Narrative Review

Comorbidities and the COVID-19 pandemic dynamics in Africa

A.A. Anjorin[1], A.I. Abioye[2], O.E. Asowata[3,4], A. Soipe[5], M.I. Kazeem[6], I.O. Adesanya[7], M.A. Raji[8], M. Adesanya[9,8,10], F.A. Oke[11], F.J. Lawal[12], B.A. Kasali[13] and M.O. Omotayo[14,15]

1 *Department of Microbiology (Virology Research), Lagos State University, Ojo, Lagos, Nigeria*
2 *Population Health Science Program & Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA,USA*
3 *Africa Health Research Institute, Durban, South Africa*
4 *School of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa*
5 *Department of Medicine, Division of Nephrology, Upstate Medical University, Syracuse, NY,USA*
6 *Department of Biochemistry, Lagos State University, Ojo, Lagos, Nigeria*
7 *CPT US Army Reserve, Houston, TX,USA*
8 *Bayou City Physicians, Houston, TX,USA*
9 *Department of Microbiology and Immunology, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia*
10 *Nursing Department, University of Texas at Arlington, Arlington, TX,USA*
11 *Department of Internal Medicine, Brookdale University Hospital Medical Centre, New York City, NY,USA*
12 *Department of Infectious Diseases, Medical College of Georgia, Augusta University, Augusta, GA,USA*
13 *Independent Researcher, Seattle, WA,USA*
14 *Centre for Global Health and Division of Pediatric Global Health, Massachusetts General Hospital, Boston, MA,USA*
15 *Department of Pediatrics, Harvard Medical School, Boston, MA,USA*

Abstract   The debate around the COVID-19 response in Africa has mostly focused on effects and implications of public health measures, in light of the socio-economic peculiarities of the continent. However, there has been limited exploration of the impact of differences in epidemiology of key comorbidities, and related healthcare factors, on the course and parameters of the pandemic. We summarise what is known about (a) the pathophysiological processes underlying the interaction of coinfections and comorbidities in shaping prognosis of COVID-19 patients, (b) the epidemiology of key coinfections and comorbidities, and the state of related healthcare infrastructure that might shape the course of the pandemic, and (c) implications of (a) and (b) for pandemic management and post-pandemic priorities. There is a critical need to generate empirical data on clinical profiles and the predictors of morbidity and mortality from COVID-19. Improved protocols for acute febrile illness and access to diagnostic facilities, not just for SARS-CoV-2 but also other viral infections, are of urgent importance. The role of malaria, HIV/TB and chronic malnutrition on pandemic dynamics should be further investigated. Although chronic non-communicable diseases account for a relatively lighter burden, they have a significant effect on COVID-19 prognosis, and the fragility of care delivery systems implies that adjustments to clinical procedures and re-organisation of care delivery that have been useful in other regions are unlikely to be feasible. Africa is a large region with local variations in factors that can shape pandemic dynamics. A one-size-fits-all response is not optimal, but there are broad lessons relating to differences in epidemiology and healthcare delivery factors, that should be considered as part of a regional COVID-19 response framework.

keywords COVID-19, SARS-CoV-2, Africa, pandemic, comorbidities, coinfections

Sustainable Development Goals (SDGs): SDG 3 (good health and well-being), SDG 16 (peace, justice and strong institutions), SDG 17 (partnerships for the goals)

Introduction

Most countries in the world, including Africa, have experienced the outbreak of coronavirus disease-2019 (COVID-19) pandemic caused by severe acute respiratory coronavirus-2 (SARS-CoV-2) [1, 2]. COVID-19 presents with a wide range of illnesses ranging from self-limiting respiratory tract illness to multi-organ failure and

ultimately death, especially in individuals having comorbidities. A common pathophysiologic dynamic is the utilisation of host angiotensin-converting enzyme-2 (ACE-2) to initiate direct viral invasion and gain access into target cells [3, 4]. Mechanistically, the host serine protease TMPRSS2 activates SARS-CoV-2 spike (S) protein after binding to the ACE-2 receptor [4, 5].

A large number of deaths from COVID-19 pandemic have occurred in the United States, China, the United Kingdom, Italy, Iran and Spain, with relatively fewer deaths recorded in Africa. Of over 25 million confirmed cases globally, with more than 840 000 deaths across 213 countries, over 27 700/1 187 786 deaths (case fatality ratio (CFR): 2.34%) have been recorded in 55 African countries as at 23 August 2020 [6]. The relatively lower toll of COVID-19 in Africa may be due to differences in genetic or climatic factors, or perhaps the epidemic is just beginning to burgeon on the continent. The debate around the pandemic response on the continent has mostly focused on the potential implications of standard public health measures of physical distancing, given the socioeconomic peculiarities of the continent [7]. However, there has been limited exploration of the impact of differences in epidemiology of key comorbidities, and related healthcare factors, in shaping the course and parameters of the pandemic, particularly severity and prognosis of the infected cases. In this paper, we summarise what is known about (a) the pathophysiological processes underlying the interaction of coinfections and comorbidities in shaping prognosis of COVID-19 patients, (b) the epidemiology of key coinfections and comorbidities, and the state of related healthcare infrastructure that might shape the course of the pandemic on the African continent; and (c) implications of (a) and (b) for pandemic management and post-pandemic priorities on the continent (Table 1).

COVID-19 and coinfections

Evidence of increased susceptibility to SARS-CoV-2 among patients with existing infections with other pathogens is slim. While elaboration of the pathophysiological processes shaping prognosis is an ongoing endeavour, it is widely noted that patients with comorbidities and those with low immunity are more likely to have a worse prognosis and an increased risk of death when coinfection with other viral respiratory pathogens or secondary microbial pathogens occurs.

Malaria

Malaria is an endemic disease in the tropical regions of the world. An estimated 228 million cases and about 405 000 deaths were attributed to malaria globally in 2018 with the African region accounting for 93% (213 million) of these cases [8]. The majority of malarial morbidity and mortality are associated with *Plasmodium falciparum* which is predominantly found in Africa [8]. Children aged 5 years and younger are the most vulnerable age group affected by malaria although this age group has been relatively spared of COVID-19 mortality and severe morbidity so far. Of note, recent data suggest that COVID-19-infected children are often mildly symptomatic and are considered less important spreaders of SARS-CoV-2 than adults [9].

As COVID-19 cases continue to rise globally, there is increasing concern that a more severe COVID-19 course could be seen among malaria-infected individuals. However, the clinical and immunological responses of malaria-infected patients to COVID-19 are yet to be specifically investigated. The potential for the disruptive effect of COVID-19 on health systems which are most fragile in malaria-endemic countries, potentially undermining malaria treatment and prevention effort in these countries, is also of concern [10]. In addition, malaria and COVID-19 have some common symptoms such as fever, headache and body weakness and aches. Therefore, malaria endemicity may complicate clinical diagnosis of COVID-19 especially in areas where access to testing is insufficient.

The under-diagnosis of non-malarial aetiology of acute febrile illness (AFI) in sub-Saharan Africa is common [11–13]. In Nigeria, up to 83% of children <5 years of age who were managed for acute febrile illness were still treated as malaria cases despite negative microscopy for *Plasmodium* [14]. Other studies have shown that locales in highly endemic areas for malaria maintain a low level of parasitemia without clinical symptomatology [15]. Thus, even in the presence of malaria parasitemia, clinical symptoms might still be due to coinfections. Therefore, the possibility of a patient suffering from both malaria and COVID-19 should always be explored using valid diagnostic tests [16].

Viral respiratory infections

The comorbidity of SARS-CoV-2 with influenza and other non-SARS-CoV-2 respiratory viruses exacerbates the conditions of COVID-19 patients [17].The host factor enhancing the initiation of the viral pathogenesis and spread is the localisation of SARS-CoV-2 receptor in several parts of the human body including the respiratory tract, small intestine epithelial cells and immune cells. Coinfection often results in pneumonia, hypoxia, dyspnoea, acute respiratory distress syndrome, multiple organ

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Table 1 Interactions and implications of selected COVID-19 comorbidities in Africa

	Comorbidity/coinfection	Clinical diagnosis/ treatment/prognosis	Public health programmes	Key research gaps
Selected coinfections				
1	Malaria	May complicate COVID-19 clinical diagnosis	Acute disruptions due to COVID-19 pandemic can constrain malaria control efforts	Clinical and immunological responses of malaria-infected patients to COVID-19 are yet to be specifically investigated, and effect on prognosis is unknown
2	Viral respiratory infections (not COVID-19)	May complicate COVID-19 clinical diagnosis, and worsen prognosis	Need to strengthen network of laboratories for diagnosis of viral pathogens	Epidemiology of viral respiratory coinfections in African populations
3	Secondary bacterial/fungal infections	May complicate COVID-19 clinical diagnosis	Need to strengthen network of laboratories for diagnosis of bacterial/fungal pathogens	Epidemiology of microbial coinfections, effects on COVID-19 prognosis and causative pathogen susceptibility profiles in African populations
4	HIV/TB	No known relationship	Acute disruptions due to COVID-19 pandemic can constrain HIV/TB control efforts	Effects of coinfection on clinical prognosis
Selected comorbidities				
5	Obesity	May worsen COVID-19 prognosis	Acute disruptions due to pandemic response can exacerbate behavioural risk factors in the overweight: poor diet, physical inactivity	Causal effect of obesity on COVID-19 outcomes
6	Undernutrition	No known relationship	Prolonged disruptions due to pandemic response can precipitate undernutrition and nutritional deficiencies in vulnerable households	Effects of zinc supplementation on COVID-19 prognosis Causal effect of micronutrient deficiencies and chronic malnutrition on COVID-19 outcomes Causal effect of COVID-19 on acute malnutrition
7	Cardiovascular disease (CVD)	May worsen COVID-19 prognosis	Disruptions due to pandemic response can exacerbate behavioural risk factors Disruption in routine health care and medical supplies can increase risk of CVD events	Causal effect of CVD on COVID-19 outcomes
8	Renal disease	May worsen COVID-19 prognosis	Disruption of routine health services due to pandemic response, and concerns about infection can constrain access to renal replacement therapy	Feasible models of dialysis patient flow that limit infection risk Long-term effect of COVID-19 on renal function in survivors
9	Hepatic disease	No known relationship	Fear of COVID-19, and mis-information can lead to increased rates of consumption of hepatotoxic materials for prophylaxis	Effective management protocols in COVID-19 patients with hepatic disease Effect of herbal medications for COVID-19 may cause hepatotoxicity
10	Diabetes	May worsen COVID-19 prognosis	Disruptions due to pandemic response can exacerbate behavioural risk factors Disruption in routine health care and medical supplies can increase risk of CVD events	Effectiveness of diabetes mellitus (DM) management strategies in patients with COVID-19 infection and DM

failure, shock and ultimately death [18, 19]. In a study reported by Kim *et al.* (2020), the most prevalent respiratory tract viral coinfections in COVID-19 patients were enterovirus/ rhinovirus (6.9%), RSV (5.2%), non-SARS-CoV-2 CoVs (4.3%), human metapneumovirus (1.7%), influenza and parainfluenza viruses (0.9%), while SARS-CoV-2 and influenza coinfection of 4.4% was reported by Ding *et al.* (2020) [20, 21]. Also, Richardson *et al.* (2020) reported coinfection in COVID-19 patients including entero/rhinovirus (52.4%), coronavirus (non-COVID-19) (16.7%) and respiratory syncytial virus (9.5%).

Furthermore, malaise exacerbation and ground glass opacity with partial filling of the lung alveoli were reported in cases of coinfection with COVID-19 and influenza [22, 23]. The pathophysiological effect of such coinfection involves SARS-CoV-2 attacking type II pneumocytes, the alveolar epithelial cells that produce surfactant which helps to reduce surface tension in the alveoli. Decreased surfactant production leads to subsequent alveolar collapse and decrease in lung compliance, which is critical to normal lung function, resulting in hypoxia and severe tachypnoea. It is noteworthy that the acute respiratory distress syndrome caused by COVID-19 pneumonia is somewhat atypical with a relatively higher lung compliance compared to severity of hypoxaemia seen in typical acute respiratory distress syndrome [24]. As the inflammation from COVID-19 infection progresses, collapse of more air sacs sets in and the pneumonia worsens with accompanying hypoxia and hypoxaemia. About 20% of COVID-19 pneumonia patients progress into a secondary and deadlier stage of the lung injury with breakdown of alveolar membrane and capillary barrier, alveolar fluid infiltration or pulmonary oedema and CO_2 accumulation leading to hypercapnia with accompanying dyspnoea followed by acidosis, with ultimate acute respiratory failure [25, 26]. According to the WHO report, 20% of COVID-19 patients had severe (dyspnoea and lung infiltrates >50% of the lung field) and critical (respiratory failure and septic shock) morbidity that resulted in hospitalisation requiring oxygen and ventilation, with an average of 20 times mortality rate more than seasonal influenza mono-infection while over 80% of them died as a result of underlying disease/comorbidity [27, 28].

Other studies have also suggested that coinfection of respiratory tract viruses with SARS-CoV-2 may influence morbidity and mortality [29–31]. This may be due to immune dysregulation by the underlying viral diseases.

Secondary microbial infections

The outcome of viral pneumonia may be complicated by coinfections with other microbial agents. Studies have shown that patients with influenza respiratory tract infections had poorer clinical outcome when bacterial agents such as *Staphylococcus aureus* (*S. aureus*), *Streptococcus pneumoniae* (*S. pneumoniae*) *Haemophilus influenzae* (*H. influenzae*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Streptococcus pyogenes* (*S. pyogenes*) complicated the primary state [32–35].

A study conducted by Golda *et al.* (2011) using human coronavirus NL63 (HCoV-NL63), a leading cause of viral croup in children, revealed enhanced binding of *S. pneumoniae* to respiratory epithelial cells in culture [34]. While the clinical significance of this study is not clear, secondary bacterial infections coexisting with viral pneumonia particularly in high-risk groups such as the elderly and young children have been associated with significant morbidity and mortality [34].

With the current COVID-19 pandemic, epidemiological data on secondary microbial agents associated with morbidity or mortality in infected patients are scarce [5].

In a recent review of 24 studies, mostly from Asian countries, UK and the United States, Langford et al analysed non-duplicate data from 3338 COVID-19 patients, which revealed that bacterial infection was more common in very ill patients [36]. Patients with bacterial coinfection represented 6.9% of their studied population [36]. The authors also noted that bacterial agents such as *S. aureus* and *S. pneumoniae*, which are frequent secondary bacterial agents of infection in viral illnesses, occur infrequently in this cohort of COVID-19 patients; the most common bacterial agents were however not stated [36]. In their conclusion, Langford et al stated that bacterial infections were not a frequent occurrence in patients with COVID-19; thus, antibiotics should be used only when indicated.

In another cohort of 3834 COVID-19 patients from 30 studies from China, United States and Spain reviewed by Lansbury et al, *Mycoplasma pneumoniae, P. aeruginosa, H. influenzae, Klebsiella pneumoniae, Acinetobacter baumannii, Chlamydia specie, Enterococcus faecium,* methicillin-resistant *Staphylococcus aureus and Serratia marscencens* were common bacterial agents associated with coinfection [37]. Further review of their data showed fungal agents such as *Candida albicans, Aspergillus flavus, Aspergillus fumigatus and Candida glabrata* were associated with secondary fungal infection, while respiratory syncytial virus and influenza A virus were reported as viral coinfecting agents in 14 studies [37]. The authors noted that bacterial coinfection occurred in 7% of the total studied population and concluded that bacterial coinfection is not a frequent finding with COVID-19 patients. *S. aureus, S. pneumoniae* and *S. pyogenes* were noted as less important bacterial agents of coinfection [37].

In a retrospective analysis of data of another cohort of 989 COVID-19 patients from Spain, Garcia-Vidal et al reported the predominance of *S. aureus* and *S. pneumoniae* as bacterial agents of coinfection in patients with community acquired infections, while *P. aeruginosa* and *E. coli* were predominately associated with hospital acquired bacterial superinfections [37, 38].

There is still paucity of data on microbial coinfection agents complicating the clinical course and outcome of COVID-19 patients in Africa. A recent case report from Morocco presented a patient with laboratory-confirmed COVID-19 infection who developed infective endocarditis while being managed; the patient had pre-existing medical conditions as noted in the report. Blood culture yielded coagulase-negative staphylococcus species [39].

Zhou et al reported sepsis as the most common complication leading to death [5]. Half of the patients who died had secondary infections [5]. The microbes associated with these patients, the antibiotic treatment guidelines deployed and the susceptibility profile of the implicated agents were not indicated in the report.

Data from available studies show that most coinfections occur in critically ill patients and those with pre-existing medical conditions. These group of patients will require invasive medical interventions that will further pre-dispose them to nosocomial pathogens. It may thus be postulated that secondary microbial coinfection with SARS-CoV-2 may reflect the prevailing agents of nosocomial infection in the managing facility.

Limited data in the literature on the guidelines steering laboratory investigation for coinfection in the various published cohort studies continue to be a recurring issue. Superimposed bacterial infection is common in viral pneumonia; however, due to our incomplete and evolving understanding of the SARS-CoV-2 and the patient population at risk of severe infections, common bacterial and fungal agents in the African context, as well as their susceptibility profiles, need to be urgently investigated. This will help in effective management of patients and judicious use of antimicrobial agents.

In addition to coinfections and superimposed infections, SARS-CoV-2 infection presenting with gastrointestinal symptoms can be mistaken for other common illnesses such as gastroenteritis. Although the frequency and volume of diarrhoea reportedly associated with SARS-CoV-2 is less than in *Vibrio cholerae* infection, without a high index of suspicion and adequate testing, an assessment of other differential diagnoses of infectious diarrhoea may be made. Cytokine storm resulting from SARS-CoV-2 also presents like sepsis and can be misdiagnosed as superimposed bacterial infection in low resource settings where acute illness care may be administered by low skilled health workers.

HIV and TB

Before the current pandemic, HIV/AIDS control was mainly hampered in the African region by coinfection with tuberculosis. It has been speculated that the immunodeficient status that influences the vulnerability of HIV-infected people to TB could also increase their susceptibility to COVID-19 [40].

In a recent study using single-cell transcriptomic analysis, the authors demonstrated an increased expression of ACE2 in specific cells of human lung tissues during HIV and TB coinfection compared to uninfected controls suggesting a potential higher risk of SARS-CoV-2 infection among these HIV/TB coinfected individuals [41]. However, the actual response of HIV and TB coinfected individuals to SARS-CoV-2 infection remains unknown.

There is currently no epidemiological relationship between HIV and COVID-19, even though people living with HIV have been regarded as a vulnerable group for COVID-19 [42]. The lack of an increase in COVID-19 incidence among HIV-infected individuals relative to the general population especially within the extremely high HIV endemic areas of Africa may either be a testament to a highly successful COVID-19 infection prevention protocol or may question the hypothesised vulnerability of people living with HIV to this novel virus. Nonetheless, UNAIDS has warned that older people living with HIV or those with HIV and heart or lung disease may be at a higher risk of SARS-CoV-2 infection with severe morbidity [43].

Clinical reports from China suggest that HIV-infected individuals especially those on combination antiretroviral therapy (cART) can recover from COVID-19-associated pneumonia without severe complications [44–46]. As most African countries continued to restrict movement due to the pandemic, the potential impact on HIV and TB control and care delivery services, especially in African countries with the most fragile healthcare systems, will likely be damaging. Majority of people were likely unable to travel to clinics or health centres to get medical supplies such as HIV and TB medicines, pre-exposure prophylaxis (PrEP), condoms, contraceptives, sterile needles and syringes [43]. WHO has recommended dispensing of HIV medicines for three months or more, community access to HIV and TB treatment and a proper understanding of how to contact clinics by telephone as measures to prevent unnecessary exposure to COVID-19 infection while accessing necessary care and supplies [43]. Besides, people living with HIV can draw on their

resilience, surviving and thriving to support their families and community to manage the potential fear, anxiety and stigma associated with COVID-19 [39] specially in sub-Saharan Africa.

COVID-19 and non-communicable comorbidities

It is widely noted that pre-existing non-communicable conditions worsen the prognosis of COVID-19 infections particularly in patients with cardiovascular, respiratory and metabolic conditions. The incidences of these conditions have been on the rise in Africa due to increasing adoption of western lifestyles. Fragility of health systems in most African countries may limit continuity of care for chronic diseases due to disruptions in routine health service provision as a result of the COVID-19 pandemic.

Obesity

In Africa, the prevalence of overweight and obesity is increasing [47] making it imperative to understand how obesity may influence the trajectory of COVID-19 on the continent. Early reports from Europe and China have shown higher prevalence of obesity among patients hospitalised with COVID-19 or who develop adult respiratory distress syndrome [48–52]. These studies either had limited data to adjust for key confounders, or inadvertently blocked any plausible causal path from nutritional status to COVID-19 disease severity [53].

Our understanding of the pathology of obesity and COVID-19 suggests a plausible causal relationship between the two. First, early studies suggest that cytokine release syndrome is central to the occurrence of severe COVID-19 [54], associated with extensive inflammation and destruction of pulmonary tissue [5, 18]. IL-6 is produced by multiple cells in the body including adipocytes, and its levels are likely elevated in obese individuals [55]. Second, adipose tissue may be a reservoir for viral replication and shedding [56].

Epidemiological phenomena may also account for the increased association of COVID-19 with worse outcomes among obese patients. First, obesity is associated with elevated risk of multiple comorbidities which are themselves associated with increased risk of severe COVID-19. Second, obesity is associated with certain socio-economic disparities that have been shown or can be reasonably expected to lead to worse COVID-19 outcomes. In high-income countries, the burden of obesity is greater in the lower socio-economic strata and in neighbourhoods with poor access to healthcare infrastructure. The extent to which obesity may modify the clinical trajectory of the disease in Africa is unclear due to differences in obesity epidemiology, and population studies are warranted.

Undernutrition

The prevalence of undernutrition among Africa's children [57] and elderly is particularly high [58–60], and could complicate COVID-19 outcomes in Africa. First, early reports suggest that elderly people are at greater risk of adverse outcomes following COVID-19 [61], and undernutrition is likely a key mediating factor [61–63]. Undernutrition may also contribute to high mortality among patients with chronic illnesses such as malignancies. Primary studies of undernutrition in COVID-19 among the elderly have however determined nutritional status based on serum levels of albumin or prealbumin [5, 63, 64]. Concentration of both biomarkers is reduced in acute infections, requiring cautious interpretation for nutritional assessment [65]. None of these studies also adjusted for potential confounders.

Undernutrition in a state of immunodeficiency [66] and a significant adverse impact on the course of SARS-CoV-2 infection is likely. Protein energy malnutrition is associated with anaemia, susceptibility to infections and immune dysfunction [67]. Production of immune cells is lowered, and response to antigens from pathogens and vaccines is weakened [67, 68]. In addition, undernutrition is often accompanied by multiple micronutrient deficiencies. Micronutrients act as cofactors for multiple enzymes in the body and may reduce viral replication and improve overall outcomes [69, 70].

Finally, there is potential for reverse causation in the relationship of COVID-19 and undernutrition. Animal studies have shown that coronavirus infections could lead to weight loss, from catabolic processes unmatched by dietary replenishment [71–74]. Well-designed population studies may clarify the role of undernutrition in COVID-19.

Cardiovascular disease

COVID-19 has been shown to have particularly worse outcomes in patients with chronic medical conditions, especially cardiovascular disease [75, 76]. Preliminary data from a recent study in China [77] that evaluated the clinical characteristics of patients admitted for COVID-19 infection showed that 31% of patients had comorbid hypertension and up to 15% had cardiovascular disease (CVD).

Pathophysiological pathways noted in COVID-19 patients are similar to those observed in patients with cardiovascular diseases even without COVID-19

infection. Hence, COVID-19 infection may intensify the process in patients with cardiovascular disease. The worse prognosis of COVID-19 infection seen in CVD patients might also be an epidemiological phenomenon since CVD is relatively prevalent among those who are generally pre-disposed to increased severity of infections such as the elderly, diabetics, obese and people with impaired immunity [76].Cells with abundant and upregulated ACE-2 receptors such as cardiac cells are more susceptible to increased COVID-19 viral load with increased severity of injury from the viral infection. These receptors are upregulated in conditions with excessive activation of the renin–angiotensin system (RAS) like ischaemic heart disease, hypertension (HTN) and congestive heart failure (CHF) [78, 79]. Once ACE-2 receptors bind to SARS-CoV-2, they are no longer available to facilitate breakdown of angiotensin II (Ang II), a potent vasoconstrictor.

Significant elevation of cytokines and chemokines has been reported in patients infected with SARS-CoV which is very similar to SARS-CoV-2 infection [77]. Cytokine release syndrome, the excessive and uncontrollable release of pro-inflammatory cytokines as a result of inflammatory response triggered by stimulation of the immune system, was identified as a negative prognostic factor in hospitalised SARS patients [77].

Renal disease

It is estimated that chronic kidney disease (CKD) affects 10–15% of the global population [80], while patients presenting with SARS-CoV-2 infection have shown varying degrees of renal involvement [81]. The uniform pathway through which SARS-CoV-2 exerts renal injury continues to be debated. A recent study reported that the human kidney, which has ACE2 expressed on the surface of its cells, is a unique target for SARS-CoV-2 [82]. Further, it has been noted that renal infection with SARS-CoV-2 leads to direct tubular injury as well as glomerular damage [81–83]. However, more recent reports suggest that cytokine effect and heightened immune responses mediate the injuries noted in the kidneys of COVID-19-infected patients [84, 85].

Patients with underlying kidney disease and those undergoing dialysis were found to have increased mortality when infected with SARS-CoV-2 [86]. This should be viewed in the context of the increased risk of infection caused by a weakened immune system in patients undergoing dialysis [87]. Likewise, acute kidney injury (AKI) has been reported to occur in approximately 25% of patients presenting with SARS-CoV-2 infection [5, 88, 89]. Metabolic and fluid balance derangements arising

from AKI often require optimisation with renal replacement therapy (RRT) modalities, in which case continuous renal replacement therapy (CRRT) has been recommended to be a preferred RRT choice to limit healthcare personnel exposure risks to COVID-19 [90–93].

Further, the RRT option utilised to manage COVID-19 patients presenting with AKI depends on the patient's clinical status, availability of suitable technology and the availability of necessary skill set which is often deficient in African settings. Data on the outcome associated with RRT provision for AKI in COVID-19 positive patients indicate a reduced risk of mortality in patients treated with CRRT [94]. Nonetheless, patients who develop AKI in the context of COVID-19 infection should be followed up for renal function monitoring after recovery from SARS-CoV-2 because a history of AKI pre-disposes to repeat AKI and CKD [95–97].

Data from countries where COVID-19 infection has been studied revealed that end-stage renal disease (ESRD) patients are at increased risk of contracting the infection [98]. The CDC and other policy makers continue to make improvements to recommendations on how to safely provide dialysis to COVID-19 patients in the inpatient and outpatient settings [93, 99]. Most African countries are resource-limited and face challenges in terms of providing the necessary infrastructure, as well as renal replacement therapies essential for ESRD management [100]. The lack of necessary infrastructure to meet the needs of the chronic dialysis-dependent population in Africa makes the situation more dire in the context of the ongoing pandemic. This raises concerns about capacity to adopt the model of treatment being implemented in medical facilities providing dialysis treatment to patients in the United States during this pandemic. In such model, there is the creation of a separate shift or different unit where COVID-19 patients are dialysed. Similarly, patients classified as symptomatic persons under investigation (PUI) are dialysed in cohorts [101, 102]. This model demands additional resources and infrastructure which is quite lacking in most African countries.

Hepatic disease

Liver injury associated with SARS-CoV-2 infection is defined as any liver damage occurring during disease progression and treatment of COVID-19 in patients with or without pre-existing liver disease [103]. COVID-19 liver infection has been postulated to involve direct viral entry which is mediated by ACE2 expression in cholangiocytes [104]. Despite prior evidence of viral infection of liver cells in patients with severe acute respiratory syndrome (SARS) [105], recent studies have reported the absence of

acute or chronic liver failure in COVID-19 patients [18, 106–111]. In addition, liver biopsy reports of COVID-19 patients revealed microvascular steatosis as well as lobular and portal activity which indicates that liver dysfunction could have resulted from either SARS-CoV-2 infection or drug-induced liver injury [112]. Given the equivocal explanation for liver dysfunction seen in COVID-19-positive patients [64, 103, 112], there is paucity of specific recommendation for the management of liver impairment in COVID-19 patients. As such, management focuses on regular monitoring of liver biochemistries, general supportive care and trial of medications targeting the modulation of the ACE2 receptor [64, 103, 113, 114].

Globally, liver disease accounts for approximately 2 million deaths per year with a high prevalence of viral hepatitis and drug-induced liver injury [115]. In Africa, there is rampant use of herbal preparations to manage illnesses due to cultural factors and poor access to healthcare services. The use of such herbal remedies may inadvertently lead to hepatic injury. As the SARS-CoV-2 pandemic continues across the world and across Africa, there is a tendency for the African populace to manage the presenting symptoms of COVID-19 infection with local remedies for which a hepatotoxicity profile has not been characterised. As such, liver impairment from hepatotoxic herbal remedy ingestion may manifest in African patients when admitted to the hospital for COVID-19.

Diabetes mellitus

Diabetes mellitus is a chronic metabolic disorder characterised by hyperglycaemia due to defects in insulin secretion and/or action [116]. It is one of the fastest growing global health emergencies of the 21st century affecting 463 million people in 2019 and it is projected to reach 578 million people by the year 2030 [117]. The disease affects 19.4 million people in Africa and results in the death of about 366 200 individuals annually. Out of 100 diabetic patients in the world, four of them are Africans [117].

Diabetes is a chronic inflammatory condition characterised by multiple metabolic and vascular abnormalities which affect response to pathogens. Hyperglycaemia promotes increased synthesis of advanced glycation end products (AGEs) and pro-inflammatory cytokines, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation [118, 119]. This inflammatory process may contribute to the underlying mechanism that leads to a higher propensity for infections with worse outcomes in patients with diabetes.

The first line of defence against COVID-19, innate immunity, is compromised in patients with uncontrolled

hyperglycaemia thereby allowing unhindered proliferation of the pathogen within the host. Even short-term hyperglycaemia has been shown to transiently stun the innate immune system [120]. Moreover, diabetes mellitus is characterised by exaggerated pro-inflammatory cytokine response notably interleukin IL-1, IL-6 and tumour necrosis factor (TNF)-α in the absence of appropriate stimulation [121]. This may be further exaggerated in response to a stimulus as seen in patients with COVID-19 [122].

In type-2 diabetes, endothelial dysfunction and vascular inflammation favouring the development of a hypercoagulable pro-thrombotic state are also part of the pathogenesis of other chronic conditions and may aggravate the condition of diabetic patients with COVID-19.

Previous studies reported that diabetes mellitus worsens the prognoses for different viruses including SARS-CoV and MERS-CoV [122, 123]. Individuals with diabetes have an increased risk of infections including influenza and pneumonia which makes it imperative that such people are vaccinated against these infections [123]. In addition, diabetes mellitus is a major contributor to mortality from COVID-19 ranging from 7.3 to 35.5%. Similarly, reports have shown that diabetes mellitus is an independent contributing factor to the severity of complications experienced by COVID-19 patients [63, 88, 118, 124–126]. This is an indication that diabetic patients infected by COVID-19 are pre-disposed to severe complications and mortality, just like other previous coronavirus diseases.

Conclusion

The COVID-19 pandemic has advanced to community transmission stage in many places in Africa. The impact of comorbidities on infection-fatality rate has been widely noted in other regions that are in more advanced stages of the pandemic. As Africa learns from such regions, the response to the ongoing pandemic and planning for post-pandemic programmes should take into consideration peculiarities in the epidemiology of comorbidities and coinfections, relevant pathophysiological and healthcare delivery factors with potential to impact pandemic dynamics and post-pandemic effects, as well as a critical need to generate empirical data on the predictors of morbidity and mortality from COVID-19. Improved diagnostic and management protocols for acute febrile illness, and access to diagnostic facilities not just for SARS-CoV-2 but also other viral infections are of importance. Chronic non-communicable diseases have been noted to have significant influence on COVID-19 prognosis although these conditions account for a relatively

lighter burden in Africa. The burden is growing and the fragility of care delivery systems implies that adjustments to clinical procedures and re-organisation of care delivery that have been useful in other regions are unlikely to be feasible. Africa is a large region with local variations in factors that can shape pandemic dynamics and a one-size-fits-all response will not be optimal but there are broad lessons relating to differences in epidemiology and healthcare delivery factors that should be carefully considered as part of a regional COVID-19 response framework.

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Corresponding author Moshood Omotayo, Center for Global Health, Massachusetts General Hospital, Boston, MA, USA. Phone: +1-617-726-0972, Email: momotayo@mgh.harvard.edu