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 firstconfirmedcase on January 20, 2020, coronavirus disease (COVID-19)casesoccurred sporadically during the initial stages. AfterFebruary 19,a large number of patients was identified fromreligious groups andlong-term care facilities. Subsequently, weexperienced anexponential rise in the number of confirmedcasesnationwide[1]. The spread of the infection hasbeenmitigated by adherence to social-distancing measures,mask-wearing,contact-tracing, and isolation of confirmed cases.Although thenumber of confirmed cases reached 10752 with 244 deathsas of April28, the acute upward slope appears to havebeenflattened[2].

Sex has already been a factor of marked importance in theshorthistory of COVID-19. According to several studies, men havehighermorbidity and mortality to COVID-19 than women[3,4].Somestudies suggest that sex hormone may affect the susceptibilitytosevere acute respiratory syndrome coronavirus 2(SARS-CoV-2)infection and subsequent mortality[3-6]. Basedon thesefindings, a clinical trial is recruiting COVID-19 patientstoevaluate the effect of female sex hormone on clinical outcomesofpatients as administering oestrogen to adult men orpost-menopausalwomen who have low level of female hormone(ClinicalTrials.govIdentifier: NCT04359329). Presently, only fewliterature describingthe effect of sex hormone on morbidity andmortality of COVID-19 isavailable. Understanding the effects of sexhormone on COVID-19 mayassist in the identification of high-riskpatients, prognosisprediction, and triage of patients forhospitalization during thecurrent pandemic.

Epidemiologic findings in South Korea were different toothercountries. Confirmed cases are more common in women, andCOVID-19is most prevalent in young adults[7]. Here, weevaluatesex-specific characteristics of patients withlaboratory-confirmedCOVID-19 in this epidemiologic setting of SouthKorea

usingnationwide claims data and aim to investigate theeffects of thefemale sex hormone on the clinical course and diseaseseverity ofCOVID-19.

Methods

Patient data

We performed a retrospective cohort study using theHealthInsurance Review and Assessment (HIRA) dataset consisting ofadultpatients (age≥ 20) with laboratory-confirmed COVID-19betweenJanuary 20, 2020 and April 8, 2020, in South Korea. TheSouthKorean government operates a mandatory nationwide insurancesystem(National Health Insurance) which covers all forms ofhealthservices, including hospitalization, ambulatory care,andpharmaceutical services. All health care utilization informationisregistered under a comprehensive database operated by theHIRA.Medical institutions then submit the healthcareutilizationinformation in electronic forms for reimbursementpurposes, andthis information is integrated into the HIRA claimsdatabase, whichcovers the entire population of South Korea(approximately 51million). The database thus contains informationon most patients,including ambulatory care histories, principaldiagnoses,prescriptions, procedures, and comorbidities using theKoreanStandard Classification of Diseases and Causes of Death,7thedition (KCD-7), a modified version of InternationalClassificationof Disease 10th revision (ICD-10). Details of HIRAare describedelsewhere[8].

The KCD-7 codes for the diagnosis of COVID-19 andsubjects'comorbidities are described in Supplementary Table 1.Underlyingcomorbidities were defined as the reimbursement of theKCD-7 codeof study diseases, within 5 years prior to the diagnosisofCOVID-19. Drug codes of oestrogen therapy, oestrogen +progesteronetherapy, and tibolone were used to identify the use ofhormonereplacement therapy (HRT) in female patients. Recent use ofHRT wasdefined as the prescription of HRT drug codes for more than1 monthafter 2019. Never use of HRT was defined as no prescriptionof HRTdrug code for the 5 years covered by the database.

Statistical analysis

Descriptive analysis was used to compare thesex-specificcharacteristics of COVID-19 patients. Continuousvariables werecompared using the independent t-test, andcategorical variableswere compared using the chi-squared test orFisher's exact test.Cox proportional hazard model was used toanalyse the risk factorsfor mortality. The effect of HRT on theclinical outcomes of womenwas evaluated using subgroup analysis ofage-matched case-controldata with a 1:3 ratio of women who had beenprescribed HRT for thepast year to those who did not. Allstatistical analyses wereperformed using SAS Enterprise Guide (SASInstitute Inc., Cary, NC,USA). Analysis results with $P < 0.05$were consideredstatistically significant. The study protocol wasapproved by theInstitutional Review Board (3-2020-0072) of YonseiUniversityCollege of Medicine, Gangnam Severance Hospital (Seoul,Republic ofKorea), and the protocol adhered to the tenets of theDeclarationof Helsinki. Since the study was retrospective and

thestudyparticipants were anonymized, the institutional review boardwaivedthe requirement for written consent from thepatients.

Data availability

The datasets generated or analysed during the current studyareavailable from the corresponding author on reasonablerequest.

Results

Figure 1 showed the trend of patients withlaboratory-confirmedCOVID-19 between January 20, 2020 and April 8,2020, in SouthKorea. During the period, a total of 10384 patientsinfected withSARS-CoV-2 were reported to Korea Centers for DiseaseControl andPrevention. Of those, 5061 adult patients with confirmedCOVID-19were included in our study. Clinical characteristics andoutcomesof the patients were reported in Table 1. Confirmed caseswere morecommon in women (2832 [56%]) than in men (2229 [44%]). Themean agewas 45.62±18.05 years in men and 44.88±17.49 years inwomen. Therewere sex- and age-specific disparities of COVID-19 inthe number ofconfirmed cases (Figure 2-A). COVID-19 was mostprevalent in the20–39 age group for both sexes (993 [44.55%] in menand 1250[44.14%] in women). In addition, the number of patients washigherin women than men in all age groups, except for the 70s. Themostcommon comorbidity was hypertension (296 [13.3%] in males and316[11.2%] in females, P = 0.022), followed by diabetes (234[10.5%])in males and chronic pulmonary disease (293 [10.3%]) infemales.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 stayforpatients admitted to the ICU was longer for men than forwomen(19.7±11.80 vs. 14.75±9.23, P = 0.016); however, the length ofstayfor hospitalized patients, in general, was longer for womenthanfor men (5.02±7.40 vs. 6.0±8.03, P < 0.001). Mortality ratewashigher in men (n=42, 1.88%) than women (n=42, 1.48%), but therewasno significant difference (P = 0.267). The mortalitycasesincreased with age, and the largest number was observed intheage>70 group (28 men [9.69%] and 31 women [10.65%])(Figure2-B). Multivariable Cox analysis revealed that independentriskfactors for mortality were older age more than 65 (hazardratio[HR], 14.335; 95% confidential interval [CI],8.239-24.942),cardiovascular disease ([HR], 2.316; 95% CI,1.053-5.094), andmalignancy ([HR], 4.332; 95% CI, 1.533-12.242),rather than sex(Table 2).

In a subgroup analysis, clinical characteristics of 53recentusers and 159 never users of HRT drugs were compared (Table3). Themean 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 notobserved,non-HRT user was more likely to receive oxygen therapy (1[1.89%]vs 10 [6.29%], *P*=0.298), while length of stay forpatientsadmitted to the ICU was longer in recent HRT user(19.0±15.56 vs15.67±7.87, *P*=0.685). Between both groups,only one deathwas reported in the HRT never user group during thefollow-upperiod.

Discussion

To our knowledge, this study is the first report with alargenumber of confirmed cases evaluating the effect of sex hormoneonthe clinical outcome of COVID-19. In this study, confirmedcaseswere most prevalent in young women. Older age andunderlyingcomorbidities rather than sex had a stronger associationwithmortality. HRT did not have a statistically significantassociationwith clinical outcomes in peri- and post-menopausalwomen. Thesefindings suggest that female sex hormone may not have aprotectiverole in morbidity and mortality of COVID-19.

Male dominant susceptibility to viral respiratory infectionswaspreviously suggested[9,10]. Several studies havereporteda male-biased sex ratio in cases confirmedwithCOVID-19[11-13]. In the Middle East respiratorysyndromecoronavirus (MERS-CoV) outbreak in South Korea, the numberofinfected men was higher than that of infected women (59.7%vs.40.3%)[14]. However, epidemiologic studies of severeacuterespiratory syndrome coronavirus (SARS-CoV) infection showedthatinfected female patients are more common inseveralcountries (55.7% in Hong Kong, 61.0% in Toronto, 66.0%inSingapore, and 63.2% in Guanzhou)[15]. Wealsodemonstrated that the number of patients infected withSARS-CoV-2were more common in women. In South Korea, the largestnumber ofcases of COVID-19 is associated with specificreligiousgroups[1]. The predominance of women in thosereligiousgroups could be reflected in the female-biased sex ratiowithin ourdomestic COVID-19 outbreak. In addition, the occupationalhazardsof a crowded workplace could be a risk factor forSARS-CoV-2infection. In South Korea, the COVID-19 outbreak emergedat a callcentre, where the workers were at a high risk of coming incontactwith each other[16]. In this call centre, theaffectedindividuals were predominantly women. We believe that thesesocialand cultural factors could have led to sex-specificdisparities inCOVID-19 morbidity in South Korea.

In contrast to the studies conducted in other countries,ourstudy showed that COVID-19 was most prevalent in women of the20–39age group. This finding is also seen in another study usingdatareported to the Korea Centers for Disease ControlandPrevention[7,17]. In 2015, the MERS-CoV outbreak inSouthKorea spread through in-hospital infections[14,18].Hence,during the COVID-19 outbreak, clinicians activelyperformeddiagnostic tests to prevent in-hospital transmission. Inaddition,the Korean government established a wide range ofindications fordiagnostic testings, so that any individual wantingto be testedcan undergo the test, even if symptoms are not severe.Therefore,many healthy young adults with mild or no symptoms couldbe testedand diagnosed. Our results may represent the realepidemiology ofCOVID-19 encompassing asymptomatic to severecases.

Data from several countries showed a male-biased sex ratioinCOVID-19 mortality[11,13,19]. In previous micemodels,female hormones had a protective effect on mortality duetoSARS-CoV infection[3]. McCoy et al. suggestedthatandrogens, which could play an important role in SARS-CoV-2entryinto the host cell, seemed to be implicated inCOVID-19mortality[4]. However, in our study, male sex wasnot anindependent risk factor for mortality, and there wasnostatistically significant association between HRT and theclinicaloutcomes of peri- and post-menopausal women. Although ourstudy didnot corroborate a role of female hormones againstSARS-CoV-2infection, further studies, which include emerging

casesacrossseveral countries, are required to determine the effect ofsexhormones during COVID-19 infection.

This study has several limitations. First, due to the natureofHIRA data, it was impossible to investigate detailedpatientinformation, such as smoking history, viral loads,laboratoryresults, and radiologic findings, which could influenceclinicaloutcomes. Second, we cannot rule out the possibilityofunderestimated number of male patients due to asymptomatic ormildinfections in COVID-19. A cohort study of patients withsubclinicalmanifestations is needed to determine the sex ratio ofentireSARS-CoV-2 infections. Third, because of the limited numberofwomen receiving HRT, we could not fully evaluate the effect ofsexhormone on clinical outcomes of COVID-19. In addition,menopausalstatus of female patients could not be evaluated.However,considering that the mean age of menopause, 49.3±0.1 years,isrelatively younger in Korea than that ofothercountries[20], the patients included in subgroupanalysismay represent peri- and post-menopausal women.

In conclusion, this study may provide indirectepidemiologicevidence on the effect of female sex hormone on theprevalence andclinical outcome of COVID-19. Our report could assistin theeffective planning of valuable health care resource use andpatientmanagement 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;formalanalysis, J.H.L. and J.A.L.; investigation, J.H.L. andJ.A.L.; datacuration, J.H.L. and S.C.Y.; writing—original draftpreparation,J.H.L. and Y.C.K.; writing—review and editing, Y.G.S.,Y.B.W., andY.S.P.; supervision, Y.C.K. and S.H.C. All authors haveread andagreed to the published version of the manuscript.

Conflicts of Interest: The authors declarenoconflict of interest.

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Tables

Table 1. Clinical characteristics and outcomes of 5061 adultpatients 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.(%)			
Cardiovasculardisease	18(0.81)	31(1.09)	0.994
Cerebrovasculardisease	13(0.58)	6(0.21)	0.032
Hypertension	296(13.28)	316(11.16)	0.022
Heartfailure	51(2.29)	82(2.90)	0.18
Diabetes	234(10.50)	185(6.53)	0.079
Pulmonarydisease	188(8.43)	241(8.51)	0.924
Malignancy	21(0.94)	18(0.64)	0.216
Chronickidney disease	15(0.67)	10(0.35)	0.107
Chronicliver disease	2(0.09)	3(0.11)	>0.999
Treatments, no.(%)			
Oxygentherapy	144(6.46)	131(4.63)	0.004
Invasivemechanical ventilation	7(0.31)	3(0.11)	0.098
Extracorporeal membraneoxygenation	1(0.04)	1(0.04)	0.865
Renalreplacement therapy	7(0.31)	6(0.21)	0.476
Clinicaloutcomes			
ICUadmission, no. (%)	60(2.69)	53(1.87)	0.049
Lengthof ICU stay, days	19.7±11.80	14.75±9.23	0.016
Lengthof hospital stay for admitted patients,days	5.02±7.40	6.0±8.03	<0.0001
Mortality, no.(%)	42(1.88)	42(1.48)	0.2674

ICU; intensive care unit

Table 2. Multivariable Cox proportional hazard model for mortalityof 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 (≥65Vs. < 65)			
< 65(reference)	reference		
≥ 65	14.335	8.239,24.942	<0.001
Comorbidities			
Cardiovasculardisease	2.316	1.053,5.094	0.037
Cerebrovasculardisease	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
Pulmonarydisease	0.586	0.265,1.296	0.187
Malignancy	4.332	1.533,12.242	0.006
Chronickidney disease	1.256	0.305,5.179	0.752

Table 3. Clinical characteristics and outcomes of women who havebeen prescribed HRT for the past year compared with those who didnot using age-matched case-control data with a 1:3ratio.

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.(%)			
Cardiovasculardisease	.	.	NA
Cerebrovasculardisease	.	.	NA
Hypertension	5(9.43)	17(10.69)	0.795
Heartfailure	0	6(3.77)	0.1514
Diabetes	4(7.55)	11(6.92)	0.877
Pulmonarydisease	5(9.43)	15(9.43)	>0.999
Malignancy	1(1.89)	0	0.25
Chronickidney disease	0	3(1.89)	0.314
Chronicliver disease	.	.	NA
Treatments, no.(%)			
Oxygentherapy	1(1.89)	10(6.29)	0.211
Invasivemechanical ventilation	0	2(0.63)	0.412
Extracorporeal membraneoxygenation	0	1(0.63)	0.563
Renalreplacement therapy	0	1(0.63)	0.563
Clinicaloutcomes			
ICUadmission, no. (%)	2(3.77)	6(3.77)	>0.999
Lengthof ICU stay, days	19.0±15.56	15.67±7.87	0.21
Lengthof hospital stay for admitted patients,days	6.89±8.65	6.91±9.11	0.677
Mortality	0	1(0.63)	0.563

HRT, hormone replacement therapy; ICU, intensive careunit.

Figures

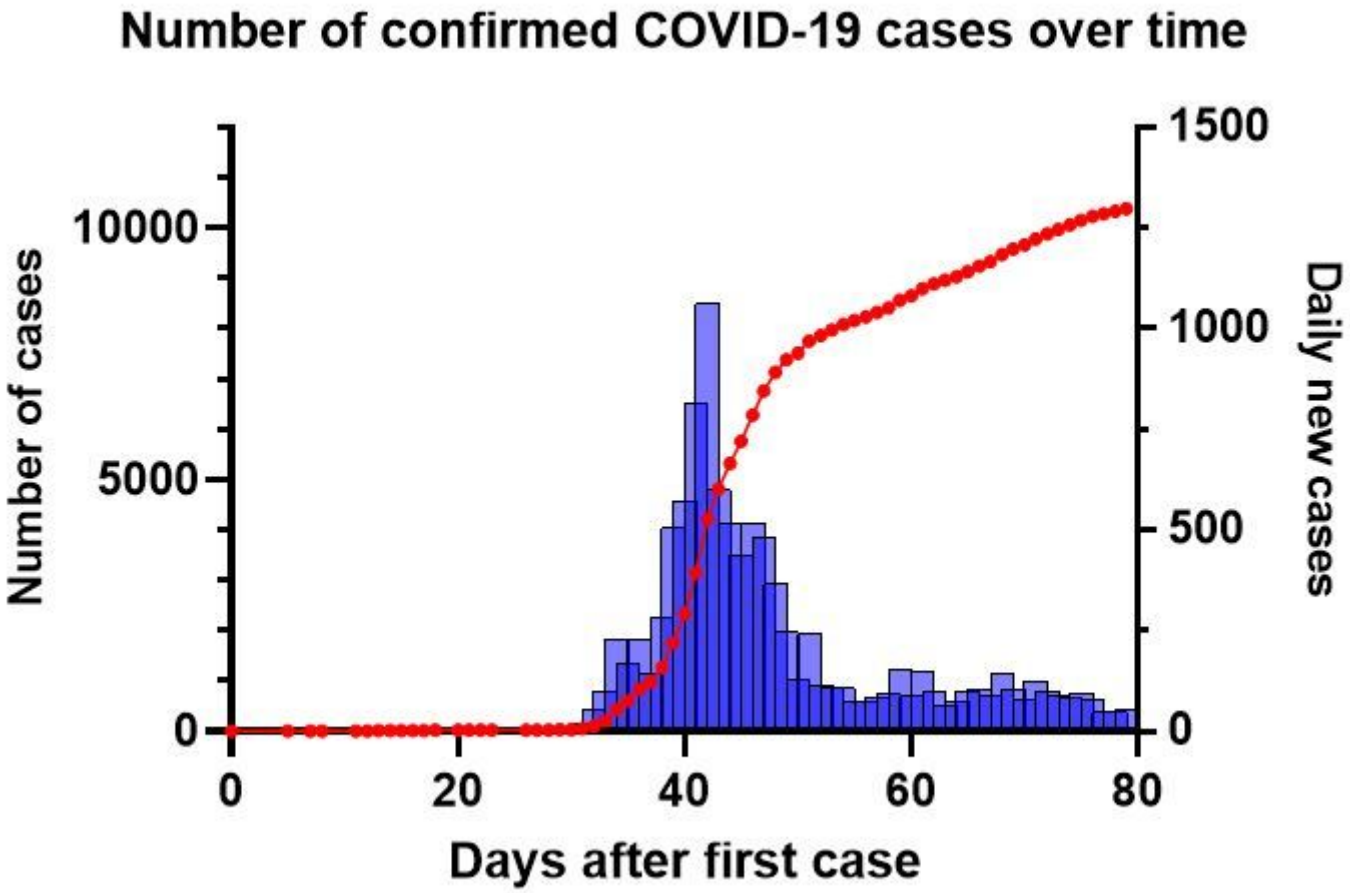

Figure 1

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

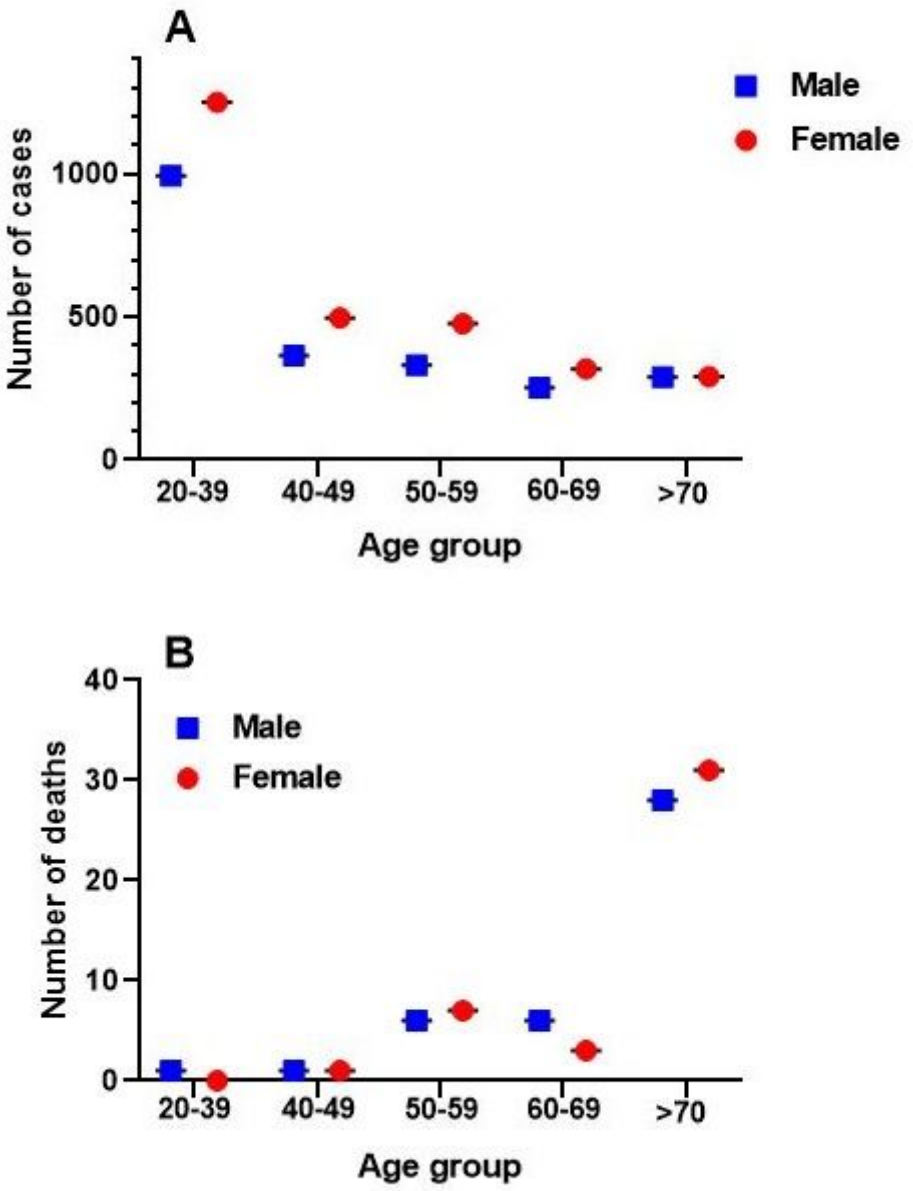

Figure 2

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

Supplementary Files

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- Supplementarydata0528.docx