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Association of thoracic skeletal muscle index with prognosis and treatment response in patients at risk of malnutrition – a secondary analysis of a randomized trial

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Data Share Statement: Data described in the manuscript, code book, and analytic code will be made available upon request pending finalization of other secondary projects related to the trial

Abstract

Background

Measurement of skeletal muscle index at single cross-sectional images in computed tomography has been suggested to improve the objective assessment of muscle mass and diagnosis of sarcopenia. While most studies have focused on lumbar vertebrae, we examined the association of the skeletal muscle index at the thoracic vertebrae level with clinical outcomes and response to nutritional support.

Methods/Design

This is a post-hoc, secondary analysis of the multicenter, randomized-controlled EFFORT trial. We investigated the association of low skeletal muscle index at the 12th thoracic vertebra (T12), defined as the lowest sex-specific quartile, with adverse outcome within 30 days after hospital admission (primary endpoint).

Results

We had complete data of 663 of 2028 patients from the EFFORT trial. Mean skeletal muscle index was 22.4±5.8 cm^2/m^2 and 19.6±5.5 cm^2/m^2 in male and female patients, respectively, and correlated well with different nutritional parameters including nutritional risk based on the NRS 2002 (adjusted coefficient -0.63, 95%CI -1.25 to -0.01, p=0.047), BMI (adjusted coefficient 0.74, 95%CI 0.66 to 0.82, p<0.001) and handgrip strength (adjusted coefficient 0.15, 95%CI 0.11 to 0.2, p<0.001). However, in multivariate regression analyses, low skeletal muscle index was not a significant predictor for either clinical outcome nor for treatment response.

Conclusion

Within this cohort of medical patients at risk for malnutrition, skeletal muscle index measured at the thoracic vertebrae, provided low prognostic information regarding clinical outcomes and nutritional treatment response. Focusing on the lumbar vertebrae may be the more promising approach.

Introduction

Sarcopenia is defined as reduced muscle mass or muscle quality in the context of impaired muscle function and has been shown to predict poor clinical outcome in different patient populations, particularly in patients with malnutrition.[1-4] In the context of malnutrition, sarcopenia has now been considered as a core component and has been integrated into the diagnostic workup according to the GLIM (Global Leadership Initiative on Malnutrition) criteria. [5] Yet, there is an on-going debate on how to best define sarcopenia.[6, 7]

Indeed, there is need to better validate the different available tools to assess muscle mass and muscle function, including different imaging modalities as well as functional tests. Yet, computer tomography (CT)-based diagnosis of sarcopenia has emerged as reliable and objective method to assess muscle mass. CT-based measures allow the estimation of skeletal muscle as well as visceral and subcutaneous adipose tissue from one cross-sectional slice. Previous studies used the skeletal muscle index (SMI) which calculates the area of total skeletal muscle (cm2) at L3 divided by the height squared (m2) for quantification of muscle mass. [5, 6, 8] Skeletal muscle mass at L3 correlated well with whole body muscle mass and with clinical outcomes in several studies [1, 9-12] and also in a previous analysis from our patient cohort. Still, the main disadvantage is radiation exposure, which limits the usefulness of CT as a primary screening tool. Yet, due to frequent use of CT scans in clinical routine, particularly in hospitalized patients, use of these scans for assessing muscle mass is an intriguing possibility to gain clinically relevant information. However, the third lumbar vertebra is only available on abdominal and abdomino-pelvic CT scans and a large portion of patients may only get thoracic CT scans in routine care, i.e. for exclusion of pulmonary embolism and for assessing lung infection. So far, only a few studies have evaluated the correlation of skeletal muscle mass in thoracic and abdominal CT scans,[8, 13-15] and the reliability and predictive value regarding clinical outcomes remains understudied.

Herein, our aim was to examine the association of SMI at level T12 with different nutritional and clinical outcomes, as well as response to nutritional support in a well-characterised cohort of hospitalised medical patients at nutritional risk from a previous randomized-controlled trial.[16]

Methods

Study design and setting

This study is a post-hoc, secondary analysis of the prospective, randomized, open-label, multicentre EFFORT study (The Effect of early nutritional support on Frailty, functional Outcomes, and Recovery of malnourished medical inpatients Trial).[16] Eight secondary and tertiary care hospitals in Switzerland participated in study: The University Hospital in Bern, the Cantonal hospitals in Aarau, Lucerne, Solothurn, St. Gallen, Münsterlingen and Baselland, as well as the hospital in Lachen. All these hospitals used a validated screening tool for malnutrition based on the nutritional risk screening 2002 (NRS 2002) score.[17] Patients with a total score of 3 or more were considered to be at high nutritional risk.

The trial was approved by the ethic committee of Northwestern Switzerland (EKNZ; 2014_001) and registered in ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02517476).

Patient population

The inclusion criteria for the EFFORT study included a NRS 2002 score ≥ 3 points, the age over 18 years, an expected length of hospital stay of ≥ 4 days and the informed consent of the patients. Exclusion criteria were initial admission to intensive care or surgical units, hospital admission because of anorexia nervosa, terminal illness, acute pancreatitis, acute liver failure, stem cell transplantation, cystic fibrosis, after gastric bypass surgery, inability to ingest oral nutrition, already receiving nutritional support or existing contraindications for nutritional support. After giving informed consent, the patients were randomly assigned (1:1) to either the intervention group to receive individualised nutritional support or the control group to receive usual standard hospital food.

For the present secondary analysis, all patients of the original EFFORT trial who received an abdominal, abdomino-pelvic or thoracic CT scan containing level T12 within 3 months of trial inclusion were eligible.

Nutritional Procedures during the trial

After inclusion, patients were randomized 1:1 into the intervention group and control group using an interacting web system, with variable block sizes and stratification according to site and the severity of malnutrition. The intervention group received individualised nutritional support according to an

implementation protocol [18], while the control group received usual hospital food without nutritional support. Nutritional support was started in the intervention group as soon as possible, but certainly within 48 hours after hospital admission. Protein and energy goals were defined for each patient at admission by a trained registered dietician. The aim of the individualised nutritional support was to meet these goals. Energy requirements were calculated using weight-adjusted Harris-Benedict equation [19]. Daily protein requirements were set at 1.2-1.5 g/kg body weight to adjust for higher protein breakdown during acute disease [20], with lower targets for patients with acute renal failure (0.8 g per kg of body weight). To achieve this, an individualised nutrition plan was established for each patient by a trained nutritionist. This plan was initially based on oral nutrition from the hospital kitchen (including adaptations according to patient preferences, food fortifications and in-between-meals) and oral nutritional supplements [21, 22]. If after 5 days at least 75% of energy and protein goals could not be achieved by oral nutrition, an extension of nutritional support to enteral tube feeding or parenteral feeding was recommended. After 24-48h, a reassessment of nutritional support was performed by a trained registered nutritionist based on the patient's daily food records. At discharge, patients in the intervention group received nutritional counseling and, if necessary, a prescription for nutritional supplements in the out-patient setting.

Patients in the control group received usual standard hospital food, adapted to their ability and preferences to eat, with no nutritional counseling or recommendation for additional support.

Image review and evaluation

In a first step, centrally trained research assistants identified and reviewed the quality of all the original Digital Imaging and Communications in Medicine (DICOM) images at level T12. In a second step, the research assistants evaluated the CT scans and selected a single slice at level T12 using the SliceOmatic Software version 5.0 (TomoVision, Montreal, Quebec, Canada). Images with incomplete depiction of T12, skeletal muscle tissue out of the image field as well as low image contrast which did not allow reliable discrimination between muscle tissue and organ margins were excluded. There were no anatomical variations that led to exclusion.

Muscle and visceral tissue were distinguished from subcutaneous adipose tissue using tissue-specific Hounsfield Units (HU) ranges and anatomical knowledge. According to the Alberta protocol[23], the Hounsfield ranges were set as follows: -29 to 150 HU for skeletal muscle, -190 to -30 HU for subcutaneous and intramuscular adipose tissue, and -150 to -50 HU for visceral adipose tissue. Muscles

included in the cross-sectional measurements at T12 with different muscle groups including the erector spinae, latissimus dorsi, external and internal oblique, rectus abdominis and external and internal intercostal muscles. Every slice was evaluated twice to improve the interrater reliability to >99%. After the first round, all research assistants adjusted their slicing and measuring criteria. The mean of total muscle areas of both segmentation rounds were used as the reference for this analysis.

Quantification of muscle mass

For the quantification of muscle mass, the skeletal muscle index (SMI) was used, which is calculated from the total muscle area at level T12, divided by the patient height (m^2). Because there are no internationally accepted cut-off values for the diagnosis of sarcopenia based on thoracic level CT scans, we defined low SMI for patients with an SMI within the lowest sex-specific SMI quartile. The cut-off for females was 30.6cm^2/m^2 and for males 42.6 cm^2/m^2.

Clinical Outcomes

In line with the original trial, the primary composite endpoint was adverse outcome within 30 days after hospital admission,[16] including all-cause mortality, admission to intensive care unit, major complications, rehospitalisation rate and functional decline. We also had several additional short and long-term outcomes including all-cause mortality within 30 days and180 days, readmission to hospital care within 30 days, length of hospital stay and functional decline within 30 days. Rehospitalisation was considered as a non-elective admission to hospital care within 30 days after discharge. Functional decline was measured by the Barthel's Index. The cut-off for a decrease was defined as a reduction of 10% within 30 days. The assessment of the endpoints was done by trained study nurses blinded to the randomization by structured interviews via phone calls at 30 days and at 180 days after trial inclusion. When necessary, the survival status was confirmed by contacting the patient’s general practitioner or family members.

Statistical analyses

Categorical variables are expressed as counts and percentages, continuous variables as means and standard deviations. For the assessment of the predictive factors of SMI we used a linear regression

model. For the multivariate regression we adjusted for the confounders C-reactive protein (CRP) and serum albumin, as well as for handgrip strength. Pearson correlation was used to compare thoracic and lumbar SMI. To examine associations of SMI at T12 with clinical outcome we used a logistic regression model for binary outcomes and linear regression models for continuous variables. The multivariate regression calculations were adjusted for age, BMI, nutritional support intervention, contributing center, presence of major comorbidities, i.e. stroke, COPD, hypertension, diabetes and chronic heart. Further, an analysis with subgroups to investigate differences in specific patient groups (age ≥80 years, NRS 2002 score ≥4 points, male gender and the presence of a tumor or frailty) was conducted. The effect of nutritional support was assessed by logistic regression and with stratification by SMI. All statistical analyses were performed with the Stata 15.1 Software (Stata Corp, College Station, TX, USA). Statistical significance for two-sided tests was set for p-values < 0.05.

Results

Patient population

Of the 2028 EFFORT trial patients, 663 (32.7%) had a thoracic, abdominal or abdomino-pelvic CT scan with T12 available and were included in this study (**Table 1**). A total of 294 (44.3%) patients were female and mean age was 70.5 (± 13.3) years. The mean SMI at T12 was 22.4 cm^2/m^2 (±5.8) for males and 19.6 cm^2/m^2 (±5.5) for females. There was a strong correlation between SMI at level L3 and T12 (r=0.74, p<0.001). A total of 167 (25%) patients had a low sex-specific SMI based on our definition. Patients with low SMI had a significantly lower BMI and body weight, a higher nutritional risk based on NRS 2002 and lower handgrip strength (22.6 kg vs. 26.1 kg). There were no differences in regard to main diagnoses or comorbidities (**Table 1**).

Association of low SMI and clinical markers

In a first step, we investigated the association of SMI with different nutritional markers (**Table 2**). We found a positive association of SMI with weight, with an increase in the SMI of 0.22 per one kilogram higher weight (95% CI 0.2 – 0.24; p<0.001). This association was also robust when adjusting for different confounding factors including for albumin, C-reactive protein (CRP) and handgrip strength (adjusted coefficient 0.23, 95%CI 0.20 to 0.25, p<0.001). A similar association was also found for BMI, the NRS

2002and handgrip strength with significant results in the unadjusted and adjusted analyses. The area under the curve for all parameters, however, suggested only low-to-moderate discrimination.

Association of low SMI and clinical outcomes

In a second step, we investigated the association of low SMI with different clinical outcomes (**Table 3**). The risk for adverse outcome was similar in patients with high SMI (135/496, 27.2%) compared to patients with low SMI (52/167, 31.1%) resulting in a non-significant adjusted odds ratio (OR) of 1.37 (95%CI 0.89 to 2.11, p=0.157). Similarly, there were no significant associations for most other secondary endpoints including all-cause mortality at 30 and 180 days, except for the risk of functional decline from baseline to day 30 (adjusted OR 1.75, 95%CI 1.01 to 3.05, p=0.048).

We also performed a subgroup analysis stratifying patients based on their risk for low SMI (i.e. patients ≥80 years of age and patients with NRS 2002 total score ≥4), which showed similar mostly non-significant results. The results of the subgroup analyses are presented in the appendix (**Supplementary Table 1**).

Association of low SMI and response to nutritional support

Finally, we investigated the potential of SMI to predict response to nutritional support by comparing differences in clinical outcomes among intervention group and control group patients according to low or high SMI measurements (**Table 4**). Regarding our primary endpoint, adverse clinical outcome within 30 days, the OR for the nutritional support intervention was 0.82 (95%CI 0.55 to 1.22) in the group of patients with high SMI and slightly lower in patients with low SMI (OR 0.61, 95%CI 0.32 to 1.18), a difference in effect that was not significant in the interaction analysis (p=0.327). Results were similar for most endpoints, except for functional decline where the nutritional intervention was significantly more effective in patients with low SMI compared to high SMI (OR 0.40 vs. 0.55, p interaction=0.025).

Discussion

The main results of this study investigating the association of low thoracic skeletal muscle mass with clinical outcome and treatment response in patients at nutritional risk are as follows. First, we found significant and independent associations of the SMI with different nutritional parameters including BMI, nutritional risk as assessed by the NRS 2002 and handgrip strength suggesting that thoracic SMI is an additional nutritional parameter that may help to better characterize patients and identify patients at nutritional risk based on a routine examination. Second, the prognostic implications of low thoracic skeletal muscle mass were only moderate with non-significant results in an adjusted regression analysis and with low area under the curve values. Third, there was only little evidence that low thoracic skeletal muscle mass would help to identify patients that show a more pronounced response to nutritional support for most outcomes, except for decline in functionality where indeed patients with low thoracic skeletal muscle mass had more benefit compared to patients with high thoracic skeletal muscle mass.

Our study is important in regard to the current discussion about use of GLIM criteria to diagnose malnutrition.[5, 24] The Global Leadership Initiative on Malnutrition (GLIM) has recently proposed such criteria.[5, 24] GLIM proposes a relatively straightforward two-step approach, with initial screening to identify patients at risk followed by a more in-depth assessment to diagnose malnutrition and grade its severity.[5, 24] While several such methods have been proposed in the past,[25] GLIM was designed to provide a more specific diagnosis of malnutrition, and includes three phenotypic criteria (unintentional weight loss, low body mass index (BMI), and reduced muscle mass), and two aetiological criteria (reduced food intake or assimilation, and inflammation or disease burden).[7] At least one phenotypic criterion and one aetiologic criterion must be present to reach a diagnosis of malnutrition based on the GLIM criteria. However, while the prognostic validity of GLIM is established, it remains unclear whether these criteria can be helpful to guide treatment.[26] Herein, individual markers of muscle healthy may help to select patients regarding treatment.[27] Still, this analysis found little value of thoracic CT scans for this purpose.

Today, there is limited research on the usefulness of the SMI in thoracic CT scans to predict clinical outcomes. Nemec et al. showed an association of low SMI measured at T12 with longer hospital stays in a population of patients undergoing transcatheter aortic valve replacement (TAVR).[8] Olson et al. found an increased risk of mortality in patients with thoracic CT-based sarcopenia undergoing thoracic endovascular aortic repair (TEVAR) compared with non-sarcopenic subjects.[14] However, in the study

by Olson a different method was used for assessing skeletal muscle mass compared to our study, normalizing the cross-sectional area by total body area using the Mosteller formula, rather than normalizing by height. Miller et al. examined skeletal muscle mass of the erector spinae muscles and the pectoralis muscles separately in patients receiving lobectomy.[28] The erector spinae SMI, measured at T12, was associated with lower survival after 30 days and prolonged length of stay, which was not the case for SMI of the pectoralis muscles. Tanimura et al. showed similar results in a population of patients with COPD with higher mortality risk in patients with low erector spinae muscle at T12.[29] Moon et al. found an association of low SMI at T4 and T12 level with higher mortality, however after adjustment for confounders the results for the measurements at T12 were no longer statistically significant. These results and associations with different clinical outcomes may in part be explained by the wide variety in study methodology and differences in the assessment of muscle mass. Herein, we believe our results of a relatively large and well-characterized cohort of medical inpatients at nutritional risk is important and suggests only little additional value of thoracic CT scans to predict outcomes.

Currently, there is no well-defined cut-off value for SMI at level T12 for the diagnosis of sarcopenia. While some studies suggested cut-off values based on their own patient populations, using these cut-offs in our cohort did not well match the population and >95% of patients would have been classified as having low SMI.[8, 13, 15] This difference may be explained by higher age and higher frequencies of frailty and comorbidities among the EFFORT population, while Nemec et al. and Olson et al. included patients with a predominantly cardiovascular risk profile, and Derstine et al. examined a healthy population. Importantly, this shows the need to validate cut-offs within the population of patients where an examination is being done.

Interesting, in the EFFORT study, there were more routine CT scans with T12 done compared to L3 CT scans, showing that in clinical routine thoracic scans may be more widely available in this population of medical inpatients. Still, our results do not support the use of the SMI in single cross-sectional images at level T12 for the definition of clinically relevant sarcopenia due to the lack of prognostic information derived from these measurements. Thus, measurements at level L3 may be the preferred option.

This study has some strengths and limitations. EFFORT was based on a prospective, randomized, multicenter study, and therefore the population included for analyses was large and well characterized. To our knowledge, this is the first study to investigate an association between low SMI on thoracic CT

scans with response to nutritional support in patients at high nutritional risk. The main limitation includes the limited power of the analysis due to no consecutive performance of CT scans and a risk of selection bias.

Conclusion

Within this cohort of medical patients at high risk for malnutrition, skeletal muscle index measured at the thoracic vertebra provided low prognostic information regarding clinical outcomes and nutritional treatment response. Focusing on the lumbar vertebrae may be the more promising approach.

Overview of Tables

Table 1. Baseline characteristics overall and stratified by the lowest and the other three quartiles

Table 2. Association of SMI with clinical markers

Table 3. Association of low SMI with clinical outcomes

Table 4. Association of low SMI with therapeutic response

Supplementary material

Supplementary Table 1. Association of low SMI and clinical outcomes in different subgroups

Table 1. Baseline characteristics overall and stratified by SMI

Characteristic	Overall	High SMI*	low SMI*	p value
	(n=663)	(n=496)	(n=167)	
Socio-demographics				
Age , mean (SD)	70.5 (13.3)	70.4 (13.3)	70.9 (13.6)	0.70
Biological sex - Male	369 (55.7%)	276 (55.6%)	93 (55.7%)	0.99
Nutritional history				
BMI (kg/m2), mean (SD)	25.2 (5.0)	26.3 (4.9)	21.7 (3.4)	<0.001
Body weight (kg), mean (SD)	72.3 (16.3)	75.8 (16.3)	62.3 (11.2)	<0.001
NRS, mean (SD)	4.08 (.89)	4.02 (.88)	4.25 (.90)	0.003
NRS 2002 score = 3	203 (30.6%)	162 (32.7%)	41 (24.6%)	0.012
NRS 2002 score = 4	242 (36.5%)	188 (37.9%)	54 (32.3%)	
NRS 2002 score = 5	182 (27.5%)	121 (24.4%)	61 (36.5%)	
NRS 2002 score = 6	36 (5.4%)	25 (5.0%)	11 (6.6%)	
Weight loss				0.39
≤5% in 3 months	321 (48.4%)	241 (48.6%)	80 (47.9%)	
>5% in 3 months	88 (13.3%)	63 (12.7%)	25 (15.0%)	
>5% in 2 months	95 (14.3%)	77 (15.5%)	18 (10.8%)	
>5% in 1 month	159 (24.0%)	115 (23.2%)	44 (26.3%)	
Loss of appetite within the last 30 days				0.71
No	78 (11.8%)	57 (11.5%)	21 (12.6%)	
Yes	585 (88.2%)	439 (88.5%)	146 (87.4%)	
Food intake of normal requirement preceding week - no (%)				0.10
> 75%	64 (9.7%)	48 (9.7%)	16 (9.6%)	
50-75%	212 (32.0%)	163 (32.9%)	49 (29.3%)	
25-50%	277 (41.8%)	213 (42.9%)	64 (38.3%)	
<25%	110 (16.6%)	72 (14.5%)	38 (22.8%)	
Severity of illness - no (%)				0.71
very mild	12 (1.8%)	10 (2.0%)	2 (1.2%)	
mild	386 (58.2%)	286 (57.7%)	100 (59.9%)	
moderate	257 (38.8%)	195 (39.3%)	62 (37.1%)	
severe	8 (1.2%)	5 (1.0%)	3 (1.8%)	
CRP mean (SD)	8.24 (9.12)	8.14 (8.93)	8.54 (9.68)	0.63
Albumin mean (SD)	29.61 (6.63)	29.78 (6.37)	29.16 (7.32)	0.36
Muscle mass				
T12 Skeletal Muscle Index in males in cm2/m2; mean (SD)	22.44 (5.79)	24.70 (4.85)	15.73 (1.72)	<0.001
T12 skeletal Muscle Index in females cm2/m2; mean (SD)	19.61 (5.51)	21.65 (4.82)	13.53 (1.45)	<0.001
Handgrip strength mean (SD)	25.2 (11.8)	26.1 (12.4)	22.6 (9.6)	0.002
Main admission diagnosis, n (%)				
Infection	192 (29.0%)	146 (29.4%)	46 (27.5%)	0.64
Oncologic disease	215 (32.4%)	156 (31.5%)	59 (35.3%)	0.35
Cardiovascular disease	38 (5.7%)	30 (6.0%)	8 (4.8%)	0.55
Frailty	59 (8.9%)	42 (8.5%)	17 (10.2%)	0.50
Lung disease	40 (6.0%)	27 (5.4%)	13 (7.8%)	0.27
Gastrointestinal disease	50 (7.5%)	39 (7.9%)	11 (6.6%)	0.59

Neurological/ psychiatric disease	14 (2.1%)	11 (2.2%)	3 (1.8%)	0.74
Renal disease	14 (2.1%)	11 (2.2%)	3 (1.8%)	0.74
Metabolic disease	13 (2.0%)	12 (2.4%)	1 (0.6%)	0.14
Other	14 (2.1%)	12 (2.4%)	2 (1.2%)	0.34
Comorbidities, n (%)				
Hypertension	353 (53.2%)	272 (54.8%)	81 (48.5%)	0.16
Tumor	326 (49.2%)	239 (48.2%)	87 (52.1%)	0.38
Renal failure	175 (26.4%)	135 (27.2%)	40 (24.0%)	0.41
Coronary heart disease	163 (24.6%)	125 (25.2%)	38 (22.8%)	0.53
Diabetes mellitus	120 (18.1%)	98 (19.8%)	22 (13.2%)	0.056
Chronic heart failure	82 (12.4%)	62 (12.5%)	20 (12.0%)	0.86
COPD	96 (14.5%)	74 (14.9%)	22 (13.2%)	0.58
Peripheral artery disease	39 (5.9%)	27 (5.4%)	12 (7.2%)	0.41
Stroke	42 (6.3%)	34 (6.9%)	8 (4.8%)	0.34
Dementia	12 (1.8%)	9 (1.8%)	3 (1.8%)	0.99

Abbreviations: SMI= skeletal muscle index; SD= standard deviation; BMI= body mass index; NRS 2002= Nutritional risk screening 2002; COPD= chronic obstructive pulmonary disease

*low SMI defined as the lowest quartile of SMI, high SMI defined as the other three quartiles of SMI of this study population.

Table 2. Association of SMI with clinical markers

Parameter	Univariate regression	ROC Area	Female	Male	*P interaction*	Multivariate regression*****
	Coefficient (95% CI) p value		Coefficient (95% CI) p value	Coefficient (95% CI) p value		Coefficient (95% CI) p value
Nutritional marker						
NRS, per point increase	-0.82 (-1.32 to -0.33), p=0.001	0.57	-0.32 (-1.03 to 0.39), p=0.373	-1.25 (-1.9 to -0.59), p<0.001	*0.381*	-0.63 (-1.25 to -0.01), p=0.047
Weight, per Kg	0.22 (0.2 to 0.24), p<0.001	0.25	0.2 (0.16 to 0.24), p<0.001	0.23 (0.2 to 0.26), p=0.00	*<0.001*	0.23 (0.2 to 0.25), p<0.001
Weight loss*	-0.32 (-0.67 to 0.04), p=0.081	0.50	-0.2 (-0.7 to 0.3), p=0.434	-0.59 (-1.06 to -0.11), p=0.015	*0.445*	-0.39 (-0.82 to 0.04), p=0.076
BMI, per 1 unit increase	0.71 (0.64 to 0.78), p<0.001	0.20	0.58 (0.49 to 0.67), p<0.001	0.84 (0.75 to 0.94), p<0.001	*0.000*	0.74 (0.66 to 0.82), p<0.001
Clinical marker						
Handgrip Strength	0.13 (0.1 to 0.17), p<0.001	0.43	0.04 (-0.06 to 0.14), p=0.43	0.11 (0.06 to 0.16), p<0.001	*0.433*	0.15 (0.11 to 0.2), p<0.001
Loss of appetite	0.98 (-0.4 to 2.36), p=0.165	0.49	1.1 (-0.99 to 3.19), p=0.302	1.21 (-0.55 to 2.97), p=0.176	*0.315*	1.62 (-0.07 to 3.31), p=0.061
Food intake**	-0.17 (-0.68 to 0.35), p=0.523	0.54	-0.33 (-1.1 to 0.44), p=0.396	0.03 (-0.63 to 0.69), p=0.933	*0.409*	-0.01 (-0.65 to 0.63), p=0.978
Disease severity***	0.23 (-0.58 to 1.05), p=0.577	0.50	0.08 (-1.03 to 1.2), p=0.882	0.18 (-0.94 to 1.3), p=0.75	*0.885*	0.16 (-0.9 to 1.22), p=0.763
Blood marker						
Albumin, per 1g/dl	0.05 (-0.03 to 0.13), p=0.232	0.48	-0.03 (-0.13 to 0.08), p=0.603	0.12 (0.01 to 0.23), p=0.026	*0.617*	0.03 (-0.06 to 0.12), p=0.541
CRP****	0 (0 to 0.01), p=0.836	0.50	0.05 (-0.02 to 0.12), p=0.13	-0.05 (-0.11 to 0.02), p=0.173	*0.138*	0.00 (-0.01 to 0.01), p=0.975

Abbreviations: NRS = Nutritional risk screening 2002; BMI= body mass index; ROC= receiver operator characteristic

*Weight loss refers to 4 categories: (≤5% in 3 month, >5% in 3 month, <5% in 2 month, <5% in 1 month)

**Food intake refers to 4 categories: (>75%, 50-75%, 25-50%, <25% of normal requirement preceding week)

***Disease severity refers to 4 categories: (very mild, mild, moderate, severe)

**** Refers to CRP in mg/l on day of admission divided by 10

***** Adjusted for albumin, C-reactive protein (CRP), handgrip strength

Table 3. Association of low SMI with clinical outcomes

	high SMI	**low SMI***		**AUC**
	n(%) of Patients with high SMI*	n(%) of Patients with low SMI*	OR or Coefficient (95% CI), p value, adjusted**	
	n=496	**n=167**		
Primary endpoint				
Adverse clinical outcome within 30 days	135 (27.2%)	52 (31.1%)	1.37 (0.89, 2.11), p=0.157	0.52
Short-term endpoints				
30-day all-cause mortality	45 (9.1%)	19 (11.4%)	1.65 (0.86, 3.18), p=0.132	0.52
Rehospitalisation within 30 days	53 (10.7%)	19 (11.4%)	1.06 (0.57, 1.96), p=0.864	0.51
Mean length of stay, days (SD)	10.0 (6.9)	10.1 (7.5)	0.42 (-0.94, 1.78), p=0.548	-
Decline Barthel index score (points)) after 30 days	68 (13.7%)	29 (17.4%)	1.75 (1.01, 3.05), p=0.048	0.53
Long-term endpoints				
180-day all-cause mortality	147 (29.6%)	47 (28.1%)	1.08 (0.69, 1.7) p=0.732	0.49

Abbreviations: SD= standard deviation; OR= odds ratio; CI= confidence interval; AUC= area under the curve

*CT based low SMI defined as the lowest quartile
**adjusted for age, BMI, nutritional support intervention, contributing center, presence of stroke, COPD, hypertension, diabetes, chronic heart failure

Table 4. Effects of nutritional support on clinical outcomes of patients in the lowest and in the other three quartiles of SMI

	high SMI			low SMI			
	Control group (n=243)	**Intervention group (n=253)**	**OR or Coefficient (95% CI), p value unadjusted**	**Control group (n=79)**	**Intervention group (n=88)**	**OR or Coefficient (95% CI), p value unadjusted**	**p for interaction**
Primary endpoint							
Adverse clinical outcome within 30 days	71 (29.2%)	64 (25.3%)	0.82 (0.55, 1.22), p=0.327	29 (37%)	23 (26%)	0.61 (0.32, 1.18), p=0.142	0.327
Short-term endpoints							
30-day all-cause mortality	25 (10.3%)	20 (7.9%)	0.75 (0.4, 1.39), p=0.357	12 (15%)	7 (8%)	0.48 (0.18, 1.29), p=0.148	0.357
Rehospitalisation within 30 days	26 (10.7%)	27 (10.7%)	1 (0.56, 1.76), p=0.992	9 (11%)	10 (11%)	1 (0.38, 2.6), p=0.995	0.992
Length of hospital stay	10.0 (6.4)	10.1 (7.4)	0.12 (-1.1, 1.34), p=0.842	11.4 (7.6)	9.0 (7.1)	-2.35 (-4.61, -0.09), p=0.042	
Decline Barthel index Score	42 (17.3%)	26 (10.3%)	0.55 (0.32, 0.93), p=0.025	18 (21%)	9 (11%)	0.4 (0.18, 0.93), p=0.034	0.025
Long-term endpoints							
180-day all-cause mortality	75 (30.9%)	72 (28.5%)	0.89 (0.61, 1.31), p=0.558	25 (32%)	22 (25%)	0.72 (0.37, 1.42), p=0.341	0.558

Abbreviations: OR= odds ratio; CI = Confidence Interval

* low SMI defined as the lowest quartile, high SMI defined as the other three quartiles of SMI in this study population

Supplementary Table 1. Association of low SMI and clinical outcomes in different subgroups

	high SMI	**low SMI***		**AUC**	**Male**	**Female**	**NRS ≥ 4**	**Age ≥ 80 years**
	n(%) of patients with high SMI	n(%) of patients with low SMI*	OR or *Coefficient (95% CI)		OR or Coefficient (95% CI)	OR or Coefficient (95% CI)	OR or Coefficient (95% CI)	OR or Coefficient (95% CI)
			p value, adjusted**		p value, adjusted**	p value, adjusted**	p value, adjusted**	p value, adjusted**
	n=496	**n=167**						
Primary endpoint								
Adverse clinical outcome within 30 days	135 (27.2%)	52 (31.1%)	1.6 (1.03 to 2.5), p=0.037	0.52	1.58 (0.87, 2.87), p=0.131	1.1 (0.56, 2.16), p=0.775	1.48 (0.89, 2.44), p=0.13	1.73 (0.74, 4.02), p=0.203
Short-term endpoints								
30-day all-cause mortality	45 (9.1%)	19 (11.4%)	1.63 (0.83 to 3.21), p=0.158	0.52	2.19 (0.92, 5.21), p=0.076	1.21 (0.41, 3.58), p=.737	1.85 (0.88, 3.92), p=0.106	3.33 (1.02, 10.86), p=0.046
Rehospitalisation within 30 days	53 (10.7%)	19 (11.4%)	1.22 (0.65 to 2.29), p=0.534	0.51	0.79 (0.33, 1.88), p=0.589	1.33 (0.53, 3.37), p=0.545	0.98 (0.47, 2.06), p=0.967	0.98 (0.23, 4.19), p=0.98
Mean length of stay, days (SD)	10.0 (6.9)	10.1 (7.5)	-0.23 (-1.62 to 1.16), p=0.743	-	0.28 (-1.7, 2.27), p=0.779	0.26 (-1.65, 2.17), p=0.789	1.02 (-0.64, 2.68), p=0.229	-0.2 (-2.67, 2.28), p=0.876
Decline Barthel's Index score (points) after 30 days	68 (13.7%)	29 (17.4%)	1.5 (0.85 to 2.66), p=0.161	0.53	2.02 (0.96, 4.26), p=0.065	1.47 (0.61, 3.54), p=0.393	1.67 (0.88, 3.18), p=0.117	3.6 (1.33, 9.78), p=0.012
Long-term endpoint								
180-day all-cause mortality	147 (29.6%)	47 (28.1%)	0.82 (0.5 to 1.35), p=0.445	0.49	1.03 (0.56, 1.89), p=0.929	1.22 (0.6, 2.47), p=0.579	1.09 (0.65, 1.83), p=0.745	0.73 (0.32, 1.68), p=0.457

Abbreviations: SD= standard deviation; OR= odds ration; AUC= area under the curve; BMI= body mass index; NRS= nutritional risk screening 2002

*CT based low SMI defined as the lowest quartile

** adjusted for age, BMI, nutritional support intervention, contributing center, presence of stroke, COPD, hypertension, diabetes, chronic heart failure

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