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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Letters to the Editor

In-Hospital Mortality Risk of Older Patients With COVID-19 Infection

To the Editor:

I read the recent article published in this journal and written by Covino et al[1] with great interest. The authors conducted a prospective study to evaluate the risk factors of mortality in adult COVID-19 patients aged ≥80 years. The adjusted hazard ratios (HRs) (95% CIs) of severe disease, ≥3 comorbidities, male sex, and vulnerability for the in-hospital death were 1.87 (1.31-2.59), 1.54 (1.11-2.13), 1.46 (1.14-1.87), and 6.93 (1.69-28.27), respectively. Regarding the severity of frailty, the adjusted HR (95% CI) of highest frailty for the in-hospital death was 12.55 (2.96-53.21). I have comments on the statistical validity, sex difference, and body mass index (BMI).

First, the number of deceased patients without frailty was 2, and they set patients without frailty as a control group. Although the numbers of deceased patients with moderate and severe frailty were 128 and 157, unstable estimates of mortality risk by frailty may be observed in wide ranges of HR. The authors should increase the number of controls to keep stable estimates by multivariate analysis with Cox regression model.

Second, the authors handled patients with a median age of 85 years. As life expectancy at birth in males is shorter than that in females, the mortality risk in males would predominantly increase in this population. HR of males against females for death may be increased in subjects without COVID-19 infection, and stratified analysis by sex should be added to specify the risk factors of mortality in patients with COVID-19 infection. In addition, interaction among independent variables in multivariate analysis cannot be fully adjusted, if the authors do not consider an interaction model among independent variables.

Finally, Kananen et al[2] evaluated the association between BMI and mortality in older COVID-19 patients with a median age of 83 years. The adjusted odds ratio (95% CI) of patients with BMI <18.5 for in-hospital mortality was 2.30 (1.17-4.31), and malnutrition was also a risk of in-hospital mortality. In contrast, increased BMI was not significantly associated with in-hospital mortality. Poor nutritional status is closely related to the increased risk of mortality in older subjects in general, and risk assessment of mortality should be comprehensively evaluated in patients with COVID-19 infection by including variables on nutritional status.

The authors declare no conflicts of interest.

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Reply to "In-Hospital Mortality Risk of Older Patients With COVID-19 Infection"

To the Editor:

We are delighted by the interest in our research by Dr Kawada and we welcome the opportunity to better clarify the results of our recent study on COVID-19 patients aged ≥80 years old.[1] In the study, we explored the overlapping effect between clinical covariates and baseline frailty status, in older patients hospitalized for COVID-19. Our results underlined the independent effect of severe frailty on the risk for in-hospital death, as well as male sex, the severity of disease at presentation, and overall comorbidities ≥3.

As noted by Dr Kawada, the group of patients with no or mild frailty [Clinical Frailty Scale (CFS) score = 1-3] was reduced (61 patients overall), with only 2 (3.3%) deaths in this group. Conversely, in the mild frailty group (CFS score = 4-6) there were 417 patients (128 deaths, 30.7%), and in the severely frail group (CFS score = 7-9) there were 251 patients (157 deaths, 62.5%). This has led to some uncertainty in the estimation of the exact hazard ratio for death using the first category as a reference and dividing the frailty scale into 3 groups. Nevertheless, it should be noted that the sample size is adequate for the overall estimation. Assuming the well-known rule of 10 cases needed for each liberty degree at multivariate analysis, we would have needed at least 100 events for the multivariate analysis (consistently, in our study we had 287 events). Moreover, evaluating the CFS variable as a linear scale in a Cox regression model, we obtained an estimated hazard ratio of 1.4 for each point of CFS score, which gives an about 10-fold risk of death for a patient with CFS score = 8¸ which is pretty similar to the 12-fold estimated risk reported in the article for the group CFS score = 7-9. Indeed, apart from the overall estimated HR, the crude figures of mortality

clearly indicate that frail patients have an increased risk of death, which is the major finding conveyed by our research.

Because life expectancy is lower in males, it could be speculated that in the older cohorts, such as the one evaluated in our study, the risk of death for males could be increased. However, given the short length of our follow-up (the end point was in-hospital mortality), we do not think that this could justify the observed excess in male mortality. Similarly, several authors evidenced the increased risk for mortality among male patients with COVID-19,[2] independent of the age group.

Finally, as noted by Dr Kawada, we did not consider the BMI among the evaluated variables. The overlapping relationship among low BMI, malnutrition, and sarcopenia is a key determinant of the frailty status. Although a low BMI may be a component of sarcopenia, the 2 conditions are not the same, neither is malnutrition.[3] Moreover, particularly in older adults, limiting the analysis to BMI could not reflect the nutritional and sarcopenic condition of the patients.

We look forward to improving our analysis, including these suggestions, to better clarify the reasons underlying the excess mortality observed in older COVID-19 patients.

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