

COVID-19 Comorbidities**Authors**

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Chapter One

Introduction of COVID-19 comorbidities

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Introduction

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic that initially started in Wuhan, China, and spread extremely quickly, making its way to over 180 countries. As the novel coronavirus continues to evolve, there are still many limitations to our knowledge of who exactly this virus would impact critically. Older adults and people of any age who have underlying medical conditions, such as hypertension and diabetes, have shown worse prognosis .

The virus causes different clinical pictures in infected people. In 80% of the cases, it is asymptomatic, or it causes mild upper respiratory tract symptoms. However, pneumonia along with fever, cough, dyspnea, and fatigue occurs in 20% of the patients, which progresses in some cases, leading to respiratory failure as well as multiple organ failure. In the symptomatic cases, the severity and outcome of the disease varies with age and other health conditions .The primary reservoir of the virus, number of the infected people, and the transmission route are important factors in the virus transmission. SARS CoV-2 is more transmissible and its R_0 is 3.28. Surviving in aerosols, it infects a significant number of people . The virus is easily transmitted between family members, acquaintances, and those with friendly contact with asymptomatic infected individuals and patients as a cluster . The virus is also transmitted during the incubation period . In addition, it remains for a significant time on teflon, glass, surgical gloves, and steel .

In other studies, obesity and smoking were associated with increased risks. In Italy, higher risks have also been reported in men than in women which could be partly due to their higher smoking rates and subsequent comorbidities.

However, the relative importance of different underlying health conditions is unclear, owing to inadequate adjustment for important confounding factors such as age, sex, and smoking status; insufficient follow-up (10); and likely under-reporting of pre-existing conditions. In China, health records are often incomplete or inaccurate and chronic conditions are underdiagnosed .

SARS-CoV-2 is considered as zoonotic . It is known that this coronavirus is 96% identical in complete genome level in comparison to a horseshoe bat coronavirus (*Rhinolophus affinis*), who lives in some regions of China and that has been proposed as its reservoir (Figure 1).

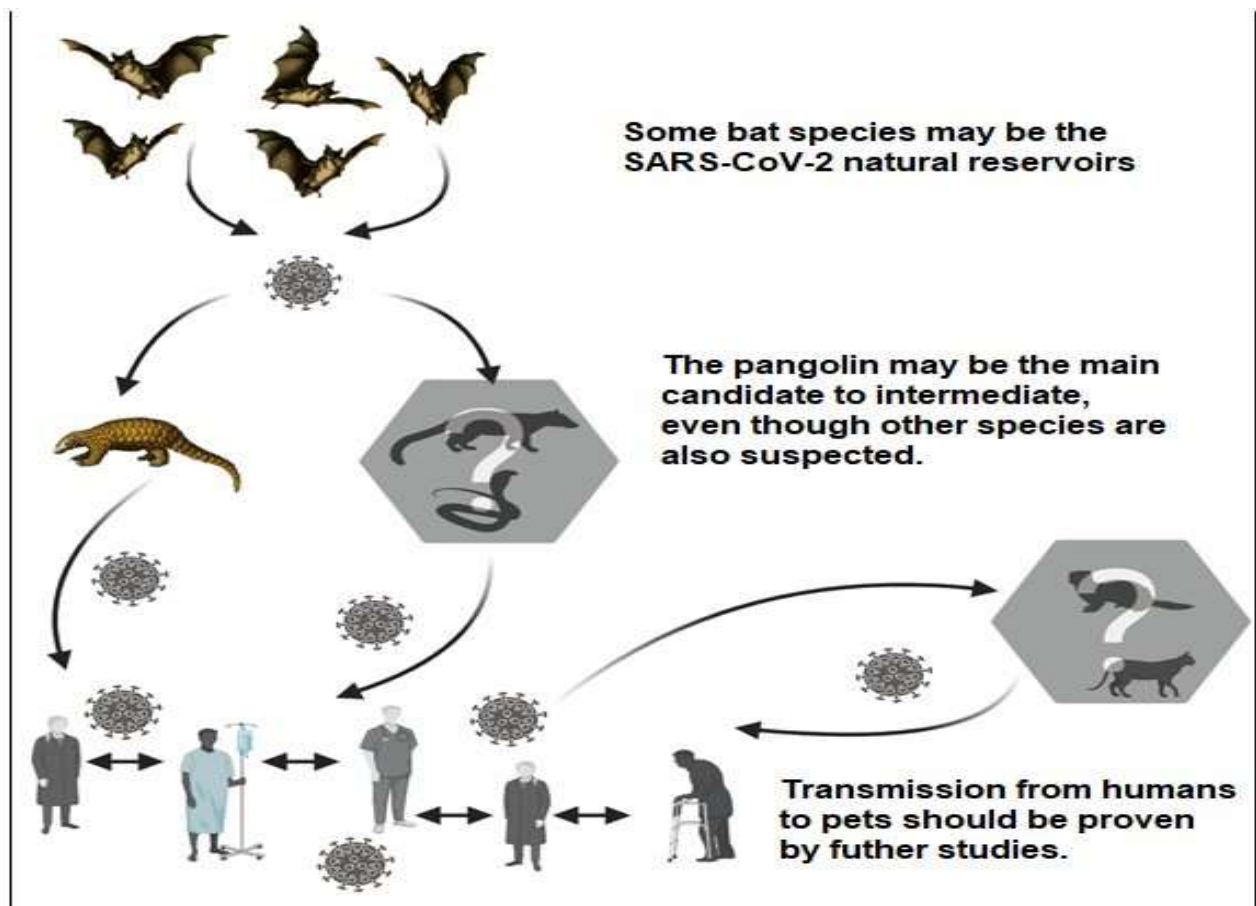


Figure 1. SARS-CoV-2 coronavirus is a zoonotic agent that has been transmitted from animals to humans. Figure created with computer program BioRender.com

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Chapter Two

Chronic Respiratory Diseases and COVID-19

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An international pandemic caused by a new coronavirus (SARS-CoV-2) was announced on March 11,2020 . The virus, that was initial identified in December

2019, is accountable for coronavirus disease (COVID-19) , a new illness with a dominant respiratory tropism.

Patients suffer from chronic respiratory diseases (CRD) such as obstructive pulmonary disease (COPD), asthma, interstitial lung disease (ILD) , lung cancer ,pleural disease, venous thromboembolic disease were promptly represented to be at risk of intense forms of COVID-19 .Indeed ,COVID-19 is accountable for different respiratory symptoms , ranging from cough with dyspnea to acute respiratory distress syndrome (ARDS) in its almost intense manifestations . In equal ,it has been presented patients with COVID-19 have raised risk for venous thromboembolic illness[4]. There is attention that the respiratory complications of COVID-19 could be harmful in patients with previously chronic respiratory disease .

Chronic Obstructive Pulmonary Disease and COVID-19

The existence of chronic obstructive pulmonary disease (COPD) is related with a raised risk of mortality in patients with community acquired pneumonia due to local/systemic inflammation ,compromised host response ,or raised production of mucus in COPD patients . In a study estimating 1,099 laboratory screened patients with COVID-19 in China, COPD was determined in 1.1% of patients . In a meta –analysis estimating the occurrence of underlying illnesses in COVID-19 patients demanding hospitalization ,0.95% patients were present to have COPD [10]. In other meta –analysis demonstrating the risk factors related to patients with COVID-19 ,Where they found to have 5.97 fold raised risk.

The smoking ,which considerers the most significant risk factor for COPD, is also a determined risk factor for infection with COVID-19 .The clarified meta-analysis of COVID-19 patients exist that 7.63% of the patients were smoking .

Moreover work indicating the effect of COPD and smoking in patients with intense COVID-19 appeared that smokers were 1.98 times more to have severe infection than non smokers .

Higher expression of angiotensin –converting enzymes 2 (ACE-2) receptors has been reported in smokers and COPD patients , assisting the entrance of SARS-CoV-2 into the cell.

Therapy and follow –up recommendations for COPD patients during the pandemic have been supplied by both the global initiative for chronic obstructive lung disease (GOLD) and National Institute for health and care excellence (NICE) It must be registered that a minimum of 30- day supply of treatment is distributed to each patient .Pulmonary function tests should not achieved unless essential.

An effective use of both inhaler and oral treatments should be warranted in COPD patients. Use of a nebulizer is not advised during pandemic, while metered dose inhalers with spacer apparatuses are preferred .Anyway, washing of hands should be achieved before and after using the inhaler apparatuses. Devices like spacers and mouthpieces should be cleaned with soapy water and used individually . Though inhaled corticosteroids are recognized to increase the risk of pneumonia, there is no proof that they increase the risk of COVID-19. Thus, it is recommended that COPD patients persist their oral and inhaler corticosteroids during pandemic of COVID-19 . No variations are recommended in the home oxygen therapies and in the use of noninvasive mechanical ventilation (NIMV) . NIMV should be achieved in well-ventilated rooms, also, away from members of the family, if probable . In hospitals, NIMV must be utilized in negative pressure rooms using a bacteria filter and total face mask. The mask should be worn and then turned on the apparatus ;when finishing the procedure ,initial, the device should be turned off

, and then the mask must be discarded . Filters must be used and exchanged every 24 hours .

Asthma and COVID-19

Though viruses are recognized to excite an asthma attack, there is no data proposing that COVID-19 is more prevalent in patients with asthma [18]. In one study inclusive 140 patients in China hospital, asthma was not represented to be a hazard factor for COVID-19 .

Global beginning for Asthma made recommendations for the handling of patients with asthma during pandemic of COVID-19. Patients with asthma have been recommended to persist their recent medications ,inclusive inhaled corticosteroids . Along with inhaled treatments, chronic oral steroid therapy should be used at the lowest efficient dose . Using the spacers instead of nebulization treatment will decrease the transmission risk in acute attacks. Routine PFT should be delayed .

The Canadian Thoracic Society suggested continued treatment with anti-IgE and IL-5 monoclonal antibodies through pandemic of COVID-19 . In addition, potential side effects and interactions of drug have been recorded by Turkish National Society of Allergy and Clinical Immunology for the drugs generally used during the pandemic .

Though symptoms proposed of an asthma attack, like cough and shortness of breath, can also happen in COVID-19 patients , other symptoms such as high fever , loss of smell and sensibility of taste may elucidate potential SARS-CoV-2 infection. Like patients with the latest group of manifestations should be recommended to require medical help .

Interstitial Lung Disease and COVID-19

An important ratio of patients with interstitial lung disease(ILD) are at a raised risk of infection with COVID-19 because of a number of agents like advanced age and side effects of medical treatments managed .This presuppose close adhesion to social segregation . Routine PFT also bronchoscopic and tomographic follow –up tests should be delayed. Patients with fever should be estimated for potential COVID-19 infection.

Antifibrotic factors used for the therapy of idiopathic pulmonary fibrosis(IPF) do not sound to demonstrate extra risks and thus should not be blocked . It is not a problem if the patients having antifibrotic medication diagnosed with COVID-19 not have their treatment for a short time(4-8 weeks) .It should also preserved in mind that antifibrotic drugs can be linked with increased liver enzymes levels .

In the newly screened patients with IPF, antifibrotic treatment can be began on the basis of PFTs and blood tests achieved within the previous 6 months. In ILD patients ,having immunosuppressive treatment, the lowest efficient dose should be persistent. Lymphocytopenia ,which can happen in patients with sarcoidosis , does not discompose a particular risk and doesn't demand stoppage of the immunosuppressive treatment.

Therapy for quietly progressing ILD like chronic hypersensitivity pneumonitis can be delayed throughout the pandemic, and if demanded , prednisolone at a maximum dose of 20 mg can be began .In the patients with quickly progressing ILD ,for example, intravenous cyclophosphamide ,vasculitis, can be used in situation of steroid failure or passivity .Prophylactic antibiotics should as well presented to the patients who request intravenous treatment. Rituximab use should be delayed until the ending of the pandemic . Acute respiratory distress syndrome

(ARDS) can be related with fibrosis in patients with genetic propensity .It has been proved that some patients may evolve ARDS when infected with COVID-19 and thus may require extensive follow-up after the pandemic for potential fibrotic changes.

Lung Cancer and COVID-19

Patients with cancer are weakly belong to age, immunosuppressive treatment, and comorbidity . In one set ,18 of the 1,590 patients with promoted COVID-19 had a history of cancer . In addition , these patients had a higher risk and worse assessment of COVID-19 infection .

Through the pandemic, an optimum equilibrium between COVID-19 risk and cancer progress risk should be sought, with reducing of hospital acceptance. Moreover, the most suitable and lower ,invasive modes should be selected for diagnosis and staging. Before continuance, regarding should be given to whether dilatory the screening work-up and procedures of staging will compromised the result. It may be preferable to evade bronchoscopy and endobronchial ultrasonography in patients with less risk for cancer .As specified ,positron emission tomography must be used to recognize alternate biopsy targets. Before surgery, if probable ,the pulmonary functions should be estimated with soft spirometry or shuttle gait test replacing of total PFT .

A staging order has been suggested by some researchers to estimate the risk of infection in patients have lung cancer requesting surgery .The authors estimated patients with age less than of 70 years and with less than 2 comorbidities as less risk of infection. They explained patients with T4 (size of the major tumor), N2 (the site of lymph nodes including cancer),or oligometastases as raise risk of progress .Surgery is recommended when the risk of infection is depressed .

Nonsurgical choices should be reflected in high risk of progression and infection with COVID-19. For patients with less risk of progression and high risk of infection, individualized approach should be selected , and if conceivable , definitive therapy should be delayed for three months .

Delay of radiotherapy should be regarded in patients with 1-2 stage of disease .If practical hypofractionated regimens must be preferred . Whether to give chemotherapy during the period of pandemic should be established according to the biology of tumor .The radiological appearances of COVID-19 may identical to progress of lung cancer . Pneumonitis can also be stimulated by immune checkpoint suppressor therapy . Thus ,clinicians must maintain a raise level of awareness when determining the treatment .

Pleural Disease and COVID-19

Pleural disease includes pleural effusion and pneumothorax .In the context of COVID-19 ,both are represented to be so abnormal that they must oblige clinicians to require alternate diagnosis .

Pleural Effusion

A pleural effusion is collection of liquid, atypically found in the pleural space , result in an increasing production of fluid and/or minimized lymphatic absorption.It is the almost manifestations of pleural disease , and it is causes range from cardiopulmonary disturbance and systemic inflammation to malignancy . The major principle is the procedures of diagnostic should be persisted in patients with dubious cancer .In this consideration ,cytological test of the pleural liquid seems to consider the most suitable method .If it cannot be achieved ,needle biopsy under

ultrasound or thoroscopic orientation can be tried. Worsening dyspnea in a patient with malignant pleural effusion may require drainage by catheters or aspiration. Talc pleurodosis using a thoracic tube must be evaded. Usual therapy is specified to patients with dubious or assured empyema. It must preserve in mind that the pleural effusion is unusual occurrence through the course of infection with COVID-19.

Pneumothorax

Pneumothorax is unusual aggregation of air in the pleural space between the lung and chest wall. Symptoms typically comprise unexpected onset of severe pain in one side of chest and shortness of breath[33]. A primary spontaneous pneumothorax is that one happens without a cause and lung disease. A secondary spontaneous pneumothorax happens in the existence of lung disease. In patients with COVID-19, preservative management should be regarded if the symptoms are lower. Chest tube replacing may be requested for severe cases. In patients with permanent air leakage, should be used closed system.

Venous Thromboembolic Disease and COVID-19

The infection with COVID-19 is associated with a raised tendency of thrombosis in both venous and arterial systems leading to inflammation, endothelial dysfunction, hypoxemia, and stasis. The risk related to venous thromboembolism (VTE) is raised in patients infected with COVID-19, particularly in the crucially sick patients demanding admission to the intensive care unit. Such, abnormal coagulation parameters are related with poor assessment in COVID-19 patients. Clinicians should doubtful VTE as unexpected worsening of hypoxemia and tachycardia promote or the blood pressure declines in patients with COVID-19. As embolism is doubted, computed tomography (CT)

pulmonary angiography must preferably be carried out instead of standard noncontrast CT. Duplex ultrasonography must be used when clinical doubt of pulmonary embolism (PE) is high and CT PE is unattainable or as there is clinical doubt of deep venous thrombosis. The anticoagulant doses advised by the British Thoracic Society for VTE include enoxaparin 0.4 mg once a day for standard risk patients with creatine clearance (CrCl) > 30 ml/min and 0.4 mg enoxaparin twice a day for patients with high risk with CrCl > 30 mL/min. It would be unharmed to increase the period of thromboprophylaxis to 4 weeks in patient with COVID-19 pneumonia. In state of VTE doubt, dose of low molecular weight heparin must be given. The period of treatment is commonly 3 months.

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Chapter Three

Chronic liver disease and its relationship to COVID-19

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Today, chronic liver diseases are regarded as a major public health concern worldwide. According to the global burden of liver diseases, how various underlying liver conditions affect hepatic damages in COVID-19 cases demands to be seriously investigated. Currently, there are insufficient findings about the incidence of chronic liver disease in individuals with COVID-19. In a recent meta-analysis by Mantovani et al., 11 observational studies involving a total of 2,034 cases with COVID-19 were included to evaluate the correlation between liver injury and COVID-19 infection. Overall, the prevalence of chronic liver disease was reported to be 3% (95% CI 2–4%; $I^2 = 29.1\%$) at baseline which was relatively low. Also, patients with more severe disease, patients referred to the intensive care unit (ICU) and patients with ARDS had higher levels of AST and ALT than those with milder disease. For example patients admitted to ICU had higher serum levels of AST (52 IU/L) and ALT (35 IU/L) than those not referred to ICU [i.e., AST: (29 IU/L); ALT (23 IU/L)]. Similarly, the same results were obtained for total bilirubin levels.

The incidence of hepatic damage during COVID-19 infection ranged from 14.8% up to 53%, mostly presented by abnormal levels of ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) accompanied by increased total bilirubin ranges. In another retrospective study of 148 consecutive COVID-19 cases, the incidence rates of tests involved in liver function elevation included ALT (18.2%), AST (21.6%), LDH (35.1%), GGT (17.6%), ALP (4.1%), and total bilirubin (6.1%). The level of serum albumin decreased in more severe cases and the range for albumin testing was ~26.3–30.9 g/L. In clinical practice, it is necessary to differentiate the onset of abnormal hepatic function, although it occurs at the diagnosis time or in the course of treatment. In addition, lymphopenia, thrombocytopenia, anemia, and

coagulation abnormalities as well as low albumin are issues observed in both liver diseases and COVID-19 infection .

Hypoalbuminemia has been reported in severe COVID-19 patients. Previously, hypoalbuminemia was considered to be a negative prognostic marker, both in patients with chronic liver disease and in individuals with SARS and MERS. Supplementing of amino acids to a patient's diet is an important step to hepatic albumin synthesis in clinical condition. This highlights the critical roles of nutritional supplements during early stages of COVID-19. Also, the hepatocyte albumin synthesis is downregulated by interaction of cytokines which are produced during cytokine storm induced by SARS-CoV-2. Both mechanisms contribute to intense hypoalbuminemia that, combined with fluid losses because of fever, is responsible for shock and hypovolemia identified in COVID-19 cases in critical care settings .

Interestingly, severe COVID-19 patients have higher rates of hepatic disorders . The ratio of increasing hepatic damage in severe cases of COVID-19 was remarkably higher than cases with mild disease . In deceased COVID-19 cases, the occurrence of liver damage reaches up to 78% . In a study from Iran, it was shown that the count of platelets and lymphocytes were notably lower in COVID-19 cases than healthy controls. Also, the levels of ALT, AST, and ALP were higher in COVID-19 patients as compared to healthy group. Moreover, the risk of transfer to ICU and critical care unit (CCU) was forcefully related to increased AST and total bilirubin levels, and the rate of mortality remarkably increased with elevated AST levels . It was reported that the elevation of AST level was 62% in ICU cases in contrast to 25% of cases who did not require ICU (1). Furthermore, Shi *et al.* reported that COVID-19 patients who were diagnosed at subclinical period and before onset of clinical symptoms had

considerably lower rate of elevated AST than cases diagnosed after symptom onset. Hence, hepatic damage has been more prevalent in severe COVID-19 patients compared to mild cases .

Till now, our knowledge about the pathogenic role of SARS-CoV-2 in hepatic damage is very limited. As aforementioned, similar to SARS-CoV, SARS-CoV-2 exploits ACE2 as its entry receptor . Despite high expression of ACE2 receptor on biliary cells, hepatocellular liver injury has been observed in a relatively broad range of patients with COVID-19 .

Findings of hepatic damage in COVID-19 patients remain to be seriously investigated. Various mechanisms have been proposed for liver injury during COVID-19 infection; some of them are as follows: (1) immune-mediated hepatitis, (2) direct cytopathic effect (CPE) of the virus, (3) drug-induced liver injury secondary to medications used for the treatment of COVID-19 disease, (4) secondary to infection-induced systemic inflammation, (5) hepatic congestion secondary to positive end-expiratory pressure (PEEP) ventilation, and (6) pre-existing liver injury .

Immune dysfunctions including decrease in CD4⁺ T-cell levels; lymphopenia and cytokine storm are prevalent features in COVID-19 patients and may be considered as important factors associated to severity of disease and death . Liver damage in severe forms of the disease is associated with activation of coagulation and fibrinolytic cascades, decreased platelet counts, and neutrophil to lymphocyte ratio, as well as increased levels of serum ferritin; although, these biomarkers are all non-specific (4). In severe COVID-19 infection, the plasma levels of CK, LDH, or myoglobin could also be increased. Hence, merely aminotransferase elevations (especially if AST>ALT) in COVID-19 infected patients might have non-hepatic origin such as COVID-19-induced myositis .

COVID-19 and Chronic Liver Diseases

The risk of getting COVID-19 infection in patients with chronic liver diseases and cirrhosis are not well-understood, because such cases have impaired immunity and worse outcomes in ARDS than other of the critically infected and sick population . Yet, there has been no report regarding liver injury happening in COVID-19 cases with chronic liver diseases, including chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) . This means that for the chronic HBV and HCV patients with viral suppression who are following long-term therapy or are in immunotolerant phases, evidence of hepatic damage, and viral replication after co-infection with SARS-CoV-2 should to be deeply investigated. In addition, effects of glucocorticoids on prognosis of the disease among COVID-19 cases with autoimmune hepatitis need to be evaluated. Also, COVID-19 cases with hepatic cirrhosis or hepatocellular carcinoma (HCC) may be more prone to COVID-19 infection due to their systemic immunocompromised conditions. Severe complications including variceal hemorrhage, hepatic encephalopathy, serious infections, and death rate in such cases demand to be checked in large clinical scales. In view of systemic immunocompromised state, more intensive surveillance and systematic therapeutic approach are required for severe cases of patients with COVID-19 infection with underlying advanced hepatic disease, particularly in elderly cases with comorbidities. Also, subsequent studies should concentrate on the causes of hepatic damage in COVID-19 cases and the impact of concurrent hepatic diseases on therapeutic outcomes of COVID-19 infection . Below, we explained more about different types of chronic liver diseases including viral hepatitis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and liver cirrhosis during COVID-19 outbreak. We also focused on liver transplant

recipients and post-transplant drugs used in patients with COVID-19 infection. Finally, we discussed about the therapeutic medications administered in COVID-19 patients with underlying liver injuries and their significant considerations.

Viral Hepatitis

People with underlying cirrhosis of the liver, including those caused by viral hepatitis, may have the potential for a higher risk of developing severe COVID-19 illness and/or more problems from their existing liver disease if they get a COVID-19 infection, with prolonged hospitalization and increased mortality. These patients need to take careful precautions to avoid COVID-19 infection. COVID-19 may affect the processes and procedures for screening, diagnosis, and treatment of viral hepatitis.

The effect of COVID-19 on patients with hepatitis B virus (HBV) is not well understood; more studies are required to understand the interactions of these infections. Little is known about the effect of hepatitis C virus (HCV) on the course of COVID-19. People with viral hepatitis who are older than 65 years of age or have other medical conditions, such as chronic lung disease, obesity, diabetes mellitus, heart disease, and kidney disease, are at a higher risk for severe illness from COVID-19.

COVID-19 infection and some of the medications for treatment may be associated with liver injury.

The safety of returning to work or other in-person activities depends on the severity of your liver disease, whether you have other medical problems, current COVID-19 transmission in your community, and whether measures to prevent transmission are being practiced (physical distancing, wearing face coverings, handwashing or using a hand sanitizer, isolating COVID-19 cases).The

European Association for the Study of the Liver (EASL) believes that chronic viral hepatitis does not augment the risk of more severe COVID-19 infection; while Xiaoping et al. (21) in a study on 15 HBV patients of 123 COVID-19 cases found that COVID-19-HBV coinfection were more likely to induce hepatic injury with severe consequences and death. The American Association for the Study of Liver Diseases (AASLD) recommends that hepatitis B and hepatitis C patients who are on the antiviral therapy should continue their treatments. Also, treatment for chronic HBV and HCV infection in patients negative for COVID-19 can be offered if clinically indicated. Hepatitis B medication therapy in COVID-19 cases should not be initiated except for a clinical suspicion of hepatitis B flare . Interferons (IFNs) have already been administrated for the treatment of MERS and SARS. Recently, application of interferon alfa-2b was investigated against SARS-CoV-2 in its nebulized form among 77 patients . Chinese guidelines suggested interferon alfa by nebulization . In a recent case series, three patients with severe form of COVID-19 pneumonia also were treated with pegylated interferon alfa-2a (180 µg per week and only 1 or 2 doses subcutaneously) . Cases experienced clinical improvement without development to ARDS and more rapid viral clearance. But, it is hard to analogize this finding to broader cases . Also, tenofovir which is known as one of the nucleotide reverse transcriptase inhibitors (NRTIs), is extensively used for the treatment of chronic HBV and can bind to SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) with binding capabilities similar to those of native nucleotides. However, its effectiveness as a potential medication against COVID-19 should be thoroughly investigated. In addition, RNA synthesis nucleos(t)ide analog inhibitors, acting as chain terminators of viral RNA, like tenofovir disoproxil fumarate (TDF), abacavir, or lamivudin, potentially could be effective for COVID-19 infection . Above all, commencement of direct

acting antivirals (DAAs) for chronic HCV in COVID-19 cases is not permitted and it is reasonable to be delayed . Liver Impairment and Patients with Chronic Hepatitis C and COVID-19

As the global prevalence of hepatitis C virus (HCV) and SARS-CoV-2 infections are geographically variable, epidemiological data across Europe may help improve our understanding of the reciprocal impact of SARS-CoV-2 and HCV. the prevalence of COVID-19 among HCV patients who achieved cure using a sofosbuvir/velpatasvir (SOF/VEL) combination antiviral treatment in all cases. The interplay between a pre-existing liver disease and SARS-CoV-2 infection may be important for patients' outcomes, since chronic hepatitis C is still a health burden in many European countries. Even though the exact impact of SARS-CoV-2 infection on the liver is unknown, abnormalities in liver biochemistry are typical in COVID-19 cases, arising in 15–65% of patients infected with SARS-CoV-2 .

SARS-Associated Viral Hepatitis Caused by a Novel Coronavirus ,liver impairment is commonly reported in up to 60% of patients who suffer from severe acute respiratory syndrome (SARS). Some researchers found the clinical course and liver pathology in three SARS patients with liver impairment. three patients who fulfilled the World Health Organization case definition of probable SARS and developed marked elevation of alanine aminotransferase were included ,liver impairment is common and has been reported in up to 70% of patients suffering from SARS. The majority of these patients have been treated with antibiotics, antiviral medications, and steroids, which are potentially hepatotoxic. Hence, whether or not SARS-CoV infection can lead to liver damage but there are another viruses can associated with liver damage but remains unknown.

Corona viral hepatic pathogenesis

SARS-CoV-2 has been linked to mild-to-moderate liver injury as revealed by elevated serum aminotransferases (ALT/AST), bilirubin, hypoproteinemia and prothrombin time prolongation, supported by liver histopathology . Single-cell RNA sequencing data from two distinct cohorts of COVID-19 patients have shown elevated expression of Angiotensin Converting Enzyme-2 receptor in cholangiocytes (59.7%) than hepatocytes (2.6%), indicating that SARS-CoV-2 might directly affect intrahepatic bile ducts . clinical study of 194 COVID-19 patients, 30 patients (15.46%) showed liver dysfunction Although in some COVID-19 cases, mild derangement of liver function was observed, patients with different durations of symptoms showed no evidence that were later associated with greater liver function derangement.

severe cases of COVID-19, liver dysfunction is also observed with greater activation of coagulative and fibrinolytic pathways along with altered platelets, neutrophil and lymphocytes profiles and chronic liver disease patients with impaired immunity because of classical hepatitis viruses (HBV, HCV, HDV and HEV) or other hepatotropic viruses (HGV, GBV, TTV and SENV) infection or nonalcoholic fatty liver disease/nonalcoholic steatohepatitis are more susceptible to COVID-19, and may present worse outcomes from acute respiratory distress syndrome compared with the other critically ill patients. viruses induce elevations of liver function biomarkers, very likely related to liver inflammation or hepatocytes damage as a result of interacting cytotoxic T-cells and Kupffer cells so SARS-CoV-2 is also proposed to cause viral hepatitis while inducing a dysregulated innate immune response. SARSCoV- 2-encoded nonstructural and accessory proteins are suggested to modulate induction of cellular interferon and cytokines, enabling the virus to evade antiviral mechanism of interferon-stimulated genes .

Does having hepatitis B put me at increased risk of severe disease from COVID-19 infection? researchers have found that those with hepatitis B and COVID-19 did not differ from those who only had COVID-19, in terms of disease severity, time to recovery, duration of hospitalization or treatment response ,another studies also found that the risk of HBV re-aesome reactivation among patients who received steroids or interferon to treat COVID-19 ,there is some evidence that people with cirrhosis are at risk for more severe outcomes from COVID-19 infection ,the past months have found that the COVID-19 disease process itself could be associated with liver injury. So, it is important for those who know they have hepatitis B to talk with doctors who are treating them for COVID-19, so that they can closely monitor liver function and liver injury, and consider prophylactic antiviral treatment as necessary.

Conclusions

COVID-19 infection can involve multiple organs other than respiratory tract and lungs, in particular liver. A noticeable incidence of liver damage accompanied by abnormal ranges of AST, ALT, ALP, bilirubin, and albumin levels has been reported during COVID-19 disease. Different mechanisms have been suggested for liver injury during COVID-19 infection including immune-mediated hepatitis, direct CPE of the virus, drug-induced liver injury secondary to medications used for the treatment of COVID-19, infection-induced systemic inflammation, hepatic congestion secondary to PEEP ventilation and pre-existing liver disease. Hence, regular monitoring of liver functions in COVID-19 cases can result in an early diagnosis of liver disease. On the other hand, one of the major concerns during COVID-19 outbreak is the population with a history of pre-existing chronic liver diseases, their management, medical treatment, and important consideration. Liver injury cases are recommended to be treated with

medications that could both prevent inflammatory responses and protect liver function. In addition, important considerations in COVID-19 patients with mild and severe liver diseases are highly advised. Further studies should focus on drugs application which may induce liver injury, such as antimicrobials (for example; macrolides) and the effect of liver-related comorbidities on treatment and consequence of COVID-19 infection.

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Chapter Four

Gender and Covid-19

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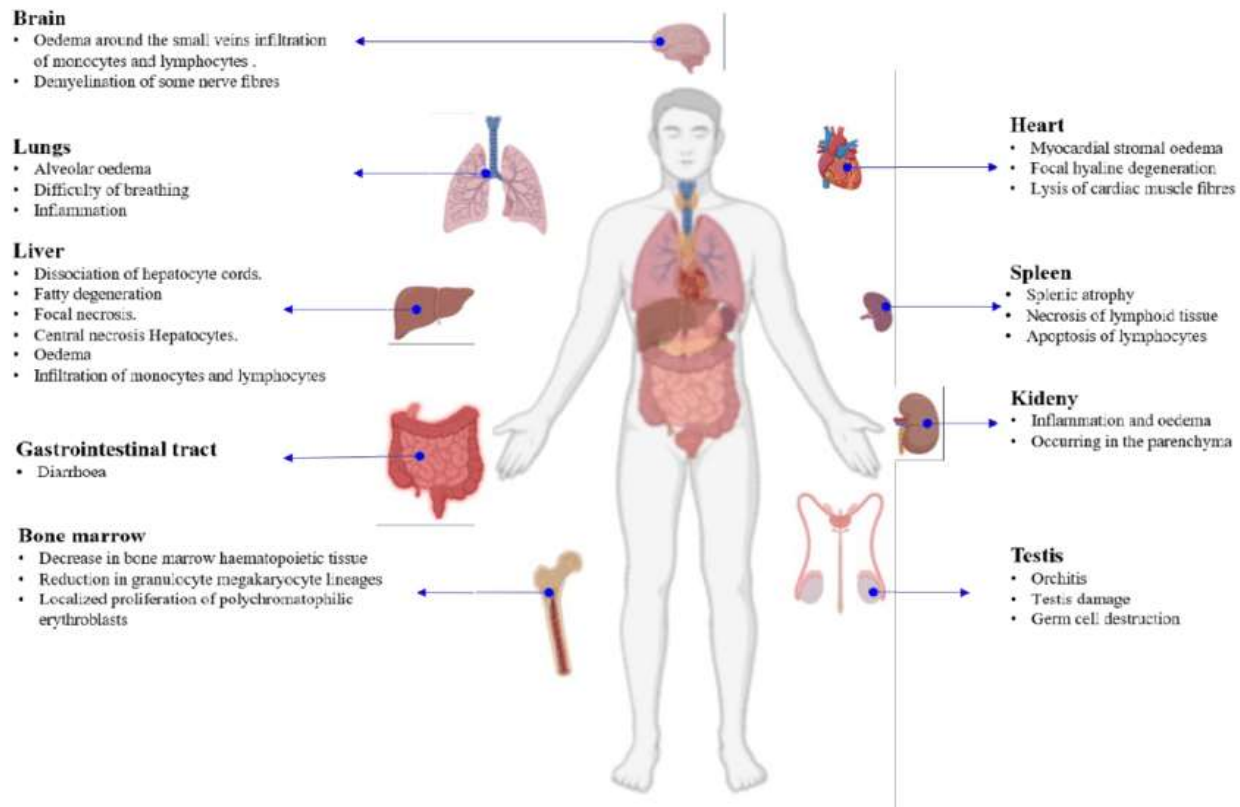
Microbiology and immunology

University of Babylon, College of Science for women

Gender and Covid- 19

Pathogenic bacteria, Clinical immunology, immunogenetic Covid -19 became a big socio-economic and healthy issue over world . Numerous viral infection and even epidemics have been recognized over the last 20 years started with severe acute respiratory syndrome(SARS-1) in 2002-2003 then H1N1 in 2009 followed by the recently epidemic SARS-COV 2 2019 that discovered in Wuhan –China .Corona virus is one of RNA viruses that cause corona virus disease ,this virus classified with the genus Beta coronavirus and subgenus Sarbecovirus that highly identical with other two bat-derived strains .A big healthy problem and widely fastly spread of this virus infection led to make it as a pandemic at 2020 .

Although the main target of this virus is the respiratory system including upper and lower respiratory tract . It is able to invade other body organs and systems such as vascular endothelial cells, lungs, kidneys.heart, brain, liver, intestine, pharynx, urino-genetal and other tissue via the presence of ACEC2 receptor and their ability to enter blood stream and transferred to other organs and tissues.Since this virus have ability to transition to many tissues and organs ,it have ability to contribute with their contents of proteins ,enzymes and hormones ,from these hints its ability to infection and established may be differ with these variations including gender hormonal variations.



(Figure1) Organs affected with covid -19 (Belmehdi *et al* 2021)

It is essential firstly to give short identifications and differences for gender and sex .Sex defined in different issue most of them refer s to the biological aspects of an individual as determined by their anatomy, which is produced by their chromosomes, hormones and their interactions generally male or female as assigned at birth . Whereas gender refers to a social construction relating to behaviors. Gender identity is a personal, internal perception of oneself and so the gender category someone identifies with may not match the sex they were assigned at birth where an individual may see themselves as a man, a woman, as having no gender, sometimes people identify on a spectrum between man and woman.

Association of Covid with gender and sex

The present study deals with investigate the variations of covid -19 infection ,severity and mortiltly among men and women . In general, differences in women's and men's bodies due to their sex (biology) is playing a role in people's risk of illness and death due to COVID-19. To attribute gender differences in COVID-19 outcomes solely to biology however ignores the role that social environments,

structures and norms are playing, and obscures the actions that can be taken to address these drivers. The idea that sex and gender are playing a role in the covid-19 outbreak is essential to building an effective, equitable response to the pandemic, clear gender differences in COVID-19 health outcomes, not all governments are reporting data separately by women and men.

The global pandemic covid-19 give an attention to gender since it is one of the essential parameters of all infections and most diseases .Although, both men and women were infected by the pandemic Covid-19 and the severity and mortality rate consist both ,there is some eco and socio –psychological factors led to investigate the rate and severity of infection with gender variation . In several nations, women reported more worry and anxiety during the early phases of the lockdown, hence the suicide rate among women in the United Kingdom and Spain is higher than it has been since 2004. Women from ethnic minorities and those living in poverty are particularly vulnerable to healthcare marginalization, the disproportionately high prevalence of COVID-19 infection and death among African Americans in the United States is sobering proof of the impact of institutional inequality. If left neglected, these health disparities are likely to worsen as the pandemic spreads.

Covid and gender sexual activity

Covid 19 outbreak reveals an alteration in sexual relationship and changes in sexual behaviour of men and women all over the world led to reduce of the weekly sexual intercourse through the period of the pandemic . Sexual behaviour of women and men aged 18-45 years reveals a noticeable changes during the Covid-19 outbreak through a survey conducted 25% of the respondents had a decrease in sexual desire, and this decrease was more in men than women ($P = .001$) . Another online survey conducted for good education level individuals in Bangladesh, India and Nepal region, no significant difference was detected in the sexual activities of the participants before and during the pandemic.

An UK survey reported decrease the mean number of weekly sexual intercourse during the pandemic as 3.23 in men and 0.88 in women. We can be concluded that covid affected gender through many physio-psychological activities including number of sexual intercourses for female and male gender, married .young age, income level and alcohol consumption. According to Global Health 5050 data,

the number of confirmed cases in COVID-19 and the death rate are high among men than women in different countries. The importance of Sex- disaggregated data are clearly appear for understanding the risk distribution of disease in the population, and the extent to which sex and gender affect clinical outcomes.

Prevalence and Susceptibility

The prevalence of symptomatic COVID-19 was found to be higher in men than in women. The high prevalence of smoking and alcohol consumption contributed to the high prevalence of COVID-19 among men. Women had a decreased risk of death in the 2003 Severe Acute Respiratory Syndrome (SARS, caused by SARS-CoV-1 infection epidemic and SARS-CoV-2 infection, in which men have a greater death risk than women.

According to epidemiological reports based on infectious disease notification, the prevalence of infectious disease is similar in both sexes. Angiotensin converting enzyme 2 (ACE2), which is the functional receptor for SARS is engaged in sex-dependent susceptibility, could be represented by an enzymatic system involved in this different sex propensity. According to a few studies on the reproductive system, SARS-CoV can directly infect the testis, and leukocyte infiltration can disrupt the function of the Leydig cell, affecting testosterone synthesis. The autoimmune reaction on the tubule could be activated as a result of this infection. In addition, women's innate and adaptive immunity is stronger than men's also they had high resistance to viral infections. Furthermore, the men prevalence in ICU unit increases and ranging from 1.5 to 2.0:1 up to 4:1 in a recent Italian study.

As emphasized for previous outbreaks of global concern (i.e. MERS, H1N1, H5N1, SARS, Zika), the study of gender dimension, which is both physical and social constructed, is important to understand the pathogenic mechanisms and to eventually design better therapeutic strategies. Considering mortality, women are significantly more likely than men to survive the infection, in accordance with recent literature on Covid-19. The role of estrogen on endothelium and vascular function have been suggested. The decreased severity of Covid-19 in women could be attributed to gender-related variables influencing at least one of the following: (1) the virus's mode of cell entry; (2) immunological and inflammatory regulation during infection; and (3) endothelium and vascular function. Gastrointestinal symptoms hitherto been inconsistently linked to prognosis, are more common.

Impact of pandemic on gender responsibility

Women and home responsibility

Women in most countries, particularly in developing and Middle Eastern countries, have a greater share of family responsibilities, child care, children's education, and domestic arrangements than men. Women's well-being and relationship satisfaction suffered as a result of this mismatch. In countries with these unequal responsibilities in home work, it is particularly noticeable. It could be interesting to look into the relationship between COVID-19 infection rates and pandemic effects. In Japan and South Korea, which have a lower COVID-19 infection rate than the other four nations, there are no statistically significant variations in economic losses owing to the COVID-19 pandemic between men and women. The number of cases with covid 19 among 1000 people in Japan and Southkorea was 0.11 ,0.21 lower than that in Italy ,United kingdom and United state 3.4,2.5and 3.2respectively,while in china appear most lower 0.06 because of their social distance policy .

Social relational and violence

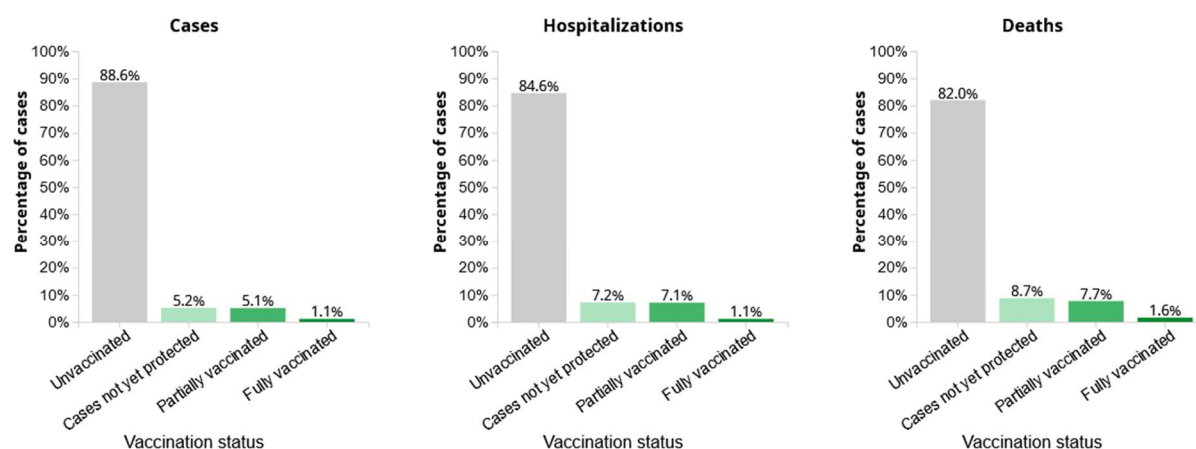
One of the most results of Pandemic covid -19 is short time work or keep home for a long time ,the presence of all family individuals at same and small space place led to social problem among family individuals ,women generally are the most victim of these closeness. This issue is appear clearly in traditional families and closed cultural countries so this pandemic has also given rise to new forms of control and manipulation. Women, and individuals from minorities gender groups, are more likely to be the victims of such violence than cis-men . Some family members' contumacy for quarantine regulations causes them to lose control and support, making them less likely to seek help or go to the hospital The COVID-19 isolation measures put women with disabilities, who are already at a higher risk of relationship and sexual assault, in even more danger.

In Iraq , Harmful and Gender based violence appear clearly in an study includes 11 province ,this study pointed increased in bad practice and violence against women during quarantine and covid pandemic 2020 .Covid -19 and its quarantine formed an increased in individuals problems and livelihood in most countries especially low-income countries these appear clearly with women than men , an survey study

in Kenya reported that women are reporting loss of all incomes during COVID-19. This study pointed that 20% of women lost all income compared to 12% of men since the onset of COVID-19 compared to 12 per cent of men. However, these income losses led to women worries to access food and healthcare.

Vaccination and gender :

Vaccines were produced from different medical companies all over the world, some of these vaccines get acceptance of world health organization, the main used and acceptable vaccines are AstraZeneca, Pfizer and sinopharm, moderna and johnson and Johnson and others, all of them have ability to protection although the differences in their preparation. Although the effected role of all vaccines there is still a small percentage of the population who are vaccinated so the cases rate may be raise for unvaccinated peoples. An study in Canada show the high rate of covid infection and death rate among unvaccinated persons than lower rate for vaccinated (figure2).



(Figure 2) Distribution of Covid 19 cases with vaccination status

The same report refer also to high rate of female 1.4 % vaccinated than male 0.8% and this give an explanation for low mortality rate in women than male. From the first COVID-19 vaccine in December 2020 to Sept. 8, 2021, more than 5.56 billion vaccine doses have been administered in an effort to fight the pandemic. Bloomberg says vaccines are available in 184 countries (but Reuters lists it at 202 countries) at a rate of 37.3 million doses daily (a slight decrease over recent weeks).

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Chapter Five

Malignancy comorbidity of covid-19

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Malignancy comorbidity of covid-19

Introduction:

The COVID-19 pandemic is considered to be one of the most important and dangerous threats affecting human health worldwide, and since this virus is a puzzle, Some people have mild symptoms while others have no symptoms at all, but they still carry the virus and transmit it to others, and there are individuals who show severe symptoms and can have a severe phenotype that leads to respiratory failure as a result of cytokine release syndrome a discrepancy has been observed between infection severity, response to treatment, and mortality in people to SARS-CoV-2 infection. Compared to the healthy population, people with malignant are found to be more likely to have complications from COVID-19 .

It was found that this virus increases the complications and the overall risk of death in malignant patients due to the abnormal growth of cells anywhere in the body, with the possibility of spreading to other parts very quickly and it can invade nearby tissues or travel to the bloodstream or lymph nodes, where they can spread to other tissues inside the body, and this is called metastatic cancer. Medicines used to treat different types of cancer suppress or kill fast-growing cells, such as white blood cells, T and B lymphocytes in the bone marrow, thus weakening the immune system and putting a person at greater risk of contracting COVID-19. Also, people with malignancy who are undergoing hormonal or chemotherapy treatment are more likely to develop severe COVID-19 symptoms that can lead to death

Risk factors of malignancy comorbidity of covid-19:

There are many factors that associated with severe COVID-19 illness and high mortality in malignant patients, which confirm that COVID-19 affects malignant patients much worse than the healthy population. They including: age (Mortality

increases with age), gender (Male mortality more than female), Types of malignant tumors in cancer patients (Solid tumor patients had higher prevalence of death compared to those with hematological malignancy), race, smoking and inhibition in immune response with medical conditions that need support of ventilator or ICU care such as high blood pressure, coronary artery disease, and congestive heart failure .

It was noted that it did not find a significant difference in deaths related to COVID in patients undergoing chemotherapy or radiotherapy compared to patients not undergoing treatment. Revealed that post-SARS-CoV-2 infection, and the patients who eventually died were found to have lower hemoglobin, higher WBC and neutrophil counts, elevated inflammatory markers, D-Dimer, lactate and lactate dehydrogenase .

COVID-19 increases malignant mortality in the long run due to late diagnosis; stop or change in treatment Therefore, the best way to properly control tumor treatment is to prevent the risk of infection with COVID-19 through vaccination for all cancer patients, regardless of the type of treatment, because no interaction between different types of vaccines and anti-cancer therapies are currently indicated

The types and stages of malignant tumors and the treatments used with it constitute additional risk factors for infection with COVID-19. There are many cancer cases associated with infection with covid-19, such as leukemia, lung or breast cancer, which is more common than other types of cancers, as a high death rate was observed in patients as four times the risk of SARS-CoV-2 infections. It has also been associated with a diagnosis of acute myeloid leukemia, aggressive non-Hodgkin's lymphoma or plasma cell tumors, and severe or critical COVID-19 . Moreover, early diagnosis and knowing the stages of cancer has reached also plays an important role in increasing the risk of death in cases accompanying the late 19th, especially with the increased ability of the tumor to spread to nearby tissues and distant nodes, or spread to other organs, which is the latest stage of it. People with stage IV metastatic cancer are more likely to have a severe COVID-19 infection than those with a localized tumor . Due to the increased risk of acute infection with COVID-19, cancer patients, especially those with active metastasis, should have priority in early diagnosis of COVID-19-specific symptoms and appropriate treatment as these patients represent a highly vulnerable group compared to COVID-19. In non-cancer patients .

The immune response in COVID-19 patients suffering from malignancy:

The relationship between cancer and the immune system is a complex one due to the rapid development of cancerous tumors across tissues and its effect on the humoral and cellular systemic and mucosal immunity through a change in the levels of antibodies and T cells and their secretions of cellular kinetics, and a decrease and dysfunction in the antigen presenting cells. So The immunosurveillance is very important to control and reduce the infection through anti-tumorigenic role, which includes NF- κ B as an essential effector. It was found that anti-tumor treatments and radiation also have a strong impact on immune responses and thus the malignant patients are more susceptible to viral infection, especially covid-19. Antibody titers not only constitute complete protection against SARS-CoV-2, but also immune cells, especially SARS-CoV-2-specific memory T cells, may be protected even in negative patients . Patients with severe COVID-19 have been observed to have the following symptoms: dyspnea, lymphopenia, hypoproteinemia, increased levels of alanine aminotransferase, lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer. with the levels of IL-2R, IL-6, IL-10 and TNF- α are significantly increased, indicating an inflammatory storm [12]. In addition to increased levels of other biomarkers and organ damage indicators (leukocytes, neutrophils, and lactate dehydrogenase), coagulation-related indicators (D-dimer-linked, prothrombin time, activated partial thromboplastin times), and N-terminal pro-type B peptides in cancer patients with COVID-19 .

The decrease in lymphocytes in cancer patients indicates that the virus tends to reduce host immunity in addition to its effect on T lymphocytes, especially CD4 T cells and CD8 T cells, which leads to a decrease in T lymphocytes and interferon production. From the above, the patients with cancer and those with COVID-19 are more likely to die compared to uninfected patients. As patients with hematological malignancies have higher levels of immunosuppression and are more susceptible to respiratory viral infection than patients with solid tumors .

Instructions for malignant patients infected with COVID-19

There are many guidelines and recommendations to reduce the incidence of COVID-19 in malignant patients who are considered a high-risk population, maintain their psychological and physical health, and how to ensure their protection from the pandemic infections according to . as follows:

1- The necessity of vaccinating malignant patients with COVID-19 vaccines to reduce the risk of contracting it, with the availability of medical advice to determine the appropriate time for vaccination

2- Pharmacological monitoring of the treatments of cancer patients and knowledge of possible drug interactions between them and the drugs used to treat COVID-19 and preventive antimicrobials with consulting a hematologist or oncologist before prescribing any treatment from them, taking into account the type of tumor condition for each patient individually, the history of the disease and the type of chemotherapy and its effects.

3- Physicians should discuss the benefits and risks of current cancer treatment with their patients during the COVID-19 pandemic. Studies show that cancer patients who have undergone cancer treatment and tested positive for COVID-19 have more severe outcomes compared to untreated patients. It is important to be informed of recent COVID-19 research to make better decisions regarding treatment and health care recommendations for patients.

4- Adopting other general advice that has been recommended to the general public, including monitoring fever (38°C or above), sterilizing and cleaning hands frequently, avoiding touching the face, using masks and a face covering, avoiding people as much as possible, and maintaining a distance of not less than 6 feet (2 m). Cancer patients are advised to get additional necessary medications in case they need to stay at home for a long time and the malignant patients are advised to reduce hospital visits to prevent them from contracting unnecessary infections and depend on telecommunication technology.

It is important to postponing chemotherapy or surgery, intensive therapy, more personal protection, communication, and a separate treatment strategy for treating COVID-19 patients with cancer. As SARS-CoV-2 is an emerging infection for humans worldwide, no matter how advanced the medical fields are, many infections across species are expected in the future. Therefore, scanning for other viruses is also necessary to enhance our preparedness for future disease outbreaks.

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Chapter Six

The Genetic Factors Associated with Risk of COVID-19 Mortality

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The Genetic Factors Associated with Risk of COVID-19 Mortality

Introduction

The SARS-COV-19 or COVID-19 is a new generation member of SARS family characterized by aggressive and mortal effects in several cases, this RNA virus used ACE receptors on different human cells to infect, the lung cells are main target of COVID-19, other pathways can be affected by infection, and damage was observed in different human organs, all this happened under the control of genetic factors that varieties among individuals and populations, other factors may be involved in the response to COVID-19 infections like environment factors, epigenetic factors and viral dose, different gene polymorphisms may be shared in the immune response, coagulation pathways, Regulatory Regions Variations of some genes, genes related to Susceptibility and severity, human Receptors gene variation and other genes were discussed in this concise review, from these overviews can be concluded that the genetic factor can be used as a predictor of severity of COVID-19 infection that benefit to prevent comorbidity and mortal effects, in addition to therapeutic strategies, and medication types.

The Immune System related genes

1- Human Leukocyte Antigens Gene Complex (HLA)

The Antigens of human leukocyte are a group of proteins produced by expressing MHC genes which contributed in the immune response to pathogens, the chronic viral infection result when the CD8⁺ or CD4⁺ T cells couldn't determine the HLA class I or II antigens or lower production of the HLA molecules. Reports proved the HLA's role in some clinical heterogeneity of the disease. Thus, the variability in this locus can be explained the differential risk susceptibility in some populations, also the role of HLA molecules in immune response alteration to COVI-19 to detect risk subjects and the design of personalized therapy. the association of HLA alleles with COVID-19 infection classified into three groups regarding to risk in different populations, first the high risk alleles included A*25:01, B*46:01 and C*01:02. The low risk group included A*02:02, B*15:03,

and C*12:03, and the mortality or severity alleles group included A*11, B*51:01, C*01, C*05, C*14:02, DQB1*04 and DRB1*08

2-Cytokine Genes

One of the immune responses to COVID-19 infection is cytokine storm, it is a complex process which represents by huge immune response out of the control. In cytokine storm different immune cells were activated to generation different cytokine molecules, the cytokine genes related to storm are:

2.1 Interleukin 6 IL-6

Interleukin 6 is the pro-inflammatory cytokine and play major role in cytokine storm that lead to mortality risk, the genetic variations have been contributed in excessive production of IL-6, some variation in *IL6* gene (HGNC:6018) has been reported with different disorders. The rs1800795 (-174C) allele, and rs1800796 (-572C) in the promoter region have been found to be related with IL-6 plasma level elevation and upper respiratory tract infection risk and other disease. A third variant (rs1800797) located in the promoter of *IL6* has been reported that it associated with COVID-19 cytokines storm, moreover, other variants in *IL6* including rs140764737, rs142164099, rs2069849, rs142759801, rs190436077, rs148171375, rs13306435 and five variants in *IL6R* including rs2229237, rs2228144, rs2228145, rs28730735, rs143810642 have been predicted to expression changes and combination of *IL6* with *IL6R* that can be implicated in the COVID-19 pathogenesis and complication.

2.2 Tumor necrosis factors –alfa

The variation of *TNF-α* gene impact in cytokine storm has been described in different infectious disease, some *TNF-α* polymorphisms in promoter region were detected in different positions, like -1031 (T/C), -238 (G/A), -851 (C/T), -857 (C/A), -419 (G/C), -308 (G/A), -49 (G/A), -376 (G/A), -863 (C/A), and -162 (G/A), These variants have been associated with autoimmune diseases. The *TNF* (HGNC:11892) rs1800629 variant found to be related to other cytokine and respiratory infections (9,10). the rs1800629 (g.4682G>A) has been associated with COVID-19 infection in different population.

2.3 The Interleukin-1 gene (IL-1)

Interleukin-1 (IL-1) is a prototype pro-inflammatory cytokine, two forms are existed; IL-1 α and IL-1 β , the IL-1 is effected on every type of cells, the genetic polymorphism of this gene found related to some disease, about 18 SNP have been found to be associated with venous thrombosis may be related with COVID-19 complications, these SNPs included : *IL1B* (HGNC:5992), *IL1RN* (HGNC:6000), *IL1R1* (HGNC:5993), and *IL1R2* (HGNC:5994), Moreover 25 haplotypes recorded to be related with deep vein thrombosis . The relation with COVID-19 still under investigations, the previous studies recorded that the SNPs in the *IL1B* rs1143633 g.8890G>A, *IL1R1* rs3917332, g.102180064A>T and *IL1RN* rs2232354, g.16866T>G were association with Venous thrombosis in COVID-19 manifestations .

2- The Regulatory Regions Variations of Other Cytokine Genes

The regulatory loci of other cytokines gene variants have been studied . For example the non- equivalent variations can be impacted in the final proteins of TGF- β and IFN- α , and the variants alteration the IL-10 and IL-2 transcriptional activity, Investigation reported that some of these variations related with some health problems like infectious disease susceptibility, venous thrombosis and cytokine storm which may accompany COVID-19 complications, like rs1800629 g.4682G>A in TNF related with infectious disease susceptibility like COVID-19 . There is poor information about the SNPs directly related to COVID-19 infections, but perhaps associated with COVID-19 complications and genes expression alterations that contribute in other disease .

The Fc-gamma Receptors (Fc γ R) have an important role in activation of immune response to generate different pro-inflammatory cytokines, like GM-CSF, IL-8 and IL-6 (18). A SNP (rs1801274) Fc fragment of IgG Receptor IIa (*FCGR2A*, HGNC:3616) found to be linked to severe pneumonia causes by A/H1N1. the variant in this SNP causes alteration position 131 to arginine from histidine, and the homozygous was elevated in patients with severe pneumonia in comparison with healthy . the polymorphism in this receptor may be contributed in immune response to COVID-19 infection .

Other cytokines implicated in lung damage by cytokine storm during virus infection, like influenza virus infection it has been referred to a strong up-regulation of cytokine gene expressions, like *CCL2* (HGNC:10618), *IL6*, *IL8* (*CXCL8*, HGNC:6025), *CXCL9* (HGNC:7098), *CCL5* (HGNC:10632), and *CXCL10* (HGNC:10637); in addition to inflammasome genes differential expression *IL1B* (HGNC:5992), *NLRP3* (HGNC:16400) and cytokine genes included *TNF* and *IFNB1* (HGNC:5434), moreover cytokine receptor genes *TNFRSF1B* (HGNC:11917) and *IL4R* (HGNC:6015). A study reported Toll-like receptor 3 (*TLR3*, HGNC:11849) inborn errors and interferon regulatory factor 7 (*IRF7*, HGNC:6122) dependent type I IFN immunity correlated to life-threatening COVID-19 pneumonia. In spite of the low percentage of variation in gene polymorphism in patients the output indicated that other IFN variants were may be contributed in the severity of COVID-19. On the other hand a research reported that *TLR7* (HGNC:15631) harmful variants pointed in 2.1% of severely affected COVID-19 in males and in asymptomatic patients, the functional gene expression was decreased in *TLR7* expression in patients than the control group.

The inter-ethnic variations also impact in the cytokine gene expression related to COVID-19 like *IL2*, *IL6*, *TGFB1IL10*, *TNF*, and *IFNG* (19, 25). For example *IL2* (HGNC:6001) alleles associated with Asians, Africans and Caucasians. However the alleles of *IL6* and *IL10* high expression was found to link with Hispanics, Africans and Asians, than Caucasians population in addition to decreased expression *IFNG* (HGNC:5438) in the Asians population than Caucasians Human Receptors genes variation of COVID-19

4.1- Angiotensin converting enzyme 2 receptor gene

The Angiotensin converting enzyme 2 receptor gene (ACE 2) plays major role in processing to facilitate viral entry to cells by acid-dependent proteolytic cleavage of the S protein with Trans membrane Serine Protease 2 (TMPRSS2) and CTSL (26). The function of ACE2 is a loss after binding with COVID-19 viral particles (27). The genetic variation of this receptor (HGNC:13557, rs2285666, c.439+4G>A) causes alterations in the transcriptional activity. The variant related to receptor stability also studied, there are three common missense alterations were reported in ACE2 included p.Asn720Asp, p.Gly211Arg and p.Lys26Arg, it's may

be interfering with protein structure and stability, meanwhile other variant may be linked to spike proteins of COVID-19 such as p.Leu351Val and p.Pro389His . About eight SNPs were detected by different approaches in ACE2 included rs961360700, rs146676783, rs143936283, rs759579097, rs766996587, rs370610075, rs73635825, and rs781255386, its reported that these variants are rare in different populations and none of them would deactivate this receptor interaction with SARS-CoV-2 proteins .

Another variant (HGNC:2707) represented by deletion/insertion (D/I) in intron sixteen was proposed to be related with COVID-19 in the early stages of pandemic . Later it has been found to be implicated in the COVID-19 severity in patients with hypertension . The studies clarified that there was an association of DD allele of ACE2 with several disease while others refer to that the genotyping of ACE2 does not pose a perceptible risk . Studies found that the ACE1 also contributed in some disease like cardiovascular diseases, but the interaction between DD in ACE1 and other genes or biomarker still under investigation, and its early to consider that the ACE1 DD as effected factor, especially more than 55% of individuals have D allele, however, in multifactorial disease this mutation has slightly effects . Again, The DD genotyping may have significant affected if it combined with other related genes and may be play vital role in comorbidities development, also it may lead to sever outcome if it linked with other factor like COVID-19 infection .

4.2 The Alpha-1 antitrypsin (AAT)

In SARS-CoV-2 infection the Alpha-1 antitrypsin (AAT) suppresses the key protease Transmembrane Serine Protease 2 (TMPRSS2) cleaves the viral spike protein to facilitate infection. The AAT disorder found to be linked with some disease, differential genetic expression was recorded with population diversity the lower expression level TMPRSS2 (HGNC:11876) found in Africans while high expression in East Asians also gender was effected in the level of expression. Investigations found several variations in genes encoded to proteins associated to COVID-19 entry to the host cells for instance TMPRSS2, ELANE (HGNC:3309), TMPRSS11A (HGNC:27954), and CTSL (HGNC:2537), about 48 polymorphisms found in these genes which effected in several populations.

3- the COVID-19 Susceptibility and Severity related genes

There are additional genes coding proteins linked to COVID-19 susceptibility and severity. In last year two studies deal with genome-wide association studies (GWAS) were implemented in European populations and UK with USA individuals, the outcome found correlation the regions 9q34.2 3p21.31 with COVID-19 severity. In more details the a study conducted by Ellinghaus et al. recorded the role of *ABO* (HGNC:79) rs657152, at region 9q34.2 and *LZTFL1* (HGNC:6741) rs11385942, at locus 3p21.31 with genetic susceptibility to COVID-19. Moreover the non-genetic factors found to be a risk factor of hospitalization and the SNPs *LZTFL1* rs13078854 and *ABO* rs9411378 were associated with COVID-severity and diagnosis

The *LZTFL1* gene encodes the ubiquitously expressed protein leucine zipper transcription factor-like 1, which is a strong production in lung cells of human (43). However the mechanism of this genes role in COVID-19 severity or susceptibility didn't clear in publications but some gene located near the 3p21.31 could lead to association, these genes are *CCR9* (HGNC:1610), *SLC6A20* (HGNC:30927), *FYCO1* (HGNC:14673), *CXCR6* (HGNC:16647), and *XCR1* (HGNC:1625).

The Chinese patients with COVID-19 show accompaniment with covid-19 severity and gene locus located at *TMEM189* (*PEDS1*, HGNC:16735)–*UBE2V1*

(HGNC:12494), that contributed in the signaling pathway of IL-1, a potential monogenic impact of function variants loss in *GOLGA3* (HGNC:4426) and *DPP7* (HGNC:14892) was proposed when investigations searched the rare variants in families where a differential clinical outcome was observed among siblings in pedigree analysis . Significant Associations among several loci were observed in patients with COVID-19 with critical illness from intensive care units, these associations observed in a gene cluster encoded to restriction enzyme activators as antiviral molecules, these genes, including *OAS1* (HGNC:8086), *OAS2* (HGNC:8087), and *OAS3* (HGNC:8088); beside tyrosine kinase 2 encoded genes (*TYK2*, HGNC:12440); within dipeptidyl peptidase 9 encoded genes (*DPP9*, HGNC:18648); in addition to in receptor of interferon gene *IFNAR2* (HGNC:5433)

4- The genes of anticoagulant pathways

As a result of systemic coagulopathies happened like Disseminated Intravascular Coagulation (DIC) and venous thromboembolism in COVID-19 cases with critical infections . The genetic factors have been found to be prognostic test to predict the coagulation complications which helps to start appropriate treatment. As well as the Mannose-Binding Lectin (MBL) and MBL-correlated serine protease (MASP)-1/3 involvements in coagulation was investigated, the deficiency can be taken into account as a risk factor for DIC during sepsis complication; thus the genetic variants resulted to decreased proteins or deficiency in their functions that were positively associated with coagulopathies secondary to COVID-19 .

Furthermore, other genes in the pathways of anticoagulant have been studied such as protein C gene variants (*PROC*, HGNC: 9451), factor V Leiden (*F5*, HGNC:3542), and AT deficiency (*SERPINC1*, HGNC:775) found to be contributed in coagulation dysfunction. Also the serpin plasminogen activator inhibitor 1 (*SERPINE1*, HGNC:8583) variants found to be effected in the levels encoded proteins, its considered as fibrinolysis main inhibitors furthermore its associated with DIC development. Moreover the fibrinogen genes variants trigger the pro-coagulant pathways resulted to form microvascular thrombi in different organs .

5- *FXIIIB and PV92*

The FXIIIB is a factor of coagulation in plasma and the PV92 (CDH13) has been found to be associated with hypertension and cadherin. The polymorphism of Deletion /insertion was observed for both genes in the locus including Alu insertion sequence. The study found that the FXIIIB and PV92 and ACE1 genes were overlap and associated with COVID-19 symptoms among European, Japanese and 2 Africans individuals, the outcomes show that II or ID in Japanese individuals and many DD or ID types in Europeans individuals.

6- Neanderthal Haplotype

The recent interesting data suggested by Zeberg and Pääbo that proposed the severity of COVID-19 infection increased by genetic locus about 50 kb located in chromosome 3 and this segment inherited from Neanderthals, also they clarified that 50 % of south Asian populations carried this segments while in Europe about 16% of population carried it (52). In contrast this trait rarely inherited by East Asians because of there has been low effects of COVID-19 pandemic in Asia populations than in Europe, this may be because that the Asian populations have resistance to COVID-19 infection resulted from the previously infected by Middle East respiratory syndrome (MERS) and SARS (53). The Neanderthal haplotypes need more investigations to explain the role of it in negative selection relation to COVID-19 symptoms, developments and host immunity.

7- Epidermal Growth Factor Receptor (EGFR)

The Epidermal Growth Factor Receptor gene has been found to be related to the COVID-19 infection, investigation found that the covid-19 replication can be prevented by EGFR signaling inhibition, and this explained the low mortality percentages in the East Asia.

8- *Epigenetic Factors*

The Epigenetic is some of the mechanisms used in the cells to control on the gene expression and the levels of proteins, several pathways of methylation mechanisms including methylation of DNA modification of histone and noncoding of RNA-

mediated mechanisms, studies found that COVID-19 able to interfere with epigenetic mechanism of host to alter immune response . COVID-19 and influenza viruses found to be controlled on the response of interferon stimulated gene by polycomb repressive complex 2-mediated H3K27me3 in the promoter region , however the mechanisms which used by COVI-19 for interference with epigenetic didn't know to yet, but potential epigenetically regulated factors were reported . The epigenetic scar is a pattern of exposed enhancers and promoters of host-defense genes ,It became clear that the epigenetic scar alleviate the severity of COVID-19 severity by previous infected of common cold or other coronavirus members .it has been found that COVID-19 proteins able to interact with human proteins which are used in gene expression regulation and epigenetics, the dysregulation of epigenetic was found to be linked to fatality risk of Covid-19 , Senapati et al. found that the excessive expression of CD26 through epigenetic modification at rs13015258-C allele is critical and could explain the higher COVID-19 infected fatality rate among Diabetes mellitus patients. Ten epigenetic factors associated with covid-19 infection included up regulation factors DTX3L, HDAC7, HDGF, PRDM1, PRMT1, and TRIM16 and down regulation factors FOXO1, HELLS, PADI3, and PPARGC1A.

Conclusion

The COVID-19 is a big health and scientific challenge in the last two years, the differentiations in the infection rates, healing rates and mortality rates among populations lead to conclude that this infection is a complex multifactorial disease, the genetic factors have the main role in the infection development and severity, as a result of variations of pathways contributed in COVID-19 infection severity, development, complications and healing, the genetic polymorphisms in each of these stages have major role represented by types of proteins structures and activity that interpreted by the genetic polymorphisms of encoded genes

Additionally; the regulation of gene expression as well as excessive or down expression which implemented via regulatory genes, epigenetics and environmental factors, which may be stimulated several genes transcription and translations which in turn can be effected in the immune response, coagulation pathways, respiratory and detoxification systems. The genetic predisposition among families effect in the COVID-19 infection and development also.

The study of genetic polymorphisms and the epigenetic factors can be contributed in the prediction the COVID-19 severity that benefit in the treatment strategies and prevent severe complications, this trait need to involve modern technologies and high through output tools like next generation sequencing to prevent more mortality and complications in the population, especially the COVID-19 virus have high ability to variations and produced a new strain that may use developed a new infections pathways.

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Chapter Seven

Covid-19 infection in the diabetic patients

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Covid 19 infection in the diabetic patients

The diabetes disease is considered as an important member of the Covid 19 comorbidity it was defined as a chronic inflammatory illness or condition characterized by multiple metabolic and certain vascular abnormalities that may affect our immune response to the pathogens. Although the exact pathophysiological mechanisms are still not really understood, it has been observed that major of severe and fatal cases that infected with COVID-19 have recorded in the elderly or in patients with underlying comorbidities, particularly diabetes mellitus, chronic lung, renal disease and blood pressure hypertension, in addition to the cancer . Therefore, the relationship or the association between COVID-19 infection and diabetes is really obvious; Diabetes is one of the leading causes of morbidity and mortality throughout the world, the condition is related with several macro-vascular besides to the micro-vascular complications, which ultimately impact affect the overall patient's survival .

Generally, the relationship between diabetes and many infections has long been medically recognized, especially influenza viral infection and pneumonia, are often most common and really more serious in the older people whom infected with type 2 diabetes mellitus (T2DM) disease condition . Although, the scientific evidence remains argumentative or controversial concerning whether the diabetes *per se* was indeed increases the patients susceptibility and impacts outcomes from these infections, or the reason was to the cardiovascular and/or the renal comorbidities that are usually associated with diabetes are considered the main influent factors involved .

It is now known that both diabetes and also uncontrolled glycaemia were reported as significant proved physiological predictors of illness severity and increase mortality rate in patients infected with different viruses, including the 2009 pandemic influenza A subtype (H1N1), SARS-CoV in addition to MERS-CoV (9,10,11).

In the present SARS-CoV-2 global pandemic, some studies did not found a clear clinical association between diabetes and severe disease. Nevertheless, most

of the medical reports were show that older patients with certain chronic diseases such as diabetes were at the higher risk for severe COVID-19 infection and higher mortality rates .

Few clinical data were exist concerning the glucose metabolism and the developing of acute health complications of diabetes (e.g., ketoacidosis) in COVID-19 patients. The infection of SARS-CoV-2 in patients with diabetes is might possibly triggers a higher stress medical conditions, with real greater releasing of exact hyperglycemic hormones, e.g., glucocorticoids and also catechol amines, that leading to increased blood levels of glucose besides to the abnormal blood glucose variability .

Interestingly, a previous retrospective study from Wuhan city was found out that about 10% of the patients with T2DM and COVID-19 were contracted at least one illness episode of hypo-glycemia (i.e $>3.9\text{mmol/L}$). Scientifically, the blood hypo-glycemia has shown to change or mobilize the pro-inflammatory monocytes (macrophages) and increase level of platelet reactivity, which significantly contribute to a higher cardiovascular mortality in patients suffering from diabetes .

Until now, it remains clearly unknown how that exactly the certain inflammatory and/or immune response was happen in these patients; Moreover, whether hyper- or hypoglycemia might change or cause alteration in the SARS-CoV-2 virulence, or may the virus itself interferes with insulin production or the body glycemic control. Additionally, the impact of usual diabetes medicine and drug treatment in COVID-19 outcomes, also the clinical therapeutic approaches that were used for COVID-19 on blood glucose regulation now remains certainly unspecified .

The hyper-glycemia in addition to the insulin resistance usually promote increased synthesis and production of the glycosylation end products (AGEs) besides to the pro-inflammatory cytokines and the oxidative stress, in addition to the stimulation the production of many adhesion molecules which mediate the tissue inflammation process. This biological process may compose the specific underlying physiological mechanism that leads to a certain higher propensity to the most infections, which leads to worse fate or outcomes at the diabetic patients .

In essence, many defects in the body immune response have been certainly associated with the hyper-glycemia. Nevertheless, the exact clinical relevance of trace in vitro disturbances, which are really still not fully understood. The poor medically controlled diabetes most often cause an inhibition in the lymphocyte proliferative response to many different types of immunological stimuli, as well as impaired functions of monocyte/macrophage in addition to neutrophil. Generally, the abnormal delayed type hypersensitivity reaction in addition to dysfunction in the complement activation that reported in patients with diabetes as well. In vitro studies, was also shown that epithelial cells of the lung were exposure to a high glucose concentrations which induce significant increases of influenza viral load and severity of infection, moreover, rising of the viral replication rate; The aforementioned finding was logically indicate that hyperglycemia might cause enhancement in the *in vivo* viral replication rates .

In specific animal models, a certain structural lung tissue changes have been correlate to diabetes, such as marked augmentation in vasculature and capillary permeability besides to microcytic collapsing of the alveolar epithelium. Additionally, many patients with diabetes were significantly showed an intensive certain reduction in the specific forced vital capacity level (FVC) besides to the level of the exact forced expiratory volumes at one second of time (FEV1), which is usually related with the increasing of blood and plasma glucose values .

1-Morbidity and mortality Rates in diabetic cohorts with COVID-19 infection:

Substantially, many of medically evolving data were clearly explain that the patients of COVID-19 with diabetes are usually associated with critical or clinically severe disease, which varying from about 14 to 32 percent in different previous medical studies . On the other hand, other clinical studies were gave more elevated results; For instance, In China, a certain study involved about 138 patients, Wu *et al.* (24), was recorded that 72 percent of COVID-19 patients with comorbidities including diabetes were urgently required or need admission to a specific ICU, in comparing to about 37 percent of patients without above comorbidities.

Nevertheless, in the clinical meta-analysis of eight different studies, were showed that the odds ratio (OR) of medically severe COVID-19 cases were not significantly higher at patients with diabetes, unlike the blood pressure hypertension for example [OR, 2.36; 95% CI, 1.46 to 3.83] and CVD as well .

On the other hand, another meta-analysis medical study from China conducted by Chen *et al.* (25) found a marked significant correlation between the severity of COVID-19 infection and diabetes. Moreover, mortality rate was also higher in diabetic individuals whom infected with COVID-19 .

The National Chinese Center for Disease Control and Prevention was recorded a case fatality rate (CFR) of 2.3% (1023 deaths among 44,672 confirmed cases) In a scientific clinical report of about 44,672 patients infected with COVID-19

Nevertheless, the CFR was as significantly higher as 10.5%, 7.3% and 6.0% in patients with CVD, diabetes and blood pressure hypertension, respectively .

Obliviously, according to the aforementioned studies, the values of morbidity and mortality rate were higher in Covid 19 patient when it associated with diabetes .

2- The pathogenesis of the illness and outcome of diabetes in patients infected with COVID19:

The patients with COVID-19 usually contract pathologic lymphocytopenia in addition to thrombocytopenia beside to leukopenia, which are extremely more dominant among those with severe form of the disease. Moreover, increasing in the levels of specific pro-inflammatory cytokines, such as interleukin-6 (IL-6) and also elevated level of C-reactive protein, in addition to the increasing of the coagulation activity, associated by higher values of d-dimer concentration levels, which also observed in the severity of infection . Generally, certain imbalance was observe between blood coagulation and fibrinolysis process, with elevated levels of plasma clotting factors, also establishment of a relative inhibition of the whole body fibrino-lytic system. The insulin resistance and T2DM as well are associated with endothelial dysfunction, besides to the enhancement of platelet aggregation and their activation. These physiologic abnormalities may enhance the development of the hyper-coagulable rate in addition to pro-thrombotic state .

Interestingly, atherosclerosis in blood circulation and the vascular inflammation in addition to the endothelial dysfunction are also consider as part of the pathogenesis of other pathological chronic medical conditions, for instance, blood pressure hypertension and CVDs .

In Essence, previous animal studies concerning SARS-CoV were record that the older ages are correlate to certain defects in specific lymphocytes (T-cell and B-cell) function and exacerbate the levels of inflammation markers. Therefore, T2DM alone and/or relationship with older age, blood pressure hypertension and/or CVDs may participate in a weak control of SARS-CoV-2 replication cycle besides to elongation of the duration of the pro-inflammatory immune response, which most often leads to bad or poor prognosis of the infection .

The replicative cycle of the viral particles start by the entry of the virion into intact host cells, which considered as a crucial component step of the viral replication and cross-species transmission as well, especially for all members of coronaviridae family. Upon the attachment of the virion to the intact host cell through certain viral glycoproteins termed as viral spikes, bind to certain host cells which express specific receptors that called as angiotensin-converting enzyme 2 (ACE2). Thereafter, the host cell proteases will cleaves this spike (S) to produce S1 and S2 spikes, which later on allows the virion to enter the intact host cell and complete viral replication cycle, (ACE2) receptors has been previously recorded as the main specific receptors for SARS-CoV in addition to SARS-CoV-2 .

In China, a previous medical study clinically compared about 39 of SARS-CoV patients without any previous history of diabetes, who did not receive any type of steroid treatment, with same number of matched healthy siblings, the study found out that twenty of above SARS-CoV patients contract diabetes during hospitalization period. The pancreatic islets are express large quantity of (ACE2) receptors it was obviously suggest that SARS-CoV may cause damage to pancreatic islets and thus induce an acute insulin dependent type of diabetes mellitus. For this reason, the pancreatic tissue damage might also be exist in SARS-CoV2 patients .

Another Previous studies have explain that the sloping in the mortality rate in addition to lowering of the need to specific endotracheal intubation in Covid 19

patients suffering from pneumonia who were in continued use of a certain ACE inhibitors (ACEIs) and also specific angiotensin receptor blockers (ARBs).

Knowingly, the clear immuno-modulatory role of these aforementioned medications play an important and significant effect and thus inhibit the pulmonary besides to the systemic body inflammatory immune response through decreasing the levels of inflammatory cytokines .

Generally, the exact susceptibility to SARS-CoV2 illness might not be significantly higher in patients with diabetes. However, it is obviously clear that diabetes most often associated with the worse outcomes in patients with COVID-19. Nevertheless, the percentage of infection with SARS-CoV 2 in diabetic patients is approximately same as in that of general population .

3- Potential implications for the clinical management at those patients:

It is of crucial important to get complete information about the clinical management of SARS-COV 2 infected patient with diabetes. An important medical trial involve results from more than one hundred patients was conducted in China at 2020; This study showed that chloroquine drug considered as valuable choice in comparing with control group, particularly, in the lowering and shortening of the viral infection course. Furthermore, the administration of above drug significantly reduce the exacerbation of pneumonia, besides to the helping of the viral negative conversion in addition to the improvement of the radiological pictures of those patients without any important clinical side effects .

Additionally, many previous medical studies concerning diabetes, have found out that the administration of hydroxy-chloroquine drug will induce a marked improvement of the glycemic control at certain decompensated, treatment-refractory infected patients with diabetes . Interestingly, the exact physiological mechanism regarding the hypoglycemic effect of the hydroxy-chloroquine remains slightly vague; However, the inflammation usually correlated with clear impairment of glucose control. Indeed, previous medical studies explained that chloroquine drug stimulate the specific C peptide response, which potentially leads to elevation of the certain b-cell function in the pancreas, inhibition of the intracellular insulin degradation, Moreover, increasing of insulin accumulation.

Therefore, precautions should be taken when the chloroquine is administered to diabetic patients associated with COVID19 infection .

It is clearly important to conduct the interim guidance of WHO on medical management and clinical care of SARS-CoV-2 infection, particularly the advices concerning use of corticosteroids outside certain clinical trials. For instance, the hyperglycemic effect and the impact of the hydroxy-chloroquine or chloroquine drugs on the medical cases, so a certain special cautions must precisely consider in diabetic patients whom infected with Covid 19 .

Unfortunately, the recommended and real data concerning the optimum management of patients with diabetes infected by Covid 19 are scarce, besides to exact clinical information regarding the patients with SARS-COV 2 who contract glycemic de-compensation. Numerous enrolled reasons are necessitate blood glucose monitoring and specific consideration for drug interactions may reduce developing of bag clinical symptoms and exacerbated outcomes . Importantly, we should not ignore the probability of hypoglycemic problems due to the main interplay among treatment therapy, pathogenesis of SARS-COV 2 in addition to the exact physiological disturbances of diabetes. The occurrence of comorbidities and exact diabetes-related and besides to complications, age of the patients in addition to another factors

Interestingly, a special care and attention must be establish for patients with diabetic renal disorders, besides to patients with diabetes-related heart complications; because they are also at a high risk of severe infection with SARS-COV 2 and bad prognosis. Therefore, excessive health vigilance and disease screening for the diabetic patients regarding infection with SARS-COV 2 are drastically needed .

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Chapter eight

Heart failure in COVID-19 Patients

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Heart failure in COVID-19

Heart failure (HF) is a group of signs and symptoms induced by the heart's malfunction resulted in a reduction in blood supply through the body; its manifestations caused by a structural and/or functional anomaly of the heart, that interrupts its filling with blood or its pumping of it throughout each heart beat . Frequently, the manifestations of HF comprise dyspnea, fatigue, and leg oedema. However, chest pain, including angina, does not typically take place owing to HF .

The most frequent causes of HF embrace coronary artery disease, together with a past myocardial infarction (heart attack), high blood pressure, valvular heart disease, atrial fibrillation, excess alcohol intoxication, infection, and cardiomyopathy of an unknown reason. Such causes lead to HF by altering either the heart structure or its function . HF regularly only influences one side of the hear; either the right or left side; nevertheless, it may involve both sides. The most well-known type is left-sided HF and occur once the left ventricle wouldn't pump sufficient blood throughout the body. Consequently, blood loads up in the pulmonary veins. This results in dyspnea, breathing problems or coughing, particularly during application of effort. The left-sided ventricular HF also included two types dependent on whether the capacity of the left ventricle to contract, or to relax, is influenced; HF with reduced ejection fraction (HFrEF), and HF with preserved ejection fraction (HFpEF) .

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients presented with earlier existing comorbidities such as HF are at a predominantly high risk of morbidity and mortality from this viral infection . In COVID-19, the general worldwide mortality rate of about 6.9% whereas in COVID-19 patients with established cardiovascular disease who generally encounter severe prognosis and a mortality rate of more than 10% in some reports .

HF that can be experienced at various stages over the span a COVID-19 patient presentation. New or existing HF in the setting of COVID-19 can introduce a group of unique challenges that can complicate presentation, management, and

prognosis . A cautious awareness of the hemodynamic and diagnostic inferences is essential for suitable triage and management of these patients. Abnormal cardiac biomarkers are common in COVID-19 and can initiate from an assortment of mechanisms that encompass the viral entry *per se* by an aid of the ACE2 receptors, direct cardiac injury, increased thrombotic activity, stress cardiomyopathy, and among others .

Patients with a history of Chronic HF are prone to develop acute decompensation after a diagnosis of COVID-19. The taking out of guideline-directed medical treatment was linked to higher mortality rate . HF patients are at particular raised risk owing to their reduced immunity, overall weakness, and reduced hemodynamic aptitude to cope with more severe infections. Most studies on HF patients have overlooked that monocytes seem to produce more TNF- α and less IL-10 than healthy subjects, which together with the extensive systemic inflammatory response related with severe COVID-19 infections necessitates improved cardiac performance and high cardiac output, something that HF patients are generally incapable of .

Alongside with the more aggressive COVID-19 infection, HF patients are at a substantial advanced risk of acute aggravations, and multiple mechanisms may be in charge of stimulating and aggravating this process. Acute infections lead to the release of proinflammatory cytokines and the recruitment of proinflammatory macrophages and granulocytes, lead to a severe inflammatory storm which may amplify the initial injury . In combination with the amplified metabolic request, this can result in cardiac depression and either new-onset HF or acute decompensation of chronic HF . The coagulation dysfunction triggered by the sepsis might play as another contributor. High rates of coagulation abnormalities and thrombotic events was shown in patients . Previous studies have also addressed that 15–29% of COVID-19 patients, the virus causes kidney impairment in the setting of acute kidney injury which may result in volume overload that may intensify an established chronic HF .

New onset of HF was noticed in hospitalized COVID-19 patients regardless of HF-free history. Such observation is owing to the direct consequences of the virus or the systemic inflammation on the heart. Severe acute myocarditis can be a manifestation of the infection leading to cardiogenic shock that can lead to

multiorgan dysfunction syndrome (MODS) and death. Furthermore, the prothrombotic state can lead to pulmonary embolism and consequently acute right ventricular failure . Stress cardiomyopathy-like depiction can also be observed owing to the comprehensive inflammatory response and sympathetic activation, leading to a additional classic acute HF decompensation with raised up filling pressures and pulmonary edema .

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Chapter Nine

Post Covid-19 Fungal Infections

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Post Covid-19 Fungal Infections

INTRODUCTION

The coronavirus disease 2019 has infected tens of millions of people worldwide within the last year. a new infection mostly manifested as viral pneumonia, started as a local epidemic but developed within a few months into a worldwide pandemic with high morbidity and mortality rates. According to the published reports, a portion (7.2%) of COVID-19 patients are sometimes co-infected by other microbial pathogens . However, the incidence of fungal secondary in COVID-19 patients remains unclear .

Many Patients with serious illness are ten times more prone to develop bacterial or fungal secondary infections than secondary viral infections . all studies of coronavirus fungal infections reported occurrence during the post covid fungal infections, mostly 14 days after the appearance of COVID-19 symptoms .

The viral disease specialized coronavirus may be allowed secondary fungal disease through a propensity to cause respiratory infection by affecting the immune system leading to dysregulation and reduced numbers of T. cells , CD4+T, and CD8+T cells, altering the natural immunity .

1. Fungal infection and COVID -19

Some mycosis infection symptoms are the same as those of coronavirus, including fever, cough, and shortness of breath . Diagnosis fungal infection by laboratory testing is very important to determine if a person has a mycosis infection or COVID-19 , some patients can have COVID-19 and a fungal infection at the same time .

The fungal co-infection almost in patients with coronavirus include aspergillosis or invasive candidiasis. These infections are reported with increasing frequency and may be associated with acute illness and death.

The patient by Awareness can be prevent these infections which that essential to reduce delays in diagnosis and therap in order to help prevent these infections deadly .

1.1 . Aspergillosis pulmonary associated coronavirus

The Aspergillosis which infections caused by the fungus *Aspergillus* but the Scientists are still learning about fungal co-infection in patient with severe coronavirus. In the past, scientists thought aspergillosis pulmonary occurred almost entirely in patients with immune systems very weakness .

However, the Patients with pulmonary aspergillosis show also without weakened immune systems but who have a cut respiratory infections caused by viruses, including influenza. Several a new anrecent reports describe COVID-19-associated pulmonary aspergillosis (CAPA) .

In this case (CAPA) the information available was indicated the following :-

*Can be occurs in patients with severe COVID-19 sach as patients on ventilators in ICUs

*In this infections (CAPA), the serum GM ELA usually occurs negative, so that limits the reliability of serum-based diagnosis of CAPA [19].

*This infections can be severe illness and finally dead[8].

1.2. The infection Candidiasis in patients with COVID-19

This infections caused by the fungus *Candida such as Candida auris*.these fungal co-infection in patients hospitalized for COVID-19 are at risk for healthcare-associated infections (HAIs), including candidemia, or bloodstream infections caused by *Candida* . *Candida auris*,it has caused outbreaks of severe infections in healthcare facilities.these infections almost commonly in the United States which can be spread in long –term care facilities caring for Patients with acut medical conditions .

According to the published reports, since the start of the coronavirus pandemic, *C. auris* has been in COVID-19 units of acute care hospitals.

These outbreaks during the COVID-19 pandemic may be related to changes in routine infection control practices, such as limited availability of gloves and gowns, or reuse of these items, and in should be changed cleaning and disinfection practices. However, occurred a new *C. auris* infections without links to known cases or healthcare abroad have been identified recently in multiple states, suggesting an increase in undetected transmission. Finally fungal infections resistant to antifungal treatment have also been described in patients with coronavirus[18]. Early diagnosis and monitoring for post covid fungal infections and antifungal resistant infections such as *C. auris*, azole-resistant *Aspergillus* are key to reducing death from coronavirus in patients with severe COVID-19 fungal co-infections.

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Chapter Ten

Covid-19 and Risk familial hypercholesterolemia

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Introduction

COVID-19 severity has been linked to cardiovascular risk factors, such as obesity, high blood pressure, diabetes, and high cholesterol. The level of Cholesterol abnormalities such as unusually low or high low-density lipoprotein (LDL) levels and elevated triglyceride levels increase mortality rates in those with COVID-19 infection, but research on the causal link between the two is ongoing. The COVID-19 illness continues to cause increased morbidity and mortality, and due to the slow pace of vaccination COVID-19 will probably remain a global burden to health systems for a long time. Unfortunately, the necessary prevention and treatment strategies of COVID-19 have led to restriction measures that are hampering the routine care of common chronic metabolic conditions like hypercholesterolemia, hypertension, hyperglycemia (diabetes), and obesity.

It is of specific worry that during the intense period of COVID-19, the control of prior metabolic infections will in general deteriorate which again expands the danger for entanglements and a helpless result in these patients , A critical supporter of these difficulties is endothelial dysfunction which is related with COVID-19 . Also, previous metabolic illnesses like obesity , diabetes, hypercholesterolemia, furthermore, hypertension are conditions that apply consistent weight on the endothelium. This Commentary will examine the effect of COVID- 19 on endothelial capacity especially in patients with sever hypercholesterolemia, like familial hypercholesterolemia (FH), a metabolic condition known to in itself unfavorably influence endothelial function. Short remarks on other metabolic conditions related with endothelial dysfunction are made.

During the infection of cells of the respiratory tract by the Coronavirus , Disease 2019 (COVID-19), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interacts with the angiotensin-converting enzyme receptor 2 (ACE2). Although lipid lowering therapy is generally considered safe in patients with COVID-19 pneumonia and acute respiratory distress syndrome (ARDS), there are theoretical concerns regarding their contribution to infectivity and safety. Based on

the baseline characteristics of patients admitted to a critical care unit due to COVID-19 from Lombardy, Italy, hypercholesterolaemia was found to be a comorbid condition in 18% of the patients. One study of patients with COVID-19 found that 35.3% had underlying atherosclerotic cardiovascular disease and that death rate was 50% . New York City data indicated that 26 percent of patients hospitalized with COVID-19 were reported to have hyperlipidaemia as a comorbid condition and 10 percent were reported to have coronary artery disease . The prevalence of hyperlipidaemia and coronary artery disease (CAD) was higher among non-hospitalised COVID-19 patients than among hospitalised patients (27% versus 24%). As a result, it does not require ventilation or any other supportive methods. In a multivariate regression analysis assessing risk factors for hospitalisation, including age, cancer, chronic kidney disease, CAD, hypertension, hyperlipidaemia, heart failure, obesity, pulmonary disease, race, male sex and tobacco use, the odds ratio (OR) for hyperlipidaemia (OR 0.67; $p = 0.003$) suggested a relative reduction in the individual proportional risk for hospital admission. patients were on statins or other lipid lowering therapies.

recently reported Hu et al. lower serum cholesterol levels amongst COVID-19 patients , leading some to suggest temporary cessation of lipid lowering therapy . However, lipid parameters often fall in cytokine-mediated inflammation as a consequence of the acute phase response rather than having a causative or pathological contribution towards infection. It is reasonable to assume that patients with a previous history of myocardial injury are at higher risk for further events, thereby justifying the need for maintaining their lipid lowering therapy as far as possible. High cholesterol, therefore, is a significant contributor to blood vessel injury that can lead to atherosclerosis. If you have COVID-19 or high cholesterol, you are at high risk of cardiovascular complications, but when the two are present at the same time, you are at especially high risk of experiencing:

- Blood clots
- Heart attack
- Stroke

Complications of High Cholesterol and COVID-19 , When LDL builds up in the blood, it can narrow or clog the arteries, raising your risk of having a:

- Heart attack
- Stroke
- Heart condition

COVID-19 puts the body in a pro-inflammatory state, damaging the heart and lung tissues while also increasing the risk of coagulopathy or blood clots. Those with high cholesterol and COVID-19 are at even higher risk of experiencing a cardiovascular event. If you are obese or have high cholesterol levels, you may require more rigorous social distancing or shielding from people to avoid COVID-19 infection and subsequent complications. High Cholesterol Treatments and COVID-19 , If you are already taking cholesterol-lowering drugs like statins, you should continue to do so until advised otherwise by a healthcare professional, even if you are diagnosed as COVID-19 positive. If you have been recently diagnosed with high cholesterol levels, your healthcare provider may recommend lowering LDL levels using statins, cholesterol-lowering medications, to lessen the degree of injury to your blood vessels from COVID-19 attack. In high-risk patients having severe COVID-19 disease, statin therapy may be initiated to prevent life-threatening cardiovascular complications. Of note, some statins may cause severe side effects such as muscle aches and liver damage. If you are experiencing statin-associated muscle symptoms, inform a healthcare professional. Statin therapy may need to be discontinued if skeletal muscle symptoms and elevated liver enzymes persist.

2- Familial hypercholesterolemia patients with COVID-19 are at increased risk

Familial hypercholesterolaemia (FH) is an inherited disease (Heterozygous familial hypercholesterolemia (HeFH))is the most common monogenic inherited metabolic disease. with an estimated prevalence of 1 in 250. It is characterized by a

lifelong two- to threefold elevation of plasma LDL cholesterol concentration, which if untreated induces premature ASCVD and a markedly increased risk of an acute coronary event in middle-aged FH patients. These epidemiological data suggest that, compared with non-FH patients, FH patients with COVID-19 may be at higher risk of cardiac complications, particularly if the underlying genetic disease has remained undetected. Concern is justified because a high proportion of critically ill COVID-19 patients are under the age of 50. Below this age, clinicians typically overlook the possibility of an increased risk of premature coronary artery disease, even amongst patients with FH in whom subclinical stenosing coronary artery disease may already start to develop during their early 30s.

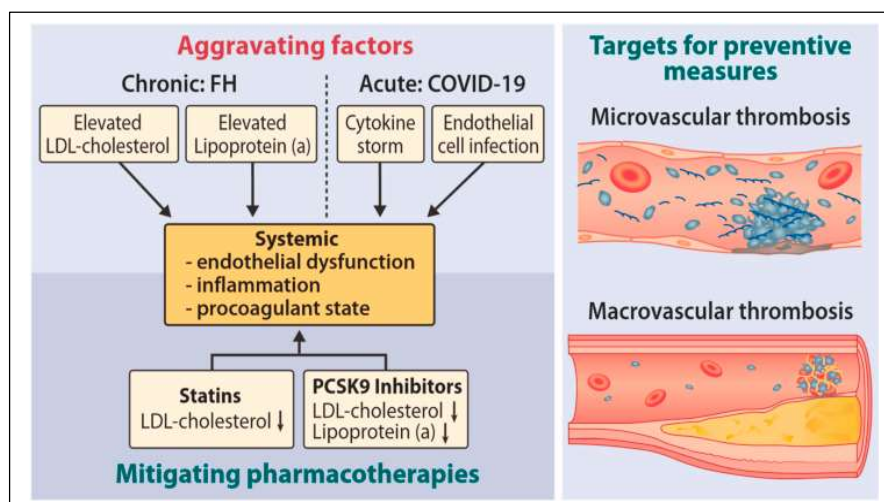
Important The discovery is the link between cytomegalovirus Antibody and Atherosclerosis, Watch in An atherosclerosis risk study was conducted in the local observed in individuals with high levels of lipoprotein (a) and fibrinogen . May such a link Also apply to FH patients who, on average, Higher levels of lipoprotein (A) compared to levels with general population and, therefore, may have a higher risk of an atherothrombotic event whilst suffering from COVID-19 and even after recovery. The potential synergism between viral infection and the resulting hypercoagulability related to increased lipoprotein(a) levels merits further investigation.

There are a few significant contemplations when treating a FH patient with Coronavirus, including

1- the need to increase cholesterol-lowering treatment because of potential coronary endothelial dysfunction caused by the viral infection .

2-Statin treatment, the primary LDL cholesterol-lowering pharmacotherapy for patients with FH, may protect against endothelial dysfunction and an acute coronary event and, therefore, should not be discontinued in patients undergoing intensive care, especially those with established coronary artery disease. Because PCSK9 inhibitors effectively lower LDL cholesterol and prevent acute coronary events in FH, their use should also be continued. PCSK9 inhibitors have a good safety profile; however, experience of their use in severely ill COVID-19 patients is limited and worthy of evaluation .

3-patients with FH are likely to be at increased long-term risk of an atherothrombotic event following COVID-19, as previously observed in FH patients with Chlamydia pneumoniae infection as well as in the general population with influenza or cytomegalovirus infection. Thus, pharmacotherapy for severe hypercholesterolaemia in an FH patient with COVID-19 should not be discontinued during infection and, due to possible excess risk of ASCVD, could even be intensified following recovery from COVID-19. Of importance, however, the potential advantages of intensifying lipid-lowering therapy for FH patients after the first COVID-19 epidemic, and the potential disadvantages of a lack of intensification, need to be explored in future epidemiological investigations.



(Figure1) The diagram shows a two-hit scenario for the development of clinical cardiovascular disease in patients with familial hypercholesterolemia (FH) and COVID-19.

The COVID-19 more dangerous for those with high cholesterol, COVID-19 is more likely to cause an inflammatory reaction that can lead to injured blood vessels, massive blood clotting throughout the body, and a higher likelihood of having a heart attack or stroke. High cholesterol is an independent risk factor for heart health. COVID-19 infection heightens the possibility of having a heart attack or stroke. High cholesterol levels have also been associated with increased coagulopathies (blood clots) in those with COVID-19. As such, BMI and LDL cholesterol have become important metrics alongside other known characteristics such as age and ethnicity in the risk assessment of vulnerability to COVID-19 infection. The medicine must be taken to keep the body safe and eating a low-sodium diet are keys to living a heart-healthy life. Adults over age 20 should have

their cholesterol tested every five years, and individuals with a family history should be especially diligent.

To prevent high cholesterol:

- Eat heart-healthy foods like colorful vegetables and whole grains.
- Reduce saturated fats and eliminate trans fats. Saturated fats, found primarily in red meat and full-fat dairy products, are the biggest culprits in raising your total cholesterol, so they should be consumed in moderation. Junk food and processed meals may be high in trans fat and should be avoided.
- Lose weight.
- Exercise for at least 30 minutes a day.
- Quit smoking.
- Limit alcohol use.
- Manage stress.

Lifestyle changes alone can lower cholesterol or maintain healthy numbers. Foods that help lower your cholesterol include:

- Green, leafy vegetables
- Oats
- Whole grains
- Fatty fish
- Beans
- Eggplant and okra
- Fresh fruits such as apples, strawberries, grapes, and citrus fruits
- Soy

When lifestyle changes are coupled with strict adherence to social distancing protocols, the risk of catching COVID-19 plummets. To decrease your risk of infection:

- Limit the number of people you come into contact with.
- Wear a mask, especially around people.
- Wash your hands with soap and water for at least 20 seconds.
- Wipe surfaces with sanitation wipes.
- If you are taking a cholesterol-lowering medication—such as a statin—without major side effects, continue to take it unless told to do otherwise by a healthcare professional.

Increase level of cholesterol can be the result of an unhealthy diet, genetics, being overweight, or smoking. The most important steps to avoiding COVID-19 complications are adhering to social distancing guidelines, getting vaccinated, and pinpointing the cause of your high cholesterol. Oftentimes, the cause of your high cholesterol is multifactorial in nature. Fortunately, a few small lifestyle changes, while not always easy, may greatly improve your heart health. Limiting unhealthy foods, exercising regularly, and checking in regularly with a healthcare professional can go a long way to living a happy, healthy, and COVID-19-free life.

Lipid, Cholesterol, and Viral Entry host cell

For basic characterization of SARS-CoV-2 and CVD, it is Important for understanding the virus with the host cell. Corona virus is one stranded virus, RNA virus positive meaning with with a lipid envelope. The virus contains four structural proteins: nucleocapsid Protein, membrane protein, envelope protein, and spike protein (S-glycoprotein) that mediate Attachment to the angiotensin converting receptor 2 (ACE2). Lipid rafts are subdomains of the plasma membrane enriched in cholesterol and glycosphingolipids, which have been shown to play an important role in viral entry into host cells. The abundant presence of cholesterol within lipid rafts is thought to play an essential role in promoting viral infectivity. Lipid rafts are important for the interaction between the S protein and ACE2 receptor as well as for facilitating the process of viral endocytosis. However, the

localisation of ACE2 on lipid rafts has been a topic of controversy, e.g., Lu et al. showed that ACE2 was largely co-localized with the raft marker caveolin-1 and GM1, and that ACE2 was shifted to the non-raft environment after depletion of cholesterol. In addition, lipid rafts also contain caveolins, clathrins, and dynamin, which may be as important as cholesterol in the process of viral entry, as figure 2

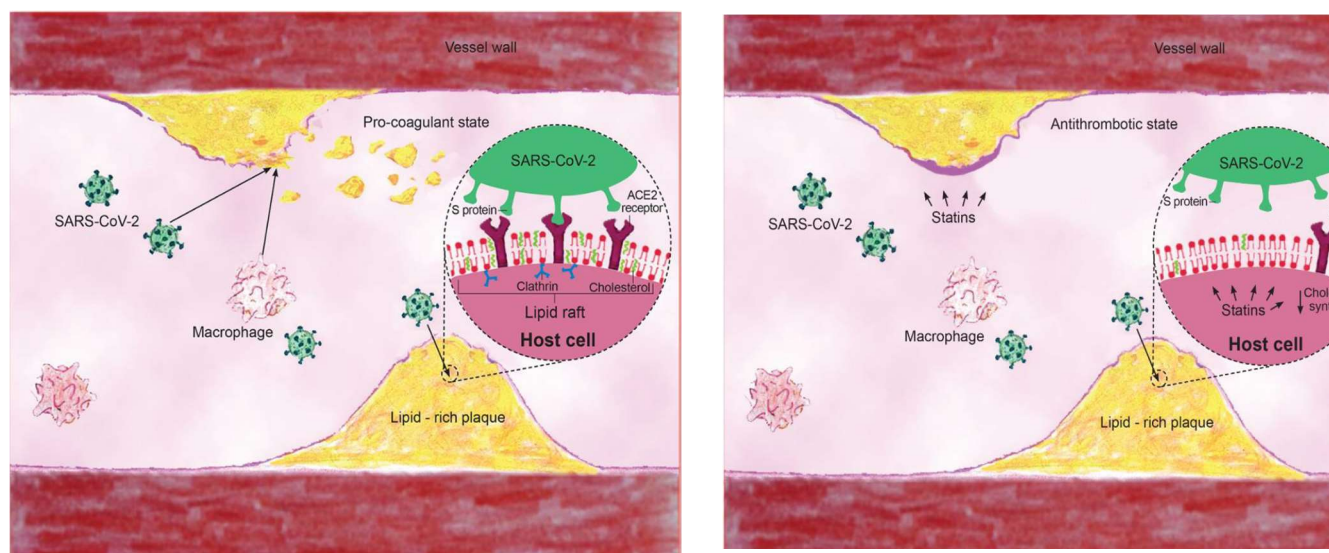


Figure 2 the mechanism of the role of cholesterol and statins in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the left figure shown Lipid rafts rich in cholesterol serve as docking sites for angiotensin-converting enzyme 2 (ACE2) receptors and viral attachment via the S protein of SARS-CoV-2, which is then taken into the cells by clathrin. also, acute infection with SARS-COV-2 and macrophages via paracrine factors can lead to plaque instability and embolization causing occlusion of distal microvasculature. the right figure shown Statins disrupt lipid rafts and viral binding; reduce cholesterol; and have plaque stabilizing, antithrombotic, and anti-inflammatory properties.

The role of cholesterol in the body and entry into the Corona virus has been studied for several coronaviruses including SARS-CoV, murine coronavirus, porcine delta coronavirus, and infectious bronchitis virus. Thus, cholesterol is found in the cell membrane and viral envelope. Contribute to the replication of the coronavirus by serving as a major component in the entry of the virus. more, Cholesterol has recently been shown to be involved in the binding and alteration of oligomeric status in The N-terminal fusion peptide of SARS-CoV, which is required for virus entry into the host cell. The impact of cholesterol on coronavirus infectivity was further supported by examining the effect of depleting cholesterol on SARS-CoV infection, which resulted in a significant reduction in viral mRNA.

It was observed that cholesterol depletion impaired viral entry and virus-induced fusion, suggesting that cholesterol is important during the post-binding stages .

3- PCSK9 inhibitors to enhance the antiviral action of interferon

orderly survey by Lee et al, breaking down the danger factors for COVID-19 mortality and revealing no relationship with higher danger of mortality in COVID-19 for hyperlipidemia, uniquely in contrast to other conventional cardiovascular danger factors like diabetes mellitus and hypertension. Additionally, the utilization of ACE inhibitors or ARBs was related with decreased danger of mortality, though no affiliation was found for statins. In this state focus our comments on the endothelial function-enhancing effect of the PCSK9 inhibitors. A useful role in efficiently lowering the plasma cholesterol level in hypercholesterolemia Patients with COVID-19, especially in patients with familial hypercholesterolemia (FH), Recently suggested.

These patients have endothelial dysfunction caused by a Elevated serum LDL-C, which is often accompanied by Elevated lipoprotein(a) level. This inherited phenotype then leads to hyperlipidemia of pro-thrombotic changes in endothelial cells, and consequent enhancement of endothelial platelets The interactions are likely to be further enhanced during SARS-CoV-2 infection. Furthermore, recent data suggest that the benefit of PCSK9 inhibitors may not be limited to their endothelial function-enhancing effect alone. Protection must be related to a decrease in the circulating PCSK9 level and the ensuing enhanced production of interferon beta. By using a PCSK9 inhibitor the prognosis of COVID-19 should be improved via the efficient lowering of the LDL-C level and via preventing the reduction in the antiviral genes expression, notably those of the type I interferons. In patients with COVID-19 and severe hypercholesterolemia, and consequently at high risk of an acute cardiovascular event, such as patients with FH, a single injection of a PCSK9 inhibitor may be considered, and the newly started drug therapy may be continued.

4- Corona Virus-19 vaccines and familial hypercholesterolemi

Myocarditis/pericarditis has been accounted for after a mRNA Coronavirus immunization in very rare cases among males aged 12-51- years . The U.S. Centers for Disease Control and Prevention has estimated that the rate of these complications is about 12.6 cases per million doses of the second dose of mRNA COVID-19 vaccination. Although the mechanism behind these complications is not clear, it has been speculated that they are due to an immune response to the genetically engineered mRNA in the vaccine, which then would further activate immunological pathways. However, so far there are no reports of FH patients with myocarditis after COVID-19 vaccination. In any case, the benefits of COVID-19 vaccinations clearly overweight the risk of rare adverse events related to the vaccination. And in the conclusion , there should be no hesitation to continue with statin therapy in severe hypercholesterolemic patients with COVID- 19, whether they are FH patients or not. We argue that in FH patients with COVID-19 the clinicians need even consider intensifying statin therapy aswell as the addition of other lipid-lowering agents, such as ezetimibe and PCSK9 inhibitors. On top statins, the PCSK9 inhibitors lower serum Lp(a) level by about 30% and serum LDL-C by about 60% . Thus, PSCK9 inhibitors need to be considered particularly in FH patients with an elevated level of Lp(a) .

In addition, PCSK9 inhibitors may potentially enhance the antiviral function of endogenously produced interferon . This call for an effective hypolipidemic prevention applies during the time of the COVID-19 pandemic and beyond. The length of the vulnerable period requiring intensification of LDL cholesterollowering therapy cannot be predicted at the moment. However, we need to recognize that cardiovascular diseases and FH are among the comorbidities that carry a high risk of complications for COVID-19 patients [14,48]. When considering that the vasculopathic effects of COVID-19 may persist, a long-term follow-up of individualized therapies in FH patients is warranted. It would be also important to collect epidemiologic follow-up data of the FH patients who have suffered COVID-19, and then analyze the benefits of a long-lasting particularly effective lipid lowering therapy .

The question in the minds of the number of people is if the cholesterol is high, is it possible to get the vaccine? The answer it is Yes. The Data shows that getting

the COVID-19 vaccine protects you from contracting and transmitting the disease. It also helps to protect others in society who are particularly vulnerable or susceptible to infection, especially those with high cholesterol who do not present with obesity or other noticeable markers of disease. While getting the COVID-19 vaccine decreases your risk of severe disease in those with high cholesterol levels, you should also adopt a healthy lifestyle that includes eating a diet high in fruits and vegetables, and routinely exercising to maximize your protection against the disease and its negative health impacts. Thus far all FDA-approved vaccine candidates—Pfizer-BioNtech, Moderna, and Johnson & Johnson—have been proven to be nearly 100% effective in preventing severe cases, hospitalizations, and death from COVID-19.

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Chapter eleven

The relationship between infection with COVID-19 disease and death in the elderly

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The relationship between infection with COVID-19 disease and death in the elderly

Introduction

The Centers for Disease Control and Prevention (CDC) defines "older adults" as anyone who is 60 years of age or older and who usually has a severe chronic disease.

The consequences of the global pandemic, Covid-19, have affected all aspects of life, the most important of which are economic, health and social. The effect of the pandemic on health were severe and deadly on specific groups of people, called high-risk group such as children, the elderly, pregnant women and those suffering from a chronic disease debilitating health because of its impact on their immunity, such as diabetes, hypertension, cardiovascular diseases, etc.

A recent study conducted by the London School of Economics and published in the Guardian newspaper indicated that the elderly, who are usually weak in structure and suffer from most chronic diseases of the era, have low immunity , rapid and severe disease infection, the Covid-19 pandemic has caused many risks. For this category of elderly. The results of one study, indicated that 75% of coronavirus-related deaths in aged care facilities worldwide are due to elderly people. This necessitates rethinking the relationship of the elderly to such emergency epidemics and examining the impact of the Coronavirus pandemic on them in particular. Raising awareness of their health needs and supporting them in preparing for the virus; securing health care for them; improving the role of the health care workforce in maintaining their health; and to view their needs as a “issue of rights.”

Harmful changes due to covid-19 infection

To understand what is happening, it must be noted that when a virus can penetrate the human body, the cells are in the front lines to confront it, either slightly or strongly.

Not only the first cells do this role, but they also notify other cells so that they are ready to fight the "external enemy", and when this response occurs, inflammation occurs in order to overcome the infection.

At this moment, the so-called "innate and non-specialized immune system" contributes to fighting infection, by eliminating damaged cells and proteins that cannot perform their tasks, and this task continues even when the body is free of the virus.

In the case of elderly people, the immune system becomes unable to get rid of this "waste" because its size increases significantly, according to what explains the researcher specializing in immunology, Eric Verden.

Experts add that when a person ages, what is known as the "unspecialized innate immune system" becomes in a continuous state of alert and inflammation towards external infection, and this response is not beneficial to health.

In addition, the aging cells in the body's tissues secrete inflammatory substances on their own, and the reason is that they experience a great change with age.

For this reason, a person over 65 years of age often has a higher level of immune system proteins such as "cytokines" that are responsible for inflammation.

These proteins related to the immune system are found more in the elderly than in the young, and this factor increases health disorders in this group.

These transformations confuse the messages that the immune system sends to counter the disease, which leads to a failure to reach the desired target.

Atypical symptoms in people infected with the virus

The elderly were classified as “very vulnerable” among various other age groups in societies, because they are most vulnerable to chronic diseases and their complications, to deteriorating functional ability, and disability, and because of discrimination against the elderly and its negative consequences for them.

As health care improves, the number of older people increases year by year, and so do their needs, as well as their contributions to the world. The composition of the world's population has changed dramatically in recent decades. Between 1950 and 2010, life expectancy worldwide increased from 46 to 68 years, and in 2015, the World Health Organization reported that the global average human life expectancy was (71.4) years. 69.1 for males, and 73.8 for females. This is the fastest increase since the 1960s.

The same report also indicates that more than 700 million people in the world are over the age of 60; East and Southeast Asia is home to the largest number of older people (261 million), followed by Europe and North America (more than 200 million), and by 2050 they will number more than two billion. According to the United Nations, all regions of the world will experience an increase in the size of the older population between 2019 and 2050. Globally, the number of people aged 60 or over is expected to rise by 46 percent (from 962 million to 1.4 billion) outnumbering young people, as well as children under the age of 10.

In the Kingdom of Saudi Arabia, the elderly Saudis aged 60 years and over constitute (6.5 percent) of the total population of the Kingdom, according to the demographic survey of the General Authority for Statistics for the year 2017.

Chronic diseases are the most prevalent among the elderly, as for those who enjoy good health in old age, this is the result of following a healthy lifestyle since childhood.

It is known that COVID-19 patient has three symptoms: fever, persistent cough and shortness of breath. But the elderly, who are the age group most at risk of severe complications or death from this condition, may not have any of these three symptoms, but rather have a number of other “atypical” symptoms, which complicates efforts to ensure that they receive appropriate treatment in a timely manner.

Alternatively, older adults may appear "disabled" and more tired than usual and less hungry and may appear more disoriented, restless and unbalanced, and not behave as they normally do early on after contracting the virus. They may sleep more than usual or stop eating, appear unusually apathetic or confused, and may become dizzy and fall. Sometimes older people stop talking or simply collapse.

Their immune response is altered, and they are less likely to show typical signs of infection. Dr. Joseph Oslander, professor of geriatrics at Schmidt College at Florida Atlantic University, says the immune response of a person at an older age may be affected, their response to infection may slow, and their ability to regulate temperature may be altered. He noted that some older adults, whether due to age-related changes or from pre-existing neurological problems such as stroke, may alter their cough reflexes. Others, due to cognitive impairment, may not be able to report their symptoms.

Symptoms that may be missing in the elderly

According to the “timesofindia” website, everyone is equally susceptible to infection with Covid-19, but the risk of complications is higher among the elderly

and people with weakened immunity. Now, a new study indicates that a particular presentation of COVID-19 may appear differently for people who they are over 65 years old, which makes it easy to miss.

As we all know that high fever is the early symptom of corona virus disease , but people over 65 years of age have a low temperature, this can easily be missed or confused with common fever.

According to the Mayo Clinic, a person's normal body temperature remains somewhere between 37°C to 37.2°C, when the temperature rises to (38°C) is considered a fever, however, a study from King's College London indicates that body temperature what is normal for an individual and what constitutes a fever may vary by age.

The researchers participating in the study stated that “aging affects the temperature in health and acute infection,” and based on the results of this study, the team of researchers concluded that 37.2 degrees is equivalent to 38 degrees in the case of people over 65 and can be a sign of infection with corona virus. Low-grade fever and increased risk Data show that about 55 percent of people infected with COVID-19 have a fever in the early days, this can be missed in the case of the elderly because the current temperature is very high, there are high chances that people over 65 years old will not reach the 38 degree mark, will delay the detection of infection caused by the Corona virus and obtaining the appropriate treatment in time, which could put their lives at risk, in the case of the elderly, it is important to be very careful, even the slightest change in body temperature or health should not be taken lightly.

Delirium could be a sign of COVID-19 in the elderly

As appear from the results of the study on the elderly patients with COVID-19, especially those using ventilators, are known to be prone to delirium, and it may be caused due to the spread of the coronavirus.

Precautionary recommendations

As for the recommendations to protect the elderly from the risk of infection with the emerging Coronavirus, and those who suffer from chronic diseases, that is, the most vulnerable to complications when contracting the disease, they are as follows:

- Stay at home and stay away from gatherings.
- Avoid contact with a person with symptoms of the emerging Coronavirus.
- Wash hands with soap and water frequently for 40 seconds, and use hand sanitizer after sneezing or coughing, and before cooking or eating food for 20 seconds.
- Avoid touching eyes, nose and mouth with unwashed hands.
- Covering the mouth and nose when coughing or sneezing with a tissue, or inside the elbow.
- Clean and disinfect frequently touched items and surfaces in the home, using either regular household cleaners or (chlorine) bleach diluted at 250 milliliters (1 cup) of water for every 5 milliliters (1 teaspoon) of bleach, being careful not to mix the bleach Never with other chemical products, and use it in a well-ventilated area.
- Use electronic applications to order food and medicine needs.
- Use apps to deliver your prescription, community medicine consultant.

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