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LETTER TO THE EDITOR

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The J-shaped relationship between body mass index and mortality in patients with COVID-19: A dose-response meta-analysis

The coronavirus disease 2019 (COVID-19) pandemic has caused a considerable number of deaths. Identifying individuals at higher risk of critical illness and death is critical for planning prevention strategies, such as assigning vaccination priority. Several studies have linked obesity to more severe illness and higher mortality in COVID-19 patients.[1–4] However, the relationship between underweight and COVID-19 mortality remains inconclusive; previous dose-response meta-analyses did not include the underweight population in their evidence synthesis.[5,6] We conducted a systematic review and dose-response meta-analysis to investigate the relationship between body mass index (BMI) and mortality in both obese and underweight patients with COVID-19.

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[7] The protocol was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (registration number: INPLASY2020120090). We searched the PubMed, Embase, Cochrane Library, Scopus and Web of Science databases from inception until February 11, 2021 using the keywords "COVID-19", "body mass index", "obesity", "overweight", "underweight" and "mortality." Details of the search strategies and article selection process are shown in the Supplementary Materials. We included studies if they: (i) reported mortality risk for patients with COVID-19; (ii) divided patients into at least three different BMI categories and reported the relative risk (RR) of mortality for each category; and (iii) reported adjusted estimates (adjustment for age and sex at minimum). We only included studies that reported at least three BMI categories and the numbers of patients and deaths for each BMI category to investigate a potential nonlinear trend in dose-response meta-analysis. Both clinical trials and observational studies that provided sufficient data were eligible. Review articles, case reports, editorials, letters and conference abstracts were excluded. Studies that reported only crude estimates without adjusting for confounders were excluded. The primary outcome was mortality. Three reviewers (H.K.H., K.B. and D.P.H.) independently assessed the relevant articles to identify eligible studies, three reviewers (H.K.H., K.B. and D.P.H.) independently extracted the data, and two reviewers (K.B. and D.P.H.) assessed the quality of the studies using the Newcastle-Ottawa Scale.[8] Discrepancies were resolved via discussion among the study team.

We first conducted a meta-analysis for the difference in the risk of mortality between the highest and the lowest category of BMI using a DerSimonian and Laird random-effects model (the high vs. low meta-analysis).[9] We then conducted the random-effects dose-response meta-analysis to estimate the linear and nonlinear trends in the association between BMI and mortality.[10] The linear trend was estimated by using the generalized least squares model described by Greenland and Longnecker.[11] We used the two-stage approach to estimating the nonlinear trend by first fitting a restricted cubic splines model with knots at the 10th, 50th and 90th percentiles for each study and then undertaking a multivariate meta-analysis for the model variables.[12] The Wald test was used to test for nonlinearity by comparing the model fit between the linear and nonlinear models. When the BMI level was presented as a range, the dose was assigned using the midpoint of the upper and lower boundaries; for the open-ended highest and lowest BMI categories, the width between the boundaries was assumed to be equal to that of the adjacent category. RRs for mortality with 95% confidence intervals (CIs) were used to report the outcome. For the dose-response meta-analysis, a sensitivity analysis was conducted by pooling only studies specifically evaluating underweight patients (BMI < 18.5 kg/m^2). We assessed heterogeneity among studies with I^2 statistics. The heterogeneity was considered low, moderate and high for I^2 < 50%, 50% to 75%, and > 75%, respectively.[13] Potential publication bias was assessed using funnel plots, Egger's test and Begg's test.[14,15] A leave-one-out sensitivity analysis was performed to evaluate the influence of each study on the overall pooled estimate. All statistical tests were two-sided, with the significance level set at 5%. Statistical analyses were conducted using Stata version 15.1 (StataCorp, College Station, Texas) and R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Institutional ethical approval was not required because this was a meta-analysis of primary published studies only.

Of the 7443 potential studies screened, 4455 duplicate studies, 2393 irrelevant studies, and 567 studies without usable data on this topic were excluded, yielding 28 studies comprising 112 682 patients for the analysis (Figure S1).[1,16–42] The characteristics of the included studies are summarized in Table 1. The mean ages of the patients ranged from 51 to 71 years, the proportion of female participants ranged from 9% to 67%, and the sample sizes ranged from 191 to 25 952. The majority of the included studies were conducted in the United States and Europe and were retrospective cohort studies. Among them, 13 studies evaluated underweight patients specifically.[16,18,19,21,22,24,26,28–31,34,41] All the included studies had an

TABLE 1 Summary of the 28 studies included in the dose-response meta-analysis

First author and year	Study design	Country	Study population	Patient inclusion period	Sample size, n	Mean age, years	Female, %	BMI categories, kg/m^2	Outcome measurement
Anderson 2020[16]	Retrospective cohort	United States	Adults hospitalized with laboratory confirmed SARS-CoV-2 infection in NewYork-Presbyterian /Columbia University Irving Medical Centre and the affiliated Allen Hospital	March 10 to April 24, 2020	2466	67[a]	42	<18.5; 18.5–24.9; 25.0–29.9; 30–34.9; 35–39.9; ≥40	In-hospital mortality
Baronia 2020[17]	Retrospective cohort	Italy	Patients tested positive for SARS-CoV-2 RNA admitted to the Fondazione Poliambulanza di Brescia hospital	March 1 to April 11, 2020	191	66[a]	28.1	<25; 25–29.9; ≥30	In-hospital mortality
Czernichow 2020[18]	Prospective cohort	France	Patients tested positive for SARS-CoV-2 and hospitalized in one of the Assistance Publique-Hôpitaux de Paris hospitals	February 1 to April 30, 2020	5795	59.8	34.6	<18.5; 18.5–24.9; 25–29.9; 30–34.9; 35–39.9; ≥40	30-day mortality
Eastment 2020[19]	Retrospective cohort	United States	All VA patients tested positive for SARS-CoV-2 in the inpatient or outpatient setting	February 28 to June 21, 2020	25 952	61.7	10.9	<18.5; 18.5–24.9; 25–29.9; 30–34.9; 35–39.9; ≥40	30-day mortality
Fai2r 2020[20]	Retrospective cohort	France	COVID-19 patients with inflammatory rheumatic disease	Feb 24 to April 17, 2020	694	56.1	66.6	<30; 30–39.9; ≥40	21-day mortality
Goyal 2020[21]	Retrospective cohort	United States	Persons hospitalized with confirmed COVID-19 at two new York City hospitals	March 3 to may 15, 2020	1687	66.5[a]	40	<18.5; 18.5–24.9; 25–29.9; 30–39.9; ≥40.0	In-hospital mortality
Gu 2020[22]	Retrospective cohort	United States	Patients tested or treated for COVID-19 at the University of Michigan (Michigan medicine)	March 10 to April 22, 2020	1139	53.0	53.4	<18.5; 18.5–24.9; 25–29.9; ≥30	Both inpatient and nonhospitalized mortality
Gupta 2020[23]	Retrospective cohort	United States	Adults with COVID-19 who were admitted to participating ICUs at 65 hospitals across the United States	March 4 to April 4, 2020.	2215	60.5	35.2	<25; 25–29.9; 30–34.9; 35–39.9; ≥40	28-day in-hospital mortality

TABLE 1 (Continued)

First author and year	Study design	Country	Study population	Patient inclusion period	Sample size, n	Mean age, years	Female, %	BMI categories, kg/m^2	Outcome measurement
Hajifathalian 2020[24]	Retrospective cohort	United States	Adult patients admitted with confirmed COVID-19 in two hospitals (an academic tertiary care referral centre and a smaller community hospital) in New York City	March 4 to April 9, 2020	770	63.5	39	<18.5; 18.5–29.9; ≥30	In-hospital mortality
Halasz 2020[25]	Retrospective cohort	Italy	Patients with laboratory-confirmed COVID-19 treated with invasive ventilation and admitted to the ICU of Guglielmo da Saliceto Hospital in Piacenza (Italy)	February to April, 2020	242	64	18.2	18.5–24.9; 25–29.9; 30–34.9; 35–39.9; ≥40	30-day mortality
Hendren 2021[26]	Retrospective cohort	United States	Patients hospitalized with COVID-19 at 88 US hospitals enrolled in the American Heart Association's COVID-19 cardiovascular disease registry	Up to July 2020	7606	63[a]	45	<18.5; 18.5–24.9; 25–29.9; 30–34.9; 35–39.9; ≥40	In-hospital mortality
Iannelli 2020[27]	Retrospective cohort	France	Patients with morbid obesity admitted for COVID-19	January 1 to may 15, 2020	8286	59.1	48.2	30–39.9; 40–50; >50	COVID-19-related death
Ioannou 2020[28]	Retrospective cohort	United States	VA enrollees tested positive for SARS-CoV-2 identified using data from the Veterans' Affairs corporate data warehouse	February 28 to may 14, 2020	10 131	63.6	9	<18.5; 18.5–24.9; 25–29.9; 30–34.9; ≥35	All-cause mortality at any time after the index date
Kabarriti 2020[29]	Retrospective cohort	United States	Patients with COVID-19 presented for care to the Montefiore Medical Centre whether or not they were admitted as inpatients	March 14 to April 15, 2020	5902	58[a]	53	<18.5; 18.5–34.9; ≥35	All-cause mortality (before April 27, 2020)
Kim 2020[30]	Retrospective cohort	Korea	Confirmed COVID-19 patients, collected by the Centres for Disease Control and Prevention of Korea	All participants released from isolation by 30 April, 2020	4057	Not reported	58	<18.5; 18.5–22.9; 23–24.9; ≥25	Mortality during follow-up period
Kim 2021[31]	Retrospective cohort	United States	Patients with COVID-19 admitted to 12 Northwell	March 1 to April 27, 2020	10 861	65[a]	40.5	<18.5; 18.5–24.9; 25–29.9; 30–	In-hospital mortality

(Continues)

TABLE 1 (Continued)

First author and year	Study design	Country	Study population	Patient inclusion period	Sample size, n	Mean age, years	Female, %	BMI categories, kg/m^2	Outcome measurement
			health system acute-care hospitals in New York					34.9; 35–39.9; ≥40	
Klang 2020[32]	Retrospective cohort	United States	Patients with COVID-19 who were hospitalized in a large academic hospital system in New York City	March 1 to May 17, 2020	3406	Not provided[b]	42.4	<30; 30–39.9; ≥40	In-hospital mortality
Nakeshbandi 2020[33]	Retrospective Cohort	United States	Patients with COVID-19 hospitalized at SUNY downstate health sciences University in New York (a COVID-19-only hospital)	March 10 to April 13, 2020	504	68	48	18.5–24.9; 25–29.9; ≥30	30-day in-hospital mortality
Nimkar 2020[34]	Retrospective case series	United States	Patients with COVID-19 admitted to a teaching community hospital in new York City	March 10 to may 13, 2020	370	71[a]	44.3	<18.5; 18.5–24.9; 25–29.9; ≥30	In-hospital mortality
Olivas-Martínez 2021[35]	Prospective cohort	Mexico	Consecutive adult patients hospitalized with severe confirmed COVID-19 pneumonia at a SARS-CoV-2 referral Centre in Mexico City	February 26 to June 5, 2020	800	51.9	39	18.5–24.9; 25–29.9; 30–34.9; 35–39.9; ≥40	In-hospital mortality
Palaiodimos 2020[36]	Retrospective cohort	United States	First 200 patients who presented to the emergency room and were admitted to the inpatient medicine service or ICU with laboratory-confirmed COVID-19 at the Montefiore Medical Centre	March 9 to March 22, 2020	200	64[a]	51	<25; 25–34; ≥35	In-hospital mortality
Petrilli 2020[37]	Prospective cohort	United States	Patients with confirmed COVID-19 at NYU Langone Health, which includes more than 260 outpatient office sites and four acute care hospitals	March 1 to April 8, 2020	5279	54[a]	50.5	<25; 25–29.9; 30–39.9; ≥40	In-hospital mortality
Rottoli 2020[38]	Retrospective cohort	Italy	Patients admitted to the hospital who had a confirmed COVID-19 diagnosis who were hospitalized in Sant'Orsola Hospital in Bologna, Italy	March 1 and April 20, 2020.	482	66.2	37.3	<30; 30–34.9; ≥35	30-day mortality

TABLE 1 (Continued)

First author and year	Study design	Country	Study population	Patient inclusion period	Sample size, n	Mean age, years	Female, %	BMI categories, kg/m^2	Outcome measurement
Schmidt 2021[39]	Prospective cohort	France, Switzerland, and Belgium	Patients admitted to the ICU with laboratory-confirmed SARS-CoV-2 infection	February 25 to may 4, 2020	4244	63[a]	26	<25; 25–29.9; 30–34.9; 35–39.9; ≥40	90-day mortality
Shah 2020[40]	Retrospective cohort	United States	All hospitalized patients with confirmed COVID-19 at Phoebe Putney Health System (three Phoebe Putney hospitals)	March 2 to may 6, 2020	522	63[a]	58.2	<30; 30–39.9; ≥40	In-hospital mortality
Smati 2021[1]	Retrospective cohort	France	Patients with type 2 diabetes and confirmed COVID-19 admitted to 68 French hospitals	10 March to April 10, 2020	1965	70.1	35.5	18.5–24.9; 25–29.9; 30–34.9; ≥35	7-day mortality
Tartof 2020[41]	Retrospective cohort	United States	Kaiser Permanente Southern California members diagnosed with COVID-19 by diagnostic codes or positive laboratory test results	February 13 to May 2, 2020	6916	49.1	55	<18.5; 18.5–24.9; 25–29.9; 30–34.9; 35–39.9; 40–44.9; ≥45	21-day mortality
Yoshida 2021[42]	Retrospective cohort	United States	Sequentially hospitalized adults admitted for COVID-19 at two tertiary care academic hospitals in New Orleans, LA	February 27 to July 15, 2020	776	60.5[a]	61.4	<25; 25–29.9; 30–34.9; 35–39.9; ≥40	In-hospital mortality

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; VA, Veterans Affairs; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

[a]Median is presented.

[b]572 patients were younger than 50 years and 2834 patients were older than 50 years.

acceptable quality, with a Newcastle-Ottawa Scale score of ≥7 points (Table S1).

In the high versus low meta-analysis, we found that COVID-19 patients with a high BMI had an increased risk of mortality (pooled RR 1.33, 95% CI 1.15–1.53; $P < 0.001$), with moderate heterogeneity ($I^2 = 54.2\%$; Figure S2). There was no evidence of publication bias according to Egger's test ($P = 0.270$), Begg's test ($P = 0.260$), or the funnel plot (Figure S3). The leave-one-out sensitivity analysis demonstrated that the pooled RR was robust (Figure S4).

In the dose-response meta-analysis, a positive dose-response relationship between BMI and mortality was found based on the linear model. The mortality of patients with COVID-19 increased by 1.6% for each 1-kg/m^2 increase in BMI (pooled RR 1.016, 95% CI 1.008–1.025), with high heterogeneity ($I^2 = 75.9\%$). However, a significant nonlinear relationship between BMI and mortality was observed (Wald test: $P_{\text{non-linearity}} < 0.001$). We demonstrated a J-shaped curve, indicating that both underweight and obese patients had a higher mortality than those with normal weight (Figure 1A). A BMI of approximately 27 kg/m^2 appeared to be associated with the lowest mortality risk. Using a BMI of 15 kg/m^2 as the reference, the RRs for mortality decreased with BMI initially, and this trend continued until a BMI of approximately 27 kg/m^2 (RR 0.836, 95% CI 0.708–0.987). The relationship between BMI and mortality was then reversed, and an upward trend was observed when BMI exceeded 27 kg/m^2; the RRs at BMI values of 30, 35, 40 and 45 kg/m^2 were 0.855 (95% CI 0.707–1.033), 0.965 (95% CI 0.785–1.186), 1.166 (95% CI 0.942–1.443) and 1.443 (95% CI 1.152–1.807), respectively. There was a moderate between-study heterogeneity ($I^2 = 62.3\%$). In the sensitivity analysis of the 13 studies with data on underweight patients, the J-shaped relationship between BMI and mortality remained unchanged, and the nonlinear fit was significantly better than the linear fit (Figure 1B), further supporting the robustness of our findings.

To our knowledge, this is the first dose-response meta-analysis to demonstrate a J-curved relationship between BMI and COVID-19 mortality, indicating that both underweight and obese COVID-19 patients had a higher mortality risk than patients with normal weight. Our findings are supported by previous studies which suggested a more severe respiratory virus infection or respiratory mortality in both underweight and obese patients.[43–45] We found that overweight patients (BMI 25-30 kg/m^2) seemed to have the lowest COVID-19 mortality risk, which was compatible with some previous evidence evaluating all-cause mortality in the general population.[46] However, the observed association between overweight and lower mortality may be subject to the problems of reverse causation and confounding by smoking or other confounders discussed previously in the literature.[47] As our meta-analysis comprises observational studies only, causality and underlying mechanisms could not be explored and still require further investigation. Despite these limitations, our findings have important public health implications. Awareness of vulnerable populations is critical when developing strategies for prevention, control, and treatment in the current pandemic. For example, the supply of COVID-19 vaccines is limited worldwide; thus, determining the vaccine priority group was a crucial issue. Patients with obesity are already considered a risk group for assigning high vaccine priority,[48,49] but underweight patients have not received comparable attention. Our meta-analysis shows a poor prognosis of both underweight and obese COVID-19 patients, so we suggest that the underweight should also be considered an at-risk group when assigning vaccine priority.

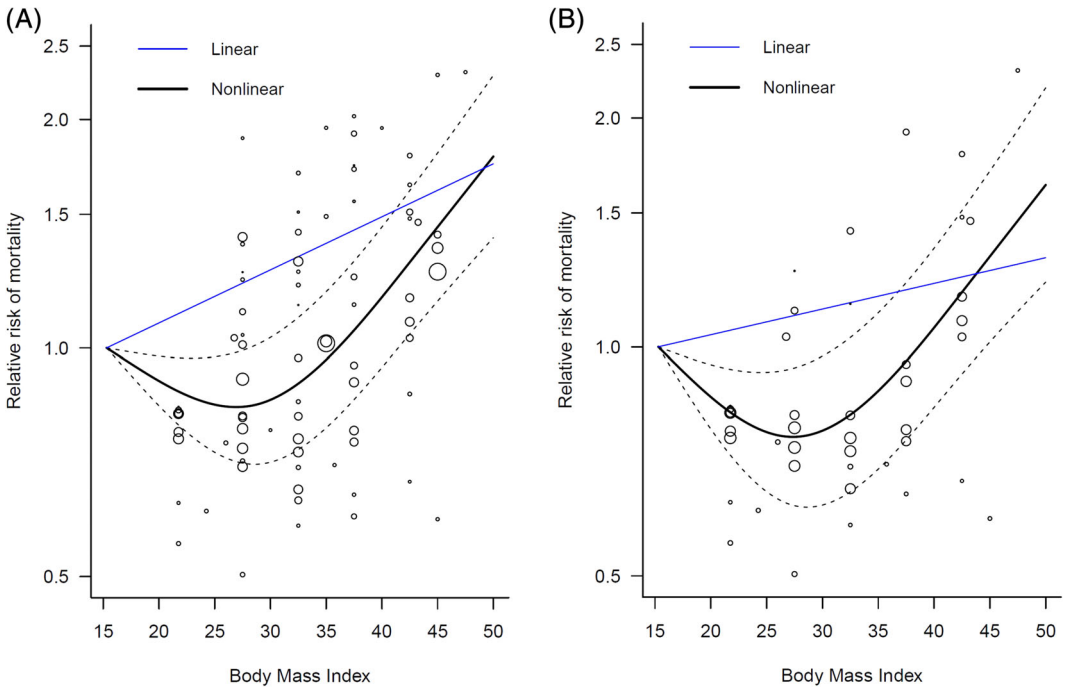

FIGURE 1 Dose-response relationship between body mass index and mortality in patients with COVID-19. (A) Full analysis using all studies listed in Table 1. (B) Sensitivity analysis that included only 13 studies with specific data on underweight patients

This meta-analysis has some limitations. First, the majority of the included studies were retrospective, the presence of unadjusted confounders may have biased the relationship between BMI and mortality, and we were unable to determine whether there was a causal relationship between body weight and COVID-19 mortality. Second, the BMI thresholds for overweight and obesity differed between Asian and Western countries; however, only one Asian study met the inclusion criteria and thus we could not conduct a subgroup analysis of Asian populations. Moreover, the relationship between BMI and the risk of COVID-19 has been found to differ according to ethnicity.[50] The differences in obesity rates may explain some of the variations in the COVID-19 mortality rates among countries.[51] Owing to these limitations, more high-quality studies from different countries and ethnic groups are necessary to validate our findings.

KEYWORDS

body mass index, COVID-19, meta-analysis, mortality, obesity, underweight

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AUTHOR CONTRIBUTIONS

Author contributions were as follows. Study conception and design: Huei-Kai Huang and Yu-Kang Tu. Acquisition of data: Huei-Kai Huang, Khulood Bukhari, Carol Chiung-Hui Peng, Duan-Pei Hung and Rachel Huai-En Chang. Analysis and interpretation of data: Huei-Kai Huang, Ming-Chieh Shih and Yu-Kang Tu. Preparation of manuscript: Huei-Kai Huang and Yu-Kang Tu. Critical revisions: Huei-Kai Huang, Ming-Chieh Shih, Shu-Man Lin, Kashif M. Munir and Yu-Kang Tu. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.