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# Oxidative and Inflammatory Biomarkers of Lung injury in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) patients living with HIV

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**Abstract**

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although both COVID-19 and HIV infections have been declared as pandemic at different times and both are known to cause lung injury, very few research has been done to determine the possibility of worsened lung injury in HIV patients infected with COVID-19. This systematic review attempts to determine the oxidative and inflammatory biomarkers associated with acute lung injury in HIV-positive population co-infected with COVID-19. Published studies in three databases were searched from January 1, 2019, to October 27, 2020. The search identified eight studies (with a total of 76 patients) that met the inclusion criteria and were included in the qualitative analysis of the systematic review. Among the eight studies, three were case reports describing 1–3 patients, four case series including 4–31 patients, and one was a cohort study. The Joanna Briggs Institute critical appraisal tools were used to assess the included studies. Qualitative analysis was used due to the heterogeneity of the study designs and the biomarkers measured. At present, C-reactive protein, Interleukin-6, D-dimer, and Lactate dehydrogenase have been found associated with the severity of disease, prognosis, and lung injury in HIV-positive patients coinfected with COVID-19. The causal association between elevated levels of these biomarkers and acute lung injury is still unknown; therefore, prospective studies are needed to determine biomarkers of lung injury useful for the prognosis and outcome of COVID-19 infection in the HIV population.

## Introduction

Coronavirus disease (COVID-19) infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was announced a pandemic by the World Health Organization on March 11, 2020, and as at August 28, 2020, 24,299,923 cases have been confirmed globally with 827,730 confirmed deaths from 216 countries. [1] (Averting HIV and AIDS, 2018). Meanwhile, HIV/AIDS has also been referred to as global pandemic with 37.9 million people living with HIV (PLWH) and 770,000 deaths from AIDS in 2018. The advent of COVID-19 pandemic has resulted in clash of pandemics. [2] (Del Amo *et al*., 2020). The first portal of infection is the upper respiratory tracts where SARSCOV-2 virus is transmitted through inhalation of droplets and aerosols by binding to the ACE2 (Angiotensin Converting Enzyme) receptor in the nasal mucosa [3] (Raftery and Samstag, 2020). Acute lung injury is the main feature observed on chest computer tomography in severe COVID-19 infection resulting from cascades of inflammation involving pro-inflammatory cytokines and chemokines which include Interleukin-6 (IL-6), Interferon gamma-induced protein 10, macrophage inflammatory protein 1$\alpha$, macrophage inflammatory protein Beta and macrophage inflammatory protein 1 [4] (Tay *et al*., 2020). Meanwhile, HIV infection is associated with various respiratory diseases and is an independent risk factor for non-infectious pulmonary complications such as chronic obstructive pulmonary disease (COPD), diffusing capacity impairment, asthma, and pulmonary hypertension despite antiretroviral therapy (ART) use. These conditions contribute to the increased mortality rate in this population. Systemic inflammation (IL6, CRP), monocytes activation (IL-2, sCD163 [soluble cluster of differentiation 163]) microbial translocation (lipopolysaccharide), and endothelial dysfunctions (endothelial-1) are linked to different non-infectious pulmonary diseases in HIV infection [5] (Therapy, 2019).

Reactive oxygen species (ROS) have been implicated as playing a central role in the pathogenesis of lung injury in both COVID-19 and HIV infections. The huge replication of SARS-CoV-2 in the epithelial cells of the lungs and the endothelial cells of the vessels in COVID-19 infection leads to large ROS production which is responsible for the destruction of CD8 cytotoxic and Cluster of diffentiation 4 (CD4) helper T cells [3], [6] (Chen *et al*., 2020; Raftery and Samstag, 2020). This results in the suppression of adaptive immune system [7] (Vardhana and Wolchok, 2020) and failure of production of antiviral antibodies and contributes to the lymphopenia observed in COVID-19 infection [3] (Raftery and Samstag, 2020). The imbalance oxidative stress response triggers pro-inflammatory cytokine storm with activation of redox-sensitive transcription factors (nuclear factor kappa-light-chain-enhancer of activated B cells) and interactions between cytokines Tumor necrosis factor-alpha (TNF-alpha) and Interleukin-1 [3] (Raftery and Samstag, 2020).

Different studies in HIV patients revealed oxidative stress, systemic inflammation, cellular senescence, immune activation, and endothelial dysfunction as central factors to the development of COPD in HIV-positive population [8] (Cribbs *et al*., 2020). The pathogenesis of lung disease in HIV infection involves an increase in monocyte, macrophage activation, and inflammatory markers (including IL-1, IL-6, IL-8 (Interleukin-8), and IL-15 (Interleukin-15), TNF- alpha, Granulocyte-macrophage colony stimulating factor (GM-CSF), and MIP-lα [9] (Agostini C, 1996). Individuals with HIV have significantly greater lung disease compared to healthy individuals due to viral replication, chronic inflammation, and defective immunity [8], [10] (Cribbs *et al*., 2020; Duncan *et al*., 2020).

### *Justification*

It has been established that severe infection and worse prognosis are experienced by older patients and those with comorbidities (hypertension, diabetes, cardiovascular disease, lung disease, and chronic kidney disease) [11] (Sanyaolu *et al*., 2020) but few case series have been reported globally on the incidence of COVID-19 infection in PLWH [2] (Del Amo *et al*., 2020).

HIV infection has not been identified as a risk factor for the development of severe COVID-19 infection rather, the state of suppressed immunity and ART are said to be protective [12] (Kanwugu and Adadi, 2021). Although both COVID-19 and HIV infections have been declared as pandemic at different times [13] (Eisinger *et al*., 2021) and both are known to cause lung injury, very few researches have been done to determine the possibility of worsened lung injury in HIV patients infected with COVID-19.

## Methods

The aim of the study is to explore the evidence available in the literature on the oxidative and inflammatory biomarkers associated with lung injury in HIV patients coinfected with COVID-19. Furthermore, to determine any difference in the outcome of COVID-19 infection among PLWH compared with their HIV-negative counterparts. The biomarkers included in the study were: Lymphocytes, platelets, hemoglobin (Hb), D-dimer, Lactate dehydrogenase (LDH), CRP, Erythrocyte sedimentation rate (ESR), IL-6, CD4 count, ferritin, and chest X-ray/computerized tomography (CT).

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, an exhaustive search was done using three databases: PubMed, Scopus, and Google Scholar.

### *Search strategy*

Search terms used in PubMed included the following: (HIV positive individuals) OR (p HIV) OR (people living with human immunodeficiency virus) OR (people living with acquired immune deficiency syndrome) OR (ploids) OR (HIV seropositive patients) AND (covid-19 positive patients) OR (coronavirus positive patients) OR (SARS-COV-2 positive patients) AND (biomarkers) OR (cytokines) OR (chemokines) OR (TNF-alpha) OR (tumor necrosis factor alpha) OR (IL-6) OR (Interleukin-6) OR (ifn-gamma) OR (interferon-gamma) OR (CRP) OR (c-reactive protein) OR (sCD163) OR (sCD-14) OR (Interleukin-1) OR (IL-1) OR (Interleukin-8) OR (IL-8) OR (Interleukin-15) OR (IL-15) OR (granulocyte-macrophage colony-stimulating factor) OR (GM-CSF) OR (macrophage inflammatory protein) OR (MIP) AND (lung injury) OR (impaired diffusion capacity) OR (abnormal lung function tests) OR (lung functional abnormalities) OR (lung structural abnormalities).

Search terms used in Scopus

1. “HIV positive individuals” OR PLWHIV OR “people living with Human Immunodeficiency Virus” OR “HIV seropositive patients”
2. “COVID-19 positive patients” OR “Coronavirus positive patients “OR “SARS-Cov-2 patients
3. Biomakers OR cytokines OR chemokines OR TNF-alpha* OR IL-6* OR IFN-gamma* OR “C- reactive protein” OR sCD-163* OR sCD-14* OR IL-1* OR IL-8* OR IL-15* OR “Granulocyte macrophage colony stimulating factor”* OR “Macrophage Inflammatory Protein”*
4. “Lung injury” OR “impaired diffusion capacity “OR “abnormal lung function tests” OR “Lung functional abnormalities” OR “lung structural abnormalities”
5. Google Scholar Search terms: HIV-positive COVID-19 positive lung injury oxidative inflammatory biomarkers.

### Study selection

Articles were included if they reported on the adult population; 18 years or above, HIV/AIDS patients co-infected with COVID-19, written in English, of any study design (case report, case series, cross-sectional, case-control, cohort and clinical trial) and published between January 1, 2019 and October 27, 2020. Abstracts were reviewed and articles with data on HIV/AIDS co-infected with COVID-19 who reported laboratory findings, especially inflammatory and oxidative biomarkers, with the outcome of the co-infection included. Authors independently screened all identified studies and assessed full texts to determine eligibility. Studies are excluded if they fail to present original empirical data (reviews, commentaries), and did not report any clinical data or laboratory findings of patients with HIV and COVID-19 co-infection. Duplicate records were excluded and disagreements over the inclusion of studies for data extraction were resolved through discussion or feedback from the senior author. The flow diagram of the literature search and study selection process is described in Figure 1.

### Data extraction

The following variables were extracted from the included studies: Lymphocytes, platelets, Hb, D-dimer, CRP, ESR, CD4 count, LDH, Ferritin, IL-6, others (procalcitonin, troponin, etc.), and radiological chest findings and outcome of the disease. The deranged biomarkers from each of the study were captured on the extraction table. Comorbidities coexisting with HIV included asthma, coronary artery disease, hypertension, hyperlipidemia, renal disease, hypothyroidism, syphilis, diabetes mellitus, COPD, obesity, atrial fibrillation, heart failure, pulmonary hypertension, bipolar disorder, hepatitis C virus, peripheral vascular disease, and malignancy. Data extraction was carried out using an extraction table which included; the surname of the first author, year of publication, study characteristics, laboratory biomarkers highlighting the deranged biomarkers, chest radiological findings, comorbidities, and outcome (Table 1).

### Quality assessment

The quality of the included papers was assessed using modified Joanna Briggs Institute's critical appraisal tools and the quality presented using numeric score. Selected studies were examined for inclusion criteria, sample size, description of study participants, setting, and the appropriateness of the statistical analysis. Methodological quality was independently assessed by two reviewers, and disagreements were resolved through discussion. Quality assessments were performed with different tools based on different study designs. Tools had eight items for case reports, ten items for case series, and 11 items for cohort studies. Quality assessment

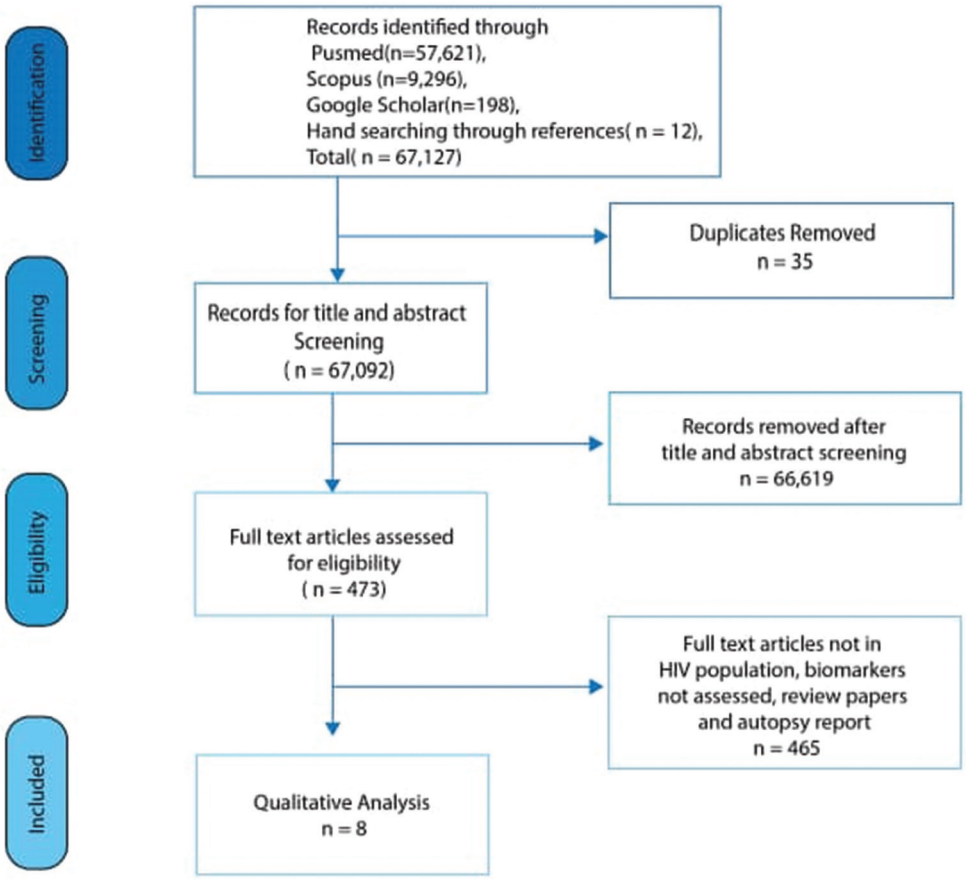


*Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow chart*

**Table 1: Study characteristics, outcomes, and laboratory biomarkers**

| Study | Country | Size (n) | Period | Age (years) | Male (n) | Design | Laboratory biomarkers | Deranged biomarkers | CXR/CT findings | Comorbidities | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pata *et al*., 2019 | USA | 3 | September 2020 | 50.3 | 2 | Case series | Hb<br>WBC<br>Platelets<br>ESR<br>CRP<br>PT<br>INR<br>APTT<br>D-dimer<br>Ferritin,<br>Fibrinogen<br>Troponin 1<br>Procalcitonin | Case 1: ESR-110 mm/h PT- 18 s INR- 1.54 APTT- 31.3 s D-dimer (max)- 2631 (<0.5) Fibrinogen- 801 mg/dL (200–400) LDH- 725U/L (140–280) CRP- 184 mg/L (<10) CD4 count- 157 cells/uL (500–1400)<br>Case 2: ESR- >120 mm/h PT- 11.9 s INR- 1.02 APTT- 32.3 s D-dimer (max)- 1.436 ng/mL Fibrinogen-482 mg/dl LDH- 956 U/L CRP- 341 mg/L Ferritin- 5.045 ng/mL CD4 count- 41 cells/uL<br>Case 3: ESR- 67 Mm/h PT- 15.9 s INR- 1.36 APTT- 33.4 s D-dimer- 4,491 ng/mL LDH- 905 U/L CRP- NA Ferritin- 5.045 ng/mL (20–250) CD4 count- 307 cells/Ul | 1. Multifocal patchy consolidations<br>2. Extensive bilateral patchy alveolar density in both lungs<br>3. Patchy infiltrates both lungs with ground-glass pattern | 1. Asthma, CAD, Hypertension, hyperlipidaemia HIV<br>2. End stage renal disease on dialysis, HIV<br>3. HIV | All recovered and discharged home |
| Blanco *et al*., 2020 | Spain | 5 | March–April 2020 | 37.8 | 3 | Case series | WBC<br>Lymphocyte<br>Platelets<br>LDH<br>CRP<br>D-dimer<br>Ferritin<br>Procalcitonin | Patient 1: NA<br>Patient 2: LDH-316U/L (140-280) CRP-30 mg/dL (<10) D-dimer->10,000 ng/mL (<0.5) Ferritin-1020 ng/mL (12–300) Patient 3: D-dimer-400 ng/mL<br>Patient 4: LDH–465U/L D-dimer-300 ng/mL Ferritin-1044 ng/mL<br>Patient 5: LDH-1149U/L CRP-40 mg/dL Ferritin-866 ng/mL | 2 normal CXR reports<br>1 Bilateral GGO<br>1 right basal interstttial infiltrate<br>1 right basal pneumonia with pleural effusion | 3 have none<br>1 hypothyroidism<br>1 asthma | 2 admitted in the ICU<br>4 recovered 1 left at the ICU |
| Zhang *et al*., 2020 | China | 2 | February–March 2020 | 30.5 | 2 | Case reports | Lymphocyte count<br>lymphocyte %<br>CRP<br>IL-6<br>Albumin<br>CD4 count | Patient 1: Lymphocyte %:17%(20–50)<br>CRP: 39.71 mg/L (0–4)<br>Hyperactive CRP: >10 mg/L (0–4)<br>Albumin: 38.2g/L (40–55)<br>IgM: 30.12 (<10)<br>IgG: 63.52 (<10)<br>IL-6: 688.40 pg/mL<br>CD4 count: 13 cells/uL (500–1600)<br>Patient 2: CRP: 96.51 mg/L (0–4) Hypersensitive CRP: >10 mg/L (0–4) Albumin: 33.2g/L (40–55) | 1. Bilateral multiple GGO worsened progressively with elevated IL-6<br>2. Multiple exudates in both lungs, then multiple large, slightly high density shadows in both lungs mostly with ground glass changes in the middle and outer zones | Both patients are Treponema pallidum positive HIV diagnosis for both patients were also made in this admission | Both discharged home in stable condition |
| Shalev *et al*., 2020 | USA | 31 | March–April 2020 | 60.7 | 24 | Case series | CD4 count<br>Viral load<br>CRP<br>Ferritin<br>D-dimer<br>Procalcitonin | CRP max, ug/mL-182.2 (1.1 to>300)<br>Ferritin max, ug/mL-1356.7 (80–7490)<br>D-dimer max, ug/mL-6.9 (0.3–20)<br>Procalcitonin max, ug/mL-2.2 (0.04–26.9) | 20 (64.5%) of the 30 patients showed abnormalities consistent with viral pneumonia | Hypertension<br>Diabetes Mellitus<br>Chronic kidney disease Asthma/ COPD Obesity | Alive-23<br>Deceased-8 |
| Karmen-Tuohy *et al*., 2020 | USA | 21 HIV-positive 42 non-HIV | March–April 2020 | HIV+: 60.04 ± 11.77 non-HIV: 61.48 ± 20.13 | HIV+: 19 non-HIV: 38 | Retrospective matched cohort study | Ferritin,<br>D-dimer,<br>Troponin<br>CRP<br>LDH | LDH peak, U/L: HIV+: 477.04 ± 210.37 (n = 21) Non-HIV: 436.30 ± 223.02 (n = 37) CRP peak, mg/L: HIV+: 185.13 ± 107.35 (n = 20) Non-HIV: 128.06 ± 99.29 (n = 38) Ferritin peak ng/mL: HIV+: 1446 (493–2209), n = 20 Non-HIV: 1156 (314–2148), n = 36 Procalcitonin peak, ng/mL: HIV+: 0.22 (0.11–0.42), n = 20 Non-HIV: 0.11 (0.06–0.28), n = 35 D-dimer peak, ng/mL:<br>< 1000: HIV+: 11 (57.9%), Non-HIV: 26 (76.5%)<br>1000–6000: HIV+: 5 (26.3%), Non-HIV: 6 (17.6%) >6000: HIV+: 3 (15.8%), Non-HIV: 2 (5.9%) | Abnormal initial chest X-ray: Bilateral: HIV+: 18 (94.7%), Non-HIV: 23 (85.2%) Unilateral: HIV+: 1 (5.3%), Non-HIV: 4 (14.8%) | Hypertension: HIV+: 7 (33.3%) Non-HIV: 16 (38.1%) Hyperlipidaemia: HIV+: 4 (19%) Non-HIV: 9 (21.4%) Coronary Artery Disease: HIV+: 1 (4.8%) Non-HIV: 3 (7.1%) Peripheral vascular disease: HIV+: 1 (4.8%) Non-HIV: 1 (2.4%) Asthma/COPD: HIV+: 4 (19%) Non-HIV: 6 (14.3%) Diabetes: HIV+: 4 (19%) Non-HIV: 8 (19%) Malignancy: HIV+: 3 (14.3%) Non-HIV: | Invasive Ventilation: HIV+: 5 (23.8%) Non-HIV: 5 (11.9%) Needed ICU: HIV+: 6 (28.6%) Non-HIV: 7 (16.7%) Died/ transferred to hospice: HIV+: 6 (28.6%) Non-HIV: 10 (23.8%) |

*(Contd...)*

**Table 1:** ***(Continued)***

| Study | Country | Size (n) | Period | Age (years) | Male (n) | Design | Laboratory biomarkers | Deranged biomarkers | CXR/CT findings | Comorbidities | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 3 (7.1%) Chronic Kidney Disease: HIV+: 4 (19%) Non-HIV: 7 (16.7%) | |
| Suwanwongse *et al.*, 2020 | USA | 9 | March–April 2020 | 58 | 7 | Case series | Ferritin, d-dimer, CRP, IL-6 | Ferritin, mg/dL (mean): 570 (56–1.010) n = 6 D-dimer, ng/mL (mean): 5,734.86 (176–37,946) n = 7 CRP, ng/dL (mean): 13.96 (0.25–37) n = 7 IL-6, pg/mL (mean): 133.8 (50–251) n = 5 | 1 normal chest X-ray<br>4 bilateral GGO<br>1 bilateral interstitial infiltrates<br>3 multifocal infiltrates | Tertiary Syphilis-1 HCV-3 Obesity-1 Hyperlipidaemia-4 Hypertension-5 COPD-4 Atrial fibrillation-2 Heart failure-1 Diabetes-3 Pulmonary hypertension-1 | Survived-2 Died-7: Septic shock from C-19:3 Hypoxemic RSF from C-19:2 ARDS from C-19:2 |
| Aydin *et al.*, 2020 | Turkey | 4 | Mar-20 | 37.3 | 4 | Case series | Ferritin, fibrinogen, CRP, LDH | Case1: Fibrinogen- 464 mg/dL (200–400)<br>Ferritin- 339 ng/mL (20–250)<br>LDH- 308 U/L (140–280)<br>CRP- 27 mg/L (<10)<br>Lymphocyte- 360 mm/mm$^3$ (1000–4800)<br>CD4 count- 2.8 mm$^3$ (500–1400)<br>Case 2: Lymphopaenia- 670/mm$^3$<br>LDH- 575 U/L CRP- 152 mg/L Ferritin- 819 ng/mL<br>D-dimer- 1.5 mg/L (<0.5)<br>Case 3: 5-fold CRP elevation CD4 count- 448/mm$^3$ other lab investigations were within normal limits<br>Case 4: Platelets- 94,000/mm$^3$ (150,000–400,000)<br>Lymphocytes- 900/mm$^3$<br>CD4 count- 396/mm$^3$<br>3-fold CRP elevation other parameters were normal | All showed ground-glass lesions | Case 1: HBV/bipolar disorder Case 2: Hypertesion Diabetes COPD Obesity Case 3: None reported Case 4: None reported. | Recovered-3 Dead-1 |
| Wang *et al*., 2020 | China | 1 | February–March 2020 | 37 | 1 | Case report | CRP<br>LDH<br>GGT<br>HBDH<br>ALB<br>AST<br>ALT<br>IL-6 | CRP- 96.51 mg/L(<10) GGT- 136 U/L (0–30) LDH-423 U/L (140–280) a-HBDH- 318 IU/L (96–190) IL-6-9.87, 141.4 pg/mL (5–15) | Bilateral diffuse ground glass appearance with some patchy consolidations | Syphilis | Recovered |

CT: Computerized tomography, Hb: Hemoglobin, WBC: White blood count, ESR: Erythrocyte sedimentation rate, INR: International, normalized ratio, APTT: Activated partial thromboplastin Time, LDH: Lactate dehydrogenase, HBDH: Hydroxybutyrate dehydrogenase, CRP: C-reactive protein, CXR: Chest X-ray, ICU: Intensive care unit, IL: Interleukin, CD: Cluster of differentiation, COPD: Chronic obstructive pulmonary disease, GGT: Gamma-glutamyl transferase, ALB: Albumin, AST: Aspartate aminotransferase, ALT: Alanine transaminase, CAD: Coronary artery disease, HIV: Human immunodeficiency virus, GGO: Ground glass opacities, PT: Prothrombin time, RSF: Respiratory failure.

tools and scores are presented in Tables 2 and 3. The Joanna Briggs Institute critical appraisal tools (https://joannabriggs.org/ebp/critical_appraisal_tools) were used to assess the methodological quality of the included papers. Tables 3a-c present the details of quality assessment tools and scores given to each item.

## Results

A review of three databases (PubMed, Scopus, and Google Scholar) identified 67,127 publications that reported on either COVID-19 infection, lung injury,

**Table 2: Biomarkers assessed in the included studies**

| Biomarkers | Studies (size) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Parameter | *Wang et al*. [15] | *Zhang et al*. [16] | *Pata et al*. [17] | *Altuntas et al*. [19] | *Blanco et al*. [14] | *Suwanwongse et al*. [18] | *Karmen-Touhy* [21] | *Shalev et al*. [20] |
| CRP | Elevated | Elevated in 2 | Elevated in 2 | Elevated in all | Elevated in 2 of 4 | Elevated in 3 of 9 | Elevated (18) | Elevated mean |
| LDH (140–280 U/L) | Elevated | NA | Elevated in all | Elevated in 2 | Elevated in 3 of 4 | NA | Elevated (5) | NA |
| D-dimer (<500 ng/mL) | NA | NA | Elevated in all | Elevated in 1 | Elevated in 3 of 3 | Elevated in all 7 | Elevated (17) | Elevated mean |
| Ferritin (10–300) | NA | NA | Elevated in 1 | Elevated in 2 | Elevated in 3 of 3 | Elevated in all 7 | Elevated (19) | Elevated |
| IL-6 (0–16.4 pg/mL) | Elevated | Elevated in 2 | NA | NA | NA | Elevated in all 5 | NA | IL-6 |
| Procalcitonin (<0.15 ng/mL) | NA | NA | Elevated in 1 of 2 | Normal in 1 | Normal in 1 | NA | Elevated (20) | Elevated mean |
| Fibrinogen (200–400 mg/dL) | NA | NA | Elevated in 2 | Elevated in 1 | NA | NA | NA | NA |
| Albumin (33–55 g/L) | Normal and dropped | Low in 2 | NA | NA | NA | NA | NA | NA |
| WBC (4,500–11,000/mL) | Initially normal but dropped | Normal in 2 | Normal in 3 | Low in 1 | Elevated in 2 of 5 | Elevated in 2 | Normal (20) | NA |
| Lymphocyte (800–5000/mcL) | Initially normal but dropped | Drop in the 2 | Elevated in 1 | Lymphopaenia in 3 | Normal in all | NA | Normal (21) | NA |
| Lymphocye % (20–40%) | NA | Dropped | NA | NA | NA | Low in 6 of 9 | NA | Low: 12.6 (mean) |
| Platelets | NA | NA | NA | Low in 1 | NA | NA | NA | NA |
| Troponin (0–0.4) | NA | NA | NA | NA | NA | Normal (18) | Normal (18) | NA |
| AST | NA | NA | NA | NA | NA | NA | NA | NA |
| ALT | NA | NA | NA | NA | NA | NA | NA | NA |
| GGT (0–30 U/L) | Elevated | NA | NA | NA | NA | NA | NA | NA |
| HCRP | NA | Elevated in 2 | NA | NA | NA | NA | NA | NA |
| IgG (SARS-CoV-2) | Neg | Elevated in 1, normal in 2 | NA | NA | NA | NA | NA | NA |
| IgM (SARS-CoV-2) | Neg | Elevated in 1, normal in 2 | NA | NA | NA | NA | NA | NA |
| RT-PCR assay | Neg | Neg in 2 | NA | Positive in all | Positive in all | NA | Positive in all | Positive in all |
| ESR | | NA | Elevated in all | NA | | NA | NA | NA |
| HIV RNA | NA | NA | <20 in 2, 35 in 1 | Neg in 1 (died) | <50–45500 | ND in 4 1 unknown | <50 (15 of 17) | <37 (28) |
| CD4 count (500–1200/mm) | Low: 34 | Very low: 13,23 | 157,41,307 | 2.8–1385 | 13–1140 | 179-1827 | Low: 298 mean (19) | Low: 3967 (mean) |

CRP: C-reactive protein, LDH: Lactate dehydrogenase, IL: Interleukin, WBC: White blood count, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutamyl transaminase, HCRP: High sensitivity C-reactive protein, IgG: Immunoglobulin G, IgM: Immunoglobulin M, RT-PCR: Reverse transcription polymerase chain reaction, RNA: Ribonucleic acid: RNA, NA: Not available, Neg: Negative, ND: Not detectable, ESR: Erythrocyte sedimentation rate.

**Table 3a: Critical appraisal for case-report studies included in the review**

| First Author (Ref) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Total score |
|---|---|---|---|---|---|---|---|---|---|
| Wang *et al*. [15] | Yes | No | Yes | Yes | Yes | Yes | No | Yes | 6/8 |
| Pata *et al*. [16] | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | 7/8 |
| Zhang *et al*. [13] | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | 7/8 |

Were patient's demographic characteristics clearly described?
Was the patient's history clearly described and presented as a timeline?
Was the current clinical condition of the patient on presentation clearly described?
Were diagnostic tests or assessment methods and the results clearly described?
Was the intervention (s) or treatment procedure (s) clearly described?
Was the post-intervention clinical condition clearly described?
Were adverse events (harms) or unanticipated events identified and described?
Does the case report provide takeaway lessons?

**Table 3b: Critical appraisal for case-series studies included in the review**

| First Author (Ref) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Blanco *et al*. [14] | No | No | No | Yes | Yes | Yes | Yes | Yes | No | Yes | 6/10 |
| Altuntas Aydin *et al*. [19] | No | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Yes | 7/10 |
| Suwanwongse *et al*. [18] | No | No | No | Yes | No | Yes | Yes | Yes | No | Yes | 5/10 |
| Shalev *et al*. [20] | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | 8/10 |

Were there clear criteria for inclusion in the case series?
Was the condition measured in a standard, reliable way for all participants included in the case series?
Were valid methods used for the identification of the condition for all participants included in the case series?
Did the case series have consecutive inclusion of participants?
Did the case series have a complete inclusion of participants?
Was there clear reporting of the demographics of the participants in the study?
Was there clear reporting of clinical information of the participants?
Were the outcomes or follow-up results of cases clearly reported?
Was there clear reporting of the presenting site (s)/clinic (s) demographic information?
Was statistical analysis appropriate?

**Table 3c: Critical appraisal for cohort studies included in the review**

| First Author (Ref) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | Total score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Karmen-Tuohy *et al*. [21] | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 8/11 |

Were the two groups similar and recruited from the same population?
Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Was the exposure measured in a valid and reliable way?
Were confounding factors identified?
Were strategies to deal with confounding factors stated?
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
Were the outcomes measured in a valid and reliable way?
Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
Was follow-up complete, and if not, were the reasons to loss to follow up described and explored?
Were strategies to address incomplete follow-up utilized?
Was appropriate statistical analysis used?

oxidative or inflammatory biomarkers, and COVID-19 infection among PLWH. After the removal of duplicates (n = 35), 67,092 articles were assessed for the title and abstract screening. The full texts of 473 articles were assessed for eligibility, and 465 were excluded, among which were those not specific to HIV population, those without the assessment of biomarkers, review papers, and autopsy reports. The search identified eight studies that met the inclusion criteria and were included in the qualitative analysis of the systematic review. Of the eight studies, three were case reports describing 1–3 patients, four case series including 4–31 patients, and one were a cohort study. Four studies were from the USA, two from China, and one each from Spain and Turkey. The publication dates ranged from April 15 to December 12, 2020. The Joanna Briggs Institute critical appraisal tools assessment scores ranged from 6 to 7 for case reports (out of eight possible points), 5–8 (out of 10 possible points) for case series, and the cohort study scored eight (out of 11 possible points). The scores were not directly compared since the assessment was done using different assessment tools based on the study design. A total of 76 patients with COVID-19 and HIV coinfection were assessed in the review with different levels of completeness of demographic and clinical data (Table 4).

Most patients were male (62, 81.6%), 12 (15.7%) were female while 2 (2.63%) were transgender. The mean age of patients was 55.6 years and almost all the participants (72, 94.7%) were on ART before COVID-19 coinfection, the remaining 4 (5.3%) participants that were HAART-naïve were newly diagnosed on admission for COVID-19 infection [14], [15], [16] (Blanco *et al*., 2020; Wang *et al*., 2020; Zhang *et al*., 2020). The multi-morbidity reported included hypertension (35, 46%), obesity (11,14%), hyperlipidemia (9, 11.8%), COPD (18, 23.7%), diabetes (21, 27.6%), CVD (4.5, 3%), renal insufficiency (12,15.8%), hypothyroidism (1, 1.3%), syphilis (4, 5.3%). The following biomarkers were found abnormal; CRP, LDH, IL-6, D-dimer, ferritin, HCRP, fibrinogen, procalcitonin, and CRP was the commonest abnormal biomarker reported (14, 18.4%). Only three (3.9%) of the participants had normal chest findings on either chest X-ray or chest computer tomography (CT), others all have varying features consistent with viral pneumonia; from multifocal infiltrates, interstitial infiltrates, exudates, and ground glass opacities which may be patchy or extensive. All that reported lung changes indicated that the infection affected both lung fields.

Table 5 shows the reported symptoms, severity, and the final outcome of HIV and COVID-19 coinfection among participants. The most common of the symptoms were fever (40/52.6%), cough (18/23.7%), and dyspnea (17/22.4%). Other symptoms reported include gastrointestinal symptoms (5/6.6%), headache (3, 3/9%), arthralgia/myalgia (2/2.6%), and sore throat (1/1.32%).

COVID-19 was reported as mild in 8 of 55 (14.5%), moderate in another 8 patients (14.5%), severe in 31 patients (56.3%), and critical in 7 patients (12.7%). All the patients were hospitalized, 10 were admitted in the intensive care unit, 22 of 76 (28.9%) were reported dead, 39 (51%) discharged, 11 (14.5%) transferred while 3 (3.9%) patients were still on admission.

### *Complete blood count biomarkers*

#### *Lymphocytes (cells/mL)*

All the included studies provided data on the lymphocyte count of the subjects. One of the included studies [17] (Pata *et al*., n.d.), recorded normal WBC in all the three cases reported while others observed either a mixture of normal or markedly elevated WBC [14], [18] (Blanco *et al*., 2020; Suwanwongse and Shabarek, 2020), a consistent drop in lymphocyte count [15], [16] (Wang *et al*., 2020; Zhang *et al*., 2020) or lymphopenia in all cases [19], [20] (Altuntas Aydin *et al*., 2020; Shalev *et al*., 2020). The only cohort study observed slightly higher total WBC among the HIV-infected cohort compared to non-HIV subjects: 8.3 (7.1–12.4) and 7.3 (5.5–11.6), respectively [21] (Karmen-Tuohy *et al*., 2020).

#### *Platelets (cells/mL)*

Three of the studies reported normal platelet count [17], [16], [22], (Blanco *et al*., 2020; Pata *et al*., n.d.; Zhang *et al*., 2020), one observed a reduction in platelet count [19] (Altuntas Aydin *et al*., 2020) while 4 studies presented no data on the platelet counts of the subjects [15], [18], [20], [21]. (Karmen-Tuohy *et al*., 2020; Shalev *et al*., 2020; Suwanwongse and Shabarek, 2020; Wang *et al*., 2020).

#### *CD4 count*

All the studies provided data on the CD4 count of the subjects, which ranged between 13 and 1827 cells/cubic millimeter.

There were mixtures of CD4 count levels recorded by the included studies, the lowest was 13 cells/mL in two ART-naive participants [15], [16] (Blanco *et al*., 2020; Zhang *et al*., 2020), and both were cured while the highest 1827 cells/mL died of septic shock due to COVID-19 infection. This supports the theory that HIV-related lymphopenia may be protective against severe clinical manifestations despite susceptibility to COVID-19 [22] (Chen *et al*., 2020). Although lymphopenia in healthy patients infected with SARS-CoV-2 signifies severe progression of the disease, lymphopenia in HAART-naive HIV-infected patients due to uncontrolled viral replication changes the hyperactive immune response to COVID-19

**Table 4: Demographics of participants**

| Study | Age | Sex | ART | CD4 count | Viral load | Multimorbidity | At least 1 morbidity | Hypertension | Obesity | Hyperlipidaemia | COPD | DM | CVD | Renal insufficiency |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aydin *et al.*, 2020 | 34 | M | Yes | 2.8/mm$^3$ | 434782 copies/ml | Yes | NA | NA | NA | NA | NA | NA | NA | NA |
| | 44 | M | Yes | 1385/mm$^3$ | Negative | Yes | NA | Yes | Yes | NA | Yes | Yes | NA | NA |
| | 35 | M | Yes | 448/mm$^3$ | Negative | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| | 36 | M | Yes | 396/mm$^3$ | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Zhang *et al.*, 2020 | 24 | M | No | 13 cells/microL | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| | 37 | M | No | 23 cells/microL | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Blanco *et al.*, 2020 | 40 | TG | Yes | 616 cells/microL | < 50 | None | None | NA | NA | NA | NA | NA | NA | NA |
| | 49 | M | Yes | 445 cells/microL | < 50 | NA | Yes | NA | NA | NA | NA | NA | NA | NA |
| | 29 | M | Yes | 604 cells/microL | < 50 | None | None | NA | NA | NA | NA | NA | NA | NA |
| | 40 | M | Yes | 1140 cells/microL | < 50 | NA | Yes | NA | NA | NA | Yes (Asthma) | NA | NA | NA |
| | 31 | TG | No | 13 cells/microL | 45,5 | None | None | NA | NA | NA | NA | NA | NA | NA |
| Wang *et al.*, 2020 | 37 | M | No | 34/uL | NA | NA | Yes | NA | NA | NA | NA | NA | NA | NA |
| Pata *et al.*, 2020 | 67 | F | Yes | 157 cells/uL | < 20 | Yes | NA | Yes | NA | Yes | NA | NA | Yes | NA |
| | 31 | M | Yes | 41 cells/uL | 35 | NA | Yes | NA | NA | NA | NA | NA | NA | Yes |
| | 32 | M | Yes | 41 cells/uL | 35 | NA | Yes | NA | NA | NA | NA | NA | NA | Yes |
| Suwanwongse *et al.*, 2020 | 37 | M | Yes | 425 cells/uL | < 20 | Yes | NA | NA | NA | NA | NA | NA | NA | NA |
| | 31 | M | Yes | 636 cells/uL | Not detected | Yes | NA | NA | Yes | Yes | NA | NA | NA | NA |
| | 70 | M | Yes | 1827 cells/uL | Not detected | Yes | NA | Yes | NA | Yes | Yes | NA | Yes | NA |
| | 76 | F | Yes | 698 cells/uL | < 30 | NA | Yes | NA | NA | NA | NA | Yes | NA | NA |
| | 63 | M | Yes | 243 cells/uL | < 30 | NA | Yes | Yes | NA | NA | NA | NA | NA | NA |
| | 52 | M | Yes | 504 cells/uL | 31 | NA | Yes | NA | NA | NA | NA | Yes | NA | NA |
| | 58 | M | No | 179 cells/uL | Not detected | Yes | NA | Yes | NA | Yes | Yes | Yes | NA | NA |
| | 52 | M | Yes | Unknown | Unknown | Yes | NA | Yes | NA | Yes | Yes | NA | NA | NA |
| | 76 | F | Yes | 420 cells/uL | Not detected | Yes | NA | Yes | NA | NA | Yes | NA | Yes | NA |
| Karmen-Tuohy *et al.*, 2020 | 60.04 ± 11.77* (no. 21) | M: 19 (90.5%); F: 2 (9.52%) | Yes | 298 (135–542), (no. 19, 90.5%) | ≤ 50 (no. 20,95%) | Yes | NA | 7 (33.3%) | NA | 4 (19%) | 4 (19%) | 4 (19%) | 1 (4.8%) | 4 (19%) |
| Shalev *et al.*, 2020 | 60.7 (23–89)* (no. 31) | M: 24 (77.4%); F: 7 (22.6%) | Yes | 396 (89–924) (no. 31, 100%) | < 200 copies/mL (no. 30, 96.8%) | Yes (no. 22, 71%) | NA | 21 (67.7%) | Yes (no. 9,33.3.%) | NA | 8 (25.8%) | 13 (41.9%) | NA | 7 (22.6%) |

| Study | HBV/HCV | Hypothyroidism | Others | Smoking | Chest finding on auscultation | Oxygen saturation on admission | Abnormal biomarker | Chest X-ray/CT chest |
|---|---|---|---|---|---|---|---|---|
| Aydin *et al.*, 2020 | Yes (HBV) | NA | Bipolar disorder | NA | Bilateral coarseness both lungs | NA | Fibrinogen, ferritin, CRP, LDH | Multiple GGO in the bilateral lower lung |
| | NA | NA | NA | NA | NA | 92% | LDH, CRP, Ferritin, AST, D-dimer | Bilateral patch-like paving-stone view, large GG lesions |
| | NA | NA | NA | NA | NA | 95% | CRP | Bilateral peripheral, incomplete GG, density infiltrations |
| | NA | NA | NA | NA | NA | NA | CRP | Bilateral extended GG opacities |
| Zhang *et al.*, 2020 | NA | NA | Syphilis | NA | NA | NA | CRP, IL-6, HCRP | Bilateral GGO |
| | NA | NA | Syphilis | NA | NA | NA (95% on day 4, 80% lowest) | CRP, IL-6, HCRP | Multiple exudates both lungs |
| Blanco *et al.*, 2020 | NA | NA | NA | NA | NA | 100% | NA | Normal |
| | NA | Yes | NA | NA | NA | <90% | LDH, CRP, D-dimer, Ferritin | Bilateral GGO |
| | NA | NA | NA | NA | NA | 97% | D-dimer | Normal |
| | NA | NA | NA | NA | NA | 94% | LDH, D-dimer, Ferritin | Right basal interstitial infiltrate |
| | NA | NA | NA | NA | NA | <90% | LDH, CRP, Ferritin | |
| Wang *et al.*, 2020 | NA | NA | Syphilis | NA | NA | 85–90% | LDH, CRP | Multiple infiltrations both lungs |
| Pata *et al.*, 2020 | NA | NA | NA | NA | NA | 86.40% | D-dimer, LDH, Fibrinogen, CRP | Multifocal patchy consolidations |
| | NA | NA | NA | NA | NA | 91.20% | D-dimer, Fibrinogen, LDH, CRP, Procalcitonin, Troponin | Extensive bilateral patchy alvolar density |
| | NA | NA | NA | NA | NA | 91.20% | D-dimer, Fibrinogen, LDH, CRP, Procalcitonin, Troponin | Extensive bilateral patchy alvolar density |

(Contd...)

**Table 4: *(Continued)***

| Study | HBV/HCV | Hypothyroidism | Others | Smoking | Chest finding on auscultation | Oxygen saturation on admission | Abnormal biomarker | Chest X-ray/CT chest |
|---|---|---|---|---|---|---|---|---|
| Suwanwongse *et al.*, 2020 | Yes | NA | Syphilis | NA | NA | 100% | D-dimer | Normal |
| | NA | NA | NA | NA | NA | 95% | D-dimer | Bilateral multifocal infiltrate |
| | Yes (HCV) | NA | NA | NA | NA | 70% | IL-6, FER | Bilateral GGO |
| | NA | NA | NA | NA | NA | 88-90% | CRP, D-dimer, Ferritin | Bilateral GGO |
| | NA | NA | NA | NA | NA | 95% | Ferritin | Bilateral GGO |
| | NA | NA | NA | NA | NA | 75% | CRP, D-dimer, Ferritin | Bilateral GGO |
| | NA | NA | NA | NA | NA | 85% | CRP, D-dimer, IL-6 | Bilateral interstitial infiltrated |
| | Yes (HBV) | NA | NA | NA | NA | 96% | D-dimer | Bilateral multifocal infiltrate |
| | NA | NA | Pulmonary hypertension | NA | NA | 82% | D-dimer, IL-6 | Bilateral multifocal infiltrate |
| Karmen-Tuohy *et al.*, 2020 | NA | NA | Peripheral vascular disease: 1 (4.8%); Malignancy: 3 (14.3%) | Former: 3 (14.3%); Current: 2 (9.5%); Never/Unknown: 16 (76.2%) | NA | NA | Ferritin, D-dimer, CRP, LDH | Abnormal initial chest X-ray-19 (90.5%): consolidation, infiltrate or opacity. Bilateral-18 (94.7%); Unilateral: 1 (5.5%) |
| Shalev *et al.*, 2020 | NA | NA | NA | Current or former smoker: 13 (42%) | NA | NA | CRP, Ferritin, D-dimer | Chest X-ray abnormalities consistent with viral pneumonia: 20 (64.5%) |

*mean: M: Male, F: Female, TG: Transgender, NA: Not available, HCV: Hepatitis C, HBV: Hepatitis B virus, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IL: Interleukin, HCRP: High sensitivity, GG: Ground glass, GGO: Ground glass opacities.

infection and therefore protective [23] (Mascolo *et al*., 2020). One of the included studies with the largest case series observed that all HIV-positive patients coinfected with COVID-19 were on ART and virologically suppressed [20] (Shalev *et al*., 2020). The hospital which was the location of the study is an active inpatient care center for people with uncontrolled HIV and AIDS-related complications. Despite the kind of people this hospital serves and its location in New York where one-quarter of PLWH are not virologically suppressed, none of those with uncontrolled HIV or AIDS have been admitted for COVID-19 infection.

Another included study that reported high mortality also observed a lower average CD4 count of the participants than in other studies [18] (Suwanwongse and Shabarek, 2020). This is in contrast to the hypothesis of more favorable outcome for HIV-positive patients co-infected with COVID-19 due to the prevention of excessive cytokine storm from lymphopenia and immunosuppression which are hallmarks of HIV infection [23] (Mascolo *et al*., 2020). It was proposed that HIV lymphopenia delays the clearance of the virus and promote the progression of the disease and that the pathogenesis of cytokine storm in severe COVID-19 may be from dysregulation of B lymphocytes so that HIV-related T-cell suppression does not confer any protective role on COVID-19 infection.

### *Biomarkers*

#### *C-reactive protein (CRP)*

CRP was significantly higher in HIV-positive patients than in non-HIV patients (HIV+: 185.13 ± 107.35 vs. non-HIV: 128.06 ± 99.29, p = 0.024) in the only cohort study of included in this review [22] (Karmen-Tuohy *et al*., 2020). There was a weak association between highest CRP values and mortality among HIV-positive patients in the same study (odds ratio: 1.026, 95% CI: 1.002–1.051, n = 20). The study with the highest mortality (77%) [19] (Suwanwongse and Shabarek, 2020), reported normal CRP levels in four out of seven patients assessed, elevated CRP was observed in three of the seven, and normal in two of the mortality cases. Four of the included studies reported elevated CRP in all the participants assessed, while Blanco observed normal levels in two of the four assessed [16], [17], [19], [20] (Altuntas Aydin *et al*., 2020; Pata *et al*., n.d.; Shalev *et al*., 2020; Zhang *et al*., 2020).

#### *Interleukin 6 (IL-6)*

IL-6 was assessed in three out of the eight included studies [15], [16], [18] (Suwanwongse and Shabarek, 2020; Wang *et al*., 2020; Zhang *et al*., 2020). The levels were high in all three studies and increased drastically within 5 days in one of them [15] (Wang *et al*.,

**Table 5: COVID-19 Symptoms reported in each study**

| | Covid-19 symptoms | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Fever | Cough | Dyspnoea | Head ache | Arthralgia /myalgia | Sore throat | GIT symptoms | Others | Severity: M/MD/S/C | Hospitalized | ICU | Death | Discharged | Transferred |
| Aydin, 2020 | | | | | | | | | | | | | | |
| Case 1 | Yes | Yes | Yes | NA | NA | NA | NA | NA | NA | Yes | No | No | Yes | No |
| Case 2 | Yes | Yes | Yes | NA | NA | NA | NA | NA | S | Yes | Yes | Yes(2nd day of admission) | No | No |
| Case 3 | NA | Yes | NA | NA | NA | NA | Yes (non-bloody diarrhoea) | Severe weakness | M | Yes | No | No | Yes | No |
| Case 4 | Yes | Yes | NA | NA | NA | NA | NA | NA | M | Yes | No | No | Yes(7th day of admission) | No |
| Zhang, 2020 | | | | | | | | | | | | | | |
| Case 1 | Yes | NA | Yes | NA | NA | Yes | Yes (poor appetite) | NA | MD | Yes | NA | No | NA | Yes |
| Case 2 | Yes | NA | Yes | NA | NA | NA | NA | Chest pain | MD | Yes | No | No | NA | Yes (day 27) |
| . | | | | | | | | | | | | | | |
| Blanco,2020 | | | | | | | | | | | | | | |
| Patient 1 | Yes | Yes | Yes | NA | NA | NA | NA | Malaise | M | Yes | No | No | Yes(1 day) | No |
| Patient 2 | Yes | Yes | NA | NA | NA | NA | NA | NA | S | Yes | Yes | NA | NA: still on admission | NA |
| Patient 3 | Yes | Yes | Yes | Yes | NA | NA | NA | Malaise | M | Yes | No | No | Yes (3rd day) | No |
| Patient 4 | Yes | Yes | Yes | Yes | NA | NA | NA | Malaise | MD | Yes | No | No | Yes(4) | No |
| Patient 5 | Yes | Yes | Yes | NA | NA | NA | NA | NA | S | Yes | Yes | No | Yes(12) | No |
| Wang,2020 | | | | | | | | | | | | | | |
| | Yes | Yes | NA | NA | NA | NA | NA | Chest pain, palpitations | MD | Yes | NA | No | NA | Yes |
| Pata,2020 | | | | | | | | | | | | | | |
| | Yes | NA | Yes | NA | NA | NA | Yes (non-bloody diarrhoea) | Weakness | MD | Yes | NA | No | Yes | NA |
| | NA | Yes | Yes | NA | NA | NA | Yes(abdominal pain) | NA | S | Yes | Yes | No | Yes (16th day) | NA |
| | NA | Yes | Yes | NA | NA | NA | Yes (abdominal pain) | NA | S | Yes | Yes | No | Yes (16th day) | NA |
| | YES | Yes | Yes | Yes | Yes | NA | NA | Feeling unwell | M | Yes | NA | No | Yes (10th day) | NA |
| Suwanwongse,2020 | | | | | | | | | | | | | | |
| Patient 1 | NA | Yes | NA | NA | Yes | NA | NA | Rhinorrhea | M | Yes | NA | No | Yes (LOS-1) | NA |
| Patient 2 | Yes | Yes | Yes | NA | NA | NA | NA | NA | M | Yes | NA | No | Yes (3rd day) | NA |
| Patient 3 | NA | NA | Yes | NA | NA | NA | NA | NA | S | Yes | NA | Yes (day 12) | No | NA |
| Patient 4 | Yes | Yes | NA | NA | NA | NA | NA | NA | S | Yes | NA | Yes (day 7) | No | NA |
| Patient 5 | Yes | NA | NA | NA | NA | NA | Yes (watery diarrhoea), vomiting) | NA | MD | Yes | NA | Yes (day 13) | No | NA |
| Patient 6 | NA | NA | Yes | NA | NA | NA | NA | NA | S | Yes | NA | Yes | No | NA |
| Patient 7 | Yes | Yes | Yes | NA | NA | NA | NA | NA | S | Yes | NA | Yes | No | NA |
| Patient 8 | NA | Yes | Yes | NA | NA | NA | NA | NA | S | Yes | NA | Yes | No | NA |
| Patient 9 | NA | Yes | Yes | NA | NA | NA | NA | NA | S | Yes | NA | Yes | No | NA |
| Karmen-Tuohy,2020 (N=21) | NA | NA | NA | NA | NA | NA | NA | NA | NA | Yes | 6(28.6%) | 6(28.6%) | 15(71.4%) | NA |
| Shalev, 2020 (N=31) | Yes:23 (74.2%) | NA | NA | NA | NA | NA | NA | NA | M:1(3.2%) MD:2(6.5%) S:21(67.7%) C:7(22.6%) | Yes | NA | 8(25.8%) | 13(41.9%) | 8(25.8%) |
| | 40 | 18 | 17 | 3 | 2 | 1 | 5 | | | | 10 | 22 | 25 | |

* M- Mild, MD-Moderate, S-Severe, C-Critical, ICU-Intensive Care Unit.

2020). Despite the use of IL-6 inhibitor (Tocilizumab) in this particular case to fight inflammation, there was no reduction in the patient's IL-6 levels. Although one of the studies reported the use of IL-6 receptor antagonist (Tocilizumab) in two of the patients, IL-6 level was not assessed in the study [20] (Shalev *et al*., 2020). Serum IL-6 has been found to be associated to the severity of COVID-19 infection in the general population and the inclusion in diagnostic workup to stratify disease severity has been proposed [16] (Zhang *et al*., 2020).

*Other biomarkers*

D-dimer, LDH, and ferritin are other important biomarkers of COVID-19. They are all associated with inflammation and coagulation observed in COVID-19 [24] (Hong *et al*., 2021). The severity of the infection determines the changes in levels of these biomarkers this can be used as a guide to treatment options and admission to ICU [25] (Kermali *et al*., 2020). Six of the included studies reported on D-dimer with a total size of 62 (81.6%) patients evaluated, LDH was reported in five of eight studies, assessed in a total of 24 (31.2%) patients while ferritin was reported in six of the eight included studies, assessed in 63 of 76 (82.9%) subjects. These biomarkers were all elevated in all subjects assessed.

***Lung findings***

There were various levels of abnormalities discovered in the lungs of HIV-positive patients co-infected with COVID-19 from interstitial infiltrate, multiple exudates, and ground glass opacities. One of the studies [18] (Suwanwongse and Shabarek, 2020), observed similar typical CXR abnormalities representing c-19 pneumonia seen among all HIV patients regardless of CD4 count. The only cohort study included in the review reported that a greater percentage of HIV-positive patients had an abnormal finding of consolidation, infiltrate, or opacity on initial chest imaging than non-HIV patients (HIV+: 19 [90.5%] vs. non-HIV: 27 [64.3%]), although no statistical difference was seen between the groups. [22] (Karmen-Tuohy *et al*., 2020). Another study noted the progression of lung abnormalities as the disease condition progressed. The ground glass opacity was initially seen mainly at the periphery of the lungs, but progressively worsened from days 4, 12, 15, and 25. The lung infection volume was found to have increased in equal proportion through the artificial intelligence technology of chest CT [16] (Zhang *et al*., 2020).

## Discussion

About 20% of patients infected with SARS-CoV-2 (COVID-19) develop potentially life-threatening pathologies involving acute inflammation, cytokine storm, septic shock complications, coagulation dysfunction, metabolic acidosis, hypoxia, and multiple organ failure in the general population. [26] (Guo *et al*., 2020). Despite the immunosuppression and comorbidities associated with HIV/AIDS, the susceptibility to COVID-19 and the risk of mortality among PLWHA is still largely unknown [27] (Ssentongo *et al*., 2021). Damage to the immune system and lung infection are the main pathological changes reported in COVID-19 infection. The role of biomarkers in determining the severity of the infection has been established in the general population [28] (Malik *et al*., 2020). This review was aimed at identifying biomarkers of lung injury in the HIV-positive population.

The activation of specific biomarkers In COVID-19 infection among PLWH was established in this review. The specific biomarkers included CRP, LDH, D-dimer, ferritin, IL-6, procalcitonin, and fibrinogen. There have been conflicting hypothesis about the severity of COVID-19 infection in PLWH; a school of thought proposed more favorable outcome for HIV-positive patients co-infected with COVID-19 due to HIV-related lymphopenia and immunosuppression resulting in the prevention of excessive cytokine storm [23] (Mascolo *et al*., 2020). One of the included studies [18] (Suwanwongse and Shabarek, 2020), a case series of nine patients all on HAART and suppressed viral load with HIV RNA undetected in 4 of them recorded a high mortality rate. Seven patients (77.8%) succumbed to the infection from septic shock to acute respiratory distress syndrome. Two possible explanations for this observation were that HIV-related lymphopenia delays the clearance of viruses and promote the progression of the disease. Secondly, it was proposed that the pathogenesis of cytokine storms in severe COVID-19 may originate from the uncontrolled B lymphocytes; hence, no protective role against COVID-19 provided by HIV-related T-cell suppression [18]. (Suwanwongse and Shabarek, 2020) Furthermore, the largest case series reported from an active in-patient care hospital in New York observed that all the HIV-positive patients coinfected with COVID-19 were on HAART and that there had been no record of any patient with uncontrolled HIV or AIDS been admitted for COVID-19 [20] (Shalev *et al*., 2020). CRP is the most frequently assessed prognostic biomarker assessed by all the included studies, followed by D-dimer, ferritin, LDH, procalcitonin, IL-6, and then fibrinogen.

CRP, a key protein of acute phase response, is universally used as a diagnostic maker for existing inflammation [29] (Potempa *et al*., 2020). The activation of IL-6 that occurs in COVID-19 infection (Sabaka *et al*., 2021) causes the signaling of the liver by IL-6 which further results in the increase production of CRP at the initial phase of inflammation [29] (Potempa *et al*., 2020). All the studies in our review assessed CRP and reported elevated levels. The cohort study identified significantly higher level of CRP in HIV-positive patients

than in non-HIV patients (HIV+: 185.13 ± 107.35 vs. non-HIV: 128.06 ± 99.29, p = 0.024) and a weak association between the highest CRP values and mortality among HIV-positive patients (odds ratio: 1.026, 95% CI: 1.002–1.051, n = 20). A study concluded that CRP level at admission is a simple and independent factor that can be used for early detection of severity of COVID-19 infection [30] (Ahnach *et al*., 2020). Moreover, CRP levels in the early stage of COVID-19, positively correlates with lung lesion and could reflect severity of disease [31] (Wang, 2020). Sharifpour *et al*, [32] discovered from their study that severe complications are likely to be experienced by patients with CRP >64.75 mg/L In this review, CRP was assessed by all the included studies, and the level was elevated in all the patients assessed. This supports other studies on the importance of CRP as a diagnostic marker of COVID-19 infection.

Ferritin is a storage protein for iron and also involved in cellular defense against inflammation [33] (Kartawidjaja, 2020). It contributes to cytokine storm syndrome observed in COVID-19 infection by causing immune dysregulation, especially at very high levels [34] (Vargas-vargas and Cortés-rojo, 2020). Patients with underlying diabetes are more prone to severe complications from COVID-19 from the higher serum level; they exhibit compared to non-diabetic patients [35] (Arora, 2017). The degree of inflammation existing on admission is dependent on high ferritin levels which are also predictive of in-hospital mortality [36] (Lino *et al*., 2021). A cross-sectional study in Israel observed a correlation between elevated ferritin levels and the severity of the disease. Severe patients had significantly higher levels of ferritin (2817.6 ng/mL) than non-severe patients (708.6 ng/mL) p = 0.02 [37]. (Dahan *et al*., 2020). Furthermore, ferritin levels beyond the 25$^{th}$ percentile were associated with a more severe pulmonary involvement, independently of age and gender in a retrospective study [38]. (Carubbi *et al*., 2021). On the other hand, Zinc; another essential metal has a varied impact on human immunity. Zinc deficiency results in increased vulnerability to infections including COVID-19. Chronic dysfunctional inflammatory responses have also been reported in zinc deficiency [39] (Syed Khalid *et al*., 2020).

LDH is an enzyme found in various cells in the body where it functions in the process energy production. The increase in concentration of LDH indicates tissue damage and suggests lung injury, especially in patients with severe pulmonary interstitial disease [40]. (Bartziokas and Konstantinos, 2021). Severe COVID-19 infection, a severe form of interstitial pneumonia, causes cytokine-mediated tissue damage and release of large quantity of LDH into the system which results into acute respiratory distress syndrome which is the hallmark of the disease [41] (Henry *et al*., 2020). A Pooled analysis by Henry *et al*., revealed 6-fold increase in odds of developing severe COVID-19 infection and 16-fold increase in odds of mortality from the infection. In LDH which indicates tissue hypoperfusion, has been identified as a potential prognostic biomarker COVID-19 patients [42], [43], [44]. (Huang *et al*., 2020; Kang and Park, 2016; Martha *et al*., 2021).

D-dimer is a fibrin-degradation product which becomes elevated in thrombotic events and signifies fibrinolysis [45]. (Demelo-Rodriguez *et al*., 2020). Activation of coagulation cascade Secondary to systemic inflammatory response syndrome in COVID-19 patients is responsible for the high D-dimer levels found in these patients [46]. (Eljilany and Elzouki, 2020). D-dimer level on admission >2.0 μg/mL has been found to effectively predict in-hospital mortality in patients with COVID-19 [17], [47], [48], [49] (Porfidia and Pola, 2020; Yao *et al*., 2020; Zhang *et al*., 2020; Zhang *et al*., 2020). A retrospective study conducted by He *et al*. [50] on the poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients, also realized that a D-dimer value of 2.025 mg/L was the ideal cutoff to conclude on a prognosis of death. The factors that influenced the level of D-dimer in COVID-19 patients include advanced age, male gender, dyspnea, and underlying diseases [50], [51]. (Giannis *et al*., 2020; He *et al*., 2021). D-dimer values can also be used as an early biomarker to decide on patients who will benefit from CT pulmonary angiography to exclude the presence of pulmonary embolism, one of the common complications observed in COVID-19 patients [52] (Palmer, 2020).

IL-6 is a very important cytokine, the production of which is central to many inflammatory diseases (Lu) and high levels of IL-6 were correlated with pulmonary inflammation and extensive lung damage (Lu). Acute phase proteins such as CRP, serum amyloid A, fibrinogen, haptoglobin, and a1-antichymotrypsin are the products of the activation of the liver by IL-6 [53] (Vatansever and Becer, 2020). IL-6 is considered a potential predictor and a determinant of patients that will require hospitalization from severe COVID-19 infection [54] (Sabaka *et al*., 2021), and the concentration of IL-6 > 24 pg/mL at initial assessment predicted with good precision, the development of hypoxemia. IL-6 is considered central to the cytokine storm experienced in severe COVID-19 and antibodies developed against IL-6 receptors are been used in the management of COVID-19 [54] (Sabaka *et al*., 2021). Two of the included studies made the diagnosis of HIV after the patient was admitted for COVID-19 infection [16], [31] (Wang *et al*., 2020; Zhang *et al*., 2020). The decision to screen the patient for HIV was made due to poor response to treatment options. The cohort study emphasized the need to screen for secondary bacterial infection which may worsen the prognosis of the infection in HIV-positive patients [22] (Karmen-Tuohy *et al*., 2020). Our review revealed a variety of abnormalities observed in the lungs of HIV-positive patients co-infected with COVID-19 regardless of CD4 count and 89% of cases

with abnormalities compatible with viral pneumonia were correlated with disease severity in one of the case series [18] (Suwanwongse and Shabarek, 2020). Another study noted the progression of lung abnormalities as the disease condition worsened [16] (Zhang *et al*., 2020).

This study reported high severity of COVID-19 infection among PLWH (56.9%), significantly higher CRP than in non-HIV patients, and various levels of lung abnormalities in HIV-positive patients coinfected with COVID-19 regardless of CD4 count.

### *Limitations*

There are few literatures that addressed the relationship between biomarkers and COVID-19 infection in the HIV population. Most of the studies included were case series and reports which made quantitative analysis difficult due to heterogeneity.

## Conclusion

This systematic review has identified the inflammatory biomarkers associated with severity of disease, prognosis, and lung injury in HIV-positive patients coinfected with COVID-19. A number of biomarkers are associated with the pathogenesis of COVID-19 infection [46] (Eljilany and Elzouki, 2020, and assessing these biomarkers early at presentation can be useful in making a choice of treatment, severity, prognosis of the disease, and close monitoring of the patient. This will be much more beneficial in the HIV population who are already disadvantaged due to their state of immunosuppression and other underlying non-communicable diseases they have that make the co-infection with COVID-19, a form of double burden in this population. Prospective studies are needed to determine the effect of inflammatory biomarkers on occurrence of lung injury, the prognosis, and outcome of COVID-19 infection in the HIV population.

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