Original article

Creatinine-to-cystatin C ratio estimates muscle mass correlating the markers of the patients with severe motor and intellectual disabilities

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Abstract

Aim: The creatinine-to-cystatin C ratio (CCR) has been acknowledged as a potential marker of muscle mass. The purpose of the present study was to evaluate the relationship between CCR and nutritional status in a bioelectrical impedance analysis (BIA) of patients with severe motor and intellectual disabilities (SMID).

Methods: This study included 39 patients with SMID (17 males, 22 females) over 16 years of age were included retrospectively. CCR was calculated as serum creatinine (mg/dL)/cystatin C (mg/L) × 10. The BIA parameters such as the phase angle (PhA), fat free mass (FFM), appendicular skeletal muscle mass (ASM) and appendicular skeletal muscle mass index (ASMI) values were measured using BIA. Correlation analyses between CCR and the BIA parameters were conducted.

Results: The mean CCR is 4.47 ± 1.34. Significant positive relationships between CCR and FFM, PhA, ASM, ASMI were identified ($r = 0.3373$, $p = 0.0357$. $r = 0.4273$, $p = 0.0093$. $r = 0.5008$, $p = 0.0012$. $r = 0.4706$, $p = 0.0025$ and $r = 0.4751$, $p = 0.0022$, respectively).

Conclusions: The study indicated that CCR in the patients with SMID is a useful parameter that allows for the muscle mass to be estimated easily and accurately. This means that evaluating CCR could be used as a simple and important screening tool for PhA, FFM and muscle mass.

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1. Introduction

The patients with severe motor and intellectual disabilities (SMID) are almost not able to intake orally, are inserted nasogastric tube or undergone gastrostomy, and require intensive nutritional support by caregivers because of the presence of severe neurological and metabolic disabilities. Accurately evaluating nutritional status of them should be fundamental. However, As the scoliosis and body compositions of the patients were abnormal and severe, calculating subjective nutritional assessments from physical measurements is difficult for physicians [1].

Body composition assessment is an important tool for evaluating nutritional status. A variety of methods of analyzing the body composition, including bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry, computed tomography and magnetic resonance imaging have been used to evaluate the body composition of the patient. BIA is the electrical tool for analyzing the body composition by measuring the biological impedance against a subtle alternating current. The merits of BIA are as belows; 1) An alternative and noninvasive method of analyzing the body composition, 2) Light in weight, portable and usable at the bedside, 3) Less expensive than dual-energy X-ray absorptiometry, computed tomography and magnetic resonance imaging, 4) No technical skill to operate [2,3]. The estimation of the components of the body structure such as fat mass (FM), fat free mass (FFM) and appendicular skeletal muscle mass (ASM) were calculated by BIA. FM and FFM associate with physical fitness of the human body composition. Especially, FFM which includes internal organs, bone, muscle, water, and connective tissue is the metabolically active tissue in the body and the body compartment with the greatest influence on metabolic rate. FFM is comprised of the nonfat components of the human body. ASM is defined as the sum of skeletal muscle mass of the arms and the legs. The Phase angle (PhA), which reflects cellularity and cell membrane or cell function as BIA parameter, is regarded as a composite measurement of tissue reactance and resistance [4]. This parameter reflects the amount and the quality of soft tissues. In our previous study, the body mass index (BMI) and FFM of the patients with SMID were lower than those values in normal subjects [1]. Moreover, PhA values of patients with SMID were also considerably lower than that of normal subjects. Low PhA reflected a risk factor of frailty [1]. Another previous study, FFM of patients with SMID calculated BIA accurately predicted resting energy expenditure using indirect calorimetry [5]. FFM were useful to predict the nutritional levels of the patients with SMID.

Creatinine is a waste product from the normal breakdown of muscle tissue. The level of serum creatinine has been considered as a potential marker reflecting muscle mass. However, the level of serum creatinine level is influenced by renal function, it is not accurate to evaluated the amount of muscle mass in clinical practice [6]. Cystatin C (CysC), which is another marker of glomerular filtration, is produced not only by muscle mass but also all nucleated cells. The proximal tubule reabsorbed the filtered CysC which is completely metabolized later. For calculating the glomerular filtration rate (GFR), the serum CysC level is more accurately than serum creatinine level [6].

Recently, Creatinine-to-Cystatin C ratio (CCR; serum creatinine [mg/dL]/serum CysC [mg/L] × 10) has been reported to be associated with a fair measurement of muscle mass estimation and named "Sarcopenia Index". Barret et al. reported that there were positively correlation between CCR and muscle volume and between CCR and physical function used to assess by BIA [7]. In a cross-sectional study of patients of Japanease adult over 60 years old, Tabara et al. reported that there was significant association between CCR and femoral abdominal cross sectional area muscle mass measured by computed tomography and hand grip strength. CCR was useful as a marker of muscle mass and muscle strength, especially in elderly subjects which had low muscle mass and weak muscle strength [8]. CCR was recommended as a practical screening marker for sarcopenia [7,8]. Sarcopenia was a skeletal muscle disorder involving the loss of muscle mass and function that is associated with increased functional disorder, frailty, and mortality, and was identified as a poor prognostic factor in patients with postoperative complications, cancers, chronic diseases such as osteoporosis, cirrhosis, and heart failure. However, no previous reports have estimated the relationship between CCR and parameters which are calculated BIA such as PhA, FFM and ASM in the patients with SMID. Therefore, in this study, we aimed to evaluate whether CCR is a reliable parameter for evaluating the muscle mass of the patients with SMID by using BIA.

2. Patients and methods

2.1. Patients

Thirty-nine patients with SMID over 16 years old (male/female, n = 17/22; mean age, 27.8 ± 11.0 years; range: 16–49 years) who were admitted for medical examination of neurological gastrointestinal motility in Kurume University Hospital between April 2014 and April 2020 were included retrospectively.

All the patients were scored 1 on Oshima's classification, bedridden with enteral feeding tube or gastrostomy tube for enteral nutrition. Of 39 patients, 37 patients presented with cerebral damage in the neonatal period or infancy, of which characteristics were presented in

Table 1
The cause of cerebral damage.

	n
West syndrome	1
Cerebral infarction	5
Lissencephaly	2
Sequelae of cerebral hemorrhage	4
Holoprosencephaly	1
Congenital cytomegalovirus infection	2
Hypoxic ischemic encephalopathy	8
Neonatal jaundice	1
Encephalopathy	2
Rett syndroma	2
Spina Bifida	2
Adrenoleukodystrophy	1
Unknown	6

Table 1, 1 patient presented with aromatic L-amino acid decarboxylase deficiency and the other patient presented with Dubowitz type spinal muscular atrophy. The patients who suffered from organ failures or lost or gain over 5% weight in the previous 3 months or lost or gain over 10% weight in the previous 6 months were excluded. Informed consents were obtained from the patients' caregivers or families before calculation. Baseline nutritional assessments which were the subjective global assessment (SGA) parameters, including age, height, weight and BMI were measured. The serum laboratory measurements which were total protein, albumin, transthyretin, creatinine and CysC were also measured at the day of calculated SGA and BIA. Estimated GFR (eGFR; ml/min/1.73 m^2) using creatinine and CysC calculated using the equations based on the guidelines of Japanese Society of Nephrology for Japanese patients, as follows: Male, eGFR using creatinine ($eGFR_{crn}$) = 194 × creatinine$^{-1.094}$ × age$^{-0.287}$; Female, $eGFR_{crn}$ = male GFR_{crn} × 0.739; Male eGFR using CysC (GFR_{CysC}) = (104 × CysC$^{-1.019}$ × 0.996^{age}) − 8; and Female $eGFR_{CysC}$ = (104 × CysC$^{-1.019}$ × 0.996^{age} × 0.929) − 8 [9].

This study was performed after obtaining informed consents from the parents and/or caregivers. This study was approved by the ethics committee for clinical research of Kurume University School of Medicine (approval No.17302).

2.2. Bioelectrical impedance analysis

The BIA measurements were calculated with InBody S20 device (Biospace, Tokyo, Japan). The patients were conducted with 8 surface electrodes (equipped thumb and middle fingers of hands and feet) and the obtained data were automatically analyzed by the BIA. The BIA parameters were as follows; PhA, FFM, FM, ASM and appendicular skeletal muscle mass index (ASMI). To calculated ASMI, ASM was converted by dividing the height

of the patient in meters squared (kg/m^2) [10–13]. Patients were fasted for more than 2 h. Parenteral nutrition was not received during calculated BIA. Patients has contracture and should stretch arms and legs as much as possible. Arms and legs were separated from each other and from the trunk were placed in the supine position during calculated BIA. A thermoneutral environment at a temperature was 26–28 °C. The PhA was determined at 50 kHz single frequencies and was calculated using the sum of the impedance and reactance of the right arm, trunk, and right leg and according to the following formula: PhA (°) = Arctangent (Reactance/Resistance × 180/π). FFM and FM were separated from body weight.

2.3. Statistical analysis

First, the SGA parameters (age, height, weight and BMI), the BIA parameters (PhA, FFM, FM, ASM and ASMI) and serum nutritional parameters (total protein, albumin, transthyretin, creatinine, CysC and CCR) were calculated and compared among each gender. Second, we investigated the consistent probability between $eGFR_{crn}$ and $eGFR_{CysC}$ in patient with SMID. Third, correlation analysis were conducted between CCR and SGA parameter and the BIA parameters. Comparisons between 2 groups among each gender were made using the Mann–Whitney U test. Spearman's correlation coefficients were used to identify relationships between two variables. The obtained data was expressed as the mean ± standard deviation. To indicate statistical significance, p-values < 0.05 were considered in this study. All of the statistical analysis were performed using by the JMP $^®$ Pro 14 software package (SAS., Cary, NC, 1989–2019. USA).

3. Results

Of all the patients, the SGA parameters, the BIA parameters and the serum nutritional parameters and the male and female patients with SMID were shown in Table 2. Comparing the SGA parameters, BIA parameters and the serum nutritional parameters between male and female patients with SMID, age, height, body weight, FFM, ASM, ASMI, Creatinine and CCR of male patient were significantly higher than those of female patients. No significant differences were observed in the other parameters between the male and female patients. The mean $eGFR_{CysC}$/$eGFR_{crn}$ ratio was 2.13 ± 0.83. All cases without one case ($eGFR_{CysC}$/$eGFR_{crn}$ ratio was 0.936), $eGFR_{CysC}$/$eGFR_{crn}$ ratio were over 1 (Table 2).

The relationships between CCR and SGA, and BIA parameters in the correlation analysis were shown in Table 3. There were significantly positive relationships between the CCR and body weight, PhA, FFM, ASM

Table 2
The parameters in the groups of patients with severe motor and intellectual disabilities

	Total (n = 39)	Male (n = 17)	Female (n = 22)	*p value*
SGA parameter				
Age (y)	27.8 ± 11.0	31.8 ± 11.1	24.8 ± 10.2	0.0200
Height (m)	137.7 ± 9.87	143.8 ± 9.25	133 ± 7.55	0.0001
Body Weight (kg)	28.3 ± 7.90	30.6 ± 7.09	26.5 ± 8.18	0.0336
Body Mass Index (kg/m2)	14.9 ± 4.03	14.8 ± 3.13	15.1 ± 4.68	0.7445
BIA data				
Phase Angle (°)	3.51 ± 1.67	4.10 ± 2.02	3.03 ± 1.17	0.0746
Fat free mass (kg)	19.4 ± 4.01	22.4 ± 3.62	17.1 ± 2.56	<0.0001
Fat mass (kg)	8.90 ± 7.05	8.28 ± 6.40	9.38 ± 7.63	0.7533
ASM (kg)	5.16 ± 3.20	7.13 ± 3.22	3.63 ± 2.26	0.005
ASMI (kg/m^2)	2.61 ± 1.41	3.39 ± 1.41	2.01 ± 1.11	0.0031
Serum nutrition maker				
Total protein (g/dL)	7.23 ± 0.68	7.13 ± 0.76	7.30 ± 0.61	0.8874
Albmin (g/dL)	3.99 ± 0.43	4.02 ± 0.10	3.97 ± 0.09	0.4965
Transthyretin (mg/dL)	25.4 ± 5.56	26.2 ± 6.48	24.8 ± 4.82	0.8207
Creatinine (mg/dL)	0.35 ± 0.13	0.40 ± 0.16	0.30 ± 0.09	0.0251
Cystatin C (mg/L)	0.76 ± 0.19	0.80 ± 0.22	0.73 ± 0.16	0.3571
eGFR$_{crn}$ (ml/min/1.73 m)	256.8 ± 158.3	261.6 ± 196.2	253.1 ± 126.5	0.6813
eGFR$_{CysC}$ (ml/min/1.73 m)	116.4 ± 29.8	115.4 ± 35.1	117.2 ± 25.9	0.7022
eGFR$_{crn}$/eGFR$_{CysC}$	2.13 ± 0.83	2.15 ± 0.98	2.11 ± 0.72	0.7979
Creatinine-to-cystatin C ratio	4.47 ± 1.34	4.95 ± 1.56	4.09 ± 1.02	0.0459

SGA: subjective global assessment, BIA: bioelectrical impedance analysis, BMI: body mass index skeletal mass index
ASM: appendicular skeltal muscle mass, ASMI: appendicular skeletal mass index,
Creatinine-to-cystatin C ratio =(Creatinine/Cystatin C)*10

Table 3
The analysis of correlations between CCR and the parameters in patients with severe motor and intellectual disabilities

	Total (n = 39)		Male (n = 17)		Female (n = 22)	
Variables	r	*p value*	r	*p value*	r	*p value*
SGA parameter						
Age (y)	0.1652	0.3149	0.3122	0.2224	−0.0931	0.6804
Height (m)	−0.0183	0.8474	0.043	0.8696	0.1773	0.4299
Body Weight (kg)	0.3373	0.0357	0.0737	0.7786	0.3991	0.0658
Body Mass Index (kg/m2)	0.2336	0.1523	0.0049	0.9851	0.3809	0.0803
BIA data						
Phase Angle (°)	0.4273	0.0093	0.2118	0.4311	0.2602	0.2680
Fat free mass (kg)	0.5008	0.0012	0.6859	0.0024	0.3478	0.1128
Fat mass (kg)	0.0573	0.7290	−0.1275	0.6259	0.2773	0.2115
ASM (kg)	0.4706	0.0025	0.3946	0.1170	0.3552	0.1048
ASMI (kg/m^2)	0.4751	0.0022	0.3676	0.1466	0.3382	0.1237

SGA: subjective global assessment, BIA: bioelectrical impedance analysis, BMI: body mass index, AMM: appendicular skeltal muscle mass, ASMI: appendicular skeletal mass index, CCR:Creatinine-to-cystatin C ratio =(Creatinine/Cystatin C)*10

and ASMI (r = 0.3373, p = 0.0357. r = 0.4273, p = 0.0093. r = 0.5008, p = 0.0012. r = 0.4706, p = 0.0025, and r = 0.4751, p = 0.0022, respectively). In the male patients, significant positive closed relationship between the CCR and FFM (r = 0.6859, p = 0.0024) was observed. There were no correlations between CCR and SGA parameters, and the BIA parameters without FFM in male patients. In female patients, there were no relationships between CCR and SGA parameters, and the BIA parameters (Table 3 and Fig. 1).

4. Discussion

To the best of our knowledge, this study might be the first report to evaluate the relationship between CCR and muscle mass in patients with SMID used to assess by BIA and to suggest the CCR was positively correlated with nutritional markers in BIA such as FFM and PhA. These findings are clinically relevant because evaluating the nutritional status in the patients with SMID were difficult to be calculated due to their abnormal body compositions.
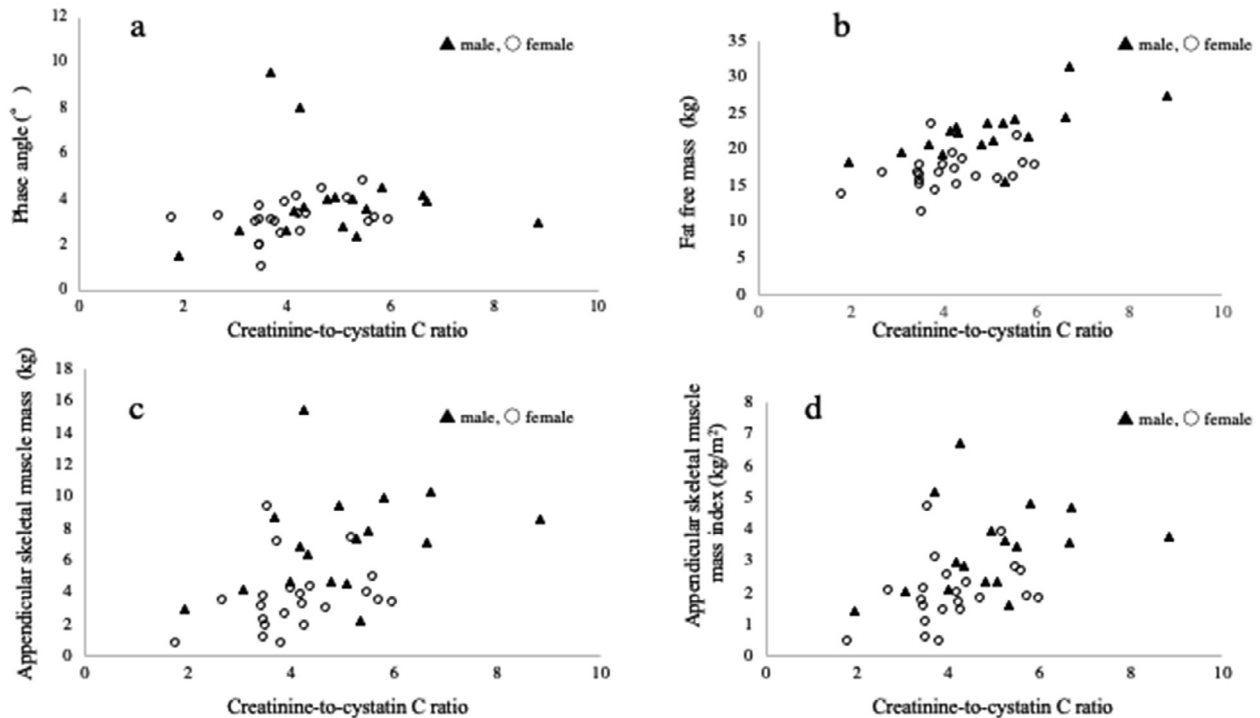
Fig. 1. The scattergram of Phase angle, fat free mass, appendicular skeletal muscle mass or appendicular skeletal muscle mass index and creatinine-to-cystatin C ratio in patients with severe motor and intellectual disabilities. (a) The scattergram of Phase angle and creatinine-to-cystatin C ratio (b) The scattergram of fat free mass and creatinine-to-cystatin C ratio (c) The scattergram of appendicular skeletal muscle mass and creatinine-to-cystatin C ratio (d) The scattergram of appendicular skeletal muscle mass index and creatinine-to-cystatin C ratio.

In this study, ASMI in the patients with SMID were very low, because appendicular skeletal muscles in the patients with SMID did not move as voluntary motions. In the Asian Working Group for sarcopenia, the cutoff values of ASMI were 7.0 kg/m^2 for males and 5.4 kg/m^2 for females measured by dual energy X-ray absorptiometry and were 7.0 kg/m^2 for males and 5.7 kg/m^2 for females measured by BIA [10–13]. In our study, the mean ASMI values was 2.61 ± 1.41 kg/m^2 and was very low in comparison with normal healthy subjects.

In our study, the mean eGFR$_{CysC}$/eGFR$_{crn}$ ratio was over 2 and had a great difference in ability between eGFR$_{CysC}$ and eGFR$_{crn}$ because of low skeletal muscle mass. Serum creatinine measurements are less valuable than CysC due to the reduced skeletal muscle mass and eGFR using CysC is also useful [14]. Braat et al. reported that in the elderly persons, when eGFR$_{crn}$ is determined to be high because of their low muscular volume, the determination of creatinine clearance by urine collection should be used. [14]. Moreover, the CCR was positively correlated with the muscle mass in the normal healthy subjects. Osaka et al. reported that the mean CCR of 309 identified patients with type 2 diabetes was 9.0 ± 1.0 (10.0 ± 2.0 in male and 8.0 ± 2.0 in female) [15]. Tabara et al. reported the mean CCR of 553 healthy subjects in men aged 60 years or older were 10.7 ± 1.6 and that of 796 apparently healthy subjects in

women were 8.6 ± 1.3 [8]. In this study, the mean CCR was 4.47 ± 1.34 and the CCR values of the patients with SMID were apparently low compared healthy patients in other studies [7.8]. As health subjects, the CCR value was as useful for assessing FFM and ASMI in the patients with SMID.

PhA is one of the electrical compartments measured by BIA that does not require direct measurement of body weight and height and non-invasive, and it seems to be an objective variable nutritional status that is the measurement about the nutritional level of human body. Since the body composition of patients with SMID is different from that of normal subjects, the accuracy of BIA for patients with SMID is an important problem. As our previous study, the PhA in the patients with SMID demonstrated lower than those in the healthy Asian subjects [1]. The electrical properties of their bodies in the patients with SMID was likely to be influenced by the poor physical activity. There was a significant relationship between in low PhA and serum albumin, the length of hospital stay days and the mortality rate [16–19]. Since PhA is influenced by the intracellular to extracellular water ratio, the reduction in PhA evaluated ill patients were seemed to reflect reduction in skeletal mass In our study, PhA was positively correlated with CCR. This result suggested that CCR in the patients with SMID was potentially in a useful as nutritional

parameter. On the other hands, no significant differences between CCR and any other parameters were observed in each gender excluded CCR and FFM in male patients. This result might be due to small sample size in each gender. In this study, phase angle and ASMI of 2 male patients were over 8° and over 5 kg/m^2. There were measurement data largely deviating from the correlation of phase angle and CCR, and ASMI and CCR, it was determined that 2 male patients had abnormality in the myotonia of the extremities. The patients had more skeletal muscle of arms than other patients. So, the patients were less correlated with other patients.

There were some limitations in this study. First, patients with SMID had various healthconditions and were in a wide age distribution, in the small sample size and in a single center study. Second, Recently, abnormal thyroid function was known to impact on both creatinine and CysC concentrations. Creatinine concentrations increased and CysC concentrations decreased, with hypothyroidism [20]. In this study, there was no data about the thyroid function of the patients with SMID. Thus, a further prospective and multicentral study with omnifarious age and health matched patients with SMID should be performed. Third, there was no data on walking speed and grip strength which were skeletal muscle function required to diagnose body functional composition. Moreover, there was no data on assessment muscle mass measured by computed tomography and dual energy X-ray absorptiometry. According to the indications reported in European Society for Clinical Nutrition and Metabolism guidelines, the use of BIA in clinical practice is not indicated for routine assessment in patients with an unbalanced state of hydration and underweight subjects or those with grade III obesity [21]. There was no data of the accuracy of BIA for the assessment of FFM and ASM in SMID patients using other reference methods. As an unbalanced state of hydration and underweight were common in patients with SMID, BIA measurements might have overestimated FFM and thus underestimated the presence of low muscle mass. It was difficult to clarify whether CCR or BIA measures were better in assessing body composition in patients with SMID. Further studies are therefore needed to measure other outcome measures or external indexes that can be used to clarify this issue.

In conclusion, based on the results of our preliminary study, CCR might be a potential nutritional marker in the patients with SMID. This means that evaluating CCR could be used as a simple and important screening tool for PhA, FFM and muscle mass.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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