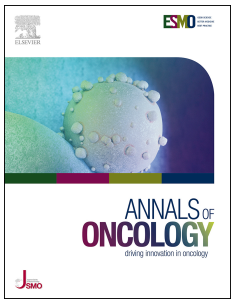

Nutritional support during the hospital stay reduces mortality in patients with different types of cancers: Secondary analysis of a prospective randomized trial

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Nutritional support during the hospital stay reduces mortality in patients with different types of cancers:

Secondary analysis of a prospective randomized trial

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Running title: Nutritional support in cancer patients

Abstract

Introduction: Nutritional support in patients with cancer aims at improving quality of life. Whether use of nutritional support is also effective in improving clinical outcomes remains understudied.

Methods: In this preplanned secondary analysis of patients with cancer included in a prospective, randomized-controlled, Swiss, multicenter trial (EFFORT), we compared protocol-guided individualized nutritional support (intervention group) to standard hospital food (control group) regarding mortality at 30-day (primary endpoint) and other clinical outcomes.

Results: We analyzed 506 patients with a main admission diagnosis of cancer, including lung cancer (n=113), gastrointestinal tumors (n=84), hematological malignancies (n=108) and other types of cancer (n=201). Nutritional risk based on Nutritional Risk Screening [NRS 2002] was an independent predictor for mortality over 180 days with a (age-, sex-, center-, type of cancer-, tumor activity- and treatment-) adjusted hazard ratio of 1.29 (95% CI 1.09 to 1.54; p=0.004) per point increase in NRS. In the 30-day follow-up period, 50 patients (19.9%) died in the control group compared to 36 (14.1%) in the intervention group resulting in an adjusted odds ratio of 0.57 (95% CI 0.35 to 0.94; p=0.027). Interaction tests did not show significant differences in mortality across the cancer type subgroups. Nutritional support also significantly improved functional outcomes and quality of life measures.

Conclusion: Compared to usual hospital nutrition without nutrition support, individualized nutritional support reduced the risk for mortality and improved functional and quality of life outcomes in cancer patients with increased nutritional risk. These data further support the inclusion of nutritional care in cancer management guidelines.

Keywords: nutrition, outcomes, cancer, malnutrition, randomized trial,

Highlights

- Nutritional risk in patients with cancer was an independent prognostic indicator regarding 6-month mortality
- In patients with cancer and increased nutritional risk, individualized nutritional support during the hospital stay reduced mortality
- Nutritional support also improved functional and quality of life outcomes.

Introduction

Effective anti-cancer strategies are based on combination of disease-modifying therapies and supportive and palliative care. The goal of supportive and palliative care is to address needs of patients with cancer and thus enhance quality of life.[1] Early and simultaneous delivery of disease-modifying therapy and palliative care has been demonstrated to improve clinical outcomes. However, the specific role of nutritional care in favoring a better outcome in patients with cancer remains understudied.

Malnutrition affects about 30% of oncological and hematological malignancy patients and is associated with higher mortality, impaired functional status and longer hospital stays.[2-4] The clinical presentation of malnutrition in patients with cancer may vary from loss of appetite and/or weight, to loss of muscle mass with sarcopenia, to severe tumor cachexia. [5] Several factors put patients with cancer at high malnutrition risk including tumor-derived cytokine release causing loss of appetite and anorexia, and side effects of cancer treatment again interfering with appetite and normal food intake.[6-8] In addition, once admitted to the hospital, patients with cancer are at high risk for further deterioration of the nutritional status due to fasting for diagnostic studies, treatment side effects and overall suboptimal nutritional management.

To prevent adverse clinical outcomes associated with malnutrition, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends identifying cancer patients at nutritional risk through early screening, followed by nutritional counseling and nutritional support.[6, 7] Different screening tools are recommended for this purpose, including the Nutritional Risk Screening (NRS 2002).[9] [10, 11] However, there is relatively little evidence regarding this recommendation for the population of hospitalized patients with cancer and previous trial data has been

somewhat inconclusive.[5, 12] While some trials looking at patients with colorectal cancer found improved outcomes associated with nutritional support interventions,[13, 14] other trials have not provided evidence that in favor of using nutritional interventions.[12] Whether malnutrition is indeed a modifiable risk factor and improved by nutritional interventions has therefore been questioned.

Herein, we performed a preplanned secondary analysis of a randomised multicentre trial in Switzerland [4, 15], investigating the effect of nutritional support during the hospital stay compared to usual care hospital food on mortality and other clinical outcomes in patients with different types of cancer.

Methods

Study design

This is a secondary analysis of the subset of patients with cancer as a main admission diagnosis included in the EFFORT (Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients) trial.[4] Effort was an investigator-initiated, open-label, randomized, controlled trial in eight Swiss hospitals investigating the effect of early individual nutritional support on medical outcomes in patients at risk of malnutrition. The trial protocol and the results of the main trial, as well as secondary outcomes, have been published previously.[4, 11, 16-22] The Ethics Committee of Northwest and Central Switzerland (EKNZ) approved the study protocol in January 2014 (EKNZ; 2014_001).

Patient population

All participating centers had an active malnutrition screening in place using the NRS 2002. This score is a well-established tool for assessing malnutrition risk based on a patient's nutritional status and disease severity with a total score ranging from 0-7

points.[9, 11] A score of 3 points or more indicates increased nutritional risk. For the purpose of this study, we stratified the nutritional risk of patients based on NRS (i.e., moderate, high and very high risk defined as NRS 3, 4 and ≥5 points).

For the initial trial, we enrolled adult patients with a NRS total score ≥3 points and an expected length of hospital stay of >4 days. Exclusion criteria were initial admission to intensive care units or surgical units; patients with terminal illness; admission diagnosis of anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis or stem-cell transplantation and history of gastric bypass surgery. Also, patients unable to ingest food orally, already receiving nutritional support or existing contraindications for nutritional support, and those previously included in the study were excluded. All patients eligible for this secondary analysis had a documented main admission diagnosis of cancer, which was confirmed and validated by a complete chart review after hospital discharge. The reporting of the proportion of patients with cancer thus differs from the original trial where diagnosis was based on admission data only. We also classified patients based on the type of cancer based on a complete review of the medical records. Tumor activity was defined as “active” if patients received antitumor treatment in the previous year or if the first diagnosis of cancer was made on admission. We also included “non-active” patients with cancer in the analysis if above mentioned definition was not met, but cancer was a main admission diagnosis.

Procedures

After trial inclusion, we randomized patients by use of an interactive web system 1:1 to the intervention group receiving individualised nutritional support according to an implementation protocol[23], or the control group receiving usual hospital food without nutritional support. In the intervention group, nutritional support was initiated as soon as possible after randomization within 48 hours of hospital admission.

Patients received individualized nutritional support to reach protein and energy goals, defined for each patient upon hospital admission by a trained registered dietician. Energy requirements were predicted using the weight-adjusted Harris-Benedict equation.[24] Daily protein intake was set at 1.2–1.5 g/kg body weight to adjust for higher protein breakdown during acute disease[25], with lower targets for patients with acute renal failure (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 food adjustment according to patient preferences, food fortification (e.g., enrichment of hospital food by adding protein powder) and providing patients with between-meal snacks) and oral nutritional supplements[26, 27]. 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. 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. Upon hospital discharge, patients received dietary counselling and, if indicated, a prescription for oral nutritional supplements in the outpatient setting. There was no planned follow-up regarding nutritional intake in the outpatient setting. Control group patients received standard hospital food according to their ability and desire to eat, with no nutritional consultation and no recommendation for additional nutritional support.

Outcomes

The primary endpoint was all-cause mortality within 30 days. The main secondary endpoints was adverse outcome, a composite endpoint predefined for the initial trial[4, 16], that includes all-cause mortality, admission to the intensive care unit from

the medical ward, non-elective hospital readmission after discharge, and major complications including adjudicated nosocomial infection, respiratory failure, a major cardiovascular event (e.g., stroke, intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism, acute renal failure, gastro-intestinal events (including hemorrhage, intestinal perforation, acute pancreatitis) or a decline in functional status of 10% or more from admission to day 30 measured by the Barthel's index. A detailed description of outcomes is provided in the **Appendix**.

Additional hospital outcomes included admission to intensive care, non-elective hospital readmission within 30 days and mean length of hospital stay and functional outcome such as a decline in functional status of 10% or more within 30 days, and functional impairment (measured by the Barthel's Index and quality of life assessed with the European Quality of Life 5 Dimensions Index, including the EQ-5D VAS visual-analogue scale). Barthel's scores range from 0 to 100, with higher scores indicating better performance of activities of daily living. The European Quality of Life 5 Dimensions index (EQ-5D) ranges from 0 to 100, with higher scores indicating better quality of life. EQ-5D VAS (including visual-analogue scale) ranges from 0 to 100, with higher scores indicating better health status.

As an additional secondary outcome, we also assessed mortality after a follow-up time of 6 month, where we had information from 1995 of 2028 patients (98%) included in the initial trial.[17]

Statistical analyses

For this secondary analysis, we used a similar statistical approach as in the original trial[4, 16]. We tested the hypothesis that individualised nutritional support is superior to usual hospital food with regard to mortality and other secondary endpoints. We performed all analyses in the intention-to-treat population, which included all patients

with a main admission diagnosis of cancer who had undergone randomisation unless they withdrew consent. Categorical variables are presented as counts (percentages) and continuous variables as means and standard deviations (SD).

First, we investigated the prognostic implications of nutritional risk by calculation of regression analysis regarding NRS and clinical outcomes adjusted for important confounders (patient age, sex, study center, cancer subgroups, tumor activity and treatment). We calculated Cox regression models for time-to-event analyses with reporting of hazard ratios (HR) and illustrated the probability of all-cause mortality in Kaplan-Meier survival curves. We used logistic regression for binary data and linear regression for continuous outcomes. Second, we compared outcomes between randomization arms by means of regression analysis adjusted for study center, Barthel's Index at admission and NRS at baseline (as predefined in our protocol).[15] We used logistic regression for all binary outcomes with reporting of odds ratios (ORs) and corresponding 95% confidence intervals (CI's), and linear regression for continuous outcomes with reporting of coefficients (differences). Finally, we conducted subgroup analyses for patient age, sex, risk for malnutrition by NRS, cancer type subgroups, tumor activity and treatment, and reason for admission. We calculated interaction analysis to test for effect modification by main prognostic factors.

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

Results

This analysis includes 506 patients with a confirmed main diagnosis of cancer at hospital admission. with a confirmed main diagnosis of cancer at hospital admission

(255 intervention group patients and 251 controls) from an original cohort of 2028 EFFORT trial patients **Supplemental Figure 1** shows the detailed patient flow. Overall, patients had different types of cancers and a high burden of comorbidities. The most frequent types of cancer were lung cancer (n=113), hematological malignancies (n=108) and gastrointestinal tumors (n=84). The most common reason for hospitalization was cancer treatment, new cancer diagnosis and failure to thrive associated with the cancer diagnosis. Detailed baseline characteristics are shown in **Table 1** for both groups.

Caloric and protein intake of patients during the in-hospital study period is listed in **Appendix, Supplemental Table 1**. Compared to control group patients, intervention group patients had a significantly higher mean caloric (1411 vs 1154 kcal/day) and protein (52.7 vs 44.2 g protein/day) intake during the index hospital stay.

Association of nutritional risk with mortality and other endpoints

Nutritional risk as measured using NRS 2002 was strongly associated with mortality over the 180-day follow-up with an adjusted HR of 1.37 (95% CI 1.15 to 1.61), p<0.001) per point increase in NRS. **Figure 1** shows the time to death stratified by NRS with shorter time until death with higher NRS groups. We also observed an association between NRS and the composite endpoint of adverse outcomes (adjusted OR per point increase in NRS of 1.42 [95% CI 1.11 to 1.83]; p=0.006). Similar results were found for mean length of hospital stay, functional decline and impairment in quality of life (**Table 2**).

Effect of nutritional support on clinical outcomes

A total of 50 patients (19.9%) in the control group died within 30 days compared to 36 (14.1%) in the intervention group resulting in an adjusted OR of 0.57 [95% CI 0.35 to

0.94; p=0.027] (**Table 3**). These results were also illustrated in Kaplan Meier estimates stratified by randomization group (**Figure 2**).

We also investigated effects of nutritional support regarding mortality over 6 months of follow-up. We recorded 128 (52.7%) deaths in the control group compared to 115 death (47.3%) in the intervention group resulting in an adjusted HR of 0.83 (95%CI 0.65 to 1.08, p=0.18) (see **supplemental figure 3** in the Appendix).

Compared to the intervention group, there was a higher risk in the control group for functional decline in activities of daily living (defined by Barthel scale) (adjusted OR 0.59 [95% CI 0.38 to 0.93]; p=0.021). In addition, patients receiving nutritional support showed significant improvements in quality of life as defined by EQ-5D Index (adjusted coefficient 0.08 [95% CI 0.01 to 0.15]; p=0.016) and by EQ-5D VAS (adjusted coefficient 6.16 [95% CI 0.51 to 11.8]; p=0.033). No significant differences were found for other secondary outcomes including the composite outcome, length of hospital stay and non-elective hospital readmission (**Table 3**).

Subgroup analysis for mortality and adverse outcome

We also performed several pre-planned subgroup analyses to investigate whether effects of nutritional support were similar among patients with different sociodemographic characteristics, different types of cancers, tumor activity and treatment, and reason for admission. Overall, there was no evidence for effect modification among subgroups for mortality (**Figure 3**). Similarly, regarding the composite endpoint of adverse outcome, no significant effect in interaction analysis was found for any subgroup (**Appendix, Supplemental Figure 2**).

Discussion

The principal findings of this secondary analysis of a large-scale, randomized, controlled nutritional trial focusing on hospitalized patients with different types of cancer are twofold. First, nutritional risk was strongly associated with mortality at 6 months, which was independent of different other prognostic indicators and cancer activity. Second, compared to a control group of patients receiving standard hospital food without nutritional support, the use of individualized nutritional support to reach nutritional goals resulted in a significant improvement in mortality and other functional outcomes at short-term. These effects were consistent among different types of cancers and other predefined subgroups.

Several aspects of this analysis are noteworthy. Firstly, we observed a strong increase in mortality in patients with higher nutritional risk, corroborating previous reports in this patient population. [10, 11, 28] Indeed, patients with an NRS of ≥5 points had a 19% higher risk of long-term mortality compared to those with 3 points. The results remained similar when adjusting the analysis for other prognostic indicators and cancer-associated factors, suggesting that nutritional status independently predict outcome in this population of patients. Further strong associations were found between NRS and other clinically-relevant secondary outcomes. Risk screening by NRS thus allows to identify a group of cancer patients at highest risk for adverse outcome where clinical attention is indicated.

Second, While the negative prognostic implications of deteriorating nutritional status in patients with cancer have previously been demonstrated, conclusive evidence regarding clinical effects of nutritional support in this population is currently scarce with international societies giving only weak recommendations regarding

318 treatment.[6, 7, 28] Importantly, clinicians may be reluctant to provide nutritional
319 support to patients with cancer with low appetite but rather focus on anti-cancer
320 treatments to improve the underlying problem.[12] Herein, our data provide evidence
321 that patients show strong benefit from nutritional support, with a greater than 5%
322 reduction in mortality (i.e., from 19.9% to 14.1%). Interestingly, this effect was found
323 independent of type of cancer and cancer activity, although some of the subgroups
324 investigated were small and do not allow firm conclusions. Clearly, the subgroup
325 analysis was underpowered with risks for type II error. In fact, visual inspection of the
326 forest plots suggests some numerical heterogeneities (e.g., patients with only
327 moderate nutritional risk [NRS 3 points] and patients with cancer-associated pain as
328 their main reasons for admission) pointing to possible lack of effect or even harm
329 regarding adverse outcome in these subgroups. Importantly, there may be
330 differences among cancer patients regarding the potential benefit from nutrition. For
331 example, patients with chronic catabolism driven by cancer-related systemic
332 inflammation may be less likely to show benefit from nutritional support. Yet, we did
333 not collect such data in our trial for more specific phenotyping of patients and were
334 thus not able to test this hypothesis. Clearly, prospective trials are needed with more
335 homogenous groups of patients regarding type of cancer and treatment to
336 understand which clinical situation provides the best opportunity for intervention.
337 Nevertheless, our results support the clinical relevance of simultaneously addressing
338 patients' oncological and nutritional needs, and provide a possible explanation to the
339 recently reported discrepancies in outcomes for patients enrolled in clinical trials and
340 those in registries.[29] Considering that patients with cancer with comorbidities,
341 including malnutrition, are less likely to be offered to participate to a clinical trial,[30]
342 prevention and treatment of malnutrition may confer additional benefits. Also,

concurrent care may enhance patients with cancer' quality of life, an issue frequently overlooked even under the protected umbrella of a clinical trial.[31]

Third, unlike other trials investigating the effect of specific nutritional formulas,[32] we used a variety of nutritional support strategies with the support of trained dieticians to reach nutritional goals. Our trial does thus not provide evidence for effects of single nutritional components, but rather suggests that the overall strategy of providing nutritional support to reach different nutritional goals during a hospital stay for an acute illness is beneficial for patients with cancer. Because nutritional support after discharge was not standardized, and not part of the main protocol focusing on in-hospital nutrition, the impact of continuing nutrition in the outpatient setting remains undefined from our data. Clearly, there is need for additional trials validating our findings in the population of cancer patients including also continued outpatient treatment.

Fourth, we also found significant improvements in functional and quality of life outcomes – a majority concern of patients with cancer [33-37]. A previous trial found no effect of nutritional intervention on quality of life and physical function in patients with cancer[38] and meta-analysis on the topic reported heterogenous results with insufficient overall evidence[39]. Again, as these previous studies focused on different populations and clinical settings, it is important to continue nutritional research in this highly vulnerable population of patients.

Fifth, similar to our study, previous reports found a high prevalence of malnutrition in different types of cancer including gastrointestinal cancers (e.g., pancreatic and gastroesophageal cancer), and in lung cancer and hematological malignancies.[40] A

majority of studies focused on patients with gastrointestinal malignancies as malnutrition may appear early in these types of cancers[41] and nutrition may also improve surgical outcomes for this population[42]. As a limitation, we excluded surgical patients in our initial trial.

Another important population is patients receiving antitumor treatment because treatment-related severe side-effects may lead to anorexia and weight loss.[43-46] Several studies with patients undergoing specific therapies have reported improved outcomes with nutritional support[14, 47]. One Danish trial described the association between intensive, individual dietary counseling and improved weight maintenance and higher provision of protein and energy amounts in patients with gynecologic, gastric or esophageal cancer being treated with radiotherapy and/or chemotherapy.[48, 49] These findings are in line with our report as we also had a large proportion of patients receiving antitumor therapy in the previous year.

Our trial has several strengths and limitations. The main strength is that it is a secondary analysis of a prospective, randomized trial consisting of a large unselected and heterogeneous population. As a result, our patient sample represents a broad spectrum of cancer sites, treatment types and disease severities.
Study limitations include the lack of blinding of participants and personnel, and some variation in the achievement of the individualized caloric and protein. We also excluded patients at end-of-life due to ethical considerations. Regarding tumor activity, we did not break down the individual antitumor therapies. Also, our control group did not receive nutritional care, including supplements, which is standard in some hospitals for patients at nutritional risk. Thus, it is not clear whether our intervention would have been superior to such a standard. While mortality effects

were significant in our analysis, we did not find strong reductions in the risk for adverse outcome – a composite endpoint including severe complications, ICU admission, functional decline and rehospitalization in addition to mortality. In our main trial, we decided to focus on in-hospital nutrition only and nutritional support after discharge was not standardized, and not part of the main protocol. The impact of continuing nutrition in the outpatient setting thus remains undefined from our data. Clearly, there is need for additional trials validating our findings in the population of cancer patients including also continued outpatient treatment. Finally, as only inpatients from the medical ward were included, we have no information about patients primarily hospitalized for surgery.

In conclusion, among hospitalized patients with cancer at nutritional risk, individualized nutritional support reduced the risk for mortality as compared to standard hospital food. These data support malnutrition screening upon hospital admission followed by an individualized nutritional support strategy in this vulnerable patient population. Also, they strengthen the evidence in favor of inclusion of nutritional care in the multi-professional and multidisciplinary management of patients with cancer and in relevant guidelines.

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Disclosures

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Author contributions

LB, CB, JH and PS were responsible for the data analysis and interpretation of this secondary analysis. LB, CB, JH and PS drafted the final manuscript with all authors contributing to critical revision of the manuscript. PS was responsible for obtaining funding. AB, LH, MB, NK, PT were involved in data collection and approved the final version of the manuscript.

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

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

The data underlying this article cannot be shared publicly due to the privacy of patients who participated in this trial. The data will be shared on reasonable request to the corresponding author.

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588
589

590 **Tables and Figure Legend**

591

592 **Figure 1.** Kaplan-Meier estimates stratified by NRS 2002 for 180-day mortality

593 **Figure 2.** Kaplan-Meier estimates of cumulative incidence of all-cause mortality

594 within 30 days according to randomization group

595 **Figure 3.** Odds ratios for mortality within 30 days in prespecified subgroups

596

597 **Table 1: Patient baseline characteristics**BMI = Body Mass Index, NRS =
598 Nutritional Risk Screening 2002; *Other hematological malignomas include essential
599 Thrombozytopenia, Multiple Myeloma and similar illnesses; **Others include
600 pleuramesothelioma, Cancer of unknown Primary and similar
601
602 **Table 2: Association of NRS score and primary and secondary outcomes.**
603 Data represent # of events (%), unless otherwise stated. All odds ratios were
604 calculated with a logistic regression for binary data and linear regression for
605 continuous data. Models were adjusted for patient age, sex, study center, cancer
606 subgroups, tumor activity and treatment. Continuous values as median and IQR,
607 categorical/binary values as absolute number and percentage.
608 *Combined adverse outcome was a composite endpoint and includes all-cause
609 mortality, admission to the intensive care unit from the medical ward, non-elective
610 hospital readmission after discharge, and major complications including adjudicated
611 nosocomial infection, respiratory failure, a major cardiovascular event (i.e., stroke,
612 intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism,
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614 perforation, acute pancreatitis) or a decline in functional status of 10% or more from
615 admission to day 30 measured by the Barthel's index
616 NRS= Nutritional Risk Screening, EQ-5D= Euroquol-5 Dimensions, VAS= Visual
617 Analogue Scale
618
619 **Table 3: Effect of nutritional support on primary and secondary outcomes**
620 Data are number of events (%), unless otherwise stated. All odds ratios were
621 calculated with a logistic regression for binary data and linear regression for
622 continuous data. Models were adjusted for initial nutritional risk screening score and
623 study center. Continuous values as median and IQR, categorical/binary values as
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632 admission to day 30 measured by the Barthel's index
633 NRS= Nutritional Risk Screening 2002, EQ-5D= Euroquol-5 Dimensions, VAS=
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Table 1: Patient baseline characteristics

	Control group	Intervention group
N	251	255
Sociodemographics		
Male sex (%)	152 (60.6%)	146 (57.3%)
Mean age (years) (SD)	71.5 (12.4)	69.2 (13.5)
Nutritional assessment		
Mean BMI (kg/m2) (SD)	24.8 (4.4)	24.2 (5.0)
Mean bodyweight (kg) (SD)	72.8 (13.3)	69.7 (15.8)
NRS 2002 score (%)		
3 points	56 (22.3%)	69 (27.1%)
4 points	88 (35.1%)	88 (34.5%)
5 points	87 (34.7%)	81 (31.8%)
>5 points	20 (8.0%)	17 (6.7%)
Tumor subgroups		
Lung cancer	49 (19.5%)	64 (25.1%)
Gastrointestinal tumors	51 (20.3%)	33 (12.9%)
Colon carcinoma	15 (6.0%)	10 (3.9%)
Rectum carcinoma	14 (5.6%)	6 (2.4%)
Pancreas carcinoma	13 (5.2%)	6 (2.4%)
Hepatocellular carcinoma	9 (3.6%)	11 (4.3%)
Hematological tumors	54 (21.5%)	54 (21.2%)
Leukemia	13 (5.2%)	18 (7.1%)
Lymphoma	39 (15.5%)	34 (13.3%)
Other hematological malignomas*	2 (0.8%)	2 (0.8%)
Other tumors	97 (38.6%)	104 (40.8%)
Breast carcinoma	19 (7.6%)	17 (6.7%)
Prostate carcinoma	16 (6.4%)	20 (7.8%)
Gynecological cancers	12 (4.8%)	14 (5.5%)
Kidney and urothelial cancers	14 (5.6%)	12 (4.7%)
Ear, nose, throat Carcinoma	4 (1.6%)	6 (2.4%)
Genital cancer	4 (1.6%)	3 (1.2%)
Skin cancer	5 (2.0%)	1 (0.4%)
Others**	23 (9.2%)	31 (12.2%)
Tumor activity and treatment		
Inactive	35 (13.9%)	23 (9.0%)
Active	216 (86.1%)	232 (91.0%)
Reason for admission		
Cancer associated failure to thrive	58 (23.1%)	62 (24.3%)
Cancer associated pain	36 (14.3%)	30 (11.8%)
Cancer associated fever and infection	36 (14.3%)	31 (12.2%)
Cancer treatment and other indications	66 (26.3%)	80 (31.4%)
First diagnosis for cancer	55 (21.9%)	52 (20.4%)

BMI = Body Mass Index, NRS = Nutritional Risk Screening 2002; *Other hematological malignomas include essential Thrombozytopenia, Multiple Myeloma and similar illnesses; **Others include pleuramesothelioma, Cancer of unknown Primary and similar

Table 2: Association of NRS score and primary and secondary outcomes.

	NRS 3 points (N=125)	NRS 4 points (N=176)	NRS >4 points (N=205)	type of analysis	Regression analysis per point increase in NRS (unadjusted) (95% CI und p-value)	Regression analysis per point increase in NRS (adjusted) (95% CI and p-value)
Primary outcome						
All-cause mortality within 30 days	15 (12.0%)	31 (17.6%)	40 (19.5%)	HR	1.27 (0.96 to 1.67), p=0.093	1.20 (0.91 to 1.60), p=0.199
Secondary outcomes						
All-cause mortality within 180 days	47 (37.6%)	80 (45.5%)	116 (56.6%)	HR	1.33 (1.17 to 1.56), p=0.001	1.37 (1.15 to 1.61), p=0.0001
*Combined adverse outcome within 30 days	32 (25.6%)	64 (36.4%)	83 (40.5%)	OR	1.38 (1.09 to 1.74), p=0.008	1.42 (1.11 to 1.83), p=0.006
Additional hospital outcome						
Admission to an intensive care unit within 30 days	3 (2.4%)	6 (3.4%)	1 (0.5%)	OR	0.56 (0.25 to 1.25), p=0.159	0.53 (0.21 to 1.34), p=0.180
Non-elective hospital readmission within 30 days	11 (8.8%)	16 (9.1%)	26 (12.7%)	HR	1.23 (0.87 to 1.75), p=0.245	1.29 (0.90 to 1.86), p=0.162
Mean length of index hospital stay (days)	9.0 (6.8)	10.7 (7.4)	11.0 (7.5)	coefficient	0.91 (0.11 to 1.72), p=0.027	1.04 (0.22 to 1.87), p=0.013
Functional outcome						
Decline in functional status of ≥ 10% from admission to day 30	17 (13.6%)	40 (22.7%)	55 (26.8%)	OR	1.47 (1.11 to 1.94), p=0.006	1.50 (1.12 to 2.01), p=0.006
Mean Barthel score at day 30 (points)	96.12 (8.89)	95.06 (10.39)	93.90 (11.28)	Coefficient	-1.11 (-2.26 to 0.04), p=0.058	-1.53 (-2.69 to -0.36), p=0.010
Mean EQ-5D Index at day 30 (points)	0.72 (0.35)	0.65 (0.39)	0.60 (0.39)	Coefficient	-0.06 (0.1 to -0.02), p=0.008	-0.06 (-0.10 to -0.02), p=0.009
Mean EQ-5D VAS at day 30 (points)	51 (28)	45 (30)	42 (31)	Coefficient	-4.74 (-8.36 to -1.13), p=0.01	-4.18 (-7.88 to -0.47), p=0.027

Data represent # of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for patient age, sex, study center, cancer subgroups, tumor activity and treatment. Continuous values as median and IQR, categorical/binary values as absolute number and percentage.
*Combined adverse outcome was a composite endpoint and includes all-cause mortality, admission to the intensive care unit from the medical ward, non-elective hospital readmission after discharge, and major complications including adjudicated nosocomial infection, respiratory failure, a major cardiovascular event (i.e., stroke, intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism, acute renal failure, gastro-intestinal events (including hemorrhage, intestinal perforation, acute pancreatitis) or a decline in functional status of 10% or more from admission to day 30 measured by the Barthel's index
NRS= Nutritional Risk Screening, EQ-5D= Euroquol-5 Dimensions, VAS= Visual Analogue Scale

Table 3: Effect of nutritional support on primary and secondary outcomes

	Control (N=251)	**Intervention group** (N=255)	**type of analysis**	**Regression analysis (adjusted)** (95% CI and p-value)
Primary outcome				
All-cause mortality within 30 days	50 (19.9%)	36 (14.1%)	OR	0.57 (0.35 to 0.94), p=0.027
Secondary outcomes				
Clinical outcome				
Combined adverse outcome within 30 days	93 (37.1%)	86 (33.7%)	OR	0.81 (0.56 to 1.19), p=0.288
Additional hospital outcomes				
Admission to an intensive care unit within 30 days	6 (2.4%)	4 (1.6%)	OR	0.62 (0.16 to 2.5), p=0.503
Non-elective hospital readmission within 30 days	22 (8.8%)	31 (12.2%)	OR	1.53 (0.85 to 2.75), p=0.159
Mean length of stay stay of index hospital stay (days)	10.4 (6.9)	10.4 (7.8)	HR	1.14 (0.93 to 1.40), p=0.206
Functional outcome				
Decline in functional status of ≥ 10% from admission to day 30	67 (26.7%)	45 (17.6%)	OR	0.59 (0.38 to 0.93), p=0.021
Mean Barthel Index score at day 30 (points)	94.72 (10.68)	94.98 (10.21)	Coefficient	0.6 (-1.16 to 2.36), p=0.506
Mean EQ-5D Index at day 30 (points)	0.62 (0.39)	0.67 (0.37)	Coefficient	0.08 (0.01 to 0.15), p=0.016
Mean EQ-5D VAS at day 30 (points)	43 (30)	48 (29)	Coefficient	6.16 (0.51 to 11.8), p=0.033
Long-term mortality				
All-cause mortality within 180 days	128 (52.7%)	115 (47.3%)	HR	0.83 (0.65 to 1.08), p=0.18

Data are number of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for initial nutritional risk screening score and study center. Continuous values as median and IQR, categorical/binary values as absolute number and percentage.

*****Combined adverse outcome was a composite endpoint and includes all-cause mortality, admission to the intensive care unit from the medical ward, non-elective hospital readmission after discharge, and major complications including adjudicated nosocomial infection, respiratory failure, a major cardiovascular event (i.e., stroke, intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism, acute renal failure, gastro-intestinal events (including hemorrhage, intestinal perforation, acute pancreatitis) or a decline in functional status of 10% or more from admission to day 30 measured by the Barthel's index

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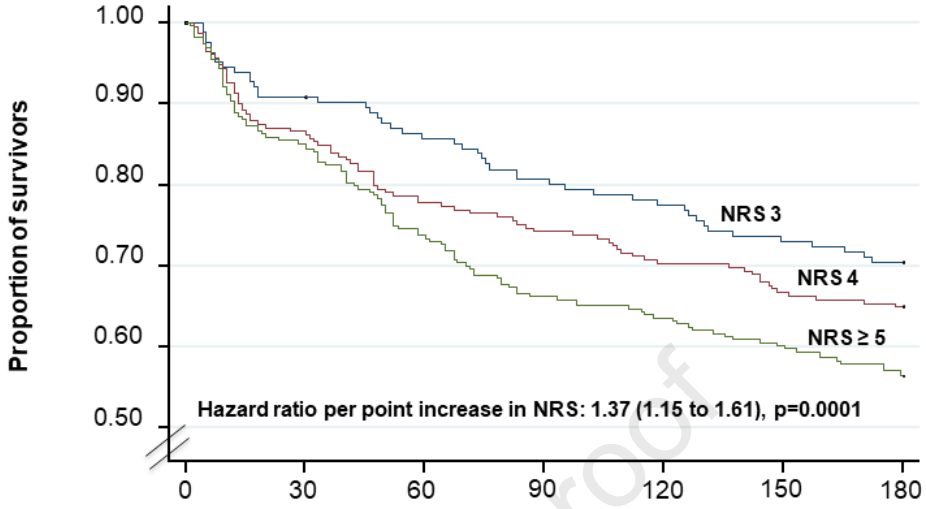
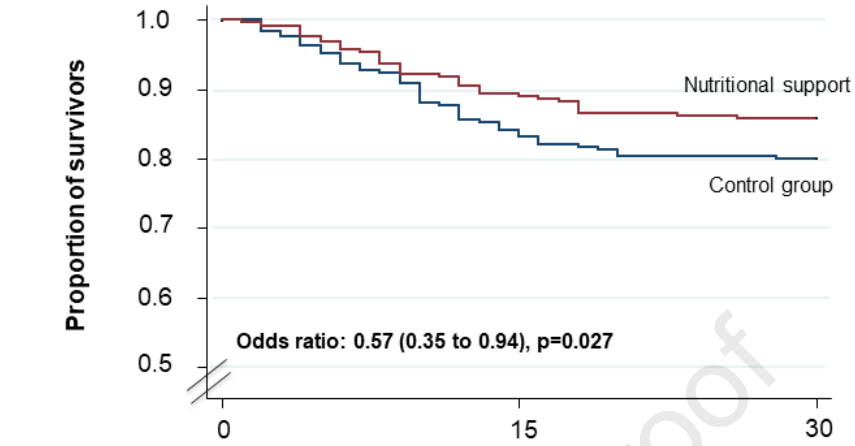


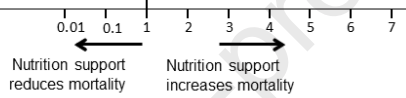
Number at risk

Moderate nutrition risk (NRS 3)	125	110	97	89	84	77	73
High nutrition risk (NRS 4)	176	145	122	114	105	97	93
Very high nutrition risk (NRS ≥5)	205	165	132	112	105	96	86



Number at risk			
Control group	251	211	201
Intervention group	255	228	219

	Control group (n/N (%))	Intervention group (n/N (%))	Adjusted odds ratio (95% CI)	P interaction
All patients	50/251 (19.9%)	36/255 (14.1%)	0.57 (0.35 to 0.94)	
Age (years)				
Age <65	8/58 (14%)	10/87 (11%)	0.66 (0.20 to 2.17)	0.902
Age 65-75	15/78 (19%)	10/68 (15%)	0.53 (0.20 to 1.40)	
Age>75	27/115 (23.5%)	16/100 (16.0%)	0.59 (0.28 to 1.23)	
Sex				
Male	34/152 (22.4%)	23/146 (15.8%)	0.51 (0.27 to 0.98)	0.714
Female	16/99 (16.2%)	13/109 (11.9%)	0.49 (0.20 to 1.22)	
Risk for malnutrition				
NRS 3 points	6/56 (11%)	9/69 (13%)	1.33 (0.42 to 4.19)	0.891
NRS 4 points	22/88 (25%)	9/88 (10%)	0.19 (0.07 to 0.52)	
NRS ≥5 points	22/107 (20.6%)	18/98 (18.4%)	0.83 (0.38 to 1.82)	
Cancer subgroups				
Lung cancer	10/49 (20%)	13/64 (20%)	0.98 (0.28 to 3.35)	0.532
Gastrointestinal cancers	12/51 (24%)	4/33 (12%)	0.25 (0.06 to 1.10)	0.459
Hematological cancers	11/54 (20%)	6/54 (11%)	0.38 (0.11 to 1.38)	0.334
Other cancers	17/97 (17.5%)	13/104 (12.5%)	0.65 (0.27 to 1.55)	0.409
Tumoractivity and treatment				
Inactive	4/35 (11%)	1/23 (4%)	0.25 (0.02 to 2.95)	0.273
Active	46/216 (21.3%)	35/232 (15.1%)	0.56 (0.33 to 0.94)	
Reason for admission				
Cancer associated failure to thrive	19/58 (33%)	12/62 (19%)	0.36 (0.13 to 0.95)	0.427
Cancer associated pain	9/36 (25%)	5/30 (17%)	0.85 (0.17 to 4.27)	0.794
Cancer associated fever and infection	3/36 (8%)	4/31 (13%)	0.41 (0.03 to 6.12)	0.190
Cancer treatment and other reasons	8/66 (12%)	8/80 (10%)	0.74 (0.21 to 2.63)	0.470
First diagnosis for cancer	11/55 (20%)	7/52 (13%)	0.55 (0.16 to 1.81)	0.731



Nutrition support reduces mortality

Nutrition support increases mortality