Human immunodeficiency virus and mortality from coronavirus disease 2019: A systematic review and meta-analysis

Introduction

At the end of December 2019, the first cases of a newly discovered acute respiratory illness named coronavirus disease 2019 (COVID-19) were reported in Wuhan, China. By January 2021, >88.3 million infections and 1.9 million deaths worldwide had been reported. The COVID-19 disease has various clinical manifestations, ranging from mild symptoms such as fever, cough and anosmia to life-threatening conditions including shock, respiratory failure, arrhythmia, overwhelming sepsis and neurological impairment. Meta-analyses have identified several comorbidities, medicines and abnormal laboratory test results associated with a poor outcome. Persons living with human immunodeficiency virus (PLWH) are at-risk population in view of their impaired immunity. This impairment increases susceptibility to tuberculosis, opportunistic infections and cancer. In 2019, an estimated 38 million people globally were living with HIV; 1.7 million new (incident) infections and 690 000 deaths were reported that year. Human immunodeficiency virus–infected individuals with immune suppression (impaired T-cell and humoral responses), unsuppressed HIV RNA viral load (untreated or with treatment failure) and comorbid disease (diabetes mellitus, cardiovascular and renal impairment) may be at risk of the life-threatening forms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, this hypothesis requires additional evidence. Results from observational studies have been conflicting. This meta-analysis aims to explore the impact of HIV and SARS-CoV-2 co-infection on the mortality outcomes of COVID-19 based on available observational studies.
Research methods and design

Eligibility criteria

This is a systematic review and meta-analysis of published observational studies. Articles were selected if they fulfilled the following entry criteria: compliance with the PICO framework, namely P = confirmed positive COVID-19 patients, I = patients living with HIV, C = HIV-uninfected persons and O = mortality in COVID-19-confirmed patients not attributable to unrelated conditions such as trauma. The studies included were randomised clinical trials, cohort, case-cohort and crossover design, and the full-text paper had to be available and to have been published. Excluded studies included non-original research such as review articles, letters or commentaries; case reports; studies in a language other than English; studies of children and youths <18 years of age and pregnant women.

Search strategy and study selection

A systematic search of PubMed and Europe PMC provided many papers. Additional articles were located by analysing the papers cited by the authors of the identified studies. The search terms included ‘HIV’ or ‘human immunodeficiency virus’ or ‘immunocompromised’ or ‘immune-deficient’ or ‘AIDS’ or ‘acquired immunodeficiency syndrome’ and ‘SARS-CoV-2’ or ‘coronavirus disease 2019’ or ‘COVID-19’ or ‘novel coronavirus’ or ‘nCoV’. The selected time-range included 01 December 2019 to 19 January 2021. Only English-language articles were evaluated. Details of the search strategy are listed in Table 1. Studies of HIV and SARS-CoV-2 co-infection with a valid definition of ‘mortality’ were included. The search strategy is presented in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.

The initial investigation located 10 733 studies. After the removal of duplicates, 8,653 records remained. A further 8,585 studies were excluded after screening of the titles and abstracts failed to match with the inclusion and exclusion criteria. Of the 68 full-text articles evaluated for eligibility, 22 that lacked control or comparator groups were excluded, and 15 more were excluded because they lacked outcomes pertinent to our study. Three articles that were not in the English language were rejected. The final meta-analysis included 28 observational studies that reported on 18 255 040 COVID-19-infected persons, of whom 48 703 were co-infected with both HIV and SARS-CoV-2 (see Figure 1). Of the included articles, 25 were retrospective and 3 were prospective (see Table 2).

Data extraction and quality assessment

The study’s outcome of interest was mortality from COVID-19. This was defined as the number of patients with COVID-19 whose death could not be attributed to a cause other than COVID-19. Two authors performed the data extraction. Relevant demographic, laboratory and clinical information was recorded on a dataform: age, gender, ethnicity, the number of PLWH, the number of patients with a CD4 cell count of <200 cells/μL, the use of antiretroviral therapy (ART) and the mortality outcomes of both HIV-infected and HIV-uninfected participants. Two authors independently assessed the quality of each study using the Newcastle–Ottawa Scale. The selection, comparability and outcome of each study were assigned a score from zero to nine. Studies with scores of ≥7 were considered to be of good quality (see Table 3). All included studies were rated ‘good’. In summary, all studies were deemed fit to be included in the meta-analysis.

Statistical analysis

Review Manager version 5.4 (Cochrane Collaboration) and the Comprehensive Meta-Analysis version 3 software were used in the meta-analysis, and Mantel-Haenszel’s formula gave odds ratios (ORs) and 95% confidence intervals (CIs). The heterogeneity was assessed using the I² statistic with values of <25%, 26% – 50% and >50% providing low, moderate and high degrees of heterogeneity, respectively. Significance was obtained if the two-tailed P-value was ≤0.05.

### Table 1: Literature search strategy

| Database | Keywords | No. of results |
|----------|----------|----------------|
| PubMed   | (“hiv” [MeSH Terms] OR “hiv” [All Fields]) AND (“acquired immunodeficiency syndrome” [MeSH Terms] OR (“acquired” [All Fields] AND “immunodeficiency” [All Fields]) OR “acquired immunodeficiency syndrome” [All Fields] OR “aids” [All Fields]) AND (“COVID-19” [All Fields] OR “COVID-19” [MeSH Terms] OR “COVID-19 Vaccines” [All Fields] OR “COVID-19” [MeSH Terms] OR “COVID-19” [All Fields] OR “COVID-19 Serological Testing” [All Fields] OR “covid-19 nucleic acid testing” [MeSH Terms] OR “COVID-19 Serological Testing” [All Fields] OR “covid-19 serological testing” [MeSH Terms] OR “COVID-19 Testing” [All Fields] OR “covid-19 testing” [MeSH Terms] OR “SARS-CoV-2” [All Fields] OR “sars-cov-2” [MeSH Terms] OR “SARS-CoV-2” [All Fields] OR “sars-cov-2” [MeSH Terms] OR “Severe Acute Respiratory Syndrome Coronavirus 2” [All Fields] OR “ncov” [All Fields] OR “2019 ncov” [All Fields] OR ((“coronavirus” [MeSH Terms] OR “coronavirus” [All Fields] OR “COVID” [All Fields]) AND 2019/11/01[PubDate] : 3000/12/31[PubDate]))) | 1626 |
| Europe PMC | “HIV” OR “human immunodeficiency virus” OR “immunocompromised” OR “immune-deficient” OR “AIDS” OR “acquired immunodeficiency syndrome” AND “SARS-CoV-2” OR “coronavirus disease 2019” OR “COVID-19” | 9107 |

**FIGURE 1**: PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.
The qualitative risk of publication bias was assessed using Begg’s funnel plot analysis.

**Results**

**HIV and mortality**

Our pooled analysis indicated that HIV was associated with mortality from COVID-19 [OR = 1.19 (95% CI 1.01–1.39), \( p = 0.03; I^2 = 72\%\), random-effect modelling] (see Figure 2).

**Meta-regression**

However, meta-regression showed that the association between HIV and mortality from COVID-19 was unaffected by age \((p = 0.208)\), gender \((p = 0.608)\) (see Figure 3a), Black
TABLE 3: Newcastle–Ottawa quality assessment of observational studies.

| First author | year | Study design | Selection | Comparability | Outcome | Total score | Result |
|--------------|------|--------------|-----------|---------------|---------|-------------|--------|
| Berenguer J et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Bhaskaran K et al. | 2020 | Cohort | **** | * | *** | 9 | Good |
| Boullé A et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Braunstein SL et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Cabello A et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Chilimuri S et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Docherty AB et al. | 2020 | Cohort | **** | * | *** | 9 | Good |
| El-Sohi AA et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Garibaldi BT et al. | 2020 | Cohort | **** | * | *** | 9 | Good |
| Geretti AM et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Gudipati S et al. | 2020 | Cohort | ** | ** | *** | 7 | Good |
| Hadi YB et al. | 2020 | Cohort | ** | ** | *** | 7 | Good |
| Harrison SL et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Hsu HE et al. | 2020 | Cohort | ** | ** | *** | 7 | Good |
| Huang J et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Jassat W et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Kabarriti R et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Karnen-Tuohy S et al. | 2020 | Cohort | ** | ** | *** | 7 | Good |
| Kim D et al. | 2020 | Cohort | *** | ** | **** | 9 | Good |
| Lee SG et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Maciel EL et al. | 2020 | Cohort | ** | ** | *** | 7 | Good |
| Marcello RK et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Miyashita H et al. | 2020 | Cohort | *** | ** | *** | 7 | Good |
| Ombajo LA et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Parker A et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Sigel K et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Stoeckle K et al. | 2020 | Cohort | *** | ** | *** | 8 | Good |
| Tesoriero JM et al. | 2020 | Cohort | ** | ** | *** | 7 | Good |

Note: Asterisk denotes scores.

FIGURE 2: Forest plot that demonstrates the association of HIV with mortality from COVID-19 outcome.
ethnicity ($p = 0.389$), CD4 cell count of <200 cells/µL ($p = 0.353$) (see Figure 3b) or ART ($p = 0.647$) (see Figure 3c).

**Subgroup analysis**

The subgroup analysis revealed that the association between HIV and mortality from COVID-19 was only statistically significant for studies from African regions [OR = 1.13 (95% CI = 1.04–1.23), $p = 0.004$; $I^2 = 0\%$, random-effect modelling] and the United States of America (USA) [OR = 1.30 (95% CI = 1.08–1.59), $p = 0.006$; $I^2 = 61\%$] but not for studies from Asia [OR = 2.41 (95% CI = 0.16–36.57), $p = 0.53$; $I^2 = 76\%$], or Europe [OR = 0.90 (95% CI = 0.70–1.15), $p = 0.40$; $I^2 = 5\%$].

**Publication bias**

The funnel plot analysis revealed a qualitatively symmetrically inverted funnel plot for the association between HIV and a mortality outcome, suggesting no publication bias. This is demonstrated in Figure 4.

**Discussion**

This systematic review and meta-analysis of 28 studies not only analyse the association between HIV and mortality from COVID-19 but evaluate the role of confounding factors such as age, gender, ethnicity, CD4 cell count and ART in this cohort.

An association was found between HIV and mortality from COVID-19. However, this did not appear to be influenced by the confounding factors above. Instead, the subgroup analysis found that mortality from COVID-19 in PLWH was more likely to be reported in studies from Africa and the USA, rather than Asia or Europe. Factors unique to Africa, such as the large background prevalence of HIV, delayed access to healthcare (poor health ‘awareness’, an inadequate healthcare infrastructure and logistical challenges to accessing care) and ready access to alternate, non-Western, traditional health practitioners and medicines, are likely to have influenced outcomes.\(^46\)\(^,47\) Similarly, the COVID-19 epidemic in the USA disproportionately affected the poor, people of colour and the socially marginalised such as drug users and the institutionalised. In both regions, PLWH may have been ‘over-represented’ in published studies.

Our pooled data confirmed an association of higher mortality from COVID-19 in PLWH.

Firstly, HIV infection may cause severe depletion of the gut-associated lymphoid tissue, with a predominant loss of memory CD4+ T cells.\(^48\) Human immunodeficiency virus-induced T-cell lymphopenia, which disrupts the innate and

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**FIGURE 3:** Bubble-plot for meta-regression. Meta-regression analysis showed that the association between HIV and mortality from COVID-19 was not affected by gender (a), CD4 cell count (b) or ART (c).

**FIGURE 4:** Funnel plot for the association of HIV with mortality from COVID-19 outcomes.
adaptive immune response, may predispose patients to Mycobacterium tuberculosis infection and progression to active disease, which increases the risk of latent tuberculosis reactivation by 20-fold.\textsuperscript{49,50} Previously published studies regarding COVID-19 have revealed that the presence of tuberculosis was associated with higher severity and mortality from COVID-19.\textsuperscript{51,52} Secondly, some proportions of PLWH may have incomplete immune reconstitution and evidence of persistent immune activation.\textsuperscript{53} They may show an abnormal innate and adaptive immune response, characterised by the elevation of macrophages, cytokines [tumour necrosis factor alpha, interleukin (IL)-1, IL-6, IL-8 and IL-10], acute phase proteins [serum amyloid A, C-reactive protein (CRP)], elements of the coagulation cascade (D-dimer and tissue factor), increased turnover and exhaustion of T cells, increased turnover of B cells and hyperimmunoglobulinaemia.\textsuperscript{54,55} These conditions may contribute to the development of cytokine storms and severe outcomes in COVID-19. Furthermore, elevated CRP, D-dimer and IL-6 have been associated with severe COVID-19 based on meta-analysis studies.\textsuperscript{53,56} Thirdly, exhaustion of T-cell lymphocytes, which is observed in HIV progression, may also be exacerbated during COVID-19 infection, possibly as a result of the SARS-Cov-2 infection’s synergistic activity with HIV, which gradually results in T-cell lymphocyte apoptosis.\textsuperscript{57} This exhaustion of T-cell lymphocytes was associated with the progression and severe manifestation of COVID-19.\textsuperscript{58,59}

Limitations

Firstly, only a limited number of our included studies reported on CD4 cell counts, viral loads and ART – a fact that is likely to have impacted the precision of the meta-regression analysis of this study. Indeed, most studies focussed on the characteristics of COVID-19 patients rather than its effects on PLWH. Secondly, the studies utilised in this review and meta-analysis were primarily observational and thus, may reflect occult confounders or biases unique to the particular study. Finally, we included some preprint studies to minimise the risk of publication bias; however, we made exhaustive efforts to ensure that only sound studies were included that we expect will eventually be published. We hope that this study can give further insight into the management of COVID-19 patients.

Conclusion

Our meta-analysis of observational studies indicates that HIV had an association with a mortality outcome from COVID-19; however, larger observational studies or even randomised clinical trials are needed to confirm our results and elucidate additional associations. Patients living with HIV must take extra precautions and always adhere to health-promoting protocols. They must be prioritised to receive COVID-19 preventive therapy: the SARS-CoV-2 vaccine. Where feasible, practical use must be made of telemedicine and virtual-based practice to provide continuous care to PLWH throughout this pandemic. Every effort must be made to identify co-infected PLWH and to link them with clinicians and treatment centres skilled in COVID-19 care. Gaps in ART-related care, such as medicine stockouts, must be identified by local healthcare providers and authorities. Finally, HIV co-infection must be included in future risk stratification models for COVID-19 management.

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Authors’ contributions

T.L.H., J.R., K.C. and A.K. formulated the research questions; T.L.H. and J.R. developed the study protocol, analysed the data and wrote the manuscript. T.L.H., J.R., K.C. and A.K. did the systematic review. A.K. supported and supervised the work. All authors reviewed the manuscript and approved the final version.

Ethical considerations

This article followed all ethical standards for research without direct contact with human or animal subjects.

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Data availability

The data analysed in this study were a reanalysis of existing data, which are openly available at the locations cited in the reference section.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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