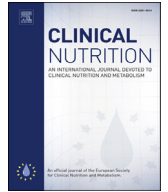




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## Randomized Control Trials

## Six-month outcomes after individualized nutritional support during the hospital stay in medical patients at nutritional risk: Secondary analysis of a prospective randomized trial

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## SUMMARY

**Background:** Among medical inpatients at risk of malnutrition, the use of individualized nutritional support during the hospital stay was found to reduce complications and improve mortality at short-term. We evaluated clinical outcomes at 6-months follow-up.

**Methods:** We randomly assigned 2028 patients to receive protocol-guided individualized nutritional support to reach protein and energy goals (intervention group) or hospital food as usual (control group) during the hospital stay. The intervention was discontinued at hospital discharge and further nutritional support was based on the discretion of the treating team. We had complete follow-up information of 1995 patients (98%), which were included in the final analysis. The primary endpoint was all-cause mortality at 6-months. Prespecified secondary end points included non-elective hospital readmissions, functional outcome and quality of life.

**Results:** At 6-month, 231 of 994 (23.2%) intervention group patients had died compared to 246 of 999 (24.6%) control group patients, resulting in a hazard ratio for death of 0.90 (95%CI 0.76 to 1.08,  $p = 0.277$ ). Compared to control patients, intervention group patients had similar rates of hospital readmission (27.3% vs. 27.6%, HR 1.00 (95%CI 0.84 to 1.18),  $p = 0.974$ ), falls (11.2% vs. 10.9%, HR 0.96 (95%CI 0.72 to 1.27),  $p = 0.773$ ) and similar quality of life and activities of daily living scores.

**Interpretation:** While individualized nutritional support during the hospital stay significantly reduced short-term mortality, there was no legacy effect on longer term outcomes. Future trials should investigate whether continuation of nutritional support after hospital discharge reduces the high malnutrition-associated mortality rates in this vulnerable patient population.

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## 1. Introduction

Malnutrition is a serious public health problem affecting 30–50% of medical inpatients [1–4]. Acute and chronic illnesses have strong effects on protein and energy homeostasis, protein catabolism, hormonal function and appetite leading to weight loss and sarcopenia with progressive deterioration of nutritional status [5]. Poor nutritional status, in turn, is associated with higher mortality and morbidity, functional decline, prolonged hospital stay, and increased health care costs [2,6]. To prevent these malnutrition-related adverse medical outcomes, current clinical nutrition guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) [4] and the American Society for Parenteral and Enteral Nutrition (ASPEN) [7] recommend an active approach with early start of nutritional support in hospitalized patients at nutritional risk. These recommendations are based on physiological rationales and also several randomized trials and meta-analyses of such trials showing that nutritional support provided during hospitalization has a beneficial effect on clinical outcomes [8–12]. Among these trials, the *Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial* (EFFORT) recently reported positive effects of individualized nutritional support during the hospital stay in medical inpatients at risk for malnutrition [13]. Intervention group patients included in EFFORT received protocolized individual nutritional support to reach protein and energy goals, which was, however, terminated after hospital discharge. Compared to control group patients, patients receiving individual nutritional support had a significant reduction in risks for complications and mortality at short-term, i.e., within 30 days, with also improvements in quality of life and functional outcomes.

Still, it remains unclear whether an intervention that focuses on the inpatient time period only will affect clinical outcomes over a prolonged period, or whether additional nutritional interventions in the outpatient setting would be necessary to improve and sustain malnutrition-related adverse outcomes and mortality. Herein, we evaluated the predefined clinical outcomes at 6-months follow-up in participants included in the EFFORT trial [13].

## 2. Materials and methods

### 2.1. Study design, registration and oversight

EFFORT was a pragmatic, investigator-initiated, open-label, non-blinded, randomized-controlled trial, that was undertaken in eight Swiss hospitals. The rationale for the trial, design details, and eligibility criteria have been published previously [14]. Also, the main analysis including all short-term outcomes within 30 days has been published [13]. The ethical committee of the Northwestern part of Switzerland (EKNZ; 2014\_001) approved the study protocol for all participating sites, and the trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT02517476) in August 2015 (<https://clinicaltrials.gov/ct2/show/NCT02517476>). All patients gave written informed consent for participation in the trial.

### 2.2. Sites, patient selection and randomization

Participating sites were secondary and tertiary care hospitals in Switzerland, and all routinely screened patients for risk of

malnutrition with the Nutritional Risk Screening 2002 (NRS) [15,16]. 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), and a higher score is associated with higher risk for adverse outcomes. To be eligible for the trial, a NRS total score of 3 points or more was mandatory. Additionally, we only included patients with an expected length of hospital stay of  $\geq 5$  days. The trial had different exclusion criteria, including initial admission to an intensive care unit or surgical unit, inability to ingest oral nutrition, ongoing nutritional treatment before trial inclusion, terminal conditions (i.e., end-of-life situation), anorexia nervosa, acute pancreatitis and liver failure, cystic fibrosis or stem cell transplantation, history of gastric bypass surgery, and any contraindications for nutritional support. Also, patients previously included in the trial were not allowed to be included in the trial again during follow-up.

Patients were randomly assigned in a 1:1 ratio with variable block size, stratified according to site and the severity of malnutrition, with the use of an interactive web-response system, to receive either individualized nutritional support (intervention group) or hospital food as usual (control group).

### 2.3. Study interventions

The nutritional support intervention focused on nutritional treatment during the initial hospital stay. All intervention group patients received individual nutritional support within 48 h after admission to reach protein and energy goals according to a previously published consensus protocol [17] and in accordance with recent international guidelines [4]. Individualized energy and protein goals were defined for each individual patient upon hospital admission by a trained registered dietician. We used the weight-adjusted Harris–Benedict equation to estimate energy requirements [18]. Daily protein intake goals were set at 1.2–1.5 g/kg body weight per day [19]. For patients with renal failure we defined lower targets (0.8 g per kg of body weight). To reach these goals, an individual nutritional plan was developed by a trained registered dietician for each patient. This plan was initially based on oral nutrition provided by the hospital kitchen (including adaptation of meals to patient's preferences, additional nutritionally dense snacks and fortified foods) and oral nutritional supplements [10,20]. 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, which was, however, rarely the case. Nutritional intake was reassessed every 24–48 h throughout the hospital stay by a trained registered dietician based on daily food records for each patient.

All intervention group patients received dietary counseling addressing malnutrition at hospital discharge. Even though continuation of nutritional support interventions in the outpatient setting were not generally recommended in the protocol and remained at the discretion of the treatment team, about 1 patient in 4 did receive continued nutritional support after hospital discharge.

Control group patients received hospital food as usual according to their ability and desire to eat, with no nutritional counseling and no recommendation for additional nutritional support.

#### 2.4. Outcome measures

The primary endpoint of the present analysis was all-cause mortality within 6-months follow-up. Secondary endpoints included non-elective hospital readmissions, falls with and without fractures, weight change and quality of life and functionality scores. To assess activities of daily living, we used the Barthel's index with (scores ranging from 0 to 100 and higher scores indicating better functional status [21]. Quality of life was assessed with the European Quality of Life 5 Dimensions index (German Version, EQ-5D index) with values ranging from 0 to 1 and higher scores indicating better quality of life. This also includes a visual-analogue scale (EQ-5D VAS) with a score ranging from 0 to 100 and higher scores indicating better health status.

All outcome data were obtained through systematic telephone calls at day 180 after trial inclusion, which were conducted blinded to group assignment. Mortality of patients during follow-up was verified by inquiring family members or the patient's family physician.

#### 2.5. Statistical analysis

The sample-size calculation and the design for the short-term (30-day) analysis have been described previously [13,14]. For the 6-months analysis, data were included for all the patients who had more than 30 days of follow-up. All analyses were performed according to the intention-to-treat principle. The 6-months event rates were the percentages of patients who died within 180 days after randomization. We fitted a cox regression model adjusted for main prognostic factors (Barthel's index and NRS scores at baseline) and study center as predefined in the study protocol. We report hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). We used a similar statistical approach for secondary

endpoints, with use of linear regression models for continuous outcomes. For graphical display, we also used the Kaplan–Meier method to calculate the probability of the primary outcome and all-cause mortality within 180 days of randomization. We also performed a post hoc landmark analysis using a cutoff point of 30 days after randomization, with HRs calculated separately for events that occurred within 30 days and those that occurred between 30 days and 6 months.

We conducted all analyses with STATA 15.1 (StataCorp. 2015. *Stata Statistical Software: Release 15*. College Station, TX, USA: StataCorp LP).

### 3. Results

#### 3.1. Patients

From April 2014 to February 2018 we screened 5015 patients and included 2028 into the initial analysis at 30 days post randomization. During the 6-month follow-up, 35 patients (1.7%) were lost to follow-up. The final analysis cohort consisted of 994 intervention group patients and 999 control group patients (Fig. 1).

The mean age of patients was 73 years, 52% were male, mean BMI was 24.8 kg/m<sup>2</sup> and 31%, 38% and 31% of patients had a NRS score of 3, 4 and  $\geq 5$ , respectively. The main diagnoses for hospital admission were infections (30%), cancer illness (19%), cardiovascular disease (10%) and frailty (9%). Overall, patients had a high burden of comorbidities particularly coronary heart disease (28%), congestive heart failure (18%), cancer (33%), chronic kidney disease (32%) and diabetes (21%). Baseline characteristics were similar between groups in regard to age, gender, nutritional risk main diagnosis at hospital admission and comorbidities. Baseline characteristics stratified according to randomization arm are presented in Table 1.

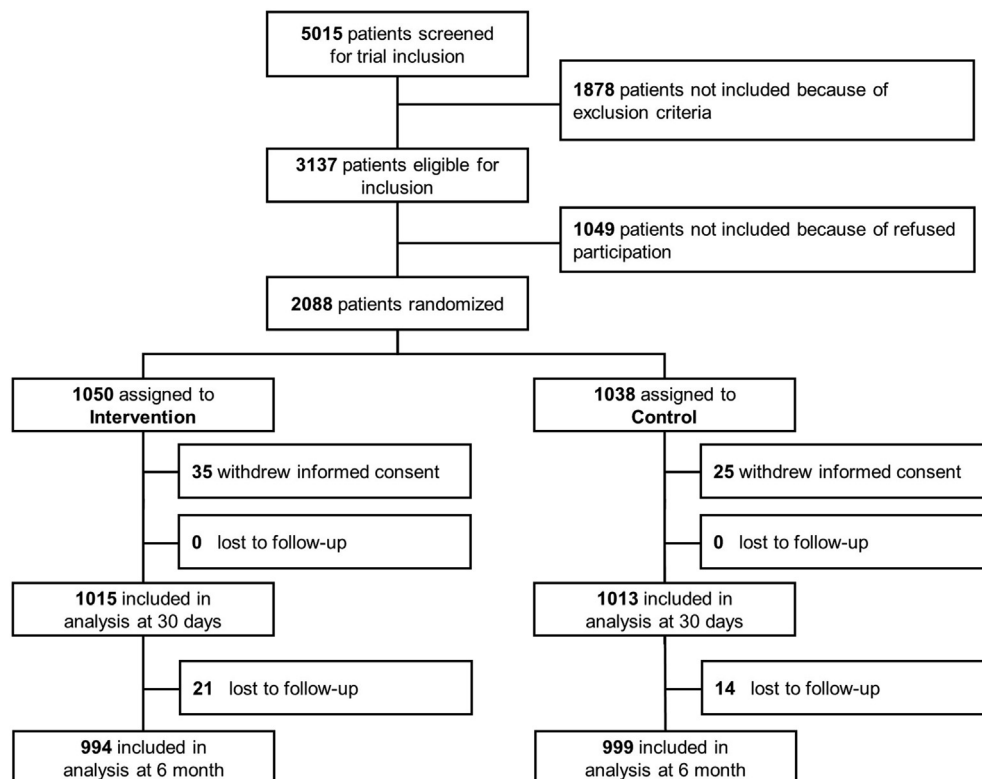


Fig. 1. Flow of patients.

**Table 1**  
Baseline characteristics of Patients. Percentages may not total 100 because of rounding.

Characteristic	Control group (N = 999)	Intervention group (N = 994)	p-value
<b>Socio-demographics</b>			
Age - yr	73.0 (13.9)	72.7 (13.9)	0.70
Male sex - no. (%)	531 (53.2%)	510 (51.3%)	0.41
<b>Nutritional history</b>			
<sup>a</sup> Body Mass Index (BMI) - kg/m <sup>2</sup>	24.7 (5.2)	24.9 (5.4)	0.39
Body weight - kg	70.9 (16.3)	71.0 (17.1)	0.52
<b><sup>b</sup>Nutritional risk screening score 2002 - no. (%)</b>			
3 points	310 (31.0%)	302 (30.4%)	0.96
4 points	377 (37.7%)	381 (38.3%)	
5 points	258 (25.8%)	261 (26.3%)	
>5 points	54 (5.4%)	50 (5.0%)	
<b>Main diagnosis at hospital presentation - no. (%)</b>			
Cardiovascular disease	113 (11.3%)	92 (9.3%)	0.13
Infection	311 (31.1%)	294 (29.6%)	0.45
Metabolic disease	29 (2.9%)	29 (2.9%)	0.98
Gastrointestinal disease	67 (6.7%)	96 (9.7%)	0.016
Renal disease	34 (3.4%)	32 (3.2%)	0.82
Cancer	171 (17.1%)	197 (19.8%)	0.12
Lung disease	75 (7.5%)	50 (5.0%)	0.023
Neurological disease	51 (5.1%)	40 (4.0%)	0.25
Failure to thrive	94 (9.4%)	93 (9.4%)	0.97
Other	25 (2.5%)	28 (2.8%)	0.66
<b>Comorbidities - no. (%)</b>			
Coronary heart disease	276 (27.6%)	285 (28.7%)	0.60
Chronic heart failure	179 (17.9%)	174 (17.5%)	0.81
Hypertension	546 (54.7%)	553 (55.6%)	0.66
Cerebrovascular disease	87 (8.7%)	74 (7.4%)	0.30
Peripheral arterial disease	104 (10.4%)	79 (7.9%)	0.057
Chronic renal failure	316 (31.6%)	317 (31.9%)	0.90
Diabetes	210 (21.0%)	212 (21.3%)	0.87
COPD	155 (15.5%)	145 (14.6%)	0.56
Dementia	36 (3.6%)	38 (3.8%)	0.80
Malignant disease	327 (32.7%)	333 (33.5%)	0.72

COPD denotes chronic obstructive pulmonary disease.

Metabolic disease included hypoglycemia, hyperglycemia, ketoacidosis, electrolyte disturbances including hyponatremia and hypernatremia, hypokalemia and hyperkalemia among others.

<sup>a</sup> The body-mass index is the weight in kilograms divided by the square of the height in meters.<sup>b</sup> Total score on nutritional risk screening ranges from 0 to 7, with a score of  $\geq 3$  identifying patients at nutritional risk and higher scores indicating higher risk.

### 3.2. Nutritional intake during the trial and upon hospital discharge

During the trial, significantly more intervention group patients reached energy and protein goals compared to control group

patients (energy goals were reached in 79% and protein goals in 76% of intervention group patients vs. 54% and 55% in control group patients). On hospital discharge, oral nutritional supplements were prescribed in 241/994 (24.2%) of patients in the intervention group

**Table 2**  
Primary and secondary endpoints.

Variable	Intervention group (N = 994)	Control group (N = 999)	p-value	Regression analysis (HR or coefficient and 95%CI)
<b>Primary outcome - no (%)</b>				
All-cause mortality	231 (23.2%)	246 (24.6%)	0.47	0.90 (0.76–1.08), p = 0.277
<b>Secondary outcomes - no (%)</b>				
Non-elective hospital readmission	274 (27.6%)	273 (27.3%)	0.91	1.00 (0.84–1.18), p = 0.974
Falls	108 (10.9%)	112 (11.2%)	0.80	0.96 (0.72–1.27), p = 0.773
Falls with fracture	18 (1.8%)	14 (1.4%)	0.47	1.27 (0.63–2.58), p = 0.506
<b>Quality of life and functional outcomes</b>				
<b>Activities of daily living</b>				
Barthel score - points	13.6 ( $\pm 7.9$ )	13.4 ( $\pm 8.1$ )	0.61	0.27 (–0.43 to 0.97), p = 0.447
Decline in functional status of $\geq 10\%$	916 (92.2%)	928 (92.9%)	0.53	0.41 (–5.01 to 5.83), p = 0.882
<b>Quality of Life</b>				
EQ-5D Visual-analogue scale - points	50.9 ( $\pm 34.9$ )	50.7 ( $\pm 35.5$ )	0.90	–1.16 (–3.34 to 1.02), p = 0.296
EQ-5D index	0.83 ( $\pm 0.21$ )	0.83 ( $\pm 0.21$ )	0.81	0.00 (–0.02 to 0.02), p = 0.802
<b>Weight change</b>				
Weight at 6-months (kg)	70.0 ( $\pm 16.0$ )	69.0 ( $\pm 16.0$ )	0.23	1.11 (–0.51 to 2.73), p = 0.180
Weight change from baseline to 6-months (kg)	–0.80 ( $\pm 6.1$ )	–0.90 ( $\pm 6.0$ )	0.71	0.06 (–0.57 to 0.68), p = 0.862

All hazard ratios were calculated with cox regression for time to event data and linear regression for continuous data. Models were adjusted for prognostic factors (initial NRS score, baseline Barthel index) and study center.

For decline in functional status we used the Barthel index and compared initial scores on admission with scores at 6-month; CI denotes confidence interval. EQ-5D denotes European Quality of Life 5 Dimensions.

To estimate decline in functional status we used the Barthel index (scores range from 0 to 100, with higher scores indicating better functional status) and compared initial scores on admission with scores at 6-month; To estimate quality of life we used the European Quality of Life 5 Dimensions index (values range from –0.205 to 1, with higher scores indicating better quality of life) including the visual–analogue scale (EQ-5D VAS) (scores range from 0 to 100, with higher scores indicating better health status).

compared to 21/999 (2.1%) of patients in the control group. The initial weight was similar in both groups and (70.9 and 71 kg) and decreased similarly over 6-months in both groups by 0.9 and 0.8 kg with no difference between groups.

### 3.3. Primary endpoint: mortality at 6-months

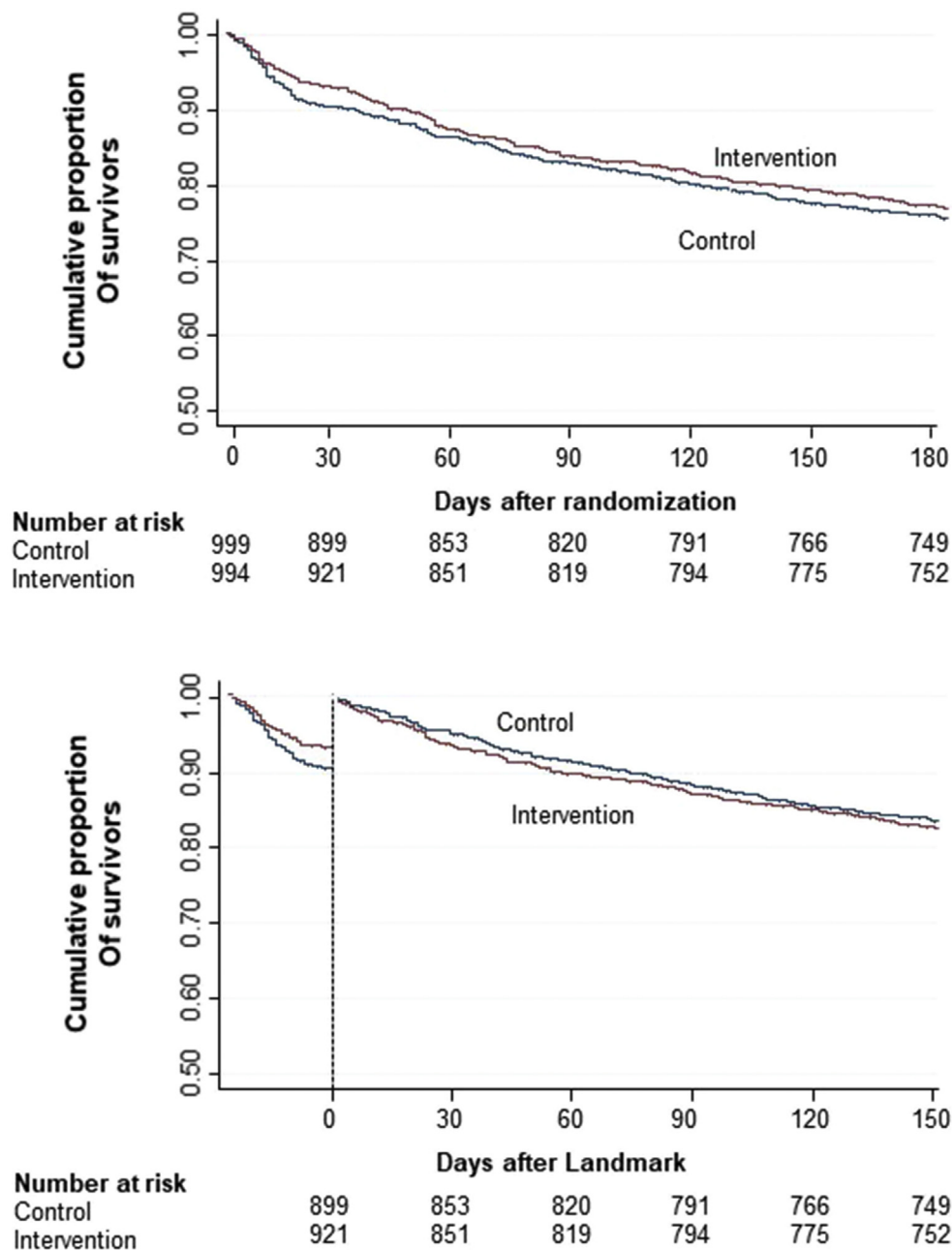
Within 6 months, 231 of 994 (23.2%) died in the intervention group compared to 246 of 999 patients (24.6%) in the control group (adjusted hazard ratio 0.90 [95%CI 0.76 to 1.08],  $p = 0.277$ ) (Table 2). Kaplan Meier estimates showed a non-significant difference between groups in regard to the time to death (Fig. 2A).

A post-hoc landmark analysis revealed a difference between the two groups in mortality within the first 30 days (adjusted HR 0.66 (95%CI, 0.48 to 0.89),  $p = 0.007$ ), but mortality was similar in the

two groups thereafter with 154 dying in the intervention group and 145 patients the in the control group (HR, 1.06 (95% 0.85 to 1.33),  $p = 0.595$ ) (Fig. 2B). Predefined subgroup analyses revealed consistency of the results across all subgroups (Fig. 3).

### 3.4. Secondary endpoints

Secondary outcomes are shown in Table 2. There was no difference in the rates of non-elective hospital readmission, falls and fractures due to falls in the 6-months follow-up. Activities of daily living measured with the Barthel index were similar at 6-months with also similar proportion of patients showing a decline of  $\geq 10\%$  from baseline. Also, there was no difference in quality of life using the EQ5D questionnaire overall, and for the visual analog scale.



**Fig. 2.** Kaplan–Meier estimates of the cumulative incidence of all-cause mortality (A) and Landmark analysis (B). Panel A shows the Kaplan–Meier curves for the time to death within 6-months ( $p$  log rank 0.45). Panel B shows the Landmark analysis for the time to death after 30 days ( $p$  log rank 0.52).

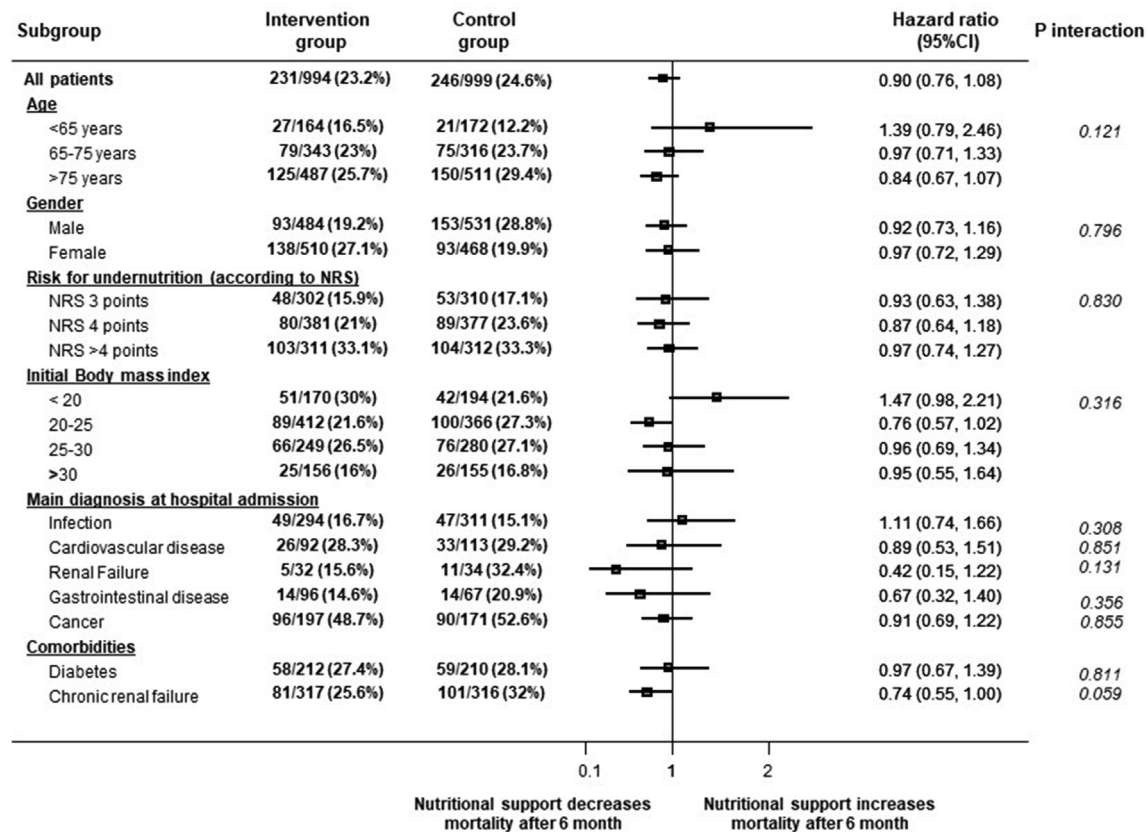


Fig. 3. Hazard ratios for all-cause mortality (primary outcome) in prespecified subgroups. There were no significant interactions between group assignment and any of the subgroups tested. The body-mass index is the weight in kilograms divided by the square of the height in meters. NRS denotes nutritional risk screening 2002.

#### 4. Discussion

EFFORT, as a multicenter randomized trial, compared clinical effects of individualized nutritional support during the hospital stay with the provision of usual care (routine hospital food) in medical inpatients at nutritional risk. We previously reported that the risk for treatment failure and death from any cause was lower with individual nutritional support in the 30-day analysis of this trial [13]. In the present analysis, we found that mortality did not differ significantly between the two groups at 6-month post randomization. The same was true for secondary endpoints, including rehospitalization, falls and activities of daily living as well as quality of life scores.

Importantly, the EFFORT trial investigated the effects of providing nutritional support during the acute phase of illness in hospitalized patients. With an average hospital length of stay of 10 days, the individual nutritional support intervention period was short and only about one fourth of patients received further nutritional support in the outpatient setting after hospital discharge. This may explain while outcomes at short term showed a significant benefit in our trial, but not over a prolonged follow-up period of 6 months. Importantly, several trials such as the NOURISH trial that offered continued nutritional support in the outpatient setting reported also significant effects of nutritional support on mortality at longer term [9,22,23]. Thus, there is a strong rationale to continue individual nutritional support for patients discharged from the hospital with existing risk for or manifest malnutrition. However, there is need for additional research to confirm this hypothesis in a well-conducted and robust trial.

There is increasing evidence showing the beneficial effects of nutritional interventions on medical outcomes in at-risk patients [8,24,25]. A recent meta-analysis confirmed that nutritional support during the hospital stay is associated with a 27% reduction in the odds of mortality [8]. Additionally, the risk for rehospitalization and prolonged length of hospital stays were improved in patients receiving individual nutritional support compared to control patients. Also, from a cost-benefit perspective, nutritional support has been shown to be highly cost-efficient because the costs for dietary counseling and nutritional products are relatively low compared to potential high savings when complications or hospital readmissions are reduced [26–28]. Future research should also look at cost-benefits of continued individual nutritional support in the outpatient setting by comparing costs of the intervention to potential benefits for the patient and the payer.

Within the EFFORT trial, we included a broad and unselected population of consecutive multimorbid medical inpatients with different acute illnesses and chronic co-morbidities. While the short-term beneficial effects of nutritional support were robust and similar in subgroups according to patient age, gender, severity of nutritional risk and underlying disease, none of the subgroups showed benefit at long term. Interestingly, while the short-term effects were more pronounced in patients with chronic kidney disease, a condition known to predispose patients to protein-energy wasting [29], this group of patients did not show significant benefit over 6-month, indeed. Still, the relatively small number of patients with chronic kidney disease included in that subgroup and the overall short period of nutritional intervention may explain the absence of significant results. Future studies should focus on the vulnerable group of patients with chronic kidney disease in

regard of nutritional support interventions, and also aim to identify predictors for treatment response – or non-response to further increase the efficacy of this intervention [30,31].

Our trial has limitations. First, our intervention focused mainly on the hospital stay and only a minority of patients received nutritional support in the outpatient setting after discharge. In fact, in both groups patients lost weight between baseline and the 6-month follow-up period (−0.90 Kg in the control group and −0.80 Kg in the intervention group), which may suggest a further deterioration on nutritional status post hospital discharge. Weight at follow-up was reported by patients, but not measured centrally. Also, about 20% of intervention group patients did not fully reach energy and protein goals despite use of the nutritional protocol implemented by trained dietitians. Similar to real-life experience, several patient, treatment, and hospital factors (e.g., delay or refusal to start enteral or parenteral nutrition by the patient, early discharge of patients, diagnostic exams interfering with nutritional support) may have prevented full adherence to the protocol. Second, EFFORT was a pragmatic trial, and blinding of participants and personnel was deemed to be impractical. Still, outcomes assessed after 30-days and 6-months were blinded. Third, our control group received hospital food as usual, which may vary from hospital to hospital and within countries. Forth, our trial design does not allow to make firm conclusions regarding the underlying reasons for lack of effect at long-term. This may be due to the lack of continuing the nutritional intervention with individualized use of proteins and calories, lack of use of micronutrients, lack of dietician involvement, among others. Also, the high burden of disease including cancer and heart disease put the patient population at high risk for reaching the primary endpoint of our analysis (mortality) and thus may lead to underestimation of any positive effects of nutrition in acutely ill patients suffering less severe or less lethal comorbidity.

Understanding the optimal use of individual nutritional support to effectively prevent and treat malnutrition is highly complex. Particularly, the optimal timing of nutritional support in regard to best time to start nutrition and optimal duration of the intervention have not well been established. The EFFORT trial showed that a nutritional intervention to reach protein and energy goals in medical inpatients at nutritional risk that focuses on the inpatient setting effectively reduces the risk of adverse outcomes and mortality within 30 days, but there is no apparent legacy effect. There is now a strong need to study effects of outpatient nutritional support interventions (possibly combined with other strategies to increase muscle mass, such as increased physical activity) in the nutritionally vulnerable population of medical patients.

### Funding of the trial

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. The members of the steering committee (Supplementary Appendix) designed the trial, collected and analyzed the data, prepared the manuscript, and decided to submit the manuscript for publication. The members of the steering committee take responsibility for the accuracy of the data set and adherence to the protocol. There was no commercial involvement in the trial.

### Author contribution

Prof. Philipp Schuetz was the principal investigator of this trial and was responsible for obtaining funding, drafting the trial

protocol, data analysis and interpretation, and writing of the final report.

Rebecca Fehr, Valerie Baechli, Martina Geiser, Manuela Deiss, Pascal Tribolet, Nina Kaegi-Braun, Sarah Schmid, Carmen Benz, Silvia Mattmann and Claudia Brand were involved in drafting the trial protocol, data collection and approved the final version of the manuscript.

Filomena Gomes, Alexander Kutz, Thomas Bregenzer, Claus Hoess, Vojtech Pavlicek, Stefan Bilz, Sarah Sigrist, Michael Brändle, Christoph Henzen, Robert Thomann, Jonas Rutishauser, Drahomir Aujesky, Nicolas Rodondi and Jacques Donzé were involved in drafting the trial protocol, supervision of study sites, drafting of the final manuscript and approved the final version of the manuscript.

Zeno Stanga and Beat Mueller were involved in obtaining funding, drafting the trial protocol, supervision of study sites, drafting of the final manuscript and approved the final version of the manuscript.

### Conflict of interest

The study was investigator-initiated and supported by a grant from the Swiss National Science Foundation to P.Schuetz (SNSF Professorship, PP00P3\_150531) and the Forschungsrat of the Kantonsspital Aarau (1410.000.058 and 1410.000.044). The institution of P.Schuetz has previously received unrestricted grant money unrelated to this project from Nestle Health Science and Abbott Nutrition. The institution of Z.Stanga received speaking honoraria and research support from Nestle Health Science, Abbott Nutrition and Fresenius Kabi. All other authors report no conflicts of interest.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2020.08.019>.

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