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Value of handgrip strength to predict clinical outcomes and therapeutic response in malnourished medical inpatients: *Secondary analysis of a randomized controlled trial*

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Abbreviations:

BMI: body mass index

HGS: handgrip strength

ICU: intensive care unit

LOS: length of hospital stay

NRS 2002: Nutritional Risk Screening 2002

OR: odd ratio

VIF: variance inflation factor

Abstract

Background: Disease-related malnutrition is associated with loss of muscle mass and impaired functional status. Handgrip strength (HGS) has been proposed as an easy-to-use tool to assess muscle strength in clinical practice.

Objective: We investigated the prognostic implications of HGS in patients at nutritional risk with regard to clinical outcomes and response to nutritional support.

Design: This was a secondary analysis of the randomized controlled, multicenter, EFFORT trial, which compared the effects of individualized nutritional support with usual hospital food in medical inpatients at nutritional risk. Our primary endpoint was 30-day all-cause mortality. The association between sex-specific HGS and clinical outcomes was investigated using multivariable regression analyses, adjusted for randomization, age, weight, height, nutritional risk, admission diagnosis, comorbidities, interaction terms and study center. We used interaction terms to investigate possible effect modification regarding the nutritional support intervention.

Results: Mean HGS in the 1,809 patients with available handgrip measurement was 17.0 (±7.1) kg for females and 28.9 (±11.3) kg for males. Each decrease of 10 kg in HGS was associated with increased risk of 30-day mortality (female: adjusted OR 2.11 (95% CI 1.23, 3.62), p=0.007, male: adjusted OR 1.44 (1.07, 1.93), p= 0.015) and 180-day mortality (female: adjusted OR 1.45 (95% CI 1.0, 2.10), p=0.048, male: adjusted OR 1.55 (1.28, 1.89), p<0.001). Individualized nutritional support was most effective in reducing mortality in patients with low HGS (adjusted OR 0.29 (95% CI 0.10, 0.82) in patients in the ≤10thpercentile vs. OR 0.98 (95% CI 0.66, 1.48) in patients in >10thpercentile, p for interaction 0.026).

Conclusions: In medical inpatients at nutritional risk, handgrip strength provided significant prognostic information about expected mortality and complication risks and

helps to identify which patients benefit most from nutritional support. Handgrip strength may thus improve individualization of nutritional therapy.

Keywords: handgrip strength, malnutrition, nutritional support, functional decline, mortality

Introduction

According to current literature, 30-50% of polymorbid medical inpatients are at risk for malnutrition, a condition that is strongly associated with higher mortality and morbidity, functional decline, prolonged hospital stay and increased health care costs (1-3). During hospitalization, several factors contribute to a further deterioration of nutritional status, including disease-related anorexia, immobilization as well as inflammatory and endocrine stress response (4, 5). Reduced nutrients intake leads to serious protein and energy deficits, which again result in muscle wasting, impairment of muscle strength and functional capacity, respectively, in addition to increased susceptibility to complications and higher mortality (4, 6).

Handgrip strength (HGS) has been proposed as an easy-to-use, noninvasive, objective and inexpensive tool to detect and monitor changes in nutritional status, and to predict functional decline during hospitalization and post discharge (7-10). Use of HGS has thus been endorsed by numerous international clinical nutrition guidelines (11-14) and may provide additional information about the severity of malnutrition. The Global Leadership Initiative on Malnutrition (GLIM) criteria for the diagnosis of malnutrition listed HGS as a possible criterium to define malnutrition (15). However, it remains unclear whether HGS measurement may help support individualization of nutritional therapy by identifying patients with favorable or lack of response to nutritional treatment (16, 17).

The current study is a preplanned secondary analysis of the Effect of Early Nutritional Support on Frailty, Functional Outcome, and Recovery of Malnourished Medical Inpatients Trial (EFFORT) (18) specifically analyzing if HGS in medical inpatients at nutritional risk provides additional prognostic information on various long- and short-term clinical outcomes, and whether HGS may help predict patient response to nutritional support.

Materials and Methods

Study design and setting

This is a secondary analysis of the EFFORT, which was a pragmatic, investor-initiated, open-label, randomized controlled trial conducted in eight Swiss hospitals between April 2014 and February 2018. The original study investigated the effects of protocol-guided individualized nutritional treatment algorithm on medical outcomes in patients at nutritional risk. The protocol and the main results have been published previously (18, 19).

The Ethics Committee of Northwest / Central Switzerland (EKNZ) approved the study protocol in January 2014 (EKNZ; 2014_001). The eight participating sites were secondary and tertiary care hospitals in Switzerland and included the University Clinic in Aarau, the University Hospital in Bern, the cantonal hospitals in Lucerne, Solothurn, St. Gallen, Muensterlingen, Baselland, and the hospital in Lachen.

Patient population

For our analysis, we included all patients from the original trial with recorded HGS measurements at time of admission. EFFORT had originally enrolled consecutive adult patients with a Nutritional Risk Screening 2002 (NRS 2002) total score ≥3 points, an expected length of hospital stay (LOS) >4 days and willingness to provide informed consent. Patients initially admitted to an intensive care unit or surgical unit were excluded. Other exclusion criteria were inability to tolerate oral nutrition intake, nutritional support at time of admission, existence of certain diseases (anorexia nervosa, acute pancreatitis, acute liver failure or cystic fibrosis), terminal condition, stem cell transplantation, history of gastric bypass surgery, contraindications for nutritional support, and previous inclusion in the trial.

148 ***Assessment of handgrip strength***

149 At time of admission, trained dieticians performed HGS measurement with a
150 dynamometer (North Coast Medical Exacta™ Hydraulic Hand Dynamometer (20)).
151 Unit of measurement was kilograms and measurements were performed in seated
152 position using the dominant hand at a 90°angle position without contacting any
153 surface (21). The patients performed three attempts, interrupted by a one-minute
154 break, and the highest result was collected.

155

156 ***Assessment of nutritional status and nutritional intervention***

157 All sites routinely screened their newly admitted patients with the Nutritional Risk
158 Screening 2002 (NRS 2002)(22) within 24-48 h. This is a validated tool that includes
159 the assessment of nutritional status (based on weight loss, body-mass index (BMI)
160 and general condition or food intake), as well as disease severity (stress metabolism)
161 and age. Parameters used to assess nutritional status and disease severity score
162 from 0-3 points and age >70 years adds one extra point. Patients with an NRS ≥3
163 points are considered “at risk” of malnutrition and were eligible for inclusion in the
164 trial.

165 In the intervention group, nutritional support based on an individualized treatment
166 algorithm was initiated as soon as possible after 1:1 randomization and within 48 h
167 after hospital admission (23, 24). Registered dietitians defined individualized energy
168 and protein goals and designed a nutritional plan initially based on oral nutrition. A
169 stepwise escalation to enteral tube feeding and parenteral nutrition was planned if
170 nutritional goals were not reached (<75%) within 5 days. Nutritional intake and the
171 need to adapt the nutrition care plan was reassessed every 24-48 h during hospital
172 stay. The intervention was discontinued upon hospital discharge and further

nutritional support including oral nutritional supplements was left to the discretion of the treating team.

Control group patients received usual hospital food without further nutritional consultation.

Outcomes

Our primary endpoint was 30-day all-cause mortality. We prespecified short-term and long-term secondary endpoints. Short-term outcomes were defined as follows: adverse clinical outcomes within 30 days, defined as the primary composite endpoint of the original trial (including all-cause mortality, admission to intensive care unit (ICU), 30-day readmission rate, major complications and functional decline), as well as the individual components of the composite endpoint and length of hospital stay. Thirty-day readmission rate was defined as non-elective hospital readmission after discharge. Major complications included nosocomial infection, respiratory failure, a major cardiovascular event, acute renal failure or gastro-intestinal failure during hospitalization. Performance of daily living activities was assessed by Barthel index (with a scale ranging from 0 to 100, being a higher score indicative of less disability with self-care and mobility), and functional impairment was defined as a decline in the Barthel index of 10% or more.

Long-term secondary outcomes were defined as follows: mortality, quality of life and incidence of falls during the 180-days follow-up period. Quality of life was assessed using: a) the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), which ranges from 0 to 1, with higher scores indicating better life quality, and b) the EQ-5D visual analogue scale (VAS) from 0 to 100, with higher scores indicating better health status.

Outcome assessment was performed by blinded study nurses who performed a structured telephone interview at 30 days and 180 days after inclusion of the participant in the trial. Family members or family physicians were contacted when verification of survival status was necessary.

Statistical analysis

Categorical and binary variables are expressed as counts and percentages, and continuous variables as means and standard deviations. To compare the baseline characteristics between the intervention and the control group we used Student's t-test for the continuous and Pearson's chi-square test for categorical and binary variables.

To investigate the different predictors of HGS we calculated uni- and multivariate linear regression models and reported coefficients and 95% confidence intervals (CI). Multivariate regression analysis included sex, age, weight, height, NRS 2002 score, main diagnoses (i.e., oncologic, cardiovascular, infectious, renal, frailty), comorbidities (i.e., hypertension, tumor, renal insufficiency, chronic heart failure and diabetes mellitus). Because sex is a known predictor of HGS, we performed sex-specific analysis using interaction terms to assess possible effect modification of sex on other predictors of HGS. We also investigated potential interactions between age and other covariates, and found age to be a significant effect modifier of the association between HGS and weight, height, the main diagnosis of frailty and the comorbidity of diabetes.

To validate the sex-specific multivariate regression model, we assessed normal distribution of prediction errors visually and performed a Cameron & Trivedi's test to assess their homoskedasticity. Furthermore, we validated the multivariate regression model by means of the variance inflation factors (VIF), which showed low collinearity

among all the covariates (highest VIF 1.80 for “oncologic disease as main diagnosis”). For further analyses, we used sex-specific regression models. In the adjusted models we included important confounders and interaction terms (as specified in the multivariate regression analysis for predictors of HGS) as well as randomization group and study center.

The association between sex-specific HGS and clinical outcomes was investigated using logistic regression analyses for categorical variables with reporting of odd ratios (ORs) and linear regression for continuous variables with reporting of coefficients which corresponds to differences.

Finally, we studied the effect of nutritional support on 30-day mortality and performed logistic regression models adjusted for the same covariates as mentioned above. We included interaction terms in the statistical models to investigate whether there was evidence for effect modification due to HGS at admission (“low HGS” vs “high HGS”). Low HGS was defined as ≤10^{th} percentile of the population (female: ≤8kg, male ≤16kg), while high HGS was defined as >10^{th} of sex-specific percentile. In this context, we calculated separate Kaplan-Meier survival curves according to HGS subgroups and used Cox regression analysis to report hazard ratios (HRs).

All statistical analyses were performed with STATA 15.1 (Stata Corp, College Station, TX, USA). A *P* value <0.05 (for a 2-sided test) was considered to indicate statistical significance. We did not adjust p-values for multiple testing.

Results

Patient population

Of the initial population of 2,028 patients providing informed consent, complete data on initial HGS measurement from 1,809 (89.2%) individuals were available (**Figure 1**). Baseline characteristics for all patients included in this analysis, stratified

according to sex and randomization status, are shown in **Table 1**. The overall mean (SD) HGS was 23.3 (±11.2) kg, with lower values in females (17.0 ±7.1) compared to males (28.9 ±11.3). Patients had a mean age of 72.3 years and 47.4% were females. The most common admission diagnoses were infectious disease (31.0%), followed by oncologic disease (17.6%) and cardiovascular disease (10.0%). Patients had high levels of comorbidities, particularly hypertension (53.7%), tumor (32.1%), chronic kidney failure (31.0%), coronary heart disease (28.5%), diabetes mellitus (21.2%) and chronic heart failure (17.2%). After stratification by sex, baseline characteristics were equally distributed between the control and intervention groups, except for a higher incidence of oncologic and gastroenterological main diagnosis in the male intervention group.

Association between patient, disease factors and handgrip strength

As a first step, we investigated predictors for low HGS in our population. **Table 2** shows associations of various baseline characteristics with HGS resulting from a multivariate regression model. Being a male was associated with higher HGS (difference between female and males: 8.36 kg (95% CI 7.41, 9.31), p<0.001), while increasing age was associated with lower HGS (decrease per year -0.25 kg (-0.28, 0.22), p<0.001). Anthropometric measurements such as weight and height showed positive association with HGS (increase per kg body weight 0.1 kg (95% CI 0.07, 0.13), p<0.001; increase per cm 0.2 kg (95% CI 0.14, 0.26), p<0.001). Nutritional risk assessed on admission was associated with lower HGS (difference between NRS ≥5 points and NRS 3 points: -1.25 kg (95% CI -2.24, -0.26, p=0.013)).

HGS did not differ according to admission diagnoses. With regard to comorbidities, there was an association between lower HGS values and tumor, chronic kidney failure, chronic heart failure, and diabetes mellitus.

In the sex-specific analyses most associations remained robust. However, there was a significant interaction between sex and several anthropometric and disease-specific predictors of HGS (age, weight, height, renal insufficiency and chronic heart failure (p for interaction < 0.05, see Table 2). Similarly, we found interactions between age and male sex, weight, height, admission diagnosis of frailty and the comorbidity diabetes, p for interaction < 0.05).

Associations between baseline factors and HGS from univariable analyses are shown in **Supplementary Table 1**.

Association of handgrip strength and clinical outcomes

As a second step, we investigated the sex-specific prognostic value of HGS with regard to clinical endpoints (**Table 3**). For female patients a 10 kg decrease in HGS was associated with more than a doubling of the 30-day all-cause mortality risk (adjusted OR 2.11 (1.23, 3.62), p=0.007). Male patients also showed this association with an increase of almost 50% of the 30-day mortality (adjusted OR 1.44 (1.07, 1.93), p=0.015). Regarding our primary endpoint, gender was a statistically significant effect modifier (p for interaction 0.047).

We also found a significant association between HGS and the composite endpoint "adverse clinical outcome" (female: adjusted OR 1.38 (95% CI 1.03, 1.84), p<0.030, male: adjusted OR 1.33 (1.11, 1.59), p=0.002), major complications (female: adjusted OR 1.65 (1.02, 2.67), p=0.040, male: adjusted OR 1.56 (1.16, 2.09), p= 0.003), LOS (female: adjusted difference 1.05 days (95% CI 0.37, 1.74), p<0.003; male: adjusted difference 1.16 days (95% CI 0.67, 1.65), p<0.001). Also, in female patients, lower HGS was associated with a ≥10% decrease in functional status (adjusted OR 1.7 (1.11, 2.61), p= 0.015). Additionally, there were significant

associations between HGS and long-term endpoints such as 180-day all-cause mortality (female: adjusted OR 1.45 (95% CI 1.00, 2.1), p=0.048; male: adjusted OR 1.56 (95%CI 1.28, 1.89), p<0.001) and quality of life measures, as well as falls in the subgroup of females (adjusted OR 1.80 (95% CI 1.23, 2.68), p=0.003). Except for the primary outcome, there was little difference between female and male patients in regard to these associations (see Table 3, p for interaction).

Effect of nutritional support on 30-day mortality according to handgrip strength groups

As a final step, we investigated whether low HGS (≤10th percentile) could predict the response to nutritional treatment intervention in male and female patients. Compared to patients with higher HGS measurements (>10th percentile), patients within the lowest sex-specific handgrip decile (≤8 kg for females and ≤16 kg for males) showed a significantly pronounced reduction of 30-day mortality in response to nutritional treatment (adjusted OR 0.29 (95% CI 0.10, 0.82) vs. 0.98 (95% CI 0.66, 1.48). This difference was also significant when tested for effect modification (p-for interaction 0.026). Our sex-specific analysis showed a significant difference between male and female patients: Male patients with a HGS ≤10th percentile showed a pronounced association between nutritional support and mortality compared to female patients with low HGS (**Table 4)**. The effect of nutritional support on 30-day mortality stratified by HGS groups is also illustrated in a Kaplan Meier curve (**Figure 2 A&B**).

Discussion

The present secondary analysis produced three main findings. First, there are several strong predictors of reduced HGS: older age, female sex, shorter height and low weight, poor nutritional status as well as certain comorbidities, particularly

malignant disease, chronic kidney disease, chronic heart failure and diabetes mellitus. Second, in addition to other clinical outcomes, there is a marked negative association between HGS and mortality. Third, the most favorable response to nutritional support was found in patients with lowest sex-specific HGS (≤10th percentile).

There is abundant literature on potential influence factors of HGS in healthy controls, as well as in hospitalized medical patients (25, 26). The most frequently proposed influence factors to date are height, weight, sex and age (8, 26, 27). Our analysis found a negative association of HGS with age and female sex, as well as a positive association with height and weight, and is therefore in line with existing literature. Furthermore, we found a significant association between HGS and the degree of malnutrition expressed by higher scores of the NRS 2002. Similar findings have been published by Norman et al, who described decreased HGS in malnourished hospitalized patients using the Subjective Global Assessment (SGA) (28). Therefore, along with being a marker of functional capacity, HGS might also be a possible marker for malnutrition. (29).

Our analysis also showed a significant association of HGS and different clinical outcomes, most notably with short- and long-term mortality. In fact, an incremental decrease of handgrip strength by 10 kg resulted in more than doubling in 30-day mortality in females and a 50% increase in 30-day mortality in males. Long-term 180-day all-cause mortality was also significantly higher with lower HGS (approximately 50% in both sexes). These results persisted after adjustment for important confounders such as socio-demographic factors, nutritional status, main admission diagnosis, comorbidities and study center. Hence, this confirms a strong and independent prognostic value of HGS to predict mortality at short- and long-term.

These findings are in line with previous studies demonstrating similar associations (29-31). The clinical implications of the increased risk as assessed by HGS measurement needs further evaluation.

Finally, HGS may even be used to predict the response to nutritional intervention. In our analysis, subjects in the lowest sex-specific handgrip decile (<10th percentile) particularly benefited from nutritional support in regards to reduction of mortality. HGS may thus facilitate the individualization of nutritional therapy. To the best of our knowledge, we are the first to demonstrate this effect. While the current concept of selecting patients for the provision of nutritional support mainly focuses on the nutritional history of patients including changes in appetite and weight as assessed through malnutrition screening tools (16, 32, 33), other patient and illness related factors such as severity of inflammation (34), specific comorbidities and specific nutritional blood markers (35) may provide additional information. Herein, HGS may provide additional information that could be helpful in identifying patients who will most benefit from a nutritional support intervention. Considering the important influence of gender on our results, sex-specific HGS cut-off values should be used in the future for decision making.

The present analysis has several strengths and limitations worth mentioning. One strength of this study is its unselected and heterogeneous non-critically ill medical population, prospectively included and randomized in the EFFORT trial (18, 19). High adherence to the study protocol in the main trial further increased the value of data collected. Even though approximately 20% of patients in the intervention group did not reach their estimated energy or protein goals (45% of the patients in the control group and 18% of the nutritional intervention group), nevertheless results did not lose validity. On the contrary, one can expect that additional provision of energy will

reduce mortality in the intervention group even more. Additionally, reaching the nutritional goal did not differ significantly between the patients with high (67.8%) and the patients with low HGS (66.7%), p=0.740.

There were, however, some weaknesses: First, it was a secondary analysis with limitations in terms of power. Due to the small sample size, there is a possibility of type II error in the analysis of the predictive value of HGS for the benefit of nutritional support, especially in the sex-specific analysis. Within our analysis, we performed several exploratory analyses and included a high number of covariates into statistical models with the risk for model overfitting type I error. Validation of our results is thus necessary. Secondly, in regard to the initial EFFORT trial it included non-blinded patients and dieticians. Data on handgrip strength was not available for the whole study population, which could lead to a potential selection bias. Furthermore, we did not include critically ill and surgical patients, which makes our findings only applicable to medical inpatients.

In conclusion, for medical inpatients at nutritional risk, HGS provided significant prognostic information on expected mortality and complication risks and helped in the identification of patients who most benefit most from nutritional support. The result is a more personalized approach and improved cost-effectiveness of nutritional interventions.

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Tables and Figure Legends

Table 1. Baseline characteristics overall, and stratified by sex and randomization[1)]

	Overall	Female			Male		
		No nutritional support	Nutritional support		No nutritional support	Nutritional support	
	(n=1809)	(n=428)	(n=429)	p value[1)]	(n=481)	(n=471)	p value[1)]
Handgrip strength (mean, SD)	23.3 (11.2)	17.0 (6.7)	17.0 (7.5)	0.970	29.0 (11.4)	28.8 (11.2)	0.780
Sociodemographic factors							
Age (years), mean (SD)	72.3 (14.2)	72.9 (13.8)	73.2 (14.4)	0.780	72.2 (14.2)	71.1 (14.2)	0.240
Nutritional status							
BMI (kg/m2), mean (SD)	24.9 (5.3)	24.6 (5.7)	24.7 (5.9)	0.710	25.1 (4.8)	25.2 (4.8)	0.690
Weight (Kg), mean (SD)	71.0 (16.7)	65.5 (15.3)	65.4 (16.4)	0.980	75.8 (15.7)	76.0 (15.9)	0.810
NRS 2002 score = 3	573 (31.7%)	129 (30.1%)	126 (29.4%)	0.610	159 (33.1%)	159 (33.8%)	0.410
NRS 2002 score = 4	690 (38.1%)	162 (37.9%)	176 (41.0%)		187 (38.9%)	165 (35.0%)	
NRS 2002 score ≥ 5	546 (30.2%)	137 (32.0%)	127 (29.6%)		135 (28.1%)	147 (31.2%)	
Main diagnosis, n (%)							
Infection	560 (31.0%)	128 (29.9%)	129 (30.1%)	0.960	163 (33.9%)	140 (29.7%)	0.170
Oncologic disease	319 (17.6%)	72 (16.8%)	69 (16.1%)	0.770	78 (16.2%)	100 (21.2%)	0.047
Cardiovascular disease	181 (10.0%)	50 (11.7%)	37 (8.6%)	0.140	49 (10.2%)	45 (9.6%)	0.740
Frailty	176 (9.7%)	45 (10.5%)	46 (10.7%)	0.920	43 (8.9%)	42 (8.9%)	0.990
Lung disease	109 (6.0%)	26 (6.1%)	20 (4.7%)	0.360	39 (8.1%)	24 (5.1%)	0.062
Gastrointestinal disease	153 (8.5%)	31 (7.2%)	42 (9.8%)	0.180	30 (6.2%)	50 (10.6%)	0.015
Neurological/psychiatric disease	88 (4.9%)	25 (5.8%)	23 (5.4%)	0.760	25 (5.2%)	15 (3.2%)	0.120
Renal disease	59 (3.3%)	12 (2.8%)	13 (3.0%)	0.840	16 (3.3%)	18 (3.8%)	0.680
Metabolic disease	54 (3.0%)	16 (3.7%)	17 (4.0%)	0.860	13 (2.7%)	8 (1.7%)	0.290
Other	46 (2.5%)	6 (1.4%)	9 (2.1%)	0.440	17 (3.5%)	14 (3.0%)	0.630
Comorbidities, n (%)							
Hypertension	971 (53.7%)	228 (53.3%)	238 (55.5%)	0.520	260 (54.1%)	245 (52.0%)	0.530
Tumor	580 (32.1%)	114 (26.6%)	123 (28.7%)	0.510	174 (36.2%)	169 (35.9%)	0.920
Renal failure	560 (31.0%)	123 (28.7%)	130 (30.3%)	0.620	158 (32.8%)	149 (31.6%)	0.690
Coronary heart disease	515 (28.5%)	96 (22.4%)	99 (23.1%)	0.820	157 (32.6%)	163 (34.6%)	0.520
Diabetes mellitus	384 (21.2%)	79 (18.5%)	74 (17.2%)	0.640	110 (22.9%)	121 (25.7%)	0.310
Chronic heart failure	311 (17.2%)	73 (17.1%)	55 (12.8%)	0.082	86 (17.9%)	97 (20.6%)	0.290

NRS 2002 = Nutritional Risk Screening 2002[1)] statistical tests of difference were Student's t-test for the continuous and Pearson's chi-square test for categorical variables

Table 2. Predictors of handgrip strength

	Patients without characteristic (Reference group)	**Patients with characteristic**	**Overall** n=1809		**Female** n=857		**Male** n=952		**p for interaction for sex**
	HGS mean (SD),	HGS mean (SD)	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	
Sociodemographic									
Male sex	17.01 (7.09)	28.87 (11.28)	8.36 (7.41, 9.31)	<0.001	-		-		
Age	-	-	-0.25 (-0.28, -0.22)	<0.001	-0.17 (-0.20, -0.13)	<0.001	-0.32 (-0.36, -0.27)	<0.001	<0.001
Anthropometric measurements	-	-							
Weight (kg)	-	-	0.10 (0.07, 0.13)	<0.001	0.03 (0.00, 0.06)	0.064	0.16 (0.12, 0.20)	<0.001	<0.001
Height (cm)	-	-	0.20 (0.14, 0.26)	<0.001	0.21 (0.15, 0.28)	<0.001	0.16 (0.07, 0.25)	<0.001	0.036
Nutritional status									
NRS 2002 score = 3	-	25.12 (11.58)	reference		reference		reference		
NRS 2002 score = 4	-	23.57 (11.64)	-0.66 (-1.55, 0.24)	0.151	-0.81 (-1.81, 0.20)	0.115	-0.46 (-1.87, 0.94)	0.518	0.903
NRS 2002 score ≥ 5	-	20.9 (9.79)	-1.25 (-2.24, -0.26)	0.013	-1.46 (-2.55, -0.37)	0.009	-1.01 (-2.58, 0.57)	0.210	0.105
Main diagnosis									
Oncologic disease	22.98 (11.21)	24.52 (11.17)	1.0 (-0.28, 2.29)	0.126	0.15 (-1.32, 1.62)	0.843	1.21 (-0.78, 3.20)	0.232	0.737
Cardiovascular disease	23.55 (11.20)	20.58 (11.06)	0.29 (-1.17, 1.74)	0.698	-0.21 (-1.79, 1.38)	0.797	0.38 (-1.97, 2.73)	0.752	0.452
Infection	22.97 (11.27)	23.89 (11.08)	0.21 (-0.76, 1.17)	0.676	0.61 (-0.46, 1.68)	0.262	-0.11 (-1.65, 1.43)	0.889	0.669
Renal failure	23.29 (11.27)	22.10 (9.36)	-0.75 (-2.93, 1.43)	0.502	0.76 (-1.78, 3.30)	0.558	-1.44 (-4.76, 1.89)	0.396	0.315
Frailty	23.42 (11.11)	21.66 (12.04)	-0.68 (-2.05, 0.69)	0.333	-0.92 (-2.38, 0.54)	0.217	-0.32 (-2.58, 1.95)	0.784	0.738
Comorbidities									
Hypertension	25.17 (11.46)	21.60 (10.74)	-1.14 (-2.08, -0.20)	0.623	-1.05 (-1.96, -0.13)	0.025	1.13 (-0.16, 2.42)	0.087	0.606
Malignant disease	23.12 (11.44)	23.54 (10.72)	-1.09 (-1.98, -0.21)	0.018	0.16 (-0.95, 1.27)	0.779	-1.61 (-3.05, -0.18)	0.028	0.190
Chronic kidney disease	24.44 (11.50)	20.60 (10.06)	-2.20 (-3.29, -1.11)	0.016	-0.85 (-1.85, 0.15)	0.094	-1.26 (-2.64, 0.11)	0.072	0.021
Chronic heart failure	23.88 (11.46)	20.25 (9.39)	-1.46 (-2.41, -0.52)	<0.001	-0.69 (-1.96, 0.57)	0.282	-3.31 (-4.98, -1.63)	<0.001	0.003
Diabetes mellitus	23.49 (11.49)	22.36 (10.11)	-1.14 (-2.08, -0.20)	0.002	-0.14 (-1.27, 0.98)	0.805	-2.17 (-3.59, -0.76)	0.003	0.158

Multivariate linear regression analysis including all baseline characteristics listed in this table. Values are means (SD) and regression coefficients (95% CI).

NRS 2002 = Nutritional Risk Screening 2002

Table 3: Association of handgrip strength with short- and long-term outcomes grouped by gender (adjusted analysis)

	A) Female (n=857)				B) Male (n=952)				p for interaction
	Patients with no event **(Reference group)**	Patients with event	HGS decrease (- 10kg)		Patients with no event **(Reference group)**	Patients with event	HGS decrease (- 10kg)		
	Mean HGS (SD)	Mean HGS (SD)	OR or *Coefficient (95% CI), adjusted[1)]	p value	Mean HGS (SD)	Mean HGS (SD)	OR or *Coefficient (95% CI), adjusted[1)]	p value	
Primary endpoint									
30-day all-cause mortality	17.23 (7.06)	13.49 (6.69)	2.11 (1.23 to 3.62)	0.007	29.24 (11.09)	24.91 (12.48)	1.44 (1.07 to 1.93)	0.015	0.047
Short-term endpoints									
Adverse clinical outcome within 30 days	17.31 (7.07)	15.9 (7.07)	1.38 (1.03 to 1.84)	0.030	29.78 (11.2)	26.23 (11.1)	1.33 (1.11 to 1.59)	0.002	0.644
Admission to ICU	17.02 (7.13)	16.4 (4.73)	1.58 (0.68 to 3.68)	0.288	28.99 (11.31)	24.71 (9.41)	1.61 (0.99 to 2.61)	0.056	0.983
Any major complication	17.15 (7.08)	15.06 (6.94)	1.65 (1.02 to 2.67)	0.040	29.29 (11.34)	24.07 (9.39)	1.56 (1.16 to 2.09)	0.003	0.913
Mean length of stay (days)	-	-	*1.05 (0.37, 1.74)	0.003			*1.16 (0.67 to 1.65)	0.000	0.822
Non-elective hospital readmission within 30 days	16.94 (7.12)	17.79 (6.7)	0.84 (0.56 to 1.28)	0.417	28.91 (11.4)	28.47 (10.09)	1.02 (0.8 to 1.31)	0.881	0.394
Decline in functional status of ≥10% after 30 days	17.29 (7.07)	14.26 (6.74)	1.7 (1.11 to 2.61)	0.015	29.37 (11.06)	25.59 (12.18)	1.26 (1 to 1.59)	0.054	0.072
Mean Barthel index score (points) after 30 days	-	-	*-2.23 (-3.26 to -1.19)	<0.001	-	-	*-1.81 (-2.49 to -1.14)	0.000	0.513
Long-term endpoints									
180-day all-cause mortality	17.49 (7.11)	14.83 (6.58)	1.45 (1.0, 2.1)	0.048	30.18 (11.24)	25.1 (10.53)	1.55 (1.28 to 1.89)	0.000	0.645
Mean EQ-5D VAS (points) after 180 days	-	-	*-3.8 (-6.57 to -1.02)	0.008	-	-	*-2.12 (-3.99 to -0.24)	0.027	0.146
Mean EQ-5D index (points) after 180 days	-	-	*-0.05 (-0.08 to -0.03)	<0.001	-	-	*-0.01 (-0.03 to 0)	0.059	0.012
Incidence of one or more falls within 180 days	17.35 (7.11)	14.71 (6.33)	1.8 (1.23 to 2.63)	0.003	29.09 (11.21)	26.2 (11.3)	1.21 (0.94 to 1.55)	0.138	0.082

HGS = handgrip strength. ICU indicates intensive care unit.

Multivariable logistic regression models reporting gender-specific odd ratios (95% CI). Linear regression models were used for continuous variables resulting in regression coefficients (marked with*)

[1)] adjusted for randomization, age, weight, height, NRS 2002, main diagnosis (oncologic disease, infection, renal disease, failure to thrive), and comorbidities (hypertension, tumor, chronic kidney failure, chronic heart failure, diabetes mellitus), study center as well interaction terms of age and weight/height/main diagnosis of frailty/comorbidity diabetes and .

HGS = handgrip strength. ICU indicates intensive care unit.

Uni- and multivariable logistic regression models reporting odd ratios (95% CI). Linear regression models were used for continuous variables resulting in regression coefficients (marked with*)

[1)] adjusted for randomization, age, weight, height, NRS 2002, main diagnosis (oncologic disease, infection, renal disease, failure to thrive),comorbidities (hypertension, tumor, chronic kidney failure, chronic heart failure, diabetes mellitus), interaction terms (age and weight, age and height, age and diabetes, age and frailty) as well as study center.

Table 4: Association of nutritional support with 30-day all-cause mortality stratified by handgrip strength subgroups

	No nutritional support	Nutritional support				
	Death within 30-days (n,%)	Death within 30-days (n,%)	unadjusted OR (95% CI)	p for interaction	Adjusted[1)] OR (95% CI)	p for interaction
Overall						
Low HGS	17/99 (17.2%)	9/123 (7.3%)	0.38 (0.16, 0.90)	0.070	0.29 (0.1, 0.82)	0.026
High HGS	56/810 (6.9%)	50/777 (6.4%)	0.93 (0.62, 1.37)		0.98 (0.66, 1.48)	
Female						
Low HGS	8/45 (17.8%)	5/59 (8.5%)	0.43 (0.13, 1.41)	0.202	0.82 (0.11, 6.16)	0.149
High HGS	19/383 (5%)	19/370 (5.1%)	1.04 (0.54, 1.99)		1.24 (0.62, 2.46)	
Male						
Low HGS	9/54 (16.7%)	4/64 (6.3%)	0.33 (0.10, 1.15)	0.160	0.06 (0.00, 0.67)	0.023
High HGS	37/427 (8.7%)	31/407 (7.6%)	0.87 (0.53, 1.43)		0.96 (0.57, 1.62)	

HGS = handgrip strength.

Association between nutritional support and 30-day mortality rate stratified by HGS groups. Overall analysis with sex-specific HGS cutoffs and sex subgroup analyses.

HGS low = patients with HGS ≤ 10^{th} percentile of the sex-specific population (female ≤8 kg, male ≤16 kg).

HGS high = patients with HGS > 10^{th} percentile of the sex-specific population (female >8kg, male >16kg)

[1)] adjusted for age, weight, height, NRS 2002 score, main diagnosis (oncologic disease, infection, renal disease, failure to thrive),comorbidities (hypertension, tumor, chronic kidney failure, chronic heart failure, diabetes mellitus), interaction terms (age and weight, age and height, age and diabetes, age and frailty*) and study center.

*excluded in the female analysis due to small number of events

Figure 1. Flow of patients through the trial

HGS = handgrip strength.

Figure 2. Kaplan-Meier estimate for time to death within 30 days according to handgrip strength group

HGS = handgrip strength.

HGS low = patients with HGS ≤10th percentile of the sex-specific population (female ≤8 kg, male ≤16 kg).

HGS high = patients with HGS >10th percentile of the sex-specific population (female >8 kg, male >16 kg).

[1)] adjusted for age, weight, height, NRS 2002 score, main diagnosis (oncologic disease, infection, renal disease, failure to thrive),comorbidities (hypertension, tumor, chronic kidney failure, chronic heart failure, diabetes mellitus), interaction terms (age and weight, age and height, age and diabetes, age and frailty*) and study center.

*excluded in the female analysis due to small number of events