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Immunological Responses and Survival Outcome in HIV and SARS-CoV-2 Coinfected Patients

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ABSTRACT

The coronavirus disease 2019 (COVID-19) has created a worldwide crisis, raising fears and concerns regarding clinical outcomes in patients with comorbidities. Some of the highly prevalent communicable and non-communicable diseases worldwide are cardiovascular diseases, diabetes, HIV/AIDS, and hepatitis B and C, which reduce the host immune responses to concurrent acute infections. Despite over 170 million confirmed cases of COVID-19 worldwide as of 24 June 2021, insufficient data is reporting the prognosis of HIV and SARS-CoV-2 co-infection. This narrative review aims to present current knowledge on the impact of SARS-CoV-2 on people living with HIV/AIDS, in terms of immunological responses and clinical outcome. Although some studies have been performed and are in progress to determine the impact of SARS-CoV-2 infection on patients living with HIV/AIDS, controversies still exist whether COVID-19 severity and mortality are higher among this special subgroup or similar to the general population.

Keywords: SARS-CoV-2 and HIV co-infection; COVID-19 mortality; immunological response to HIV; immunological response to SARS-CoV-2; HIV/SARS-CoV-2 co-infection survival

INTRODUCTION

There is an ongoing need for the surveillance and study of infectious diseases and the current pandemic of COVID-19, attests to that fact. From December 2019 till 24 June 2021, SARS-CoV-2 infection has affected more than 170 million people all around the globe [1]. The current threat of the SARS-CoV-2 pandemic in the human population that already have a significant burden of cardiovascular diseases, human immunodeficiency virus (HIV) infection, hepatitis B & C, has markedly increased the mortality rate and already taken a toll of 3.5 million people [1]. The epidemiological, clinical, immunological, and biological studies done to date for SARS-CoV-2 and HIV co-infection have revealed that HIV and SARS-CoV-2 may cause variable effects at the population, individual, cellular, and molecular levels [2].

Current evidence indicates that the risk of severe COVID-19 illness and fatal outcome increases with age, male gender and with comorbidities like cardiovascular disease, diabetes, chronic obstructive lung disease, obesity, and renal failure [3]. The people living with HIV (PLWH) [4,5] may be more likely to have severe SARS-CoV-2 infection than uninfected people, especially individuals with comorbidities, lower CD4 cell counts, or uncontrolled HIV RNA viral load. Contrary to this, antiretroviral therapy and immunosuppression in HIV patients might modify the vulnerability of these patients to COVID-19 and the clinical course of the illness [6]. HIV infected people with normal CD4 T-cell count, suppressed viral load, without other comorbidities, and who are well-optimized on antiviral treatment may not be at an increased risk of severe or critical SARS-CoV-2 infection [7,8]. However, in the USA, nearly 50% of the PLWH are older than 50 years and comorbidities like cardiovascular disease, chronic lung disorders are more prevalent among this special group [9].

This review aims to present current knowledge on the impact of SARS-CoV-2 and HIV co-infection in terms of immunological responses and survival outcome.

METHOD

For this scoping review, the authors searched PubMed, Scopus, Web of Science, Embase, preprint databases, and Google Scholar, using the terms "COVID-19" in HIV patients, "SARS-CoV-2 impact on HIV patients", and "HIV and SARS-CoV-2 pathogenesis". We selected 21 original articles which reported cases of COVID-19 in HIV-infected individuals, specifically. These studies included case reports and observational case series of HIV-patients with COVID-19 published from China, Turkey, Spain, Germany, UK, Italy, South Africa, and the United States. Reports from the WHO, CDC, and European AIDS agencies were also included. Further literature is searched for the immunological responses occurring in HIV and SARS-CoV-2 infections. The findings are abridged narratively.

DISCUSSION

The effects of HIV and SARS-CoV-2 on the Host Immune System

The pathogenic mechanism of both HIV and SARS-CoV-2 revolves around the immune cells and cytokine system. The formal causes depletion of immune cells and dysregulation of cytokine production whereas the latter is associated with hyperproduction of chemical mediators produced by activated immune cells, resulting in cytokine storm which is the hallmark of COVID-19 severe/critical disease. HIV infection is caused by two specific viruses which are HIV-1 and HIV-2 in the human population. HIV-2 is less virulent as compared to HIV-1 and associated with a more functional and constant T-cell immunity [10].

The immunological changes associated with HIV depends upon many other variables in addition to its types, such as early diagnosis, control with antiretroviral drugs, and the chronicity of the infection. The majority of the HIV infection is caused by HIV-1. The immunological changes seen in PLWH include depletion in CD4+ T-cell (T-helper lymphocytes) count, subsequently altered CD4 and CD8 (cytotoxic T lymphocytes) ratio, and cytokine dysregulation [11]. During the acute phase of HIV infection, there is a gradual loss of peripheral CD4 T-cells, whereas chronic infection is associated with the massive production of proinflammatory cytokines due to immune system activation. Some of the causes of depletion of CD4 T-cells are apoptosis, impaired production of T lymphocytes by the thymus, and destruction by activated HIV-specific CD8+ T-cells [10]. Altered function of the immune system such as a decrease in T cell responses to antigens as well as weak humoral immune responses due to the direct effects of HIV aggravates the immune deficiency caused by depletion of CD4+ T cells. Cytokine dysregulation also plays an important role in the pathogenesis of HIV infection. The rise in serum levels of pro-inflammatory and inflammatory cytokines like IL-2, IL-4, and interferon type II (IFN-γ) contribute to viral replication and subsequent immunodeficiency.

The secretion of IL-2 and antiviral IFN-γ, which is crucial for intracellular infection, by T-helper 1 cells is generally reduced in HIV -1 infection [11]. It is reported that IFN-γ can inhibit viral replication and enhance antigen presentation. On the other hand, the production of IL-4, IL-10, proinflammatory cytokines, and tumour necrosis factor (TNF)-alpha by T-helper 2 cells, which are important for extracellular infection, is increased. This dysregulation of cytokine production to a certain degree explain the vulnerability of HIV-infected individuals to infection by intracellular microbes.

The exact immunologic mechanism of SARS-CoV-2 infection still needs to be investigated and confirmed. However, an immune response initiated by the first line of leukocytes defense against the novel coronavirus, that ended up into the cytokine storm through a complex chain of events, involving antigen-presenting cells and T-helper cells is highly suggested [12,13]. Activated T-helper cells proliferate and differentiate into CD4+ T cells and CD8+ T cells. CD4+ T-cells further differentiate into T-helper 1 and T-helper 2, with different cytokine profiles as mentioned earlier. Balanced secretory activity of T-helper 1 and T-helper 2 cells is evidenced in healthy adults with COVID-19 infection, whereas in PLWH this activity is dysregulated which can affect the clinical course and outcome of the SARS-CoV-2 and HIV co-infection. Besides the cytokine mechanism in COVID-19 patients, it has been observed that viral clearance is mediated by CD8+ T lymphocytes and natural killer cells, which is significant for the positive disease outcome [14]. However in progressive cases of HIV infection, there is a gradual loss of CD4 T-cells, the CD8 T-cell remains elevated initially and during the chronic phase of HIV infection until the late phase where depletion of both CD4+ and CD8+ T-cells occurs [15].

Impact of COVID-19 on People living with HIV

The term *syndemic* is used for the occurrence of two or more diseases that act synergistically to enhance or intensify the clinical course and outcome of disease [16], and the SARS-CoV-2/HIV co-infection needs to be addressed by larger studies to facilitate early diagnosis and management in this vulnerable group.

There are approximately 38 million diagnosed cases of HIV/AIDS globally, and by adding thousands of undiagnosed cases the number would be much higher [17]. Although this subset of comorbidity mostly affected the younger age group, the mortality rate due to COVID-19 is higher among older adults. However, it is a known fact that ageing is accelerated in people living with HIV, attributed to the "ageing effect" of HIV [18].

Various studies have been performed and are in progress to determine the impact of the SARS-CoV-2 pandemic on PLWH and their correlation in terms of clinical outcome, however, it remains ambiguous whether COVID-19 severity and mortality are higher among this special group [4,7]. From history, it has been identified that the influenza viruses and SARS were not associated with increased morbidity and mortality in PLWH [19,20]. The European AIDS Clinical Society stated that "there is no evidence for a higher COVID-19 infection rate or different disease course in people with HIV than in HIV-negative people" so far [21].

Most of the systematic reviews, case reports, and meta-analysis available indicated that PLWH did not have negative clinical outcomes due to COVID-19 [4]. However, the number of cases observed was small, and clinical studies on large scale are needed to achieve better insight and accurate information.

Late in January 2020, an isolated case of COVID-19 in Wuhan city of China was reported by Zhou et al. [22] The patient was male, 61 years old, a heavy smoker and a known case of type 2 diabetes. Initially, he was treated as an ambulatory case, but his clinical condition deteriorated, and he was later hospitalized due to fever, difficulty in breathing, and increasing lymphopenia. Multiple bilateral ground-glass opacities and consolidation were found on the chest CT. The patient received all the recommended treatment for COVID-19, but the lymphopenia got worse and the lymphocyte count reached 0.56 × 10g/L and a low CD4+T-cells percentage at 4.75%. He was tested for HIV and the result came as positive [22]. The patient was already on anti-HIV drug (lopinavir/ritonavir) treatment recommended for SARS-CoV-2 pneumonia by the Chinese health authority along with broad-spectrum antibiotics, gamma-globulin, corticosteroids and supplemental oxygen therapy. His clinical condition improved over two weeks and his throat swabs were tested negative for SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) assay. This case is unique as the disease outcome was positive despite age and comorbidities.

Another report of two COVID-19 cases from China revealed similar results [23]. Both the patients were known cases of HIV with other comorbidities. They fully recovered from a moderate SARS-CoV-2 illness after receiving conventional treatment recommended for COVID-19. It is indicated that lymphopenia and the use of lopinavir/ritonavir might be the reason for positive clinical outcome in these patients. Similar findings have been documented by Altuntas et al. [24] by reporting three cases of SARS-CoV-2 in PLWH in which the viral load was suppressed with regular use of antiviral treatment.

A small case series followed by researchers in Barcelona Spain during the outbreak, March 2020 reported five (0.92%) positive HIV cases among a cohort of 543 consecutive patients with SARS-CoV-2 infection admitted to the hospital [25]. The findings of this study emphasized a very low incidence for HIV/SARS-CoV-2 co-infection and complete recovery from COVID-19 in all of these five patients. These results were supported by an observational prospective study at a tertiary university hospital in Madrid, Spain following-up regularly 2873 adult patients with HIV, reported consecutive HIV-infected individuals aged 18 years or older with a diagnosis of suspected or confirmed 51 COVID-19 cases (incidence 1·8%) as of April 30, 2020 [26]. Similar clinical, laboratory and radiographical features were observed among patients co-infected with SARS-CoV-2 and HIV when compared with reports of the general population. However, the prevalence of comorbidities was significantly higher among this group. Lower CD4 cell counts due to chronic HIV infection affected COVID-19 pathogenesis and viral kinetics. There is a possibility of HIV induced immune dysfunction and humoral dysregulation on the immune responses and elimination of SARS-CoV-2 [27]. Suwanwongse and Nehad have reported through a case series, a higher mortality rate among patients who had significantly lower CD4+ T-cells count [28]. This opposes the hypothesis that HIV/SARS-CoV-2 coinfected patients have a positive outcome because of prevention from vigorous cytokine storms due to the lymphopenia and the immunosuppressive state of PLWH. This negative outcome in HIV/SARS-CoV-2 infected individuals with very low CD4 cell count may be attributed to a reduced number of T-lymphocytes, which are required for host immunity response to SARS-CoV-2 and subsequent delay in viral clearance. Besides the cytokine storm, severe COVID-19 may arise due to the B lymphocytes humoral dysregulation [29].

Harter et al. performed a retrospective analysis of a case series of 33 HIV patients co-infected with SARS-CoV-2, who were attending 12 participating German HIV centers, to determine the clinical course and survival in this special population. All HIV positive patients were either on antiretroviral drugs or taking protease inhibitors. Three (9%) out of the total number of patients had a fatal outcome and died, whereas 91% recovered with 76% affected with mild infection only [30]. The above findings do not support excess morbidity and mortality among patients co-infected with HIV and SARS-CoV-2.

A report from a reference hospital for the management of HIV infection in Italy documented the clinical course and disease outcome in patients co-infected with HIV and SARS-CoV-2 [31]. The database included nearly 6000 patients with HIV, the majority of them were male, around 50 years old, with suppressed viral load, and CD4 T-cell count of more than 500 cells/ mm^3. Among these, 47 patients were identified with proven or probable SARS-CoV-2 infection. A large proportion of these patients had at least one comorbidity which is frequently prevalent among older age groups in the general population. However, the risk of mortality and severity of disease was lower when compared to HIV-negative or HIV untreated cases of the same age group. The cytokine storm which is said to be the main pathological mechanism causing tissue damage in SARS-CoV-2 infection remained milder, and thus the clinical symptoms and signs. These positive outcomes may be achieved since many of these patients were receiving antiretroviral drugs and lopinavir/ritonavir, tocilizumab, and darunavir/cobicistat were all considered for compassionate use against SARS-CoV-2 infection [32]. The deficient or suppressed immune response due to immunosuppressive therapy and CD4+ T-cell count above 500 cells/mm^3 may have a possible role in the positive outcome among these patients.

Another case series reported by Alexis et al. regarding the management of COVID-19 in patients with HIV at a health care facility in Newark, the center of the HIV epidemic of New Jersey, identified a similarity in the presentation of co-infected HIV and SARS-CoV-2 cases with what has been reported for the general population. In this series 27 PLWH were diagnosed with COVID-19 by a positive result on an RT-PCR assay of a specimen collected on a nasopharyngeal swab. A mild form of COVID-19 was observed in 14 (51%) of these co-infected patients and all of them were managed as out-patients [33]. The rest of them were hospitalized and needed specialized care. Most of them were above 50 years of age with male predominance and more than half of these patients had a clinical history of either cardiovascular disease, diabetes, or renal dysfunction. In all of these HIV infected cases, the viral load was low and the CD4 T-cell count was elevated, indicating that the HIV infection was well controlled, and no mortality or morbidity was reported due to COVID-19.

A province-wide cohort of COVID-19 cases from Western Cape, South Africa and two other studies from national databases in the United Kingdom have reported a significant increase in mortality risk among HIV and SARS-CoV-2 coinfected cases [34,35]. Nearly 50% of the patients from the South African cohort were reported as an active or past case of tuberculosis, which itself is an added hazard. The data from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) database, consisting of 53,992 cases of COVID-19, and from the Open SAFELY dataset [5,36], from primary care practices through the UK, also identified that PLWH co-infected with SARS-CoV-2 had significantly higher mortality than non-HIV individuals, after adjusting for age, ethnicity, and other comorbidities. Data regarding HIV-related determinants such as antiretroviral therapy, viral load, CD4 T-cell count, and medical history of opportunistic infections, is lacking in both of these studies which creates a discrepancy in the findings. However, multimorbidity and older age are identified as the major factors for severe morbidity and mortality among COVID-19/HIV co-infected patients [37].

CONCLUSION

This paper presented a scoping review of the immunological effects of HIV and SARS-CoV-2 on the host and the survival outcome of HIV/SARS-CoV-2 co-infected cases. There are multiple mediating and moderating factors that affect the clinical course and survival outcome among this special group and the currently available data is lacking in many aspects. The impact of COVID-19 on PLWH is still controversial. There is an urgent need for the provision of resources and multidisciplinary approaches for the diagnosis, treatment, and prevention of both HIV and SARS-CoV-2 as the pandemic progresses. More studies of SARS-CoV-2 infection in patients with HIV are needed in the older population, drug users, those with comorbidities and, with uncontrolled viral load in all socio-economic settings.

AUTHOR CONTRIBUTIONS

Conceptualization, ZO; Original draft preparation, UAJ, SAJ; Review and editing, UAJ, ZO. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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