# Indices calculated by serum creatinine and cystatin C as predictors of liver damage, muscle strength and sarcopenia in liver disease

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**Abstract.** Serum creatinine (Cr)-based glomerular filtration rate (CrGFR) is overestimated in liver disease. The present study evaluated whether the difference in CrGFR and cystatin C (CysC) GFR (dGFR) is significant in liver disease. The Cr-to-CysC ratio and sarcopenia index (SI) have been reported to correlate with muscle volume. An estimated total body muscle mass with Cr, CysC and calculated body muscle mass (CBMM) has also been reported to correlate with muscle mass. The applicability of dGFR, SI and CBMM for liver disease were evaluated. A total of 313 patients with liver damage were evaluated for Child-Pugh score, albumin-bilirubin (ALBI) score, model for end-stage liver disease, fibrosis-4, Cr, CysC, Cr-based estimated GFR (CreGFR), CysCGFR and grip strength. Of the 313 patients, 199 were evaluated using cross-sectional computed tomography (CT) of the third lumbar vertebra to determine the skeletal muscle (SM) mass. dGFR, CBMM and SI were compared to liver damage, muscle strength and muscle mass. In the 313 patients, dGFR was correlated with age, ALBI and grip strength; CBMM was correlated with body mass index (BMI) and grip strength; and SI was correlated with BMI and grip strength. In patients evaluated with CT, the correlation coefficients for CBMM and SI with SM were 0.804 and 0.293, respectively. Thus, CBMM and SI were associated with sarcopenia. The relationship between dGFR and ALBI does not differ with different grades of CrGFR-based chronic kidney disease (CKD). dGFR is a marker of liver damage and muscle strength regardless of CKD. CBMM and SI are markers for sarcopenia in liver disease.

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*Abbreviations:* eGFR, estimated glomerular filtration rate; Cr, creatinine; CysC, cystatin C; SI, sarcopenia index; CBMM, calculated body muscle mass; CH, chronic hepatitis; LC, liver cirrhosis; CPS, Child-Pugh score; ALBI, albumin-bilirubin score; MELD, model for end-stage liver disease; TB, total bilirubin; BIA, bioelectrical impedance analysis

*Key words:* creatinine, cystatin C, estimated glomerular filtration rate, liver function, muscle strength

## Introduction

Assessment of glomerular filtration rate (GFR) using the serum creatinine (Cr)-based method provides very inaccurate results and tends to overestimate GFR in patients with liver disease (1). In chronic liver disease, decreased Cr production correlates with decreased hepatic creatine synthesis, and decreased skeletal muscle (SM) mass is thought to overestimate Cr-based GFR (CrGFR) (1,2). Conversely, serum cystatin C (CysC)-based estimated GFR (CysCGFR) shows improved correlation with measured GFR and improved predictability for overall survival and incidence of acute kidney injury compared with CrGFR (2-4). CysC appears to be more sensitive than Cr for patients with declining GFR in chronic liver disease (3-5). However, CysC positively correlates with body mass index (BMI) and is more strongly correlated with waist circumference and inflammation (6-8). In patients with chronic kidney disease (CKD) with eGFR >60 ml/min/$m^2$, the medium value of Cr was well within the normal range, whereas the median value of CysC was found to be higher than the upper reference limit (7). As reported, liver disease can also cause fluctuations in CysC level (9). Several cystatin C-based equations have been proposed, although they have not been shown to be superior to Cr-based equations (10). However, whether the difference between CrGFR and CysCGFR is significant in patients with liver disease has not been investigated.

Recently, Cr-to-CysC ratio (Cr/CysC x100), the so-called sarcopenia index (SI), has been reported to be associated with a fair measure of muscle mass estimation among patients admitted in the intensive care unit and can modestly predict the time in hospital and 90-day mortality among patients who do not have acute kidney injury at the time of measurement (11). SI correlates with muscle volume in patients with critical illness (11,12), lung transplant candidates (13), patients with type 2 diabetes (14) and patients with hepatocellular carcinoma (15). Cr production is relatively constant when the muscle mass is stable. Since CysC is excreted by all nucleated cells, the effect of muscle mass on CysC production is less than that on Cr. Therefore, SI is presumed to be associated with SM mass and sarcopenia. Sarcopenia is a harmful condition in patients with liver disease and cirrhosis (16) in patients who undergo liver transplantation (17) and in patients with hepatoma (18,19). In 2015, the Japan Society of Hepatology (JSH) decided to establish its own assessment criteria for sarcopenia in liver disease due to the high number of patients with liver disease and sarcopenia (20). As per the JSH criteria, when the handgrip strength was below 26 k in men and 18 kg in women, the muscle volume was evaluated by computed tomography (CT) or bioelectrical impedance analysis (BIA). As SI was not evaluated for its usefulness in liver disease, the present study compared SI and sarcopenia using the JSH criteria.

A new equation to estimate total body muscle mass using serum Cr and CysC level, the so-called calculated body muscle mass (CBMM), has also been developed (21), where Cr is correlated with muscle mass and CysC is correlated with body fat mass after adjusting the GFR value. After eliminating GFR, an equation to estimate total body muscle mass was generated. There was an agreement between muscle mass calculated and that measured by dual-energy X-ray absorptiometry in both the derivation and validation cohort ($P<0.001$, adjusted $R^2=0.829$, $\beta=0.95$ and $P<0.001$, adjusted $R^2=0.856$, $\beta=1.03$, respectively) (21). CBMM is calculated using body weight (BW) in kg, Cr and CysC.

The present study evaluated the applicability of CBMM in liver disease in addition, it evaluated the significance in the difference between CrGFR and CysCGFR in liver disease, with a focus on the relationship among differences in GFR, SI, CBMM and liver damage. Subsequently, in patients who underwent abdominal CT, body composition, including SM mass, was measured and their correlation with GFR, SI, CBMM and muscle mass were compared.

## Patients and methods

*Patients*. A total of 313 patients with liver dysfunction were admitted to Nagasaki Harbor Medical Center between April 2017 and October 2018. The median age of patients was 66 years, (range, 25-92) and there were 167 females and 146 males in the recruited cohort. In the outpatient department, patients were evaluated for the cause of liver disease (including hepatitis C virus, hepatitis B virus, autoimmune hepatitis and primary biliary cholangitis), clinical stage of liver disease [normal, chronic hepatitis and liver cirrhosis (22)], degree of liver damage [Child-Pugh score (CPS)] (23,24), albumin-bilirubin score (ALBI)] (25), model for end-stage liver disease (MELD) (26), fibrosis-4 (27), renal function (serum Cr, CysC, CrGFR and CysCGFR), BMI [BW (kg)/height (m)/height (m)] and grip strength (kg) (Table I). All patients were screened for hepatocellular carcinoma using imaging examinations (ultrasonography, CT and /or magnetic response imaging).

This was a retrospective observational study. Informed consent was obtained from each patient included in the study and they were guaranteed the right not to join the study or to leave whenever they wished. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as evidenced by the approval of the study by the Human Research Ethics Committee of Nagasaki Harbor Medical Center (approval no. H30-031).

*Measurements*. Laboratory and anthropometric measurement data were obtained for each patient during the hospital visit. Laboratory examinations included the assessment of total bilirubin (TB, mg/dl), albumin (mg/dl), alanine aminotransferase (U/l), aspartate aminotransferase (U/l), platelet ($10^4/\mu$l), prothrombin time (percentage and international normalized ratio), Cr (mg/dl) and CysC (mg/l). Estimated GFR (eGFR; ml/min/1.73 $m^2$) was calculated using the equations based on the guidelines of Japanese Society of Nephrology for Japanese patients, as follows: Male $CrGFR=194 \times Cr^{-1.094} \times Age^{-0.287}$; female, CrGFR = male CrGFR x 0.739; male $CysCGFR = (104 \times CysC^{-1.019} \times 0.996^{Age})-8$; and female $CysCGFR=(104 \times CysC^{-1.019} \times 0.996^{Age} \times 0.929)-8$.

Patients' diseases were staged according to the level of CrGFR in ml/min/1.73 $m^2$: G1, >90; G2, 60-89; G3a, 45-59; G3b, 30-44; and G4, 15-29 (28). The difference between CrGFR and CysCGFR (dGFR) was calculated as follows: CrGFR-CysCGFR. SI was calculated as follows: Cr/CysC x 100. CBMM was calculated according to the Cr, CysC and BW according to a previous study (21). CBMM index was calculated as follows: CBMM/height (m)/height (m).

Hand grip strength was evaluated in 302 patients. Grip strength was measured using a dynamometer (Smedlay's Dynamo Meter; TTM) with participants standing in an erect position with both arms at their sides. The maximum result of two tests was used for further analysis. Female patients with mean grip strength <18 kg were categorized under the low strength group and male patients with mean grip strength <26 kg were categorized into the low strength group according to the JSH criteria (20).

*CT analysis of the body composition*. Of the 313 patients, 199 were evaluated by CT (Table II). In these patients, cross-sectional CT images at the third lumbar vertebra (L3) were analyzed using Slice-O-Matic version 5.0 (TomoVision) to determine SM, abdominal adipose tissue area [visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) area and intra-muscle adipose tissue]. Muscle areas included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques and rectus abdominis muscles. Tissue Hounsfield unit (HU) thresholds were employed: -29 to 150 HU for SM; -190 to -30 for SAT; and -150 to -50 for VAT (19). SM was normalized for height in meters squared and expressed as $cm^2/m^2$ as skeletal muscle index (SMI). VAT/SAT ratios were also calculated to explore abdominal adipose tissue distributions. In addition, mean muscle attenuation (MA) was calculated using the same

Table I. Clinical characteristics.

| Factors | Mean (SD) or number |
|---|---|
| Age, years | 65.138 (14.043) |
| Sex | |
| Female | 167 |
| Male | 146 |
| Height, m | 1.599 (0.097) |
| Body weight, kg | 60.721 (12.185) |
| BMI | 23.579 (4.288) |
| Disease | |
| AIH | 15 |
| HBV | 78 |
| HCV | 80 |
| PBC | 27 |
| Other | 113 |
| Clinical stage | |
| Normal | 29 |
| LC | 114 |
| CKD grade | |
| G1 | 55 |
| G2 | 172 |
| G3a | 16 |
| G3b | 16 |
| G4 | 8 |
| G5 | 5 |
| CKD | |
| 1-2 | 227 |
| 3-5 | 86 |
| CPS | 5.543 (1.171) |
| CP | |
| A | 268 |
| B | 39 |
| C | 6 |
| ALBI | -2.631 (0.587) |
| 1 | 207 |
| 2 | 92 |
| 3 | 14 |
| MELD | 8.605 (3.767) |
| Fib-4 | 4.079 (3.926) |
| Cr, mg/dl | 0.866 (0.650) |
| CrGFR, mL/min./1.73 $m^2$ | 71.051 (22.477) |
| CysC, mg/l | 1.255 (0.670) |
| CysCGFR, ml/min./1.73 $m^2$ | 63.335 (25.165) |
| dGFR | 7.716 (19.234) |
| SI | 69.704 (19.902 |
| CBMM | 34.601 (8.435) |
| BCAA | 30 |
| Carnitine | 4 |
| Grip strength, kg | 20.128 (9.495) |
| Strength, low | 188 |

SI=Cr/CysC x100. CBMM is calculated by Cr, CysC and body weight. Grip strength was evaluated in 302 cases. Female patients with a mean grip strength <18 kg were categorized as low strength and male patients with a mean grip strength <26 kg were categorized as low strength. SD, standard deviation; CKD, chronic kidney disease; BMI, body mass index; AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; LC, liver cirrhosis; CPS, Child-Pugh score; ALBI, albumin-bilirubin index; MELD, model for end-stage liver disease; Fib-4, fibrosis-4; Cr, creatinine; CysC, cystatin C; GFR, glomerular filtration rate; dGFR, difference between CrGFR and CysCGFR; SI, sarcopenia index; CBMM, calculated body muscle mass; BCAA, branched-chain amino acid; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table II. Muscle and fat volume in 199 patients with CT evaluation.

| Factors | Mean (SD) or number |
|---|---|
| SM | 111.582 (29.056) |
| IMAT | 7.542 (6.767) |
| VAT | 111.423 (81.066) |
| SAT | 131.221 (76.139) |
| MA | 30.506 (7.613) |
| SMI | 42.975 (8.301) |
| Low muscle volume | 76 |
| Sarcopenia | 54 |
| Low strength/normal SMI | 66 |
| Low SMI/normal strength | 18 |
| Normal SMI and strength | 61 |

SD, standard deviation; SM, skeletal muscle; IMAT, intra-muscular adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; MA, muscle attenuation; SMI, skeletal muscle mass index.

CT images to assess SM quality (Table II). A low muscle volume is <39 $cm^2/m^2$ of the SMI in women and <42 $cm^2/m^2$ of the SMI in men. Sarcopenia is diagnosed as low grip strength and low muscle volume based on the JSH guidelines for sarcopenia (20).

*Statistical analysis*. Data were analyzed using StatView version 5.0 (SAS Institute, Inc.). Data are presented as mean ± standard deviation. Laboratory result variables were compared using correlation analysis, t-tests (for differences between two groups), one-way analysis of variance with a post-hoc Tukey's test (for differences among three or more groups) or a $\chi^2$ test. A multivariate analysis was performed with multi-linear regression analysis and logistic regression analysis. Correlation was evaluated based on Pearson's correlation coefficient (R). P<0.05 was considered to indicate

Table III. Association between dGFR, SI and CBMM with clinical factors.

| | dGFR | | | | SI | | | | CBMM | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Factors | R | P-value | β | P-value | R | P-value | β | P-value | R | P-value | β | P-value |
| Age[a] | 0.260 | <0.0001 | 0.232 | <0.0001 | -0.355 | 0.0002 | 0.004 | 0.8857 | -0.184 | 0.0680 | - | - |
| BMI[a] | -0.015 | 0.8032 | - | - | 0.047 | 0.6375 | - | - | 0.628 | <0.0001 | 0.371 | <0.0001 |
| CPS | 0.238 | <0.0001 | 0.031 | 0.7221 | -0.222 | 0.0227 | 0.010 | 0.7391 | -0.048 | 0.6298 | - | - |
| ALBI[a] | 0.309 | <0.0001 | 0.167 | 0.0321 | -0.262 | 0.0070 | 0.029 | 0.4141 | 0.011 | 0.9102 | - | - |
| MELD | 0.117 | 0.0441 | 0.014 | 0.8173 | 0.031 | 0.7557 | - | - | 0.099 | 0.3162 | - | - |
| Fib-4 | 0.287 | <0.0001 | 0.094 | 0.1273 | -0.313 | 0.0012 | -0.027 | 0.3507 | -0.066 | 0.5014 | - | - |
| Grip strength[a] | -0.175 | 0.0025 | 0.203 | 0.0011 | 0.398 | <0.0001 | 0.173 | <0.0001 | 0.496 | <0.0001 | 0.636 | <0.0001 |
| SI | -0.841 | <0.0001 | - | - | - | - | - | - | 0.666 | <0.0001 | - | - |
| CBMM[a] | -0.428 | <0.0001 | - | - | 0.690 | <0.0001 | - | - | - | - | - | - |
| dGFR | - | - | - | - | -0.738 | <0.0001 | - | - | -0.355 | 0.0002 | - | - |
| Cr | -0.122 | 0.0362 | - | - | 0.469 | <0.0001 | - | - | 0.298 | 0.0019 | - | - |
| CrGFR | 0.283 | <0.0001 | - | - | -0.213 | <0.0001 | - | - | -0.128 | 0.1924 | - | - |
| CysC | 0.162 | 0.0052 | - | - | 0.074 | 0.4556 | - | - | 0.091 | 0.7022 | - | - |
| CysCGFR | -0.491 | <0.0001 | - | - | 0.344 | 0.0003 | - | - | 0.199 | 0.1588 | - | - |

[a]Significant factor. dGFR is calculated as follows: CrGFR-CysCGFR. SI is calculated as follows: Cr/CysC x100. CBMMI is CBMM/height (m)/height (m). BMI, body mass index; ALBI, albumin-bilirubin index; Fib-4, fibrosis-4; Cr, creatinine; CysC, cystatin C; GFR, glomerular filtration rate; dGFR, difference between CrGFR and CysCGFR; SI, sarcopenia index; CBMM, calculated body muscle mass; CPS, CPS, Child-Pugh score.

statistical significance. A sufficient sample size in was analyzed in the present study.

## Results

*dGFR only contributes to liver damage, whereas CBMM contributes to grip strength more than deGFR and SI.* The relationships between dGFR, SI and CBMM with clinical factors were analyzed (Table III). Age, CPS, ALBI, MELD and FIB-4 were positively correlated with dGFR and grip strength negatively correlated with dGFR. CrGFR was positively correlated and CysCGFR was negatively correlated with dGFR. For SI, Cr was divided by CysC, which reflected the low Cr and high CysC and negative correlation with dGFR. SI was positively correlated with grip strength and negatively correlated with age, CPS, ALBI and FIB-4. CBMM was positively correlated with BMI and grip strength. In a multilinear regression analysis, age, ALBI and grip strength were correlated with dGFR, grip strength was correlated with SI, BMI and CBMM. Notably, sex differences were reflected in CBMM but not in dGFR; patients with CKD G3-5 had lower dGFR but not CBMM compared with patients with CKD G1-2 (Table IV). Patients with worse stage disease (CH/LC in clinical stage, B/C in CP and 2/3 in ALBI) had excessive dGFR ($P<0.05$, Table IV). Patients with low grip strength had higher dGFR compared with those with normal strength. Conversely, CBMM in the female group and low grip strength group were lower compared with the male group and normal strength group (Table III). dGFR is only a contributing factor for ALBI. dGFR, CBMM and SI were correlated with grip strength, but CBMM had the largest R (CBMM R=0.496; SI R=0.398; and dGFR R=-0.175).

*CBMM correlates better with muscle volume than SI.* The relationship between CBMM and CT-based body composition was analyzed in 199 patients (Tables II, V and VI). Of the 199 patients, 76 had low muscle volume, and 54 of the 76 patients with low muscle volume were diagnosed with sarcopenia. The positive correlation between CBMM with SM (R=0.804) was greater than its correlations with VAT, SAT and MA but not with CPS and ALBI (Table V). SI showed a weak positive correlation with SM (R=0.293), and a negative correlation with CPS and ALBI. It was evaluated whether ALBI and CKD had an influence on the relationship between CBMM and body compositions (Table VI). As SM, grip strength, age, VAT, SAT and MA were statistically correlated with CBMM in the correlation analysis, these factors were evaluated by a multilinear regression analysis. SM, grip strength and VAT were contributing factors for CBMM; in addition, SM and grip strength were contributing factors regardless of ALBI and CKD. VAT contributed to CBMM regardless of CKD and G1 of ALBI but not for G2-3. SI was positively correlated with grip strength and weakly correlated with SMI. However, the R values for these relations with SI were lower than those for the relations with CBMM (Table II).

*dGFR correlates with age and grip strength and ALBI but not with SM; CBMM correlates with SM and grip strength.* The relationship between dGFR and body composition was assessed in 199 patients evaluated by CT (Table VII). dGFR

Table IV. Association between dGFR and CBMM with clinical factors.

A, dGFR

| Factors | Mean (SD) | P-value |
|---|---|---|
| Sex[a] | | 0.9805 |
| Female | 7.691 (15.841) | |
| Male | 7.745 (22.554) | |
| Stage | | <0.0001 |
| Normal | 2.083 (16.379) | |
| CH | 4.298 (20.401) | |
| LC | 14.246 (16.239) | |
| CP | | 0.0001 |
| A | 6.054 (18.974) | |
| B | 15.759 (17.298) | |
| C | 29.667 (18.817) | |
| ALBI 1/2/3 | | <0.0001 |
| 1 | 5.640 (14.815) | |
| 2 | 20.515 (16.934) | |
| 3 | 25.850 (11.897) | |
| Grip strength[a] | | 0.0003 |
| Low | 11.194 (14.947) | |
| Normal | 3.190 (22.763) | |
| CKD | | 0.0333 |
| 1-2 | 9.139 (20.797) | |
| 3-5 | 3.960 (13.718) | |

B, CBMM

| Factors | Mean (SD) | P-value |
|---|---|---|
| Sex[a] | | <0.0001 |
| Female | 28.809 (4.958) | |
| Male | 41.227 (6.490) | |
| Stage | | 0.6980 |
| Normal | 34.235 (7.921) | |
| CH | 35.091 (7.921) | |
| LC | 34.8 2 (8.917) | |
| CP | | 0.4878 |
| A | 34.375 (8.605) | |
| B | 36.104 (7.341) | |
| C | 34.949 (7.484) | |
| ALBI | | 0.2662 |
| 1 | 34.878 (8.751) | |
| 2 | 33.609 (7.548) | |
| 3 | 37.027 (8.991) | |
| Grip strength[a] | | <0.0001 |
| Low | 31.891 (7.63) | |
| Normal | 38.925 (7.929) | |
| CKD | | 0.2793 |
| 1-2 | 34.283 (8.345) | |
| 3-5 | 35.44 (8.662) | |

[a]Significant factor. dGFR is calculated as follows: CrGFR-CysCGFR. SD, standard deviation; CKD, chronic kidney disease; CH, chronic hepatitis; LC, liver cirrhosis; CP, Child Pugh; ALBI, albumin-bilirubin index; GFR, glomerular filtration rate; dGFR, difference between creatinine GFR and cystatin GFR; CBMM, calculated body muscle mass.

was positively correlated with CBMM, MA and grip strength, negatively correlated with age and ALBI, and was not correlated with SM and SMI. CBMM, grip strength, age and ALBI were correlated with dGFR based on the multilinear regression analysis (Table VII). dGFR in CKD G1-2 was influenced by CBMM, grip strength, age and ALBI and in CKD G3-5 was influenced by age and ALBI (Table VII). The low grip strength group had lower CBMM and higher dGFR compared with the normal group (Table VIII). Additionally, the low muscle volume group had lower CBMM compared with the normal group, without any difference in dGFR (Table VIII). Similarly, the sarcopenia group, which included patients with low grip strength and low muscle volume, had lower CBMM compared with the normal group, without any difference in dGFR (Table VIII). CBMM and dGFR differed with sarcopenia, low grip strength and normal muscle volume, low muscle volume and normal grip strength, and normal grip strength and normal muscle volume (Table IX). SI was also lower in the low strength and sarcopenia group compared with the normal group (Table IX). In the multivariate analysis, factors correlated with sarcopenia were found to be CBMM and SI but not dGFR (Table X).

## Discussion

The present study did not intend to evaluate the difference between true GFR and Cr-based GFR. Rather, it clarified whether dGFR, that is the difference between CrGFR and CysCGFR, correlated with ALBI and grip strength in liver disease. Overestimated CrGFR, which is almost identical to dGFR, is speculated to contribute to liver damage and muscle strength. Conversely, CBMM, calculated by Cr, CysC and BW, correlated with grip strength and SM. Thus, CBMM is speculated to contribute to muscle function and volume and is a major factor contributing to sarcopenia, but it did not correlate with liver function. SI is also similar to CBMM and it was correlated with muscle strength and volume and contributed to sarcopenia but did not correlate with ALBI. However, SI was a weaker relation factor for muscle strength, muscle volume and sarcopenia than CBMM.

In the present study, dGFR was found to be a marker of muscle strength and liver function. The cause of dGFR is the overestimation of CrGFR, which was caused by the decreased

Table V. Association between CBMM, CBMMI and SI with muscle volume.

| | CBMMI | | CBMM | | SI | |
|---|---|---|---|---|---|---|
| Factors | R | P-value | R | P-value | R | P-value |
| SMI | 0.643 | <0.0001 | 0.640 | <0.0001 | 0.187 | 0.0900 |
| SM | 0.624 | <0.0001 | 0.804 | <0.0001 | 0.293 | 0.0070 |
| Grip strength | 0.513 | <0.0001 | 0.713 | <0.0001 | 0.459 | <0.0001 |
| CPS | -0.004 | 0.95 | 0.068 | 0.3415 | -0.217 | 0.0481 |
| ALBI | -0.055 | 0.446 | 0.013 | 0.8521 | -0.281 | 0.0099 |
| Age | -0.083 | 0.2451 | -0.261 | 0.0002 | -0.367 | 0.0006 |
| IMAT | 0.136 | 0.0566 | 0.042 | 0.5573 | -0.169 | 0.1272 |
| VAT | 0.564 | <0.0001 | 0.537 | <0.0001 | 0.233 | 0.0334 |
| SAT | 0.376 | <0.0001 | 0.329 | <0.0001 | 0.030 | 0.7861 |
| VAT/SAT | 0.384 | <0.0001 | 0.373 | <0.0001 | 0.220 | 0.0458 |
| MA | 0.129 | 0.0709 | 0.283 | <0.0001 | 0.334 | 0.0019 |

Low muscle volume is >39 $cm^2/m^2$ of SMI in female and 42 $cm^2/m^2$ of SMI in male; sarcopenia is low grip strength and low muscle volume; CKD is based on serum creatinine. CKD, chronic kidney disease; CBMM, calculated body muscle mass; CBMMI, CBMM index; SI, sarcopenia index; CPS, Child-Pugh score; SM, skeletal muscle; IMAT, intra-muscular adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; MA, muscle attenuation; SMI, skeletal muscle mass index.

Table VI. Association between ALBI with muscle volume and grip strength.

| | | | ALBI | | | | CKD | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All | | G1, n=126 | | G2-3, n=74 | | G1-2, n=145 | | G3-5, n=55 | |
| Factors | β | P-value | β | P-value | β | P-value | β | P-value | β | P-value |
| SM | 0.446 | <0.0001 | 0.429 | <0.0001 | 0.633 | <0.0001 | 0.397 | <0.0001 | 0.488 | 0.0002 |
| Grip strength | 0.345 | <0.0001 | 0.379 | <0.0001 | 0.279 | 0.0138 | 0.381 | <0.0001 | 0.340 | 0.0019 |
| Age | 0.014 | 0.7572 | 0.026 | 0.6197 | 0.061 | 0.4859 | -0.031 | 0.5299 | -0.062 | 0.5191 |
| VAT | 0.234 | <0.0001 | 0.218 | <0.0001 | 0.093 | 0.3573 | 0.181 | 0.0005 | 0.235 | 0.0284 |
| SAT | 0.073 | 0.1058 | 0.075 | 0.1232 | 0.073 | 0.4374 | 0.131 | 0.0107 | -0.127 | 0.2009 |
| MA | -0.015 | 0.7624 | 0.019 | 0.7320 | -0.183 | 0.0862 | 0.018 | 0.7375 | -0.089 | 0.4062 |

Low muscle volume is >39 $cm^2/m^2$ of SMI in female and 42 $cm^2/m^2$ of SMI in male; sarcopenia is low grip strength and low muscle volume; CKD is based on serum creatinine. CKD, chronic kidney disease; SI, sarcopenia index; ALBI, albumin-bilirubin index; SM, skeletal muscle; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; MA, muscle attenuation.

creatine production in the liver and Cr production in the muscle (29). A previous study showed that the overestimation of CrGFR, which is the difference between true eGFR and CrGFR, was observed in 47% of patients with cirrhosis and was associated with female sex, CPS grade B/C and decreased SM volume (4). dGFR correlated with CPS, ALBI, MELD and FIB-4, but ALBI was found to only influence dGFR based on a multi-linear regression analysis. ALBI is calculated using albumin and TB values and has attracted attention as a prognostic factor for liver disease (25,30). CPS is used to determine the degree of ascites and hepatic encephalopathy and is evaluated based on the clinician's judgement; conversely, ALBI is independent of the clinician's judgment. MELD can overestimate Cr in liver disease; conversely, calculation of ALBI is not used in Cr value. FIB-4 is a useful marker for liver fibrosis but not for liver function (30). It may reflect the relationship between Cr product loss in the liver and ALBI-influenced dGFR in liver disease.

Previous studies demonstrated that Cr is a biomarker of muscle volume (29,31), but the present study showed that dGFR was correlated with grip strength but not with SMI. CysCGFR was reported to be correlated with hand grip strength (32), and a previous study showed that low grip strength was associated with age, female sex, height, depression and mobility problems

Table VII. Association between dGFR and muscle volume.

| | All | | | | CKD1-2 | | CKD3-5 | |
|---|---|---|---|---|---|---|---|---|
| Factors | R | P-value | β | P-value | β | P-value | β | P-value |
| CBMM[a] | -0.432 | <0.0001 | -0.554 | <0.0001 | -0.510 | <0.0001 | -0.334 | 0.0684 |
| SM | -0.060 | 0.4442 | - | - | - | - | - | - |
| IMAT | 0.33 | 0.6462 | - | - | - | - | - | - |
| VAT | -0.078 | 0.2752 | - | - | - | - | - | - |
| SAT | -0.077 | 0.2793 | - | - | - | - | - | - |
| MA | -0.186 | 0.0087 | -0.064 | 0.3816 | -0.065 | 0.4397 | -0.153 | 0.189 |
| SMI | -0.011 | 0.8725 | - | - | - | - | - | - |
| Grip strength | -0.157 | 0.0270 | 0.345 | 0.0003 | 0.323 | 0.0051 | 0.199 | 0.1824 |
| Age | 0.213 | 0.0025 | 0.158 | 0.0257 | 0.208 | 0.0111 | 0.356 | 0.0032 |
| ALBI[a] | 0.339 | <0.0001 | 0.346 | <0.0001 | 0.362 | <0.0001 | 0.499 | <0.0001 |

[a]Significant factor. CBMM, calculated body muscle mass; SM, skeletal muscle; IMAT, intra-muscular adipose tissue; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; MA, muscle attenuation; SMI, skeletal muscle mass index; dGFR, difference between creatinine GFR and cystatin GFR.

Table VIII. Association between CBMM, dGFR and SI with grip strength and muscle volume.

| | CBMM | | dGFR | | SI | |
|---|---|---|---|---|---|---|
| Factors | Mean (SD) | P-value | Mean (SD) | P-value | Mean (SD) | P-value |
| Grip strength | | <0.0001 | | 0.0003 | | <0.0001 |
| Low, n=62 | 12.904 (2.244) | | 11.194 (14.947) | | 64.587 (16.056) | |
| Normal, n=79 | 14.096 (2.260) | | 3.190 (22.763) | | 76.586 (20.508) | |
| Volume | | <0.0001 | | 0.6479 | | 0.0811 |
| Low, n=76 | 12.100 (1.829) | | 10.853 (16.884) | | 64.968 (14.502) | |
| Normal, n=130 | 13.913 (2.233) | | 9.667 (18.551) | | 69.72 (20.855) | |
| Sarcopenia | | <0.0001 | | 0.2143 | | 0.0067 |
| Presence, n=54 | 13.773 (2.172) | | 13.131 (14.520) | | 61.966 (12.877) | |
| Absence, n=145 | 11.747 (1.734) | | 9.823 (17.378) | | 69.16 (17.617) | |

SD, standard deviation; CBMM, calculated body muscle mass; SI, sarcopenia index; dGFR, difference between creatinine GFR and cystatin GFR.

Table IX. CBMM, dGFR and SI between patients with low strength/low volume, low strength/normal volume, low volume/normal strength and normal strength/normal volume.

| | CBMM | | dGFR | | SI | |
|---|---|---|---|---|---|---|
| Factors | Mean (SD) | ANOVA | Mean (SD) | ANOVA | Mean (SD) | ANOVA |
| Sarcopenia, n=54 | 11.747 (1.734) | | 13.131 (14.520) | | 61.966 (12.877) | |
| Low strength/normal volume, n=66 | 13.520 (2.103) | | 14.138 (14.085) | | 62.95 (16.478) | |
| Low volume/normal strength, n=18 | 13.234 (1.831) | | 3.106 (22.018) | | 75.463 (15.462) | |
| Normal, n=61 | 14.207 (2.289) | <0.0001 | 7.136 (18.197) | 0.0140 | 74.02 (17.462) | <0.0001 |

SD, standard deviation; CBMM, calculated body muscle mass; SI, sarcopenia index; dGFR, difference between creatinine GFR and cystatin GFR.

Table X. CBMM and SI contribute to sarcopenia.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Factors | P-value | Odds | 95% CI | P-value | Odds | 95% CI |
| CBMM | <0.0001 | 0.849 | 0.799-0.903 | <0.0001 | 0.773 | 0.702-0.852 |
| dGFR | 0.214 | 1.012 | 0.993-1.031 | 0.1347 | 1.027 | 0.992-1.123 |
| SI | 0.0079 | 0.971 | 0.95-0.992 | 0.0067 | 1.07 | 1.019-1.123 |

CI, confidence interval; CBMM, calculated body muscle mass; SI, sarcopenia index; dGFR, difference between creatinine GFR and cystatin GFR.

in elderly patients at a primary care unit, but eGFR was not evaluated in that study (33). In addition to muscle atrophy, physical inactivity and protein energy wasting conspire to impair muscle strength (34), and hand grip strength was the only mortality factor (35) that is not associated with muscle volume (36). The decrease in muscle strength is significantly more rapid than the concomitant loss of muscle mass (37). Tamai *et al* (15) described that the eGFRcre/eGFRcys ratio could be a useful predictive marker for survival in patients with hepatocellular carcinoma. As the relationship between dGFR and grip strength was clarified in the present study, the relationship between dGFR and the prognosis of liver disease should be evaluated. Additionally, as CysC is a stable marker for GFR, regardless of the liver function (3), a combination of Cr and CysC may be an important marker for liver and muscle function in healthy individuals.

CKD grade by CrGFR in patients was fundamental to evaluate dGFR. In patients with CKD G3-5, dGFR correlated with age and ALBI but not with grip strength. Since dGFR in CKD G3-5 is smaller compared with CKD G1-2, grip strength may be affected by worsening CKD stage, whereas CBMM was correlated with SM regardless of CKD stage and ALBI grade. CBMM was hypothesized to be a universal marker of muscle mass and strength based on the results of the present study.

CBMM is also a useful maker for muscle strength and volume. Unlike dGFR, CBMM correlated with sarcopenia. Sarcopenia has a poor prognosis (16-19) and is a severe fibrosis factor (38) in liver disease, but evaluation of muscle volume and strength require several different techniques. Muscle strength is evaluated by CT or BIA using the JSH criteria. To the best of the authors' knowledge, the present study was the first to report that CBMM contributed to grip strength, muscle volume and sarcopenia in liver disease. It is hypothesized that CBMM may serve as a diagnostic marker for sarcopenia in liver disease.

SI was also correlated with SM and sarcopenia. However, compared to CBMM, the correlation coefficient of SI and SM was weak, and the odds ratio of SI for sarcopenia was also weaker compared with CBMM. Recently, SI was reported to not be correlated with sarcopenia (39). In liver disease, Cr/CysC is correlated with muscle mass and liver function (15). In the present study, the correlation coefficient of SI and grip strength was larger than that of SI and SM, and SI in the low grip strength group and sarcopenia group was lower compared with the normal group. Given the above results, it was hypothesized that SI indicated muscle strength rather than muscle mass and was a weaker marker for muscle strength and volume than CBMM.

The present study has some limitations. The proportion of patients with CKD G3-5 and CPS B/C was small. Thus, evaluating the relationship between dGFR, CBMM, SI, muscle volume and grip strength in end-stage liver and renal disease was difficult. Sarcopenia and grip strength are known prognostic factors for chronic disease, survival times could not be evaluated due to the short observation period. However, the present study clarified that dGFR is the marker of liver function and muscle strength, and CBMM is a marker of muscle volume and strength or sarcopenia in liver disease. Additionally, the present study demonstrated that dGFR increased in patients with advanced liver disease and with low muscle strength. Therefore, Cr and CysC may be important markers for the evaluation of the liver and muscle function in patients with liver disease.

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**Availability of data and materials**

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

**Authors' contributions**

TI wrote the paper, analyzed the data and designed the study. HM, SM, YM, MY, SY, MK, YT, TH, HY, RU, NH, RH, NT and KN collected the data. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Informed consent was obtained from each patient included in the study and they were guaranteed the right not to join the study or to leave whenever they wished. The study protocol

conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as evidenced by the approval of the study by the Human Research Ethics Committee of Nagasaki Harbor Medical Center (approval no. H30-031).

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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