRS (Q=6.21, df=2, P=0.0447) for 2020 and 2021, contrary to 2022 (P = 0.5839) (R^2 = 0.55) (Supp. File 1), study setting (single or multiple) was insignificant (P = 0.4621) (R^2 = 0.00) (Supp. File

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2), and the region / country of study population (Q = 5.75, df = 1, p = 0.0165) (R^2 = 0.11) (Supp. File 3). The combined impact of all covariates in the model explained at least some of the variance in effect size (Q = 20.93, df = 4, p = 0.0003), and the proportion of variance explained by covariates on comparing the model with and without the covariates was very significant (Tau^2 = 0.1067, Tau = 0.3266, I^2 = 86.5%, Q = 73.99, df = 10, P = 0.0000) (R^2 = 0.78) (Supp. File 4).

Moderation analysis for studies detailing COVID-19 mortality revealed no association with the nature of study site (single or multiple) (Q = 3.58, df = 1, p = 0.0584) (R^2 = 0.09) (Supp. File 5). The region / country of study population was associated with COVID-19 mortality (Q = 19.71, df = 4, P = 0.0006) (R^2 = 0.60) (Supp. File 6)., while the year of the study did not independently predict COVID-19 mortality (Q = 0.70, df = 2, P = 0.7043) (Supp. File 7). The combined impact of all covariates in the model explained at least some of the variance in effect size (Q = 28.84, df = 7, P = 0.0002). Further, the proportion of variance explained by covariates on comparing the model with and without the covariates was significant (Tau^2 = 0.0834, Tau = 0.2887, I^2 = 87.5%, Q = 168.02, df = 21, p = 0.0000) (R^2 = 0.67) (Supp. File 8).

Discussion

The purpose of this study was to systematically review and conduct meta-analysis using the most current data from studies on the incidence of COVID-19 related cytokine release syndrome and mortality relative to HIV serostatus, alongside the associated covariates via meta-regression. Further, it aimed at ascertaining the parameters defining cytokine release syndrome predicted by HIV infection and estimate the combined proportion effect of all covariate in studies detailing CRS and mortality.

To our knowledge, this is one unique meta-analysis amongst peer-reviewed literature assessing the risk of HIV on the incidence COVID -19 related mortality by further investigating the cytokine release syndrome which is highly associated with the ultimate death in COVID-19 infection (Que et al., 2022). Principally, the present meta - analysis found that HIV seropositive status portrays an increased risk for COVID-19 related mortality at approximately twenty percent in comparison to HIV seronegative counterpart population. Similarly, this HIV seropositive status became even more significant in predicting cytokine release syndrome by over fifty percent. Following sensitivity analysis of good-quality studies only, risk for both COVID-19 related mortality and cytokine release syndrome were more significant. Overall, there was a high degree of heterogeneity amongst studies detailing the COVID-19 related cytokine release syndrome and mortality, which greatly reduced following sensitivity analysis. The two outcomes remained significant on inclusion of only good-quality studies suggesting these analyses represent true effects as per the generated prediction intervals. A high level of heterogeneity was only observed with inclusion of few studies in assessing the effect of HIV on either COVID-19 related cytokine release syndrome or mortality, likely to substantial inter-study variation. The egger's regression test indicated low impact of publication bias on our results.

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The cumulative incidence of mortality with HIV seropositive status was at an average excess of 20% (RR=1.197), this was similar to a recent meta-analysis which reported almost same results in odds ratio suggesting that, people living with HIV infection had a higher risk of mortality from COVID-19 than those without HIV infection (OR=1.252, 95% CI 1.027–1.524)(Dong et al., 2021). Among the COVID-19 patients with HIV infection, the mortality rate due to COVID-19 was 3.6 %, and among the COVID-19 patients without HIV infection, the mortality rate due to COVID-19 was 0.5% this is commensurate with a meta-analysis findings that showed a 3.44% and 0.42% respectively(Dong et al., 2021), while with COVID-19 related cytokine release syndrome, the cumulative incidence of 4.6 % and 2.4 in HIV seropositive and seronegative patients respectively in this study that distinctively demonstrates a higher incidence with HIV infection similar to some study findings (Karmen-Tuohy et al., 2020; Peng et al., 2020)

Our finding that HIV infection is associated with increased COVID-19 related mortality further validates previous research findings from several smaller meta-analyses and primary studies (Davies, 2020; Dong et al., 2021; Mellor et al., 2021; Ssentongo et al., 2021) in a most recent data from a larger patient population, achieved through a more rigorous, prospectively registered methodology. The finding that HIV clearly predicts more significantly the experience of cytokine release syndrome, also confirms previous findings from primary studies (Cabello et al., 2021; Ho et al., 2020; Hoffmann et al., 2021; N. Liu et al., 2021). The association of both cytokine release syndrome and the COVID-19 mortality with HIV seropositive status in the context of this current findings is biologically plausible as in normal circumstances, CRS is linked with ARDS which leads to COVID-severity prior to death(Hu et al., 2021).

Alongside other co-morbidities, HIV has been found to advance the clinical severity of COVID-19 culminating to death(Essien et al., 2021). In addition, HIV infection increases severity from both bacterial and viral infections through the induction of mechanical and structural changes in the respiratory tract and alteration of cell and humoral-mediated immune responses(Eybpoosh et al., 2021). In the context of respiratory viruses, HIV infection has been reported to cause increased hospital and ICU admissions with influenza infection, greater severity with respiratory syncytial virus bronchiolitis and increased mortality with viral pneumonia(Garbino et al., 2008).

Analysis of HIV infection to the risk of COVID-19 mortality by the study setting showed significance with multiple Centre studies [RR = 1.305, 95% CI 1.092 -1.559] (P = 0.003) an outcome similar to a multicenter meta-analysis (Dandachi et al., 2021; Feng et al., 2020; D. Liu et al., 2020). With hypothesis that studies in our meta-analysis stemmed from one similar region with its own overall true effect on sub-subgroup analysis, fixed effect model was used and people with HIV infection had a higher risk of COVID-19 mortality than those without HIV infection in the United States (RR=1.422, 95% CI 1.233–1.639). A similar risk was also achieved in South Africa from 4 studies, our subgroup analysis found that people living with HIV infection also had a higher risk of COVID-19 mortality than those without HIV infection (RR=1.123, 95% CI 1.052–1.198). However, no significant association between HIV infection and the mortality risk of COVID-19 was found in the United Kingdom (RR=0.819, 95% CI 0.651–1.1030). This finding is very consistent with another meta-analysis which showed; USA (OR=1.520, 95% CI 1.252–1.845),

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South Africa (OR=1.122, 95% CI 1.032–1.220) and United Kingdom (OR=0.878, 95% CI 0.657–1.174). The reason for this difference might be related to SARS-CoV-2 virus mutations in different countries (Nagy et al., 2021; WHO, 2021). Further, access and affordability of health services in different countries could also affect(Amimo et al., 2021; Singh et al., 2021).

In regards to cytokine release syndrome, its parameters were critical care services (ICU) admission, mechanical ventilation, increased intubation rates, elevated interleukin - 6, clinical severity of COVID-19 and inpatient services. These trends were similar to other studies which demonstrated that HIV infection is associated with ICU admission, mechanical ventilation (Karmen-Tuohy et al., 2020), intubation (Nishikimi et al., 2021; Wadman et al., 2020), mechanical ventilation (Grasselli et al., 2020), interleukin-6 (Henry, De Oliveira, et al., 2020; Sayah et al., 2021; Shekhawat et al., 2021; Ulhaq & Soraya, 2020), clinical severity of COVID-19 inpatient services(Henry, Cheruiyot, et al., 2020; Moutchia et al., 2020). In this current study, mechanical ventilation and ICU admission clearly showed an association with HIV sero-positive status with similar trend of increased risk (Karmen-Tuohy et al., 2020) but this is contrary to another study which found no difference in HIV infection and non-infection (Braunstein et al., 2021; Dandachi et al., 2021; Nagarakanti et al., 2021). On the contrary (Geretti et al., 2021) reported no differences between HIV-negative patients and PLWH in the risk of admission to ICU.

Meta-regression analysis showed that, the year (2020, 2021 and not 2022) and the region a study was conducted were associated with COVID-19 related cytokine release syndrome and mortality ($P<0.05$), unlike the study setting sites. This trend has been explained by the data on cumulative mortality globally where the case fatality rates were higher in 2020 and in a reducing trajectory in 2021 and a flattening curve in 2022 (Horwitz et al., 2021; James & Menzies, 2021). Generally, the combined impact of all covariates in the model explained at least some of the variance in COVID-19 related cytokine storm and mortality, similar to existing findings in countries and region related factors (Asfahan et al., 2020; Hashim et al., 2020). Further studies show that, patients located in America experienced higher mortality rates from COVID-19 infection (aOR, 7.441; 95% CI, 3.546-15.617) (Albitar et al., 2020), which in the context of this study, formed the largest population from 13 of all the twenty two studies.

Conclusion

Our study indicated a consistent and statistically significant effect of HIV on COVID-19 related cytokine release syndrome and mortality even after heterogeneity investigation all in random effects model with egger's regression test indicating no major publication bias. ICU admission, mechanical ventilation and intubation were the key CRS parameters predicted by HIV infection in COVID-19 patients. With a fixed effect model, region of study greatly influenced COVID-19 related mortality alongside HIV infection. The proportion of variance explained by covariates was significant with the year and region of study being the major co-variates associated with both COVID-19 related CRS and mortality. Public health interventions should be carefully tailored and implemented on HIV infected persons with COVID-19 to reduce the risk of severity associated with cytokine release syndrome and mortality. An intensive and regular focus is required to detect early occurrences of clinical conditions in similar viral pandemics or COVID-19 resurgence.

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Author contributions: **J.M.K.** conceived the study. **MJ.** performed the literature search. **J.M.K.** and **F.M.W.** contributed equally to the screening and qualitative analysis, with support from J.K.O. and **M.J**. **J.M.K.** performed the meta-analysis. **J.M.K.** and **J.K.O.** wrote the first draft of the article. **J.M.K., J.K.O., MJ., F.M.W.,** critically reviewed and edited the article and consented to publication.

Conflicts of interest

There are no conflicts of interest.

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