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Research Article

Serum myostatin at dialysis initiation may predict 1-year mortality and hospitalization

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Short title: myostatin at starting dialysis predicts mortality

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Abstract

Objective: Myostatin, which is known as a negative skeleton muscle regulator, is associated with mortality in maintenance hemodialysis patients. However, the significance of serum myostatin concentrations at dialysis initiation has not been established. We investigated the relation between serum myostatin concentrations and mortality or hospitalization within one year in incident dialysis patients.

Methods: After a patient initiating hemodialysis or peritoneal dialysis during 2016–2018 was enrolled, the patient's serum myostatin at dialysis initiation was measured. Composite outcomes comprising mortality and hospitalization within 1 year after dialysis initiation were compared between two groups divided according to myostatin levels. The Cox proportional hazards model was used to assess significant relations between myostatin and outcomes.

Results: This study examined 104 incident dialysis patients with mean age of 65.5±14.0 (68% male). Kaplan–Meier analyses indicated the 1-year hospitalization-free and survival rate as significantly lower in the lower myostatin group than in the higher myostatin group (p = .0020). Cox proportional hazards regression analyses revealed that the value of myostatin logarithm at dialysis initiation was inversely associated with the occurrence of a composite outcome, independently of age (hazard ratio 0.16, 95% confidence interval 0.05–0.57). Receiver operating characteristic (ROC) analysis showed the area under the curve of serum myostatin for predicting death or hospitalization within 1 year as higher than those of clinical indices of nutritional disturbance and frailty.

Conclusion: Serum myostatin concentration at dialysis initiation is inversely associated with adverse outcomes in these dialysis-initiated patients.

Introduction

In recent years, the age at incidence of end-stage kidney disease (ESKD) requiring dialysis treatment has increased worldwide. For that reason and others, ESKD patients often face various health difficulties earlier after starting dialysis [1-3]. Aging and kidney dysfunction can induce sarcopenia [4], loss of muscle mass and strength, and can induce frailty, a state of increased vulnerability caused by loss of reserves for stress, along with detrimental changes in nutrition and body composition. Sarcopenia, which affects physical function, is associated with adverse outcomes including falls and hospitalization of dialysis patients [5-7]. Both older age and advanced chronic kidney disease (CKD) including ESKD have been recognized as risk factors for skeletal muscle loss [8,9].Although the mechanisms of sarcopenia in elderly ESKD patients have not been fully understood, multiple factors such as malnutrition, inflammation, and uremic toxins are thought to be intricately involved [6,8]. Moreover, sarcopenia, frailty, and nutritional disturbance are mutually related. All are known to be associated with prognosis in elderly patients undergoing dialysis [10]. Therefore, it is necessary to identify a marker reflecting skeletal muscle status from the start of dialysis and to evaluate such a marker's relation to frailty and nutritional status.

Myostatin, known as growth development factor-8 (GDF-8), is a transforming growth factor-β superfamily cytokine that is secreted mainly from muscle cells [6,8]. Myostatin acts on muscle satellite cells to suppress the muscle volume in general. However, it has been suggested that it might also act outside of musculature and might have a role in physiological and pathological processes such as metabolic disorders, cardiovascular disease, and chronic kidney disease [11]. Myostatin blood concentrations are higher in CKD and dialysis patients than in healthy subjects [6,8,12]. In maintenance dialysis patients, blood myostatin concentrations are positively associated with skeletal muscle mass and strength, with low concentrations reportedly associated with a poor prognosis [13-15]. Nevertheless, the association between myostatin at dialysis initiation and prognosis has not been adequately investigated.

This study investigates whether serum myostatin concentrations at dialysis initiation can predict mortality or hospitalization within one year after initiating dialysis. We also examine relations between myostatin and the clinical frailty scale, an index of frailty, and the geriatric nutritional risk index (GNRI) and nutritional risk index for Japanese hemodialysis (NRI-JH), which are indices of nutritional status.

Materials and Methods

Study design and Patients

We conducted a retrospective cohort study including adult (age 18 years and older) patients who started chronic dialysis (either peritoneal dialysis or hemodialysis) as their first kidney replacement therapy between August 1, 2016 and March 31, 2018 in a tertiary care hospital. Only incident dialysis patients were included in this study: patients who required dialysis transiently for AKI and patients who withdrew successfully from dialysis were not included. Peritoneal dialysis included both continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), All patients who started hemodialysis were inducted into conventional hemodialysis. No patient was receiving hemodiafiltration. All the patients started dialysis under inpatient care according to our usual clinical practice policy. After discharge from our hospital, hemodialysis patients continued treatment at other dialysis clinics near their home. Peritoneal dialysis patients were managed by our hospital. When discharging a patient to home after dialysis initiation was difficult, the patient was transferred to another hospital to continue hemodialysis. Written informed consent was obtained from all patients at dialysis initiation. The exclusion criteria were the following: (1) lost to follow-up within 1 month after dialysis initiation; (2) patients who had been hospitalized for more than 3 months before dialysis initiation; and (3) patients whose laboratory data or blood samples could not be obtained at dialysis initiation, i.e. before the start of the first session for hemodialysis and before the first dwell of dialysate for peritoneal dialysis. In addition, (4) patients with acute kidney injury with temporary dialysis but who had been weaned off before discharge from the hospital were not included in this study. This study, which was conducted in accordance with the principles outlined in the Declaration of Helsinki, was approved by the Institutional Review Board of The University of Tokyo (#11239).

Data collection

Basic information of the participants was obtained from their electronic medical records: age, gender, cause of ESKD, history of cardiovascular disease (CVD), the patient's dialysis modality, and whether or not induction was scheduled. Their data of systolic and diastolic blood pressure and body mass index (BMI) on the day of dialysis initiation were obtained from electronic medical records. Laboratory data from immediately before dialysis initiation were also obtained from electronic medical records: hemoglobin (Hb), albumin (Alb), blood urea nitrogen (BUN), serum creatinine (Cr), estimated glomerular filtration rate (eGFR), corrected calcium, phosphate, uric acid, C-reactive protein (CRP), total cholesterol (T.chol), triglyceride, hemoglobin A1c, and brain natriuretic peptide (BNP).

To assess the nutritional risk to the patients, the geriatric nutritional risk index (GNRI) and nutritional risk index for Japanese hemodialysis (NRI-JH) at dialysis initiation were evaluated according to methods described in the literature [16,17]. GNRI was calculated using the data of Alb, body weight, and ideal body weight (based on BMI value of 22 calculated by body height). The NRI-JH score was calculated using data of age, BMI, Alb, Cr, and T.chol to classify risks of nutritional disturbance into three levels: low risk (0–7 points), intermediate risk (8–10 points), and high risk (11–13 points).

Frailty at dialysis initiation was assessed as described earlier [18]. Briefly, the degree of frailty was assessed using the clinical frailty scale (CFS) ver. 2.0 translated into Japanese on a scale of 1–9 with permission from the licensor [19]. Two nurses, each with more than two years of experience at a dialysis center, independently assessed frailty using CFS by referencing a medical chart at dialysis initiation. The mean value of the results of the two nurses' assessments was regarded as the patient's CFS score, with 5 or higher defined as frail for this study [18].

Serum myostatin measurement

Serum samples collected at dialysis initiation were stored at -80°C. Stored serum samples were thawed and measured to assess the myostatin concentration using a commercial ELISA kit (GDF-8/Myostatin Quantikine ELISA Kit, #DGDF80; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol.

Outcomes

The primary outcome was the composite of all-cause mortality and unexpected hospitalization within one year after dialysis initiation. The secondary outcome was all-cause mortality within one year after dialysis initiation. The occurrence and date of the first observed outcome for each patient since the start of dialysis were investigated. Patient prognostic data were obtained through electronic medical records and telephone surveys. Patient survival was censored at kidney transplantation or at the date of last follow-up.

Statistical analysis

All statistical analyses were conducted using software (BellCurve for Excel; Social Survey Research Information Co., Ltd., Tokyo, Japan). Continuous data are expressed as mean ± standard deviation or median (interquartile range). Student *t*-tests and Mann–Whitney U-tests were used to compare continuous variables between two groups. Chi-square test and Fisher's exact test were used to compare categorical variables. Spearman's correlation test was applied to examine correlation between myostatin and clinical parameters. The Kaplan–Meier method and the log-rank test were used to compare differences in primary and secondary outcomes between the groups divided according to the serum myostatin concentrations. Univariate and multivariate Cox proportional hazards regression analyses were performed to examine significant factors associated with the primary outcome. Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive ability of variables, including myostatin, for primary outcomes. Results for which a *p*-value less than .05 was obtained were inferred as representing significant difference.

Results

Study participant characteristics

Of the 112 patients who started chronic dialysis during the study period, 104 patients were included in the analysis (Fig. S1). Baseline characteristics and laboratory data are shown in Table 1. The mean age was 65.5±14.0

years old; 71 (68%) were male. The most common cause of ESKD was diabetic kidney disease (*n*=36, 35%) followed by chronic glomerulonephritis (*n*=24, 23%) and nephrosclerosis (*n*=16, 15%). Regarding dialysis modalities, HD and PD were selected respectively in 94 (90%) and 10 (10%) patients. Of the 10 patients inducted into PD, 4 and 6 had CAPD and APD, respectively. The primary outcome was observed in 39 (38%) patients, for whom 1-year mortality was 13% (13 deaths). The causes of death included malignancy (*n*=3, 23%), infection (*n*=2, 15%), CVD (*n*=1, 8%), others (*n*=3, 23%), and unknown (*n*=4, 31%). The causes of unexpected hospitalization (*n*=32) included CVD (*n*=9, 28%), infection (*n*=6, 19%), malignancy (*n*=5, 16%), emergent vascular access troubles (*n*=3, 9%), and others (*n*=9, 28%).

When all patients were divided into two groups based on the median value of myostatin concentrations (3751 pg/ml), the lower myostatin group had significantly higher incidence of primary outcome (54% vs. 21%, $p < .01$), 1-year mortality (23% vs. 2%, $p < .01$), eGFR [5.6 (4.5, 6.4) vs. 4.5 (3.6, 5.6) ml/min/1.73 m^2, $p < .01$], CRP [0.71 (0.12, 3.63) vs. 0.13 (0.05, 0.29) mg/dl, $p < .01$], BNP [287 (105, 1376) vs. 153 (62, 429) pg/ml, $p < .01$], and prevalence of frail (33% vs. 8%, $p < .01$) compared with the higher myostatin group. By contrast, the proportion of planned dialysis initiation (46% vs. 73%, $p < .01$), systolic blood pressure [143±24 vs. 155±19 mmHg, $p < .01$], and Cr [7.4 (6.4, 8.9) vs. 10.1 (8.3, 11.5) mg/dl, $p < .01$] were significantly lower in the low myostatin group. Classification by NRI-JH was significantly different between the two groups ($p < .01$).

Relation between myostatin and clinical factors

Results of Spearman's correlation test between myostatin concentrations and other clinical parameters are shown in Table S1. Significant positive correlation was found between myostatin and each of systolic blood pressure (r=0.26, $p < .01$), diastolic blood pressure (r=0.23, $p = .02$), Cr (r=0.47, $p < .01$), and T.chol (r=0.23, $p = .02$). In addition, significant negative correlation was found between myostatin and each of age ($r = -0.29$, $p < .01$), eGFR ($r = -0.33$, $p < .01$), CRP ($r = -0.47$, $p < .01$), and NRI-JH score ($r = -0.30$, $p < .01$).

Figure 1 presents results of myostatin level comparisons between two groups divided based on each nominal scale. Myostatin concentrations were significantly different between groups of frail and non-frail and between those of low and medium/high risk of NRI-JH, although results did not differ by gender, diabetes, CVD history, or dialysis modality (Figs. 1A–1F). Patient groups with adverse outcomes, 1-year death or hospitalization, and 1-year mortality each had significantly higher serum myostatin concentrations than the corresponding groups without them (Figs. 1G and 1H).

Relation between outcomes and myostatin

Using Kaplan–Meier analysis and log-rank testing, the composite outcome of 1-year mortality or hospitalization after the initiation of dialysis was compared between groups with lower and higher myostatin concentrations (Fig. 2). Results showed lower myostatin levels to be associated with decreased 1-year survival or hospitalization-free rate ($p = .0020$, Fig. 2A). Similarly, the 1-year survival rate in the lower myostatin group was significantly lower than that in the higher myostatin group ($p = .0021$, Fig. 2B).

To evaluate the relation between composite outcome and several variables including myostatin, analyses were conducted using univariate and multivariate Cox proportional hazard models (Table S2 and Table 2, respectively). The univariate analysis results showed significant relations between outcome and age, systolic blood pressure, Alb, Cr, eGFR, logarithm of CRP, T.chol, NRI-JH score, CFS score, and logarithm of serum myostatin (Table S2). The analyses were adjusted for factors which have been reported as associated with increased risk of all-cause mortality: age, gender, systolic blood pressure, Alb, Cr, CRP, NRI-JH score, and CFS score (Table 2) [17,18,20-22]. Higher myostatin levels are associated significantly with a lower risk of 1-year mortality or hospitalization in all models.

Prognostic predictive ability of myostatin

To elucidate the predictive ability of serum myostatin at dialysis initiation for death or hospitalization within 1 year, ROC analyses were conducted (Fig. 3). Regarding the composite outcome, the area under the curve (AUC) [95% confidence interval (95% CI)] was 0.76 [0.66–0.86]; the cutoff value of myostatin was 3367 pg/ml with 71% specificity and 72% sensitivity (Fig. 3A). In contrast, AUCs [95% CI] of the serum Cr, NRI-JH score, and CFS score for

the composite outcome were 0.74 [0.65–0.84], 0.64 [0.53–0.74], and 0.66 [0.55–0.77], which are comparable or tended to be lower than those of myostatin (p = .83, .053, and .09, respectively). For 1-year mortality, AUC [95% CI] of myostatin was 0.85 [0.74–0.95]; the cutoff value was 2839 pg/ml with 79% specificity and 77% sensitivity (Fig. 3B). The AUCs [95% CI] of the serum Cr, NRI-JH score, and CFS score were, respectively, 0.73 [0.61–0.84], 0.72 [0.60–0.84], and 0.72 [0.59–0.86]. Those were significantly lower or tended to be lower than those of myostatin (p = .10, .03 and .06, respectively). Serum myostatin had moderate diagnostic ability for frailty (CFS >=5): AUC [95% CI] was 0.78 [0.66–0.90]. The cutoff value was 3340 pg/ml with 66% specificity and 81% sensitivity (Fig. S2).

Discussion

This report is the first of a study demonstrating that lower concentrations of myostatin at the initiation of dialysis are associated significantly with mortality or hospitalization within one year. Possible reasons for the association of myostatin with prognosis include sarcopenia, frailty, and poor nutritional status. The present study also showed an association between serum myostatin concentration and these factors. We found inverse correlation between myostatin concentration in the blood and the values of indices or the presence of nutritional disturbance and frailty, as evaluated respectively by NRI-JH and CFS. Myostatin might have equivalent or better predictive ability for short-term prognosis in incident dialysis patients than the capabilities of either NRI-JH or CFS, each of which is known to be associated with dialysis patient survival.

The median of the serum myostatin concentration in this study for all eligible patients was 3751 pg/ml, which is considered higher than that of healthy people and which is consistent with earlier studies [12,14,15,23]. Earlier studies using the assay kit from the same company as that cited in this report demonstrated mean blood myostatin concentrations of 3060–4620 pg/ml in CKD patients and of 2573–7590 pg/ml in dialysis patients, with the median value for our study subjects initiating dialysis falling within both ranges [12]. Several factors such as low physical activity, inflammation, and uremic toxins are thought to contribute to increased production of myostatin from muscle cells, and to contribute to reduced clearance from the kidney, thereby causing elevation of circulating myostatin concentrations [12,24,25]. Myostatin is known as a negative regulator of skeleton muscle, but the effects of increased blood myostatin concentration in ESKD patients on changes in muscle mass are not fully understood. Numerous reports have described positive correlation between blood myostatin levels and indices of muscle mass and strength in dialysis patients, which is an apparent contradiction considering the physiological actions of myostatin [6,12,14,15,23,26-28]. These findings suggest that circulating myostatin in ESKD patients might be a biomarker of sarcopenia by reflecting muscle mass and functions, rather than being a cause of muscle loss [14]. A meta-analysis indicated low muscle mass and low muscle strength as related independently to increased mortality risk in dialysis patients [7]. Poor outcomes in low myostatin concentration groups might reflect these conditions.

In our study, serum myostatin concentrations at dialysis initiation were significantly lower in patients classified as medium-risk or high-risk by NRI-JH than in patients classified as low-risk. Findings from an earlier study indicated circulating myostatin as positively correlated with Alb and negatively correlated with the Malnutrition Inflammation Score (MIS) in maintenance hemodialysis patients, suggesting lower myostatin levels with worse nutritional status [27]. Nutritional intake might enhance myostatin secretion from muscle cells [14,29]. Therefore, positive correlation between serum myostatin concentrations and nutritional status is suggested. Increased catabolism because of nutritional disorders might contribute to reduction of myocytes, a major source of myostatin, resulting in decreased muscle mass and circulating myostatin levels. Nutritional disorders might partially explain the poorer prognosis with lower myostatin levels in incident dialysis patients.

This report is the first of a study showing the blood myostatin concentration at dialysis initiation to be significantly lower in the frail group, as classified based on CFS, than in the non-frail group. We also observed that serum myostatin has moderate predictive ability for frailty (Fig. S2). Because frailty is known to be associated with mortality, especially in elderly people, accurate diagnosis of frailty must be made as early as possible, and especially at dialysis initiation [18,30,31]. Some frailty assessment tools require interviews, several physical measurements of patients, and clinical judgment by health-care providers, any of which might compromise the

inter-rater reliability. A simple and objective marker for diagnosing frailty can be combined with existing tools for more accurate frailty assessment. The results of our study indicate circulating myostatin as a potential objective marker for frailty in incident dialysis patients, although further research is needed.

From ROC analysis conducted for our study, we found that the predictive ability of serum myostatin for 1-year death or hospitalization tended to be higher than that of the NRI-JH score and CFS score. During the dialysis initiation period, NRI-JH might not always reflect the prognostic risk accurately because factors such as inflammation from acute illness and weight gain from excessive water retention might affect the Alb and BMI values used to calculate its score. For CFS, clinical judgment might not always agree among raters. Therefore, serum myostatin, evaluated simply by collecting and measuring blood samples, might be an accurate and useful marker for predicting the prognosis of patients starting dialysis. However, although a cut-off value of 1647 pg/ml for myostatin to predict mortality in prevalent hemodialysis patients was proposed in an earlier study, it might not be easy to establish a clear cut-off value for myostatin levels because many factors, including assay technique, age, and gender, strongly influence myostatin measurements [12,14]. Further research to establish it for patients starting dialysis is warranted.

Our study had several limitations. First, because this was a single center study with a small number of patients, it remains unclear whether the results are applicable to patients starting dialysis at other hospitals. Second, factors which were not considered, such as muscle mass by body composition analysis and muscle strength (e.g. handgrip), might have affected these study results. Third, we did not measure other circulating factors reported as regulators of skeleton muscle, such as IGF-1 and activin A. Fourth, we only measured serum myostatin concentrations at dialysis initiation. Therefore, sequential changes were not evaluated. To address these limitations, a large, multicenter prospective cohort study must be conducted.

In conclusion, this study demonstrated that serum myostatin concentrations at dialysis initiation are significantly and inversely associated with mortality and hospitalization rate within one year. Myostatin might be a useful objective marker for predicting the adverse prognoses of incident dialysis patients. Additional studies must be conducted to elucidate whether the maintenance of higher circulating concentrations of myostatin can extend the healthy survival of dialysis patients.

Statements

Acknowledgment

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Statement of Ethics

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of The University of Tokyo (#11239). Written informed consent was obtained from all patients.

Conflict of interest Statement

The authors declare that they have no competing financial or other interest or personal relation that could have influenced this paper or the study it describes.

Funding Sources

The authors declare that they have no relevant financial interests.

Author Contributions

This study was designed by Yoshifumi Hamasaki. Material preparation, data collection, and analyses were performed by Midori Sakashita, Yoshifumi Hamasaki, Rikako Oki, Yohei Komaru, and Yoshihisa Miyamoto. The first draft of the manuscript was written by Midori Sakashita and Yoshifumi Hamasaki, and was revised by Teruhiko Yoshida, Ryo Matsuura, Kent Doi, and Masaomi Nangaku.

Data Availability Statement

The data which support the findings of this study are available from the corresponding author, [Y.H.], upon reasonable request.

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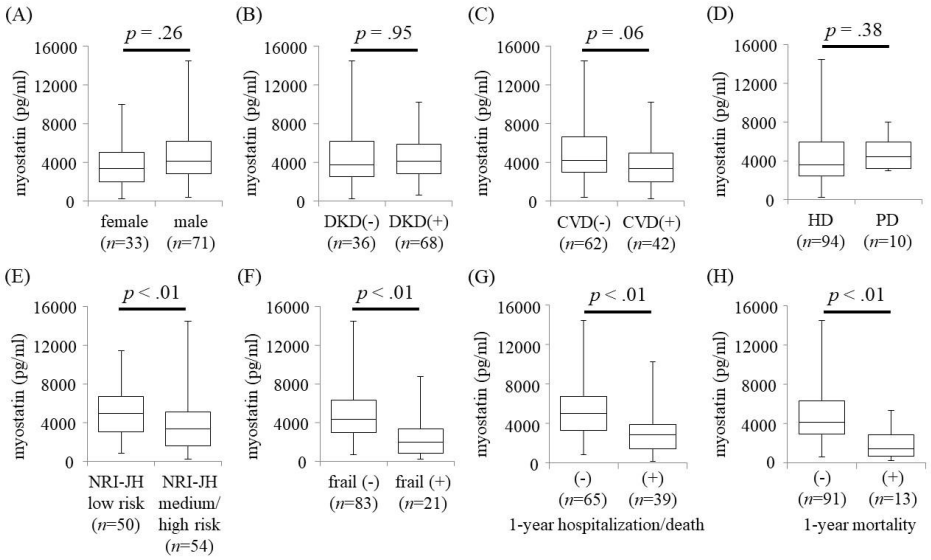
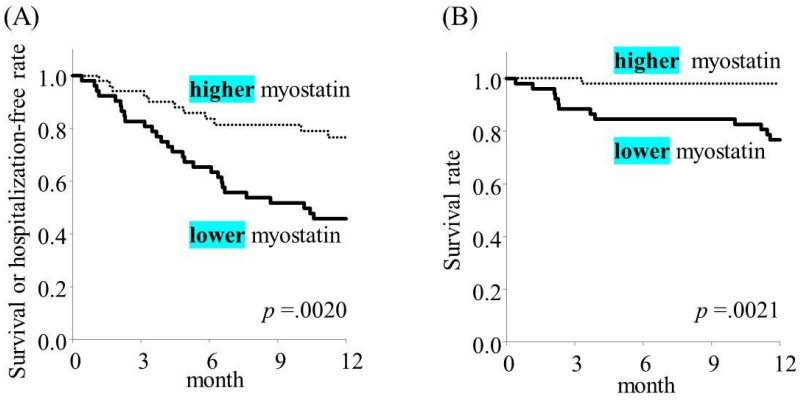
Figure Legends

Figure 1. Comparison of serum myostatin levels between two groups.
Serum myostatin levels were compared between groups divided based on gender (A), DKD (B), CVD history (C), dialysis modality (D), NRI-JH risk classification (E), frailty (F), and outcomes of 1-year death or hospitalization (G) and mortality (H).

Figure 2. Kaplan–Meier analysis for composite outcome (survival or hospitalization-free rate) (A) and survival rate (B) within 1 year after starting dialysis.

Figure 3. Receiver operating characteristic (ROC) analyses assessing the predictive ability of serum myostatin, serum creatinine (Cr), NRI-JH score, and CFS score for outcomes (death or hospitalization (A) or mortality (B) within 1 year after starting dialysis).





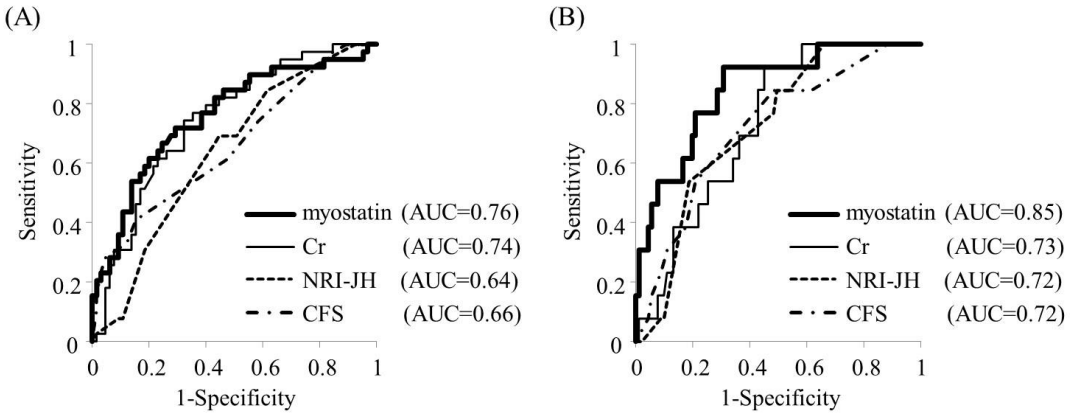


Table 1. Patient characteristics and comparison among groups according to serum myostatin level

Variable	all (*N*=104)	lower myostatin (*N*=52)	higher myostatin (*N*=52)	*p*
age [y.o.]	65.5±14.0	68.1±13.8	62.9±13.8	.06
male gender [*n* (%)]	71 (68%)	33 (63%)	38 (73%)	.40
cause of ESKD [*n* (%)]				.36
DKD	36 (35%)	17 (33%)	19 (37%)	
chronic glomerulonephritis	24 (23%)	9 (17%)	15 (29%)	
nephrosclerosis	16 (15%)	10 (19%)	6 (12%)	
others/unknown	28 (27%)	16 (31%)	12 (23%)	
CVD history [*n* (%)]	42 (40%)	24 (46%)	18 (35%)	.32
planned initiation of dialysis	62 (60%)	24 (46%)	38 (73%)	< .01
dialysis modality (HD/PD)	94/10	49/3	45/7	.32
systolic blood pressure [mmHg]	149±22	143±24	155±19	< .01
diastolic blood pressure [mmHg]	74±16	71±17	78±13	.02
body mass index [kg/m^2]	23.4 (20.9, 27.1)	23.0 (20.4, 26.8)	23.8 (21.9, 27.2)	.44
Hb [g/dl]	9.1 (8.1, 9.8)	8.7 (7.9, 9.5)	9.3 (8.6, 10.0)	.050
Alb [g/dl]	3.2 (2.8, 3.6)	3.1 (2.7, 3.6)	3.2 (2.9, 3.6)	.30
BUN [mg/dl]	91.6 (75.9, 106.2)	95.7 (78.2, 112.0)	90.6 (75.0,100.8)	.19
Cr [mg/dl]	8.6 (7.1, 10.9)	7.4 (6.4, 8.9)	10.1 (8.3, 11.5)	< .01
eGFR [ml/min/1.73 m^2]	5.2 (3.9, 6.2)	5.6 (4.5, 6.4)	4.5 (3.6, 5.6)	< .01
corrected Ca [mg/dl]	8.7 (8.3, 9.1)	8.7 (8.2, 9.1)	8.8 (8.4, 9.1)	.22
IP [mg/dl]	5.7 (5.0, 6.7)	5.6 (5.0, 6.5)	5.8 (5.2, 6.9)	.39
UA [mg/dl]	6.9 (6.1, 8.6)	6.9 (6.2, 8.9)	7.3 (6.1, 8.4)	.92
CRP [mg/dl]	0.20 (0.08, 1.17)	0.71 (0.12, 3.63)	0.13 (0.05, 0.29)	< .01
T.chol [mg/dl]	162 (130, 183)	157 (118, 183)	167 (139, 183)	.19
TG [mg/dl]	122 (86, 159)	122 (86, 159)	124 (87, 160)	.91
HbA1C [%]	5.6 (5.3, 6.2)	5.5 (5.2, 6.1)	5.7 (5.3, 6.2)	.42
BNP [pg/ml]	207 (73, 927)	287 (105, 1376)	153 (62, 429)	.03
GNRI	97.8 (90.3, 108.1)	96.1 (88.3, 108.3)	98.0 (94.5, 108.1)	.26
NRI-JH [*n* (%)]				< .01
low risk (score 0–7)	50 (48%)	18 (35%)	32 (61%)	
medium risk (score 8–10)	45 (43%)	27 (52%)	18 (35%)	
high risk (score 11–13)	9 (9%)	7 (13%)	2 (4%)	
frailty (CFS score >=5) [*n* (%)]	21 (20%)	17(33%)	4(8%)	< .01
serum myostatin [pg/ml]	3751 (2656, 5935)	2624 (1449, 3227)	5953 (4996, 7655)	< .01
death within 1 year [*n* (%)]	13 (13%)	12 (23%)	1 (2%)	< .01
hospitalization/death within 1 year [*n* (%)]	39 (38%)	28 (54%)	11 (21%)	< .01

Table 2. Results from multivariate Cox proportional hazards model for 1-year death or hospitalization

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
serum myostatin (logarithm)	0.12 (0.04–0.32)	< .01	0.18 (0.06–0.54)	< .01	0.12 (0.03–0.40)	< .01	0.16 (0.05–0.57)	< .01	**0.08 (0.03–0.24)**	**< .01**
age	1.03 (1.00–1.06)	.03	1.02 (0.996–1.05)	.09	1.03 (1.00–1.06)	.03	1.03 (1.01–1.06)	.02	**1.03 (1.01–1.06)**	**.01**
male gender	1.85 (0.89–3.83)	.10							**1.74 (0.84–3.60)**	**.14**
systolic blood pressure	0.99 (0.98–1.01)	.31								
Alb			0.69 (0.36–1.33)	.27						
Cr			0.88 (0.76–1.02)	.08						
CRP (logarithm)					1.02 (0.63–1.62)	.95				
T.chol					0.996 (0.99–1.00)	.25				
NRI-JH score							1.06 (0.93–1.21)	.39		
CFS score							1.14 (0.85–1.52)	.38		
planned dialysis initiation									**0.81 (0.40–1.64)**	**.55**

Alb, albumin; Cr, creatinine; CRP, C-reactive protein; T.chol, total cholesterol; NRI-JH, nutritional risk index for Japanese hemodialysis patients; CFS, clinical frailty scale.