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.

Obesity Research & Clinical Practice xxx (xxxx) xxx

Contents lists available at ScienceDirect

Obesity Research & Clinical Practice

journal homepage: www.elsevier.com/locate/orcp

Association between metabolic syndrome and mortality in patients with COVID-19: A nationwide cohort study

Hyo Jin Park [a], Jin-Hyung Jung [b], Kyungdo Han [c], Jean Shin [a], Yoojeong Lee [a], Yujin Chang [a], Kyeyeung Park [d], Yoon Jeong Cho [e], Youn Seon Choi [a], Seon Mee Kim [a,*], Ga Eun Nam [a,*]

[a] Department of Family Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea
[b] Department of Biostatistics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[c] Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea
[d] Department of Family Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea
[e] Department of Family Medicine, Daegu Catholic University School of Medicine, Daegu, Republic of Korea

ARTICLE INFO

Keywords:
Metabolic syndrome
COVID-19
SARS-CoV-2
Mortality
Women

ABSTRACT

Objectives: We investigated the association between metabolic syndrome (MetS) and mortality among coronavirus disease 2019 (COVID-19) patients in Korea.
Methods: We analyzed 3876 individuals aged ≥ 20 years who were confirmed with COVID-19 from January 1 to June 4, 2020 based on the Korea National Health Insurance Service (NHIS)-COVID-19 database and had undergone health examination by NHIS between 2015 and 2017. Multivariable Cox proportional hazard regression analyses were performed.
Results: Of total participants, the prevalence of MetS was 21.0% (n = 815). During 58.6 days of mean follow-up, 3.1 % (n = 120) of the participants died. Compared to individuals without MetS, COVID-19 patients with MetS had a significantly increased mortality risk after adjusting for confounders in total participants (hazard ratio [HR]: 1.68, 95 % confidence interval [CI]: 1.14–2.47) and women (HR: 2.41, 95 % CI: 1.17–4.96). A low high-density lipoprotein cholesterol level in total participants (HR: 1.63, 95 % CI: 1.12–2.37) and hyperglycemia in women (HR: 1.97, 95 % CI: 1.01–3.84) was associated with higher mortality risk. The mortality risk increased as the number of MetS components increased among total participants and women (P for trend = 0.009 and 0.016, respectively). In addition, MetS groups had higher mortality risk in aged ≥ 60 years (HR: 1.60, 95 % CI: 1.07–2.39), and never-smokers (2.08, 1.21–3.59).
Conclusions: The presence of MetS and greater number of its components were associated with increased mortality risks particularly in female patients with COVID-19. Managing MetS may contribute to better outcomes of COVID-19.

1. Introduction

Since it was first reported in Wuhan, China in December 2019, coronavirus disease 2019 (COVID-19) infection has spread rapidly around the world, with approximately 400 million infected people worldwide and more than 1 million infected people in South Korea until recently [1]. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) of the coronaviridae family [2]. Fortunately, the mortality and fatality rates of coronavirus infection are decreasing over time since the first appearance of SARS-CoV-2 [3]. In South Korea, as of the end of March 2022, the mortality rate from COVID-19 is approximately 0.13 % [4]. However, the virus is still spreading, and following the appearance of the delta variant in October 2020, the omicron variant appeared in November 2021 [5]. Although COVID-19 vaccine booster shots effectively lower the severity of COVID-19 infection [6], the so-called breakthrough infections have increased owing to the strong infectivity of the virus [7].

As the spread of SARS-CoV-2 is becoming more serious, many studies exploring the risk factors related to mortality from COVID-19 have been conducted [8,9]. Several studies have suggested that cardiometabolic diseases including metabolic syndrome (MetS) may affect the prognosis of COVID-19 [10]. The prevalence of MetS continues to increase

* Corresponding authors.
E-mail addresses: ksmpdh@korea.ac.kr (S.M. Kim), namgaaa@hanmail.net (G.E. Nam).

https://doi.org/10.1016/j.orcp.2022.10.011
Received 7 July 2022; Received in revised form 19 October 2022; Accepted 21 October 2022
Available online 31 October 2022

worldwide, along with the increase in the prevalence of obesity. Recently, the prevalence of MetS in South Korea increased and was 22.9 % in 2018 [11]. MetS is generally associated with insulin resistance and cardiometabolic factors, including hypertension, diabetes, hyperlipidemia, and obesity, and it is one of the most important factors related to the increasing mortality rate from cardiovascular diseases [12]. Thus, it is important to clarify the mortality risk in patients with COVID-19 with concomitant MetS or have some risk factors for MetS. MetS is known to be associated with elevated C-reactive protein levels as well as inflammation [13]. Recently, the relationship between MetS and the course of infectious diseases caused by some bacteria and viruses has also been studied; however, the exact mechanism of how MetS affects the progression of infectious diseases remains unclear [14,15]. Moreover, most studies on the association between MetS and outcomes of COVID-19 have been conducted in patients with severe cases, such as patients who needed hospitalization treatment or intensive care unit (ICU) admission [16]. As COVID-19 has a relatively low mortality rate, studies on the general population, including patients with mild symptoms, are also essential.

Therefore, this study aimed to investigate the association of MetS and its components with the mortality risk among patients with COVID-19 in South Korea using a nationwide database. In addition, we identified several vulnerable subgroups among patients with COVID-19 regarding the association between MetS and mortality.

2. Methods

2.1. Data source and study population

This study used the National Health Insurance Service (NHIS)-COVID-19 cohort database provided by the Korean National Health Insurance Corporation. This database was established in cooperation with the NHIS and Korea Disease Control and Prevention Agency (KDCA). The KDCA provided information, including the date on which infection was confirmed, for patients with confirmed SARS-CoV-2 infection, tested using polymerase chain reaction (PCR), from January 1 to June 4, 2020, as well as the final results of the course of COVID-19. The database included not only the information of individuals with severe infections requiring hospitalization but also that of those with asymptomatic or mild symptoms who did not require hospital admission. In South Korea, in the early stages of the COVID-19 pandemic, asymptomatic patients or those with mild symptoms were closely observed and treated at centers managed by the Korean government. The database identified the information of people with COVID-19 in terms of their past health examination results provided by the NHIS between January 1, 2015, and December 31, 2017, including their sociodemographic characteristics and health behavior information. The database followed the International Classification of Diseases (ICD-10) codes for disease diagnosis and classification. The data for the participant's health and the results of their health examination provided by the NHIS were collected before they were diagnosed with COVID-19.

Among 230,327 individuals who underwent COVID-19 PCR testing between January 1 and June 4, 2020, we initially included 8070 individuals who were confirmed to be positive in the test. Of these, we excluded individuals aged < 20 years ($n = 357$), those who had not received a health examination provided by the NHIS between January 1, 2015, and December 31, 2017 ($n = 3779$), and those who had missing data ($n = 58$). Finally, this study involved 3876 patients who were diagnosed with COVID-19. Supplementary appendix presents the flow diagram of the study participant selection procedure. This study was conducted as per the tenets of Declaration of Helsinki and the institutional review board of the Korea University Anam Hospital accepted the protocol of this study (No. 2020AN0282).

2.2. Study outcome

Participants were followed up from the index date when SARS-CoV-2 infection was confirmed in the PCR test until the date of all-cause mortality or until July 31, 2020. The data from the Korean National Statistical Office were used to calculate all-cause mortality which includes both COVID-19-related deaths and all other causes of death.

2.3. Definition of MetS and covariates

Anthropometric and laboratory measurements were performed after participants fasted for at least 8 h, and comorbidities were defined using a combination of health examination results, disease diagnoses, and ICD-10 prescription codes. Height, weight, waist circumference (WC), and blood pressure (BP) were measured, and body mass index (BMI) was calculated by dividing the participants' weight (kg) by the square of their height (m). Laboratory test results included the levels of fasting serum glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and creatinine. MetS was defined based on the modified criteria of the National Cholesterol Education Program Adult Treatment Panel III, while abdominal obesity was based on the Asian-specific WC cutoff [17]. Individuals were diagnosed with MetS if they had three or more of the following: (1) a WC of $\geq$ 90 cm for men and $\geq$ 85 cm for women [18]; (2) a serum triglyceride level of $\geq$ 150 mg/dL or were treated with lipid-lowering medication; (3) a serum HDL-C level of $<$ 40 mg/dL for men or $<$ 50 mg/dL for women; (4) a BP of $\geq$ 130/85 mmHg or were treated with antihypertensive medication; and (5) a fasting blood glucose level of $\geq$ 100 mg/dL or were treated with antidiabetic medication. The use of lipid-lowering, antihypertensive, and antidiabetic medications was defined as $\geq$ 1 prescription per year under the ICD-10 codes E78, I10–I13 or I15, and E11–E14, respectively.

Hypertension was defined as BP of $\geq$ 140/90 mmHg or antihypertensive medication use and type 2 diabetes as fasting blood glucose level of $\geq$ 126 mg/dL or antidiabetic medication use. Dyslipidemia was defined as a serum total cholesterol level of $\geq$ 240 mg/dL or lipid-lowering medication use. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation, and a value of $<$ 60 mL/min/1.73 m^2 was used to define chronic kidney disease.

Information on the participants' demographics and health-related behaviors was collected using a standardized self-report questionnaire. Participants considered to be in the low-income level were defined as those receiving medical aid from the government or had household income in the bottom 20 % of the population. Based on the smoking history of participants, ever-smokers included both ex-smokers and current smokers. Alcohol drinker was defined as a person who consumed more than 0 g in a day. Regular exerciser was defined as a person who carried out moderate-intensity exercise for $\geq$ 5 days per week or vigorous-intensity exercise for $\geq$ 3 days per week.

2.4. Statistical analysis

The statistical analysis was performed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA). Our final analysis included all COVID-19 patients regardless of the severity of COVID-19 symptoms or the type of treatment in COVID-19 patients. We compared the means of continuous variables using the independent t-test and percentages of categorical variables using the chi-square test according to the presence or absence of MetS in patients with COVID-19. We used the Kaplan-Meier method for the graphs to figure out the probability of mortality related to the presence of MetS and the number of MetS components satisfied in patients with COVID-19. The mortality rates were calculated by dividing the number of events by 1000 person-days. We performed a multivariable Cox proportional hazard regression analysis to examine the associations of MetS, each component of MetS, and the number of

Table 1
Baseline characteristics by the presence of metabolic syndrome in patients with COVID-19.

Characteristics	Without MetS	With MetS	P-value
N	3061	815	
Age (≥60 years)	1059 (34.6)	457 (56.1)	< 0.001
Sex (male)	1056 (34.5)	389 (47.7)	< 0.001
Ever smoker	611 (20.0)	256 (31.4)	< 0.001
Alcohol drinker	991 (32.4)	233 (28.6)	0.039
Regular exercisers	623 (20.4)	127 (15.6)	0.002
Low income	865 (28.3)	217 (26.6)	0.356
Weight (kg)	61.1 ± 10.7	70.4 ± 13.1	< 0.001
BMI (kg/m^2)	23.3 ± 3.0	26.6 ± 3.5	< 0.0001
WC (cm)	78.1 ± 8.4	88.9 ± 8.5	< 0.0001
Systolic BP (mmHg)	118.2 ± 13.7	133.2 ± 14.7	< 0.001
Diastolic BP (mmHg)	73.3 ± 9.4	81.0 ± 9.9	< 0.001
Fasting glucose (mg/dL)	96.1 ± 20.4	119.4 ± 42.1	< 0.001
Total cholesterol (mg/dL)	193.7 ± 36.5	199.2 ± 41.2	< 0.001
HDL-C (mg/dL)	59.5 ± 18.9	46.8 ± 11.5	< 0.001
LDL-C (mg/dL)	114.0 ± 32.6	115.4 ± 37.4	0.315
Triglycerides (mg/dL)	101.6 ± 56.7	191.8 ± 102.0	< 0.001
Creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.5	< 0.001
eGFR (mL/min/1.73 m^2)	92.3 ± 22.3	84.8 ± 22.6	< 0.001
Hypertension	213 (7.0)	267 (32.8)	< 0.001
Type 2 diabetes	146 (4.8)	186 (22.8)	< 0.001
Dyslipidemia	330 (10.8)	129 (15.8)	< 0.001
Chronic kidney disease	85 (2.8)	79 (9.7)	< 0.001

Values are presented as the number (percentage) or as the mean ± standard deviation.
Abbreviations: COVID-19, coronavirus disease 2019; MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

components with mortality risk in total participants and each sex group. We also calculated hazard ratios (HRs) and 95 % confidence intervals (CIs). In model 1, covariates were not adjusted. In model 2, we adjusted for age, sex, smoking status, alcohol consumption, physical activity, income level, BMI, and chronic kidney disease. Stratified analyses of the association between MetS and mortality risk were also performed in subgroups based on age, smoking status, and type 2 diabetes after adjusting for all confounding variables. A P-value of < 0.05 was used to indicate statistical significance.

3. Results

3.1. Baseline characteristics

From January 1 to June 4, 2020, a total of 3876 individuals were confirmed to have COVID-19 %, and 21.0 % of them (n = 815) were revealed to have MetS. Table 1 shows the baseline characteristics of the study participants according to the presence or absence of MetS. The proportion of individuals aged ≥ 60 years and men was significantly higher in individuals with MetS than in those without MetS (both P < 0.001). The proportion of ever-smokers was higher in those with MetS than in those without MetS (P < 0.001), and the proportion of alcohol drinkers and regular exercisers was lower in those without MetS than in those with MetS (P = 0.039 and P = 0.002, respectively). The percentage of patients with a low economic status was similar between the two groups. The mean values of the cardiometabolic parameters, including weight, BMI, WC, systolic/diastolic BP, fasting blood glucose, and serum levels of total cholesterol, triglycerides, and creatinine, were greater in those with MetS than in those without MetS (all P < 0.001). Individuals with MetS were more likely to have comorbidities, including hypertension, type 2 diabetes, dyslipidemia, and chronic kidney disease, than those without MetS (all P < 0.001).

3.2. Association between MetS and mortality risk in patients with COVID-19

During the follow-up period (mean = 58.6 days), 3.1 % (n = 120) of the participants died. Fig. 1 presents the Kaplan–Meier curves of the probabilities of mortality according to the presence of MetS and the number of MetS components satisfied. The cumulative mortality rates were significantly higher in those with MetS than in those without MetS (log-rank P < 0.001). The probabilities generally increased as the number of MetS components increased (log-rank P < 0.001).

Table 2 shows the mortality rates and HRs (95% CIs) of mortality according to the presence of MetS and its components in COVID-19 patients. The mortality rate in total participants was 3.8-fold higher in those with MetS than in those without. The presence of MetS was significantly associated with increased mortality risk compared with the absence of MetS in both models (model 1, HR: 3.73, 95 % CI: 2.61–5.34; model 2, HR: 1.68, 95 % CI: 1.14–2.47). Regarding each component of MetS, a low serum HDL-C level was significantly associated with increased mortality risk compared with a high HDL-C level, even after adjusting for all potential confounding variables (HR: 1.63, 95 % CI:

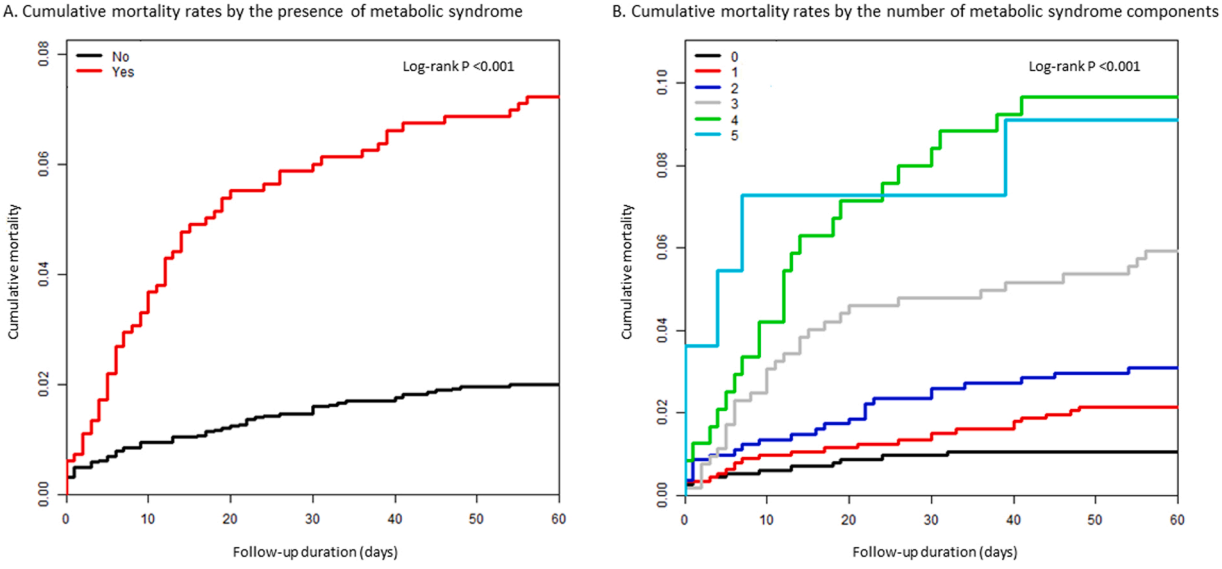

Fig. 1. Cumulative mortality rates by the presence of metabolic syndrome and the number of metabolic syndrome components.

Table 2
Association of Metabolic Syndrome and its Components with Mortality Risk in Patients with COVID-19.

MetS or component		N	Mortality	Person-days	Mortality rate[a]	Hazard ratio (95 % confidence interval)			
						Model 1[b]	P-value	Model 2[c]	P-value
Total participants									
MetS	No	3061	61	181,012	0.34	1 (reference)		1 (reference)	
	Yes	815	59	46,262	1.28	3.73 (2.61–5.34)	< 0.001	1.68 (1.14–2.47)	0.009
Abdominal obesity[d]	No	3011	70	177,581	0.39	1 (reference)		1 (reference)	
	Yes	865	50	49,693	1.01	2.53 (1.76–3.64)	< 0.001	1.21 (0.77–1.91)	0.415
High triglycerides[e]	No	2953	78	173,822	0.45	1 (reference)		1 (reference)	
	Yes	923	42	53,452	0.79	1.74 (1.20–2.53)	0.004	1.35 (0.92–1.97)	0.125
Low HDL-C[f]	No	2901	69	171,073	0.40	1 (reference)		1 (reference)	
	Yes	975	51	56,201	0.91	2.23 (1.55–3.21)	< 0.001	1.63 (1.12–2.37)	0.011
High BP[g]	No	2555	52	150,874	0.35	1 (reference)		1 (reference)	
	Yes	1321	68	76,400	0.89	2.56 (1.78–3.67)	< 0.001	1.00 (0.69–1.47)	0.991
Hyperglycemia[h]	No	2434	47	144,054	0.33	1 (reference)		1 (reference)	
	Yes	1442	73	83,220	0.88	2.67 (1.85–3.85)	< 0.001	1.36 (0.94–1.98)	0.107
Men									
MetS	No	1056	44	61,450	0.72	1 (reference)		1 (reference)	
	Yes	389	38	21,748	1.75	2.41 (1.56–3.71)	< 0.001	1.43 (0.90–2.29)	0.132
Abdominal obesity[d]	No	1038	47	60,262	0.78	1 (reference)		1 (reference)	
	Yes	407	35	22,936	1.53	1.94 (1.25–3.00)	0.003	1.19 (0.68–2.06)	0.547
High triglycerides[e]	No	983	54	56,715	0.95	1 (reference)		1 (reference)	
	Yes	462	28	26,483	1.06	1.11 (0.70–1.75)	0.658	1.32 (0.82–2.11)	0.251
Low HDL-C[f]	No	1166	52	67,690	0.77	1 (reference)		1 (reference)	
	Yes	279	30	15,508	1.93	2.48 (1.58–3.88)	< 0.001	1.55 (0.98–2.48)	0.064
High BP[g]	No	792	37	45,816	0.81	1 (reference)		1 (reference)	
	Yes	653	45	37,382	1.20	1.48 (0.96–2.29)	0.076	0.83 (0.53–1.32)	0.434
Hyperglycemia[h]	No	780	33	45,461	0.73	1 (reference)		1 (reference)	
	Yes	665	49	37,737	1.30	1.77 (1.14–2.76)	0.011	1.17 (0.74–1.85)	0.499
Women									
MetS	No	2005	17	119,562	0.14	1 (reference)		1 (reference)	
	Yes	426	21	24,514	0.86	5.95 (3.14–11.27)	< 0.001	2.41 (1.17–4.96)	0.017
Abdominal obesity[d]	No	1973	23	117,319	0.20	1 (reference)		1 (reference)	
	Yes	458	15	26,757	0.56	2.85 (1.49–5.45)	0.002	1.32 (0.57–3.06)	0.525
High triglycerides[e]	No	1970	24	117,107	0.21	1 (reference)		1 (reference)	
	Yes	461	14	26,969	0.52	2.51 (1.30–4.86)	0.006	1.21 (0.62–2.37)	0.584
Low HDL-C[f]	No	1735	17	103,383	0.16	1 (reference)		1 (reference)	
	Yes	696	21	40,693	0.52	3.12 (1.64–5.91)	0.001	1.72 (0.89–3.31)	0.106
High BP[g]	No	1763	15	105,058	0.14	1 (reference)		1 (reference)	
	Yes	668	23	39,018	0.59	4.09 (2.14–7.85)	< 0.001	1.53 (0.77–3.03)	0.221
Hyperglycemia[h]	No	1654	14	98,593	0.14	1 (reference)		1 (reference)	
	Yes	777	24	45,483	0.53	3.69 (1.91–7.14)	< 0.001	1.97 (1.01–3.84)	0.047

Abbreviations: COVID-19, coronavirus disease 2019; MetS, metabolic syndrome; reference, reference; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.
[a] Mortality per 1000 person-days.
[b] Model 1 was unadjusted.
[c] Model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, body mass index, and chronic kidney disease.
[d] Waist circumference of ≥ 90 cm for men and ≥ 85 cm for women
[e] Serum triglyceride level of ≥ 150 mg/dL or were treated with lipid-lowering medication
[f] Serum HDL-C level of < 40 mg/dL for men or < 50 mg/dL for women
[g] Systolic/diastolic BP ≥ 130/85 mmHg or treatment with antihypertensive medication.
[h] Plasma fasting glucose ≥ 100 mg/dL or treatment with antidiabetic medication.

1.12–2.37). Although the mortality rate was greater in individuals with high WC, high serum triglycerides, high BP, or high fasting glucose levels than in the other groups for each component, these associations were attenuated after adjusting for the confounding variables. After dividing participants by sex, there was no significant association of MetS and each component with mortality risk among men with COVID-19. However, among women with COVID-19, those with MetS were associated with a 2.41-fold higher mortality risk compared to those without MetS (HR: 2.41, 95 % CI: 1.17–4.96). As for the components of MetS, women with hyperglycemia showed a significantly higher mortality risk than those without (HR: 1.97, 95 % CI: 1.01–3.84).

Table 3 presents the HRs of mortality according to the number of MetS components in COVID-19 patients. After adjusting for the confounding variables, the HRs in total participants and women tended to increase as the number of MetS components increased (P for trend = 0.009 and 0.016, respectively).

3.3. Subgroup analyses in relation to the association between MetS and mortality risk in patients with COVID-19

Table 4 presents the associations between MetS and COVID-19 mortality in additional subgroups according to age, smoking status, and type 2 diabetes status. The presence of MetS was associated with significantly greater mortality risk compared to the absence of MetS in COVID-19 patients who were aged ≥ 60 years (HR: 1.60, 95 % CI: 1.07–2.39), and those who were never smoked (HR: 2.08, 95% CI: 1.21–3.59) after adjusting for all confounding variables.

4. Discussion

Our study revealed that MetS is associated with an increased mortality risk in patients with COVID-19 and this association was prominent in female COVID-19 patients. All five components of MetS were associated with a higher mortality rate, and among these components, a low HDL-C level in total participants and hyperglycemia in women was significantly associated with the mortality risk, respectively. In further

Table 3
Association between the number of metabolic syndrome components and mortality risk in patients with COVID-19.

Number of MetS components	N	Mortality	Person-days	Mortality rate[a]	Hazard ratio (95 % confidence interval)	
					Model 1[b]	Model 2[c]
Total participants						
0	1135	12	67,504	0.18	1 (reference)	1 (reference)
1	1119	24	66,170	0.36	2.04 (1.02–4.07)	1.18 (0.58–2.37)
2	807	25	47,338	0.53	2.96 (1.49–5.88)	0.94 (0.46–1.91)
3	522	31	29,978	1.03	5.74 (2.95–11.18)	1.42 (0.70–2.87)
4	238	23	13,234	1.74	9.53 (4.74–19.15)	2.28 (1.07–4.85)
5	55	5	3050	1.64	9.07 (3.20–25.75)	2.80 (0.92–8.50)
P for trend					< 0.001	0.009
Men						
0	286	10	16,674	0.60	1 (reference)	1 (reference)
1	407	16	23,797	0.67	1.12 (0.51–2.47)	0.82 (0.37–1.84)
2	363	18	20,979	0.86	1.43 (0.66–3.09)	0.66 (0.30–1.48)
3	242	19	13,760	1.38	2.28 (1.06–4.90)	0.84 (0.37–1.90)
4	128	17	6929	2.45	3.98 (1.82–8.69)	1.59 (0.67–3.77)
5	19	2	1059	1.89	3.12 (0.68–14.22)	2.45 (0.49–12.25)
P for trend					< 0.001	0.164
Women						
0	849	2	50,830	0.04	1 (reference)	1 (reference)
1	712	8	42,373	0.19	4.79 (1.02–22.53)	2.92 (0.61–13.94)
2	444	7	26,359	0.27	6.72 (1.40–32.34)	2.18 (0.44–10.81)
3	280	12	16,218	0.74	18.58 (4.16–83.01)	4.90 (1.02–23.46)
4	110	6	6305	0.95	23.71 (4.79–117.47)	5.87 (1.08–31.87)
5	36	3	1991	1.51	37.47 (6.26–224.26)	6.61 (0.95–45.85)
P for trend					< 0.001	0.016

[a] Mortality per 1000 person-days.
[b] Model 1 was unadjusted.
[c] Model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, body mass index, and chronic kidney disease.

subgroup analysis, MetS was related to an increased mortality risk in patients with COVID-19 who aged 60 years or older and never smoked. These results highlight that MetS may be an important risk factor for death particularly in women diagnosed with COVID-19. Furthermore, our findings may be applicable to the management of individuals with MetS to prevent poor outcomes from COVID-19, and suggest that prevention of COVID-19 may be necessary in people vulnerable to MetS.

The results of our study correspond with those of earlier studies reporting that the presence of MetS is related to mortality in patients with COVID-19 [19]. Our findings are also consistent with the results of previous studies showing a linear association between the number of MetS components and mortality risk of COVID-19 patients [20]. It is also in line with studies showing that MetS and its related comorbidities are significantly associated with COVID-19-related deaths [21]. Our study, in addition to previous studies showing higher rates of COVID-19 mortality and ICU admissions with MetS, demonstrates that MetS and its components can be important factors in predicting the prognosis of COVID-19 [22]. However, most of the recent studies mentioned analyzed only severely ill patients. Our study included not only severely ill patients who needed inpatient treatment but also patients with asymptomatic or mild symptoms. The results of our study may be applicable to the general population.

The mechanism by which MetS or the components of MetS affect mortality in patients with COVID-19 has not yet been fully elucidated. However, several possible causes can be proposed to explain our findings. First, the presence of MetS is itself an important factor in increasing all-cause mortality, as well as mortality in individuals with cardiovascular disease and diabetes [23]. In previous studies, individuals with MetS were very susceptible to COVID-19 [24], and at the same time, MetS was an important factor in exacerbating the severity of outcomes of COVID-19 [19]. Second, MetS was closely related to the renin-angiotensin-aldosterone system in the human body. Angiotensin-converting enzyme 2 (ACE2) acts as an important enzyme in this system [25]. ACE2 also acts as a receptor for the SARS-CoV-2 virus when it initially enters target cells [26]. The overexpression of ACE2 in patients with MetS and COVID-19, is related to the increased abnormal activity of cytokines and causes endothelial dysfunction, which is eventually associated with the worsening severity of COVID-19 [27]. Therefore, individuals who already have MetS prior to COVID-19 are not only more susceptible to COVID-19 but also have a more severe form of the disease than those without MetS, and their mortality rate may be much higher. Third, among the components of MetS, a mechanism that increases the mortality rate of COVID-19 from the perspective of cholesterol can be proposed. Cholesterol is present in the cell membrane, and the presence of adequate cholesterol helps maintain the stability of the cell membrane, which acts as a gateway before SARS-CoV-2 penetrates the cell [28]. In addition, cholesterol is known to be involved in intracellular transcription factors or cell signaling systems [29]. In a recent study on animals, intracellular cholesterol is known to increase the infectivity of SARS-CoV-2 in cells [30]. Low HDL-C levels have been found to be associated with the severity of disease in systemic inflammatory or other infectious diseases [31,32]. Thus, low HDL-C levels may be a risk factor for increased severity and mortality of COVID-19 [33].

Interestingly, there was a sex difference in that female COVID-19 patients with MetS exhibited an significantly higher mortality risk than those without MetS, however, this association was not observed in men. It has been reported that men had generally higher mortality rates than women in COVID-19 patients [34]. However, there have been other previous studies showing that women with type 2 diabetes had a higher mortality rate, similar to men, than women without type 2 diabetes [35]. In the aspect that type 2 diabetes and MetS share common mechanisms, sex-specific association between MetS and mortality in our study supports the previous results. Accordingly, female COVID-19 patients with hyperglycemia were significantly related to increased mortality risk in our study. Among the components of MetS, hyperglycemia is the most relevant indicator for type 2 diabetes [36]. In addition, women are known to more likely to have regular health checkups and health-related behaviors than men [37], and women in good health may have a decreased cardiometabolic risk such as high insulin sensitivity, better body composition, and low inflammatory reactions [35]. However, in our study, women with MetS or hyperglycemia may lose these advantages due to COVID-19 condition. Consideration of sex-specific association may be helpful for better prognosis of COVID-19, and further

Table 4
Subgroup analysis of the association between metabolic syndrome and mortality risk in patients with COVID-19.

Subgroup	N	Mortality	Person-days	Mortality rate[a]	HR (95 % CI)[b]
Age (years)					
< 60					
MetS (-)	2002	4	119,966	0.03	1 (reference)
MetS (+)	358	5	21,252	0.24	3.02 (0.64–14.32)
P-value					0.163
≥ 60					
MetS (-)	1059	57	61,046	0.93	1 (reference)
MetS (+)	457	54	25,010	2.16	1.60 (1.07–2.39)
P-value					0.023
Smoking status					
Never-smoker					
MetS (-)	2450	30	145,661	0.21	1 (reference)
MetS (+)	559	33	31,995	1.03	2.08 (1.21–3.59)
P-value					0.008
Ever-smoker					
MetS (-)	611	31	35,351	0.88	1 (reference)
MetS (+)	256	26	14,267	1.82	1.29 (0.73–2.29)
P-value					0.383
Type 2 diabetes					
No					
MetS (-)	2807	41	166,655	0.25	1 (reference)
MetS (+)	534	22	31,059	0.71	1.47 (0.83–2.60)
P-value					0.185
Yes					
MetS (-)	254	20	14,357	1.39	1 (reference)
MetS (+)	281	37	15,203	2.43	1.26 (0.70–2.25)
P-value					0.442

Abbreviations: COVID-19, coronavirus disease 2019; MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval.

[a] Mortality per 1000 person-days.

[b] Calculated using multivariable Cox proportional hazard regression analysis after adjusting for age, sex, smoking status, alcohol consumption, physical activity, income, body mass index, and chronic kidney disease.

studies are warranted to confirm the association.

The subgroup analysis demonstrated a significantly higher mortality risk among individuals aged 60 years or older with MetS than among those without MetS. However, this association was not significant in individuals younger than 60 years. This is consistent with the results of several previous studies showing that the mortality rate of COVID-19 is higher in the elderly than in the non-elderly [38,39]. Elderly individuals not only have more underlying diseases, such as hypertension and diabetes [40], but their immunity decreased and mortality risk increased owing to the strong inflammatory reactions to COVID-19 [41]. Therefore, the current quarantine policy that classifies the elderly as a high-risk group for COVID-19 seems to be appropriate. Meanwhile, MetS was associated with an increased mortality risk in never-smokers with COVID-19. There have been limited evidence on the association between MetS and COVID-19 prognosis according to smoking status. Moreover, conflicting findings have been reported on the association between smoking and COVID-19 prognosis. [42]. A few studies reported smoking might have potentially protective effects on the prevalence and outcomes of COVID-19 [43]. Those studies suggested hypotheses that the effects of smoking on chronic inflammation and ACE2 expression might cause a positive result of COVID-19. It is necessary to investigate the exact effect of smoking on the association between MetS and COVID-19.

Our study has several limitations. First, this study is insufficient in proving a causal relationship between MetS and mortality risk in COVID-19 patients owing to its retrospective design. Second, since recent health examination data before the enrollment of study participants were used, there were time intervals between the enrollment and health examination. Moreover, the time of the health examinations varied among the participants. Third, the fact that the data used in our study were from the early pandemic period in South Korea could serve as a limitation.

The COVID-19 pandemic has continued for much longer than was expected, and in the future, COVID-19 is expected to become a seasonal disease that is most prevalent at a specific time every year as was in the case of the previous swine flu virus [44]. The most important thing is that healthcare providers and governments in each country have to lower the severity and mortality rate. Therefore, our findings are expected to help identify important risk factors and minimize the mortality rate. As our study used data from the general population of a relatively large number of South Koreans who were not vaccinated in the early stages of the COVID-19 pandemic, the results demonstrate the general impact of MetS on the severity of COVID-19. The mortality rate of COVID-19 allows us to determine the severity of COVID-19, and the possibility of adjusting for various confounding variables including sociodemographic characteristics, health behaviors, clinical variables and comorbidities is a major strength of our study. In addition, based on the comparison of the HRs of the mortality rate, the high risk groups related MetS in the prognosis of COVID-19 appear to be more clearly identified.

5. Conclusion

The presence of MetS and the greater number of its components were associated with mortality risk particularly in women diagnosed with COVID-19. Prevention and management of MetS and its related factors may be essential to reduce the risk of severe outcomes from COVID-19. Further research is needed to determine the association between MetS and COVID-19 prognosis.

Funding

This study was supported by Korea University medicine, fund raised for COVID-19 research.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.orcp.2022.10.011.

References

[1] World Health Organization. WHO coronavirus disease (COVID-19) dashboard. Available at: ⟨https://covid19.who.int/⟩. 2020 [Accessed 28 July.2020].
[2] Kumar A, Singh R, Kaur J, Pandey S, Sharma V, Thakur L, et al. Wuhan to world: the COVID-19 pandemic. Front Cell Infect Microbiol 2021;11:596201.
[3] Horwitz LI, Jones SA, Cerfolio RJ, Francois F, Greco J, Rudy B, et al. Trends in COVID-19 risk-adjusted mortality rates. J Hosp Med 2021;16:90–2.
[4] Korea Disease Control and Prevention Agency, Coronavirus (COVID-19), Republic of Korea: cases in Korea. Available at: ⟨http://ncov.mohw.go.kr/en/bdBoardList.do?brdId=16&brdGubun=161&dataGubun=&ncvContSeq=&contSeq=&board_id=⟩. 2022 [Accessed 29 March.2022].
[5] Centers for Disease Control and Prevention, SARS-CoV-2 variant classifications and definitions. Available at: ⟨https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html⟩. 2021 [Accessed 1 March.2022].

[6] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. N Engl J Med 2021;385:1393–400.
[7] Del Rio C, Omer SB, Malani PN. Winter of Omicron – the evolving COVID-19 pandemic. JAMA 2022;327:319–20.
[8] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020; 146:110–8.
[9] Albitar O, Ballouze R, Ooi JP, Sheikh Ghadzi SM. Risk factors for mortality among COVID-19 patients. Diabetes Res Clin Pract 2020;166:108293.
[10] Costa FF, Rosário WR, Farias ACR, de Souza RG, Duarte Gondim RS, Barroso WA. Metabolic syndrome and COVID-19: an update on the associated comorbidities and proposed therapies. Diabetes Metab Syndr 2020;14:809–14.
[11] Huh JH, Kang DR, Kim JY, Koh KK. Metabolic syndrome fact sheet 2021: executive report. Cardiometab Syndr J 2021;1:125–1334.
[12] Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis 2017;11:215–25.
[13] Fröhlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, et al. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. Diabetes Care 2000;23:1835–9.
[14] Refaeli R, Chodick G, Haj S, Goren S, Shalev V, Muhsen K. Relationships of H. pylori infection and its related gastroduodenal morbidity with metabolic syndrome: a large cross-sectional study. Sci Rep 2018;8:4088.
[15] Masyuko SJ, Page ST, Kinuthia J, Osoti AO, Polyak SJ, Otieno FC, et al. Metabolic syndrome and 10-year cardiovascular risk among HIV-positive and HIV-negative adults: a cross-sectional study. Medicine 2020;99:e20845.
[16] Wu S, Zhou K, Misra-Hebert A, Bena J, Kashyap SR. Impact of metabolic syndrome on severity of COVID-19 illness. Metab Syndr Relat Disord 2022;20:191–8.
[17] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and Blood institute; American heart association; World heart federation; International atherosclerosis society; and International association for the study of obesity. Circulation 2009;120:1640–5.
[18] Kim BY, Kang SM, Kang JH, Kang SY, Kim KK, Kim KB, et al. Korean society for the study of obesity guidelines for the management of obesity in Korea. J Obes Metab Syndr 2020;2021(30):81–92.
[19] Jeon WH, Seon JY, Park SY, Oh IH. Association of metabolic syndrome with COVID-19 in the Republic of Korea. Diabetes Metab J 2022;46:427–38.
[20] Kim NH, Kim KJ, Choi J, Kim SG. Metabolically unhealthy individuals, either with obesity or not, have a higher risk of critical coronavirus disease 2019 outcomes than metabolically healthy individuals without obesity. Metabolism 2022;128: 154894.
[21] Denson JL, Gillet AS, Zu Y, Brown M, Pham T, Yoshida Y, et al. Metabolic syndrome and acute respiratory distress syndrome in hospitalized patients with COVID-19. JAMA Netw Open 2021;4:e2140568.
[22] Lohia P, Kapur S, Benjaram S, Pandey A, Mir T, Seyoum B. Metabolic syndrome and clinical outcomes in patients infected with COVID-19: Does age, sex, and race of the patient with metabolic syndrome matter? J Diabetes 2021;13:420–9.
[23] Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care 2005;28:1769–78.
[24] Scalsky RJ, Chen YJ, Desai K, O'Connell JR, Perry JA, Hong CC. Baseline cardiometabolic profiles and SARS-CoV-2 infection in the UK Biobank. PLOS One 2021;16:e0248602.
[25] de Lucena TMC, da Silva Santos AF, de Lima BR, de Albuquerque de Albuquerque Borborema ME, de Azevêdo Silva J. Mechanism of inflammatory response in associated comorbidities in COVID-19. Diabetes Metab Syndr 2020;14:597–600.
[26] Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653–9.
[27] Pinto BGG, Oliveira AER, Singh Y, Jimenez L, Gonçalves ANA, Ogava RLT, et al. ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19. J Infect Dis 2020;222:556–63.
[28] Kočar E, Režen T, Rozman D. Cholesterol, lipoproteins, and COVID-19: basic concepts and clinical applications. Biochim Biophys Acta Mol Cell Biol Lipids 2021; 1866:158849.
[29] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782–93.
[30] Palacios-Rápalo SN, De Jesús-González LA, Cordero-Rivera CD, Farfan-Morales CN, Osuna-Ramos JF, Martínez-Mier G, et al. Cholesterol-rich lipid rafts as platforms for SARS-CoV-2 entry. Front Immunol 2021;12:796855.
[31] Trinder M, Boyd JH, Brunham LR. Molecular regulation of plasma lipid levels during systemic inflammation and sepsis. Curr Opin Lipido 2019;30:108–16.
[32] Saballs M, Parra S, Sahun P, Pellejà J, Feliu M, Vasco C, et al. HDL-c levels predict the presence of pleural effusion and the clinical outcome of community-acquired pneumonia. Springerplus 2016;5:1491.
[33] Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, et al. Hypolipidemia is associated with the severity of COVID-19. J Clin Lipido 2020;14:297–304.
[34] Her AY, Bhak Y, Jun EJ, Yuan SL, Garg S, Lee S, et al. Sex-specific difference of in-hospital mortality from COVID-19 in South Korea. PLOS One 2022;17:e0262861.
[35] Kautzky-Willer A. Does diabetes mellitus mitigate the gender gap in COVID-19 mortality? Eur J Endocrinol 2021;185:C13–7.
[36] Lee MK, Han K, Kim MK, Koh ES, Kim ES, Nam GE, et al. Combinations of metabolic syndrome components and the risk of type 2 diabetes mellitus: a nationwide cohort study. Diabetes Res Clin Pract 2020;165:108237.
[37] Deeks A, Lombard C, Michelmore J, Teede H. The effects of gender and age on health related behaviors. BMC Public Health 2009;9:213.
[38] Yanez ND, Weiss NS, Romand JA, Treggiari MM. COVID-19 mortality risk for older men and women. BMC Public Health 2020;20:1742.
[39] Sasson I. Age and COVID-19 mortality: a comparison of Gompertz doubling time across countries and causes of death. Demogr Res 2021;44:379–96.
[40] Imam Z, Odish F, Gill I, O'Connor D, Armstrong J, Vanood A, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med 2020;288:469–76.
[41] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
[42] Reddy RK, Charles WN, Sklavounos A, Dutt A, Seed PT, Khajuria A. The effect of smoking on COVID-19 severity: a systematic review and meta-analysis. J Med Virol 2021;93:1045–56.
[43] Muhammad SU, Tariq JS, Muhammad SK, Urvish KP, Izza S, Jawad A, et al. Is there a smoker's paradox in COVID-19? BMJ Evid Based Med 2021;26:279–84.
[44] Murray CJL, Piot P. The potential future of the COVID-19 pandemic: will SARS-CoV-2 become a recurrent seasonal infection? JAMA 2021;325:1249–50.