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Original Research Article

Extrapulmonary manifestations of SARS-CoV-2 in a tertiary care centre in South India

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ABSTRACT

Background: COVID-19 is primarily a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, extrapulmonary manifestations were also quite frequently seen among the patients. Aims and objective of the study was to assess the extrapulmonary manifestations of COVID-19 in a selected group of patients.
Methods: The study was conducted at RVM Hospital, Siddipet on patients aged between 18-99 years, confirming to the World Health Organization (WHO) criteria for COVID-19. A total of 307 patients have been taken into consideration for this study.
Results: Cardiovascular, neurological, gastrointestinal (GIT) were the most common extrapulmonary systems being affected apart from hematological and endocrine systems. Coronary artery disease (67%) was the most common cardiac abnormality noted and ischemic stroke (86%) was the most common neurological problem. Type 1 DM, diarrhoea, conjunctivitis, hypothyroidism were the other diseases frequently encountered.
Conclusions: COVID-19, whilst being primarily a respiratory disease, can also affect the various systems in the body. Having said that, the most common extrapulmonary manifestations noted were cerebrovascular accidents (CVAs), myocardial infarctions (MI), pancreatitis and diarrhea.

Keywords: COVID-19, SARS-CoV-2, Extrapulmonary manifestations

INTRODUCTION

COVID-19 was a dreadful disease affecting many parts of the world. The condition, first identified in Wuhan, China on the 31 of December, 2019, rapidly spread to different parts of the country and eventually caused a pandemic across the globe.[1] COVID-19 remains an international public health problem with the epidemiological graph showing multiple peaks. While the mortality rate associated with the infection seems to have taken a dip, there is no hiding that among the at-risk population (i.e., the geriatric population, those with an immunocompromised status and so on), COVID-19 remains a major threat.

COVID-19 mainly affects the respiratory tree with symptoms ranging from mild upper respiratory tract (URT) symptoms to severe pulmonary damage leading to the need for invasive or non-invasive ventilation and/or death. The symptoms of COVID-19 might be ranging from flu-like symptoms to severe acute respiratory distress syndrome (ARDS) or ARDS-like manifestations. Viral pneumonia has also been implicated in the pathogenesis of COVID-19.[2] The clinical criteria involved in the diagnosis of the disease include any acute onset of any three or more of fever, cough, weakness or fatigue, headache, myalgia, sore throat, coryza, dyspnoea, nausea, anorexia and diarrhoea.[2]

COVID-19, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a distinct coronavirus from the one responsible for the 2002-2003

SARS outbreak, known as SARS-CoV-1.[3] The virus is believed to have been transmitted to humans via horseshoe bats (*Rhinolophus sinicus*) and other intermediate hosts to which individuals may have been exposed at wild food markets. COVID-19 is still an ongoing pandemic and is largely responsible for 70,31,216 deaths worldwide (as per WHO). COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) on 30 January 2020, with only 171 deaths, a figure that went up to 18 million by the end of December 2020.[2] As per World Health Organization (WHO), a confirmed case of COVID-19 is a person with a positive nucleic acid amplification test (NAAT) regardless of any clinical or epidemiological criteria. A person can be deemed as a confirmed COVID-19 case if they are rapid antigen test (RAT) positive and are meeting either/both clinical and epidemiological criteria for the condition.[2]

A study was conducted in our institution to find the extra pulmonary manifestations of COVID -19 and the sequelae associated. The study was done to emphasise that there are not only pulmonary symptoms but the patients often presented even with the extra pulmonary symptoms.

Pathogenesis

SARS-CoV-2 brings about its entry into target cells by binding to angiotensin converting enzyme 2 (ACE 2) receptors and also has a higher binding affinity to ACE2 receptors as compared to SARS-CoV-1 (responsible for the 2002-04 SARS outbreak) (Figure 1).[4]

Direct viral toxicity

The virus can be transmitted via direct or indirect respiratory tract exposure. The respiratory tract, in particular, has a high expression of ACE2 receptors and the SARS-CoV-2 virus, in general, has a higher binding affinity towards ACE2 receptors as compared to SARS-CoV-1.[5] This also forms the basis for RT-PCR testing. Live SARS-CoV-2 virus and the viral subgenomic mRNA can be isolated from the Upper Respiratory Tract, which can aid in the establishment of the diagnosis.[6] Tropism for ACE2 receptors for the virus also exists for renal parenchymal cells, myocardial tissue, Gastrointestinal epithelium, neurologic tissues, and pharyngeal tissues.[7] Studies have also confirmed the pulmonary and extrapulmonary expression of ACE2 and TMPRSS2 receptors (Figure 2). This explains one of the reasons behind the extrapulmonary manifestations of the disease.

Dysregulated immune response

SARS-CoV predominantly infects the airway and alveolar cells and also has an impact on the hematopoietic cells such as dendritic cells (DCs), monocyte-macrophages, and other peripheral blood mononuclear cells such as lymphocytes, natural killer cells, and so on. Infection of the DCs induces a mild expression of antiviral cytokines IFN-αβ which pales in comparison to the profound upregulation of the pro-inflammatory chemokines CCL2, CCL3, CCL5, and CXCL10.[8] A mild upregulation in the pro-inflammatory cytokines TNF and IL-6 have also been noted.

T-cell lymphodepletion may predispose to the overactivation of the innate immune response, invariably leading to cytokine-release syndrome and a dysregulated immune response.[9] In patients with severe SARS disease, there are high levels of pro-inflammatory cytokines (IL-1, IL-12, IL-6, IFN-γ, and TGF-β) in comparison with those with an uncomplicated disease. High levels of IL-6 are also associated with a poor prognosis and consequent mortality.[10] Elevated levels of Interferons (IFN-γ and IFN-β) have also been studied in those with lethal SARS with an increase in the levels of IFN-stimulated genes (ISGs) such as CXCL10 and CCL2, pointing toward the role of interferons in the immunopathogenesis of SARS.[11] It has also been brought to light that the elevated levels of D-dimer, erythrocyte sedimentation rate, and acute phase reactants such as C-reactive protein, ferritin, and lactate dehydrogenase are associated with progressively poor outcomes and mortality.

Dysregulation of RAAS

ACE-2 is a membrane-bound aminopeptidase to which the spike protein of the SARS-CoV-2 binds, which in turn results in the downregulation of the said receptor in addition to the viral entry and replication that occurs at the same backdrop. ACE-2 is essential for cleaving angiotensin I, to inactive angiotensin and angiotensin 1,9, and angiotensin II to angiotensin 1,7, which essentially has anti-inflammatory properties.[12]

Endothelial cell damage and thromboinflammation

The presence of viral particles has been demonstrated in the arterial and venous endothelium of organs such as the lungs.[13] This explains why ACE-2 mediated entry of the SARS-CoV-2 and the associated inflammation has been implicated in the pathogenesis of immunothrombosis in patients with COVID-19. Excessive thrombin production, activation of complement pathways, thromboinflammation, and inhibition of fibrinolysis are the byproducts of infection-mediated endothelial cell injury and endothelialitis (demonstrated by the presence of macrophages and neutrophils in the endothelial cells).[14]

It is also understood that platelet-neutrophil cross-communication coupled with macrophage activation can lead to a proinflammatory state by facilitating the formation of neutrophil extracellular traps (NETs), cytokine release, and fibrin and microthrombi formation.[15] The resultant extracellular traps damage the endothelium and activate the intrinsic and extrinsic coagulation pathways, giving rise to a prothrombotic state. Acute lung injury in COVID-19 also facilitates the release of hypoxia inducible factor 1 (HIF-1) which also promotes a thrombotic state.[16]

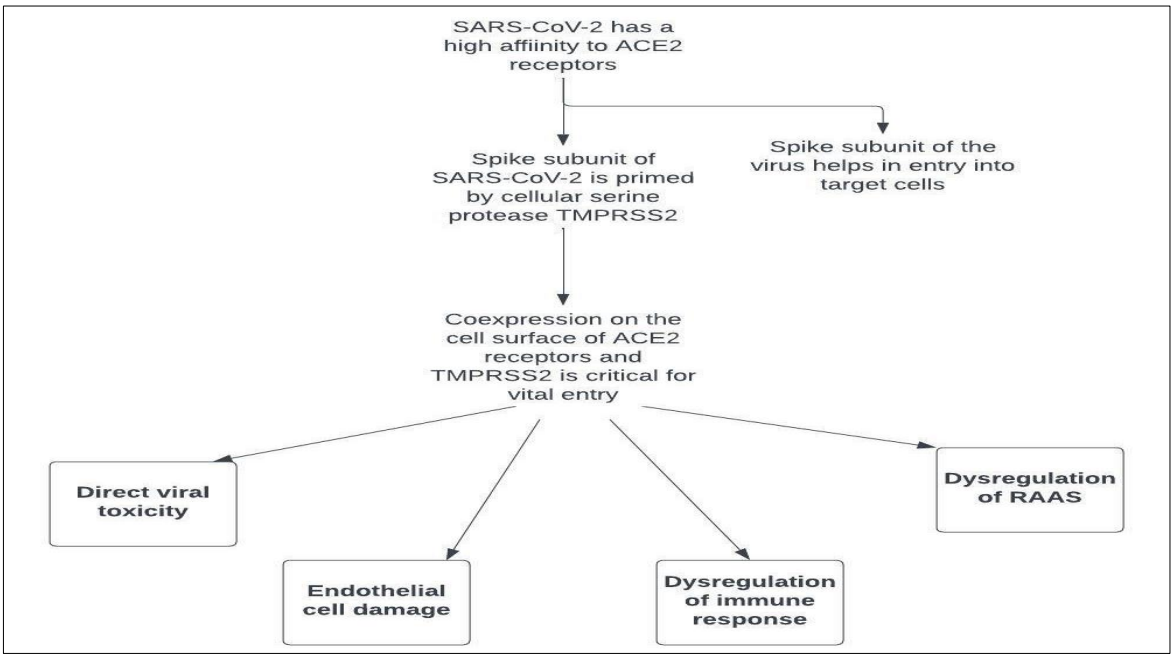

Figure 1: Pathogenesis of COVID 19.

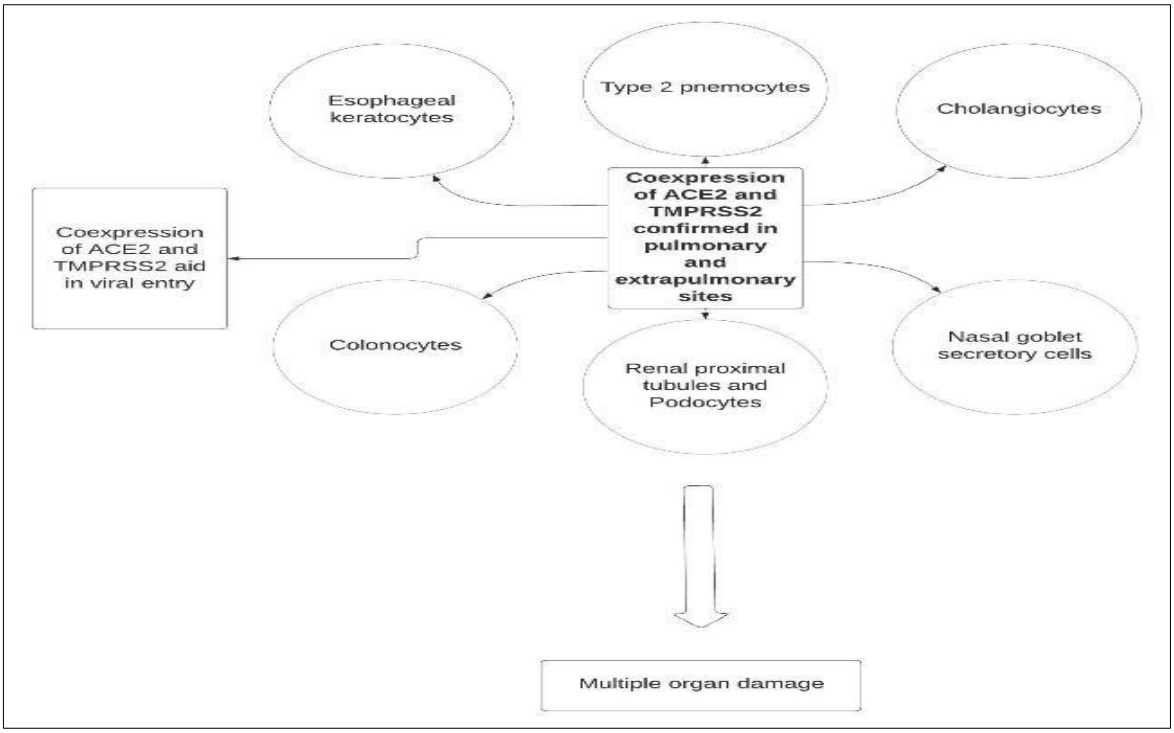

Figure 2: Pulmonary and extrapulmonary sites of ACE2 and TMPRSS2 expression.

Cardiovascular manifestations

Cardiac complications (of COVID-19) can manifest as heart failure, myocardial injury, arrhythmias, and cardiovascular syndromes, especially shock.[17] There is a particularly high expression of ACE2 receptors in cardiovascular tissues including cardiac myocytes, fibroblasts, endothelial cells, and smooth muscle cells.[18] The pathogenesis of SARS-CoV-2 involving the cardiovascular system is mediated by: direct viral injury, and direct viral infection of the endothelium (endothelial cell damage).[19]

Cytokine storm as a part of systemic inflammatory response syndrome (SIRS) has also been implicated in the causative factors behind the cardiovascular complications of COVID-19.[20]

Renal manifestations

It has already been brought to light the presence of ACE-2 receptors in the renal parenchyma. Moreover, lymphocytic endothelialitis in the kidney in addition to the presence of viral inclusion particles in the glomerular basement membrane points towards microvascular damage secondary to endothelial cell damage. SIRS may also lead to acute kidney injury (AKI).[21] Patients affected by COVID-19 can also develop collapsing focal segmental glomerulosclerosis with the underlying mechanism behind it being narrowed down to the deposition of immunocomplexes of the viral antigen or virus-induced specific effector mechanisms.[22] SARS-CoV-2 mediated podocyte injury may also occur which may lead to the development of albuminuria. ARDS, volume depletion, interstitial nephritis, and rhabdomyolysis, all of which are linked with COVID-19 patients, are also implicated in their respective roles in the development of renal manifestations (or more specifically, AKI) in COVID-19.[23]

Hematological manifestations

ACE-2-dependent/independent entry into lymphocytes is one of the main mechanisms by which lymphopenia or leukocytopenia occurs in COVID-19 patients. The other mechanisms by which lymphopenia, which is a negative prognostic marker, can also be caused due to apoptosis mediated lymphocyte depletion, and the inhibitory effect of increasing lactic acid levels on lymphocyte proliferation. Spleen atrophy (accompanied by extensive lymphoid tissue destruction), which has been implicated in patients with COVID-19, can also lead to lymphopenia.[24] Lymphopenia is commonly seen and it has been approximated that at least 67-90% of the patients affected develop lymphopenia. It is also a marker of impaired cellular immunity.

Hypoxia in combination with the direct viral mediated effects can also cause high rates of thrombotic complications. Moreover, there is an increase in the ACE-2 receptor expression in the endothelial cells following SARS-CoV-2 infection which can predominantly lead to endothelialitis and thus thromboinflammation. Thrombocytopenia has also been documented in some studies and is associated with worse patient outcomes.[25]

Endocrinological manifestations

Diabetes has become an important extrapulmonary manifestation in patients with COVID-19. Patients who already had pre-existing diabetes were at risk of developing poor glycaemic control with the development of ketoacidosis, which was either hyperglycaemic or euglycemic. That being said, some patients who did not have pre-existing diabetes also presented with ketosis or deranged blood glucose levels. One of the plausible explanations behind the poor insulin control in COVID-19 can be narrowed down to the evidence of ACE-2 receptors in the β-islet pancreatic cells, pointing towards the role of direct viral-mediated cellular damage in causing poor glycaemic control.[26] Studies also suggest that elevated cytokine levels can impair the insulin-secreting function of the β-islet cells and apoptosis.[27]

The thyroid gland is also an important target of SARS-CoV-2. It is understood that the thyroid also expresses ACE-2 receptors on its surface, making its involvement in the disease pathogenesis possible.[28] Abnormal thyroid function has been reported during the COVID-19 illness, either during the disease course or the timeline following its resolution. Having said that, non-thyroidal illness syndrome (NTIS), subacute thyroiditis, hypothyroidism, and thyrotoxicosis are some of the thyroidal manifestations of COVID-19.[29]

Central nervous system manifestations

SARS-CoV-2 can also affect the central nervous system (CNS). Its entry into the CNS is mediated by the nasal route as the nasal epithelium has the highest concentration of ACE-2 receptors, explaining why anosmia was one of the more common presentations among COVID-19 patients.[30] Other possible routes for the viral entry into CNS have been postulated to be via the lamina cribrosa, olfactory bulb, or retrograde axonal transport. Cytokine storm can bring about pro-inflammatory or prothrombotic sequelae, affecting the brain vasculature and the blood-brain barrier.

Ophthalmic manifestations

Ophthalmic symptoms in those infected with COVID-19 are uncommon but there have been reports linking the SARS-CoV-2 virus causing ocular manifestations. While the mechanisms behind the same remain unclear, there are explanations that could shed light on the pathophysiology of ocular manifestations of COVID-19. One of the theories that have been postulated is the direct inoculation of the ocular surface with SARS-CoV-2 via nasal droplets or aerosolized viral particles. Direct migration via the nasolacrimal duct or the hematogenous spread of the virus through the lacrimal gland has also been touted as possible mechanisms.[31] It is also understood that ACE-2 receptors are present on the corneal surface and limbus and at low levels, on the conjunctival surface as well.[32] Therefore, direct viral invasion could potentially be one of the mechanisms behind the ocular manifestations.

Gastrointestinal tract manifestations

The presence of ACE-2 receptors on the intestinal glandular cells points towards direct virus-mediated tissue damage.[33] That being said, viral RNA has also been isolated from faecal samples highlighting that gastrointestinal tract (GIT) is also a potential source of transmission of the disease. In addition, the presence of infiltrating plasma cells, lymphocytes, and interstitial edema is indicative of inflammation-mediated tissue

damage. Microvascular small bowel injury in patients with COVID-19 has also been highlighted as one of the important mechanisms behind the GIT manifestations of the infection.

Peripheral vascular disease

Cytokine storm in the later stages or depending upon the disease severity establishes a pro-inflammatory and pro-coagulatory state which facilitates the development of thrombosis in the vasculature. There are also reduced levels of nitric oxide (NO) in patients with COVID-19. Endothelial dysfunction, coagulopathy, vascular leakage, and inflammation can also bring about vascular changes and increased platelet activation. In severe cases, thrombocytopenia, elevated D-dimer and fibrinogen levels indicative of disseminated intravascular coagulation (DIC) follow.

The disease mainly affects the lung parenchyma in the form of pneumonia and ARDS. While the pulmonary manifestations are the usual norm of the disease, several extra-pulmonary showings of COVID-19 have also been noted. The condition can also affect the central nervous system, the cardiovascular system, the digestive tract, and so on. This paper is aimed at exploring the various extra pulmonary manifestations of SARS-COV-2 disease.

METHODS

The study was undertaken at RVM Institute of Medical Sciences and Research Centre, Siddipet. This is a prospective study done from April 2020 to August 2022. The data was collected from the patients who were admitted to RVM hospital due to SARS-CoV-2 in the study period.

Inclusion criteria

All persons who were diagnosed with COVID-19 (NAAT positive or RAT positive and/or NAAT positive and CORADS >5). Patients of 18 years of age and above have been considered for the study.

Exclusion criteria

Pregnant women and lactating mothers with COVID-19 infection have been left out of the study. All COVID-19-positive patients below the age of 18 have also been excluded from the data.

Sample collection and investigations

The consent from all the patients was obtained for all investigations for the duration of their stay in the hospital. Blood analysis and radiological investigations were carried out to assess the severity and extent of the COVID-19 infection in the affected patients. Results were analysed using statistical package for the social sciences (SPSS) version 20.

RESULTS

Our investigation delved into the clinical evidence gleaned from a cohort of 307 patients who tested positive for COVID-19. There were 210 males and 97 females who were affected with the disease. Most of the patients were in the age group 66–75 years (70) followed by 56–65 years (Table 1).

Notably, we observed a significant prevalence of extrapulmonary manifestations among patients, particularly affecting the cardiovascular and central nervous systems. Moreover, we documented intriguing manifestations of the virus, including pulmonary thromboembolisms, superior mesenteric artery thrombosis, as well as hematological abnormalities such as leucopenia and thrombocytopenia. Additionally, we observed ocular pathologies like central retinal vein and artery occlusions, which manifested following the onset of the disease, adding further complexity to its clinical profile (Figure 3).

Table 1: Distribution of cases in relation to age.

Age group (years)	Number
18–25	20
26–35	25
36–45	32
46–55	40
56–65	60
66–75	70
76–85	40
86–95	20

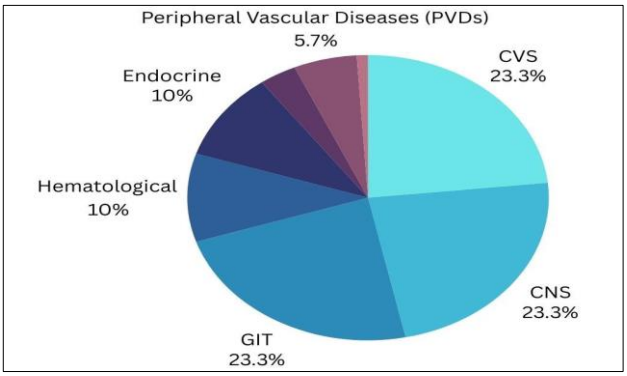

Figure 3: Distribution of extrapulmonary manifestations of COVID-19.

In the present study, 70 patients presented with cardiovascular manifestations. 48 patients from this select group had ACS/CAD, with 30 developing STEMI and 18 developing NSTEMI. 15 patients progressed to heart failure. Seven patients developed myocarditis and seven patients developed pericarditis with pericardial effusion. 15 patients developed myocarditis (raised trop-I). Many entered into the stage of heart failure (raised BNP, NT pro BNP) as well. This was the most common sequelae and the

majority of the patients were also lost to follow-up (Figure 4). Among the patients treated, 10 of them developed renal manifestations (AKI) with five developing haematuria and five, albuminuria (Figure 5).

In our study, 30 patients had developed poor glycaemic control with 10 patients (out of those 30 patients) developing type 1 DM in the subsequent follow-up.

There were also transient thyroid abnormalities with five patients developing transient hyperthyroidism and four developing hypothyroidisms. However, some of them had attained euthyroid states by the time of their follow up. Hypothyroidism was the most common observation found among patients who failed to attain euthyroid states.

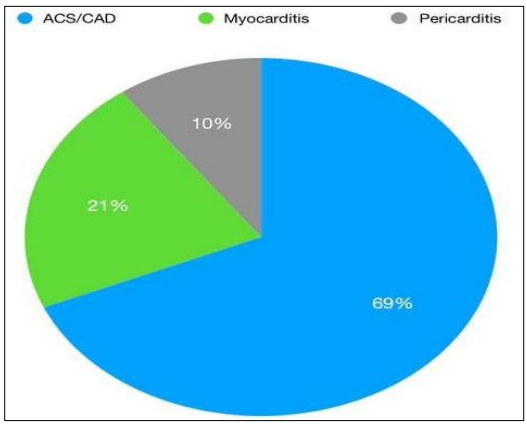

Figure 4: Cardiovascular manifestations in 70 patients.

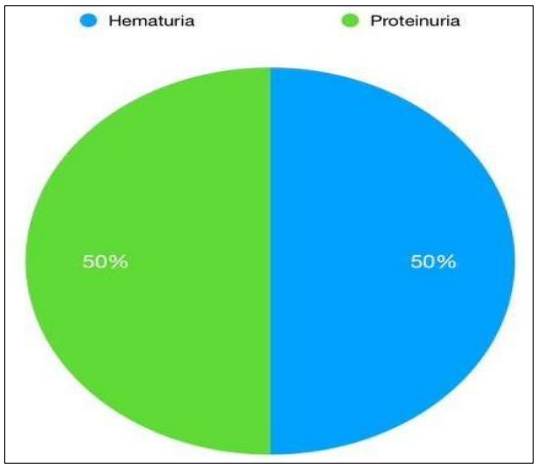

Figure 5: Renal manifestations.

In this study, 60 patients developed an ischaemic stroke within 1 to 2 weeks of the onset of COVID (in most cases) with computed tomography (CT) and magnetic resonance imaging (MRI) brain changes also confirming the same. Furthermore, 7 patients developed Guillain-Barre syndrome with generalized weakness and reflex reduction being among the more common symptoms. Three patients also had central sinus venous thrombosis (CSVT). Anosmia, dysgeusia, and encephalopathy were also observed in admitted patients. One of the more intriguing aspects of CNS involvement in COVID-19 was the complaints of vertigo, which was also commonly come across in the follow-up discussions. Along with vertigo, sleep disturbances, memory loss, headache, anosmia, dysgeusia, peripheral neuropathy, and ataxia were commonly observed in the follow-up patients of COVID-19 (Figure 6).

There were frequent complaints of eye redness and foreign body sensations among our patient pool. Conjunctivitis was also reported in several cases. Two patients however, developed central retinal artery occlusion (CRAO) with one developing central retinal vein occlusion (CRVO). It has to be understood that all other causes of CRAO and CRVO were ruled out before arriving at the conclusion that SARS-Cov-2 was the causative agent.

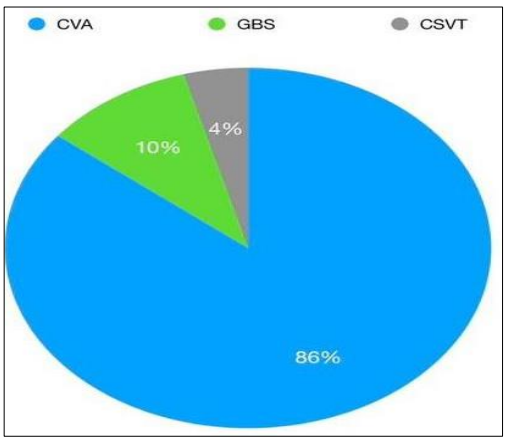

Figure 6: CNS manifestations.

In the given pool of patients, leukopenia was seen with an N/L ratio greater than 3:1. In that, lymphopenia was predominant and was associated with a poor prognosis. 23 patients developed thrombocytopenia with 10 requiring SDP transfusions for malena.

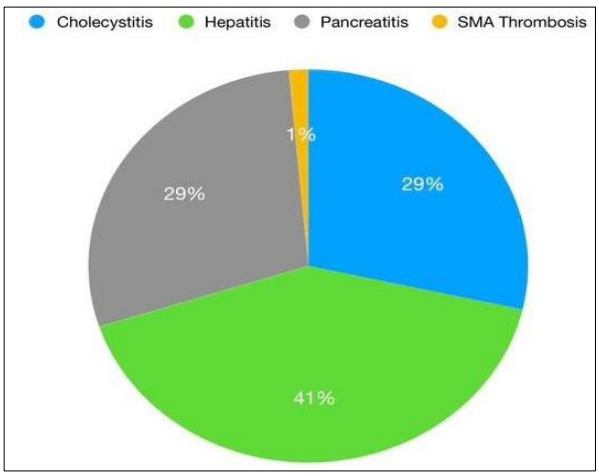

Figure 7: GIT manifestations.

The majority of the patients in our study had diarrhoea, proving it to be one of the more common extrapulmonary manifestations of COVID-19. Further, 29 patients had raised liver enzymes (AST, ALT) less than 5 times the upper limit in their respective liver function tests (LFTs) indicative of viral hepatitis. Liver involvement could be due to ACE2 receptors in the biliary and liver epithelial cells. 20 patients also displayed cholecystitis while 20 patients had raised serum amylase and lipase as a result of a new-onset pancreatitis. One patient had developed severe cramping abdominal pain and further investigation revealed that they had sudden-onset superior mesenteric artery (SMA) thrombosis. Ascites, lower GI bleeds and abdominal pain were secondary to the development of the above-mentioned conditions (Figure 7).

In our study, 10 patients had developed pulmonary thromboembolism while 7 patients developed deep vein thrombosis (DVT). Five patients had arterial thromboses with digital gangrene affecting both upper and lower limbs. Acute limb ischemia was also seen in severe COVID-19 infection, especially in the geriatric and obese patients and in those with underlying cardiac comorbidities (Figure 8).

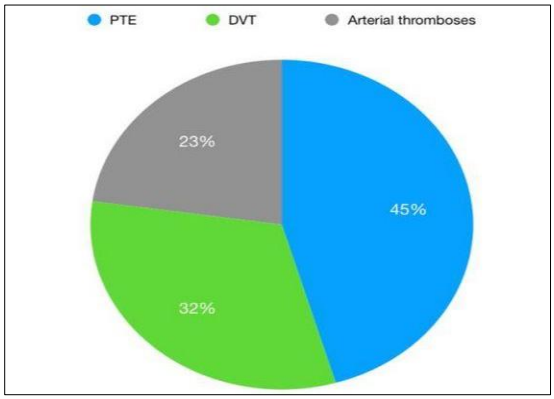

Figure 8: Peripheral vascular disease among COVID-19 patients.

Post-infection sequelae

While a fraction of the patients in our study were lost to follow-up, many reported feeling chronically fatigued in the weeks following discharge. Some patients also developed autoimmune arthritis post the infection while many had complaints of myalgia. Chest pain, cough, and insomnia were also commonly observed among the ones who returned for follow-up. Many patients also complained of feeling anxious and depressed and not being able to remember things they would usually expect themselves to remember (memory loss).

DISCUSSION

The present study emphasises on the extrapulmonary manifestations of COVID 19. The clinical spectrum of SARS-CoV2 infection ranges from asymptomatic infection to critical and fatal illness. Cardiovascular, neurological and gastro intestinal systems were the most commonly affected systems.

Cardiac manifestations like myocardial injury, myocarditis, ischaemic injury, right heart strain (corpulmonale), systemic inflammatory response syndromes, heart failure, cardiac arrythmias leading to sudden cardiac death were seen. The frequency of cardiac complications is similar to other studies.[34]

Neurological complications like anosmia, dysgeusia, headache, vertigo, cognitive impairment, encephalopathy, insomnia, cerebrovascular accident (CVA) and Guillian Barre syndrome (GBS) were seen. Among the neurological sequelae, ishemic stroke was the most common (86.7%). The incidence of stroke was less in other studies.[34]

Diarrhoea was the most common gastrointestinal complication noticed in our study similar to other studies.[35] This is due to the high cellular expression of ACE2 receptors in intestinal epithelial cells. Thrombotic complications were noted among 5.6% of patients in our study. The incidence of thrombotic complications were much higher in other study.[36]

Renal abnormalities like albuminuria and proteinuria were seen in 50% of cases in our study whereas albuminuria was 34% and hematuria was 63% in another study.[37]

Endocrine manifestations like abnormal thyroid functions and deranged blood sugars were noticed. Patients with uncontrolled diabetes mellitus are more likely to have serious complications, more ICU admissions, longer length stay and death due to SARS COVID 19. Other studies confirmed that pancreatic β cell injury occurs in COVID-19 infection leading to elevated amylase and lipase levels.[38]

Limitations

This study is limited, mainly with the patients lost to follow-up and with the patients who left in spite of medical advice whilst affected by COVID-19.

CONCLUSION

While SARS-CoV-2 usually affects the respiratory tract and can be associated with significant mortality and morbidity, emphasis also needs to be given to the extrapulmonary manifestations of the disease. While COVID-19 infection, depending on its severity can seriously impair the lung function of a patient causing irreversible fibrotic changes. It is also imperative to understand that it can cause equally severe and cause important tissue damage in organs such as the heart, brain, liver, pancreas, kidney, and blood vasculature causing a variety of complications such as fatigue, cognitive dysfunctions (as observed in long COVID syndrome)

vertigo, insomnia, psychological symptoms like anxiety depression, while also posing significant clinical challenges.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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