Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Asian Nursing Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Asian Nursing Research

journal homepage: www.asian-nursingresearch.com

Research Article

Sex-Based Differences in Outcomes of Coronavirus Disease 2019 (COVID-19) in Korea

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ARTICLE INFO

Article history:
Received 4 November 2021
Received in revised form
5 July 2022
Accepted 31 July 2022

Keywords:
COVID-19
death
risk factors
sex

SUMMARY

Purpose: This study examined the factors affecting mortality and clinical severity score (CSS) of male and female patients with Coronavirus Disease 2019 (COVID-19) using clinical epidemiological information provided by the Korea Disease Control and Prevention Agency.
Methods: This is a retrospective, observational cohort study. From January 21 to April 30, 2020, a total of 5624 patients who were released from quarantine or died were analyzed.
Results: The factors influencing release or death that differed by sex were high heart rate and malignancy in males and chronic kidney disease in females. In addition, the factors influencing progression to severe CSS were high BMI (severe obesity) and rheumatic disease in males and high temperature, sputum production, absence of sore throat and headache, chronic kidney disease, malignancy, and chronic liver disease in females. Older age, low lymphocyte count and platelets, dyspnea, diabetes mellitus, dementia, and intensive care unit (ICU) admission affected mortality in all the patients, and older age, low lymphocyte count and platelets, fever, dyspnea, diabetes mellitus, dementia, and ICU admission affected progression to severe stage of CSS.
Conclusions: This study is expected to contribute to the general results by analyzing nationally representative data. The results of this study present an important basis for development of differentiated nursing and medical management strategies in consideration of factors that influence treatment effects and outcomes according to sex of patients with COVID-19.

Introduction

The World Health Organization (WHO) declared the Coronavirus Disease 2019 (COVID-19) was a pandemic on March 11, 2020 [1]. As of July 4, 2022, a total of 546,357,444 patients were reported to have COVID-19, and 6,336,415 were reported to have died from the disease [2]. In comparison, severe acute respiratory syndrome (SARS) was identified first on November 16, 2002 and confirmed in 8096 patients, causing 774 deaths in 29 countries through July 2003, but was not judged to be a global pandemic. COVID-19 is believed to be one of the most serious health crises ever.

Detecting the causative agent of COVID-19 and providing appropriate isolation and treatment by sharing information is a top priority. Therefore, several studies have analyzed clinical epidemiological data. Studies based on early epidemiological data found that males were more likely to be infected than females [3,4]. A study of severely ill patients with COVID-19 identified a larger proportion of males than females, indicating that COVID-19 varies by sex, and that male patients are more susceptible to severe COVID-19 [5,6]. In particular, severity and complications were more severe in male patients, and this was premised on pathophysiological evidence that the potential functional regulation of angiotensin-converting enzyme 2 (ACE2) by estrogen results in sex differences between morbidity and mortality [7–11]. Conversely, androgens can be a predisposing factor to greater severity of COVID-19 in males [12]. Additionally, although the mechanism of these sex differences is not fully understood, factors such as

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https://doi.org/10.1016/j.anr.2022.07.003

Please cite this article as: Kim J et al., Sex-Based Differences in Outcomes of Coronavirus Disease 2019 (COVID-19) in Korea, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.07.003

socioeconomic status, lifestyle habits (e.g., smoking and drinking rates), personal hygiene patterns (e.g., hand washing), healthcare-seeking behavior, and access to healthcare might partially explain the sex-based differences [5,13,14]. The mortality and severity of patients with COVID-19 differ according to sex, indicating it is an important variable in prevention and treatment of COVID-19. However, most studies have generally reported differences in incidence, mortality, and severity according to epidemiological characteristics [5,6,15,16]. A meta-analysis of 4420 patients with SARS-CoV-2/COVID-19 by Brady et al. [17] found that sex/gender was included as an analytical variable in only 178 (4%). In other words, there have been no reports on systematic analysis of specific and various factors for effective medical management, such as clinical findings, comorbid diseases, and blood tests, according to sex. A study of patients with COVID-19 in Korea identified risk factors for progression to severe stage [18] using models that predicted clinical severity and duration of hospitalization [19] but failed to account for sex differences. A study using data from the Korea Disease Control and Prevention Agency (KDCA) daily reports also analyzed dynamic patterns among age and sex groups and found that epidemics among young adults resulted in the epidemic spreading across the entire population, whereas overall sex differences in the COVID-19 epidemic were moderate; however, other related factors could not be analyzed [20]. In light of the current results, researchers of SARS-CoV2 and COVID-19 are urged to systematically apply sex-specific methodologies [17]. This should include performance of sex-specific analyses and reporting of sex-disaggregated results for identification of differences in treatment effects [21].

Therefore, this study uses clinical epidemiological information recorded by the KDCA from patients confirmed to have COVID-19 to identify and compare factors that affect mortality and clinical severity score (CSS) of male and female patients. The predictive variables selected in this study (age, body mass index [BMI], clinical findings at hospitalization, comorbidities, etc.) were found to be related to COVID-19 outcomes in previous studies [18–20]. In addition, as much information as can be obtained from the early clinical process, it could be very useful in identifying the risk of mortality and CSS in male and female patients before or at the early stage of diagnosis of COVID-19. Therefore, the results of this study will provide data for planning evidence-based nursing and medical management strategies by sex for the prevention and treatment of COVID-19.

Methods

Study design and samples

This is a retrospective observational cohort study using patient clinical epidemiological information provided by the KDCA (http://www.kdca.go.kr/). The clinical epidemiological information was collected for COVID-19 patients with confirmed COVID-19 who were con-firmed to be released from quarantine or died as of April 30, 2020. Confirmed cases include those who have been confirmed as infected with the infectious disease pathogen according to the diagnostic testing standard, regardless of clinical manifestations [22]. The raw data included 5628 patients; each variable did not have many missing values and patients with missing values were excluded from the analysis. A total of 5624 patients (2317 males, 3307 females) were included in the final analysis.

Measurements

Epidemiological and clinical characteristic data were obtained by healthcare providers at admission. Patients were followed until the end of hospitalization. During hospitalization, patients were monitored by the KDCA of the National Medical Center.

Epidemiological and clinical characteristics

The age, BMI, initial examination findings (heart rate, temperature), clinical findings at hospitalization (fever, cough, sputum production, sore throat, rhinorrhea, dyspnea, headache, confusion), comorbid diseases (diabetes mellitus, hypertension, chronic kidney disease, malignancy, chronic liver disease, rheumatic disease, dementia), intensive care unit (ICU) admission, and complete blood count (lymphocytes and platelets) of the patients were analyzed.

Definition of outcome

The first treatment effect was mortality according to the following criteria. Confirmed cases who display symptoms are discharged if they meet the clinical and testing criteria. (1) According to the clinical criteria, a person should not exhibit a fever without taking fever reducers and show improvements in clinical symptoms for at least 72 hours after 10 days on onset. (2) For the testing criteria, a person should not exhibit a fever without taking fever reducers and show improvements in clinical symptoms after 7 days on onset. Thereafter, the person should test negative on PCR tests twice in a row with at least a 24-hour interval. Confirmed cases who do not display symptoms are discharged if they do not exhibit any clinical symptoms for 10 days on confirmation. According to the testing criteria, they should test negative on PCR tests twice in a row with at least a 24-hour interval after 7 days on confirmation [22]. Death was defined as in-hospital mortality.

The second treatment effect was CSS. The CSS represents clinical severity of patients with COVID-19. The original CSS provided by the KDCA is scored from 1 to 8, with the lowest stage 1 indicating no disruption of daily life and the highest stage 8 indicating death. In this study, appropriate treatment was determined by reclassifying severity into four stages from the original 8 stages according to patient condition. These CSS stages (Stage 1: No disruption to daily life; Stage 2: Hindrance to daily life but no oxygen required; Stage 3: Oxygen treatment, multi-organ damage, and extracorporeal membrane oxygenation (ECMO); Stage 4: Death) were classified and analyzed.

Data analysis

Data were analyzed using SAS 9.4 program [23]. Epidemiological and clinical characteristics of the patients were analyzed as the frequency, percentage, mean, and standard deviation, and Chi-square test was used to examine the differences in epidemiological and clinical characteristics between male and female patients. Pearson's correlation coefficient analysis was used to identify the associations between CSS and age, heart rate, temperature, lymphocytes, platelets variables in male and female patients. Multiple binary/ordinal stepwise logistic regression was performed to investigate the major factors affecting treatment effect and outcomes (mortality, CSS) in male and female patients, considering the useable major factors such as age, BMI, rhinorrhea, dyspnea, confusion, diabetes mellitus, chronic kidney disease, malignancy, dementia, ICU admission, lymphocytes, platelets, and so on. The stepwise logistic regression was used to remove variables that were not required to explain the dependent variable. The variance inflation factors (VIF) of all selected independent variables are below 3, which means multicollinearity does not exist in these regression models. The threshold for statistical significance for this study was $p < .05$.

Please cite this article as: Kim J et al., Sex-Based Differences in Outcomes of Coronavirus Disease 2019 (COVID-19) in Korea, Asian Nursing Research, https://doi.org/10.1016/j.anr.2022.07.003

Ethical considerations

This study was approved for information disclosure by the KDCA. The research was approved by the Institutional Review Board of the associated institute (IRB No. SMUIRB, ex-2020-005). To ensure the anonymity and confidentiality of participants, personal information was provided and used through a secured closed system.

Results

Participants' characteristics

A total of 5624 participants was in the final analysis, including 2317 males (41.2%) and 3307 females (58.8%). Of the 5624 confirmed patients with COVID-19, 5383 (95.7%) were released from quarantine and 241 (4.3%) died. The mortality rate for males was 5.5%, higher than that for females (3.5%). There were significant differences between male and female patients according to release or death, CSS, age, BMI, temperature, cough, sputum production, sore throat, headache, diabetes mellitus, chronic liver disease, dementia, ICU admission, lymphocyte, and platelets (Table 1).

Correlation coefficients for variables

To identify bivariate correlations, Pearson's correlation coefficient analyses were performed and confirmed that predictor variables had an association with CSS (Table 2).

Multiple binary logistic regression for mortality

To identify factors affecting mortality, multiple binary logistic regression was conducted by dividing all patients into quarantine

Table 1 *Epidemiological and Clinical Characteristics.*

Variables	Categories	Men ($n = 2317$)	Women ($n = 3307$)	Total	X^2	p
		n (%) or M ± SD	n (%) or M ± SD	n (%) or M ± SD		
Release or death[a]	Release	2190 (97.5)	3193 (96.6)	5383 (95.7)	13.74	<.001
	Death	127 (5.5)	114 (3.5)	241 (4.3)		
Clinical severity score (CSS)[a]	No disruption to daily life	1804 (78.2)	2647 (80.5)	4451 (79.5)	18.53	<.001
	Hindrance to daily life but no oxygen required	118 (5.1)	212 (6.4)	330 (5.9)		
	Oxygen treatment, multi-organ damage, and extracorporeal membrane oxygenation (ECMO)	201 (11.2)	317 (9.6)	575 (10.3)		
	Death	127 (5.5)	114 (3.5)	241 (4.3)		
Age (years)[a]	60<	1604 (69.2)	2235 (67.6)	3839 (68.3)	12.04	0.007
	60–69	377 (16.3)	539 (16.3)	916 (16.3)		
	70–79	232 (10.0)	313 (9.5)	545 (9.7)		
	≥80	104 (4.5)	220 (6.7)	324 (5.8)		
BMI[a]	<18.5	87 (4.7)	173 (6.8)	260 (5.9)	154.52	<.001
	18.5–22.9	614 (33.0)	1253 (48.9)	1867 (42.2)		
	23.0–24.9	487 (26.1)	551 (21.5)	1038 (23.5)		
	25.0–29.9	576 (30.1)	476 (18.6)	1052 (23.8)		
	≥30	99 (5.3)	109 (4.3)	208 (4.7)		
HR		86.17 ± 15.40	85.58 ± 14.82	85.82 ± 15.06	1.56	0.459
	<60	48 (2.3)	59 (1.9)	107 (2.0)		
	60–100	1762 (82.9)	2615 (84.0)	4377 (83.6)		
	≥100	316 (14.9)	438 (14.1)	754 (14.4)		
Temperature[a]		36.90 ± 0.57	36.98 ± 0.54	36.94 ± 0.56	41.48	<.001
	<36.1	68 (3.2)	66 (2.1)	134 (2.6)		
	36.1–37.2	1602 (74.4)	2191 (69.3)	3793 (71.4)		
	37.3–38.2	416 (19.3)	835 (26.4)	1251 (23.5)		
	38.3–40.4	66 (3.1)	70 (2.2)	136 (2.6)		
Fever	Yes	521 (22.5)	784 (23.7)	1305 (23.2)	1.14	0.286
Cough[a]	Yes	918 (39.6)	1423 (43.0)	2341 (41.6)	6.52	0.011
Sputum production[a]	Yes	592 (25.6)	1027 (31.1)	1619 (28.8)	20.14	<.001
Sore throat[a]	Yes	290 (12.5)	591 (17.9)	881 (15.7)	29.57	<.001
Rhinorrhea	Yes	239 (10.3)	382 (11.6)	621 (11.0)	2.12	0.145
Dyspnea	Yes	263 (11.4)	403 (12.2)	666 (11.8)	0.91	0.340
Headache[a]	Yes	299 (12.9)	668 (20.2)	967 (17.2)	50.92	<.001
Confusion	Yes	16 (0.7)	19 (0.6)	35 (0.6)	0.30	0.586
DM[a]	Yes	325 (14.0)	366 (11.1)	691 (12.3)	11.07	0.001
Hypertension	Yes	506 (21.8)	695 (21.0)	1201 (21.4)	0.55	0.459
CKD	Yes	26 (1.1)	29 (0.9)	55 (1.0)	0.85	0.358
Malignancy	Yes	49 (2.1)	96 (2.9)	145 (2.6)	3.37	0.066
CLD[a]	Yes	48 (2.2)	35 (1.1)	83 (1.6)	9.62	0.002
Rheumatoid disease	Yes	12 (0.6)	26 (0.8)	38 (0.7)	1.46	0.227
Dementia[a]	Yes	71 (3.2)	153 (4.9)	224 (4.2)	8.70	0.003
ICU admission[a]	Yes	115 (5.0)	74 (2.3)	189 (3.4)	31.11	<.001
Lymphocytes (%)[a]		27.60 ± 12.28	30.12 ± 11.14	29.15 ± 11.66	46.27	<.001
	<20	428 (27.2)	455 (18.3)	883 (21.8)		
	20–39	913 (58.0)	1579 (63.3)	2492 (61.4)		
	≥40	232 (14.8)	450 (18.0)	682 (16.8)		
PLT ($10^3/\mu L$)[a]	<150	263 (16.6)	237 (25.5)	500 (12.2)	44.99	<.001
	150–399	1298 (81.7)	2212 (88.7)	3510 (86.0)		
	≥400	27 (1.7)	45 (1.8)	72 (1.8)		

Note. BMI = body mass index; CKD = chronic kidney disease; CLD = chronic liver disease; DM = diabetes mellitus; HR = heart rate; ICU = intensive care unit; PLT = platelets.
[a] Indicates that the proportions of male and female are significantly different at significance level 0.05 by Chi-square test.

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Table 2 *Correlation Coefficients for Variables in Males and Females.*

Variables	Men			Women		
	Clinical severity score (CSS)			CSS		
	r	95% CI		r	95% CI	
		Low	High		Low	High
Age[a]	0.43***	0.40	0.47	0.38***	0.35	0.40
HR[a]	0.11***	0.07	0.15	−0.00	−0.04	0.03
Temperature	0.16***	0.12	0.20	0.11***	0.07	0.14
Lymphocytes[a]	−0.41***	−0.44	−0.38	−0.34***	−0.37	−0.31
PLT	−0.20***	−0.23	−0.16	−0.17***	−0.20	−0.14

*$p < .05$, **$p < .01$, ***$p < .001$.
Note. HR = heart rate; PLT = platelets.
[a] Indicates that the correlation coefficients of male and female are significantly different at significance level 0.05 by Fisher's z-test.

release or death (Table 3). Older age, high heart rate, low lymphocyte count and platelets, rhinorrhea, dyspnea, confusion, diabetes mellitus, malignancy, dementia, and ICU admission were factors influencing mortality among all patients.

Older age, high heart rate, low lymphocyte count and platelets, dyspnea, diabetes mellitus, malignancy, dementia, and ICU admission affected mortality among male patients. When other variables were controlled, the odds ratio of release was 25.22 times lower in the younger than 60-year-old group, 7.73 times lower in the 60-69-year-old group, and 5.23 times lower in the 70-79-year-old group compared with patients 80 years or older. When heart rate increased by 1 beat per min, the odds ratio of release was 0.97 times higher than that of death; when the number of lymphocytes increased by 1%, the odds ratio of release was 1.10 times higher than that of death. In clinical findings, the odds ratio of release in the absence of dyspnea was 2.62 times (1/0.38) higher than in the presence of dyspnea. For comorbid diseases, the odds ratio of release was 2.16 times (1/0.46), 5.78 times (1/0.17), and 9.71 times (1/0.10) higher in the absence of diabetes mellitus, malignancy, or dementia, respectively. In addition, the odds ratio of release was 10.64 times (1/0.09) higher in cases not admitted to the ICU.

Older age, low lymphocyte count and platelets, dyspnea, diabetes mellitus, chronic kidney disease, dementia, and ICU admission affected mortality of female patients. The odds ratio of release was 67.1 times lower in the younger than 60-year-old group, 35.7 times lower in the 60-69-year-old group, and 4.64 times lower in the 70-79-year-old group compared with death in patients 80 years or older. When the number of lymphocytes increased by 1%, the odds ratio of release was 1.11 times higher than that of death. In clinical findings, the odds ratio of release in the absence of dyspnea symptoms was 5.88 times (1/0.17) greater than that in patients with symptoms. For comorbid diseases, the odds ratio of release was 2.96 times (1/0.34), 9.43 times (1/0.11), and 2.80 times (1/0.36) higher in the absence of diabetes mellitus, chronic kidney disease, and dementia, respectively. In addition, the odds ratio of release was 17.24 times (1/0.06) higher in cases not admitted to the ICU.

Multiple ordinal logistic regression for clinical severity score

For testing the proportional odds assumption, *p* values of score Chi-squares are .607 (for male), .512 (for female), and .538 (for total), which indicate that the proportional odds assumption is reasonable.

Multiple ordinal logistic regression was performed to identify the factors affecting CSS (Table 4). Older age, high BMI (severe obesity), low lymphocyte count and platelets, fever, sputum production, absence of sore throat and headache, rhinorrhea, dyspnea, confusion, diabetes mellitus, malignancy, dementia, and ICU admission affected progression to severe CSS in all patients.

Older age, high BMI (severe obesity), low lymphocyte count and platelets, fever, dyspnea, diabetes mellitus, rheumatic disease, dementia, and ICU admission were found to affect progression to severe CSS in male patients. When the coefficients were increased and other variables were controlled, the odds ratio of stage 1 CSS (No disruption to daily life) in the under 60-, 60-69-, and 70-79-

Table 3 *Multiple Binary Logistic Regression for Mortality.*

Variables		Men			Women			Total		
		OR	95% CI		OR	95% CI		OR	95% CI	
			Low	High		Low	High		Low	High
Age	60<	25.22***	7.45	85.44	67.15***	12.52	360.27	33.43***	12.76	87.56
	60–69	7.73***	2.87	20.85	35.73***	4.88	261.57	10.72***	4.66	24.67
	70–79	5.23**	1.96	13.95	4.63**	1.66	12.96	4.88***	2.39	9.94
	≥80	Ref.			Ref.			Ref.		
BMI	<18.5				0.15	0.02	1.18	0.79	0.18	3.43
	18.5–22.9				0.81	0.12	5.40	1.80	0.48	6.66
	23.0–24.9				1.66	0.18	15.00	3.98	1.00	15.80
	25.0–29.9				0.63	0.09	4.25	1.39	0.38	5.08
	≥30				Ref.			Ref.		
HR		0.97*	0.95	1.00				0.98*	0.97	1.00
Rhinorrhea								6.93*	1.28	37.48
Dyspnea		0.38*	0.18	0.83	0.17***	0.07	0.43	0.34***	0.19	0.61
Confusion								0.13*	0.02	0.84
DM		0.46*	0.22	0.96	0.34*	0.14	0.85	0.38**	0.21	0.67
CKD					0.11*	0.02	0.61			
Malignancy		0.17**	0.05	0.61				0.20**	0.07	0.55
Dementia		0.10***	0.03	0.33	0.36*	0.13	0.98	0.21***	0.10	0.44
ICU admission		0.09***	0.04	0.21	0.06***	0.02	0.17	0.08***	0.04	0.15
Lymphocytes (%)		1.10***	1.05	1.15	1.11***	1.06	1.16	1.11***	1.08	1.15
PLT ($10^3/\mu L$)		1.00**	1.00	1.00	1.00*	1.00	1.00	1.00***	1.00	1.00
χ^2/df		290.08/11***			304.60/14***			606.37/17***		

*$p < .05$, **$p < .01$, ***$p < .001$.
Note. BMI = body mass index; 95% CI = 95% confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus; HR = heart rate; ICU = intensive care unit; OR = odds ratio; PLT = platelets; Ref = reference group.
Excluded predictors are temperature, fever, cough, sputum production, sore throat, headache, hypertension, chronic liver disease, and rheumatoid disease.

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Table 4 *Multiple Ordinal Logistic Regression for Clinical Severity Score (CSS).*

Variables		Men			Women			Total		
		B	95% CI		B	95% CI		B	95% CI	
			Low	High		Low	High		Low	High
Age	60<	2.73***	8.31	28.53	2.03***	4.64	12.55	2.16***	5.90	12.62
	60–69	1.96***	3.81	13.14	1.68***	3.12	9.26	1.66***	3.52	7.83
	70–79	1.55***	2.49	8.95	0.90**	1.46	4.11	1.13***	2.07	4.59
	≥80	Ref.			Ref.			Ref.		
BMI	<18.5	0.57	0.66	4.76				0.33	0.75	2.56
	18.5–22.9	1.24**	1.61	7.35				0.55*	1.07	2.79
	23.0–24.9	1.07**	1.37	6.19				0.58*	1.09	2.92
	25.0–29.9	0.64	0.91	3.91				0.16	0.73	1.91
	≥30	Ref.						Ref.		
Temperature					−0.32*	0.55	0.96			
Fever		−0.97***	0.27	0.53	−0.60**	0.38	0.80	−0.89***	0.33	0.51
Sputum production					−0.39**	0.51	0.90	−0.32**	0.58	0.90
Sore throat					0.50*	1.09	2.48	0.40*	1.08	2.06
Rhinorrhea								0.45*	1.04	2.38
Dyspnea		−1.29***	0.19	0.41	−1.48***	0.17	0.32	−1.37***	0.20	0.33
Headache					0.52**	1.15	2.47	0.38*	1.08	1.97
Confusion								−1.33*	0.080	0.88
DM		−0.50**	0.42	0.88	−0.67***	0.36	0.73	−0.62***	0.42	0.70
CKD					−1.42**	0.09	0.66			
Malignancy					−0.87**	0.23	0.78	−0.85**	0.27	0.69
CLD					−1.03*	0.14	0.94			
Rheumatoid disease		−2.12**	0.03	0.53						
Dementia		−1.78***	0.08	0.37	−1.20***	0.17	0.53	−1.30***	0.17	0.43
ICU admission		−2.24***	0.06	0.18	−2.08***	0.07	0.23	−2.19***	0.08	0.17
Lymphocytes (%)		0.06***	1.05	1.09	0.05***	1.04	1.07	0.06***	1.05	1.07
PLT ($10^3/\mu L$)		0.00**	1.00	1.00	0.00***	1.00	1.00	0.00***	1.00	1.00
χ^2/df		625.09/15***			661.02/17***			1282.53/20***		

*$p < .05$, **$p < .01$, ***$p < .001$.
Note. BMI = body mass index; 95% CI = 95% confidence interval; CKD = chronic kidney disease; CLD = chronic liver disease; DM = diabetes mellitus; ICU = intensive care unit; PLT = platelets; Ref = reference group.
Excluded predictors are heart rate, cough, and hypertension.

years age groups increased compared with that of the 80-year-old group. In BMI, the odds ratio of stage 1 CSS was increased in the normal and overweight groups compared with the group of severe obesity.

Older age, high temperature, low lymphocyte count and platelets, fever, sputum production, absence of sore throat and headache, dyspnea, diabetes mellitus, chronic kidney disease, malignancy, chronic liver disease, dementia, and ICU admission were found to affect progression to severe CSS in female patients. When the coefficients were increased and other variables were controlled, the odds ratio of having stage 1 CSS in the under 60-, 60-69-, and 70-79-years age groups increased compared with those of the 80-year-old group.

Discussion

This study used clinical epidemiological information of COVID-19 patients to determine the factors affecting mortality and CSS of male and female patients in 5624 confirmed cases of COVID-19. The results showed differences according to sex.

In this study, male and female patients showed a significant difference according to mortality and CSS. In this retrospective observational cohort study among COVID-19 patients in Korea, the mortality rate was 5.4% for males and 3.45% for females. In CSS, there were 11.2% male and 9.6% female patients with stage 3 (oxygen treatment, multi-organ damage, and ECMO). In addition, 5.0% of males and 2.3% of females used the ICU during the hospitalization period. In a study of patients hospitalized for COVID-19 at Wuhan Hospital in China [16], among 168 severely ill patients (86 males and 82 females), the mortality rate was 12.8% for males and 7.3% for females. As a result of examining the odds ratio of intensive treatment unit (ITU) admission through a meta-analysis of 3,111,714 cases reported worldwide, it was found that male patients were more than three times more likely to die than females [6]. The results of this study were similar to the difference in prognosis according to sex in other COVID-19-related studies.

Factors that influenced mortality in all patients included older age, low lymphocyte count and platelets, dyspnea, diabetes mellitus, dementia, and ICU admission. In a study of patients with confirmed COVID-19 in China [24], the risk factors for severe pneumonia or death were age over 60, hypertension, diabetes mellitus, cardiovascular disease, chronic lung disease, and cancer. In a meta-analysis study, it was shown that comorbid diseases such as hypertension, diabetes mellitus, cardiovascular disease, and respiratory diseases can have a significant effect on the prognosis of COVID-19 [15]. Moon et al. [25] reported that elderly age can influence the clinical course of COVID-19 and COVID-19-related mortality through immune aging or high prevalence of comorbid diseases. A study of adult patients with COVID-19 in England and Wales [26] showed that hypertension, dementia, chronic lung disease, and diabetes mellitus were associated with death. The results of this study were similar to the results of domestic and foreign studies that showed a high mortality rate among the elderly with comorbid diseases. Among complete blood counts, lymphocytes are important for immunological responses such as cytokines and chemokines [27,28]. When abnormal lymphocytes and abnormal platelets enter the immune system, patients were believed to be vulnerable and COVID-19 symptoms could be exacerbated [18,27,28]. In terms of the biological mechanisms and in viral-associated hyperinflammatory syndromes, mediators (which primarily kill viral infected cells by stimulating CD8 + cells) are secreted during eradication of the virus, which inadvertently inhibits bone marrow function and activates platelets, resulting in thrombocytopenia [29]. In addition, COVID-19 starts with systemic

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symptoms such as muscle pain, chills, fatigue, with a dry cough and dyspnea occurring from several days to one week after infection [30]. Among the systemic symptoms, dyspnea was a factor affecting mortality in both male and female patients.

In this study, the initial examination findings and comorbid diseases showed differences according to sex. Heart rate and malignancy were associated with mortality in men, whereas chronic kidney disease was associated with mortality in women. Although heart rate was a significant factor in these results, most participants had normal heart rates and showed no significant change in practice. These results must be interpreted with caution and verified in a larger number of patients. New COVID-19 vaccines and treatments are being developed [31], but the prolonged pandemic is causing major socioeconomic and medical concerns in limited nursing and medical resource settings. Taking this into account, it is thought that the risk of death related to COVID-19 and the related nursing and medical system burden can be reduced if appropriate prevention and treatment are provided according to comorbid diseases of male and female patients.

The factors affecting progression to severe CSS in all patients were older age, low lymphocyte count and platelets, fever, dyspnea, diabetes mellitus, dementia, and ICU admission. As a result of analyzing the characteristics of COVID-19 pneumonia according to severity at a hospital in Wuhan, 36 of 138 pneumonia patients needed intensive treatment, and the average age of these 36 people was 66 years, with underlying diseases such as hypertension and diabetes mellitus [32]. The most common symptom of COVID-19 is fever [29]. Previous studies have shown that high body temperature increases the risk of progressing to the severe stage of COVID-19 [33]. The present study showed a similar trend in the relationship between comorbid diseases, clinical findings, and CSS. The results of this study can be used for early assessment of patients to identify those that might require intensive care from those who will experience mild disease.

The factors influencing progression to severe CSS that differed according to sex were high BMI (severe obesity) and rheumatic disease in men and high temperature, sputum production, absence of sore throat and/or headache, chronic kidney disease, malignancy, and chronic liver disease in women. Several studies have shown that high BMI increases the risk of progressing to the severe stage of COVID-19 [34,35]. In the context of metabolic syndrome, obesity has been shown to provide an inflammatory environment by rapidly increasing the cytokine storm associated with COVID-19 severity [36]. In the present study, BMI and CSS in women were not related, but in men, the odds ratio of stage 1 CSS was higher in the normal and overweight groups than in the group with a BMI of 30 or higher. Nurses caring for patients with COVID-19 should educate male patients on obesity management as a means of reducing the risk of progression to severe CSS. In Italy, analysis of the sex-related clinical predictors of ICU hospitalization through a cross-sectional observation multicenter national survey revealed that obesity was more frequent in both males and females admitted to the ICU [37]. As such, sex-based differences in the relationship between BMI and CSS were not consistent. Further studies on sex-based differences are needed. In addition, symptoms of upper respiratory tract infection such as sore throat were rare in COVID-19 patients [30], and absence of sore throat was found to affect progression to severe CSS in female patients. Based on the results of the present study, sex differences in CSS might also be caused by comorbid diseases. In addition, more influencing factors such as rheumatic disease and chronic liver disease were identified in COVID-19 CSS in male and female patients, respectively, which has implications for prevention and treatment.

This study is a comprehensive comparative analysis of factors influencing mortality and CSS of male and female patients using the clinical epidemiological information of COVID-19 patients provided by the KDCA. The results of this study will be used as important information to develop nurses' infection expertise. Nursing management strategies for new infectious diseases such as COVID-19 should be based on evidence, and it is important to develop strategies for preemptive and tailored nursing care to vulnerable populations. Therefore, nurses should provide differentiated nursing management for each patient by identifying various factors that affect treatment effects and outcomes according to sex, thereby reducing the risk of developing into severe COVID-19 or mortality. However, the present study has some limitations. It is not clear whether the results of this study can be generalized to other regions of the world, so a study that specifically analyzes various factors related to sex differences in COVID-19 patients in various countries is necessary. In this study, we did not report gender differences in the statistical significance of each predictor, and evaluated based on the results of previous studies. In the future, specific studies are needed to investigate the difference in the predictors presented in this study. Currently, since the validity verification was not performed while modifying the CSS scale in the study, the validity verification should be performed by accumulating related data for the precision of the study. In addition, it was not possible to collect and analyze data on various diagnostic tests, medications, and lifestyle factors by male and female patients as a retrospective study. Research should take into account not only biological differences, but also social and behavioral differences (lifestyle habits, health care seeking behavior, etc.). Lastly, the strain of coronavirus, the type of vaccine, the number of inoculations, and treatment information are not reflected in these data. In the future, repeated studies including various factors are needed, and prospective studies are needed to confirm mechanisms between symptoms, comorbidities, mortality, and CSS.

Conclusions

This study is expected to contribute to the general results by analyzing nationally representative data using the clinical epidemiological information of COVID-19 patients provided by the KDCA. It is significant in that it identifies factors affecting mortality and the CSS of COVID-19 male and female patients and identified differences according to sex. In this study, factors influencing mortality that differed according to sex were high heart rate and malignancy in men and chronic kidney disease in women. In addition, factors influencing CSS that differed by sex were high BMI and rheumatic disease in men and high temperature, sputum production, absence of sore throat and/or headache, chronic kidney disease, malignancy, and chronic liver disease in women. Therefore, classifying patients as at high risk of mortality and severe CSS according to sex and managing patients considering risk factors as such clinical findings at hospitalization and comorbid diseases can lead to effective management of COVID-19 patients. Understanding the specific factors that affect COVID-19 treatment effects and outcomes by sex is important for nursing and medical management, including prevention and treatment. As COVID-19 continues to spread, it is important to be aware of vulnerable populations, and there is a need to tailor ongoing and planned prevention and treatment according to sex. Ultimately, the results of this study can be used to efficiently allocate nursing and medical resources by identifying the factors affecting mortality and CSS according to sex. Understanding sex differences in COVID-19 outcomes is expected to contribute to the development of individualized nursing and

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medical management strategies for COVID-19 and new infectious diseases.

Data statement

The data in this study were obtained from the Korea Disease Control and Prevention Agency (KDCA). All data generated or analyzed during this study are included in this published article.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The authors thank Korea Disease Control and Prevention Agency for offering and using COVID-19 patients clinical epidemiological information as a research source.

References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 − 11 March 2020 [internet]. Geneva: WHO; 2020 [cited 2020 Jul 13]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19−11-march-2020
2. World Health Organization. WHO coronavirus disease (COVID-19) dashboard [internet]. Geneva: WHO; 2022 [cited 2022 Jul 4]. Available from: https://covid19.who.int/
3. Prinelli F, Trevisan C, Noale M, Franchini M, Giacomelli A, Cori L, et al. Sex-and gender-related differences linked to SARS-CoV-2 infection among the participants in the web-based EPICOVID19 survey: the hormonal hypothesis. Maturitas. 2022;158:61−9. https://doi.org/10.1016/j.maturitas.2021.11.015
4. Vahidy FS, Pan AP, Ahnstedt H, Munshi Y, Choi HA, Tiruneh Y, et al. Sex differences in susceptibility, severity, and outcomes of coronavirus disease 2019: cross-sectional analysis from a diverse US metropolitan area. PLoS One. 2021;16(1):e0245556. https://doi.org/10.1371/journal.pone.0245556
5. Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med. 2020;8(4):e20. https://doi.org/10.1016/S2213-2600(20)30117-X
6. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020;11(1):6317. https://doi.org/10.1038/s41467-020-19741-6
7. Ahmed SB, Dumanski SM. Sex, gender and COVID-19: a call to action. Can J Public Health. 2020;111(6):980−3. https://doi.org/10.17269/s41997-020-00417-z
8. Grandi G, Facchinetti F, Bitzer J. The gendered impact of coronavirus disease (COVID-19): do estrogens play a role? Eur J Contracept Reprod Health Care. 2020;25(3):233−4. https://doi.org/10.1080/13625187.2020.1766017
9. Groban L, Wang H, Sun X, Ahmad S, Ferrario CM. Is sex a determinant of COVID-19 infection? Truth or myth? Curr Hypertens Rep. 2020;22(9):62. https://doi.org/10.1007/s11906-020-01073-x
10. Kelada M, Anto A, Dave K, Saleh SN. The role of sex in the risk of mortality from COVID-19 amongst adult patients: a systematic review. Cureus. 2020;12(8):e10114. https://doi.org/10.7759/cureus.10114
11. Pinna G. Sex and COVID-19: a protective role for reproductive steroids. Trends Endocrinol Metab. 2021;32(1):3−6. https://doi.org/10.1016/j.tem.2020.11.004
12. Giagulli VA, Guastamacchia E, Magrone T, Jirillo E, Lisco G, De Pergola G, et al. Worse progression of COVID-19 in men: is testosterone a key factor? Andrology. 2021;9(1):53−64. https://doi.org/10.1111/andr.12836
13. Wenham C, Smith J, Morgan R. COVID-19: the gendered impacts of the outbreak. Lancet. 2020;395(10227):846−8. https://doi.org/10.1016/S0140-6736(20)30526-2
14. Galasso V, Pons V, Profeta P, Becher M, Brouard S, Foucault M. Gender differences in COVID-19 attitudes and behavior: panel evidence from eight countries. Proc Natl Acad Sci U S A. 2020;117(44):27285−91.
15. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect. 2020;81(2):e16−25. https://doi.org/10.1016/j.jinf.2020.04.021
16. Meng Y, Wu P, Lu W, Liu K, Ma K, Huang L, et al. Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: a retrospective study of 168 severe patients. PLoS Pathog. 2020;16(4):e1008520. https://doi.org/10.1371/journal.ppat.1008520
17. Brady E, Nielsen MW, Andersen JP, Oertelt-Prigione S. Lack of consideration of sex and gender in COVID-19 clinical studies. Nat Commun. 2021;12(1):1−6. https://doi.org/10.1038/s41467-021-24265-8
18. Kim SR, Nam SH, Kim YR. Risk factors on the progression to clinical outcomes of COVID-19 patients in South Korea: using national data. Int J Environ Res Public Health. 2020;17(23):8847. https://doi.org/10.3390/ijerph17238847
19. Oh B, Hwangbo S, Jung T, Min K, Lee C, Apio C, et al. Prediction models for the clinical severity of patients with COVID-19 in Korea: retrospective multicenter cohort study. J Med Internet Res. 2021;23(4):e25852. https://doi.org/10.2196/25852
20. Yu X, Duan J, Jiang Y, Zhang H. Distinctive trajectories of the COVID-19 epidemic by age and gender: a retrospective modeling of the epidemic in South Korea. Int J Infect Dis. 2020;98:200−5. https://doi.org/10.1016/j.ijid.2020.06.101
21. Arnegard ME, Whitten LA, Hunter C, Clayton JA. Sex as a biological variable: a 5-year progress report and call to action. J Womens Health. 2020;29(6):858−64. https://doi.org/10.1089/jwh.2019.8247
22. Korea Disease Control and Prevention Agency. Coronavirus disease-19, Republic of Korea [internet]. Osong: KDCA; 2021 [cited 2021 May 31]. Available from: http://ncov.mohw.go.kr/en/baroView.do?brdId=11&brdGubun=112&dataGubun=&ncvContSeq=&contSeq=&board_id=; 2021
23. Allison PD. Logistic regression using SAS: theory and application. 2nd ed. SAS Institute; 2012.
24. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. Am J Roentgenol. 2020;214(5):1072−7. https://doi.org/10.2214/AJR.20.22976
25. Moon H, Kim K, Kang EK, Yang HJ, Lee E. Prediction of COVID-19-related mortality and 30-day and 60-day survival probabilities using a nomogram. J Korean Med Sci. 2021;36(35):e248. https://doi.org/10.3346/jkms.2021.36.e248
26. Mohamed MO, Gale CP, Kontopantelis E, Doran T, de Belder M, Asaria M, et al. Sex differences in mortality rates and underlying conditions for COVID-19 deaths in England and Wales. Mayo Clin Proc. 2020;95(10):2110−24. https://doi.org/10.1016/j.mayocp.2020.07.009
27. Chen H, Lin C, Fan Z, Yu W, Cao M, Ke C, et al. Serum cytokines and clinical features in patients with fever and thrombocytopenia syndrome. Clin Chim Acta. 2019;494:22−30. https://doi.org/10.1016/j.cca.2019.02.034
28. Lin Z, Long F, Yang Y, Chen X, Xu L, Yang M. Serum ferritin as an independent risk factor for severity in COVID-19 patients. J Infect. 2020;81(4):647−9. https://doi.org/10.1016/j.jinf.2020.06.053
29. Yeo WS, Ng QX. Distinguishing between typical Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2. Med Hypotheses. 2020;144:110263. https://doi.org/10.1016/j.mehy.2020.110263
30. Park SE. Epidemiology, virology, and clinical features of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). Clin Exp Pediatr. 2020;63(4):119−24. https://doi.org/10.3345/cep.2020.00493
31. National Institutes of Health. COVID-19 treatment guidelines [internet]. Bethesda: NIH; 2022 [cited 2022 Jan 29]. Available from: https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/
32. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus−infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061−9. https://doi.org/10.1001/jama.2020.1585
33. Rod JE, Oviedo-Trespalacios O, Cortes-Ramirez J. A brief-review of the risk factors for COVID-19 severity. Rev Saude Publica. 2020;54:60. https://doi.org/10.11606/s1518-8787.2020054002481
34. Gao F, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care. 2020;43(7):e72−4. https://doi.org/10.2337/dc20-0682
35. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. Clin Infect Dis. 2020;71(5):896−7. https://doi.org/10.1093/cid/ciaa415
36. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Investig. 2017;127(1):1−4. https://doi.org/10.1172/JCI92035
37. Iaccarino G, Grassi G, Borghi C, Carugo S, Fallo F, Ferri C, et al. Gender differences in predictors of intensive care units admission among COVID-19 patients: the results of the SARS-RAS study of the Italian Society of Hypertension. PLoS One. 2020;15(10):e0237297. https://doi.org/10.1371/journal.pone.0237297

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