

COVID-19 in Chronic Diseases

Kronik Hastalıklarda COVID-19

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ABSTRACT

The novel coronavirus disease, namely COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide and resulted in a crucial global health problem. Various studies and meta-analyses have demonstrated that chronic disease, including diabetes mellitus, hypertension, cardiovascular diseases, and chronic obstructive pulmonary disease, are considered as risk factors for the disease severity, poor prognosis, and mortality in COVID-19. Although the exact reasons for the association between these comorbidities and disease severity and mortality risk of COVID-19 have not clarified, immune dysregulation and hyperinflammation in these chronic diseases might be contributing factors to the progression of the COVID-19. Furthermore, most of the patients with chronic inflammatory rheumatologic disease have the impairment of immune system and inflammatory response due to underlying pathogenesis of their diseases, and thus they might be prone to SARS-CoV-2 infection. We have focused the attention on most common chronic diseases frequently observed in COVID-19 and rheumatologic diseases which may be related to infection and their association with course of COVID-19.

Key Words: SARS-CoV-2, COVID-19, chronic disease, comorbidity, severity of the disease

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ÖZET

Yeni koronavirüs enfeksiyonuna (COVID-19) neden olan şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) hızlı bir şekilde bütün dünyaya yayılarak önemli bir global sağlık problemi haline geldi. Çeşitli çalışmalar ve meta-analizler diyabetes mellitus, hipertansiyon, kardiyovasküler hastalıklar ve kronik obstrüktif akciğer hastalığı gibi kronik hastalıkların COVID-19'da hastalık şiddeti, kötü prognoz ve mortalite için risk faktörü olduklarını göstermiştir. Bu komorbiditeler ile COVID-19'un hastalık şiddeti ve mortalite riski arasındaki ilişkinin kesin olarak nedenleri açığa kavuşturulamamış olmasına rağmen, bu kronik hastalıklarda görülen immün disregülasyon ve hiperinflamasyon hastalık progresyonuna katkıda bulunan faktörler olabilirler. Ayrıca kronik inflamatuvar romatolojik hastalığı olan çoğu hastada, altta yatan hastalığın patogeneziyle ilgili olarak gelişen immün sistemde ve inflamatuvar yanıtta bozukluk sebebi ile SARS-CoV-2 enfeksiyonuna yatkınlıkları olabilir. Bu derlemede COVID-19'da en sık görülen kronik hastalıklara ve enfeksiyon ile ilişkili olabilecek romatolojik hastalıklara ve bu hastalıkların COVID-19 seyri ile ilişkisine odaklandık.

Anahtar Sözcükler: SARS-CoV-2, COVID-19, kronik hastalık, komorbidite, hastalığın şiddeti

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INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), a newly identified member of betacoronaviruses has become a global catastrophe (1-3). First SARS-CoV-2 infection cases were observed in patients with atypical pneumonia characterized by fever, fatigue, dry cough, and dyspnea in the Chinese Province of Wuhan (4). SARS-CoV-2 infection, named coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO), has rapidly spread all over the world, leading to a pandemic and serious global health problem (5). SARS-CoV-2 is composed of a non-segmented single-stranded positive-sense RNA, a lipid bilayer envelope, and main structural proteins including envelope (E), nucleocapsid (N), spike (S), and membrane (M) proteins which play significant roles in the virus entry and infectivity (6-8). The genomic analysis has demonstrated that the genomic sequence of SARS-CoV-2 is closely similar to SARS-CoV-2 (79.5% identity) and bat-CoV RATG13 (96% identity) (9). Therefore, the bat is implicated as a natural host of SARS-CoV-2. In the light of the reports of patients and retrospective case series, COVID-19 has a wide range of clinical severity, ranging from the asymptomatic or mild disease which usually represents the large part of patients to the severe disease, which progresses acute respiratory syndrome (ARDS), primary respiratory failure, and multi-organ failure (10). The recent meta-analysis has demonstrated that the overall estimated proportion of severe cases and the mortality rate is 25.6% and 3.6%, respectively (11). The frequently seen comorbidities in hospitalized patients with COVID-19 are hypertension (HTN), coronary artery disease (CAD), diabetes mellitus (DM), obesity and chronic respiratory failure (12). The important fact of course of the disease is that severe cases required intensive care unit (ICU) admission were prominently older age, and have at least one comorbidity, including HTN, DM, and cardiovascular diseases (CVDs) than patients with non-required ICU admission (13). The important meta-analysis has elucidated that critical/mortal patients with COVID-19 have a significantly higher proportion of chronic diseases like CVD, DM, and chronic respiratory disease compared to non-critical patients (14). The case fatality risk (number of deaths/number of those diagnosed) of patients without comorbidities is 0.9% while chronic diseases significantly remarkably increase this risk (15). The immune dysregulation in COVID-19 might be related to underlying comorbidities which are considered as risk factors for the severity of COVID-19 and affect the prognosis of COVID-19 (16, 17). In this review, we have aimed to focus on the most common comorbidities in patients with COVID-19 and their possible roles in the disease progression.

METHODS

We performed systemic literature search from Pubmed and Google Scholar databases until 2 May 2020 with using combination of following keywords: "SARS-CoV-2", "COVID-19", "comorbidity", "chronic disease", "diabetes mellitus", "hypertension", "cardiovascular disease", "chronic respiratory disease", and "rheumatologic disease". We included case reports, retrospective studies, systemic reviews, meta-analyses, clinical guidelines, and recommendations. We reviewed relevant references cited in retrieved articles. The literature search was limited to studies published in English.

COVID-19 in patients with diabetes mellitus

DM is one of the most important chronic diseases, resulting in severe macrovascular and microvascular complications, and the estimation of the global diabetes prevalence is 9.3% in 2019 and rising to 10.2% in 2030 (18). The association between DM and increased susceptibility to infections is well-known, particularly in older patients (19). Several studies have supported the immune dysregulation in DM by inhibition of neutrophil chemotaxis, phagocytic dysfunction of monocytes, impaired T cell-mediated response, and inefficient microbial clearance, all of which might be a potential reason of the increase in risk of infections (20-24). Hyperglycemia enhances the production of adhesion molecules on endothelial cells, which promotes the adherence of leukocytes (25). The plasma concentration of proinflammatory cytokines, including interleukin (IL)-6, IL-8, and tumor necrosis alpha (TNF- α) in diabetic patients is higher than non-diabetic controls (26). The synthesis of advanced glycation end products (AGEs) induced by hyperglycemia and insulin resistance leads to the production of potent inflammatory cytokines such as interferon-gamma (IFN- γ) and an increase in basal cytokine secretion (27, 28). These results might offer evidences of immune dysregulation in patients with DM.

In COVID-19, the level of IL-6, IL-8, IFN- γ , and TNF- α is elevated in both mild and severe cases, while severe cases possess significantly higher cytokine levels except for IFN- γ compared to non-severe cases (29). IL-6 and IFN- γ are the major contributing cytokines of macrophage activation syndrome whose serologic markers and clinical symptoms markedly resemble severe COVID-19 (30-33). Furthermore, the increased level of IL-6 is significantly related to lung infiltration of ARDS in COVID-19 (34). In particular, diabetic patients in COVID-19 have substantially higher level of inflammatory markers, involving IL-6, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum ferritin, tissue injury related enzymes, and computerized tomography (CT) imaging score compared to non-diabetes patients (35), suggesting laboratory evidence of poor prognosis in DM patients. Those laboratory findings were supported with clinical observations. DM is one of the most frequently observed comorbidities in COVID-19 patients. According to the result of meta-analysis, the prevalence of DM in COVID-19 is 7.7%, while the proportion of DM in critical cases increases up to 44.5% (16). Besides, the novel study included 5700 hospitalized patients with COVID-19 from the New York City Area has reported that 33.8% of patients have DM (12). According to reports from the Chinese Center for Disease Control, the case-fatality rate in DM is 7.3% in contrast to the overall case-fatality rate of 2.3% (15). The novel meta-analysis has shown that DM is associated with poor outcome of COVID-19, including mortality, severe disease, ARDS, and disease progression. Moreover, DM has a strong relationship with poor outcome in non-hypertensive patients with younger than 55 years old (36). DM is considered as a risk factor of disease severity and poor prognosis in SARS-CoV-2 infection as in epidemic betacoronavirus infections such as SARS-CoV and MERS-CoV previously demonstrated (37, 38).

COVID-19 in patients with cardiovascular disease and hypertension

CVDs is the major factor of mortality and morbidity worldwide and responsible for approximately one third of all deaths (39, 40). The prevalence of CVD remarkably increases with aging which is an independent risk factor of the mortality in COVID-19 (41-43). The presence of CVDs is substantial risk factors of disease severity and mortality in COVID-19. The study included 191 patients from China has shown that the most frequent comorbidity is HTN (30%) followed by DM (19%) and CAD (8%) and these ratios are elevated in non-survivor patients (4). The meta-analysis, including 1.576 patients with COVID-19 from China has elicited that patients had comorbidities with 21.1% having HTN, 9.7% with DM and with 8.4% CVD. Moreover, severe cases more likely to have HTN (odds ratio, (OR):2.36, (95% confidence interval (CI):1.46-3.83)), respiratory system disease (OR:2.46, CI:1.76-3.44), and CVDs (OR:3.42, CI:1.88-6.22) (44). The results of the inpatient reports, the most seen comorbidity is HTN (56%), and other observed CVDs are CAD (11.1%) and chronic congestive heart failure (6.9%) (12). In addition to the frequency of these chronic diseases, the mortality rate of patients having HT or CVD is markedly higher. The case fatality risk of CVD and HTN in infected patients is 10.5% and 6%, respectively, in contrast to the overall mortality rate (2.3%) without age adjustment (15). The recent multicentered study included 8910 hospitalized patients from different countries has elicited that the independent risk factors of mortality in hospitalized patients are older age (greater than 65 years), CAD, heart failure, arrhythmias, chronic obstructive pulmonary disease (COPD) and current smoking. However, HTN was not detected as a risk factor of mortality in COVID-19 by contrast with previous studies (43). This conflicting result might be related to previous analyses with the lack of adjustment for age. The exact underlying mechanism of the association between CVDs and the disease severity and the mortality rate of COVID-19 has not clearly comprehended yet. The increment in the incidence of CVD with aging, the impairment of immune system, and the involvement of angiotensin-converting enzyme 2 (ACE2) in the cardiovascular system might be potential explanations for this association (42, 45-47).

The S glycoproteins on the surface of CoVs, contain two domains (S1 and S2) which are responsible for binding to host cell, the fusion of viral-host cell membrane, and the entry to host cell (8). S1 domain attaches to ACE2 on host cells as the cellular entry receptor (9). ACE2, a type 1 transmembrane protein, is expressed on cells in heart, gastrointestinal tract, blood vessels, oral and nasal mucosa, kidney and particularly type 2 alveolar cells in lung (48, 49). ACE2, a main member of the renin-angiotensin system (RAS), converts angiotensin (Ang) I to Ang 1-7 and Ang I to Ang 1-9, which are protective proteins for the cardiovascular system (50).

The dysregulation of RAS/ACE2 plays a vital role in the pathophysiology of CVD and HTN; therefore, this system might be considered as a possible underlying factor for the relationship between COVID-19 and HTN or CVD. ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are frequently used in CVD, HTN, and DM. A few animal studies have displayed that RAS inhibitors lead to a compensatory increase in tissue level of ACE2 (51, 52). However, the number of studies has emerged that there is not definite relationship between plasma level of ACE2 and the use of RAS inhibitors. In fact, the upregulation of ACE2 in human tissues by RAS inhibitors has not been supported by any evidence (53). European Society of Cardiology, the American Heart Association, Heart Failure Society of America and American College of Cardiology have strongly recommended the continuation of RAS inhibitors (54, 55).

When focused on the effects of SARS-CoV-2 infection on cardiovascular system, it leads to detrimental cardiovascular complications, including myocardial injury, myocarditis, acute myocardial infarction, acute heart failure, a wide range of arrhythmia, and cardiomyopathy all of which could be fatal (56). Various possible factors might be incriminated to cardiovascular complications in COVID-19, and these are direct virus injury to myocardium; aberrant inflammatory response; impairment of myocardial demand due to hypoxia and increased cardiometabolic demand; plaque rupture and coronary thrombosis induced by systemic inflammation and enhanced shear stress; adverse effects of several therapies such as corticosteroids anti-viral drugs, and electrolyte imbalances such as hypokalemia, resulting in lethal arrhythmias (57, 56, 58, 59).

Acute cardiac injury (assessed with an elevation of Troponin I/T or creatine kinase) is occurred in at least 8% of patients with COVID-19. However, the incidence of acute cardiac injury in severe/ICU patients is 13 folds higher than in non-ICU/severe patients (58). The elevation of troponin T level is considered as an independent risk factor for the mortality in hospitalized patients with COVID-19 (60). Similarly, the increase in cardiac troponin I level is an independent risk factor for critical disease (61). The investigation including 187 patients has evaluated the association between myocardial injury and underlying CVDs in patients with COVID-19 and demonstrated that myocardial injury prominently more observed in patients with CVD and other chronic diseases such as DM, COPD and chronic kidney disease. The level of plasma troponin T is positively correlated with inflammatory marker, CRP. Furthermore, the mortality rate of patients with elevated troponin T levels notably increased compared to patients with normal troponin T levels. Nevertheless, patients with CVD and increased troponin T have the highest mortality rate, which implicates that CVD might prone to myocardial injury, resulting in high risk for mortality (62).

COVID-19 in patients with chronic respiratory diseases

The most prominent target tissue of SARS-CoV-2 infection is doubtlessly lungs. SARS-CoV-2 promotes enormously production of proinflammatory cytokines which mediate 'the cytokine release syndrome' which result in serious complications such as ARDS (29, 63). It might be presumed that patients with chronic respiratory diseases (CRDs) like COPD, asthma, and interstitial lung disease (ILD) are prone to SARS-CoV-2 infection and severe or critical disease. However, it is unknown whether patients with ILD or asthma have more severe disease of COVID-19 or susceptibility of SARS-CoV-2 infection.

COPD is one of the major chronic inflammatory disorder throughout the world and increasing with aging. COPD is characterized by persistent chronic inflammation, mediating with macrophages, T cells and neutrophils, and increased proinflammatory cytokines, in lung parenchyma and airways and destruction of lung parenchyma (64-66). COPD is one of the most remarkable risk factors for developing severe disease in COVID-19. COPD in patients increases nearly four-fold the risk of severe COVID-19 compared to patients without COPD (67). The mortality rate of patients with COPD in COVID-19 is 6.3% without age adjustment (15). Moreover, results of the recent study included 1.590 inpatients has displayed that COPD is considered as a risk factor (hazard ratio (HR) 2.68, 95 % CI 1.42-5.08) for poor outcomes (admission to ICU, invasive ventilation or death) after adjustment of smoking and age status in addition to DM (HR 1.59, 95 %CI 1.03-2.45) and HTN (HR 1.58, 95%CI 1.07-2.32) (68). The dysregulation of immune system, impairment of resolution of inflammation, and defect in repair mechanism in COPD might contribute progression and severity of COVID-19 (69, 66). Although the effect of ACE2 expression on COPD might be a feasible reason for disease severity, unfortunately, there is limited data in the literature. The just reported investigation has demonstrated increased ACE2 expression on epithelial cells of lower airways in COPD compared to non-COPD (70). However,

several animal models studies have shown the protective effect of ACE2 in acute lung injury and COPD (71-73).

COVID-19 in patients with rheumatologic diseases

Rheumatologic diseases contain a wide range of inflammatory disorders through various type of arthritis, autoimmune connective tissue disorders to vasculitis. Most of the rheumatic patients use numerous types of immunosuppressive and immunomodulatory therapies to control the diseases and their activities. Besides, the impairment of immune system can be detected in nature of rheumatologic diseases. Thus, patients with inflammatory rheumatologic diseases are inclined to increased risk of infections compared to the general population (74-78). Besides, as mentioned before comorbidities such as chronic respiratory disease, CVD, HTN and DM, considered as risk factors for poor outcome in COVID-19, are frequently observed in patients with rheumatologic diseases (79-82). Moreover, COVID-19 leads to acute interstitial lung disease and acute lung injury (29, 83).

Therefore, the course of COVID-19 might be unfavorably affected in patients with the lung involvement of rheumatologic diseases such as rheumatoid arthritis (RA), systemic sclerosis (SSc), Sjogren's syndrome (SS), and other connective tissue disorders, as in chronic respiratory diseases (84-88). However, only a few descriptive analyses have demonstrated rheumatologic patients with COVID-19. The study involved 530 patients, mostly having RA or spondyloarthropathies (SpA), treated with immunosuppressive targeted therapies, has detected only three patients with mild COVID-19 confirmed with a positive nasopharyngeal swab (89). The similar study evaluating COVID-19 in 320 patients having RA or SpA treated with immunosuppressive targeted therapies has shown that COVID-19 was determined in four patients and four symptomatic patients were reported. Severe respiratory complications and death were not observed in patients with COVID-19 or symptomatic individuals (90). The descriptive analysis of 123 patients with connective tissue disorders from Italy has found that COVID-19 was detected in the only patient who had SSc treated with rituximab and hydroxychloroquine and developed severe disease and died. Fourteen patients had respiratory symptoms consistent with the viral infection, and their symptoms resolved rapidly. The disease activity was stable in most of the patients (91). Although the immunosuppressive effects of rheumatologic drugs are significant doubt, some anti-rheumatologic therapies, including IL-6 antagonists, anakinra, intravenous immunoglobulin, chloroquine (CQ) and hydroxychloroquine (HCQ) might be suggested as potential treatment for COVID-19 because of their anti-viral and immunomodulatory effects (33). Even though lack of exact evidence for the management of rheumatologic treatment in COVID-19, there are expert opinion recommendations for rheumatic disease with COVID-19. According to American College of Rheumatology Guidance, glucocorticoids should be used at the lowest effective doses to control rheumatologic disease and not be suddenly stopped due to the possibility of hypothalamic-pituitary-adrenal axis suppression. If patients have vital organ threatening diseases like lupus nephritis or vasculitis, high-dose glucocorticoids might be initiated. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), immunosuppressants, biologics, and JAK inhibitors may be recommended to continue in patients with a stable rheumatic disease without SARS-CoV-2 exposure or COVID-19 in order to prevent the flare of the disease. In patients with SARS-CoV-2 exposure, the continuation of hydroxychloroquine/chloroquine, sulfasalazine and non-steroidal anti-inflammatory drugs may be recommended while the interruption of immunosuppressant, non-IL-6 biologics and JAK inhibitors are recommended until negative test result for COVID-19 or two weeks symptom-free period. The use of csDMARDs except for HCQ/CQ, immunosuppressants, non-IL-6 biologics, and JAK inhibitors is recommended to cease in patients with reported or possible COVID-19 (92).

CONCLUSION

Most frequently seen comorbidities such as DM, CVDs, HTN, and COPD are closely related to the severity of disease and mortality of COVID-19. These chronic diseases and their underlying pathologic inflammatory response and immune dysregulation might be responsible for the progression of SARS-CoV-2 infection.

Besides, rheumatologic patients might be considered at risk for COVID-19 due to their immunocompromised situation from their underlying impairment of the immune system and the use of immunosuppressant and targeted immunomodulatory therapies. On the other hand, we need further urgent investigations to explain the relationship between these chronic diseases and pathogenesis of SARS-CoV-2 for proper management of COVID-19. Patients with these chronic diseases should be carefully monitored, and these patients should be promoted to adopt more restrictive measures for minimizing potential exposure of SARS-CoV-2.

Conflict of interest

No conflict of interest was declared by the authors.

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