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Original Article

Differences in COVID-19 mortality in males and females: Is estrogen hormone attributing to sex differences?

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ABSTRACT

Objectives: Globally, the case fatality ratio is more in males versus females. Some studies have suggested estrogen hormone decreases susceptibility to SARS CoV-2. We have analyzed the observed sex differences in COVID-19 behavior in males and females and the clinical profiles of females of different age groups of COVID-19 patients and discussed their symptoms, laboratory evaluations, and associated comorbidities.

Material and Methods: The patients were tested for COVID-19 through real-time RT-PCR (Reverse Transcription Polymerase Chain Reaction) assay. The data obtained were studied for the epidemiological, clinical, and laboratory characteristics from their medical records.

Results: The mortality rate in females was 12.33% (36/292) whereas mortality in males was 19.63% (84/428). In between group analysis, 8.7% (14/161) of females died in the <40 years age group versus 16.8% (22/131) in more than 40 years age group whereas in males, the mortality was 13.7% (21/153) in <40 years versus 22.9%(63/275). The mortality rate in women older than 40 years was greater than mortality in younger females emphasizing the protection provided by estrogen hormone in them. The proportion of patients who expired due to COVID-19 significantly differs by age cutoff of 40 years, X2 (1, n = 428). The difference is statistically significant at $P < 0.05$. Males more than 40 years are more likely to expire.

Conclusion: Sex-related differences in coronavirus pandemic have been found pointing toward the protective role of estrogen hormone and other differences in immunological behavior in males and females. Downregulation of ACE2 expression, thereby reducing viral entry, might also be contributory to decreasing mortality in females.

Keywords: COVID-19, Coronavirus, Perimenopausal females, Sex differences, Estrogen protection RT-PCR, Estrogen estradiol COVID-19, SARSCoV-2, Comorbidity

INTRODUCTION

Men are more susceptible to viral infections than women. Globally, the case fatality ratio is more in males versus females. Sex-related differences in coronavirus pandemic have been found. More intensive care admissions have been found in males compared to females. This study is designed to evaluate the sex differences in SARSCoV-2 outcomes and has emphasized the gender differences in COVID-19 behavior.

MATERIAL AND METHODS

This study was conducted in a dedicated COVID-19 facility with a retrospective analysis of the data collected between April 2020 and July 2020. Nasal and oral swab samples were collected from patients suspected of having COVID-19. Patients who had a clinical diagnosis of COVID-19 but were RT-PCR negative were excluded from this study. Informed consent was obtained from patients. Ethical clearance was obtained from our institutional committee and it follows the ethical principles of the World Medical Association Declaration of Helsinki. Epidemiological, clinical, laboratory, chronic illnesses (comorbidities) and radiological characteristics, and treatment and outcomes data were obtained from medical records and these data were reviewed and analyzed by a trained team of our institute. Laboratory and radiological parameters included were complete blood count, ESR, liver function test, renal function test, blood sugar, CRP, and ferritin levels. A fever was noticed when oral temperature >99*F. As our hospital is dedicated to L2 and L3 facilities, we admitted only moderate and severe cases of COVID-19. Data were analyzed using SPS Software. $P < 0.05$ was considered statistically significant.

RESULTS

Total of 720 SARSCoV-2-positive patients were admitted from April to July 2020 out of which 292 patients were females

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and 428 were males. Out of these 292 females, 161 females were <40 years of age and 131 females were more than 40 years of age that is perimenopausal and menopausal. The median age at admission was 58.30 (42–82 years). Maximum patients were house workers (112/131), 18 patients were working in a different occupation and one was paramedical staff working in our COVID hospital. Out of 131, 71 patients (54.20%) presented with a severe acute respiratory infection (SARI), the average SPO2 in patients who presented with SARI was 81. 26% (45–95) at room air at admission. Due to respiratory failure/ARDS, 17/131 (12.98%) patients expired despite ventilatory support who presented with SARI

Symptoms

Fever was the most prevalent symptom 56.49% (74/131) in patients with COVID-19, followed by breathlessness 52.67% (69/131), cough 35.11% (46/131), myalgia 9.16% (12/131), sore throat 8.40% (11/131), and chest pain, and diarrhea in 5.34% (07/131) equally. The other symptoms in these patients were abdominal pain in 02, epistaxis in 01, hemoptysis in 01, bleeding per rectum, and altered sensorium in 01 patients.

Laboratory investigation

About 34% of patients had low hemoglobin and 35.6% had low platelet counts. About 18.8% had lymphopenia while 12.3% had lymphocytosis. About 19.1% had leukocytosis. Markers of infection C-reactive protein (C-RP) were increased in 78% of patients, serum ferritin was increased in 63% and ESR was increased in 18%. LDH was increased in 44% of patients. Deranged renal function was seen in 46.23% of patients. Liver enzymes (SGPT/SGOT) were deranged in 56% of patients. Serum albumin was decreased in 46.4%. A small number of patients had dyselectrolemia, but 54% had decreased calcium levels. About 18% of patients had urinary tract infection. Nine patients had ketones in their urine and five were diabetic. About 38% of patients presented with increased blood sugar level at the time of admission and level of hyperglycemia was associated with poor outcome. When stratified by severity, those patients who had thrombocytopenia, increased CRP/ferritin and decreased calcium/albumin had poor outcome.

Chest X-Ray findings

The chest X-ray findings in patients who survived revealed that 40.37% (44/109) were normal, 17.43% (19/109) had unilateral consolidation while the rest 42.20% (46/109) had Bilateral consolidation at the time of admission. The left lung was involved more than the right. Among those patients who expired, unilateral consolidation was found in the chest X-ray of 31.82% (07/22), 54.55% (12/22) had bilateral consolidation, and 3/22 had normal X-ray of their lungs.

Comorbidities

Common comorbidities associated in our study were diabetes mellitus (DM), hypertension (HTN), cardiovascular diseases (CVD), chronic kidney diseases (CKD), and chronic liver disease (CLD). DM was associated with a total of 38 patients (29%) of which eight patients who have diabetes, expired. A total of 5 patients of DM presented with diabetic ketoacidosis and three patients were well managed but two patients could not survive. HTN was associated with total of 37 patients (28.24%), in which eight patients expired. CKD was associated with 17 patients (12.98%) of which 13 patients were on maintenance hemodialysis (HD). Three patients with CKD could not survive. Chronic lung diseases such as COPD, asthma, and old treated lung tuberculosis were found to be associated with nine cases out of which four could not survive. Hypothyroidism was associated with 08 patients (6.11%), two patients could not survive. A total of six patients were admitted with a previous history of CVD while one patient presented with the acute coronary syndrome (ACS). This patient of ACS along with one patient with rheumatic heart disease expired. CLD was associated with 6 females (04.58%) and 2 patients with CLD expired. Malignancy was associated with 4 females (03.05%). Other comorbidities found in this study were acute pancreatitis (one), cholelithiasis (two), fracture of lower limbs (two), and general tonic clinic seizure (one).

Treatment and outcome

Due to low oxygen saturation and other comorbidities, 32.82% (43/131) of patients were admitted to ICU. All patients in ICU were given oxygen through different types of masks, HFNC and BIPAP. A total of 32 patients required mechanical ventilation. Antibiotics, steroids, paracetamol, and low molecular weight heparin were administered in maximum patients according to need along with the standard of care treatment. Inj Remdesvir was given to 36 patients. We also transfused convalescent plasma in four patients, two survived. The patients who were admitted to wards and HDU were managed with standard of care treatment and needed as when. A total of 14 patients were given renal replacement therapy (HD) including 13 patients, already on HD. We also encouraged our patients to do Yoga and lung expanding exercises. We managed DM and steroid/stress induced hyperglycemia with insulin. Other symptoms were managed accordingly. One patient with cholelithisis was managed surgically due to non-responding pain. Fracture of the lower limbs was managed conservatively with traction in both patients. In two patients with CLD, paracentesis was done due to non-responding ascites.

A total of 22 patients expired during hospitalization, 20 patients due to respiratory failure/ARDS and two

patients due to sudden cardiac arrest. Maximum death was in patients who had associated comorbidities such as DM, HTN, CKD, and chronic lung diseases. The median age of expired patients was 61.18 (48–76 years). Mortality was more in uncontrolled DM and HTN patients. Mortality was also associated with thrombocytopenia, increased CRP/ferritin, decreased calcium/albumin and hyperglycemia at the time of admission. Oxygen requirement and involvement of lung parenchyma were also directly associated with poor outcome.

Gender- and age-related differences in mortality

The mortality rate in females was 12.33% (36/292) [Table 1] whereas mortality in males was 19.63% (84/428). In between group analysis, 8.7% (14/161) of females died in the <40 years age group versus 16.8% (22/131) in more than 40 years age group whereas in males, the mortality was 13.7% (21/153) in <40 years versus 22.9% (63/275). The mortality rate in women above forty years was greater than mortality in younger females emphasizing the protection provided by estrogen hormone in them [Table 2]. The proportion of patients who expired due to COVID-19 significantly differs by age cutoff of 40 years, X2 (1, n = 428). The difference is statistically significant at $P < 0.05$. Males more than 40 years are more likely to expire. *Mortality was greater in males compared to females further strengthening the role of estrogen*.

DISCUSSION

A total of 720 patients (292 females and 428 males) were admitted in our facility during study periods. Male preponderance could also be partly explained by sex ratio in our country and usually males are in occupation; therefore, more exposed to COVID-19. We included females of age >40 years only and analyzed their data. Fever (56.49%) was the most prevalent symptom in our patients followed by breathlessness (52.6%) and cough (35.11%) as in study by Huang *et al*.[1] who reported fever in 98% cases and Wang *et al*.[2] (98.6%) and Guan[3] (87.9%) where fever is the most common symptom. Cough was present in 76%, 59.4%, and 69.7% cases, respectively. Fever was present in only 56.49% cases.

Elevated CRP was reported in 78% in our study, 91% of cases by Zhang *et al*.[4] and 86% cases by Chen *et al*.[5] and Liu *et al*.[6] in 83%. This inflammatory response is responsible for the associated organ damage.

Thrombocytopenia (35.6%) followed by leukocytosis (19.1%) and lymphopenia (18.8%). Thrombocytopenia was reported in 36.2% of all cases by Guan and 41.7% cases by Liu *et al*. However, the prevalence of thrombocytopenia in severe cases was greater in the former study whereas it was more common in non-severe cases in the latter study. DM was the most commonly associated comorbidity seen in 29% cases followed by HTN (28.24%) and CKD (12.98%). Garg *et al*.[7] found that age is the independent risk factor for mortality and also reflected in our findings.

Cai *et al*.[8] reported that patients with deranged liver function tests have a higher risk of progressing to a severe disease. Tezcan *et al*.[9] concluded that hyponatremia is a sign of poor prognosis in patients with COVID-19 disease.

Table 1: Mortality according to sex age distribution.

Age (Years)	Female *n*=292		Male *n*=426		Total *n*=718	
	No of death	Percentage	No of Death	Percentage	No	%
<= 9	2	0.68	0	0.00	2	0.28
10–19	6	2.05	2	0.47	8	1.11
20–29	2	0.68	4	0.94	6	0.84
30–39	4	1.37	7	1.64	11	1.53
40–49	2	0.68	14	3.29	16	2.23
50–59	6	2.05	18	4.23	24	3.34
60–69	10	3.42	28	6.57	38	5.29
70–79	4	1.37	9	2.11	13	1.81
80+	0	0.00	2	0.47	2	0.28
Total	36	12.33	84	19.72	120	16.71

Table 2: Mortality in women below and above 40 years.

Age (Years)	Female *n*=292		Male *n*=426		Total *n*=718		*P*-value	Result
	No	%	No	%	No	%		
<40	14	4.82	13	3.05	27	3.76	<0.01	Highly Significant
>40	22	7.53	71	16.66	93	12.95		
Total	36	12.33	84	19.71	120	16.71		

Mortality rate was 0.5% in women versus 1.2% for male almost double in a study in China.[10]

More males developed severe respiratory failure 89% versus 10.7% in female.[11]

In a study, it was found that myocardial injury was increased but myocardial ACE2 expression was decreased after intranasal inoculation of SARS virus.[15]

CONCLUSION

COVID-19 has less mortality in females compared to males probably attributed to protection provided by estrogen hormone and better immunological behavior in females. Deranged renal function test was the most prevalent laboratory investigation in patients having the COVID-19 disease. Lung disease was the most prevalent comorbidity followed by HTN in patients with coronavirus disease.

Strength of study – very few studies have focused on the protective effect of estrogen hormone on morbidity in COVID-19 in females in India. Further research should be aimed at studying the association of COVID-19 with sex and the cause of gender differences in behavior should be evaluated.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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