

Is menopause a potential risk factor for severity of COVID-19: A retrospective cross-sectional study?



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ABSTRACT

Background: The world is struggling with the rising number of covid-19 cases. Few studies are available to propose the effect of menopause on covid-19. We are submitting a research article targeted at identifying menopause as an independent risk factor for severe Covid-19.

Aims and Objectives: Determine whether menopausal women are at higher risk of developing severe Covid-19 infection as compared to menstruating women of the same age group.

Materials and Methods: A retrospective cross-sectional study that included patients ages varies from 40 to 55 years from the medical record department of LNMC Bhopal, India. We enrolled 65 female patients after analysing records of 2500 patients. We divided the entire study population into two groups, the menopause group, and the non-menopausal group.

Result: Out of 65 patients, 27 patients were in the menopause group, and 38 patients were in the non-menopause group. The mean D-dimer in the menopause group is 1100.78 ng/ml and in the non-menopause group is 727.63 ng/ml, which is statistically significant. (p-value 0.04) The mean value of C-Reactive protein is 27.11 mg/l and 16.74 mg/l among the menopause and non-menopause groups, respectively (p-value 0.041). Twelve out of 17 patients who develop moderate-to-severe disease belong to the menopause group and five patients in the non-menopause group (p-value 0.005). **Conclusion:** In the present study, we witnessed that the disease is more severe in the menopause group than in the non-menopause group (p<0.005). This study can help recognize the high-risk cases and may be helpful to plan the treatment policies for the menopausal women who contract the Covid-19.

Key-Words: Covid-19; Menopause; D-Dimer; C-Reactive Protein; Immunity

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INTRODUCTION

The world is struggling with the rising number of Covid-19. World health organization has reported 150 million cases so far, with 3.2 million deaths.¹ Rigorous research and investigations are underway to understand the risk factor, pathophysiology, management, and complication of Covid-19. Patients infected with coronavirus may present mild-moderate to severe symptomatic illness and occasionally progress to acute respiratory distress syndrome (ARDS) and deaths.² The body's immune system, age, and inherent co-morbidities decide the varied

presentation of the disease. World health organization has found Various risk factors such as diabetes mellitus, hypertension, coronary artery disease, cerebrovascular accident, renal failure, malignancy for severe covid-19. The immune system, gender, age, and the inherent co-morbidities put individuals at more risk than others and decide the diverse presentation of the disease ranging from mild asymptomatic to acute respiratory distress syndrome.³ Some observed that males are more affected with severe covid-19 than women.^{4,5} Therefore, males are at higher risk; an explanation for the same is that 17 beta-estradiol down-regulates expressions of angiotensin-converting enzyme-2

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(ACE-2) mRNA in epithelial cells, which is the entry point for the virus into the host.^{6,7} Ding et al., found that estrogen and severe Covid-19 are inversely proportional so that menopause can be a potential risk factor for severe Covid-19.⁸ Few studies are available to propose the effect of menopause on Covid-19. We are submitting a research study targeted at identifying menopause as an independent risk factor for severe Covid-19.

MATERIALS AND METHODS

A retrospective study that included patient's ages varies from 40 to 55 years from the medical record department of LNMC and J.K. Hospital Bhopal. We collected the record of those patients who got admitted between August 2020 to January 2021. None of our patients was vaccinated.

RT-PCR assay diagnosed all patients on Nasopharyngeal swab, which is the confirmatory testing as per guidelines provided by the world health organization.¹ We found sixty-five female patients in the study as per the inclusion criteria and exclusion criteria after analysing records of two thousand five hundred patients. We divided the entire study population into two groups. Group one included females who attained menopause (not menstruating for at least one year) and group two incorporated women who are still menstruating. The study started with Institutional ethical clearance. Written informed consent was waived, as it was a retrospective study.

Data Collection

Information regarding the study population was gathered from the Medical record department of LNMC and J.K. Hospital and filled in an M.S. Excel sheet. Both groups underwent laboratory investigations, like complete blood counts, liver function test, kidney function test, serum sodium, serum potassium, C-Reactive protein, serum LDH, serum ferritin, D-Dimer, and HRCT Chest. The study also solicits information concerning clinical presentation. We did categorization regarding the severity of the disease according to a standard guideline issued by WHO.¹

Inclusion Criteria

All-female between ages 40 years to 55 years

Exclusion Criteria

We have excluded the patients with co-morbidities such as diabetes mellitus, hypertension, cerebrovascular accident, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, bronchial asthma, malignancy, history of hysterectomy, women on hormone replacement therapy, taking immunosuppressant drugs, and pregnant females.

Study design: A retrospective observational study

Study period: August 2020 to January 2021

Treatment: We adopted the standard treatment protocol suggested by the world health organization¹⁵ and the Indian council of medical research. Both the group received the same treatment as per the severity of the disease (Table 1).

STATISTICAL ANALYSIS

The presentation of the Categorical variables was done in the form of numbers and percentages (%). On the other hand, we use mean \pm S.D. and median values to show the presence of the continuous variables. The data normality was checked by using the Kolmogorov-Smirnov test. In the cases in which the data was not normal, we used non-parametric tests. We implemented the following statistical tests for the results:

1. The comparison of the quantitative variables was analysed using Mann-Whitney Test (for not normally distributed data) and the Independent t-test (for normally distributed data).
2. The association of the qualitative variables was analysed using the Chi-Square test. The data entry was done in the Microsoft Excel spreadsheet, and the final analysis was done using Statistical Package for Social Sciences (SPSS) software. For statistical significance, the p-value of less than 0.05 was significant.

RESULT

We found twenty-seven patients in the menopause group and thirty-eight in the non-menopause group. Table 2 showed the clinical characteristics of the patients. The mean age in the menopause group was 49.74 years and in the non-menopause group 43.37 years. There is no statistically significant difference in the symptoms between the groups except in the dyspnoea, which is more common among the menopause group (40.74%) than 15.79% in the non-menopause group (p-value 0.024). It is clear from Table 3 that haematological parameters, liver function test, kidney function test, and serum electrolytes are comparable in both the groups and we did not report any statistically significant difference in values between the two groups. Table 4 shows mean D-dimer in the menopause group is 1100.78 ng/ml and in the non-menopause group is 727.63 ng/ml, which is statistically significant. (p-value 0.04). It is evident from the table that the value of D-dimer (ng/mL) in the menopause and non-menopausal groups range from 92 to 4213, 125 to 2325, respectively. Spikes of the D-Dimer values are there among both groups. The standard deviation is 825.43 and 427.54 in the menopause and non-menopause groups,

Table 1: Treatments received by the study participants

Treatment	Mild Category	Moderate Category	Severe Category
Antivirals	Hydroxychloroquine	Remdesivir	Remdesivir
Steroids	None	dexamethasone	dexamethasone
Anti-il-6 therapy	None	none	None
Symptomatic/supportive	Paracetamol Vitamin c Zinc Etc.	Paracetamol Vitamin c Zinc oxygen etc.	Paracetamol Vitamin c Zinc Oxygen or high flow nasal cannula or Non-invasive/ invasive ventilation Etc.

Table 2: Comparison of symptoms between menopause and non-menopause

Symptoms	Menopause (n=27)	Non menopause (n=38)	Total	P value
Age(years)				
Mean \pm SD	49.74 \pm 3.97	43.37 \pm 3.51	46.02 \pm 4.85	<.0001*
Median(25th-75th percentile)	50(47.5-52)	42(40-45)	45(42-50)	
Range	41-58	40-54	40-58	
Body mass index(kg/m ²)				
Mean \pm SD	24.95 \pm 3.13	25.33 \pm 2.12	25.17 \pm 2.58	0.429*
Median(25th-75th percentile)	24.6(23.4-26)	25(24-26.3)	25(24-26)	
Range	20-31	21.5-30	20-31	
Symptoms				
Fever	16 (59.26%)	25 (65.79%)	41 (63.08%)	0.591#
Cough	19 (70.37%)	25 (65.79%)	44 (67.69%)	0.697#
Bodyache	15 (55.56%)	24 (63.16%)	39 (60%)	0.538#
Shortness of breath	11 (40.74%)	6 (15.79%)	17 (26.15%)	0.024#
Lost taste	12 (44.44%)	11 (28.95%)	23 (35.38%)	0.198#
Lost smell	12 (44.44%)	11 (28.95%)	23 (35.38%)	0.198#

*-Mann Whitney test, #-Chi-square test

respectively. We calculated the median value in both the group to overcome this wide distribution in the D-dimers values. Women with mild disease have lower D-dimer levels. Among menopausal women (n=27), 15 (55.55%) had mild disease; these patients had a lower range of D- Dimer. The mean value of C-Reactive protein is 27.11 mg/l and 16.74 mg/l among menopause and non-menopause groups, respectively. (p-value 0.041). However, the value of LDH and serum ferritin is comparable and not statistically significant. Table 5 indicates seventeen patients developed a moderate-to-severe disease and forty-eight patients had mild disease. Twelve out of seventeen patients who develop moderate-to-severe disease belong to the menopause group and five patients in the non-menopause group (p-value 0.005).

DISCUSSION

Enough data is not available to link menopause as an independent risk factor for the severe Covid-19. We found only a few articles showing some effect of sex hormone on Covid-19. Our study has covered an age group between 40 to 55 years. The idea behind taking this age range is that this is the age range of menopause; we have not included

women more than this age group to exclude the effect of age on the Covid-19. The mean age in the menopause group is 49.74 years and among the non-menopause group is 43.37 years. It is a fact that age is a risk factor for severe covid-19. Patients aged over 50 years are at 15.4 folds increased risk of mortality because of covid-19 than patients less than 50 years of age.⁹ The gradual decay in the immune system in postmenopausal women is linked to the deprivation of estrogen.¹⁰ We have excluded the patients with co-morbidities such as diabetes, hypertension, chronic kidney disease, chronic liver disease, coronary artery disease, cerebrovascular accident, and obesity to eliminate the effect of these factors on the severity of the disease. The level of sex hormones affects immunity. As we noted in earlier studies, a high level of estrogen that occurs during reproductive age protects women from viral infections. Estrogen influences many components of innate immunity. Loss of estrogen after menopause causes decreased immunity and may put women at higher risk of contracting moderate-to-severe covid-19.¹¹ We did not report any statistically significant difference in the symptoms between the group, but women in the menopausal group had more dyspnoea than non-menopause. The present study shows no difference in the haematological parameters among study groups.

Table 3: Comparison of laboratory parameters between menopause and non-menopause

Laboratory parameters	Menopause (n=27)	Non-menopause (n=38)	Total	P-value
Total leucocyte count(mm ³)				
Mean ± SD	6004.44 ± 1934.24	6126.32 ± 2172.64	6075.69 ± 2062.17	0.931*
Median (25th-75th percentile)	5700(4700-6750)	5500(4850-6875)	5600(4800-6800)	
Range	3400-10500	3000-12500	3000-12500	
Neutrophils (%)				
Mean ± S.D.	62.74 ± 11.64	60.79 ± 8.6	61.6 ± 9.94	0.439 ^s
Median (25th-75th percentile)	62(55-68)	61.5(54.25-67.5)	62(55-68)	
Range	44-90	43-76	43-90	
Lymphocyte (%)				
Mean ± S.D.	32.67 ± 10.86	34.55 ± 8.16	33.77 ± 9.35	0.427 ^s
Median (25th-75th percentile)	32(27-40)	34(28.25-41.75)	34(27-41)	
Range	7-50	20-50	7-50	
Platelets(lacs/mm ³)				
Mean ± S.D.	2.79 ± 0.7	2.62 ± 0.93	2.69 ± 0.84	0.408 ^s
Median (25th-75th percentile)	2.78(2.25-3.16)	2.54(1.845-3.112)	2.67(2.05-3.16)	
Range	1.1-3.88	1.18-5.25	1.1-5.25	
Hemoglobin(gm%)				
Mean ± SD	11.95 ± 1.78	11.93 ± 1.78	11.94 ± 1.77	0.954 ^s
Median (25th-75th percentile)	12(11.1-12.7)	12(11.125-13.15)	12(11.1-12.9)	
Range	6.3-16.8	8-16.2	6.3-16.8	
Urea(mg/dl)				
Mean ± S.D.	24.7 ± 8.53	24.11 ± 10.83	24.35 ± 9.87	0.566*
Median (25th-75th percentile)	21(19-29.5)	23.5(17-26.75)	22(18-28)	
Range	13-46	10-71	10-71	
Creatinine(mg/dl)				
Mean ± S.D.	0.83 ± 0.18	0.81 ± 0.27	0.82 ± 0.23	0.57*
Median (25th-75th percentile)	0.8(0.7-0.965)	0.79(0.685-0.867)	0.8(0.7-0.95)	
Range	0.5-1.2	0.03-1.5	0.03-1.5	
Total bilirubin(mg/dl)				
Mean ± S.D.	0.5 ± 0.33	0.48 ± 0.31	0.49 ± 0.31	0.956*
Median (25th-75th percentile)	0.4(0.3-0.6)	0.4(0.3-0.5)	0.4(0.3-0.6)	
Range	0.2-1.4	0.2-1.5	0.2-1.5	
SGOT(U/L)				
Mean ± SD	25.81 ± 8.37	25.95 ± 9.64	25.89 ± 9.07	0.81*
Median (25th-75th percentile)	25(21.5-32)	25(18-32)	25(18-32)	
Range	10-47	13-61	10-61	
SGPT(U/L)				
Mean ± S.D.	34.37 ± 11.78	33.08 ± 15.84	33.62 ± 14.2	0.311*
Median (25th-75th percentile)	31(26-43)	28.5(19.25-44.25)	29(22-43)	
Range	17-58	16-76	16-76	
Albumin(g/dl)				
Mean ± S.D.	3.56 ± 0.43	3.48 ± 0.41	3.52 ± 0.42	0.543*
Median (25th-75th percentile)	3.6(3.35-3.7)	3.5(3.2-3.7)	3.6(3.2-3.7)	
Range	2.7-4.5	2.6-4.5	2.6-4.5	
Sodium(mmol/L)				
Mean ± SD	137.63 ± 6.49	139.32 ± 4.33	138.62 ± 5.35	0.543*
Median (25th-75th percentile)	140(132-142)	140(136-142)	140(136-142)	
Range	125-146	129-147	125-147	
Potassium(mmol/L)				
Mean ± S.D.	3.88 ± 0.38	3.96 ± 0.44	3.92 ± 0.42	0.814*
Median (25th-75th percentile)	3.9(3.7-4.05)	3.85(3.7-4.2)	3.9(3.7-4.1)	
Range	3.2-5.1	3.2-4.9	3.2-5.1	

* -Mann Whitney test,^s-Independent t-test

In contrast, a study conducted by Neha et al. found that the total leukocyte count (TLC) (7800 ± 264.6 vs. 5850 ± 264.6) was higher ($P < 0.01$) in the menopausal group as compared to the non-menopause group.¹² Our study shows the C- Reactive protein and D-Dimer were higher among menopausal groups, and the difference is statistically significant, while Neha et al., observed

little such difference. We witnessed in the present study that moderate to severe disease is more common in the menopause group than in the non-menopause group ($p < 0.005$). This observation reveals the importance of the hormonal milieu in women, which might be protective against severe covid-19. Nevertheless, a study conducted by Bonaccorsi et al., said that menopause does not enhance

Table 4: Comparison of inflammatory markers between menopause and non-menopause.

Inflammatory markers	Menopause (n=27)	Non-menopause (n=38)	Total	P-value
D-Dimer(ng/mL)				
Mean ± SD	1100.78 ± 825.43	727.63 ± 427.54	882.63 ± 645.61	0.041*
Median (25th-75th percentile)	932(558-1444.5)	707(434.5-925.75)	768(465-1025)	
Range	92-4213	125-2325	92-4213	
Serum ferritin(ng/mL)				
Mean ± SD	307.38 ± 190.79	287.68 ± 342.92	295.87 ± 287.87	0.101*
Median (25th-75th percentile)	351(180-413.5)	135.5(69.5-417.75)	208(85-423)	
Range	13.35-856	17-1532	13.35-1532	
LDH (U/L)				
Mean ± SD	381.93 ± 304.07	313.63 ± 259.29	342 ± 278.53	0.358*
Median (25th-75th percentile)	233(168.5-595.5)	237(109.5-435.75)	233(145-452)	
Range	79-951	36-862	36-951	
CRP (mg/L)				
Mean ± S.D.	27.11 ± 18.36	16.74 ± 9.39	21.05 ± 14.65	0.041*
Median (25th-75th percentile)	19(14-42)	14.5(9.75-18)	16(12-26)	
Range	6-75	8-46	6-75	

* -Mann Whitney test

Table 5: Menopause and severity of Covid-19

Group	Mild (n=48)	Moderate/ Severe (n=17)	Total	P value
Menopause	15 (31.25%)	12 (70.59%)	27 (41.54%)	0.005#
Non-menopause	33 (68.75%)	5 (29.41%)	38 (58.46%)	
Total	48 (100%)	17 (100%)	65 (100%)	

-Chi-square test

the risk of severe disease.¹³ Lee et al., did not find a positive correlation between menopause with severe disease.¹⁴ On the other hand, Neha et al.,¹² found a statistically significant difference in oxygen demand, hospital stay, and progression to severe illness in the menopause group compared to the non-menopause group. Our analysis also observed similar conclusions that the Covid-19 is more severe among postmenopausal women.

CONCLUSION

This study on females with covid-19 provided more insight into menopause as a risk factor for moderate-severe disease. We report that the illness is more severe among post-menopause women. This study can help recognize the high-risk cases and may be helpful to plan the treatment policies for the menopausal women who contract the Covid-19. Since the sample size is small, we require further studies to establish the findings.

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Authors Contribution:

VA-Concept and design of the study; Interpreted the results; prepared the first draft of the manuscript; revision of the manuscript; **RB**- Concept and design of the study, reviewed the literature and manuscript preparation; **AB**- Concept, coordination, review of literature and manuscript preparation; **NSK**- Coordination, data collection; **AG**- Statistically analysed and interpreted, preparation of manuscript and revision of the manuscript

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