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ORIGINAL STUDY

Effect of sex hormones on coronavirus disease 2019: an analysis of 5,061 laboratory-confirmed cases in South Korea

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Abstract

Objective: To evaluate the effect of female sex hormones on the clinical outcomes of coronavirus disease 2019 patients using national claims data.

Methods: This retrospective cohort study used the Health Insurance Review and Assessment data of 5,061 adult patients with laboratory-confirmed coronavirus disease 2019 in South Korea from January 20 to April 8, 2020. To evaluate the effect of hormone therapy on clinical outcomes among women, subgroup analyses using age-matched case-control data were performed.

Results: Coronavirus disease 2019 was most prevalent in women in the 20-39 years age group (1,250 [44.14%]). Men were more likely to receive oxygen therapy (144 [6.46%] vs 131 [4.63%], $P = 0.004$), be admitted to the intensive care unit (60 [2.69%] vs 53 [1.87%], $P = 0.049$), and have a longer length of stay after admission to the intensive care unit (19.70 ± 11.80 vs 14.75 ± 9.23, $P = 0.016$). However, there was no significant difference in the mortality rate (men vs women: 42 [1.88%] vs 42 [1.48%], $P = 0.267$). In the multivariable Cox analysis, older age and underlying comorbidities, but not sex, were independent risk factors for mortality. Hormone therapy was not significantly associated with clinical outcomes.

Conclusions: This study, using nationwide data, suggests that female sex hormones are not associated with the morbidity and clinical outcomes of coronavirus disease 2019 in South Korea.

Key Words: Big data – COVID-19 – Hormone therapy – SARS-CoV-2 – Sex characteristics.

I
n South Korea, since the identification of the first confirmed case on January 20, 2020, coronavirus disease 2019 (COVID-19) cases have been identified sporadically in the early stages of the outbreak. After February 19, several patients were identified from religious groups and long-term care facilities. Subsequently, an exponential rise in the number of confirmed cases nationwide was observed.[1] Infection spread has been mitigated by adherence to social-distancing measures, mask-wearing, contact-tracing, and isolation of confirmed cases. Although the number of confirmed cases reached 10,752 with 244 deaths as of April 28, the acute upward slope seems to have been flattened.[2]

Sex has been observed to be a factor of marked importance in the short history of the COVID-19 pandemic. According to several studies, men have higher rates of COVID-19-related morbidity and mortality than women.[3,4] Some studies have

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suggested that sex hormones may affect the susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and subsequent mortality.[3-6] Based on these findings, a clinical trial is recruiting COVID-19 patients to evaluate the effect of female sex hormones on the clinical outcomes of patients by administering estrogen to adult men or postmenopausal women with low levels of female sex hormones (ClinicalTrials.gov Identifier: NCT04359329). Presently, only a few published studies on the effects of sex hormones on the morbidity and mortality of COVID-19 are available. Understanding the effects of sex hormones on SARS-CoV-2 infection may assist in the identification of high-risk patients, prognosis prediction, and triage of patients for hospitalization during the current pandemic. The sex-specific disparities in morbidity and mortality of COVID-19 observed in several countries may be considered as indirect evidence of the effects of sex hormones on SARS-CoV-2 infection. However, these findings have not been reported in all countries, and sex-specific morbidity and mortality vary significantly by region. Moreover, only a few studies have reported a female-dominant sex ratio for COVID-19 morbidity. In South Korea, confirmed cases were more common in women, and COVID-19 was the most prevalent in young adults.[7] For understanding this disease better, it is worthwhile to examine the epidemiological findings in South Korea, which are different than those in other countries. In this study, we evaluated the sex-specific characteristics of patients with laboratory-confirmed COVID-19 in an epidemiologic setting in South Korea using nationwide claims data and investigated the effects of female sex hormones on the clinical course and disease severity of COVID-19.

METHODS

Patient data

We performed a retrospective cohort study using the Health Insurance Review and Assessment (HIRA) dataset, consisting of data from adult patients (age ≥ 20 y) with laboratory-confirmed COVID-19 between January 20, 2020, and April 8, 2020, in South Korea. The South Korean government operates a mandatory nationwide insurance system (National Health Insurance), which covers all forms of health services including hospitalization, ambulatory care, and pharmaceutical services. All healthcare utilization information is registered under a comprehensive database operated by the HIRA. Medical institutions submit the healthcare utilization information via electronic forms for reimbursement purposes, and this information is integrated into the HIRA claims database, which covers the entire population of South Korea (approximately 51 million). Thus, the database contains information on most patients, including data on ambulatory care histories, principal diagnoses, prescriptions, procedures, and comorbidities, based on the Korean Standard Classification of Diseases and Causes of Death, 7th edition (KCD-7), a modified version of the International Classification of Disease 10th revision. Details of the HIRA database are described elsewhere.[8]

The KCD-7 codes for the diagnosis of COVID-19 and patients' comorbidities are described in the supplementary table (Supplemental Table 1, http://links.lww.com/MENO/A649). Underlying comorbidities were defined as the reimbursement of the KCD-7 code of study diseases within 5 years prior to the diagnosis of COVID-19. Drug codes for estrogen therapy, estrogen plus progestogen therapy, and tibolone were used for identifying the use of hormone therapy (HT) in female patients. Recent use of HT was defined as the prescription of HT drug codes for more than 1 month after January 2019. Nonuse of HT was defined as no prescription of HT drug codes for the 5 years covered by the database.

Diagnosis and treatment

During the study period, all patients with COVID-19 were diagnosed and treated according to the guidelines published by the Korea Centers for Disease Control.[2] The reverse-transcription polymerase chain reaction test was used for detecting SARS-CoV-2. Sputum, nasal, and oropharyngeal samples were collected from the individuals. Clinical specimens were tested with reagents, authorized for emergency use, in public facilities, medical institutions, or entrusted facilities. A person who tested positive was confirmed to be infected with SARS-CoV-2, regardless of the presence of any clinical symptoms. After confirming the diagnosis, patients were classified based on their condition. Patients with mild disease with no need for hospitalization or special treatments were monitored at residential treatment centers. Meanwhile, those with moderate-to-severe disease were admitted to medical institutions. At medical institutions in South Korea, several patients were treated according to the management protocol issued by the Korean Society of Infectious Diseases, Korean Society for Antimicrobial Therapy, and Korean Society for AIDS. The treatment guidelines have been revised and updated during the outbreak. The latest guidelines on antiviral therapy for COVID-19 were issued on May 19, 2020.[9] When antiviral therapy was considered for patients with laboratory-confirmed COVID-19, the majority were treated with hydroxychloroquine or lopinavir/ritonavir as soon as possible. Combination therapy with type I interferon or ribavirin was initiated in patients showing an inadequate clinical response despite hydroxychloroquine or lopinavir/ritonavir administration.

Statistical analysis

Comparisons between male and female COVID-19 patients were performed using descriptive statistics. The results were presented as numbers (percentages) for categorical variables and means $\pm$ standard deviations for continuous variables. Continuous variables were compared using an independent t test, and categorical variables were compared using the chi-squared test or Fisher exact test. Cox proportional hazard regression analysis was performed for identifying the risk factors of mortality among the covariate variables of sex, age ≥ 65 years, and seven comorbidities (cardiovascular disease,

Number of confirmed COVID-19 cases over time
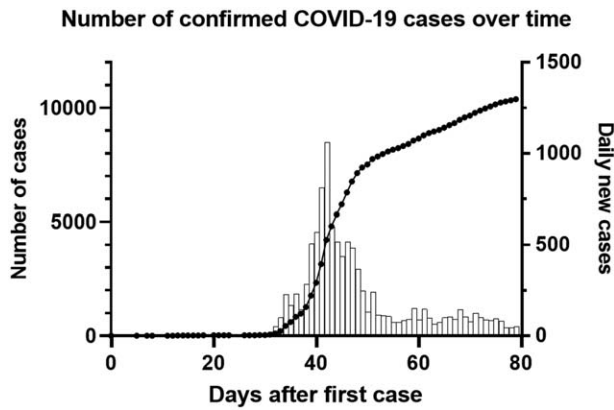
FIG. 1. Trend of confirmed coronavirus disease cases over time between January 20, 2020, and April 8, 2020, in South Korea.

cerebrovascular disease, hypertension, diabetes, pulmonary disease, malignancy, and chronic kidney disease).

HT was usually prescribed for women in their 40s-60s. To attenuate the age effect for evaluating the association of HT with the clinical outcomes of female patients, a propensity score matching technique was adopted. The propensity score was calculated using a logit model for matching recent HT female patients in the treatment group and never HT female patients in the control group according to age and predicting probabilities within a caliper of 0.25. A 1:3 propensity score matching was fulfilled to match the recent HT patients with non-HT patients and confirmed the age balanced between the recent HT and non-HT patients. All statistical analyses were performed using SAS Enterprise Guide (SAS Institute Inc., Cary, NC). Results with a P value of < 0.05 were considered statistically significant. The study protocol was approved by the institutional review board (3-2020-0072) of Yonsei University College of Medicine, Gangnam Severance Hospital (Seoul, Republic of Korea), and the protocol adhered to the tenets of the Declaration of Helsinki. Since the study was retrospective and the study participants were anonymized, the institutional review board waived the requirement for written consent from the patients.

RESULTS

Figure 1 shows the trend of patients with laboratory-confirmed COVID-19 between January 20, 2020, and April 8, 2020, in South Korea. During the period, a total of 10,384 patients infected with SARS-CoV-2 were reported to the Korea Center for Disease Control and Prevention. Of those, 5,061 adult patients with confirmed COVID-19 were included in our study. The clinical characteristics and outcomes of the patients are reported in Table 1. Confirmed cases were more common in women (2,832 [56%]) than in men (2,229 [44%]). The mean age was 45.62 ± 18.05 years in men and 44.88 ± 17.49 years in women. There were sex- and age-specific disparities in the number of confirmed COVID-19 cases (Fig. 2A). COVID-19 was the most prevalent in the 20-39 years age group for both sexes (993 [44.55%] in men and 1,250 [44.14%] in women). Additionally, the number of patients was higher among women than among men in all age groups. The most common comorbidity was hypertension (296 [13.3%] men and 316 [11.2%] women, $P = 0.022$), followed by diabetes (234 [10.5%]) in men and chronic pulmonary disease (241 [8.51%]) in women. The rates of oxygen therapy administration (144 [6.46%] vs 131 [4.63%], $P = 0.004$) and intensive care unit (ICU) admission (60 [2.69%] vs 53 [1.87%], $P = 0.049$) were higher in men than in women. The length of stay after admission to the ICU was longer in men than in women (19.7 ± 11.80 vs 14.75 ± 9.23, $P = 0.016$); however, the length of stay in hospitalized patients in general was longer in women than in men (6.0 ± 8.03 vs 5.02 ± 7.40, $P < 0.001$). There was no significant difference in the

TABLE 1. *Clinical characteristics and outcomes of 5,061 adult patients with confirmed COVID-19 in South Korea*

Variables	Male ($n = 2,229$)	Female ($n = 2,832$)	P value
Age, y	45.62 ± 18.05	44.88 ± 17.49	0.140
Comorbidities, no. (%)			
Cardiovascular disease	18 (0.81)	31 (1.09)	0.994
Cerebrovascular disease	13 (0.58)	6 (0.21)	0.032
Hypertension	296 (13.28)	316 (11.16)	0.022
Heart failure	51 (2.29)	82 (2.90)	0.18
Diabetes	234 (10.50)	185 (6.53)	0.079
Pulmonary disease	188 (8.43)	241 (8.51)	0.924
Malignancy	21 (0.94)	18 (0.64)	0.216
Chronic kidney disease	15 (0.67)	10 (0.35)	0.107
Chronic liver disease	2 (0.09)	3 (0.11)	>0.999
Treatments, no. (%)			
Oxygen therapy	144 (6.46)	131 (4.63)	0.004
Invasive mechanical ventilation	7 (0.31)	3 (0.11)	0.098
Extracorporeal membrane oxygenation	1 (0.04)	1 (0.04)	0.865
Renal replacement therapy	7 (0.31)	6 (0.21)	0.476
Clinical outcomes			
ICU admission, no. (%)	60 (2.69)	53 (1.87)	0.049
Length of ICU stay, d	19.7 ± 11.80	14.75 ± 9.23	0.016
Length of hospital stay for admitted patients, d	5.02 ± 7.40	6.0 ± 8.03	<0.001
Mortality, no. (%)	42 (1.88)	42 (1.48)	0.267

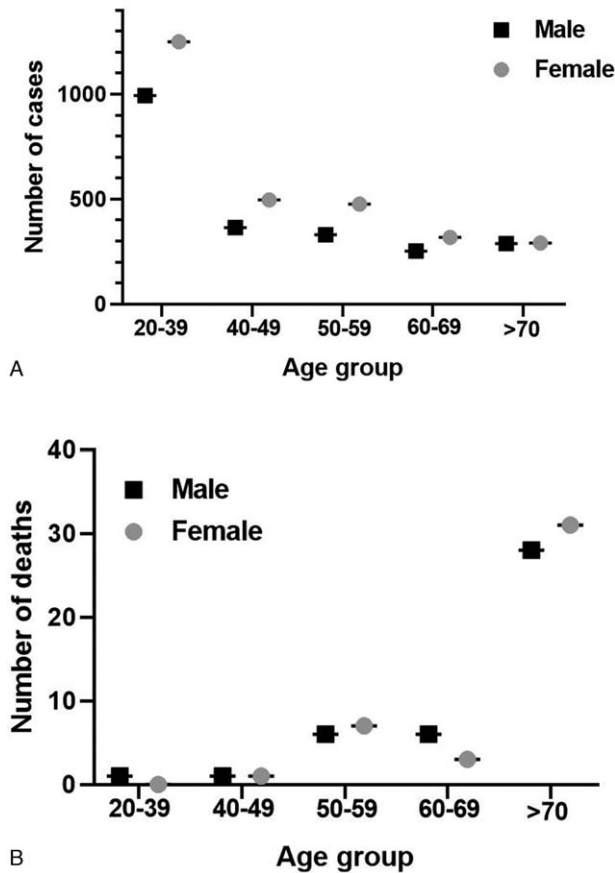COVID-19, coronavirus disease 2019; ICU, intensive care unit.

FIG. 2. Sex- and age-specific disparities in coronavirus disease cases. (**A**) Confirmed cases; (**B**) mortality cases.

mortality rate between men ($n = 42$, 1.88%) and women ($n = 42$, 1.48%) ($P = 0.267$) (Table 1). The mortality increased with age, and the largest number was observed in the >70 years age group (28 men [9.69%] and 31 women [10.65%]) (Fig. 2B). The multivariable Cox analysis revealed that age >65 years (hazard ratio [HR], 14.335; 95% confidence interval [CI], 8.239-24.942), cardiovascular disease (HR, 2.316; 95% CI, 1.053-5.094), and malignancy (HR,

4.332; 95% CI, 1.533-12.242) were the risk factors for mortality (Table 2).

In the subgroup analysis, the clinical characteristics of 53 recent HT users and 159 non-HT users were compared (Table 3). The mean ages were 49.40 ± 11.04 and 49.40 ± 10.97 years in the corresponding groups, respectively. Hypertension was the most common comorbidity in recent HT users (5 [9.43%]) and in non-HT users (17 [10.69%]). Although statistical significance was not observed, non-HT users were more likely to receive oxygen therapy (10 [6.29%] vs 1 [1.89%], $P = 0.211$), whereas recent HT users were likely to have a longer length of stay after admission to the ICU (19.0 ± 15.56 vs 15.67 ± 7.87 d, $P = 0.210$). In these groups, only one death was reported in the non-HT user group during the follow-up period.

DISCUSSION

To our knowledge, this is the first study to include a large number of confirmed cases that evaluated the effect of sex hormones on clinical outcomes of COVID-19. In this study, confirmed cases were the most prevalent in young women. Older age and underlying comorbidities, but not sex, had strong associations with mortality. HT use did not have a significant association with clinical outcomes in peri- and postmenopausal women. These findings suggest that female sex hormones may not have a protective role against COVID-19-related morbidity and mortality.

Male-dominant susceptibility to viral respiratory infections has been previously suggested.[10,11] Several studies have reported a male-biased sex ratio in confirmed COVID-19 cases.[12-14] In the Middle East respiratory syndrome coronavirus outbreak in South Korea, the number of cases was higher in men than in women (59.7% vs 40.3%).[15] However, epidemiologic studies on SARS-CoV infection have shown that the proportions of female patients were higher in several countries and regions (55.7% in Hong Kong, 61.0% in Toronto, 66.0% in Singapore, and 63.2% in Guangzhou).[16] Similarly, we demonstrated that the number of female patients infected with SARS-CoV-2 was higher. In South Korea, specific religious groups were associated with the largest number of

TABLE 2. *Multivariable Cox proportional hazard model for mortality of patients with confirmed COVID-19*

Variables	Hazard ratio	95% Confidence interval	*P* value
Sex (female vs male)			
Male (reference)	Reference		
Female	0.854	0.549-1.327	0.482
Age (≥65 vs <65)			
<65 (reference)	Reference		
≥65	14.335	8.239-24.942	<0.001
Comorbidities			
Cardiovascular disease	2.316	1.053-5.094	0.037
Cerebrovascular disease	0.471	0.065-3.435	0.458
Hypertension	1.238	0.758-2.021	0.691
Diabetes	1.524	0.909-2.553	0.110
Pulmonary disease	0.586	0.265-1.296	0.187
Malignancy	4.332	1.533-12.242	0.006
Chronic kidney disease	1.256	0.305-5.179	0.752

COVID-19, coronavirus disease 2019.

TABLE 3. *Clinical characteristics and outcomes of women who have been prescribed HT for the past year compared with those who did not using age-matched case-control data with a 1:3 ratio*

Variables	HT recent users (n = 53)	HT never users (n = 159)	P value
Age, y	49.40 ± 11.04	49.40 ± 10.97	0.925
Comorbidities, no. (%)			
Cardiovascular disease	.	.	NA
Cerebrovascular disease	.	.	NA
Hypertension	5 (9.43)	17 (10.69)	0.795
Heart failure	0	6 (3.77)	0.151
Diabetes	4 (7.55)	11 (6.92)	0.877
Pulmonary disease	5 (9.43)	15 (9.43)	>0.999
Malignancy	1 (1.89)	0	0.250
Chronic kidney disease	0	3 (1.89)	0.314
Chronic liver disease	.	.	NA
Treatments, no. (%)			
Oxygen therapy	1 (1.89)	10 (6.29)	0.211
Invasive mechanical ventilation	0	2 (1.26)	0.412
Extracorporeal membrane oxygenation	0	1 (0.63)	0.563
Renal replacement therapy	0	1 (0.63)	0.563
Clinical outcomes			
ICU admission, no. (%)	2 (3.77)	6 (3.77)	>0.999
Length of ICU stay, d	19.0 ± 15.56	15.67 ± 7.87	0.210
Length of hospital stay for admitted patients, d	6.89 ± 8.65	6.91 ± 9.11	0.677
Mortality	0	1 (0.63)	0.563

HT, hormone therapy; ICU, intensive care unit.

COVID-19 cases.[1] The predominance of women in those religious groups could be reflected in the female-biased sex ratio in our domestic COVID-19 outbreak. Additionally, the occupational hazards of a crowded workplace could be a risk factor for SARS-CoV-2 infection. In South Korea, the COVID-19 outbreak emerged at a call center, where the workers were at a high risk of coming in contact with each other.[17] At this call center, the affected individuals were predominantly female. We believe that these social and cultural factors could have led to sex-specific disparities in COVID-19 morbidity in South Korea.

In contrast to the studies conducted in other countries, our study showed that COVID-19 was the most prevalent in women in the 20-39 years age group. This finding was also observed in another study using data reported to the Korea Centers for Disease Control and Prevention.[8,18] In 2015, the Middle East respiratory syndrome coronavirus outbreak in South Korea spread through in-hospital infections.[15,19] Hence, during the COVID-19 outbreak, clinicians actively performed diagnostic tests for preventing in-hospital transmissions. Additionally, the Korean government established a wide range of indications for diagnostic testing such that any individual could get tested, even if the symptoms were not severe. Therefore, many healthy young adults with mild or no symptoms could get tested and diagnosed. Our results may represent the real epidemiology of COVID-19, encompassing asymptomatic to severe cases.

Data from several countries have shown a male-biased sex ratio in COVID-19 mortality.[12,14,20] In previous mice models, female hormones had a protective effect on mortality related to SARS-CoV infection.[4] McCoy et al suggested that androgens, which may play an important role in SARS-CoV-2 entry into the host cell, were implicated in COVID-19 mortality.[5] However, in our study, male sex was not an independent risk factor for mortality, and there was no significant association between HT use and the clinical outcomes of peri- and postmenopausal women. Although our study did not corroborate the protective role of female hormones against SARS-CoV-2 infection, further studies including emerging cases across several countries are required for determining the effects of sex hormones on SARS-CoV-2 infection.

This study has several limitations. First, owing to the nature of HIRA data, it was impossible to investigate detailed patient information, such as smoking history, viral loads, laboratory results, and radiologic findings, which could influence the clinical outcomes. In addition, we could not evaluate the exact interaction between female sex hormone levels and clinical outcomes because of the limited laboratory data available. Second, we cannot rule out the possibility of the underestimation of the number of male patients owing to asymptomatic or mild infections. A cohort study of patients with subclinical manifestations is needed for determining the sex ratio of the overall SARS-CoV-2 infections. Third, because of the limited number of women who received HT, we could not fully evaluate the effect of sex hormones on the clinical outcomes of COVID-19. Moreover, it is difficult to determine whether the patient was using the prescribed medications using claims data, and thus, HT use was evaluated based on drug codes for HT. Fourth, the menopausal status of female patients could not be evaluated. However, considering that the mean age at menopause (49.3 ± 0.1 y) is relatively lower in Korea than in other countries,[21] the patients included in the subgroup analysis may represent peri- and postmenopausal women.

CONCLUSIONS

This study provides indirect epidemiologic evidence on the effects of female sex hormones on the prevalence and clinical outcomes of COVID-19. Female sex hormones were not

associated with the morbidity and mortality of COVID-19 in South Korea. Furthermore, we showed that HT use was not associated with the clinical outcomes. Our findings could assist in the effective allocation of valuable health care resources and patient management during the current pandemic.

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