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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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...
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 ≥ 90 cm for men and ≥ 85 cm for women [18]; (2) a serum triglyceride level of ≥ 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 ≥ 130/85 mmHg or were treated with antihypertensive medication; and (5) a fasting blood glucose level of ≥ 100 mg/dL or were treated with antidiabetic medication. The use of lipid-lowering, antihypertensive, and antidiabetic medications was defined as ≥ 1 prescription per year under the ICD-10 codes E78, I10–113 or I15, and E11–E14, respectively.

Hypertension was defined as BP of ≥ 140/90 mmHg or antihypertensive medication use and type 2 diabetes as fasting blood glucose level of ≥ 126 mg/dL or antidiabetic medication use. Dyslipidemia was defined as a serum total cholesterol level of ≥ 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 m² 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 ≥ 5 days per week or vigorous-intensity exercise for ≥ 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
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 MetS (log-rank P < 0.001). The probabilities generally increased as the number of MetS components increased (log-rank P < 0.001). 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: 0.05 was used to indicate statistical significance.

![A. Cumulative mortality rates by the presence of metabolic syndrome](image1.png)

![B. Cumulative mortality rates by the number of metabolic syndrome components](image2.png)

**Fig. 1.** Cumulative mortality rates by the presence of metabolic syndrome and the number of metabolic syndrome components.
1.2–2.37). 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: 1.17–4.86). 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).

| MetS or component | N | Mortality | Person-days | Mortality rate | Hazard ratio (95% confidence interval) |
|-------------------|---|-----------|-------------|---------------|-------------------------------------|
| Total participants | | | | Model 1 | P-value | Model 2 | P-value |
| 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 | 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 | 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 | 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 | 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 | No | 2433 | 47 | 144,054 | 0.23 | 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) |
| Abdominal obesity | No | 1038 | 47 | 60,262 | 0.78 | 1 (reference) | 1 (reference) |
| Yes | 407 | 35 | 22,936 | 1.53 | 2.61 (1.56–3.71) | <0.001 | 1.43 (0.90–2.29) | 0.132 |
| High triglycerides | 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 | 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 (1.28–2.48) | 0.064 |
| High BP | 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 | 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) |
| Abdominal obesity | No | 426 | 21 | 24,514 | 0.86 | 5.95 (3.14–11.27) | <0.001 | 2.41 (1.17–4.96) | 0.017 |
| Yes | 455 | 15 | 21,748 | 1.75 | 2.85 (1.49–5.45) | 0.002 | 1.32 (0.57–3.06) | 0.525 |
| High triglycerides | 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 | 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 | No | 1763 | 15 | 105,058 | 0.14 | 1 (reference) | 1 (reference) |
| Yes | 668 | 23 | 39,018 | 0.59 | 4.09 (2.14–8.85) | <0.001 | 1.53 (0.77–3.03) | 0.221 |
| Hyperglycemia | 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.

1. Mortality per 1000 person-days.

2. Model 1 was unadjusted.

3. Model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, body mass index, and chronic kidney disease.

4. Waist circumference of ≥90 cm for men and ≥85 cm for women

5. Serum triglyceride level of ≥150 mg/dL or were treated with lipid-lowering medication

6. Serum HDL-C level of <40 mg/dL for men or <50 mg/dL for women

7. Systolic/diastolic BP ≥130/85 mmHg or treatment with antihypertensive medication.

8. Plasma fasting glucose ≥100 mg/dL or treatment with antidiabetic medication.

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
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]. In 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 a 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 be 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 3

| Number of MetS components | N  | Mortality | Person-days | Mortality rate<sup>a</sup> | Hazard ratio (95% confidence interval) |
|---------------------------|----|-----------|-------------|---------------------------|---------------------------------------|
|                           |    |           |             |                           | Model 1<sup>b</sup>                     | Model 2<sup>c</sup>                     |
| 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)                     |

<sup>a</sup> Mortality per 1000 person-days.

<sup>b</sup> Model 1 was unadjusted.

<sup>c</sup> Model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, body mass index, and chronic kidney disease.
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. Available at: [http://ncov.mohw.go.kr/en/bdBoardList.do?brdId=161&brdGubun=161&dataGubun=161&contSeq=board_id]. 2020 [Accessed 28 July, 2020].
[3] Horwitz L, 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: [https://ncov.mohw.go.kr/en/bdBoardList.do?brdId=161&brdGubun=161&dataGubun=&contSeq=&comSeq=&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/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;385:1393–405.

[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 patients in Wuhan. J Allergy Clin Immunol 2020;146:110–8.

[9] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the National heart, lung, and Blood institute; American heart association; World heart federation; International diabetes federation; International diabetes association. Circulation 2009;120:1640–50.

[10] 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;2020:301-81–92.

[11] Deeks A, Lombard C, Michelmore J, Teede H. The effects of gender and age on COVID-19 mortality risk for older men and women. BMC Public Health 2020;20:1742.

[12] 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.

[13] Velders M, Hooijkaas T, Zondag D, Vermeulen I, Weijers P, van der Meer M, et al. Microbiota composition 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.

[14] 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.

[15] 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.

[16] de Lucena TMC, da Silva Santos AF, de Lima BR, de Albuquerque Borborema M, de Azevedo Silva J. Mechanism of inflammatory response in associated comorbidities in COVID-19. Diabetes Metab Syndr 2020;14:597–600.

[17] Vaduganathan M, Vardeny O, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653–9.

[18] Pinto BGG, Oliveira AER, Singh Y, Jimenez L, Gonçalves ANA, Ograla RTL, 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.

[19] Kocar E, Rezen T, Rozman D. Cholesterol, lipoproteins, and COVID-19: basic concepts and clinical applications. Biochim Biophys Acta Mol Cell Lipids 2021;1866:158849.

[20] 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;324:792–93.

[21] Pinto BGG, Oliveira AER, Singh Y, Jimenez L, Gonçalves ANA, Ograla RTL, 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.

[22] Pinto BGG, Oliveira AER, Singh Y, Jimenez L, Gonçalves ANA, Ograla RTL, 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.

[23] 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;2020:301-81–92.

[24] Rezaei R, Chodick G, Haji 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.

[25] Wu S, Zhou K, Misra-Hebert A, Bena J, Kashyap SR. Impact of metabolic syndrome on 10-year cardiovascular risk among HIV-positive and HIV-negative adults: a cross-sectional study. Medicine 2020;99:e20845.