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Elevated risk of severe COVID-19 outcomes among underweight patients in Japan: A national registry-based study

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Abstract: We conducted a study to determine the impact of body mass index (BMI) (underweight, normal weight, and overweight) on the severity of COVID-19 across different periods of variant predominance using a large-scale data registry of hospitalized COVID-19 patients in Japan (COVIREGI-JP), involving 46,291 Japanese patients aged 20–89 years. Severity was classified based on the most intensive treatment received throughout the hospitalization. Multiple logistic models were used to assess the risk of severe disease, and adjusted odds ratios (ORs) for BMI < 18.5, 18.5–20, and ≥ 25 relative to BMI of 20.1–24.9 were calculated by sex and age group. The risk of severe COVID-19 and death was high among those with BMI < 18.5 [OR (95% CI): 1.88 (1.52–2.33), 1.59 (1.22–2.07)] as well as those with BMI ≥ 25 [1.38 (1.20–1.60), 1.87 (1.50–2.34)] for both men and women, respectively. The risk was extremely high among those with BMI < 18.5 when the Omicron variant was predominant [2.41 (1.66–3.49) for men, 2.96 (1.77–4.97) for women]. An important point to note is that being underweight as well as obesity increased the risk of severe COVID-19 and death. More attention should be paid to underweight individuals when predicting COVID-19 risk.

***Keywords*:** COVID-19, infectious disease, BMI, obesity, lean

1. Introduction

Numerous studies have examined possible associations between body mass index (BMI) and COVID-19 severity, hospitalization, and death. Most studies have reported obesity as a risk factor for all three (*1-9*). Because of the small number of people studied, the risk for each BMI category by sex and age has not been established. In Europe and the US, the number of thin people (BMI < 18.5) is quite low, so there have also been only limited studies on the severity of COVID-19 and death in underweight individuals (*10-12*). To the best of our knowledge, no studies have analyzed the severity of COVID-19 among underweight individuals by variant. In Japan, the prevalence of people with BMI < 18.5 is higher, and there is a tendency toward increased numbers of people in the lower normal weight range (18.5 ≤ BMI ≤ 20.0) among older adults ≥ 65 years of age (*13*).

Therefore, we conducted the present study to evaluate associations between being underweight and COVID-19 severity and death by sex and age, by SARS-CoV-2 variant (Omicron or not), and by the four categories of underweight, lower normal weight, normal weight, and overweight (including obesity).

2. Study design

2.1. Data source and ethical approval

This study was approved by the ethics review board (NCGM-S-004352-02) of the Japan Institute for Health Security (JIHS, formerly NCGM: National Center for Global Health and Medicine). Informed consent was

waived due to the retrospective nature of the study. This research was conducted in accordance with the Declaration of Helsinki.

This study used data from COVIREGI-JP, a large-scale registry of hospitalized COVID-19 patients in Japan, which contains data on patients' characteristics and clinical course during hospitalization (*e.g.,* admission and discharge dates, treatments and dates, and survival or death). Prior to beginning this work, we informed the registry on the JIHS' website (the primary investigator's affiliation), provided a webinar for journalists, a press release, *etc.*, and asked hospitals to participate in COVIREGI-JP and voluntarily register patients' information. A total of 531 hospitals was involved with this registry system. The details have been reported elsewhere (*14-16*).

The inclusion criteria for enrollment were: *i*) a positive SARS-CoV-2 test (*14*); and *ii*) inpatient treatment at a healthcare facility. If a patient had a history of multiple COVID-19 hospitalizations and met the aforementioned inclusion criteria, each admission was included separately in the registry. However, those data were excluded from the current analysis. This was because multiple hospitalization data for a particular patient could not be linked and therefore the most intensive treatment during hospitalization, which was the outcome criterion for the present study, could not be identified. The purpose here was to avoid the inclusion of duplicate data. Non-Japanese citizens were also excluded to minimize any potential effects of ethnicity.

2.2. Patients

There were 75,148 patients registered in the COVIREGI-JP who were hospitalized between January 26, 2020 and December 14, 2022 and who were discharged or dead by December 15, 2022. We defined the non-Omicron and Omicron variant–predominant periods (referred to as the non-Omicron and Omicron periods) as the periods before and after December 1, 2021, respectively. Patients were excluded from the analysis in the following order: non-Japanese citizens (n = 10,473), sex missing (n = 22), outside of the age range of 20-89 years (n = 8,080), transferred from another hospital (n = 5,615), transferred to another hospital (n = 4,891), still hospitalized (n = 1,470), treatment details missing (n = 383), and admission and/or discharge dates missing (n = 177). Finally, therefore, the analysis included 46,291 patients aged 20–89 years (26,467 men and 19,824 women).

2.3. Definition of disease grades

We graded the severity of COVID-19 based on the most intensive treatment received throughout the hospitalization, as shown in the header of Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*), as follows: grade 0 (no oxygen, *i.e.,* patients were never given supplemental oxygen); grade 1 (patients were given a nasal cannula or oxygen mask); grade 2 [patients were given high-flow oxygen or non-invasive positive pressure ventilation (NIPPV)]; grade 3 [invasive mechanical ventilation (IMV)]; grade 4 [extracorporeal membrane oxygenation (ECMO)]; and grade 5 (death during hospitalization regardless of treatment). We considered pooled grades 3, 4 and 5 as "severe" for these analyses, but grade 5 (death) was also analyzed separately.

2.4. Statistical analysis

The frequency distributions of COVID-19 grades and other categorical data are shown as percentages. Continuous variables were summarized as the mean and standard deviation (SD). The BMI categories of patients with severe grade 3/4/5 (IMV/ECMO/death) and separately grade 5 (death) were compared to those with grade 0 (no oxygen, reference group) using multiple logistic regression and expressed as the odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, date of admission, smoking, and comorbidities. There were too many types of comorbidities (25 diseases), so the comorbidities to adjust for were selected using a stepwise procedure with $p < 0.10$ for entry and removal. Grades 1 and 2 were excluded from the primary analysis in order to focus on the risk of severe grades (3 and above) by comparing them to grade 0. The inclusion of grade 2 could obscure the association between BMI and the severity of COVID-19, so the ORs for grade 2/3/4/5 were also calculated for sensitivity analyses, with grade 0 as the reference group. The entire observation period was divided into 2-month intervals and the date of admission was categorized by interval and coded as a dummy variable for statistical adjustment. The separated analysis was conducted by the Omicron period and the non-Omicron period. A two-sided p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. The key findings of this study

3.1. Characteristics of patients

The mean duration of hospitalization, including the day of admission, was 13.5 days (range: 1 to 762) for patients admitted to hospital because of a positive test for SARS-CoV-2.

The ages, smoking status, BMI, and prevalence of comorbidities in these COVID-19 patients are shown in Table 1. The mean age was 55.7 years for men and 57.2 years for women. The mean BMI was 24.9 kg/m^2 for men and 23.1 kg/m^2 for women. The frequency of the BMI categories — underweight, lower normal weight,

Table 1. Characteristics and comorbidities of the COVID-19 patients registered in Japan

Items	Men (*n* = 26,467)		Women (*n* = 19,824)	
	n	%	*n*	%
Age (20–89 years)				
Mean ± standard deviation	55.7 ± 18.4		57.2 ± 20.7	
Smoking history*				
Currently smoking (until shortly before the onset of symptoms)	5,963	22.5% (25.6%)	1,866	9.4% (11.1%)
Former smoking	8,403	31.7% (36.1%)	2,120	10.7% (12.6%)
Never smoking	8,887	33.6% (38.2%)	12,796	64.5% (76.2%)
Unknown	3,214	12.1%	3,042	15.3%
BMI (kg/m^2)*				
Mean ± standard deviation	24.9 ± 5.8		23.1 ± 4.7	
< 18.5 (underweight)	1,152	4.4% (5.0%)	2,087	10.5% (12.4%)
18.5–20.0 (lower normal weight)	1,426	5.4% (6.2%)	2,383	12.0% (14.1%)
20.1–24.9 (normal weight)	10,713	40.5% (46.7%)	7,781	39.3% (46.1%)
≥ 25 (overweight/obesity)	9,638	36.4% (42.0%)	4,625	23.3% (27.4%)
unknown	3,538	13.4%	2,948	14.9%
Comorbidities				
Myocardial infarction	676	2.6%	170	0.9%
Congestive heart failure	796	3.0%	515	2.6%
Peripheral vascular disease	521	2.0%	260	1.3%
Cerebrovascular disorders	1,820	6.9%	1,124	5.7%
Hemiplegia	245	1.2%	654	1.4%
Dementia	1,098	4.1%	1,703	8.6%
COPD	945	3.6%	167	0.8%
Chronic lung diseases other than COPD	496	1.9%	229	1.2%
Bronchial asthma	1,253	4.7%	1,449	7.3%
Mild liver disease	340	1.7%	1,239	2.7%
Moderate to severe liver dysfunction	61	0.3%	193	0.4%
Peptic ulcer	250	0.9%	141	0.7%
Hypertension	8,534	32.2%	5,559	28.0%
Hyperlipidemia	4,061	15.3%	2,942	14.8%
Mild diabetes	4,525	17.1%	2,209	11.1%
Severe diabetes	763	2.9%	256	1.3%
Diabetes mellitus (mild and severe)	5,288	20.0%	2,465	12.4%
Obesity	2,281	8.6%	1,044	5.3%
Moderate to severe renal dysfunction	701	2.6%	304	1.5%
Maintenance hemodialysis before hospitalization	377	1.4%	159	0.8%
Solid cancers	1,224	4.6%	717	3.6%
Leukemia	98	0.4%	74	0.4%
Lymphoma	224	0.8%	160	0.8%
Metastatic solid cancers	401	1.5%	200	1.0%
Connective tissue disease	237	0.9%	497	2.5%
HIV infection	105	0.4%	1	0.0%

*Percentage values in parentheses are for excluding the "unknown" category.

normal weight, overweight, and "unknown" — were 4.4%, 5.4%, 40.5%, 36.4%, and 13.4%, respectively for men and 10.5%, 12.0%, 39.3%, 23.3%, and 14.9% for women. Many patients had hypertension (32.2% of men and 28.0% of women), hyperlipidemia (15.3% of men and 14.8% of women), diabetes (20.0% of men and 12.4% of women), and obesity (8.6% of men and 5.3% of women) as comorbidities (Table 1).

3.2. Lower weight patients have an extremely high risk of death

The risks of grade 3/4/5 (IMV/ECMO/death) and grade 5 (death) were mostly higher in men than in women (except for the very small number of deaths in the 40-49-year-old group) and increased with age for both sexes (Figure 1, Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*). The risks of grade 3/4/5 and grade 5 were higher in the elderly group than in the younger group.

ORs and 95% CIs by BMI (relative to BMI 20.1–24.9 kg/m^2) by grade, with grade 0 as the

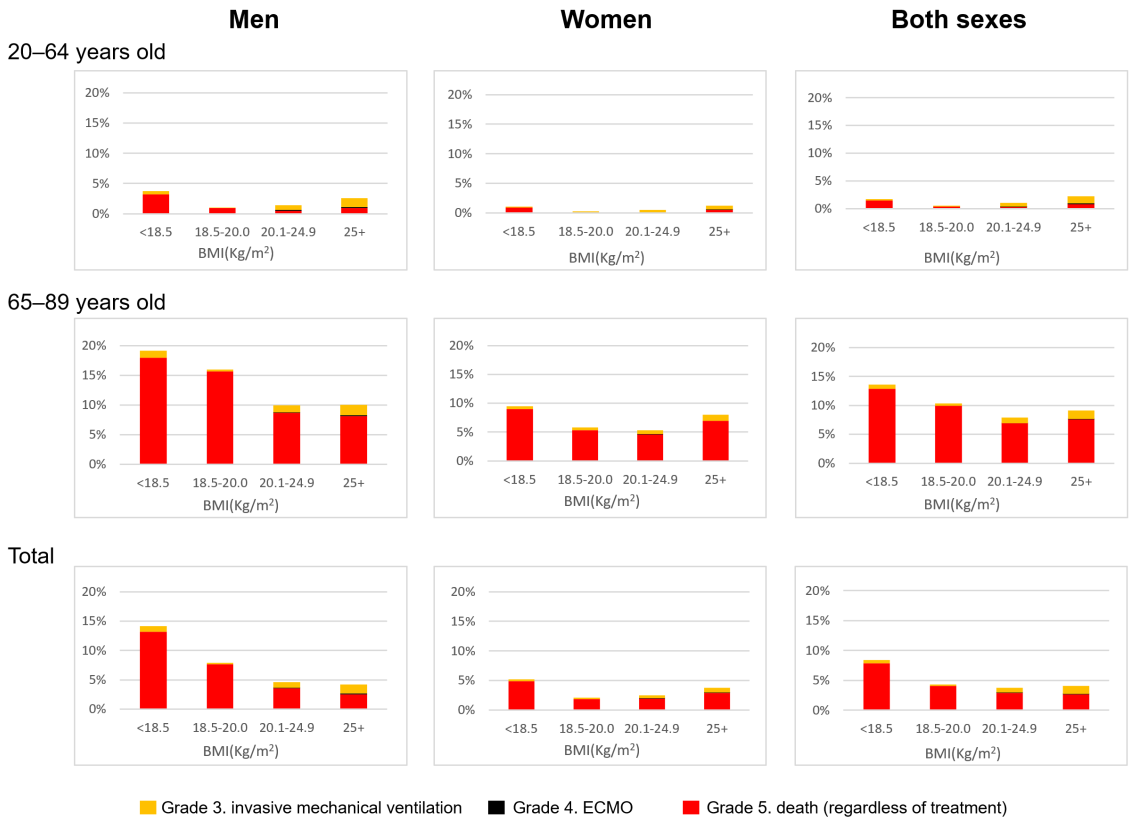

Figure 1. The frequency of each grade by sex and age groups among COVID-19 patients registered in Japan.

reference group, for the entire period are shown in Figure 2A and Supplemental Table S2-A (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*). Patients with BMI < 18.5 and ≥ 25 had a significantly increased risk of grade 3/4/5 COVID-19 and death in all age groups. In the younger group (20–64 years), the risk of death increased particularly when the BMI was < 18.5 (OR 4.84 for men, 8.50 for women, and 5.75 for both). In older adults (65–89 years), BMI < 18.5 was associated with a significantly increased risk of grade 3/4/5 and death. For the risk of COVID-19 severity and death, the proportion of patients in the lower normal weight range (18.5 ≤ BMI ≤ 20.0) was significantly higher in men, and for those overweight (BMI ≥ 25) it was significantly higher in women.

3.3. The risk remained elevated even during the Omicron period, when general severity was declining

An analysis was conducted separately for the time when the Omicron variant was preponderant, and for the period when other variants were. The strength of the association between BMI and severity of and death from COVID-19 differed between these two periods. For the non-Omicron period, the trend differed slightly according to age (Figure 2B, 2C, and Supplemental Table S2-B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*). Young people with BMI < 18.5 and ≥ 25 had an increased risk of grade 3/4/5 and death, whereas older men with BMI < 18.5 had an increased risk of grade 3/4/5 and death [OR (95% CI): 1.54 (1.15–2.06), 1.61 (1.19–2.18)], and older women with BMI ≥ 25 had a significantly increased risk [2.10 (1.60–2.76), 2.13 (1.58–2.85)].

In the period when Omicron was predominant, no younger women with 20.1 ≤ BMI ≤ 24.9 died (Figure 2B and 2C, and Supplemental Table S2-C, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*), but patients with BMI < 18.5 had a significantly increased risk of grade 3/4/5 and death among both sexes [OR (95% CI): 2.61 (1.94-3.51)]. However, there was no significantly increased risk of grade 3/4/5 and death for patients with BMI ≥ 25.

4. Discussion

This study examined body size and the risk of severe COVID-19 and death. To the best of our knowledge, this is the first study showing that the risk of COVID-19 severity grade 3/4/5 and death significantly increased in underweight individuals with a BMI < 18.5, and especially among younger people, regardless of the variant period.

A U-shaped association was observed between BMI and COVID-19 severity for whole period (Figure 2A and Supplemental Table S2-A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=110*). Comparing the period dominated by the

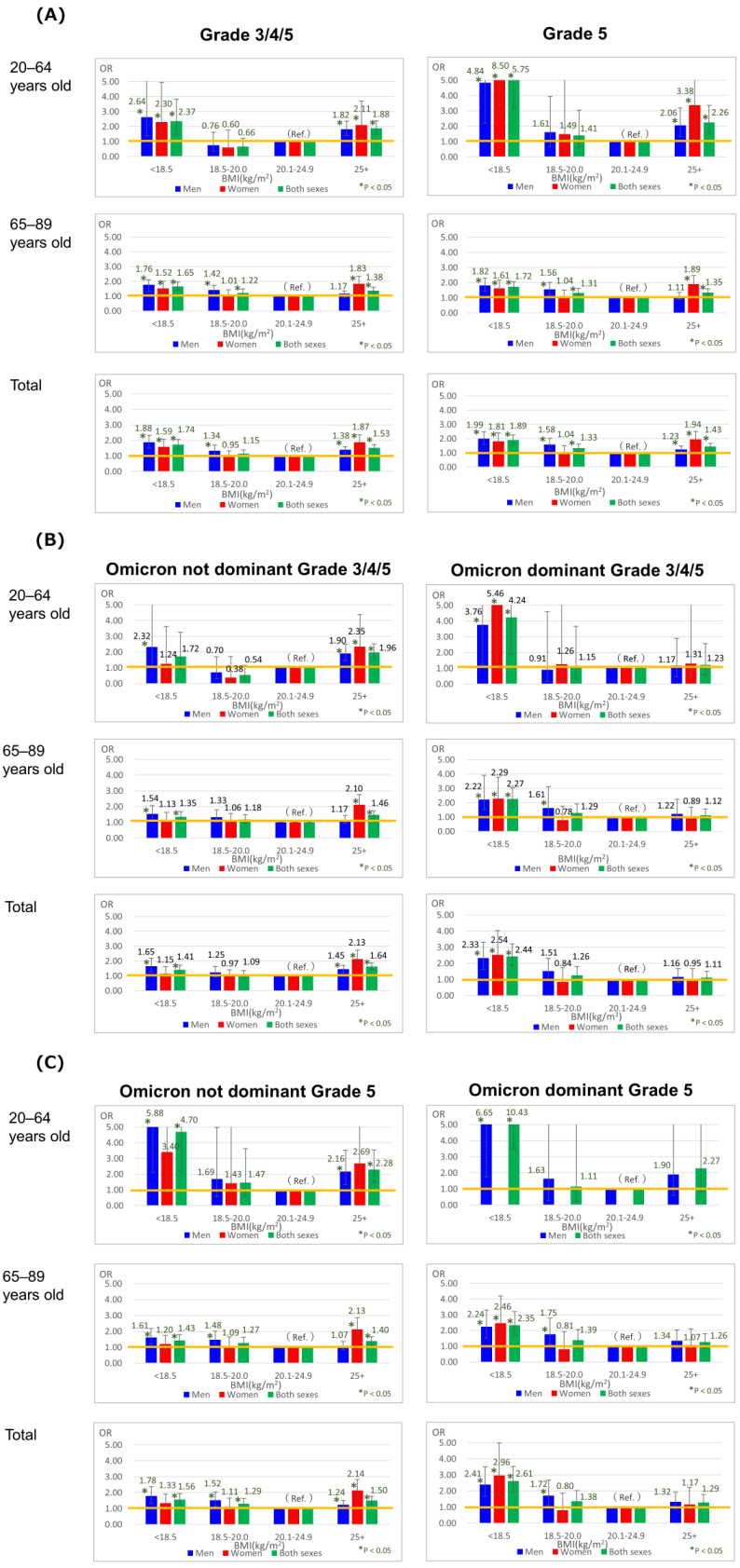

Figure 2. (A) Association between BMI and grades of COVID-19 severity; **(B)** Association between BMI and grades of COVID-19 severity by SARS-CoV-2 variant (Omicron or not); **(C)** Association between BMI and death of COVID-19 by SARS-CoV-2 variant (Omicron or not). Odds ratio (OR) and 95% confidence interval (CI) for each grade (using "Grade 0" as a reference) according to BMI by a multiple logistic regression model; 10-year dummy variables were used to adjust for age, and dummy variables for 2-month intervals were used to adjust for date of admission. ORs (95% CIs) in bold indicate statistical significance at $p < 0.05$. Comorbidities were selected by a stepwise procedure using $p < 0.10$ for entry and removal. None of the comorbidities was selected for adjustment.

Omicron variant with that of other prevalent variants revealed a slightly different trend. Notably, during the Omicron period, overweight individuals did not have a significantly increased risk of COVID-19 severity and death. In contrast, during the period when other variants were dominant, overweight individuals had a significantly higher risk of COVID-19 severity. This analysis was also performed separately for older and younger patients.

Although many studies have examined the relationship between BMI and COVID-19 severity and death, only a handful of studies have separately analyzed the impact of being underweight with BMI < 18.5 (*10-12*). However, no studies have analyzed COVID-19 severity and death among individuals with a BMI < 18.5 grouped by age and variant. Reasons for this may include the small number of people in the overall analysis and the fact that the number of people with BMI < 18.5 was too small for some ethnic groups to be analyzed (*13*). Moreover, no studies have examined whether different SARS-CoV-2 variants influenced the association between BMI and COVID-19 severity and death. Therefore, the present study determined the risk of severe disease and death in 49,291 subjects from a large national registry dataset, which was analyzed by age group (20–64 and 65–89 years) and BMI < 18.5. In addition, the effect of viral variant-specific differences on pathogenesis was also analyzed.

In the present study, underweight people had a significantly increased risk of death. The mechanism responsible for this is not clear, but it is thought to be influenced by a frail constitution. Another possibility is that the system that prioritized the elderly and obese resulted in differences in vaccination status, which prevented an increase in the risk of severe illness and death during the period when Omicron was predominant. However, there was no significant association between BMI status and vaccination coverage (data not shown).

The present study had several limitations. Patients with a history of two or more COVID-19 hospitalizations were excluded because the most intensive treatment was not identifiable, and duplicate data needed to be avoided. That said, a strength of this study is that we were able to perform a variant-specific analysis of COVID-19 and evaluate the risk of severe illness and death for patients with a BMI < 18.5, and especially for lower normal weight individuals with BMI of 18.5–20.0 among the elderly. Since the analysis was performed on hospitalized patients, the status of care was known, and the analysis could be performed using worst-case data during hospitalization.

It is important to note the tendency toward underweight and lower normal weight in the elderly as well as obesity. We found that the strength of the association between body size and COVID-19 differed between the period when the Omicron variant predominated and the period when other variants were dominant. We suggest that more attention should be given to underweight individuals and those with lower normal weight in predicting the risk of COVID-19 severity and mortality. Prevention and treatment of COVID-19 has been a priority for overweight and elderly people. Underweight people should also be prioritized regardless of age in the future.

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