COVID-19 Comorbidities

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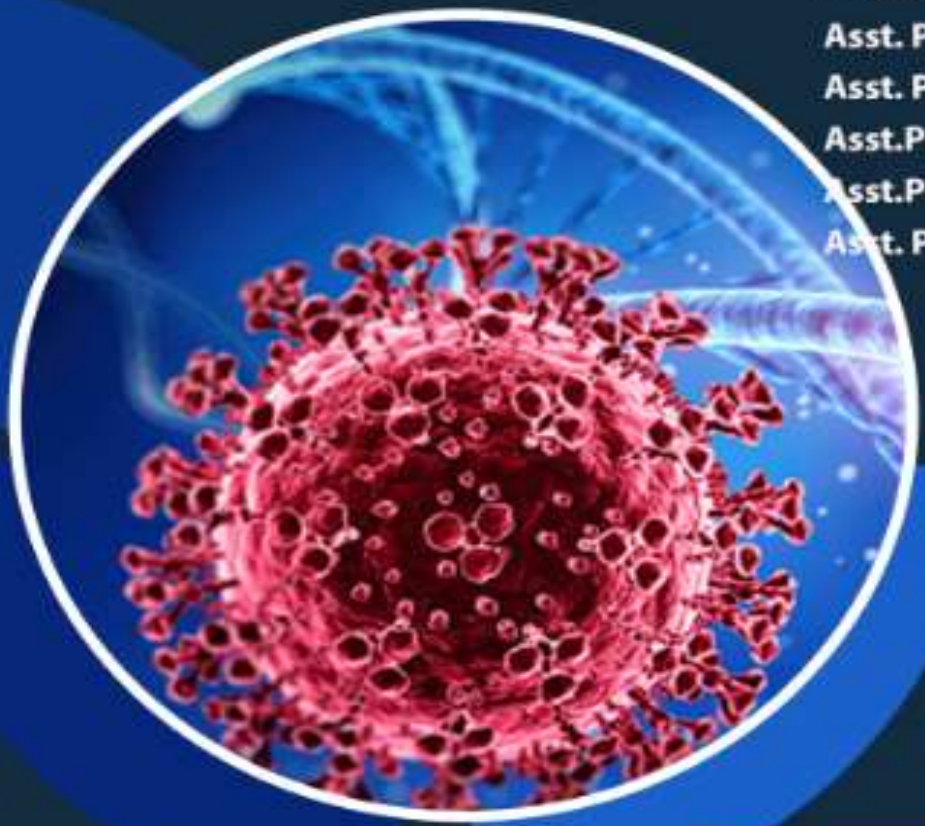
Authors
Prof. Dr. Maitham G. Yousif
Prof. Dr. Abdulnabi J. Abid
Prof. Dr. Fadhil Alamrani
Prof.Dr.Musa N. Mezher
Prof. Dr. Samah A. Kadhum
Prof. Dr. Nawal M. Utba
Prof. Dr. Karar M. Abdul-Sada
Prof.Dr. Habeeb W. Kadhum
Asst. Prof.Dr. Bahaa A. Razzaq
Asst. Prof.Dr.Ghaidaa J. M.
Asst.Prof. Dr. Mona N. Al-Terehi
Asst.Prof. Dr. Huda R.Hashim
Asst. Prof. Dr. Zahraa H. Alqaim



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Authors

Prof. Dr. Maitham Ghaly Yousif

Prof. Dr. Abdulnabi Jawid Abid

Prof. Dr. Fadhil Alamrani

Prof.Dr.Musa Nima Mezher

Prof. Dr. Samah Ahmed Kadhum

Prof. Dr. Nawal Mohammed Utba

Prof. Dr. Karar Mohammed Abdul-Sada

Prof.Dr. Habeeb Waseel Kadhum Shubber

Assistant Prof. Dr. Bahaa A. Razzaq

Assistant Prof.Dr.Ghaidaa Jihadi Mohammed

Assistant Prof. Dr. Mona N. Al-Terehi

Assistant Prof. Dr. Huda Raheem Hashim Al-Mosway

Assistant. Prof. Dr. Zahraa Haleem Alqaim

List of Contact

Chapter One

Introduction of COVID-19 comorbidities

Prof. Dr. Maitham Ghaly yousif

Medical Microbiology and immunology

University of Al-Qadisiyah College of Science/Department of Biology

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 R0 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 womenwhich 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).

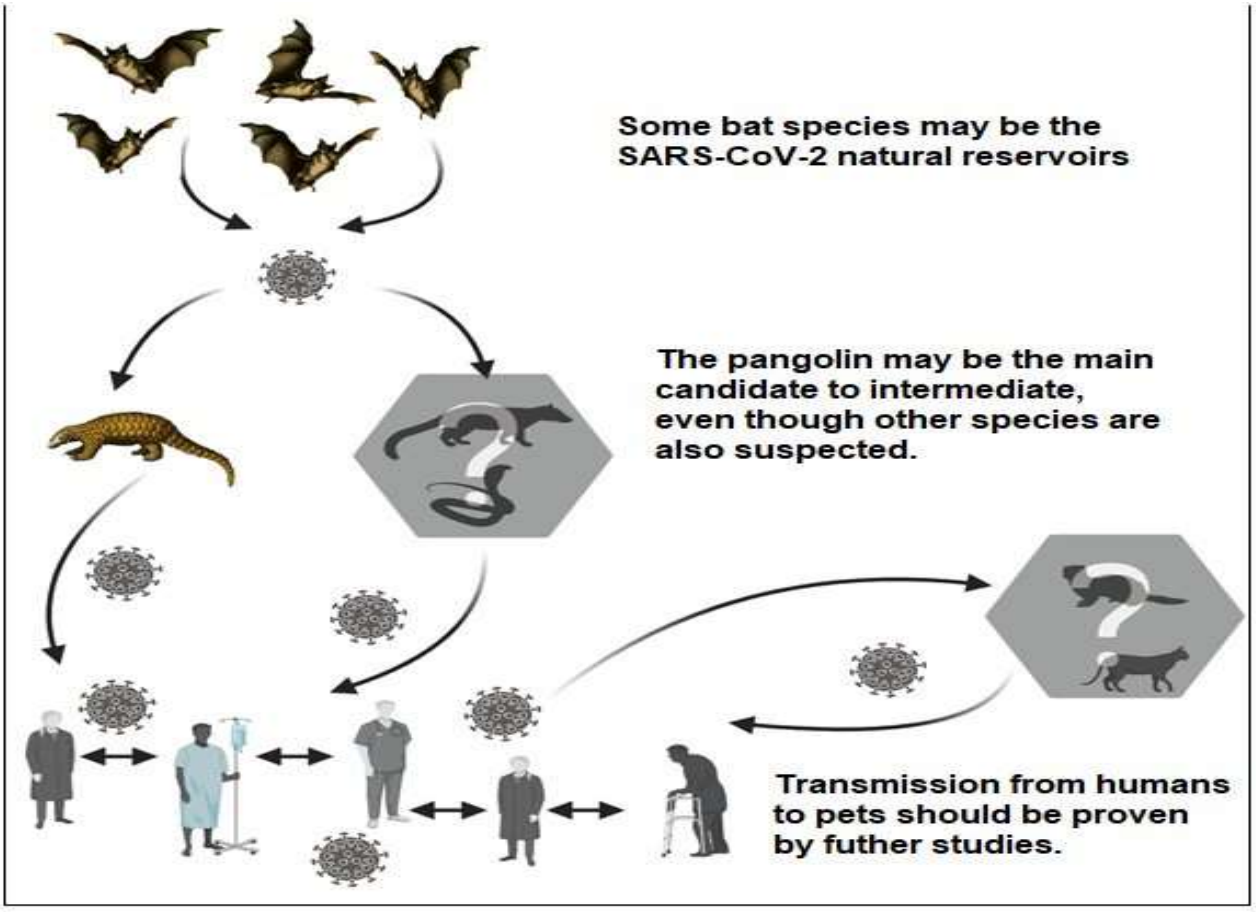


Figure 1. SARS-CoV-2 coronavirus is a zoonotic agent that has been transmitted from animals to humans. Figure created with computer program BioRender.com

References:

1-Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis, and practical considerations. Diabetes Metab Syndr Clin Res Rev. 2020;14(4):303–10.

2-Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395 (10223), 497-506.

3-Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020; 27 (2), taaa021.

4-van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020; 382 (16), 1564-7.

5-Chan JF-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020; 395 (10223), 514-23.

6-Li P, Fu J-B, Li K-F, et al. Transmission of COVID-19 in the terminal stage of incubation period: a familial cluster. Int J Infect Dis. 2020; 96, 452-3.

7-Huang R, Zhu L, Xue L, et al. Clinical findings of patients with coronavirus disease 2019 in Jiangsu Province, China: a retrospective, multi-center study. 2020.

8-Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus–Infected pneumonia in Wuhan, China. JAMA2020;323: 1061-9. doi:10.1001/jama. 2020. 1585 pmid:32031570.

9-Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA2020. doi:10.1001/jama.2020.4344.

10-Kobayashi T, Jung SM, Linton NM, et al. Communicating the risk of death from novel coronavirus disease (COVID-19). J Clin Med2020;9:580. doi: 10.3390/ jcm9020580.

11- Fang L, Gao P,Bao H, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med2018;6:421-30. doi:10.1016/S2213-2600(18)30103-6.

12-Li D, Lv J, Liu F, et al. Hypertension burden and control in mainland China: Analysis of nationwide data 2003-2012. Int J Cardiol2015;184:637-44. doi:10.1016/j.ijcard. 2015. 03.045.

13- Bonilla-Aldana D, Villamil-Gómez W, Rabaan A, Rodríguez-Morales J. Una nueva zoonosis viral de preocupación global: COVID-19, enfermedad por coronavirus 2019. Iatreia 2020;33(2): 107-10.

14- WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. WHO Speeches. 2020. Disponible en: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---20-march-2020 (consultado el 28 de abril de 2020).
15-Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020; 87(4): 281-6. DOI: https://doi.org/10.1007/s12098-020-03263-6.
16- Cortés ME. Enfermedad por coronavirus 2019 (COVID-19): Importancia de la comunicación científica y de la enseñanza actualizada de las zoonosis. Rev Peru Investig Salud. 2020; 4(2): 87-8.
17-Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579(7798): 270-3.
18- Zhang Y-Z, Holmes EC. A Genomic Perspective on the Origin and Emergence of SARS-CoV-2. Cell 2020; 181(2): 223-7.

Chapter Two

Chronic Respiratory Diseases and COVID-19

Assistant Prof.Dr.Ghaidaa Jihadi Mohammed

University of Al-Qadisiyah College of Science Department of Biology

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 be 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 requirement 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 thoracoscopic 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 thromobembolism(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 carried out instead of standard nonconstrant 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 inclusive enoxaparin 0.4 mg once a day for standard risk patients with creatine clearance (CrCl) > 30 ml/min and o.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 throboprophylaxis 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 .

Reference

1. Ahrenfeldt LJ, Nielsen CR, Möller S, et al.Burden and prevalence of risk factors for severe COVID-19 disease in the ageing European population - A SHARE-based analysis. Res Sq 2020.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China Lancet Lond Engl 2020; 395: 497–506. doi:10.1016/S0140-6736(20)30183-5
3. Chung M, Bernheim A, Mei X, et al. CT Imaging features of 2019 novel coronavirus (2019-nCoV). Radiology 2020; 295: 202–207. doi:10.1148/ radiol. 2020200230
4. Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation 2020; 142: 184–186. doi:10.1161/CIRCULATIONAHA.120.047430
5. Petersen E, Koopmans M, Go U, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. Lancet Infect Dis 2020; 20: e238–e244. doi:10.1016/S1473-3099(20)30484-9
6. Burn E, You SC, Sena AG, et al.An international characterisation of patients hospitalised with COVID-19 and a comparison with those previously hospitalised with influenza. MedRxiv Prepr Serv Health Sci 2020.
7. Restrepo MI, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. Eur Respir J. 2006;28:346–51. doi: 10.1183/09031936. 06. 00131905.
8. Lippi G, Henry BM. Chronic Obstructive Pulmonary Disease is associated with severe coronavirus disease 2019 (COVID-19) Respir Med. 2020 doi: 10.1016/j.rmed.2020.105941. doi: 10.1016/j. rmed.2020. 105941.
9. Guan WJ, Ni Z, Hu Y, et al. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 doi: 10.1056/ NEJMoa 2002032.
10. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalance of underlying diease in hospitalized patients with COVID-19: A systematic review and meta-analysis. Arch Acad Emerg Med. 8:e35. 202.

11. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY) 2020; 12:6049–57. doi: 10.18632/aging.103000.
12. Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of Covid-19: A systemic review and meta-analysis. J Med Virol. 2020;15 doi: 10.1002/jmv.25889. doi: 10.1002/ jmv.25889.
13. Leung JM, Yang CX, Tam A, et al. ACE-2 Expression in the small airway epithelia and smokers and COPD patients: Implications for COVID-19. Eur Respir J. 2020. pii.2000688.
14. Global Initiative for Chronic Obstructive Lung Disease. [Access date: 23 April 2020]. Available from: https://goldcopd.org/gold-covid19-guidance
15. COVID-19 rapid guideline: community- based care of patients with chronic obstructive pulmonary disease (COPD) NICE guideline. Published: 9 April 2020 Available from: www.nice. org.uk/ guidance/ng168.
16. Bhutani M, Hernandez P, Bourbeau J, et al. Addressing therapeutic questions to help Canadian health care professionals optimize COPD management for their patients during the COVID-19 pandemic. Canadian Journal of Respiratory Critiacal Care and Sleep Medicine. [Access date: 23 April 2020]. In press. Version 1.0 submitted for publication in the CJRCCSM on April 8, 2020. Available from: https://cts-sct.ca/covid-19/covid-19-copd/
17. Guidance for the role and use of non-invasive respiratory support in adult patients with COVID-19 (confirmed or suspected) Apr 6, 2020. [Access date: 23 April 2020]. Ver 3. Available from: https://www.england.nhs.uk/ coronavirus/wp-content/uploads/sites/52/2020/03/specialty-guide-NIV-respiratory - support- and-coronavirus-v3.pdf.
18. Celebioglu E. Asthma and COVID-19. Asthma Allergy Immunol. 2020;18:56–7. doi: 10.21911/aai.531.
19. Zhang IJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, Chine. Allergy. 2020;75:1730–41. doi: 10.1111/all.14238.
20. Global Initiative for Asthma. [Access date: 20.4.2020]. Available from: https:// ginasthma.org/covid-19-gina-answer-to-frequently-asked-question - on-asthma-management/
21. Licskai C, Yang CL, Ducharme FM, et al. Addressing therapeutic questions to help Canadian health care professionals optimize asthma management for their patients during the COVID-19 pandemic. Canadian Journal of Respiratory Critiacal Care and Sleep Medicine. [Access date: 23

April 2020]. In press. Version 1.0 submitted for publication in the CJRCCSM on April 7 2020. Available from: https://cts-sct.ca/covid-19/covid-19-asthma/

22. Turkish National Society of Allergy and Clinical Immunology. [Accessed date: 20.4.2020]. Available from: https://www.aid.org.tr/covid-19-pandemisinde-agır-astım-yonetimi/
23. Advice for healthcare professionals treating people with asthma (adults) in relation to COVID-19. [Access date: 23 April 2020]. Available from: https:// www.brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community/
24. British Thoracic Society Advice for managing Intersititial lung disease patients during COVID-19 pandemic. [Access date: 20 April 2020]. Available from: https://brit-thoracic.org.uk/about-us/covid-19 information-for-the-respiratory-community/
25. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335–7. doi: 10.1016/ S1470-2045(20)30096-6.
26. Lung cancer and mesothelioma service guidance during the COVID-19 pandemic. [Access date: 21 April 2020]. Available from: https://brit-thoracic. org.uk/about-us/covid-19-information-for-the-respiratory-community
27. Cafarotti S, Patella M. Lung cancer surgical management during the outbreak of COVID-19. J Thorac Oncol. 2020;15:e81. doi: 10.1016/j. jtho.2020.03.027.
28. Calabro L, Peters S, Soria JC, et al. Challenges in lung cancer theraphy during the COVID-19 pandemic. Lancet Respir Med. 2020 doi: 10.1016/S2213-2600 (20)30170-3.
29. Simpson S, Kay FU, Abbara S, et al. Radiological Society of North America Expert Consensus Statement on reporting chest CT findings related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA – Secondary Publication. J Thorac Imaging 2020 ; 35: 219–227. doi:10.1097/ RTI. 0000000000000524
30. Jany, B; Welte, T. "Pleural Effusion in Adults—Etiology, Diagnosis, and Treatment". Deutsches Ärzteblatt International.2019; **116** (21): 377–386. doi: 10.3238 /arztebl.2019.0377
31. Pleural services during the COVID-19 Pandemic. [Access date: 24 April 2020]. Available from: https://brit-thoracic.org.uk/about-us/covid-19-information - for- the- respiratory - community/
32. Ye Zheng, Zhang Yun, Wang Yi, et al. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): A pictorial review. Eur Radiol. 2020;30:4381–9. doi: 10.1007/s00330-020-06801-0.

33. Bintcliffe, Oliver; Maskell, Nick (8 May 2014). "Spontaneous pneumothorax". BMJ (Clinical Research Ed.). 348: g2928. doi:10.1136 / bmj.g 2928
34. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow up. J Am Coll Cardiol. 2020;75:2950–73. doi: 10.1016/j.jacc. 2020.04.031.
35. Fa Klok, Kruip MJHA, van der meer NJM, et al. Incidens of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145–7. doi: 10.1016/j.thromres.2020.04.013.
36. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844–7. doi: 10.1111/jth.14768.
37. Rotzinger DC, Beigelman-Aubry C, von Garnier C, Qanadli SD. Pulmonary embolism in patients with COVID-19: Time to change the paradigm of computed tomography. Thromb Res. 2020;190:58–9. doi: 10.1016/j.thromres. 2020.04.011.
38. Obi AT, Barnes GD, Wakefield TW, et al. Practical diagnosis and treatment of suspected venous thromboembolism during COVID-19 pandemic. J Vasc Surg Venous Lymphat Disord. 2020;8:526–34. doi: 10.1016/j.jvsv.2020.04.009.
39. BTS Guidance on venous thromboembolic disease in patients with COVID-19. [Access date: 24 April 2020]. Available from: https://brit-thoracic.org.uk/ about-us/covid-19-information-for-the-respiratory-community/

Chapter Three

Chronic liver disease and its relationship to COVID-19

Prof.Dr.Musa Nima Mezher

University of kufa College of Science Department of Biology

Microbiology and Immunology

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 fibrinolyticpathways 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.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. (2020).

2. Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease 2019 (COVID-19) and prevalence of chronic liver disease: a meta-analysis. Liver Int. (2020) 40:1316–20.

3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.*. . Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. (2020) 2020:e201585.

4. Fan Z, Chen L, Li J, Tian C, Zhang Y, Huang S, *et al.* . Clinical features of COVID-19 related liver damage. medRxiv. (2020).

5- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al.* . Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. (2020) 8:475–81.

6. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, *et al.* Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. (2020) 368:m792

7. Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, *et al.* . Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Rep. (2020) 2:100113.

8. Ramadori G. Hypoalbuminemia: an underestimated, vital characteristic of hospitalized COVID-19 positive patients?. Hepatoma Res. (2020)

9. Goldsmith CS, Tatti KM, Ksiazek TG, Rollin PE, Comer JA, Lee WW, *et al*. . Ultrastructural characterization of SARS coronavirus. Emerging Infect Dis. (2004) 10:320–6. 10.3201/eid1002.030913

10. Su L, Ma X, Yu H, Zhang Z, Bian P., Han Y, *et al*. The different clinical characteristics of corona virus disease cases between children and their families in China - the character of children with COVID-19. Emerg Microbes Infect. (2020) 9:707–13. 10.1080/22221751.2020.1744483

11. Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, *et al*. . COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy. (2020)

12. Omrani-Nava V, Maleki I, Ahmadi A, Moosazadeh M, Hedayatizadeh-Omran A, Roozbeh F, *et al*. Evaluation of hepatic enzymes changes and association with prognosis in COVID-19 patients. Hepat Mon. (2020)

13. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, *et al*. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. (2020) 20:425–34. 10.1016/S1473-3099(20)30086-4

14. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. (2020) 40:998–1004. 10.1111/liv.14435

15. Banales JM, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. Nat Rev Gastroenterol Hepatol. (2019) 16:269–81.

16. . Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. (2020) 8:e21. 10.1016/S2213-2600(20)30116-8

17. Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, *et al*. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol. (2020) 10.1016/j.jhep.2020.03.044.

18. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. (2020) 5:428–30.

19. Bangash MN,Patel J,Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol.(2020) 5:529–30. 10.1016/S2468-1253(20)30084-4

20. Gacouin A, Locufier M, Uhel F, Letheulle J, Bouju P, Fillatre P, *et al*. Liver cirrhosis is independently associated with 90-day mortality in ARDS patients. Shock. (2016) 45:16–21.

21. Su TH, Kao JH. The clinical manifestations and management of COVID-19-related liver injury. J Formos Med Assoc. (2020) 119:1016–8. 10.1016/j.jfma.2020.04.020

22. Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, *et al*. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. Hepatology. (2020). 10.1002/hep.31281.

23. Zhou Q, Chen V, Shannon CP, Wei XS, Xiang X, Wang X, *et al*. Interferon-a2b treatment for COVID-19. Front Immunol. (2020) 11:1061

24. El-Lababidia RM, Mooty M, Maria-Fernanda Bonilla MF, Nouran Salem MNM. Treatment of severe pneumonia due to COVID-19 with peginterferon alfa 2a. IDCases. (2020) 21:e00837.

27. Varghese L, Zachariah P, Vargas C, LaRussa P, Demmer RT, Furuya YE, et al. . Epidemiology and clinical features of human coronaviruses in the pediatric population. J Pediat Inf Dis Soc. (2018) 7:151–8. 10.1093/jpids/pix027

28. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J. (2020) 39:355–68. 10.1097.

29. Ebrahimi M, Saki A, rahim F. Laboratory findings, signs and symptoms, clinical outcomes of Patients with COVID-19 Infection: an updated systematic review and meta-analysis. medRxiv. (2020). 10.1101/2020.03.25.20043703 .

30. Rismanbaf A, Zarei S. Liver and kidney injuries in COVID-19 and their effects on drug therapy; a letter to editor. Arch Acad Emerg Med. (2020) 8:e17

Chapter Four

Gender and Covid-19

Prof. Dr. Abdulnabi Jawid Abid

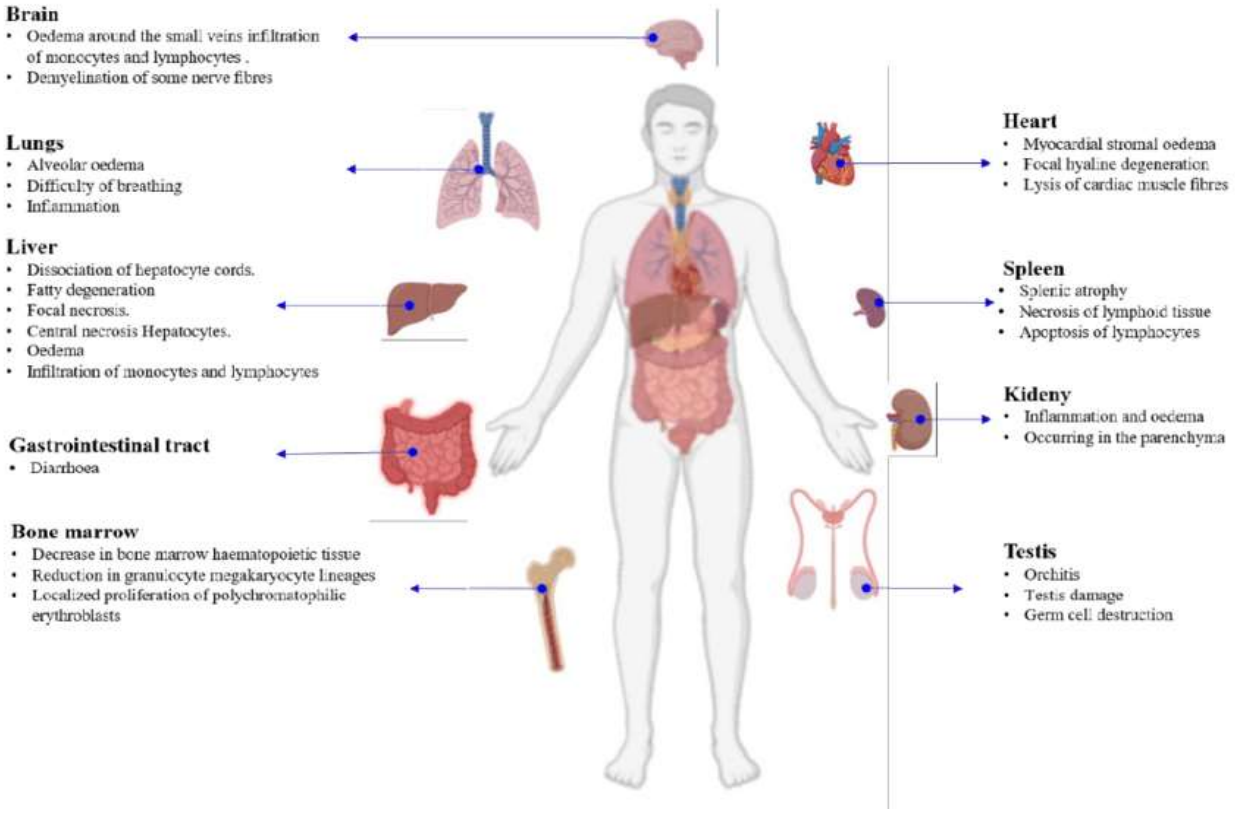
Microbiology and immunology

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 sever 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 spreed 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 mortilty 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-psycological 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

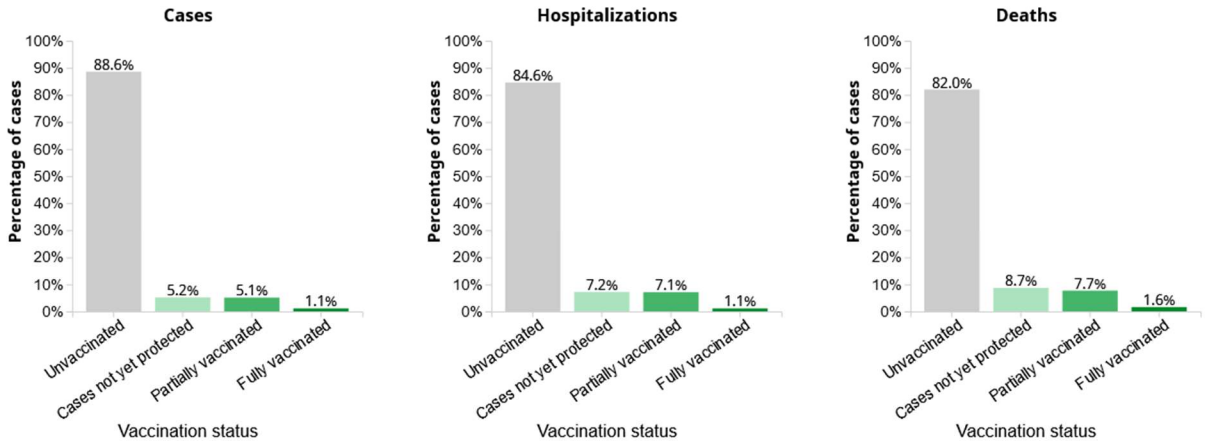
One of the most results of Pandemic covid -19 is short time work or keep home for a long time ,the presence of all family individuals at same and small space place led to social problem among family individuals ,women generaly are the most victim of these closeness. This issue is appear clearly in traditional 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 abilty to protection although the differences in their preparation .Although the effected role of all vacines 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 female1.4 % 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).

References

1.Wadman ,M, Couzin-Frankel J, Kaiser J, at al(2020). How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes. Jun;2020https://www.sciencemag.org/news/2020/04/.

2. Belmehdi O , Hakkour,M 2 , El Omari,N 3 , et al (2021) Molecular Structure, Pathophysiology, and Diagnosis of COVID-19 .Biointerface Research in Applied Chemistry,11(3).:10215-10237. https://doi.org/10.33263/BRIAC113.1021510237

3. Warrington, C. (2020, October 4). "It's essential that intervention is possible": Women, isolation, and suicide. The Independent. https://www.independent.co.uk/life-style/women-suicide-taking-own-lives-pandemic-loneliness-isolation-coronavirus-help-b673630.html

4. Ray, R. (2020). Why are Blacks dying at higher rates from COVID-19? The Brookings Institution. https://www.brookings.edu/blog/fixgov/2020/04/09/why-are-blacks-dying-at-higher-rates-from-covid-19

5. Baran,Oand Aykac,A,(2020). The effect of fear of covid-19 transmission on male sexual behaviour: A cross-sectional survey study. Int J Clin Pract. 2021 Apr;75(4):e13889.doi: 10.1111/ijcp.13889. Epub 2020 Dec 12.

6. Li W, Li G, Xin C, Wang Y, Yang S. Challenges in the practice of sexual medicine in the time of COVID-19 in China. J Sex Med. 2020;17:1225–1228. [PMC free article] [PubMed]

7. Arafat SMY, Alradie-Mohamed A, Kar SK, Sharma P, Kabir R. Does COVID-19 pandemic affect sexual behaviour? A cross-sectional, cross-national online survey. Psychiatry Res. 2020;289:113050. [PMC free article] [PubMed] [Google Scholar]

8. Jacob L, Smith L, Butler L,et al. COVID-19 social distancing and sexual activity in a sample of the British Public. J Sex Med. 2020;17:1229-1236. [PMC free article] [PubMed]

9.Wenham C, Smith J, Morgan R, et al. COVID-19: the gendered impacts of the outbreak. Lancet 2020;395:846–8.

10. Abate,BB ; Kassie ,Am ; Kassaw,MW ,et al (2020).Sex difference in coronavirus disease (COVID-19)a systematic review and meta- analysis.BMJ 2020;10:e040129.doi:10.1136/bmjopen-2020-040129.

11. Mehra MR, Desai SS, Kuy S, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2007621

12. Italian Health Institute (ISS). Covid-19 13 May 2020 report. https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_13maggio%20ITA.pdf. Last visited 20 May, 2020.

13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.

14. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16:626–38. https://doi.org/10.1038/nri.2016.90.

15.Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region—case series. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2004500.

16. Gausman J, Langer A. Sex and gender disparities in the COVID-19 pandemic. J Women's Health. 2020;29:465–6. https://doi.org/10.1089/jwh.2020.8472.

17. Knowlton AA, Lee AR. Estrogen and the cardiovascular system. Pharmacol Ther. 2012;135:54–70. https://doi.org/10.1016/j.pharmthera.2012.03.007.

18. Mikula, G., Riederer, B., Bodi, O. (2011). Perceived justice in the division of domestic labour: Actor and partner effects. Personal Relationships, 19, 680–695

19. Dang,HH and Nguyen,CV (2020). Gender Inequality during the COVID-19 Pandemic: Income, Expenditure, Savings, and Job Loss. IZA Institute of labor economics, DP No. 13824.

20. Azcona, G., Bhatt, A., Encarnacion, J., Plazaola-Castano, J., Seck, P., Staab, S., Turquet, L. (2020). From insights to action: Gender equality in the wake of COVID-19. UN Women. https://www.unwomen.org.

21. Mahmood ,KI;Sherzad ,AS;M-Amen,KM et al (2021)The Impact of COVID-19 Related Lockdown on the Prevalence of Spousal Violence Against Women in Kurdistan Region of Iraq. Journal of Interpersonal Violence, First Published 26 Feb 2021:1-25.

22. United Nation In Kenya (2020). AN ASSESSMENT OF THE GENDERED EFFECTS OF THE CCOVID 19 PANDEMIC ON HOUSEHOLDS.GENDER PRESPECTIVE. https://data.unwomen.org/sites/default/files/documents/Publications/COVID-19_Kenya.pdf.

23. PHAC Report Government of Canada(2021)COVID-19 daily epidemiology update Updated: September 3, 2021, https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.htm

24.Central for Disaster Philanthropy(CDP)(2021).Disaster Covid -19Coronavirus.September 8,2021.

Chapter Five

Malignancy comorbidity of covid-19

Prof. Dr. Samah Ahmed Kadhum

Department of Clinical Laboratory Sciences

College of Pharmacy University of Babylon

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 dead 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 immunosurveillan is very important to control and reduse the infection through anti-tumorigenic role, which includes NF-kB 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-dimmer-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 paws 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.

References:

1. Pathania AS, Prathipati P, Abdul BAA, Chava S, Katta SS, Gupta SC, Gangula PR, Pandey MK, Durden DL, Byrareddy SN, and Challagundla KB. COVID-19 and Cancer Comorbidity: Therapeutic Opportunities and Challenges. Theranosticsv 2021; 11(2): 731–753.

2. Liang W, Guan W, Chen R, Wang W, Li J, Xu K. Caichen L, Qing A, Weixiang L, Hengrui L, Shiyue L, and Jianxing H. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. The Lancet Oncology. 2020;21:335–7

3. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, *et al*. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov. 2020;10:783–91.

4. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F. *et al*. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol. 2020;7:e737-e45.

5. Sanchez-Pina JM, Rodriguez Rodriguez M, Castro Quismondo N, Gil Manso R, Colmenares R, Gil Alos D. *et al.* Clinical course and risk factors for mortality from COVID-19 in patients with haematological malignancies. Eur J Haematol. 2020;105:597-607.

6. Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A. *et al*. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. Cancer Discov. 2020;10:935–41.

7. Fillmore NR, La J, Szalat RE, Tuck DP, Nguyen V, Yildirim C, Do NV, Brophy MT and Munshi NC. Prevalence and Outcome of COVID-19 Infection in Cancer Patients: A National Veterans Affairs Study. JNCI: 2021; 113(6):691–698.

8. Martin S, Kaeuffer C, Leyendecker P, Tuzin N, Tazi Y, Schaff-Wendling F, Kleinheny T, Husson-Wetzel S, Pamart G ,Limacher JM, Clerc O, Dicop E, Kurtz JE, Barthélémy P and Ganter J. COVID-19 in Patients with Cancer: A Retrospective Study of 212 Cases from a French SARS-CoV-2 Cluster During the First Wave of the COVID-19 Pandemic. The Oncologist. 2021,26(9):e1656-e1659.

9. Lisa Derosa, Cléa Melenotte, Franck Griscelli, Bertrand Gachot, Aurélien Marabelle, Guido Kroemer & Zitvogel L. The immuno-oncological challenge of COVID-19. Nature Cancer, 2020, 1: 946–964

10. Garassino MC, Whisenant JG, Huang LC, Trama A, Torri V, Agustoni F, Baena J, Banna G, Berardi R, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol. 2020 , 21(7):914-922.

11. Allen B, Hiam K, Burnett E *et al*. Systemic dysfunction and plasticity of the immune macroenvironment in cancer models. Nat Med 2020; 26: 1125– 1134.

12- Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, *et al*. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020; 130:2620–29.

13- Mao R, Liang J, Shen J, Ghosh S, Zhu LR, Yang H, *et.al*. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol. 2020; 5:425–27.

14- Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K, Lu H, Liu J, Yang J, Dong Y, Pan D, Shu C, Li J, *et al*.. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020; 21:904–13.

15- Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020; 71:762–68.

16- Shah V, Ko Ko T, Zuckerman M, *et al*. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King's College Hospital experience. Br J Haematol. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32526039.

17- Yang K, Sheng Y, Huang C, *et al*. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):904-913. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32479787

18- Rubinstein SM, Steinharter JA, Warner J, Rini BI, Peters S, Choueiri TK. The COVID-19 and Cancer Consortium: A Collaborative Effort to Understand the Effects of COVID-19 on Patients with Cancer. Cancer Cell. 2020;37:738–41.

19- Lau SK, Woo PC, Yip CC, Tse H, Tsoi HW, Cheng VC. *et al.* Coronavirus HKU1 and other coronavirus infections in Hong Kong. J Clin Microbiol. 2006;44:2063–71.

20- Kumar D, Dey T. Treatment delays in oncology patients during COVID-19 pandemic: A perspective. J Glob Health. 2020;10:010367.

Chapter Six

The Genetic Factors Associated with Risk of COVID-19 Mortality

Asst. Prof. Dr. Mona N. Al-Terehi

University of Babylon College of Science

Biotechnology Branch

The Genetic Factors Associated with Risk of COVID-19 Mortality

Introduction

The SARC-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 COVI-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:

2.1Interleukin 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 .

2.2Tumor 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 COVD-19 infection in different population .

2.3The Interleukin-1 gene (IL-1)

Interleukin-1 (IL-1) is a prototype pro-inflammatory cytokine, two forms are existed; IL-1alpha and IL-1beta, 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 (FcγR) 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 .

4.2The 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 ATT 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 region*s* 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 and 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 SARC (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.

References

1- Gao J, Zhu C, Zhu Z, Tang L, Liu L, Wen L, et al. The human leukocyte antigen and genetic susceptibility in human diseases. J Bio-X Res (2019) 2:112–20. doi: 10.1097/jbr.0000000000000044.

2- Turrieta-Zuazo I, Rita CG, García-Soidán A, de Malet Pintos-Fonseca A, Alonso-Alarcón N, Pariente-Rodríguez R, et al. Possible role of HLA class-I genotype in SARS-CoV-2 infection and progression: A pilot study in a

cohort of Covid-19 Spanish patients. Clin Immunol (2020) 219:108572. doi: 10.1016/j.clim.2020.108572

3- Tavasolian F, Rashidi M, Reza Hatam G, Jeddi M, Zavaran Hosseini A, Hussain Mosawi S, et al. Immune Response, and Susceptibility to COVID-19. Front Immunol (2021) 11:601886. doi: 10.3389/fimmu.2020.601886

4- Fricke-Galindo Ingrid, Falfán-Valencia Ramcés, TITLE=Genetics Insight for COVID-19 Susceptibility and Severity: A Review JOURNAL=Frontiers in Immunology,12, 2021, 1057

5- Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the Eye of the Cytokine Storm. Microbiol Mol Biol Rev (2012) 76:16–32. doi: 10.1128/mmbr.05015-11

6- Sanderson SC, Kumari M, Brunner EJ, Miller MA, Rumley A, Lowe GD, et al.Association between IL6 gene variants -174G>C and -572G>C and serum IL-6levels: Interactions with social position in the Whitehall II cohort. Atherosclerosis (2009) 204:459–64. doi: 10.1016/j.atherosclerosis.2008.09.019

7- Brull DJ, Montgomery HE, Sanders J, Dhamrait S, Luong L, Rumley A, et al. Interleukin-6 gene -174G > C and -572G > C promoter polymorphisms are strong predictors of plasma interleukin-6 levels after coronary artery bypass surgery. Arterioscler Thromb Vasc Biol (2001) 21:1458–63. doi: 10.1161/hq0901.094280

8- Doyle WJ, Casselbrant ML, Li-Korotky HS, Cullen Doyle AP, Lo CY, Turner R, et al. The interleukin 6-174 C/C genotype predicts greater rhinovirus illness. J Infect Dis (2010) 201:199–206. doi: 10.1086/649559

9- Patel JA, Nair S, Revai K, Grady J, Saeed K, Matalon R, et al. Association of proinflammatory cytokine gene polymorphisms with susceptibility to otitis media. Pediatrics (2006) 118:2273–9. doi: 10.1542/peds.2006-0764

10- Revai K, Patel JA, Grady JJ, Nair S, Matalon R, Chonmaitree T. Association between cytokine gene polymorphisms and risk for upper respiratory tract infection and acute otitis media. Clin Infect Dis (2009) 49:257–61. doi: 10.1086/599833

11- Michalek J, Svetlikova P, Fedora M, Klimovic M, Klapacova L, Bartosova D, et al.Interleukin-6 gene variants and the risk of sepsis development in children. Hum Immunol (2007) 68:756–60. doi: 10.1016/j.humimm.2007.06.003

12- Humphries SE, Luong LA, Ogg MS, Hawe E, Miller GJ. The interleukin-6 -174 G/C promoter polymorphism is associated with risk of coronary heart disease and systolic blood pressure in healthy men. Eur Heart J (2001) 22:2243–52. doi: 10.1053/euhj.2001.2678

13- Eze IC, Imboden M, Kumar A, Adam M, von Eckardstein A, Stolz D, et al. A common functional variant on the pro-inflammatory Interleukin-6 gene may modify the association between long-term PM10 exposure and diabetes. Environ Heal (2016) 15:39. doi: 10.1186/s12940-016-0120-5

14- Terry CF, Loukaci V, Green FR. Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. J Biol Chem (2000) 275:18138–44. doi: 10.1074/jbc.M000379200

15- Strafella C, Caputo V, Termine A, Barati S, Caltagirone C, Giardina E, et al. Investigation of genetic variations of IL6 and IL6r as potential prognostic and pharmacogenetics biomarkers: Implications for covid-19 and neuroinflammatory disorders. Life (2020) 10:1–10. doi: 10.3390/ life10120351

16- Saleh, A., Sultan, A., Elashry, M. A., Farag, A., Mortada, M. I., Ghannam, M. A., Saed, A. M., & Ghoneem, S. (2020). Association of TNF-α G-308 a Promoter Polymorphism with the Course and Outcome of COVID-19 Patients. *Immunological investigations*, 1–12. Advance online publication. https://doi.org/10.1080/08820139.2020.1851709

17- Van Minkelen R, De Visser MCH, Houwing-Duistermaat JJ, Vos HL, Bertina RM, Rosendaal FR. Haplotypes of IL1B, IL1RN, IL1R1, and IL1R2 and the risk of venous thrombosis. Arterioscler Thromb Vasc Biol (2007) 27:1486–91. doi: 10.1161/ATVBAHA.107.140384

18- Dettke M, Loibner H. Different types of FC gamma-receptors are involved in anti-Lewis Y antibody induced effector functions in vitro. Br J Cancer (2000) 82:441–5. doi: 10.1054/bjoc.1999.0940

19- Hoffmann SC, Stanley EM, Cox ED, DiMercurio BS, Koziol DE, Harlan DM, et al. Ethnicity greatly influences cytokine gene polymorphism distribution. Am J Transpl (2002) 2:560–7. doi: 10.1034/j.1600-6143.2002.20611.x

20- Sankaran D, Asderakis A, Ashraf S, Roberts ISD, Short CD, Dyer PA, et al. Cytokine gene polymorphisms predict acute graft rejection following renal transplantation. Kidney Int (1999) 56:281–8. doi: 10.1046/j.1523-1755.1999.00536.x.

21- Dettke M, Loibner H. Different types of FC gamma-receptors are involved in anti-Lewis Y antibody induced effector functions in vitro. Br J Cancer (2000) 82:441–5. doi: 10.1054/bjoc.1999.0940.

22- Zúñiga J, Buendía-Roldán I, Zhao Y, Jiménez L, Torres D, Romo J, et al. Genetic variants associated with severe pneumonia in A/H1N1 influenza infection. Eur Respir J (2012) 39:604–10. doi: 10.1183/09031936.00020611.

23- Hang Q, Liu Z, Moncada-Velez M, Chen J, Ogishi M, Bigio B, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science (2020) 370:eabd4570. doi: 10.1126/science.abd4570

24- Fallerini C, Daga S, Mantovani S, Benetti E, Picchiotti N, Francisci D, et al. Association of Toll-like receptor 7 variants with life-threatening COVID-19 disease in males: findings from a nested case-control study. Elife (2021) 10: e67569. doi: 10.7554/eLife.67569.

25- Manchanda PK, Kumar A, Bid HK, Mittal RD. Interleukin-1band receptor antagonist (IL-1Ra) gene polymorphisms and the prediction of the risk of end-stage renal disease. Biomarkers (2006) 11:164–73. doi: 10.1080/ 13547500500525383.

26- Muus C, Luecken M, Eraslan G, Waghray A, Heimberg G, Sikkema L, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. bioRxiv (2020). doi: 10.1101/2020.04.19.049254.

27- Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of

the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res (2020) 126:1456–74. doi: 10.1161/ CIRCRESAHA.120.317015.

28- Debnath M, Banerjee M, Berk M. Genetic gateways to COVID-19 infection: Implications for risk, severity, and outcomes. FASEB J (2020) 34:8787–95. doi: 10.1096/fj.202001115R

29- Asselta R, Paraboschi EM, Mantovani A, Duga S. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY) (2020) 12:10087–98. doi: 10.18632/aging.103415.

30- Elisa B, Rossella T, Ottavia S, Andrea C, Giovanni B, Alessandro B, et al. ACE2 gene variants may underlie interindividual variability and susceptibility to COVID-19 in the Italian population. medRxiv (2020) 28:1602–14. doi: 10.1101/2020.04.03.20047977 04.03.20047977.

31- Othman H, Bouslama Z, Brandenburg JT, da Rocha J, Hamdi Y, Ghedira K, et al. Interaction of the spike protein RBD from SARS-CoV-2 with ACE2: Similarity with SARS-CoV, hot-spot analysis and effect of the receptor polymorphism. Biochem Biophys Res Commun (2020) 527:702–8. doi: 10.1016/j.bbrc.2020.05.028.

32- Delanghe JR, Speeckaert MM, De Buyzere ML. The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. Clin Chim Acta (2020) 505:192–3. doi: 10.1016/ j.cca.2020.03.031

33- Bosso M, Thanaraj TA, Abu-Farha M, Alanbaei M, Abubaker J, Al-Mulla F. The Two Faces of ACE2: The Role of ACE2 Receptor and Its Polymorphisms in Hypertension and COVID-19. Mol Ther - Methods Clin Dev (2020) 18:321–7. doi: 10.1016/j.omtm.2020.06.017

34- Gómez J, Albaiceta GM, García-Clemente M, López-Larrea C, Amado-Rodríguez L, Lopez-Alonso I, et al. Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome. Gene (2020) 762:145102. doi: 10.1016/j.gene.2020.145102.

35- Shafiee, S.M.; Firoozrai, M.; Salimi, S.; Zand, H.; Hesabi, B.; Mohebbi, A. Angiotensin converting enzyme DD genotype not associated with increased risk of coronary artery disease in the Iranian population. Pathophysiology 2010, 17, 163–167. [Google Scholar] [CrossRef]

36- Wuyts, B.; Delanghe, J.; de Buyzere, M. Angiotensin I-converting enzyme insertion/deletion polymorphism: Clinical implications. Acta Clin. Belg. 1997, 52, 338–349. [Google Scholar] [CrossRef]

37- Staessen, J.A.; Ginocchio, G.; Wang, J.G.; Saavedra, A.P.; Soubrier, F.; Vlietinck, R.; Fagard, R. Genetic variability in the renin-angiotensin system: Prevalence of alleles and genotypes. J. Cardiovasc. Risk **1997**, 4, 401–422.

38- Yamamoto, N.; Yamamoto, R.; Ariumi, Y.; Mizokami, M.; Shimotohno, K.; Yoshikura, H. Does Genetic Predisposition Contribute to the Exacerbation of COVID-19 Symptoms in Individuals with Comorbidities and Explain the Huge Mortality Disparity between the East and the West? *Int. J. Mol. Sci.* **2021**, *22*, 5000. https://doi.org/10.3390/ijms22095000.

39- Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell **2020**, 181, 271–280.e8.

40- Zeberg, H.; Paabo, S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. Nature **2020**, 587, 610–612.

41- Ortiz-Fernández L, Sawalha AH. Genetic variability in the expression of the SARS-CoV-2 host cell entry factors across populations. Genes Immun (2020) 21:269–72. doi: 10.1038/s41435-020-0107-7.

42- Vargas-Alarcón G, Posadas-Sánchez R, Ramírez-Bello J. Variability in genes related to SARS-CoV-2 entry into host cells (ACE2, TMPRSS2, TMPRSS11A, ELANE, and CTSL) and its potential use in association studies. Life Sci (2020) 260:118313. doi: 10.1016/j.lfs.2020.118313.

43- Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med (2020) 283:1522–34. doi: 10.1056/NEJMoa2020283 NEJMoa2020283

44- Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Somnez T, Coker D, et al. Trans-ethnic analysis reveals genetic and non-genetic associations with COVID-19 susceptibility and severity. medRxiv (2020). doi: 10.1101/ 2020.09.04.20188318

45- Wang F, Huang S, Gao R, Zhou Y, Lai C, Li Z, et al. Initial whole-genome sequencing and analysis of the host genetic contribution to COVID-19 severity and susceptibility. Cell Discovery (2020) 6:83. doi: 10.1038/s41421-020-00231-4.

46- Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, et al. Genetic mechanisms of critical illness in Covid-19. Nature (2020) 591:92–8. doi: 10.1038/s41586-020-03065-y.

47- Levi M, Thachil J. Coronavirus Disease 2019 Coagulopathy: Disseminated Intravascular Coagulation and Thrombotic Microangiopathy—Either, Neither, or Both. Semin Thromb Hemost (2020) 46:781–4. doi: 10.1055/s-0040-1712156

48- Takahashi K, Chang WC, Takahashi M, Pavlov V, Ishida Y, La Bonte L, et al. Mannose-binding lectin and its associated proteases (MASPs) mediate coagulation and its deficiency is a risk factor in developing complications from infection, including disseminated intravascular coagulation. Immunobiology (2011) 216:96–102. doi: 10.1016/j.imbio.2010.02.005.

49- Sommeijer DW, Reitsma PH. Genetic Risk Factors for Disseminated Intravascular Coagulation. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience (2013).

50- 72Gialeraki, A.; Politou, M.; Rallidis, L.; Merkouri, E.; Markatos, C.; Kremastinos, D.; Travlou, A. Prevalence of prothrombotic polymorphisms in Greece. Genet. Test. **2008**, 12, 541–547.

51- Gonzalez-Giraldo, Y.; Rodriguez-Duenas, M.; Forero, D.A. Development of Novel High-Resolution Melting-Based Assays for Genotyping Two Alu Insertion Polymorphisms (FXIIIB and PV92). Mol. Biotechnol. **2016**, 58, 197–201.

52- Zeberg, H.; Paabo, S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. Nature **2020**, 587, 610–612.

53- Yamamoto, N.; Bauer, G. Apparent difference in fatalities between Central Europe and East Asia due to SARS-COV-2 and COVID-19: Four hypotheses for possible explanation. Med. Hypotheses **2020**, 144, 110160.

54- Klann, K.; Bojkova, D.; Tascher, G.; Ciesek, S.; Münch, C.; Cinatl, J. Growth Factor Receptor Signaling Inhibition Prevents SARS-CoV-2 Replication. Mol. Cell **2020**, 80, 164–174.e4.

55- Menachery, V. D., Eisfeld, A. J., Schäfer, A., Josset, L., Sims, A. C., Proll, S., Fan, S., Li, C., Neumann, G., Tilton, S. C., Chang, J., Gralinski, L. E., Long, C., Green, R., Williams, C. M., Weiss, J., Matzke, M. M., Webb□ Robertson, B. J., Schepmoes, A. A., … Baric, R. S. (2014). Pathogenic influenza viruses and coronaviruses utilize similar and contrasting approaches to control interferon□stimulated gene responses. mBio, 5(3), e01174□01114.

56- Ayaz, S., & Crea, F. (2020). Targeting SARS□CoV□2 using polycomb inhibitors as antiviral agents. Epigenomics, 12(10), 811–812.

57- Mantovani, A., & Netea, M. G. (2020). Trained innate immunity, epigenetics, and Covid□19. New England Journal of Medicine, 383(11), 1078–1080.

58- Yildirim Z, Sahin OS, Yazar S, Bozok Cetintas V. Genetic and epigenetic factors associated with increased severity of Covid-19. Cell Biol Int. 2021 Jun;45(6):1158-1174. doi: 10.1002/cbin.11572. Epub 2021 Mar 1. PMID: 33590936; PMCID: PMC8014716.

59- Gordon, D. E., Jang, G. M., Bouhaddou, M., Xu, J., Obernier, K., White, K. M., O'Meara, M. J., Rezelj, V. V., Guo, J. Z., Swaney, D. L., Tummino, T. A., Hüttenhain, R., Kaake, R. M., Richards, A. L., Tutuncuoglu, B., Foussard, H., Batra, J., Haas, K., Modak, M., …Krogan, N. J. (2020). A SARS□CoV□2 protein interaction map reveals targets for drug repurposing. Nature, 583(7816), 459–468

60- Mueller, A. L., McNamara, M. S., & Sinclair, D. A. (2020). Why does COVID□19 disproportionately affect older people? Aging (Albany NY), 12(10), 9959–9981.

61- Senapati, S., Kumar, S., Singh, A. K., Banerjee, P., & Bhagavatula, S. (2020). Assessment of risk conferred by coding and regulatory variations of TMPRSS2 and CD26 in susceptibility to SARS□CoV□2 infection in human. Journal of Genetics, 99, 99

62- Khan, M. A.□A.□K., & Islam, A. B. M. M. K. (2020). SARS□CoV□2 proteins exploit host's genetic and epigenetic mediators for the annexation of key host signaling pathways that confers its immune evasion and disease pathophysiology. bioRxiv

Chapter Seven

Covid-19 infection in the diabetic patients

Prof.Dr.Karar Mohammed Abdul-Sada

College of Veterinary Medicine, University of Kufa

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 >3.9mmol/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 lympho-cytopeniain 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 .

References:

1- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020:1–13. https://doi.org/10.1056/NEJMoa2002032. PubMed PMID: 32109013. Epub 2020/02/29. PubMed PMID: 32109013.

2- Wu Zunyou, McGoogan Jennifer M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention.JAMA 2020;323(13):1239. https://doi.org/ 10.1001/jama.2020.2648.

3- Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.03.017. Epub 2020/ 03/17 PubMed PMID: 32173574.

4- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID19 in Wuhan, China: a retrospective cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)30566-3. Epub 2020/03/15. PubMed PMID: 32171076.

5- Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besanc¸on S, et al. Global and regional estimates and projections of diabetes-related health expenditure: results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract 2020;162:108072. https://doi.org/ 10.1016/j.diabres.2020.108072.

6- McDonald HI, Nitsch D, Millett ERC, Sinclair A, Thomas SL. New estimates of the burden of acute community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using linked electronic health records. Diabet Med 2014;31(5):606–14. https://doi.org/ 10.1111/dme.2014.31.issue-510.1111/dme.12384.

7- Li Sen, Wang Jiaxin, Zhang Biao, Li Xinyi, Liu Yuan. Diabetes mellitus and cause-specific mortality: a population-based study. Diabetes Metab J 2019;43(3):319. https://doi.org/ 10.4093/dmj.2018.0060.

8- Knapp Sylvia. Diabetes and infection: is there a link? - A mini-review. Gerontology 2013;59(2):99–104. https://doi.org/ 10.1159/000345107.

9- Schoen Karla, Horvat Natally, Guerreiro Nicolau FC, de Castro Isac, de Giassi Karina S. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infect Dis 2019;19(1). https://doi.org/10.1186/s12879-019-4592-0.

10- Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006;23(6):623–8. https://doi.org/10.1111/j.1464- 5491.2006.01861.x. Epub 2006/06/09. PubMed PMID: 16759303.

11- Banik Gouri Rani, Alqahtani Amani Salem, Booy Robert, Rashid Harunor. Risk factors for severity and mortality in patients with MERS-CoV: analysis of publicly available data from Saudi Arabia. Virol Sin 2016;31(1):81–4. https://doi.org/ 10.1007/s12250-015-3679-z.

12- Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.03.017. Epub 2020/ 03/17 PubMed PMID: 32173574.

13- Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020. https://doi. org/10.1515/cclm-2020-0198. Epub 2020/03/03 PubMed PMID: 32119647.

14- Wang Aihong, Zhao Weibo, Xu Zhangrong, Gu Jianwen. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Res Clin Pract 2020;162:108118. https://doi.org/ 10.1016/j.diabres.2020.108118.

15- Zhou J, Tan J. Diabetes patients with COVID-19 need better care. Metabolism 2020. https://doi.org/10.1016/j. metabol.2020.154216. Epub 2020/03/30.

16- Iqbal A, Prince LR, Novodvorsky P, Bernjak A, Thomas MR, Birch L, et al. Effect of hypoglycemia on inflammatory responses and the response to low-dose endotoxemia in humans. J Clin Endocrinol Metab 2019;104(4):1187–99. https:// doi.org/10.1210/jc.2018-01168. Epub 2018/09/27.

17- Petrie John R, Guzik Tomasz J, Touyz Rhian M. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Canadian J Cardiol 2018;34 (5):575–84. https://doi.org/10.1016/j.cjca.2017.12.005.

18- Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 1999;26(3–4):259–65. https://doi.org/10.1111/j.1574-695X.1999. tb01397.x. Epub 1999/11/27 PubMed PMID: 10575137.

19- Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabete Metab 1992;18(3):187–201. Epub 1992/05/01. PubMed PMID: 1397473.

20- Ilyas R, Wallis R, Soilleux EJ, Townsend P, Zehnder D, Tan BK, et al. High glucose disrupts oligosaccharide recognition function via competitive inhibition: a potential mechanism for immune dysregulation in diabetes mellitus. Immunobiology 2011;216(1–2):126–31. https://doi.org/10.1016/ j.imbio.2010.06.002. Epub 2010/08/03. PubMed PMID: 20674073; PubMed Central PMCID: PMCPMC3088832.

21- Kohio Hinissan P, Adamson Amy L. Glycolytic control of vacuolar-type ATPase activity: a mechanism to regulate influenza viral infection. Virology 2013;444(1-2):301–9. https://doi.org/10.1016/j.virol.2013.06.026.

22- Popov D, Simionescu M. Alterations of lung structure in experimental diabetes, and diabetes associated with hyperlipidaemia in hamsters. Eur Respir J 1997;10(8):1850–8. https://doi.org/10.1183/09031936.97.10081850. Epub 1997/08/ 01 PubMed PMID: 9272930.

23- Lange P, Groth S, Kastrup J, Mortensen J, Appleyard M, Nyboe J, et al. Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. Eur Respir J 1989;2 (1):14–9. Epub 1989/01/01 PubMed PMID: 2651148.

24- Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in wuhan, China. JAMA Intern Med. Published online March 13, 2020. doi:10.1001/jamainternmed.2020.0994 (Accessed on March 31, 2020).

25- Chen Y, Gong X, Guo J. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. https://www.medrxiv.org/content/10.1101/2020.03.25.20043133v1.

26- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. J Am Med Assoc 2020 Feb 24. https://doi.org/10.1001/jama.2020.2648.

27- Singh A K , Gupta R, Ghosh A , Misra A. Review: Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 14 (2020) 303e310. https://doi.org/10.1016/j.dsx.2020.04.004.

28- Dunn EJ, Grant PJ. Type 2 diabetes: an atherothrombotic syndrome. Curr Mol Med 2005;5(3):323–32. https://doi.org/ 10.2174/1566524053766059. Epub 2005/05/17. PubMed PMID: 15892651.

29- Letko Michael, Marzi Andrea, Munster Vincent. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 2020;5 (4):562–9. https://doi.org/10.1038/s41564-020-0688-y.

30- Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426(6965):450–4. https:// doi.org/10.1038/nature02145. Epub 2003/12/04. PubMed PMID: 14647384.

31- Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, et al. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses 6 diabetes research and clinical practice 162 (2020) 108142 2019;11(1). https://doi.org/10.3390/v11010059. Epub 2019/01/ 17. Epub 2019/01/17PubMed PMID: 30646565; PubMed Central PMCID: PMCPMC6357155.

32- Yang Jin-Kui, Lin Shan-Shan, Ji Xiu-Juan, Guo Li-Min. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47(3):193–9. https://doi. org/10.1007/s00592-009-0109-4.

33- Henry Christopher, Zaizafoun Manaf, Stock Eileen, Ghamande Shekhar, Arroliga Alejandro C, White Heath D. Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia. Bayl Univ Med Cent Proc 2018;31(4):419–23. https://doi.org/10.1080/ 08998280.2018.1499293.

34- Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11(8):875–9. https://doi.org/10.1038/nm1267. Epub 2005/07/12. PubMed PMID: 16007097.

35- Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest 2020. https://doi.org/10.1007/s40618-020- 01236-2.

36- Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies.Biosci Trends. 2020;14(1):72–3. https://doi.org/10.5582/bst.2020.01047. Epub 2020/02/20. PubMed PMID: 32074550.

37- Rekedal LR, Massarotti E, Garg R, Bhatia R, Gleeson T, Lu B, et al. Changes in glycosylated hemoglobin after initiation of hydroxychloroquine or methotrexate treatment in diabetes patients with rheumatic diseases. Arthritis Rheum 2010;62 (12):3569–73. https://doi.org/10.1002/art.27703. Epub 2010/08/ 20. PubMed PMID: 20722019; PubMed Central PMCID: PMCPMC2992611.

38- Gerstein HC, Thorpe KE, Taylor DW, Haynes RB. The effectiveness of hydroxychloroquine in patients with type 2 diabetes mellitus who are refractory to sulfonylureas–a randomized trial. Diabetes Res Clin Pract 2002;55(3):209–19. https://doi.org/10.1016/s0168-8227(01)00325-4. Epub 2002/02/ 19. PubMed PMID: 11850097.

39- Emami Jaber, Pasutto Franco M, Mercer John R, Jamali Fakhreddin. Inhibition of insulin metabolism by hydroxychloroquine and its enantiomers in cytosolic fraction of liver homogenates from healthy and diabetic rats. Life Sci 1998;64(5):325–35. https://doi.org/10.1016/S0024-3205(98) 00568-2.

40- World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance, 13 March 2020 Geneva2020 [28/ 03/2020]. Available from: https://www.thelancet.com/action/ showPdf?pii=S0140-6736%2820%2930317-2.

41- Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395(10223):473–5. https://doi.org/10.1016/S0140- 6736(20)30317-2. Epub 2020/02/12. PubMed PMID: 32043983.

42- Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS CoV-2 in Wuhan, China. Allergy 2020. https://doi.org/10.1111/ all.14238. Epub 2020/02/23 PubMed PMID: 32077115.

43- Hussain A , Bhowmik B , Moreira N C. Review: COVID-19 and diabetes: Knowledge in progress. Diabetes Research and Clinical Practice. 162 (2020) 108142. https://doi.org/10.1016/j.diabres.2020.108142 0168-8227.

Chapter eight
Heart failure in COVID-19 Patients

Prof. Dr. Nawal Mohammed Utba
Virology and Immunology
University of Baghdad College of Science

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 .

References:

1- National Guideline Centre (UK) (2018). "Chronic HF in Adults: Diagnosis and Management". National Institute for Health and Care Excellence: Clinical Guidelines.

2- O'Connor CM (2005). Managing Acute Decompensated HF a Clinician's Guide to Diagnosis and Treatment. London: Informa Healthcare. p. 572.

3- National Clinical Guideline Centre (UK) (August 2010). Chronic HF: National clinical guideline for diagnosis and management in primary and secondary care: Partial update. National Clinical Guideline Centre. pp. 19–24.

4- Chronic HF: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update. National Clinical Guideline Centre. August 2010. pp. 38–70.

5- Bader F., Manla Y., Atallah B., Starling R. (2020). HF and COVID-19. Heart Fail Rev. 2020 Jul 27: 1–10.

6- Novel CP. (2020). The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi ;41(2):145.

7- Chatrath N, Kaza N, Pabari PA, et al. The effect of concomitant COVID-19 infection on outcomes in patients hospitalized with HF. ESC Heart Fail. Published online October 11, 2020. doi:10.1002/ehf2.13059.

8- Italia L, Tomasoni D, Bisegna S, Pancaldi E, Stretti L, Adamo M and Metra M (2021). COVID-19 and HF: From Epidemiology During the Pandemic to Myocardial Injury, Myocarditis, and HF Sequelae. Cardiovasc. https://doi.org/10.3389/fcvm.2021.713560

9- Rey J, Caro-Codón J, Rosillo S, Iniesta A, Castrejón-Castrejón S, Marco-Clement I, Martín-Polo L, Merino-Argos C, Rodríguez-Sotelo L, García-Veas J , Martínez-Marín L, Martínez-Cossiani M, Buño A , Gonzalez-Valle L, Herrero A , López-Sendón J , Merino J. (2020). HF in COVID-19 patients: prevalence, incidence and prognostic implications. Eur J Heart Fail.;22(12):2205-2215.

10- Ng TM, Toews ML. (2016). Impaired norepinephrine regulation of monocyte inflammatory cytokine balance in HF. World J Cardiol.; 8(10):584–589.

11- Tufan A, GÜLER AA, Matucci-Cerinic M. (2020) COVID-19, immune system response, hyperinflammation and repurposing anti-rheumatic drugs. Turk J Med Sci 50(SI-1):620–632.

12-Kumar A, Parrillo JE, Kumar A (2002) Clinical review: myocardial depression in sepsis and septic shock. Crit Care 6(6):500.

13-Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers DA, Kant KM, Kaptein FH, van Paassen J, Stals MA, Huisman MV, Endeman H (2020) Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 191:148–150.

14- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062.

15- Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 46(5): 846–848.

16-Scally C, Abbas H, Ahearn T, Srinivasan J, Mezincescu A, Rudd A, Spath N, Yucel-Finn A, Yuecel R, Oldroyd K, Dospinescu C. (2019) Myocardial and systemic inflammation in acute stress-induced (Takotsubo) cardiomyopathy. Circulation 139(13):1581–1592.

Chapter Nine

Post Covid-19 Fungal Infections

Assistant Prof.Dr. Huda Raheem Hashim Al-Mosway

University of Al-Muthanna

College of Basic Education Department of Science

Microbiology Medical Mycology

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 pub-lished reports,a portion(7.2%) of COVID-19 patients are sometimesco-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 occurrenceduring 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 at the same to those of coronavirus, including fever, cough, and shortness of breath . Diagnosis fungal infection by laboratoty testing is very important to determin 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 acut 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 pub-lished 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.

Reference

1. Jiang W, Li W, Xiong L, Wu Q, Wu J, He B, Shen J, Pang R, Luo T, Guo Y, Yang Y, Han Y, Dai W, et al. Clinical efficacy of convalescent plasma therapy on treating COVID-19 patients: Evidence from matched study and a meta-analysis. Clin Transl Med. 2020; 10:e259.

https://doi.org/10.1002/ctm2.259 PMID:33377664

2. X. Chen, B. Liao, L. Cheng, X. Peng, X. Xu, Y. Li, et al., The microbial co-infectionin COVID-19, Appl. Microbiol.

3. Petrikkos, G., Skiada, A., Lortholary, O., Roilides, E., Walsh, T.J., Kontoyiannis, D.P .,2012. Epidemiology and clinical manifestations of mucormycosis. Clin. Infect. Dis. 54 (Suppl 1), S23–S34. https://doi.org/10.1093/cid/cir866.

4. Hoenigl M. Invasive fungal disease complicating COVID-19: when it rains it pours Infect Dis. 2020 Sep 5.

5. K.A. Marr, A. Platt, J.A. Tornheim, S.X. Zhang, K. Datta, C. Cardozo, et al.,Aspergillosis complicating severe coronavirus disease, Emerging Infect. Dis.27 (1) (2021) 18.

6. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: We should be preparedexternal icon. J Mycol Med 2020 Jun

7.Wael F. Ismaiel a, Mohamed H. Abdelazim a, Ibrahim Eldsoky b, Ahmed A. Ibrahim a Mahmoud E. Alsobky a, Ebtesam Zafan c, Abdulkarim Hasan.2021. The impact of COVID-19 outbreak on the incidence of acute invasive fungal rhinosinusitis. American Journal of Otolaryngology–Head and Neck Medicine and Surgery 42 (2021) 103080.

8. Benedetti MF, Alava KH, Sagardia J, et al. COVID-19 associated pulmonary aspergillosis in ICU patients: Report of five cases from Argentinaexternal icon. Med Mycol Case Rep. 2020 Dec 7.

9. Mohamed A, Rogers TR, Talento AF. COVID-19 associated invasive pulmonary aspergillosis: diagnostic and therapeutic challengesexternal icon. J Fungi. 2020 Jul 22.

10. Beer KD, Jackson BR, Chiller T, Verweij PE, Van de Veerdonk FL, Wauters J. Does pulmonary aspergillosis complicate COVID-19?external icon Crit Care Exp. 2020 Sep .

11. Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer DA, Fuchs F, et al. COVID-19 associated pulmonary aspergillosisexternal icon. Mycoses. 2020 May 15.

12. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive studyexternal icon. Lancet. 2020 Jan 30.

13. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysisexternal icon. J Infect. 2020 May 27.

14. Verweij PE, Gangneu J, Bassetti M, Bruggemann RJM, Cornely OA, Koehler P, et al. Diagnosing COVID-19-associated pulmonary aspergillosisexternal icon. Lancet Microbe. 2020 May ,10.

15. Heard KL, Hughes S, Mughal N, Moor LSP.COVID-19 and fungal superinfection. Lancet Microbe 2020;1(3):e107. https://doi.org/10.1016/S2666-5247(20)30065-3

16. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literatureexternal icon. Mycopathologia. 2021 Feb 5.

17. Nucci M, Barreiros G, Guimarães LF, Deriquehem VA, Castiñeiras AC, Nouér SA. Increased incidence of candidemia in a tertiary care hospital with the Covid-19 pandemicexternal icon. Mycoses. 2020 Dec 4

18. Rabagliati R, Rodríguez N, Núñez C, Huete A, Bravo S, Garcia P. COVID-19-Associated Mold Infection in Critically Ill Patients, Chile. Emerging infectious diseases. 2021 May.

19. K.A. Marr, A. Platt, J.A. Tornheim, S.X. Zhang, K. Datta, C. Cardozo, et al.,Aspergillosis complicating severe coronavirus disease, Emerging Infect. Dis.27 (1) (2021) 18.

20. Posteraro B, Torelli R, Vella A, Leone PM, De Angelis G, De Carolis E, et al. Pan-echinocandin-resistant Candida glabratabloodstream infection complicating COVID-19: a fatal case reportexternal icon. J Fungi. 2020 Sep 6.

21. Meijer EFJ, Dofferhoff ASM, Hoiting O, Buil JB, Meis JF. Azole-resistant COVID-19-associated pulmonary aspergillosis in an immunocompetent host: a case reportexternal icon. J Fungi. 2020 Jun 6.

Chapter Ten

Covid-19 and Risk familial hypercholesterolemia

Asst. prof, Dr. Zahraa Haleem Alqaim

Al-Mustaqbal University College, Anesthesia of Department

Medical Genetic , Biotechnology ,

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 co-morbid 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 co-morbid condition and 10 percent were reported tohave 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.

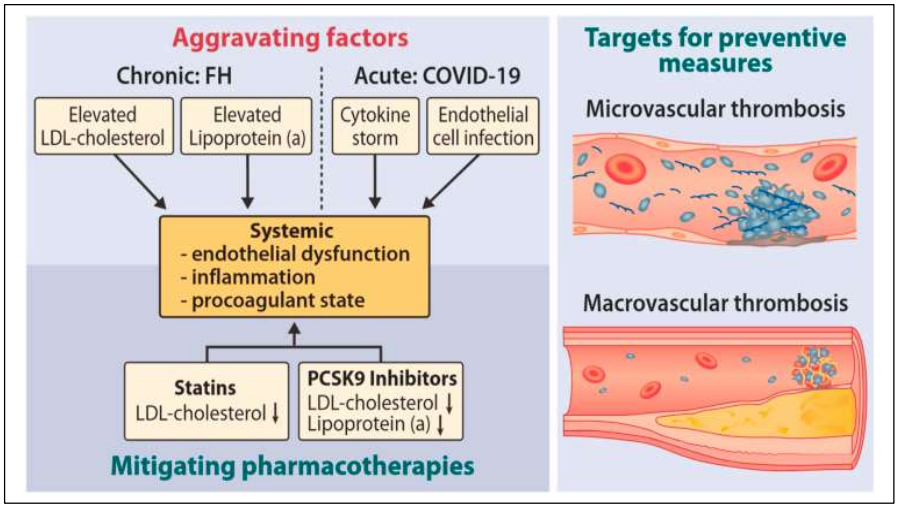
There are a few significant contemplations when treating a FH patient with Coronavirus, including

1- the need to increase cholesterol-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 Chlamydiapneumoniae 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 ز 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

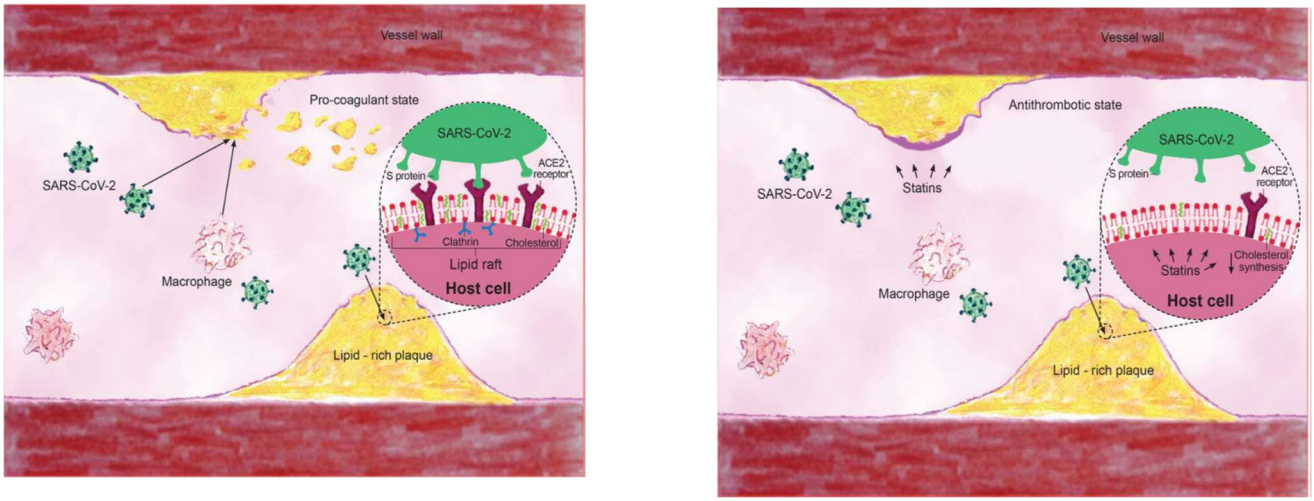


Figure 2 the mechanism of the role of cholesterol and statins in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the left figure shown Lipid rafts rich in cholesterol serve as docking sites for angiotensin-converting enzyme 2 (ACE2) receptors and viral attachment via the S protein 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 e_ect 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 al1, 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.

Reference

1- Hill MA, Sowers JR, Mantzoros CS. Commentary: COVID-19 and obesity pandemics converge into a syndemic requiring urgent and multidisciplinary action. Metabolism 2021;114:154408.

2- Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. Newonset diabetes in covid-19. N Engl J Med 2020;383:789e90.

3- le Roux CW. COVID-19 alters thinking and management in metabolic diseases. Nat Rev Endocrinol 2021;17:71e2.

4- P_aez-Franco JC, Torres-Ruiz J, Sosa-Hern_andez VA, Cervantes-Díaz R, Romero- Ramírez S, P_erez-Fragoso A, et al. Metabolomics analysis reveals a modified amino acid metabolism that correlates with altered oxygen homeostasis in COVID-19 patients. Sci Rep 2021;18(11):6350.

5- Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care 2020;24: 353.

6- X. Ou, Y. Liu, X. Lei, et al., Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV, Nat. Commun. 11 (2020) 1620.

7- G. Grasselli, A. Zangrillo, A. Zanella, et al., Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 323 (16) (2020) 1574–1581.

8- T. Guo, Y. Fan, M. Chen, et al., Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiology 5 (7) (2020) 811–818.

9- C.M. Petrilli, S.A. Jones, J. Yang, et al., Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study, BMJ 369 (2020) m1966.

10- X. Hu, D. Chen, L. Wu, et al., Low serum cholesterol level among patients with COVID-19 infection in wenzhou, China, China (February 21, 2020), http://doi.or g/10.2139/ssrn.3544826. [6] T. Greenhalgh, G.C.H. Koh, J. Car, Covid-19: a remote assessment in primary care, BMJ 368 368 (2020) m1182.

11- K.E. Herbert, C. Erridge, Regulation of low-density lipoprotein cholesterol by intestinal inflammation and the acute phase response, Cardiovasc. Res. 114 (2018) 226–232.

12- Q. Feng, W.Q. Wei, S. Chaugai, et al., Association between low-density lipoprotein cholesterol levels and risk for sepsis among patients admitted to the hospital with infection, JAMA Netw Open 2 (2019), e187223.

13- A. Golucci, F.A.L. Marson, A.F. Ribeiro, R.J.N. Nogueira, Lipid profile associated with the systemic inflammatory response

14-Aung N, Khanji MY, Munroe PB, Petersen SE. Causal inference for genetic obesity, cardiometabolic profile and covid-19 susceptibility: a mendelian randomization study. *Front Genet*. 2020;11. doi:10.3389/fgene.2020.586308

15-Cao X., Yin R., Albrecht H., Fan D., Tan W. Cholesterol: a new game player accelerating vasculopathy caused by SARS-CoV-2? *Am. J. Physiol. Endocrinol*. Metabol. 2020;319:E197–E202. doi:10.1152/ajpendo.00255.2020

16- Aung N, Khanji MY, Munroe PB, Petersen SE. Causal inference for genetic obesity, cardiometabolic profile and COVID-19 susceptibility: a mendelian randomization study. *Frontiers in Genetics*. 2020. doi:10.3389/fgene.2020.586308

17- Hennig BJW, Hellier S, Frodsham AJ et al. Association of lowdensity lipoprotein receptor polymorphisms and outcome of hepatitis C infection. Genes Immun 2002;3:359–67. Erratum in Genes Immun 2007; 8: 707.

18- Wu Q, Zhou L, Sun X et al. Altered lipid metabolism in recovered SARS patients twelve years after infection. Sci Rep 2017; 7: 9110.

19- Kontula K, Vuorio A, Turtola H, Saikku P. Association of seropositivity for Chlamydia pneumoniae and coronary artery disease in heterozygous familial hypercholesterolaemia. Lancet 1999; 354: 46–7.

20- Nieto FJ, Sorlie P, Comstock GW et al. Cytomegalovirus infection, lipoprotein(a), and hypercoagulability: an atherogenic link? Arterioscler Thromb Vasc Biol 1997; 17: 1780–5.

21-Vuorio A, Watts GF, Schneider WJ, Tsimikas S, Kovanen PT. Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities. J Int Med 2020; 287: 2–18.

22- Peretz A, Azrad M, Blum A. Influenza virus and atherosclerosis. QJM 2019; 112: 749–55.

23- Khademi F, Momtazi-Borojeni AA, Reiner _Z, Banach M, Al- Rasadi KA, Sahebkar A. PCSK9 and infection: a potentially useful or dangerous association? J Cell Physiol 2018; 233: 2920–7.

24- Madjid, M.; Safavi-Naeini, P.; Solomon, S.D.; Vardeny, O. Potential e_ects of coronaviruses on the cardiovascular system: A review. JAMA Cardiol. 2020. [CrossRef]

25- Baglivo, M.; Baronio, M.; Natalini, G.; Beccari, T.; Chiurazzi, P.; Fulcheri, E.; Petralia, P.P.; Michelini, S.; Fiorentini, G.; Miggiano, G.A.; et al. Natural small molecules as inhibitors of coronavirus lipid-dependent attachment to host cells: A possible strategy for reducing SARS-COV-2 infectivity? Acta Biomed. 2020, 91, 161–164. [PubMed]

26- Jeon, J.H.; Lee, C. Cholesterol is important for the entry process of porcine deltacoronavirus. Arch. Virol. 2018, 163, 3119–3124. [CrossRef] [PubMed]

27- Li, G.; Li, Y.; Yamate, M.; Li, S.; Ikuta, K. Lipid rafts play an important role in the early stage of severe acute respiratory syndrome-coronavirus life cycle. Microbes Infect. 2007, 9, 96–102. [CrossRef] [PubMed]

28- Lu, Y.; Liu, D.X.; Tam, J.P. Lipid rafts are involved in SARS-CoV entry into vero E6 cells. Biochem. Biophys. Res. Commun. 2008, 369, 344–349. [CrossRef]

29- Choi, K.S.; Aizaki, H.; Lai, M.M.C. Murine coronavirus requires lipid rafts for virus entry and cell-cell fusion but not for virus release. J. Virol. 2005, 79, 9862–9871. [CrossRef]

30- Guo, H.; Huang, M.; Yuan, Q.; Wei, Y.; Gao, Y.; Mao, L.; Gu, L.; Tan, Y.W.; Zhong, Y.; Liu, D.; et al. The important role of lipid raft-mediated attachment in the infection of cultured cells by coronavirus infectious bronchitis virus beaudette strain. PLoS ONE 2017, 12, e0170123. [CrossRef]

31- Lee KH, Kim JS, Hong SH, Seong D, Choi YR, Ahn YT, Kim KS, Kim SE, Lee S, Sim W, Kim D, Jun B, Yang JW, Yon DK, Lee SW, Kim MS, Dragioti E, Li H, Jacob L, Koyanagi A, Abou Ghayda R, Shin JI, Smith L. Risk factors of COVID-19 mortality: a systematic review of current literature and lessons from recent retracted articles. Eur Rev Med Pharmacol Sci 2020; 24: 13089-13097.

32- Vuorio A, Watts GF, Kovanen PT. Familial hypercholesterolaemia and COVID-19: triggering of increased sustained cardiovascular risk. J Intern Med 2020; 87: 746-747.

33- Mechanick JI, Rosenson RS, Pinney SP, Mancini DM, Narula J, Fuster V. Coronavirus and cardiometabolic syndrome: JACC Focus Seminar. J Am Coll Cardiol 2020; 76: 2024-2035.

34- Li Z, Liu Q. Proprotein convertase subtilisin/kexin type 9 inhibits interferon β expression through interacting with ATF-2. FEBS Lett 2018; 592: 2323-2333.

35- Gan ES, Tan HC, Le DHT, Huynh TT, Wills B, Seidah NG, Ooi EE, Yacoub S. Dengue virus induces PCSK9 expression to alter antiviral responses and disease outcomes. J Clin Invest 2020; 130: 5223-5234.

36- Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines [published online ahead of print, 2021 Jul 20]. Circulation 2021. https:// doi.org/10.1161/CIRCULATIONAHA.121.056135.

37- Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military

38- Iqbal Z, Ho JH, Adam S, France M, Syed A, Neely D, et al. Managing hyperlipidaemia in patients with COVID-19 and during its pandemic: an expert panel position statement from HEART UK. Atherosclerosis 2020;313: 126e36.[b] Vuorio A, Watts GF, Schneider WJ, Tsimikas S, Kovanen PT. Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities. J Intern Med 2020;287:2e18.

39- Vuorio A, Kovanen PT. PCSK9 inhibitors for COVID-19: an opportunity to enhance the antiviral action of interferon in patients with hypercholesterolaemia. J Intern Med 2021;289:749e51.

40- Gao X, Dong Q. A Bayesian framework for estimating the risk ratio of hospitalization for people with comorbidity infected by SARS-CoV-2 virus. J Am Med Inf Assoc 2021;28:472e6.

41- Kovanen PT, Raal F, Vuorio A. Patients with familial hypercholesterolemia and COVID-19: efficient and ongoing cholesterol lowering is paramount for the prevention of acute myocardial infarction. Am J Prev Cardiol 2021;7:100224.

42- Vuorio A, Ramaswami U, Holven KB. Editorial: genetics of familial hypercholesterolemia: new insight. Front Genet 2021;12:669373.

43- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162B2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577

Chapter eleven

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

Professor Dr. Habeeb Waseel Kadhum Shubber

Medical Parasitology

University of Al-Qadisiyah College of Science

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.

References

1. https://www.skynewsarabia.com/amp/technology/13747212.

2.https://aawsat.com/home/article

3. https://www.masrawy.com/howa_w_hya/health/details/2021/2/18/1972883

4. https://arabic.cnn.com/health/article/2021/02/04/younger-adults-biggest-covid-spreaders

5. https://www.albayan.ae/one-world/overseas/2020-09-24-1.3968900

6. https://www.masrawy.com/howa_w_hya/health/details/2021/4/28/2013715 /

Chapter Twelve

Patient with a previous surgical history of cardiac surgery as a co-morbidity in COVID-19

Prof.Dr.Fadhil Alamrani and Dr.Bahaa A. Razzaq

Kufa University, College of Medicine

Patient with a previous surgical history of cardiac surgery as a co-morbidity in COVID-19

Introduction

COVID-19 epidemic is caused by a coronavirus-2 virus (SARS-CoV-2) and represents the third attack of the highly pathogenic coronavirus into the population. SARS-CoV-2 and the previous viruses, SARS coronavirus-1 in 2002 and Middle East respiratory syndrome coronavirus in 2012, are RNA viruses. These viruses can cause various respiratory complaints, ranging from mild symptoms (fever, cough, malaise, fatigue, anosmia, and anorexia) to acute respiratory distress syndrome (ARDS). [(1)(2)]

COVID-19 has had a profound impact on cardiac surgery patients. A significant decrease in access to surgical treatment has forced surgeons to prioritize patients and follow strict COVID-19 protocols to protect surgeons, staff, and patients. [(3)]

Cardiovascular disease and COVID-19

From the onset of the COVID-19 pandemic, it has been clear that mortality rates from COVID-19 are higher in the male sex and increasing age. Early studies show a shorter duration from the onset of disease to death in people aged 70 and over, with the most significant fatalities in those >85. These are the same risk factors for cardiovascular disease and its associated co-morbidities. [(4)(5)(6)] Patients with heart failure are at increased risk for hospitalization, poor outcome, and death from COVID-19. A notable difference in mortality was observed between patients with and without heart failure, with heart failure patients having higher mortality. [(7)]

Although the primary reported mortality rate was about 2-3% in China, it reached 10% among patients with underlying cardiovascular diseases. The preliminary epidemiological investigations in Italy showed a high prevalence of underlying cardiovascular diseases in more than 40% of the infected patients. A high prevalence of hypertension (HTN), ischemic heart disease, and diabetes were reported among deceased patients in Italy. In addition, they showed a higher prevalence of underlying cardiovascular diseases among ICU admitted patients due to coronavirus infection. Previous experiments in different pandemic situations showed that the cardiovascular system had been affected in many ways. Earlier studies on SARS-CoV and MERS-CoV reported that cardiovascular co-morbidities directly correlated with the risk of infection, the severity of disease, and the mortality rate. [(8)(9)]

Cardiovascular complications of COVID-19 infection

Myocardial infarction is one of the most serious cardiac complications of viral respiratory infections. It was first detected in the influenza pandemic in 1990. However, in seasonal outbreaks of influenza, sporadic cases are detected yet. In this situation, viral infections provide a suitable condition for peeling the coronary plaques via inducing inflammatory cytokine. So, these plaques are exposed to thrombotic materials in vessels. This complication is also probable in patients with acute respiratory syndrome due to COVID-19 Acute heart injury is also among the major complications after the severe type of COVID-19 infection. [8][9]

The SARS-CoV-2 virus not only injures the lung but also attacks other tissues, including the heart. Non-ischemic myocardial injury, which is detected by high levels of cardiac troponin, results from acute heart injury in these patients. Recent studies in COVID-19 patients reported high levels of troponin in more than 46% of dying patients, while high levels of troponin were detected only in 1% of the survivors. Furthermore, it seems that the level of troponin at the onset of the infection in the deceased group was higher. The troponin increment was faster and more notable in this group. Myocarditis is also a common form of myocardial insult among these patients. In a recent retrospective study, myocarditis was considered a cause for death in 33% of deceased patients due to COVID-19. Chest pain and dyspnea were common among the subjects of COVID-19 myocarditis. In their chest X-rays, enlargement of the heart could be detected. Their CT scan showed heart enlargement and pleural effusion, which shared common features with COVID-19 pneumonia. In some cases, ST-segment elevation and increased cardiac troponin levels were also present, which could be the features of myocardial infarction without coronary vessel obstruction. Vascular complications were also observed. In one study, small and mid-sized pulmonary artery thrombosis was observed in post-mortem biopsies of COVID-19 cases. Cardiac arrhythmia was another less common cardiac complication of COVID-19. This complication usually presented with tachycardia and heart palpitation and was mostly detected in ICU admitted patients with severe pneumonia. [10][11][12][13]

Patients with a history of CABG

To date, there is no sufficient data regarding how COVID-19 affects coronary artery bypass graft vessels, in particular the saphenous vein graft patency. SARS-CoV-2 could bind ACE2 in the saphenous vein in CABG patients and, therefore, lead to graft failure through vascular inflammation and vascular and endothelial dysfunction. Moreover, the inflammatory effects of cytokines also lead to activated vascular endothelial cells and endothelial injury with resultant prothrombotic properties. Also, the increased pro-inflammatory cytokines, including TNFα and IL-6, from human saphenous vein under inflammatory conditions has been shown, suggesting the possible interaction of vascular inflammation, endothelial dysfunction, and the risk of thrombosis in saphenous vein graft failure. Chen et al. demonstrated that SARS-CoV-2 attacks the human heart pericytes, which can cause capillary endothelial dysfunction and microcirculation disorder. The authors suggest that these patients are more vulnerable to cardiac damage by COVID-19. [14][15]

Patients with prosthetic valves

Unfortunately, there is no published evidence about the outcome of SARS-Co-2 in patients with underlying valvular heart diseases. So, we investigated the available data on other viral infections with respiratory systems involvement. A case report by Qian *et al.* reported that influenza infection with respiratory syndromes might increase the risk of myocarditis and heart blocks in patients with valvular heart disease. [16] Warfarin is one of the most common drugs prescribed in patients with prosthetic valves and interacts with drugs used in COVID-19 treatment. Heparin and Enoxaparin are two reasonable alternatives for warfarin among COVID-19 patients. [17][18]

Patients with a history of surgery for congenital heart disease

The new coronavirus disease outbreak in 2019 (COVID-19) represents a dramatic challenge for healthcare systems worldwide. As to viral tropism, lungs are not the only COVID-19 target, but also the heart may be involved in a not-small percentage of the infected patients. Myocarditis-related cardiac dysfunction and potentially life-

threatening arrhythmias are the main aftermaths. A few studies showed that myocardial injury in adult patients is often linked with a fatal outcome. Conversely, scientific evidence in children is sparse, although several reports were published with the description of cardiac involvement in COVID-19 pediatric patients. In these young subjects, a background of surgically treated congenital heart disease seems to be a predisposing factor. [19] Danielle D. Strah *et al*. reported increased hospital morbidities and costs for patients with CHD affected by COVID-19.[20]

COVID-19 in the immediate post-operative period

Unrecognized complications are seen during the pandemic, like acute biological leaflet thrombosis after aortic valve replacement with biological valve. COVID-19 has proven highly pro-coagulable; this creates an additional challenge for perfusionists. We need to reconsider anticoagulants in patients for whom these would not have been the usual practice. The risk of acute respiratory distress syndrome is also potentially greater in COVID-19 patients undergoing surgery that requires cardiopulmonary bypass. This risk is due to the associated pro-inflammatory response with CPB and increase of circulating cytokines from COVID-19. As such, off-pump options may need to be chosen. [21][22]

The outcome of cardiac surgical patients who contracted COVID-19 infection perioperatively is extremely poor. Patients infected with Covid-19 had more than five times greater chance of dying than those without Covid-19 after cardiac surgery. The mortality rate of Covid-19 appears to be particularly higher in those diagnosed after surgery. To offer time-critical urgent cardiac surgery, units must implement rigorous protocols to maintain a COVID-19 protective environment to minimize additional life-threatening complications related to this virus infection. [23]

References

1. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status. Mil Med Res. 2020;7:11.

2. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region—case series. N Engl J Med. 2020;382:2012–2022.

3. Engelman, D.T., et al., Adult cardiac surgery and the COVID-19 pandemic: Aggressive infection mitigation strategies are necessary in the operating room and surgical recovery. J Thorac Cardiovasc Surg, 2020. 160(2): p. 447-451.

4. Li X, Guan B, Su T, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. Heart 2020; 106: 1142–1147.

5. Sun P, Lu X, Xu C, et al. Understanding of COVID-19 based on current evidence. J Med Virol 2020; 92: 548–551.

6. NHS. Cardiovascular disease, https://www.nhs.uk/conditions/cardiovascular-disease/ (2018, accessed 18 March 2021).

7. Emir Yonas. aIdrus Alwi, Raymond Pranata, et al. Effect of heart failure on the outcome of COVID-19 — A meta-analysis and systematic review. The American Journal of Emergency Medicine Volume 46, August 2021, Pages 204-211.

8. Di Pasquale G. Coronavirus COVID-19: quali implicazioni per la Cardiologia? Giornale Italiano di Cardiologia. 2020;21(4):243-5.

9. Clerkin KJ, Fried JA, Raikhelkar J, et al. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease. Circulation. 2020.

10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020.

11. Welt FG, Shah PB, Aronow HD, et al. Catheterization Laboratory Considerations During the Coronavirus (COVID-19) Pandemic: From ACC's Interventional Council and SCAI. Journal of the American College of Cardiology. 2020.

12. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. European Heart Journal. 2020.
13. Lax SF, Skok K, Zechner P, et al. Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome: Results From a Prospective, Single-Center, Clinicopathologic Case Series. Annals of internal medicine. 2020.

14. Bochenek ML, Schäfer K. Role of endothelial cells in acute and chronic thrombosis. Hamostaseologie. 2019;39(2):128-39. doi:10.1055/s-0038-1675614.
15. Daci A, Özen G, Uyar İ, et al. Omega-3 polyunsaturated fatty acids reduce vascular tone and inflammation in human saphenous vein. Prostaglandins Other Lipid Mediat. 2017;133:29-34. doi:10.1016/j.prostaglandins.2017.08.007.

16. Qian L, Zheng J, Xu H, Shi L, Li L. Extracorporeal membrane oxygenation treatment of a H7N9-caused respiratory failure patient with mechanical valves replacement history:
A case report. Medicine. 2016;95(40):e5052.

17. Peterson D, Van Ermen A. Increased warfarin requirements in a patient with chronic hepatitis C infection receiving sofosbuvir and ribavirin. American Journal of Health-System Pharmacy. 2017;74(12):888-92.

18. Puglisi G, Smith S, Jankovich R, et al. Paritaprevir/ritonavir/ombitasvir+ dasabuvir plus ribavirin therapy and inhibition of the anticoagulant effect of warfarin: a case report. Journal of clinical pharmacy and therapeutics. 2017;42(1):115-8.

19. Sanna, G., Serrau, G., Bassareo, P.P. et al. Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. Eur J Pediatr 179, 1079–1087 (2020). https://doi.org/10.1007/s00431-020-03699-0.

20. Danielle D. Strah, Katie A. Kowalek, Kevin Weinberger, et al. Worse Hospital Outcomes for Children and Adults with COVID-19 and Congenital Heart Disease. Pediatric Cardiology, 11 October 2021, https://doi.org/10.1007/s00246-021-02751-6.

21. Harky A, Poole G, Axiaq A, et al. COVID-19 and cardiac surgery: do outcomes differ? J Card Surg 2020; 35:3391–3394.

22. Manghat NE, Hamilton MCK, Joshi NV, et al. Acute post-operative thrombosis of an aortic valve prosthesis and embolic myocardial infarction in a coronavirus

disease 2019 (COVID-19)-positive patient-an unrecognized complication. JTCVS Tech 2020: 4; 111–113.

23. Julie Sanders, Enoch Akowuah, Jackie Cooper. Cardiac surgery outcome during the COVID-19 pandemic: a retrospective review of the early experience in nine UK centres. Journal of Cardiothoracic Surgery (2021) 16:43. https://doi.org/10.1186/s13019-021-01424-y.