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Short Communication

Undernourished patients do not have increased risk of severe COVID-19 outcomes

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Background: Undernutrition has been previously identified as a deleterious factor in acute infections. In covid-19 infection, obesity is a risk-factor of severe evolution, but initial undernutrition has not been evaluated yet.
Methods: We retrospectively analyzed correlation between nutritional status at admission and severe outcomes (intensive care unit admission, invasive mechanical ventilation requirement and death) of patients hospitalized for confirmed covid-19 infection.
Results: Risk of intensive care unit admission and invasive mechanical ventilation requirement was not significantly different between undernutrition and normoweight sub-groups, but increased in excessive weight sub-group (ODDR (IC 95%) 1.048 (1.011-1.086), p = 0.011). Risk of death was the same in all sub-groups.

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Conclusion: Undernutrition didn't appear as a factor of severe outcomes in covid-19 infection.

Introduction

Known risk factors of severe coronavirus disease 2019 (COVID-19) identified to date include: male gender, older age, obesity, hypertension, diabetes mellitus, and cardiovascular diseases [1].

Regarding acute infections and specifically COVID-19 infection, obesity has been confirmed as a risk factor for ICU admission (ICU) and the need for invasive mechanical ventilation (IMV) [2]. However, until now, undernutrition was investigated only in terms of consequences of COVID-19, but not as a risk factor *per se* [3,4].

We aimed to assess whether malnutrition could be a risk factor for severe COVID-19 infection defined by at least one of the following criteria: ICU admission, IMV need, or death. At admission, according to the **Global Leadership Initiative of Malnutrition (GLIM),** a low Body Mass Index (BMI) was the nutritional phenotype criteria to classify the patients as undernourished.

Materials and methods

This **observational longitudinal case-control study** included 660 participants with PCR-confirmed COVID-19 infection from the database NOSO-COR of **4 university hospitals** in France, between February 1st and April 10th 2020. All participants provided written informed consent.

Diagnosis of malnutrition according to the **GLIM criteria** requires at least one etiologic criterion among reduced food intake or assimilation, inflammation or disease burden and at least one phenotypic criterion among involuntary weight loss, low BMI and reduced muscle mass [5]. In our study, etiologic criterion of malnutrition was fulfilled due to COVID-19 induced inflammation. Moreover, reduced food intake or assimilation: the other etiologic criterion was also respected in most cases due to COVID-19 illness progression (nausea, vomiting, diarrhea, anosmia, dysgeusia). Phenotypic criteria were assessed using BMI. Nutritional status sub-groups defined by the GLIM classification were: **underweight (UW)** for patients with a BMI < 20 kg/m2 if < 70 years old and < 22 for those > 70 years old [5], **excessive weight** (**EW**) for patients with BMI > 25 kg/m2 and **normal weight (NW)**. To determine the specific impact of the virus, a non COVID-19 **control group** included 177 patients hospitalized in the same ICU, during the same period the previous year (2019).

The statistical analysis was performed using IBM SPSS Statistics 19. All results were expressed as mean ± mean standard error (MSE) for continuous variables and frequency (percentage) for categorical variables. A student t-test or Mann-Whitney U-test was used for the comparison of continuous variables and the chi-squared was used for the comparison of the categorical variables. Associations between BMI or patients characteristics (such as age, sex or medical history) and the need for IMV or death occurrence have been assessed by using univariate and multivariate logistic regression as well as a Kaplan-Meier survey for the impact of the BMI on the ICU duration. A p-value level <0.05 was considered significant.

Results

At admission, out of 660 hospitalized COVID-19 patients, 127 (18.5%) were UW and 364 (55.1%) EW.

The admission in ICU concerned 166 (25.2%) patients. UW patients were less prevalent than NW (n = 16 (9.6%) vs n = 43 (25.9%), p = 0.014), and EW (n = 16 (9.6%) vs n = 107 (64.5%), p < 0.001) (Fig. 1-a).

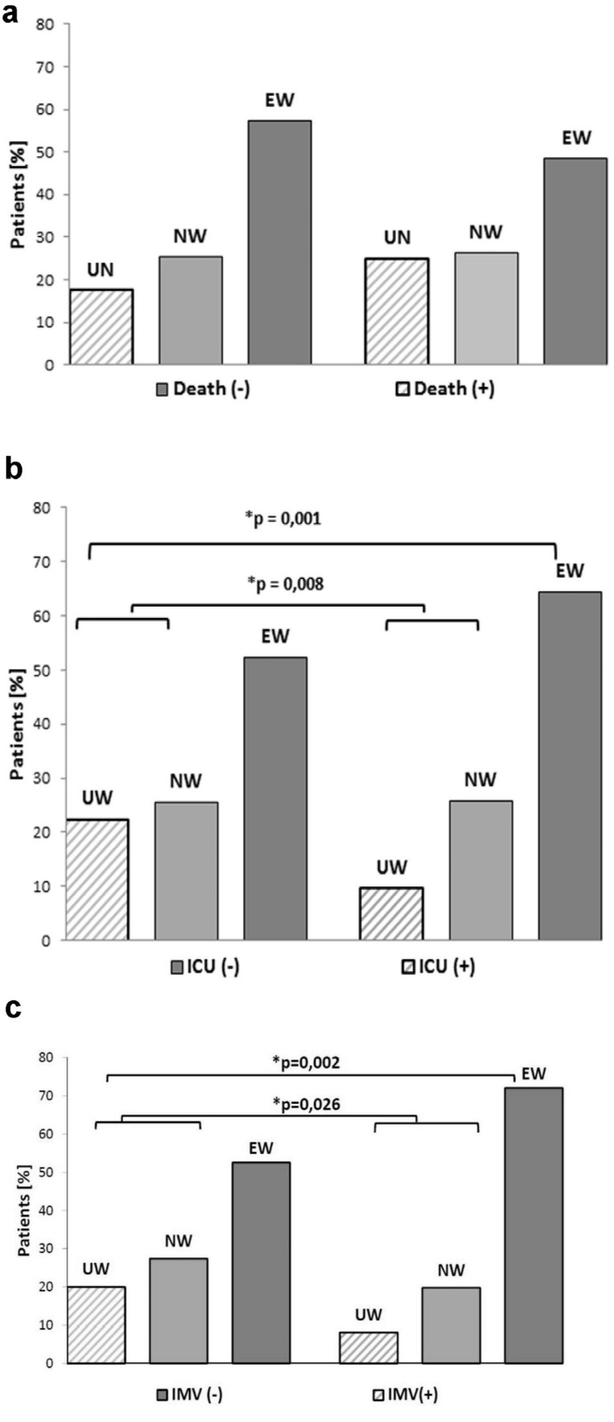

Figure 1. Description of severe outcomes for patients hospitalized for COVID-19 infection according to their nutritional status. UW: underweight patients; NW: normoweight; EW: Excessive weight; ICU+: admission to intensive care unit; ICU-: no admission to intensive care unit; IMV+: Invasive mechanical ventilation requirement; IMV-: no invasive mechanical ventilation requirement; Death+: dead patients.

IMV was required for 86 (13%) patients, and 145 (21.9%) patients died. There was no significant difference between UW and NW subgroups. However, **IMV and death were significantly less prevalent in the UW group compared to the EW group** ($p = 0.002$ and $p = 0.017$ respectively) (Fig. 1-b and 1-c).

After adjustment for age, sex and comorbidities, the risk of severe COVID-19 outcomes increased significantly with age and male gender, but not with underweight. **ICU admission risk was not significantly different between the UW and NW sub-groups, but increased for EW** (ODDR (IC 95%) 1.048 (1.011–1.086), $p = 0.011$). **IMV requirement was the same for the UW and NW** subgroups, but doubled for obese subjects. Concerning **length of stay in ICU**, there was no statistically significant difference between the three nutritional subgroups with a mean length of stay in ICU of 14.5(±11.8), 13.5 (±11.11) and 13.3 (±10.6) days for UW, NW and EW respectively. **Risk of death was the same** for all sub-groups.

Compared to the ICU control group, UW COVID-19 patients had the same prevalence and the same risk of IMV and death. However, EW COVID-19 patients had a higher IMV needs (107 (64.8%) vs 92 (52.0%), $p = 0.016$), and had an increased risk of death ($p = 0.003$).

Discussion

Previous studies showed that COVID-19 infection can potentially lead to malnutrition, and a higher risk of malnutrition may worsen the evolution of patients with viral pneumonia [6]. In addition, our data suggest that pre-existing malnutrition, based on GLIM criteria, does not affect the prognosis of patients hospitalized for SARS-COV2 infection.

Our study is one of very few studies to evaluate malnutrition as a risk factor of severe forms of COVID-19. **We did not find any association between pre-existing malnutrition and severe COVID-19 outcomes**. Our finding is supported by a previous study concluding that malnutrition was not associated with the risk of transfer to ICU or death of COVID-19 patients [7,8]. On the other hand, a retrospective study conducted in Wuhan, found that patients admitted in ICU for COVID-19 infection had a significant lower BMI compared to patients in non-ICU unit [4,9]. Moreover, in ICU group, patient with a higher mNUTRIC score, score used for the evaluation of the risk of malnutrition, had a higher risk of death. However, no patients included in this study had a BMI below 18.5. Finally, the mNUTRIC score is not a diagnosis score but a score of risk of malnutrition and was done only for patients admitted in ICU.

On the opposite, obesity is a well-known risk factor of severe evolution in SARS-Cov2. This difference could be the result of a chronic low-grade inflammation and increased inflammatory cytokines produced by pro-inflammatory immune cells accumulating in adipose and impairing the host immune response in obesity [10]. In addition, obesity is a metabolic disease associated with numerous underlying risk factors for COVID-19, including hypertension, dyslipidaemia, type 2 diabetes (T2D) and chronic kidney or liver disease which are all described to have deleterious effect during infection with COVID-19 [11]. Resistance to insulin and hyperglycemia impair immune cell function directly or indirectly via oxidants generation and glycation products. On the other hand, malnutrition and in particular protein energy malnutrition (PEM) has been linked to immunosuppressive phenotype due to decreased levels of adipokine and leptin [12]. Leptin has been shown to shift the immune response from an anti-inflammatory profile to a more pro-inflammatory one validating the immunosuppressive profile seen in leptin-deficient malnourished patients. Accordingly, malnutrition appears to counteract severe complications brought on by the cytokine storm as the consequence of the infection by SARS-Cov2 [12]. In stunting, another suggested protective mechanism is atrophy of primary lymphoid organs, reducing T- and B-cell numbers, leading to leukopenia. This reduced number of immune cells may acts as a protective factor against the “cytokine storm” described in the severe SARS and defined by an exacerbated secretion of pro inflammatory cytokines associated with an overreaction of the immune system [13].

Moreover, our study has some limitations. Firstly, BMI was the only phenotypic criterion used to define the nutritional status for the GLIM screening; however, as underlined by recent statement, the diagnosis of undernutrition cannot be limited to a “low” BMI [14]. Indeed, BMI is a highly individual measure since the weight range corresponding to a “normal” BMI for a given person could allow a variability in weight up to 35%. Thereby, a recent loss of weight of 10%, could maintain a patient on a "normal" BMI despite a proven malnutrition. On the contrary, a "low" BMI is not always a sign of malnutrition since it does not consistently reflect body composition. On another side, some authors differentiate the unintentional and intentional weight loss, which does not, seems to have the same consequences according to gender and ethnicity. Further studies should discriminate between standardized BMI and individual optimal weight. Secondly, there was a lack of specific biological nutritional markers not performed in clinical routine during the pandemic; however, the strength of our study is the use of GLIM criteria for the definition of malnutrition, known to be the most reliable tool for nutritional status determination. Thirdly, we cannot rule out local ethical decisions to limit the admission of the elderly and therefore possibly underweight patients to the ICU; however, mortality rate was evaluated for the entire cohort.

Nevertheless, malnutrition as part of COVID-19 morbidity requires essential nutritional measures to alleviate its deleterious consequences. COVID-19 infection can potentially lead to malnutrition, and malnutrition may worsen the evolution of patients with viral pneumonia [6].

In conclusion, malnutrition doesn't seem to be a risk factor for severe form of COVID-19.

Ethics approval and consent to participate

The study has been approved by the institutional review board of the Hospices Civils de Lyon under the reference of CNIL 20_5235.

Availability and data materials

The authors confirmed the data availability upon request.

Consent for publication

Consent for publication had been waved due to the retrospective design of the study.

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Conflicts of interest

The authors declare that they have no competing interests. All authors read and approved the final manuscript.

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References

[1] Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med 2020;180(11):1436–47.
[2] Kjøllesdal MKR, Smith GD, Ariansen I, Kinge JM, Degerud E, Næss Ø. The association between BMI and mortality using early adulthood BMI as an instrumental variable for midlife BMI. Sci Rep 2018;8(1):11499.
[3] Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obes Silver Spring Md 2020; 28(7):1195–9.
[4] Li T, Zhang Y, Gong C, Wang J, Liu B, Shi L, et al. Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. Eur J Clin Nutr 2020;74(6):871–5.
[5] Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. Clin Nutr Edinb Scotl 2019;38(1):1–9.

[6] Short KR, Kedzierska K, van de Sandt CE. Back to the future: lessons learned from the 1918 influenza pandemic. Front Cell Infect Microbiol 2018;8:343.
[7] Bedock D, Bel Lassen P, Mathian A, Moreau P, Couffignal J, Ciangura C, et al. Prevalence and severity of malnutrition in hospitalized COVID-19 patients. Clin Nutr ESPEN 2020;40:214–9.
[8] Huang H-K, Bukhari K, Peng CC-H, Hung D-P, Shih M-C, Chang RH-E, et al. The J-shaped relationship between body mass index and mortality in patients with COVID-19: A dose-response meta-analysis. Diabetes Obes Metab 2021;23(7):1701–9.
[9] Li G, Zhou C-L, Ba Y-M, Wang Y-M, Song B, Cheng X-B, et al. Nutritional risk and therapy for severe and critical COVID-19 patients: A multicenter retrospective observational study. Clin Nutr Edinb Scotl 2021;40(4):2154–61.
[10] Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes 2005 2013;37(3):333–40.
[11] Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. Obes Rev Off J Int Assoc Study Obes 2020;21(11):e13128.
[12] Schoeman D, Fielding BC. Leptin deficiency, caused by malnutrition, makes you susceptible to SARS-CoV-2 infection but could offer protection from severe COVID-19. mSphere 2021;6(3):e00031-21.
[13] Silverio R, Gonçalves DC, Andrade MF, Seelaender M. Coronavirus disease 2019 (COVID-19) and nutritional status: the missing link? Adv Nutr Bethesda Md 2021;12(3):682–92.
[14] Golubnitschaja O, Liskova A, Koklesova L, Samec M, Biringer K, Büsselberg D, et al. Caution, « normal » BMI: health risks associated with potentially masked individual underweight-EPMA Position Paper 2021. EPMA J 2021;12(3):243–64.