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

Influence of obesity on incidence of thrombosis and disease severity in patients with COVID-19: From the CLOT-COVID study

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ABSTRACT

Background: The influence of obesity on the development of thrombosis and severity of coronavirus disease 2019 (COVID-19) remains unclear.
Method: The CLOT-COVID study was a retrospective multicenter cohort study enrolling 2894 consecutive hospitalized patients with COVID-19 between April 2021 and September 2021 among 16 centers in Japan. The present study consisted of 2690 patients aged over 18 years with available body mass index (BMI), who were divided into an obesity group (BMI ≥30) ($N = 457$) and a non-obesity group (BMI <30) (N = 2233).
Results: The obesity group showed more severe status of COVID-19 at admission compared with the non-obesity group. The incidence of thrombosis was not significantly different between the groups (obesity group: 2.6 % versus non-obesity group: 1.9 %, $p = 0.39$), while the incidence of a composite outcome of all-cause death, or requirement of mechanical ventilation or extracorporeal membrane oxygenation during hospitalization was significantly higher in the obesity group (20.1 % versus 15.0 %, $p < 0.01$). After adjusting confounders in the multivariable logistic regression model, the risk of obesity relative to non-obesity for thrombosis was not significant (adjusted OR, 1.39; 95 % CI, 0.68–2.84, $p = 0.37$), while the adjusted risk of obesity relative to non-obesity for the composite outcome was significant (adjusted OR, 1.85; 95 % CI, 1.39–2.47, $p < 0.001$).
Conclusions: In the present large-scale observational study, obesity was not significantly associated with the development of thrombosis during hospitalization; however, it was associated with severity of COVID-19.

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Introduction

A large proportion of patients that develop coronavirus disease 2019 (COVID-19) have asymptomatic or mild symptoms; however, some patients present with respiratory failure and hemodynamic instability, requiring admission to an intensive care unit and advanced respiratory support, sometimes leading to multiple organ failure and death [1–4]. In addition, COVID-19 often causes coagulopathy, especially in severe COVID-19, which leads to thromboembolic complications, especially venous thromboembolism (VTE) [5–7]. Therefore, it is important to identify risk factors of thrombosis and worsening of COVID-19 severity, and to conduct prophylactic anticoagulation therapy and aggressive anti-virus therapy suitable for patients classified as high risk.

Obesity is a well-known independent risk factor of VTE for medical hospitalized patients [8,9]. In addition, obesity is associated with requirement of respiratory support under intubation and development of acute respiratory distress syndrome and other respiratory failure [10]. Thus, in COVID-19, obesity may lead to increased risks of development of thrombosis and worsening of COVID-19 severity. Previous studies have reported an association between obesity and worsening of COVID-19 severity [11–17]. However, the impact of obesity on thrombosis has not been fully evaluated. Therefore, the present study aimed to compare patient characteristics and clinical outcomes between obese and non-obese patients and evaluate the impact of obesity on thrombosis and the severity of COVID-19 using data from a large-scale multicenter observational study in Japan.

Methods

Study design and study population

The CLOT-COVID Study (thrombosis and antiCoaguLatiOn Therapy in patients with COVID-19 in Japan Study: UMIN000045800) was a physician-initiated, retrospective, multicenter cohort study involving consecutive hospitalized patients with COVID-19 from 16 centers in Japan between April 2021 and September 2021. The design of the study was previously reported in detail [18]. A total of 2894 consecutive patients who were diagnosed with COVID-19 using a positive polymerase chain reaction test were enrolled through the hospital databases. The present study population consisted of 2690 adult patients with available body mass index (BMI) data after excluding 138 patients without height or body weight recorded at admission and 66 patients below the age of 18 years. Obesity was defined as 30 $kg/m^2 \leq$ BMI according to World Health Organization criteria [19]. The entire population was divided into an obesity group and a non-obesity group (Fig. 1).

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the relevant review boards or ethics committees at all participating centers. We obtained informed consent in the form of an opt-out on each hospital's website due to the use of clinical information obtained during routine clinical practices. This study is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

Data collection and definitions for patient characteristics

We collected the patients' data, clinical management, and follow-up information from the hospital charts or hospital databases according to the pre-specified definitions. The physicians at each institution entered the data entry into an electronic case report form. In addition, data were manually checked at the general office for missing or contradictory input and values out of the expected range.

We defined patients who did not require oxygen as mild COVID-19, those who required oxygen as moderate COVID-19, and those who required mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO) as severe COVID-19 [18,20,21]. Pharmacological thromboprophylaxis managements were defined as the usage of any anticoagulants except for their usage for the treatment of thrombosis. The definitions of other diseases are described in Online Appendix 1.

Clinical outcomes

The primary outcome in the present study was thrombosis during the hospitalization. Thrombosis included VTE, ischemic stroke, myocardial infarction, and systemic arterial thromboembolism. VTE was defined as pulmonary embolism and/or deep vein thrombosis objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography, pulmonary angiography, contrast venography, or ventilation/perfusion lung scintigraphy) or by autopsy. Ischemic stroke was defined as stroke either requiring or prolonging the hospitalization with symptoms lasting >24 h. Myocardial infarction was defined according to the universal myocardial infarction guidelines [22].

The secondary outcome measures were VTE alone, major bleeding, all-cause death, and a composite outcome of all-cause death or requirement of MV or ECMO during hospitalization. Major bleeding was defined using International Society on Thrombosis and Haemostasis major definition [23].

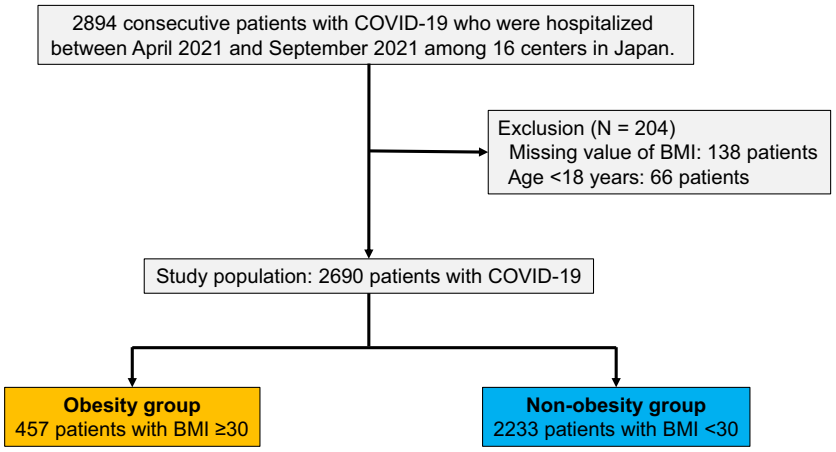

Fig. 1. Study flow chart.
COVID-19, coronavirus disease 2019; BMI, body mass index.

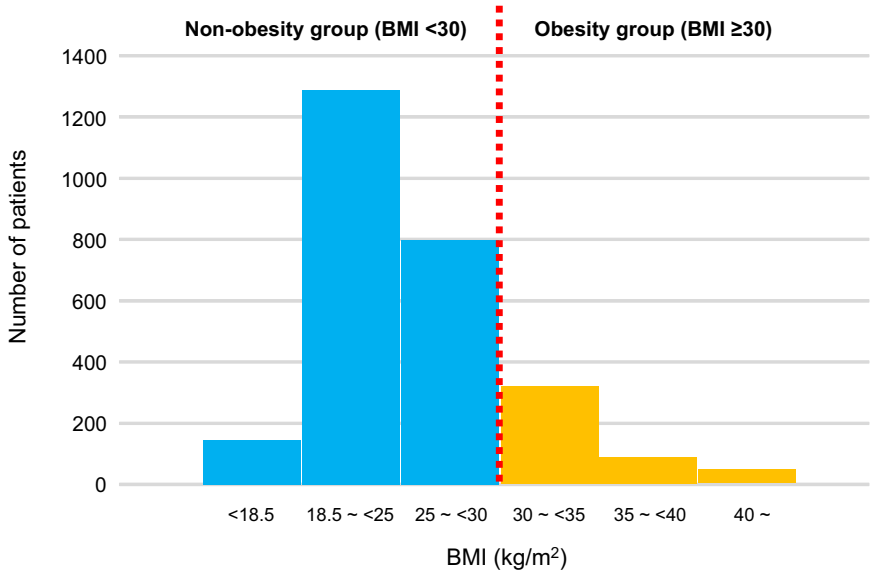

Fig. 2. Distribution of body mass index in the entire population.
BMI, body mass index.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous values were presented as the mean and standard deviation for parametric data or as the median and interquartile range for nonparametric data. Categorical variables were compared using chi-square test, as appropriate; otherwise, Fisher's exact test. Continuous variables were compared using Student's *t*-test or Wilcoxon's rank-sum test based on the normality of distribution. The clinical outcomes were presented as numbers of events and percentages with the 95 % confidence intervals (CI). The incidence of thrombosis was assessed by stratified analysis according to severity of COVID-19 at admission. To adjust for possible confounding factors, a multivariable logistic regression model was used to estimate the adjusted odds ratio (OR) and the 95 % CI of obesity with a reference of non-obesity for development of thrombosis and a composite outcome of all-cause death, or requirement of MV or ECMO. Based on previous reports [5,8,12,14,24,25] and clinical relevance, we selected 5 risk-adjusting variables of baseline characteristics (age, sex, D dimer levels at admission >1.0 μg/*ml, severity of COVID-19 at admission, and pharmacological thromboprophylaxis*) for thrombosis and VTE alone, and 7 risk-adjusting variables of baseline characteristics (age, sex, hypertension, diabetes mellitus, heart disease, respiratory disease, active cancer) for the composite outcome. All statistical analyses were performed using JMP version 13.0.0 software (SAS Institute Inc., Cary, NC, USA). All reported *p*-values were 2-tailed, and statistical significance was set at a *p*-value <0.05.

Results

Patient characteristics at admission

In the entire study population, the median BMI was 24.7 (21.7, 28.1) kg/m^2. The obesity group and the non-obesity group accounted for 457 patients (17 %) and 2233 patients (83 %), respectively. In detail, there were 146 patients (5.4 %) with BMI <18.5 kg/m^2, 1288 patients (47.9 %) with 18.5 ≤ BMI <25 kg/m^2, 799 patients (29.7 %) with 25 ≤ BMI <30 kg/m^2, 321 patients (11.9 %) with 30 ≤ BMI <35 kg/m^2, 89 patients (3.3 %) with 35 ≤ BMI <40 kg/m^2, and 47 patients (1.7 %) with 40 kg/m^2 < BMI (Fig. 2). Median BMI in the obesity and non-obesity groups was 32.9 (31.0, 35.7) kg/m^2 and 23.8 (21.3, 26.2) kg/m^2, respectively.

The obesity group was younger than the non-obesity group (47 years versus 55 years, $p < 0.01$); however, there was no significant difference in sex or D-dimer levels at admission between the two groups (Table 1). The obesity group showed higher prevalence of hypertension and diabetes mellitus than the non-obesity group; however, there was no significant difference in lung disease and history of VTE or bleeding between the two groups. The obesity group had more severe status of COVID-19 at admission than the non-obesity group (mild: 54 % versus 60 %, moderate: 36 % versus 32 %, and severe: 11 % versus 7.9 %, $p = 0.02$) (Table 1).

Pharmacological thromboprophylaxis management and imaging examinations.

The obesity group more often received pharmacological thromboprophylaxis than the non-obesity group (55 % versus 42 %, $p < 0.01$). There was no significant difference in ultrasound examination of the lower extremities and contrast-enhanced computed tomography examination during hospitalization between the two groups (Table 1).

Clinical outcomes during hospitalization

The incidence of thrombosis during hospitalization was 2.0 %, in which the most frequent thrombosis was VTE (72 %). Both groups showed an increased incidence of thrombosis in the patients with increased severity of COVID-19 (Fig. 3); however, the difference between the groups was not significant [obesity group: 2.6 % (1.5–4.5 %) versus non-obesity group: 1.9 % (1.4–2.5 %), $p = 0.39$]. There was also no significant difference in the incidence of VTE alone between the groups [obesity group: 2.2 % (1.2–4.0 %) versus non-obesity group: 1.3 % (0.9–1.9 %), $p = 0.15$]. Similarly, the incidence of major bleeding was not significantly different [2.4 % (1.3–4.3 %) versus 2.0 % (1.5–2.7 %), $p = 0.59$] (Table 2). On the other hand, there was a significant difference in the incidence of the composite outcomes of all-cause death or requirement of MV or ECMO during hospitalization (obesity group: 20 % versus non-obesity group: 15 %, $p < 0.01$); however, there was no significant difference in the incidence of all-cause death (4.4 % versus 5.6 %, $p = 0.29$).

After adjusting confounders in the multivariable logistic regression model, the risk of obesity relative to non-obesity for thrombosis remained

Table 1
Patient characteristics and management strategies during hospitalization.

	Total N = 2690	Obesity group (BMI ≥ 30) N = 457	Non-obesity group (BMI < 30) N = 2233	*p*-value
Baseline characteristics				
Age (years)	54 ± 16	47 ± 13	55 ± 17	<0.01
Male	1759 (84 %)	304 (67 %)	1455 (65 %)	0.58
Body weight (kg)	69.9 ± 17.5	94.9 ± 16.3	64.8 ± 12.7	<0.01
Height (cm)	165.2 ± 9.5	166.3 ± 9.5	165.0 ± 9.5	0.01
Body mass index (kg/m^2)	24.7 (21.7–28.1)	32.9 (31.0–35.7)	23.8 (21.3–26.1)	<0.01
D-dimer level at admission (μg/mL) (N = 2615)	0.8 (0.5–1.3)	0.8 (0.5–1.2)	0.8 (0.5–1.3)	0.13
Comorbidities				
Hypertension	833 (31 %)	184 (40 %)	649 (29 %)	<0.01
Diabetes mellitus	567 (21 %)	157 (34 %)	410 (18 %)	<0.01
Heart disease	234 (8.7 %)	28 (6.1 %)	206 (9.2 %)	0.03
Respiratory disease	276 (10 %)	50 (11 %)	226 (10 %)	0.60
Active cancer	57 (2.1 %)	1 (0.2 %)	56 (2.5 %)	<0.01
History of major bleeding	27 (1.0 %)	3 (0.7 %)	24 (1.1 %)	0.60
History of VTE	15 (0.6 %)	3 (0.7 %)	12 (0.5 %)	0.73
Severity of COVID-19 at admission				
Mild	1584 (59 %)	245 (54 %)	1339 (60 %)	0.02
Moderate (Need oxygen)	880 (33 %)	163 (36 %)	717 (32 %)	
Severe (Need mechanical ventilation /ECMO)	226 (8.4 %)	49 (11 %)	177 (7.9 %)	
Pharmacological thromboprophylaxis during hospitalization				
Anticoagulants	1190 (44 %)	250 (55 %)	940 (42 %)	<0.01
Prophylactic dose of unfractionated heparin	647/1190 (54 %)	139/250 (56 %)	508/940 (54 %)	0.48
Therapeutic dose of unfractionated heparin	155/1190 (13 %)	27/250 (11 %)	128/940 (14 %)	
Prophylactic dose of low-molecular-weight heparin	197/1190 (17 %)	33/250 (13 %)	164/940 (17 %)	
Therapeutic dose of low-molecular-weight heparin	0/1190 (0 %)	0/250 (0 %)	0/940 (0 %)	
Direct oral anticoagulants	162/1190 (14 %)	46/250 (18 %)	116/940 (12 %)	
Warfarin	17/1190 (1.4 %)	2/250 (0.8 %)	15/940 (1.6 %)	
Others	12/1190 (1.0 %)	3/250 (1.2 %)	9/940 (1.0 %)	
Imaging examinations during hospitalization				
Ultrasound examination of the lower extremities	37 (1.4 %)	8 (1.8 %)	29 (1.3 %)	0.57
Contrast-enhanced CT examination	121 (4.5 %)	20 (4.4 %)	101 (4.5 %)	0.89

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using the Student's t-test or Wilcoxon's rank sum test based on distribution.
BMI, body mass index; VTE, venous thromboembolism; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; CT, computed tomography.

insignificant (adjusted OR, 1.39; 95 % CI, 0.68–2.84, $p = 0.37$) (Table 3). Similarly, the risk of obesity relative to non-obesity for VTE alone was insignificant (adjusted OR, 1.47; 95 % CI, 0.66–3.27, $p = 0.35$). On the other hand, the adjusted risk of obesity relative to non-obesity for the composite outcome during the hospitalization was still significant (adjusted OR, 1.85; 95 % CI, 1.39–2.47, $p < 0.01$).

Discussion

The main findings of the present study were as follows: 1) obesity was associated with severe status of COVID-19 during hospitalization; and 2) there was not a statistically significant difference in the incidence of VTE between the groups.

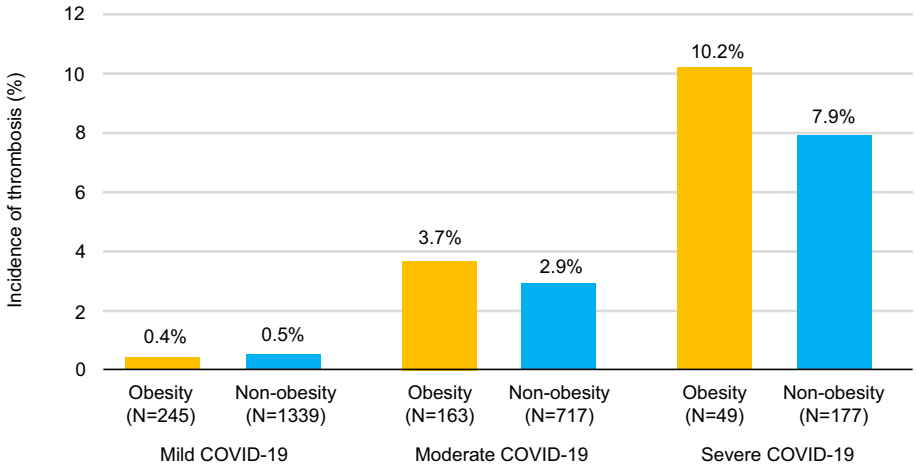

Fig. 3. Incidence of thrombosis comparing obesity and non-obesity group according to the severity of COVID-19 at admission.
COVID-19, coronavirus disease 2019.

Table 2
Clinical outcomes during hospitalization.

	Total N = 2690	Obesity group (BMI ≥ 30) N = 457	Non-obesity group (BMI < 30) N = 2233	*p*-value
Thrombosis	54 (2.0 % [1.5–2.6 %])	12 (2.6 % [1.5–4.5 %])	42 (1.9 % [1.4–2.5 %])	0.39
VTE	39 (1.5 % [1.1–2.0 %])	10 (2.2 % [1.2–4.0 %])	29 (1.3 % [0.9–1.9 %])	0.15
Arterial thrombotic events	12 (0.4 % [0.3–0.8 %])	2 (0.4 % [0.1–1.6 %])	10 (0.4 % [0.2–0.8 %])	–
Ischemic stroke	9/12 (75 %)	1/2 (50 %)	8/10 (80 %)	–
Myocardial infarction	2/12 (17 %)	1/2 (50 %)	1/10 (10 %)	–
Systemic arterial thromboembolism	1/12 (8 %)	0/2 (0 %)	1/10 (10 %)	–
Other thrombosis	6 (0.2 % [0.1–0.5 %])	0 (0.0 % [0.0–0.8 %])	6 (0.2 % [0.1–0.6 %])-	–
Major bleeding	56 (2.1 % [1.6–2.7 %])	11 (2.4 % [1.3–4.3 %])	45 (2.0 % [1.5–2.7 %])	0.59
All-cause death	145 (5.4 % [4.6–6.3 %])	20 (4.4 % [2.9–6.7 %])	125 (5.6 % [4.7–6.6 %])	0.29
All-cause death, or need MV or ECMO during hospitalization	426 (15.8 % [14.5–17.3 %])	92 (20.1 % [16.7–24.0 %])	334 (15.0 % [13.5–16.5 %])	<0.01

Clinical outcomes are presented as numbers of events and percentages with the 95 % confidence intervals, which were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used.
BMI, body mass index; VTE, venous thromboembolism; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

Consistent with a lot of previous reports [1,11,12,14,16,25–33], the present study identified that obesity was independently associated with severe status of COVID-19 during hospitalization. Obesity may lead to an impaired immune system and reduced respiratory function [10,34]. Gene expression of angiotensin-converting enzyme 2 receptor, a cellular receptor for the virus, is up-regulated in adipose tissue in patients with obesity, which may facilitate the entry of the virus into cells [35]. The underlying mechanism may account for obesity causing disease progression in COVID-19 patients. There was consistency between our observation with a large dataset from Japan and previous studies; however, the risk of worsening of COVID-19 may vary according to differences in race or ethnicity, resource availability in each country, and different virus variants; thus, caution should be taken in generalizing these results.

Several previous reports suggested obesity led to an increased risk of thrombosis associated with COVID-19 [21,25,36], but the issue remains controversial. Hendren et al. reported that class II obesity ($35 \leq BMI < 40\ kg/m^2$) increased with the risk of VTE, but class I ($30 \leq BMI < 35\ kg/m^2$) and class III ($40\ kg/m^2 \leq BMI$) did not increase significantly, and did not find that obesity consistently conferred risk of developing VTE [25]. The present study showed an increased incidence of thrombosis in the patients with increased severity of COVID-19, and obesity did not statistically significantly lead to an increased rate of thrombosis. Previous reports from Japan showed patients with VTE had higher BMI, but also had more severe status of COVID-19 [21,36]. Thus, these findings may indicate that development of VTE was attributable mainly to increased severity of COVID-19, but not to obesity. Additionally, our findings are consistent with a recent meta-analysis that found that some risk factors of VTE, including obesity, were not associated with VTE in patients with COVID-19 [37]. These results support the hypothesis that immune-thrombosis is implicated in the thrombosis associated with COVID-19 [38]. Severe status of COVID-19 may lead to hyperactivation of the immune system, causing hypercoagulation presenting with D-dimer elevation and vascular endothelial dysfunction, resulting in immune-thrombosis in small to large vessels [38]. Patients with obesity should be treated with sufficient attention to disease progression; however, obesity might not be a strong risk factor of thrombosis, which suggested that patients with obesity might not have to receive routine pharmacological thromboprophylaxis especially among clinically stable patients.

Study limitations

The present study has several limitations. First, the present study was based on an observational study and the clinical management including vaccination, anti-viral treatment, and prophylactic anticoagulation was determined by the discretion of the attending physicians, which may have influenced the clinical outcomes. In addition, VTE screening had not been performed in all patients, which could lead to the underdiagnosis of thrombosis. Second, the number of patients with severe obesity (BMI ≥ 35) was small, which may have influenced our evaluation of the association between severe obesity and thrombosis. Finally, the present study investigated only clinical outcomes during hospitalization; thus, the influence of obesity on thrombosis after hospital discharge *remains unclear.*

Conclusions

In the present large-scale observational study, obesity was not significantly associated with the development of thrombosis during hospitalization; however, it was associated with severity of COVID-19.

Table 3
Crude and adjusted clinical outcomes.

	Non-obesity group (BMI < 30) (Reference) N = 2233	Obesity group (BMI ≥ 30) N = 457				
	Numbers of events during hospitalization (percentages)	Numbers of events during hospitalization (percentages)	Crude OR (95 % CI)	*p*-value	Adjusted OR (95 % CI)	*p*-value
Thrombosis	42 (1.9 %)	12 (2.6 %)	1.41 (0.73–2.69)	0.30	1.39 (0.68–2.84)	0.37
All-cause death, or need MV or ECMO during hospitalization	334 (15.0 %)	92 (20.1 %)	1.43 (1.11–1.85)	<0.01	1.85 (1.39–2.47)	<0.01

Crude and adjusted ORs and 95 % CIs were estimated by the multivariable logistic regression model using non-obesity group as the reference. We selected 5 risk-adjusting variables of baseline characteristics (age, sex, D dimer levels at admission >1.0 μg/ml, severity of COVID-19 at admission, and pharmacological thromboprophylaxis) for thrombosis, and 7 risk-adjusting variables of baseline characteristics (age, sex, hypertension, diabetes mellitus, heart disease, respiratory disease, active cancer) for the composite outcome.
BMI, body mass index; OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.08.011.

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