Feasibility of computed tomography-based assessment of skeletal muscle mass in hemodialysis patients

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Abstract

Background: Sarcopenia is a major health issue especially in patients on maintenance hemodialysis. Low skeletal muscle mass is included in the diagnostic criteria for sarcopenia. The skeletal muscle mass is usually evaluated by modalities such as bioimpedance analysis (BIA) or dual-energy x-ray absorptiometry, however the assessment of skeletal muscle mass using computed tomography (CT) images has not been established. The purpose of the study was to investigate the feasibility of the assessment of skeletal muscle mass using CT image in hemodialysis patient.

Methods: Skeletal muscle mass index (SMI) was measured by BIA and psoas muscle index (PMI) was measured by cross-sectional CT image in 131 patients. The relationship between SMI and PMI and the diagnostic ability of PMI for low muscle mass were evaluated. Furthermore, the patients were followed up and long-term survival in patients with low and high PMI were compared.

Results: PMI measured at L3 vertebral level was strongly correlated with SMI ($r = 0.597$, $p < 0.001$). Age, sex, and SMI were the influencing factor for PMI. Patients with low PMI showed higher incidence rates of mortality during the follow up.

Conclusions: PMI assessed by CT image can be an alternative to BIA in patients with hemodialysis.

Key words: sarcopenia, psoas muscle, bioimpedance analysis, muscle wasting

Introduction

Sarcopenia is recognized as one of the major health issues especially in the elderly population. Sarcopenia is an independent risk factor for bone fracture [1], dementia [2], and cardiovascular events [3]. A population-based studies have shown that approximately 8% of the elderly subjects were sarcopenic [4, 5]. In addition to the fact that patients with chronic kidney disease are at higher risk for sarcopenia compared to healthy individuals [6, 7], sarcopenia was shown to be the risk factor of death in hemodialysis patients [8]. Therefore, it is important to adequately assess and manage sarcopenia in patients with end-stage renal disease.

The diagnosis of sarcopenia is based on the existence of low skeletal muscle mass combined with low muscle strength and/or physical performance. The skeletal muscle mass can be evaluated by various kinds of modalities including bioimpedance analysis (BIA) and dual-energy x-ray absorptiometry, those are included in the diagnostic criteria from several working groups of sarcopenia [9, 10]. However, it depends on the dialysis facilities whether these modalities could be applied to their patients. Besides that, no previous study investigated the gold-standard modality and relevant cut off value for assessing sarcopenia in patients with hemodialysis. Therefore, it is important to establish a method that could be an alternative to BIA for assessing muscle mass in these patients.

Computed tomography (CT) has been proposed as an alternative for the evaluation of skeletal muscle mass. Assessment of skeletal muscle mass using CT images was reported to be useful in predicting mortality in chronic liver disease [11, 12]. Although this technique can be applied to patients with hemodialysis, the feasibility of

CT-based assessment of muscle mass in hemodialysis patients has not been evaluated. In the present study, we aimed to investigate the influencing factor and the diagnostic ability of the CT-based assessment of muscle mass in hemodialysis patients.

Methods

Study population

This study included 138 patients on maintenance hemodialysis who underwent CT scanning of the abdomen and BIA between April 2018 and October 2018. Skeletal muscle mass was evaluated by BIA using InBody (InBody Japan, Tokyo, Japan). In order to eliminate the influence of excess body fluid, BIA was performed after a session of hemodialysis, and the dry weight (estimated ideal weight) of the patient was determined according to their physical findings, chest X-ray examination, and serum brain natriuretic peptide or human atrial natriuretic peptide levels. Patients who were congestive at the time of BIA and patients with a past history of amputation of an extremity was excluded from the study. The patient's height was measured and skeletal muscle mass index (SMI) was calculated by adjusting the skeletal muscle mass for height (kg/m^2). Patients with SMI less than 7.0 kg/m^2 in male and 5.7 kg/m^2 in female were defined as muscle wasting [9]. The patients were followed up until May 2020 and all-cause death and the time until death was recorded. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethical committee of the Tottori University Hospital (approval number: 19A222).

Evaluation of muscle mass by CT image

Abdominal CT scanning performed within 3 months of BIA were referred for

the assessment of muscle mass. Cross-sectional area of bilateral psoas muscle at the lower border of the L3 vertebral, umbilical and iliac crest levels were manually traced and measured (Fig.1) using an imaging software (SYNAPSE 4.0, FUJIFILM, Tokyo, Japan). One experienced physician (T.T.) measured the psoas muscle area. Single measurement was taken at each site of the CT images. Psoas muscle index (PMI), a total area of the bilateral psoas muscle area adjusted by height (kg/m^2), was used for the analysis.

Statistical analysis

Continuous variables were expressed as mean ± SD or median (range). The differences between groups were analyzed by chi-square test, Student's t test, or Mann-Whitney U test according to the data distribution. Kolmogorov-Smirnov test was used for assessing the distribution. The correlations between psoas muscle area or PMI and skeletal muscle or SMI were analyzed using Pearson's correlation coefficient as both of the variables were normally distributed. Multiple linear regression analysis, in which age, sex, duration of hemodialysis, SMI, and Kt/V were included as explanation variants, was performed to investigate influencing factors of PMI. No multicollinearity was suspected among the explanation variants. The diagnostic ability and the cut off value of PMI for low skeletal muscle mass was analyzed by receiver operating characteristic (ROC) curves. Long term survival was compared using the Kaplan-Meier survival curve analysis and log-rank test. Cox proportional hazards regression analysis was performed to investigate the hazard ratio of PMI in the model. Statistical analyses were performed using GraphPad Prism (7.0. for Windows, GraphPad Software, San Diego, CA, USA) and StatFlex ver 6.0 for Windows (Artec, Osaka, Japan). A two-tailed

p-value less than 0.05 was considered as statistically significant.

Results

Patient characteristics

Patients included in the analyses were summarized in Fig.2 and Table 1. Among the 131 patients analyzed, 4 male and 4 female patients were diagnosed with muscle wasting. Diabetic nephropathy was the major cause of kidney disease (n = 40). Patients diagnosed with muscle wasting were significantly older and had smaller body size. Duration of the hemodialysis and efficiency of dialysis did not differ among groups. We did not see any differences in SMI between patients with or without diabetic nephropathy (p = 0.89)

Relationships between BIA and CT-based assessment

The coefficient of variation of five repeated measurement in the same subject was 3.7% at L3 vertebral, 3.8% at umbilical, and 2.1% at iliac crest levels. There were no significant differences between left and right psoas muscle area in each site (p value of 0.15 at L3 vertebral, 0.92 at umbilical, and 0.51 at iliac crest, respectively). Since psoas muscle mass was measured at three different levels, we investigated the relationships between skeletal muscle mass and psoas muscle mass at each level. Univariate analysis revealed that psoas muscle area measured at L3 vertebral, umbilical, and iliac crest levels showed significant correlations between skeletal muscle mass (each $p < 0.001$). PMI measured at these three levels significantly correlated to SMI as well (each $p < 0.001$, Table 2). Bland-Altman analyses showed that the mean difference and the standard deviations between SMI and PMI were 2.81 ± 1.48 at L3 vertebral,

-1.59 ± 2.73 at umbilical, and 1.50 ± 1.52 at iliac crest levels, respectively (Fig.3). Since most of the previous reports using CT measured muscle mass at L3 vertebral level, we further investigated the feasibility of PMI at L3 vertebral level.

Multiple linear regression analysis, in which age, sex, duration of hemodialysis, SMI, and Kt/V were included as explanation variables, was performed to investigate the influencing factor for PMI. Patient's age (stdβ = -0.322, $p < 0.001$), sex (stdβ = 0.380, $p < 0.001$), and SMI (stdβ = 0.312, $p = 0.001$) were the independent influencing factor for PMI (Table 3). No multicollinearity was observed between the explanation variables.

Diagnostic ability of PMI for muscle wasting

During a median follow-up of 24 month (interquartile range = 19.0-24.0), 8 patients (7 male and 1 female) died. In order to investigate the mortality in patients with low PMI, the subjects were classified by three different way and analyzed by the Kaplan-Meier curve analysis. In the first model, the subjects were divided into two groups according to the cut off value derived from BIA. ROC curve analyses were separately performed in male and female, and PMI assessed at L3 level distinguished muscle wasting with the cut off value of 3.91 in male (area under the curve of 0.961) and 3.35 in female (area under the curve of 0.654). As a result, 19.1% (13 male and 12 female) were defined as muscle wasting. In the second model, the cut off values defined as 2SD in healthy young subjects (i.e. 6.36 in male and 3.92 in female) were used [13]. This model diagnosed 48.9% (46 male and 18 female) of the patients as muscle wasting. In the third model, the patients were classified by tertile of PMI (i.e. PMI of 4.58 and 6.38). The lowest PMI groups included 16 male and 27 female, whereas the highest PMI groups included 41 male and 3 female. The Kaplan-Meier curves of the three

models revealed that patients with low PMI had higher incidence rate of mortality during the follow-up period ($p < 0.001$, $p = 0.022$, and $p = 0.028$, respectively) (Fig.4). Univariate and multivariate cox proportional hazards regression analysis adjusted for age and sex revealed that low PMI was the independent predictor of long-term mortality (Table 4 and 5).

Discussion

In the present study, we demonstrated that PMI evaluated by abdominal CT images strongly correlated with SMI. Age, sex and SMI were the influencing factors for PMI. Patients with low PMI had higher incidence rate of mortality. PMI evaluated by CT images can be an alternative for the assessment of muscle mass in hemodialysis patients.

Assessment of muscle mass using CT has been reported to be useful for predicting mortality in patients with cancer, chronic debilitating diseases, and after liver transplantation or gastrointestinal surgery [11, 14–16]. Recently, this method has also been applied to evaluate low muscle mass in patients with chronic kidney disease [17]. In previous reports evaluating the availability of CT, total area of the skeletal muscle or thickness of psoas muscle at the single slice image was used for the quantification, and muscle mass quantified at the L3 vertebral level was reported to be well correlated to whole body skeletal muscle mass [18]. In the present study, PMI measured at the L3 vertebral, umbilical and the iliac crest levels well correlated to the SMI. Although previous reports recommended to measure PMI at L3 vertebral level, considering the simplicity of the measurement and the small discrepancy between SMI, iliac crest is easily verified and can be an option for the assessment of PMI. Umbilical level seemed

to be inferior to the other levels for the measurement of PMI.

In the present study, age and sex independently influenced the PMI. This result is compatible with the previous investigations that showed higher prevalence of sarcopenia with ageing [4, 5, 19]. A number of studies have also demonstrated a significant difference in muscle mass between male and female. Therefore, a cut off value for diagnosing muscle wasting may be separately determined each [9]. In the present study, the area under the curve of the ROC curve in male was remarkably high. On the other hand, the diagnostic ability of PMI in women seemed to be inferior to that in male. This discrepancy between sex might be explained by the speed of muscle atrophy and the target muscle quantified by each modality. In a large cohort of 4000 subjects in Japan, trunk muscle mass tended to decrease rapidly in the elderly men, whereas it was rather preserved in the elderly women [20]. Since we evaluated psoas muscle mass, which is a component of trunk muscle, we might possibly detect only a small variation in PMI in female. There is another possibility that only a small number of the patients were defined as muscle wasting by BIA in this study. This might abate the reliability of ROC curve analysis. In the present study, we investigated three different models to investigate the predicting ability to long-term survival; one based on the results from BIA, one from previously reported 2SD of PMI in healthy young subject, and the other derived from tertile of PMI in this study. The Kaplan-Meier curve analysis showed that low PMI in these three models could predict poor outcome. In particular, low PMI, defined based on BIA and tertile of PMI, was an independent predictor of poor outcome even adjusted for age and sex. In previous reports investigating PMI and long-term outcomes, the cut off value depended on each study [11, 21], and these results can not be directly applied to Asian population. In addition,

the cut of values in patients with hemodialysis has not been reported. The prevalence of muscle wasting varies depending on the modality, cut off value, and the patient's renal function (i.e. on dialysis or not) (22). Therefore, it would be important to use different cut off to evaluate muscle mass in patients on hemodialysis. Our results propose the possibility that PMI assessed by CT images could be an alternative to SMI in patients with hemodialysis.

It is well recognized for nephrologist/urologist that hemodialysis patients are at high risk for developing renal cell carcinoma. CT is one of the recommended modalities for screening renal tumor [23]. Therefore, it is reasonable to take advantage of the screening CT not only for detecting renal cell carcinoma, but also for assessing trunk muscle mass. Ultrasound might be another modality for the assessment of muscle mass [24] especially in extremities. Since segmental body composition alters according to the health status [25], further study linking site-specific muscle wasting and the long-term survival would be beneficial.

There are some limitations in this study. Since hemodialysis patients tend to gain excess fluid that may affect the result of BIA, an ideal modality for assessing muscle mass in these patients is desired. Although the present study is based on the small number of subjects, the present study would be a help in diagnosing low muscle mass in patients with hemodialysis.

In conclusion, we revealed that PMI evaluated by CT images well correlated to SMI assessed by BIA, and the CT-based assessment of muscle mass could be an alternative in hemodialysis patients.

Declarations

Funding: Not applicable.

Conflicts of interest: The authors declare that they have no conflict of interest.

Availability of data: All data generated or analyzed during this study are included in this published article.

Author's contributions: Conceptualization: Tomoaki Takata, Kentaro Yamada, Ayami Ida, Masaya Ogawa, Shintaro Hamada, Marie Yamamoto, Yukari Mae, and Takuji Iyama; Data acquisition; Tomoaki Takata, Aki Motoe, and Katsumi Tanida; Formal analysis and investigation; Tomoaki Takata, Sosuke Taniguchi: Writing – original draft preparation; Tomoaki Takata: Writing – review and editing: Munehiro Taniguchi, Akihisa Nakaoka: Supervision; Hajime Isomoto.

Ethical approval: This study was conducted retrospectively from data obtained for clinical purposes. This study was approved by the ethical committee of the Tottori University Hospital (approval number: 19A222), and was conducted according to the declaration of Helsinki.

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Figure legends

Figure 1. Measurement of psoas mass area on CT image. Representative CT image showing the measurement of bilateral psoas muscle area at the lower border of the L3 vertebra. The psoas muscle masses were also measured at umbilical and iliac crest levels.

Figure 2. Study design. Of the 139 patients who underwent CT scanning of the abdomen and BIA using InBody, 131 patients were included in the analysis.

Figure 3. Bland-Altman plots of the SMI and PMI. The mean differences and standard deviations between SMI and PMI were 2.86 ± 1.48 at L3 vertebral **(a)**, -1.59 ± 2.73 at umbilical **(b)**, and 1.50 ± 1.52 at iliac crest level **(c)**. SMI, skeletal muscle mass index; PMI, psoas muscle index.

Figure 4. Kaplan-Meier survival analysis classified into three different models

(a) Model 1: The patients were divided into two groups by the cut off value of 3.91 in male and 3.35 in female derived from the receiver operating curve analysis of skeletal muscle mass index. The overall survival rate was significantly lower in patients with low PMI ($p < 0.001$). **(b)** Model 2: The patients were divided into two groups by the cut off value of 6.36 in male and 3.92 in female. The overall survival rate was significantly lower in patients with low PMI ($p = 0.022$). **(c)** Model 3: The patients were divided into

three groups according to tertile of PMI (4.58 and 6.38). The overall survival rate of patients with the lowest PMI was significantly lower than those in the highest PMI (p = 0.028).

Supplementary Figure. Scheme of the assessment of muscle mass. Representative computed tomography images from patient with high and low PMI were shown.

Tables

Table 1. Patient's characteristics

Muscle wasting	-	+	P-value
Number	123	8	
Age	66.3 ± 12.4	76.5 ± 15.0	0.028
Sex (male / female)	84/39	4/4	0.44
Cause of renal disease			
Diabetic nephropathy	39	1	
Chronic glomerulonephritis	22	3	
Polycystic kidney disease	15	0	
Nephrosclerosis	6	1	
Other/unknown	41	3	
Duration of hemodialysis (month)	203 (4-1219)	217 (95-632)	0.46
Height (m)	1.62 ± 0.10	1.53 ± 0.08	0.012
Body weight (kg)	59.1 ± 12.8	42.6 ± 5.9	<0.001
Muscle mass (kg)	22.8 ± 5.2	13.1 ± 2.3	<0.001
SMI (cm^2 / m^2)	8.59 ± 1.31	5.56 ± 0.49	<0.001
Psoas muscle area (L3 vertebral, cm^2)	15.11 ± 5.38	7.83 ± 2.55	<0.001
PMI (L3 vertebral, cm^2 / m^2)	5.68 ± 1.71	3.35 ± 1.18	<0.001
Psoas muscle area (umbilical, cm^2)	16.64 ± 5.80	10.55 ± 4.00	0.004
PMI (umbilical, cm^2 / m^2)	10.20 ± 3.25	6.84 ± 2.36	0.005
Psoas muscle area (iliac crest, cm^2)	18.77 ± 6.10	11.58 ± 3.49	0.001
PMI (iliac crest, cm^2 / m^2)	7.05 ± 1.88	4.89 ± 1.20	0.002
Kt/V	1.79 ± 0.34	1.93 ± 0.53	0.24

SMI: skeletal muscle mass index; PMI: psoas muscle index

Table 2. Univariate correlations

	r	p value
Between skeletal muscle mass		
Psoas muscle area (L3 vertebra, cm2)	0.736	<0.001
Psoas muscle area (umbilicus, cm^2)	0.686	<0.001
Psoas muscle area (iliac crest, cm^2)	0.770	<0.001
Between SMI		
PMI (L3 vertebral, cm2 / m2)	0.597	<0.001
PMI (umbilical, cm2 / m2)	0.574	<0.001
PMI (iliac crest, cm2 / m2)	0.624	<0.001

SMI: skeletal muscle mass index; PMI: psoas muscle index

Table 3. Multiple linear regression analysis for PMI (L3 vertebra)

	Std β	95% CI of std β	VIF	p value
Age	-0.322	-0.487-0.157	1.422	<0.001
Male	0.380	0.204-0.555	1.600	<0.001
Duration of hemodialysis	-0.055	-0.202-0.093	1.149	0.46
SMI	0.312	0.126-0.498	1.835	0.001
Kt/V	0.089	-0.074-0.251	1.327	0.28

SMI: skeletal muscle mass index. Akaike's information criterion: 380.2

Table.4 Univariate analysis of overall mortality (n = 131)

Characteristic	HR (95% CI)	P value
Male	3.59 (0.44-29.15)	0.23
Age	1.06 (0.99-1.13)	0.077
Duration of hemodialysis	1.00 (1.00-1.00)	0.65
Height	199.13 (0.04-100000)	0.23
Body Weight	0.99 (0.94-1.05)	0.74
Muscle mass	0.96 (0.85-1.09)	0.56
SMI	0.67 (0.42-1.08)	0.10
Psoas muscle area	1.00 (1.00-1.00)	0.035
PMI	0.46 (0.27-0.79)	0.005
Kt/V	0.17 (0.02-2.03)	0.16

HR: hazard ratio; CI: confidence interval; SMI: skeletal muscle mass index; PMI: psoas muscle index

Table.5 Multivariate analysis of overall mortality (n = 131)

	Characteristic	HR (95% CI)	P value
Model 1	Male	6.11 (0.71-52.32)	0.099
	Age	1.02 (0.95-1.09)	0.62
	PMI		
	High	Reference	-
	Low	9.90 (1.83-53.66)	0.008
Model 2	Male	3.08 (0.38-25.27)	0.29
	Age	1.04 (0.97-1.11)	0.27
	PMI		
	High	Reference	-
	Low	4.96 (0.55-44.64)	0.15
Model 3	Male	9.45 (1.06-84.57)	0.045
	Age	1.01 (0.94-1.08)	0.78
	PMI		
	Highest	Reference	-
	Middle	1.18 (0.07-20.40)	0.91
	Lowest	12.65 (1.06-150.89)	0.045

Model 1: patients were classified according to the cut off of 3.91 in male and 3.35 in female.

Model 2: patients were classified according to the cut off of 6.36 in male and 3.92 in female.

Model 3: patients were classified according to the tertile (4.58 and 6.38).

HR: hazard ratio; CI: confidence interval; PMI: psoas muscle index

Figure 1

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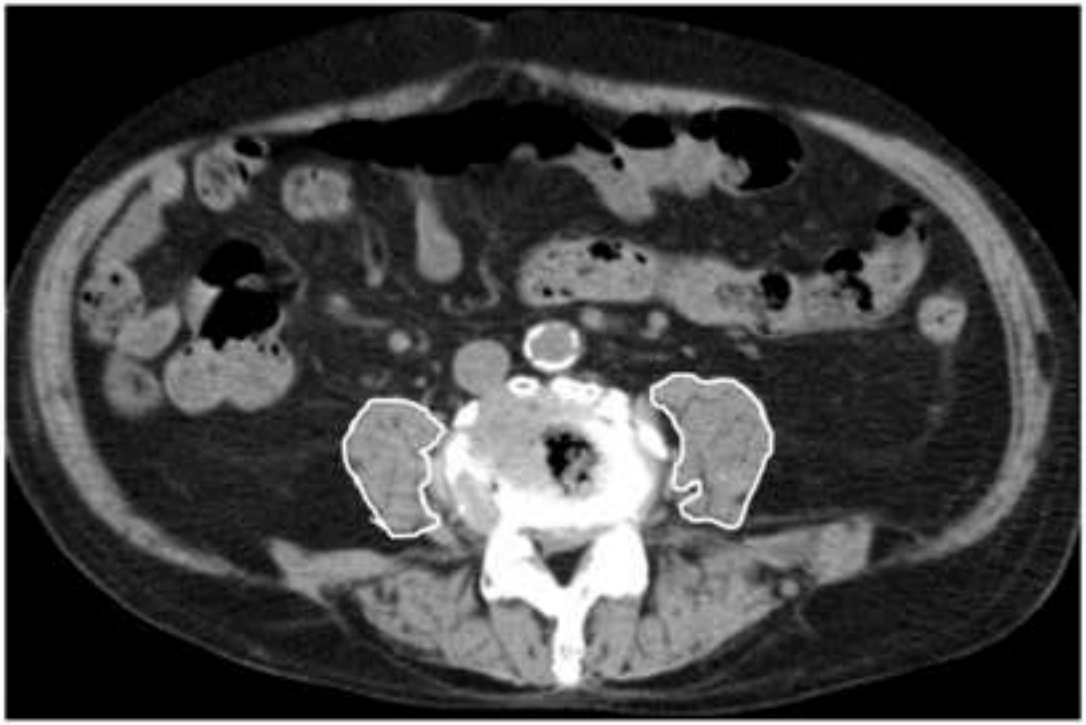

Figure 2

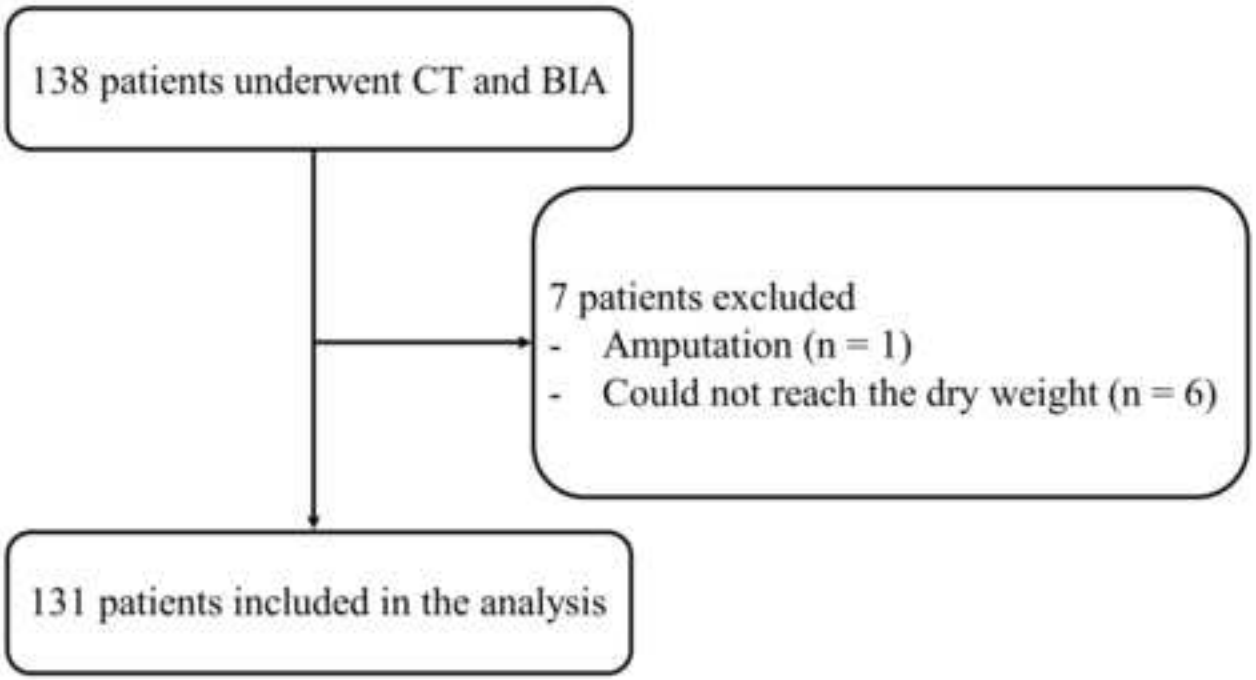

Figure 3

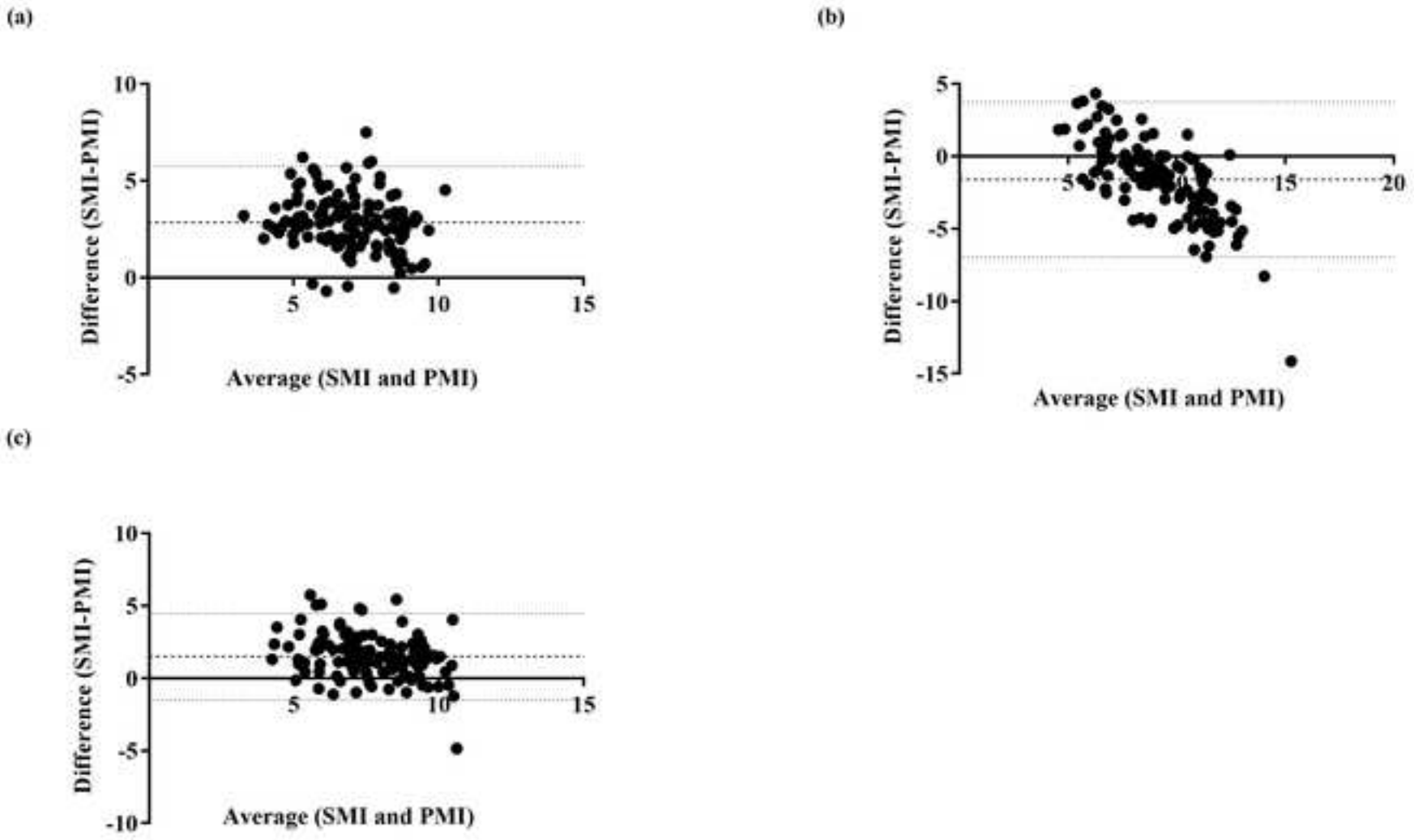

Figure 4