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Original article

Three-month mortality in permanently bedridden medical non-oncologic patients. The BECLAP study (permanently BEdridden, creatinine CLearance, albumin, previous hospital admissions study)

Antonio Brucato[a,b], Alberto Ferrari[c,*], Mara Tiraboschi[a], Alberto Zucchi[d], Chiara Cogliati[e], Daniela Torzillo[e], Francesco Dentali[f], Luca Tavecchia[f], Vera Gessi[f], Alessandro Squizzato[f], Sara Moretti[f], Eleonora Tamborini Permunian[f], Alessandra Carobbio[c], Luca Pasina[g], Fabio De Stefano[a], Enrico Tombetti[b], Davide Cumetti[a], Gianni Tognoni[h], Tiziano Barbui[c]

[a] *Dipartimento di Scienze Biomediche e Cliniche, Università degli Studi d Milano, Ospedale Fatebenefratelli, Italy*
[b] *Ospedale Papa Giovanni XXIII, Bergamo, Italy*
[c] *Research Foundation, Papa Giovanni XXIII Hospital, Bergamo, Italy*
[d] *Epidemiology Unit, Health Protection Agency, Bergamo, Italy*
[e] *Internal Medicine Department, L. Sacco Hospital, ASST fbf-sacco, Milan, Italy*
[f] *Department of Medicine and Surgery, University of Insubria, Varese, Italy*
[g] *Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy*
[h] *Dipartimento di Anestesia-Rianimazione e Emergenza Urgenza, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

A B S T R A C T

Objective: To predict the 3-months mortality in permanently bedridden medical non-oncologic inpatients.

Patients and Methods: 2788 consecutive patients admitted in 5 Italian Internal Medicine units from January 2016 through January 2017 were prospectively screened; 644 oncologic patients were excluded; 2144 non-oncologic patients (1021 female) were followed-up for mortality for 6 months. Main outcome was 3-months mortality in permanently bedridden inpatients with at least 2 of: creatinine clearance < 35 ml/min; albumin < 2.5 g/dl; at least 2 hospital admissions in the previous 6 months. Advanced dementia and dysphagia were also recorded.

Results: Mean age of the 2144 patients was 73.9 (SD, 14.9) years; 374 (17%) were permanently bedridden, 435 (20%) had a creatinine clearance < 35 ml/min, 217 (10%) albumin < 2,5 g/dl, 112 (5%) at least 2 hospital admissions in the previous 6 months. Seventy-seven (4%) patients were permanently bedridden with at least 2 of the above mentioned items, and 48 of them died within 3 months (62%) ($p < 0.001$;95% CI 51–73%). Regression coefficients of the variables associated with 3-months mortality in multivariate analysis in 998 patients of unit 1 (training cohort) were used to create a simple score, which was validated in the 1146 patients of the other units (validation cohort) and performed well in predicting the 3-months mortality (https://www.ejcrim.com/beclap/).

Conclusions: Approximately two out of three non-oncologic medical patients permanently bedridden having 2 of the abovementioned items are dead 3 months after index admission; a simple score including bedridden status, creatinine clearance, albumin, dysphagia, age and sex may help discuss management priorities.

1. Introduction

Prediction of short term prognosis of medical frail patients is relevant to avoid unintended iatrogenic side-effects and to plan the priorities [1-4]. Scant evidence is available to assess the risk of short-term mortality of non-oncologic elderly frail patients and many prognostic scores have been proposed [1,5].

Busy Internists need simple instruments, easy to use. Being permanently bedridden indicates a severely compromised performance status [6]; kidney failure is a major contributor to poor outcomes [7]; albumin level is a well-known prognostic factor [8-10], and recent hospital admissions indicate that patients' stability is deteriorating [11].

We published an exploratory analysis [12] showing that bedridden status, severely reduced kidney function, recent hospital admissions and hypoalbumin were associated with high risk of three-months mortality in non-oncologic patients after discharge from internal medicine and geriatric hospital wards in an Italian registry (REPOSI). That study had some limitations: the registry was not specifically designed to evaluate the risk of three-month mortality; moreover, follow-up at three months was lacking for about one third of patients.

Specifically designed prospective studies with no drop-outs are needed to further validate these data.

* Corresponding author.
E-mail addresses: antonio.brucato@unimi.it (A. Brucato), aferrari@fondazionefrom.it (A. Ferrari), tbarbui@asst-pg23.it (T. Barbui).

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Aim of the present study was to prospectively assess the 3-months mortality in consecutive non-oncologic permanently bedridden inpatients (BE) with at least 2 of the following variables (whose association with mortality is well established) [6-11]: creatinine clearance < 35 ml/min (CL); albumin < 2.5 g/dl (A); at least 2 hospital admissions in the previous 6 months (P) (BECLAP). Advanced dementia (AD) and dysphagia (DY) are less clearly associated with short-term mortality [11-16], so we recorded these items as secondary outcomes. The second step was to assess the effect of each variable on 3-months mortality, with the corresponding regression coefficients. The third step was to create a prognostic score in a training cohort that was then assessed in a validation cohort.

2. Methods

2.1. Study design and patients

This is a prospective cohort study performed in 5 Italian Internal Medicine units (Bergamo, Milano, San Giovanni Bianco, Varese1 and Varese2). Enrollment started in January 2016 and ended in January 2017; each patient was followed-up for mortality for 6 months, with no drop-outs, and follow-up ended in July 2017. Bergamo Hospital, the promoter center, is a big tertiary hospital; San Giovanni Bianco is a small local hospital; Milano and Varese are university teaching hospitals. The units are heterogeneous; their wide diagnosis-related groups are showed in eTable 1: case mix indexes ranged from 0.91 to 1.39; 2788 consecutive patients admitted in the 5 units were screened (Fig. 1). Oncologic patients (644) were excluded. 2144 non-oncologic patients were evaluated for the following pre-specified variables: to be in a permanent bedridden status (inability to walk or stand upright during the whole hospital stay), creatinine clearance < 35 ml/min; albumin < 2.5 g/dl; at least 2 hospital admissions in the previous 6 months.

The first step was to assess the mortality at three-months in patients permanently bedridden and with at least 2 of the other conditions (BECLAP: Bedridden, creatinine Clearance, Albumin, Previous hospital admission). According to the pre-specified protocol only the above-mentioned variables (BECLAP) were assessed for the main outcome, but advanced dementia and dysphagia were also recorded to evaluate their possible role in a predictive score. The second step was to assess the effect of each variable on mortality at 3 months, with the corresponding regression coefficients. The third step was to create a score based on the variables that were statistically significant in a multivariate analysis performed in a predefined training cohort; the score's predictivity was then assessed in a validation cohort (1146 patients admitted in the other 4 units).

The Ethics committees at each participating center approved the study.

2.2. Inclusion and exclusion criteria and definitions

2788 consecutive patients admitted in the 5 units were screened (Fig. 1). Oncologic patients (644) were excluded. A patient was considered ``oncologic'' when a malignant solid or hematological neoplasm was present during the hospital stay or when treated with chemotherapy or radiotherapy in the previous 6 months; patients with only non-melanoma skin cancers were considered non-oncological in absence of metastasis.

Permanent bedridden status was defined as the inability to walk or stand upright during the whole hospital stay. This parameter was deemed easier to assess as compared to the use of other indexes of performance status, such as the Barthel index, Karnofsky index, etc.

Creatinine clearance (the last value recorded during the hospital stay) was calculated according to the Cockcroft-Gault equation since this equation is easily available and it takes into account age, weight and sex.

The first value of albumin (g/dl) recorded during the hospital stay was used as therapeutic infusions of albumin may alter subsequent measurements.

All hospital admission in the previous 6 months, urgent or planned, in any hospital unit, either medical or surgical, were recorded.

Advanced dementia was defined as profound memory deficits (e.g., inability to recognize family members), minimal verbal abilities, inability to ambulate independently, inability to perform any activities of daily living, and urinary and fecal incontinence (Stage 7 on the Global Deterioration Scale, ranging from 1 to 7, with higher stages indicating worse dementia); in this condition Mini-mental state examination (MMSE) cannot be administered [17].

Dysphagia was defined as the presence of evident difficulty in oral feeding; positioning of a nasogastric tube of percutaneous endoscopic

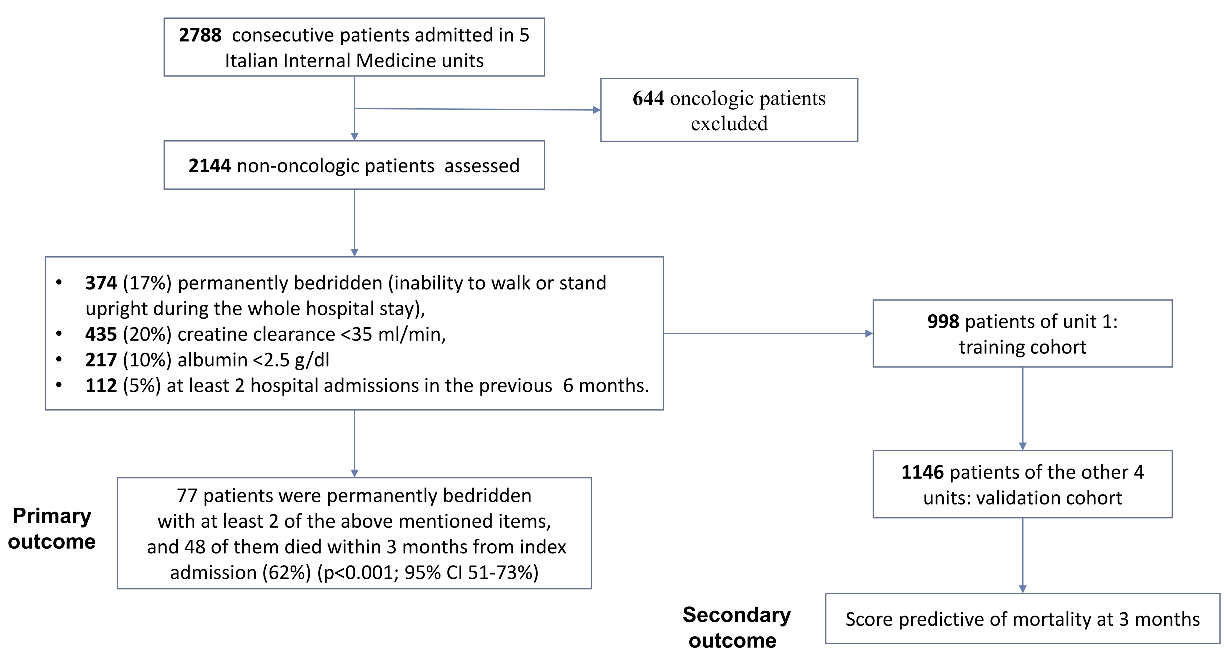

Fig. 1. Flow chart of the study.

gastrostomy (PEG) was recorded [14].

2.2.1. Follow up, outcomes and measures

Main outcome was 3-months mortality in non-oncological permanently bedridden patients (BE) and with at least 2 of: CL, A and P.

Mortality data were provided by the Cause of Death Registry (managed by Regional Health Authority), without lost to follow-up.

Secondary outcomes were: the effects of CL, A and P, plus also advanced dementia (AD) and dysphagia (DY), on mortality at 3 and 6 months, and the elaboration of a score able to predict 3-months mortality in medical non-oncologic patients; 998 patients in the unit 1 (Bergamo) were the derivation cohort and 1146 patients in the other units were the validation cohort

2.3. Sample size and statistical analysis

Required sample size was estimated considering the effect of a single covariate on survival under Cox proportional hazards model, assuming hypothesis testing is performed by two-tailed Wald's test on the coefficients estimated by partial likelihood.

The expected risk model includes the effect of more non-independent covariates, therefore a degree of multiple correlation was assumed ($R^2 = 0.50$).

In a previous 2011 unpublished analysis performed on 300 consecutive patients in unit 1, observed 3-months mortality was ≈12–15%. Assuming a conservative 10% estimate and a low effect size (regression coefficient = 0.8), about 1000 patients would be needed to achieve 80% power under an alpha Type I error of 5%.

Categorical variables and mortality are presented as absolute and relative frequencies (percentages). A summary of mortality is presented stratified for each risk factor and for combined classes of risk. Quantitative variables are summarized and presented as Mean ± Standard Deviation. The effect of single categorical variables on survival at three and six months was assessed in univariate analyses by plotting the Kaplan-Meier survival curves stratified by the variable of interest and performing the log-rank test. Multivariate analyses on survival were performed using Cox proportional hazards models, and the effect of the single variables on the outcome was assessed by two tailed Wald's tests on the coefficients.

Coefficients estimated in the predefined training cohort (998 patients admitted in unit 1) from the Cox model were used for production of a prognostic score which was then validated by plotting the Receiver Operating Characteristic (ROC) curve and computing the corresponding Area Under Curve (AUC). For calibration, we ran logistic regression of mortality on the score in the training set and then ran the Hosmer-Lemeshow test with ten quantiles on the validation set, considering a non-significant *p*-value as evidence of good calibration.

P-values below 0.05 were considered significant in all the analyses.

The entire analysis was performed on Stata, version 13.

3. Results

2788 consecutive patients admitted in the 5 Italian Internal Medicine units were screened; 644 oncologic patients were excluded; 2144 non-oncologic patients were analyzed (1021 female) (Fig.1). Baseline features are described in Table 1.

3.1. Main outcome

Three-hundreds seventy-four (17%) patients were permanently bedridden, 435 (20%) had a creatinine clearance < 35 ml/min, 217 (10%) albumin < 2.5 g/dl and 112 (5%) at least 2 any hospital admissions in the previous 6 months. Seventy-seven patients (4%) satisfied the predefined ``condition": BE with at least 2 of: CL; A and P; 48 of them died within 3 months from index admission (62%) ($p < 0.001$ Condition vs. no Condition; 95% CI 51–73%). Fig.2 reports the Kaplan-Meier survival curves at 3 months for the condition (main outcome). Two Cox regression models including also effects of age, sex, and center were estimated and the Wald test on the coefficients confirmed the highly significant effect of the Condition on survival at three months (HR = 5.62, $p < 0.001$).

Table 1
baseline features of non-oncologic patients, with overall 3-months mortality.

	N (%) Tot = 2144
Age (years)	
Mean ± SD	73.9 ± 14.9
Median (IQR)	78.0 (67.0, 85.0)
Sex	
Female	1021 (47.6%)
Male	1124 (52.4%)
Creatinine Clearance < 35 ml/min	435 (20.3%)
Mean ± SD	63.2 ± 33.9
Median (IQR)	57.0 (38.8, 82.3)
Albumin < 2.5 g/dL	217 (10.1%)
Mean ± SD	3.2 ± 0.5
Median (IQR)	3.2 (2.8, 3.6)
Permanently bedridden	374 (17.4%)
At least 2 admissions in the previous 6 months	112 (5.0%)
Advanced Dementia	313 (14.6%)
Dysphagia	224 (10.5%)
Overall 3-months mortality	306 (14%)
	Of whom 127 during the index admission

3.2. Secondary outcomes

3.2.1. Effects of single parameters on 3-months mortality

Table 2 describes the observed 3-months mortality for each separate combination of variables: just 1 variable; 2 coexisting variables; 3 coexisting variables.

Log-rank tests were highly significant for each variable ($p < 0.01$ o $p < 0.001$) (see Fig.3). Thus, we ran a multivariate analysis in order to confirm the predictivity of these parameters using a Cox proportional hazards model including the variables mentioned above (model 1, eTable 2). For greater accuracy, in this analysis albumin and creatinine clearance where dealt with as continuous variables. The model included age, sex and center as adjusting factors. Bedridden status, creatinine clearance, albumin, ($p < 0.001$) and dysphagia ($p < 0.01$) were highly associated with 3-months mortality in the multivariate analysis; at least 2 hospital admissions in the previous 6 months had a borderline statistical significance ($p = 0.062$), while advanced dementia was not significantly associated (eTable 2). The center effect on mortality was significant ($P = 0.007$), probably related to the different case mix indexes of the units (see eTable 1).

Fig. 3 reports the Kaplan-Meier survival curves at 3 (and 6) months stratified for each significant variable: BE, CL, A, DY.

3.2.2. Prognostic score

As per pre-definite protocol, we then re-calculated the regression coefficients of the variables of interest, plus age and sex, in a new model (model 2) fitted in the derivation subset of the 998 patients of unit 1 (Bergamo), to create a score predictive of the probability of death at 3 months (eTable 2). The regression coefficients associated to each significant variable (plus age and sex) were multiplied × 10 and used to assign a prognostic score according to the following formula (supplementary excel calculator):

$$Score = 0.1 \times Age + 3.6(if\ male) - 8.2 \times Albumin - 0.2 \times Creatinine\ Clearance + 14.3(if\ bedridden) + 6.9\ (if\ dysphagic) + 50$$

The score includes an arbitrary constant of 50 used to avoid

Table 2
Matrix describing in detail the observed 3-months mortality for each separate combination of variables: just 1 variable; 2 coexisting variables; 3 coexisting variables.

3-months observed mortality by combination of parameters[a]						
All patients (2144)						
	BE	A	CL	AD	P	DY
BE	163/374 (43.6%)					
A	51/98 (52.0%)	78/217 (35.9%)				
CL	64/102 (62.7%)	23/48 (47.9%)	126/435 (29.0%)			
AD	111/232 (47.8%)	39/70 (55.7%)	48/89 (53.9%)	131/313 (41.9%)		
P	22/39 (56.4%)	15/29 (51.7%)	15/32 (46.9%)	21/33 (63.6%)	35/112 (31.3%)	
DY	84/170 (49.4%)	31/51 (60.8%)	37/55 (67.3%)	77/155 (49.7%)	13/23 (56.5%)	96/224 (42.9%)
Bedridden only (374)						
		A	CL	AD	P	DY
A		51/98 (52.0%)				
CL		15/25 (60.0%)	64/102 (62.7%)			
AD		33/59 (55.9%)	40/61 (65.6%)	111/232 (47.8%)		
P		11/17 (64.7%)	11/14 (78.6%)	17/26 (65.4%)	22/39 (56.4%)	
DY		27/46 (58.7%)	32/42 (76.2%)	70/137 (51.1%)	12/17 (70.6%)	84/170 (49.4%)

[a] BE: Permanently Bedridden; CL: Creatinine Clearance < 35 mL/min; A: Albumin < 2.5 g/dL; P: two or more hospital admissions in the previous six months; AD: Advanced Dementia; DY: Dysphagia.

returning negative scores. We had no lost to follow-up at 3 months so we were also able to perform a logistic regression of 3-months mortality on the score (OR = 1.13, 1.10–1.15).

The curve describing the increment of the probability of death at 3 months predicted by the logistic model as a function of score is reported in Fig 1-online-only. Scores and the corresponding risks for some relevant values are reported in eTable 3.

The score was then validated in the validation cohort: 1146 patients of the other 4 units; its predictivity was assessed plotting the corresponding ROC curve (Fig. 2-online-only). The area under the curve was 0.82, indicating a very good predictivity of the score. Hosmer-Lemeshow Chi^2 was 13.82 with $p = 0.181$, confirming that predicted and expected mortality do not differ significantly in the validation set. The corresponding calibration plot of predicted vs. observed mortality is shown in Fig.3-online only.

An excel file to calculate the score with corresponding probabilities of death at 3 months is available as supplementary material, and a calculator is freely available at https://www.ejcrim.com/beclap/.

3.2.3. 6-month mortality

Fig. 3 shows the Kaplan-Meier survival curves also at 6 months (with the log-rank tests) for the condition studied and for each single variable; eTable 4 is a matrix reporting observed 6-months mortality for each separate combination of variables. Of note 56/77 (73%) patients fulfilling the predefined condition were dead at 6 months (Fig. 2) and several combinations of variables showed strikingly elevated mortality (see eTable 4).

Log-rank tests were highly significant for each variable (< 0.001) (see Fig.2) (univariate analysis), and all the variables, including dementia, were statistically associated with 6-months mortality.

4. Discussion

Prognosis has a central role in clinical decision-making [2], but most studies address medium-long term prognosis, e.g. mortality at 1 year [1]. Still what is crucial in clinical decisions is short-term prognosis, i.e. 3-months mortality, that was not addressed as primary outcome in prognostic studies [1,2,18,19]. Indeed, life expectancy of three months is now deemed a condition in which palliative care should be considered [3,16,20], activating protocols that have been associated with a better quality of life but also prolonged survival in patients with advanced cancers [21], probably due to fewer iatrogenic side effects in fragile patients; it is not known whether this is true for non-oncologic patients [16,22].

In this prospective observational study 2144 consecutive non-oncologic inpatients admitted in Italian units of internal Medicine were analyzed: only 77 were permanently bedridden during the entire hospital stay and had at least 2 of CL, A, P; 48 of them were dead 3 months after index admission (62%). Many more patients showed different combinations of variables (see Fig. 1, Table 2 and eTable 4). In these patients clinical decisions are often difficult, also for uncertainty regarding short-term prognosis; a simple score (BECLAP-D Score) was then calculated in a derivation cohort and validated in a validation cohort, to help discuss management priorities in these frail patients.

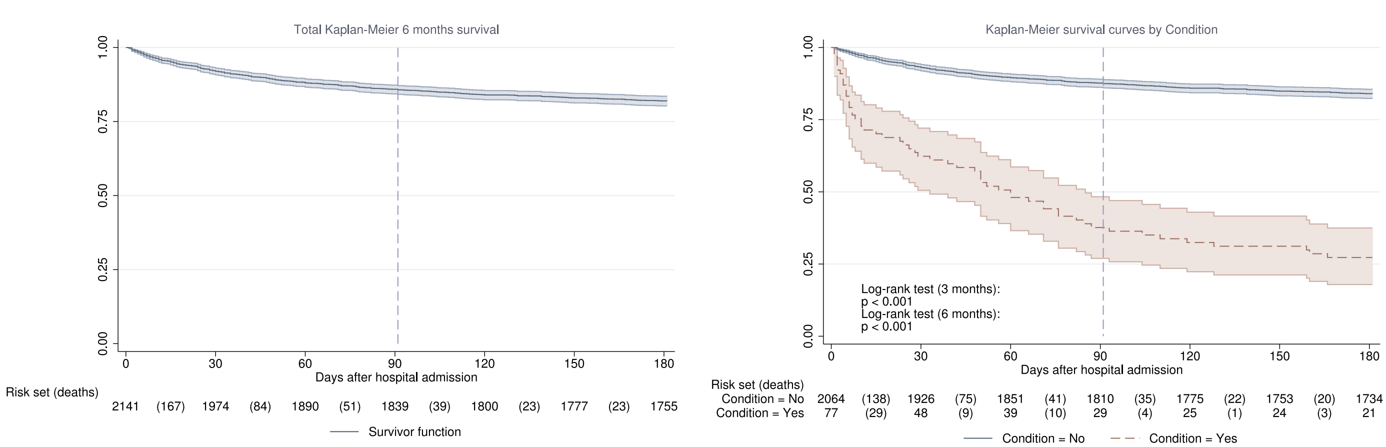

Fig. 2. Kaplan-Meier survival curves at 3 at 6 months (with the log-rank tests) for the condition studied (main outcome): permanently bedridden plus at least 2 of creatinine clearance < 35 ml/min, albumin < 2.5 g/dl and at least 2 hospital admissions in the previous 6 months.

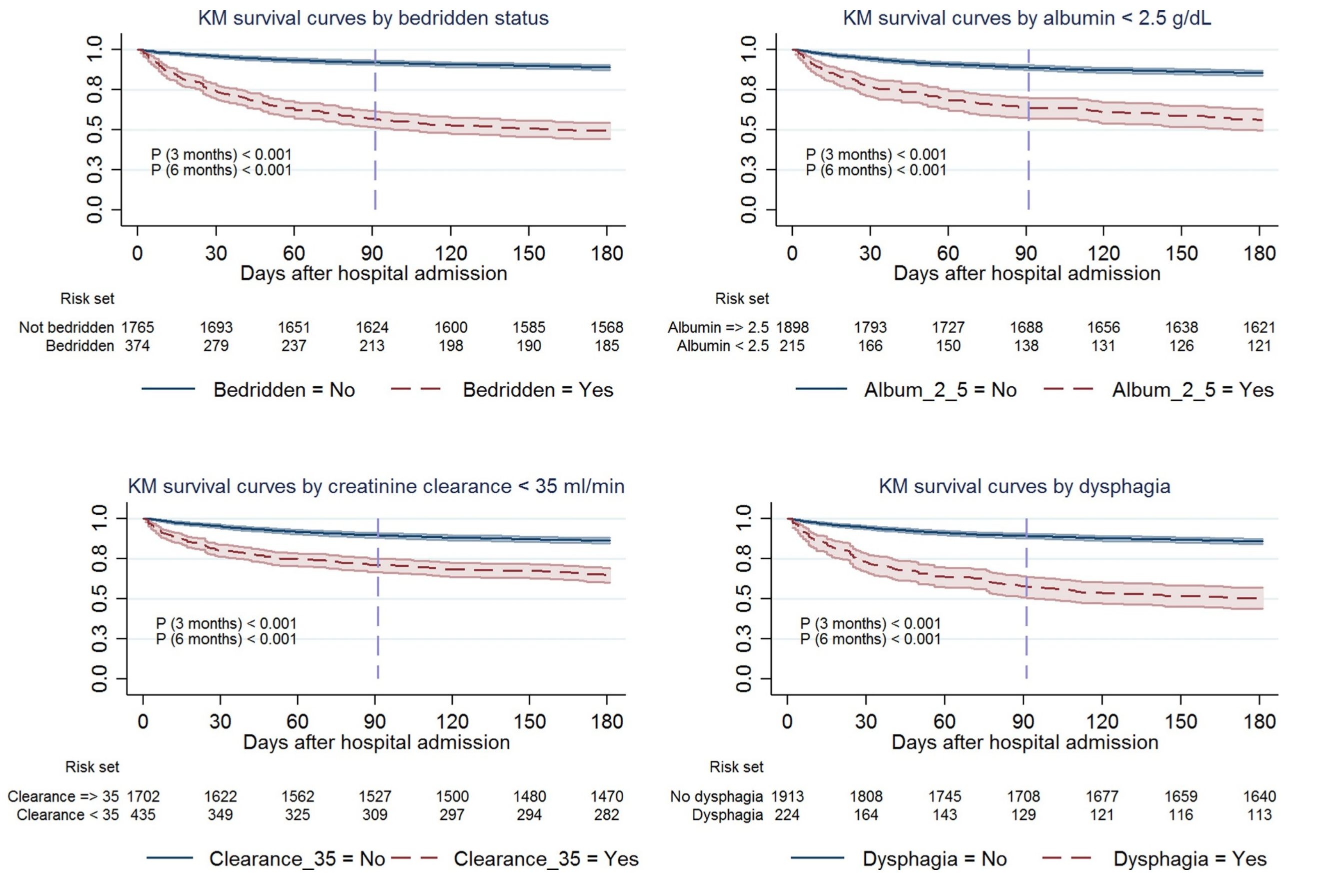

Fig. 3. Kaplan-Meier survival curves at 3 at 6 months (with the log-rank tests) for each single variable: to be permanently bedridden, albumin < 2,5 g/dl, creatinine clearance < 35 ml/min and dysphagia.

The score also includes dysphagia and is available on line (web addenda).

Overall, we selected items that are easily assessed in a clinical context but also prognostically relevant according to our recent exploratory analysis [12] and to previously published studies [6-11]. Being permanently bedridden obviously indicates a severely compromised performance status [6], and it is a very simple parameter to assess, while the Bartel index is not routinely adopted in the internal medicine wards, because it is time consuming.

Low albumin levels are a predictor of poor prognosis [8], are associated with in-hospital mortality [9], may reflect malnutrition, but are also a potential marker of diseases, such as cirrhosis and heart or kidney failure [9,10]. Recent hospital admissions may indicate that the relative stability of the fragile patients is deteriorating [11]. Finally, the possible impact on short term mortality of dementia and dysphagia, an emerging issue in medical elderly patients, is less well established [13-17], and for this reason we collected these variables just as secondary outcomes.

Many studies addressed the prognosis of medical non-oncologic patients, and scores have been developed [2,15] but there are some caveats. Firstly, several scores are disease-specific [15], i.e. for heart [23], liver [24] or kidney failure [25], but many fragile medical non oncologic patients have coexisting conditions, including geriatric syndromes [4,26,27].

Secondly, most scores appear too complex for routine clinical use [19,28-31].

Thirdly, many scores predict mortality at medium-long term, i.e. at 12 months, a time window that is less relevant for clinical decision-making [19,28,30-42]. Other studies addressed 6-months mortality [8,43], and often for specific diseases such as heart failure, dementia, cirrhosis [15]. Three-months mortality was evaluated in 2 studies [18,19]: in the first study it was evaluated together with other less hard outcomes, such as functional decline and high-healthcare demand [18]. In the second study Sancarlo [19] validated a Multidimensional Prognostic Index for 1-year mortality initially proposed by Pilotto [31], addressing also mortality at 1 and 3 months, and simplifying it, but that index was still based on a total of 51 items in 8 domains of the comprehensive geriatric assessment, making it difficult to apply in clinical practice.

Many of these indices rely on administrative datasets [32,44], and the accuracy of ICD-9 codes has been called into question [2].

Finally, most studies included oncologic patients [19,28,31,44].

Compared to most of these scores, our instrument is based on items that are more easily assessed in a clinical context, and we think that short term prognosis, i.e. 3-months mortality, is more relevant to clinical decision-making.

There are no widely accepted validation criteria for discrimination and calibration of prognostic indices [1]. On our part, we found an AUC (c-statistic) of 0.82, and we tested calibration using Hosmer-Lemeshow test, which confirmed that predicted and expected mortality do not differ significantly in the validation set. All points of the calibration plot laid close to the bisector (Fig.3-online only). Notably, our score performed well even in presence of differences in case mix indexes between centers.

Further study will be needed to accurately assess the short-term prognosis in non-oncologic inpatients, and to evaluate whether the early activation of palliative care in active care (``simultaneous care'') [3,16,45] will improve the quality and duration of life in non-oncologic medical inpatients with limited life expectancy.

5. Limitations

Our study has several limitations. First, it is a national (Italian) study and, therefore, BECLAP-D score should be validated in patients from other countries. However, the main characteristics of the ``modern" non-oncologic medical inpatient are becoming similar in most industrialized countries. Second, the score should be validated by investigators not involved in its elaboration to become widely accepted. On the other hand, a strength of our study is the absence of drop-out for the main outcome (mortality).

6. Conclusions

Short-term prognosis, i.e. 3-months mortality, is rarely addressed in clinical studies, still it is of extreme relevance. This prospective observational study analyzed 2144 medical non-oncologic inpatients; of them 77 were permanently bedridden (unable to walk or stand upright during the whole hospital stay) and had at least 2 of: creatinine clearance < 35 ml/min; albumin < 2.5 g/dl; at least 2 hospital admissions in the previous 6 months: approximately 2 out of 3 of these patients (62%) were dead 3 months after index admission. A simple score (BECLAP-D Score), including these variables plus dysphagia, was accurate in predicting early mortality in frail medical non-oncologic patients, and may help physicians to identify management priorities and avoid therapeutic obstinacy.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2019.10.016.

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