Original Article

Combined grip strength and calf circumference as a useful prognostic system in patients with liver diseases: a large cohort study

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Background: Sarcopenia and body composition can be associated with mortality in chronic liver diseases (CLDs). We sought to identify predictors in CLD patients (n=631, 309 males) and create a prognostic model using easily available indexes.

Methods: Reference values for low-grip strength (GS) were 26 kg in men and 18 kg in women. Reference values for low-skeletal muscle index (SMI) were 7.0 kg/m^2 in men and 5.7 kg/m^2 in women using bioelectrical impedance analysis (BIA). Reference values for low-calf circumference (CC) were 34 cm in men and 33 cm in women. Reference values for high-waist circumference were 85 cm in men and 90 cm in women. Using significant factors in the multivariate analysis contributing to the overall survival (OS), we created a simple predictive model. Akaike information criterion (AIC) was compared.

Results: Men (P<0.0001), presence of liver cirrhosis (LC) (P<0.0001), presence of hepatocellular carcinoma (HCC) (P<0.0001), low-GS (P<0.0001), low-CC (P<0.0001), serum albumin (P=0.0355), estimated glomerular filtration rate (P=0.0461), hepatitis B virus (P=0.0044) and hepatitis C virus (P<0.0001) were significant factors contributing to the OS by the multivariate analysis. The study subjects were classified into the 4 groups (combined GS-SMI system): (I) low-GS and low-SMI (sarcopenia, n=73); (II) low-GS and high-SMI (n=65); (III) high-GS and low-SMI (n=110); and (IV) high-GS and high-SMI (n=383). The cumulative OS rates were well stratified among 4 groups (overall P<0.0001, AIC =360.895). The study subjects were also classified into the 4 groups (combined GS-CC system): (I) low-GS and low-CC (n=60); (II) low-GS and high-CC (n=78); (III) high-GS and low-CC (n=70); and (IV) high-GS and high-CC (n=423). The cumulative OS rates were also well stratified among 4 groups (overall P<0.0001, AIC =349.521). In receiver operating characteristic (ROC) curve analysis for CC based on the OS, the optimal cutoff point in men was 34.6 cm [area under the ROC (AUC) =0.70, sensitivity =0.558, specificity =0.842], and that in women was 32.8 cm (AUC =0.72, sensitivity =0.619, specificity =0.787).

Conclusions: CC can be an alternative marker for muscle mass in CLD patients. Our proposed combined GS-CC system can be helpful in the community settings without special equipment for muscle mass measurement.

Keywords: Chronic liver disease (CLD); grip strength (GS); skeletal muscle mass; calf circumference (CC); predictive model

Submitted Oct 14, 2020. Accepted for publication Jan 25, 2021.
doi: 10.21037/atm-20-6901
View this article at: http://dx.doi.org/10.21037/atm-20-6901

Introduction

More than three decades have passed since Rosenberg's proposal of sarcopenia in elderly people in 1989 (1). Sarcopenia, which is characterized by skeletal mass loss and muscle strength loss and/or physical activity decline, is frequently encountered in chronic liver diseases (CLDs) because of the disease burden itself as well as aging (2-6). CLD patients with sarcopenia can involve both impaired protein synthesis and accelerated muscle proteolysis in skeletal muscle (5,6). Sarcopenia in CLDs has been recently gaining much research interest due to its prognostic significance (3,7-10). A previous meta-analysis reported the close association between sarcopenia and mortality in CLD patients (3). However, it is controversial as to which of muscle strength or muscle mass is a stronger predictor in CLD patients. For the past 2 or 3 decades, sarcopenia researches have mainly focused on muscle mass (11). While in our recent study, we emphasized the significance of grip strength (GS) on composite hepatic events in CLD patients (12). Hanai *et al*. reported that reduced GS rather than skeletal muscle mass or fat mass was significantly linked to an increased risk of mortality in cirrhotic patients (13). GS well reflects muscle strength for the entire body, and also reflects nutritional status as muscle function responses earlier to starvation status (14-16). A previous large observational study showed that measuring of GS is a simple and cost-effective method for risk stratification of prognosis (17). Additionally, an increase of GS significantly contributed to a reduced risk of cancer-related death (18).

How to employ convenient markers in the daily clinical practice is essential from the perspective of suppressing medical costs. Body composition measurement is suitable for nutritional assessment in routine clinical settings because it is simple and minimally invasive (19-21). In particular, calf circumference (CC) is recommended to measure in the revised Asian Working Group for Sarcopenia (AWGS) guidelines on the earlier detection of sarcopenic persons (22). While the measurement of waist circumference (WC) is used for the assessment of metabolic syndrome (23). However, prognostic impacts of anthropometric measurements in CLD patients are unclear.

A prognostic model using simple indexes that can be used by anyone is very useful in the daily medical care. It is particularly significant in facilities without advanced medical equipment. In this study, we sought to identify prognostic markers for CLD patients, and also create a prognostic model as a useful tool for clinicians. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6901).

Methods

Patients

Using a retrospective computerized database, 631 CLD individuals who visited our hospital between January 2013 and April 2020 were collected. CLD was defined as a condition in which hepatitis was confirmed to persist for more than 6 months. Data for muscle strength (i.e., GS) and muscle mass using bioelectrical impedance analysis (BIA), and data for body composition (CC and WC) at baseline (i.e., at the beginning of the follow-up) were collected. Diagnosis for liver cirrhosis (LC) and hepatocellular carcinoma (HCC) were determined according to the current guidelines (24,25). The most suitable interventional strategy for each underlying liver disease was performed (24,26,27). HCC therapy was based on the current guidelines (25,28,29). No patient received liver transplantation in the follow-up period. Patients with far advanced HCC, other advanced malignancies, severe heart failure, severe ascites or severe malnutrition were not included. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) with ethical approval from the institutional review board in our hospital (approval number 3469). An opt out method was employed considering the retrospective nature of this study.

GS, SMI, CC and WC

Reference values for low-GS were 26 kg in men and 18 kg in women based on the Japanese Society of Hepatology (JSH) guidelines (30). Likewise, reference values for low-skeletal muscle index [SMI, SMI indicates appendicular muscle mass divided by height squared (kg/m^2)] were 7.0 kg/m^2 in men and 5.7 kg/m^2 in women using BIA (30). BIA is currently the standard method for the assessment of skeletal muscle mass in CLDs (29). Reference values for low-CC were 34 cm in men and 33 cm in women based on the AWGS guidelines (22,31). Reference values for high-WC were 85 cm in men and 90 cm in women based on the Japanese criteria for visceral fat obesity (23). All of anthropometric measurements were done by an expert nutritionist.

Primary outcome measure and study design of our study

The primary outcome measure was the overall survival (OS, all-cause mortality). Study subjects were followed from the anthropometric measurement at baseline until death or the last follow-up visit. First, factors contributing to the OS were identified using univariate and multivariate analyses. Second, using sarcopenia-related variables or body composition-related variables, prognostic systems were created. Predictability in each prognostic model was assessed.

Statistics

In the univariate analyses of items contributing to the OS, the median value for each item was selected for the classification of our cohort. Factors with a P value <0.05 (univariate analysis) were entered into the multivariate Cox hazard model. Survival curves were created by the Kaplan-Meier method with the log-rank test. Akaike information criterion (AIC) in each prognostic system was tested (32). The smaller the AIC value, the better the model was considered (32). In the analysis of correlation between parameters, Pearson's correlation coefficient (r) was employed. Receiver operating characteristic curve (ROC) analysis was done for estimating the area under the ROC (AUC) for CC with the optimal cutoff value determined by Youden index (33). A P<0.05 denotes statistical significance [statistical analysis software: JMP 14 (SAS Institute Inc., Cary, NC, USA)].

Results

Patient backgrounds

Our patient backgrounds (n=631, 309 males) were presented in *Table 1*. The median (interquartile range, IQR) age was 65 (52.0, 71) years. The median follow-up interval was 3.53 years. LC was seen in 226 patients (35.8%: Child-Pugh A/B/C in 166/53/7 patients, respectively). Forty-nine men (15.9%) had a GS decrease, while 89 women (27.6%) had a GS decrease (30). Seventy-six men (24.6%) had an SMI decrease, while 107 women (33.2%) had an SMI decrease (30). Forty-nine men (15.9%) had a CC decrease, while 81 women (25.2%) had a CC decrease (22). Two hundred and six men (66.7%) had a WC increase, while 103 women (32.0%) had a WC increase (23).

Causes of death and cumulative OS rates for all cases

During the observation period, 64 patients (10.1%) succumbed: liver failure-related death in 28 patients, HCC progression-related death in 17 and other causes in 19. The 1-, 3- and 5-year cumulative survival rates for all cases were 97.5%, 91.2% and 85.8% (*Figure 1*).

Uni- and multivariate analyses of factors contributing to the OS

The univariate analysis of factors associated with the OS identified that 13 factors were significant: age ≥65 years (P<0.0001), gender (P=0.0020), liver disease etiology (P=0.0002), low-GS (P<0.0001), low-SMI (P=0.0002), low-CC (P<0.0001), presence of LC (P<0.0001), presence of HCC (P<0.0001), aspartate aminotransferase >27 IU/L (P=0.0055), serum albumin ≥4.2 g/dL (P<0.0001), prothrombin time ≥92.1% (P=0.0031), platelet count ≥17.8×10^4/mm^3 (P=0.0014) and estimated glomerular filtration rate (eGFR) >81 mL/min/1.73 m^2 (P=0.0433) (*Table 2*). Multivariate analysis of the 13 factors identified that men (P<0.0001), presence of LC (P<0.0001), presence of HCC (P<0.0001), low-GS (P<0.0001), low-CC (P<0.0001), serum albumin ≥4.2 g/dL (P=0.0355), eGFR >81 mL/min/1.73 m^2 (P=0.0461), hepatitis B virus (P=0.0044) and hepatitis C virus (P<0.0001) were significant factors contributing to the OS (*Table 3*). Hazard ratio and 95% confidence interval for each variable were demonstrated in *Table 3*.

Cumulative OS rates in combined GS and SMI, and in combined GS and CC

Muscle strength and muscle mass are well established and validated prognostic markers (12,22,30). Thus, the study subjects were classified into the 4 groups (combined GS-SMI system): (I) subjects with low-GS and low-SMI (type A, sarcopenia, n=73); (II) subjects with low-GS and high-SMI (type B, n=65); (III) subjects with high-GS and low-SMI (type C, n=110); and (IV) subjects with high-GS and high-SMI (type D, n=383). AIC value on OS was calculated. The OS rates were well stratified among 4 groups (overall P<0.0001, AIC =360.895) (*Figure 2A*).

Next, considering the results of multivariate analysis, the study subjects were also classified into the 4 groups (combined GS-CC system): (I) subjects with low-GS and low-CC (type E, n=60); (II) subjects with low-GS and high-CC (type F, n=78); (III) subjects with high-GS and low-CC (type G, n=70); and (IV) subjects with high-GS and high-CC (type H, n=423). The OS rates were well stratified among 4 groups (overall P<0.0001,

Table 1 Patient backgrounds (n=631)

Variables	All cases (n=631). Number or median value (interquartile range)
Age (years)	65 (52.0, 71.0)
Gender, male/female	309/322
Liver disease etiology, HBV/HCV/others	90/286/255
Liver cirrhosis, yes/no	226/405
Hepatocellular carcinoma, yes/no	22/609
Body mass index (kg/m^2)	22.9 (20.7, 25.8)
Grip strength (kg), male	34.5 (28.6, 40.9)
Grip strength (kg), female	21.1 (17.7, 23.9)
Skeletal muscle index (kg/m^2), male	7.55 (7, 8.07)
Skeletal muscle index (kg/m^2), female	6.0 (5.5, 6.5)
Calf circumference (cm), male	37.3 (35, 39.6)
Calf circumference (cm), female	34.7 (33.0, 37.5)
Waist circumference (cm), male	89.5 (83.0, 96)
Waist circumference (cm), female	84.7 (77.7, 93.5)
Total bilirubin (mg/dL)	0.8 (0.6, 1.1)
Serum albumin (g/dL)	4.2 (3.8, 4.5)
ALBI score	−2.82 (−3.08, −2.53)
ALBI grade, 1/2/3	442/173/16
Prothrombin time (%)	92.1 (82, 101.4)
Platelet count (×10^4/mm^3)	17.8 (12.2, 22.8)
Aspartate aminotransferase (IU/L)	27 (21.0, 40)
Alanine aminotransferase (IU/L)	23 (16.0, 41)
eGFR (mL/min/1.73m^2)	81 (70.0, 95)

HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; eGFR, estimated glomerular filtration rate.

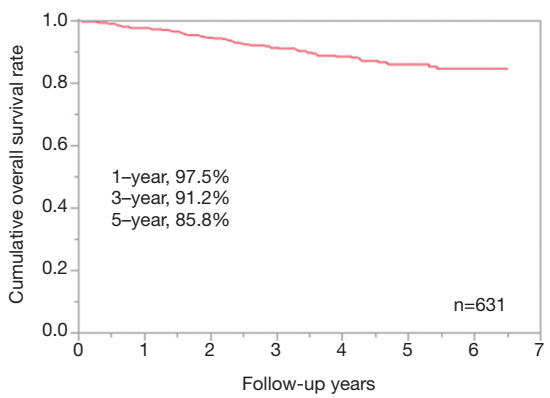

Figure 1 Mortality rates for all cases (n=631).

AIC =349.521) (*Figure 2B*).

Subgroup analysis according to gender (combined GS-SMI system *vs.* combined GS-CC system)

To confirm the validity of our proposed combined GS-CC system, we performed subgroup analyses (four sections below "Cumulative OS rates in combined GS and SMI, and in combined GS and CC"). In men (n=309), the OS rates were well stratified by GS and SMI [type A (n=24), type B (n=25), type C (n=52) and type D (n=208)] (overall P<0.0001, AIC =251.335). (*Figure 3A*) Likewise, the OS rates were well stratified by GS and CC [type E (n=21), type F (n=28), type G

Table 2 Univariate analyses of variables contributing to overall survival (n=631)

Variables	Number of each group	Univariate, P value
Age (years) ≥65, yes/no	297/334	<0.0001
Gender, male/female	309/322	0.0020
Cause of liver diseases, HBV/HCV/others	90/286/255	0.0002
Grip strength, high/low	138/493	<0.0001
Skeletal muscle index, high/low	183/448	0.0002
Calf circumference, high/low	130/501	<0.0001
Waist circumference, high/low	309/322	0.4017
Presence of liver cirrhosis, yes/no	226/405	<0.0001
Presence of hepatocellular carcinoma, yes/no	22/609	<0.0001
Aspartate aminotransferase ≥27 IU/L, yes/no	317/314	0.0055
Alanine aminotransferase ≥23 IU/L, yes/no	329/302	0.1479
Serum albumin ≥4.2 g/dL, yes/no	332/299	<0.0001
Total bilirubin ≥0.8 mg/dL, yes/no	352/279	0.1421
Prothrombin time ≥92.1%, yes/no	320/311	0.0031
Platelet count $\geq 17.8\times10^4/mm^3$, yes/no	317/314	0.0014
eGFR ≥81 mL/min/1.73 m^2, yes/no	323/308	0.0433
Body mass index ≥22.9 kg/m^2, yes/no	324/307	0.0928

HBV, hepatitis B virus; HCV, hepatitis C virus; eGFR, estimated glomerular filtration rate.

(n=28) and type H (n=232)] (overall P<0.0001, AIC =190.833) (*Figure 3B*).

In women (n=322), the OS rates were well stratified by GS and SMI [type A (n=49), type B (n=40), type C (n=58) and type D (n=175)] (overall P=0.0011, AIC =157.273) (*Figure 3C*). Similarly, the OS rates were well stratified by GS and CC [type E (n=39), type F (n=50), type G (n=42) and type H (n=191)] (overall P<0.0001, AIC =137.698) (*Figure 3D*).

Subgroup analysis according to age (combined GS-SMI system *vs*. combined GS-CC system)

In patients over 65 years (n=297), the OS rates were well stratified by GS and SMI [type A (n=59), type B (n=47), type C (n=65) and type D (n=126)] (overall P<0.0001, AIC =239.657) (*Figure 4A*). Likewise, the OS rates were well stratified by GS and CC [type E (n=50), type F (n=56), type G (n=46) and type H (n=145)] (overall P<0.0001, AIC =235.501) (*Figure 4B*).

In patients less than 65 years (n=334), the OS rates were well stratified by GS and SMI [type A (n=14), type B (n=18), type C (n=45) and type D (n=257)] (overall P<0.0001, AIC =122.593) (*Figure 4C*). Similarly, the OS rates were well stratified by GS and CC [type E (n=10), type F (n=22), type G (n=24) and type H (n=278)] (overall P<0.0001, AIC =116.241) (*Figure 4D*).

Subgroup analysis according to the LC status (combined GS-SMI system *vs*. combined GS-CC system)

In patients with LC (n=226), the OS rates were well stratified by GS and SMI [type A (n=33), type B (n=40), type C (n=43) and type D (n=110)] (overall P<0.0001, AIC =217.659). (*Figure 5A*) Likewise, the OS rates were well stratified by GS and CC [type E (n=31), type F (n=42), type G (n=31) and type H (n=122)] (overall P<0.0001, AIC =210.434) (*Figure 5B*).

In patients with non-LC (n=405), the OS rates were well stratified by GS and SMI [type A (n=40), type B (n=25), type C (n=67) and type D (n=273)] (overall P<0.0001, AIC =104.64). (*Figure 5C*) Similarly, the OS rates were well stratified by GS and CC [type E (n=29), type F (n=36), type G (n=39) and type H (n=301)] (overall P<0.0001,

Table 3 Multivariate analyses of variables contributing to overall survival (n=631)

Variables	Multivariate analysis		
	Hazard ratio	95% confidence interval	P value
Age ≥65 years	1.177	0.585–2.298	0.6400
Male	3.464	1.938–6.362	<0.0001
Presence of liver cirrhosis	6.041	2.467–15.266	<0.0001
Presence of hepatocellular carcinoma	10.260	5.111–20.371	<0.0001
Low-grip strength	6.110	3.393–11.213	<0.0001
Low-calf circumference	5.031	2.621–9.835	<0.0001
Low-skeletal muscle index	1.435	0.712–2.917	0.3136
Serum albumin ≥4.2 g/dL	0.474	0.227–0.951	0.0355
Platelet count ≥17.8×10^4/mm^3	0.500	0.247–1.037	0.0624
Prothrombin time ≥92.1%	0.696	0.315–1.574	0.3794
Aspartate aminotransferase ≥27 IU/L	1.180	0.633–2.234	0.6039
eGFR ≥81 mL/min/1.73 m^2	0.553	0.305–0.990	0.0461
Cause of liver disease			
HBV-related	0.297	0.111–0.698	0.0044
HCV-related	0.184	0.098–0.335	<0.0001
Others		Reference	

eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus.

AIC =107.584) (*Figure 5D*).

Subgroup analysis in patients without HCC at baseline (combined GS-SMI system *vs*. combined GS-CC system)

In non-HCC patients at baseline (n=609), the OS rates were well stratified by GS and SMI [type A (n=67), type B (n=59), type C (n=107) and type D (n=376)] (overall P<0.0001, AIC =286.784) (*Figure 6A*). Likewise, the OS rates were well stratified by GS and CC [type E (n=56), type F (n=70), type G (n=67) and type H (n=416)] (overall P<0.0001, AIC =272.938). Due to the small number of HCC cases (n=22), we did not perform subgroup analysis in HCC patients (*Figure 6B*).

Correlation between CC and SMI according to gender

The association in CC and SMI was investigated using Pearson's correlation coefficient (r). In men, significant correlation between CC and SMI was found (r=0.80, P<0.0001) (*Figure 7A*). Similarly, in women, significant correlation between CC and SMI was found (r=0.86, P<0.0001) (*Figure 7B*).

Cutoff values of CC in male and female based on the OS

The AWGS guidelines set the cutoff values of CC 34 cm in men and 33 cm in women (23). To confirm the validity of these cutoff points in AWGS, ROC analyses were performed. In ROC analysis for the cutoff value of CC based on the OS, the optimal cutoff point in men was 34.6 cm (AUC =0.70, sensitivity =0.558, specificity =0.842), and that in women was 32.8 cm (AUC =0.72, sensitivity =0.619, specificity =0.787) (*Figure 8A*,*B*).

Discussion

As mentioned earlier, a prognostic model using easily available indexes appears to be very helpful in the daily medical care. In this study, we primarily aimed to create a simple prognostic system both in community settings and hospital settings. Especially in facilities that cannot

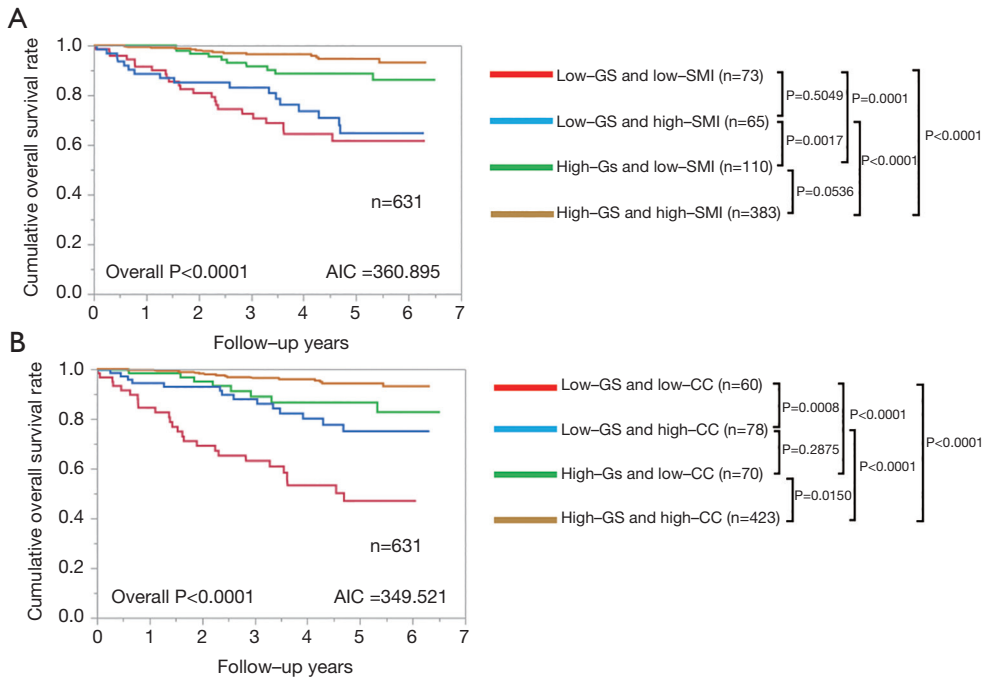

Figure 2 Mortality rates stratified by GS and SMI or CC for all cases. (A) Mortality rates stratified by GS and SMI for all cases. (B) Mortality rates stratified by GS and CC for all cases. GS, grip strength; SMI, skeletal muscle index; CC, calf circumference.

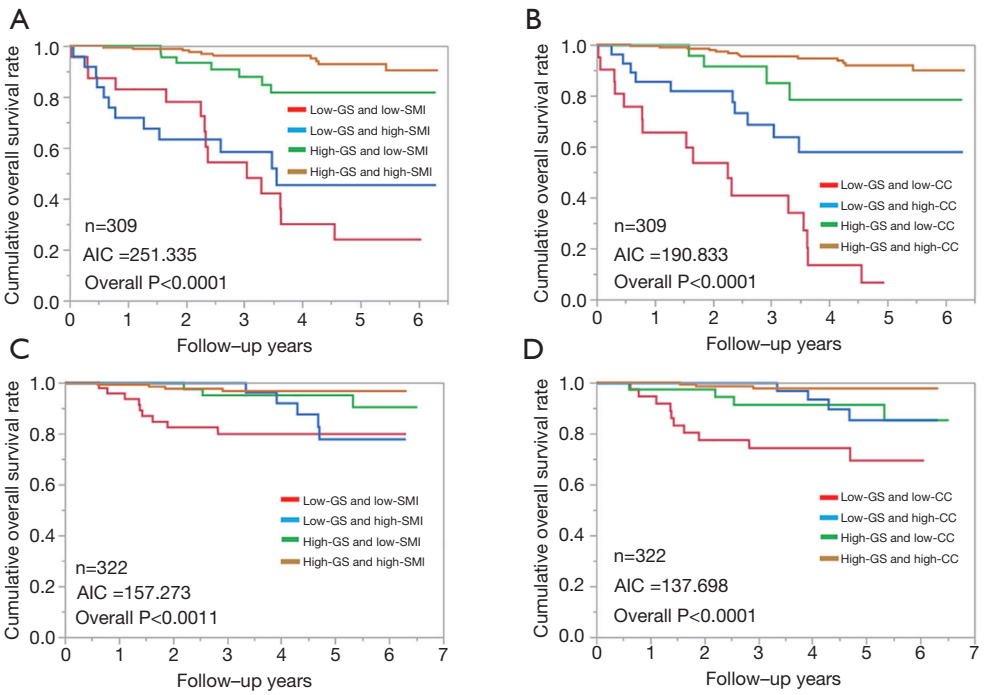

Figure 3 Mortality rates stratified by GS and SMI or CC according to gender. (A) Mortality rates stratified by GS and SMI in men. (B) Mortality rates stratified by GS and CC in men. (C) Mortality rates stratified by GS and SMI in women. (D) Mortality rates stratified by GS and CC in women. GS, grip strength; SMI, skeletal muscle index; CC, calf circumference.

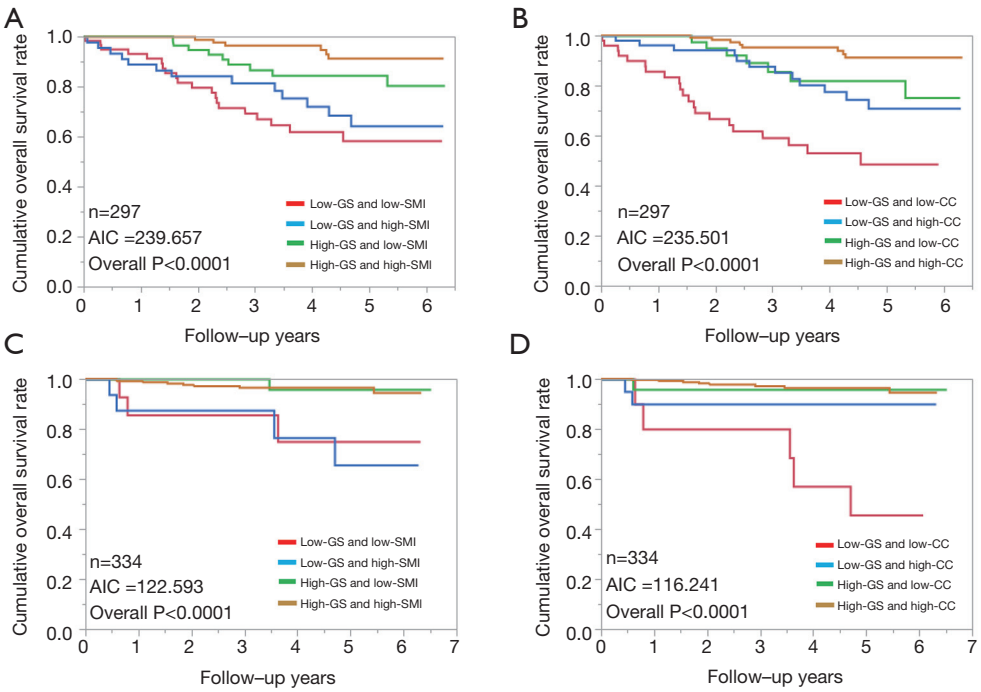

Figure 4 Mortality rates stratified by GS and SMI or CC according to age. (A) Mortality rates stratified by GS and SMI in patients over 65 years. (B) Mortality rates stratified by GS and CC in patients over 65 years. (C) Mortality rates stratified by GS and SMI in patients less than 65 years. (D) Mortality rates stratified by GS and CC in patients less than 65 years. GS, grip strength; SMI, skeletal muscle index; CC, calf circumference.

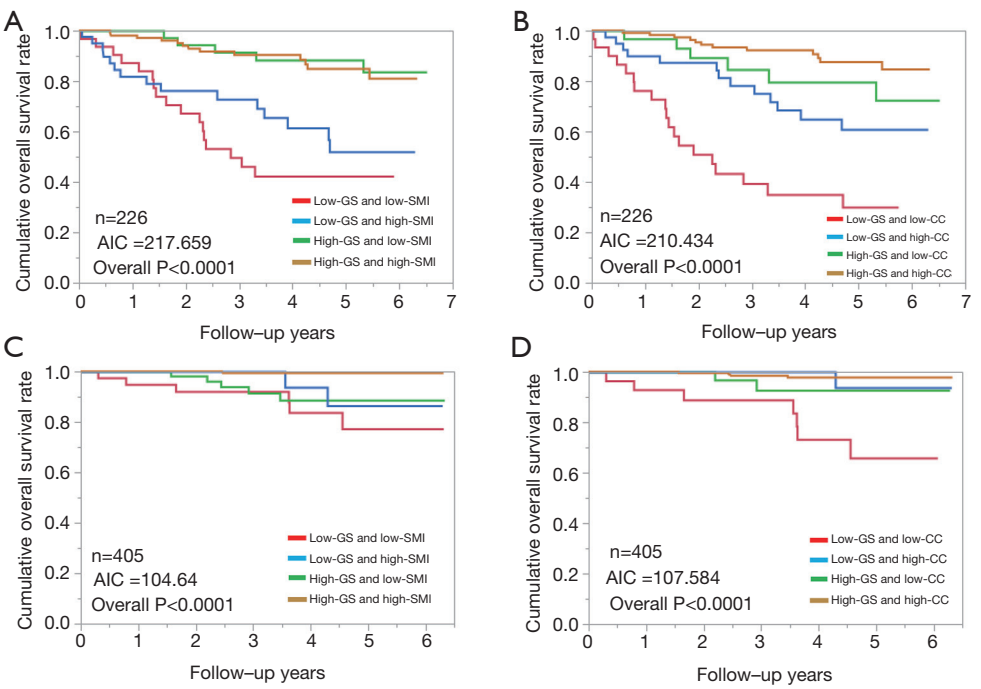

Figure 5 Mortality rates stratified by GS and SMI or CC according to the LC status. (A) Mortality rates stratified by GS and SMI in LC patients. (B) Mortality rates stratified by GS and CC in LC patients. (C) Mortality rates stratified by GS and SMI in non-LC patients. (D) Mortality rates stratified by GS and CC in non-LC patients. GS, grip strength; SMI, skeletal muscle index; CC, calf circumference; LC, liver cirrhosis.

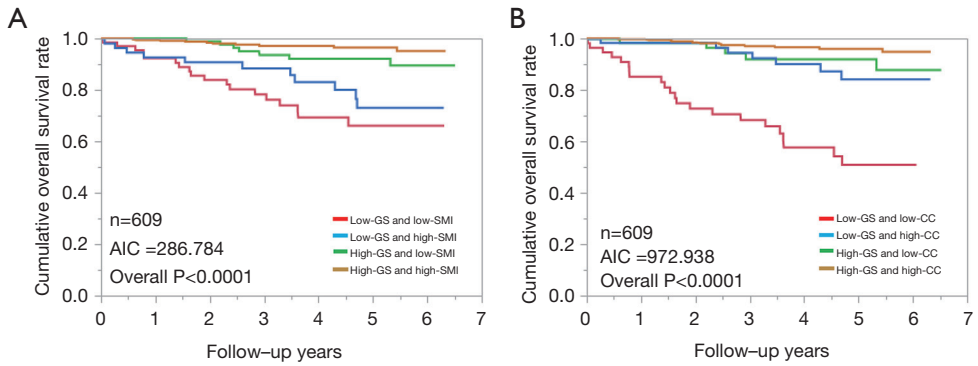

Figure 6 Mortality rates stratified by GS and SMI or CC in patients without HCC. (A) Mortality rates stratified by GS and SMI in patients without HCC. (B) Mortality rates stratified by GS and CC in patients without HCC. GS, grip strength; SMI, skeletal muscle index; CC, calf circumference; HCC, hepatocellular carcinoma.

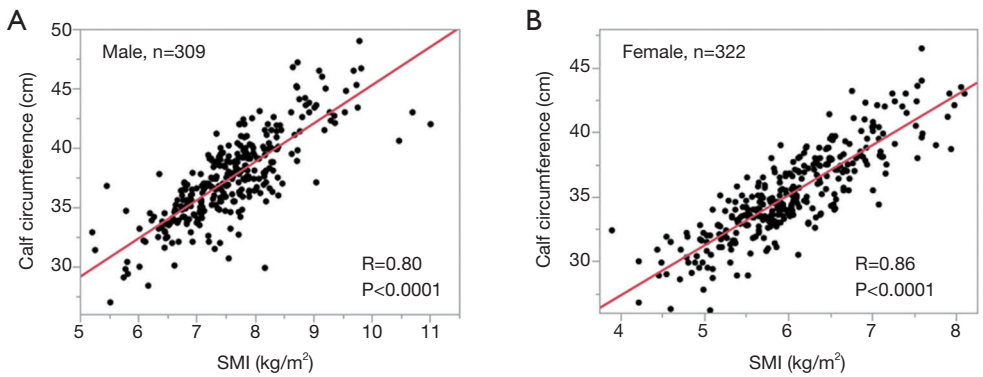

Figure 7 Correlation between CC and SMI in men (A) and women (B). CC, calf circumference; SMI, skeletal muscle index.

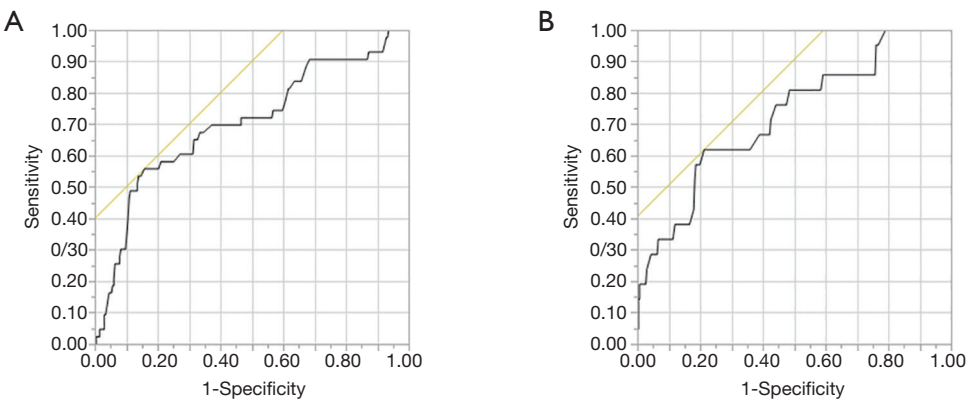

Figure 8 ROC analysis of calf circumference based on the overall survival in men (A) and women (B). ROC, receiver operating characteristic curve.

measure muscle mass, anthropometry measurements are of great significance due to its convenience for use. Different algorithms between the community situations and the hospital situations are presented in the revised Asian guidelines (22). In the community situations, characteristically, muscle mass measurement is not

mandatory (22). Our study is probably the first report presenting the impact of CC on the OS in CLDs using a large cohort (n=631). Multiple results were presented, but we believe that all the results are clinically meaningful and worthy of reporting.

In our results, lower GS (hazard ratio =6.110, P<0.0001) and lower CC (hazard ratio =5.031, P<0.0001) were independent adverse factors contributing to the OS. Additionally, AIC values of combined GS-CC system were smaller than those of GS-SMI system for the entire cohort and all subgroups except for non-LC cases. These results denoted that our proposed combined GS-CC system can be a useful stratification system in CLD patients, which shed some lights on the daily clinical practice. On the other hand, skeletal muscle atrophy undoubtedly occurs with aging (11). However, in the multivariate analysis, advanced age was not a significant factor linked to the OS (P=0.6400), while presence of LC (hazard ratio =6.041, P<0.0001) and higher serum albumin level (hazard ratio =0.474, P=0.0355) were significant as well as low-GS and low-CC. These results may be attributed to the impact of secondary sarcopenia caused by CLD itself on OS rather than age-associated primary sarcopenia. A lot of previous reports demonstrated the prognostic significance of skeletal muscle mass as an independent predictor linked to the mortality, however, SMI was not significant in our multivariate analysis (2,34-40). Clinical impacts of GS and CC on the OS may diminish the impacts of SMI on the OS, but these results do not always deny the importance of skeletal muscle mass on the mortality in patients with CLDs. While the hazard ratio of GS on the OS was 6.110, which was higher than that of the presence of LC (6.041), also demonstrating strong impact of GS on the OS. Both CC and SMI are markers for skeletal muscle mass. Nevertheless, the HRs of CC and SMI on the OS were largely different (5.031 *vs.* 1.435). Reference values for low-CC and low-SMI may be linked to our results.

As expected, CC had a strong correlation with SMI both in men (r=0.80) and women (r=0.86) in our data. Kawakami *et al.* demonstrated that CC had a strong positive correlation with appendicular skeletal muscle and SMI in 526 adults (31). Hiraoka *et al.* reported the finger-circle test as an easy and effective screening method for early stage of muscle atrophy (41). All of these are in line with our current results.

Looking at Kaplan-Meier curves of combined GS-SMI system and combined GS-CC system, we noticed a significant difference in the two systems. In comparison of type A and B, the difference of OS did not reach significance, whereas in comparison of type E and F, the difference of OS reached significance. Our proposed GS-CC stratification system can identify the group with the worst prognosis. We would like to emphasize this point as the major strength of our proposed GS-CC stratification system compared to GS-SMI stratification system. In CLD patients with lower GS and lower CC, earlier intervention should be considered. While in our non-LC patients, 14 patients (3.5%) died in the follow-up period. Of these, only one patient died of liver-related disease. One patient died of amyotrophic lateral sclerosis. The majority of causes of death in non-LC patients were cancer-related (not HCC) deaths. In our LC patients, 50 patients (22.1%) died in the follow-up period. Of these, 44 patients died of liver-related disease. In non-LC patients with adverse predictors (i.e., lower GS, lower SMI, or lower CC), the possibilities of diseases other than liver diseases should be taken into account. As described, AIC values of combined GS-CC system were smaller than those of GS-SMI system for all subgroups except for non-LC cases. This may be attributed to the difference of cause of death between non-LC patients and LC patients.

Male was an independent adverse predictor in our analysis. One possible reason for these is that the prevalence of HCC at baseline between male and female was significantly different [5.2% (16/309) *vs.* 1.9% (6/322), P=0.0290]. Decreased eGFR was also an independent adverse predictor. Several reports have stressed the prognostic significance of eGFR in CLD patients, which were in agreement with our results (42-44). While, BMI and WC (adiposity-related markers) were not associated with the OS in our study, although a recent large prospective cohort study demonstrated the prognostic significance of excess adiposity (45). The reason for these discrepancies between studies remains unclear. Antiviral therapies have dramatically improved in recent years (46,47). The favorable hazard ratios in our patients with viral causes compared with non-viral causes seem to be attributable to the advancement of antiviral therapies. On the other hand, it is of note that in our ROC analysis of CC based on the OS, the optimal cutoff points were 34.6 cm in men and 32.8 cm in women, which were almost similar to the AWGS data (34 cm in men and 33 cm in women). Our results support the validity of the AWGS recommendations. Our study is the first study presenting the optimal cutoff point of CC in CLD patients using the OS data. This point should also be noted.

Several limitations to our study should be mentioned. First, this single-center study had a retrospective nature. Second, the observation period (median, 3.53 years) may not be enough for the survival analysis especially in non-LC patients as the number of deaths in non-LC patients is expected to be small. Third, our cohort was heterogeneous including various etiologies for underlying liver diseases and various degrees of liver functional reserve. Fourth, the number of HCC patients was small (n=22), and thus whether our proposed prognostic system can be applied to HCC patients is unclear. Fifth, various interventions for each subject have been done during the follow-up period, making bias for the OS. Caution must be therefore taken in interpreting the results and external validation will be needed in future studies. Despite the limitations, the current study results denote that our proposed GS-CC prognostic system in patients with CLDs can be a useful stratification system. The usefulness of this system can be prominent in community settings without BIA or computed tomography. CC can be an alternative marker for SMI in patients with CLDs. In conclusion, we would like to emphasize the importance of GS-CC system as a useful prognostic model for patients with CLDs.

Acknowledgments

The authors would like to thank Yasuko Higuchi in our hospital for the anthropometry measurement. This work was partly supported by Hyogo Innovative Challenge, Hyogo College of Medicine, Japan.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-6901

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-6901

Peer Review File: Available at http://dx.doi.org/10.21037/atm-20-6901

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6901). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) with ethical approval from the institutional review board in our hospital (approval number 3469). An opt out method was employed considering the retrospective nature of this study.

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Cite this article as: Nishikawa H, Yoh K, Enomoto H, Nishimura T, Nishiguchi S, Iijima H. Combined grip strength and calf circumference as a useful prognostic system in patients with liver diseases: a large cohort study. Ann Transl Med 2021;9(8):624. doi: 10.21037/atm-20-6901

