A Comprehensive Review on COVID-19 Infection and Comorbidities of Various Organs

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Abstract- In the Coronavirus disease 2019 (COVID-19) pandemic, underlying diseases such as cardiovascular disease, respiratory illness, liver and kidney disease or malignancies, have a critical prognostic role for these patients. Due to the increased risk of mortality in patients with established or new-onset comorbidities, we decided to conduct a study to further investigate the possible comorbidities and treatment recommendations of COVID-19. All articles published by March 25, 2020, on the new coronavirus infection were reviewed and for cutaneous manifestation as a new emerging concern, by April 25, 2020. ScienceDirect, Google Scholar, Scopus, PubMed databases were searched, and keywords such as "COVID-19", "2019-nCoV", "Coronavirus2019", "SARS-CoV-2", and "comorbidity" have been used. The most important comorbidity in elderly patients with confirmedCOVID-19 was cardiovascular disease, followed by diabetes and chronic respiratory disease, respectively, and on the other hand, COVID-19 itself could cause acute heart, lung, liver, kidney, and skin disease. Also, the prevalence of underlying diseases in dead patients or patients with severe COVID-19 is higher than the others. Considering treatment, drug interactions, and careful drug adjustment based on hepatic and renal metabolism are essential. The results of this study showed that the mortality rate and ICU admission in people with the underlying disease is higher than in other people. Also, we must pay attention to the possible multi-organ damages and comorbidities for the protection and successful treatment of COVID-19. There are some comorbidities like primary cutaneous manifestations that may have diagnostic or prognostic values in the COVID-19 course.

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Introduction

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The new coronavirus disease 2019 (COVID-19) is a class of RNA viruses that belongs to the ancient coronavirus family, which is widespread among mammals and humans (1). With the rapid spread of the disease in China and then to other parts of the world, the new coronavirus, scientifically known as SARS-CoV-2, and the resulting disease, COVID-19, have caused great concern and panic among the world's population. The disease was recently recognized as a pandemic by the World Health Organization (2). The disease caused by the new coronavirus (COVID-19) has been confirmed in Iran since February 20, 2017, according to official reports (3). The disease (11 April 2020) has more than 1,524,161 cases worldwide. In Iran, 66,220 cases have been confirmed with PCR testing so far (4).

COVID-19 pneumonia is characterized by symptoms such as fever, fatigue, dry cough, and lymphopenia. Many elderly patients with the severe illness have underlying conditions such as cardiovascular disease, respiratory illness, liver disease, kidney disease, or malignant tumors (5). These patients often die from their underlying diseases. Due to the risk of transmitting a group of infectious diseases, we should pay close attention to the main treatment for comorbidities when treating pneumonia, especially in elderly patients with severe comorbidities. COVID-19 not only cause pneumonia but also can damage other organs such as the heart, liver, and kidneys, as well as organs such as the blood and immune system (6). Eventually, patients die from multiple organ failure, shock, acute respiratory distress syndrome, heart failure, arrhythmia, and renal failure (7,8). Therefore, possible multiple organ damage and protection and prevention should be considered in the treatment of COVID-19 (9). Given the increased risk of mortality with comorbidities, we decided to conduct a study to further investigate the role of comorbidities and treatment recommendations in COVID-19.

Materials and Methods

In this comprehensive review study, all articles published by March 25, 2020, in English on the new coronavirus infection were reviewed. Following databases were searched for this manuscript: ScienceDirect, Google Scholar, Scopus, PubMed using the following keywords: "COVID-19", " 2019 novel coronavirus (2019-nCoV)", "Coronavirus 2019", " Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)", and "comorbidity." The world's leading health websites such as the World Health Organization and the Centers for Disease Control and Prevention (CDC) have also been used to obtain the latest statistics and information on the disease. Information related to clinical features and tips for the comorbidity has been extracted from the above articles and websites. In this article, the official information websites of the Ministry of Health of Iran have also been used.

In the initial search, 1360 articles were extracted, and after deleting the repetitive items and evaluating the title and abstract, 104 articles were selected. After reviewing the full text of the articles, 71 articles had the necessary conditions to participate in the present study as comorbidities of COVID-19 infection. For cutaneous manifestation since it was a new emerging concern, we updated our search up to April 25, 2020, and selected other 12 articles for entering this review. Finally, 83 articles met the criteria to enter the study.

Epidemiology

Studies have shown that the estimated mortality rate in China is about 2.3% or 2.9% and 4.3%, respectively. In the March 3, 2020 report by the World Health Organization (WHO), this estimate was 3.4% (10). At the time of data release, no deaths occurred in the under-9 age group in china, but in the 70- to 79-year-old age group, the mortality rate was 8.0%, and in the 80-year-old age group and above, the mortality rate was 14.8% among patients (11,12). Case Fatality Rate (CFR) is 10.5% for cardiovascular disease, 7.7% for diabetes, 6.3% for chronic respiratory disease, 6.0% for blood pressure and 6.6% for cancer (7). Gender differences may also be present in patients with COVID-19 with severe clinical status. Men are more likely to have a more complex clinical condition, and in a hospital setting, the results are worse than for women (13). Because immune-related genes are located on the X chromosome, and sex hormones that affect innate and acquired immune responses may justify more male susceptibility to the infection (14).

Pathogenesis

Coronary spike surface glycoprotein of coronaviruses plays a key role in binding to cell surface receptors and plays a key role in tissue proliferation. Previous studies have shown that the SARS virus uses the enzyme angiotensin-converting enzyme type 2 as a cellular receptor to enter the cell. Recent studies have also shown that the new coronavirus SARS-CoV-2 also uses the enzyme type 2 angiotensin-converting enzyme as a receptor for entry into the cell (15,16).

A comparative analysis showed that ACE2

expression in kidney cells was not less than in the lungs, the esophagus, small intestine, and the large intestine, so the kidney may be an important target organ for SARS-Cov-2 (17). This receptor is also expressed in myocyte cells, which can cause these cells to be directly attacked by the COVID-19 (18). The angiotensin 2 converting enzyme (ACE2) is a membrane-bound aminopeptidase that plays an important role in cardiovascular and immune systems. ACE2 is involved in heart function and high blood pressure, and diabetes (19).

Pulmonary involvement

A recent study shows that SARS-CoV-2 has an ACE2 cell input receptor similar to SARS-CoV. In general, ACE2 protein is expressed in alveolar cells, bronchial epithelium, and vascular endothelium, so the SARS-CoV-2 protein binds to ACE2 and leads to acute lung damage and pulmonary edema (20,21). On the other hand, the Cytokine storm, which leads to an over-immune response and uncontrolled inflammatory responses, causes severe organ disease, including lung damage. Therefore, these results may explain the acute lung dysfunction in critical illness (22). Coronavirus SARS-CoV-2 effectively reproduces in the upper respiratory tract. Infected people produce large amounts of the virus in their upper respiratory tract during a Preliminary period, which leads to further spread of the virus to others (23). Coronavirus SARS-CoV-2 is also prone to cells in the lower respiratory tract, and by multiplying in these areas, it can lead to lesions in the lower respiratory tract (23).

Pneumonia is the most common pulmonary involvement in COVID-19. Depending on the severity of the symptoms, patients are categorized into mild, moderate, severe, and very severe. Patients with very severe symptoms should be referred to the ICU. A recent meta-analysis found that the average age of hospitalized people in the ICU was 62-year-old, and the most common symptoms in the very severe cases were cough (67.2%), fever (62.9%), and shortness of breath (61.2%). Preliminary CT findings showed that the lesions involved two or more lobes and were mainly distributed in the peripheral areas of the lungs. The findings may be related to the anatomy of the right lower lobe bronchus, which is thick and short, making it easy for the virus to invade. Primary lesions are rarely calcified (6%). Relatively clear manifestations, including Ground Glass view, vascular thickening (80%), halo mark sign (64%), crazy paving pattern (40%), and air bronchogram sign (48%), are seen in the early stages of the disease. External pulmonary fibrosis and manifestations, such as enlarged mediastinal and pulmonary lymph nodes, pleural effusion, and thickening of the pleura, are not present in the primary lesions of COVID-19 pneumonia. These findings may be seen in the next stage and the severe form of the disease. Patients with severe disease may develop acute respiratory distress syndrome (ARDS) (24). In three studies performed on hospitalized patients, 31.7%, 23.2%, and 26.1% of patients were admitted to the ICU, respectively, and the percentage of patients with ARDS was 29.3%. 17.2 and 19.6, respectively, and 4.9%, 4.0%, and 12.3% of these patients were intubated, respectively (25).

There have been reports of a previous history of COPD or asthma in admitted patients. Huang *et al*., and Wang *et al*., have reported the prevalence of Chronic obstructive pulmonary disease (COPD), approximately 2% and 2.9%, respectively (6,26). Subsequently, Chen *et al*., has been reported Respiratory system disease to be approximately 1% (8), which differs from the estimated COPD prevalence in different parts of China (between 1.2 and 8.9%) (27). In addition, no interstitial lung disease, no history of smoking, bronchiectasis, or asthma have been reported. A study by Zang*et al*., conducted on 140 patients with COVID-19, showed that asthma or other allergic diseases were not reported by any of the patients.

Chronic obstructive pulmonary disease COPD and recent smoking were seen in 1.4% of patients. This study shows that allergic diseases, asthma, and COPD are not risk factors for SARS-CoV-2 infection. Age, the high number of underlying diseases, and severe laboratory abnormality were associated with severe disease (28). Ding *et al*., have reported pulmonary changes such as localized and necrotic hemorrhage, pulmonary alveolitis, bronchitis, and desquamation of alveolar epithelial cells in SARS (29-31). In fact, in this study, the results showed general pulmonary lesions, including alveolar edema with bleeding and bronchiolitis and alveolitis, along with inflammatory damage to epithelial cells. Note that extensive interstitial pulmonary fibrosis, vessel wall thickening, lumen stenosis, and obstruction were often observed under a microscope (32).

In a new clinical trial in France that publishes data in the middle of evaluation, concomitant administration of chloroquine and azithromycin together could significantly clear the pneumonia of COVID-19 within six days (33). There are no definitive treatments for COVID-19 therapies, and several clinical trials are currently underway by the WHO, the results of which

will be announced soon. Favipiravir and ribavirin analog nucleosides can stop the virus from reproducing. Theoretically, Remdesivir was the most effective drug among animal samples, and its effect was even greater than that of Kaletra® (Lopinavir/Ritonavir) as well as interferon (chines Guideline for COVID-19). The neuraminidase inhibitors, including oseltamivir, zanamivir, and peramivir, which are effective in influenza, have been used extensively for COVID-19 but have not been published in the studies. And other peptide fusion drugs such as Arbidol and RNA synthase inhibitors and even Sovodak, an Iranian drug, are being clinically tested. Immunosuppressive drugs and poly or monoclonal antibodies are other evaluated therapies (34-36).

Cardiac involvement

Although the symptoms of the virus were initially thought to be unique to the respiratory system, some patients developed severe cardiovascular damage, and in addition, mortality in patients with the underlying cardiovascular disease increased (6). Therefore, it is important to know the proper mechanism of action of COVID-19 on the cardiovascular system. In addition, many patients were referred with cardiac symptoms such as palpitations or chest tightness (chest tightness) instead of coughing and fever, which eventually led to COVID-19 (37).

In one study, the prevalence of the cardiovascular disease, blood pressure, and the incidence of an acute heart attack during admission among COVID-19 patients was 14.6%, 14.5%, and 12.2%, respectively. In another study evaluating hospitalized patients with COVID-19 showed that 14.5%, 31.2%, and 7.2% had CVD, high blood pressure, and acute heart attack. Also, 26% of them required ICU, the prevalence of hypertension (HTN) and cardiovascular diseases (CVD) among ICU admitted patients was 58% and 25%, respectively (6,26). Another study examining the causes of mortality from COVID-19 found that patients with underlying cardiovascular disease were significantly more likely to die, so that 7% of patients died from myocardial infarction (MI) and 33% died from MI and ARDS. For the first time in this paper, fulminant myocarditis was reported (38). In another study in Wuhan, China, the virus significantly affects heart function, and a history of coronary heart disease (CHD) and increased cardiac troponin I (cTnI) levels are two independent variables predicting disease status (39). In a study of 82 deaths from COVID-19, 80.5% of those were over the age of 60 with an average age of 72 years, 56% had a history of high blood pressure, and 20.6% had a history of underlying cardiovascular disease, and 14.6% of them died of heart failure (39). In a meta-analysis of 6 studies and 1527 patients, the percentage of hypertension, cardiovascular, and diabetes among COVID-19 patients was 17.1%, 16.4%, and 9.7%, respectively, and this prevalence was doubled and tripled in hospitalized and ICU patients, respectively. About 8% of patients with COVID-19 had an acute heart attack. These results suggest that cardiac diseases could increase the severity of COVID-19 disease and that COVID-19 itself could cause heart damage (40).

The viral infection is a common cause of heart damage such as myocarditis. Adenovirus, enterovirus, and herpes viruses are well known to be the most common infectious causes of heart damage (41). Since coronavirus was first reported in 1980 (42), studies have shown that coronavirus is an uncommon but undeniable pathogen for heart damage (42,43). Coronaviruses are likely to cause apoptosis or myocardial necrosis by storms of inflammatory cytokines such as IL-6 & CRP (44) or direct attack of heart cells by COVID-19 through ACE2 receptors (18). In a cohort study in china conducted on patients with COVID-19. The findings of this study showed that high sensitive-troponin I (hs-TnI) levels were higher in the elderly with comorbidities such as blood pressure at the time of hospitalization and hs-TnI levels higher than 6.126 pg/mL (NL: 0-28 pg /ml) is associated with higher mortality during hospitalization. High hs-TnI is also associated with elevated levels of inflammatory factors (neutrophils, Interleukin 6

(IL-6), C-reactive protein (CRP), and Procalcitonin (PCT)) and decreased immune levels (lymphocytes, monocytes, and Cluster of differentiation 4 (CD4)+ and Cluster of differentiation 8 (CD8)+T cells). Elevated levels of Creatine kinase-MB (CK-MB) at the time of hospitalization in male patients with a history of recent smoking were associated with higher mortality. This association was also observed at elevated lactate dehydrogenase (LDH) and alpha-hydroxybutyrate dehydrogenase (α-HBDH) levels. Researchers recommend that patients with suspected heart damage, especially older men with a history of high blood pressure and smoking, be evaluated for heart damage and that lower levels of hs-TnI be considered positive (45).

Evaluation of a 50-year-old patient who died of acute respiratory syndrome from COVID-19 and a pathology sample from the heart revealed that there was little mononuclear infiltration, and no evidence of direct damage to the heart was found (46). ACE2 levels can be

increased by the use of angiotensin 2 converter enzyme inhibitors or angiotensin receptor inhibitors, and because ACE2 is a SARS-CoV-2 functional receptor, the use of ACE inhibitors or angiotensin-receptor blockers should be considered carefully (37). In a comprehensive review conducted in 2020, most of the world's leading scientific associations emphasized the continued use of ACE inhibitors or angiotensin-receptor blockers, and numerous studies have shown that ultimately the weight is for or against ACE inhibitors or angiotensin-receptor blockers, and more detailed studies should be performed (47). The American Heart Association's recommendation for the use of the renin-angiotensin-aldosterone system (RAAS) antagonists in patients taking these drugs with heart problems have been advised to continue, and if you have CVD with COVID-19. It was decided to make a case-by-case decision based on the patient's characteristics (48).

Diabetes

Diabetes is one of the most common comorbidities associated with COVID-19. In a recent meta-analysis, its prevalence was estimated to be about 9.7% in patients with COVID-19 (41). People with diabetes, especially the elderly, are at risk for infections, especially the flu and pneumonia. With good glycemic control, this risk, although not completely eliminated, is reduced. All people with diabetes (over two years of age) are recommended for pneumococcal vaccination of 13 valances and 6 to 12 months later, type 23 valance (Advisory Committee on Immunization Practices (ACIP) recommendation) and annual flu dose [49, 50]. Patients with diabetes have a severe illness when they become infected with respiratory viruses. In fact, diabetes has been identified as a significant risk factor for death in the Middle East respiratory syndrome (MERS), Severe acute respiratory syndrome (SARS), and Hemagglutinin 1 neuraminidase 1(H1N1) influ (51-53).

Due to the inherent immune response defect, diabetics develop a more severe illness after SARS-CoV-2 infection. In addition, COVID-19 in diabetic patients has a much greater potential for the rapid progression of acute respiratory distress syndrome and septic shock, which may eventually lead to multiple organ failure (54).Compared with patients who did not receive ICU care, patients admitted to the ICU with COVID-19 were more likely to have underlying diabetes (22.2% versus 5.9%)(30). Information about COVID-19 is currently limited in patients with diabetes. In a study of 26 deaths from COVID-19 in Wuhan, China, 42.3% of dead patients were diabetic (55). In a study of 140 patients with COVID-19 in Wuhan, China, diabetes did not pose a risk factor for serious illness (28). However, another study of 150 patients (68 deaths and 82 improved patients) in Wuhan found that the number of comorbidities was a significant predictor of mortality (38). An analysis of 11 studies of laboratory abnormalities in patients with COVID-19 did not indicate an increase in blood sugar or diabetes as a predictor of severe disease (56). China's largest epidemiological report of 72,314 confirmed COVID-19 cases with diabetes has a 7.3% higher mortality rate than 4.3% of patients without diabetes (57). Clinical findings indicate mortality of 2.3% to 15.5% in diabetic patients with COVID-19 (6,8,26). In Iran, in terms of the incidence of underlying diseases in the number of deaths, the highest incidence of diabetes was 16% among 514 deaths (58).

Because the MERS-CoV receptor binds to human dipeptidyl peptidase IV (DPP-IV), a transgenic mouse model that expressed the DPP-IV receptor on alveolar lung cells was used to study the effect of diabetes on worsening disease severity. This study showed a link between diabetes and weight loss and increased pulmonary inflammation, and the infiltration of macrophages in the lungs was similar to the clinical manifestations of the disease (59). Coronaviruses are also linked to ACE receptors. In addition, ACE2 expression is increased in patients with type 1 and type 2 diabetes, which is often treated with ACE inhibitors and Angiotensin II Receptor Blockers (ARBs) (60). ACE2 is also increased by thiazolidinedione and ibuprofen (61).

Liver

Liver damage in patients with coronavirus infection may be directly due to a viral infection of the liver cells. The liver may also be damaged by medications, which can cause severe changes in the liver. In addition, severe inflammation caused by a storm of cytokines and hypoxia— caused by pneumonia—may play a role in liver damage. Liver damage in mild COVID-19 cases is often transient and can return to normal without any specific treatment (62).

Data show that 11-12% of COVID-19 patients have liver disease, and 14-53% of reported cases have abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Patients with severe COVID-19 appear to have more liver dysfunction. In a study by Huang *et al.,* An increase in AST was observed in 8 cases (62%) of 13 patients in the intensive care unit (ICU) compared with seven cases (25%) of 28

hospitalized patients (6). In a cohort study of 1,099 patients from 552 hospitals in 31 provinces, patients with severe disease had abnormal levels of liver enzymes compared with non-severe patients (63). In addition, in another study of asymptomatic COVID-19 patients that were confirmed by CT scan, the prevalence of AST abnormalities was significantly lower than symptomatic patients. Therefore, liver damage is more common among severe cases of COVID-19 (64).

About 2 to 10% of patients with COVID-19 are directly affected by COVID-19, and SARS-CoV-2 RNA has been detected in stool and blood samples (65). Both SARS-CoV-2 and SARS-CoV bind to the angiotensin-converting receptor 2 (ACE2) receptor for entry into the target cell, where the virus multiplies and subsequently infects other cells in the upper respiratory tract and lung tissue (26). Patients then begin to experience clinical signs and symptoms. Pathological studies in patients with SARS confirmed the presence of the virus in liver tissue, although the viral titer was relatively low because virus components were not observed (66). Another study found that 54% of patients with COVID-19 have an increased level of gamma-glutamyltransferase during hospitalization, and an increase in alkaline phosphatase levels was observed in 1.8% of patients with COVID-19 during hospitalization (62). Zang *et al*., showed that ACE2 receptor expression in cholangiocytes has increased, and this study suggests that SARS-CoV-2 may be directly linked to positive ACE2 cholangiocytes to regulate liver function (67).

A study published on March 5, 2020, which evaluated 148 proven patients with COVID-19, has reported the prevalence of liver enzyme abnormalities as follows: 35.1%, 21.6%, 18.2%. 17.6%, 4.1% of patients had an abnormal level of LDH, AST, ALT, GGT, ALP, respectively, and 50.7% of these patients had some degree of hepatic impairment at the time of hospitalization. After hospitalization, some patients developed functional liver damage, and the study evaluated all of the patients' medications, antibiotics, and antiviral drugs, indicating that Lopinavir/ritonavir prescription in patients with abnormal liver function was 25% higher compared with normal liver function group. Due to the fact that liver dysfunction is associated with impaired immune function and increases the length of hospital stay, especially in the elderly with multiple comorbidities, this study suggests a review of the use of the lopinavir/ritonavir diet (68). A study of covid therapy found that lopinavir/ritonavir had no effect on the negative conversion rate of SARS-CoV-2 (69). In particular, due to the high efficacy of remdesivir over lopinavir/ritonavir in association with interferon, the therapeutic method can be revised (35). In the case of chronic liver diseases such as chronic hepatitis B or autoimmune disease, attention should be paid to previous immunosuppression and concurrent infection with COVID-19, and in patients with a history of bile duct stenosis, the viral effects of the virus on the ducts should be considered (62). The Iranian drug SOVODAC (Sofosbuvir/Daclatasvir) has been used experimentally and unpublished to treat cases of COVID-19 in Iran.

Renal involvement

The prevalence of renal dysfunction (hematuria, proteinuria, and renal dysfunction) was high among hospitalized patients (mean 63 years) with COVID-19, and after modification of the disruptive factors, renal dysfunction was associated with a higher risk of death in hospitalized patients (70). Also, after a lung infection, the virus can enter the bloodstream, accumulate in the kidneys, and cause damage to the kidney cells. In Reverse transcription-polymerase chain reaction (RT-PCR) of kidney cells, the kidney cells were positive in 15% of cases (6). Acute kidney injury (AKI) may occur as a result of synergistic viral cytopathic attacks and systemic inflammatory responses, especially in severe cases. In SARS, the rate was 6.7%, and in COVID-19 in a cohort study, the prevalence of (AKI) was 3.2% in hospitalized patients and also it was higher (9.1%) in patients with high creatinine at baseline comparing with patients with normal basal creatinine (2.0%). The mortality rate in patients with abnormal basal creatinine was 30.9%, which is clearly 9.2% higher than in people with normal basal creatinine. In addition, abnormalities in urinalysis, such as protein or blood excretion in the urine, increase the mortality within the hospital.

Therefore, in the treatment of COVID-19, early prevention from renal impairment, including adequate hemodynamic support and not using nephrotoxic drugs, is of particular importance, and also considering early renal replacement therapy may improve patient prognosis.

Chloroquine and lopinavir/ritonavir, which are commonly used to treat COVID-19, do not require dose adjustment based on creatinine. Oseltamivir, which is commonly used in Iranian medical protocols, must be reduced by 30 mg twice daily for 30 to 60 mg GFR (glomerular filtration rate) and 30 mg daily for 10 to 30 mg GFR based on creatinine clearance. Antibiotic drugs used in Iran for the prophylaxis of secondary infection are fluoroquinolones that require dose adjustment based on creatinine clearance and cephalosporin 3rd

generation drugs (71).

Cutaneous involvement

There are many recently published articles about probable primary cutaneous involvements during COVID-19 course or secondary skin involvements as aggravation of some previous skin disorders (like rosacea, seborrheic dermatitis, atopic dermatitis, neurodermatitis, acne,...) or incidence of many skin disorders due to protective hygiene-related processes (such as contact dermatitis or more severe asteatoticdermatitis due to frequent hand washing and cleansing and…) or the emergence of stress-related cutaneous conditions (like telogen effluvium, herpes reactivation, zona, psychocutaneous disorders and…) (72-75). About 20% of involved patients may have skin involvement (40% in admission time and 6% during hospitalization) that in more than 90% of cases presents as erythematous rash or widespread urticarial, without any correlation with disease severity. Although cutaneous eruption can frequently occur in COVID-19, its rate is the same as other similar viruses. This sign is a valuable diagnostic clue for further consideration and works up (72).

Also, there are many concerns about procedural dermatologic treatments, such as laser therapy or using immune-modulators for disease control (since a large group of disorders in dermatology are immune-related and needed to be treated by such drugs) (76-78). In addition, it is possible to encounter many drug reactions due to routine therapeutic options for new coronavirus like hydroxychloroquine (especially AGEP and pustular eruptions) or false seropositivity of rheumatologic skin disorders (due to auto-immunity reactions by coronavirus) or encounter many other prospective articles focusing on cutaneous, mucosal and appendageal presentations of COVID-19, related to virus itself or its management.

Most recent primary dermatologic manifestations of COVID-19, are acute acro-ischemic lesions due to probable hypercoagulative state in many patients (COVID toes), vascular skin symptoms due to the Angiotensin-converting enzyme 2 (ACE2) a cellular receptor for COVID-19 that plays a role in vascular presentations (vasculitis and thrombotic vasculopathies like violaceous macules with porcelain appearance, levidoreticlaris, necrotic and non-necrotic purpura, chilbelains and pernio-like lesions, frostbite and raynaud, eruptive cherry angioma), the mainly truncal-involved lesions like erythematous/exanthematous or petechial (dengue-like) rash, generalized urticaria or eczematous rash and chickenpox-like herpetiform lesions, acute urticaria and pyrexia…., so cutaneous manifestations are really higher than that was first reported as 0.2% in China and with better evaluation by expert eyes also increasing our knowledge in this area, skin manifestations may be seen in more than 20% of patients especially in more complicated cases and could be considered as an early diagnostic even prognostic clue in patients with better clinical situation (72,79-83).

The new coronavirus is a common old virus shared by humans and animals, with about half a billion people involved in quarantining and shutting down centers, cities, and towns around the world, and the WHO has called it a global pandemic. No treatment or vaccine has been approved so far, and its transmission through the air has recently been confirmed by airborne. Therefore, the most important way to prevent it is by staying at home. The most vulnerable to this disease are the elderly and people with comorbidities. The highest mortality rate among the elderly in the age group of 70 to 79 years was 8.0%, and in the age group of 80 years and above, the mortality rate was 14.8% among the patients and even in a study on the elderly, 23.7% was mentioned. The most common comorbidities associated with deceased patients were cardiovascular disease, diabetes, and underlying respiratory diseases, respectively. COVID-19 can cause acute heart, lung, liver, and kidney damage. Recently there are many original reports of primary cutaneous involvement of COVID-19, which could be a mirror of systemic events during the disease course and may precede evident symptomatic systemic clinical presentations. Therefore, we must pay attention to the possible multi-organ damage and its protection and prevention in the treatment of COVID-19.

The authors of this study, based on their special medical fields, have been worked on various aspects of COVID-19, including COVID-19 in the geriatric population (84), certain multi-potential drugs for the treatment of COVID-19 (85,86), and specific dermatologic concerns in the pandemic era (87-92). In the COVID-19 Pandemic, it is very important to approach to multi-organ involvement in COVID-19 setting and address the social impacts of the virus as well as controversies around its related data. In this study, we discussed about one of the hot topics in the field of the COVID-19 pandemic and comorbidities in various organs in patients with COVID-19 (93-95).

Abbreviations

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; 2019-nCoV: 2019 novel coronavirus;

CDC: Disease Control and Prevention; WHO: World Health Organization; ACE2: Angiotensin 2 converting enzyme; ARDS: Acute respiratory distress syndrome; COPD: Obstructive pulmonary disease; ICU: Intensive care unit; CVD: Cardiovascular diseases; HTN: Hypertension; MI: Myocardial infarction; CHD: Coronary heart disease; cTnI: Cardiac troponin I; hs-TnI: high sensitive-troponin I; CRP, C reactive protein; IL-6: Interleukin 6; PCT: Procalcitonin; CD4: Cluster of differentiation 4; CD8: Cluster of differentiation 8; CK-MB: Creatine kinase-MB; LDH: lactate dehydrogenase; α-HBDH: alpha-hydroxybutyrate dehydrogenase; RAAS: renin-angiotensin-aldosterone system; MERS: the Middle East respiratory syndrome; SARS: Severe acute respiratory syndrome; H1N1: Hemagglutinin 1 neuraminidase1; ACIP: Advisory Committee on Immunization Practices; DPP-IV: dipeptidyl peptidase IV.

ARBs: Angiotensin II Receptor Blockers; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RT-PCR: Reverse transcription-polymerase chain reaction; AKI: Acute kidney injury; GFR: Glomerular filtration rate

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