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.

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Original article

Body mass index and its association with COVID-19 clinical outcomes: Findings from the Philippine CORONA study

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SUMMARY

Background and aims: To explore the association between body mass index (BMI) and adverse outcomes in a large cohort of patients with coronavirus disease 2019 (COVID-19).
Methods: This is a secondary analysis of a 37-site, nationwide, multicenter, retrospective cohort study that investigated the clinical and neurological outcomes of adult patients with confirmed COVID-19 admitted from February to December 15, 2020.
Results: We analyzed 4,463 patients with BMI and outcome data. A total of 790 (17.7%) and 710 (15.9%) had the primary outcome of in-hospital mortality and need for invasive mechanical ventilation (IMV), respectively. There was no significant association between WHO BMI groups and these outcomes. Using Asia-Pacific cutoffs showed a significant association between obesity and in-hospital mortality risk ($P = 0.012$). Being underweight was an independent predictor of prolonged IMV requirement regardless of BMI criteria used ($P < 0.01$). Obesity correlated with the need for intensive care unit admission using Asia-Pacific cutoffs ($P = 0.029$). There was a significant association between any BMI abnormality and odds of severe/critical COVID-19 ($P < 0.05$). Obese patients with concomitant acute neurological presentation/diagnosis during their COVID-19 admission were shown to have lower odds of neurologic recovery ($P < 0.05$).
Conclusions: We found BMI abnormalities to be associated with several adverse clinical and neurologic outcomes, although such associations may be more evident with the use of race-specific BMI criteria.

Abbreviations: BMI, body mass index; CORONA, COVID-19 Outcomes: a Retrospective study Of Neurological manifestations and Associated symptoms; COVID-19, coronavirus disease 2019; HR, hazard ratio; IMV, invasive mechanical ventilation; IQR, interquartile range; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory coronavirus 2; WHO, World Health Organization.

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1. Introduction

More than a year since its declaration as a pandemic, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) continues to pose significant threats to public health worldwide [1]. As of January 29, 2022, the Philippines, a developing Southeast Asian country with an estimated population of 110 million people, has documented a total of 3,545,680 laboratory-confirmed cases, with 202,864 active infections and 53,891 deaths [2]. As local and global cases continue to rise, so do their negative impact on the country's strained healthcare system [3]. As such, the determination of clinical prognostic factors for patient risk stratification, management algorithms, and resource allocation strategies is needed [4].

A recent pooled evidence has demonstrated a possible association between body mass index (BMI) abnormalities and poor outcomes in COVID-19, although findings are tempered by several limitations such as paucity of included studies, heterogeneity of BMI assessment and classification schemes, and restricted analyses to effects of increased weight abd obesity [4,5]. Moreover, the exact relationship, effect size, and underlying mechanisms between abnormal BMI and clinical outcomes remain unclear. Some reports demonstrate a significant association between BMI abnormalities and poor outcomes, while others have not found such a correlation [6–12]. In studies that included both underweight and obese patients, a J-shaped association was observed in terms of risk of intubation, death, or a composite of these outcomes [13–15].

Our previous study also revealed that COVID-19-infected patients who had new-onset neurological symptoms on admission carried an increased risk of all-cause mortality and other adverse outcomes, although how BMI affects such association is still undetermined. Additionally, the existence of an obesity survival paradox, a phenomenon wherein alterations in fat accumulation and adipose microenvironment exert protective effects in critically ill patients, in COVID-19 remains speculative [6,13,16]. Furthermore, the applicability of the observed findings in other parts of the world, specially in countries that face the double burden of malnutrition, is still unknown due to limited evidence [17].

In view of these knowledge gaps, we further analyzed the dataset from a large, multicenter, retrospective cohort study of patients hospitalized for COVID-19 [18]. We hypothesize that either abnormally low or high BMI significantly affects clinical and neurologic outcome measures in this subset of patients. Where evidence exists, we also discussed possible mechanisms underlying observed associations (or lack therof) between BMI abnormalities and COVID-19 outcomes.

2. Materials and methods

2.1. Study design and source population

The Philippine CORONA Study was a nationwide, multicenter, retrospective cohort study that investigated the clinical and neurologic outcomes of adult patients with confirmed COVID-19 and were consecutively admitted in any of the 37 participating hospitals across the country between February 1 to December 15, 2020 [18]. The study obtained approval from the respective research ethics boards of all participating sites and was registered in ClinicalTrials.gov (NCT04386083). Specific details about the research design, patient enrollment, and data collection procedures were discussed in the published protocol [19].

For this study, we analyzed data from patients with available BMI information during admission, along with other relevant details including age, sex, smoking status, clinical characteristics (specific and cumulative number of comorbid conditions, neurologic history and manifestations, non-neurologic presenting symptoms, treatment/s received), and in-hospital outcomes.

2.2. Exposure

We operationalized BMI, calculated as weight in kilograms divided by the square of height in meters (kg/m^2), as our primary exposure. Weight and height measurements were recorded upon hospital admission. We analyzed BMI as a categorical variable using the World Health Organization (WHO) criteria: underweight (BMI <18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2) [19]. Patients with missing or implausible BMI data were excluded from the analyses.

2.3. Outcomes

Our primary outcomes of interest were in-hospital mortality and need for invasive mechanical ventilation (IMV). We also explored the association between BMI and several dichotomized secondary endpoints including COVID-19 severity at nadir (mild/moderate versus severe/critical), intensive care unit (ICU) admission (admitted versus not admitted), and lengths of IMV dependence (<14 versus ≥14 days), ICU admission (≤7 versus >7 days), and overall hospital stay (≤14 versus >14 days). We also explored the association of BMI with neurologic outcomes (full/partial versus no neurologic improvement) among patients who had any neurologic symptom or diagnosis on admission.

2.4. Statistical analysis

The baseline patient characteristics across the prespecified BMI criteria was summarized using descriptive statistics. Continuous variables were presented as median (interquartile range, IQR), and categorical variables as frequencies and proportions. To compare baseline sociodemographic and clinico-neurologic data between BMI strata, we used one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables, and chi-square or Fisher exact tests for categorical variables as appropriate. We applied Cox proportional hazards and binary logistic regression models to determine the relationship between BMI classification and our primary and secondary endpoints, respectively. In both models, we adjusted for a priori defined covariates such as age, sex, smoking status, hypertension, diabetes, malignancy, and chronic respiratory, cardiac, kidney, and neurologic disease [14,20] by performing multivariable regression analysis with normal BMI category as reference. To test if age and sex were possible effect modifiers, we also conducted stratified analyses with likelihood ratio test using a full model and a reduced model without the interaction terms.

Kaplan–Meier plots and log-rank tests were also done to examine the association between BMI and time-to-event data for mortality and need for IMV. Lastly, we conducted a sensitivity analysis using two BMI classification systems, namely, WHO international BMI criteria and the Asia-Pacific BMI classification, to further assess the robustness of our findings. Briefly, the Asia-Pacific classification utilizes the following trigger points based on risk for adverse health outcomes: underweight (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight/increased risk (23–27.5 kg/m^2), and obese/higher

high risk (≥27.5 kg/m^2) [19]. Given the exploratory nature of this study, no imputations were made for missing data.

All tests were two-tailed, and we set $P < 0.05$ as the threshold for statistical significance. All analyses were carried out in Stata Version 15.1 (StataCorp LLC, TX, USA).

3. Results

3.1. Baseline characteristics of analytic cohort

Among the 10,881 patients in the Philippine CORONA Study, 4463 (41%) had available BMI and outcome data and were included in the full analytic cohort (Supplementary Fig. 1). Baseline data are summarized in Table 1. The median BMI was 25.0 kg/m^2 with the following distribution per category: underweight (3.4%), normal (47.0%), overweight (32.8%), and obese (16.8%). Majority of patients were <60 years of age with a median age of 54 years (IQR: 28). Within the cohort, there were more males ($P < 0.001$) and non-smokers ($P = 0.023$) across the BMI strata. Hypertension, diabetes, and chronic respiratory disease displayed a direct trend, whereas chronic kidney disease and HIV/AIDS showed an inverse trend in relation to BMI ($P < 0.05$). On admission, 76.8% presented with at least one non-neurologic symptom, with fever, cough, and dyspnea being more frequently observed among patients with higher BMI classes ($P < 0.05$) (Supplementary Table 1). In terms of neurologic profile, the proportions of patients with chronic, as well as acute neurologic symptom or diagnosis on admission, appeared to decrease with higher BMI ($P < 0.05$). We observed significantly inhomogeneous proportions of treatment administered, with overweight and obese patients having received glucocorticoids, tocilizumab, antiviral, and antibacterial medications more frequently compared to other BMI groups ($P < 0.05$).

3.2. Outcomes

Within the study period, 790 (17.7%) patients were intubated and 710 (15.9%) died over a median hospital stay of 13 days (IQR, 8 days; $P = 0.647$), the proportions of which did not differ across BMI strata ($P = 0.974$ and 0.858 for IMV requirement and in-hospital mortality, respectively) (Table 2). In the multivariable Cox model, adjusted analysis showed no differences in estimated risks for in-hospital mortality and IMV requirement across all BMI groups (Figures 1A and B). These findings did not vary by age group nor sex (Supplementary Tables 2 and 3). Correspondingly, the time-to-mortality and -intubation data showed no significant differences across BMI categories (Figures 1C and D).

Table 1
Baseline characteristics of patients stratified by World Health Organization Body Mass Index classification.

Characteristic	All patients (Median BMI: 25.0 kg/m^2)	Underweight (BMI <18.5 kg/m^2)	Normal (BMI 18.5–24.9 kg/m^2)	Overweight (BMI 25.0–29.9 kg/m^2)	Obese (BMI ≥30 kg/m^2)	*P*
	(n = 4463)	(n = 151)	(n = 2100)	(n = 1463)	(n = 749)	
Socio-demographic data						
Age, median (IQR)	54 (28)	43 (38)	55 (31)	54 (25)	51 (25)	**<0.001**
Age group						**<0.001**
18–59 y, n (%)	2764 (61.9)	102 (67.6)	1238 (59.0)	903 (61.7)	521 (69.56)	
≥ 60 y, n (%)	1699 (38.1)	49 (32.5)	862 (41.1)	560 (38.3)	228 (30.4)	
Female, n (%)	1983 (44.4)	74 (49.0)	1013 (48.2)	575 (39.3)	321 (42.9)	**<0.001**
Ever-smoker (past/current), n (%)	436 (9.8)	19 (12.6)	229 (10.9)	131 (8.9)	57 (7.6)	**0.023**
Clinical characteristics						
Non-neurologic comorbidities						
Hypertension, n (%)	1816 (40.7)	42 (27.8)	823 (39.2)	616 (42.1)	335 (44.7)	**<0.001**
Diabetes mellitus, n (%)	1107 (24.8)	15 (9.9)	500 (23.8)	368 (25.2)	224 (29.9)	**<0.001**
Chronic cardiac disease[a], n (%)	241 (5.4)	9 (6.0)	126 (6.0)	70 (4.8)	36 (4.8)	0.366
Chronic respiratory disease[b], n (%)	307 (6.9)	9 (6.0)	142 (6.8)	86 (5.9)	70 (9.4)	**0.022**
Chronic kidney disease, n (%)	264 (5.9)	12 (8.0)	143 (6.8)	82 (5.6)	27 (3.6)	**0.009**
Chronic liver disease, n (%)	23 (0.5)	2 (1.3)	12 (0.6)	6 (0.4)	3 (0.4)	0.464
Malignancy, n (%)	100 (2.2)	7 (4.6)	51 (2.4)	25 (1.7)	17 (2.3)	0.103
HIV/AIDS, n (%)	17 (0.4)	8 (5.3)	5 (0.2)	3 (0.2)	1 (0.1)	**<0.001**
Others, n (%)	761 (17.1)	39 (25.8)	348 (16.6)	257 (17.6)	117 (15.6)	**0.019**
Number of non-neurologic comorbidities, median (IQR)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	0.199
Non-neurologic presenting symptom, n (%)	3428 (76.8)	118 (78.2)	1573 (74.9)	1130 (77.2)	607 (81.0)	**0.007**
Fever, n (%)	2000 (44.8)	55 (36.4)	899 (42.8)	673 (46.0)	373 (49.8)	**0.001**
Cough, n (%)	2160 (48.4)	69 (45.7)	986 (47.0)	714 (48.8)	391 (52.2)	0.084
Dyspnea, n (%)	1224 (27.4)	37 (24.5)	565 (26.9)	384 (26.3)	238 (31.8)	**0.028**
Sore throat, n (%)	332 (7.4)	15 (9.9)	172 (8.2)	99 (6.8)	46 (6.1)	0.118
Diarrhea, n (%)	271 (6.1)	8 (5.3)	124 (5.9)	87 (6.0)	52 (6.9)	0.730
Fatigue, n (%)	325 (7.3)	10 (6.6)	142 (6.8)	126 (8.6)	47 (6.3)	0.117
Neurologic characteristics						
Chronic neurologic disease, n (%)	192 (4.3)	8 (5.3)	108 (5.1)	53 (3.6)	23 (3.1)	**0.039**
Neurologic presenting symptom, n (%)	838 (18.8)	35 (23.2)	439 (21.0)	248 (17.0)	116 (15.5)	**0.001**
Concomitant acute neurologic diagnosis on admission, n (%)	384 (8.6)	16 (10.7)	205 (9.8)	119 (8.1)	44 (5.9)	**0.008**
Treatment/s received						
Glucocorticoids, n (%)	1487 (33.3)	40 (26.5)	664 (31.6)	508 (34.7)	275 (36.7)	**0.011**
Tocilizumab, n (%)	590 (13.2)	16 (10.7)	225 (10.7)	198 (13.5)	151 (20.2)	**<0.001**
Antiviral[c], n (%)	1040 (23.3)	26 (17.2)	437 (20.8)	348 (24.0)	229 (30.6)	**<0.001**
Antibacterial, n (%)	3758 (84.2)	119 (78.8)	1698 (80.9)	1267 (86.6)	674 (90.0)	**<0.001**
Others[d], n (%)	1277 (28.6)	32 (21.2)	510 (24.3)	467 (31.9)	268 (35.8)	**<0.001**

Abbreviations: BMI, body mass index; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IQR, interquartile range.
[a] Includes heart failure, coronary artery disease, prior history of myocardial infarction, and other cardiac conditions.
[b] Includes bronchial asthma, chronic obstructive pulmonary disease (COPD), restrictive lung disease, and other pulmonary conditions.
[c] Includes remdesivir, lopinavir, ritonavir.
[d] Includes chloroquine, hydroxychloroquine, convalescent plasma, and other therapies.

Table 2
Between-group comparison of outcomes across World Health Organization Body Mass Index classifications.

Outcomes	All	Underweight (BMI <18.5 kg/m^2)	Normal (BMI 18.5–24.9 kg/m^2)	Overweight (BMI 25.0–29.9 kg/m^2)	Obese (BMI ≥30 kg/m^2)	*P*
	(n = 4463)	(n = 151)	(n = 2100)	(n = 1463)	(n = 749)	
Final Outcomes						0.974
In-hospital mortality, n (%)	710 (15.9)	25 (16.6)	331 (15.8)	237 (16.2)	117 (15.6)	
Discharged, n (%)	373 (84.1)	126 (83.4)	1769 (84.2)	1226 (83.8)	632 (84.4)	
Time to in-hospital mortality in days, median (IQR)	17 (14)	22 (15)	16 (15)	16 (13)	18 (14)	0.051
Need for IMV, n (%)	790 (17.7)	25 (16.6)	376 (17.9)	251 (17.2)	138 (18.4)	0.858
Time to intubation in days, median (IQR)	5 (4)	4 (4)	5 (4)	5 (4)	5 (4)	0.458
Duration of IMV in days, median (IQR)	14 (12)	20 (15)	13 (12)	14 (12)	15 (12)	**0.027**
IMV dependence <14 days, n (%)	375 (47.6)	5 (20.0)	192 (51.1)	120 (48.2)	58 (42.0)	**0.011**
IMV dependence ≥14 days, n (%)	413 (52.4)	20 (80.0)	184 (48.9)	129 (51.8)	80 (58.0)	
COVID-19 severity at nadir						**0.012**
Mild/moderate, n (%)	2819 (63.2)	94 (62.3)	1375 (65.5)	907 (62.0)	443 (59.2)	
Severe/critical, n (%)	1644 (36.8)	57 (37.7)	725 (34.5)	556 (38.0)	306 (40.8)	
Admitted to ICU, n (%)	838 (18.8)	30 (19.9)	397 (18.9)	260 (17.8)	151 (20.2)	0.562
Length of ICU stay in days, median (IQR)	15 (13)	18 (17)	15 (13)	15 (13)	15 (12)	0.185
ICU stay ≤7 days, n (%)	113 (13.5)	2 (6.7)	58 (14.6)	37 (14.2)	16 (10.6)	0.419
ICU stay >7 days, n (%)	725 (86.5)	28 (93.3)	339 (85.4)	223 (85.8)	135 (89.4)	
Length of hospital stay[a] in days, median (IQR)	13 (8)	13 (9)	13 (8)	12 (9)	12 (8)	0.647
Hospital stay ≤14 days, n (%)	2972 (66.6)	98 (64.9)	1384 (65.9)	987 (67.5)	503 (67.2)	
Hospital stay >14 days, n (%)	1491 (33.4)	53 (35.1)	716 (34.1)	476 (32.5)	246 (32.8)	0.742
Neurologic outcome on discharge[b]						0.552
Full/partial neurologic recovery, n (%)	682 (87.0)	30 (85.7)	347 (88.1)	207 (87.3)	98 (83.1)	
No recovery, n (%)	102 (13.0)	5 (14.3)	47 (11.9)	30 (12.7)	20 (16.9)	

Abbreviations: BMI, body mass index; COVID-19, 2019 coronavirus disease; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range.
[a] Derived from overall length of stay for patients who were never admitted to ICU; excludes ICU length of stay for those who were admitted in the ICU.
[b] Patients who had a neurologic presentation or concomitant acute neurologic diagnosis on admission (n = 784).

Among those who were intubated, however, a higher proportion of underweight patients had longer IMV dependence compared to other BMI groups ($P = 0.011$) with a median duration of 20 days (IQR, 15 days; $P = 0.025$) (Table 2). This observation remained consistent after adjusting for multiple covariates (OR, 4.98; 95% CI, 1.80–13.78; $P = 0.002$) (Table 3). Unadjusted and adjusted analyses also revealed a significant, J-shaped association between BMI abnormalities and COVID-19 severity (unadjusted $P = 0.012$), with underweight (OR, 1.48; 95% CI, 1.03–2.14; $P = 0.035$) and obese (OR, 1.46; 95% CI, 1.22–1.76; $P < 0.001$) patients showing the highest, and overweight patients demonstrating a modest, but statistically significant, odds of developing severe/critical COVID-19 at nadir (OR, 1.19; 95% CI, 1.02–1.38; $P = 0.024$) (Tables 2 and 3). In contrast, we did not find BMI category, using WHO classification, to be independently associated with the other secondary endpoints in both unadjusted and adjusted analyses (Tables 2 and 3). In the subgroup of COVID-19 patients who had a neurologic presentation or diagnosis on admission, 784 (82.4%) had available data for analysis of neurologic outcomes. Whereas between-group comparison failed to reveal any significant differences across BMI strata, the adjusted analysis demonstrated decreased odds of full or partial neurologic recovery on discharge among obese, COVID-19-infected patients (OR, 0.48; 95% CI, 0.25–0.90; P = 0.023) (Tables 2 and 3). No significant interactions by age group or sex were found for these secondary endpoints (Supplementary Tables 2 and 3).

3.3. Sensitivity analysis

The results of the sensitivity analyses are shown in Table 4. Comparing the two BMI criteria, similar trends were seen for primary endpoints, although a significant difference in effect size (>10%) was detected for in-hospital mortality risk. While increasing weight appeared to correlate directly with the said risk, statistical significance was only reached for those classified as obese using Asia–Pacific cutoffs ($P = 0.012$). Stratification by age group showed significant differences in risk estimates for IMV requirement between the two criteria, with younger (18–59 years) overweight patients having a significantly reduced risk (HR, 0.69; 95% CI, 0.51–0.94; $P = 0.018$), and older (≥60 y) overweight and obese patients having a significantly greater risk of IMV requirement

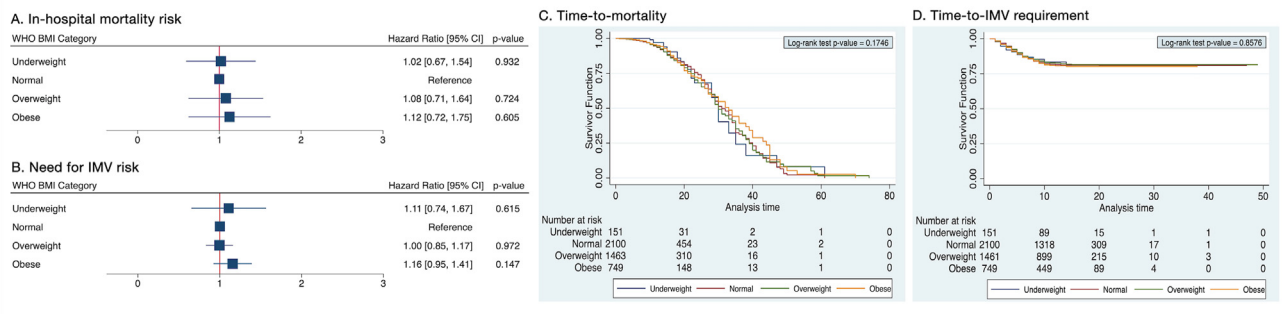

Fig. 1. Multivariable adjusted Cox proportional analysis and Kaplan–Meier estimates of primary outcomes. **A, B**. Forest plots of adjusted hazards ratio (HR) and 95% confidence intervals (CI) estimating risks for in-hospital mortality and need for invasive mechanical across BMI groups. **C, D**. Time-to-mortality and -IMV requirement across BMI groups.

Table 3
Multivariable binary logistic regression analysis of association between body mass index and secondary endpoints across body mass index categories.

BMI category[a]	Disease severity at nadir (n = 4463)		ICU admission (n = 4463)		Duration of IMV (n = 790)[b]		Length of hospital stay[c](n = 4463)		Length of ICU stay (n = 838)[d]		Neurologic outcome (n = 784)[e]	
	OR (95% CI)	*P*	OR (95% CI)	p	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR	*P*
Underweight	1.48 (1.03, 2.14)	**0.035**	1.32 (0.84, 2.07)	0.225	4.98 (1.80, 13.78	**0.002**	1.09 (0.77, 1.54)	0.639	2.14 (0.49, 9.38)	0.312	0.78 (0.24, 2.55)	0.681
Normal	Reference		Reference		Reference		Reference		Reference		Reference	
Overweight	1.19 (1.02, 1.38)	**0.024**	0.95 (0.79, 1.15)	0.624	1.13 (0.82, 1.57)	0.454	0.95 (0.82, 1.09)	0.446	1.04 (0.66, 1.63)	0.872	0.78 (0.46, 1.32)	0.348
Obese			1.21 (0.97, 1.53)	0.098	1.46 (0.98, 2.19)	0.064	0.99 (0.82, 1.18)	0.875	1.45 (0.79, 2.64)	0.228	0.48 (0.25, 0.90)	**0.023**

Abbreviations: BMI, body mass index; ICU, intensive care unit; IMV, invasive mechanical ventilation; OR, odds ratio.
[a] World Health Organization BMI criteria.
[b] Patients requiring IMV.
[c] Derived from overall length of stay for patients who were never admitted to ICU; excludes ICU length of stay for those who were admitted in the ICU.
[d] Patients requiring ICU admission.
[e] Patients who had neurologic presentation or acute neurologic diagnosis on admission.

Table 4
Sensitivity analyses comparing primary and secondary outcomes using the World Health Organization Body Mass Index criteria and Asia–Pacific public health action trigger points.

Primary Outcomes[a]	BMI Categories	WHO BMI Criteria		Asia–Pacific Pubic Health Action Trigger Points		% Difference
		Adjusted HR (95% CI)	*P value*	Adjusted HR (95% CI)	*P value*	
In-hospital mortality	Underweight	1.30 (0.80–2.10)	0.294	1.45 (0.88–2.38)	0.145	11.54
	Normal	Reference		Reference		
	Overweight	1.10 (0.91–1.34)	0.329	1.23 (0.99–1.53)	0.064	11.82
	Obese	1.21 (0.95–1.55)	0.129	**1.35 (1.07–1.71)**	**0.012**	11.57
Need for IMV	Underweight	1.09 (0.68–1.76)	0.709	1.15 (0.71–1.86)	0.575	5.50
	Normal	Reference		Reference		
	Overweight	0.99 (0.82–1.19)	0.893	1.03 (0.83–1.26)	0.812	4.04
	Obese	1.17 (0.93–1.48)	0.180	1.23 (0.99–1.53)	0.066	5.13
Need for IMV,	Underweight	1.09 (0.68–1.76)	0.709	1.03 (0.55–1.93)	0.931	−5.50
Age group 18–59 y	Normal	Reference		Reference		
	Overweight	0.99 (0.82–1.19)	0.893	0.69 (0.51–0.94)	**0.018**	−30.30
	Obese	1.17 (0.93–1.48)	0.180	0.98 (0.73–1.31)	0.868	−16.24
Need for IMV	Underweight	1.09 (0.68–1.76)	0.709	1.22 (0.70–2.12)	0.485	11.93
Age group ≥60 y	Normal	Reference		Reference		
	Overweight	0.99 (0.82–1.19)	0.893	**1.26 (1.01–1.57)**	**0.039**	27.27
	Obese	1.17 (0.93–1.48)	0.180	**1.32 (1.04–1.69)**	**0.025**	12.82
Secondary Outcomes[b]	BMI Categories	WHO BMI Criteria		Asia–Pacific Public Health Action Trigger Points		% Difference
		Adjusted OR (95% CI)	*p value*	Adjusted OR (95% CI)	*p value*	
Disease severity at nadir	Underweight	**1.48 (1.03–2.14)**	**0.035**	**1.50 (1.03–2.19)**	**0.033**	1.35
	Normal	Reference		Reference		
	Overweight	**1.19 (1.02–1.38)**	**0.024**	1.08 (0.91–1.27)	0.391	−9.24
	Obese	**1.46 (1.22–1.76)**	**<0.001**	**1.42 (1.19–1.69)**	**<0.001**	−2.74
Duration of IMV dependence	Underweight	**4.98 (1.80–13.78)**	**0.002**	**5.38 (1.91–15.12)**	**0.001**	8.03
	Normal	Reference		Reference		
	Overweight	1.13 (0.82–1.57)	0.454	1.18 (0.82–1.69)	0.365	4.42
	Obese	1.46 (0.98–2.19)	0.064	1.45 (0.99–2.13)	0.055	−0.68
Need for ICU admission	Underweight	1.32 (0.84–2.07)	0.225	1.41 (0.89–2.23)	0.146	6.82
	Normal	Reference		Reference		
	Overweight	0.95 (0.79–1.15)	0.624	1.02 (0.83–1.26)	0.822	7.37
	Obese	1.21 (0.97–1.53)	0.098	**1.28 (1.03–1.59)**	**0.029**	5.79
Length of ICU admission[c]	Underweight	2.14 (0.49–9.38)	0.312	2.17 (0.48–9.71)	0.311	1.40
	Normal	Reference		Reference		
	Overweight	1.04 (0.66–1.63)	0.872	1.05 (0.64–1.72)	0.861	0.96
	Obese	1.45 (0.79–2.64)	0.228	1.23 (0.72–2.12)	0.449	15.17
Length of hospital stay[d]	Underweight	1.09 (0.77–1.54)	0.639	1.09 (0.76–1.57)	0.626	0.00
	Normal	Reference		Reference		
	Overweight	0.95 (0.82–1.09)	0.446	0.96 (0.82–1.12)	0.623	1.05
	Obese	0.99 (0.82–1.18)	0.875	1.00 (0.85–9.71)	0.972	1.01
Neurologic Outcomes[e]	Underweight	0.78 (0.24–2.55)	0.681	0.60 (0.17–2.05)	0.414	23.08
	Normal	Reference		Reference		
	Overweight	0.78 (0.46–1.32)	0.348	0.62 (0.34–1.13)	0.118	20.51
	Obese	**0.48 (0.25–0.90)**	**0.023**	**0.40 (0.21–0.75)**	**0.005**	16.67

Abbreviations: BMI, body mass index; ICU, intensive care unit; IMV, invasive mechanical ventilation; WHO, World Health Organization.
[a] Cox proportional hazards model.
[b] Binary logistic regression analysis.
[c] Patients requiring ICU admission.
[d] Derived from overall length of stay for patients who were never admitted to ICU; excludes ICU length of stay for those who were admitted in the ICU.
[e] Patients who had a neurologic presentation or concomitant acute neurologic diagnosis on admission (n = 784).

based on Asia–Pacific cutoff points (HR, 1.25; 95% CI, 1.01–1.57; $P = 0.039$ and HR, 1.32; 95% CI, 1.04–1.69; $P = 0.025$ for overweight and obese strata, respectively). Obesity, as defined in the Asia–Pacific criteria, was also shown to be independently associated with the need for ICU admission (OR, 1.28; 95% CI, 1.03–1.59; $P = 0.029$). Similar trends in odds estimates were observed for duration of IMV dependence, COVID-19 severity at nadir, and lengths of ICU and hospital stay using both BMI criteria. Lastly, although significant differences in effect sizes were detected, the statistically significant association between BMI and neurologic outcomes remained consistent even with the use of Asia–Pacific cutoff points. No significant effect–measure interactions were found after stratifying for sex.

4. Discussion

This nationwide observational study with the largest cohort of Asian patients to date demonstrated the association, or lack thereof, of BMI abnormalities with several clinical and neurologic outcomes of patients hospitalized for COVID-19.

Compared to available nutritional data, our cohort showed a lower proportion of underweight and higher proportions of overweight and obese patients. Such differences in prevalence estimates may be expected in the context of rapidly changing patterns in diet, physical activity and mobility, food systems, and economic status [17,21–23]. In terms of baseline clinical findings, we observed higher proportions of concomitant non-communicable diseases among overweight and obese patients admitted for COVID-19. Chronic respiratory disease and dyspnea on admission were more frequently found in these subgroups, expanding prior observations showing an association between excess weight and altered respiratory biomechanics and function [9,10]. We also found higher proportions of concurrent HIV/AIDS and chronic kidney disease among underweight individuals, which may relate to the negative downstream effects of these conditions on muscle mass and weight [24,25]. Additional longitudinal assessments are needed to quantify the degree to which COVID-19 infection impacts measures of body composition and energy state.

We demonstrated an apparent nonuniform risks and time-to-mortality and intubation depending on BMI criteria used. While no association was found in terms of WHO BMI criteria, the use of lower cutoff points in the Asia–Pacific classification system showed obesity to be an independent predictor of the risks for mortality, intubation, and ICU admission, although this did not seem to significantly affect the durations of ICU and hospital stay. This finding was in agreement with past observations [6,7,9,10,13].

Diverse mechanisms of COVID-19 and the pathophysiological alterations associated with obesity may synergistically be responsible for the hightened risk of adverse outcomes oberved in our study. The increased adiposity seen in obesity promotes SARS-CoV-2 infection by virtue of the increased expression of angiotensin-coverting enzyme 2 (ACE-2), which is considered to be an essential receptor for viral entry [26,27]. Adipose tissue may also serve as a viral reservoir contributing to prolonged viral shedding [4]. Accumulating evidence also implicates immune dysregulation as a putative mechanism underlying the greater degree of severity, systemic complications, and poor outcomes among obese COVID-19 patients. Obesity promotes a chronic, proinflammatory state that, coupled with the effects of COVID-19 on the immune system, sets a vicious auto-regenerating response characterized by the elaboration of cytokines and other inflammatory mediators. These intertwined processes lead to cytokine storm, which fundamentally underlies severe/critical COVID-19 [4,10,13,27]. Obesity is also associated with altered pulmonary biomechanics, including diminished respiratory reserve volume, impaired diaphragmatic excursion, poor lung compliance, and reduced functional capacity, all of which may compromise adequate oxygenation during COVID-19 infection [9,15,27]. It is also widely known that obesity predisposes tto cardiometabolic comorbidities such as hypertension and diabetes, which by themselves are independent risk factors to poor outcomes in COVID-19 [9,13,27]. Concerning the use of BMI criteria, our data highlighted the potential utility and sensiticity of race-specific BMI criteria, which consider ethnic differences in body composition and adiposity, in estimating COVID-19 prognosis and informing discussions pertaning to resource allocation and advance care planning [10,28].

Consistent with another report, we found age to be a significant factor in the differential risk of IMV requirement observed across BMI strata [8]. Our results demonstrated that overweight and obesity, classified using race-specific criteria, conferred a greater risk of intubation among elderly individuals, whereas being overweight appeared to reduce this risk among those <60 years of age. That the latter was observed without a concomitant elevation in the mortality risk points to the possible existence of a survival paradox in COVID-19 postulated in prior studies [6,14,16]. The results of our analysis, however, suggested that the reduction of risk may only occur at a certain range of excess weight and its occurrence may be restricted to younger patients. Further studies are warranted to determine the BMI cutoff point at which the protective benefit of excess weight declines and becomes a risk factor for intubation and expound on the mechanisms that drive this shift. Available evidence centered on the general population reveals sex differences in BMI owing to innate variations in body distribution, energy metabolism, neuroendocrine regulation, and dietary behaviors [29]. Exactly how these differences contribute to outcomes in COVID-19 remains unclear due to discrepant findings in published reports [8,13,27]. We did not find sex as a significant effect modifier in our analysis of the primary and secondary endpoints, in agreement with previous data [13,27].

Our data also demonstrated that BMI abnormalities confer a significant risk for the development of severe/critical COVID-19 at nadir regardless of age, sex or BMI criteria used, with extremes of BMI (i.e., underweight and obesity) showing a more striking association compared to normal and overweight. We found it interesting that higher odds of severe/critical illness among younger, overweight patients arose in the background of a reduced risk of intubation and a nonsignificant risk of in-hospital mortality, which altogether support the age-dependent survival paradox described earlier. The direct correlation observed between BMI and COVID-19 severity was independent of cardiometabolic and other conditions related to excess weight, a finding consistent across observational reports, two of which involved primarily Asian cohorts [8,9,30,31]. In contrast to prior observations, underweight stratification appeared to be a strong, independent risk factor not only for severe COVID-19, but also for prolonged IMV requirement [8,10,15]. The relatively higher proportion of underweight patients in our cohort may partially explain this disparity, and possibly provides a more precise estimate of the impact of low BMI on these outcomes. Our findings further emphasized the importance of giving comparable attention to underweight patients in terms of prevention, hospital triage, and treatment strategies due to their significant risk for COVID-19 morbidity. One study linked this association to the underlying frailty and altered immune responses associated with being underweight [13]. Another report also found a significant, albeit tenuous, correlation between low BMI and decreased diaphragmatic thickness, an emerging predictive marker of prolonged IMV requirement among critically ill patients [32]. Future studies employing more accurate measurements of adiposity, fat-free muscle mass, pulmonary function, and inflammatory response

may help elucidate the complex relationship between BMI and respiratory complications of severe COVID-19.

Although neurologic involvement in COVID-19 has been documented in previous studies, none have addressed the contribution of BMI abnormalities on neurologic outcomes [33–35]. Our data showed that obesity may be an independent predictor of poor neurologic recovery among COVID-19 patients with an acute neurologic presentation or condition on admission. This association remained robust even after performing effect modification and sensitivity analyses. The underlying mechanisms for this finding are still unknown. It is theoretically plausible that the downstream effects of obesity described earlier overlap or act synergistically with the direct and immune-mediated neurologic injury elicited by SARS-CoV-2, although our present data cannot confirm this hypothesis [33]. The determination of exact mechanisms by which obesity contributes to the systemic and neuroinflammatory effects of COVID-19, and the magnitude by which this interaction ultimately affects neurologic and overall prognosis requires continued investigation.

This study has several limitations. As this is a secondary analysis of published data, our findings should be construed as exploratory and hypothesis-generating. Although the Philippine CORONA utilized standard operational definitions for the data extracted and outcomes assessed, it remains possible that competing risks of death and other adverse clinical and neurologic outcomes were not fully accounted for in our final analysis. Our study also acknowledges potential differential bias in management protocols between participating sites, especially in the context of rapidly evolving diagnostic and treatment paradigms in COVID-19 over time. Additionally, significant associations between underweight and COVID-19 severity and prolonged IMV dependence should be cautiously interpreted given the wide 95% CIs of the effect sizes. The study is also underpowered to detect significant relationships between underweight and other endpoints due to the smaller number of patients in this BMI class. In view of the participating sites being largely concentrated in urban areas, our study findings may not be genralizable to non-hospitalized COVID-19 patients and those admitted to small rural hospitals. Other study limitaions include the retrospective design, the large amount of missing BMI data, and the lack of accurate measurements of COVID-19 inflammatory biomarkers and viral shedding. Lastly, it should be noted that this study heavily relied on anthropometric assessment (i.e., BMI), which may not fully capture the other aspects of nutritional status. Future work should investigate the impact of sarcopenia, as well as subcellular alterations associated with malnutrition, on COVID-19 outcomes using more precise nutritional assessment tools and biochemical markers.

5. Conclusions

This large-scale study demonstrated that obesity, classified using race-specific BMI criteria, was associated with an increased risk of adverse outcomes including severe/critical COVID-19, IMV requirement, ICU admission, poor neurologic recovery, and in-hospital mortality in an Asian cohort. Although being overweight appeared to be associated with the risk for severe/critical COVID-19, this does not seem to elevate the risk of death. These findings, combined with a reduced risk of intubation seen only in the younger age group, suggest that such paradox is probably age-dependent and might only be evident within a critical range of excess weight. The threshold for, and mechanisms underlying this phenomenon merit further investigation. Due to factors such as underlying frailty, maladaptive immune responses, and altered respiratory mechanics, underweight patients may also be at risk for severe/critical COVID-19 and prolonged IMV requirement, and thus deserve comparable attention in terms of preventive and treatment strategies. Larger prospective studies with more precise nutritional assessment methods and biomarkers are needed to elucidate the complex relationship between body composition and COVID-19 outcomes.

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Author contribution

AIE: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing. NGDR: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing. CFDL: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing. MCCS: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing. VMMA: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing. RDGJ: Conceptualization, data curation, formal analysis, interpretation of data, writing-original draft, writing-review, and editing.

Declaration of competing interest

All authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Appendix A. Supplementary data

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