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Nutrition, Metabolism & Cardiovascular Diseases (2021) **31**, 3219–3226

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

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

The association between BMI and metabolically unhealthy status with COVID-19 mortality: Based on 3019 inpatients from Wuhan, China

Jing Zeng [a,1], Xiong Liu [b,1], Shengshu Wang [c], Shanshan Yang [d], Wangping Jia [c], Ke Han [c], Changjun Wang [b], Miao Liu [e,***], Yong Chen [b,**], Yao He [c,*]

[a] *Department of Endocrinology, The Second Medical Centre & National Clinical Research Centre for Geriatric Disease, Chinese PLA General Hospital, Beijing, China*
[b] *Chinese PLA Center for Disease Control and Prevention, China*
[c] *Institute of Geriatrics, Beijing Key Laboratory of Aging and Geriatrics, National Clinical Research Center for Geriatrics Diseases, State Key Laboratory of Kidney Diseases, Second Medical Center of Chinese PLA General Hospital, China*
[d] *Department of Disease Prevention and Control, The 1st Medical Center, Chinese PLA General Hospital, China*
[e] *Graduate School of Chinese PLA General Hospital, China*

Received 13 April 2021; received in revised form 25 July 2021; accepted 27 July 2021
Handling Editor: A. Siani
Available online 5 August 2021

KEYWORDS
Obesity;
Underweight;
Metabolic unhealth;
COVID-19;
Cohort study

Abstract *Background and aims:* Patients with multiple metabolic diseases are at high risk for the occurrence and death of COVID-19. Little is known about patients with underweight and metabolically healthy obesity. The aim of this study is to evaluate the impact of BMI and COVID-19 mortality in hospitalized patients, and also explore the association in different metabolically healthy (MHS) and unhealthy status (MUS).
Methods and results: A retrospective cohort study based on 3019 inpatients from Wuhan was conducted. Included patients were classified into four groups according the BMI level (underweight, normal weight, overweight and obesity), and patients with at least one of the metabolic abnormalities (diabetes, hypertension, dyslipidemia) was defined as MUS. Multiple Cox model was used to calculate the hazard ratio (HR). Compared to patients with normal weight, the HRs of overweight and obesity for COVID-19 mortality were 1.91 (95%CI:1.02–3.58) and 2.54 (95%CI:1.22–5.25) respectively in total patients, and 2.58 (95%CI:1.16–5.75) and 3.89 (95% CI:1.62–9.32) respectively in the elderly. The HR of underweight for COVID-19 mortality was 4.58 (95%CI:1.56–13.48) in the elderly. For different metabolic statuses, both underweight, overweight and obesity had obviously negative association with COVID-19 mortality in total and elderly patients with MUS. However, no significance was found in non-elderly and patients with MHS.
Conclusion: Not only overweight or obesity, but also underweight can be associated with COVID-9 mortality, especially in the elderly and in patients with MUS. More large-scale studies are needed for patients with underweight and metabolically healthy overweight or obesity.

* Corresponding author. Institute of Geriatrics, Chinese PLA general Hospital, 28 Fuxing Road, Beijing, 100853, China.
** Corresponding author. 20 Dongdajie Road, Fengtai, Beijing, 100071, China.
*** Corresponding author. 28 Fuxing Road, Beijing, 100853, China.
E-mail addresses: liumiaolmbxb@163.com (M. Liu), chenyonger@126.com (Y. Chen), yhe301@sina.com (Y. He).
[1] These two authors contributed equally to this work.

https://doi.org/10.1016/j.numecd.2021.07.030

Introduction

Coronavirus disease 2019 (COVID-19) has remained a global pandemic since its onset, and seriously affects human health and the normal operation of economy and society [1]. And now the sign of viral mutations brings new uncertainties and challenges to the prevention and treatment of the disease. Previous studies demonstrate that old age, male and patients with comorbidities (such as cardiovascular diseases, diabetes, and hypertension) have a higher risk for disease progression and mortality [2].

Obesity, as the cause of many chronic diseases, is also observed to be closely associated to similar risks of COVID-19 [3]. In China, overweight is also one of important public health problems [4], and the prevalence of overweight and obesity are projected to increase to 540 million and 150 million by 2030, respectively [5]. Previous evidences based on chronic diseases have shown that individuals with metabolically healthy obesity (MHO), in spite of none consistent definition, did not have an increased risk of cardiovascular diseases, diabetes, and total mortality [6,7]. How metabolic abnormalities might affect the relationship between overweight or obesity and COVID-19 remains unclear. In addition, few studies focused on the effect of underweight, which also accounts for a certain proportion of Chinese population [8]. Thus, in this retrospective study, we aim to evaluate the relationship of BMI and COVID-19 among hospitalized patients, and further explore the association in different metabolically healthy and unhealthy statuses.

Methods

Study design and participants

This retrospective cohort study included all of the inpatients in one hospital of Wu Han between February 4, 2020 and followed up to April 14, 2020. A total of 3059 patients with COVID-19 infection were initially in the study, and 12 patients were actually not treated in this hospital because of other complications (such as dialysis). Then, patients who had incomplete BMI data (n = 21), BMI outlier (n = 1) and were younger than 18 years old (n = 6) were excluded. Of 3019 COVID-19 patients were divided into four groups: underweight (n = 151), normal weight (n = 1303), overweight (n = 1167) and obesity (n = 398) according to different BMI level. Further follow-up for mortality was carried out during hospitalization. The median follow-up time was 39 (IQR, 30–50) day. Fig. 1 was the flow chart of participants' inclusion. The study protocol was approved by the Institution Ethic Committee of PLA general hospital, and the requirement for informed consent was waived by the ethics Committee.

Data collection

The database was from medical records on hospitalization system of our hospital, with complete records of admission, diagnosis, treatment process and discharge. All related data including demographic information, medical history, computed tomography (CT) description, blood pressure, symptoms, height, weight and laboratory test were collected. Progress to mortality during follow up was confirmed by the physicians' course records. The extracted contents were conducted by trained engineer used Python and randomly selected 5% to double cheek by trained physicians to insure the accuracy.

Definition

Following the diagnosis criteria for novel coronavirus pneumonia (trial version 5–7) [9] published by the National Health Commission, patients was diagnosed based on typical clinical symptoms and chest CT findings and/or positive result of COVID-19 RNA and/or gene, and further divided into four types according to the severity of the disease. Criteria of critical type met any of the following items: (1) respiratory failure needing mechanical ventilation; (2) shock; (3) other organ failure needing monitor and treatment in an intensive care unit. Criteria of Severe type was: (1) respiratory distress ($\geq$30 beats per min); (2) finger oxygen saturation $\leq$93% at rest; (3) ratio of arterial partial pressure of oxygen (PaO_2) to oxygen concentration (FiO_2) $\leq$300 mmHg; (4) more than 50% progression of lesion over 24–48 h in pulmonary imaging. Moderate or mild patients was diagnosed with COVID-19 but without those severe or critical features.

Body mass index (BMI) was calculated as weight (kg) divided by height (m^2) measured in indoor clothing without shoes. Given the body characteristic of the Asian population, patients were categorized into four groups according the BMI level [10]: (1) underweight: BMI$<$18.5 kg/m^2,(2) normal weight: 18.5$\leq$ BMI $<$24 kg/m^2, and (3) overweight: 24$\leq$ BMI $<$28 kg/m^2, and (4) obesity: BMI $\geq$28 kg/m^2. Diabetes, hypertension, dyslipidemia, chronic bronchitis or chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD) and cerebrovascular disease were defined based on the patient's self-reported medical history, received drug treatment, or the discharge diagnosis determined by the doctor according to related guidelines. History of respiratory disease was defined as patients who had chronic bronchitis or COPD. History of cardiovascular and cerebrovascular disease was defined as had CHD or cerebrovascular disease.

Metabolically unhealthy status (MUS) was defined according to the harmonizing joint definition of metabolic syndrome [11]. Since waist circumference and blood lipids were not included in the medical records, we defined MUS as at least had one of the metabolic abnormalities (diabetes, hypertension, dyslipidemia). Metabolically healthy status (MHS) was defined as no metabolic abnormality mentioned above.

Statistical analysis

For continuous variables, data were expressed as mean $\pm$ SD used One-Way ANOVA test and median (interquartile range, IQR) used Kruskal–Wallis H test for

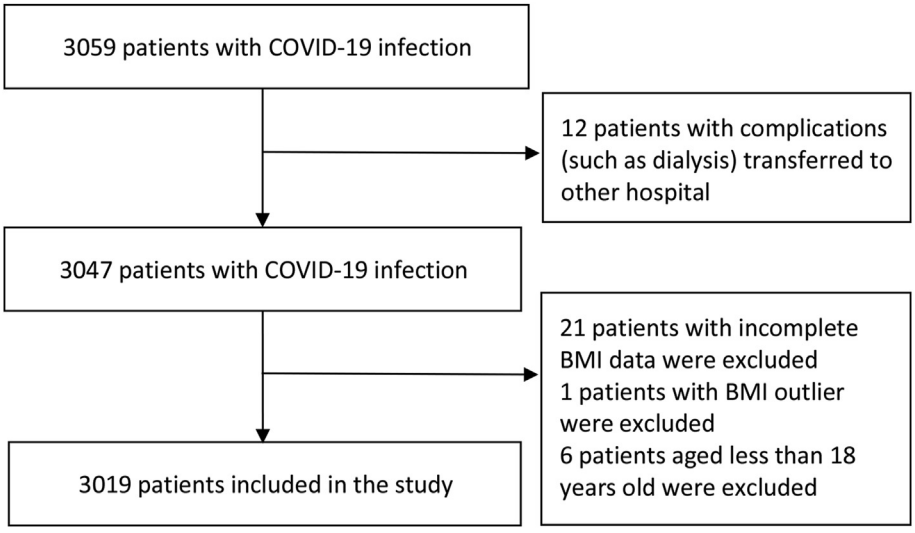

Figure 1 Flow chart of inclusion of patients.

comparisons in view of the non-normality. For categorical variables, data were expressed as number (%) and used χ^2 test for comparisons. Multivariable Cox proportional risk model was then performed to assess the association of BMI and follow-up mortality with COVID-19 and further stratified patients as metabolically healthy and unhealthy group.The hazard ratio (HR) and 95% confidence was calculated adjusted for statistical and clinical significant variables. A predefined subgroup stratified by age (65 years as the cutoff to define the elderly and the non-elderly group) was conducted. SPSS was used for data analysis and a two-sided P value < 0.05 was considered statistically significant.

Results

A total of 3019 inpatients with COVID-19 were included in our analysis, with 50.7% (1532) male and average aged 58.48 $\pm$ 14.29 years old. The average level of BMI was 24.21 $\pm$ 3.58 kg/m^2, and the proportions of underweight, normal weight, overweight and obesity significantly differed in age and MUS ($p < 0.001$) (Fig. 2). Non-elderly and patients with MUS had a higher proportion of overweight or obesity (53.3% and 57.9%, respectively), while elderly and patients with MHS had underweight (7.8% and 5.5%, respectively).

Demographic and symptomatic characteristics of each BMI group

The distribution of demographic and symptomatic characteristics in four BMI groups were compared in Table 1. The average level of blood pressure and proportion of fever, dry cough, dyspnea, CT description with ground-glass opacity, and hypertension showed an increasing trend along with the increasing BMI group ($p < 0.05$). However, patients with underweight had a highest proportion of history of respiratory, cardiovascular and cerebrovascular disease ($p < 0.01$). The mortality was much higher in patients with underweight or obesity (4%, $p = 0.001$). No difference was found in disease type of admission ($p > 0.05$).

Clinical laboratory characteristics of each BMI group

The laboratory characteristics in the four BMI groups presented in Table 2, and mostly revealed significant difference in addition to lymphocyte and neutrophil percentage, platelet count, PT, and APPT. The albumin level was lowest and BUN and D-dimer level were highest in underweight group, while the rest was relatively highest in overweight or obesity group ($p < 0.05$).HRs of BMI for mortality in patients with COVID-19

Table 3 showed the HRs and 95% CI of BMI for mortality with COVID-19. After adjusting for age, gender, disease type on admission, history of respiratory, cardiovascular and cerebrovascular disease, DBP, haemoglobin, CRP, creatinine, blood glucose, albumin, AST, LDH, and D-dimer, the findings tended to showed an increased trend ($HR > 1$)

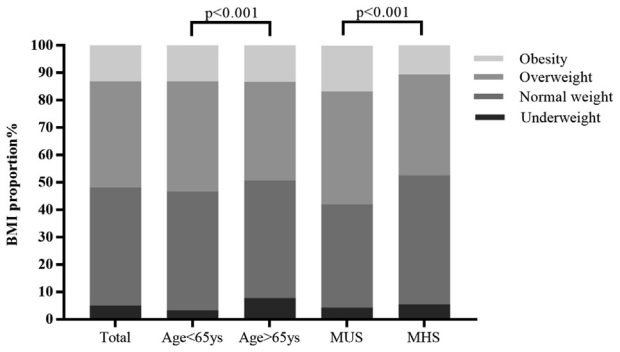

Figure 2 The distribution of BMI groups.

Table 1 Demographics and symptomatic characteristics of patients with COVID-19.

	Total (n = 3019)	Underweight (n = 151)	Normal weight (n = 1303)	Overweight (n = 1167)	Obesity (n = 398)	p value	p for trend
Age(year),mean ± SD	58.48 ± 14.29	65.87 ± 19.06	57.66 ± 14.55	58.41 ± 13.4	58.57 ± 13.8	<0.001	<0.001
Male,n(%)	1532(50.7)	43(28.5)	522(40.1)	709(60.8)	258(64.8)	<0.001	<0.001
Signs and symptoms							
DBP(mmHg),mean ± SD	81 ± 11	77 ± 11	80 ± 11	82 ± 11	82 ± 11	<0.001	<0.001
SBP(mmHg),mean ± SD	130 ± 16	128 ± 15	128 ± 16	131 ± 16	132 ± 16	<0.001	0.006
Fever,n(%)	2561(84.8)	110(72.8)	1103(84.7)	993(85.1)	355(89.2)	<0.001	<0.001
Diarrhea,n(%)	394(13.1)	14(9.3)	173(13.3)	167(14.3)	40(10.1)	0.080	0.809
Dry cough,n(%)	1561(51.7)	55(36.4)	658(50.5)	628(53.8)	220(55.3)	<0.001	<0.001
Dyspnea,n(%)	423(14.0)	21(13.9)	157(12.0)	169(14.5)	76(19.1)	0.005	0.002
Muscle ache,n(%)	658(21.8)	23(15.2)	278(21.3)	260(22.3)	97(24.4)	0.128	0.041
CT description							
Ground-glass opacity,n(%)	1859(61.6)	75(49.7)	798(61.2)	738(63.2)	248(62.3)	0.014	0.037
Patch shadow,n(%)	2033(67.3)	91(60.3)	881(67.6)	795(68.1)	266(66.8)	0.278	0.430
Comorbidities							
Metabolically unhealthy status,n(%)	1266(41.9)	55(36.4)	477(36.6)	522(44.7)	212(53.3)	<0.001	<0.001
Diabetes	528(17.5)	24(15.9)	212(16.3)	210(18.0)	82(20.6)	0.213	0.041
Hypertension	1052(34.8)	45(29.8)	382(29.3)	439(37.6)	186(46.7)	<0.001	<0.001
Dyslipidemia	89(2.9)	4(2.6)	31(2.4)	40(3.4)	14(3.5)	0.406	0.143
History of respiratory disease,n(%)	292(9.7)	30(19.9)	99(7.6)	114(9.8)	49(12.3)	<0.001	0.593
History of cardiovascular and cerebrovascular disease,n(%)	456(15.1)	40(26.5)	163(12.5)	186(15.9)	67(16.8)	<0.001	0.680
Outcomes							
Disease type of admission,n(%)						0.360	0.392
Mild-moderate	2203(73.0)	105(69.5)	968(74.3)	849(72.8)	281(70.6)		
Severe or critical	816(27.0)	46(30.5)	335(25.7)	318(27.2)	117(29.4)		
Mortality,n(%)	67(2.2)	6(4.0)	15(1.2)	30(2.6)	16(4.0)	0.001	0.012
Day of onset to death, median (IQR)	39(30–50)	39(29–48)	39(31–50)	39(29–51)	38(30–49)	0.814	–

Abbreviation:DBP, diastolic blood pressure; SBP, systolic blood pressure; IQR, interquartile range.

but did not reach significance when BMI used as continuous variable in the model. When used as categorical variables and normal weight as reference, the HR of overweight and obesity for mortality with COVID-19 was 1.91 (95%CI:1.02–3.58) and 2.54 (95%CI:1.22–5.25) in total patients.Similar result was observed in the elderly, and the HR was 2.58 (95%CI:1.16–5.75) and 3.89 (95% CI:1.62–9.32), respectively. And an apparent association was also found in elderly patients with underweight for mortality, the adjusted HR was 4.58 (95%CI:1.56–13.48). However, no significance was observed in the non-elderly.

HRs of BMI for mortality in metabolically healthy and unhealthy patients

We ascertained the association of BMI for follow-up COVID-19 mortality among patients with different metabolic statuses in Table 4. Adjusted for age, gender, disease type of admission, history of respiratory and cardiovascular and cerebrovascular disease, haemoglobin, CRP, creatinine, albumin, AST, LDH, and D-dimer, the association show an increased tendency (HR > 1) but without significance in patients with MHS. In patients with MUS, when compared to the normal weight patients, obvious significance of overweight and obesity for mortality were found in total patients, and corresponding HRs were 3.94 (95% CI:1.43–10.86) and 8.69 (95%CI:3.14–24.00), respectively. Similar significance was observed in the elderly. Additionally, the association of underweight for mortality in total and elderly patients were also observed, and corresponding HRs were 5.27 (95%CI:1.35–20.46) and 4.46 (95% CI:1.16–17.12), respectively.

Discussion

In this retrospective cohort study based on 3019 Chinese COVID-19 patients, the results revealed that overweight and obesity were independently associated with COVID-19 mortality. BMI had a U-shaped relationship among elderly patients, rather than a simple linear relationship. That is, both underweight and overweight or obesity were risk factors for COVID-19 mortality, independent of gender, comorbidities and other related covariates. More interestingly, these associations were more prominent in patients with MUS, while no statistically significance was found in patients with MHS.

Many studies have focused on the relationships between overweight or obesity and COVID-19 mortality, even several meta-analyses. The conclusions tend to be consistent that patients with overweight or obesity are at high risk of COVID-19 mortality [12–15]. In a meta-analysis of 6 studies showed that the overall risk (odds ratio) of patients with BMI of >25 kg/m^2 for COVID-19 mortality was 3.68 (95%CI: 1.54–8.83) [15]. Considering the characteristics of

Table 2 Laboratory parameters of patients with COVID-19.

	Reference values	Underweight (n = 151)	Normal weight (n = 1303)	Overweight (n = 1167)	Obesity (n = 398)	Total (n = 3019)	p value
Blood routine							
Haemoglobin(g/L), mean ± SD	130–175	111.38 ± 19.03	121.85 ± 16.37	126.28 ± 17.24	128.65 ± 16.14	123.93 ± 17.25	0.001
White blood cell count (109/L),median(IQR)	3.5–9.5	5.60(4.60–7.10)	5.70(4.60–6.90)	5.80(4.90–7.10)	5.80(4.80–7.20)	5.70(4.70–7.00)	<0.001
Lymphocyte percentage(%), mean ± SD	20–50	24.83 ± 10.94	26.71 ± 9.53	25.98 ± 10.15	26.30 ± 9.71	26.28 ± 9.88	0.081
Neutrophil percentage (%),mean ± SD	40–75	64.43 ± 12.41	62.84 ± 10.89	63.65 ± 11.60	63.33 ± 11.70	63.30 ± 11.36	0.190
Platelet count(109/L), mean ± SD	125–350	221.44 ± 83	233.79 ± 78.03	236.72 ± 84.55	231.52 ± 80.28	234.01 ± 81.18	0.150
Biochemical detection							
CRP(mg/L), median(IQR)	0–4	2.57(0.51–23.23)	1.97(0.67–6.38)	2.35(1.03–9.72)	2.81(1.50–10.48)	2.33(0.86–8.52)	<0.001
BUN (mmol/L),median(IQR)	2.6–7.5	4.75(3.85–6.86)	4.41(3.61–5.37)	4.41(3.67–5.34)	4.44(3.73–5.33)	4.41(3.64–5.40)	0.001
Uric acid (μmol/L), mean ± SD	142–340	260.79 ± 96.24	271.23 ± 80.74	299.77 ± 92.13	314.36 ± 99.84	287.43 ± 90.37	<0.001
Creatinine (μmol/L), median(IQR)	41–73	61.40(52.30–71.90)	62.90(54.10–72.40)	65.70(57.00–76.90)	68.00(58.58–79.25)	64.50(55.70–75.00)	<0.001
Blood glucose (mmol/L), median(IQR)	3.9–6.11	4.82(4.44–5.62)	4.81(4.41–5.42)	4.93(4.56–5.72)	5.11(4.64–6.07)	4.89(4.49–5.64)	<0.001
Albumin(g/L), mean ± SD	40–55	36.27 ± 4.56	37.32 ± 4.29	37.35 ± 4.27	37.19 ± 4.40	37.26 ± 4.32	0.030
ALT (IU/L), median(IQR)	7–40	14.60(10.30–23.30)	21.50(13.80–33.30)	24.60(17.00–39.50)	29.95(18.70–45.03)	23.30(15.10–37.70)	<0.001
AST(IU/L), median(IQR)	7–45	19.60(15.30–25.60)	19.70(15.40–25.20)	19.80(16.00–27.20)	21.15(16.90–30.65)	19.80(15.80–26.50)	<0.001
γ-GT(IU/L), median(IQR)	7–45	21.80(14.10–32.80)	28.30(18.30–43.20)	31.30(22.70–52.00)	36.35(25.98–59.73)	30.20(20.50–47.90)	<0.001
LDH(IU/L), median(IQR)	120–250	179.10(149.50–217.80)	179.10(152.50–207.60)	179.10(155.40–217.00)	186.00(163.35–226.33)	179.10(155.10–215.00)	<0.001
TBIL(IU/L), median(IQR)	0–14	9.30(7.00–12.20)	9.40(7.20–11.70)	9.50(7.60–12.30)	10.05(7.90–13.00)	9.50(7.40–12.10)	<0.001
DBIL(IU/L), median(IQR)	0–8	3.40(2.40–4.60)	3.20(2.40–4.00)	3.30(2.60–4.50)	3.60(2.80–4.90)	3.30(2.50–4.40)	<0.001
Coagulation indices							
PT(seconds), median(IQR)	9.2–15	12.97(12.46–13.78)	12.83(12.36–13.36)	12.83(12.40–13.40)	12.83(12.30–13.43)	12.83(12.38–13.41)	0.104
APPT(seconds), median(IQR)	21–37	28.06(27.14–30.62)	28.03(26.54–29.6)	28.03(26.57–29.55)	28.03(26.67–29.36)	28.03(26.6–29.59)	0.117
D-dimer (mg/L), median(IQR)	0–0.55	0.51(0.30–1.22)	0.42(0.24–0.69)	0.42(0.26–0.74)	0.42(0.27–0.68)	0.42(0.25–0.72)	0.002

Abbreviation: IQR, interquartile range; CRP, Creactive protein; BUN, urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamine transaminase; LDH, lactate dehydrogenase; TBIL, total bilirubin; DBIL, direct bilirubin; PT, prothrombin time; APPT, activated partial thromboplastin time.

Table 3 HRs and 95% CI of BMI for mortality in patients with COVID19.

		Crude HR(95%CI)	p value	Model1 HR(95%CI)	p value	Model2 HR(95%CI)	p value
BMI as continuous variable							
Total	BMI	1.07(1.00−1.14)	0.052	1.07(1.00−1.14)	0.044	1.03(0.97−1.11)	0.334
<65yrs	BMI	1.11(0.98−1.27)	0.110	–		1.12(0.93−1.35)	0.251
≥65yrs	BMI	1.06(0.99−1.14)	0.118	1.04(0.96−1.12)	0.351	1.01(0.93−1.09)	0.872
BMI as categorical variable							
Total	Normal	1(ref)		1(ref)		1(ref)	
	Underweight	3.61(1.40−9.32)	0.008	1.75(0.65−4.71)	0.266	1.82(0.65−5.07)	0.252
	Overweight	2.20(1.19−4.10)	0.013	1.96(1.05−3.67)	0.036	1.91(1.02−3.58)	0.043
	Obesity	3.51(1.73−7.10)	<0.001	3.01(1.47−6.15)	0.002	2.54(1.22−5.25)	0.012
<65yrs	Normal	1(ref)		1(ref)		1(ref)	
	Underweight	–		–		–	
	Overweight	2.87(0.91−9.03)	0.071	2.87(0.91−9.03)	0.071	2.15(0.56−8.15)	0.262
	Obesity	0.85(0.10−7.58)	0.882	0.85(0.10−7.58)	0.882	1.53(0.14−16.57)	0.729
≥65yrs	Normal	1(ref)		1(ref)		1(ref)	
	Underweight	3.22(1.19−8.71)	0.021	2.58(0.94−7.02)	0.065	4.58(1.56−13.48)	0.006
	Overweight	1.98(0.94−4.16)	0.072	1.86(0.88−3.92)	0.102	2.58(1.16−5.75)	0.021
	Obesity	4.22(1.94−9.19)	<0.001	4.31(1.98−9.38)	<0.001	3.89(1.62−9.32)	0.002

Model1 adjusted for age and gender; Model2 adjusted Model1 and disease type of admission, history of respiratory and cardiovascular and cerebrovascular disease,DBP,hemoglobin,CRP, creatinine, blood glucose, albumin,AST, LDH,D-dimer.

the Asian population, our study with the cutoff of 24 kg/m^2 got similar results. And some studies in younger patients also have show the negative association, but no significance was found in our results [16]. The biological mechanisms linking overweight or obesity and COVID-19 are still unclear, but the critical role of current acknowledged hypotheses is about low-grade inflammation and poor immune response [17]. Epidemiological evidences reported that the elderly have a higher risk of COVID-19 occurrence and adverse outcomes [18], and combining with overweight or obesity may be one of the explanations for the age difference.

The linear dose−response association between overweight or obesity and COVID-19 mortality basically reaches a consensus [19,20], but the impact of underweight is still controversial. Our result show that underweight was also associated with COVID-19 mortality in the elderly, that is to say, the association between BMI and COVID-19 mortality in the elderly is not a simple linear but a U-shaped curve. The elderly with BMI of <18.5 kg/m^2 are 4.58-fold as likely to have mortality as those with normal weight, independent of gender and other potentially confounding factors. This U-shaped curve was consistent with the study based on 10,861 adult patients with COVID-19 infection in New York [21]. And some studies also identified a U-shaped association between BMI and COVID-19 mortality in the middle-aged and elderly, although the CI was a little wider ($p > 0.05$) in underweight group [22−24]. Non-linear relationship was also found in younger patients, including the children [25]. As we know, low body weight partly reflects poor nutritional status, which may be related to poor nutrient intake and dysfunction in leptin signaling and further affect the immune response [26]. This result implies that studies are needed to identify such uncertain association and underlying mechanisms. Meanwhile, proper attention should also focus on the elderly patients with underweight in clinical practice.

Table 4 HRs of BMI for mortality in metabolically healthy and unhealthy COVID19 patients.

		Metabolically health HR (95%CI)	p value	Metabolically unhealth HR (95%CI)	p value
Total	Normal	1(ref)		1(ref)	
	Underweight	2.33(0.47−11.65)	0.303	5.27(1.35−20.46)	0.016
	Overweight	1.22(0.44−3.37)	0.697	3.94(1.43−10.86)	0.008
	Obesity	–		8.69(3.14−24.00)	<0.001
<65yrs	Normal	1(ref)		1(ref)	
	Underweight	–		–	
	Overweight	2.41(0.42−13.79)	0.323	10.81(0.95−122.68)	0.055
	Obesity	–		31.67(0.03−39437.44)	0.342
≥65yrs	Normal	1(ref)		1(ref)	
	Underweight	3.00(0.49−18.23)	0.234	4.46(1.16−17.12)	0.030
	Overweight	1.67(0.40−6.95)	0.484	2.44(0.81−7.29)	0.112
	Obesity	–		6.49(2.35−17.95)	<0.001

Adjusted for age,gender, disease type of admission, history of respiratory and cardiovascular and cerebrovascular disease, hemoglobin,CRP, creatinine, albumin,AST, LDH,D-dimer.

Besides, in this cohort study, patients with MUS had higher HRs for COVID-19 mortality regardless of BMI groups. Available studies also reported that patients with one or more pre-existing comorbidities would increase the mortality rate [27,28]. However, the association between underweight, overweight or obesity and COVID mortality reduced to null in patients with MHS. Previous studies based on chronic diseases have revealed that not all the population with obesity had metabolic abnormalities, which is the so-called harmless or healthy obesity [6]. Current studies have more focused on patients with overweight or obesity and various comorbidities, and there was little evidence on the patients with MHO. Whether the similar conclusion applies to COVID-19, a novel disease, is not yet clear. Our result cannot confirm this complicated association because of the wide and overlapping confidence interval. Hence, it is important to conduct large-scale prospective studies to prove the evidence and the underlying mechanisms, especially considering the impact of lifestyle. An available study has showed that physical inactivity was the biggest modifiable risk factor for severe COVID-19 outcomes, other than advanced age and organ transplant [29].

This was a cohort study with full sample from one center, and disease from onset to mortality (hard endpoint) were used to calculate time variable to avoid the time lag in transfer treatment. However, this study had the following limitations. First, in this retrospective study design, the definition of MUS was not exactly the same as the guidelines, due to lacking of blood lipid level. And due to the self-report or doctor's diagnosis, there could be a misclassification bias in the metabolically healthy or unhealthy status. Second, the measurement of obesity only used BMI level but without the data of WC or visceral fat, which was not comprehensive enough. And the definition of obesity, using a cutoff BMI >28 kg/m^2 for Asian populations, may influence the data comparison from different countries. Third, although a full sample from one center was included, the sample size of patients with underweight was still small (the power was 0.72 calculated by PASS 15.0 software). More large-scale studies are needed. Finally, we collected all data during hospitalization and did not conduct a long-term follow up after discharge.

In summary, this cohort study showed that both overweight or obesity and underweight can be associated with the COVID-9 mortality, especially in the elderly and patients with MUS. Hence, in addition to overweight or obesity, proper attention should also be paid to patients with underweight in clinical practice. Future large-scale prospective studies for patients with underweight and metabolically healthy overweight or obesity are still essential.

Authors' contribution

Conceptualizing of the study: ZJ, LM, HY, WCJ and CY; collecting and recording of the demographic, clinical, and laboratory data: ZJ, WSS, YSS, HK and JWP; analyzing of the data: ZJ and LX; drafting of the manuscript: ZJ and LX; and revising of all subsequent versions of the manuscript: ZJ, LX, LM, HY and CY. All authors read and approved the final manuscript.

Data availability

The database of the current study is not publicly available.

Declaration of competing interest

The author has no conflict of interest to declare.

Acknowledgments

The paper was funded by military fund (BWS20J009). We are grateful to all the nursing, medical, and health care professionals for their dedication in caring for the patients included in this study.

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