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Nutritional risk screening (NRS 2002) is a strong and modifiable predictor risk score for short-term and long-term clinical outcomes: *Secondary analysis of a prospective randomised trial*

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Nutritional risk screening (NRS 2002) is a strong and modifiable predictor risk score for short-term and long-term clinical outcomes:

Secondary analysis of a prospective randomised trial

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Abstract

Introduction: The Nutritional Risk Screening 2002 (NRS 2002) identifies patients at risk of malnutrition. We studied the prognostic implications of this score with regard to short-term and long-term clinical outcomes in a well-characterised cohort of medical inpatients from a previous trial.

Methods: This is a secondary analysis of an investigator-initiated, prospective randomised controlled multicenter trial in Switzerland (EFFORT) that compared the effects of an individualised nutritional support intervention with standard of care. We investigated associations between admission NRS and several short-term and long-term outcomes using multivariable regression analyses.

Results: Of the 2,028 patients, 31% had an NRS of 3, 38% of 4 and 31% of ≥5 points, and 477 (24%) died during the 180 days of follow-up. For each point increase in NRS, we found a stepwise increase in risk of 30-day mortality (adjusted Hazard Ratio (HR) 1.22 (95% CI 1.00 to 1.48), p=0.048) and 180-day mortality (adjusted HR 1.37 (95% CI 1.22 to 1.55), p<0.001). NRS was associated with length of hospital stay (adjusted difference of 0.60 days per NRS point increase, 95%CI 0.23 to 0.97, p=0.002) and functional outcomes at 180 days (adjusted decrease in Barthel index of -4.49 points per NRS point increase, 95%CI -6.54 to -2.45, p<0.001). In a subgroup analysis, associations of NRS and short-term adverse outcomes were less pronounced in patients receiving nutritional support (intervention group) compared to control group patients (adjusted HR for 30-day mortality 1.12 [95%CI 0.83 to 1.52, p=0.454] vs. 1.33 [95%CI 1.02 to 1.72, p=0.032]).

Conclusion: The NRS is a strong and independent risk score for malnutrition-associated mortality and adverse outcomes over 180 days. Our data provide strong evidence that the nutritional risk, however, is modifiable and can be reduced by the provision of adequate nutritional support.

Introduction

Malnutrition is a common condition in medical inpatients affecting approximately 30-50% in the western patient population [1-3]. Patients with poor nutritional status are more likely to suffer from adverse outcomes, have an elevated risk of mortality and morbidity, as well as experience significant socioeconomic implications [4-7]. Importantly, recent studies have found that malnutrition risk factors in medical inpatient populations are at least partly modifiable [8-10]. More specifically, two trials reported positive outcomes on mortality associated with a nutritional intervention [11, 12]. The placebo-controlled NOURISH (Nutrition effect On Unplanned Readmissions and Survival in Hospitalized patients) trial found a significant reduction in mortality over 90 days in medical inpatients treated with a high protein oral nutrition supplement [13]. Similarly, the recent EFFORT (*Effect of Early Nutritional Support on Frailty, Functional Outcomes and Recovery of Malnourished Medical Inpatients*) trial found a reduction in the risk for severe complications and mortality associated with the use of nutritional support compared to a control group not receiving additional nutritional support [11]. These findings have provided conclusive evidence to support current guideline recommendations regarding early screening of patients for malnutrition upon hospital admission and the use of nutritional support intervention for at-risk patients [14-16].

For this purpose, several screening tools for malnutrition have been proposed and validated in different patient populations [17, 18]. Of these, the Nutritional Risk Screening (NRS 2002) has become particularly well established for the medical inpatient population [19, 20]. NRS includes assessment of the patient's nutritional status (based on weight loss, Body Mass Index (BMI) and general condition or food intake) and disease severity (stress metabolism due to the degree of disease), and is associated with higher risk for adverse outcomes. Each section is scored from 0 to 3

100 points, and patients receive an extra point if they are 70 years or older [21-23].
101 Earlier observational retrospective studies also found that the NRS has prognostic
102 implications and is associated with short-term and long-term mortality [24, 25]. It
103 remains unclear, however, if the association can be explained by other disease-
104 related factors, or whether the type of nutritional support may influence the
105 connection between NRS and outcome.
106 Herein, we hypothesized that an elevated risk for malnutrition, as assessed by the
107 NRS, is associated with an increased long-term risk for mortality and that this risk is
108 modifiable through the provision of individual nutritional support. To test this
109 hypothesis, we performed a secondary analysis of a prospective, multicentre,
110 randomised trial [11] to investigate the association of NRS with different clinical
111 health outcomes at short-term and long-term follow-up, and studied the differences
112 according to the nutritional support provided to patients.

Methods

Study design and setting

This study is a secondary analysis of the overall EFFORT study population, an investigator-initiated, non-commercial, prospective and open-label randomised trial that compared the effects of individualised nutritional support intervention versus no nutritional support on medical outcomes in patients at nutritional risk (as assessed by the NRS). The trial protocol and the main results have been published elsewhere [26]. The ethics committee of northwest / central Switzerland (EKNZ) approved the study protocol in January 2014 (EKNZ; 2014_001). The eight participating sites were secondary and tertiary care hospitals in Switzerland and included the University Clinic in Aarau, the University Hospital in Bern, the Cantonal hospitals in Lucerne, Solothurn, St. Gallen, Muensterlingen and Baselland, and the hospital in Lachen. Patients were enrolled between April 2014 and February 2018.

Patient population

Adult patients with a NRS total score ≥3 points, an expected length of hospital stay (LOS) >4 days and willingness to provide informed consent were eligible. Exclusion criteria were defined as initial admission to an intensive care unit or surgical unit; the inability to tolerate oral nutrition intake; nutritional support received at time of admission; patients with a terminal condition; admission to hospital due to anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, stem cell transplantation or gastric bypass surgery; contraindications for nutritional support; and previous inclusion in the trial.

Outcomes

The primary endpoint of this study was all-cause mortality from inclusion in the trial up to day 30 and day 180.

Secondary endpoints included the composite endpoint adverse events (all-cause mortality, admission to the intensive care , readmission and major complications) as well as major complications (nosocomial infection or abscess requiring antibiotic treatment, major cardiovascular events, acute renal failure); economic outcome including total LOS, non-elective hospital readmission (defined as non-scheduled hospital readmission after discharge), and admission to the intensive care unit from the medical ward. Functional outcomes included functional impairment (assessed with the Barthel scale), quality of life (European Quality of Life 5 Dimensions Index (assessed with the European Quality of Life 5 Dimensions Index (EQ-5D)) and visual-analogue scale [EQ-5D VAS]), fractures, and accidental fall events. All outcomes were defined and assessed as short-term (30 days) and long-term (180 days) outcomes. To assess primary and secondary endpoints, all patients were contacted by blinded study nurses for a structured telephone interview after 30 days and 180 days. The survival status of all patients during follow-up was confirmed either by family members or the patient`s family physician.

The Barthel scale was used to assess the performance of activities of daily living. Functional impairment was defined as a decline of 10% or more in functional status. The EuroQol Group 5- Dimension Self-Report Questionnaire, which ranges from 0 to 1, with higher scores indicating better life quality and EQ-5D VAS, which scores from 0 to 100, with higher scores indicating better health status, were used to rate quality of life [11].

Nutritional status and procedures

Nutritional status was assessed as recommended by nursing staff within 24-48 hours after hospital admission using the NRS score[18, 27]. We scored for each predictor of the NRS (i.e. patient's nutritional status (based on weight loss, Body Mass Index [BMI] and general condition or food intake) and disease severity) between 0 to 3 points, and added an extra point for patients aged 70 years or older. A NRS total score of ≥ 3 points was considered "at risk" for malnutrition. We then divided the study population into three groups (i.e., moderate risk, high risk, very high risk) according to NRS (3 points; 4 points; ≥5 points).

Nutritional support provided during the trial

Nutritional support during the trial differed according to randomisation of patients, and details of the intervention have been published [26]. In summary, in the intervention group, nutritional support was initiated as soon as possible after trial inclusion. Patients received individualised nutritional support to reach protein and energy requirements according to a previously published consensus protocol and under the guidance of a registered dietician [15]. Energy requirements were predicted using the weight-adjusted Harris-Benedict equation [28]. Daily protein intake was set at 1.2–1.5 g/kg body weight, [29] with lower targets for patients with acute renal failure but without need of renal replacement therapy (0.8 g per kg of body weight). An individual nutritional plan was developed for each patient that was initially based on oral nutrition provided by the hospital kitchen and further increased to enteral tube feeding or parenteral feeding if at least 75% of energy and protein targets could not be reached within 5 days by oral (or enteral) feeding. In total 8, respectively 12 patients received enteral or parenteral nutrition. Nutritional intake was reassessed every 24–48 h throughout the hospital stay and compliance to the nutrition care plan was reinforced. Upon discharge from hospital, patients received dietary counselling

and, if indicated, a prescription for oral nutritional supplements to be taken in the outpatient setting.

Control group patients received standard hospital food according to their ability and desire to eat, with no additional nutritional consultation and no recommendation for supplementary nutritional support.

Study aims

The overall aim of this analysis was to investigate the prognostic implications of NRS in connection with short-term and long-term clinical outcomes in a well-characterised cohort of patients from the EFFORT intervention trial, as well as to compare differences when stratifying patients based on nutritional support received.

Sample size and statistical analyses

For this secondary analysis looking at associations of NRS and long-term mortality within 180 days, we used patients previously included in a randomized trial and the sample size was therefore based on the available number of patients included in the initial trial. Still, with 477 patients reaching the primary endpoint, this sample provides adequate power to support over 47 degrees of freedom in the models. We thus assume that inclusion of up to 47 covariates is possible in the regression models.

Categorical variables are expressed as counts (percentages, standard deviations (SD)) and continuous variables as medians (interquartile ranges [IQR], 25^{th} and 75^{th} percentiles).

We calculated regression models adjusted for important confounders (sex, comorbidities, admission diagnosis, study centre and randomisation) to explore the association between the NRS and several short-term and long-term outcomes. Models were not additionally adjusted for age as this variable is already a part of

NRS. We used Cox regression models for time-to-event data with recorded hazard ratios (HRs), logistic regression for binary outcomes with recorded odds ratios (ORs) and linear regression for continuous outcomes with recorded coefficients. We also calculated Kaplan-Meier survival curves to present the results visually.

Finally, we conducted different analyses according to the pre-specified subgroups, stratifying patients based on age, sex, and main admission diagnosis, as well as those receiving individual nutrition support for different short-term outcomes.

All statistical analyses were performed with STATA 15.1 (Stata Corp, College Station, TX, USA). A *P* value <0.05 (for a 2-sided test) was considered to indicate statistical significance.

Results

We included all 2,028 patients who were enrolled in the EFFORT trial. A total of 624 (31%) patients had a NRS score of 3 points, 775 (38%) a NRS score of 4 points and 629 (31%) a NRS score of ≥5 points. Overall, the median age of the patients was 72.6 years and 1,064 (52%) were male. When comparing patients with NRS of 3, 4 and ≥5 points, we found significant differences in regard to age, weight, admission diagnosis, and comorbidities. More detailed patient baseline characteristics, stratified by NRS and by mortality at 180 days, are shown in **Table 1**.

Association of NRS with short-term and long-term mortality (primary endpoint)

At 30-day and 180-day follow-up, a total of 173 patients (9%) and 477 patients (24%) respectively had died. Mortality showed a stepwise increase consistent with higher NRS scores at short term and long term follow-up. This was also confirmed in a multivariable regression analysis with an adjusted HR of 1.22 (1.00 to 1.48, p=0.048) for mortality at 30 days and an adjusted HR of 1.37 (1.22 to 1.55, p<0.001) for 180-day mortality (**Table 2**).

These results were also confirmed in Kaplan-Meier survival estimates showing a higher likelihood for mortality with increasing NRS scores (**Figure 1**).

Associations of NRS with secondary endpoints

We also investigated associations between NRS and different secondary endpoints (**Table 2**). We observed a stepwise increase in the incidence of adverse outcomes within 30 days - from 22.6% (3 points) to 24.0% (4 points) to 28.1% (5 points and more) with an unadjusted OR of 1.16 (95% CI 1.02 to 1.32, p=0.023) but without remaining significant after multivariate adjustment (p=0.130). There was also a significant increase in mean LOS (from 8.8 to 9.8 to 9.9 days, respectively) with an

(adjusted) increase of 0.6 days (95% CI 0.23 to 0.97) p=0.002) per increase in NRS point. In addition, there was an increase in the risk for impairment of activities of daily living as defined by Barthel scale at days 30 and 180 (coefficient of -0.65 points (95% CI -1.18 to -0.11, p=0.018) for day 30 and -7.52 points (95% CI -9.63 to -5.39, p<0.001) for day 180. Similar results were found for impairment in quality of life within 180 days, as measured by EQ-5D and the EQ-5D VAS.

Subgroup analysis for the primary endpoint

We also performed several pre-planned subgroup analyses to investigate whether the association between NRS and mortality was dependent on age, sex and main admission diagnosis. **Figure 2** shows associations of the NRS and 180-day mortality within these different subgroups. Overall, results were similar, with little difference between groups.

Subgroup analysis regarding effects of nutritional support

Finally, to understand whether the nutritional risk is modifiable through the provision of nutritional support, we performed a subgroup analysis comparing associations of NRS and outcomes stratified by nutritional support received during the trial (nutritional support group vs. control group) (**Table 3, Figure 3**). We found a stronger association of NRS and mortality within 30 days for patients not receiving nutritional support (i.e. control group patients) compared to patients receiving nutritional support (HR of 1.43 (95% CI 1.11 to 1.85) vs. 1.20 (95% CI 0.89 to 1.61). Results were similar for other endpoints including overall adverse outcomes, non-elective hospital readmission, and admission to an intensive care unit.

Discussion

The main findings of this secondary analysis from a recent multicentre trial are twofold. First, we found associations of NRS with different adverse clinical outcomes at short-term and long-term follow-up, which proofed to be independent of important confounders in multivariate analysis and showed robust results in different subgroup analyses. This demonstrates that NRS has strong prognostic implications regarding malnutrition-associated adverse clinical outcomes. Secondly, the association between NRS and adverse outcomes were less pronounced in patients receiving nutritional support compared to patients not receiving nutritional support, suggesting that the risk for adverse outcomes for patients with malnutrition is at least partly modifiable through provision of nutritional support.

There are several findings of this study worth mentioning. Firstly, the association between malnutrition and mortality has been known for some time [1, 30, 31]. A previous retrospective observational study performed in Italy, including 5,698 patients hospitalized between from October 2015 and July 2016, showed that nutritional risk identified by NRS at time of hospital admission was a good predictor of short-term (1-, 3-, 6-month) and long-term (1 year) mortality, with a doubling in mortality comparing patients scoring NRS≤3 with those NRS≥3 [24]. These finding are in line with our results, which also show an increase of 5% within 30 days and 17% within 180 days between patients with an NRS of 3 and those with ≥5 points. Importantly, we were also able to adjust our analysis for important confounders such as socio-demographic factors, main admission diagnosis and comorbidities, suggesting that malnutrition has an independent negative effect on health outcomes, which is not explained by the heavier burden of disease seen in the malnourished population. Our prospective sample of patients with detailed clinical information thereby confirms

results of other observational and retrospective studies with less rigorous statistical adjustment[24].

Secondly, our findings regarding secondary endpoints are also partly in line with multiple previous studies, which report associations between nutritional risk and various economic outcomes such as increased LOS [32-38], hospital readmission [4, 39] and admission to an intensive care unit. The economic burden of malnutrition derives mostly from extended LOS, which leads to higher use of hospital resources and thus increased costs. A prospective cohort study of 818 patients in Singapore found an increased LOS by two days when comparing well nourished with malnourished and severely malnourished patients (using the Subjective Global Assessment SGA) [39]. In our study, we were able to adjust all analysis for confounders showing that NRS might be indeed independently associated with these economic outcomes.

Thirdly, we were able to look at the association of malnutrition risk as assessed by NRS within different subgroups with different underlying main diagnosis- asking the question whether the individual situation of a patient with regard to socio-demographics, admission diagnosis, and comorbidities may influence the strength of association.[40] Overall, we found little variation within these groups, suggesting that malnutrition is a risk factor across the entire medical inpatient population and the consequence of different illnesses, rather than caused by specific conditions.[41] Screening and treatment of malnutrition should, therefore, not be limited to certain patient populations, but rather include all medical inpatients.[42] This is also in line with the EFFORT trial, which demonstrates the benefits of nutritional support independent of the medical condition.[11]

Fourthly, most studies looking at malnutrition and risk of impaired functional outcomes (such as quality of life or performance of activities of daily living) were carried out on a geriatric population [43, 44]. Functional impairments have an important impact on a patient's independence, with dramatic socio-economic implications [43]. Our analysis expands the results regarding functional outcomes to a medical inpatient population, demonstrating similar results to those known from geriatrics. Both quality of life and performance of daily activities measured by the EQ-5D and the Barthel scale decreased with an increasing NRS score. Interestingly, these associations were more pronounced for long-term outcomes and remained significant in the fully adjusted statistical model. The Barthel scale, for instance, was 42% higher in patients scoring ≥5 points in the NRS than patients scoring 3 points. Naturally the worsening of functional outcomes due to progression of sarcopenia takes time to develop and the consequences of malnutrition only become evident only after a certain period of time.

Fifth, as a new and clinically relevant main finding, we explored whether provision of nutritional support influences the association between malnutrition and adverse clinical outcomes. We focused on short-term outcomes because our intervention only looked at the initial hospital stay and not the post-discharge period. Interestingly, the association between NRS and mortality was only about half as strong in the intervention group as compared to the control group. This indicates that the adverse effects of malnutrition are at least partially modifiable. These findings again suggest that patients as being identified as at risk of malnutrition according to NRS or a similarly well-validated nutrition screening tool should receive more in-depth assessment and individualised nutritional support, if indicated.

We used the NRS as a screening tool, as recommended by the European Society of Parenteral and Enteral Nutrition (ESPEN)[18]. Other screening tools for malnutrition such as the Mini Nutritional Assessment (MNA) and its shorter form (MNA-SF), as well as the malnutrition universal screening tool (MUST) have been validated for predicting mortality and adverse outcomes in previous studies, but it remains unclear which of these tools best identifies patients who would benefit from nutritional intervention [22, 23, 45].

This trial has several strengths and limitations worth mentioning. One of the strengths of this study is that it consists on a secondary analysis of a prospective randomised trial including a large unselected and heterogeneous population [12, 46, 47]. To the best of our best knowledge this is the first adequately powered study to investigate several short-term and long-term outcomes, and include functional outcomes. Furthermore, while several observational studies investigated the predictive validity of the NRS, we were the first to demonstrate that nutritional support has an influence on the association of NRS and outcome and is thus an effect modifier. We were also able to calculate multivariate regression models and adjust the analysis for important confounders.

There are, however, some limitations to the underlying EFFORT trial; including the non-blinding of patients and dieticians, some variation in compliance with the nutritional protocol (with about 20% of patients not reaching their energy and protein goals which, however, is a conservative bias towards the here relevant endpoints), and the focus on one country which may limit external validity to other health care systems. Also, we only included patients with an NRS score of at least 3 points and thus have no data regarding patients with no nutritional risk as a control group. We

also did not include ICU patients and surgical patients and our findings thus only applies to medical inpatients limiting external validity. Lastly the selection of co-morbidities for inclusion in statistical models was based on the data collection within the initial trial.

In conclusion, as it mirrors patients' individual nutritional risk, the NRS is a strong and independent risk factor for mortality and adverse outcomes - which may in turn be modified by the adequate provision of nutritional support.

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Statement of Authorship

LH, AB, LB and PS were responsible for the data analysis and interpretation of this secondary analysis. LH, AB, LB and PS drafted the final manuscript with all authors contributing to critical revision oft he manuscript. PS was responsible for obtaining funding. RF, VB, MG, MD, PT, NK, SS, CB, SM, CB were involved in data collection and approved the final version of the manuscript.

FG, AK, TB, CH, VP, SB, SS, MB, CH, RT, JR, DA, NR, JD were involved in drafting the trial protocol, supervision of study sites, drafting of the final manuscript and approved the final version of the manuscript oft the original EFFORT trial.

ZS and BM were involved in obtaining funding, drafting the trial protocol, supervision of study sites, drafting of the final manuscript oft he original EFFORT trial and approved the final version of the current manuscript. The corresponding authors had full access to all the data used and had a shared final responsibility for the accuracy of the analysed data.

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Tables and Figure Legends

Table 1. Baseline Characteristics

Table 2. Association of NRS and clinical outcomes

Table 3: Association of NRS with short-term Outcomes, stratified by nutritional support (intervention vs control group).

Figure 1. Kaplan Meier estimate on 180-day mortality stratified by the NRS

Time to death shown for each NRS score upon admission (p≤ 0.001)

Figure 2. Subgroup analysis

Subgroup analysis for sociodemographic factors and main diagnosis. The overall effect is listed as the reference group (HR 1.31; CI 95% 1.17,1,48). “Other diagnosis” includes neuropsychological, renal, gastrointestinal and metabolic illnesses.

Figure 3. Subgroup analysis regarding mortality and non-elective readmission

Association of NRS and endpoints stratified by nutritional support (intervention vs control group). Adjusted Hazard ratios are shown for time to event outcome data, odds ratios for binary outcome data and coefficients for continuous outcomes.

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Appendix

Figure 4. Subgroup analysis regarding adverse outcomes, major complications and decline in functional status

Effects of nutritional support on primary endpoints for patients compared to the control group. Odds ratios for binary outcome data and coefficients for continuous outcomes.

Figure 5. Subgroup analysis regarding Length of stay and Barthel index

Effects of nutritional support on primary endpoints for patients compared to the control group. Coefficients are shown for continuous outcomes.

Table 2. Association of NRS and clinical outcomes

	NRS 3 (N=624)	NRS 4 (N=775)	NRS ≥5 (N=629)	*p-Value*	*Hazard ratio (HR), Odds ratio (OR), Coefficients*	Regression analysis (not adjusted) (95%CI and p-value)	Regression analysis (adjusted) (95%CI and p-value)
Primary outcomes							
Short-term outcomes							
All-cause mortality within 30 days	41 (6.6%)	62 (8.0%)	70 (11.1%)	0.012	HR	1.33 (1.09 to 1.61) p=0.004	1.22 (1.00 to 1.48) p=0.048
Long-term outcomes							
All-cause mortality within 180 days	101 (16.2%)	169 (21.8%)	207 (32.9%)	<0.001	HR	1.51 (1.34 to 1.70) p<0.001	1.37 (1.22 to 1.55) p<0.001
Secondary outcomes							
Short-term outcomes							
Complications							
Adverse outcome within 30 days	141 (22.6%)	186 (24.0%)	177 (28.1%)	0.06	OR	1.16 (1.02 to 1.32) p=0.023	1.11 (0.97 to 1.27) p=0.130
Non-elective hospital readmission within 30 days	55 (8.8%)	64 (8.3%)	61 (9.7%)	0.64	HR	1.05 (0.87 to 1.27) p=0.589	1.03 (0.85 to 1.25) p=0.759
Admission to the intensive care unit within 30 days	13 (2.1%)	24 (3.1%)	12 (1.9%)	0.29	OR	0.96 (0.67 to 1.38) p=0.837	1.08 (0.74 to 1.57) p=0.696
Any major complication	45 (7.2%)	62 (8.0%)	43 (6.8%)	0.69	OR	0.97 (0.79 to 1.20) p=0.798	0.97 (0.78 to 1.21) p=0.804
Nosocomial infection	17 (2.7%)	34 (4.4%)	28 (4.5%)	0.19	OR	1.26 (0.94 to 1.68) p=0.116	1.22 (0.91 to 1.65) p=0.182
Major cardiovascular event	4 (0.6%)	4 (0.5%)	7 (1.1%)	0.41	OR	1.39 (0.72 to 2.69) p=0.332	1.35 (0.68 to 2.67) p=0.386
Acute kidney failure	20 (3.2%)	25 (3.2%)	18 (2.9%)	0.91	OR	0.94 (0.69 to 1.30) p=0.726	0.91 (0.66 to 1.27) p=0.592
Functional outcome							
Mean length of stay within 30 days (days)	8.8 (6.1)	9.8 (6.7)	9.9 (6.8)	0.005	Coefficient	0.54 (0.18 to 0.90) p=0.003	0.6 (0.23 to 0.97) p=0.002
Mean BARTHEL score (points) within 30 days	95.58 (9.12)	95.21 (9.42)	94.29 (10.6)	0.052	Coefficient	-0.65 (-1.18 to -0.11) p=0.018	-0.53 (-1.07 to 0.02) p=0.059
Decline in functional status of >10%	64 (10.3%)	90 (11.6%)	92 (14.6%)	0.052	OR	1.23 (1.04 to 1.46) p=0.018	1.16 (0.97 to 1.38) p=0.105
Long-term outcomes							
Complications							
Non-elective hospital readmission within 180 days	168 (26.9%)	204 (26.3%)	177 (28.1%)	0.74	HR	1.11 (1.00 to 1.24) p=0.051	1.07 (0.96 to 1.19) p=0.248
Accidental fall event within 180 days	74 (11.9%)	88 (11.4%)	58 (9.2%)	0.27	OR	0.87 (0.73 to 1.04) p=0.133	0.89 (0.74 to 1.07) p=0.200
Fracture within 180 days	8 (1.3%)	17 (2.2%)	7 (1.1%)	0.2	OR	0.94 (0.60 to 1.47) p=0.79	0.93 (0.58 to 1.48) p=0.749
Functional outcomes							
Mean EQ-5D index (points)†	0.77 (0.30)	0.75 (0.33)	0.69 (0.35)	<0.001	Coefficient	-0.04 (-0.06 to -0.02) p<0.001	-0.03 (-0.05 to -0.01) p=0.015
VAS index †	60 (26)	58 (27)	55 (29)	0.007	Coefficient	-2.57 (-4.23 to -0.91) p=0.002	-1.59 (-3.23 to 0.05) p=0.058
Mean EQ-5D VAS (points) within 180 days †	56.5 (32.5)	51.5 (34.6)	44.5 (37.3)	<0.001	Coefficient	-6.02 (-8.07 to -3.96) p<0.001	-4.22 (-6.16 to -2.28) p<0.001
Mean BARTHEL score (points) within 180 days †	73.1 (34.27)	68.34 (37.74)	58.08 (42.44)	<0.001	Coefficient	-7.51 (-9.63 to -5.39) p<0.001	-4.49 (-6.54 to -2.45) p<0.001
Decline in mean BARTHEL score (points) within 180 days	284 (47.3%)	369 (49.9%)	317 (53.2%)	0.12	OR	1.13 (1.01 to 1.26) p=0.040	1.12 (0.99 to 1.27) p=0.064

Continuous values as median and IQR, categorical/binary values as absolute number and percentage.
NRS= Nutritional Risk Screening, EQ-5D= European Quality of Life 5 Dimensions index; VAS= visual-analogue scale
Adjusted for sex, admission diagnosis, comorbidities, study centre and randomization. Comorbidities include: Coronary heart disease, chronic heart failure, hypertonia, stroke, chronic renal failure, diabetes mellitus, tumor, chronic obstructive pulmonal disease, peripheral artery disease and dementia
HR= Hazard ratio; OR= Odds ratio

Table 3: Short-term Outcomes in control versus intervention group

	Hazard ratio (HR), Odds ratio (OR), Coefficients	**Regression analysis Control (non-adjusted)** (odds ratio and 95%CI and p-value)	**Regression analysis Intervention (non-adjusted)** (odds ratio and 95%CI and p-value)	**Regression analysis Control (adjusted)** (odds ratio and 95%CI and p-value)	**Regression analysis Intervention (adjusted)** (odds ratio and 95%CI and p-value)
Primary outcomes					
All-cause mortality within 30 days	HR	1.43 (1.11 to 1.85) p=0.006	1.20 (0.89 to 1.61) p=0.232	1.33 (1.02 to 1.72) p=0.032	1.12 (0.83 to 1.52) p=0.454
Secondary outcomes					
Complications					
Adverse outcome within 30 days	OR	1.22 (1.02 to 1.46) p=0.026	1.10 (0.91 to 1.32) p=0.336	1.18 (0.98 to 1.42) p=0.087	1.05 (0.86 to 1.28) p=0.630
Any major complication	OR	0.98 (0.73 to 1.31) p=0.871	0.97 (0.72 to 1.31) p=0.842	0.95 (0.70 to 1.3) p=0.750	0.98 (0.72 to 1.34) p=0.914
Acute kidney failure	OR	1.17 (0.74 to 1.85) p=0.493	0.76 (0.48 to 1.20) p=0.243	1.07 (0.67 to 1.73) p=0.771	0.75 (0.47 to 1.19) p=0.223
Economic outcome					
Mean length of stay within 30 days (days)	Coefficient	0.37 (-0.11 to 0.84) p=0.132	0.72 (0.17 to 1.26) p=0.010	0.42 (-0.07 to 0.91) p=0.092	0.80 (0.24 to 1.36) p=0.005
Non-elective hospital readmission within 30 days	HR	1.14 (0.88 to 1.48) p=0.327	0.97 (0.74 to 1.26) p=0.822	1.18 (0.90 to 1.55) p=0.227	0.90 (0.69 to 1.18) p=0.436
Admission to the intensive care unit within 30 days	OR	1.00 (0.61 to 1.64) p=0.995	0.92 (0.55 to 1.57) p=0.769	1.05 (0.63 to 1.77) p=0.840	1.09 (0.62 to 1.92) p=0.753
Functional outcome					
Mean BARTHEL score (points) within 30 days	Coefficient	-0.33 (-1.1 to 0.44) p=0.395	-0.96 (-1.72 to -0.21) p=0.012	-0.15 (-0.94 to 0.64) p=0.702	-0.87 (-1.63 to -0.10) p=0.026
Decline in functional status of >10%	OR	1.17 (0.93 to 1.46) p=0.175	1.32 (1.01 to 1.72) p=0.040	1.08 (0.85 to 1.37) p=0.546	1.28 (0.97 to 1.69) p=0.078

Continuous values as median and IQR, categorical / binary values as absolute number and percentage. NRS= Nutritional Risk Screening, EQ-5D= Euroquol-5 Dimensions, VAS= Visual Analogue Scale
*Adjusted for sex, admission diagnosis, comorbidities, study centre and randomization

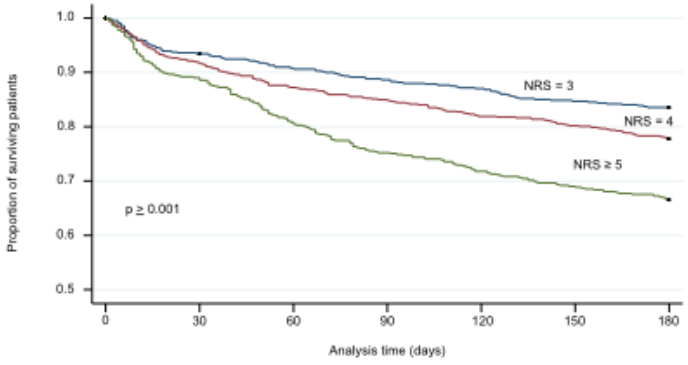
Table 1. Baseline results of patients

	Stratified according to NRS				Stratified according to Mortality		
Parameters	**NRS 3**	**NRS 4**	**NRS ≥5**	**p-Value**	**Survivors**	**Non-survivors**	**p-Value**
N	624	775	629		1551	477	
Sociodemographics							
Mean age (years)	70.20 (15.2)	71.4 (14.9)	76.5 (10.6)	<0.001	71.5	76.2	<0.001
Age group							
<65 years	143 (22.9%)	162 (20.9%)	50 (7.9%)	<0.001	307 (19.8%)	48 (10.1%)	<0.001
65-75 years	215 (34.5%)	247 (31.9%)	209 (33.2%)	<0.001	517 (33.3%)	154 (32.3%)	<0.001
>75 years	266 (42.6%)	366 (47.2%)	370 (58.8%)	<0.001	727 (46.9%)	275 (57.7%)	<0.001
Male sex [no.] (%)	344 (55.1%)	402 (51.9%)	318 (50.6%)	0.250	773 (49.8%)	291 (61.0%)	<0.001
Nutritional assessment							
Mean Body Mass Index (kg/m^2)	26.0 (5.0)	24.8 (5.3)	23.6 (5.4)	<0.001	25 (5.5)	24.2 (4.6)	0.004
Mean bodyweight (kg)	74.2 (16.6)	71.1 (16.5)	67.1 (16.3)	<0.001	71.2 (17.0)	69.9 (15.5)	0.220
NRS 2002 score (%)							
3 points					523 (33.7%)	101 (21.2%)	<0.001
4 points					606 (39.1%)	169 (35.4%)	<0.001
5 points					357 (23.0%)	167 (35.0%)	<0.001
>5 points					65 (4.2%)	40 (8.4%)	<0.001
Weight loss - no. (%)							
≤5% in 3 month	434 (69.6%)	394 (50.8%)	242 (38.5%)	<0.001	858 (55.3%)	212 (44.4%)	<0.001
>5% in 3 month	94 (15.1%)	115 (14.8%)	76 (12.1%)	<0.001	200 (12.9%)	85 (17.8%)	<0.001
>5% in 2 month	70 (11.2%)	132 (17.0%)	55 (8.7%)	<0.001	182 (11.7%)	75 (15.7%)	<0.001
>5% in 1 month	26 (4.2%)	134 (17.3%)	256 (40.7%)	<0.001	311 (20.1%)	105 (22.0%)	<0.001
Loss of appetite - no. (%)							
No	99 (15.9%)	74 (9.5%)	56 (8.9%)	<0.001	200 (12.9%)	29 (6.1%)	<0.001
Yes	525 (84.1%)	701 (90.5%)	573 (91.1%)	<0.001	1351 (87.1%)	448 (93.9%)	<0.001
Normal required food intake preceding week - no. (%)							
>75%	89 (14.3%)	69 (8.9%)	47 (7.5%)	<0.001	181 (11.7%)	24 (5.0%)	<0.001
50-75%	336 (53.8%)	202 (26.1%)	101 (16.1%)	<0.001	501 (32.3%)	138 (28.9%)	<0.001
25-50%	184 (29.5%)	378 (48.8%)	277 (44.0%)	<0.001	614 (39.6%)	225 (47.2%)	<0.001
<25%	15 (2.4%)	126 (16.3%)	204 (32.4%)	<0.001	255 (16.4%)	90 (18.9%)	<0.001
Severity of illness - no. (%)							
Very mild	33 (5.3%)	22 (2.8%)	0 (0.0%)	<0.001	53 (3.4%)	2 (0.4%)	<0.001
Mild	482 (77.2%)	548 (70.7%)	286 (45.5%)	<0.001	1021 (65.8%)	295 (61.8%)	<0.001
Moderate	105 (16.8%)	200 (25.8%)	330 (52.5%)	<0.001	458 (29.5%)	177 (37.1%)	<0.001
Severe	4 (0.6%)	5 (0.6%)	13 (2.1%)	<0.001	19 (1.2%)	3 (0.6%)	<0.001
Admission diagnosis							
Cardiovascular disease	78 (12.5%)	76 (9.8%)	51 (8.1%)	0.034	148 (9.5%)	57 (11.9%)	0.130
Infection	166 (26.6%)	234 (30.2%)	213 (33.9%)	0.02	517 (33.3%)	96 (20.1%)	<0.001

Metabolic disease	20 (3.2%)	28 (3.6%)	14 (2.2%)	0.31	54 (3.5%)	8 (1.7%)	0.045
Gastrointestinal disease	57 (9.1%)	72 (9.3%)	35 (5.6%)	0.02	136 (8.8%)	28 (5.9%)	0.042
Renal disease	13 (2.1%)	29 (3.7%)	26 (4.1%)	0.098	52 (3.4%)	16 (3.4%)	1.000
Cancer	91 (14.6%)	129 (16.6%)	154 (24.5%)	<0.001	188 (12.1%)	186 (39.0%)	<0.001
Lung disease	39 (6.2%)	50 (6.5%)	36 (5.7%)	0.85	98 (6.3%)	27 (5.7%)	0.600
Neurological disease	44 (7.1%)	34 (4.4%)	17 (2.7%)	0.001	89 (5.7%)	6 (1.3%)	<0.001
Reduced general condition	71 (11.4%)	76 (9.8%)	47 (7.5%)	0.061	167 (10.8%)	27 (5.7%)	<0.001
Other	21 (3.4%)	20 (2.6%)	14 (2.2%)	0.44	42 (2.7%)	13 (2.7%)	0.980
Comorbidity							
Coronary heart disease	175 (28.0%)	208 (26.8%)	183 (29.1%)	0.64	423 (27.3%)	143 (30.0%)	0.25
Congestive heart failure	120 (19.2%)	123 (15.9%)	110 (17.5%)	0.26	239 (15.4%)	114 (23.9%)	<0.001
Hypertension	305 (48.9%)	435 (56.1%)	369 (58.7%)	0.001	839 (54.1%)	270 (56.6%)	0.34
Stroke	51 (8.2%)	58 (7.5%)	53 (8.4%)	0.79	121 (7.8%)	41 (8.6%)	0.58
PAD	64 (10.3%)	72 (9.3%)	50 (7.9%)	0.36	137 (8.8%)	49 (10.3%)	0.34
Chronic kidney disease	184 (29.5%)	219 (28.3%)	238 (37.8%)	<0.001	459 (29.6%)	182 (38.2%)	<0.001
Diabetes	124 (19.9%)	171 (22.1%)	133 (21.1%)	0.61	311 (20.1%)	117 (24.5%)	0.036
COPD	89 (14.3%)	115 (14.8%)	99 (15.7%)	0.76	231 (14.9%)	72 (15.1%)	0.91
Dementia	25 (4.0%)	33 (4.3%)	17 (2.7%)	0.27	55 (3.5%)	20 (4.2%)	0.51
Malignant disease	178 (28.5%)	213 (27.5%)	276 (43.9%)	<0.001	388 (25.0%)	279 (58.5%)	<0.001

Continuous values as median and IQR, categorical / binary values as absolute number and percentage.
NRS-2002= Nutritional Risk Screening 2002, PAD= Peripheral Artery Disease, COPD= Chronic Obstructive Pulmonary Disease

Figure 1. Kaplan Meier estimate on 180 day mortality stratified by NRS



Number at risk

NRS = 3	624	583	551	538	528	514	507
NRS = 4	775	712	656	639	616	603	585
NRS ≥ 5	629	560	497	462	441	424	409

Figure 2. Subgroup analysis

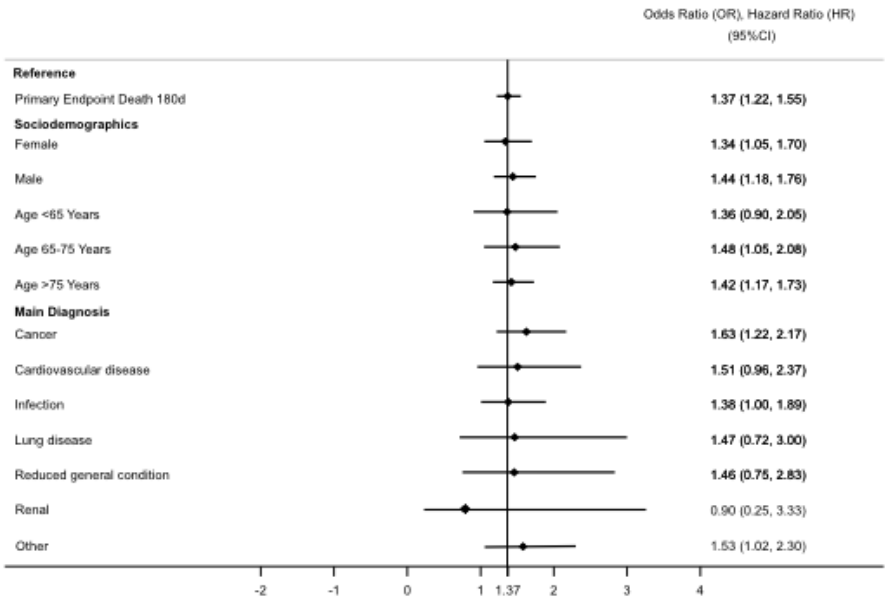
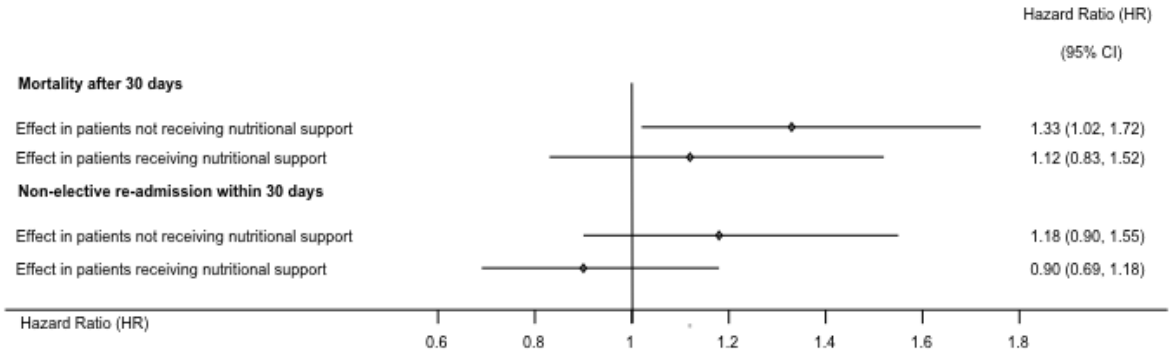


Figure 3. Analysis regarding nutritional intervention in primary endpoints



Conflict of Interest Statement and Funding sources

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