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Association of Gender, Age, and Comorbidities with COVID-19 infection in India

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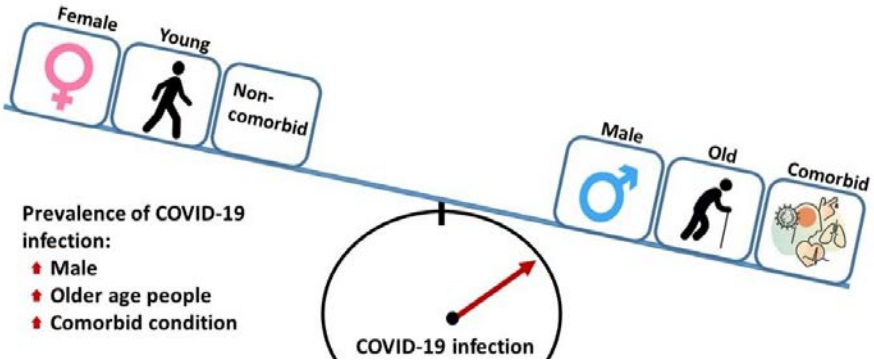
ABSTRACT



Due to a lack of data on various parameters with COVID-19 in the Indian population, this study was carried out to understand the relation among gender, age and comorbidities in Indian population. The data was collected using a questionnaire-based survey form that included questions on demographic characteristics, infection and any pre-underlying conditions (n=1146). The data showed that the male patients had suffered more from COVID-19 (58.6%). Also, the patients suffering from comorbidity are more likely to suffer from a severe form of COVID-19 and obesity/overweight was identified as the most prevalent (n=69) comorbid condition, followed by diabetes (n=35), thyroid (n=19) and hypertension (n=11). In severe COVID-19 cases, 85% of patients had a comorbid condition. In another study of COVID-19 hospitalized-cases, about 97% of patients were found to have an underlying medical condition. Among these, diabetes (55.9%) was identified as the most prevalent comorbidity. Males and older people are at a higher risk of developing COVID-19 infection in Indian population. The comorbid conditions also predisposed individuals to COVID-19 and aggravated the infection.

Keywords: COVID-19, comorbidity, age, gender, obesity, diabetes, hypertension

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) belongs to a family of Coronaviridea causing coronavirus disease-19 (COVID-19), which was declared a global pandemic on 11 March 2020 by the World Health Organization (W.H.O.). As of 15 December 2021, it has affected about 270 M people worldwide, including 34.7 M cases from India.[1] Due to its heterogeneity, the virus infects people with various degrees of symptoms. In critical cases, it can also lead to mortality in patients due to lung failure, heart attack or multiple organ failure.[2] Since coronavirus has been continuously evolving, it is difficult to anticipate its impact in the affected population. The morbidity and mortality in COVID-19 infection depend on several factors. A number of reports have claimed a higher risk of COVID-19 infection in males than in females due to higher expression of ACE2 receptors in males.[3] A number of retrospective studies have shown that older people are more predisposed to COVID-19 infection, and showed a higher

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mortality rate. Reports have also revealed that people already suffering from an underlying disease, such as obesity, hypertension and diabetes, have shown worse prognosis.[4–6]

The immune system of patients plays a key role in defense against COVID-19 infection. COVID-19 patients with over-activated immune response experience inflammation of lungs due to infiltration of cytokines, which makes their condition severe.[7] The presence of comorbidities, such as diabetes and hypertension, in COVID-19 patients adversely affects the functioning of the immune system, and therefore may impact the clinical outcome of the disease in patients. Since COVID-19 is a novel disease, its clinical treatment relies on the permutation and combination of drugs; however, COVID-19 combating drugs may interfere with the comorbid conditions and lead to worst consequences.[8] Consequently, the treatment of COVID-19 infection in comorbid patients remains a challenge due to the availability of limited treatment options.[9]

Although numerous studies are being carried out across the world to understand and combat COVID-19, yet the understanding about its demographic distribution and clinical features of patients is unpredictable, due to the novel nature of the virus. A number of studies have also been reported from India; however, since the median age of the population is 28.43 years, it would be interesting to examine the relation between COVID-19 and age that has not been studied effectively. Moreover, due to large population size, a very high percentage of Indian population is suffering from an underlying condition, and therefore, our study is focused on the role of comorbidity in severe COVID-19 cases. The study examines the progression of COVID-19 in patients of all age groups and genders suffering from any underlying disease, and evaluates their association with the risk of COVID-19 infection.

MATERIALS AND METHODS

Data source

The current study is a cross-sectional study wherein the participants from all over India were asked to fill a survey form, sharing data about their age, gender, COVID-19 status, severity of the disease, symptoms, hospitalization and comorbidity, if any. The study was approved by the IHEC of ACBR, University of Delhi as per ICMR guidelines (Ref. No.: ACBR/IHEC/DS-07/08-2020). Prior consent was taken from the participants of the study who were also informed about the purpose and nature of the study. The confirmed cases of COVID-19 were included in the data analyses and unaffected people were considered as a control group. The cases were classified as asymptomatic, mild, moderate and severe based on the symptoms and hospitalization as disclosed by the participants. The 'asymptomatic' and 'mild' cases did not report breathing issues and recovered at home without any need of hospitalization, while the 'moderate' cases reported breathing difficulties and required oxygen. The 'severe' cases required ventilator and hospitalization due to shortness of breath and other medical complexities. The reported comorbid conditions are included in the current study without any filter, while obesity was calculated based on Body-Mass-Index (BMI) from the information received on height and weight from the participants.

A parallel study of hospitalized cases is also included wherein the survey was done on patients hospitalized due to COVID-19. All those patients were categorized in 'severe' category since they all had breathing issues due to low SpO_2 and needed ventilators for days to recover. The data of this study was used to analyze the relation of age, gender and any comorbidities to the clinical outcome of the hospitalized patients and comparison with the cross-sectional study.

Data analysis

The statistical analysis of the data collected was carried out using the Chi-square test for categorical variables and expressed as a number (or percentage). The significance level of all hypothesis was tested by a two-sided α value of less than 5% to determine the effect of age, gender and different comorbidities on the infection rate of SARS-CoV-2 and severity of the disease in Indian patients.

RESULTS

Participant's demographics

A total of 1146 people from all over India participated in the online survey. The demographic characteristics of participants are given in Table 1.

Among the respondents, gender was found almost equally distributed (49.7% females and 50.3% males). The study participants had a higher representation of respondents aged 18 to 30 years (49.6%) followed by aged 31-40 years (28.5%). Body mass index (BMI) was calculated based on the height and weight reported by the participants. Around 36.8% of participants were overweight (BMI ranged 25-29.9 kg/m²), however, 8.3% of participants were obese. Of note, about 52.8% of the study participants had experienced COVID-19. About 36.9% of the study participants were academicians followed by professional and managerial occupations (32%). Around 81.8% participants were from North India.

Influence of gender and age in COVID-19 infection

The data collected showed that in a random study of 1146 people, 605 were infected with SARS-CoV-2 between 18 May, 2020 (first patient) and 26 June, 2021 (database lock). In 2020, the number of COVID-19 cases was about two times less (n=187) than that in 2021 (n=406). Among the patients, the number of males (~66% in 2020 and ~55% in 2021) with confirmed COVID-19 infection was significantly higher [Chi-square value (χ^2) =5.7, Critical value (CV)=3.8, p =0.02] than that of the females (~34% in 2020 and 45% in 2021) (Fig. 1a.). Since in India, the median age of population is ~30 years, most of the COVID-19 cases were reported in the younger population ≤40 years of age (n=437/605), while the remaining 167 cases were reported in the population >40 years (Fig. 1b; χ^2 = 2.8, CV = 3.8, p = 0.09). The most common symptoms among the affected patients were body ache, loss of smell and taste, high fever, headache, and sore throat.

Relation between comorbidities and infection

The survey-based study on the relation between COVID-19 and comorbidities showed that among a total of 605 patients, 154 had underlying diseases, such as diabetes, hypertension and heart conditions. In patients with no comorbidities (n=446), 19% showed severe symptoms as compared to ~27% (n=154) with comorbidities. The percentage of asymptomatic cases in the non-

Table 1: Demographic characteristics of the study respondents

Characteristics	n	% Study participants, n = 1146
Gender		
Female	569	49.7
Male	576	50.3
Prefer not to say	1	0.09
Age group (years)		
18-30	568	49.6
31-40	326	28.5
41-60	214	18.7
61 and above	37	3.2
Not known	1	0.09
BMI (kg/m²)		
Under weight (<18.5)	87	7.6
Normal weight (18.5-24)	519	45.3
Overweight (25-29.9)	423	36.9
Obese (>30)	95	8.3
Not known	22	1.9
COVID affected (Ever have experienced with COVID-19)		
Yes	605	52.8
No	541	47.2
Occupation Category		
Academician	422	36.8
Frontline workers	177	15.4
Housewife/ Retired/ Unemployed	161	14.1
Professionals and Managerial	367	32.0
Not known	19	1.7
Region of India		
Central	3	0.3
East	47	4.1
North	938	81.8
Northeast	27	2.4
South	34	3
West	76	6.6
Not Known	21	1.8

comorbid patients was 23%, while in the comorbid ones, it was 11% (Fig. 2a; χ^2=25.4, CV=7.8, p = 1.2E−05).

The most common underlying conditions present in the patients (χ^2=59.07, CV=7.8, p=9.2E−13) were obesity/overweight (n=69), diabetes (n=35) and thyroid (n=19), followed by hypertension (n=11) (Fig. 2b). Lung disorder was also present in 6 patients. In the case of severe patients who needed hospitalization with a long stay on ventilator, ~15% had no comorbidity, while 85% reported comorbidity after the normalization of data (Fig. 2c; χ^2=52.5, CV=3.8, p=4.15E−13).

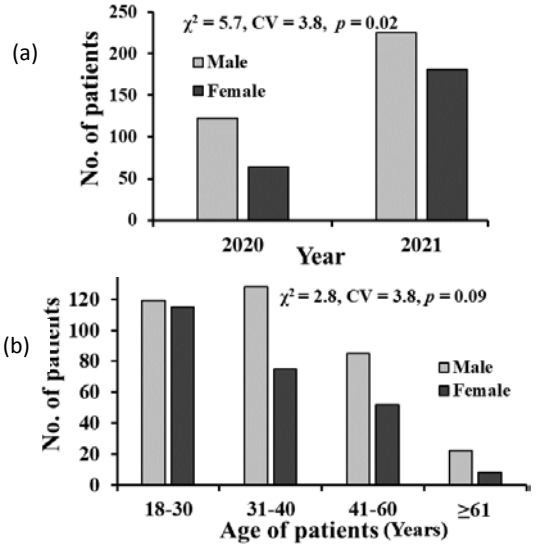

Figure 1. (a) Trend data of COVID-19 patients according to gender distributed year-wise in India (n=605). The χ^2 test for significance indicated that the no. of male patients infected with COVID-19 were higher than female (p=0.02). **(b) Age-wise burden of COVID-19 cases in India**. A relatively younger population (<40) has shown higher cases of COVID-19 (due to less median age group in India).

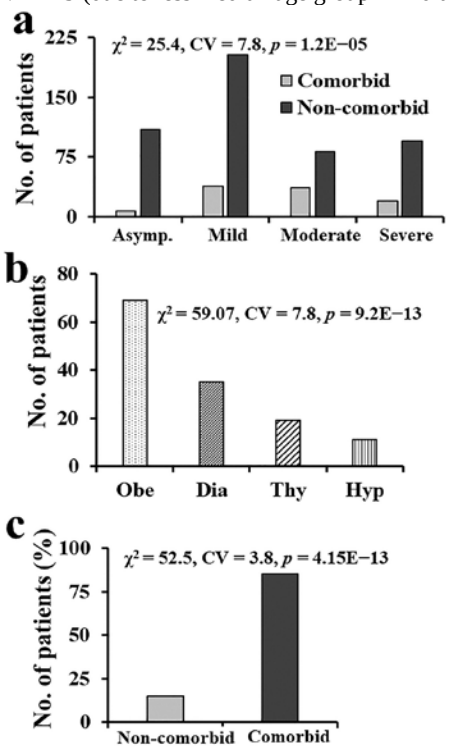

Figure 2. (a) Trend data of clinical classification of COVID-19 patients with comorbid and non-comorbid condition into asymptomatic (Asymp.), mild, moderate and severe. The χ^2 test indicated that asymptomatic cases in non-comorbid COVID-19 patients were higher compared to comorbid COVID-19 patients (p =1.2E-05). **(b) Comorbidities associated with COVID-19 infection**. The most prevalent underlying medical condition (p=9.2E-13) was obesity (Obe) followed by diabetes (Dia), thyroid (Thy) and hypertension (Hyp). **(c) Severity in COVID-19 patients in comorbid and non-comorbid conditions**. The significance analysis (χ^2) indicated that severe cases were higher in comorbid COVID-19 patients than non-comorbid COVID-19 patients (p=4.15E-13).

Hospitalized cases study

The data comprising the prevalence of various comorbidities in the COVID-19 hospitalized cases (n=114) were also collected. Out of 114 hospitalized cases, 111 patients had an underlying medical condition, while only 3 patients had no comorbidity (Figure 3a; p=4.73E−24). In the comorbid patients, 72 (~65%) were males, while only 39 (35%) were females (Figure 3b; χ^2=9.8, CV=3.8, p=0.002). The majority of patients belonged to the age group of >61 (48.6%), while only 3.6% belonged to <30 (Figure 3c; χ^2=67.3, CV=7.8, p=1.6E−14). Few hospitalized patients were showed more than one underlying disease. The most prevalent comorbidities present in the hospitalized cases (Figure 3d; χ^2=11.3, CV=11, p=0.04) were diabetes (55.9%), hypertension (48.9%), thyroid (11.7%), cardiovascular diseases (9%) and lung disorder (7%).

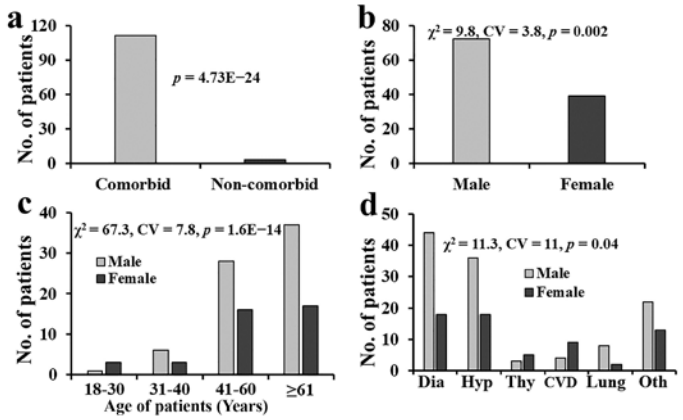

Figure 3. (a) Trend data of comorbid and non-comorbid condition in COVID-19 patients in hospitalized cases (procured from hospital, n=114). The χ^2 analysis showed that a significantly higher no. of hospitalized COVID-19 patients had an underlying medical condition (p=4.73E-24). **(b) Gender-wise distribution of hospitalized COVID-19 patients**. Statistical significance analysis (χ^2) showed that males are more prone to severe condition in COVID-19 infection compared to female (p=0.002). **(c) Age-wise distribution of hospitalized COVID-19 cases**. Trend data indicated that significantly higher COVID-19 cases (p=1.6E-14) belong to age group >61 compared to other age groups. **(d) Distribution of hospitalized male and female COVID-19 patients according to different comorbid conditions.** The most prevalent comorbid condition (p=0.04) in COVID-19 hospitalized patient was diabetes (Dia.) followed by hypertension (Hyp.), thyroid (Thy.), cardiovascular diseases (CVD), lung disorder (Lung) and others (Oth).

DISCUSSION

COVID-19 pandemic has been adversely affecting the world's population by causing different levels of morbidity and mortality. A number of studies based on the clinical underlying conditions in the patients described it as a gender-biased disease that affects males more frequently than females.[10] Studies have also reported that old age and comorbidities enhance the risk of infection, with mortality rate higher in people with pre-underlying medical conditions.[6] Based on the current study, it is evident that males are more prone to this infection than females. A meta-analysis study by Biswas et al.[11] reported that infection and mortality in the male patients were significantly higher than in the female patients. Another study revealed a global fatality rate of 7.3% in males compared to 4.4% in females.[12] Previous reported cases of SARS and Middle East respiratory syndrome (MERS) epidemic also had the similar findings of male bias mortality.[13,14] Various hypotheses have been given in support of these findings. An interesting study during the SARS epidemic demonstrated that the removal of ovaries or blocking of estrogen release using drugs in female mice led to an increased infiltration of immune cells, resulting in a severe outcome of the disease.[13] Although a precise molecular pathway of estrogen functioning in COVID-19 protection is yet to be established, several reports have already suggested the role of estrogen in providing immunity, preventing aging and controlling ACE2 levels.[13] Another reason reported is the higher expression of angiotensin-converting enzyme 2 (ACE2) under the control of male sex hormones, rendering them the prime target of SARS-CoV-2 infection.[15] As the ACE2 gene specifically lies on the X-chromosome, it expresses in higher amount in males (homozygous for all X-lying genes). However, few studies contradict the idea of the role of ACE2 in higher COVID-19 infections in males, and rather consider ACE2 a blessing in disguise that protects organ failure in severe COVID-19 cases.[16] Therefore, a thorough evaluation of ACE2 regarding its expression and role in COVID-19 needs to be conducted based on histological and clinical studies before arriving at any conclusion.

A number of studies have reported that people suffering from any underlying medical condition are at a greater risk of COVID-19 infection.[17,18] As older people are more prone to comorbidities, COVID-19 infection may lead to the development of severe symptoms and mortality in them. In agreement with the previous reports, our study has also confirmed that people with comorbid conditions are more prone to COVID-19 infection than the healthy population. The healthy population was found to be asymptomatic or had only mild symptoms of COVID-19 as compared to the comorbid population wherein the number of severe cases was higher.

In agreement with several other reports,[5,19] our survey also identified obesity as one of the most common underlying medical conditions, followed by diabetes, thyroid and hypertension. However, the hospitalization data found diabetes as the most common underlying medical condition. Nevertheless, as per reports, diabetes and hypertension are constantly associated comorbidities in COVID-19 cases.[20]

In our study of hospitalized cases, diabetes has been observed as the most prevalent comorbidity, while in the random population survey, it was positioned at the second place after obesity. The most likely reason is predominance of diabetes in the world, including India. In addition, various reasons have been identified for the prevalence of diabetes in COVID-19 patients, such as the susceptibility of hyper-inflammation leading to cytokine storm and weakening of the immune response by inducing oxidative stress. The treatment of diabetes by ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARB) may also increase the risk of COVID-19 infection by inhibiting conversion of angiotensin 1 to angiotensin 2.[21,22] Hence these treatments can increase expression of ACE2 that is considered a route for SARS-COV-2 entry. The innate immune response during COVID-19 is also hampered by the

anti-inflammatory effect of DPP4 inhibitors used in diabetes treatment.[23]

Studies have revealed that hypertensive patients are at a higher risk of severe COVID-19 infection.[24] The risk to hypertensive patients might be due to their mode of treatment in which similar drugs (ACEI and ARB) to those for diabetes are used in the treatment of hypertension.[25,26] Moreover, ACE2 expression is high in the heart, along with pericytes, fibroblasts and cardiocytes,[27] that is a predisposition for viral entry into the heart. However, in the absence of concrete information, the role of ACE2 is still unclear and the research is ongoing.

Obesity is generally considered a lifestyle disease and is mostly associated with cardiovascular disease, diabetes or hypertension. The BMI calculation in our cross-sectional study has identified obesity as the highest comorbid condition in COVID-19 patients. Previous studies have reported that obesity might weaken the immune response to infection, leading to compromised B-and T-cell activity.[28] In addition, a recent study has reported that human adipose tissue has high expression of ACE2 and acts as reservoir for SARS-CoV-2 that elicits production of inflammatory mediators in severe COVID-19 cases.[29] Thus, obese people are strongly susceptible to COVID-19 infection and its severity.

The data on the association of thyroid disease with COVID-19 is scarce; however, a few reports have suggested a strong link between them.[30] Our findings are in agreement with these reports and have identified thyroid as a potential risk factor in COVID-19 infection. The results can be explained on the basis of dysregulation of innate immune response in thyroid disease as thyroid hormones are important molecules to maintain robust innate immunity that act as a primary barrier to prevent the virus entry.[30] The levels of pro-inflammatory cytokines (TNF-α and IL-6) were also found to be higher in thyroid patients as well as in the severe cases of COVID-19 leading to cytokine storm.

In view of these findings, it is essential that a close monitoring of underlying medical conditions in COVID-19 patients is carried out to combat the disastrous effects of SARS-CoV-2. The drugs prescribed for comorbid conditions during COVID-19 infection in the patients should not act as a mediator of inflammation, enhancing the deteriorating condition in such patients.

Conclusion

In India, COVID-19 infection is more prevalent in males than in females. Older people have a higher chance of other underlying clinical conditions; hence the age, along with comorbid conditions, predisposes the individuals to COVID-19 infection and may result in a severe form of the disease that can lead to mortality. In view of the above, it is necessary for older people with comorbid conditions to protect themselves from SARS-CoV-2 infection. In addition, if such people are hospitalized, they should be accurately cross-examined for any comorbid conditions, and drugs prescribed for comorbidity or for COVID-19 infection should be carefully inspected for any side effects.

Limitations of the study

The findings revealing the correlation of age, gender and comorbidities with COVID-19 in the current study are based on a survey analysis, and hence the study may have certain limitations. The mild, moderate and severe classification of COVID-19 cases was self-reported by the participants and therefore the chances of error or misreporting of conditions may be there. The comorbidities might be under-reported by COVID-19 patients due to the lack of health awareness or poor economic conditions, and hence remain undiagnosed. In the case of obesity, in particular, people rely more on appearance than BMI, and therefore might not be able to assess their condition correctly. All the above-mentioned limitations can affect the results and statistical significance of the current study.

Authors' contributions

JT, SKY, PB designed the survey form. JT, SKY, PB, SJ, DS collected the epidemiological data. PG provided clinical data. SKY, PB and JT analyzed the data. SKY drafted the manuscript. All authors read the manuscript and approved it.

Conflicts of interest

Authors declare that there is no financial, literary or otherwise conflict of interest for publication of this work.

Ethics approval/consent to participate

The study was approved by the IHEC of ACBR, University of Delhi as per ICMR guidelines (Ref. No.: ACBR/IHEC/DS-07/08-2020). The written consent from all the participants was secured prior to the survey.

References

1. WHO coronavirus (COVID-19) Dashboard https://covid19.who.int/.
2. C. Huang, Y. Wang, X. Li, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, 395 (10223), 497–506.
3. J.M. Jin, P. Bai, W. He, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front. Public Heal.* **2020**, 8, 152.
4. F.M. Noor, M.M. Islam. Prevalence and Associated Risk Factors of Mortality Among COVID-19 Patients: A Meta-Analysis. *J. Community Health* **2020**, 45 (6), 1270–1282.
5. L.A. Callender, M. Curran, S.M. Bates, et al. The Impact of Pre-existing Comorbidities and Therapeutic Interventions on COVID-19. *Front. Immunol.* **2020**, 11, 01991.
6. A. Sanyaolu, C. Okorie, A. Marinkovic, et al. Comorbidity and its Impact on Patients with COVID-19. *SN Compr. Clin. Med.* **2020**, 2 (8), 1069–1076.
7. W. Wang, B. Su, L. Pang, et al. High-dimensional immune profiling by mass cytometry revealed immunosuppression and dysfunction of immunity in COVID-19 patients. *Cell. Mol. Immunol.* **2020**, 17 (6), 650–652.
8. V. Lumb, P. Karwal. Intravesical BCG Immunotherapy for Non-Muscle Invasive Bladder cancer during COVID-19 pandemic: Mutual impact and implications. *Chem. Biol. Lett.* **2022**, 9 (2), 267.
9. G. Chen, D. Wu, W. Guo, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J. Clin. Invest.* **2020**, 130 (5), 2620–2629.
10. J. Karlberg, D.S.Y. Chong, W.Y.Y. Lai. Do Men Have a Higher Case Fatality Rate of Severe Acute Respiratory Syndrome than Women Do? *Am. J. Epidemiol.* **2004**, 159 (3), 229–231.
11. M. Biswas, S. Rahaman, T.K. Biswas, Z. Haque, B. Ibrahim. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Intervirology* **2021**, 64 (1), 36–47.
12. E.P. Scully, J. Haverfield, R.L. Ursin, C. Tannenbaum, S.L. Klein. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat. Rev. Immunol.* **2020**, 20 (7), 442–447.
13. R. Channappanavar, C. Fett, M. Mack, et al. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *J. Immunol.* **2017**, 198 (10), 4046–4053.

14. I.G. Alghamdi, I.I. Hussain, S.S. Almalki, et al. The pattern of Middle east respiratory syndrome coronavirus in Saudi Arabia: A descriptive epidemiological analysis of data from the Saudi Ministry of Health. *Int. J. Gen. Med.* **2014**, 7, 417–423.
15. D. Gemmati, B. Bramanti, M.L. Serino, et al. COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-Chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? *Int. J. Mol. Sci.* **2020**, 21 (10), 3474.
16. D. Gurwitz. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev. Res.* **2020**, 81 (5), 537–540.
17. A. Emami, F. Javanmardi, N. Pirbonyeh, A. Akbari. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. *Arch. Acad. Emerg. Med.* **2020**, 8 (1), e35.
18. S. Richardson, J.S. Hirsch, M. Narasimhan, et al. Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA - J. Am. Med. Assoc.* **2020**, 323 (20), 2052–2059.
19. W. Guo, M. Li, Y. Dong, et al. Diabetes is a risk factor for the progression and prognosis of <scp>COVID</scp> -19. *Diabetes. Metab. Res. Rev.* **2020**, 36 (7), 3319.
20. E. Burgos-Morón, Z. Abad-Jiménez, A.M. de Marañón, et al. Relationship between oxidative stress, ER stress, and inflammation in type 2 diabetes: The battle continues. *J. Clin. Med.* **2019**, 8 (9), 2–22.
21. R. Pal, A. Bhansali. COVID-19, diabetes mellitus and ACE2: The conundrum. *Diabetes Res. Clin. Pract.* **2020**, 162, 108132.
22. L. Fang, G. Karakiulakis, M. Roth. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir. Med.* **2020**, 8 (4), e21.
23. G. Iacobellis. COVID-19 and diabetes: Can DPP4 inhibition play a role? *Diabetes Res. Clin. Pract.* **2020**, 162, 108125.
24. E. Driggin, M. V. Madhavan, B. Bikdeli, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. *J. Am. Coll. Cardiol.* **2020**, 75 (18), 2352–2371.
25. A.M. South, D.I. Diz, M.C. Chappell. COVID-19, ACE2, and the cardiovascular consequences. *Am. J. Physiol. Circ. Physiol.* **2020**, 318 (5), H1084–H1090.
26. C.S. Kow, S.T.R. Zaidi, S.S. Hasan. Cardiovascular Disease and Use of Renin-Angiotensin System Inhibitors in COVID-19. *Am. J. Cardiovasc. Drugs* **2020**, 20 (3), 217–221.
27. L. Chen, X. Li, M. Chen, Y. Feng, C. Xiong. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc. Res.* **2020**, 116 (6), 1097–1100.
28. D. Frasca, A. Diaz, M. Romero, B.B. Blomberg. Ageing and obesity similarly impair antibody responses. *Clin. Exp. Immunol.* **2016**, 187 (1), 64–70.
29. G.J. Martínez-Colón, K. Ratnasiri, H. Chen, et al. SARS-CoV-2 infects human adipose tissue and elicits an inflammatory response consistent with severe COVID-19. *bioRxiv* **2021**, 2021.10.24.465626.
30. T.I. Hariyanto, A. Kurniawan. Thyroid disease is associated with severe coronavirus disease 2019 (COVID-19) infection. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2020**, 14 (5), 1429–1430.