The effect of sex hormone on COVID-19: analysis of laboratory-confirmed 5061 patients in South Korea

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Research Article

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**Abstract**

Limited data describing the effect of sex hormone on coronavirus disease (COVID-19) is available. We evaluated the effect of sex hormone on prevalence and clinical outcomes of COVID-19. Retrospective cohort study was performed using the nationwide claims data of 5061 adult patients with laboratory-confirmed COVID-19 in South Korea, from January 20 to April 8, 2020. COVID-19 was most prevalent in women of the 20-39 age group (1250 [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 stay longer 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 mortality rates between men and women. In multivariable Cox analysis, independent risk factors for mortality were older age and underlying co-morbidities, rather than sex. To evaluate the effect of HRT among women, subgroup analysis was implemented using age-matched case-control data with a 1:3 ratio of females receiving HRT to those who did not. HRT did not have statistically significant association with clinical outcomes. This study suggests that sex hormone may not affect prevalence and clinical outcome of COVID-19 in South Korea.

**Introduction**

In South Korea, since the identification of the first confirmed case on January 20, 2020, coronavirus disease (COVID-19) cases occurred sporadically during the initial stages. After February 19, a large number of patients was identified from religious groups and long-term care facilities. Subsequently, we experienced an exponential rise in the number of confirmed cases nationwide. The spread of the infection 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 10752 with 244 deaths as of April 28, the acute upward slope appears to have been flattened.

Sex has already been a factor of marked importance in the short history of COVID-19. According to several studies, men have higher morbidity and mortality to COVID-19 than women. Somestudies suggest that sex hormone may affect the susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and subsequent mortality. Based on these findings, a clinical trial is recruiting COVID-19 patients to evaluate the effect of female sex hormone on clinical outcomes of patients as administering oestrogen to adult men or post-menopausal women who have low level of female hormone (ClinicalTrials.gov Identifier: NCT04359329). Presently, only few literature describing the effect of sex hormone on morbidity and mortality of COVID-19 is available. Understanding the effects of sex hormone on COVID-19 may assist in the identification of high-risk patients, prognosis prediction, and triage of patients for hospitalization during the current pandemic.

Epidemiologic findings in South Korea were different to other countries. Confirmed cases are more common in women, and COVID-19 is most prevalent in young adults. Here, we evaluate sex-specific characteristics of patients with laboratory-confirmed COVID-19 in this epidemiologic setting of South Korea.
using nationwide claims data and aim to investigate the effects of the female sex hormone 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 adult patients (age ≥ 20) 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 health care utilization information is registered under a comprehensive database operated by the HIRA. Medical institutions then submit the healthcare utilization information in 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). The database thus contains information on most patients, including ambulatory care histories, principal diagnoses, prescriptions, procedures, and comorbidities using the Korean Standard Classification of Diseases and Causes of Death, 7th edition (KCD-7), a modified version of International Classification of Diseases and Causes of Death, 10th revision (ICD-10). Details of HIRA are described elsewhere.

The KCD-7 codes for the diagnosis of COVID-19 and subjects' comorbidities are described in Supplementary Table 1. Underlying comorbidities were defined as the reimbursement of the KCD-7 codes of study diseases, within 5 years prior to the diagnosis of COVID-19. Drug codes of oestrogen therapy, oestrogen + progesterone therapy, and tibolone were used to identify the use of hormone replacement therapy (HRT) in female patients. Recent use of HRT was defined as the prescription of HRT drug codes for more than 1 month after 2019. Never use of HRT was defined as no prescription of HRT drug code for the 5 years covered by the database.

**Statistical analysis**

Descriptive analysis was used to compare the sex-specific characteristics of COVID-19 patients. Continuous variables were compared using the independent t-test, and categorical variables were compared using the chi-squared test or Fisher's exact test. Cox proportional hazard model was used to analyse the risk factors for mortality. The effect of HRT on the clinical outcomes of women was evaluated using subgroup analysis of age-matched case-control data with a 1:3 ratio of women who had been prescribed HRT for the past year to those who did not. All statistical analyses were performed using SAS Enterprise Guide (SAS Institute Inc., Cary, NC, USA). Analysis results with P < 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
thestudyparticipants were anonymized, the institutional review board waived the requirement for written consent from the patients.

**Data availability**

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

**Results**

Figure 1 showed 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 10384 patients infected with SARS-CoV-2 were reported to Korea Centers for Disease Control and Prevention. Of those, 5061 adult patients with confirmed COVID-19 were included in our study. Clinical characteristics and outcomes of the patients were reported in Table 1. Confirmed cases were more common in women (2832 [56%]) than in men (2229 [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 of COVID-19 in the number of confirmed cases (Figure 2-A). COVID-19 was most prevalent in the 20–39 age group for both sexes (993 [44.55%] in men and 1250 [44.14%] in women). In addition, the number of patients was higher in women than men in all age groups, except for the 70s. The most common comorbidity was hypertension (296 [13.3%] in males and 316 [11.2%] in females, P = 0.022), followed by diabetes (234 [10.5%]) in males and chronic pulmonary disease (293 [10.3%]) in females. Rates of oxygen therapy (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. Length of stay for patients admitted to the ICU was longer for men than for women (19.7±11.80 vs. 14.75±9.23, P = 0.016); however, the length of stay for hospitalized patients, in general, was longer for women than for men (5.02±7.40 vs. 6.0±8.03, P < 0.001). Mortality rate was higher in men (n=42, 1.88%) than women (n=42, 1.48%), but there was no significant difference (P = 0.267). The mortality cases increased with age, and the largest number was observed in the age > 70 group (28 men [9.69%] and 31 women [10.65%]) (Figure 2-B).

Multivariable Cox analysis revealed that independent risk factors for mortality were older age more than 65 (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), rather than sex (Table 2).

In a subgroup analysis, clinical characteristics of 53 recent users and 159 never users of HRT drugs were compared (Table 3). The mean age was 49.40±11.04 and 49.40±10.97 years, respectively. Hypertension was the most common comorbidity (5 [9.43%] vs 17 [10.69%]). Although statistically significance was not observed, non-HRT user was more likely to receive oxygen therapy (1 [1.89%] vs 10 [6.29%], P=0.298), while length of stay for patients admitted to the ICU was longer in recent HRT user (19.0±15.56 vs 15.67±7.87, P=0.685). Between both groups, only one death was reported in the HRT never user group during the follow-up period.

**Discussion**
To our knowledge, this study is the first report with a large number of confirmed cases evaluating the effect of sex hormone on the clinical outcome of COVID-19. In this study, confirmed cases were most prevalent in young women. Older age and underlying comorbidities rather than sex had a stronger association with mortality. HRT did not have a statistically significant association with clinical outcomes in peri- and post-menopausal women. These findings suggest that female sex hormone may not have a protective role in morbidity and mortality of COVID-19.

Male dominant susceptibility to viral respiratory infections was previously suggested\(^9,10\). Several studies have reported a male-biased sex ratio in cases confirmed with COVID-19\(^11-13\). In the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, the number of infected men was higher than that of infected women (59.7% vs. 40.3%)\(^14\). However, epidemiologic studies of severe acute respiratory syndrome coronavirus (SARS-CoV) infection showed that infected female patients are more common in several countries (55.7% in Hong Kong, 61.0% in Toronto, 66.0% in Singapore, and 63.2% in Guangzhou)\(^15\). We also demonstrated that the number of patients infected with SARS-CoV-2 were more common in women. In South Korea, the largest number of cases of COVID-19 is associated with specific religious groups\(^1\). The predominance of women in these religious groups could be reflected in the female-biased sex ratio within our domestic COVID-19 outbreak. In addition, 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 centre, where the workers were at a high risk of coming in contact with each other\(^16\). In this call centre, the affected individuals were predominantly women. 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 most prevalent in women of the 20–39 age group. This finding is also seen in another study using data reported to the Korea Centers for Disease Control and Prevention\(^7,17\). In 2015, the MERS-CoV outbreak in South Korea spread through in-hospital infections\(^14,18\). Hence, during the COVID-19 outbreak, clinicians actively performed diagnostic tests to prevent in-hospital transmission. In addition, the Korean government established a wide range of indications for diagnostic testing, so that any individual wanting to be tested can undergo the test, even if symptoms are not severe. Therefore, many healthy young adults with mild or no symptoms could be tested and diagnosed. Our results may represent the real epidemiology of COVID-19 encompassing asymptomatic to severe cases.

Data from several countries showed a male-biased sex ratio in COVID-19 mortality\(^11,13,19\). In previous micromodels, female hormones had a protective effect on mortality due to SARS-CoV infection\(^3\). McCoy et al. suggested that androgens, which could play an important role in SARS-CoV-2 entry into the host cell, seemed to be implicated in COVID-19 mortality\(^4\). However, in our study, male sex was not an independent risk factor for mortality, and there was no statistically significant association between HRT and the clinical outcomes of peri- and post-menopausal women. Although our study did not corroborate a role of female hormones against SARS-CoV-2 infection, further studies, which include emerging
cases across several countries, are required to determine the effect of sex hormones during COVID-19 infection.

This study has several limitations. First, due 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 clinical outcomes. Second, we cannot rule out the possibility of underestimated number of male patients due to asymptomatic or mild infections in COVID-19. A cohort study of patients with subclinical manifestations is needed to determine the sex ratio of entire SARS-CoV-2 infections. Third, because of the limited number of women receiving HRT, we could not fully evaluate the effect of sex hormone on clinical outcomes of COVID-19. In addition, menopausal status of female patients could not be evaluated. However, considering that the mean age of menopause, 49.3±0.1 years, is relatively younger in Korea than that of other countries, the patients included in subgroup analysis may represent peri- and post-menopausal women.

In conclusion, this study may provide indirect epidemiologic evidence on the effect of female sex hormone on the prevalence and clinical outcome of COVID-19. Our report could assist in the effective planning of valuable health care resource use and patient management during the current pandemic.

Declarations

Author Contributions: Conceptualization, J.H.L., Y.C.K. and S.H.C.; methodology, J.H.L., Y.C.K. and S.H.C.; formal analysis, J.H.L. and J.A.L.; investigation, J.H.L. and J.A.L.; data curation, J.H.L. and S.C.Y.; writing—original draft preparation, J.H.L. and Y.C.K.; writing—review and editing, Y.G.S., Y.B.W., and Y.S.P.; supervision, Y.C.K. and S.H.C. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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**Tables**

Table 1. Clinical characteristics and outcomes of 5061 adult patients with confirmed COVID-19 in South Korea.
| Variables                        | Male (n= 2229) | Female(n = 2832) | P-value |
|---------------------------------|----------------|-----------------|---------|
| Age, years                      | 45.61±18.05    | 44.88±17.49     | 0.14    |
| 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. (%)             |                |                 |         |
| Oxygentherapy                   | 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   |
|                          | 19.7±11.80 | 14.75±9.23 | 0.016 |
|--------------------------|------------|------------|-------|
| Length of ICU stay, days |            |            |       |
| Length of hospital stay  | 5.02±7.40  | 6.0±8.03   | <0.0001 |
| for admitted patients,   |            |            |       |
| days                     |            |            |       |
| Mortality, no. (%)       | 42(1.88)   | 42(1.48)   | 0.2674 |

ICU: intensive care unit

Table 2. Multivariable Cox proportional hazard model for mortality of patients with confirmed COVID-19.
| Variables                  | Hazardratio | 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            | 0.6912  |
| Diabetes                  | 1.524       | 0.909, 2.553            | 0.11    |
| 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   |

Table 3. Clinical characteristics and outcomes of women who have been prescribed HRT for the past year compared with those who did not using age-matched case-control data with a 1:3 ratio.
| Variables                           | HRTrecent users (n = 53) | HRTnever users (n = 159) | p-value |
|------------------------------------|--------------------------|--------------------------|---------|
| **Age, years**                     | 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)                  | 0.1514  |
| Diabetes                           | 4(7.55)                  | 11(6.92)                 | 0.877   |
| Pulmonary disease                  | 5(9.43)                  | 15(9.43)                 | >0.999  |
| Malignancy                         | 1(1.89)                  | 0                        | 0.25    |
| 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(0.63)                  | 0.412   |
| Extracorporeal membrane oxygenation| 0                        | 1(0.63)                  | 0.563   |
| Renal replacement                  | 0                        | 1(0.63)                  | 0.563   |
| **Clinical outcomes**              |                          |                          |         |
| ICU admission, no. (%)             | 2(3.77)                  | 6(3.77)                  | >0.999  |
| Length of ICU stay, days           | 19.0±15.56               | 15.67±7.87               | 0.21    |
| Length of hospital stay            | 6.89±8.65                | 6.91±9.11                | 0.677   |
| Mortality                          | 0                        | 1(0.63)                  | 0.563   |
Figures

Number of confirmed COVID-19 cases over time

Figure 1

Trend of confirmed coronavirus disease 2019 cases over time between January 20, 2020 and April 8, 2020, in South Korea.
Figure 2

Sex- and age-specific disparities in coronavirus disease 2019. A) confirmed cases B) mortality cases.

Supplementary Files

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- Supplementarydata0528.docx