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A nationwide cohort study

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ORIGINAL ARTICLE

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The impact of age and obesity on outcomes among patients hospitalized with COVID-19 in Denmark: A nationwide cohort study

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Abstract

Purpose: Obesity may alter the severity of infection with Coronavirus disease 2019 (COVID-19). Age may impact the association between body weight and severity of COVID-19 in patients with obesity. The aim of the study was to examine the association between obesity and severity of infection in a Danish cohort hospitalized with COVID-19 in the initial wave of the pandemic.

Patients and methods: Based on data from the nationwide, clinical database: COVID-DK, risks of intensive care unit (ICU) admission, invasive mechanical ventilation (IMV), and mortality were compared among patients with and without obesity. Interaction with age was examined and we used Inverse Probability of Treatment Weighting regression for confounder adjustment.

Results: Among 524 patients, 142 (27%) were admitted to the ICU, 112 (21%) required IMV, and 109 (21%) died. Compared to COVID-19 patients without

obesity, patients with obesity displayed a non-significant increased risk of ICU admission (Relative Risk [RR] 1.19, 95% Confidence Interval [CI] 0.88; 1.60), IMV (RR 1.23, CI 0.86; 1.75) and mortality (RR 1.21, CI 0.84; 1.75). COVID-19 patients with obesity, <60 years had highly increased risk of ICU admission (RR 1.92, CI 1.14; 3.24) and IMV (RR 1.95, CI 1.09; 3.49).

Conclusions: In hospitalized COVID-19 patients, obesity conferred an approximately 20% increased risk for ICU admission, IMV, and death, although these relationships did not reach statistical significance. COVID-19 patients with obesity and <60 years had an almost doubled risk of ICU admission and IMV.

KEYWORDS
body mass index (BMI), infections, mortality, obesity

1 | INTRODUCTION

Coronavirus Disease 2019 (COVID-19) may lead to severe disease, hospitalization, and risk of death.[1] Knowledge on prognostic factors for the development of severe COVID-19 is crucial to identify vulnerable populations, thereby guiding both vaccination prioritization and ensuring timely interventions as well as intensive care.

Previous studies have highlighted increasing Body Mass Index (BMI) as a potential prognostic factor for adverse outcomes of COVID-19,[2–5] including increased risk of hospitalization, admission to intensive care units (ICU), the need for invasive mechanical ventilation (IMV), and possibly mortality.[3–5] Hospitalization criteria may differ between health care systems, however, previous reports spanning geographically wide report odds ratios between 1.4 and 2.5[5–7] when comparing hospitalization risk among patients with obesity to patients without obesity. Furthermore, median duration of admission may be prolonged for patients with obesity.[8] Regarding ICU admission, a recent umbrella review from our group found that COVID-19 patients with obesity, as compared to patients without obesity, had 1.3–2.3 increased odds of ICU admission.[5] IMV display evidence of a severe disease course and pulmonary complications.[9] In patients with obesity, the risk of IMV is also increased with odds ratios of 1.5–2.6.[5,9]

The previously mentioned umbrella review observed diverging findings on associations between obesity and mortality from COVID-19, though data trended toward increased mortality.[5] In contrast, another recent umbrella review reported no increased mortality associated with obesity in COVID-19 patients.[10] As mortality is a less likely outcome than hospitalization, ICU admission, and IMV, these associations remain unclear.

Importantly, the potential augmentation of COVID-19 disease severity and mortality associated with obesity might be age dependent.[11,12] Chu et al. found obesity to be a stronger prognostic factor for a poor composite endpoint including severe COVID-19, ICU admission, IMV, mortality, and disease progression in younger adults (<60 years) as compared to older adults (≥60 years).[11] Similarly, Kompaniyets et al. observed increased risk of hospitalization and death in non-elderly (<65 years) COVID-19 patients with obesity.[12] Furthermore, Bhasin et al. reported that patients younger than 50 years admitted due to COVID-19 had a higher BMI than those aged ≥50 years.[13] The finding was consistent in subgroups including patients with diabetes and hypertension and was not observed in patients without COVID-19, suggesting that obesity confers an altered disease-burden related to age.

Obesity is associated with metabolic changes with low-grade chronic inflammation and inappropriate secretion of immunological active proteins (e.g., interleukin(IL)-6, IL-1β), derived from cells from both the immune system and the adipose tissue,[14] which create an auto-regenerating state of inflammation, ultimately immune impairment, and hypercoagulability.[15] Furthermore, obesity-related comorbidities including cardiovascular disease, diabetes mellitus, and hypertension may affect the clinical course of COVID-19 negatively,[16–18] as well as obesity-related mechanical ventilation problems such as weaning from mechanical ventilation and reduced lung volume due to excess intra-abdominal fat.[19,20] The COVID-19 pandemic coincides with an ongoing global obesity pandemic with nearly 40% of all adults living with overweight, of these 13% with obesity worldwide.[21] In Denmark, overweight and obesity estimates are approximately 53% and 18%, respectively.[22] It is therefore of utmost importance to clarify whether patients with obesity should be regarded as a high-risk group for severe COVID-19.

2 | METHODS

2.1 | Setting, study design, and participants

Denmark has a tax-financed healthcare system free-of-charge for all residents; a system that throughout the pandemic did not reach capacity limits of available hospital beds.[23] Participants were included from the national COVID-19 database (COVID-DK)[24,25] of hospitalized patients with laboratory-verified COVID-19 at six

departments of infectious diseases at hospitals in Aalborg, Aarhus, Odense, Copenhagen University Hospitals at Amager/Hvidovre, Hillerød, and Rigshospitalet in Denmark (population ~5.8 million individuals) between 27 February 2020 (the date of the first COVID-19 diagnosis in Denmark) and 4 May 2020. Using an online case-report form (REDCap)[26] COVID-DK holds information on baseline characteristics (anthropometric measures, sex, age, comorbidities, and smoking and alcohol habits), outcomes of COVID-19 (ICU admission, IMV, and overall mortality), symptoms, and signs at admission, biochemical markers, and radiological examinations. Data in COVID-DK was assessed by a local investigator through review of electronic medical records. Patients in the cohort were followed from the date of positive test for COVID-19 until the date of VTE, major bleeding, emigration out of Denmark, death, or date of last medical record review (4 May 2020). The study was approved by the Danish Board of Health (ID: 31-1522-84) and registered at the University of Southern Denmark (ID: 10.960) and the legal authorities in North Denmark Region (ID: 2020-045). Patient consent or approval from an ethical committee was not required for this study in Denmark.

2.2 | Exposure and outcomes

We divided patients into two groups by baseline BMI according to the WHO obesity classification.[21] Patients without obesity were defined as those having a BMI <30 kg/m^2 and patients with obesity as those with BMI ≥30 kg/m^2. Due to the relatively small number of patients with COVID-19, it was not possible to differentiate between different degrees of obesity (different BMI classes). Main outcomes were defined as admission to an ICU, treatment with IMV, and all-cause mortality.

2.3 | Confounding factors

Confounding factors considered possible were age, sex, and comorbidity. Comorbidities included arterial hypertension, congestive heart failure, ischemic heart disease, diabetes mellitus, hypercholesterolemia, chronic obstructive pulmonary disease (COPD)/asthma, liver disease, alcoholism, immune-suppressive treatment, and other immune-suppressive conditions. Covariates were selected based on prior literature review and clinical judgment, focusing on variables that might confound the association between BMI and the main outcome.[27–32]

2.4 | Statistical analyses

For every patient in the cohort, a propensity score (PS) was computed, that is the probability of having the exposure (e.g., having obesity vs. not having obesity), using a logistic regression model including the covariates in Table 1, excluding "Any comorbidity". The PS was used for Inverse Probability of Treatment Weighting (IPTW) with stabilized weights to create a pseudo-population in which covariate distribution was independent of BMI group and used it to estimate the average exposure effect in the cohort.[33] Stabilized weights below the 1st and above the 99th percentiles were truncated to the value of the 1st and 99th percentile, respectively. Covariate balance before and after weighting was assessed using standardized mean differences (SMD). Although there is no universally accepted criterion for a threshold of SMD to indicate imbalance, it is commonly agreed that SMD above 10% may indicate meaningful imbalance.[34]

Baseline characteristics (age and sex) and individual comorbidities (as described above) were compared according to BMI group and tabulated before and after weighting. Weighted relative risks (RRs) of the main outcomes for the entire cohort with obesity versus without obesity were estimated with robust sandwich-type 95% Confidence Intervals (CIs) using a generalized linear model with a binomial distribution and a log link. Next, potential obesity effect-modification by age group was addressed (<60 years vs. ≥60 years). Thereafter, a secondary IPTW cohort balanced on age and sex was created to estimate age-sex standardized risk differences (RDs) of the main outcomes. RDs were estimated similarly to RRs but using an identity link. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Among 749 patients admitted to a department of infectious diseases with a laboratory-verified COVID-19 and registered in the COVID-DK database between 27 February 2020, and 4 May 2020, 524 (70%) had BMI data available for analysis. Among the 524 patients hospitalized with COVID-19, 142 (27%) were admitted to the ICU, 112 (21%) required IMV, and 109 (21%) died. 175 (33%) of all COVID-19 patients had obesity. Compared with COVID-19 patients without obesity, patients with obesity were slightly younger (median age: 68 vs. 71 years, $p = 0.01$), but had more comorbidity (79% had any comorbidity vs. 69%, $p = 0.01$), with no sex differences. The characteristics of the main IPTW cohort were well balanced after weighting (Figure 1) and are compared to the unweighted cohort in Table 1. The characteristics of the secondary IPTW cohort were similarly well balanced (data not shown).

3.1 | Outcomes of COVID-19

In the unadjusted model, patients with obesity were found to have a non-significantly increased risk of ICU admission (RR 1.26, CI 0.94; 1.67, Table 2), use of IMV (RR 1.29, CI 0.92; 1.79, Table 2), and mortality (RR 1.07, CI 0.74; 1.50, Table 2). After adjustment for potential confounders using IPTW, patients with obesity had an

TABLE 1 Characteristics of patients with and without obesity before and after main inverse probability of treatment weighting

	Unweighted cohort			Main IPTW cohort		
BMI	Without obesity <30	With obesity ≥30	SMD	Without obesity <30	With obesity ≥30	SMD
Overall						
n	349	175		348	173	
Sex, *n* (%)						
Male	208 (60)	98 (56)	−0.1	203 (58)	99 (57)	0.0
Age, median (IQR)						
Years	71 (58–81)	68 (56–75)	−0.2	70 (57–80)	69 (59–76)	0.0
Comorbidity, *n* (%)						
Any comorbidity	239 (69)	139 (79)	0.3	248.9 (72)	126.6 (73)	0.0
Arterial hypertension	133 (38)	90 (51)	0.3	146.6 (42)	73.1 (42)	0.0
Congestive heart failure	23 (7)	11 (6)	0.0	23.1 (7)	12.3 (7)	0.0
Ischemic heart disease	34 (10)	22 (13)	0.1	38.4 (11)	19.2 (11)	0.0
Diabetes mellitus	61 (18)	56 (32)	0.3	76.4 (22)	39.0 (23)	0.0
Hypercholesterolemia	62 (18)	50 (29)	0.3	73.9 (21)	38.3 (22)	0.0
COPD/asthma	63 (18)	42 (24)	0.1	67.4 (19)	33.4 (19)	0.0
Liver disease	6 (2)	*n* < 5	−0.1	*n* < 5	*n* < 5	0.0
Alcoholism	11 (3)	*n* < 5	−0.1	9.6 (3)	5.6 (3)	0.0
Immuno-suppressive treatment	16 (5)	12 (7)	0.1	17.8 (5)	8.9 (5)	0.0
Other immuno-suppressive condition or comorbidity	43 (12)	18 (10)	−0.1	42.1 (12)	23.0 (13)	0.0

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting; SMD, standardized mean differences.

approximately 20% increased risk of all three clinical outcomes, albeit statistically imprecise: ICU admission RR 1.19, CI 0.89; 1.58, use of IMV RR 1.23, CI 0.88; 1.72 and mortality RR 1.21, CI 0.86; 1.71. Point estimates tended toward increased risk of all main outcomes in patients with obesity (Figure 2 and Table 2).

Next, younger patients were compared to older patients (<60 vs. ≥60 years) to assess whether age modified the association between high BMI and severe outcomes of COVID-19. For patients with obesity <60 years, there was a clearly increased risk for both ICU admission (RR 1.92, CI 1.14; 3.24) and for IMV (RR 1.95, CI 1.09; 3.49). For patients with obesity ≥60 years, there was no increased risk of ICU admission (RR 0.97, CI 0.67; 1.42) or IMV (RR 1.00, CI 0.64; 1.56). In relation to mortality, no association between obesity and mortality was observed in patients <60 years, however, fatal outcomes were too rare ($n \leq 5$) for meaningful estimation (RR 0.56, CI 0.13; 3.31). Among patients ≥60 years, the mortality RR associated with obesity was 1.20, CI 0.84; 1.73 (Figure 2 and Table 2).

As seen from Table 3, an association between obesity and higher crude risks of ICU admission (31% vs. 25%), IMV (25% vs. 20%), and death (22% vs. 20%) was found. When standardizing the differences in age and sex (i.e., younger age and female sex associated with obesity), the ICU admission RD was 6% (CI −2%; 14%), the IMV RD was 5% (CI −3%; 13%) and the mortality RD was 4% (CI −4%; 11%), though all estimates had limited statistical precision (Table 3).

4 | DISCUSSION

In this prospective nationwide cohort study, data from more than 500 patients hospitalized with COVID-19 during the initial wave of the pandemic was analyzed. Obesity was found to confer an approximately 20% increased risk for ICU admission, IMV, and death following COVID-19 but statistical precision for these findings was limited, which may hamper clear conclusions, however, our results are in line with findings from previous studies.[2,3,9] Among patients with COVID-19 younger than 60 years, obesity was associated with an almost 2-fold increased risk of ICU admission and IMV. These findings indicate substantial effect-modification of age on the impact of obesity on COVID-19 disease severity.

The strengths of the present study were its nationwide design including all COVID-19 patients admitted to a department of infectious diseases in Denmark during the study period with virtually

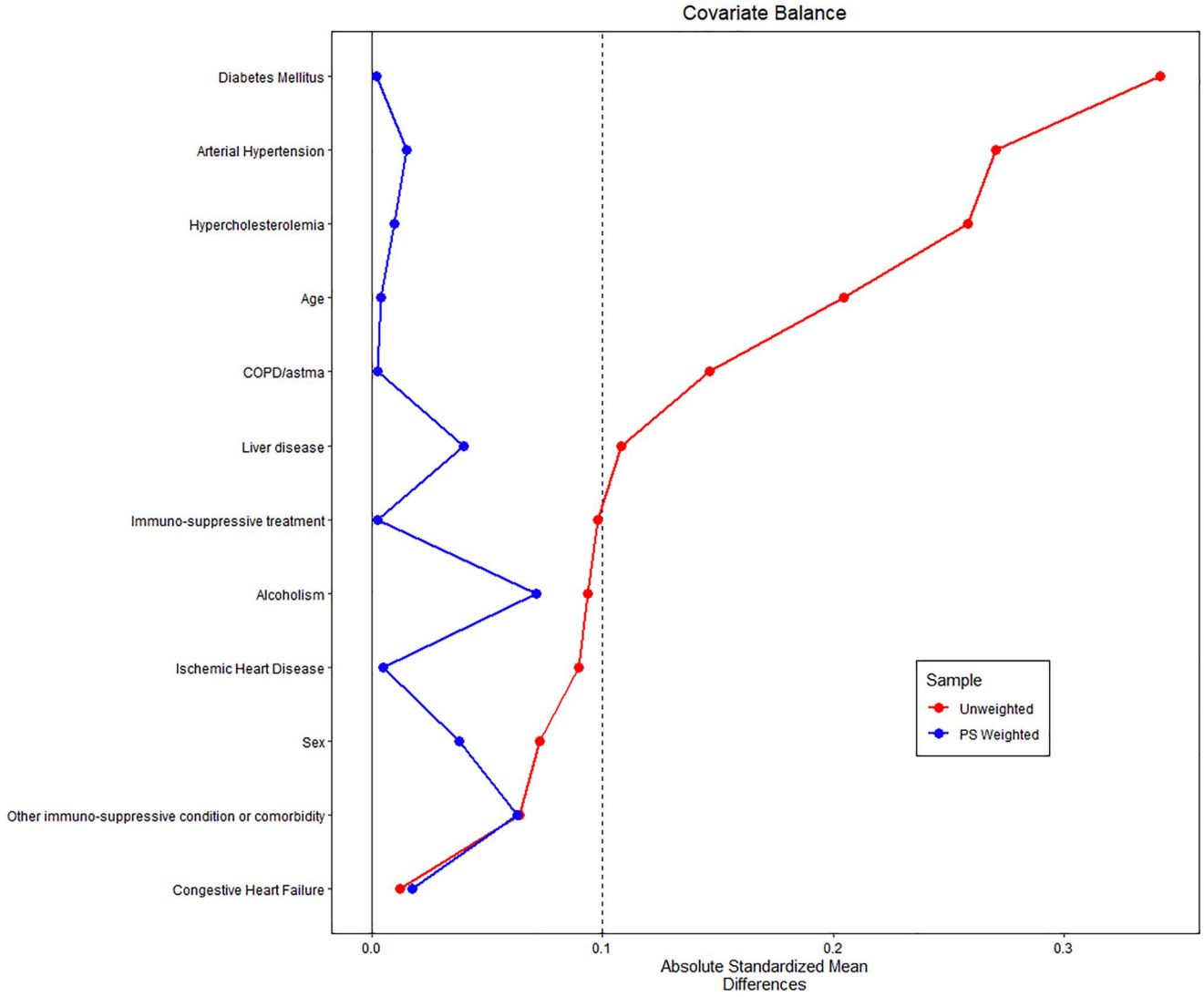

FIGURE 1 Love plot of standardized mean differences in the main inverse probability of treatment weighting cohort for each covariate before and after weighting.

TABLE 2 Crude RR and weighted RR for ICU admission, IMV, and mortality associated with obesity, overall and stratified by age

	All patients		Patients aged <60 years		Patients aged ≥60 years	
BMI	Without obesity <30	With obesity ≥30	Without obesity <30	With obesity ≥30	Without obesity <30	With obesity ≥30
ICU admission	87 (25%)	55 (31%)	20 (21%)	21 (40%)	67 (27%)	34 (28%)
Crude RR (95% CI)	1	1.26 (0.94; 1.67)	1	1.92 (1.15; 3.25)	1	1.05 (0.73; 1.48)
Model 1[a]	1	1.19 (0.88; 1.60)	1	1.92 (1.14; 3.24)	1	0.97 (0.67; 1.42)
IMV	68 (20%)	44 (25%)	17 (18%)	18 (34%)	51 (20%)	26 (21%)
Crude RR (95% CI)	1	1.29 (0.92; 1.79)	1	1.94 (1.09; 3.48)	1	1.05 (0.68; 1.58)
Model 1[a]	1	1.23 (0.86; 1.75)	1	1.95 (1.09; 3.49)	1	1.00 (0.64; 1.56)
Mortality	71 (20%)	38 (22%)	$n \leq 5$	$n \leq 5$	66 (26%)	36 (30%)
Crude RR (95% CI)	1	1.07 (0.74; 1.50)	1	0.73 (0.11; 3.27)	1	1.13 (0.79; 1.58)
Model 1[a]	1	1.21 (0.84; 1.75)	1	0.65 (0.13; 3.31)	1	1.20 (0.84; 1.73)

Abbreviations: BMI, body mass index; ICU, Intensive Care Unit admission; IMV, invasive mechanical ventilation; RR, relative risk.

[a]Weighted for sex, age, and comorbidity using IPTW.

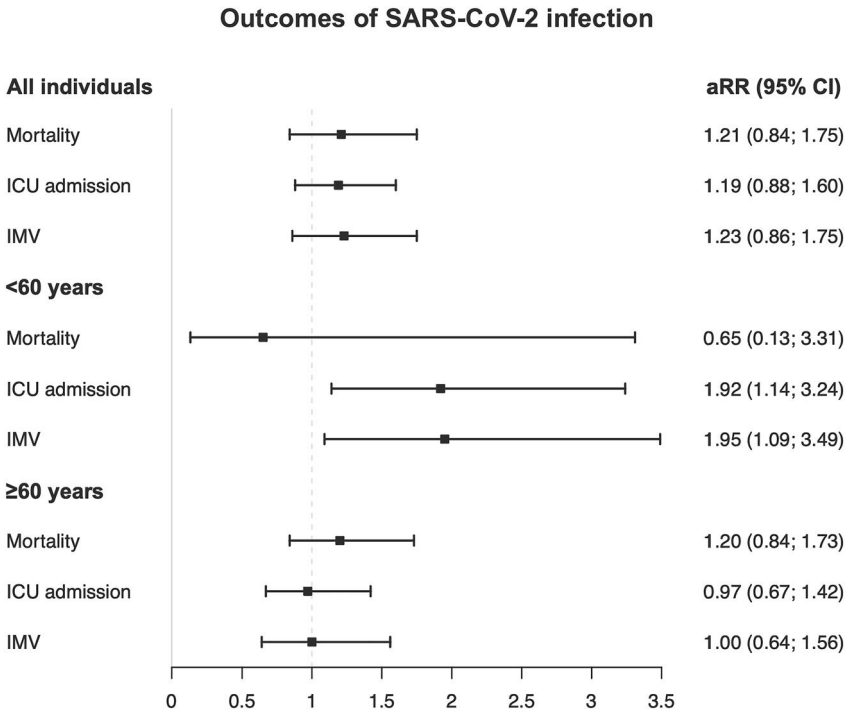

FIGURE 2 Association between having obesity and outcomes of COVID-19 in the main IPTW cohort, in patients aged <60 years, and in patients aged ≥60 years. ICU, Intensive Care Unit admission; IMV, invasive mechanical ventilation; IPTW, inverse probability of treatment weighting

TABLE 3 Crude risks and age and sex standardized RD in the secondary IPTW cohort for clinical outcomes among COVID-19 patients with and without obesity

BMI	Without obesity <30	With obesity ≥30
ICU admission		
n (%)	87 (25)	55 (31)
RD (95% CI)	Ref.	6 (−2; 14)
IMV		
n (%)	68 (20)	44 (25)
RD (95% CI)	Ref.	5 (−3; 13)
Mortality		
n (%)	71 (20)	38 (22)
RD (95% CI)	Ref.	4 (−4; 11)

Abbreviations: BMI, body mass index; ICU, Intensive Care Unit admission; IMV, invasive mechanical ventilation; IPTW, inverse probability of treatment weighting; RD, risk differences.

complete follow-up. Free access to an advanced healthcare system for all residents limits geographical and socio-economical selection bias. This study also has limitations. First, 30% of patients in COVID-DK were excluded due to unavailability of BMI data. These patients were younger (median age: 63 vs. 70 years) and less comorbid (57% had any comorbidity vs. 72%) than patients in the study population (Table S1). If clinicians less frequently measured BMI in younger versus older patients with obesity, the general obesity prevalence in the younger age group may have been underestimated, but this is not anticipated to cause significantly biased associations with the measured outcomes. Second, data on waist circumference were not available. Studies[35,36] have demonstrated that individuals can be metabolically healthy overweight (MHO), and that analyzing on waist circumference may be more representative of the real burden of obesity. Third, due to limited sample size it was not possible to make comparisons between patients with overweight (i.e., 25 kg/m^2 ≤ BMI < 30 kg/m^2), normal weight (i.e., 18.5 kg/m^2 ≤ BMI < 25 kg/m^2), and underweight (i.e., BMI <18.5 kg/m^2). Previous studies[12,37] have indicated an enhanced disease burden and mortality from COVID-19 among patients with underweight, probably related to malnourishment, impairment in immune response, or occult disease associated with weight loss.[38] Including patients with underweight in the reference group may result in an underestimation of the prognostic impact of obesity, though this is not anticipated in the present study as ≤10 patients had underweight. Fourth, not all hospitalized patients with COVID-19 in Denmark were admitted to a department of infectious diseases. Patients admitted to general medical wards likely experienced milder disease courses or treatment at specialized departments was considered futile, and the generalizability of our results may be limited to this subgroup.

While there are a few discrepancies in the literature, the observed association of obesity with increased risk of severe COVID-19 in younger patients is consistent with several other studies.[3,37,39–41] A recent US-based study limited to a single hospital comparing younger (<60 years) COVID-19 patients with severe obesity (BMI ≥35) to older COVID-19 patients with severe

obesity found an increased odds of ICU admission (Odds Ratio [OR] 3.6 [2.5; 5.3] vs. OR 1.5 [0.9; 2.3])[39] in the younger population. Thus, the present clinical cohort extends previous findings in a Danish nationwide cohort of all patients admitted to a department of infectious diseases with microbiologically confirmed COVID-19.[3,39,41] Several other studies found robust associations between obesity and COVID-19 related mortality.[3,12,37,42–45] However, a limited sample size likely conferred a statistically imprecise increased risk of death among hospitalized COVID-19 patients with obesity in the present study.

The increased severity of COVID-19 associated with obesity is hypothesized to be multifaceted. Obesity is associated with chronic low-grade inflammation, oxidative stress, and endothelial dysfunction.[14,15] A subsequent viral infection could activate the impaired immune system to create a cytokine storm which in combination with endothelial dysfunction may cause circulatory defects and multiorgan damage.[46] Moreover, obesity may lead to other comorbidities such as cardiovascular disease, diabetes mellitus, and hypertension,[16,17] which can have detrimental impact on the clinical course of COVID-19.[18] In addition, there may be mechanical problems, since obesity is associated with complications in intubation[19] and with difficulty weaning from mechanical ventilation[20] in addition to mechanically compressing the thorax hampering ventilation.[47]

5 | CONCLUSION

The present study in a Danish cohort hospitalized with COVID-19 showed that obesity conferred an approximately 20% increased risk of ICU admission, IMV, and death following COVID-19 diagnosis, but statistical precision for these findings was limited. Among patients with COVID-19 younger than 60 years, obesity was a strong prognostic factor both for ICU admission and IMV.

AUTHOR CONTRIBUTIONS

Bjørn Richelsen, Sigrid Bjerge Gribsholt and Jens Meldgaard Bruun conceived and designed the study. Anton Lund Andersen and Lars Pedersen conducted statistical analyses. Jens Meldgaard Bruun and Sigrid Bjerge Gribsholt obtained funding. Jacob Bodilsen, Reimar Wernich Thomsen, Thomas Lars Benfield, Ole Søgaard, Stig Lønberg Nielsen, Lars Haukali Omland, and Birgitte Lindegaard aided in acquisition of data. Jens Meldgaard Bruun, Sigrid Bjerge Gribsholt, Reimar Wernich Thomsen, and Bjørn Richelsen supervised the study. Anton Lund Andersen wrote first draft, which has been critically reviewed and approved by all authors.

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CONFLICT OF INTEREST

Jens Meldgaard Bruun, Sigrid Bjerge Gribsholt and Bjørn Richelsen received honoraria for lectures at Novo Nordisk Denmark A/S. Thomas Lars Benfield received grants or contracts from Novo Nordisk Foundation, Simonsen Foundation, Lundbeck Foundation, Kai Foundation, Erik and Susanna Olesen's Charitable Fund, GSK, Pfizer, Boehringer Ingelheim, Gilead Sciences, MSD, Pentabase, Roche, Novartis, Kancera AB, Janssen, and Astra Zeneca. Thomas Lars Benfield received honoraria for lectures at GSK, Pfizer, Gilead Sciences, Boehringer Ingelheim, Abbvie, and Astra Zeneca. TLB received donation of trial medication from Eli Lilly. Other authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

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