JAMDA 23 (2022) 1608.e1–1608.e8

JAMDA

journal homepage: www.jamda.com

Original Study

Can the Multidimensional Prognostic Index Improve the Identification of Older Hospitalized Patients with COVID-19 Likely to Benefit from Mechanical Ventilation? An Observational, Prospective, Multicenter Study

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ARTICLE INFO

Article history:
Received 12 February 2022
Received in revised form
13 June 2022
Accepted 25 June 2022

Keywords:
COVID-19
mechanical ventilation
noninvasive ventilation
Comprehensive Geriatric Assessment
Multidimensional Prognostic Index
mortality
prognosis

ABSTRACT

Objective: Data on prognostic tools for indicating mechanical ventilation in older people with COVID-19 are still limited. The aim of this research was to evaluate if the Multidimensional Prognostic Index (MPI), based on the Comprehensive Geriatric Assessment (CGA), may help physicians in identifying older hospitalized patients affected by COVID-19 who might benefit from mechanical ventilation.
Design: Longitudinal, multicenter study.
Settings and Participants: 502 older people hospitalized for COVID-19 in 10 European hospitals.
Methods: MPI was calculated using 8 different domains typical of the CGA. A propensity score, Cox's regression analysis was used for assessing the impact of mechanical ventilation on rehospitalization/mortality for 90 days' follow-up, stratified by MPI = 0.50. The accuracy of MPI in predicting negative outcomes (ie, rehospitalization/mortality) was assessed using the area under the curve (AUC), and the discrimination with several indexes like the Net Reclassification Improvement (NRI) and the Integrated Discrimination Improvement (IDI).
Results: Among 502 older people hospitalized for COVID-19 (mean age: 80 years), 152 were treated with mechanical ventilation. In the propensity score analysis, during the 90-day follow-up period, there were 44 rehospitalizations and 95 deaths. Mechanical ventilation in patients with MPI values $\geq$ 0.50, indicating frailer participants, was associated with a higher risk of rehospitalization/mortality (hazard ratio 1.56, 95% CI 1.09-2.23), whereas in participants with MPI values $<$ 0.50 this association was not

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The authors declare no conflicts of interest.

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https://doi.org/10.1016/j.jamda.2022.06.023

significant. The accuracy of the model including age, sex, respiratory parameters, and MPI was good (AUC = 0.783) as confirmed by an NRI of 0.2756 ($P < .001$) and an IDI of 0.1858 ($P < .001$), suggesting a good discrimination of the model in predicting negative outcomes.

Conclusions and Implications: MPI could be useful for better individualizing older people hospitalized by COVID-19 who could benefit from mechanical ventilation.

The coronavirus disease (COVID)-19 pandemic increased the interest in best medical practices in older adults with acute respiratory failure.[1] COVID-19, particularly in older people before the vaccination, was characterized by a rapid worsening of the disease, and at the same time, the limited efficacy of specific antiviral therapies increased the risk of intensive care unit (ICU) overcrowding and finally mortality.[2,3]

During the COVID-19 pandemic, the limited availability of mechanical ventilation and the advanced mean age of symptomatic patients requiring hospitalization aroused relevant ethical dilemmas that are still not solved, such as which patients best take advantage from mechanical ventilation.[4] This pandemic showed once again the need of prognostic criteria able to identify those older individuals with COVID-19 who can benefit or not from intensive treatments, such as mechanical ventilation. Moreover, evidence-based prognostic rules could be useful to optimize resources because, as widely confirmed, age and comorbidities are not sufficient.[5] A pivotal systematic review regarding the use of prognostic tools in COVID-19 showed that proposed models are poorly reported, at high risk of bias, with a probably optimistic performance.[6] Other authors concluded that clinicians should use their clinical experience, particularly in older people, waiting for validated prognostic tools.[7]

There is a general agreement that the strongest and most consistent predictors of mortality in older people include comorbidity and functional status[8] and that in this regard the Comprehensive Geriatric Assessment (CGA), which explores information on clinical, functional, and psychosocial domains of the older people,[9] seems to be very useful to give prognostic information.[10] A seminal systematic review published 1 decade ago found several prognostic indexes potentially useful in older people,[11] but these tools should be based on a multidimensional assessment, including some key factors, such as certain comorbid conditions, social support, and functional, biological, and cognitive factors.[8] The main problem for the prognosis in older people, even with COVID-19, is that one size does not fit all,[8] further motivating the clinical usefulness of the CGA. In this sense, the Multidimensional Prognostic Index (MPI) is a well-validated CGA-based prognostic tool very useful to predict short- and long-term mortality risk[12] and is commonly used in hospitalized older patients.[13] Several multicenter studies have extensively reported that MPI has an excellent accuracy and calibration in predicting negative clinical outcomes during hospitalization.[14,15] Indeed, the MPI has been validated in more than 54,000 older adults with the most common chronic and acute age-related diseases in more than 50 international studies.[16] MPI seems to be useful for better tailoring pharmacologic and nonpharmacologic interventions in older people.[17,18] Finally, the usefulness of MPI was recently confirmed in terms of prognostic importance in COVID-19 in both hospital[19,20] and nonhospital[21] settings. However, whether MPI can be used as a tool in the selection of older people with COVID-19 candidates to mechanical ventilation is still unknown, even if this tool seems to be useful for better identifying older people with acute respiratory failure who are at high risk of noninvasive ventilation (NIV) failure.[22]

Given this background, the aim of this research was to evaluate if the CGA-based MPI assessed at hospital admission can help physicians in identifying older patients with COVID-19 who might benefit from mechanical ventilation in terms of rehospitalization and mortality rate at 90 days' follow-up, across several European centers.

Materials and Methods

Study Design and Population

For the aims of this research, we included (1) patients ≥65 years of age, (2) consecutively admitted to the hospital with ascertained diagnosis of COVID-19 through nasopharyngeal swab with real-time polymerase chain reaction, and (3) able to sign an informed consent. Exclusion criteria were age <65 years, unwillingness to participate in the study, and inability to give informed consent. The period of enrollment and follow-up was between April 2020 and August 2021. At the time of enrollment, vaccines against COVID-19 were not available. The patients were enrolled after admission in each ward across 10 European centers located in Italy (5 centers, n = 272 participants included), Spain (1 center, n = 46), Czech Republic (1 center, n = 153), Portugal (1 center, n = 34), and Germany (2 centers, n = 43).

This was a prospective, observational study conducted according to the World Medical Association's 2008 Declaration of Helsinki, the guidelines for Good Clinical Practice, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[23] The ethical committees of each of the centers formally approved the study. Informed consent was given by participants who underwent initial evaluation and/or their proxies in case of an inability to understand and sign the informed consent (eg, severe dementia) for their clinical records to be used in clinical studies according to the Local Law.

Outcomes

Data regarding the outcomes of interest were ascertained using administrative data, such as death certificates and medical records during a maximum follow-up period of 90 days from the admission in each ward. The primary outcome of our research was a composite end point made of rehospitalization and all-cause mortality. Secondary outcomes were these end points, singularly considered. Dates of death were identified from death certificates and dates of readmission in hospital using medical records.

Exposure: Mechanical Ventilation

Mechanical ventilation was recorded as NIV and orotracheal intubation using medical records during hospitalization.

MPI

The MPI was made at the admission into the medical ward and included information from 8 different domains of the CGA,[12,19] in order to give clinical prognostic information. MPI was calculated using the following parameters:

1. Functional status was estimated based on the Activities of Daily Living index.[24]
2. Independence status was based on the performance of instrumental activities of daily living.[25]

3. Cognitive status was measured using the Short Portable Mental Status Questionnaire.[26]
4. Comorbidity was assessed using the Cumulative Illness Rating Scale,[27] which uses a 5-point ordinal scale (score 1-5) to estimate the severity of pathology in each of 13 systems. Based on the ratings, the Cumulative Illness Rating Scale–Comorbidity Index score, reflecting the number of concomitant diseases, was derived from the total number of categories in which moderate or severe levels (grade from 3 to 5) of disease were identified (range from 0 to 13).
5. Nutritional status was investigated with the Mini Nutritional Assessment–Short Form,[28] which includes information on several nutritional aspects.
6. Risk of developing pressure sores was evaluated through the Exton Smith Scale.[29]
7. Medication use was defined according to the Anatomical Therapeutics Chemical Classification code system (ATC classification), and the number of drugs used by patients at admission was also recorded.
8. Social domain was categorized in living alone, with family (or with other support), and in institution.

For each domain, a tripartite hierarchy was used, that is, 0 = no problems, 0.5 = minor problems, and 1 = major problems, based on conventional cutoff points derived from the literature for the singular items.[12] The sum of the calculated scores from the 8 domains was divided by 8 to obtain a final MPI risk score ranging from 0 = no risk to 1 = higher risk of mortality. MPI requires between 15 and 25 minutes for its complete execution.[15] In Supplementary Table 1, we reported as the MPI was calculated, based on the single domains' categorization.

In case of impossibility of doing the CGA (eg, hyperactive delirium), the evaluation was postponed to the following day, however, within 48 hours from admission for all participants included.[19]

Clinical, Biohumoral, and Radiologic Parameters

Clinical and radiologic data of COVID-19 infection were also registered. Among clinical signs and symptoms, we recorded information regarding fever (body temperature ≥37.5 °C), cough, diarrhea, and dyspnea. Moreover, we investigated the presence of delirium at hospital admission using the 4AT score, a short tool for delirium assessment designed to be easy to use in clinical care.[30] Radiographic findings were categorized as bilateral ground-glass opacities vs other findings, whereas CT findings in pneumonia suggestive of COVID-19 vs others, according to a standardized classification.[31] Finally, data regarding serum inflammatory parameters [ie, white blood cells, C-reactive protein (CRP) serum levels] and arterial blood gas parameters (pH, Po_2, Spo_2, Pco_2, Po_2/Fio_2 ratio) were measured using standard methods across the 10 European centers.

Statistical Analysis

All patient records and information were anonymized and deidentified before the analysis.

To minimize the effect of potential confounders, we used a propensity score matching with 1 case (mechanical ventilation) and 2 controls that never experienced this kind of intervention during hospitalization. Data on continuous variables were normally distributed according to the Kolmogorov-Smirnov test and then reported as means and standard deviation values for quantitative measures and percentages for the categorical variables, by use or not of mechanical ventilation. Levene test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch analysis of variance was used. *P* values were calculated using the Student *t* test for continuous variables and the Mantel-Haenszel χ^2 test for categorical ones.

The association between mechanical ventilation and the outcomes of interest was made using a Cox regression analysis, using a propensity-score model. The results were reported as hazard ratios (HRs) with their 95% CIs. Because the interaction MPI by mechanical ventilation in predicting the composite and the singular outcomes was significant ($P < .05$), we have reported the HRs stratified according to an MPI value less or more than 0.50 that was identified as the best cutoff as sensitivity and specificity using the Youden index.[32]

The accuracy of prognostic factors predicting negative outcomes during follow-up, in terms of area under the curve (AUC), was analyzed using different models, that is, age and sex; age, sex and Pao_2/Fio_2; and age, sex, Pao_2/Fio_2 combined with MPI score. The categorization of AUC is fully reported in Supplementary Table 2.[33,34]

The improvement in model performance was evaluated by the inclusion of MPI into the model. Calibration was analyzed using the C-statistics. The predicted probabilities derived by the models without MPI were then classified into 2 different risk categories (50%) used to build reclassification tables for patients with negative events (death or rehospitalization) and without these events. Improvement in risk prediction by adding the MPI to age, sex, and Pao_2/Fio_2 was then assessed estimating the Net Reclassification Improvement (NRI) and the Integrated Discrimination Improvement (IDI).[35,36] Briefly, the NRI focused on reclassification tables built separately for patients with and without events and quantifies the correct movement in predefined categories (upward for events and downward for nonevents); the IDI can be defined as an average over the range of all possible risk cutoffs of the improvements on sensitivity minus the worsening on specificity.

All analyses were performed using the SPSS 21.0 for Windows (IBM Corp, Armonk, NY) and Stata, 14.0. All statistical tests were 2-tailed, and statistical significance was assumed for a *P* value $< .05$.

Results

Of the 548 subjects recruited, 502 were analyzed after removing the nine without calculatable MPI scores and the 37 lost to follow-up. Overall, 174 participants died during the 90 days of follow-up, mainly in 2020 (118 participants) compared with 2021 (56).

Among the 502 people initially included, 152 (=30.3%) underwent mechanical ventilation, as shown in Table 1. The people experiencing a mechanical ventilation were significantly frailer [MPI = 0.55 ± 0.24 (mechanical ventilation) vs 0.47 ± 0.23 (no mechanical ventilation); $P = .001$], but similar in terms of mean age ($P = .11$) and the proportion of females ($P = .62$) than their counterparts. Among the clinical signs/symptoms, dyspnea ($P < .001$), fever ($P = .01$), and cough ($P < .001$) were associated more frequently to mechanical ventilation compared to patients not undergoing mechanical ventilation. A significantly higher presence of bilateral ground-glass opacities at radiographic examination was present in people that needed mechanical ventilation. Finally, participants undergoing mechanical ventilation did not differ in terms of serum inflammatory parameters compared with their counterparts, although they reported worse arterial blood gas parameters in terms of Pao_2/Fio_2, Po_2, Spo_2, and Pco_2 (Table 1).

For decreasing the role of potential confounders on outcomes of interest from the 502 people initially included, using a propensity score accounting for age, gender, and MPI, 91 patients undergoing mechanical ventilation (2 orotracheal intubation and 89 NIV) were matched to 182 controls (Table 1). People undergoing mechanical ventilation had a significantly higher presence of bilateral ground-glass opacities ($P = .001$), but not pneumonia suggestive of COVID-19 at CT scan ($P = .90$) compared to people not using mechanical ventilation during hospitalization. From a clinical point of view, cough ($P < .001$) and dyspnea ($P < .001$) were more frequently represented in people undergoing mechanical ventilation (Table 1). The arterial blood

Table 1
Baseline Clinical Characteristics by MPI Values

Parameter	All Sample			Propensity Score		
	No Mechanical Ventilation (n = 350)	Mechanical Ventilation (n = 152)	*P* Value	No Mechanical Ventilation (n = 182)	Mechanical Ventilation (n = 91)	*P* Value
Mean age, mean (SD)	79.9 (7.9)	81.1 (8.3)	.11	81.6 (7.6)	81.4 (7.6)	.78
Female gender, %	57.9	60.3	.62	40.1	45.1	.44
MPI domains, mean (SD)						
ADL score	3.5 (2.2)	2.9 (2.4)	.005	2.8 (2.0)	2.6 (1.9)	.56
IADL score	3.8 (2.9)	2.8 (2.8)	<.001	2.3 (2.0)	2.5 (2.1)	.36
SPMSQ score	3.1 (2.8)	4.2 (3.7)	<.001	3.7 (3.0)	3.9 (2.7)	.65
ESS score	15.1 (3.8)	13.7 (4.3)	<.001	13.8 (3.4)	13.8 (3.4)	.89
MNA-SF score	9.2 (3.5)	7.7 (3.6)	<.001	7.3 (2.9)	7.9 (2.8)	.08
CIRS-CI score	4.2 (2.1)	4.2 (2.3)	.88	4.1 (2.0)	4.9 (1.8)	.004
Number of medications	5.7 (3.1)	6.4 (3.2)	.04	6.5 (3.1)	6.3 (3.1)	.68
Living alone, %	22.2	42.7	.01	22.6	25.0	.81
MPI score	0.47 (0.23)	0.55 (0.24)	.001	0.58 (0.13)	0.58 (0.13)	.93
Inflammatory parameters, mean (SD)						
White cells	8.06 (5.83)	7.88 (3.97)	.70	7.39 (4.23)	7.98 (4.15)	.94
CRP	11.7 (18.2)	12.1 (16.1)	.85	10.5 (15.8)	12.4 (18.0)	.37
Arterial blood gas parameters, mean (SD)						
pH	7.44 (0.06)	7.43 (0.09)	.42	7.43 (0.05)	7.42 (0.09)	.30
Po_2/Fio_2 ratio	355 (147)	224 (98)	<.001	368 (143)	235 (106)	<.001
Po_2	68.2 (25.8)	52.7 (34.7)	.001	66.3 (25.2)	45.5 (36.8)	<.001
Spo_2	91.7 (9.9)	86.9 (13.2)	.004	92.7 (9.3)	85.5 (13.1)	<.001
Pco_2	28.8 (16.4)	36.2 (10.8)	<.001	25.7 (18.6)	35.4 (10.8)	<.001
Clinical and radiologic presentation						
Bilateral ground-glass opacities (radiograph), %	37.4	56.0	<.001	28.6	50.0	.001
Pneumonia suggestive of COVID-19 (CT), %	44.3	43.4	.92	39.6	40.7	.90
Fever, %	45.8	58.7	.01	47.8	56.7	.20
Cough, %	32.4	53.6	<.001	30.8	53.8	<.001
Diarrhea, %	12.3	17.3	.16	11.5	17.6	.19
Dyspnea, %	50.3	76.8	<.001	45.1	75.8	<.001
4AT score, mean (SD)	3.8 (4.2)	4.1 (4.5)	.46	3.58 (4.10)	4.43 (3.90)	.10

4AT, Alertness, Abbreviated Mental Test–4, Attention, Acute Change or Fluctuating Course; ADL, activities of daily living; CIRS-CI, Cumulative Illness Rating Scale–Comorbidity Index; CRP, C reactive protein; ESS, Exton-Smith Scale; IADL, instrumental activities of daily living; MNA-SF, Mini Nutritional Assessment-Short Form; SPMSQ, Short Portable Mental State Questionnaire.

gas profile indicates that the use of mechanical ventilation was related to the acute respiratory failure severity.

During the 90-day follow-up period, in the propensity-score analysis, 44 rehospitalizations and 95 deaths were observed. Table 2 shows the analyses regarding follow-up outcomes during the follow-up period using mechanical ventilation as exposure and rehospitalization and mortality as outcomes, divided according to the median value of the MPI (ie, 0.50). Mechanical ventilation was associated with a higher risk of negative outcomes (HR 1.56, 95% CI 1.09-2.23; $P = .01$), rehospitalization (HR 2.00, 95% CI 1.04-4.27; $P = .03$), and mortality (HR 2.16, 95% CI 1.34-3.48; $P = .001$), but only in frailer people (ie, people with an MPI >0.50). On the contrary, no significant association was observed between mechanical ventilation and negative outcomes in people having an MPI score <0.50 (Table 2).

The receiver operating characteristic operator curve using different combinations of age, sex, Pao_2/Fio_2 ratio and MPI as exposure and the incidence of rehospitalization/mortality during follow-up as outcome demonstrated that Pao_2/Fio_2 ratio did not increase the prognostic accuracy of age and sex (AUC = 0.674, 95% CI 0.617-0.730), while adding the MPI score led to a good predictive value (AUC = 0.783, 95% CI 0.733-0.833, $P < .001$) (Figure 1). As shown in Table 3, these findings were confirmed by the estimated NRI of 0.2756 ($P < .001$), suggesting that on adding the MPI to the model with age, sex, and Pao_2/Fio_2 ratio, about 28% of patients were correctly reclassified and the estimated IDI of 0.1858 ($P < .001$) was achieved, overall suggesting a significant improvement from a clinical point of view (Table 3).

Discussion

In this observational, longitudinal study, involving older people hospitalized across different European countries, we found that mechanical ventilation was associated with a higher risk of negative outcomes at 3 months of follow-up in frail older people hospitalized for COVID-19 compared with less frail individuals. Moreover, our

Table 2
Outcomes of Interest, Stratified for the Median MPI Value, by Use of Mechanical Ventilation in Propensity Score Analysis

	Composite Outcome*		Rehospitalization		Mortality	
	MPI ≤ 0.50	MPI > 0.50	MPI ≤ 0.50	MPI > 0.50	MPI ≤ 0.50	MPI > 0.50
Sample size	100	173	100	173	100	173
Number of events	44	95	17	27	27	68
Percentage of events	44.0	54.9	17.0	15.3	27.0	39.3
No mechanical ventilation, HR (95% CI)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Mechanical ventilation, HR (95% CI)	1.15 (0.68-1.94)	1.56 (1.09-2.23)	1.00 (0.37-2.73)	2.00 (1.04-4.27)	0.91 (0.41-2.02)	2.16 (1.34-3.48)
P value	.60	.01	.99	.03	.82	.001
P value for between strata	<.001		<.001		<.001	

*Composite outcome is made by rehospitalization and mortality during follow-up period.

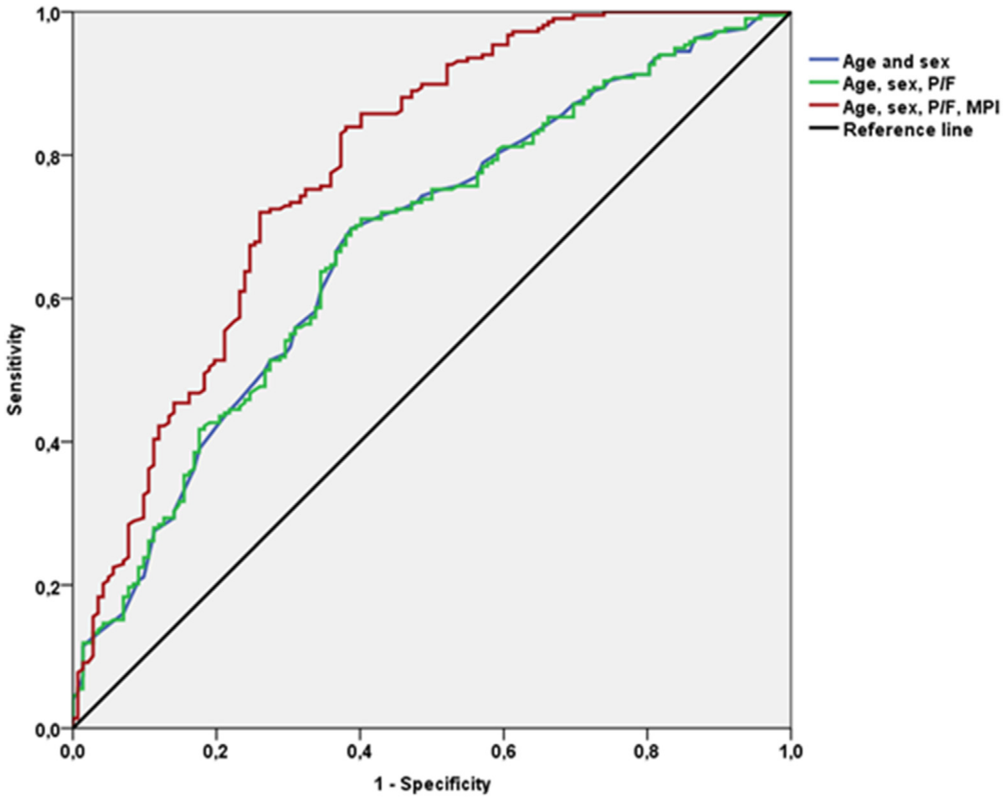

Fig. 1. Receiver operating characteristic curve using different combinations of age, sex, Pao$_2$/Fio$_2$, and MPI as exposure and the incidence of rehospitalization/mortality during follow-up.

study indicates that the Pao$_2$/Fio$_2$ ratio, that is, the ratio between arterial oxygen partial pressure (Pao$_2$) and the fractional inspired oxygen (Fio$_2$), recommended as pivotal criterion for acute respiratory distress syndrome in COVID-19 and non–COVID-19 conditions,[37] is poorly associated with prognosis in older people.

When analyzing the data of the entire cohort, we observed that physicians used more frequently mechanical ventilation in frailer patients that were more affected by some clinical signs and symptoms typical of COVID-19 such as dyspnea, fever, and cough or worse arterial blood gas parameters. However, when matching using a propensity score patients undergoing mechanical ventilation or not during follow-up, we observed that frailer patients experienced a higher risk of negative outcomes than those not using this intervention, suggesting that multidimensional frailty should be taken into account for better use of mechanical ventilation in older people with COVID-19. Even if there is significant evidence that the early use of mechanical ventilation may reduce in-hospital mortality,[38] literature suggests that mechanical ventilation is associated with a high rate of failure in older people in both noninvasive[39] and invasive forms.[40] Altogether, these data indicate that current criteria for mechanical ventilation are poorly applicable to older people, again indicating the need of prognostic tools that can help the physician in the daily clinical decision making.[8] In this sense, the Pao$_2$/Fio$_2$ ratio is widely recognized as a pivotal indicator for the need of mechanical ventilation in ARDS.[41] However, our study clearly showed that this parameter did not add anything in terms of accuracy to age and sex for predicting poor prognosis in older people. The use of the Pao$_2$/Fio$_2$ ratio was also reported in some COVID-19 experiences as important for prognosis and for using mechanical ventilation or opting not to,[42,43] but these researchers were mainly focused on adults.

Our work supported the idea that multidimensional frailty, as assessed by MPI, is probably more important than the Pao$_2$/Fio$_2$ ratio in determining prognosis in older people. Using a propensity score matching between people treated with mechanical ventilation and controls that included age, gender, and MPI, we observed that MPI could be a good prognostic tool because frailer people, indicated by an MPI value $>$ 0.50, experienced a higher risk of mortality and rehospitalization even if mechanical ventilation was used. Moreover, comparing the 2 models (ie, Pao$_2$/Fio$_2$ ratio vs MPI), we observed that

Table 3

Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI) Tables of Older Hospitalized Patients With COVID-19 Who Died or Were Rehospitalized (Events) During 90 Days of Follow-up, by Adding MPI to Pao$_2$/Fio$_2$ Ratio

Parameters			Statistics		
					P Value
IDI Age, sex, Pao$_2$/Fio$_2$ + MPI			0.1858		<.001
NRI Age, sex, Pao$_2$/Fio$_2$ + MPI			0.2756		<.001
	Events (n = 218)			Nonevents (n = 142)	
	With MPI			With MPI	
Without MPI	≤0.50	>0.50	Without MPI	≤0.50	>0.50
≤0.50	13	27	≤0.50	43	8
>0.50	16	162	>0.50	40	51

NRI, corresponding estimated Net Reclassification Improvement. NRI focused on reclassification tables and quantifies the correct movement in categories (upward for events and downward for nonevents).

IDI, corresponding estimated Integrated Discrimination Improvement. A model's discrimination is the ability to distinguish subjects who will develop an event from those who will not. IDI focused on differences between sensitivity and "1 − specificity" for all possible cutoffs for models with and without MPI and does not require predefined risk categories.

inclusion of MPI improved the accuracy from a prognostic point of view, which is necessary for taking the correct therapeutic decision in older people.[11] Finally, adding MPI to clinical and blood gas parameters can help to better discriminate older people in terms of prognosis, which is necessary for taking the correct clinical decisions. Altogether, these findings, to our knowledge the first in COVID-19, confirmed previous results showing that MPI could be useful not only for tailoring pharmacologic approaches in older people[18,44] but also for helping the physician in the areas of medicine in which less evidence is available, such as artificial nutrition or the use of mechanical ventilation in older people.[22]

The MPI is based on multidimensional assessment derived from a standardized CGA. This tool has been already recognized as a useful prognostic tool in hospitalized older adults with critical illnesses, such as pneumonia, heart failure, or acute myocardial infarction.[45–47] Also in COVID-19 condition, MPI seems to be a useful tool for clinical decision making in both hospital[19,20] and nonhospital settings.[21] In the present research, we have further shown that this tool could be used in COVID-19 patients in order to avoid unnecessary interventions (such as orotracheal intubation) in frailer patients, because this solution could be followed by a negative prognosis. Therefore, our study reported a clinical application of the MPI in a topic in which no clear indications were given, that is, in older people affected by COVID-19 and needing mechanical ventilation. As already reported by several authors during the COVID-19 epidemic, the topic of prognosis is of critical importance in older people, and our findings remind us that it is very important to assess the individual multidimensional impairment to define to the best possible extent the trajectories of acute COVID-19, beyond the patient's chronological age.[48,49]

The findings of our study must be interpreted within its limitations. First, the observational nature of this research can introduce a selection bias in the findings. Second, we were not able to separate people in NIV from those undergoing orotracheal intubation, which is important in geriatric medicine. Finally, we were not able to compare the accuracy or discrimination of the MPI compared with other indexes indicating frailty because we did not collect sufficient information for these tools.

Conclusions and Implications

MPI could be useful for physicians for better individualizing older people hospitalized by COVID-19 who could benefit from mechanical ventilation, having a good accuracy, and leading to a significant discrimination in terms of prognosis. These findings further indicate that performing a CGA that includes information on multidimensional characteristics of patients (ie, functional, cognitive, nutritional, biological, and social aspects) might help the physician to refine patient selection for mechanical ventilation and to take into consideration not just clinical, radiologic, or arterial blood gas parameters, which seem to have poor prognostic value in older people.

Acknowledgment

This article is under the auspices of the SIGOT (Italian Geriatric Hospital and Community Society) and the Special Interest Group in Comprehensive Geriatric Assessment (CGA) of the European Geriatric Medicine Society (EuGMS).

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References

1. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? *Aging (Albany NY)*. 2020;12:9959.
2. Polidori MC, Maggi S, Mattace-Raso F, Pilotto A. The unavoidable costs of frailty: a geriatric perspective in the time of COVID-19. *Geriatric Care*. 2020:6.
3. Lithander FE, Neumann S, Tenison E, et al. COVID-19 in older people: a rapid clinical review. *Age Ageing*. 2020;49:501–515.
4. James A, Verdonk F, Bougle A, Constantin JM. Non-invasive ventilation for acute respiratory failure (in COVID-19 patients): The non-ending story? *Anaesth Crit Care Pain Med*. 2020;39:549.
5. Montero-Odasso M, Hogan DB, Lam R, et al. Age alone is not adequate to determine health-care resource allocation during the COVID-19 pandemic. *Can Geriatr J*. 2020;23:152–154.
6. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of Covid-19: systematic review and critical appraisal. *BMJ*. 2020;369:m1328.
7. Sperrin M, Grant SW, Peek N. Prediction models for diagnosis and prognosis in Covid-19. *BMJ*. 2020;369:m1464.
8. Gill TM. The central role of prognosis in clinical decision making. *JAMA*. 2012;307:199–200.
9. Pilotto A, Cella A, Pilotto A, et al. Three decades of Comprehensive Geriatric Assessment: evidence coming from different healthcare settings and specific clinical conditions. *J Am Med Dir Assoc*. 2017;18:192.e1–192.e11.
10. European Medicines Agency. Physical frailty: instruments for baseline characterisation of older populations in clinical trials. 2018. Accessed January 02, 2022. https://www.ema.europa.eu/en/physical-frailty-instruments-baseline-characterisation-older-populations-clinical-trials
11. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. *JAMA*. 2012;307:182–192.
12. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a Multidimensional Prognostic Index for one-year mortality from Comprehensive Geriatric Assessment in hospitalized older patients. *Rejuvenation Res*. 2008;11:151–161.
13. Mattace-Raso F, Pilotto A. The Challenge of the Multifaceted Prognosis in the Older People and the Multidimensional Prognostic Index. *Eur Geriatr Med*. 2021;12(2):223–226.
14. Volpato S, Bazzano S, Fontana A, Ferrucci L, Pilotto A. Multidimensional Prognostic Index predicts mortality and length of stay during hospitalization in the older patients: a multicenter prospective study. *J Gerontol A Biol Sci Med Sci*. 2015;70:325–331.
15. Pilotto A, Veronese N, Daragjati J, et al. Using the Multidimensional Prognostic Index to predict clinical outcomes of hospitalized older persons: a prospective, multicenter, international study. *J Gerontol A Biol Sci Med Sci*. 2019;74:1643–1649.
16. Pilotto A, Custodero C, Maggi S, Polidori MC, Veronese N, Ferrucci L. A multidimensional approach to frailty in older people. *Ageing Res Rev*. 2020;60:101047.
17. Veronese N, Cella A, Cruz-Jentoft AJ, et al. Enteral tube feeding and mortality in hospitalized older patients: A multicenter longitudinal study. *Clin Nutr*. 2020;39:1608–1612.
18. Pilotto A, Panza F, Copetti M, et al. Statin treatment and mortality in community-dwelling frail older patients with diabetes mellitus: a retrospective observational study. *PLoS One*. 2015;10:e0130946.
19. Pilotto A, Azzini M, Cella A, et al. The Multidimensional Prognostic Index (MPI) for the prognostic stratification of older inpatients with COVID-19: a multicenter prospective observational cohort study. *Arch Gerontol Geriatr*. 2021;95:104415.
20. Verholt AB, Gregersen M, Gonzalez-Bofill N, et al. Clinical presentation and outcomes of COVID-19 in older hospitalised patients assessed by the record-based Multidimensional Prognostic Index, a cross-sectional study. *Eur Geriatr Med*. 2021;12:1147–1157.

21. Veronese N, Koyanagi A, Stangherlin V, et al. Mortality attributable to COVID-19 in nursing home residents: a retrospective study. *Aging Clin Exp Res*. 2021;33:1745–1751.
22. Custodero C, Gandolfo F, Cella A, et al. Multidimensional Prognostic Index (MPI) predicts non-invasive ventilation failure in older adults with acute respiratory failure. *Arch Gerontol Geriatr*. 2021;94:104327.
23. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349.
24. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist*. 1970;10:20–30.
25. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179–186.
26. Pfeiffer EA. Short Portable Mental Status Questionnaire (SPMSQ). *J Am Geriatr Soc*. 1975;23:1975.
27. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. 1968;16:622–626.
28. Guigoz Y, Vellas B. The Mini Nutritional Assessment (MNA) for grading the nutritional state of elderly patients: presentation of the MNA, history and validation. *Nestle Nutr Workshop Ser Clin Perform Programme*. 1999;1:3–11; discussion 11–12.
29. Bliss MR, McLaren R, Exton-Smith AN. Mattresses for preventing pressure sores in geriatric patients. *Mon Bull Minist Health Public Health Lab Serv*. 1966;25:238–268.
30. Bellelli G, Morandi A, Davis DH, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing*. 2014;43:496–502.
31. Wong CK, Wong JY, Tang EH, Au CH, Wai AK. Clinical presentations, laboratory and radiological findings, and treatments for 11,028 COVID-19 patients: a systematic review and meta-analysis. *Sci Rep*. 2020;10:1–16.
32. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. *Biom J*. 2005;47:458–472.
33. Ling CX, Huang J, Zhang H. AUC: a statistically consistent and more discriminating measure than accuracy. In: *IJCAI '03: Proceedings of the 18th International Joint Conference on Artificial Intelligence*. Morgan Kaufman Publishers Inc; 2003.
34. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. John Wiley & Sons; 2000.
35. Pencina MJ, Sr D'Agostino RB, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172.
36. Pilotto A, Sancarlo D, Aucella F, et al. Addition of the Multidimensional Prognostic Index to the estimated glomerular filtration rate improves prediction of long-term all-cause mortality in older patients with chronic kidney disease. *Rejuvenation Res*. 2012;15:82–88.
37. Tobin MJ, Jubran A, Laghi F. Noninvasive strategies in COVID-19: epistemology, randomised trials, guidelines, physiology. *Eur Respir J*. 2021;57:2004247.
38. Cabrini L, Landoni G. A novel non-invasive ventilation mask to prevent and manage respiratory failure during fiberoptic bronchoscopy, gastroscopy and transesophageal echocardiography. *Heart Lung Vessel*. 2015;7:297–303.
39. Rocco M, Conti G, Antonelli M, et al. Non-invasive pressure support ventilation in patients with acute respiratory failure after bilateral lung transplantation. *Intensive Care Med*. 2001;27:1622–1626.
40. Cheng AC, Liao KM, Ho CH, et al. The prognosis in extremely elderly patients receiving orotracheal intubation and mechanical ventilation after planned extubation. *Medicine (Baltimore)*. 2020;99:e21970.
41. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149:818–824.
42. Zinellu A, De Vito A, Scano V, et al. The Pao_2/Fio_2 ratio on admission is independently associated with prolonged hospitalization in COVID-19 patients. *J Infect Dev Ctries*. 2021;15:353–359.
43. Zeng F, Li L, Zeng J, et al. Can we predict the severity of coronavirus disease 2019 with a routine blood test. *Pol Arch Intern Med*. 2020;130:400–406.
44. Pilotto A, Gallina P, Panza F, et al. Relation of statin use and mortality in community-dwelling frail older patients with coronary artery disease. *Am J Cardiol*. 2016;118:1624–1630.
45. Pilotto A, Dini S, Daragjati J, et al. Combined use of the Multidimensional Prognostic Index (MPI) and procalcitonin serum levels in predicting 1-month mortality risk in older patients hospitalized with community-acquired pneumonia (CAP): a prospective study. *Aging Clin Exp Res*. 2018;30:193–197.
46. Cammalleri V, Bonanni M, Bueti FM, et al. Multidimensional Prognostic Index (MPI) in elderly patients with acute myocardial infarction. *Aging Clin Exp Res*. 2021;33:1875–1883.
47. Pilotto A, Addante F, Franceschi M, et al. Multidimensional Prognostic Index based on a Comprehensive Geriatric Assessment predicts short-term mortality in older patients with heart failure. *Circ Heart Fail*. 2010;3:14–20.
48. Panagiotou OA, Kosar CM, White EM, et al. Risk factors associated with all-cause 30-day mortality in nursing home residents with COVID-19. *JAMA Intern Med*. 2021;181:439–448.
49. Fisman DN, Greer AL, Tuite AR. Age is just a number: a critically important number for COVID-19 case fatality. *Ann Intern Med*. 2020;173:762–763.

Supplementary Table 1
Calculation of MPI

	Score in Each Domain		
	Low Risk (Value = 0)	Moderate Risk (Value = 0.5)	High Risk (Value = 1)
ADL	6-5	4-3	2-0
IADL	8-6	5-4	3-0
SPMSQ	0-3	4-7	8-10
ESS	16-20	10-15	5-9
MNA-SF	12-14	8-11	0-7
CIRS	0	1-2	≥3
Number of drugs	0-3	4-6	≥7
Cohabitation status	Family	Nursing home	Alone
Add the values of the single items and divide by 8		Total score MPI	

ADL, activities of daily living; CIRS, Cumulative Illness Rating Scale; CRP, C reactive protein; ESS, Exton-Smith Scale; IADL, instrumental activities of daily living; MNA-SF, Mini Nutritional Assessment-Short Form; MPI, Multidimensional Prognostic Index; SPMSQ, Short Portable Mental State Questionnaire.

Supplementary Table 2
Categorization of Area Under the Curve and Harrell *C* Statistic

Values	Area Under the Curve	*C* Statistics
0.50-0.60	Very poor	No better than random chance
0.60-0.70	Poor	Poor
0.70-0.80	Good	Good
>0.80	Very good	Strong