

# SARS-Cov-2 Infection in Postmenopausal Women. New Data on Menopause Hormone Therapy

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## Research Article

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# Abstract

## Objective

To address the factors involved in hospital admission and medical follow up in postmenopausal women with COVID-19 diagnosis.

## Methods

Retrospective observational study. Postmenopausal women aged between 40-70 years since September 2020 until June 2021 with COVID-19 diagnosis were included. Of the 300 women cohort, 50 were receiving menopause hormone therapy (MHT)

## Results

288 patients were analyzed. The mean age was 56.20 years (+/-6.06y SD). Age ( $p=0.030$ ), High blood pressure (HBP) ( $p=0.002$ ), respiratory disorders ( $p=0.003$ ), depression ( $p=0.028$ ) and fibromyalgia ( $p=0.030$ ) were associated with a greater risk for hospital admission, while MHT was found as a protective factor ( $p=0.042$ ). Being a health professional ( $p<0.001$ ), HBP ( $p=0.029$ ), respiratory disorders ( $p=0.022$ ), vitamin D deficiency ( $p=0.010$ ), depression ( $p=0.005$ ) and fibromyalgia ( $p=0.001$ ) were related with a longer follow up while MHT was related with a shorter one ( $p=0.010$ ). Regression analysis showed that HBP and respiratory disorders acted as independent factors for hospital admission while MHT and fibromyalgia were for the length of follow up.

## Conclusions

MHT has a positive impact in postmenopausal women with SARS-CoV-2 infection. HBP and respiratory disorders are associated with a higher risk of hospital admission of these patients.

## Background

Regardless of their age, postmenopausal women tend to have a more torpid evolution of SARS-CoV-2 /COVID-19, with a higher tendency to develop serious respiratory symptoms and greater mortality (1,2). This could be explained in part, due to an important role of estradiol in immunomodulation, as it helps in the regulation of several cytokines expression and the renin angiotensin aldosterone system (3). In addition, it acts as a vasodilator and exhibit endothelium protective properties by triggering the production of nitric oxide, counteracting the vasoconstriction evoked by the inflammatory response during SARS-CoV-2 infection (4).

Several observational studies have focused on the differences in gender observed during the evolution of COVID-19 and the relationship of disease severity and mortality and estrogen exposure in women. (1,2,5,6). However, other major aspects of the infection have not been yet properly assessed. One of the hallmarks of COVID-19, is the mandatory sociosanitary quarantine that is required for patients after diagnosis to avoid further dissemination of the virus. In Spain, by order of the Ministry of Health, people are urged to remain in individual rooms or in places that allows them to maintain a two meters distance from others and seek remote health assistance (telemedicine) whenever they present with compatible symptoms (7). This highly restrictive measurements involve major limitations in family and professional areas, as well as notable negative financial and personal consequences.

The objective of this study is to assess the factors related with hospital admission and health care follow up (including home isolation follow up) following COVID-19 diagnosis in postmenopausal women.

## Methods

Retrospective observational study that included 300 postmenopausal patients between 40-70 years old with SARS-CoV-2 infection proven by PCR (polymerase chain reaction) from September 2020 until June 2021 diagnosed at Miguel Servet University Hospital of Zaragoza, in Spain. Pre or perimenopausal women, non-PCR diagnoses, reinfected and vaccinated women were excluded. Of the initial 300 women, twelve were excluded due to unavailability of all clinical records.

Samples used in diagnosis, were nasopharyngeal swabs with or without oropharyngeal swabbing, taken by a trained health care professional and analyzed in the Clinical Microbiology laboratory. Patient sample was obtained using a simple randomization model using the patient database of the Gynecology department of the Hospital, collecting 30 patients each month to avoid bias generated by differences in treatment or circulating variant.

Demographic and health related data were collected form the electronic clinical record. Women working in hospitals, primary care facilities and nursing homes were classified as health care professionals. Menopause was defined retrospectively as the cessation of spontaneous

menstruation for 12 months following STRAW criteria (8). Menopause hormone therapy (MHT) group included those who started the treatment at least one month before COVID-19 diagnosis and did not suspend it during the infection. All types MHT were included (transdermic, oral, combined progestogens and estrogens, estrogens alone or tibolone). As respiratory disorders, chronic pathologies diagnosed before COVID-19 were included (asthma, chronic bronchitis, chronic obstructive pulmonary disease). Low vitamin D values were defined as a serum concentration below 30ng/ml.

The primary outcomes of the study were hospital admission and follow up length. Hospital admission was ordered by the emergency department physician following current hospital guidelines (9) which included chest X-ray abnormalities, oxygen saturation <93%, respiratory rate >30 breaths per minute, inadequate oral intake, or immunosuppression.

Health care follow up was performed by a primary care physician by telephone consultation following current Spanish Ministry of Health regulations. Sociosanitary isolation was always indicated since first symptoms, until the 10<sup>th</sup> day if the patient remained asymptomatic for three consecutive days. In asymptomatic cases, isolation began with the PCR result until the 10<sup>th</sup> day of infection. The attending physician kept a established form, specifying the end of follow up. For those patients in working age, medical follow up period, corresponded with medical sick leave, including the isolation period. A negative PCR test was required for medical discharge, with the exception of health care workers. If the patient was not working at the time, medical follow up period consisted of at least the isolation period and until clinical resolution.

This study was carried out with the approval of the Aragón Ethical committee (C.P. - C.I. PI21/277). Being a retrospective study and taking into account the anonymization process, no written informed consent was required. An informative document of the study was sent to all participants by conventional mail. Patients could request to withdraw from the study at any time. The research was conducted in accordance with Good Clinical Practice standards and the current revision of the Declaration of Helsinki.

## Statistics Analysis

Discrete variables are expressed in frequencies and percentages. The parametric distribution of the quantitative variables was studied with the Kolmogorov-Smirnov test. The variables that did not follow a normal distribution were expressed with the median and interquartile range (IQR) and those that presented a normal distribution were expressed in mean and standard deviation (SD). U Mann-Whitney test was used for the analysis of dichotomous qualitative nonparametric variables, and Kruskal-Wallis test for non-dichotomous qualitative ones. A binary logistic backward stepwise regression analysis was performed for identify the independent variables related to the hospital admission indication (yes/no). Backward stepwise multiple linear regression analysis was carried out to identify the independent variables related to days of isolation. Only variables with p-value <0.05 in the univariate analysis were used to construct the final regression model. The level of statistical significance was set at p< 0.05. The data were collected and codified using IBM Statistics Process Social Sciences 22.0 for Windows (Copyright SPSS Inc., 2013) for subsequent statistical analysis.

## Results

Mean age of participants was 56.2 years (+/-6.06SD). Fifty patients were receiving MHT treatment. Clinical, demographical and comorbidities characteristics of the participants are summarized in Table 1.

Table 1  
Baseline data of women in the sample

		n	%
Age	<60 years	197	68,4%
	≥ 60 years	91	31,6%
Health professional	No	232	81,4%
	Yes	53	18,6%
Country of origin	Spain	243	84,4%
	Latin America	27	9,4%
	Europe	14	4,9%
	Sub-Saharan	4	1,4%
BMI*	<30	173	70,0%
	≥ 30	74	30,0%
Smoker	No	250	87,7%
	Yes	35	12,3%
Diabetes	No	265	92,0%
	yes	23	8,0%
HBP <sup>§</sup>	No	210	73,2%
	Yes	77	26,8%
Autoimmune diseases	No	247	85,8%
	Yes	41	14,2%
Immunosuppressants	No	276	96,5%
	Yes	10	3,5%
Oncological history	No	269	93,4%
	yes	19	6,6%
Respiratory pathology	No	259	89,9%
	Yes	29	10,1%
Vit D deficiency	No	229	79,5%
	Yes	59	20,5%
Depression	No	217	75,3%
	Yes	71	24,7%
Fibromyalgia	No	276	95,8%
	Yes	12	4,2%
Years from menopause	0-4	95	35,3%
	≥ 5	174	64,7%
MHT <sup>^</sup>	No	238	82,6%
*BMI: body mass index			
§ HBP: high blood pressure			
^ MHT: Menopause hormone therapy			

	n	%
Yes	50	17.4%
*BMI: body mass index		
§ HBP: high blood pressure		
^ MHT: Menopause hormone therapy		

Table 2 shows the statistical analysis of clinical characteristics, demographics and use of MHT compared with hospital admission. Older age (14.7% <60y vs 25.3% >60y, OR 1.959, 95% CI 1.059-3.626, p=0.030), High Blood pressure (HBP) (28.6% vs 14.3%, OR 2.596, 95% CI 1.389-4.849, p=0.002), respiratory disorders (57.9% vs. 15.8%, OR 3.249, 95% CI 1.430-7.385, p=0.003), depression (26.8% vs. 15.2%, OR 2.037, 95% CI 1.071-3.875, p=0.028) and fibromyalgia (41.7% vs. 17.1%, OR 3.480, 95% CI 1.059-11.437, p = 0.030) appeared to be a risk factor for hospital admission with statistical significance. On the contrary, MHT was linked with a lower risk for hospital admission (8% vs. 20.2%, OR 0.334, 95% CI 0.118-1.003, p=0.042). Other variables included showed no significant association with hospital admission.

Table 2  
Factors related to hospital admission for COVID 19

		Hospital admission for COVID 19			
		No	Yes	p value	OR IC95%
Age	<60 years	168 (85.3)	29 (14.7)	0.030	1.959 (1.059-3.626)
	≥ 60 years	68 (74.7)	23 (25.3)		
Health professional	No	190 (81.9)	42 (18.1)	0.897	1.052 (0.490-2.261)
	Yes	43 (81.1)	10 (18.9)		
Country of origin	Spain	203 (83.5)	40 (16.5)	0.176	-
	Latin America	18 (66.7)	9 (33.3)		
	Europe	12 (85.7)	2 (14.3)		
	Sub-Saharan	3 (75)	1 (25)		
BMI*	<30	142 (82.1)	31 (17.9)	0.497	1.264 (0.643-2.485)
	≥ 30	58 (78.4)	16 (21.6)		
Smoker	No	202 (80.8)	48 (18.2)	0.265	0.543 (0.183-1.612)
	Yes	31 (88.5)	4 (11.4)		
Diabetes	No	220 (83)	45 (17)	0.108	2.139 (0.832-5.499)
	yes	16 (69.6)	7 (30.4)		
HBP <sup>§</sup>	No	180 (85.7)	30 (14.3)	0.002	2.596 (1.389-4.849)
	Yes	55 (71.4)	22 (28.6)		
Autoimmune diseases	No	202 (81.7)	45 (18.3)	0.860	0.924 (0.385-2.218)
	Yes	34 (82.9)	7 (17.1)		
Immunosuppressants	No	226 (81.8)	50 (18.1)	0.510	0.502 (0.062-4.055)
	Yes	9 (90)	1 (10)		
Oncological history	No	220 (81.8)	49 (18.2)	0.790	0.842 (0.236-3.002)
	Yes	16 (84.2)	3 (15.8)		
Respiratory pathology	No	218 (84.2)	41 (15.8)	0.003	3.249 (1.430-7.385)
	Yes	18 (62.1)	11 (57.9)		
Vit D deficiency	No	191 (83.4)	38 (16.6)	0.204	1.564 (0.782-3.129)
	Yes	45 (76.3)	14 (23.7)		
Depression	No	184 (84.8)	33 (15.2)	0.028	2.037 (1.071-3.875)
	Yes	52 (73.2)	19 (26.8)		
Fibromyalgia	No	229 (82.9)	47 (17.1)	0.030	3.480 (1.059-11.437)
*BMI: body mass index					
§ HBP: high blood pressure					
^ MHT: Menopause hormone therapy					

	Yes	7 (58.3)	5 (41.7)		
Years from menopause	0-4	77 (81.1)	18 (18.9)	0.997	1.001 (0.529-1.895)
	≥ 5	141 (81)	33 (19)		
MHT <sup>^</sup>	No	190 (79.8)	48 (20.2)	0.042	0.344 (0.118-1.003)
	Yes	46 (92)	4 (8)		
*BMI: body mass index					
§ HBP: high blood pressure					
^ MHT: Menopause hormone therapy					

Table 3 summarizes the relationship between studied factors and length of follow up. Working in a healthcare facility ( $p < 0.001$ ), HBP ( $p = 0.029$ ), chronic respiratory conditions ( $p = 0.022$ ), low levels of serum Vitamin D ( $p = 0.010$ ), depression ( $p = 0.005$ ) and fibromyalgia ( $p = 0.001$ ) were related with a prolonged follow up period. MHT was related with a decrease in follow up length ( $p = 0.010$ ).

Table 3  
Factors related to medical follow up for COVID 19

		Medical follow up for covid	
		Mediana (ICR)	p value
Age	<60 years	16 (314)	0.152
	≥ 60 years	20 (148)	
Health professional	No	15 (314)	<0.001
	Yes	22 (127)	
Country of origin	Spain	17 (314)	0.818
	Latin America	18 (132)	
	Europe	16 (50)	
	Sub-Saharan	12 (49)	
BMI*	<30	17 (314)	0.820
	≥ 30	16 (136)	
Smoker	No	17 (314)	0.244
	Yes	15 (71)	
Diabetes	No	17 (314)	0.586
	yes	15 (129)	
HBP <sup>§</sup>	No	16 (314)	0.029
	Yes	21 (149)	
Autoimmune diseases	No	17 (314)	0.125
	Yes	20 (116)	
Immunosuppressants	No	17 (314)	0.991
	Yes	19 (59)	
Oncological history	No	17 (314)	0.210
	yes	18 (57)	
Respiratory pathology	No	17 (314)	0.022
	Yes	21 (136)	
Vit D deficiency	No	16 (314)	0.010
	Yes	18 (71)	
Depression	No	24 (16)	0.005
	Yes	28 (21)	
Fibromyalgia	No	17 (314)	0.001
	Yes	40 (145)	
Years from menopause	0-4	15 (313)	0.221
	≥ 5	17 (149)	

\*BMI: body mass index

§ HBP: high blood pressure

^ MHT: Menopause hormone therapy

MHT	No	18 (314)	0.010
	Yes	14 (37)	
*BMI: body mass index			
§ HBP: high blood pressure			
^ MHT: Menopause hormone therapy			

Binary logistic regression analysis revealed HBP and chronic respiratory conditions were identified as independent factors for hospital admission. No other factors were found to be independently related in the binary logistic regression (Table 4)

Table 4  
Results of the binary logistic regression analysis of the factors related to hospital admission for COVID-19. Only variables with  $p < 0.05$  are included in the univariate analysis.

	$\beta$ coefficient	Standard error	Wald	Exp(B)	95% Confidence interval		p value
Age	0,466	0,334	1,944	1,594	0,828	3,07	0,173
HBP <sup>§</sup>	0.745	0.330	5.089	2,107	1,103	4,026	0.024
Respiratory pathology	1,061	0,443	5,747	2,88	1,214	6,88	0,016
Depression	0,456	0,348	1,714	1,577	0,797	3,119	0,19
Fibromyalgia	0,915	0,637	2,064	2,497	0,717	8,7	0,151
MHT <sup>^</sup>	-0,9	0,576	2,444	0,355	0,118	1,069	0,66
§ HBP: high blood pressure							
^ MHT: Menopause hormone therapy							

Multiple linear regression analysis established fibromyalgia and MHT as independent factors for longer and shorter follow up periods respectively (Table 5).

Table 5  
Results of the linear logistic regression analysis of the factors related to medical follow up for covidCOVID-19. Only variables with  $p < 0.05$  are included in the univariate analysis.

	$\beta$ _coefficient	Error desviation	$\beta$ _coefficient	t	95% Confidence interval		p value
Health professional	0,092	4,379	0,092	1,587	-1,672	15,569	0,114
HBP <sup>§</sup>	0,07	3,989	0,07	1,155	-3,247	12,458	0,249
Respiratory pathology	0,083	5,76	0,083	1,392	-3,324	19,354	0,165
Depression	0,009	4,04	0,009	0,152	-7,338	8,568	0,879
Vit D deficiency	-0,02	4,301	-0,02	-0,334	-9,904	7,028	0,738
Fibromyalgia	0,216	8,724	0,216	3,754	15,579	49,925	<0.001
MHT <sup>^</sup>	-0,116	4,464	-0,116	-2,019	-17,8	-0,225	0,044
§ HBP: high blood pressure							
^ MHT: Menopause hormone therapy							

## Discussion

The main highlight of our study is that MHT in postmenopausal women seems to be related with a quicker recovery from COVID-19, proved by a lower rate of hospital admission and a shorter follow up length. To our best knowledge, this is the first study that evaluates MHT and COVID-19 related aspects. HBP and respiratory disorders were related as independent factors for greater risk of hospital admission due to

COVID-19. MHT was linked with a fewer rate of hospital admission; although was not found as an independent factor in the multivariate analysis.

Epidemiological studies in the general population have focused in factors associated with a poor clinical outcome of COVID-19 (10, 11). In a systematic review including 207 studies and more than 75.000 patients from twelve countries, in consistency with our data, found that factors as age, HBP, and chronic respiratory conditions were related with higher disease severity and worst clinical outcome of COVID-19 (12). Epidemiological studies usually do not consider factors as depression or fibromyalgia, even when those are highly prevalent among postmenopausal women, making them a relevant target to correlate with disease progression (13–15). According to our results, both fibromyalgia and depression are related with a more severe infection and extended follow up, although only fibromyalgia proved to be an independent factor for domiciliary isolation. Taking that into account, we strongly believe that those are important factors to be included and evaluated in postmenopausal women with COVID-19.

Several studies have shown greater disease severity in men compared with women, pointing to a possible protective role of estrogens. (2, 5, 16–18). Even between pre and postmenopausal women, there are differences in prognosis regardless of age. (19). Seeland et al, in a wide epidemiological study found that postmenopausal women above 50 years old under MHT with COVID-19, had a reduction greater than 50% in mortality, driven by estrogens levels (1). Recently, another important epidemiological study using the COVID Symptom Study Smartphone Application in the United Kingdom, including around 18.000 women with COVID-19 under MHT, found that hospital admission was not greater in this group of patients, although they exhibit a higher and broader spectrum of symptoms. Only age, mass body index and smoking habit were assessed as confounding variables, nevertheless, diagnosis was made based on symptoms and prediction models and not in molecular tests, which potentially limits extrapolation of results (20).

Medical sick leave and domiciliary isolation, have deleterious implications at the social, family and working levels, without mentioning at the economical sphere. The deleterious cognitive and emotional consequences of this highly restrictive measurement, due to the physical distancing from the usual environment and dimensions in which patients have to reside during days or weeks, has been studied (21). Besides, working cessation in women who work as independents, posed great drawbacks in income (22). Lastly, it has been noted that prolonged domiciliary isolation has a negative impact in quality of life related to menopause, measured with specific quality of life instruments for menopause (23).

Because of everything mentioned above, a prompt recovery and a shorter isolation period is crucial to the wellbeing of menopausal women in all means. In our study, postmenopausal women under MHT finished their isolation and returned to daily life faster. It is possible that estrogens as a protective factor played an important role in this scenario, especially in the early stages of the infection. In addition, alleviation of climacteric symptoms by MHT could also improve patient wellbeing and avoid COVID-19 symptoms masking. For this reason, unlike some recommendations given in the early phases of the coronavirus pandemic, it does not seem reasonable to suspend MHT in symptomatic postmenopausal women with non-serious infection (24).

We believe that these results will contribute to the scaring literature regarding the management of postmenopausal COVID-19 patients and could be used as a reference for future research involved in the establishment of the the relationship between exogenous estrogens intake and viral infections outcomes. Nevertheless, the results of this work should be taken cautiously, as we are aware of the several limitations of this study. Limited number of patients presented, especially in the MHT group, impossibility to perform a comparison regarding administration route, composition or doses of MHT and a potentially source of bias arising from the analysis based on their employment status. This last one is minimized given the fact that the health care professional in charge of the follow up, was required to specify the end of follow up in an epidemiological survey.

## Conclusions

MHT can positively influence the evolution of coronavirus infection in postmenopausal women. HBP and respiratory diseases are associated with a higher rate of hospital admission in postmenopausal women with SARS-CoV-2 infection.

## Abbreviations

MHT: menopause hormone therapy

PCR: polymerase chain reaction

HBP: High Blood pressure

BMI: body mass index

## Declarations

## Ethics approval and consent to participate

This study was carried out with the approval of the Aragón Ethical committee (C.P. - C.I. PI21/277). Being a retrospective study and considering the anonymization process, no written informed consent was required. An informative document of the study was sent to all participants by conventional mail. Patients could request to withdraw from the study at any time

## Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

## Competing interests

The authors declare no conflict of interest

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There was no financial support, participant compensation, or funding for the research team.

## Authors' contributions

LB: is one of the study designers, has participated in the elaboration and writing of the article and is the current corresponding author. JN: has carried out data collection and critical revision of the manuscript. YJ: has carried out data collection and analysis and manuscript writing. AT: has carried out data collection and analysis and manuscript writing. PR: has carried out data collection and analysis. AR: has carried out data collection and critical revision of the manuscript. ML: is one of the study designers, has participated on writing of the manuscript and critical revision of it.

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