Clinical Nutrition 45 (2025) 1–9

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

A simplified multidimensional scale approach is effective in predicting mortality in hospitalized older adults and highlights the role of nutrition

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ARTICLE INFO

Article history:
Received 4 April 2024
Accepted 15 December 2024

Keywords:
Malnutrition
Older adult
Hospital
Mortality
Frailty

SUMMARY

Background & aims: Malnutrition and cognitive impairment are among the major contributors to frailty, that significantly increases the risk of mortality of older hospitalized patients. Multidimensional frailty assessment tools, such as the multidimensional prognostic index-MPI, a tool based on a standard comprehensive geriatric assessment (CGA), have proven valuable for predicting adverse outcomes, including mortality of older adults following acute illness but its application in everyday clinical practice is limited. We hypothesized that removing parameters not closely associated with mortality and sorting the patient population according to the presence or not of cognitive impairment with possible integration of common laboratory markers, could provide a simplified approach that could improve practicability in all settings with at least comparable 1-year mortality predictive value.
Methods: A retrospective cohort study was conducted in patients consecutively admitted to the Geriatric Clinic of the Maggiore University Hospital in Trieste, Italy from January 1st 2018 to December 31st 2019. Their demographics, functional, clinical, laboratory parameters and 1-year mortality were recorded. In a development cohort of 1032 consecutive patients, best predictors of mortality were selected via systematic analysis and included in simplified prognostic models and algorithms and subsequently compared for prediction of 1-year mortality. The predictive relevance of the best algorithms was then validated, in comparison to MPI, in a separate cohort of 575 consecutive patients.
Results: While all demographic and tested laboratory parameters as well as MPI domains correlated with 1-year mortality, exclusion from MPI calculation of Short Portable Mental Status Questionnaire (SPSMQ), Exton Smith scale (ESS) and Mini Nutritional Assessment (MNA) significantly reduced MPI mortality predictivity, suggesting that not all MPI domains have the same weight. Further analysis showed that in the whole study cohort and in subgroups according to cognitive function, selected models including up to 3 parameters were superior to MPI in predicting 1-year mortality. In particular, models including MNA and albumin, or Exton Smith scale proved to better predict mortality in patients without or with severe cognitive impairment, respectively. A derived diagnostic algorithm applying different models according to cognitive status showed improved predictive value compared to MPI while requiring shorter estimated assessment time. Internal validation confirmed these results [HR: 4.37 (3.02–6.31) vs 3.16 (2.18–4.61), $p < 0.0001$].
Conclusions: In older acutely ill patients, a simplified multidimensional algorithm approach based on the assessment of cognitive function followed by nutritional status with the addition of plasma albumin or of functional status in patients without or with severe cognitive impairment respectively, may significantly improve 1-year mortality prediction while reducing assessment time. Moreover, these results highlight the prognostic value of MNA in association with albumin for 1-year mortality risk screening in the

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https://doi.org/10.1016/j.clnu.2024.12.015

hospital setting and, for the first time, demonstrate its differential performance according to the presence or not of cognitive impairment.

1. Introduction

Frailty, characterized by reduced physiological reserve and increased vulnerability to stressors, affects up to 79 % of older adults acutely hospitalized [1–3] and is strongly associated with adverse outcomes, including extended length of hospital stay, discharge destination different from home and all-cause mortality [1]. Thus, routine screening for frailty in older hospital patients using standardized tools is currently recommended [4].

To detect and quantify frailty and associated risk of mortality, several screening and assessment tools to be used by healthcare professionals have been validated in different settings. These indices are usually multidimensional and combine parameters that assess various domains of frailty, including nutritional status, cognitive function, dependence, comorbidities, polypharmacy and psychosocial status [5,6]. Indeed, the panel of questionnaires used in frailty prognostic indices includes scores that, although designed to target specific areas, are per se multidimensional. As an example, the Mini Nutritional Assessment (MNA) developed for the assessment of nutritional risk/malnutrition not only provides information about anthropometry and nutrition, but also about cognitive function, medications, mobility, recent acute diseases and self-perception of health [7]. The inclusion in the MNA of several domains underscores on one side the multifactorial origin of malnutrition and on the other side the tight relationship between malnutrition and selected determinants, in particular cognitive and physical dysfunction [8]. Indeed several studies have demonstrated a strong association between malnutrition, physical frailty and impaired cognition [9–11] as well as the prognostic validity of MNA, which includes assessment of the three areas, for malnutrition, frailty and mortality in acute hospitalized older adults [12–19].

Indeed, the MNA alone is not designed to provide comprehensive information about frailty and it is generally integrated by specific questionnaires for cognitive and functional status. This results in a partial overlap and amplification of the relevance of selected areas that may ultimately influence the prognostic significance of the multidimensional assessment. At present, it is not clear from the current evidence how and to which extent individual factors included in multidimensional frailty scores should be considered in risk-adjustment models such as calculating mortality rates after admission in older adults acutely hospitalized. In order to assess this topic, we focused on individual items of the multidimensional assessment and on selected laboratory parameters to design a simplified algorithm to predict 1-year mortality in older adults acutely ill. We considered the Multidimensional Prognostic Index (MPI) [20], based on the comprehensive geriatric assessment (CGA) because it is widely used in hospitalized older patients and it is a validated tool for predicting the risk of 1-year mortality as well as the length of hospital stay, rehospitalization and institutionalization [5,21,22]. Despite its accuracy and validation as CGA-based prognostic and frailty tool the large-scale practicability of MPI is still debated, since the minimum time needed to perform it is 15 min [23], with other reports indicating that up to 30 min may be needed [24]. Therefore, the availability of a rapid algorithm to screen for mortality would allow to identify the patients at highest risk. In particular, in these patients the CGA allows for an individualized approach in recognizing domains linked to frailty that should be the target of multidimensional interventions for effective patient care. Early initiation of interventions based on the MPI domains, in particular targeted at functional, nutritional, and cognitive status are particularly important, because hospitalization accelerates the development of deconditioning, which has a negative impact on performance at discharge [25]. Therefore, preventing/treating potentially modifiable risk factors for deconditioning identified following administration of the complete CGA, i.e. malnutrition and sarcopenia, functional and cognitive deficits may contribute to improved rehabilitation post hospital stay [25]. Several studies have also shown that in older adults acutely ill nutritional support improves clinical outcomes by reducing mortality and complications [26].

Given these observations, with this study we aim at designing a simplified algorithm based on individual items of the MPI and on selected laboratory parameters to screen for the risk of 1-year mortality in hospitalized older adults. In particular, serum albumin is a blood test routinarily performed in geriatric patients, which is also an established marker of all-cause mortality risk [27,28]. Given the importance of cognitive status also for the reliability of response to questionnaires, we also aimed at exploring the potential relevance of cognitive impairment in the process of selecting single items associated with 1-year mortality in the current setting. Finally, we also aim at validating in a separate cohort the best potential multivariable prediction models.

2. Materials and methods

2.1. Study cohort

The study was conducted in two phases and was based on a secondary analysis of a retrospectively collected database. In the development phase, data from patients consecutively admitted from the Emergency Department (ED) to the Geriatric Clinic of the Maggiore University Hospital Trieste between January 1st to December 31st 2019 was included in model and algorithm design and assessment. In the validation phase, patients admitted to the same study ward from the ED between January 1st to December 31st 2018 were included. A total of 1032 patients were included in the development cohort and 575 in the validation cohort. Study cohorts are representative of ED-referrals to a geriatric ward in a teaching hospital. All the procedures performed in the study can be classified as routine care. Inclusion criteria included age≥65 years, written consent to the use of data for clinical research purposes, first episode of hospitalization in the Geriatric study ward, direct admission to the ward from the ED. Exclusion criteria: age<65 years, refusal to sign the informed consent to the use of data for clinical research purposes, missing data at the analysis, episode of rehospitalization. Data from hospital records was reviewed and missing data was found to be similar among sociodemographic groups. Patients not included for missing relevant data were 142 and 83 in the development and validation cohorts, respectively. With regard to power assessment for 1-year mortality prediction, the current study numerosity is comparable to that used in the original MPI development [20]. The study is part of the “Prevalence and prognostic impact of frailty and depression in hospitalized older adults" non registered research protocol. The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the University of Trieste (approval number 127, date of approval: January 23rd 2023).

2.2. Data collection

Participants' age, sex, educational level and living condition were recorded at admission in the Geriatric study ward. Clinical, functional and laboratory data were extrapolated from the hospital electronic archive and from patients' medical records. Laboratory parameters used in the current study were obtained upon admission to the ward. All the participants underwent, within 72 h of admission to the ward, the comprehensive geriatric assessment for multidimensional evaluation, including administration of the following scores: Basic and Instrumental Activities of Daily Living [29,30] for functional evaluation, Exton Smith scale [31] for the risk of pressure sores, Mini Nutritional assessment [7] for the risk of malnutrition, Short Portable Status Mental Questionnaire [32] for cognitive function and Cumulative Illness Rating Scale [33] for comorbidities. In addition social condition and number of drugs at admission were recorded. Assessments were performed by expert geriatricians in standard clinical practice and took place before this retrospective study was planned.

Based on this information, the Multidimensional Prognostic Index was calculated [20]. Patients scoring in the range of 0–0.33 were considered at low risk of mortality; those scoring between 0.34 and 0.66 were considered at intermediate risk of mortality; and those included between 0.67 and 1 were at high risk of mortality [20].

2.3. Study design and methodology

The methodology was designed and described according to the most recent TRIPOD guideline (TRIPOD + AI) for reporting clinical prediction models [34]. The primary study end-point was mortality – defined as death from any cause – within 12 months from hospital admission. Date of death was obtained from the official national electronic mortality register, thus preventing any potential related bias in data availability. Initial predictors considered for model development included all relevant clinical data collected in standard practice upon admission in the geriatric ward such as age, sex and BMI, all MPI factors [20] and common plasma measurements including C reactive protein, plasma glucose, creatinine, hemoglobin, albumin, sodium and potassium circulating levels. All factors were then tested for outcome prediction in the whole study cohort as well as in subgroups of patients without or with cognitive impairment. MPI factors better contributing to its prediction value were also identified. Variables that collectively resulted to be better associated with 1-year mortality, were then used to systematically design potential predicting regression models. Generated models included all combinations of up to a maximum of 3 parameters among those which showed potential comparable prediction value vs. MPI. Models which showed best prediction value in the whole study cohort or in subgroups were then used to generate potential algorithms based on a two step approach which included the use of potentially different models according to prior cognitive impairment assessment. Best algorithmic approaches were then tested for mortality prediction vs. MPI and validated in the validation cohort. No patient or member of the public was involved in study design, conduct, reporting or interpretation of the data.

2.4. Statistical analysis

Data distributions for continuous variables was assessed by Shapiro–Wilk test. Subgroup comparison was performed by independent sample t test or Mann–Whitney for normally or non-normally distributed variables, respectively. Initially, in order to identify factors predictive of 1-year mortality, the associations of all demographic, laboratory, clinical and functional parameters as well as the MPI itself were evaluated by point-biserial correlation analysis. Models were systematically designed using all of the combinations of maximum 3 parameters including at least one among those with $p > 0.2$ (broad similarity) in the prognostic difference with MPI. Receiver operating characteristic (ROC) analysis was used to evaluate continuous variables and models as predictors of 1 y mortality. Hazard ratio with confidence interval for overall mortality was assessed by COX regression. Prediction models were generated for each identified set of variables as the sum of the products of each variable for the relative regression coefficient, as calculated by COX regression in the whole study group. Model evaluation and selection was performed considering lower Schwartz Information Criterion (BIC), a method that takes into account both higher likelihood and lower number of parameters. Cutoffs for each model were identified by Youden's Index, identifying the point with maximum sum of sensitivity and specificity for 1 y mortality. HR with confidence interval for algorithm prediction of all-cause 1 y mortality was assessed in contingency table analysis. Sensitivity was considered as the probability that the algorithm predicts >50 % death probability in patients that die within 1 year (true positive rate), specificity as the probability that the algorithm predicts <50 % death probability in patients that survive 1 y (true negative rate), accuracy as the overall probability that a patient is correctly classified regarding mortality risk. Comparison of paired ROC curves, models and algorithms was performed using z-tests on AUCs or HRs with their respective standard errors. Statistical analysis was performed using SPSS for Windows version 17 (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Clinical and demographic data of the development cohort

Table 1 shows the main characteristics of the whole population and of subgroups according to the absence (SPSMQ≤4) or presence (SPSMQ>4) of moderate to severe cognitive impairment. Compared with non severely cognitively-impaired patients, those cognitively impaired were older, had lower BMI, reduced ADL, IADL and ESS scores indicating worse functional status and lower MNA score, suggesting malnutrition. On average they demonstrated a higher CIRS comorbidity score but assumed a fewer number of drugs as compared with the group with no/mild cognitive impairment; the living condition showed a higher percentage of patients living in long term health care facilities. Except for CRP, there were no significant differences in laboratory parameters between groups. Mean MPI for the whole study cohort showed a moderate risk for mortality, becoming severe in patients cognitively impaired, who also presented higher 1-year mortality rate than the subgroup with SPSMQ ≤4. Overall, patients in the MPI 3 subgroup at high mortality risk represented 22.8 % of the whole population.

3.2. Factors associated with mortality

Parameters and MPI tests were then assessed for their association with 1-year mortality. All demographic and tested laboratory

Table 1
Characteristics of study patients in the development cohort. BMI, body mass index; CGA, Comprehensive Geriatric Assessment; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CIRS, Cumulative Illness Rating Scale; SPSMQ, Short Portable Status Mental Questionnaire; ESS: Exton–Smith score; MNA, Mini nutritional assessment; MPI, Multidimensional Prognostic Index; CRP: C reactive protein. Data are expressed as mean ± standard error or median value (Mdn) with interquartile range (IQR) where specified.

Parameter	ALL (n = 1032)	SPMSQ ≤4 (n = 677)	SMPSQ >4 (n = 355)	p
Demographic				
Age (y)	84.7 ± 0.23	83.6 ± 0.27	86.9 ± 0.39	<0.001
Sex (% male)	36.7	38.2	33.9	0.18
BMI (kg/m^2)	23.7 ± 0.16	24.6 ± 0.20	22.1 ± 0.25	<0.001
1 year all-cause mortality (%)	34.9	27.5	49.2	<0.001
CGA				
Number of drugs (Mdn; IQR)	6; 4-8	6; 4-8	5; 3-7	<0.05
ADL (Mdn; IQR)	5; 2-6	6; 5-6	2; 0-4	<0.001
IADL (Mdn; IQR)	3; 0-7	5; 2-8	0; 0-2	<0.001
CIRS (Mdn; IQR)	5; 3-6	4; 3-6	6; 4-8	<0.05
SPMSQ (Mdn; IQR)	2; 1-5	1; 0-2	6; 4-8	<0.001
ESS (Mdn; IQR)	17; 14-19	18; 16-20	6; 4-8	<0.001
Living condition: Alone (%)	39	46	25	<0.001
family/Caregiver (%)	48	49	46	
Institution (%)	13	5	29	
MNA (Mdn; IQR)	20; 16-25	22;-19-25	6; 4-8	<0.001
MPI (Mdn; IQR)	0.5; 0.3–0.6	0.4; 0.3–0.5	0.6; 0.4–0.8	<0.001
MPI 1 (n; %)	302; 29.3	278; 41.1	24; 6.8	<0.001
MPI 2 (n; %)	495; 48.0	348; 51.4	147; 41.4	<0.01
MPI 3 (n; %)	235; 22.8	51; 7.5	184; 51.8	<0.001
Laboratory				
CRP (mg/L)	62.2 ± 2.41	56.5 ± 2.90	73.1 ± 4.24	<0.05
Glucose (mg/dL)	123 ± 1.62	121 ± 1.71	128 ± 3.38	<0.05
Creatinine (mg/dL)	1.2 ± 0.03	1.2 ± 0.03	1.2 ± 0.05	0.880
Hemoglobin (g/dL)	11.5 ± 0.06	11.5 ± 0.08	11.5 ± 0.11	0.635
Albumin (g/dL)	3.3 ± 0.02	3.4 ± 0.02	3.2 ± 0.03	<0.001
Sodium (mEq/L)	138 ± 0.21	138 ± 0.27	139 ± 0.33	<0.05
Potassium (mEq/L)	4.1 ± 0.02	4.2 ± 0.02	4.1 ± 0.03	<0.05

parameters, except for blood glucose and electrolytes, were associated with this outcome in point-biserial association analysis, in the whole study cohort (Table 2). In cognitively non-impaired patients, living condition and SPMSQ score were not associated with 1-year mortality, while age was not associated in patients with SPMSQ>4. Comparable results were obtained in ROC and survival analyses (Supplementary Tables 2-3). The current data confirm that MPI as well as its composing domains are associated with 1-year all-cause mortality, in the whole study cohort as well as in both SPMSQ subgroups (Table 2). MPI was also a strong predictor of all cause 1-y and overall mortality in ROC and survival analysis in the whole study cohort [HR(CI) = 14.42(9.96–20.90), $p < 0.001$], SPMSQ≤4 [HR(CI) = 12.62(7.20–22.12), $p < 0.001$] and SPMSQ>4 [HR(CI) = 13.57(6.57–28.03), $p < 0.001$] subgroups (Supplementary Tables 2-3).

3.3. MPI domains do not equally contribute to mortality prediction

In further analysis, the identification of the most relevant clinical parameters in terms of mortality prediction was also performed by evaluating the specific contribution from single items to overall MPI outcome predictive value. In the whole study cohort and subgroups, exclusion from MPI calculation of SPSMQ, ESS, MNA, living condition, CIRS and number of medications (all $p < 0.001$), while still maintaining a strong overall all-cause mortality prediction value (Table 3, Supplementary Fig. 1, Supplementary Table 3), significantly reduced it compared to full MPI. Interestingly, ADL exclusion from MPI calculation improved mortality prediction ($p < 0.05$ vs MPI) in all groups (Table 3). These results show that not all domains have the same weight, with the potential to even decrease overall index prognostic value.

3.4. Generation of predictive algorithms shows that using weighted combinations of selected factors may increase mortality prediction

Potential simplified models obtained by systematic combination of the better predicting factors (Supplementary Table 1) in regression analyses are presented in Supplementary Table 4, which also shows their predictive value for mortality as well as optimal cutoffs. Comparisons of hazard ratios for 28 models, but also single variables and clinical cutoffs, showed that 3 and 5 criteria were significantly superior to MPI in predicting 1-year mortality in the whole study cohort and in patients without cognitive impairment, respectively. None was better in those with SPMSQ>4. 12 (including MNA), 15 (including ESS and ADL), and 7 (including ESS and albumin) criteria were comparable respectively in the whole cohort and in cognitively non-impaired and impaired patients (Supplementary Table 5). Combinations of all criteria with HR higher than MPI for each subgroup were then systematically included in possible single or two step prognostic algorithms (Fig. 1, Supplementary Table 6) based on a differential approach for patients with or without cognitive impairment.

3.5. Identification of a simplified quicker assessment protocol

Generated algorithms were then tested and ranked for prediction value. Among these, 17 were significantly superior in predicting 1-year mortality respectively to MPI cutoff calculated by Youden's method, and 7 were found superior also to MPI class 2/3 clinical cutoff. Among the 17 improved algorithms, all also presented higher accuracy and specificity than MPI, while sensitivity was equal or higher in 5 (Supplementary Table 6). Among the best 7 algorithms, all include assessment of MNA and albumin in cognitively non impaired patients, while ESS is always included in

Table 2

Association analysis (point-biserial correlation) of 1-y mortality with studied parameters, in the whole study cohort as well as in subgroups of patients without or with cognitive impairment. BMI, body mass index; CGA, Comprehensive Geriatric Assessment; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CIRS, Cumulative Illness Rating Scale; SPSMQ, Short Portable Status Mental Questionnaire; ESS: Exton–Smith scale; MNA, Mini nutritional assessment; MPI, Multidimensional Prognostic Index; CRP: C reactive protein.

1-y mortality	ALL		SPMSQ ≤4		SPMSQ>4	
	rho	p	Rho	P	rho	p
Demographic						
Age	0.2065	<0.0001	0.1153	0.0027	0.2429	<0.0001
Sex (male)	0.0718	0.0215	0.0784	0.0423	0.0921	0.0841
BMI (kg/m^2)	−0.1621	<0.0001	−0.0995	0.0098	−0.1591	0.0028
CGA						
Number of drugs	0.0930	0.0028	0.0844	0.0281	0.1709	0.0012
ADL	−0.2868	<0.0001	−0.1882	<0.0001	−0.2463	<0.0001
IADL	−0.3007	<0.0001	−0.2127	<0.0001	−0.2146	<0.0001
CIRS	0.1925	<0.0001	0.1484	0.0001	0.2359	<0.0001
SPMSQ	0.2385	<0.0001	0.0746	0.0522	0.1908	0.0003
ESS	−0.3311	<0.0001	−0.2403	<0.0001	−0.2936	<0.0001
Living condition	0.1274	<0.0001	0.0013	0.9731	0.1635	0.0020
MNA	−0.3031	<0.0001	−0.2292	<0.0001	−0.2478	<0.0001
MPI	0.3456	<0.0001	0.2555	<0.0001	0.3112	<0.0001
Laboratory						
CRP	0.1699	<0.0001	0.1430	0.0003	0.1458	0.0080
Glucose	0.0594	0.0582	0.0036	0.9264	0.1209	0.0236
Creatinine	0.1276	<0.0001	0.1540	0.0001	0.1417	0.0078
Hemoglobin	−0.1313	<0.0001	−0.1221	0.0015	−0.1545	0.0036
Albumin	−0.2743	<0.0001	−0.2405	<0.0001	−0.2499	<0.0001
Sodium	0.0125	0.6894	−0.0462	0.2308	0.0670	0.2095
Potassium	−0.0161	0.6072	0.0196	0.6115	−0.0316	0.5550

Table 3

HR for all-cause mortality of MPI and MPI without single components in each study group. For each group, factors are ordered by decreasing HR. BMI, body mass index; CGA, Comprehensive Geriatric Assessment; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CIRS, Cumulative Illness Rating Scale; SPSMQ, Short Portable Status Mental Questionnaire; ESS: Exton–Smith scale; MNA, Mini nutritional assessment; MPI, Multidimensional Prognostic Index.

	HR	IC		p	p vs MPI
ALL					
MPI w/o ADL	17.6056	11.8069	26.2522	5.77E-45	<0.0001
MPI w/o IADL	14.8077	10.0155	21.8929	1.37E-41	0.1675
MPI	14.4283	9.9591	20.9031	3.19E-45	1.0000
MPI w/o SPMSQ	13.8293	9.4508	20.2364	1.13E-41	0.0271
MPI w/o ESS	13.3771	9.1944	19.4625	7.17E-42	0.0001
MPI w/o MNA	13.0156	9.0147	18.792	1.11E-42	<0.0001
MPI w/o Living condition	11.3948	8.2163	15.8030	3.65E-48	<0.0001
MPI w/o CIRS	10.2996	7.3941	14.347	2.87E-43	<0.0001
MPI w/o Number of drugs	9.96509	7.1209	13.9452	5.34E-41	<0.0001
SPMSQ ≤ 4					
MPI w/o ADL	14.7049	7.8586	27.5154	4.14E-17	<0.0001
MPI	12.6215	7.2027	22.1172	8.09E-19	1.0000
MPI w/o IADL	11.6286	6.2816	21.5270	5.79E-15	0.0194
MPI w/o MNA	11.0683	6.4618	18.9588	2.04E-18	0.0001
MPI w/o ESS	10.9871	6.3907	18.8895	4.36E-18	<0.0001
MPI w/o Living condition	10.5189	6.2957	17.5751	2.58E-19	<0.0001
MPI w/o Number of drugs	9.9820	5.8248	17.1060	5.67E-17	<0.0001
MPI w/o SPMSQ	9.6270	5.8131	15.9432	1.39E-18	<0.0001
MPI w/o CIRS	9.0643	5.4449	15.0894	2.31E-17	<0.0001
SPMSQ > 4					
MPI w/o ADL	14.8244	7.2087	30.4859	2.31E-13	0.0162
MPI w/o SPMSQ	13.6874	6.5439	28.6289	3.67E-12	0.8250
MPI	13.5707	6.5713	28.0252	1.81E-12	1.0000
MPI w/o Living condition	12.5790	6.5392	24.1975	3.31E-14	0.0466
MPI w/o ESS	12.2089	5.7596	25.8800	6.68E-11	0.0105
MPI w/o IADL	11.9222	5.9743	23.7919	2.06E-12	0.0012
MPI w/o MNA	11.2565	5.4729	23.1518	4.71E-11	<0.0001
MPI w/o CIRS	9.8284	5.115	18.8822	6.89E-12	<0.0001
MPI w/o Number of drugs	8.7085	4.3881	17.2827	6.05E-10	<0.0001

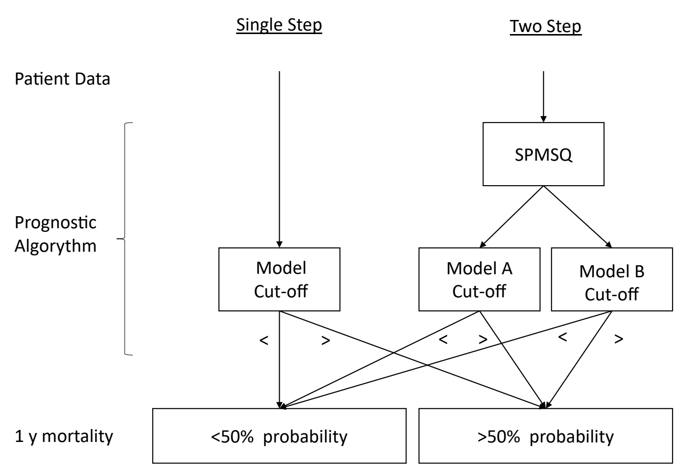

Fig. 1. Prognostic algorithm models.

algorithms to better assess patients with SPMSQ>4. Among algorithms with higher HR than MPI-1/2, 5 presented better or comparable (i.e. ±0.01) sensitivity, specificity and accuracy than MPI. Model formulas used in these best-performing algorithms were then transformed for simplified practical use by including the relative cut-off, in order that in any model values > 0 now suggest a >50 % probability of death within 1-year, and reported in Table 4. Further comparisons with regard to simplicity and shortest time of assessment was also performed (Table 4). All selected protocols had potentially lower number of items and quicker average time to be performed than MPI with regard to the study population. In particular, diagnostic algorithm 1 (DA01) including MNA and albumin in those with SPMSQ≤4 and Exton Smith score in those with

Table 4
Diagnostic algorithms. Definition of formula combinations, number of necessary tests to be performed and average timing required for diagnostic algorithms with higher HR than MPI-1/2 and better or comparable (i.e. ±0.01) sensitivity, specificity and accuracy than MPI. For practical use, formulas selected for these best performing algorithms, have been modified by including the relative cut-off value, so that values > 0 always suggest a >50 % probability of death within 1-year. DA, Diagnostic algorithm; MNA, Mini nutritional assessment; ESS: Exton–Smith scale; MPI, Multidimensional Prognostic Index. ADL, Activities of Daily Living.

Diagnostic algorythm	SPMSQ≤4		SPMSQ>4		Total number of tests (min–max)	Estimated average time (min)
	Formula	Model variables	Formula	Model variables		
DA01	F1	MNA, albumin	F2	ESS	2–3	7.9
DA02	F3	MNA, albumin, ESS	F2	ESS	2–4	9.9
DA03	F1	MNA, albumin	F4	ESS ADL	3	8.9
DA04	F1	MNA, albumin	F3	MNA, albumin, ESS	3–4	11.5
DA05	F1	MNA, albumin	F5	MPI	3–8	17.2
DA42	F5	MPI	Same	MPI	8	30.0

Formulas.
F1 = MNA*-0.0639+albumin*-0.5279 + 3.03.
F2 = ESS*-0.1286 + 2.08.
F3 = MNA*-0.0427+albumin*-0.4364 + ESS*-0.0686 + 3.4.
F4 = ADL*-0.0935 + ESS*-0.0856 + 1.83.
F5 = MPI-0.5.

SPMSQ>4, besides presenting the highest HR was also found to be the one with lower number of tests to be implemented as well as lowest average estimated time to be performed (Supplementary Table 6, Table 4) and was therefore chosen as best potential simplified assessment protocol.

3.6. Validation of the simplified approach protocol

The validation cohort characteristics reported in Supplementary Table 7 are largely comparable to the development one, except for higher ($p < 0.001$) MPI in the subgroup of patients with SPMSQ ≤4 (although in the range of intermediate mortality risk in both cohorts) and slightly higher values of plasma glucose and sodium in the overall validation cohort. The identified diagnostic protocol was then tested for validation, also in comparison to MPI, in this cohort. Results confirmed that the identified simpler diagnostic algorithm had significantly higher HR than MPI in predicting 1-year mortality, considering both clinical and calculated cut-offs (Table 5). Accuracy and specificity were also higher in the algorithm compared to MPI, while sensitivity was lower of less than 6 %. Clinical cutoff MPI-2/3 showed good accuracy but low sensitivity while MPI-1/2 had low specificity (Table 5).

4. Discussion

This study demonstrates that a simplified algorithm based on selected items of the validated Multidimensional Prognostic Index combined with a selected laboratory parameter (albumin) outperforms the MPI in predicting 1-year mortality in a cohort of acutely hospitalized older adults. In addition, if patients are prescreened for cognitive impairment using the SPSMQ, the algorithm can be further simplified while preserving its possible use on all patients in the current setting. Indeed, application of either the Exton Smith Scale in those severely cognitively impaired or the combination of MNA and plasma albumin in those cognitively intact demonstrates better accuracy and specificity than the MPI in predicting 1-year mortality. Moreover, clinical cutoff MPI-2/3, while presenting higher specificity, is much lower in sensitivity, strongly undermining its potential usefulness in a screening procedure. The simplified scale approach requires a lower number of tests and consequently of single items which can be calculated in the range of 15 (in cognitively impaired patients) or 29 (in those with no/mild cognitive impairment) versus 63 of the MPI with significant time saving (about 22 min).

Recognizing frailty has important prognostic and clinical implications for the correct management of older adults acutely ill. According to a previous metanalysis [2], the prevalence of frailty in hospitalized patients, based on MPI categorization >0.66 (class 3) is 29.8 %. Our data show a slightly lower rate in both the original and validation cohorts. Nonetheless, the relative large study population allowed us to examine study endpoints throughout all MPI subgroups, including MPI 3, which notably includes patients that are poorly represented in studies examining admissions of older adults from the Emergency Department.

Mortality is one of negative outcomes associated with frailty, in addition to falls, disability, hospitalization and nursing home admission [35]. The MPI, as well as other frailty tools are important instruments for prognosis and for individualized patient care, however none of them is regularly applied in the real world out of specialized geriatric settings, because of barriers linked to low practicability especially in terms of time needs [23] and qualified personnel availability. Thus, simplifying existing frailty detection procedures enables a broader use in everyday clinical practice also by health professionals without a specialized training. A few frailty prognostic scores are currently available for hospitalized older adults, and uncertainty in tool selection represents another reason for the lack of implementation of frailty screenings outside specialist settings [36]. Thus, while available and validated multidimensional frailty tools are indispensable instruments for prognosis of several frailty-associated negative outcomes and for

Table 5
Simplified diagnostic algorithm and 1 y mortality predictivity in the validation cohort. HR, Sensitivity, Specificity Accuracy of proposed diagnostic criteria vs 1 year all-cause mortality in comparison with MPI (Youden) and MPI-2/3 clinical cut-offs. Algorithms are ordered by decreasing HR. All p < 0.001. DA: Diagnostic algorithm; MPI, Multidimensional Prognostic Index.

	HR (CI)	p	p vs MPI	p vs MPI-2/3	Sensitivity	Specificity	Accuracy
DA01	4.3656 (3,0181–6,3148)	<0.0001	<0.0001	0.003	0.673	0.679	0.677
MPI-2/3	3,5172 (2327–5,3162)	<0.0001	0.221	1.000	0.362	0.861	0.689
MPI	3,1687 (2,1776–4,6109)	<0.0001	1.000	0.221	0.730	0.540	0.605
MPI-1/2	2,9861 (1.8449–4,8332)	<0.0001	0.558	0.101	0.878	0.294	0.495

purposes of strategic planning of supportive interventions, simplified prognostic screening algorithms focusing on selected outcomes, i.e. mortality may support the stage of identification of the frailest older adults who should undergo CGA. For the purpose of mortality prediction in frail older adults, simplified prognostic algorithms ought in any case to encompass multiple areas rather than relying solely on selected domains. Previous studies have in fact suggested that frailty scores should include at least 30 items, with a lowest practical limit of 10–15 [37]. In this view careful selection of the scores to be included plays a crucial role when the number of items is reduced. Indeed, an abbreviated form of MPI, namely BRIEF-MPI, was also proposed by the same group who designed MPI [38]. Their simplified approach, while maintaining a multidimensional structure, was, at variance with our study, mainly clinically-rather than data-driven, as its design was based on removing repetitions of domain assessment between items by empirical judgment, with nutritional assessment being arbitrarily reduced to three parameters. As a consequence, while the number of total items was indeed reduced, BRIEF-MPI still needs 8 factors for its calculation. However, its assessment, despite being conducted in a limited sample-sized cohort, demonstrated a good agreement with the full MPI, thus showing, as a proof of principle, a potential clinical relevance for simplified approaches. Moreover, the adoption of a two-step algorithmic approach allows to apply simpler models calculated on smaller number of variables to the appropriate target groups, with overall reduction in needed variables without loss of prediction value.

Notably, some scores included in the MPI are per se multidimensional because they explore several dimensions of frailty and the simplified scale approach demonstrated good construct validity and included data for most of the domains evaluated by the MPI.

Among the different domains assessed by MPI, those that reflect physical (also characterized by weight loss and sarcopenia) and cognitive frailty are relevant components and often associated [39]. Malnutrition, which contributes to frailty [13] increases the risk of mortality in older adults who are hospitalized and acutely ill [26]. Acute diseases exacerbate malnutrition because of decreased appetite, altered metabolism and increased nutritional requirements. The Mini Nutritional Assessment, originally designed for screening and diagnosing malnutrition/risk of malnutrition in older adults, is a multidimensional tool used in a variety of contexts [40]. The MNA addresses various aspects of nutritional status, including dietary intake and weight loss but also neuropsychological problems and mobility providing a holistic view of an older adult's health. The high prevalence of risk of malnutrition or frank malnutrition and the association with frailty and sarcopenia explain the large use of the Mini Nutritional Assessment in the hospital setting. A recent meta-analysis demonstrated that in older hospitalized patients, those affected by prefrailty/frailty, risk of/malnutrition and sarcopenia were respectively 84 %, 66 % and 37 % and that the three conditions frequently coexist [41]. In addition, several studies have demonstrated the MNA is an independent predictor of adverse clinical outcomes in older hospitalized patients, including risk of developing geriatric syndromes during hospitalization and post-discharge mortality [17,18]. In addition to assessing nutritional status, it can also provide information on frailty [14–16] and on the risk of functional decline [42]. The strong relevance of MNA and of selected domains of the MPI (i.e Exton Smith scale) regarding risk for 1-year mortality has been recently confirmed also by a machine-learning approach in a prospective cohort study [43].

Albumin serves as more than just a nutritional marker in older adults who are acutely ill; it also negatively reflects inflammation and severity of disease [44]. In older acute medical inpatients low serum albumin is associated with poor survival [45] and in the presence of high CRP reduced albumin levels are independent predictors of short- and long-term mortality in addition to severe frailty [46]. In view of these and other findings the role of albumin as a nutritional markers has been debated. However, a previous study demonstrated that high CRP and severe nutritional risk assessed by the Nutritional Risk Score 2002 were independently associated with hypoalbuminemia and that the three variables were independent predictors of mortality during acute diseases, confirming distinct contributions of inflammation and malnutrition to reduced survival [47]. Thus, combining MNA with albumin not only has diagnostic implications for malnutrition/risk of malnutrition and its treatment, but may also indeed be used for mortality risk stratification.

In our cohort in the presence of cognitive impairment, the use of a functional score, i.e. the Exton Smith scale improved the predictive ability for 1-year mortality as compared to both the MPI and to the simplified score including albumin and MNA. It should be underscored that MPI is a validated prognostic tool for mortality also in the presence of dementia [48]. The Exton Smith scale holds significant importance in evaluating the individual's risk of developing pressure ulcers by assessing factors such as mobility, activity, incontinence and overall mental status. Indeed, accumulating evidence has demonstrated that in the acute hospital setting cognitive impairment, irrespective of its cause, is associated with increased risk of adverse outcomes, including functional decline, increased length of hospital stay, discharge to a long-term care facility and short- and long-term mortality [49,50]. Notably, cognitive impairment and low-level functional status are associated with increased hospital admission and readmission rates and with worsen clinical outcomes [11] in frail individuals. Our results confirm these data suggesting that in patients with severe cognitive impairment the risk of 1-year mortality is mostly driven by functional status rather than by malnutrition or other laboratory parameters also reflecting severity of acute disease.

In our study the contribution of comorbidities estimated by CIRS to the prognostic model was less relevant than that of MNA, SPSMQ and Exton Smith scale. Indeed, a previous investigation demonstrated that questionnaires used for the assessment of patient complexity can be grouped in two main clusters: one with common denominator dependence and frailty in which, among others, the Exton Smith scale, SPSMQ and MNA are included and with higher prognostic relevance in terms of mortality; the other one representative of comorbidities with a less relevant role [51]. The same pattern was recognized also performing factor analysis in the current study dataset (data not shown), however CIRS alone did not show any broadly relevant similarity (i.e. $p > 0.2$) to MPI in terms of prognostic value and was therefore, as per model design methodology, not considered for inclusion in model design.

There are limitations to our study. First, it was conducted at a single geriatric academic center, limiting the generalizability of the findings to the overall population of older adults acutely ill. Second, although the simplified diagnostic algorithm yielded superior accuracy to MPI in predicting 1-year mortality, no external validation was performed.

Advantages for the simplified algorithm scale-based approach as constructed in this study include: 1) For the first time a discrimination algorithm based on cognitive function has been introduced, which is highly correlated with 1-year mortality; 2) no additional skills or data handling and quality assessment are required by healthcare professionals compared to standard CGA and MPI; 3) Internal validation was conducted, supporting a larger generalizability of the model. These features highlight the strengths of the simplified algorithm in predicting mortality in older adults acutely ill.

5. Conclusion

In conclusion, although the composite structure of MPI and of other frailty assessment tools are essential instruments to address the multidimensional nature of frailty and of associated increased risks of adverse outcomes, including mortality, the incorporation of several scores increases its complexity limiting practicality and feasibility. Our results show that a two-step procedure, which primarily involves a quick and efficient screening of older adults for mortality risk by using a simplified scale approach based on the assessment of cognitive function and then of nutritional and functional status with the inclusion of a laboratory parameter (plasma albumin) efficiently and easily predicts 1-year mortality in older hospitalized patients. In particular, the domains of nutritional status, cognitive function and functional dependence appear to be the main drivers of increased long-term mortality and – particularly malnutrition - are importantly susceptible of treatment. The proposed simplified approach strongly supports the feasibility of multiparametric assessment also in non-specialistic or resource-limited settings, where the identification of patients at higher mortality risk may in turn enable complete CGA and lead to selected targeted multidimensional interventions.

Author contributions

Conceptualization, G.G.C. and M.Z.; Methodology, G.G.C., G.S. and M.Z..; Validation, G.G.C., M.Z and G.S.; Formal analysis, G.G.C.; Investigation, M.C., E.C. and R.P.; Data curation, G.C., P.D.C., E.C., M.C. and R.P.; Writing—original draft, G.G.C. and M.Z; Writing—review & editing, G.S., P.D.C, R.B..; Supervision, G.G.C. , R.B. and M.Z. All authors have read and agreed to the published version of the manuscript.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Conflict of interest

None to be disclosed.

Acknowledgements

The authors are grateful to the participants who took part to the study. Data is available from the corresponding author upon reasonable request, pending clearance from hospital data and privacy management offices.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.12.015.

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