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Fungemia and Fungal Diseases as Complication of COVID-19

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ABSTRACT

Introduction The influence of coinfections on the morbidity and mortality of the new clinical syndrome coronavirus disease 2019 is unknown (COVID-19). Fungal agent of aspergillosis, mucormycosis, and candidiasis is the main superinfection that occurs as complicated to COVID-19; it may be related to ventilator-associated pneumonia (VAP), diabetic disease, or long time exposure to a corticosteroid that cause immune-suppressive even cytokine storm. These factors act as risk factors for fungemia and fungal shock that causes severe inflammation, disturbances in blood circulation with sepsis, and damage in many organs. Therefore, This review aimed to identify the main fungal agent and explain the pathogenesis and pathological aspect as complicated to COVID-19.

Conclusion The high rate of severe infection and mortality in patients with COVID-19's is thought to be due in part to a lack of natural immunity and raped viral replication in the lower respiratory tract, as well as superinfections, secondary infections, or coinfections, the mainly fungal agent that cause severe lung injury and acute respiratory distress syndrome (ARDS) as well as cause damage and sepsis in other organs.

Keywords COVID-19; Infection; Fungal Complication; Mycosis

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Introduction

Coronaviruses (CoVs) are single stranded and envelop RNA related to Coronaviridae family, order Nidovirales belong to sub-family: Orthocoronavirinae [1]. Sporadic and outbreak infections occur in both animals and humans as SARS-1, MERS which transmitted from animal to humans, recently pandemic SARS-2 has also revisable transmitting from human to pet animals [2]. In December 2019, SARS-2 was detected in Wuhan Seafood Market as a novel disease characterized by pneumonia with severe acute respiratory syndrome [3]. Because SARS-2 is a rapidly transmissible disease, there were about 10 million known cases and 500000 deaths in the first six months after the disease was discovered, and some cases associated with acute respiratory distress syndromes (ARDS) [4, 5]. This review aimed to identify the main fungal agent and explain the pathogenesis and pathological aspect as complicated to COVID-19.

Pathophysiological Mechanisms

COVID-19 primarily affects the respiratory and immunological systems, but it also affects other systems such as the urinary, gastrointestinal and reproductive tracts with neural and cardiovascular systems [6]. The spike protein is the main viral structural envelop for pathogenesis in the human, which binds to a human cell surface receptor protein called Angiotensin Converting Enzyme-2 (hACE2) via its receptor-binding domain (RBD). It is proteolytically activated by human proteases; also, cell entry of COVID-19 is reactivated by proprotein convertase furin, reducing its dependence on target cell proteases for entry [7] (Figure 1).

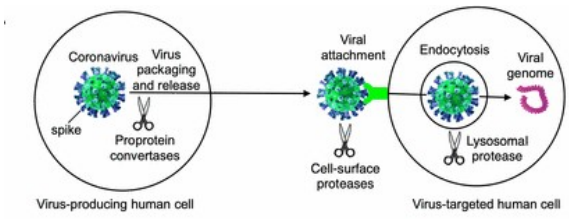

Figure 1) Host cellular proteases may trigger coronavirus spikes at various phases of coronavirus penetration [7]

SARS-cell CoVs entrance mechanism has been extensively researched. The receptor-binding domain (RBD) of SARS-CoV S1 bind to angiotensin-converting enzyme 2 (ACE2) as the virus's receptor [8]. One of the defense body mechanisms is a chemokine response and cytokine, which play a vital role in viral permission, whereas a dysregulated response might have disastrous consequences for infected patients [9]. The recruitment of hyperactive cytokines and chemokines causes a significant number of immune cells, such as macrophages, neutrophils, monocytes, and lymphocytes, to migrate from the bloodstream to the infection site [10], deregulated cytokines and chemokines have been caused by sepsis and pathological changes in different variable organs as in (Figure 2).

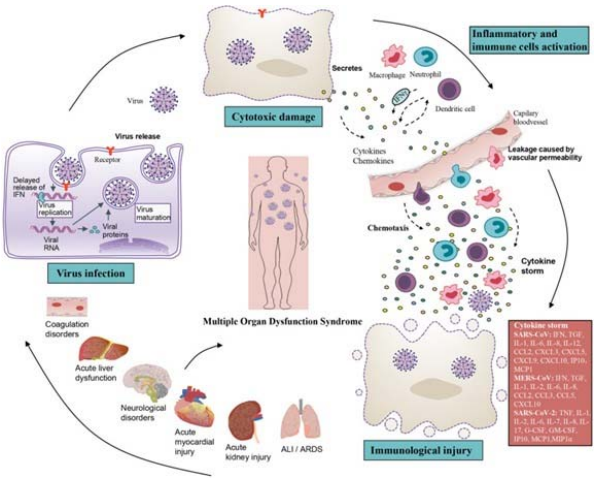

Figure 2) Pathogenesis of SARS-2, cytokine storm and inflammatory injury to vital organs [11]

COVID-19 Coinfection

SARS-CoV-2 has far outperformed any other common flu virus in terms of infection and fatality since its discovery [12]; the coinfection of SARS-CoV-2 with other microbes, such as viruses, bacteria, and fungi, plays a major role in COVID-19, which is called "Superinfection". Superinfections caused by bacteria and fungi that are complicated as COVID-19 are more common in critically sick hospitalized patients with underlying systemic disorders, immunosuppression, overdose, prolonged treatment with a corticosteroid, mechanical ventilation, prolonged hospital, and ICU stay, and advanced age. Superinfections can exacerbate coronavirus illness in an immunocompetent host [13].

Mixed fungal coinfection maybe occur as *Aspergillus fumigatus* with a *Mucorales species* and causes several clinical forms, the hypothesis for the infection are some risk factors as usage steroid drug for treatment SARS-2 may act important roles for the development of molds, providing a good environment for colonizing the patient, SARS-CoV-2 infection itself considered as an immunosuppressive state [14].

Superinfection Pathophysiology Mechanisms

Mechanical and immunological factors damage the respiratory tract's host defenses after viral infection, exposing the patient to bacterial and fungal infection [15]; pathophysiology Mechanisms involve two predisposing factors:

Mechanical ventilation: Reports suggested that, predominantly from China, secondary infections were observed in 5–27% of SARS-CoV-2 infected individuals in multiple institutions, with 50–100% of those who died [16]. Patients with severe disease

who are intensive care getting mechanical ventilation are more likely to get these infections.

-Dysregulation of the immune system of the host: The interaction between the virus and the host cell triggers an immune response, resulting in the production of anti-inflammatory cytokines like IL-4 and IL-10 as well as pro-inflammatory cytokines as IL-6, IL-2, and TNF-alpha; all these cytokines considered harmful and damage to host cells. Also, prolonged and severe antimicrobial administration may have a role in superinfection and die due to synergic effects or interaction between them [17]. A 30-year-old patient with pneumonia caused by *Staphylococcus aureus*, complicated with COVID-19, died after several days of treatment by clindamycin plus oxacillin and azithromycin for COVID-19, which was later changed to piperacillin-tazobactam and linezolid and then to meropenem, gentamicin, and linezolid; also an immunocompetent drug like corticosteroids have an important role in superinfection. Superinfections occur in many categories, as in Table 1.

Table 1) Categories and percentage of superinfections occurrence

Categories	The rate of occurrence	Reference
Bacteremia	There was a variable rate of bacteremia combined with COVID19 Among COVID-19-positive patients, research from New York City hospitals found a relatively low rate of bacteremia (1.6 percent). About 3% bacteremia was reported in the non-survivors of COVID-19 patients. While reaching 24.6% in some cases	[18-21]
Ventilator-Associated Pneumonia (VAP)	Patients with COVID-19 are exposed to severe mechanical ventilation, which leads to damage to capillary and ventilator-associated pneumonia and then changes lung microflora and predisposes the patient to secondary infection. In China, about 20% of survivors have pneumonia related to mechanical ventilation, and 6% of cases in non-survivors	[20]
Urinary Tract Infection	Urinary catheters have been the most common cause of urinary tract infection and about 1.4 to3.3% in hospitalized patients. UTI may consider predisposing. Although the data are very few UTI, the factor for superinfection occurs in 3% of COVID-19 patients.	[20, 22]
Immunosuppressive and drug interaction	Some therapy acts as immunosuppression and causes elevated blood sugar, which is a predisposing factor for superinfection. Some of the COVID-19 therapy under investigation may cause depression immune system as a corticosteroid or block important biological receptors. Also, drug resistance plays a significant role in the occurrence of superinfection	[22, 24]

Fungal Superinfection

Cases of COVID-19-induced "black fungus" are growing in some areas as the second wave of COVID-19. Aspergillosis, mucormycosis, and candidiasis infections produced by melanized fungus are examples of opportunistic mycoses that cause a wide spectrum of diseases. These affected patients take steroids and are immunocompromised. from localized infections to lethal disseminated disorders; some are transmitted from animal to human or indirect transmission from the environment as an endemic infection [18].

In COVID-19 patients with predisposing conditions, the incidence of opportunistic fungal infections is significantly higher (e.g., mechanical ventilation, cytokine storm, and diabetes). The majority of fungal infections in this group of patients, on the other hand, are related to the COVID-19 patients' difficult medical situations and the improper collection of clinical specimens. The respiratory tract represented the main target organs for COVID-19 infection and the most vital organs affected by super fungal infections (Figure 3).

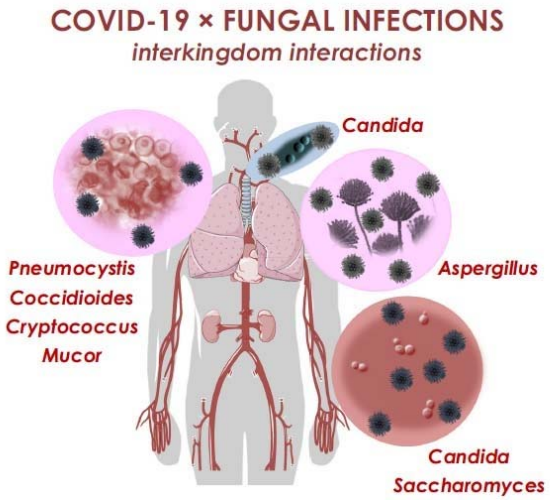

Figure 3) The SARS-CoV-2, which is represented by black spiky circles and the coinfection fungal genera of the affected patient with COVID-19, SARS-CoV-2 is represented by black spiky circles [25]

Mucormycosis (Black fungal disease) is a very uncommon infection. Mucor mold is widely distributed in plants, manure plants, and decaying vegetables and fruits. It is global and originates in air and soil, even in healthy people's noses and mucous. Mucormycosis, which has an overall mortality rate of 50%, may be triggered by steroids.

Steroids reduce inflammation in the lungs for COVID-19 and appear to help stop some of the damage that can happen when the body's immune system goes into overdrive to fight off coronavirus. But they also reduce immunity and push up blood sugar levels in people with diabetes and non-diabetic COVID-19 patients [26].

Mucormycosis hyphal angeo-invasive fungal infection associated with a high rate of morbidity and mortality, the brain, sinuses, and paranasal tissue are the main target organs;

however, it can also affect the heart, spleen, and skin, as in table [2, 27, 28].

Table 2) Mucormycosis types and target organs for infection in the most susceptible patients

Types of mucormycosis	Target organs	Patient susceptibility
Rhino cerebral	Sinus and Brain	Diabetics and patients who have a kidney transplant are both at risk.
Pulmonary	Lung	Patients with cancer or who have stem cells or an organs transplant
Gastrointestinal	Skin	Patient (premature or kids with low weight birth) with surgery or antibiotic which reduce ability resistance to germ invasion

Mucormycosis is not a contagious fungal that is transmitted through (i) inhaled spores and invade the lung and sinus, (ii) affected the skin if the infection occurs through a bite, burn. The infection then directly through circulation spreads to internal organs involve the eye, brain, spleen, heart, different pathways of causative agent entry lead to differences in clinical signs [29]. In general, atypical clinical signs take about four weeks, characterized by the nasal blockade, proptosis, crusting, edema, and facial swelling, painful necrotic skin (Figure 4), headache and fever, even chemosis, and ptosis periorbital inflammation with ophthalmoplegia with neurological signs [30, 31]. Histopathological examination revealed paranasal sinus tissue necrosis, angio-invasive, and vasculitis with granulomatous inflammation [23, 32].

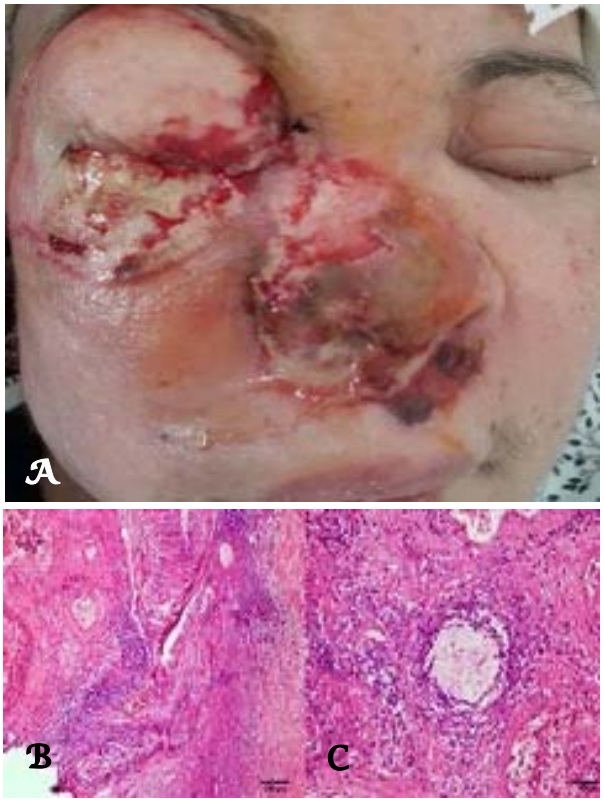

Figure 4) Fascial swelling and necrosis (A), necrotic debris in the paranasal sinus tissue with vasculitis (B), with granulomatous inflammation (C); Hematoxylin and eosin 200X [23, 31]

Invasive Pulmonary Aspergillosis (IPA) is another fungal disease that occurs as coinfection with COVID-19 because of lung damage and lowers respiratory tract, mainly occurring in patients with neutropenia and prolonged treatment with prolonged treatment corticosteroid [33]. In Wuhan, the mortality rate in patients with COVID-19 reached approximately 60–64.7% due to mechanical ventilator and invasive fungal *A. fumigatus,* which is reported as mainly coinfection and more common fungal prevalence as 70% from cases with fungal coinfection occurs with pandemic COVID-19 in the world wide country [34-36].

Cytokines Releasing Syndrome (CRS) associated with IPA**:** In severe COVID-19 patients, pro-inflammatory chemokines and cytokines such as TNFa, monocyte chemoattractant protein-1, interleukin-1b, IL-6, and IL-10 were greatly enhanced. The raised cytokine levels called (storm cytokines) may also play a role in COVID-19's deadly consequences; the histopathological examination revealed interstitial infiltrations with macrophage and monocyte in the heart, lung, and gastrointestinal mucosa and tissue necrosis in severe COVID-19 patients with high inflammatory cytokines [37]. IL-10 is one of the most important cytokines, which is considered a key for many immune responses. It mediates macrophage activity and limits the level of local tissue destruction. In the COVID-19, there is a greater activity of T helper cells (Th_2) with increased levels of IL-10, combined with a depression in the Th_1 that causes depression in the macrophage activity and elevates host susceptibility Aspergillus infection [38].

Also, IL-6 is one of the CRS that has a role in a blockage targeting the host immune system that may be effective for COVID-19. However, at the same time, it causes biological damage as disturbances in vessel permeability, cardiac arrhythmia, and reducing myocardium contractility and acute respiratory distress syndrome (ARDS) and increases susceptibility to IPA at this case, the T cells' reactivity to IL-6 is diminished [39, 40].

A. fumigatus isolated from patients a Broncho-alveolar lavage (BAL), and is characterized by septate hyphae with fruiting head and broad hyaline branching (Figure 5) and cause bilateral pneumonia and follicular lymphoma [41].

-Candidiasis invasive candidiasis is a serious healthcare-associated fungal infection that causes significant mortality rates. It is caused by various opportunistic Candida species, the most frequent *Candida albicans* and *C. glabrata* [42]. According to data from a Spanish hospital, invasive candidiasis is becoming more common among COVID-19-positive patients with a higher fatality rate. During COVID-19 pandemic events in New York City, USA, Candida spp. was one of the most commonly detected fungi in the bloodstream (candidemia) of patients with central venous catheters; Candida species were also

isolated from oropharyngeal which cause damage to the epithelial cells [43, 44].

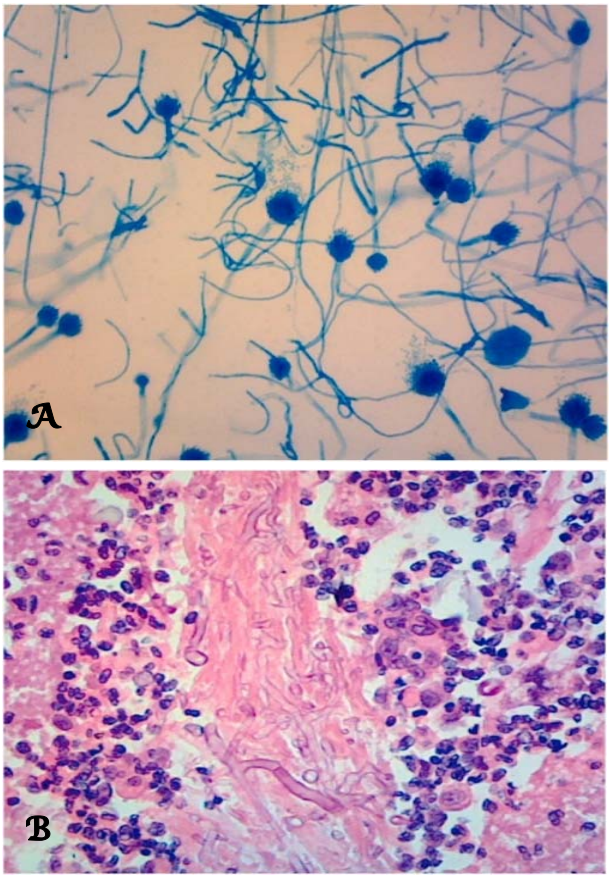

Figure 5) A: *A. fumigatus* characterized by septate hyphae with fruiting head (Lactophenol cotton blue, 200X); **B:** broad hyaline branching and cause bilateral pneumonia and follicular lymphoma (Hematoxylin and eosin, 200X), [41].

On the other hand, Saccharomyces organisms have been described as invasive infection agents in malignance or immunocompromised patients following probiotic treatment with Saccharomyces cerevisiae, which was detected in two patients hospitalized in the ICU due to severe COVID-19 [45]. Fungaemias is the translocation of the yeast to the blood circulation through mucositis and ulcers; another portal entry is through the central venous catheter [46, 47]. Yeast overgrowth and gastrointestinal (GIT) escape, produced by direct or indirect GIT damage, maybe key pathogenic factors for invasive mycoses. Haemodialysis, intestinal surgery and severe chemotherapy all these risk factors play a part in the GI leakage and lead to Sepsis-Related Organ Failure Assessment score (SOFA score) and the gravity of the disease in terms of septic shock.

Coinfections with COVID-19 and Pneumocystis also have been reported. *Pneumocystis jirovecii* is an opportunistic pathogen and an atypical unicellular fungus. Pneumocystis can produce *Pneumocystis pneumonia* or pneumocystosis, and variable lesions in many organs in immunocompromised patients (due to HIV, cancer, immunosuppressive medication, organ donation, or congenital immunodeficiencies) [48] Pneumocystis pneumonia is a kind of pneumocystis [49]. Descript the Histopathological lesions in the variable organs so in the lung detected fibrosis and thickening of the alveolar septa, microcapillary thrombus with micro-hyaline –fibrin and/ or platelet thrombus in the alveolar-capillary in addition to exudate in the alveolar and may reach to the bronchial lumen with foamy macrophage (Figure 6). There was a hyper trophy of myofiber in the hearing, alcoholic steatosis is seen in the liver with hepatitis and extensive tubular necrosis in the kidney (shock kidney), and significant medullary hemorrhage in the adrenal glands (Figure 7).

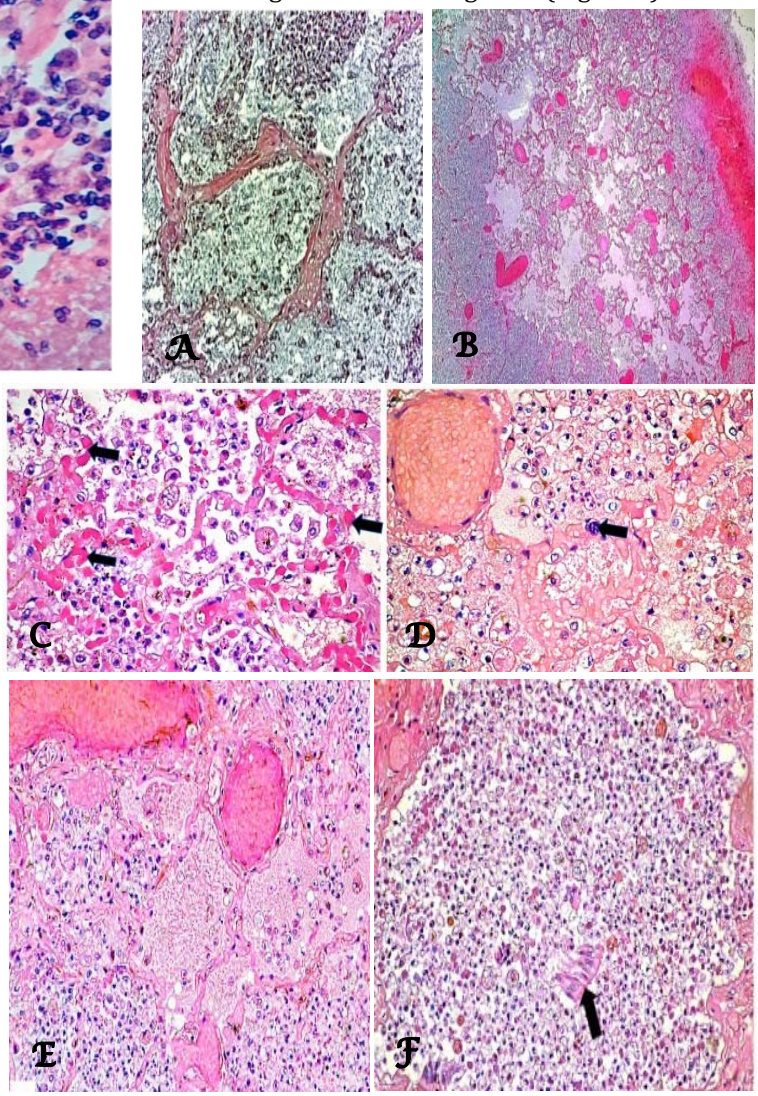

Figure 6) Histopathological examination of the lung revealed fibrosis and thickening of the alveolar septa (A) x100, microcapillary thrombus (B) x40, with micro-hyaline –fibrin (C) x200and/ or platelet thrombus in the alveolar-capillary (D) x100in addition to exudate in the alveolar (E) x400 and may reach to the bronchial lumen with foamy macrophage (F)x200; Hematoxylin and Eosin [49]

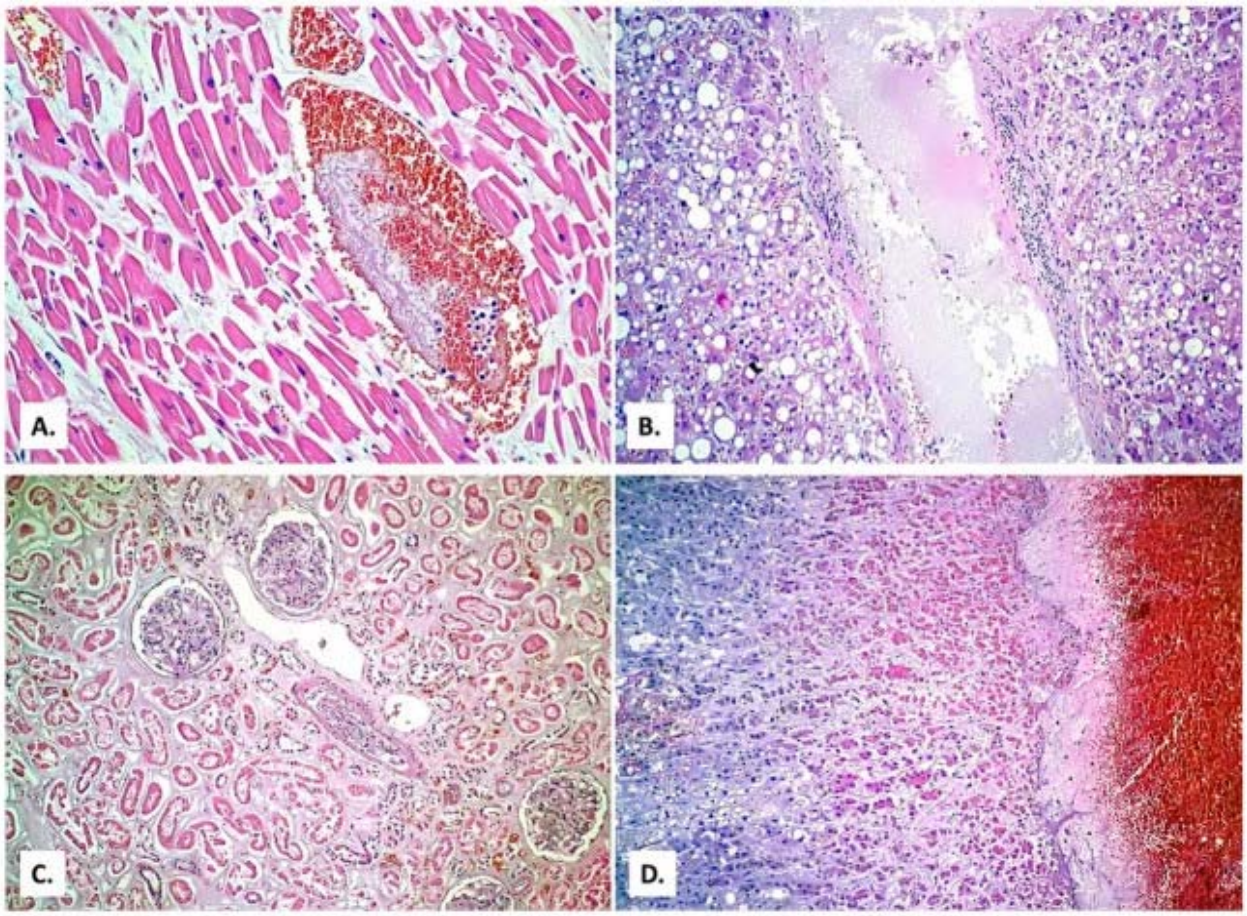

Figure 7) Histopathological examination In the hearing, there was hypertrophy of myofiber (A) × 400, alcoholic steatosis is seen in the liver with hepatitis (B) x 100 and extensive tubular necrosis in the kidney (shock kidney) (C) x200, as well as significant medullary hemorrhage in the adrenal glands (D) x40; Hematoxylin and eosin [49]

Conclusion

The high rate of severe infection and mortality in patients with COVID-19's is thought to be due in part to a lack of natural immunity and raped viral replication in the lower respiratory tract, as well as superinfections, secondary infections, or co-infections, mainly fungal agent that cause severe lung injury and acute respiratory distress syndrome (ARDS) as well as cause damage and sepsis in other organs.

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