

The Multidimensional Prognostic Index (MPI) for the prognostic stratification of hospitalized older patients with COVID-19: a prospective multicenter observational cohort study. Objectives, study design and expected outcomes (MPI_COVID-19)

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Abstract

The emergent coronavirus-19 disease (COVID-19) pandemic posed and still poses serious issues in the management of the inpatients and in the resource allocation, in particular for those patients requiring Intensive Care Unit (ICU) management. Epidemiological data clearly suggest that multimorbid older patients have the poorest prognosis. However, it is conceivable that age and number of comorbidities alone do not reflect the real condition and the expected prognosis of the patients affected by COVID-19. A different approach based on comprehensive geriatric assessment (CGA) could help to better identify older patients more at risk of dismal outcomes and who, at some

point of their clinical course, will need the ICU admission. The Multidimensional Prognostic Index (MPI) is a well-accepted tool derived from a standard CGA which allows to measure prognosis of older patients in different clinical settings including hospital. Therefore, we designed a multicenter, prospective, observational study to evaluate the role of MPI in predicting risk of ICU admission and in-hospital mortality among 500 COVID-19-positive older subjects admitted to geriatric and internal medicine wards. In addition, risk of re-hospitalization, institutionalization and death after 3 months from discharge will be assessed. The MPI yields a straightforward value from 0 to 1 and might be able to adequately stratify complex, vulnerable COVID-19 patients for best possible decision-making and treatment allocation.

Introduction

The recent diffusion of the coronavirus-19 disease (COVID-19) has reached proportions to be declared a pandemic disease as it affected more than 100,000 persons in 100 different countries.¹ According to recent epidemiological data from Italy, 96.3% of deceased patients are >60 years old and 87.7% is aged 70 years and older, showing that COVID-19 is a killer pathogen mainly in the aging population.² A source of big concern among all the Health Systems is the number of hospital and intensive care beds available to host the increasing number of older patients who need intensive interventions.

A recent document from the Italian Society of Anesthesiology and Resuscitation (SIAARTI) proposes to allocate treatments according to life expectancy.³ Though the current guidelines did not suggest that age should be the only factor determining resource allocation, the committee acknowledged that crucial for the clinical decision could be the difficulty for the frail older patients to survive the prolonged intubation required to recover from COVID-19-related pneumonia.⁴

This points to the need to stratifying patients according their prognosis based upon validated criteria. Wynants and colleagues, in a meta-analytic revision of the current literature, showed that proposed prediction models for prognosis of patients with COVID-19 infection lack of reliability and therefore could be more harmful than good.⁵ Besides age, sex and disease-specific determinants (e.g., computed tomography (CT) scans, inflammatory markers),⁵ it would be also important for the prognosis of older patients to assess functional, physical and

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psycho-social factors that can be best addressed by multidimensional tools.⁶ The Multidimensional Prognostic Index (MPI) is a prognostic tool able to predict short-term and long-term mortality in older patients in different settings including hospital. MPI is calculated based on information derived from a standard Comprehensive Geriatric Assessment (CGA) exploring different domains such as functional status, cognitive performance, risk of pressure sores, nutrition, multi-morbidity, number of drugs and co-habitation status.⁷

A consistent body of literature demonstrated that MPI has excellent accuracy and calibration in predicting length of hospital stay and clinical outcomes after hospitalization.⁸ Recently, results from the MPI_AGE European project reported that MPI was able to predict in-hospital mortality, as well as the risk of re-hospitalization, institutionalization, and access to home-care services.⁹ Nowadays, the MPI has been validated in over 54,000 older adults suffering from the most common chronic and acute age-related diseases associated with high mortality in over 50 international studies.¹⁰ It is consid-

ered one of the most commonly used tools to ascertain presence and degree of frailty in hospital and primary care.¹¹ Moreover, through the stratification of older patients in classes with different mortality risk, MPI has been shown to be a helpful instrument in the clinical decision making.¹⁰

Of note, previous studies confirmed the validity of MPI in predicting mortality of older patients hospitalized with pneumonia¹² and very recently, the MPI has been shown to predict the clinical outcome after non-invasive ventilation (NIV) in patients affected from respiratory insufficiency.¹³ However, there are no studies yet regarding the use of MPI to predict prognosis in older inpatients with COVID-19.

Objectives

Main objective

The main objective of the study is to evaluate in a population of hospitalized older patients affected by COVID-19, the reliability and accuracy of MPI in predicting: i) the admission to intensive care units (ICU) and ii) the risk of in-hospital mortality.

Secondary objectives

Secondary objectives of the study are to evaluate whether MPI could predict in this population: i) the length of stay, and the risk, over 3 months follow-up, of: ii) re-hospitalization; iii) admission to long-term care facility; iv) mortality.

Materials and Methods

Study design

This is a multicenter, prospective, observational cohort study which will enroll hospitalized older patients positive for

COVID-19 from 10 centers across the European Union (EU). At baseline, all recruited patients will undergo data collection for the calculation of the CGA-based MPI. Clinical, biological and radiological parameters about COVID-19 infection will be collected. In addition, discharge allocation, therapy plan at discharge, length of hospital stay, main diagnosis and other diagnoses will be recorded. After 3 months from discharge, patients and/or caregivers will be contacted to collect information about survival and eventual re-hospitalizations/institutionalization.

Sample size

A recent multicenter study reported that hospitalized older subjects in MPI-3 high risk group had an in-hospital mortality rate of 6.4% (in subjects at low-risk in MPI-1 group the mortality rate was 0.7%).¹⁴ Based on these data, 328 patients are sufficient to demonstrate the primary outcome, i.e. in-hospital mortality, with a first type error (alpha) of 5% and a statistic power of 80%. In this study we plan to recruit about 500 older hospitalized patients.

Setting and participants

This study will enroll a population of 500 hospitalized older patients (≥ 65 years) consecutively admitted to geriatrics and internal medicine ward.

All the patients are required to have the following inclusion criteria: i) 65 or more years old; ii) confirmed diagnosis of COVID-19 through swab with RT-PCR; iii) willingness to participate to the study. Patients younger than 65 years or unwilling/unable to participate to the study will be excluded.

Outcomes

Primary outcomes are the ICU admission from geriatrics or internal medicine wards and the in-hospital mortality.

Furthermore, we will assess as secondary outcomes: the length of hospital stay and during follow-up, until 3 months from discharge: mortality, rehospitalization, long-term care admission.

Procedures

Table 1 shows the information that will be collected at hospital admission. All the enrolled patients, who will meet the inclusion/exclusion criteria, will sign informed consent and have a standard CGA in order to collect the following information: personal data, functional, cognitive, and nutritional status, risk of pressure sores, co-morbidity, number of drugs taken, co-habitation status. Clinical data about COVID-19 infection will be recorded including signs and symptoms, day of swab, day of diagnosis, findings from standard (e.g., circulating inflammatory markers, chest X-ray, thorax ultrasound) or specific (e.g., chest CT, bronchoscopy) diagnostic tests. We will also report the following data: need of NIV or invasive mechanical ventilation, delirium assessment, discharge allocation, drug therapy at admission and at discharge, length of hospitalization, main diagnosis and secondary diagnoses coded through the ICD9-CM system. At 3 months after discharge, the patient or his/her caregiver will be contacted by phone call to determine: survival/mortality (eventually the date and cause of death), number of re-hospitalizations and/or institutionalization (Table 1).

Multidimensional Prognostic Index

The MPI is a prognostic tool based on a standardized CGA which allows to predict short- and long-term mortality in older subjects. MPI includes data derived from the eight following domains: i) Activities of Daily Living (ADL) - 6 items which evaluate the patient's functional status in daily life activities;¹⁵ ii) Instrumental Activities of Daily Living (IADL) - 8 items assessing the

Table 1. Procedures at the two different time-points in the MPI_COVID-19 study.

Recruitment (at hospital admission)	Follow-up (3 months after discharge)
Informed consent;	Survival/mortality (eventually the date and cause of death);
Demographics data;	Number of re-hospitalizations;
Standard CGA in order to calculate MPI;	Long-term care facility admission
Clinical parameters related to COVID-19 infection;	
Delirium assessment;	
Need of NIV or invasive mechanical ventilation;	
Main diagnosis and secondary diagnoses coded through the ICD9-CM system;	
Drug therapy at admission and at discharge;	
Total length of stay and discharge allocation (e.g., admission to ICU, institutionalization, home)	

MPI, Multidimension Prognostic Index; CGA, comprehensive geriatric assessment; NIV, non-invasive ventilation; ICU, Intensive Care Unit.

level of independence in the instrumental activities of daily life;¹⁶ iii) Short Portable Mental Status Questionnaire (SPMSQ) composed of 10 questions which assessed the patient's cognitive status, in particular spatio-temporal and personal orientation, memory, attention and computation ability;¹⁷ iv) Exton-Smith Scale (ESS) composed of 5 items assessing the risk of developing pressure sores;¹⁸ v) Mini-Nutritional Assessment-short form (MNA-SF) which consists of 6 items evaluating the patient's nutritional status through based on anthropometric, dietary and subjective data;¹⁹ vi) Cumulative Illness Rating Scale (CIRS) consisting of 14 items which allow to identify the pathologies present at the time of patient recruitment and their severity by calculating the comorbidity and severity index respectively;²⁰ vii) number of drugs usually taken by the patient; viii) cohabitation status which identifies the patient's socio-housing condition. To each domain is assigned a score corresponding to a risk, respectively: low (value of 0); moderate (value of 0.5); high (value of 1) (see Table 2).

The MPI is expressed as a continuous value from 0.0 (lowest risk of mortality) to 1.0 (highest risk of mortality). Appropriate and validated cut-off have been calculated to identify three levels of mortality risk as follows: MPI-1: mild risk (MPI values from 0.0 to 0.33), MPI-2: moderate risk (MPI values from 0.34 to 0.66), MPI-3: severe risk (MPI values from 0.67 to 1.0). The calculation of the final MPI will be made through the software application available at the <http://www.mpiage.eu>.

Clinical evaluation

In addition, other clinical parameters related to the COVID-19 infection will be evaluated at hospital admission: body tem-

perature (measured in C°), presence of cough, dyspnoea, diarrhea, parameters from blood gas analysis [*i.e.*, pH, pO₂, SpO₂, pCO₂, HCO₃⁻, pO₂ (mmHg)/O₂ Flux (L/min)], serum biomarkers (white blood cells, count of lymphocytes, C-reactive protein, LDH), findings from imaging techniques (*e.g.* chest x-ray, thorax ultrasound, chest CT). Given the several risk factors for delirium development in these patients (*e.g.*, age, sepsis, distance from caregivers),²¹ we will assess presence of this condition using the four 'A's Test (4AT), a screening tool for delirium which evaluates alertness, memory, attention and acute change or fluctuation in mental status.²² Finally, need of NIV or invasive mechanical ventilation, main diagnosis (and secondary diagnoses) at discharge in accordance with the ICD9-CM and drug therapy at discharge will be recorded.

Data management and conservation of documentations

The data will be managed at the E.O. Galliera Hospital - National Relevance and High Specialization Hospital, Genoa, Italy, coordinator center of the MPI_COVID-19 Project, which is designated as the center responsible for the processing and storing of personal data described above, in accordance with the rules of privacy and agreement to what is reported in this study protocol. All data will be collected in an electronic database in every center and transmitted anonymously to the coordinator center using standardized secure transmission rule in order to guarantee anonymity and protection of data.

Statistical analysis

General characteristics will be reported as frequencies (percentages) for categorical variables and mean ± standard deviation for

continuous variables. Comparisons across MPI categories will be performed using the Kruskal-Wallis test for singly ordered contingency tables, and linear by linear association test, for categorical and continuous variables, respectively.

Logistic binary regression analysis will be run, taking MPI at admission (in categories or as increase in 0.1 points) as exposure and admission to ICU, in-hospital mortality, and post-discharge (3-months) re-hospitalization, institutionalization and mortality as outcomes. The strength of the association between MPI at admission and these outcomes will be reported as odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for age, gender and center. We will also calculate the adjusted risk that come from the adjusted predicted probability of the outcome of interest for each level of MPI, when the other covariates in the model are at their means. For all the outcomes, receiver operator characteristic curves will be analyzed to compare the sensitivity and specificity of MPI in predicting these negative outcomes, measuring the relative area under the curve with the correspondent 95% CI. Two-sided alternatives with a significance level (P=0.05) will be considered for all the tests.

Monitoring and quality assurance

All partner centers will perform quality control and assurance procedures according to their internal standards and procedures. At least one technical meeting with all the centers involved in the data collection will be organized prior to the starting of the patient recruitment phase to ensure a proper implementation of the study. Moreover, at the start-up of the project the responsible for every center will conduct a meeting in their respective unit to share and adequately

Table 2. Ranges of values for each domain corresponding to the three risk levels in the Multidimensional Prognostic Index.

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

MPI, Multidimensional Prognostic Index; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; SPMSQ, Short Portable Mental Status Questionnaire; ESS, Exton-Smith Scale; MNA-SF, Mini-Nutritional Assessment Short Form; CIRS, Cumulative Illness Rating Scale.

inform the medical and nursing personnel participating to the project about the procedures for data collection. The same responsible will monitor, during the study, the personnel adherence to the collection protocol.

Ethical issues

The study will be conducted in accordance with the recommendations adopted by the 18th World Medical Assembly, Helsinki 1964 and subsequent revisions and following Good Clinical Practices.

Conclusions

This study will provide new insights on the short and long-term prognosis of older adults affected by COVID-19. Criteria merely based on age and number of comorbidities might be not such really sensitive in the early identification of healthcare needs of older patients with COVID-19. We hypothesize that a single numerical value derived from a standard CGA, as the MPI score, could help the clinicians to better identify those patients more at risk of negative outcomes and requiring more intensive health support.

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