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Non-invasive testing for sarcopenia predicts future cardiovascular events in patients with chronic kidney disease

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ABSTRACT

Background: Sarcopenia is frequently observed and associated with poor outcomes in patients with chronic kidney disease (CKD). A simple screening test for sarcopenia using age, grip strength, and calf circumference was recently developed. However, the clinical utility of this sarcopenia score in patients with CKD remains unclear.
Methods and results: We calculated the sarcopenia score of 265 patients with CKD and followed the patients for cardiovascular events. The endpoint of this study was the composite of cardiovascular hospitalization and total mortality. We divided all participants into high ($n = 166$) and low ($n = 99$) sarcopenia score groups using a simple scoring system. Patients in the high sarcopenia score group showed significantly higher plasma B-type natriuretic peptide (BNP) levels than those in the low sarcopenia score group (median: 103.1, interquartile range: 46.3–310.0 vs. 46.7, 18.0–91.8 pg/mL; $p < 0.0001$). The Kaplan–Meier curve revealed that the risk of cardiovascular events was significantly greater in the high sarcopenia score group (log-rank test: $p < 0.0001$), even after potential confounding factors were corrected using propensity score matching. Multivariate Cox hazard analysis identified a high sarcopenia score (hazard ratio: 3.04, 95% confidence interval: 1.45–6.38, $p = 0.003$) as an independent predictor of the primary endpoints. Furthermore, the combination of a high sarcopenia score and high BNP level identified patients with a significantly higher probability of future events ($p < 0.0001$).
Conclusions: This study demonstrates that this simple screening score for sarcopenia could be a useful tool for estimating the future adverse event risk in patients with CKD.

1. Introduction

Reduced muscle mass and strength, known as sarcopenia, is an important age-related physical change and is increasing due to aging of the population [1,2]. Because the presence of sarcopenia is associated with both a decreased ability to exercise and increased mortality [3,4], the clinical importance of sarcopenia has received more attention in recent years. Chronic kidney disease (CKD) is one of the main causes of sarcopenia and leads to aggravation or early exteriorization of sarcopenia [5,6]. In contrast, the presence of sarcopenia has been shown to be associated with increased mortality in patients with CKD [7,8]. Resistance training, which helps to maintain muscle mass and function, is often utilized as a therapeutic intervention for patients with CKD and sarcopenia; such training reportedly has positive effects, including a decrease in systemic inflammation, in this patient population [9,10]. In this context, early detection of sarcopenia and resultant early intervention are thought to be very important in patients with CKD.

The diagnostic criteria for sarcopenia have long been unclear. However, the European Working Group on Sarcopenia in Older People, and Asian Working Group for Sarcopenia recently established a clear criterion for the diagnosis of sarcopenia [3,11]. The guideline recommends the use of dual-energy X-ray absorptiometry, computed tomography, and magnetic resonance imaging to measure the skeletal muscle mass. Although these modalities allow precise evaluation of muscle mass, they are not available for routine use in the daily clinical practice setting. Ishii et al. [12] developed a simple screening test that can identify sarcopenia with high accuracy using three easily obtainable variables: age, hand grip strength (HGS), and calf circumference. We recently reported that this screening test can predict future adverse events in patients with heart failure (HF) [13]. However, whether this simple screening test for sarcopenia can predict the future risk of adverse cardiovascular events in patients with CKD remains unclear. In this study, we measured this simple screening score of sarcopenia in patients with CKD and determined its prognostic significance

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2. Methods

2.1. Study population

The study participants comprised 265 consecutive in-hospital patients with CKD who were admitted to Kumamoto University Hospital for a diagnostic work-up for coronary artery disease, HF, or arrhythmia from March 2012 to February 2013 and underwent measurement of both HGS and calf circumference. The definition of CKD was a low estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73 m^2) and/or the presence of proteinuria [14]. The eGFR was calculated using the Japanese Society of Nephrology formula [15]. Urinary protein was evaluated semiquantitatively using a urine dipstick test (Uro-Labstix; Siemens Japan, Tokyo, Japan), and the definition of proteinuria was ≥1+ (corresponding to urinary protein excretion of >30 mg/dL). HF was defined by the American College of Cardiology/American Heart Association Stage B or C classification, and anemia was defined by the criteria of the WHO. The study protocol conformed to the principles of the Declaration of Helsinki and was conducted after approval of the ethics committee of our institution. Written informed consent was obtained from each patient.

2.2. Protocol

HGS and calf circumference were evaluated immediately before discharge from the hospital. The HGS and calf circumference measurement techniques were as described previously [13]. In brief, HGS of the dominant hand was measured using a digital HGS dynamometer (Takei Scientific Instruments, Niigata, Japan), and the higher value of the two measurements was used for estimation of the sarcopenia score. Calf circumference was measured using a measuring tape at the maximum circumference of the nondominant leg in a sitting position with the leg bent 90° at the knee. The sarcopenia screening score was calculated using a scoring chart for the estimated probability of sarcopenia advocated by Ishii et al. [12]. In this study, we defined a high sarcopenia score as a sarcopenia screening score of ≥105 in men and ≥120 in women based on the above-mentioned study [12].

2.3. Follow-up and cardiovascular events

After calculation of the sarcopenia screening score, the patients were followed in the outpatient clinic for a median of 653 days (interquartile range, 282–1419 days). The endpoint of this study was the composite of cardiovascular events (nonfatal myocardial infarction, stroke, or hospitalization for HF decompensation) and all-cause mortality. Mortality and cardiovascular events were identified by searching the medical records and confirmed by direct contact with the patients, relatives, and caring physicians.

2.4. Blood sampling and echocardiography

Blood samples were withdrawn from resting patients in the supine position. Plasma B-type natriuretic peptide (BNP) levels were measured using the MI02 Shionogi BNP kit (Shionogi, Osaka, Japan). Serum high-sensitivity cardiac troponin T (hsTnT) levels were measured using the Elecsys 2010 Troponin T hs kit (Roche Diagnostics, Indianapolis, IN). The serum and plasma samples were kept frozen at −80 °C until performance of the laboratory assays. Echocardiography findings obtained from all patients using an Aplio XG (Toshiba, Tokyo, Japan) or Vivid 7 (GE-Vingmed Ultrasound, Horton, Norway) ultrasound system were evaluated by two independent investigators who were blinded to all clinical data. The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method. Early (E) and late atrial (A) transmitral peak flow velocities were measured from the mitral inflow velocities. The early diastolic mitral annular (e′) velocity was determined after pulsed wave tissue Doppler imaging, and the E/e′ was calculated [16].

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation. However, the BNP, high-sensitivity C-reactive protein, and hsTnT concentrations showed skewed distributions and are therefore expressed as median (interquartile range); they were log transformed before linear regression analysis and Cox proportional hazard analysis. Categorical variables are expressed as number (percentage). Continuous and categorical variables were compared using the Mann–Whitney *U* test and chi-square test or Fisher's exact test, respectively. The correlation between plasma BNP levels and sarcopenia score was evaluated using univariate and multivariate linear regression analyses, because BNP was reported to be the predictor of HF event in patients with CKD [17]. Kaplan–Meier method, log rank test, and simple and stepwise forward or forced-entry multiple Cox regression analyses were used to assess prognostic associations. We performed a receiver operating characteristic (ROC) analysis to evaluate the strength of the association between outcome and sarcopenia, age, HGS, calf circumference, or Framingham risk score (FRS) [18]. Furthermore, we performed propensity score matching to correct for some potential confounding factors in patients with CKD with a high or low sarcopenia score. Independent variables included in the propensity score model were age, sex, serum albumin concentration, and eGFR. A two-tailed p value of <0.05 denoted statistical significance. All data were statistically analyzed using the Statistical Package for the Social Sciences v24 for Windows (SPSS Japan Inc., Tokyo, Japan).

3. Results

Table 1 shows the clinical characteristics of all study participants. The study comprised 184 men (69%), and the mean patient age was 72.3 ± 9.8 years. We divided all participants into two groups according to the cut-off sarcopenia score. The high and low sarcopenia score groups comprised 166 and 99 patients, respectively. The patients in the high sarcopenia score group were older than those in the low score group. There were no significant differences in the proportions of patients with coronary artery disease and risk factors between the two groups. With respect to laboratory data, the circulating levels of BNP and hsTnT, established biomarkers of cardiovascular disease, were significantly higher in the high than low sarcopenia score group (Table 1). In contrast, the eGFR was significantly lower in patients in the high sarcopenia score group. The proportion of patients with HF and anemia was significantly higher in the high than low sarcopenia score group. Moreover, echocardiography showed significantly higher E/e′ values in the high than low sarcopenia score group. With regard to medications, loop diuretics were prescribed more frequently to patients in the high than low sarcopenia score group (Table 1). Table S1 shows the clinical characteristics of all study participants classified based on eGFR levels. Estimated GFR levels were significantly associated with the proportion of patients with high sarcopenia score. The circulating levels of BNP and hsTnT were also correlated with eGFR levels (Table S1). In univariate linear regression analysis of plasma BNP level (ln[BNP]), body mass index, atrial fibrillation, hypertension, anemia, creatinine, LVEF, and a high sarcopenia score (≥cut-off value) were associated with plasma BNP level (Table S2). Multivariate analysis showed that a high sarcopenia score was significantly associated with BNP independent of body mass index, atrial fibrillation, hypertension, anemia, creatinine, and LVEF (Table S2).

Data of 265 patients with CKD were available for analysis of mortality and cardiovascular events. During the follow-up period, 53 (20.0%) of the 265 patients died or were hospitalized for cardiovascular disease. The following events were registered: death ($n = 23$), nonfatal myocardial infarction ($n = 6$), stroke ($n = 5$), and hospitalization for HF decompensation ($n = 32$). Kaplan–Meier analysis demonstrated a significantly higher probability of death or cardiovascular events in the high than low sarcopenia score group (log-rank test: $p < 0.0001$) (Fig. 1A). Furthermore, to correct for potential confounding factors, we performed propensity score matching and categorized the patients into two groups: the matched low sarcopenia score group ($n = 51$) and the matched high sarcopenia score group ($n = 51$). There were no significant differences in patient backgrounds between these two groups after matching (Table S3). These patients were followed for a median of 725 days (interquartile range, 312–1448 days), and during this period, adverse cardiovascular events were reported in 23 (23%) of 102 propensity score-matched patients. Kaplan–Meier analysis after propensity score matching also showed that patients with CKD with a high sarcopenia score had a higher probability of adverse events than those with a low sarcopenia score (Fig. 1B). Furthermore, we divided CKD group based on the severity and examined their future risks respectively. We found that the risk of cardiovascular events was greater in the high sarcopenia score group in every groups. However, these differences did not reach statistical significance only in "30 > eGFR ≧ 15" and "15 > eGFR" groups (Fig. S1).

Univariate Cox proportional hazards analysis using all study participants showed that a high sarcopenia score, the presence of anemia, a low serum albumin, a high BNP concentration (ln[BNP]), and a low LVEF were significantly correlated with future events (Table 2). Furthermore, stepwise multivariate Cox proportional hazard analysis identified a high sarcopenia score (hazard ratio [HR]: 3.04, 95% confidence interval [CI]: 1.45–6.38, $p = 0.003$), the presence of coronary artery disease (HR: 1.97, 95% CI: 1.12–3.48, $p = 0.019$), a low serum albumin concentration (HR: 0.53, 95% CI: 0.32–0.89, $p = 0.016$), and a high BNP concentration (HR: 1.43, 95% CI: 1.16–1.77, $p = 0.001$) as independent predictors of

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