Challenges in the Management of COVID-19 Patients with Metabolic Syndrome with Special Emphasis on Gender and Age - A Review

Arunima Chaudhuri[1], Suhrita Paul[2], Tapas Ghosh[3]

[1]Department of Physiology, Burdwan Medical College, Burdwan, West Bengal, India. [2]Department of Pharmacology, Burdwan Medical College, Burdwan, West Bengal, India. [3]Department of Anatomy, Burdwan Medical College, Burdwan, West Bengal, India.

ABSTRACT

BACKGROUND

The corona virus disease-19 (Covid-19) pandemic has put human civilization into a huge challenge, especially in the field of medicine in the management of patients with co-morbidities. Health authorities across the world depend greatly on reliable data to make major decisions and this is especially true during this global pandemic. The present review was conducted to estimate the challenges in the management of Covid-19 patients with metabolic syndrome with special emphasis on gender and age.

Patients having pre-existing health conditions e.g., heart disease, diabetes are at higher risk of morbidity and mortality due to COVID-19. According to the WHO newsletter, COVID-19 has tragically claimed more than 1.5 million lives. The burden of obesity across the world has nearly tripled since 1975. In 2016, 1.9 billion adults, were overweight; 650 million were obese; 13 % of the world's adult population (11 % of males and 15 % of females) were obese in 2016. Obesity has been observed to be a high-risk factor for COVID-19 severity. Severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2) targets the angiotensin-converting enzyme 2 (ACE2) for cell entry and ACE2 is highly expressed in adipose tissue. This suggests an important role for the tissue in determining COVID-19 disease severity in obese individuals.[1-2] There has been an increase in death from diabetes by 70 % globally between 2000 and 2019, and an 80 % rise in deaths among males has been observed.

Metabolic syndrome comprises three or more of the following factors: increased waist circumference; hypertriglyceridemia; elevated blood pressure; reduced high-density lipoprotein cholesterol; hyperglycemia.[1-2] Visceral fat is known to produce higher concentrations of proinflammatory cytokines. These are then released in the bloodstream. Release of proinflammatory markers in blood stream may cause auto-amplifying cytokine production ("cytokine storms") and low-grade inflammation. Cytokine storm and low-grade inflammation can contribute to worsening of COVID-19 patients with obesity. Components of metabolic syndrome such as hypertension, type 2 diabetes mellitus (T2DM), and obesity are highly prevalent among the general population and have been observed to significantly increase the risk of hospitalization and mortality in COVID-19 patients.[1-2]

KEYWORDS

Covid-19 Pandemic, Metabolic syndrome, Aging, Gender

Corresponding Author:
Dr. Arunima Chaudhuri,
Department of Physiology,
Burdwan Medical College,
Burdwan, West Bengal, India.
E-mail: arunimachaudhuri4u@gmail.com

DOI: 10.18410/jebmh/2021/617

How to Cite This Article:
Chaudhuri A, Paul S, Ghosh T. Challenges in the management of COVID-19 patients with metabolic syndrome with special emphasis on gender and age - a review. J Evid Based Med Healthc 2021;8(38):3401-3405. DOI: 10.18410/jebmh/2021/617

Submission 11-08-2021,
Peer Review 19-08-2021,
Acceptance 10-09-2021,
Published 20-09-2021.

PATHOPHYSIOLOGY

Coronaviruses have four structural proteins: Spike protein (S); Membrane protein (M); Envelop protein (E); Nucleocapsid (N). S protein is known to be important for host attachment and penetration. ACE-2 has been identified as a functional receptor for SARS-CoV and is greatly expressed on the pneumocytes and S protein binds initially to these receptors to start host cell invasion. After binding of SARS-CoV-2 to ACE-2, the S protein undergoes activation by a two-step protease cleavage. Membrane fusion helps the virus to enter the pulmonary alveolar epithelial cells. The viral contents are then released in the cells. In the host cell, the virus undergoes replication followed by formation of a negative-strand ribonucleic acid (RNA) by RNA polymerase activity. This newly formed negative-stranded RNA helps to produce new strands of positive RNAs and finally there is synthesis of new proteins in the cytoplasm. A greater immune response is observed during this phase and there is release of C-X-C motif chemokine ligand 10 (CXCL-10) as well as interferons (IFN-β and IFN-λ) from the infected cells. The pneumocytes now release many different types of cytokines and inflammatory markers such as interleukins (IL-1, IL-6, IL-8, IL-120, IL-12); tumour necrosis factor-α (TNF-α); IFN-λ and IFN-β; CXCL-10; Monocyte chemoattractant protein-1 (MCP-1); Macrophage inflammatory protein-1α (MIP-1α). The 'cytokine storm' now acts as a chemoattractant for neutrophils, CD4 helper T cells, CD8 cytotoxic T cells. These cells are mainly responsible for acting against the virus but they also cause subsequent inflammation and lung injury. This results in apoptosis of host cells with the release of new viral particles, which then infect the adjacent type 2 alveolar epithelial cells.[1-2]

Covid 19 and Diabetic Individuals

ACE2 is expressed in pancreatic islets, vascular endothelium, adipose tissue. SARS-CoV-2-ACE2 interaction in these tissues, and other factors, governs the spectrum of the disease. A pro-inflammatory milieu interior is seen in patients with metabolic syndrome. This may also contribute towards COVID-19-mediated dysregulation of host immune responses (suboptimal immune responses; hyper inflammation; microvascular dysfunction; thrombosis).[3]

Several features of diabetes and obesity may result in the accentuation of the clinical response to SARS-CoV-2 infection. These include an impaired immune response, atherothrombotic state, accumulation of advanced glycation end products as well as a chronic inflammatory state. These may result in exaggerated cytokine response to viral infection. Exaggerated cytokine response may trigger progression of worsening of patients and lead to septic shock, acute respiratory distress syndrome (ARDS) and multi-organ failure (MOF). Infection also leads to an inflammatory response and tissue damage resulting in increased metabolic activity. There is also an increase in the mechanism by which cells ingest, degrade tissue debris as well as foreign materials.[4-8]

Diabetic subjects were found to have an increased risk of developing severe Covid-19 infection as compared to non-diabetic counterparts (OR of 2.61) as found in a meta-analysis of 31 studies (6104 subjects).[5] Another meta-analysis conducted on 14 studies which included 4659 cases from China and the USA observed that pre-existing diabetes increased the risk of death with OR 2.0.[6] A meta-analysis including 33 studies with 16003 patients observed the prevalence of diabetes in 11.2 % of cases. Diabetes increased the risk of severe disease with OR 2.75 and death with OR 1.90.[7] A meta-analysis of 30 studies including 6452 cases demonstrated that diabetes increased the risk of severe Covid-19 with OR 2.45, and of death with OR 2.12. Diabetes increased the risk with OR 2.38 in an analysis of composite poor outcomes. A subgroup analysis showed that the risk was stronger in younger cases with median age < 55 years-old (RR 3.48) as compared to older cases ≥ 55 years-old (RR 1.92).[8]

Many spectra of the innate and adaptive immune systems are impaired in diabetes and obesity. There is inappropriate T-cell action. Activity of natural killer cell activity phagocytic cell may be impaired. There may be defects in the complement pathway and chemotaxis mechanism of neutrophils. The immunocompromised body mechanisms of diabetic individuals may lead to impaired responses to many stimuli activated during infections. Impaired immune cell function may also reduce viral clearance and this has been demonstrated in a recent study conducted on diabetic patients with Covid-19 infection. The compromised immune system of diabetic individuals increases susceptibility to a potential secondary nfection.[1-8]

Chronic low-grade inflammation is seen in diabetic individuals which may be a result of excess calorie intake resulting in stimulation of pancreatic β-cell insulin secretion. This leads to an increase in oxygen consumption resulting in cell stress and mild inflammation. Adipocytes and macrophages release an increased amount of proinflammatory cytokines and chemokines and less anti-inflammatory cytokines and adipokines. These factors can then increase insulin-resistance leading to more pancreatic insulin release and thus establish a vicious cycle.[1-8]

In obese and diabetic individuals, this chronic low-grade inflammatory state may aggravate the inflammatory response to SARS-CoV-2 infection resulting in precipitation of the hypersensitivity reaction and cytokine storm. Hypersensitivity reaction and cytokine storm can lead to pneumonia, ARDS and MOF. Higher levels of IL-6, CRP, fibrinogen have also been reported in COVID-19 patients with diabetes. The cytokine storm is part of the stress response preparing the body for a severe insult with activation of the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, a tissue defense response as well as an acute-phase reaction. These help to generate pro-coagulant factors, in preparation for tissue damage.[1-6]

Age and Gender

The COVID-19 pandemic has shown a markedly low proportion of cases among children with children having lower susceptibility to infection, lower propensity to show clinical symptoms, or both. Davis NG et al. evaluated these possibilities by fitting an age-structured mathematical model

to epidemic data from China, Italy, Japan, Singapore, Canada, South Korea. In the study, it was estimated chances of infections in adults over the age of 20 were twice more likely as compared to younger population. Clinical symptoms were observed in 21 % of infections in the age group of 10 to 19, while clinical symptoms were seen in 69 % of infected people aged above 70 years. It was concluded that without effective control measures, regions with relatively older populations are likely to observe disproportionally more cases of COVID-19, particularly in the latter stages of an unmitigated epidemic.[9]

Laxminarayan R et al.[10] analysed data from Tamil Nadu and Andhra Pradesh in India. This primary data of this high-incidence setting provided a detailed description of severe acute respiratory syndrome coronavirus 2 transmission pathways and mortality. Reported cases and deaths were concentrated in young cohorts in this study which is a different finding as compared to studies conducted in higher-income countries. Life expectancy at birth in India is 69 years, China 77 years, the United States 79 years, Italy and South Korea 83 years respectively. Socio-economic factors may be a cause of the difference in concentration of cases and deaths in younger cohorts in the Indian population as compared to the above countries. 575,071 subjects were exposed to 84,965 cases. Infection probabilities were found to be 4.7 to 10.7 % for low-risk and high-risk contact types. The greatest infection risks were associated with same-age contacts. Case fatality ratios ranged between 0.05 % at ages of 5 to 17 years and increased to 16.6 % at ages of 85 years or greater.

Data from ten European countries collected during the present pandemic provides details of distribution of COVID-19 cases by sex and gender. Among working age group, women diagnosed with COVID-19 outnumbered men and this pattern was reversed around the age of retirement. Females in the age group of 20 - 59 had higher risks and incidences of Covid-19 infection. Males had infection rate peaks in the age group of 70 - 79. Women working in healthcare-related occupations had higher incidences of infections. 75 % and 85 % of professionals in health care and social work who were infected were women. The "occupational disadvantage" might account for the overall higher rate of infections among women in European countries.[11]

Cardiovascular disease (CVD) was traditionally viewed as a disease that predominantly affects males. But in the postmodern society, the relative risk for obesity and hypertension-induced morbidity and mortality and the major risk factors for CVD have been observed to be higher for women across many countries of the world. Stress may be defined as perceived threat that influences the individual's homeostasis which results in the activation of neuroendocrine and sympathetic autonomic responses. Stressful experiences are the most significant factors responsible for the development of obesity, insulin resistance, heart disease in women. The purpose of a study conducted by Murphy MO et al. was to highlight the fact that women perceive more stress, and this increased perception of stress in females leads to obesity-associated metabolic disturbances and CVD.[12] Occupational stress and other stressful events during the pandemic may be the cause of the results of Sobotka T et al.[11] which is in variance with other studies showing a female preponderance in COVID-19 patients and worse outcomes.

In a systematic review conducted by Levin AT et al.[13] an exponential relationship between age and infection fatality rate (IFR) for COVID-19 was observed. The estimated age-specific IFR was seen to increase progressively to 0.4 % at 55 years; 1.4 % at 65 years; 4.6 % at 75 years; 15 % at 85 years. 90 % variation in IFR across geographical locations and population was observed. This reflects differences in the age composition of different populations across the globe and the extent to which relatively vulnerable age groups were exposed to the virus.

The COVID-19 mortality risk is greatly increased in older ages, particularly those aged 80+ years. Case fatality rate (CFR) in China, had ranged from 0.4 % for 40 years to 49 years to 14.8 % for that 80+ years.[14] In South Korea, CFR for those 80+ years is 18.31 %.[15] In Italy, CFR observed is 0.7 % for patients aged 40 years to 49 years; 27.7 % for those > 80 years, and 96.9 % of deaths occurring in those aged 60 years and over.[16] The importance of age structure for COVID-19 transmission and fatality may partially explain the remarkable variation in fatalities across different countries. Italy has one of the oldest populations, with 23.3 % of the population over 65 years, compared to 12 % in China.[16] Italians also prefer to live close to extended family, so contact between different age groups is more and this increases the risk of transmission of the virus among vulnerable populations.[17-18]

Data was collected from 287 consecutive patients with COVID-19 at two hospitals in New Orleans by Xie J et al.[19] Metabolic syndrome was present in 66 % of patients and was significantly associated with mortality [aOR 3.42]; intensive care unit (ICU) admission (aOR 4.59); invasive mechanical ventilation (aOR 4.71); and acute respiratory distress syndrome (aOR4.7).

When considering fatalities in relative terms across age groups, no significant differences between countries in different studies have been observed. Case fatalities increase over 60 years of age. This may mostly be as a result of lowered immunity and a higher prevalence of chronic illnesses in the elderly. Another factor of heterogeneity in mortality due to COVID-19 is gender with males having a higher risk compared to females. Testosterone and oestrogen seem to be the keys to adapting the body's immune responses. The male disadvantage is evident in COVID-19 fatality. Although current disaggregated datasets are incomplete, the higher fatality rate for men may derive from gender-based immunological differences, or be associated with comorbidities, including diabetes, hypertension, cardiovascular diseases, and alcohol consumption. The researchers concluded that the underlying inflammation seen in metabolic syndrome may be the driver leading to these more severe cases. Obesity, diabetes, high blood pressure, abnormal cholesterol levels were all predictive of higher incidents of death in COVID-19 patients.[19-26]

Cytokine Storm a Challenging Management Considerations

Current management of COVID-19 includes preventive and supportive therapy. Different therapies have been advocated to prevent and treat the cytokine storm. Cytokine storm also known as cytokine release syndrome (CRS) occurs usually in critically ill patients with COVID-19. COVID-19 causes a biphasic immune response. During the incubation and mild phases, there is a specific adaptive immune response essential to eliminate the virus and to stop disease progression to severe stages. As the virus enters the cells, they are recognized by innate immune cells by pathogen-associated molecular patterns. Single-stranded RNA binds to pattern recognition receptors (PRRs). Double-stranded RNA binds to endosomal toll-like receptors as well as cytosolic retinoic acid-inducible gene-I-like receptors. These receptors stimulate signalling pathways leading to the activation and nuclear translocation of transcription factors, nuclear factor-κB, interferon regulator factors. These lead to the secretion of type I interferons, pro-inflammatory cytokines, and chemokines. Type I IFNs produced by macrophages, pneumocytes, and dendritic cells stimulate IFN-stimulated genes that inhibit viral entry and replication and enhance clearance of viruses.[20-23]

In CRS, a cytokine profile is seen which is characterized by increased IL-2, IL-6, IL-7, GCS-F, INF-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, tumour necrosis factor-α. The cytokine profile resembles secondary hemophagocytic lymphohistiocytosis which is usually triggered by viral infections. There is also huge release of proinflammatory cytokines like IL-2, IL-8 TNF-α, IL-6. These cause dysregulated hyperimmune responses. This immunopathogenesis usually leads to acute lung injury as well as acute respiratory distress syndrome. Low-dose corticosteroids and heparin have been found to be beneficial in the management of cytokine storms. The use of serine protease inhibitors (ulinastatin) has also been advised. Therapies with high-dose of vitamin C, interleukin-6 inhibitors (tocilizumab) have also been advocated. Therapies with Janus kinase inhibitors and neurokinin-1 receptor antagonists need further research and evidence. The use of blood purification strategies, as well as convalescent plasma, may be promising in some critically ill patients.[20-26]

Metabolic syndrome has been placed as an important risk factor for COVID-19 across different continents in multiple studies. In a study conducted in the U.S., among 1482 patients hospitalized with COVID-19 in fourteen states, 12 % had a history of comorbidities. Among patients having comorbidities, 49.7 % were hypertensive; 48.3 % were obese; 34.6 % had chronic liver disease, 28.3 % were diabetic; 27.8 % had cardiovascular diseases.[23] In a study conducted in China among 191 patients with COVID-19 who were followed up, 48 % had comorbidities: hypertension 30 %, diabetes 19 % and coronary disease 8 %.[24] Brazil had 347,398 cases of COVID-19 and 13,868 deaths were associated with comorbidities. Heart disease: 7318 deaths; diabetes: 5627; renal disease: 1218; neurological disease: 1159; pulmonary disease: 1061; obesity: 742; immunosuppression: 740; asthma: 397.[25] Detailed understanding of the interplay between MS, COVID-19, and proposed therapies is essential for optimal management of patients as many patients with COVID-19 have comorbidities related to MS. Costa FF et al.[22] conducted a systematic review. Results showed that patients with metabolic disorders may have a higher challenge of infection of COVID-19. These problems were found to have a negative impact on the development and prognosis of the disease and were associated with worse outcomes in patients. MS has been found to be a high-risk factor influencing the development and prognosis of the present corona virus disease. No specific drug regimen has been recommended as a cure till date. It was suggested in the review that the development of a vaccine for immunization remains the best long-term solution.

Yanai H[27] conducted a systematic review to study the association of metabolic syndrome and susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as well as the severity of COVID-19 in these patients. In patients with metabolic syndrome dysregulation of adipocytokines induce excess ACE2 expression, procoagulant state, endothelial dysfunction. All these changes may play a crucial role in the development of severe COVID-19. A review was conducted by Matias NJ et al.[28] to study the relationship between the factors inherent to MS and COVID-19. The results showed that insulin resistance caused by centripetal obesity and an environment abundant in pro-inflammatory cytokines favours the immune imbalance. The additive effect of inflammatory secretory patterns of MS with the cytokine storm of COVID-19 may be the result of worsened prognosis observed in COVID-19 patients with MS. ACE2 has been observed to be widely expressed in the respiratory epithelium and belongs to the pressure regulation mechanism. SARS-CoV-2 as well as arterial hypertension share pathways through ACE2. Dyslipidemia also promotes increased cardiovascular risk leading to thrombotic events and thus increases morbidity and mortality in infected individuals.

The viruses in this pandemic seem to have acquired the ability to exploit these mechanisms which facilitate their invasion into the cells and life-cycle. In patients with metabolic syndrome, these mechanisms are chronically activated as a result of the perturbed metabolism which seems to provide an increased opportunity for a more intense and sustained viral infection.[4]

CONCLUSIONS

There is a proinflammatory milieu interior in individuals with metabolic syndrome and abnormal immunological profile which favours the viral infection and progression of the disease with poor outcomes. MS thus represents a critical element that needs to be considered in COVID-19 patients, as it grossly impacts the prognosis of the outcome involving various mechanisms.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Parashar A. COVID-19: current understanding of its pathophysiology, clinical presentation, and treatment. Postgraduate Med J 2020;97:312–320.

[2] Krams IA, Luoto S, Rantala MJ, et al. Covid-19: Fat, Obesity, Inflammation, ethnicity, and sex differences. Pathogens 2020;9(11):887.

[3] Bansal R, Gubbi S, Muniyappa R. Metabolic syndrome and COVID 19: endocrine-immune-vascular interactions shapes clinical course. Endocrinology 2020;161(10):bqaa112.

[4] Holly JMP, Biernacka K, Maskell N, et al. Obesity, diabetes and COVID-19: an infectious disease spreading from the east collides with the consequences of an unhealthy western lifestyle. Front Endocrinol (Lausanne) 2020;11:582870.

[5] Wang X, Fang X, Cai Z, et al Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: a systemic review and meta-analysis. Research (Wash D C) 2020;2020:2402961.

[6] Tian W, Jiang W, Yao J, et al Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. J Med Virol 2020;92(10):1875–1883.

[7] Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr 2020;14(4):535-545.

[8] Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 2020;14(4):395-403.

[9] Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020;26(8):1205-1211.

[10] Laxminarayan R, Wahl B, Dudala SR, et al. Epidemiology and transmission dynamics of COVID-19 in two Indian states. Science 2020;370(6517):691-697.

[11] Sobotka T, Brzozowska Z, Muttarak R, et al. Age, gender and COVID 19 infections. https://DOI.org/10.1101/2020.05.24.20111765

[12] Murphy MO, Loria AS. Sex-specific effects of stress on metabolic and cardiovascular disease: are women at higher risk? Am J Physiol Regul Integr Comp Physiol 2017;313(1):R1-R9

[13] Levin AT, Hanage WP, Owusu-Boaitey N, et al. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. Eur J Epidemiol 2020;35(12):1123-1138.

[14] The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 2020;41(2):145-151.

[15] Salmon A. Why are Korea's COVID-19 death rates so low? Asia Times, 11 March 2020. https://asiatimes.com/2020/03/why-are-koreas-covid-19-death-rates-so-low/.

[16] United Nations, World Population Prospects 2019. https://population.un.org/wpp/DataQuery/.

[17] Kalmijn M, Saraceno C. A comparative perspective on intergenerational support. Eur Soc 2008;10(3):479–508.

[18] Istituto Nazionale di Statistica, Spostamenti Quotindiani e nuove forme di Mobilità [Daily Shifts and New Forms of Mobility]. https://www.istat.it/it/archivio/224469.

[19] Xie J, Zu Y, Alkhatib A, et al. Metabolic syndrome and COVID19 mortality among adult black patients in new Orleans. Diabetes Care 2020;44(1):188-193.

[20] Goujon A, Natale F, Ghio D, et al. Age, gender, and territory of COVID-19 infections and fatalities. EUR 30237 EN, Publications Office of the European Union, Luxembourg. 2020, ISBN 978-92-76-19180-3, DOI: 10.2760/838390, JRC120680.

[21] Mehta Y, Dixit SB, Zirpe KG, et al. Cytokine storm in novel coronavirus disease (COVID-19): expert management considerations. Indian J Crit Care Med 2020;24(6):429-434.

[22] Costa FF, Rosário WR, Farias ACR, et al. Metabolic syndrome and COVID-19: an update on the associated comorbidities and proposed therapies. Diabetes Metab Syndr 2020;14(5):809–814.

[23] Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-net, 14 STATES, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020;69(15):458-464.

[24] 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(10229):1054–1062.

[25] Ministério da Saúde (BR) Boletim epidemiológico especial COE-COVID-19: semana epidemiológica 2020.

[26] Brasília (DF) https://www.saude.gov.br/images/pdf/2020/May/29/2020-05-25---BEE17--Boletim-do-COE.pdf

[27] Yanai H. Metabolic syndrome and COVID-19. Cardiol Res 2020;11(6):360-365.

[28] Matias JN, Santos Campanari GS, de Souza AG, et al. Metabolic syndrome and COVID-19. AIMS Bioengineering 2020;7(4):242-53.