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Metabolically unhealthy individuals, either with obesity or not, have a higher risk of critical coronavirus disease 2019 outcomes than metabolically healthy individuals without obesity

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**Abstract**

**Background:** This study aimed to determine the relative and independent contributions of impaired metabolic health and obesity to critical coronavirus disease 2019 (COVID-19).

**Methods:** We analyzed 4069 COVID-19 patients between January and June 2020 in South Korea, classified into four groups according to metabolic health status and body mass index (BMI): metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy obesity (MHO), and metabolically unhealthy obesity (MUO). The primary outcome was a composite of intensive care unit (ICU) admission, invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), and death. Multivariable Cox proportional hazard regression models were used to estimate the hazard ratio (HR) for the outcome.

**Results:** The incidence rate (per 100 person-months) of critical COVID-19 was the lowest in the MHNW group (0.90), followed by the MHO (1.64), MUNW (3.37), and MUO (3.37) groups. Compared with MHNW, a significantly increased risk of critical COVID-19 was observed in MUNW (HR, 1.41; 95% CI, 1.01–1.98) and MUO (HR, 1.77; 95% CI, 1.39–2.44) but not in MHO (HR, 1.48; 95% CI, 0.98–2.23). The risk of ICU admission or IMV/ECMO was increased only in MUO; however, the risk of death was significantly higher in MUNW and MUO. The risk of critical COVID-19 increased insignificantly by 2% per 1 kg/m² BMI increase but significantly by 13% per 1 metabolically unhealthy component increase, even after mutually adjusting for BMI and metabolic health status.

**Conclusions:** Metabolic health is more important to COVID-19 outcomes than obesity itself, suggesting that metabolic health status should be considered for a precise and tailored management of COVID-19 patients.

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**1. Introduction**

Earlier observations revealed that patients with severe forms of COVID-19 were more obese than those with non-severe disease [1,2]. Multiple studies have indicated that obesity, which is generally represented by a high body mass index (BMI), is associated with the severity and mortality of COVID-19 [3–7]. However, obesity is a predisposing condition for metabolic derangement and cardiovascular diseases [8], which have also been recognized as important risk factors for adverse outcomes of COVID-19 [9,10]. Therefore, the observed association between obesity and critical COVID-19 might be biased by the effects of comorbidities. Previous studies have attempted to solve this problem by adjusting for comorbidities such as diabetes, hypertension, and dyslipidemia [11–14]; however, this might be insufficient to identify a direct relationship between obesity and COVID-19 outcomes.

Many differences in the determining characteristics of metabolic phenotypes have been observed between East Asians and other ethnic groups. For example, a substantial number of East Asian patients with type 2 diabetes were reported to be nonobese, although the prevalence of type 2 diabetes was similar to that in Caucasians [15]. This observation directed much interest to metabolically unhealthy without obesity phenotypes. However, metabolically healthy with obesity phenotypes have also been observed [16].

We hypothesized that metabolic health beyond obesity might be crucial in determining the risk of COVID-19 outcomes. The objective of this large retrospective study was to investigate the relative contribution of obesity and metabolic health status to critical outcomes of COVID-19 patients in a nationwide cohort in South Korea.
2. Materials and methods

2.1. Data source and study population

The Korean National Health Insurance Service (NHIS), which is the sole mandatory public medical insurance system for all citizens of South Korea, recently released the NHIS-COVID-19 cohort database, which included 8080 patients with COVID-19 confirmed with a SARS-CoV-2 PCR test between January 1, 2020, and June 4, 2020. The database incorporated past longitudinal information of the patients before the diagnosis of COVID-19, including demographic, medical, and pharmaceutical data from 2015 to 2020. The relevant information included medical history based on the International Classification of Disease 10th revision (ICD-10), hospitalization including ICU admission, drug prescriptions, medical procedures, and anthropometric and biochemical laboratory information including body weight, height, waist circumference, systolic and diastolic blood pressure, fasting plasma glucose, and lipid profile. In addition, this database was merged with death records managed by the Korean National Statistical Office. All patients were followed up until 4 months after the diagnosis of COVID-19 or until death. A more detailed protocol has been previously published [17]. We presented the STROBE checklist in Supplementary Table S1.

This study was approved by the Institutional Review Board of Korea University Anam Hospital (approval no. 2020AN0482). The requirement for informed consent was waived because all patient data were anonymized and de-identified.

2.2. Study definition and outcomes

This is a nationwide retrospective cohort study. Supplementary Fig. S1 shows the diagram of the selection of the study patients. Among patients with laboratory confirmed COVID-19, those with any missing variables for the identification of metabolic status were excluded. We divided these patients into four groups according to the obesity and metabolic health status: (i) metabolically healthy normal weight (MHNW), (ii) metabolically unhealthy normal weight (MUNW), (iii) metabolically healthy obesity (MHO), and (iv) metabolically unhealthy obesity (MUO). Obesity was defined as BMI ≥25 kg/m² according to the Asia-Pacific BMI criteria, calculated as weight divided by height squared (kg/m²) [18]. A metabolically unhealthy status was defined as the presence of three or more of the following factors: (i) fasting plasma glucose level ≥100 mg/dl or current use of glucose-lowering agents under the ICD-10 codes for diabetes mellitus (E10–E14), (ii) blood pressure ≥130/85 mm Hg or use of antihypertensive agents under the ICD-10 codes for hypertension (I10–I15), (iii) serum triglyceride level ≥150 mg/dl or current use of lipid-lowering agents under the ICD-10 code for dyslipidemia (E78), (iv) high-density lipoprotein-cholesterol level <40 mg/dl in men or <50 mg/dl in women or current use of lipid-

| Table 1 | Characteristics of patients with coronavirus disease 2019 according to metabolic health and obesity phenotypes. |
|---------|----------------------------------------------------------------------------------------------------------|
|         | MHNW | MUNW | MHO | MUO | p-Value |
| n (%)   | 1871 (46.0) | 728 (17.9) | 595 (14.6) | 875 (21.5) | 0.001 |
| Follow-up time, mean (SD), days | 118.0 (10.2) | 111.9 (26.2) | 117.0 (14.5) | 113.0 (24.3) | <0.001 |
| Age group, n (%) years | 20–29 | 149 (8.0) | 3 (0.4) | 39 (6.6) | 7 (0.8) |
| 30–39 | 228 (12.2) | 9 (1.2) | 40 (6.7) | 41 (4.7) |
| 40–49 | 430 (23.0) | 45 (6.2) | 124 (20.8) | 112 (12.8) |
| 50–59 | 604 (32.3) | 179 (24.6) | 192 (32.3) | 238 (27.2) |
| 60–69 | 326 (17.4) | 246 (33.8) | 96 (16.1) | 276 (31.5) |
| ≥70 | 95 (5.1) | 165 (22.7) | 41 (6.9) | 135 (15.4) |
| ≥80 | 39 (2.1) | 81 (11.1) | 13 (2.2) | 66 (7.5) |
| Male sex, n (%) | 522 (27.9) | 300 (41.2) | 298 (50.1) | 410 (46.9) | <0.001 |
| BMI, mean (SD), kg/m² | 21.8 (2.0) | 22.7 (1.7) | 27.0 (2.1) | 27.9 (2.6) | <0.001 |
| WC, mean (SD), cm | 74.6 (6.8) | 80.2 (6.5) | 85.8 (7.3) | 90.7 (7.4) | <0.001 |
| HDL-C, mean (SD), mg/dl | 79.6 (6.1) | 83.5 (5.5) | 88.8 (6.6) | 92.9 (7.2) | <0.001 |
| Total cholesterol, mean (SD), mg/dl | 21.8 (2.0) | 22.7 (1.7) | 27.0 (2.1) | 27.9 (2.6) | <0.001 |
| Triglyceride, mean (SD), mg/dl | 74.6 (6.8) | 80.2 (6.5) | 85.8 (7.3) | 90.7 (7.4) | <0.001 |
| LDL-C, mean (SD), mg/dl | 79.6 (6.1) | 83.5 (5.5) | 88.8 (6.6) | 92.9 (7.2) | <0.001 |
| Hemoglobin, mean (SD), g/dl | 21.8 (2.0) | 22.7 (1.7) | 27.0 (2.1) | 27.9 (2.6) | <0.001 |
| Creatinine, mean (SD), mg/dl | 21.8 (2.0) | 22.7 (1.7) | 27.0 (2.1) | 27.9 (2.6) | <0.001 |
| AST, mean (SD), IU/L | 21.8 (2.0) | 22.7 (1.7) | 27.0 (2.1) | 27.9 (2.6) | <0.001 |
| ALT, mean (SD), IU/L | 21.8 (2.0) | 22.7 (1.7) | 27.0 (2.1) | 27.9 (2.6) | <0.001 |
| Smoking, n (%) | 1577 (84.3) | 500 (68.7) | 444 (74.6) | 612 (69.9) | <0.001 |
| Never | 200 (10.7) | 120 (16.5) | 96 (16.1) | 79 (9.0) | <0.001 |
| Former | 94 (5.0) | 58 (8.0) | 51 (8.6) | 79 (9.0) | <0.001 |
| Alcohol consumption, n (%) | 313 (16.7) | 106 (14.6) | 159 (26.7) | 203 (23.2) | <0.001 |
| Regular exercise, n (%) | 805 (43.0) | 338 (46.4) | 262 (44.0) | 429 (49.0) | 0.023 |
| Moderate-to-vigorous physical activity, n (%) | 93 (5.0) | 45 (6.2) | 32 (5.4) | 45 (5.1) | 0.066 |
| Low SES, n (%) | 430 (23.0) | 246 (33.8) | 96 (16.1) | 276 (31.5) | 0.001 |
| Comorbidities, n (%) | 178 (24.5) | 117 (19.7) | 199 (22.7) | 0.214 |
| Hypertension | 200 (10.7) | 464 (63.7) | 95 (16.0) | 551 (63.0) | <0.001 |
| Diabetes mellitus | 33 (1.8) | 264 (36.3) | 8 (1.3) | 287 (32.8) | <0.001 |
| Dyslipidemia | 162 (8.7) | 597 (82.0) | 41 (6.9) | 617 (70.5) | <0.001 |
| Cardiovascular disease | 227 (12.1) | 294 (40.4) | 66 (11.1) | 252 (33.4) | <0.001 |
| Chronic kidney disease | 8 (0.4) | 22 (3.0) | 4 (0.7) | 35 (4.0) | <0.001 |
| Chronic pulmonary disease | 384 (20.5) | 227 (33.8) | 96 (16.1) | 276 (31.5) | 0.001 |

Abbreviations: MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; SD, standard deviation; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SES, socioeconomic status.

a Socioeconomic status was identified according to the medical insurance premium in the database, in which low socioeconomic status was defined as the lower 30%.
lowering agents under the ICD-10 code for dyslipidemia (E78), and (v) waist circumference > 90 cm in men or ≥85 cm in women based on the International Diabetes Federation criteria for Asians [18,19].

The primary outcome was a composite of ICU admission, invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), and death of any cause from the diagnosis of COVID-19 to the end of follow-up.

2.3. Statistical analyses

Continuous data are presented as mean ± standard deviation (SD) values for normally distributed variables and as medians and interquartile ranges for nonnormally distributed variables. Categorical data are presented as frequencies and percentages. ANOVA and Pearson’s χ² test were used to compare baseline characteristics among the four groups.

We calculated the incidence of the primary composite outcome by dividing the total number of events by the total follow-up period (per-son-months). Kaplan–Meier analysis followed by the log-rank test was used to examine differences in the cumulative incidence of the composite primary outcome according to the metabolic health and obesity phenotypes. We also used multivariable Cox proportional hazard regression models to analyze the hazard ratios (HRs) for the study outcomes according to each metabolic health and obesity phenotype. Model 1 was adjusted for age and sex, and model 2 was adjusted for all possible confounders including age, sex, smoking, alcohol consumption, physical activity, socioeconomic status, previous history of chronic pulmonary disease including asthma and chronic obstructive pulmonary disease. As general obesity (represented by a high BMI) and metabolic health are closely associated with each other, we further investigated their independent roles in the development of critical COVID-19 by further adjusting for BMI and metabolically healthy status mutually. For handling the missing data, available-case analyses (also known as pairwise deletion) were used without additional data handing.

All reported p-values were two-sided, and statistical significance was set at p < 0.05. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

Of patients with laboratory confirmed COVID-19 from the original NHIS-COVID-19 cohort database (n = 8080), those with any missing variables (n = 4011) for the identification of metabolic status, including BMI, waist circumference, fasting plasma glucose, blood pressure, and serum levels of triglyceride and high-density lipoprotein-cholesterol, were excluded. Finally, a total of 4069 patients were selected.

3.1. Baseline patient characteristics

The mean (±SD) age of the patients was 55.5 ± 14.2 years, and 2539 (62.4%) were female. The mean BMI was 24.0 kg/m². A total of 879 patients (21.6%) had a history of cardiovascular disease, 1310 (32.2%) had hypertension and 1013 (24.9%) had chronic pulmonary disease. The baseline characteristics of patients in the four groups according to metabolic health and obesity status are listed in Table 1. In general, patients in the metabolically unhealthy groups (MUNW and MUO) were older than those in the metabolically healthy groups (MHNW and MHO). The proportion of male patients was the lowest in MHNW, followed by MUNW, MUO, and MHO. Metabolic parameters, including systolic/diastolic blood pressure and serum glucose/triglyceride levels, were higher in the metabolically unhealthy groups than in the metabolically healthy groups. Metabolically unhealthy patients also had a higher prevalence of comorbidities, including hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, chronic kidney disease, and chronic pulmonary disease than metabolically healthy patients.

3.2. Severe COVID-19 outcomes according to metabolic health and obesity status

During about 4 months of follow-up, 289 (7.1%) critical COVID-19 outcomes occurred. The incidence rate (per 100 person-months) of the outcomes was higher in metabolically unhealthy patients (3.37 in both MUNW and MUO) than in metabolically healthy patients (0.90 in MHNW and 1.64 in MHO). Table 2 shows the HRs for the composite and individual COVID-19 outcomes in the four groups. Compared with the MHNW group as the reference, all three other groups had significantly higher HRs for the composite of critical COVID-19 outcomes in an unadjusted model (1.79 [1.19–2.70], 3.58 [2.59–4.95], and 3.59 [2.63–4.91] in MHO, MUNW, and MUO, respectively), indicating that both obesity and impaired metabolic health are important risk factors for critical COVID-19. However, after adjusting for confounding variables (in two different models), patients with a metabolically unhealthy status (MUNW and MUO groups) still had a significantly higher risk of critical COVID-19, but patients in the MHO group did not. In model 2, the risk of critical COVID-19 was 41% higher in the MUNW group and 77% higher in the MUO group than in the MHNW group. The MUNW and MUO groups also had a significantly higher risk of death than the MHNW group, although the risks of ICU admission and IMV or ECMO requirement were higher only in the MUO group. Kaplan–Meier curves showed a time-dependent risk

| Table 2 | Severe COVID-19 outcomes according to metabolic health and obesity phenotypes. |
|---------|--------------------------------------------------------------------------------|
| Events, n | Incidence rate, per 100 person-months | Hazard ratio (95% CI) | Unadjusted | Model 1 | Model 2 |
| Composite of severe COVID-19 outcomes | | | | | |
| MHNW 64 | 0.90 | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| MUNW 86 | 3.37 | 3.58 (2.59–4.95) | 1.42 | 1.41 |
| MHO 36 | 1.64 | 1.79 (1.19–2.70) | 1.42 (0.94–2.14) | 1.48 (0.98–2.23) |
| MUO 103 | 3.37 | 3.59 (2.63–4.91) | 1.80 | 1.77 |
| ICU admission | | | | | |
| MHNW 47 | 0.66 | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| MUNW 50 | 1.96 | 2.82 (1.89–4.20) | 1.43 | 1.45 |
| MHO 29 | 1.32 | 1.96 (1.24–3.12) | 1.92 (1.00–2.55) | 1.92 (0.95–2.54) |
| MUO 69 | 2.26 | 3.26 (2.25–4.72) | 1.92 | 1.92 |
| IMV or ECMO | | | | | |
| MHNW 15 | 0.21 | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| MUNW 24 | 0.91 | 4.19 (2.20–7.98) | 1.83 | 1.87 |
| MHO 12 | 0.53 | 2.54 (1.19–5.42) | 1.99 (0.93–4.27) | 2.02 (0.94–4.33) |
| MUO 35 | 1.10 | 5.11 (2.79–9.36) | 2.72 | 2.65 |
| Death | | | | | |
| MHNW 21 | 0.29 | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| MUNW 52 | 1.94 | 6.36 (3.95–10.89) | 1.85 | 1.90 |
| MHO 12 | 0.52 | 1.81 (0.89–3.67) | 1.30 (0.64–2.65) | 1.44 (0.71–2.94) |
| MUO 52 | 1.60 | 5.43 (3.27–9.01) | 2.23 | 2.22 |

Abbreviations: COVID-19, coronavirus disease 2019; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MUO, metabolically healthy obesity; MHO, metabolically unhealthy obesity; ICU, intensive care unit; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

Model 1 was adjusted for age and sex.

Model 2 was adjusted for age, sex, smoking, alcohol consumption, physical activity, socioeconomic status, and previous history of chronic pulmonary disease, including asthma and chronic obstructive pulmonary disease.
of each outcome in the four groups (Fig. 1). All outcomes were determined to occur early, mostly within 30 days after the diagnosis of COVID-19.

3.3. Severe COVID-19 outcomes according to BMI category and the number of metabolically unhealthy components

In an unadjusted model, the risk of critical COVID-19 was increased by 2% per 1 kg/m² increase in BMI and by 13% for every 1 component increase in metabolically unhealthy parameters (Table 3). However, after reciprocal adjustment for each variable and other confounding factors (in model 2), only the number of metabolically unhealthy parameters was associated with the risk of critical COVID-19.

4. Discussion

In this retrospective cohort study, we found that impaired metabolic health was a stronger predictor of critical COVID-19 than obesity itself in the Korean population. Notably, metabolically unhealthy individuals, either with obesity or not, had a higher risk of critical COVID-19 outcomes, including ICU admission and death, than metabolically healthy individuals without obesity. In contrast, metabolically healthy individuals with obesity were not associated with critical COVID-19. In addition, the risk of COVID-19 outcomes linearly increased with increasing number of metabolically unhealthy components independently of BMI, whereas BMI did not distinguish patients at a risk of critical COVID-19.

Metabolically unhealthy traits, generally manifesting as metabolic syndrome, have been proposed as important risk factors for adverse outcomes of COVID-19. Although the exact mechanisms underlying this association remain unknown, immunomodulation (such as a hyperimmune response) and increased expression of ACE2 (which is the viral entry receptor of SARS-CoV-2) partly explain the association between metabolic syndrome and COVID-19 outcomes [20,21]. However, these mechanisms may also be applicable to obesity-related COVID-19 outcomes. Thus, further studies are required to elucidate this issue.

Obesity is a heterogeneous condition. For example, individuals with the same BMI can show various phenotypes in terms of adipocyte biology, fat distribution, and body composition [22]. One of the important factors determining metabolically healthy and unhealthy obesity is the amount or distribution of visceral adipose tissue (VAT). Previous studies found that Asian diabetic patients had more VAT than Caucasian diabetic patients with the same waist circumference, which can explain the higher susceptibility of lean Asians to type 2 diabetes [23]. Given the close association of VAT with insulin resistance, and further with metabolic syndrome, this parameter could be a determinant of the metabolic health status at a given BMI [24]. Several studies have indicated that VAT could be an important indicator of COVID-19 severity. In a small-sample study, VAT was an independent risk factor for severe COVID-19 outcomes, but not BMI [25]. Another study showed that high VAT (≥128.5 cm²) was a crucial factor in predicting COVID-19 severity [26]. Although we were unable to validate this association in our cohort, we assumed that a higher proportion of VAT in the MUNW group than in the MHNW group might have contributed to the risk of critical COVID-19. Metabolically unhealthy phenotype is also related to adipose tissue dysfunction and inflammation, which ultimately result in ectopic fat deposition and insulin resistance [27]. Indeed, upregulation of inflammatory cytokines including TNF-α and IL-6 was frequently observed in patients with insulin resistance, even without general obesity [20]. This partly explains hyperimmune response to infectious insult including SARS-CoV-2 and adverse outcomes of COVID-19 in MUNW people.
Another possible factor is reduced muscle mass characteristic of MUNW individuals [16]. Reduced muscle mass has been proposed to be independently associated with insulin resistance and increased susceptibility to adverse respiratory outcomes, including pneumonia and sepsis [28,29].

Nonetheless, the available evidence from multiple geographical regions generally supports that obesity contributes to the adverse outcomes of COVID-19. However, previous reports had substantial inconsistencies in terms of study population and measured outcomes. A linear association between BMI and the need for ICU admission or mortality risk from COVID-19, J-shaped or U-shaped associations with infection and death outcomes, although it was not significant even after adjusting for BMI, suggesting an important role for BMI in the development of severe COVID-19 and mortality in this study [57,30,32].

Given that the proposed cutoff values of high BMI for death risk ranged from 30 to 40 kg/m² in previous studies, the possibility exists that the much lower incidence of high BMI in our study and the National Health Insurance Service, which developed the Korean Health Insurance Cohort study and the National Health Insurance Service, which developed the NHIS-COVID-19 cohort database.

**Declaration of competing interest**

The authors report no potential conflicts of interest relevant to this article.

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Appendix A. Supplementary data

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