JMID/
Journal of Microbiology and Infectious Diseases

2021; 11 (2):45-57
doi: 10.5799/jmid.951471

RESEARCH ARTICLE

Complications of Covid-19: A Systematic Review and Meta-Analysis

Aishat Temitope Alonge, Babatunde Isaac Ademusire, Chinweoge Frances Epum, Boluwatife Adeleye Adewale, Opeoluwa Samuel Adefarati

College of Medicine, University of Ibadan, Nigeria

ABSTRACT

Objectives: COVID-19, primarily a respiratory disease, can have complications that affect all organ systems of the body. There is a paucity of systematic reviews on all the complications. In this systematic review and meta-analysis, we set out to summarize the complications of COVID-19 in all body systems and their prevalence.

Methods: PubMed and Google Scholar were searched for eligible articles using predefined criteria. Database searching and extraction were performed by independent reviewers.

Results: We identified 74 case reports/series and 15 observational studies. In both the case reports/series and observational studies, pulmonary complications were the most commonly reported, particularly pneumonia, followed by neurological complications in case reports/case series and hematological complications in observational studies. Atrial arrhythmias (1.7%) and acute myopericarditis (1.7%), liver injury (3.3%), acute kidney injury (8.8%), deep venous thrombosis (2.2%), ischemic stroke (12.2%), herpes zoster (1.1%), and diabetic ketoacidosis (1.1%) were the most reported cardiovascular, gastrointestinal, renal, hematological, neurological, dermatological, and endocrine complications respectively in case reports/series. However, acute myocarditis (100%), hypoproteinemia (15.9-28.8%), transient acute renal failure (49.9-90.1%), acute coagulopathy (16.5-28.4%), and ischemic stroke (1.3-3.9%) had the highest pooled prevalence for cardiovascular, gastrointestinal, renal, hematological, and neurological complications respectively in observational studies.

Conclusion: The complications of COVID-19 are multi-systemic with pulmonary complications being the most commonly reported. Notwithstanding, healthcare professionals should be aware that COVID-19 is a differential diagnosis for even the rare but equally debilitating complications and should screen patients who develop these complications to rule out COVID-19 during the pandemic and beyond. *J Microbiol Infect Dis 2021; 11(2): 45-57.*

Keywords: *Covid-19, SARS-CoV-2, Complications, Sequelae, Systematic review*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory disease that was firstly recorded in Wuhan China as a group of unexplained pneumonia cases and has since then become a global pandemic [1]. Coronaviruses are transmitted between humans and animals and commonly presents in humans with symptoms like fever, headache, fatigue, sore throat, cough, breathlessness, and some other common respiratory symptoms [2–4].

It has been shown from various studies that COVID-19 affects all the systems of the human body and this may be due to either weakening of the immune system caused by the infection or by replication and dissemination of the virus outside the lungs [5]. Therefore, we conducted a systemic review of the complications of COVID-19 by analyzing and summarizing different case reports/series and observational studies.

METHODS

Inclusion and exclusion criteria

We conducted this systematic review following the Preferred Reporting Items for Systematic and Meta-analysis (PRISMA) protocols and guidelines. We included studies (case reports, case series, and observational studies) reporting

Correspondence: Dr. Aishat Temitope Alonge, College of Medicine, University of Ibadan, Nigeria
aishattemitopealonge@gmail.com
Received: 19 November 2020 Accepted: 31 May 2021

complications seen in COVID-19 patients during the pandemic. We excluded studies that did not report the complications seen in COVID-19 patients. Systematic reviews, articles that are abstracts-only or without full text, non-English articles, and articles not freely available were also excluded.

Outcomes of interest

The primary outcome was to identify all the complications of COVID-19 among infected patients during the COVID-19 pandemic. We also aimed to report the prevalence of these complications.

Search strategy

Database searching was carried out by two reviewers independently (BIA and CFE) from July 1, 2020, till July 17, 2020. A comprehensive initial search was carried out using PubMed and Google Scholar. The PubMed database was searched using the following terms: (COVID-19 OR coronavirus OR SARS-COV-2) AND (symptom[Title] OR sign[Title] OR clinical characteristics[Title] OR clinical feature[Title]) and (COVID-19 OR coronavirus or SARS-COV-2) AND (Complication[Title/Abstract]). Related titles and abstracts were subsequently screened to select studies that met the inclusion criteria. Eligible articles were further screened by applying the predefined inclusion and exclusion criteria. Manual searching was done by ATA, BAA, and OSA using the reference lists, citation lists, and related articles of all the eligible articles. The last publishing date of the article included in this study is July 16, 2020. All articles identified had already been included from the first search. Figure 1 shows the flow diagram of the screening process of studies included in this systematic review and meta-analysis.

Data extraction

The data from included studies were extracted using a customized template and entered into Microsoft Excel by two autonomous reviewers (BIA and CFE). A third reviewer (ATA) resolved the differences between the two autonomous authors. The following data were extracted: authors' names, year of publication, journal, country of patient recruited, year of recruitment, year of research, the population of the study, sample size, follow up duration, study design, sample size, respiratory complications, cardiovascular complications, gastrointestinal complications, renal complications, hematological complications, neurological complications, dermatological complications, and endocrine complications. Complications that do not strictly fit into a particular body or functional system were classified as others. The number of reported complications in various organ systems was entered for each study.

Statistical analysis

Data was exported into Statistical Package for the Social Sciences (SPSS) version 23 for analysis – case report/series and observational studies separately. Counts and proportions were computed for each complication. The proportion for the observational studies was computed as the number of positive findings relative to the total sample size of studies that reported the complication. The 95% confidence intervals of proportions reported in the observational studies were determined using an online calculator [6].

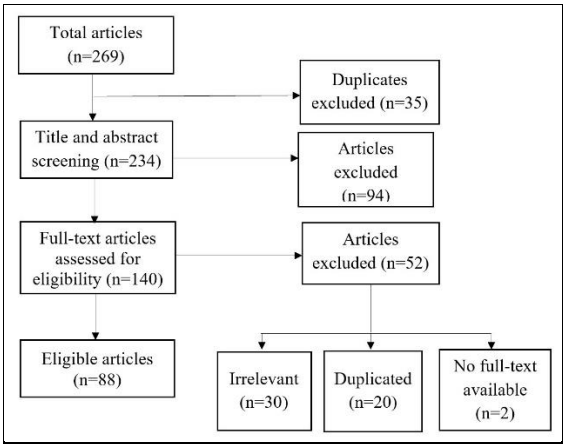

Figure 1. Flow diagram showing the screening process of studies included in this systematic review.

RESULTS

Eighty-eight papers published in 2020 were included in this systematic review; 51 case reports, 22 case series, 2 prospective studies, and 12 retrospective studies; 1 consisted of both a case-control study and case series. Only 3 of the studies had an experimental and control group in the design, while the rest were purely experimental groups. The majority (25) of the studies had patients recruited from the United States, 14 from Italy, 12 studies recruited from the United Kingdom, and 11 from China. The largest study so far is a prospective cohort study – with patients recruited from 24 countries – on

pulmonary complications and mortality of COVID-19.

From the 74 published case reports/series, 38 reported pulmonary complications, 14 reported cardiovascular complications, 3 reported gastrointestinal complications, 8 reported renal complications, 10 reported hematological complications, 24 reported neurological complications, 2 reported dermatological complications, and 2 reported endocrine complications.

Among the observational studies, 10 studies reported pulmonary complications, 6 cardiovascular, 4 gastrointestinal, 6 renal, 6 hematological, and 2 neurological complications. Details on the included studies and the reported complications could be seen in the Additional File 1. The pooled prevalence estimates from the observational studies show that pneumonia (41.4%; 95% CI: 38.6 – 44.1%) and acute respiratory distress syndrome (ARDS) (22.2%; 95% CI: 20.2 – 24.1%) were the commonest respiratory complications (Table 1). There were 5 cases given a diagnosis of COVID-19 associated pulmonary aspergillosis (CAPA) and 4 cases of Aspergillosis colonization.

The pooled prevalence estimates of common complications associated with COVID-19 were 25.6% (95% CI: 25.6 – 41.0%) for myocardial injury and 20.0% (95% CI: 5.7 – 43.7%) for pericardial effusion (Table 2). Acute coagulopathy (22.5%; 95% CI: 16.5 – 28.4%) was the commonest hematological complication associated with COVID-19 (Table 3). There were only 2 observational studies that reported neurological complications, reporting low prevalence of ischemic stroke (2.3%; 95% CI: 1.3 – 3.9%), seizures (0.47%; 95% CI: 0.01 – 2.60%) and hemorrhagic stroke (2.3%; 95% CI: 0.8 – 5.5%) (Table 4). Of the 51 case reports and 23 case series published with 181 patients in total, there were 121 (67%) males and 60 (33%) females. Pulmonary complications were most commonly reported, followed by neurological, then renal complications. Pneumonia was the commonest respiratory complication (Table 1), whereas ischemic stroke was the commonest neurological complication (Table 4).

There were 1,830 reported complications reported from the 15 observational studies included in this review. Pulmonary complications constituted the majority (65.7%) of the reported complications, followed by hematological complications (8.1%). There were 101 (5.5%) cardiovascular complications (Table 2), 97 (5.3%) gastrointestinal complications, 87 (4.8%) renal complications (Table 5) and 21 (1.1%) neurological complications (Table 4).

Other commonly reported complications (Table 6) include transient acute renal failure (70.0; 95% CI: 49.9 – 90.1%), hypoproteinemia (22.4%; 95% CI: 15.9 – 28.8%) and electrolyte disorders (29.8%; 95% CI: 22.8–36.9%).

DISCUSSION

Respiratory complications

COVID-19 causes more damage to the respiratory system more than any other system. The respiratory route is the main route of entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as angiotensin-converting enzyme 2 (ACE2) receptors are well expressed on the lung alveolar epithelial cells. These receptor proteins are also found in the gastrointestinal system and the venous and arterial endothelium which are probably responsible for vascular and hematological complications [7].

Our findings reveal that about 4 in 10 hospitalized COVID-19 cases have pneumonia (Table 1) commonly presenting with fever, cough, and dyspnea. The risk factors for this level of illness severity in COVID-19 patients include old age, immunosuppression, diabetes mellitus, and cardiovascular and lung comorbidities [8]. Similar to influenza virus-induced pneumonia, the condition can be further complicated by acute respiratory distress syndrome (ARDS). However, ARDS in COVID-19 can be somewhat atypical with a later onset time (8-12 days) than stipulated by Berlin criteria (1 week) [9]. COVID-19 induced ARDS patients may in fact have normal lung compliance [10].

These complications progress to respiratory failure which is the most likely cause of COVID-19 mortality. Invasive Aspergillosis must be excluded if antibacterial therapy becomes ineffective and disease is rapidly advancing, particularly in immunocompromised patients [11].

Table 1. Respiratory complications of COVID-19.

Respiratory Complications, n=107 (59.1)	Case reports/series (N = 181)	Observational studies		
	n (%)	Number of studies reporting complication	n/N (%)*	95% Confidence Interval (CI)
Acute respiratory distress syndrome	4 (2.2)	6	387/1747 (22.2)	20.2 – 24.1
Pneumothorax	8 (4.4)	2	2/253 (0.8)	0.1 – 2.9
Invasive Aspergillosis	1 (0.6)	1	9/147 (6.1)	2.8 – 11.6
Respiratory failure only	6 (3.3)	1	6/161 (3.7)	1.4 – 8.1
Pneumonia	36 (19.9)	3	501/1211 (41.4)	38.6 – 44.1
Unexpected ventilation		1	240/1128 (21.3)	18.9 – 23.7
Pulmonary embolism	21 (11.6)	4	58/2190 (2.6)	2.0 – 3.4
Pleural effusion	3 (1.7)			
Acute chest syndrome	2 (1.1)			
Mediastinal emphysema	1 (0.6)			
Giant bulla	2 (1.1)			
Pneumomediastinum	12 (6.6)			
Subcutaneous emphysema	6 (3.3)			
Hydropneumothorax	1 (0.6)			
Pulmonary capillary leak syndrome	2 (1.1)			
Diffuse alveolar hemorrhage	2 (1.1)			

*pooled prevalence of complications in the observational studies expressed as the number of reported complications divided by the total sample size of studies reporting the complication

Table 2. Cardiovascular complications of COVID-19.

Cardiovascular Complications, n=17 (9.3)	Case reports/series (N = 181)	Observational studies		
	n (%)	Number of studies reporting complication	n/N (%)*	95% Confidence Interval (CI)
Myocardial injury	1 (0.6)	2	48/144 (33.3)	25.6 – 41.0
Heart failure only		1	9/161 (5.6)	2.6 – 10.6
Malignant arrhythmia		1	3/161 (1.9)	0.4 – 5.4
Myocardial infarction	1 (0.6)	2	6/549 (1.1)	0.4 – 2.4
Ventricular tachycardia/ Ventricular fibrillation		1	11/187 (5.9)	2.9 – 10.5
Acute myocarditis	2 (1.1)	1	20/20 (100)	100
Pericardial effusion	1 (0.6)	1	4/20 (20.0)	5.7 – 43.7
Acute effusive pericarditis with cardiac tamponade	1 (0.6)			
Intramural hematoma	1 (0.6)			
Atrial arrhythmia	3 (1.7)			
Acute myopericarditis	3 (1.7)			
Acute thrombosis of aortic prosthetic graft	1 (0.6)			
High degree atrioventricular block	1 (0.6)			
Left ventricular thrombus	1 (0.6)			
Takotsubo cardiomyopathy	1 (0.6)			

*pooled prevalence of complications in the observational studies expressed as the number of reported complications divided by the total sample size of studies reporting the complication

Table 3. Hematological complications of COVID-19.

Hematological Complications, n=16 (8.8)	Case reports/series (N = 181)	Observational studies		
	n (%)	Number of studies reporting complication	n/N (%)*	95% Confidence Interval (CI)
Acute coagulopathy		1	42/187 (22.5)	16.5 – 28.4
Deep venous thrombosis	4 (2.2)	4	27/1144 (2.4)	1.6 – 3.4
Venous abdominal thrombosis	1 (0.6)			
Arterial abdominal thrombosis	3 (1.7)	1	11/400 (2.8)	1.4 – 4.9
Disseminated intravascular coagulation	1 (0.6)	3	39/820 (4.8)	3.4 – 6.5
Bleeding events	4 (2.2)	1	19/400 (4.7)	2.9 – 7.4
Non-vessel thrombotic complication		1	8/400 (2.0)	0.9 – 3.9
Superficial venous thrombosis		1	2/400 (0.50)	0.06 – 1.81
Methemoglobinaemia in glucose-6-phospate deficiency	1 (0.6)			
Vasocclusive crisis	2 (1.1)			

*pooled prevalence of complications in the observational studies expressed as the number of reported complications divided by the total sample size of studies reporting the complication

Table 4. Neurological complications of COVID-19.

Neurological Complications, n= 82 (45.3)	Case reports/series (N = 181)	Observational studies		
	n (%)	Number of studies reporting complication	n/N (%)*	95% Confidence Interval (CI)
Ischemic stroke	22 (12.2)	2	14/602 (2.3)	1.3 – 3.9
Guillain-Barre syndrome (GBS)	12 (6.6)			
Basal ganglia involvement	1 (0.6)			
Rhombencephalitis	1 (0.6)			
Myasthenia Gravis crisis	1 (0.6)			
Encephalopathy	2 (1.1)			
Phrenic nerve paralysis	1 (0.6)			
Cerebral vasculitis	2 (1.1)			
Subarachnoid hemorrhage	5 (2.8)			
Posterior reversible encephalopathy syndrome	3 (1.7)			
Polyneuritis cranialis	1 (0.6)			
Intracerebral hemorrhage	7 (3.9)	1	1/214 (0.47)	0.01 – 2.60
Seizures	13 (7.2)	1	1/214 (0.47)	0.01 – 2.60
Hypoxic ischemic brain injury	7 (3.9)			
Transient ischemic attack	1 (0.6)			
Hemorrhagic stroke	3 (1.7)	1	5/214 (2.3)	0.8 – 5.5

*pooled prevalence of complications in the observational studies expressed as the number of reported complications divided by the total sample size of studies reporting the complication

Table 5: Gastrointestinal, renal, and dermatological complications of COVID-19.

Complications	Case reports/series (N = 181)	Observational studies		
	n (%)	Number of studies reporting complication	n/N (%)*	95% Confidence Interval (CI)
GASTROINTESTINAL	9 (5.0)			
Liver injury	6 (3.3)	3	49/331 (14.8)	11.0 – 18.6
Gastrointestinal bleeding		1	3/161 (1.9)	0.4 – 5.4
Pancreatic injury		1	9/52 (17.3)	7.0 – 27.6
Ischemic colitis	1 (0.6)			
Hypoproteinemia		1	36/161 (22.4)	15.9 – 28.8
Acute pancreatitis	2 (1.1)			
RENAL	23 (12.7)			
Renal insufficiency		2	15/253 (5.9)	3.3 – 9.8
Acute kidney injury	16 (8.8)	3	58/940 (6.2)	4.7 – 8.0
Transient acute renal failure	7 (3.9)	1	14/20 (70.0)	49.9 – 90.1
DERMATOLOGICAL	2 (1.1)			
Herpes zoster (shingles)	2 (1.1)			

*pooled prevalence of complications in the observational studies expressed as the number of reported complications divided by the total sample size of studies reporting the complication

Table 6: Endocrine, and others complications of COVID-19.

Complications	Case reports/series (N = 181)	Observational studies		
	n (%)	Number of studies reporting complication	n/N (%)*	95% Confidence Interval (CI)
ENDOCRINE	3 (1.7)			
Subacute thyroiditis	1 (0.6)			
Diabetic ketoacidosis	2 (1.1)			
OTHERS	13 (7.2)			
Multiple organ dysfunction syndrome	2 (1.1)	2	51/253 (20.2)	15.2 – 25.1
Electrolyte disorders		1	48/161 (29.8)	22.8 – 36.9
Sepsis		1	17/161 (10.6)	5.8 – 15.3
Shock		1	20/20 (100)	100
Atypical Kawasaki disease		1	10/20 (50.0)	28.1 – 71.9
Rhabdomyolysis	11 (6.1)	1	23/214 (10.8)	6.6 – 14.9

*pooled prevalence of complications in the observational studies expressed as the number of reported complications divided by the total sample size of studies reporting the complication

The outbreak of COVID-19 is not yet up to a year; the majority of reported complications are within three months of infection. The long-term effects of the infection on the respiratory system are still unknown. Drawing inferences from the sequelae of the 2002 Severe Acute Respiratory Syndrome (SARS) outbreak, the National Health Service, United Kingdom enlists chronic cough, fibrotic lung disease, bronchiectasis, and pulmonary vascular disease as potential long-term complications of COVID-19. Much is still unknown about COVID-19. Therefore, adequate follow-up clinic presentation and chest imaging of COVID-19 pneumonia patients should be recommended in order to detect long-term harbingers of complications and respond promptly [12,13].

Cardiovascular complications

Pre-existing cardiovascular conditions are established predictors of poor outcomes of SARS-CoV-2 infection. Certain cardiovascular complications have also been associated with COVID-19 [14]. These may result from systemic inflammation, the direct effect of the virus on cardiomyocytes via ACE2 receptors, and increased demand on the heart due to ongoing systemic inflammation [15,16]. The mechanisms by which COVID-19 results in cardiovascular complications are not well understood. A likely explanation for the incidence of myocardial infarction is that systemic inflammation causes disruption of atherosclerotic plaques. Moreover, since the activation of ACE2 receptor promotes the excretion of potassium ions, this may result in hypokalemia which puts the heart at risk of arrhythmia [15]. Adverse drug reactions are also potential causes of cardiovascular complications. Hydroxychloroquine with or without azithromycin can disrupt the electrical activity of the heart [17]. Multiple organ dysfunction syndromes (MODS) and shock are associated with severe COVID-19 infection and can eventually lead to death [18].

Hematological complications

Acute coagulopathy disseminated intravascular coagulation, and deep venous thrombosis were the commonest hematological complications found in this systematic review and meta-analysis (Table 3). Previous studies associated sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) with severe COVID-19 cases, especially in non-survivors.

Gastrointestinal complications

From our findings, liver injury was the most frequent gastrointestinal complication (Table 5). Studies reported that autopsies done on COVID-19 patients confirmed the presence of the virus in the liver tissues of patients. The underlying mechanisms for hepatic injury in patients with COVID-19 are still not fully understood. However, a study showed that the SARS-CoV-2 receptor ACE2 was highly expressed in bile duct cells. This suggests that SARS-CoV-2 may directly bind to ACE2-positive bile duct cells, leading to liver dysfunction [19]. Another likely explanation for liver injuries associated with COVID-19 is drug hepatotoxicity. Studies reported cases of drug-induced liver injury during treatment of COVID-19 patients with antiviral, antibiotic, and steroid medications. Some patients treated with Remdesivir during the pandemic were also reported to have elevated liver enzymes. Hypoproteinemia was a commonly encountered complication in severe and critical COVID-19 patients; this may have resulted from malnutrition or liver injuries [20].

Bioinformatics analysis revealed that ACE2 was also highly expressed in the glandular cells of gastric and duodenal epithelia. Invasion of the ACE2-expressing enterocytes by SARS-CoV-2 can lead to malabsorption, unbalanced intestinal secretion, activated enteric nervous system, and result in diarrhea. This invasion might explain other gastrointestinal complications, including gastrointestinal bleeding that was reported in this study [21].

Renal complications

Acute kidney injury was found to be the commonest renal complication; this was followed by renal insufficiency and acute renal failure (Table 5). Researchers found that ACE-2 receptor of SARS-CoV-2 was highly expressed in renal tubules and cells including mesangial cells, podocytes, and parietal epithelium of the Bowman's Capsule, this might be responsible for the renal complications [22,23].

Although mechanisms for the renal manifestations of COVID-19 are still not fully understood, a study proposed a complex multifactorial pathway which includes the

following: (i) direct viral involvement and replication in the kidneys leading to dysfunction; (ii) local disruption in renin-angiotensin-aldosterone system homeostasis (iii) lung protective fluid management strategy during treatment of ARDS and (iv) as a result of a systemic inflammatory response "cytokine storm" [23]. A recent study also demonstrated that the SARS-CoV-2 virus can directly infect human renal tubules consequently leading to acute renal tubular injury [23].

Increased incidence of venous thromboembolic events was also reported in critically ill COVID-19 patients admitted to the intensive care unit [24].

COVID-19 infection has been associated with coagulation abnormalities characterized by the elevation of coagulation biomarkers. There were reports of increases in procoagulant factor levels including fibrinogen and increases in D-dimers in COVID-19 patients. This reflects an inflammatory status characterized by coagulation activation and endothelial dysfunction and has been described to be a predictor of death associated with high mortality [24]. The expression of SARS-CoV-2 receptor ACE2 on venous and arterial endothelium is probably responsible for vascular and hematological complications [7].

Neurological complications

There are few observational studies that assess neurological complications of COVID-19. Cerebrovascular accidents and Guillain-Barre syndrome are mostly reported in case reports/series. There are gaps in the understanding of the neurotropism of SARS-CoV-2. Notwithstanding, possible routes of SARS-CoV-2 neuro-invasion have been proposed involving the olfactory epithelium, trans-synaptic spread through peripheral nerves, and lymphatic or hematogenous transfer [25].

Dermatological complications

Dermatological complications of COVID-19 were reported in just a few case reports/series. These complications are either due to direct invasion of the virus or due to a reaction of the immune system of the body [26]. Herpes zoster is one of the skin complications of COVID-19 and was reported in a case report in which there was a reactivation of the varicella-zoster virus in a patient with COVID-19 [27].

Endocrine complications

Diabetic ketoacidosis (DKA) and subacute thyroiditis are two of the endocrine complications in patients with COVID-19 reported by a few case reports. Subacute thyroiditis is a late complication of COVID-19 that presents with fever, cough, hoarseness, and odynophagia [28,29]. DKA, on the other hand, is a hyperglycemic crisis that is due to insulin deficiency. A previous study showed that there is an increased risk of DKA in diabetic patients with COVID-19 [30,31].

Other complications

Other complications like multiple organ dysfunction syndromes, electrolyte disorders, sepsis, shock, atypical Kawasaki disease, and rhabdomyolysis can also result from COVID-19 infection. MODS is an end-stage disease that includes acute kidney injury, thrombosis, acute cardiac injury, stroke, viral liver injury, pulmonary embolism, atelectasis, etc. [32]. Hypocalcemia, hypokalemia, and hypernatremia are the common electrolyte disorders that can be caused by COVID-19 infection and may be due to gastrointestinal losses by vomiting or diarrhea [33].

This review is limited by the fact that it was conducted at a time the pandemic is still ongoing. As such, newer complications other than those reported may still arise. Also, the exact causes of many complications are not yet fully understood. Further studies will be needed to elucidate these.

Conclusions

This review identifies systemic complications associated with COVID-19 infection and the prevalence of these complications. Pulmonary complications such as pneumonia, ARDS, amongst others, are the most reported across all study types, with endocrine and neurological complications least reported. The higher prevalence of pulmonary complications further supports existing literature that the respiratory system is the most affected in COVID-19 infections. With an increase in the number of cases worldwide, this study adds to the existing literature on COVID-19 complications and helps

improve the current knowledge of healthcare professionals of the impact of COVID -19 infections. It buttresses the need to be on the watch for arising complications across all body systems in patients with COVID 19 infections and ensure prompt treatment and care to avoid debilitating effects associated with the complications.

ACKNOWLEDGMENTS

Availability of data and materials

Data generated or analyzed during this study are included in this published article, and/or its supplementary information file will be provided by the corresponding author if demanded.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

Funding: Not applicable

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