Original Article

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Body Composition as Prognostic Markers for Survival of Patients with Non-Metastatic Non-Small-Cell Lung Cancer

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Abstract:

Objective: Lung cancer is the leading cause of cancer-related deaths. Although, previous research have shown that patients with non-small-cell lung cancer (NSCLC), with a higher body mass index (BMI), have a lower risk of death, only a few studies have examined the effects of body composition. Hence, this study examined the prognostic value of skeletal muscle mass and fat mass in patients with non-metastatic NSCLC.

Material and Methods: This was a retrospective cohort study; from 2008 to 2012. Eighty-eight of 130 non-metastatic NSCLC patients underwent computed tomography to assess paravertebral skeletal muscle, subcutaneous adipose tissue (SAT), and visceral adipose-tissue (VAT) at the 3rd lumbar vertebral level. Spearman correlation analysis was used to analyze body-composition correlations. Cox regression analysis was used to determine prognostic markers.

Results: Higher SAT and VAT indices were associated with a higher-survival probability (HR, 0.79; p-value=0.001 and, HR 0.88; p-value=0.016, respectively). In contrast, higher SAT density and VAT/SAT ratio were associated with a lower survival probability (HR 1.16, p-value=0.012; HR 1.28, p-value=0.006, respectively). Lower performance status and TNM stage 3 were associated with lower-survival probability (HR 2.60; p-value=0.004, HR 1.92; p-value=0.035, respectively).

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Conclusion: The VAT index predicts a better prognosis for patients with non-metastatic lung cancer; however, visceral-fat distribution, as measured by a high VAT/SAT ratio, is associated with a worse prognosis.

Keywords: body composition, fat mass, non-metastatic non-small cell lung cancer, obesity paradox, prognosis, skeletal muscle, survival

Introduction

Despite advancements in the treatment of lung cancer, it remains the most common cause of cancer-related deaths worldwide[1]. More than half of the patients with lung cancer die within one year of diagnosis, and the 5-year survival rate is 18.2%[2]. In addition to Tumor, Node, Metastasis (TNM) stage, age, performance status[3] and treatment regimens[4], there is evidence that body weight, in terms of body mass index (BMI), affects survival in patients with cancer[5]. BMI increment was also associated with a higher risk of disease progression, or death due to colon[6], prostate[7] and breast cancers[8]. In contrast, the mortality rate of lung cancer patients; especially those with non-small cell lung cancer (NSCLC), is lower in patients with higher BMI than in those with lower BMI[9,10]. The benefit of obesity, known as the "obesity paradox," has gained enormous attention from researchers, and has been debated as to whether there is a real benefit to being obese.

However, whether the effect of the obesity paradox relies on body composition, the ratio of fat and/or muscle mass, is still controversial. Skeletal muscle mass is a proxy for muscle quantity and quality, as determined by the skeletal muscle index and density. Low skeletal muscle mass, also known as sarcopenia, has been proven to be a poor predictor of survival in patients with prostate, head and neck, gastric and lung cancers in previous systematic reviews and meta-analyses[11-14]. Additionally, low skeletal muscle density, which indicates a greater amount of fat in skeletal muscle, has been associated with poor survival in breast cancer patients[15]. However, these systematic reviews have demonstrated heterogeneity and research is limited on this topic in non-metastatic cancers. In addition, few studies have considered the relationship between fat mass and survival in patients with non-metastatic NSCLC. The objectives of this study were to assess the correlations between body composition markers; specifically skeletal muscle mass and fat mass in addition to their prognostic determinants in the survival of non-metastatic NSCLC patients.

Material and Methods

This retrospective study was conducted in a university hospital in the lower region of Southern Thailand, which is the main referral center for cancer patients. Adults aged ≥18 years, diagnosed with non-metastatic NSCLC, stages I to IIIc, according to TNM-8 lung cancer staging[16]; from January 2008 and December 2012, were included. Those who did not have computed tomography (CT) findings at diagnosis or undetermined CT findings for body composition analysis were excluded. This study was approved by the appropriate ethics committee and was conducted in accordance with the Declaration of Helsinki.

The data were obtained from two sources: the Hospital Information System (HIS) and the death register. Information on patients aged ≥18 years who were diagnosed with NSCLC using the International Classification of Diseases, 10th revision (ICD-10) codes of C34, C341, C342, C343, C348, and C349 were retrieved. Non-metastatic status and staging were reviewed from medical notes, and CT staging by a principal investigator to aquire the patients based on the inclusion criteria. The availability and interpretability of CT imaging were checked, and patients were excluded where there was an undetermined analysis of body composition. Patient information and death status were reviewed and recorded independently from body composition measures.

Overall survival was defined as the interval between the time of diagnosis and the time of death from any cause. The main variables of interest in this study were: BMI and body composition. BMI was calculated as body weight (kg) divided by height squared (m^2). The World Health Organization (WHO) BMI criteria for Asian populations were used to define patients as underweight (<18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2), overweight (23.0-24.9 kg/m^2) or obese (≥25 kg/m^2)[17]. Body composition was evaluated using CT imaging; including: the skeletal muscle index, muscle density, subcutaneous adipose tissue (SAT) index, SAT density, visceral adipose tissue (VAT) index, VAT density and VAT/SAT ratio. The cross-sectional areas (cm^2) of the paravertebral skeletal muscle, SAT, and VAT at the level of the third lumbar vertebra were measured using C++ software. The Hounsfield Unit (HU) was used to differentiate the muscle from SAT or VAT, using the ranges of -29 to 150, -190 to -30, and -150 to -50 HU, respectively[18].

The skeletal muscle index, SAT index, and VAT index (cm^2/m^2) were calculated by dividing the skeletal muscle, SAT, and VAT by the square of height (m^2). Skeletal muscle density, SAT density, and VAT density were indicated by the mean HU of the individual measures. The VAT/SAT ratio was defined as the ratio of the VAT to SAT. The covariates were age, gender, tumor staging, and performance status; as defined by the Eastern Cooperative Oncology Group (ECOG).

Data were entered into EpiData (version 3.1) and analyzed using R version 4.0.3 (2020 The R Foundation for Statistical Computing, Vienna, Austria). The correlations among all body compositions measured were analyzed with Pearson's correlation coefficient, and the absolute value of R was used to grade the strength of the association: 0-0.29 was considered negligible, 0.30-0.49 was considered low, 0.50-0.69 was considered moderate, 0.70-0.89 was considered high, and 0.90-1.00 was considered as a very high correlation[19]. The cut-off thresholds of body composition were determined using the receiver operating characteristic curve (ROC) method, which determines the maximal hazard ratio (HR) based on log-rank statistics[20]. Kaplan-Meier curves and log-rank tests were used for survival time analysis. The prognostic value of CT-derived body composition indices (all continuous) for overall survival was analyzed using Cox proportional hazards regression. Covariates that showed statistical significance in univariate analysis (p-value<0.2) were included in the Cox multivariate analysis. Statistical significance was set at p-value<0.05.

The sample size was calculated using a survival formula, in which the difference in five-year survival probability between high and low degrees of adiposity was 20%; according to a previous study[21]. Based on a type one error of 5%, a type two error of 20%, and an unequal sample size (k=4), there were 18 patients in the exposure group (n1=18) and 73 patients in the non-exposure group (n2= 73), leading to a total of at least 91 patients being required.

Results

During the study period, 1,864 patients were diagnosed with lung cancer, of which the majority were metastatic or small-cell lung cancer (n=1,734); resulting in 130 non-metastatic non-small cell lung cancer patients. Of these, 42 patients did not have CT for body composition evaluation, resulting in 88 remaining patients.

The characteristics of the patients are presented in Table 1. Age of patients ranged from 43.1 to 87.3 years, with a mean age of 64.5 years. Three-quarters of them were male, and one-third were overweight to obese (n=26/88, 29.6%). Approximately half of them were TNM stage III, and the majority (87%) were in ECOG score 0-1.

Table 1 Characteristics of included patients (n=88)

Characteristics	N=88
Age (years)	
Mean (S.D.)	64.5 (10.2)
Sex	
Men	70 (79.5%)
Women	18 (20.5%)
BMI (kg/m^2) [a]: mean (S.D.)	21.3 (3.9)
BMI classification[a]	
Underweight	21 (24.4%)
Normal	39 (45.3%)
Overweight	11 (12.8%)
Obese	15 (17.4%)
Comorbid diseases	
No	48 (54.5)
Yes	40 (45.5%)
Hypertension	14 (15.9%)
Dyslipidaemia	7 (8%)
Diabetes	6 (6.8%)
CAD	4 (4.5%)
TNM tumor staging	
I	16 (18.2%)
II	30 (34.1%)
III	42 (47.7%)
ECOG[b]	
0	16 (18.8%)
1	58 (68.2%)
≥2	11 (13%)

BMI=body mass index, CAD=coronary artery disease, ECOG=eastern cooperative oncology group performance status
missing data (n=2)[a] and (n=3)[b]

Body composition values and their correlations

The correlations of individual body compositions are shown in Figure 1. Positive correlations were found between BMI and SAT, the VAT index (r=0.59; p-value<0.001 and r=0.58; p-value<0.001, respectively), SAT and VAT index (r=0.59; p-value<0.001) and SAT density and VAT density (r=0.57; p-value<0.001). On the other hand, there was a negative correlation between the SAT index and SAT density (r=-0.68; p-value<0.001), VAT index, VAT density (r=-0.37; p-value<0.001) and SAT density (r=-0.61; p-value<0.001). Table 2 presents body composition and survival-related thresholds. Of these measures, the VAT index was the most depleted, with three-quarters of the patients having VAT index depletion. Skeletal muscle index and skeletal muscle mass, on the other hand, were the least deficient. The median skeletal muscle index, SAT index, VAT index and VAT/SAT ratio were 14.57, 14.92, 25.64, and 1.73, respectively.

Overall survival by univariate analysis and multivariate analysis

The median overall survival was 8.7 months. Univariate Cox regression analysis showed that TNM staging, performance status, SAT index, SAT density, VAT index and VAT/SAT ratio were significantly associated with overall survival (Table 3): Kaplan-Meier Curves are shown in Figure 2. Factors showing a p-value of less than 0.2 in univariate analysis were included in the first model, and only four factors remained in the final model; as shown in Table 4. Patients who were in TNM stage III (aHR 2.13 (1.05-4.32); p-value=0.035), had an ECOG ≥2 (aHR 2.90 (1.24-6.79); p-value=0.014) and had a higher VAT/SAT ratio (aHR 1.61 (1.17-2.22); p-value=0.003) were associated with reduced overall survival. A longer overall survival was found in patients with a higher VAT index (aHR=0.74 (0.60-0.92); p-value=0.005).

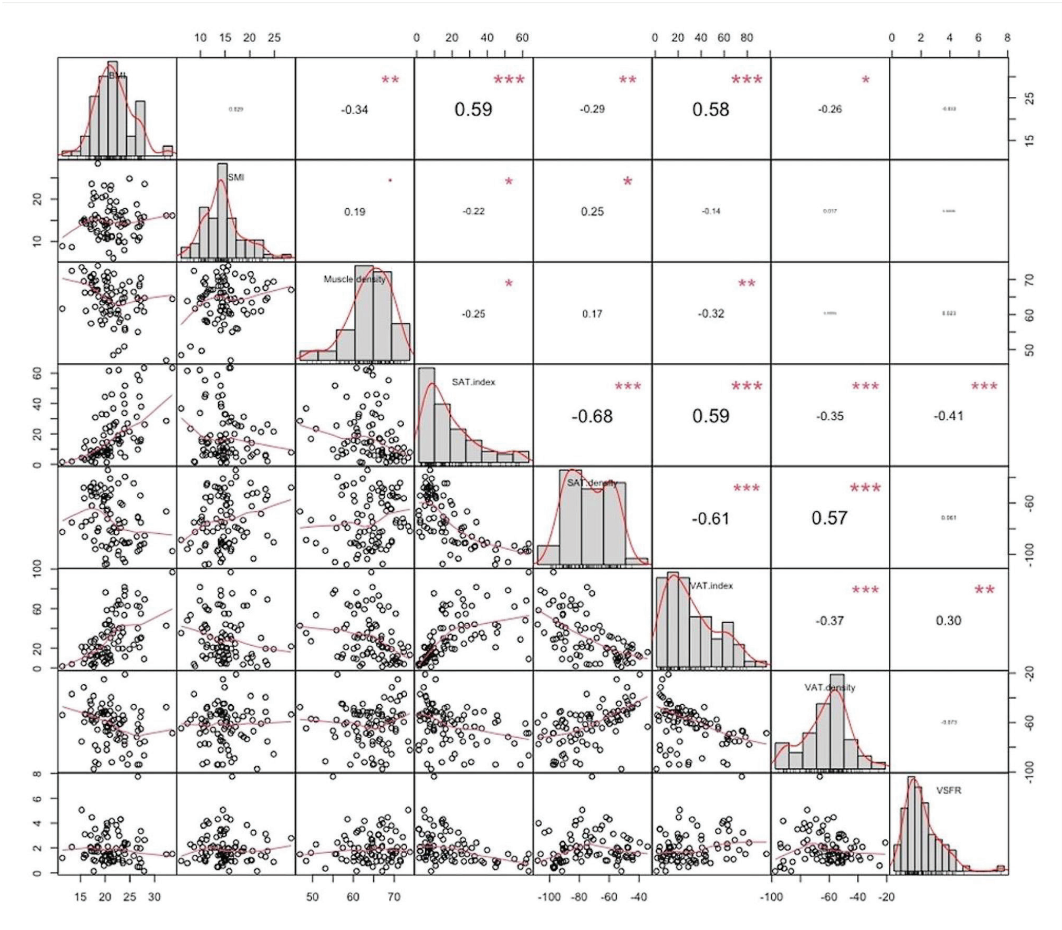

Figure 1 Correlations of body composition parameters

Table 2 Body composition values and survival-related thresholds

Body composition	Median [IQR]	Survival-related thresholds by optimal stratification methods	
		Threshold	Percentage of depletion (%)
Skeletal muscle index (cm^2/m^2)	14.57 (12.21, 15.05)	10.93	13.6
Muscle density (HU)	64.65 (60.95, 68.400)	58.2	13.6
SAT index (cm^2/m^2)	14.92 (7.09, 26.86)	9.16	34.1
SAT density (10 HU)	-74.94 (-90.95, -54.97)	-78.58	45.5
VAT index (cm^2/m^2)	25.64 (12.89, 43.87)	42.71	71.6
VAT density (per 10 HU)	-62.29 (16.25)*	-59.5	43.2
VAT/SAT ratio	1.73 (1.12, 2.65)	2.65	75

IQR=interquartile range, SAT=subcutaneous adipose tissue index, SAT density, VAT=visceral adipose-tissue index, VAT density, VAT/SAT ratio
*=mean (S.D.)
All patients were sarcopenic, according to the CT= computed tomography diagnostic criteria of sarcopenia for the population of South China (male ≤38.89 cm^2/m^2, female ≤33.28 cm^2/m^2)[22]

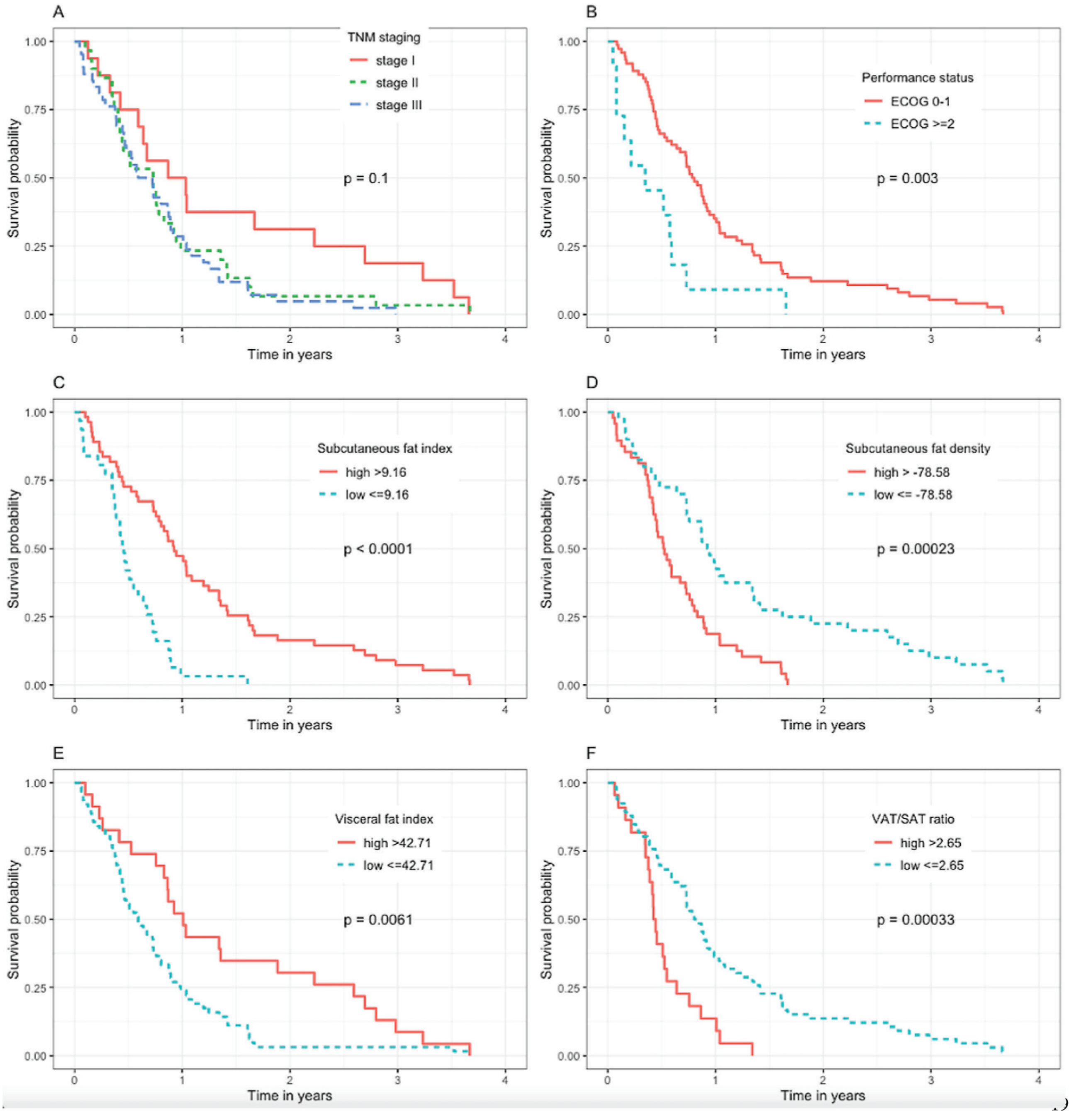

Figure 2 Kaplan–Meier curves, based on TNM staging (A), performance status (B), SAT in-dex (C), subcutaneous fat density (D), VAT index (E) and VAT/SAT ratio (F)

Table 3 Univariate cox regression analysis of body composition parameters and clinical conditions for overall survival

Factors	HR	p-value
Age (years)	1.01 (0.99-1.03)	0.472
Sex		
Male	Ref	-
Female	0.61 (0.35-1.04)	0.070
TNM Tumor staging		
I	Ref	-
II	1.63 (0.87-3.04)	0.127
III	1.92 (1.05-3.50)	0.035
ECOG		
0-1	Ref	
≥2	2.60 (1.34-4.97)	0.004
BMI (kg/m^2)	0.96 (0.90-1.01)	0.122
Skeletal muscle index (per 10 cm^2/m^2)	1.23 (0.71-2.13)	0.470
Skeletal muscle density (per 10 HU)	0.86 (0.56-1.32)	0.490
SAT index (per 10 cm^2/m^2)	0.79 (0.68-0.91)	0.001
SAT density (per 10 HU)	1.16 (1.03-1.30)	0.012
VAT index (per 10 cm^2/m^2)	0.88 (0.80-0.98)	0.016
VAT density (per 10 HU)	1.08 (0.95-1.24)	0.242
VAT/SAT ratio	1.28 (1.07-1.53)	0.006

BMI=body mass index, HR=hazard ratio, ECOG=eastern cooperative oncology group performance statu, SAT=subcutaneous adipose tissue VAT=visceral adipose-tissue

Table 4 Final model of multivariate cox regression analysis of body composition parameters; adjusted with clinical conditions for overall survival

Factors	Adjusted HR (95% CI)	p-value
VAT index (per 10 cm^2/m^2)	0.74 (0.60-0.92)	0.005
VAT/SAT ratio	1.61 (1.17-2.22)	0.003
TNM Tumor staging		
I	Ref	
II	1.76 (0.87-3.58)	0.110
III	2.13 (1.05-4.32)	0.035
ECOG		
0-1	Ref	
≥ 2	2.90 (1.24-6.79)	0.014

BMI=body mass index, HR=hazard ratio, ECOG=eastern cooperative oncology group performance status, SAT=subcutaneous adipose tissue, VAT=visceral adipose-tissue

Discussion

Non-metastatic NSCLC was likely to have high indices, but low density of SAT and VAT with a low skeletal muscle index. Subcutaneous and visceral adipose tissue indices were positively correlated with BMI, but negatively correlated with density. There was no correlation between the skeletal muscle index and BMI. For overall survival, a high VAT index was a favorable predictive marker, but the VAT/SAT ratio had a negative effect after adjusting for TNM staging and ECOG performance status, which were independent predictors of survival.

The median SAT and VAT indices indicating fat mass found in this study were lower than those found in a prior study[23]; even though the technique for measuring fat mass in non-metastatic NSCLC was the same. This can be explained by the different degrees of cancer cachexia observed in the samples. The skeletal muscle index at the L3 paravertebral area in non-metastatic NSCLC was slightly higher than that reported in a previous study that included patients with metastatic lung cancer[24]. This finding supports the hypothesis that both fat and skeletal muscle mass are related to disease severity, even in the non-metastatic stage.

To date, few studies have reported the correlation between body composition index in lung cancers; additionally, the techniques and measurements used were different[21,25,26]. In this study, subcutaneous and visceral adipose tissue indices were positively correlated with BMI, indicating the degree of adiposity, which was consistent with previous studies; even though the measurement used was not the same. The negative correlation between subcutaneous and visceral adipose tissue indices and density in this study could be explained by the fact that the fat cells in our non-metastatic NSCLC patients were non-fibrotic normal fat cells, resulting in the detection of low density[27]. This study showed no correlation between --

Conclusion

Fat mass, in terms of SAT and VAT indices, are associated with a favorable prognosis in non-metastatic lung cancer patients; particularly those with sarcopenia. In contrast, visceral fat distribution, in terms of a high VAT/SAT ratio, is associated with poor prognosis. As a result, a staging CT scan may be used to assess patients' body composition and identify those whom are at high risk of mortality. This allows for the provision of specialized nutritional support for a better outcome.

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Conflict of interest

There are no potential conflicts of interest to declare.

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