Evaluation of Skeletal Muscle Mass in Patients with Chronic Liver Disease Shows Different Results Based on Bioelectric Impedance Analysis and Computed Tomography

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\textbf{Objective:} We aimed to evaluate the difference between computed tomography (CT)-based and bioelectrical impedance analysis (BIA)-based assessment of sarcopenia in patients with chronic liver disease (CLD).

\textbf{Methods:} We enrolled a total of 257 patients who were evaluated with or without sarcopenia. Sarcopenia was defined as a low skeletal muscle mass index (SMI) with low muscular strength by the Japan Society of Hepatology. To evaluate whether or not the different methods influence the diagnosis of sarcopenia for patients with CLD, we assessed the number and characteristics of mismatches between the low SMI using BIA versus CT.

\textbf{Results:} The numbers of patients with low SMI using BIA or CT were 53 (20.6\%) and 114 (44.3\%) patients, respectively. Multivariate analysis revealed that hepatic ascites and body weight were independent factors of mismatch between SMI using BIA versus CT (hazard ratio [HR] 3.232, \( p < 0.001 \); HR 2.347, \( p = 0.005 \), respectively). The median OS in patients with sarcopenia based on CT was significantly lower than that in patients without sarcopenia (\( p = 0.006 \)). In contrast, there was no difference between patients with sarcopenia based on BIA (\( p = 0.217 \)).

\textbf{Conclusion:} Muscle mass in patients with CLD may be overestimated by the BIA method compared to CT when assessing sarcopenia, especially in cases of fluid retention.

\textbf{Introduction}

Sarcopenia is defined as a syndrome with decline in muscle mass and strength associated with functional decline [1]. It is well known that the end-stage liver disease...
with protein-energy malnutrition is correlated with the high frequency of disease-related sarcopenia and leads to high mortality, infection risk, postoperative complications, and long hospitalizations [2, 3].

Early detection and immediate intervention is imperative to improve the overall prognoses in patients with disease-related sarcopenia due to liver disease [4]. Various therapies including dietary protein, vitamin D supplementation, and resistance exercise have been useful for sarcopenia [4–6]. Especially, branched-chain amino acids supplementation was reported to improve the nutritional status in patients with severe chronic liver disease (CLD) [7].

However, these reports were based on the definition of primary sarcopenia produced by the Asian Working Group for Sarcopenia (AWGS) and the European Working Group on Sarcopenia in Older People. There were no criteria or data for disease-related sarcopenia [8, 9]. To solve this problem, the Japan Society of Hepatology (JSH) established new criteria for patients with disease-related sarcopenia [10]. This criterion was composed of the evaluation of muscle mass and muscle strength, which was based on the AWGS [8]. The characteristic point of this criterion was to select the measurement method to estimate the muscle mass by computed tomography (CT) and bioelectrical impedance analysis (BIA). In large epidemiologic studies, the application of BIA to measure body composition was reported to be a relatively quick and noninvasive method for reliable measurements of body composition [11]. Therefore, BIA was recommended to evaluate the skeletal muscle mass on the AWGS criteria [8]. On the other hand, CT required specialized equipment to evaluate muscle mass and density [12]. However, CT may be able to measure muscle mass for patients with severe CLD more accurately than with BIA because BIA is easily affected by the amount of water in the body [13]. Therefore, we need to carefully interpret muscle mass evaluation in patients with ascites and edema of the lower limbs, which is one of the complications of liver cirrhosis. To our knowledge, there are limited data to evaluate the difference between CT- and BIA-based assessments of skeletal muscle mass in patients with CLD. Therefore, we aimed to evaluate the difference of CT and BIA for the diagnosis of sarcopenia.

**Materials and Methods**

**Ethical Considerations**

The Japanese clinical trial registration system UMIN-CTR is a registration site that meets the ICMJE standards, and this study is registered in UMIN ID UMIN000041121 and approved by the research Ethics Committee in Tokushukai Medical Group (Number: TGE1230) and Kitasato University School of Medicine (Number: C21-171). This study is a retrospective observational study. Informed consent was obtained from all individual participants included in the study by the opt-out method as described in our hospital Website.

**Eligibility Criteria**

This retrospective study was conducted at two centers between January 2015 and March 2021. We enrolled patients who met the following inclusion criteria: (1) the presence of CLD, (2) men and women over 20 years old, (3) muscular strength measured by a handgrip dynamometer, and (4) skeletal muscle mass index (SMI) measured by BIA and CT. A total of 293 patients met all inclusion criteria in both institutes. Of these, 36 patients were excluded because of (1) the presence of a malignant tumor other than hepatocellular carcinoma (HCC) and/or (2) cardiac, respiratory, and/or renal failure. Therefore, the remaining 257 patients were evaluated for sarcopenia (Fig. 1).

CLD was subdivided into chronic hepatitis, compensated cirrhosis, and decompensated cirrhosis. The diagnosis of liver cirrhosis was based on the images of atrophic changes in the liver lobe, splenomegaly, varices, and/or ascites. Decompensated cirrhosis was defined as any cirrhosis with complications, such as variceal bleeding, hepatic encephalopathy, and/or ascites [14]. The causes of CLD included hepatic virus infection, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD). Hepatitis-C virus (HCV) infection was confirmed by the plasma levels of HCV RNA and/or HCV antibody. Hepatitis-B virus (HBV) infection was confirmed by hepatitis-B surface antigen and/or the plasma levels of HBV-DNA. Alcoholic liver disease was associated with CLD with...
daily alcohol consumption of \(>60\) g for men or \(>40\) g for women. NAFLD should be diagnosed histologically, which proved the presence of intrahepatic triglyceride content of \(>5\%\) of liver weight. However, the progression of liver fibrosis leads to the disappearance of characteristic findings such as steatosis and Mallory bodies. Therefore, NAFLD was diagnosed with CLD in patients who habitually drink alcohol \(<20\) g/day and the appropriate exclusion of other causes of CLD [15].

Sarcopenia Definition

Sarcopenia was diagnosed based on the criteria for patients with CLD, recommended by a working group from JSH [10]. Their consensus definition was based on low SMI with low muscular strength. Low muscular strength and low SMI were defined as follows.

Muscular Strength

Muscular strength was measured using a handgrip dynamometer (Digital Hand Grip Dynamometer, A5401; Takei Scientific Instruments Co., Ltd.). The patient’s grip strength was tested in two trials each, and the average grip force (kg) was calculated for each individual. Low grip strength was defined as a grip strength measurement of \(<26\) kg for men and \(<18\) kg for women.

Muscle Mass Measurement

SMI was measured as the skeletal muscle mass using CT and BIA. Measurements of SMI using CT were the cross-sectional area of the skeletal muscles (cm\(^2\)) at the third lumbar vertebra (L3) divided by height squared \([L3 \text{ SMI} = \text{cm}^2/\text{m}^2]\) [12]. The skeletal muscles were composed of the erector spinae, external oblique, internal oblique, psoas major, rectus abdominis, quadratus lumborum, and the transversus abdominis. Cross-sectional CT images at L3 were made using the Slice-O-Matic software (v5.0; Tomovision, Montreal, Canada). Low SMI using CT was defined as an SMI measurement of \(<42.0\) cm\(^2/\text{m}^2\) for men and \(<38.0\) cm\(^2/\text{m}^2\) for women. SMI based on the BIA was evaluated as the muscle mass of all 4 limbs using BIA by dividing the square of the height. Low SMI using BIA was defined as an SMI measurement of \(<7.0\) kg/m\(^2\) for men and \(<5.7\) kg/m\(^2\) for women. Segmental body composition was measured using InBody S10 (InBody Japan Inc., Tokyo, Japan) or Multi-Frequency Body Composition Analyzer MC-180 (Tanita Corporation, Tokyo, Japan). The measurement procedure of InBody S10 required the electrode pads contact the patient’s hands and feet. The hand electrodes were placed on all the participants’ fingers. The foot electrode was positioned between the examinee’s ankle (the ankle bone) and the calcaneus (the heel bone). The measurement procedure of Multi-Frequency Body Composition Analyzer MC-180 required the subject to stand in bare feet on the analyzer and to hold a pair of handgrips. Both are medical machines that use eight electrodes and have a multi-frequency measurement principle and measure the trunk, right arm, left arm, right leg, and left leg separately.

Study Design

To evaluate whether or not the different methods influence the diagnosis of sarcopenia for the patients with CLD, we assessed the numbers and characteristics of mismatches between the low SMI using BIA and that using CT based on the JSH criteria. We also compared the overall survival (OS) in patients with and without sarcopenia based on CT and BIA to evaluate the appropriate methods for patients with CLD. OS was defined as the number of days from the evaluation of sarcopenia to either death or September 10, 2020, whichever came first.

Clinical Characteristics

All enrolled participants were assessed for base characteristics: physical assessment, prescription drugs, heavy episodic drinking, presence of HCC, nutritional status, degree of fibrosis progression, and laboratory data. The diagnosis of HCC was based on the images before the sarcopenia evaluation. The laboratory data evaluated the white blood cell count, hemoglobin level, platelet count, creatinine level, blood urea nitrogen level, aspartate aminotransferase level, alanine aminotransferase level, total bilirubin, serum albumin, ammonia, alpha-fetoprotein, prothrombin time, and glycated hemoglobin A1c.

### Table 1. Baseline clinical characteristics

| Clinical characteristics | All patients |
|--------------------------|-------------|
| Patients, \(n\)          | 257         |
| Age, years              | 69±10.8     |
| Gender: male, \(n\) (%) | 163 (63.4)  |
| Weight, kg              | 61±12.5     |
| Body mass index, kg/m\(^2\) | 23±3.8     |
| Etiology: HCV/HBV/alcohol/NASH/etc., \(n\) | 85/36/68/53/15 |
| HCC, \(n\) (%)          | 25 (9.7)    |
| Stage 1/2/3/4, \(n\)    | 31/28/33/8  |
| CH/compensated LC/decompensated LC, \(n\) (%) | 50/103/104 |
| Hypertension, \(n\) (%)  | 94 (36.6)   |
| Grip strength, kg        | 24.9 (8.8)  |
| SMI (CT), cm\(^2/\text{m}^2\) | 4.0 (5.9)  |
| SMI (BIA), kg/m\(^2\)    | 7.6 (1.6)   |
| Phase angle              | 5.1 (1.6)   |
| CP scores               | 109/49/29/30/14/15/5/5/1 |
| ALBI score              | −2.38±0.62  |
| Grades 1/2/3            | 138/140/22  |
| Fib-4 index             | 5.62 (6.59) |
| BCAA supplementation, \(n\) (%) | 82 (31.9)   |
| White blood cells, /μL   | 4,921 (1,694) |
| Hemoglobin, g/dL         | 13.4 (9.4)  |
| Platelets, ×10\(^9\)/μL  | 13.7 (8.1)  |
| Prothrombin time, \%     | 79 (19)     |
| Serum albumin, g/dL      | 3.7 (0.6)   |
| BUN, mg/dL               | 16.7 (7.8)  |
| Serum creatinine, mg/dL  | 1.37 (6.66) |
| eGFR, mL/min/1.73 m\(^2\) | 64 (21)    |
| ALT, IU/L                | 43 (31)     |
| AST, IU/L                | 30 (22)     |
| Total bilirubin, mg/dL   | 1.2 (1.0)   |
| Serum sodium, mMg/L      | 139 (9)     |
| HbA1c, %                 | 6.0 (1.1)   |
| Ammonia, μg/dL           | 60 (50)     |
| AFP, ng/mL               | 213 (1,678) |

Data are expressed as mean, number (%), or mean (standard deviation). HCV, hepatitis-C virus; HBV, hepatitis-B virus; CP, Child-Pugh; ALBI, albumin-bilirubin; BCAA, branched-chain aminoacid; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HbA1c, hemoglobin A1c; AFP, alpha-fetoprotein.
Statistical Analyses

Statistical significance was defined as $p < 0.05$. Statistical analyses were analyzed using SPSS software (version 24.0; IBM Corp., Armonk, NY, USA) and were compared between the two groups using the $\chi^2$ test and the $t$-test. The log-rank test and the Kaplan-Meier method were used to compare differences between patients with and without sarcopenia in the patients' survival rates. A multivariate logistic regression analysis was performed to calculate the hazard rate for the variables entered, which were significantly associated with the characteristics of mismatches between low SMI using BIA and CT by univariate analysis. Statistical analyses were reviewed by the Statista Corporation, Kyoto, Japan.

Results

Subjects

Table 1 shows the patients’ baseline characteristics. The mean age was $69.2 \pm 10.8$ years. The number and frequency of men were 163 and 63.4%. The etiologies of the CLD were HBV ($n = 36$), HCV ($n = 85$), alcohol ($n = 68$), NAFLD ($n = 53$), and others ($n = 15$). Of patients with HCV, 34 patients achieved a sustained viral response with antiviral therapy. The numbers of chronic hepatitis and compensated and decompensated cirrhosis were 50 (19.5%), 103 (40.1), and 104 (40.5%), respectively. There were 25 (9.70%) patients with HCC.

Sarcopenia Frequency Using BIA and CT

The mean hand grip was $24.9 \pm 8.8$ kg. The number and population of low muscular strength was 107 (41.6%). The mean SMI using BIA and CT was $7.6 \pm 1.6$ and $40.0 \pm 5.9$, respectively. The phase angle (PhA) using BIA was $5.1 \pm 1.6^\circ$. The numbers of patients with low SMI using BIA and CT were 52 (20.2%) and 124 (48.2%) patients, respectively. As a result, the number and frequency of patients with sarcopenia using BIA and CT were 28 (10.9%) and 68 (26.5%) patients, respectively (Fig. 2).

Based on the analysis using CT to evaluate SMI, progression fibrosis was related to the frequency of sarcopenia (CLD = 5/50, compensated liver cirrhosis = 25/103, and decompensated liver cirrhosis = 38/104, respectively;
However, based on the analysis using BIA to evaluate SMI, there was no correlation between progression fibrosis and the frequency of sarcopenia (CLD = 1/50, compensated liver cirrhosis = 19/103, and decompensated liver cirrhosis = 8/104, respectively; \( p = 0.791 \)) (Fig. 3).

**Risk Factors for Mismatches between BIA- and CT-Based Assessment of SMI**

Univariate analysis revealed that low hand grip strength, body weight, hepatic ascites, albumin, and hemoglobin were independent factors correlated with mismatches between BIA- and CT-based assessment of sarcopenia (Table 2). Multivariate analysis revealed that hepatic ascites and body weight were independent factors of mismatches between SMI using BIA and CT (hazard ratio 3.232, 95% confidence interval [CI] 1.755–5.954, \( p < 0.001 \); hazard ratio 2.347, 95% CI 1.290–4.269, \( p = 0.005 \), respectively) (Table 2).

**BIA-Derived PhA in Sarcopenia**

To evaluate quality for the measurement of muscle mass using BIA, PhA was analyzed in patient with and without sarcopenia based on BIA. For man, PhA in the sarcopenia and nonsarcopenia groups was 4.4 ± 0.8° and 5.4 ± 1.9°, respectively. For woman, PhA in the sarcopenia and nonsarcopenia groups was 4.4 ± 0.7° and 4.7 ± 0.7°, respectively. The PhA was significantly lower in the sarcopenia group than that in the nonsarcopenia (man, \( p = 0.079 \), and woman, \( p = 0.045 \)).

**OS Based on the Sarcopenia Using BIA and CT**

The cause of deaths in the enrolled patients during the study period was liver failure (\( n = 24 \)), HCC (\( n = 23 \)), varix rupture (\( n = 6 \)), infection (\( n = 5 \)), sudden death (\( n = 3 \)), cancers other than HCC (\( n = 3 \)), hemorrhage (\( n = 1 \)), and gastrointestinal perforation (\( n = 1 \)). The frequency of deaths in patients with sarcopenia and nonsarcopenia based on CT analysis was 35.3% (24/68) and 22.2% (42/189), respectively. The median OS in patients with and those without sarcopenia was 1,365 days and 1,828 days, respectively (95% CI: 1,153–1,578 days and 1,710–1,945 days, respectively). The median OS in patients with sarcopenia was significantly lower than that in patients without sarcopenia (\( p = 0.006 \)).

In contrast, the frequency of deaths of patients with and that of those without sarcopenia based on the analysis using BIA was 35.7% (10/28) and 24.4% (56/229), respectively. The median OS of patients with and that of those without sarcopenia was 1,326 days and 1,758 days, respectively (95% CI: 1,043–1,609 days and 1,643–1,873 days, respectively). There was no difference between OS of patients with sarcopenia and that of nonsarcopenia patients (\( p = 0.217 \)) (Fig. 4).
Table 2. Univariate and multivariate analyses of factors affecting mismatch between SMI using BIA and CT

| Variable                                      | Univariate analysis |          | Multivariate analysis |          |
|-----------------------------------------------|---------------------|----------|-----------------------|----------|
|                                               | HR (95% CI)         | p value  | HR (95% CI)           | p value  |
| Age                                           | 1.000               | 0.296    | 1.000                 | 0.005    |
| <70.0                                         |                     |          |                       |          |
| ≥70.0                                         | 1.336 (0.776–2.301) |          |                       |          |
| Gender                                        |                     |          |                       |          |
| Male                                          | 1.536 (0.882–2.673) | 0.129    |                       |          |
| Female                                        | 1.000               |          |                       |          |
| Body weight                                   |                     |          |                       |          |
| <60                                           | 1.000               | 0.004    | 1.000                 | 0.005    |
| ≥60                                           | 2.264 (1.296–3.955) |          | 2.347 (1.290–4.269)   |          |
| Sarcopenia (hand grip)                        |                     |          |                       |          |
| –                                             | 1.000               | 0.003    |                       |          |
| +                                             | 2.291 (1.319–3.978) |          |                       |          |
| HCC                                           |                     |          |                       |          |
| –                                             | 1.000               | 0.962    |                       |          |
| +                                             | 1.022 (0.408–2.561) |          |                       |          |
| Hepatic ascites                               |                     |          |                       |          |
| –                                             | 1.000               | <0.001   | 1.000                 | <0.001   |
| +                                             | 3.142 (1.738–5.682) |          | 3.232 (1.755–5.954)   |          |
| Hepatic encephalopathy                        |                     | 0.404    |                       |          |
| –                                             | 1.000               |          |                       |          |
| +                                             | 1.308 (0.696–2.459) |          |                       |          |
| Total bilirubin                               |                     | 0.966    |                       |          |
| <2.0                                          | 1.000               |          |                       |          |
| ≥2.0                                          | 1.036 (0.422–2.210) |          |                       |          |
| Albumin                                       |                     | 0.001    |                       |          |
| <3.5                                          | 2.521 (1.448–4.388) |          |                       |          |
| ≥3.5                                          | 1.000               | 0.185    |                       |          |
| <30.0                                         | 1.000               |          |                       |          |
| ≥30.0                                         | 1.469 (0.831–2.597) |          |                       |          |
| Platelet count                                |                     | 0.651    |                       |          |
| <10.0                                         | 1.136 (0.653–1.976) |          |                       |          |
| ≥10.0                                         | 1.000               |          |                       |          |
| Hemoglobin                                    |                     | 0.034    |                       |          |
| ≤10                                           | 2.081 (1.056–4.105) |          |                       |          |
| ≥10                                           | 1.000               |          |                       |          |

AST, aspartate aminotransferase; HR, hazard ratio.

Discussion

To our knowledge, this is the first study to evaluate the difference between BIA- and CT-based assessment of sarcopenia using the JGH (Jewish General Hospital) criteria in patients with CLD. Currently, four main techniques have been commonly used to estimate muscle mass: BIA, dual energy X-ray absorptiometry (DXA), CT, and magnetic resonance imaging [16]. Valid, standardized, reliable, accurate, and cost-effective tools are necessary for the identification of muscle mass. BIA is a method of estimating body composition by passing a weak electric current through the body and measuring the resistance value [11]. This measurement has the convenience of completing the measurement in a few minutes with immediate results. In daily practice, the BIA method can be used to evaluate muscle mass accurately and timely according to changes in symptoms. In fact, the PhA using BIA had a tendency to be lower in the sarcopenia group compared with the nonsarcopenia group. The PhA is obtained from the resistance and reactance, which values that indicate the phase shift that occurs when a current is
passed through a muscle cell in the BIA measurement method [17, 18]. It is a value that represents the density of muscles, that is, the quality of muscles [19]. However, contemporary measurements make it difficult to accurately determine sarcopenia. BIA is easily affected by the amount of water in the body. Therefore, muscle mass indicated with BIA should be interpreted carefully in patients with severe ascites or edema [16].

In point of fact, there were numerous mismatched cases in the evaluation of muscle mass indicated using BIA and that using CT in the decompensated phase compared with that in the chronic hepatitis and compensated phases. Ascites and edema in the decompensated phase were recognized as fat and/or muscle instead of water by the BIA method which measures the difference in impedance of the current flowing through the body [11, 13]. As a result, it implies that overestimating muscle mass leads to a decreased number of sarcopenia diagnosis. In the present study, the frequency of sarcopenia based on the assessment using BIA was relatively low compared with that using CT. Therefore, the diagnosis of sarcopenia in the decompensated phase should be appropriately evaluated by a cross-sectional area of several muscles on CT imaging. As a diagnostic method, CT imaging plays a critical role in the early detection of sarcopenia [20].

This criterion could be applicable to various fields to diagnose disease-related sarcopenia. However, muscle mass in patients with edema and ascites may be overestimated, and the frequency of sarcopenia may not be accurately assessed. If patients with CLD are overestimated by using the BIA method to assess sarcopenia, appropriate treatment, such as nutritional and exercise interventions, may be delayed and may affect prognosis [21]. It is well known that CLD with disease-related sarcopenia is associated with a poor prognosis. Therefore, accurate diagnoses are important to improve the overall prognoses in patients with disease-related sarcopenia [22]. Iwasa et al. [23] reported that dividing the skeletal muscle mass of only the arms by height (arm index) was useful in avoiding the effects of severe edema. SMI, which uses upper and lower limb muscle mass, has been shown to be unsuitable for patients with lower limb edema. In the future, it will be necessary to evaluate fluid retention, such as ascites, and to select an appropriate assessment method using the BIA and/or CT methods. In addition, when using BIA, patients with ascites or edema may want to consider the cut-off value and evaluate sarcopenia only by using the upper arm, which is less susceptible to edema.

Furthermore, the measurement of the skeletal muscle mass by BIA varies depending on the device. Different devices were used, which might add extra variability and lead to misdiagnosis. In fact, there is a great difference between InBody S10 and MC-180 as follows. (1) The frequency for measuring impedance is 1–1,000 kHz for InBody S10 and 5–500 kHz for MC-180. The difference of frequencies from these two BIA devices influences the assessment of body composition in cirrhotic patients [24]. (2) Direct segmental multi-frequency BIA (DSM-BIA), which was
performed using the S10, was more accurate than conventional BIA devices [25]. (3) MC-180 was corrected by the measurements of skeletal muscle mass of the dual energy X-ray absorptiometry method for Japanese people.

It is unclear to what degree violating BIA measurement assumptions will alter the predicted SMI. In the present study, the frequency of sarcopenia based on two different devices was similar despite acutely violating the preliminary measurement BIA assumptions across a range of different methods. The minor variations of the measurement may be smaller than what would be expected [26].

This study has some limitations. First, it was a retrospective study. Second, edema was not assessed. Fluid retention can only be examined in ascites. Third, the equipment used for the BIA differs between the two facilities in this study. When evaluating SMI in pathological conditions accompanied by fluid retention such as liver cirrhosis, it is important to select an appropriate BIA measuring device and also evaluate water content by site. We will investigate this and report it in an upcoming article.

Conclusion

Due to the characteristics of the measurement principle of BIA, overestimation of muscle mass is predicted to be affected by fluid retention. It is necessary to assess edema before determining muscle mass using the BIA method.

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board Ethics Committees of Tokushukai Medical Group (Number: TGE1230) and Kitasato University School of Medicine (Number: C21-171). This study was a retrospective observational study. Informed consent was obtained from all individual participants included in the study by the opt-out method of our hospital Website, which was approved by the Research Ethics Committees of Tokushukai Medical Group and Kitasato University School of Medicine.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Nahoko Kikuchi, Haruki Uojima, Hisashi Hidaka, Shuichiro Iwasaki, Naohisa Wada, Kousuke Kubota, Takahide Nakazawa, Akitaka Shibuya, Makoto Kako, Teruko Sato, and Chika Kusano contributed equally to this work; Nahoko Kikuchi and Haruki Uojima collected and analyzed the data; Haruki Uojima drafted the manuscript; Hisashi Hidaka and Makoto Kako designed and supervised the study; Shuichiro Iwasaki, Naohisa Wada, Kousuke Kubota, Takahide Nakazawa, Akitaka Shibuya, Teruko Sato, and Chika Kusano offered technical or material support.

Data Availability Statement

The technical appendix, statistical code, and dataset are available from the corresponding author (email: kiruha@kitasato-u.ac.jp). All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
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