

The association between prealbumin, all-cause mortality and response to nutritional treatment in patients at nutritional risk.

Secondary analysis of a randomized-controlled trial

Brief title: Prealbumin in patients at nutritional risk

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Abstract

Introduction Due to the shorter half-life as compared with albumin, serum prealbumin concentrations have been proposed to be useful nutritional biomarkers for the assessment of patients at nutritional risk. In a post-hoc analysis of patients at nutritional risk from a randomized-controlled nutritional trial, we therefore tested the hypothesis that (a) prealbumin is associated with higher all-cause 180-day mortality rates and that (b) individualized nutritional support compared to usual care nutrition more effectively improves survival at 30 days in patients with low prealbumin levels compared to patients with normal prealbumin levels.

Methods We performed a pre-specified cohort study in patients included in the pragmatic, Swiss, multicenter, randomized-controlled EFFORT trial comparing the effects of individualized nutritional support with usual care. We studied low prealbumin concentrations (<0.17 g/l) in a subgroup of 517 patients from one participating centre.

Results A total of 306 (59.2%) patients (mean age 71.9 years, 53.6% men) had low admission prealbumin levels (<0.17 g/L). There was a significant association between low prealbumin levels and mortality at 180-days [115/306 (37.6%) vs. 47/211 (22.3%), fully adjusted hazard ratio (HR) 1.59, 95%CI 1.11 to 2.28, p=0.011]. Prealbumin levels significantly improved the prognostic value of the Nutritional Risk Screening total score regarding mortality prediction at short- and long-term. The difference in mortality between patients receiving individualized nutritional support and usual care nutrition was similar for patients with low prealbumin levels compared with patients with normal prealbumin levels [HR 0.90 (95%CI 0.51 to 1.59) vs. HR 0.88 (95%CI 0.35 to 2.23)] with no evidence for interaction (p=0.823).

Conclusion Among medical inpatients at nutritional risk, low admission prealbumin levels correlated with different nutritional markers and higher mortality risk; but patients with low or high prealbumin levels had a similar benefit from nutritional support. Further studies should identify nutritional markers that help further personalize nutritional interventions.

Trial Registration: ClinicalTrials.gov Identifier: NCT02517476

Clinical Relevancy Statement

In this secondary analysis of a Swiss multicenter trial including 517 patients at risk of malnutrition, patients with low serum prealbumin concentrations had significantly higher mortality rates, but there was no evidence that nutritional support is more effective in lowering mortality in patients with low vs. normal prealbumin concentrations. In a population of medical patients at risk for malnutrition, low serum prealbumin concentrations had prognostic implications and indicated higher mortality risk, but did not predict response to nutritional treatment.

Introduction

Malnutrition is frequent among the population of elderly and polymorbid medical patients and is strongly associated with higher mortality, complications and impairments in quality of life and functional abilities.¹⁻⁴ There is increasing evidence demonstrating that risks of malnutrition can be lowered, at least partly, by addressing malnutrition through active screening followed by a specific nutritional intervention to achieve improvement of clinical outcomes.^{3,5,6} In fact, several trials and meta-analyses of such trials have shown positive effects of nutritional support within the population of medical inpatients.⁵⁻⁸ The largest trial in the medical inpatient setting was the *Effect of Early Nutritional support on Frailty and Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial* (EFFORT), a pragmatic Swiss multicenter trial that included 2028 medical inpatients at nutritional risk and that compared an individualized nutritional support strategy with usual nutritional care.⁵ While this study and other trials found significant reductions in the risk for severe complications and mortality in the overall population of medical inpatients, secondary analyses suggested that there are patients that show more or less benefit from the intervention opening the door for a more personalized approach.^{3,9} In fact, different analyses showed that some nutritional biomarkers may help to identify patients who will have more or less benefit from nutritional support including biomarkers of inflammation (i.e., C-reactive protein [CRP]), markers of kidney function and markers of sarcopenia.¹⁰⁻¹³ Other markers such as albumin¹⁴ or different metabolomic parameters were not helpful.^{15,16} Further knowledge of specific nutritional biomarkers to predict response to nutritional treatment may allow better phenotyping patients and help focus specific interventions on patients who may benefit the most.

Among potential nutritional biomarkers, there is particular interest in visceral proteins such as serum albumin that has been used to characterise patients since the 1970's.¹⁷ In fact, baseline albumin levels were associated with higher risk for mortality among patients in the EFFORT trial but albumin was not helpful in stratifying patients regarding response to nutritional treatment confirming results of other similar studies.¹⁴ However, one major drawback of

albumin as a nutritional marker is its long half-life of about 20 days and that its concentration is affected by inflammation and fluid balance. Yet, prealbumin (transthyretin), has a much shorter half-life of about 2 days and thus may be more accurate for the characterization of patients in the acute care setting.¹⁸⁻²⁰ However, there is currently insufficient data from larger trials investigating the possible benefits of measurement of prealbumin among patients at nutritional risk. Answering this question may help to use prealbumin as a nutritional biomarker in the future to identify patients at high risk of adverse outcome that should receive nutritional care. Herein, in a post-hoc analysis of patients at nutritional risk from a randomized-controlled nutritional trial⁵, we therefore tested the hypothesis that (a) prealbumin is associated with higher all-cause 180-day mortality rates and that (b) individualized nutritional support compared to usual care nutrition more effectively improves survival at 30 days in patients with low prealbumin levels compared to patients with normal prealbumin levels.

Methods and Materials

Study design and setting

We performed a pre-specified retrospective cohort study in patients included in the pragmatic, Swiss, multicenter, randomized-controlled EFFORT trial comparing the effects of individualized nutritional support with usual care. We studied low prealbumin concentrations (<0.17 g/l) in a subgroup of 517 patients from one participating centre. EFFORT was a prospective, randomized-controlled trial studying the effect of early individual nutritional support compared with usual care nutrition in patients at nutritional risk in eight Swiss hospitals from April 2014 to February 2018.⁵ The trial was approved by the ethics committee of Northwestern Switzerland (EKNZ; 2014_001) and registered at ClinicalTrials.gov in August 2015. (<https://clinicaltrials.gov/ct2/show/NCT02517476>) The trial protocol, eligibility features and main results were previously published.^{5,21}

Patient population

The initial EFFORT trial population included 2028 patients at nutritional risk (defined by a Nutritional Risk Screening (NRS 2002) total score ≥ 3 points).^{22,23} The NRS includes the patient's current nutritional status and the severity of the underlying disease.⁶ Each part scores between 0 to 3 points, plus 1 point for age above 70 years (max. 7 points). For this secondary analysis, we only focused on 517 patients (25.5%) from one participating centre (Kantonsspital Aarau), where prealbumin levels were measured routinely in a blinded fashion as a preplanned substudy, without communication of results to physicians.

All adult patients were eligible for the trial when there was an expected length of hospital stay ≥ 5 days and if they provided informed consent. Exclusion criteria were initial admission to an intensive care unit or a surgical unit, inability for oral ingestion of food, already established nutritional support on admission, terminal illness, prior gastric bypass surgery, anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, stem cell transplantation or contraindications for nutritional support and previous inclusion in the trial. Patients were randomly assigned (1:1) either to the intervention group (individualized nutritional support), or the control group (standard hospital food). The intervention group received individualized nutritional support within 48 hours of admission to reach protein and energy goals according to a previously published consensus protocol and in accordance with recent international guidelines.^{24,25} Individualized energy and protein goals were defined for each patient upon hospital admission by a trained registered dietician using weight-adjusted Harris-Benedict equation to estimate energy requirements.²⁶ Daily protein intake goals were set at 1.2-1.5 g/kg body weight per day with lower targets of 0.8 g/kg body weight for patients with renal failure.²⁷ To reach these goals, an individualized nutritional plan was developed based initially on oral nutrition provided by the hospital kitchen and oral nutritional supplements.^{28,29} A further increase in nutritional support to enteral tube feeding or parenteral feeding was recommended if at least 75% of energy and protein targets could not be reached through oral feeding within 5 days. Patients in the control group received usual care nutrition according to their ability and

desire to eat, with no nutritional consultation and no recommendation for additional nutritional support.

We prospectively collected different medical and nutritional information in patients including medical diagnosis according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes, sociodemographic and anthropometric data, baseline muscle strength, and functional status (using the Barthel-Index).³⁰

Patient groups and outcomes

To understand the prognostic potential of prealbumin, we stratified the patient population into two groups based on their serum prealbumin levels at admission with a cut-off of 0.17 g/L as recommended.³¹ We additionally, stratified patients based on their baseline inflammation status using a CRP cut-off level of 100 mg/L as suggested previously.^{10,32}

The primary endpoint for this analysis was all-cause mortality within 180 days for the prognostic analyses based on data from a long-term follow-up analysis.³³ For the analysis regarding response to nutritional treatment we used short-term all-cause mortality within 30 days similar to the initial trial.⁵ To assess response to nutritional treatment we compared whether the difference in mortality in patients in the intervention group receiving individualized nutritional support and control patients would be different according to low or normal prealbumin levels at the 0.17 g/L cut-off. Other secondary endpoints included the composite endpoint of adverse outcomes (consisting of all-cause mortality, admission to the intensive care, readmission, major complications, functional decline), length of hospital stay (LOS) and non-elective hospital readmission after 30 and 180 days. All endpoints are in line with the original publication and collected through a structured telephone interview at 30 and 180 days after inclusion in the trial.⁵

Statistical analyses

All analyses were performed in the intention-to-treat population, including all patients with available serum prealbumin concentrations. Continuous variables were expressed as mean

and standard deviations (SD) for normally distributed data or as median and interquartile range (IQR) for skewed data, discrete variables as counts and percentages. We compared frequencies using Pearson's χ^2 test and continuous variables using a two-sample t-test or a Wilcoxon rank-sum test. We used Cox regression models for time-to-event data reporting hazard ratios (HR), logistic regression for binary outcomes reporting odds ratios (OR) and linear regression for continuous outcomes reporting coefficients (Coef) with corresponding 95% confidence intervals (CI). We performed models for prognostic and predictive analysis adjusted for different predefined confounders (age, sex, main diagnosis, comorbidities, randomization as well as CRP and NRS). To investigate possible subgroup effects (effect modification) with regard to admission prealbumin concentrations, we included interaction terms in the statistical models. We also used the Kaplan-Meier method to visualise outcome data over time by calculating the probability of all-cause mortality within 30 days of randomization.

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

Results

Patient population

From the 2028 patients enrolled in the EFFORT trial, prealbumin levels were available from one study center for 517 (25.5%) (**Figure 1**), of whom 306 (59.2%) patients had low prealbumin levels (<0.17 g/L). Mean patient age (SD) was 71.9 (13.3) years and 277 (53.6%) were male. All patients were at nutritional risk, with 140 (27.1%), 191 (36.9%) and 186 (36.0%) having NRS scores of 3, 4 or 5 and more points. Overall, patients had a high burden of comorbidities and of 511 patients with available CRP measurements, 159 (31.12%) patients had high inflammation with CRP levels ≥ 100 mg/L. **Table 1** shows additional baseline characteristics stratified by prealbumin level. Additional baseline tables stratified by CRP concentrations and randomization can be found in the **Supplementary document**.

Association of admission prealbumin concentrations and clinical outcomes

In a first step, we investigated the prognostic value by calculating the associations of prealbumin with 30- and 180-day outcomes (**Table 2**). In terms of long-term mortality after 180 days, patients with low prealbumin levels had an almost doubling in mortality resulting in an unadjusted HR of 1.88 (95%CI 1.34 to 2.64; $P < 0.001$). These results remained robust in an adjusted model including CRP (HR of 1.52 (95%CI 1.04 to 2.22; $P = 0.03$)) and in a model also including NRS (HR 1.59 (95%CI 1.11 to 2.28; $P = 0.011$)). To further visualize 180-day mortality among different patient subgroups, we calculated Kaplan-Meier survival curves. **Figure 2** shows survival curves stratified by the two prealbumin groups (**Figure 2A**), as well as groups additionally stratified by nutritional risk (i.e., NRS 3-4 points vs. ≥ 5 points) and inflammation (CRP < 100 mg/L vs. ≥ 100 mg/L) (**Figure 2B-E**). All results were significant except for the subgroup of patients in the high inflammation group ($p = 0.066$).

Regarding other adverse outcomes within 30 days, we found significant associations of low baseline prealbumin concentrations with the composite endpoint adverse outcome and length of hospital stay in unadjusted and the adjusted models. For short-term mortality, associations were again significant in the unadjusted models but not in fully adjusted models.

We also compared the prognostic value of prealbumin with established outcome parameters including albumin and NRS with regard to the area under the curve (**Supplementary Table 3**). With an AUC of 0.62, prealbumin showed the best discrimination regarding 180-day mortality and significantly improved the NRS score from AUC 0.60 to 0.66 ($p < 0.001$).

Association of prealbumin concentrations and effectiveness of nutritional support

To understand whether treatment response to nutritional treatment would differ according to admission prealbumin levels, we compared effects of the initial randomization (intervention vs. control) in subgroups of patients according to prealbumin (**Table 3**). These analyses are displayed in a Kaplan-Meier survival function (**Figure 3**) and a forest plot (**Figure 4**). Patients

with normal vs. low prealbumin levels had a similar response to nutritional treatment with regard to 30-day mortality (OR for nutritional support 0.88 vs. 0.90, P interaction=0.823). The same effect was observed within the different CRP subgroups with no evidence for a subgroup effect. Similarly, no differences were found for the composite endpoint adverse outcome and length of hospital stay for these analyses.

Association of nutritional parameters and prealbumin concentrations

Finally, we investigated the association of other nutritional parameters with prealbumin concentration in a linear regression analysis (**Supplemental Table 4**). Change in albumin concentration was associated with significant change in prealbumin, with an increase of 0.071 (95%CI 0.06 to 0.082; $P < 0.001$) units prealbumin for every 10 unit increase in albumin level. Other significant associations were found for CRP, NRS, BMI chronic kidney failure, with lower coefficients. These results are also graphically displayed with correlation graphs between prealbumin and albumin as well as NRS in the **Supplementary Figures**.

Discussion

In this secondary analysis of a large randomized clinical trial, we investigated the prognostic value of serum prealbumin at admission to predict mortality at 180 days and response to nutritional treatment. Our results indicate that among medical inpatients at nutritional risk, prealbumin was a strong prognostic marker for long-term mortality as well as other adverse outcomes with robust results in different statistical models adjusted for other prognostic indicators. Also, prealbumin appeared to be the strongest prognostic indicator when compared with albumin and NRS, and improved the NRS score regarding prognostication. However, the difference in mortality in intervention group patients receiving individualized nutritional support compared to control group patients receiving usual care nutrition was similar in subgroups of patients with normal and low prealbumin levels suggesting that despite its prognostic value,

admission prealbumin concentrations are not helpful in selecting patients for nutritional treatment in a population with elevated nutrition risk (NRS ≥ 3).

Our finding that prealbumin is a prognostic factor among nutritionally at-risk patients is largely in line with previous results.^{31,32,34,35} The strength of this analysis includes the large and well-characterized patient cohort with collection of different nutritional parameters and prospectively collected short- as well as long-term outcomes. We were thus able to rigorously adjust our analyses for potential confounders including markers of inflammation. Importantly, these adjusted analyses for the inflammatory marker CRP suggest that prealbumin provides independent information from inflammation – a condition well known to influence plasma proteins and its precursors, as also shown in the correlation analyses (**Table 4**).³⁴ Still, even though our analysis shows that prealbumin is a strong prognostic factor, it does not offer insight on whether low prealbumin concentrations are part of the pathway to increased mortality or whether it is simply a surrogate marker for more severe illness and therefore correlates with higher mortality. As a limitation to this report, we only had admission prealbumin levels and it thus remains unclear whether prealbumin dynamics over time could help predict clinical outcomes and whether it would be useful to monitor prealbumin concentrations in hospitalized patients to understand the risks for treatment failure.

While nutritional factors likely play an important role regarding the concentration of prealbumin, in the hospital setting there are several other important parameters influencing prealbumin including inflammation and the severity of illness.^{31,36} Thus, similar to albumin, some researchers argue that prealbumin should be considered as a negative acute phase protein reflecting more the acute situation and systemic inflammation and less the nutritional status.^{31,36} In addition, prealbumin concentrations are influenced by different diseases including kidney- or liver failure, as prealbumin is primarily produced in the liver and degraded by the kidneys.^{18,37} Still, some authors see prealbumin as a protein that also reflects the nutritional status of patients.^{18,19,38,39} In fact, a recent study suggested specific cut-offs of transthyretin to define malnutrition.³² Our data also confirm that prealbumin is highly correlated with the NRS score, but may not substitute a nutritional assessment.

Importantly, while most studies have correlated prealbumin with nutritional parameters and clinical outcomes, there is a lack of studies looking at this marker to predict response to nutritional treatment. Herein, this report is to our knowledge the first to investigate the role of prealbumin as a predictor for the effectiveness of nutritional support. In our analysis, response to nutritional treatment did not differ in patients with high or low admission prealbumin concentrations and we found no significant interaction between prealbumin concentrations and effectiveness of nutritional support. However, our data suggest that treatment differs according to the baseline inflammatory status of patients – a result that concurs with a previous analysis from our trial.¹⁰ It is also in line with other trials suggesting less pronounced effects of nutritional support in severely ill patients and in patients with a high degree of inflammation.^{13,40,41} Thus, our results indicate that among medical inpatients at nutritional risk, prealbumin is not an optimal nutritional biomarker to select patients for nutritional support. This conclusion is also supported by a recent consensus paper stating that visceral proteins should not be measured to diagnose malnutrition or guide the indication for nutritional support.^{31,42}

This secondary analysis has several strengths and limitations. To our knowledge, this is the first secondary analysis based on a randomized controlled clinical trial data to investigate whether low prealbumin concentrations are associated with effectiveness of nutritional support. Nonetheless, we only measured prealbumin levels, albumin and CRP but did not measure other biomarkers such as retinol-binding protein.^{34,43} We only had prealbumin in about one fourth of the initial trial population limiting the power of the analysis. This analysis was not done based on a power calculation, but we used all subjects with available prealbumin levels from one site. There was no evidence for a site effect in the original study, but the smaller sample size of this sub-study may explain why confidence intervals were large and effects were not significant, while there was a significant effect reported in the original EFFORT trial.

There are also limitations regarding the underlying trial including selection bias due to inclusion and exclusion criteria, lack of a control group not at nutritional risk, the pragmatic design with some patients not reaching their nutritional goals among others. Thus, results of this secondary

analysis should be rather viewed as hypothesis generating and not definite. For sure, a prospective validation in an independent sample is needed.

In conclusion, this secondary analysis of a randomized clinical trial suggests that among medical inpatients at nutritional risk, low admission prealbumin levels correlate well with different nutritional markers and indicate higher mortality risk, but are not helpful in identifying patients who may or may not respond to nutritional support. Further studies are required to identify nutritional markers that help to further personalize nutritional interventions.

Article Information

C.Bretscher, M.Buergin, G.Gurzeler, N Kaegi, Z.Stanga, B.Mueller and P schuetz equally contributed to the conception and design of the research; C.Gressies, P.Tribolet, D.Lobo and D.Evans contributed to the design of the research and to the interpretation of the data; C.Bretscher and P Schuetz drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflict of interest disclosure:

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The Funders had no rule in design and conduct of this study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit manuscript for publication.

Abbreviations

EFFORT Effect of Early Nutritional treatment on Frailty, Functional Outcomes and Recovery of Malnourished, Medical Inpatients Trial

NRS-2002/NRS Nutritional Risk Screening 2002

ESPEN European Society of Clinical Nutrition and Metabolism

MNA-SF Mini Nutritional Assessment Short Form

MUST Malnutrition Universal Screening Tool

LOS length of hospital stay

EQ-5D 5-level European Quality of Life 5 Dimensions index

EQ-5D VAS self-assessment visual analogue scale

SD Standard Deviation

IQR Interquartile Range

HR Hazard ratio

OR Odds ratio

Coef Coefficient

CI Confidence Intervals

ICD-10 International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

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Table 1. Baseline Characteristics Overall and stratified by Prealbumin concentration

	Overall	Prealbumin ≥ 0.17 g/L	Prealbumin < 0.17 g/L	P value
n	517	211 (40.8%)	306 (59.2%)	
Sociodemographics				
Male sex	277 (53.6%)	107 (50.7%)	170 (55.6%)	0.28
Age				
Mean Age (years), mean (SD)	71.9 (13.3)	72.2 (14.0)	71.8 (12.9)	0.73
Age groups				
<65 years, n (%)	93 (18.0%)	37 (17.5%)	56 (18.3%)	
65-75 years	185 (35.8%)	70 (33.2%)	115 (37.6%)	
>75 years	239 (46.2%)	104 (49.3%)	135 (44.1%)	
Nutritional assessment				
Mean body mass index (kg/m ²), mean (SD)	24.9 (5.2)	25.6 (5.0)	24.5 (5.3)	0.015
Mean body weight (kg), median (IQR)	69.4 (60.2, 82.2)	70.7 (61.5, 82.8)	68.1 (59.1, 82.2)	0.24
NRS 2002 score n (%)				
3 points	140 (27.1%)	65 (30.8%)	75 (24.5%)	
4 points	191 (36.9%)	76 (36.0%)	115 (37.6%)	
≥ 5 points	186 (36.0%)	70 (33.2%)	116 (37.9%)	
Weight loss, n (%)				
$\leq 5\%$ in 3 months	271 (52.4%)	107 (50.7%)	164 (53.6%)	
>5% in 3 months	80 (15.5%)	31 (14.7%)	49 (16.0%)	
>5% in 2 months	62 (12.0%)	24 (11.4%)	38 (12.4%)	
>5% in 1 month	104 (20.1%)	49 (23.2%)	55 (18.0%)	
Loss of appetite, n (%)	459 (88.8%)	178 (84.4%)	281 (91.8%)	0.008
Food intake of normal requirement in the past week, n (%)				
>75%	48 (9.3%)	24 (11.4%)	24 (7.8%)	
50-75%	136 (26.3%)	53 (25.1%)	83 (27.1%)	
25-50%	215 (41.6%)	94 (44.5%)	121 (39.5%)	
<25%	118 (22.8%)	40 (19.0%)	78 (25.5%)	
Severity of illness, n (%)				
very mild	13 (2.5%)	11 (5.2%)	2 (0.7%)	<0.001
mild	313 (60.5%)	137 (64.9%)	176 (57.5%)	
moderate	185 (35.8%)	61 (28.9%)	124 (40.5%)	
severe	6 (1.2%)	2 (0.9%)	4 (1.3%)	
Laboratory measurements				
Admission prealbumin level (g/L), median (IQR)	0.15 (.1, .2)	0.22 (.18, .26)	0.11 (.08, .14)	<0.001
Admission CRP level (mg/L), median (IQR)	43 (12, 120)	12 (4, 38)	81.5 (32.5, 160)	<0.001
Admission albumin level (g/L), median (IQR)	27.5 (23.6, 31.3)	30.7 (27.3, 33.3)	25.4 (22, 28.4)	<0.001
Main admission diagnosis n (%)				
Cardiovascular disease	62 (12.0%)	32 (15.2%)	30 (9.8%)	0.065
Infection	133 (25.7%)	38 (18.0%)	95 (31.0%)	<0.001
Cancer	137 (26.5%)	44 (20.9%)	93 (30.4%)	0.016
Pulmonary disease	28 (5.4%)	10 (4.7%)	18 (5.9%)	0.57
Frailty	31 (6.0%)	16 (7.6%)	15 (4.9%)	0.21
Other	114 (22.1%)	63 (29.9%)	51 (16.7%)	<0.001
Comorbidities n (%)				
Coronary heart disease	113 (21.9%)	50 (23.7%)	63 (20.6%)	0.4
Congestive heart failure	101 (19.5%)	46 (21.8%)	55 (18.0%)	0.28
Hypertension	301 (58.2%)	134 (63.5%)	167 (54.6%)	0.043
Cerebrovascular disease	48 (9.3%)	18 (8.5%)	30 (9.8%)	0.62
Peripheral arterial disease	50 (9.7%)	27 (12.8%)	23 (7.5%)	0.046
Chronic kidney disease	182 (35.2%)	102 (48.3%)	80 (26.1%)	<0.001
Diabetes	112 (21.7%)	49 (23.2%)	63 (20.6%)	0.47
COPD	70 (13.5%)	24 (11.4%)	46 (15.0%)	0.23
Dementia	17 (3.3%)	6 (2.8%)	11 (3.6%)	0.64
Malignant disease	200 (38.7%)	67 (31.8%)	133 (43.5%)	0.007

Table 2. Prognostic value of prealbumin to predict clinical outcomes

*Model 1 unadjusted; Model 2 adjusted for age, sex, main diagnosis, comorbidities, randomization, CRP; Model 3 adjusted for age, sex, main diagnosis, comorbidities, randomization, NRS.

	Prealbumin ≥ 0.17 g/L	Prealbumin < 0.17 g/L	Model 1*		Model 2*		Model 3*	
	n (%) or mean (SD)	n (%) or mean (SD)	OR, HR or Coef (95% CI)	P value	OR, HR or Coef (95% CI)	P value	OR, HR or Coef (95% CI)	P value
Short- and long-term mortality								
All-cause mortality within 30 days (HR)	18/211 (8.5)	48/306 (15.7)	1.9 (1.1-3.26)	0.021	1.41 (0.75-2.64)	0.281	1.6 (0.9-2.85)	0.109
All-cause mortality within 180 days (HR)	47/211 (22.3)	115/306 (37.6)	1.88 (1.34-2.64)	<0.001	1.52 (1.04-2.22)	0.03	1.59 (1.11-2.28)	0.011
Secondary short-term outcomes (30 days)								
Adverse outcome	46/211 (21.8)	100/306 (32.7)	1.74 (1.16-2.61)	0.007	1.65 (1.04-2.63)	0.033	1.65 (1.06-2.57)	0.027
Non-elective hospital readmission (HR)	13/211 (6.2)	28/306 (9.2)	1.51 (0.78-2.92)	0.218	1.72 (0.85-3.5)	0.133	1.53 (0.75-3.09)	0.239
Length of hospital stay	7.658768 (5.4)	9.895425 (7.1)	2.24 (1.11-3.37)	<0.001	2.27 (1.01-3.53)	<0.001	2.36 (1.16-3.57)	<0.001
Secondary long-term outcomes (180 days)								
Non-elective hospital readmission (HR)	63/211 (29.9)	85/306 (27.8)	1.07 (0.77-1.48)	0.701	0.98 (0.69-1.41)	0.933	1.02 (0.72-1.44)	0.911

Table 3. Predictive Value of prealbumin regarding effectiveness of nutritional support

*Adjusted for NRS, Barthel Score

	Prealbumin ≥ 0.17 g/L				Prealbumin < 0.17 g/L				Interaction terms
	Intervention group	Control group	Regression analysis*		Intervention group	Control group	Regression analysis*		
	n (%) or mean (SD)	n (%) or mean (SD)	OR, HR or Coef (95% CI)	P value	n (%) or mean (SD)	n (%) or mean (SD)	OR, HR or Coef (95% CI)	P value	
All-cause mortality within 30 days (HR)									
All patients	9/110 (8.2)	9/101 (8.9)	0.88 (0.35-2.23)	0.792	23/154 (14.9)	25/152 (16.5)	0.9 (0.51-1.59)	0.726	0.823
CRP < 100 mg/l	6/94 (6.4)	9/87 (10.3)	0.59 (0.21-1.65)	0.314	10/94 (10.6)	11/77 (14.3)	0.71 (0.3-1.68)	0.436	0.325
CRP ≥ 100 mg/l	2/13 (15.4)	0/13 (0)	n.a.	n.a.	12/58 (20.7)	14/75 (18.7)	1.23 (0.3-2.69)	0.608	n.a.
Adverse outcome									
All patients	27/110 (24.6)	19/101 (18.8)	1.36 (0.7-2.66)	0.363	49/154 (31.8)	51/152 (33.6)	0.92 (0.57-1.48)	0.727	0.328
CRP < 100 mg/l	24/94 (25.5)	18/87 (20.7)	1.31 (0.65-2.63)	0.457	31/94 (33)	23/77 (29.9)	1.17 (0.61-2.25)	0.636	0.443
CRP ≥ 100 mg/l	2/13 (15.4)	1/13 (7.7)	1.73 (0.11-26.09)	0.691	17/58 (29.3)	28/75 (37.3)	0.72 (0.34-1.52)	0.392	0.546
Length of hospital stay									
All patients	7.05 (4.9)	8.33 (5.7)	-1.32 (-2.76-0.12)	0.073	10.4 (7.8)	9.39 (6.3)	1.04 (-0.56-2.64)	0.203	0.138
CRP < 100 mg/l	7.24 (5.1)	8.29 (5.8)	-1.07 (-2.66-0.53)	0.189	10.73 (7.2)	8.78 (5.3)	1.92 (-0.04-3.88)	0.055	0.23
CRP ≥ 100 mg/l	6.08 (3.7)	9.15 (5.4)	-2.66 (-6.47-1.16)	0.163	10.09 (8.7)	10.01 (7.1)	0.21 (-2.54-2.96)	0.88	0.276

Figure 1. Study flow diagram

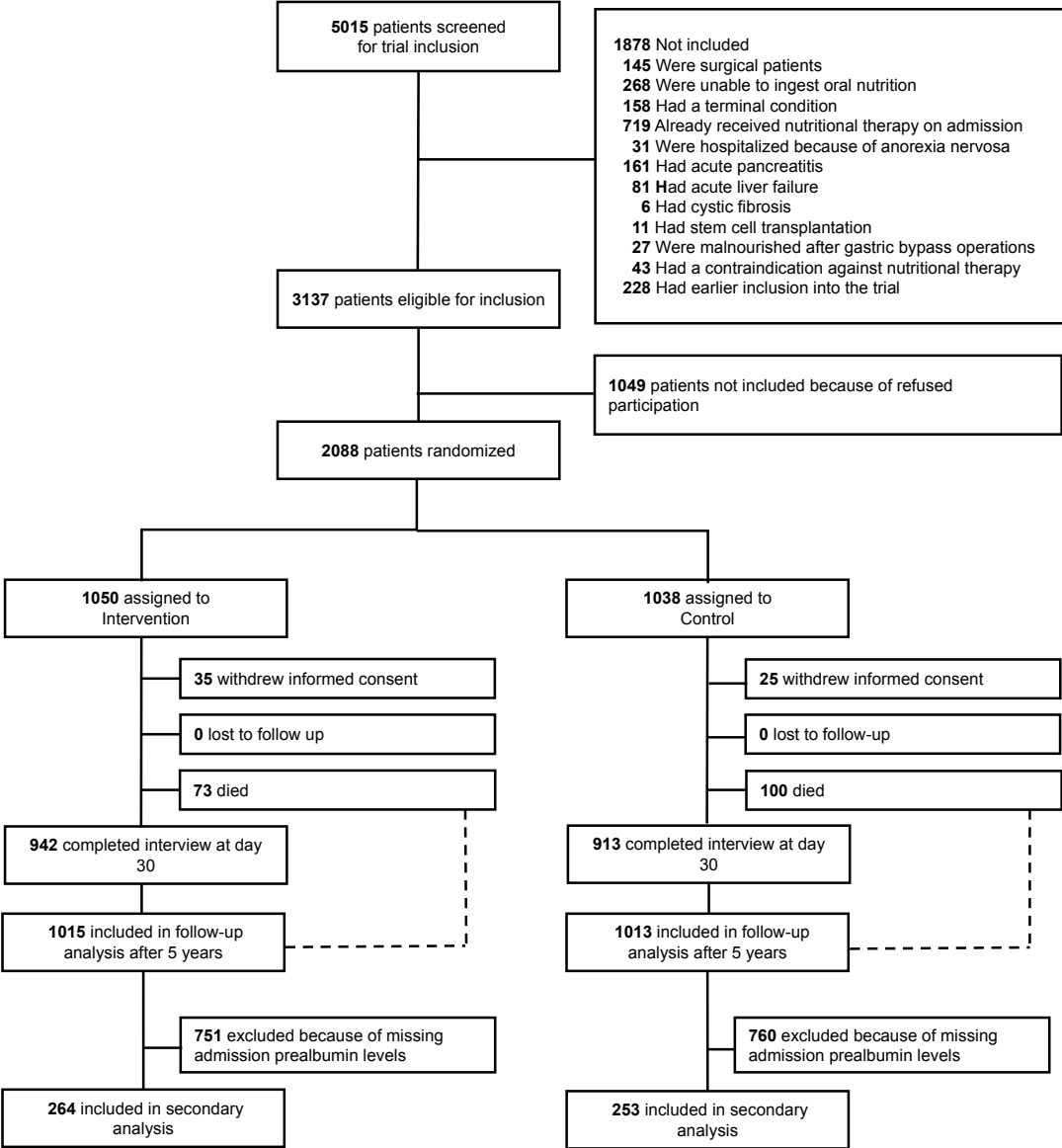
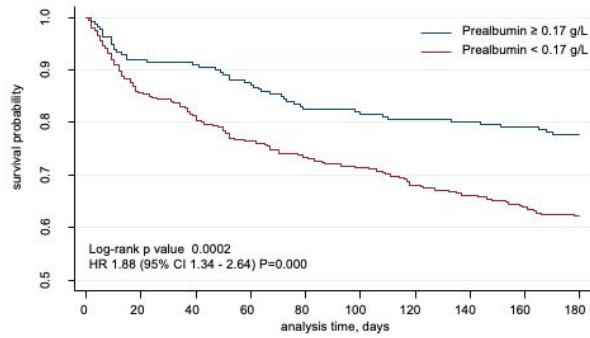


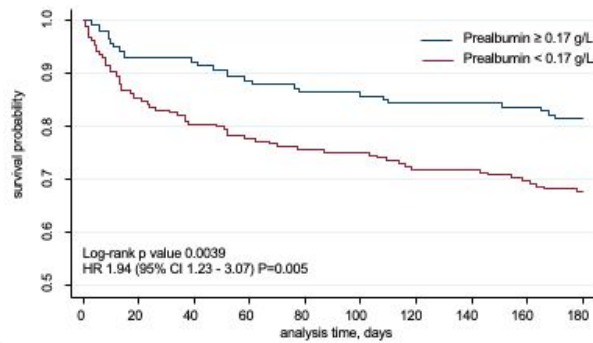
Figure 2. Kaplan-Meier survival estimates for prognostic value

Figure 2A. 180 day mortality in overall population



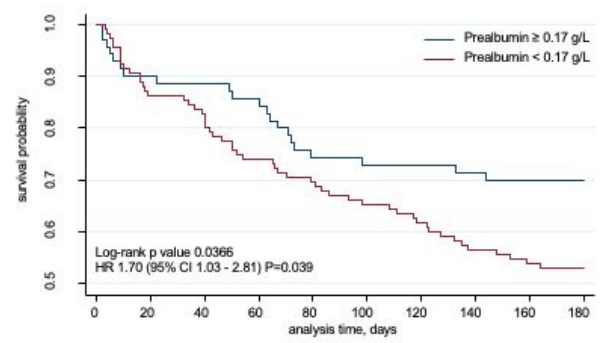
Number at risk		0	20	40	60	80	100	120	140	160	180
Prealbumin ≥ 0.17 g/L		211	194	192	185	174	173	170	169	167	164
Prealbumin < 0.17 g/L		306	262	246	231	222	216	206	200	193	188

Figure 2B. 180 day mortality among patients with moderate nutritional risk (NRS 3-4 points)



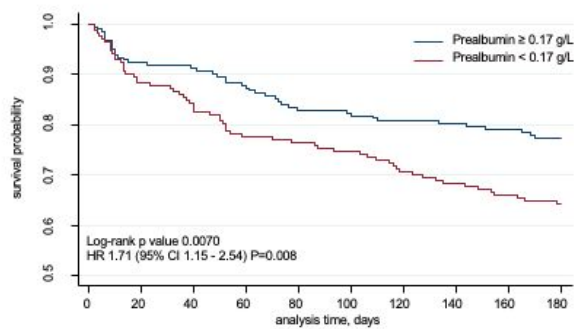
Number at risk		0	20	40	60	80	100	120	140	160	180
Prealbumin ≥ 0.17 g/L		141	131	130	125	122	122	119	119	118	115
Prealbumin < 0.17 g/L		190	162	151	146	142	141	135	135	131	127

Figure 2C. 180 day mortality among patients with high nutritional risk (NRS ≥ 5 points)



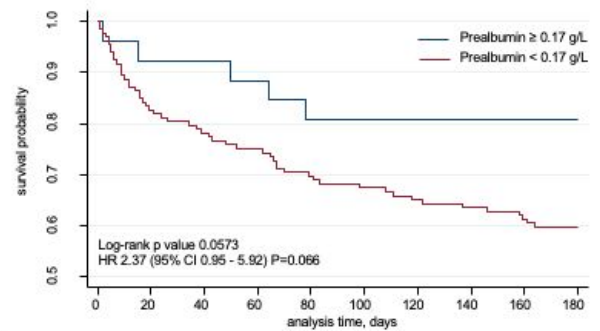
Number at risk		0	20	40	60	80	100	120	140	160	180
Prealbumin ≥ 0.17 g/L		70	63	62	60	52	51	51	50	49	49
Prealbumin < 0.17 g/L		116	100	95	85	80	75	71	65	62	61

Figure 2D. 180 day mortality among patients with low to moderate inflammation (CRP < 100 mg/L)



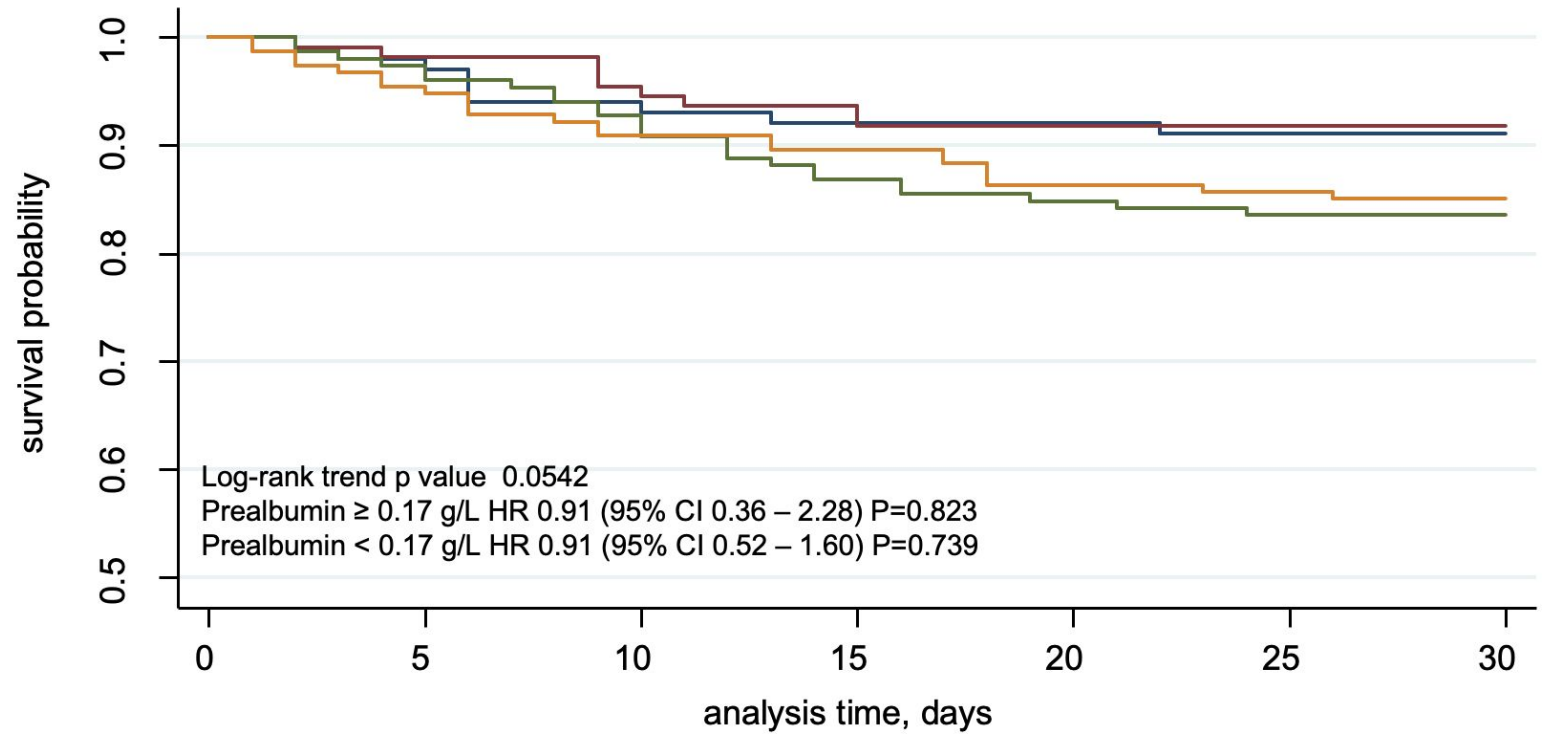
Number at risk		0	20	40	60	80	100	120	140	160	180
Prealbumin ≥ 0.17 g/L		181	167	165	159	150	149	146	145	143	140
Prealbumin < 0.17 g/L		171	151	143	132	130	127	120	116	112	109

Figure 2E. 180 day mortality among patients with high inflammation (CRP ≥ 100 mg/L)



Number at risk		0	20	40	60	80	100	120	140	160	180
Prealbumin ≥ 0.17 g/L		26	24	24	23	21	21	21	21	21	21
Prealbumin < 0.17 g/L		133	110	102	98	91	88	85	83	80	78

Figure 3. Kaplan-Meier survival estimates for predictive value



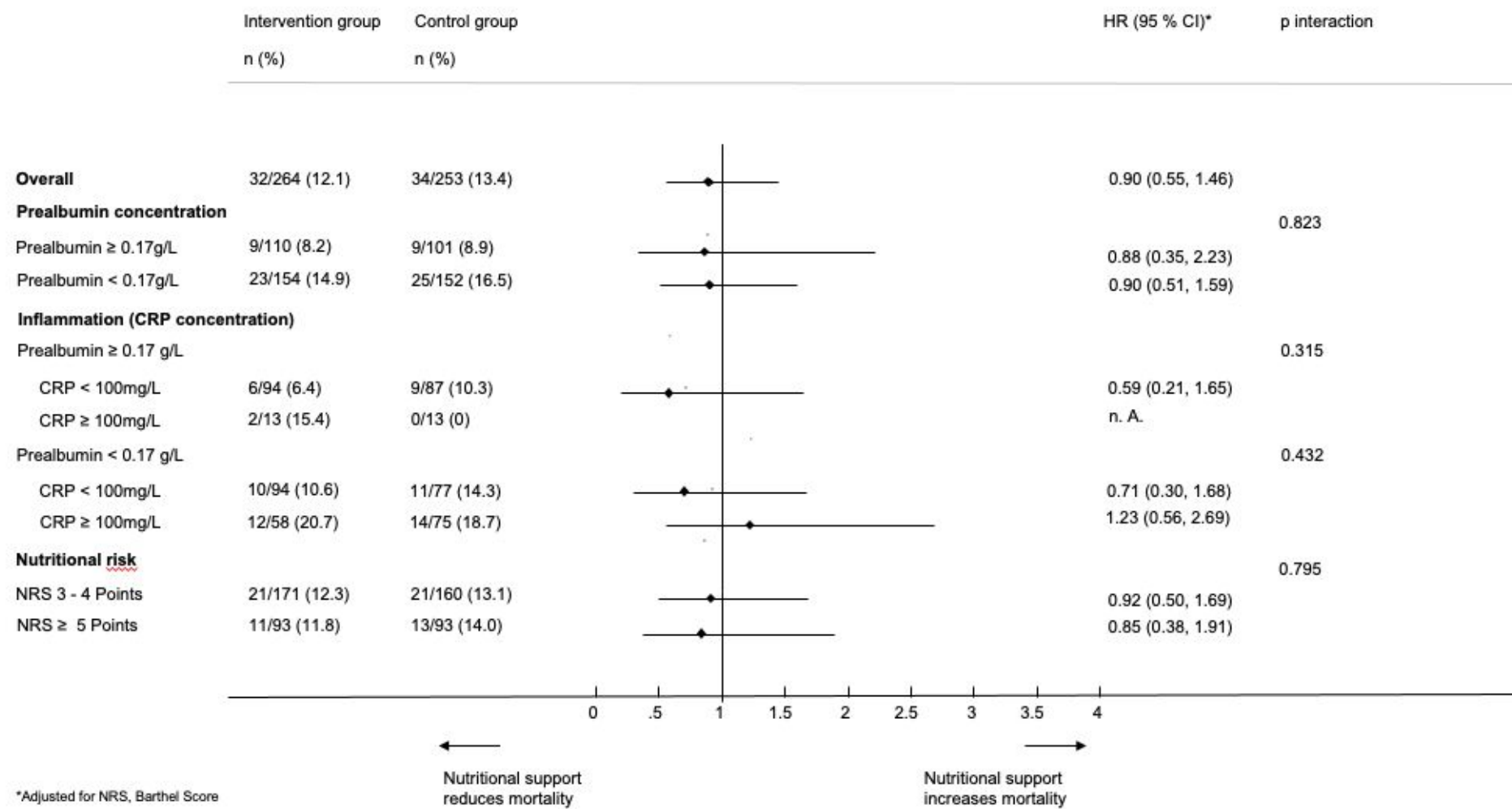
Prealbumin \geq 0.17 g/L

Control group	—	101	99	95	93	93	92	92
Intervention group	—	110	108	105	103	101	101	101

Prealbumin $<$ 0.17 g/L

Control group	—	152	148	141	132	129	127	127
Intervention group	—	154	147	140	138	133	132	131

Figure 4. Forest plot for 30-day mortality, subgroup analysis for response to nutritional support.



Supplementary Materials

The association between prealbumin, all-cause mortality and response to nutritional treatment in patients at nutritional risk.

Secondary analysis of a randomized-controlled trial

Brief title: Prealbumin in patients at nutritional risk

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Definition of outcomes assessed during the initial trial

- The primary composite endpoint consists of adverse clinical outcomes within 30 days defined as follows:
 - (a) Mortality defined as all-cause mortality from inclusion to day 30
 - (b) ICU admission defined as admission to the intensive care unit from the medical ward from inclusion to day 30
 - (c) Non-elective hospital readmission defined as non-scheduled hospital readmission after discharge from the index hospital stay to day 30
 - (d) Major complications defined as the following complications occurring from inclusion (i.e., not present at the time of inclusion) to day 30
 - I. Adjudicated nosocomial infection or abscess requiring antibiotic treatment
 - II. respiratory failure with need for invasive or non-invasive ventilation (continuous positive airway pressure, CPAP)
 - III. major cardiovascular events including stroke, intracranial bleeding, cardiac arrest, myocardial infarction with and without invasive procedure and pulmonary embolism
 - IV. acute renal failure (defined by 2x increase of baseline creatinine or new requirement of dialysis due to volume overload or electrolyte disturbance)
 - V. gastro-intestinal events (hemorrhage, intestinal perforation, pancreatitis [defined as 2 out of 3 criteria: abdominal pain, 3-fold increase in lipase or pancreas-specific amylase, characteristic imaging findings])
 - (e) decline in functional status of 10% or more from admission to day 30 measured by the Barthel's index.¹ This index measures performance in activities of daily living and comprises two groups of items, one related to self-care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use), the other related to mobility (ambulation, transfers, and stair climbing). We used the German translation which has a score ranging from 100 to 0 with lower scores indicating more severe disability.

- *Secondary endpoints* assessed were defined as follows:
 - (a) each single component of the primary endpoint at day 30
 - (b) Longterm mortality at 180 days
 - (c) daily protein and energy intake as assessed by clinical nurses and trained registered dieticians using food records for each patients` meal

- (d) total length of hospital stay defined as total in-hospital days during the index hospital stay from inclusion to day 30
 - (e) quality of life measured on admission and at 30-day day using the EuroQol Group 5-Dimension Self-Report Questionnaire.² This included the European Quality of Life 5 Dimensions index (values range from 0 to 1, with higher scores indicating better life quality) and the visual-analogue scale (EQ-5D VAS) (scores range from 0 to 100, with higher scores indicating better health status).
- Safety endpoints including side effects from nutritional therapy are daily assessed until hospital discharge and are defined as:
 - a) adverse gastrointestinal effects defined as obstipation, diarrhea, nausea, vomiting, abdominal pain
 - b) complications related to enteral nutrition (defined as any complications associated with tube feeding) or parenteral nutrition (defined as any complications associated with central venous catheter)
 - c) refeeding syndrome defined according to a recent consensus definition^{3,4} as electrolyte shifts (e.g., decrease in Phosphate, Magnesium, Potassium) suggestive of refeeding syndrome in conjunction with typical clinical symptoms (e.g., peripheral or acute lung edema)
 - d) liver or gall bladder dysfunction
 - e) hyperglycemia (defined as persistent levels >10mmol/l in patients without diabetes or well controlled diabetes)

Supplementary table 1. Baseline Characteristics Overall and stratified by CRP serum concentration

	Overall	CRP ≥ 100 mg/l	CRP < 100 mg/l	P value
n	517	159 (30.8%)	352 (68.1%)	
Sociodemographics				
Male sex	277 (53.6%)	90 (56.6%)	185 (52.6%)	0.4
Age				
Mean Age (years), mean (SD)	71.9 (13.3)	69.7 (14.3)	72.9 (12.7)	0.012
Age groups				
<65 years, n (%)	93 (18.0%)	36 (22.6%)	56 (15.9%)	
65-75 years	185 (35.8%)	60 (37.7%)	123 (34.9%)	
>75 years	239 (46.2%)	63 (39.6%)	173 (49.1%)	
Nutritional assessment				
Mean body mass index (kg/m ²), mean (SD)	24.9 (5.2)	25.6 (5.7)	24.6 (4.9)	0.059
Mean body weight (kg), median (IQR)	69.4 (60.2, 82.2)	73.6 (62.7, 84.5)	68.0 (59.0, 80.6)	0.022
NRS 2002 score n (%)				
3 points	140 (27.1%)	30 (18.9%)	109 (31.0%)	
4 points	191 (36.9%)	64 (40.3%)	126 (35.8%)	
≥5 points	186 (36.0%)	65 (40.9%)	117 (33.2%)	
Weight loss, n (%)				
≤5% in 3 months	271 (52.4%)	84 (52.8%)	183 (52.0%)	0.93
>5% in 3 months	80 (15.5%)	26 (16.4%)	54 (15.3%)	
>5% in 2 months	62 (12.0%)	20 (12.6%)	42 (11.9%)	
>5% in 1 month	104 (20.1%)	29 (18.2%)	73 (20.7%)	
Loss of appetite, n (%)				
459 (88.8%)	148 (93.1%)	306 (86.9%)	0.041	
Food intake of normal requirement in the past week, n (%)				
>75%	48 (9.3%)	12 (7.5%)	35 (9.9%)	0.42
50-75%	136 (26.3%)	38 (23.9%)	97 (27.6%)	
25-50%	215 (41.6%)	67 (42.1%)	147 (41.8%)	
<25%	118 (22.8%)	42 (26.4%)	73 (20.7%)	
Severity of illness, n (%)				
very mild	13 (2.5%)	2 (1.3%)	11 (3.1%)	<0.001
mild	313 (60.5%)	69 (43.4%)	240 (68.2%)	
moderate	185 (35.8%)	84 (52.8%)	100 (28.4%)	
severe	6 (1.2%)	4 (2.5%)	1 (0.3%)	
Laboratory measurements				
Admission prealbumin level (g/L), median (IQR)	0.15 (.1, .2)	0.1 (.07, .14)	0.17 (.12, .22)	<0.001
Admission CRP level (mg/L), median (IQR)	43 (12, 120)	160 (130, 210)	21 (6.5, 45)	<0.001
Admission albumin level (g/L), median (IQR)	27.5 (23.6, 31.3)	24 (20.7, 26.7)	28.9 (25.9, 32.6)	<0.001
Main admission diagnosis n (%)				
Cardiovascular disease	62 (12.0%)	2 (1.3%)	58 (16.5%)	<0.001
Infection	133 (25.7%)	79 (49.7%)	52 (14.8%)	<0.001
Cancer	137 (26.5%)	48 (30.2%)	89 (25.3%)	0.25
Pulmonary disease	28 (5.4%)	7 (4.4%)	21 (6.0%)	0.47
Frailty	31 (6.0%)	8 (5.0%)	23 (6.5%)	0.51
Other	114 (22.1%)	13 (8.2%)	99 (28.1%)	<0.001
Comorbidities n (%)				
Coronary heart disease	113 (21.9%)	25 (15.7%)	86 (24.4%)	0.027
Congestive heart failure	101 (19.5%)	17 (10.7%)	84 (23.9%)	<0.001
Hypertension	301 (58.2%)	87 (54.7%)	209 (59.4%)	0.32
Cerebrovascular disease	48 (9.3%)	12 (7.5%)	36 (10.2%)	0.34
Peripheral arterial disease	50 (9.7%)	9 (5.7%)	41 (11.6%)	0.035
Chronic kidney disease	182 (35.2%)	40 (25.2%)	141 (40.1%)	0.001
Diabetes	112 (21.7%)	31 (19.5%)	80 (22.7%)	0.41
COPD	70 (13.5%)	21 (13.2%)	47 (13.4%)	0.96
Dementia	17 (3.3%)	0 (0.0%)	17 (4.8%)	0.005
Malignant disease	200 (38.7%)	75 (47.2%)	123 (34.9%)	0.009

Supplementary table 2. Baseline Characteristics Overall and stratified by randomization group

	overall	Control	Intervention	P value
n	517	253 (48.9%)	264 (51.1%)	
Sociodemographics				
Male sex	277 (53.6%)	134 (53.0%)	143 (54.2%)	0.78
Age				
Mean Age (years), mean (SD)	71.9 (13.3)	71.5 (13.7)	72.3 (13.0)	0.48
Age groups				
< 65 years, n (%)	93 (18.0%)	51 (20.2%)	42 (15.9%)	
65-75 years	185 (35.8%)	84 (33.2%)	101 (38.3%)	
>75 years	239 (46.2%)	118 (46.6%)	121 (45.8%)	
Nutritional assessment				
Mean body mass index (kg/m2), mean (SD)	24.9 (5.2)	24.7 (5.2)	25.1 (5.3)	0.34
Mean body weight (kg), median (IQR)	69.4 (60.2, 82.2)	68.1 (59.5, 82.2)	70.0 (60.8, 82.2)	0.39
NRS 2002 score n (%)				
3 points	140 (27.1%)	68 (26.9%)	72 (27.3%)	
4 points	191 (36.9%)	92 (36.4%)	99 (37.5%)	
≥5 points	186 (36.0%)	93 (36.8%)	93 (35.2%)	
Weight loss, n (%)				
≤5% in 3 months	271 (52.4%)	134 (53.0%)	137 (51.9%)	
>5% in 3 months	80 (15.5%)	39 (15.4%)	41 (15.5%)	
>5% in 2 months	62 (12.0%)	35 (13.8%)	27 (10.2%)	
>5% in 1 month	104 (20.1%)	45 (17.8%)	59 (22.3%)	
Loss of appetite, n (%)	459 (88.8%)	224 (88.5%)	235 (89.0%)	0.86
Food intake of normal requirement in the past week, n (%)				
>75%	48 (9.3%)	30 (11.9%)	18 (6.8%)	
50-75%	136 (26.3%)	63 (24.9%)	73 (27.7%)	
25-50%	215 (41.6%)	103 (40.7%)	112 (42.4%)	
<25%	118 (22.8%)	57 (22.5%)	61 (23.1%)	
Severity of illness, n (%)				
very mild	13 (2.5%)	4 (1.6%)	9 (3.4%)	
mild	313 (60.5%)	150 (59.3%)	163 (61.7%)	
moderate	185 (35.8%)	96 (37.9%)	89 (33.7%)	
severe	6 (1.2%)	3 (1.2%)	3 (1.1%)	
Laboratory measurements				
Admission prealbumin level (g/L), median (IQR)	0.15 (.1, .2)	0.15 (.09, .19)	0.15 (.1, .21)	0.23
Admission CRP level (mg/L), median (IQR)	43 (12, 120)	56.5 (11, 130)	37 (12, 110)	0.20
Admission albumin level (g/L), median (IQR)	27.5 (23.6, 31.3)	27 (23.3, 31.3)	27.8 (23.8, 31)	0.52
Main admission diagnosis n (%)				
Cardiovascular disease	62 (12.0%)	30 (11.9%)	32 (12.1%)	0.93
Infection	133 (25.7%)	78 (30.8%)	55 (20.8%)	0.009
Cancer	137 (26.5%)	68 (26.9%)	69 (26.1%)	0.85
Pulmonary disease	28 (5.4%)	15 (5.9%)	13 (4.9%)	0.61
Frailty	31 (6.0%)	13 (5.1%)	18 (6.8%)	0.42
Other	114 (22.1%)	45 (17.8%)	69 (26.1%)	0.022
Comorbidities n (%)				
Coronary heart disease	113 (21.9%)	51 (20.2%)	62 (23.5%)	0.36
Congestive heart failure	101 (19.5%)	51 (20.2%)	50 (18.9%)	0.73
Hypertension	301 (58.2%)	137 (54.2%)	164 (62.1%)	0.066
Cerebrovascular disease	48 (9.3%)	21 (8.3%)	27 (10.2%)	0.45
Peripheral arterial disease	50 (9.7%)	27 (10.7%)	23 (8.7%)	0.45
Chronic kidney disease	182 (35.2%)	88 (34.8%)	94 (35.6%)	0.84
Diabetes	112 (21.7%)	58 (22.9%)	54 (20.5%)	0.50
COPD	70 (13.5%)	37 (14.6%)	33 (12.5%)	0.48
Dementia	17 (3.3%)	6 (2.4%)	11 (4.2%)	0.25
Malignant disease	200 (38.7%)	96 (37.9%)	104 (39.4%)	0.74

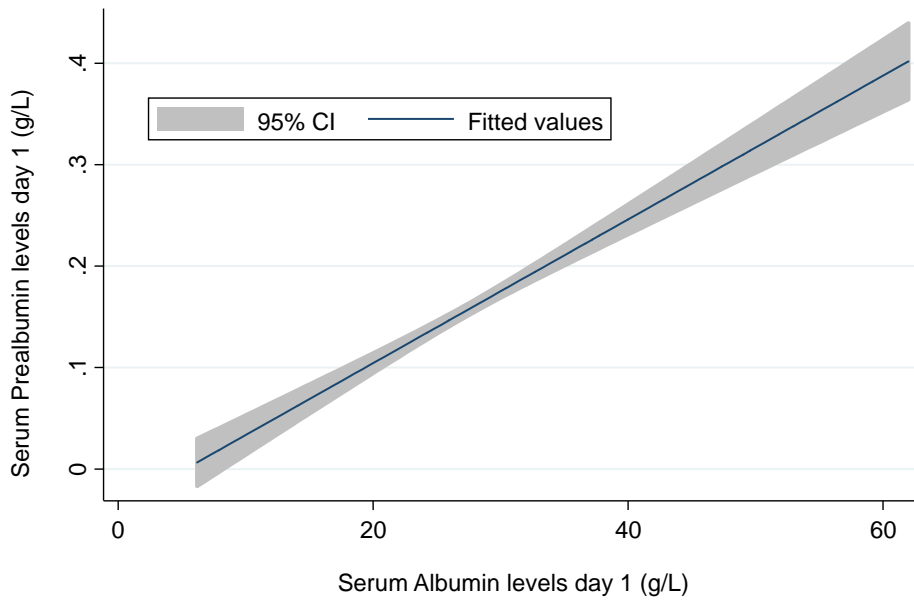
Supplementary table 3. Prognostic value of prealbumin, albumin and NRS in regard to the area under the curve (AUC)

	n (%) or n (SD)	Prealbumin	Albumin		NRS		NRS + Prealbumin	
		AUC (95% CI)	AUC (95% CI)	P value	AUC (95% CI)	P value	AUC (95% CI)	P value vs NRS
Short- and long-term mortality								
All-cause mortality within 30 days	66/517 (12.8)	0.63 (0.56-0.71)	0.56 (0.48-0.64)	0.0822	0.49 (0.42-0.56)	0.0028	0.63 (0.56-0.71)	0.0023
All-cause mortality within 180 days	162/517 (31.3)	0.62 (0.57-0.68)	0.58 (0.53-0.63)	0.1256	0.4 (0.36-0.45)	<0.001	0.66 (0.61-0.71)	<0.001
Secondary short-term outcomes (30 days)								
Adverse outcome	146/517 (28.2)	0.59 (0.53-0.64)	0.53 (0.47-0.59)	0.0515	0.47 (0.42-0.53)	0.0032	0.59 (0.54-0.64)	0.0055
Non-elective hospital readmission	41/517 (9.1)	0.53 (0.44-0.62)	0.51 (0.42-0.61)	0.746	0.48 (0.4-0.56)	0.4793	0.52 (0.43-0.62)	0.6104
Secondary long-term outcomes (180 days)								
Non-elective hospital readmission	148/517 (28.6)	0.47 (0.42-0.53)	0.47 (0.41-0.52)	0.7876	0.52 (0.47-0.58)	0.1948	0.55 (0.49-0.6)	0.3873

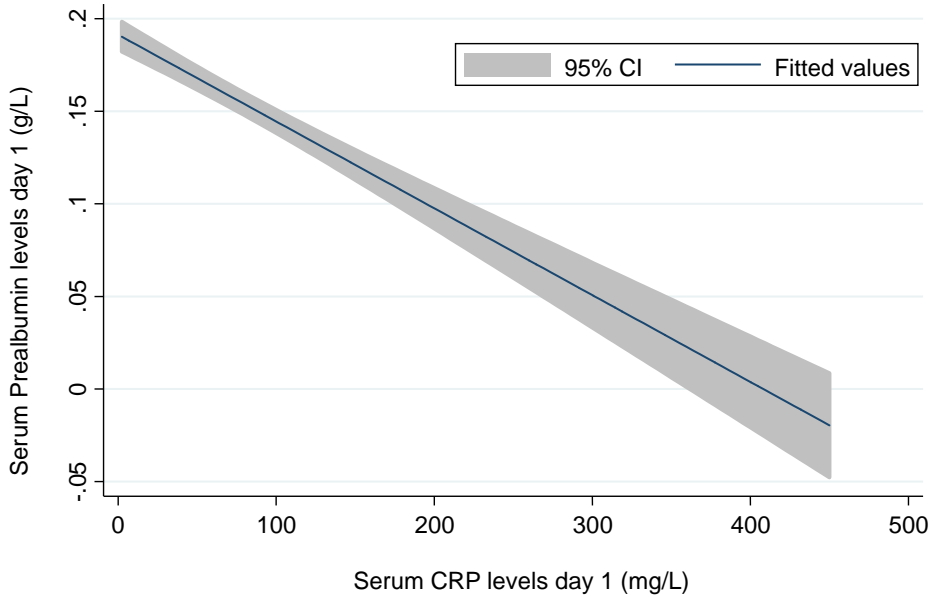
Supplemental Table 4. Linear regression analysis investigating associations of different variables on prealbumin level in g/L

	Univariate analysis		Multivariate analysis	
	Coef (95% CI)	P value	Coef (95% CI)	P value
Albumin (change by 10 units)	0.071 (0.060, 0.082)	<0.001	0.047 (0.035, 0.059)	<0.001
CRP (change by 100 units)	-0.047 (-0.054, -0.040)	<0.001	-0.030 (-0.038, -0.022)	<0.001
NRS (change by 1 unit)	-0.009 (-0.017, -0.002)	0.015	0.001 (-0.005, 0.008)	0.655
BMI (change by 1 unit)	0.002 (0.001, 0.003)	0.003	0.002 (0.001, 0.003)	0.001
Kidney failure	0.038 (0.024, 0.052)	<0.001	0.028 (0.016, 0.040)	<0.001
Cancer	-0.016 (-0.030, -0.003)	0.021	0.002 (-0.010, 0.014)	0.775

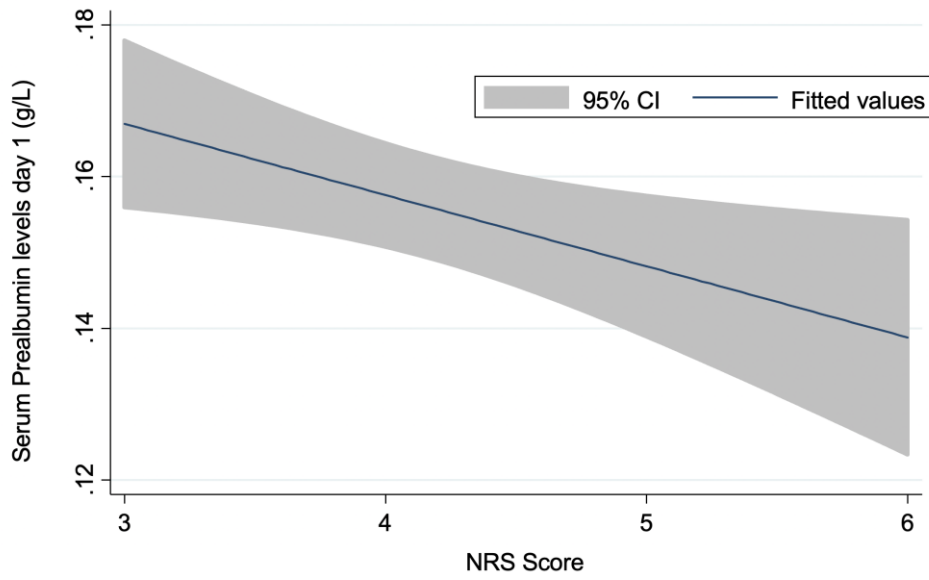
Supplementary figure 1. Correlation of prealbumin with albumin



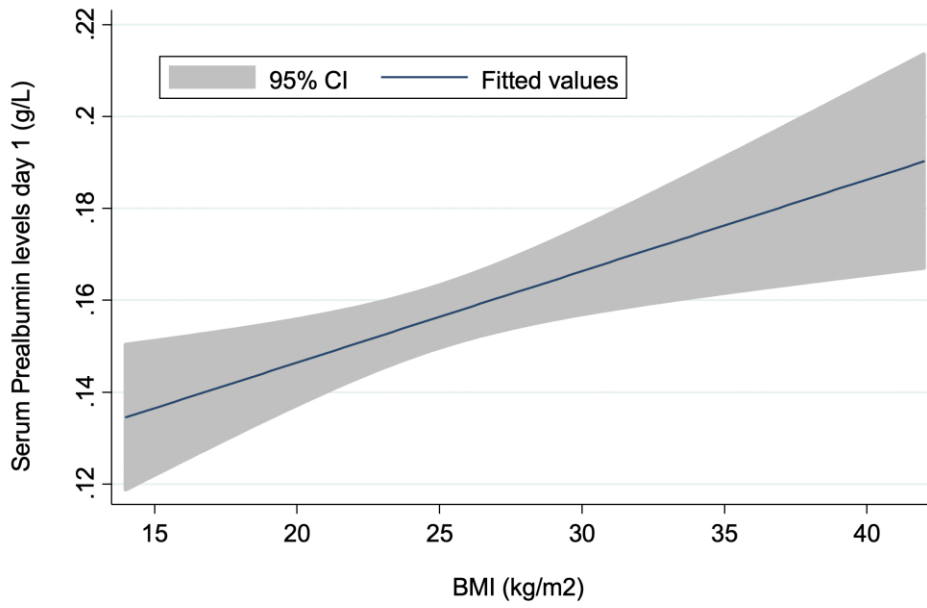
Supplementary figure 2. Correlation of prealbumin with CRP



Supplementary figure 3. Correlation of prealbumin with NRS



Supplementary figure 4. Correlation of prealbumin with BMI



References

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