Nina Kaegi ORCID iD: 0000-0003-4015-295X

Dileep Lobo ORCID iD: 0000-0003-1187-5796

David Evans ORCID iD: 0000-0001-7366-3567

Philipp Schuetz ORCID iD: 0000-0001-6400-4949

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

Céline Bretscher, MD [a,b*]; Michelle Buergin [a,b*]; Gianna Gurzeler [a,b*]; Nina Kägi-Braun, MD [a]; Carla Gressies[a], Pascal Tribolet[a,c], Prof Dileep N. Lobo, MD [d,e]; David C. Evans, MD [f]; Prof Zeno Stanga, MD [g]; Prof Beat Mueller, MD [a,b]; and Prof Philipp Schuetz, MD [a,b] for the EFFORT study team

[*]equally first authors

[a] Medical University Department, Division of General Internal and Emergency Medicine, Kantonsspital Aarau, Aarau, Switzerland

[b] Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland

[c] Department of Health Professions, Bern University of Applied Sciences, Bern, Switzerland;

[d] Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Queen's Medical Centre, Nottingham, UK

[e] MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham, Queen's Medical Centre, Nottingham, UK

[f] Trauma / Critical Care Surgery, Ohio Health Grant Medical Center, Columbus, Ohio, USA

[g] Division of Diabetology, Endocrinology, Nutritional Medicine, and Metabolism, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jpen.2470.

Correspondence and reprint requests:

Prof. Dr. med. Philipp Schuetz, MD, MPH
University Department of Medicine
Kantonsspital Aarau
Tellstrasse
CH-5001 Aarau, Switzerland
E-mail: schuetzph@gmail.com

Manuscript word count: 2715

Keywords: malnutrition; nutritional support; outcomes; prealbumin; biomarker; visceral proteins

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 medicals 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 metanalyses 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 albumin[14] 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 trial[5], 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 1.2.64; 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 levelv. 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 morality 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 (**Supplementary 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 shcuetz 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:

Funding/Support:

The Swiss National Science Foundation (SNSF) (PP00P3_150531) and the Research Council of the Kantonsspital Aarau (1410.000.058 and 1410.000.044) provided funding for the trial. The funders had no role in data collection, analysis, interpretation, writing of the manuscript and the decision to submit. There was no commercial involvement in the trial.

The Institution of P.Schuetz has previously received unrestricted grant money unrelated to this project from Neste Health Science and Abbott Nutrition. The institution of Z.Stanga received speaking honoraria and research support from Neste Health Science, Abbott Nutrition and Fresenius Kabi. All other authors report no conflicts of interest.

Role of the Funder/ Sponsor:

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	Prealbumin <0.17	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				0.49
<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/m2), 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,	70.7 (61.5, 82.8)	68.1 (59.1, 82.2)	0.24
NRS 2002 score n (%)				0.26
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 (%)				0.54
<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				0.18
>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 (%)				**<0.001**
very mild	13 (2.5%)	11 (5.2%)	2 (0.7%)	
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,	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	**Prealbumin**	**Model 1***		**Model 2***		**Model 3***	
	n (%) or	n (%) or	OR, HR or	P	OR, HR or	P	OR, HR or	P
Short- and long-term mortality								
All-cause mortality	18/211 (8.5)	48/306	1.9 (1.1-3.26)	**0.021**	1.41 (0.75-	0.281	1.6 (0.9-2.85)	0.109

All-cause mortality	47/211	115/306	1.88 (1.34-	**<0.001**	1.52 (1.04-	**0.03**	1.59 (1.11-	**0.011**
Secondary short-term outcomes								
Adverse outcome	46/211	100/306	1.74 (1.16-	**0.007**	1.65 (1.04-	**0.033**	1.65 (1.06-	**0.027**
Non-elective hospital	13/211 (6.2)	28/306 (9.2)	1.51 (0.78-	0.218	1.72 (0.85-3.5)	0.133	1.53 (0.75-	0.239
Length of hospital stay	7.658768	9.895425	2.24 (1.11-	**<0.001**	2.27 (1.01-	**<0.001**	2.36 (1.16-	**<0.001**
Secondary long-term outcomes								
Non-elective hospital	63/211	85/306	1.07 (0.77-	0.701	0.98 (0.69-	0.933	1.02 (0.72-	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**				
	Intervention group	**Control group**	**Regression analysis***		**Intervention group**	**Control group**	**Regression analysis***		**Interaction terms**
	n (%) or mean (SD)	n (%) or mean (SD)	OR, HR or Coef (95%	P value	n (%) or mean (SD)	n (%) or mean	OR, HR or Coef (95%	P value	P interaction*
All-cause mortality within 30 days (HR)									
All	9/110 (8.2)	9/101	0.88	0.792	23/154	25/152	0.9	0.726	0.823
CRP	6/94 (6.4)	9/87	0.59	0.314	10/94 (10.6)	11/77	0.71	0.436	0.325
CRP	2/13 (15.4)	0/13 (0)	n.a.	n.a.	12/58 (20.7)	14/75	1.23	0.608	n.a.
Adverse outcome									
All	27/110	19/101	1.36	0.363	49/154	51/152	0.92	0.727	0.328
CRP	24/94 (25.5)	18/87	1.31	0.457	31/94 (33)	23/77	1.17	0.636	0.443
CRP	2/13 (15.4)	1/13	1.73	0.691	17/58 (29.3)	28/75	0.72	0.392	0.546
Length of hospital stay									
All	7.05 (4.9)	8.33	-1.32 (-	0.073	10.4 (7.8)	9.39	1.04 (-	0.203	0.138
CRP	7.24 (5.1)	8.29	-1.07 (-	0.189	10.73 (7.2)	8.78	1.92 (-	0.055	0.23
CRP	6.08 (3.7)	9.15	-2.66 (-	0.163	10.09 (8.7)	10.01	0.21 (-	0.88	0.276

Figure 1. Study flow diagram

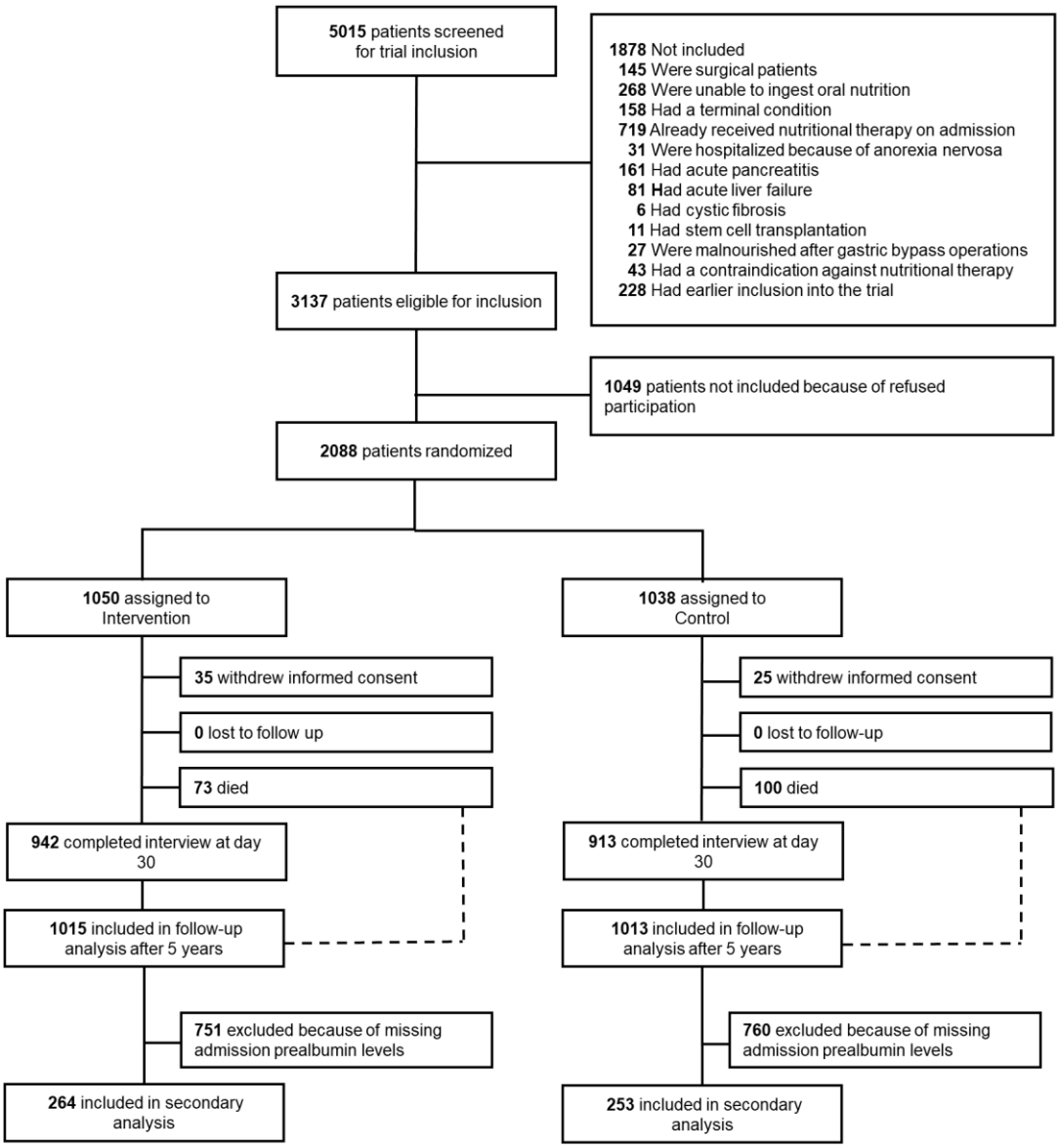

Figure 2. Kaplan-Meier survival estimates for prognostic value

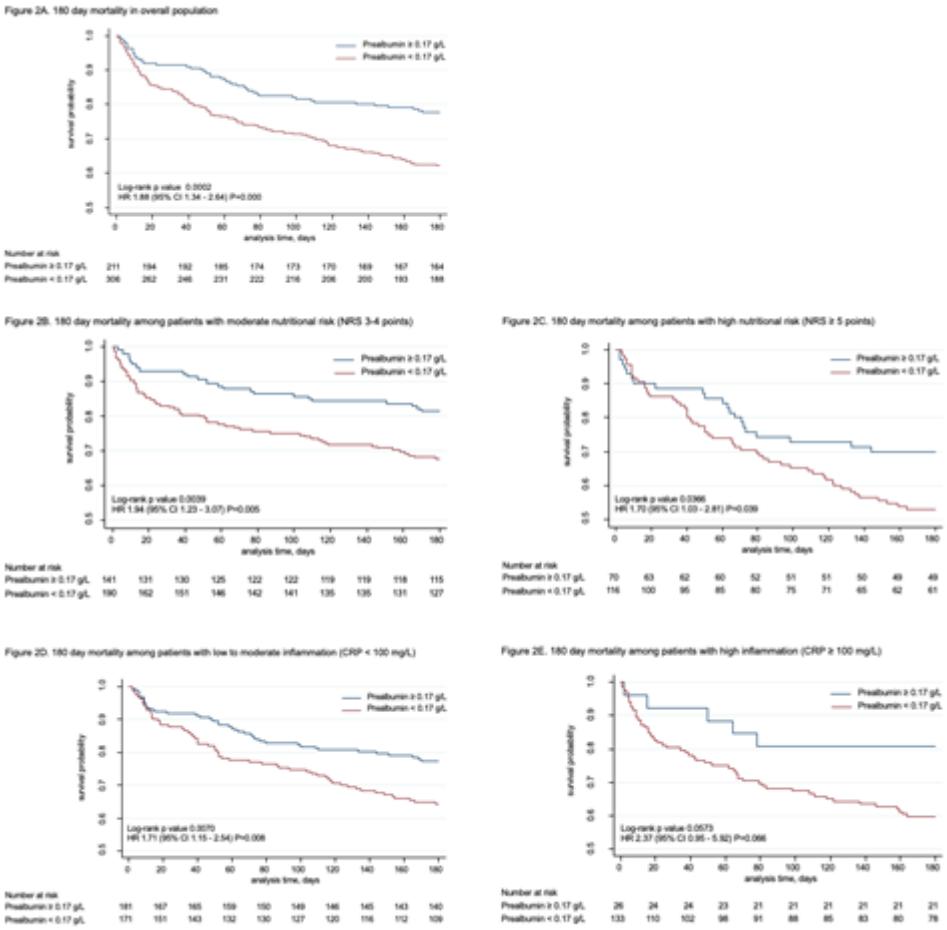

Figure 3. Kaplan-Meier survival estimates for predictive value

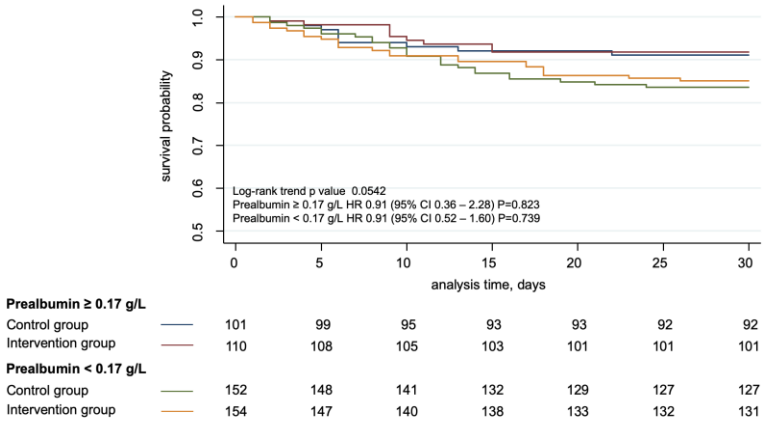

Figure 4. Forest plot for 30-day mortality, subgroup analysis for response to nutritional support.