Prediction of early- and long-term mortality in adult patients acutely admitted to internal medicine: NRS-2002 and beyond

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ARTICLE INFO

Accepted 11 April 2019

Keywords:
Comorbidity
Glasgow Prognostic Score
Malnutrition
Modified Early Warning Score
Norton scale
Nutritional Risk Screening 2002

SUMMARY

Background & aims: In hospitalized patients malnutrition is a risk factor for adverse clinical outcomes. The Nutritional Risk Screening 2002 (NRS-2002) represents a quick and simple tool to identify malnutrition risk in this population. No study tested the predictive power of NRS-2002 on mortality adjusting for confounders related to patient's complexity, thus considering conditions such as functional status, illness-related severity and inflammation. The aim of this study was to explore the independent prognostic power and the relative weight of NRS-2002 screening tool to predict inhospital and post-discharge (up to 1 year) mortality, adjusting for variables representing the non-disease specific multidimensional complexity of patients admitted to Internal Medicine wards.

Methods: Retrospective observational study including 5698 consecutive patients acutely admitted to an Internal Medicine Department. Logistic regression models were run to test the predictive power of the NRS-2002 on patient mortality at different time intervals, adjusted for age, sex, Charlson comorbidity index, Glasgow Prognostic Score (GPS), BUN/creatinine ratio, Modified Early Warning Score (MEWS), and Norton index. The performance of the logistic models in predicting mortality was measured through the *c*-statistic. The different time of death between patients scored upon admission as NRS-2002 < 3 or ≥ 3 was evaluated through crude Kaplan-Meier curves and multivariate Cox proportional hazard analysis.

Results: Patients classified at high malnutrition risk (NRS-2002 ≥ 3) showed a higher and earlier mortality (Log-rank test: $p < 0.001$) compared to subjects in the NRS-2002 "low-risk" group. NRS-2002 ≥ 3 was an independent significant ($p < 0.01$) predictor of mortality in logistic regression at every time interval. Among the considered covariates, Charlson index, GPS and Norton scale showed a steadily higher OR than NRS-2002 in predicting both early and late mortality. The multivariate models demonstrated a very good discrimination for hospital and mid-term (up to 90 days) mortality. Being classified at risk for malnutrition (NRS-2002 ≥ 3) on admission independently increased the risk of one-year death (HR $= 1.431$; 95% CI: 1.277–1.603; $p < 0.001$) compared to the patients who were scored at low malnutrition risk.

Conclusions: Malnutrition risk identified upon hospital admission by NRS-2002 independently contributes to early and late mortality in a population including a majority of elderly. However, risk of malnutrition has to be considered according to other factors related to comorbidities, functional status, illness severity and inflammation which reciprocally interact, concurring at worsening patient's outcome.

1. Introduction

Malnutrition is a well-recognized risk factor for adverse clinical outcomes during hospitalization. Poor nutritional status is associated with sarcopenia, impaired immune responses, increased rate of infectious complications and of readmissions, delayed recovery,

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prolonged hospital stay, reduced functional independence and significant impact on health-care costs [1–4]. Early identification of malnutrition is therefore mandatory in order to organize individual patient's care in a personalized manner. Unfortunately, up to 85% of inpatients who are malnourished or at risk of malnutrition are not recognized [5].

Screening of nutritional status is at present recommended as a routine practice through the continuum of care, particularly in the context of acute hospital settings [6]. The Nutritional Risk Screening 2002 (NRS-2002) is an effective and simple screening tool to identify risk of malnutrition in hospitalized patients [7,8]. Despite it was originally developed to identify subjects who could benefit from nutritional intervention, NRS-2002 is usually employed to screen nutritional risk [8]. Compared to different nutritional screening tools, NRS-2002 showed to be superior in identifying the risk of malnutrition during acute illness [9]. Consequently, for acute adult and older medical inpatients NRS-2002 represents a quick and simple nutritional screening tool to identify malnutrition risk in order to develop a personalized treatment plan to positively influence outcomes [10]. Several studies in different hospitalized non-intensive care populations (e.g., surgical, medical, COPD, hemodialysis patients) demonstrated that NRS-2002 is a good predictor for early- and long-term mortality, adjusting the analyses for variables such as socio-demographic factors, comorbidities, medical diagnosis and clinical laboratory data [11–18]. However, to the best of our knowledge, no study tested the predictive power of NRS-2002 on mortality considering other confounders related to patient's complexity.

Indeed, in hospitalized patients several potential determinants of clinical outcome may be simultaneously present, contributing to outline an intricate and compound clinical picture defined as “complexity” [19]. Patients' complexity is a multidimensional concept having significant implications for clinical decision-making, organization of care, allocation of resources and, ultimately, for prognosis. Unfortunately, in patients acutely admitted to Internal Medicine, definition of the determinants of complexity and of the modalities by which complexity can be measured are still unresolved issues [20]. In addition to the variables related to the frailty phenotype, which includes conditions such as cognitive dysfunction, functional dependence, risk of pressure sores, nutrition and comorbidities [20], the definition of complexity in this setting should also include clinical parameters and validated scores to assess acute illness-related severity in order to increase early predictivity of poor clinical outcome.

Defining the weight of malnutrition in determining early- and long-term mortality risk at the light of patient's complexity as described by relevant and no time-consuming information routinely assessed in daily practice can represent a strategic goal for clinicians. Unfortunately, although considering prognosis in the context of clinical decision-making is increasingly recommended as a central factor in weighing pros and cons of patient's care, many of the proposed prognostic tools are biased by low applicability in routine clinical practice [21]. For a reliable estimation of the risk of poor clinical outcomes more complex and non–disease-specific prognostic indexes need to be used [21]. They could include malnutrition and inflammation scores that demonstrated to be predictive for in-hospital mortality. Among them, the blood urea nitrogen to creatinine ratio showed to be an independent predictor for death [22] as well as a potential and independent marker of malnutrition in different populations [23–25]. The Glasgow Prognostic Score, a cumulative inflammation-based score that measures elevation of CRP and decrease in serum albumin, has been reported to be a reliable prognostic marker in different populations [26–28].

The aim of this study was therefore to explore the predictivity and the relative weight of NRS-2002 screening tool to predict inhospital and post-discharge (up to 1 year) mortality in a model including variables representing the non-disease specific multidimensional complexity of acutely hospitalized patients (age, sex, comorbidities, clinical severity, functional state, mental function and degree of nursing dependency) and some inflammation-based prognostic scores.

2. Materials and methods

2.1. Study design, setting and population

The PROPOSING IDEAS (PROgnostic factors of Poor hospital Outcome based on clinical Severity, nutrItional and NursinG indexes IDEntified on AdmiSsion) was a retrospective observational study conducted in the 650-bed University Hospital of Trieste, Italy. All consecutive adult (age $\geq$ 18 years) patients admitted from the Emergency Department to the Internal Medicine Department between October 15, 2015 and July 31, 2016 were considered eligible for inclusion in the study, irrespective of their clinical condition. Patients were excluded if their hospital admission was scheduled (elective) or if they did not consent to the use of their clinical data for study purposes.

2.2. Ethics

The study was approved by the Regional Bioethics Committee of Friuli Venezia Giulia, Italy (protocol number: 28,217; date of approval: 31/7/2018). The research was conducted according to the Declaration of Helsinki. At hospital admission, all enrolled patients or her/his legal representative authorized the use of their clinical data for study purposes.

2.3. Study variables

Nutritional Risk Screening 2002 (NRS-2002) [8] was used to detect the presence of malnutrition risk. Body weight and height were measured according to standard procedures [29]. Then BMI was calculated as the ratio between weight (kg) and height (m) squared (kg/m^2). Information about food intake and weight loss (compared to the usual weight) in preceding week/months were collected by interviewing the patients or—in the presence of altered mental status or impaired communication—her or his relatives/caregivers. Reduction of food intake was estimated by assessment of food consumed in the week before admission compared with her/his usual intake. Usual weight was collected to calculate the percentage of body weight loss before admission. The severity of disease was scored according to the patient's history and to the reason of acute hospital admission.

Comorbidities were assessed using the Charlson comorbidity index, a tool broadly used to predict ten year survival in the presence of multiple comorbidities; the final score ranges from 0 to 24; the burden of comorbidity was considered high in the presence of a threshold of $\geq$5 [30].

The Modified Early Warning Score (MEWS) [31], a physiological scoring system based on respiratory rate, body temperature, systolic blood pressure, heart rate and neurologic assessment which was originally developed as a screening tool to promptly recognize patients at risk of clinical decline, was employed to assess patient criticality. The following categories were considered: MEWS $\leq$2: low criticality; MEWS 3–4: intermediate criticality; MEWS $\geq$5: high criticality.

The Norton scale [32], a risk assessment tool considering key aspects of health representing, when compromised, conditions that can be associated to frailty (e.g., functional status, mental condition, incontinence), level of nursing dependency and prognosis [33], was

used as a surrogate marker of patients' vulnerability. The Norton scale was considered as follows: score ≥19, low risk; score 14–18, intermediate risk; score 10–13, high risk; score ≤9, very high risk.

Laboratory blood tests data, i.e. lymphocyte count, serum levels of C-reactive protein (CRP), creatinine, albumin, and blood urea nitrogen (BUN), were collected. From these data, BUN/creatinine ratio and Glasgow Prognostic Score (GPS) were calculated. BUN/creatinine ratio expresses the relative modifications in BUN and/or creatinine concentration (ratio 10–20 for normal individuals) [34]. Since in our population only 3 patients had a BUN/creatinine ratio < 10, only two categories were created (normal or high ratio). The GPS was assigned according to the following conditions: score 0 (good prognosis): CRP ≤ 10 mg/L and albumin ≥3.5 g/dL; score 1 (intermediate prognosis): CRP > 10 mg/L and albumin ≥3.5 g/dL, or CRP ≤ 10 mg/L and albumin <3.5 g/dL; score 2 (poor prognosis): CRP > 10 mg/L and albumin <3.5 g/dL.

2.4. Outcome variables

In hospital clinical practice, mortality rate is the most frequently used outcome measure to assess the quality of care [35,36]. In the present study mortality rate was measured as all-causes patients' death during hospital stay, after 30, 90, 180 days, and after one year following hospital admission.

2.5. Data sources

Data were extracted by two researchers (DDM, MZan) from three different sources: the electronic nursing assessment register for sociodemographic (e.g., age, sex), functional (e.g., Norton Index), clinical severity (MEWS) and nutritional (e.g. NRS-2002) data; the hospital electronic archive for clinical and laboratory data and outcome (comorbidity, date of admission and discharge, hospital death) variables; patient's condition (survived or dead, with the possible date of death) within one year after hospital admission was gathered from the Registry office linked to the hospital archive. All data were linked by a different researcher (GS) into a specific study database, where patients' names were anonymized after assigning an identifying code to each record.

2.6. Statistical analysis

The continuous variables were described as the mean with standard deviation (SD), and median with interquartile range (IQR). The difference between the means was analyzed using the unpaired Student *t*-test, after determining whether equal variance could be attributed to the subgroups according to Levene's test. The nominal variables were described as a number and percentage, and analyzed with contingency tables and the χ^2 test.

Several logistic regression models were run to test the predictive power of the NRS-2002 on patient mortality at different time intervals, adjusted for confounders such as age, sex, Charlson comorbidity index, GPS, BUN/creatinine ratio, MEWS, and Norton index. All variables but age were converted into dummy variables according to the defined risk threshold (e.g., 0 = NRS-2002 < 3; 1 = NRS-2002 ≥ 3) or the dicotomic categories (e.g.: 0 = male; 1 = female). Age was non normally distributed (skewness = - 1.4; kurtosis = 2.8), so that both logarithmic and square-root transformations were performed to achieve a more normal data distribution. Since the transformed data showed worst skewness and kurtosis, untransformed age data were used.

The coefficient of the determination of statistical models, that is the proportion of variance in the dependent variable predictable from the independent variables and is an important summary statistic of biological interest [37], was calculated based on the Nagelkerke R^2 [38].

The performance of the logistic models in predicting mortality was described through the receiver operating characteristic (ROC) curves and measured through the *c*-statistic, that is a standard summary for the goodness of the predictive accuracy of regression models having a binary outcome [39]. The *c*-statistic (equivalent to the area under the ROC curve) [39] defines the probability that a randomly selected patient (e.g. dead) had a higher score than a second randomly selected one (e.g. survived) [40]. Results of the *c*-statistic were interpreted according to the following criteria, previously proposed to assess the validity of the NRS-2002 tool [41]: 0.50 to 0.59: poor; 0.60 to 0.69: moderate; 0.70 to 0.79: good; 0.80 to 0.89: very good; and ≥ 0.90: excellent discrimination [42].

The different time of death between patients scored upon admission as NRS-2002 < 3 or NRS-2002 ≥ 3 was evaluated. Observations were censored until 365 days from admission (known survival). Unadjusted analysis was carried out by comparing Kaplan-Meier curves; Mantel-Cox log-rank test was adopted to assess differences in survival rates after 365 days from admission between groups. A multivariate Cox proportional hazard analysis was used to estimate patient's risk of death (proportional hazard ratio [HR]) between NRS-2002 groups, controlled for the same potential confounders considered for the logistic regression models. Given the high number of statistical comparisons performed for each variable, an alpha level of $p < 0.01$ was considered statistically significant for all performed analyses to reduce type I error rate. Statistical analyses were performed using the software SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, US).

3. Results

During the study period, 5698 patients were enrolled in the study (females; 3,248, 57.0%; males: 2,450, 43.0%). Their mean age was 80.1 ± 12.3 (median 83, IQR 75–89) years. Females were older ($p < 0.001$) than males (82.0 ± 11.9 vs. 77.6 ± 12.2 years). Table 1 shows the main characteristics of the study population. The prevalence of high malnutrition risk according to NRS-2002 was 32.2%.

Compared with the population in NRS classes 1–2, patients with a NRS-2002 score ≥3 were mostly females, were older ($p < 0.001$), had more ($p < 0.001$) comorbidities, a higher ($p < 0.001$) level of functional dependence according to Norton Scale, a higher ($p < 0.001$) level of clinical criticality as measured by MEWS, and showed worse ($p < 0.001$) values for direct and calculated laboratory variables, with the only exception of BUN/creatinine ratio ($p = 0.039$) (Table 2).

In bivariate analyses, all considered variables showed a statistically significant relationship with inhospital, 1-, 3-, 6-months and 1-year mortality, except for BUN/creatinine ratio and female gender, the latter demonstrating statistically significant relationship ($p < 0.01$) only with 6-months and 1-year mortality (Table 3). Figure 1 shows the crude Kaplan-Meier curves for the probability of survival one year after hospital admission for patients belonging to the two NRS-2002 nutritional risk categories. Patients classified at high risk of malnutrition (NRS-2002 ≥ 3) showed a higher and earlier mortality (Log-rank test: $p < 0.001$) compared to subjects in the NRS-2002 "low-risk" group.

Table 4 shows the results of the multivariate logistic regression analysis. Based on above results, BUN/creatinine ratio was excluded from multivariate analyses. NRS-2002 ≥ 3 was an independent significant ($p < 0.01$) predictor of hospital mortality at every considered time. A NRS-2002 ≥ 3 on admission determined a 1.85 times increase in the odds of hospital mortality, with an OR decreasing up to 1.55 with the increase of the time interval between

Table 1
Characteristics of patients at hospital admission, and mortality rate at different time intervals.

Variable	Data
Charlson comorbidity index [¥]	
Low comorbidity	4511; 85.7%
High comorbidity	753; 14.3%
Creatinine (mg/dL)[§]	1.2 ± 0.8 (1.0; 0.8–1.3) [5533]
Blood urea nitrogen (mg/dL)[§]	56.2 ± 38.1 (46.0; 33.0–66.0) [5473]
Albumin (g/dL)[§]	3.4 ± 0.6 (3.5; 3.0–3.8) [5202]
C-reactive protein (mg/L)[§]	55.6 ± 74.5 (21.2; 5.2–78.6) [5499]
Lymphocytes (cells x 10^3/μL)[§]	1.3 ± 1.1 (1.1; 0.7–1.6) [5216]
C-reactive protein/albumin (ratio)[¥]	
Low or normal	2.0% (109)
High	98.0% (5347)
Modified Early Warning Score[¥]	
Low risk	43.5% (2477)
Intermediate risk	27.7% (1579)
High risk	28.5% (1625)
Nutritional Risk Score 2002[¥]	
No risk (0 points)	8.4% (481)
Low risk (1 point)	5.1% (288)
Moderate risk (2 points)	49.3% (2807)
High risk (≥3 points)	37.2% (2121)
Norton scale[¥]	
Low risk	24.2% (993)
Intermediate risk	39.0% (1600)
High risk	17.1% (704)
Very high risk	19.7% (808)
Glasgow Prognostic Score[¥]	
Good prognosis	26.1% (1358)
Intermediate prognosis	30.8% (1601)
Poor prognosis	43.1% (2239)
Cumulative mortality[a,¥]	
In hospital	7.9% (452)
30 day	14.2% (808)
90 day	22.9% (1303)
180 day	29.9% (1704)
365 day	37.8% (2153)

[a] n = 5570.
[§] Mean ± standard deviation (median; inter-quartile range) [number].
[¥] Percentage (number).

admission and date of follow-up. Overall, the regression models showed an explained variance ranging from 21.6% for hospital death to 26.6% for one-year death. Figure 2 shows the ROCs for the five logistic models. The model showed the best discriminatory capability for the hospital-mortality (*c*-statistic = 0.84), with a progressive decrease in predictive accuracy with the lengthening of the follow-up interval (one-year mortality: *c*-statistic = 0.77).

The multivariate Cox regression analysis (log-likelihood = −19237.947; $p < 0.001$) showed that being classified at high risk of malnutrition (NRS-2002 ≥ 3) on admission independently increased the risk of one-year death (HR = 1.431; 95% CI: 1.277–1.603; p < 0.001) compared to the patients who were scored at low malnutrition risk (Fig. 3).

Table 2
Demographic and clinical characteristics of patients according to their malnutrition risk as described by NRS-2002 score.

Variable	NRS-2002 < 3	NRS-2002 ≥ 3	*p*-value
Age (years)[§]	78.2 ± 13.3	83.3 ± 9.3	<0.001
Sex (female)[¥]	55.1% (1972)	60.1% (1275)	<0.001
Charlson Index ≥ 3 (high comorbidity)[¥]	12.2% (412)	18.0% (341)	<0.001
Creatinine (mg/dL)[§]	1.1 ± 0.7	1.2 ± 0.8	<0.001
Blood urea nitrogen (mg/dL)[§]	52.4 ± 33.5	62.7 ± 44.1	<0.001
Albumin (g/dL)[§]	3.5 ± 0.6	3.2 ± 0.6	<0.001
C-reactive protein (mg/L)[§]	48.4 ± 69.9	67.9 ± 80.3	<0.001
BUN/Creatinine ratio (>20)[¥]	97.7% (3360)	98.5% (1987)	0.039
GPS = 2 (poor prognosis)[¥]	36.1% (1193)	55.2% (1046)	<0.001
MEWS ≥ 5 (high criticality)[¥]	23.6% (843)	37.0% (782)	<0.001
Norton scale ≤13 (high/very high risk)[¥]	29.4% (774)	50.2% (738)	<0.001

NRS-2002: Nutrition Risk Screening 2002; BUN: blood urea nitrogen; GPS: Glasgow Prognostic Score; MEWS: Modified Early Warning Score.
[§] Mean ± standard deviation [unpaired Student *t*-test].
[¥] Percentage (number) [χ^2 test].

4. Discussion

This study demonstrates the independent role of malnutrition risk, as detected by NRS-2002, in predicting patient's early and late mortality, after adjusting for patients' demographic (age and sex) and clinical characteristics (nutritional-inflammatory status, co-morbidity, clinical severity, and nursing dependency). For patients scored at high nutritional risk on admission the odds for hospital mortality was increased by 85%. The reliability of NRS-2002 as an independent prognostic factor was maintained over time, with the risk of death still increased by 55% one-year after admission. This finding was confirmed also by the proportional hazard analysis, demonstrating that being at high nutritional risk upon hospital admission generated a 43% statistically significant increase in risk of death a year away. A systematic literature review showed that NRS-2002 shows a good performance in predicting mortality for adult hospital patients, whereas the predictive validity is lower in older patients [43]. Our findings contributed to extend the predictive validity of NRS-2002 on early- and late-term mortality in a population of medical inpatients; in particular, to the best of our knowledge this is the first study demonstrating the predictive value of NRS-2002 on one-year mortality in acute medical inpatients.

Disease-related malnutrition is a major problem in hospital setting in developed countries. Therefore, early and systematic screening of nutritional risk on hospital admission is the first fundamental step to activate multidisciplinary interventions based on sharing the importance of nutrition as a key factor of hospital care, in order to reduce the risk of undesirable outcomes. Our study confirmed that NRS-2002 represents an effective and simple-to-use tool to detect this risk. Nutritional screening in older hospitalized patients is in general carried out by either the NRS-2002 or the mini-nutritional assessment (MNA), being the latter the most recommended worldwide [44]. However, some considerations need to be made when dealing with populations of hospitalized patients, especially if consists mostly of older subjects. First, the NRS-2002 showed to be better than MNA in identifying malnutrition risk in newly admitted elderly inpatients [9]. Moreover, MNA is not applicable in patients whose self-perceived health and nutrition states cannot be assessed due to conditions such as acute confusion, alteration of consciousness or dementia. Finally, administering MNA is more time consuming compared with NRS-2002, thus resulting in a greater impact on the healthcare providers' workload. Based on above reflections and on the present study findings, the NRS-2002 should be used as a standard malnutrition screening tool in acute medical inpatients.

Once identified patients who are malnourished, comprehensive nutrition care plans should be promptly activated, also redefining the roles of all clinicians involved in patient care and reconsidering the nutrition also from an ethical point of view, for example by avoiding obsolete nutrition practices or unwarranted interprofessional barriers [45]. However, the risk of death cannot be reduced only by prescribing to the patients an adequate nutritional support, since prognosis may depend also on functional status (e.g., impaired self-feeding) [46] and on factors such as the impact of systemic inflammation and severity of illness. For this reason, the present study analyzed the independent prognostic power of NRS-

Table 3
Relationships between demographic and clinical characteristics of study patients and mortality at different time interval from hospital admission.

Predictor	Hospital mortality Survivors; Deceased	30-days mortality Survivors; Deceased	90-days mortality Survivors; Deceased	180-days mortality Survivors; Deceased	365-days mortality Survivors; Deceased
Age (years)[§]	79.6 ± 12.3; 84.8 ± 9.5[d]	79.5 ± 12.4; 84.6 ± 9.4[d]	79.1 ± 12.5; 83.9 ± 9.9[d]	78.6 ± 12.7; 83.8 ± 9.8[d]	78.1 ± 12.9; 83.6 ± 9.8[d]
Sex (female)*,[¥]	56.9% (2909); 57.1% (258)[a]	56.6% (2697); 58.5% (473)[a]	57.5% (2452); 55.1% (718)[a]	58.3% (2253); 53.8% (917)[c]	58.7% (2006); 54.1% (1164)[c]
Charlson Index ≥ 5[¥]	12.9% (653); 46.9% (99)[d]	12.1% (5,63); 34.0% (184)[d]	10.6% (442); 30.0% (305)[d]	9.9% (374); 26.5% (373)[d]	9.1% (304); 24.0% (443)[d]
Creatinine (mg/dL)[§]	1.1 ± 0.7; 1.6 ± 1.0[d]	1.1 ± 0.7; 1.4 ± 1.0[d]	1.1 ± 0.7; 1.4 ± 0.9[d]	1.1 ± 0.7; 1.3 ± 0.9[d]	1.1 ± 0.6; 1.3 ± 0.9[d]
BUN (mg/dL)[§]	53.2 ± 33.9; 90.7 ± 60.3[d]	52.1 ± 32.6; 82.4 ± 55.3[d]	50.4 ± 30.7; 76.5 ± 51.7[d]	49.4 ± 29.7; 72.4 ± 49.2[d]	48.5 ± 28.8; 69.1 ± 47.0[d]
Albumin (g/dL)[§]	3.4 ± 0.6; 2.9 ± 0.7[d]	3.5 ± 0.6; 2.9 ± 0.7[d]	3.5 ± 0.6; 3.0 ± 0.6[d]	3.5 ± 0.5; 3.1 ± 0.6[d]	3.6 ± 0.5; 3.1 ± 0.6[d]
CRP (mg/L)[§]	51.0 ± 70.8; 107.4 ± 93.5[d]	48.4 ± 69.0; 100.0 ± 90.5[d]	45.9 ± 68.1; 88.6 ± 85.3[d]	44.4 ± 67.3; 81.9 ± 83.7[d]	44.8 ± 68.7; 73.4 ± 80.2[d]
BUN/Creatinine (>20)[¥]	98.0% (4907); 98.6% (435)[a]	97.9% (4533); 98.9% (751)[a]	97.7% (4060); 99.0% (1224)[b]	97.8% (3685); 98.6% (1599)[b]	97.9% (3264); 98.2% (2020)[a]
GPS = 2[¥]	40.3% (1947); 81.1% (291)[d]	37.8% (1693); 79.1% (521)[d]	34.2% (1373); 74.8% (841)[d]	32.1% (1169); 69.9% (1045)[d]	30.5% (983); 64.4% (1231)[d]
MEWS ≥ 5[¥]	25.1% (1282); 64.0% (284)[d]	23.8% (1131); 59.0% (470)[d]	22.2% (947); 50.7% (654)[d]	20.9% (809); 46.8% (792)[d]	20.1% (687); 42.7% (914)[d]
Norton scale ≤ 13[¥]	32.7% (1207); 79.5% (267)[d]	30.5% (1049); 75.2% (433)[d]	28.1% (867); 66.5% (615)[d]	26.2% (732); 61.6% (750)[d]	24.1% (591); 57.1% (891)[d]
NRS-2002 ≥ 3[¥]	34.7% (1774); 62.6% (283)[d]	33.2% (1583); 61.3% (495)[d]	31.2% (1332); 57.3% (746)[d]	29.6% (1146); 54.7% (932)[d]	28.9% (988); 50.6% (1090)[d]

a: $p \geq 0.05$; b: $0.05 < p > 0.001$; c: $p = 0.001$; d: $p < 0.001$.
BUN: blood urea nitrogen; CRP: C-reactive protein; GPS: Glasgow Prognostic Score; MEWS: Modified Early Warning Score. NRS-2002: Nutrition Risk Screening 2002.
*: compared to male population.
[§] Mean ± standard deviation [unpaired Student *t*-test].
[¥] Percentage (number) [χ^2 test].

2002 in the context of a multivariate model aimed at representing the multidimensional and non-disease specific complexity of a medical inpatient as defined based on non time-consuming information routinely assessed in clinical practice. Overall, the multivariate model demonstrated a very good discrimination power at separating patients who survived from those who died at an early (during hospitalization) and mid-term (up to 90 days) interval after hospital admission as well as for late-term mortality.

Interestingly, the explained variance of our models was low, suggesting that other variables—not included in our study—could be important in predicting hospital and post-discharge mortality. In particular, the medical diagnosis at discharge was not considered in the regression model, since all data were recorded upon hospital admission. In addition, other variables potentially related to explored outcomes and characterizing the case-mix during the whole hospital stay and in the post-discharge time (e.g., medication adherence, socioeconomic factors, functional status, psychosocial problems) were unavoidably unknown at the time of patient admission and could have contributed to explain the remaining variance. However, such a more complete risk stratification was outside the objectives of this study.

Although the present study was aimed at analyzing the adjusted prognostic power of NRS-2002, it is worth making some considerations about the results of the other considered predictors, as some of which (Charlson index, Norton scale, GPS) showed a higher OR than NRS-2002 in predicting patients' mortality. Considering

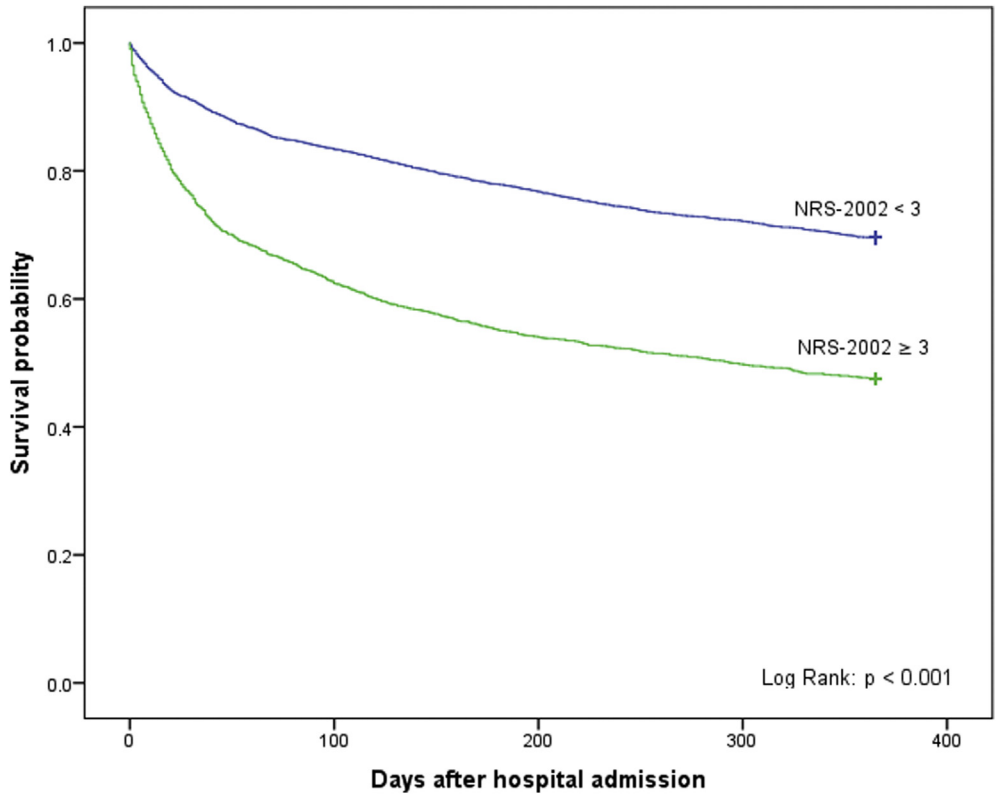

Fig. 1. Crude Kaplan–Mayer curves for patients with (NRS-2002 ≥ 3) or without (NRS-2002 < 3) high nutritional risk on hospital admission. NRS-2002: Nutritional Risk Score 2002.

Table 4
Stepwise multiple logistic regression of mortality at different time interval from hospital admission on study variables.

Predictor	Hospital mortality OR (95% CI)	30-days mortality OR (95% CI)	90-days mortality OR (95% CI)	180-days mortality OR (95% CI)	365-days mortality OR (95% CI)
NRS-2002 $\geq$ 3	1.853 (1.285–2.672)[b]	1.766 (1.383–2.254)[c]	1.803 (1.489–2.183)[c]	1.706 (1.437–2.026)[c]	1.548 (1.318–1.817)[c]
Age	e.f.m.	e.f.m.	1.019 (1.008–1.029)[c]	1.025 (1.016–1.035)[c]	1.034 (1.025–1.042)[c]
Sex (female)	e.f.m.	e.f.m.	0.758 (0.623–0.922)[a]	0.674 (0.566–0.803)[c]	0.679 (0.578–0.798)[c]
GPS = 2	3.419 (2.192–5.333)[c]	3.829 (2.888–5.076)[c]	3.599 (2.941–4.404)[c]	3.248 (2.732–3.861)[c]	2.664 (2.275–3.119)[c]
Charlson Index $\geq$ 5	3.877 (2.692–5.584)[c]	2.944 (2.258–3.838)[c]	3.266 (2.622–4.069)[c]	2.842 (2.310–3.495)[c]	2.741 (2.239–3.354)[c]
MEWS $\geq$ 5	1.979 (1.362–2.875)[c]	2.097 (1.631–2.697)[c]	1.673 (1.368–2.047)[c]	1.588 (1.323–1.907)[c]	1.472 (1.239–1.749)[c]
Norton scale $\leq$ 13	3.100 (2.041–4.708)[c]	2.948 (2.258–3.850)[c]	2.270 (1.844–2.795)[c]	2.125 (1.768–2.555)[c]	2.059 (1.736–2.442)[c]
Nagelkerke R^2	*0.216*	*0.258*	*0.285*	*0.283*	*0.266*

OR: odds ratio; CI: confidence interval; NRS-2002: Nutrition Risk Screening 2002; GPS: Glasgow Prognostic Score; MEWS: Modified Early Warning Score.
e.f.m.: excluded from the final model; a: $p = 0.005$; b: $p = 0.001$; c: $p < 0.001$.
Text in italic is referred to data describing the coefficient of the determination (R2) and the performance (c) of statistical models, while the data of the covariates are reported in normal text.

that comorbidity is a well-known strong confounding factor for elderly patients [19], it is not surprising that it resulted as a very strong predictor of mortality in our model. However, in patients acutely admitted to Internal Medicine, comorbidity alone cannot represent the complexity [19], since it deeply interacts with important prognostic determinants such as patient's illness severity and functional status [20]. The MEWS is a simple measure of acute physiologic compromise and an indicator of illness severity [47,48]. The strong relationship of increased MEWS with hospital and 30-days mortality in acute inpatients is widely demonstrated [49]. The novelty of our findings is that this relationship is extended up to one-year after hospital admission. Furthermore, our study is in line with previous data showing that Norton scale on admission was independently associated with in-hospital mortality [50]. However, differently from the cited study, our data confirmed this association for both mid- and long-term mortality. Interestingly, age did not contribute to predict early mortality. The reasons could be related mostly to the fact that 75% of the enrolled population was over 75 years old. Moreover, age was included in the calculation of the NRS-2002 score. Finally, one should consider that age is not independent of comorbidity, as each condition negatively impacts on the other in a vicious circle [51]. The fact that the risk of death was higher for men than for women could still be related to age, given that in the Italian general population life expectancy at birth is higher for women than for men [52]; however it is interesting to stress that in our sample female patients were older than males.

Among the considered covariates, the most novel finding was probably related to the role of inflammation-based prognostic scores as predictors for early-and late-term mortality. Our data demonstrated that GPS (based on C-reactive protein and albumin) could be considered as a strong independent prognostic factor since patient admission; in particular, GPS resulted in general as the strongest predictor of mortality in our model. Although inflammation-based prognostic scores combining in different ways C-reactive protein, albumin and white cells count were already described as prognostic factors for all-cause mortality in general population [53], as far as we know this is the first study

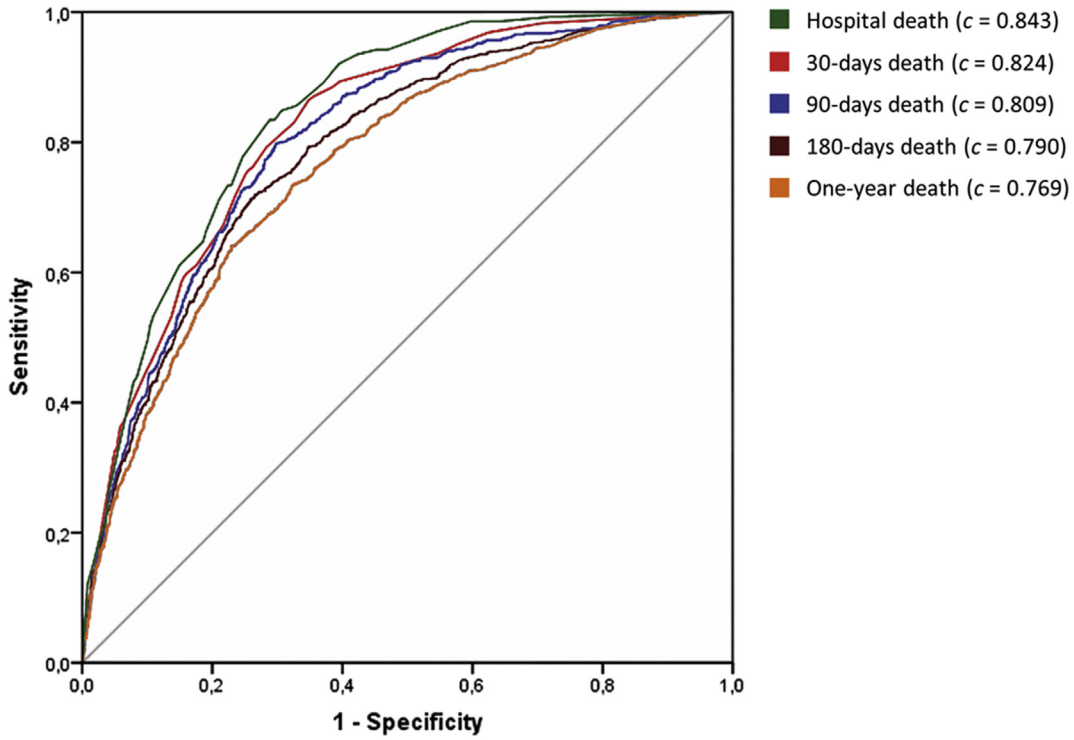

Fig. 2. Comparison of ROC curves for the five explored logistic regression models. In brackets: *c*-statistic (equivalent to the area under the ROC curve).

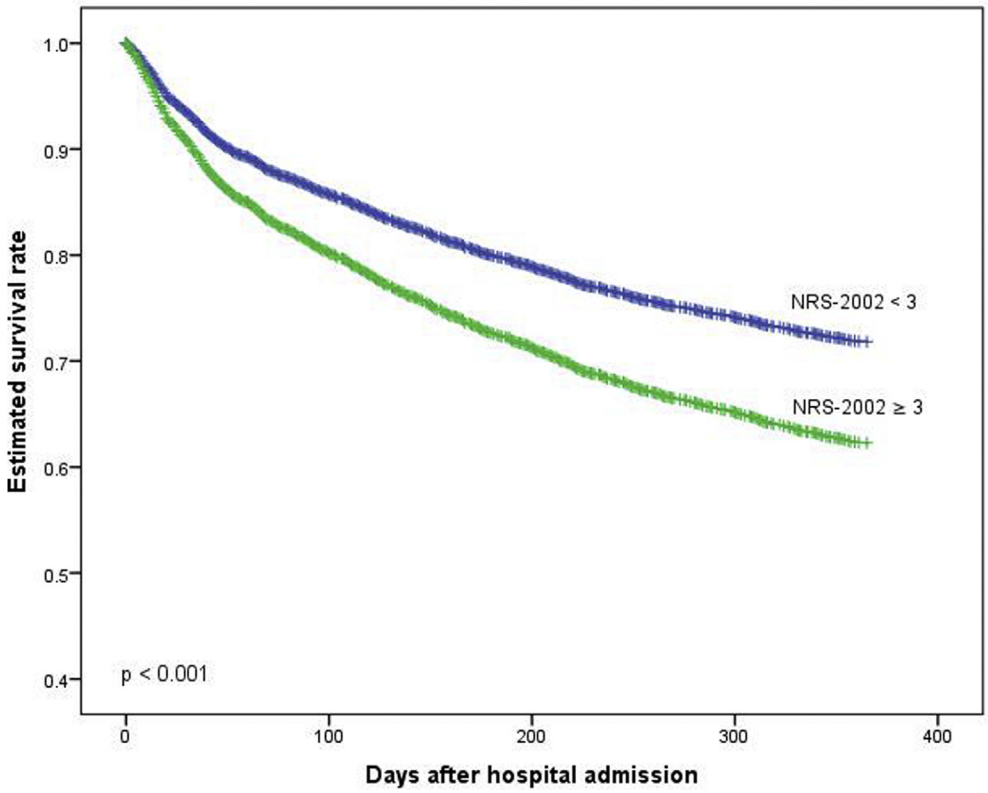

Fig. 3. Adjusted one-year survival curves for patients with (NRS-2002 $\geq$ 3) or without (NRS-2002 < 3) high nutritional risk on hospital admission, estimated with the multivariate Cox proportional hazards model. NRS-2002: Nutritional Risk Score 2002.

demonstrating this ability in a geriatric population of internal medical patients.

Based on these findings, a clinical phenotype of a patient burdened by a higher risk for early and late mortality could be outlined, who presents upon admission at least one of the following risk factors: a) several "minor" or even only one "major" comorbidities; b) high risk of malnutrition, c) both low albumin and high CRP serum levels, d) several "slightly compromised" or even only a couple of "severely compromised" vital signs, e) significantly compromised functional/cognitive status, and thus, high pressure sore risk. Since the majority of patients admitted to general medicine wards are characterized by a high level of complexity, which is due to advanced age, multiple comorbidities and increased frailty [20], identifying subjects who fall into this phenotype may be absolutely strategic also in term of resource allocation. For these patients, the resolution or support of the identified critical aspects should be considered a priority, thus ensuring her/him a higher intensity of care (e.g., a higher nurse-to-patients ratio) with the aim of reducing the risk for hospital and mid-long term mortality. Moreover, given the risk of long-term mortality, for patients survived to hospital discharge a nutritional follow-up should be provided to avoid readmissions [54] and improve clinical outcomes.

4.1. Limitations

Results of the present investigation should be generalized with caution, considering the observational and retrospective design of the study exposing to the risk of bias (e.g., a certain number missing data for some variable, caution in considering as causal the reported associations between predictors and outcome). The external validity of our findings should be confirmed through further studies, maybe prospective, by testing the predictive models in similar large populations.

5. Conclusions

Malnutrition risk identified upon hospital admission by NRS-2002 independently contributes to early and late mortality. However, malnutrition has to be considered according to a broader vision which takes into account the complexity of the patient, since other factors related to comorbidities, functional status, illness severity and inflammation reciprocally interact, concurring at outlining a complex picture with dramatic impact on patient's outcome. The use of validated, simple and routinely available screening tools can improve the ability to identify this critical phenotype of patient, laying the foundations for targeted and multidisciplinary interventions aimed at improving the prognosis.

Future studies should confirm these findings and identify additional variables able to ameliorate, upon hospital admission, the explained variance for early and late mortality, with the aim to evaluate strategies focused at treating the risk conditions to improve patient's outcome.

Funding

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

Author contributions statement

GS and MZan conceived and designed the study; IB, CC, MS and MZac performed data acquisition; DDM supervised data management in nursing registry; MZan supervised the data collection; GS

and MZan analyzed and interpreted the data and drafted the manuscript; GB contributed substantially to its revision; GS and MZan took responsibility for the paper as a whole; all Authors approved the final version of the manuscript to be submitted.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors thank the whole staff of the "Accoglimento Condiviso" Service of the Trieste University Hospital for their collaboration in data collection. Special thanks are due to Francesca Sanson for her assistance in the realization of charts.

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