Factors affecting poor prognosis of COVID-19 in people living with human immunodeficiency virus: A systematic review and meta-analysis of co-infection

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ABSTRACT

Objectives: This study aims to assess the correlation between clinical features and mortality in human immunodeficiency virus (HIV)-infected individuals with COVID-19.

Methods: A systematic literature search was conducted for cohort, cross-sectional, and case series that reported co-infection with HIV and COVID-19 published from January to September 2020. Clinical features such as age, comorbidities, CD4$^+$T lymphocyte counts, HIV RNA levels, and antiretroviral regimens were evaluated using meta-analyses and systematic reviews. Meta-analysis was performed using Stata 15.0 software.

Results: A total of 24 articles with 939 cases of HIV/COVID-19 co-infection were included in this study. The overall mortality rate was 10.3% (97/939). Older age and comorbidities including hypertension, diabetes, renal insufficiency, chronic obstructive pulmonary disease/asthma, and tumors were significantly associated with increased mortality (95% confidence interval 0.005–0.050, 0.042–2.294, 0.390–2.754, 0.513–2.848, 0.348–3.743, and 1.943–7.101, respectively, P = 0.021, 0.043, 0.012, 0.008, 0.022, and 0.005). There was no significant correlation between mortality and CD4$^+$T lymphocyte count <200/μL or >500/μL, HIV RNA level below the detection limit, or antiretroviral drugs (including tenofovir) (all P > 0.05). Improved HIV treatment, complex immune interactions, study population variability, and lack of direct SARS-CoV-2 targeting by ART likely obscure the correlation between CD4$^+$ counts or ART and COVID-19 mortality in HIV patients.

Conclusion: HIV-infected individuals with COVID-19 have a similar prognosis to the general population. However, older age, comorbidities (hypertension and diabetesetc.), and lower CD4$^+$ T-cell counts are associated with increased mortality. Mainstream anti-HIV drugs do not offer significant protection against COVID-19.

Keywords: Co-infection, COVID-19, HIV, Meta-analysis, Review

Introduction

The COVID-19 pandemic has presented unprecedented challenges to global health, with particularly severe implications for populations already vulnerable due to underlying health conditions. People living with human immunodeficiency virus (PLWH) face compounded risks, as human immunodeficiency virus (HIV) infection compromises immune function and can be accompanied by comorbidities that heighten susceptibility to severe COVID-19 outcomes. Although antiretroviral therapy (ART) has significantly improved long-term health for PLWH, some immune dysfunction persists, increasing their vulnerability to infections like COVID-19.[1] Recent studies indicate a higher risk of severe COVID-19 complications, hospitalization, and mortality among HIV-positive individuals compared to the general population. Factors such as low CD4$^+$ T-cell counts, advanced HIV disease, and HIV-related comorbidities, including hypertension, diabetes, and chronic respiratory issues, contribute to the worsened outcomes seen in this group. Despite this evidence, the extent to which HIV-related immunosuppression specifically exacerbates COVID-19 severity remains inconclusive. While some research suggests immunosuppression could lead to heightened COVID-19 complications, other studies report that immunosuppressed individuals may not experience significantly worse COVID-19 outcomes than the general population.[2]

In light of the challenges in treating COVID-19, attention has turned to repurposing antiviral drugs originally developed

for other viral infections, including those used in ART. The researchers are also investigating potential COVID-19 treatments among existing anti-RNA virus drugs. Drugs like remdesivir and lopinavir, initially considered promising, have shown limited success against COVID-19, prompting further investigation into the potential protective role of long-term ART use for PLWH.[3] ART regimens, especially those involving nucleoside reverse transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors (INSTIs), are central to managing HIV by maintaining viral suppression and improving immune function. This potential interaction between ART and COVID-19 outcomes has led researchers to question whether ART might confer indirect protection against severe COVID-19 in PLWH.[4] However, the findings across studies remain mixed. While some research suggests that certain ART components, such as tenofovir, might reduce COVID-19 severity, other studies have not confirmed these protective effects, leaving questions regarding ART's overall efficacy against COVID-19. In addition to ART, factors such as $CD4^+$ T-cell counts and HIV RNA detectability further complicate our understanding of COVID-19 prognosis in co-infected patients. For instance, PLWH with $CD4^+$ counts below 200 cells/μL indicative of significant immunosuppression are generally at risk for worse outcomes in many infections. Yet, their correlation with COVID-19 mortality is not definitively established.[5] Some studies posit that lower immune activation in these patients may provide protection against the excessive inflammatory response, or cytokine storm, which drives severe COVID-19 in the general population.[6]

Given the significant clinical implications, this systematic review and meta-analysis aim to identify the factors most strongly associated with severe COVID-19 outcomes in HIV-positive individuals. By focusing on clinical characteristics such as age, sex, comorbidities, $CD4^+$ T cell counts, HIV RNA levels, and ART regimens, this study seeks to elucidate the specific factors influencing COVID-19 prognosis in PLWH. Synthesizing data from a wide range of studies across different regions, this research aims to offer insights into the underlying drivers of COVID-19 severity in co-infected patients, ultimately informing clinical guidelines and improving patient outcomes in this high-risk population. Through this comprehensive approach, the study endeavors to clarify whether ART regimens, immune status markers, to identify other promising antiviral options or other HIV-related factors significantly impact COVID-19 outcomes, thereby contributing valuable knowledge to managing co-infection cases in clinical practice.

Materials and Methods

Literature search

The retrieval time is from January 2020 to January 2021, including online published documents. The languages are Chinese and English. English documents were chosen from Embase, PubMed database, Wanfang, CNKI, and Weipu journal resource integration service platform in the Chinese language. The search includes three types of keywords: "coronavirus," "human immunodeficiency virus" and "prognosis," among which "coronavirus" includes the English search term "coronavirus" "nCoV" "2019-nCoV" "COVID" "SARS-CoV," "HIV," "AIDS" "acquired immunodeficiency syndrome." Other English search terms are "outcome" "mortality" "death" "fatality" "severs" "ICU" "intensive care."

Literature inclusion and exclusion criteria

Literature inclusion criteria
The research objects are confirmed patients of HIV co-infection with COVID-19, including cohort studies, case–control studies, case series, and cross-sectional studies. The article's content includes demographic characteristics, clinical conditions, comorbidities, HIV control status, ART programs, and prognosis. The literature is published in a peer-reviewed journal.

Literature exclusion criteria
Literature that does not contain the original information of the case, such as reviews, comments, and correspondence, does not clearly explain the clinical information and prognosis of the case, the case has repeated inclusion relationships, and the number of cases is <4 cases.

Literature quality evaluation
Use the Joanna Briggs Institute Literature Quality Evaluation Scale.[7] The review of the literature cohort to establish comparability, inclusion or exclusion criteria, detailed description, exposure factor evaluation, variable measurement methods, confounding factor identification, confounding factor processing, outcome variable evaluation, use of statistical methods, and other methods were used to give scores. According to different literature types, the corresponding scale was used, in which the total score of the cohort study was 12, the total score of the case series was 10, and the total score of the cross-sectional study was 8. Two staff members independently completed the literature retrieval, screening, and evaluation.

Statistical analysis

Statistical analysis was performed using Stata 15.0 software. The meta-analysis calculates the case fatality rate of patients for each study, uses a random-effects model to calculate the combined value of the case fatality rate and its 95% CI, and performs a *Z* test. The heterogeneity test between studies adopts I^2 to evaluate, and there may be substantial heterogeneity when I^2 is 50–90%. The symmetry of the funnel chart evaluated the publication bias, and the Begg and Egger tests were performed simultaneously. $P > 0.05$ means that there is no publication bias. Heterogeneity in this study was managed using statistical techniques to account for variations across different studies. Meta-regression analysis is used to explore the reasons for the heterogeneity of mortality

and its possible influencing factors. This study conducted a single-factor regression analysis. Regression analysis is required for at least 5 literature reports for each risk factor to avoid over-fitting. Since the case fatality rate of the patients in this study is skewed (the case fatality rate of 5 studies is 0), the case fatality rate is subjected to double arcsine transformation before meta-analysis and regression analysis and then obtained by the inverse change of double arcsine transformation. The composite value of the case fatality rate and its 95% CI. The count data is expressed as the number of cases, and the χ^2 test compares groups. $P < 0.05$ is considered statistically significant.

Results

Search results

The review included a total of 2020 publications in Chinese and English (sourced from Embase: 618, Medline: 556, Cochrane: 278, PubMed: 548, Wanfang Data Resource System: 7, CNKI: 9, and VIP: 4). After removing 641 duplicate entries, 1312 studies were further excluded based on title and abstract, yielding 67 articles for preliminary review. Following a full-text assessment, 27 case reports, 10 correspondence articles, 3 review papers, and 3 studies not meeting inclusion criteria were excluded. Ultimately, 24 English-language studies were

retained,[8-31] comprising 8 cohort studies, 14 case series, and 2 cross-sectional studies. Together, these studies encompassed 939 patients co-infected with HIV and COVID-19. Basic study details and quality assessment scores are presented in Table 1.

Among the 939 patients, the mean age was 53.3 years, with a demographic breakdown of 78.7% males (739), 20.8% females (195), and 0.5% transgender individuals (5). For studies reporting comorbidities, 62.8% (250/398) of the patients had at least one underlying health condition. The most prevalent comorbidities included hypertension (36.4%, 243/668), diabetes (18.0%, 120/668), obesity or hyperlipidemia (13.0%, 87/668), chronic obstructive pulmonary disease (COPD) or asthma (10.5%, 70/668), and renal insufficiency (9.9%, 66/668), with an average of 1.2 comorbid conditions per patient. Among studies documenting CD4+ T cell counts, 23.8% (74/311) of patients had CD4+ T-cell counts below 200/μL. In the subset of studies reporting HIV RNA levels, 9.2% (63/683) of patients had detectable viral loads. Regarding antiviral therapy, 54.0% (503/931) of patients were on an INSTI, 17.7% (165/931) were on a protease inhibitor (PI), 23.3% (217/931) were using non-NRTIs (NNRTI), and 77.9% (725/931) were on NRTI. In addition, 12.7% (119/939) of patients required mechanical ventilation, and the overall mortality rate was 10.3% (97/939).

Table 1: Included literature and quality evaluation.

Authors name	Country	Number of patients	Research type	Quality score
Blanco *et al*.[8]	USA	5	Case series	8
Härter *et al*.[9]	Germany	32	Case series	8
Gervasoni *et al*.[10]	Italy	47	Cross-sectional	6
Childs *et al*.[11]	UK	18	analysis	5
Suwanwongse and Shabarek[12]	USA	9	Case series	5
Shalev *et al*.[13]	USA	31	Case series	8
Byrd *et al*.[14]	USA	27	Case series	9
Del Amo *et al*.[15]	Spain	236	Case series	10
Sigel *et al*.[16]	USA	88	Cohort study	11
Marimuthu *et al*.[17]	India	6	Cohort study	8
Gudipati *et al*.[18]	USA	14	Case series	7
Maggiolo *et al*.[19]	Italy	55	Case series	11
Suwanwongse and Shabarek[20]	USA	5	Cohort study	9
Ridgway *et al*.[21]	USA	5	Case series	7
Vizcarra *et al*.[22]	Spain	51	Case series	10
Calza *et al*.[23]	Italy	26	Cohort study	6
Di Biagio *et al*.[24]	Italy	69	Case series	7
Huang *et al*.[25]	China	35	Cross-sectional	11
Karmen-Tuohy *et al*.[26]	USA	21	analysis	10
Shekhar *et al*.[27]	USA	5	Cohort study	6
Okoh *et al*.[28]	USA	27	Cohort study	9
Inciarte *et al*.[9]	Spain	53	Case series	9
Etienne *et al*.[30]	French	54	Case series	8
Collins *et al*.[31]	USA	20	Cohort study	7

Mortality rate of HIV/COVID-19 co-infected patients

24 included articles mortality of forest plot and funnel, in Figure 1; mortality Begg funnel plot test $Pr > |z| = 0.274$, Egger test $P = 0.333$, no publication bias, in Table 2.

There is a correlation between the age of patients and the mortality rate, and the mortality rate of elderly patients increases ($P < 0.05$). Complicated with hypertension, diabetes, renal insufficiency, COPD/asthma, and tumors are all related to the increase in mortality (all $P < 0.05$), obesity/hyperlipidemia, cardiovascular disease, and mortality are not correlated (all $P > 0.05$). CD4+ T lymphocyte count <200/µL or HIV RNA below the detection limit were not correlated with mortality ($P > 0.05$). There was no correlation between antiviral treatment programs containing

different drugs and mortality (all $P > 0.05$). Stratified analysis of CD4+ T lymphocyte counts in HIV/COVID-19 co-infected patients. Of 60 patients with CD4+ T lymphocyte count <200/µL, 6 died; 39 patients with CD4+ T lymphocyte count 200-500/µL, 5 died; CD4+ T lymphocyte count >500/µL of the 7 patients, 3 died. There was no correlation between CD4+ T lymphocyte count and mortality ($\chi^2 = 5.936$, $P > 0.05$).

Discussion

This study included data from various medical centers worldwide, encompassing both case reports and cohort studies. Significant heterogeneity existed among the studies ($I^2 = 67.3\%$) due to differences in patient comorbidities, HIV infection control levels, and long-term anti-HIV medication
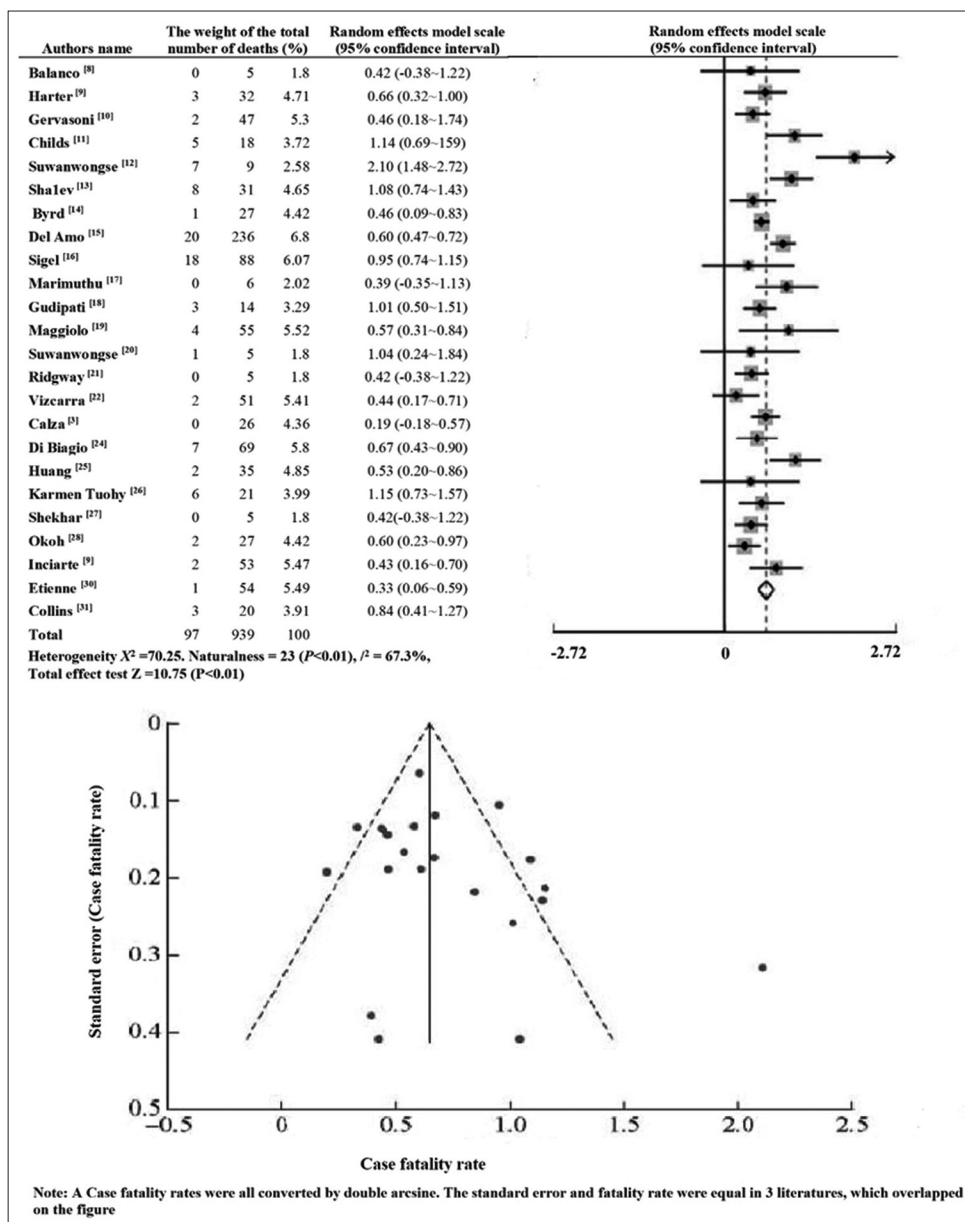

Figure 1: HIV/COVID-19 co-infected patients with forest and funnel charts for the overall mortality rate

Table 2: Meta-analysis of the relationship between clinical characteristics and mortality in HIV/Covid-19 infected patients

Variable	Number of documents	Regression system	P-values	95% CI	R² (%)
Venerable age	23	0.027	0.021	0.005–0.050	33.64
Male	23	0.366	0.545	−2.472	−6.75
At least one comorbidity	17	0. 792	0.057	−1.64	23.39
Hypertension	20	1.168	0.043	0.042–2.294	28.48
Obesity/hyperlipemia	12	0. 332	0.648	−3.144	−10.89
Diabetes	19	1.572	0.012	0.390–2.754	58.96
COPD/Asthma	16	2. 045	0.022	0.348–3.743	40.32
Cardiovascular disease	14	1.211	0.353	−5.463	−7.32
Renal dysfunction	15	1.68	0.008	0.513–2.848	63.66
Tumor	8	4. 522	0.005	1.943–7.101	100
CD4 + T lymphocyte count<200/L	14	0. 289	0.735	−3.635	−14.28
CD4 + T lymphocyte count> 500/L	14	0.149	0.790	−2.387	−15.05
HIV RNA is below the lower limit of detection	22	0. 665	0.544	−4.494	−8.3
Treatment include integrase inhibitors	23	0. 072	0.797	−1.153	−8.68
Treatment contains protease inhibitors	23	0. 234	0.710	−2.591	−7.34
Treatment with NNRTI	23	−0.441	0.175	−1.306	14.98
Treatment with NRTI	23	0. 205	0.360	−0.913	−1.99
Treatment with Tenofovir	21	0. 273	0.289	−1.048	0. 34

COPD: Chronic obstructive pulmonary disease, NNRTI: Non-nucleoside anti-reverse transcriptase inhibitor, NRTI: Nucleoside anti-reverse transcriptase inhibitor

regimens. Meta-regression analysis revealed that advanced age and comorbidities, similar to the general population, were associated with poor prognosis in HIV/COVID-19 co-infected patients.[32] Studies have reported that HIV-infected or immunocompromised patients have a better prognosis for COVID-19,[2] and the subsequent review system prompts immunocompromised patients with a poor prognosis.[3] This study did not find that HIV infection control and CD4+ T lymphocyte count levels are associated with poor prognosis, especially patients with CD4+ T lymphocyte counts <200/μL did not show a significant increase in mortality.[33-35] Some studies believe that the death of COVID-19 is a manifestation of excessive activation of inflammation, whether the reduction of CD4+ T lymphocyte count itself plays a particular "protective" effect by reducing the formation of inflammatory storms, it may need further research to clarify.

Preliminary research has high hopes for lopinavir and tenofovir,[36] And even some agencies try to change HIV infection after infection COVID-19 basis ART programs to improve the prognosis.[8,11,12,22] According to the current evidence, various conventional anti-HIV ART drugs have not found adequate protection against COVID-19 infection, severe illness, and death.[37,38] Until further evidence is obtained, no attempt should be made to change the ART regimen to prevent and treat COVID-19.[39]

In this study, the overall mortality rate of HIV/COVID-19 co-infected patients reached 10.3%, which is a certain gap with the international understanding of the overall mortality rate of COVID-19 patients. The variation in overall case fatality rates, ranging from 0.1% to 25% across regions, is largely attributable to differences in calculation methods and indicators used to

measure these rates.[40-42] This study focuses on patients diagnosed with COVID-19 after seeking medical treatment, aligning more closely with the concept of case fatality ratio, which typically yields higher values than the infection fatality ratio. The estimated case fatality rate remains the most practical clinical indicator for assessing mortality. However, the patients included in this study were ill during the early stages of the pandemic (January 2020–2021). As HIV-infected individuals constitute a significant portion of the population in certain regions, these areas often experienced more severe COVID-19 outbreaks. Consequently, medical centers in these regions reported a higher number of HIV/COVID-19 co-infection cases, potentially influencing the overall mortality rate.[43] These areas faced relatively insufficient medical resources in the epidemic's early stages and insufficient respiratory and critical support treatments. Due to lack of experience, some centers even reported 7 deaths among 9 co-infected patients in May 2020;[12] until July 2020, due to the appropriate follow-up medical resources, the reduction of overall cases, again reported on new cases co-infected patients, only one died.[20] The results of the funnel chart of the fatality rate in this study showed no obvious publication bias in the included literature and the prospective cohort study. This study showed no significant difference in the fatality rate between HIV-infected people and the general population,[16] and it further shows that when other conditions are matched, HIV infection is not a high-risk factor for the death of COVID-19 patients.[44]

Despite its value, this study still has several limitations. This study, while valuable, has several limitations. First, due to ethical considerations and preventive measures, most current research on HIV/COVID-19 co-infection is observational. Compared to randomized controlled trials, observational

studies are more prone to bias. However, this review mitigated some of these biases by including multiple study designs (cohort, cross-sectional, and case series) and excluding case reports. Conducting future studies with matched control groups could further reduce bias. Second, variations in testing rates, hospitalization criteria, and critical care availability across different settings can impact mortality rates. Large-scale single-center case-control studies should be interpreted cautiously due to these variations. Many individual studies included in this review had limited sample sizes, hindering the ability to draw definitive conclusions. Nevertheless, the systematic review and meta-analysis combined data from multiple studies to achieve statistically significant findings.

Conclusion

There has been no significant rise in the mortality rate of people with HIV who contract COVID-19 in comparison to the general population. Advanced age and comorbidities remain the primary risk factors for death from co-infection. The impact of HIV RNA and $CD4^+$ T lymphocyte count on COVID-19 mortality requires additional investigation. The study found no conclusive evidence that anti-HIV treatments can prevent COVID-19 fatalities. Therefore, altering ART regimens due to COVID-19 infection is not recommended until more clinical data is available.

Ethics Approval and Consent to Participate

All the informed consents for publication from the patients did not need to be obtained. Because no human or animal trials are involved in this research by us. Also, no direct patient's data are involved from our institution. So ethical approval consent is not required. All the data were collected from published articles.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

Not applicable.

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Not applicable yet.

Authors' Contributions

Substantial contributions to conception and design: Sayed Abdulla Jami
Data acquisition, data analysis, and interpretation: All authors
Drafting the article or critically revising it for important intellectual content: All authors
Final approval of the version to be published: All authors
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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