Long-Term Impairments Are Most Pronounced in Critically Ill Patients with COVID-19 with Severe Obesity

To the Editor:

Although obesity is an important risk factor for the development of severe coronavirus disease (COVID-19) (1), once admitted to the ICU, no clear relationship between body mass index (BMI) and short-term outcomes is present (2). Many patients experience long-term symptoms after an ICU admission with COVID-19 (3, 4), but it is unknown whether the prevalence rates of long-term symptoms differ between different BMI groups. Therefore, this study aimed to examine the differences between BMI categories in the occurrence of physical, mental, and cognitive symptoms 3 and 12 months after ICU treatment in critically ill patients with COVID-19.

Methods

In this prospective multicenter cohort study, patients with COVID-19 admitted to ICUs in 11 Dutch hospitals between March 1, 2020 and July 1, 2020 were included after obtaining informed consent (5). Patients received three questionnaires regarding their health status: pre-ICU (baseline; answered in retrospect as soon possible after ICU admission), and 3 and 12 months after ICU treatment, which could be completed by the patient or a proxy. Patients who completed the baseline and 12-month follow-up questionnaires without missing data on BMI were included in the analyses. Four hospitals were not able to provide 3-month data. Primary outcomes were occurrence of physical (fatigue and new physical problems), mental (symptoms of anxiety, depression, and post-traumatic stress disorder [PTSD]), and cognitive symptoms. Patients were categorized into BMI categories according to the World Health Organization definition: normal weight (18.5–25.0 kg/m^2), overweight (25.0–30.0 kg/m^2), obese class I (30.0–35.0 kg/m^2), and obese class II/III ($\geq$35.0 kg/m^2) (6). Differences in patient characteristics between BMI categories were tested using χ^2 or Kruskal-Wallis tests followed by *post hoc* pairwise χ^2 or Dunn's multiple comparisons tests, respectively. Differences in symptom occurrence rates between BMI categories were tested using multivariable logistic regression analysis including the following covariables: age, sex, severity of illness (Acute Physiology and Chronic Health Evaluation IV [APACHE IV]), and length of stay in the ICU. In addition, the presence of symptoms pre-ICU was included as covariable for the 3- and 12-month analysis. Furthermore, differences in change in outcome scores between baseline and both moments of follow-up were tested using linear regression analysis (available for fatigue, anxiety, depression, and cognitive impairment), including the same covariates as in the logistic regression analysis. IBM SPSS version 25 was used for the statistical analysis.

Results

A total of 302 patients participated, of whom 239 patients were included because they completed the 12-month follow-up. Included patients had similar baseline characteristics compared with nonresponders. Patients with obesity class II/III were younger, less likely male, and had a lower APACHE IV score and shorter length of stay in the ICU than normal-weight patients (Table 1). No statistically significant differences between BMI categories in baseline physical, mental, or cognitive symptoms were present (Figure 1).

Table 1. Demographic Patient Characteristics

Patient Characteristic	BMI Category*				*P* Value (Overall)
	Normal Weight, 18.5–25 kg/m^2 (*n* = 69)	Overweight, 25–30 kg/m^2 (*n* = 108)	Obesity Class I, 30–35 kg/m^2 (*n* = 41)	Obesity Class II/III, ⩾35 kg/m^2 (*n* = 21)	
Age, yr	65 (59–70)	62 (55–69)	58 (52–65)†	57 (53–61)†	<0.001
Sex, male	52 (75)	84 (78)	27 (66)	9 (43)†‡	0.01
BMI, kg/m^2	23.9 (22.9–24.6)	27.3 (26.3–28.4)†	32.6 (30.8–32.7)†‡	37.0 (36.4–39.1)†‡	<0.001
APACHE-IV	59 (49–68)	59 (49–68)	54 (43–68)	50 (42–58)†	0.02
LOS ICU, d	27 (13–39)	18 (11–31)	18 (12–28)	12 (9–20)†	0.004
LOS hospital, d	39 (25–54)	29 (20–44)	27 (18–43)	24 (15–35)†	0.006

Definition of abbreviations: APACHE-IV = Acute Physiology and Chronic Health Evaluation IV; BMI = body mass index; IQR = interquartile range; LOS = length of stay.
Data are given as median (IQR) or *n* (%).
*There were no patients with BMI < 18.5 kg/m^2.
†$P < 0.05$ compared to BMI 18.5–25 kg/m^2.
‡$P < 0.05$ compared to BMI 25–30 kg/m^2.

There is a significant interplay between the BMI categories and the incidence of physical and mental symptoms at both 3 and 12 months. This was most pronounced for the class II/III category at 3 months for symptoms of fatigue, anxiety, and PTSD (Figure 1).

At 12 months post-ICU, patients in the obesity class II/III category were still significantly more likely to experience symptoms of

Originally Published in Press as DOI: 10.1164/rccm.202202-0376LE on June 13, 2022

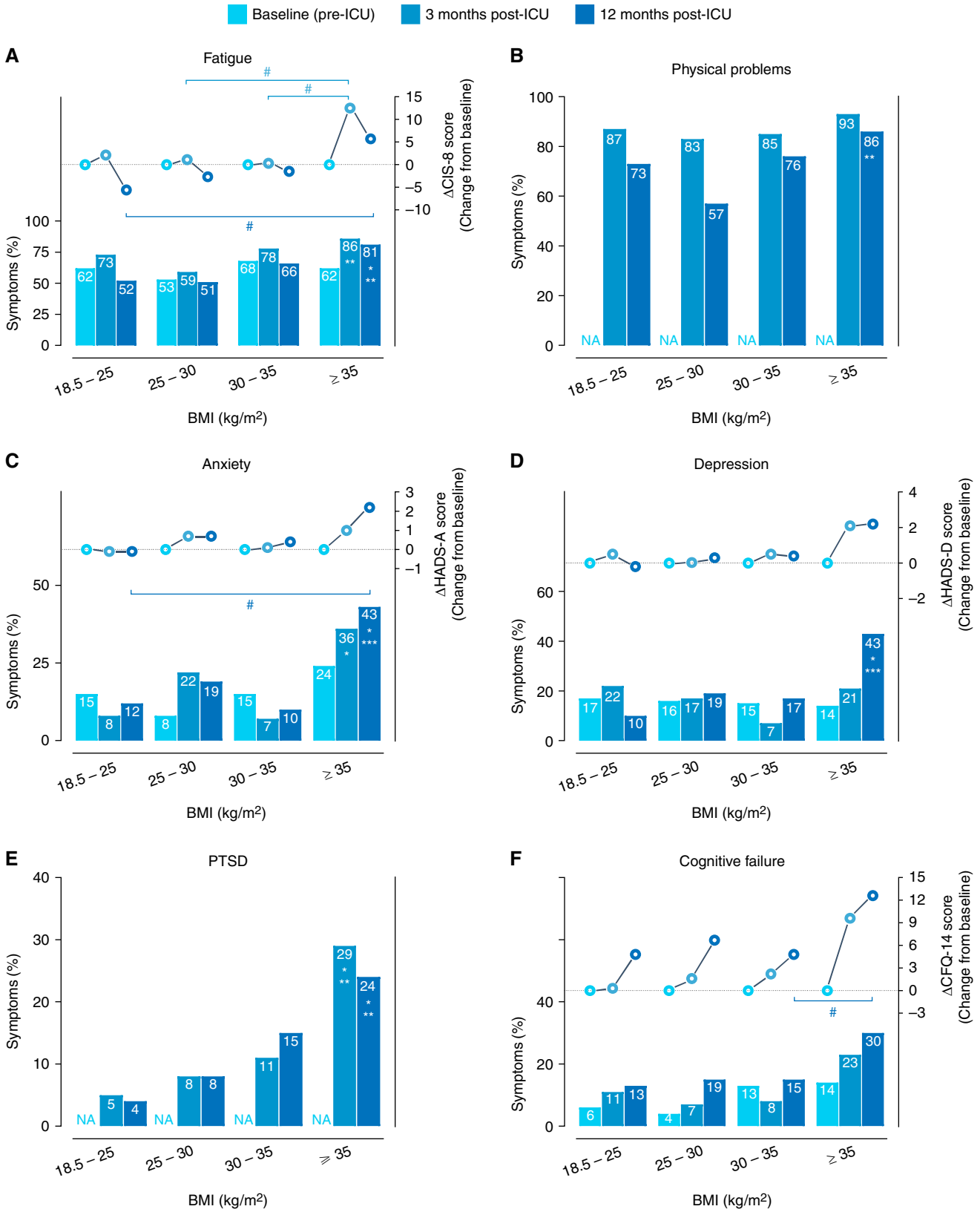

Figure 1. Prevalence of symptoms (left *y*-axis) and absolute change scores (right *y*-axis) between baseline (light blue dots) and 3-month (azure blue dots) and 12-month (dark blue dots) follow-up of (*A*) fatigue, (*B*) physical problems, (*C*) anxiety, (*D*) depression, (*E*) post-traumatic stress disorder (PTSD), and (*F*) cognitive impairment at baseline (pre-ICU), and 3 and 12 months post-ICU in different body mass index (BMI)

Figure 1. (*Continued*). categories in patients with coronavirus disease (COVID-19). Occurrence rates of PTSD as a result of ICU treatment and new physical problems as a result of ICU treatment are only available post-ICU. (*A*) Fatigue was defined by a score of ⩾27 on the Checklist for Individual Strength–Fatigue subscale (CIS-8), ranging from 8–56. (*B*) Physical problems were defined as at least one new or worsened problem (e.g., weakened condition, muscle weakness, dyspnea, abdominal problems). (*C* and *D*) Anxiety and depression symptoms were defined by a score of ⩾8 on the Hospital Anxiety and Depression Scale (HADS) anxiety (HADS-A) and depression (HADS-D) subscales, both ranging from 0–21. (*E*) Symptoms of PTSD were defined by a mean score of ⩾1.75 on the Impact Event Scale (IES)-6, ranging from 0–4. (*F*) Cognitive impairment was defined as a score of ⩾43 on the abbreviated Cognitive Failure Questionnaire (CFQ-14), ranging from 0–100. $^{*}P<0.05$ compared with BMI 18.5–25 kg/m^2, $^{**}P<0.05$ compared with BMI 25–30 kg/m^2, and $^{***}P<0.05$ compared with BMI 30–35 kg/m^2. $^{\#}$Change in outcome score between baseline and follow-up is statistically significant between groups ($P<0.05$). NA = no available data.

fatigue, physical symptoms, and symptoms of anxiety, depression, and PTSD than those in the other BMI categories (Figure 1). Cognitive symptoms were similar among BMI categories.

In addition, patients in obesity class II/III experience a greater deterioration in outcome scores than the other BMI categories for fatigue, anxiety, and cognitive impairment at 3- and 12-month follow-up (Figure 1).

Discussion

Severely obese ICU survivors with COVID-19 experience more long-term physical and mental symptoms than patients in lower BMI categories, whereas no significant differences were present before ICU admission. In contrast with the absence of an association of BMI and ICU mortality (2), these long-term symptoms may be directly related to BMI. The long-term impact of COVID-19 may be more pronounced in obese patients, or they may have limited ability to rehabilitate after their hospital stay. Therefore, future research should also focus on the role of BMI in long-term symptoms in ICU survivors who did not have COVID-19. However, regardless the underlying causes, it implicates that long-term follow-up is of explicit importance in obese patients in the ICU with COVID-19. ■

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Acute OSA Impacts Diurnal Alzheimer's Biomarkers through Nocturnal Hypoxemia and State Transitions

Alzheimer's disease (AD) has a long preclinical phase, lasting years to decades, in which proteins implicated in the pathogenesis of AD can accumulate. The National Institute on Aging and Alzheimer's Association have proposed a research framework allowing for characterization of the continuum of such brain changes even in cognitively normal older individuals (1). This AT(N) model groups fluid and imaging biomarkers into those impacting brain amyloid-β (Aβ) deposition (A), pathologic tau (T), and neurodegeneration (N). Aβ peptides are secreted from neurons and can form insoluble

Supported by AASM Foundation Focused Projects Grant JI-19–5 (K.K.), National Heart, Lung, and Blood Institute R01HL135483 (J.J.), National Institute on Aging R01AG056031 (R.S.O.), R01AG056531 (R.S.O.), R01AG056682 (A.W.V.), and R01AG066870 (A.W.V.).

Author Contributions: Conception and study design: K.K., J.J., R.S.O., and A.W.V. Data acquisition, analysis, and interpretation: K.K., J.J., A.P., O.M.B., A.E.M., C.G., L.P., T.M.W., D.M.R., I.A., R.S.O, and A.W.V. Manuscript preparation: K.K., J.J., A.P., O.M.B., R.S.O, and A.W.V.

Originally Published in Press as DOI: 10.1164/rccm.202202-0262LE on June 13, 2022