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Nutritional Status is Associated With Non-Cardiovascular Mortality but not With Cardiovascular Mortality in Maintenance Hemodialysis Patients

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Protein energy wasting, malnutrition-inflammation complex syndrome, and frailty are thought to affect mortality in chronic dialysis patients. We performed a historical cohort study to investigate effects of the nutritional status on cardiovascular（CV）and non-CV mortalities as well as CV events using Geriatric Nutritional Risk Index（GNRI）. We registered patients undergoing maintenance hemodialysis（HD）therapy from January to March in 2006 to analyze mortality and causes of death in 7-years observation. A Kaplan-Meyer curve showed that the survival rate tends to be lower in 102 patients with GNRI<92, compared to 171 patients with GNRI ≧92. In a multivariate Cox proportional hazard analysis, the GNRI was an independent predictor for all-cause mortality with hazard ratio of 0.960（95% confident interval: 0.928-0.993）after adjustment with age, gender, dialysis duration, blood access, the presence of diabetes mellitus, serum levels of calcium, phosphate, alkaline phosphatase, parathyroid hormone and C-reactive protein, and drug use of active vitamin D analog and non-calcium containing phosphate binders. The GNRI was not associated with CV death but with non-CV death after adjustment with the covariates. In parallel with these findings, there was no significant association between the GNRI and CV events. Nutritional status was significantly associated with non-CV death but not with CV death and CV events at least in our maintenance hemodialysis patients.

Key words: nutrition, hemodialysis, mortality, cardiovascular event

INTRODUCTION

The survival rate of patients with dialysis therapy is markedly reduced, compared to the healthy population［1］. Because dialysis therapy is associated with loss of amino acids, maintenance dialysis therapy has been believed to lead to highly catabolic status. Indeed, serum concentration of essential amino acids is similar before and after hemodialysis（HD）therapy, suggesting the compensation by dissolving the muscle and protein from the body. In addition, there are many other causes leading to malnutrition, which are tightly linked to inflammation and atherosclerosis. Thus, the pathophysiology has been called malnutrition-inflammation-atherosclerosis（MIA）syndrome or malnutrition-inflammation complex syndrome（MICS）, which is known to be a major complication of dialysis patients to reduce survival rate［2-5］. Malnutrition, sarcopenia and frailty have been socioeconomic issues in not only chronic kidney disease（CKD）patients but also general aged population, because they are strong

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risk factors for mortality and hospitalization [6-11]. These days, this idea is also based on protein energy wasting (PEW) and frailty, which compile nutritional and physical or generalized aspects of CKD patients, respectively. PEW, which is defined as the loss of somatic and circulating body protein and energy reserves, is usually used for CKD, especially in patients undergoing dialysis therapy [12, 13].

Malnutrition inflammation score (MIS) has been a good measure as a nutritional status of dialysis patients, since it significantly correlates with mortality, cardiovascular (CV) events, the prevalence of depressive symptoms and poor quality of life [14-17]. MIS is composed of not only objective assessment but also subjective global assessment such as dietary intake, digestive symptoms, physical function, loss of adipose tissue (triceps and biceps brachii, and breast), and loss of muscle mass. Although subjective assessment makes MIS more reliable, it is complex and time consuming. On the other hand, geriatric nutritional risk index (GNRI), which has been developed as an assessment tool for nutritional status of geriatric population, simply provides nutritional risk for subjects using serum albumin concentration, body weight and height [18-20]. Recent studies have been demonstrated that GNRI is useful for identifying mortality risk of dialysis patients and comparable to MIS and other tools [21-24].

Mortality rate of dialysis patients is considerably high especially in younger population. Among this population, CV event rates are much higher than those of healthy subjects. Indeed, heart failure is a leading cause of death in Japan and one thirds of patients undergoing dialysis therapy result in CV death [25]. A recent study shows that CV mortality is associated with nutritional status in incident HD patients [26]. However, it remains uncertain whether or not nutritional status affects CV or non-CV mortality in chronic dialysis patients and if so, to what extent the nutritional status provides an impact on CV or non-CV mortality. To clarify these issues, we conducted a historical cohort study among maintenance HD patients.

MATERIALS AND METHODS

Study design

A historical cohort study, which was performed using data from 4 institutes located in Shimane prefecture (Izumo city, Ooda city and Masuda city), started in March 2006 and was completed in March 2013. Patients undergoing maintenance HD in March 2006 were assigned for this study to analyze the follow-up survival and the first presentation of CV events. We collected baseline data for each patient from January 2006 to March 2006. Then, we examined effects of nutritional status on all-cause mortality, CV mortality, and non-CV mortality.

Subjects

This study was approved by the Institutional Review Board after reviewed by the Shimane University Institutional Committee on Ethics, and were conducted in accordance with the Declaration of Helsinki. The inclusion criteria of this study were patients undergoing maintenance HD therapy at March in 2006. The exclusion criteria were patients with less than 3 months of HD duration, with any advanced cancer, and with hospitalization due to acute and/or severe illness at that time. Two hundred seventy-three patients (157 men and 116 women) undergoing maintenance HD therapy in 4 institutes were registered. No one had any advanced cancer in 2006 at least from the medical review. Patients' background information and blood sample data from January to March in 2006 were obtained. Information including age, body weight (dry weight), type of vascular access, and the duration of dialysis therapy was obtained from the dialysis unit. Diabetes mellitus (DM) was defined as a history or the presence of diabetic retinopathy.

Regarding the modality of dialysis, a standard HD therapy (4 hours per session, 3 times a week) had been performed in most patients. The membranes with 1.5-2.5 m^2 were usually used during the study period, in order to achieve the target Kt/V of around 1.2. Dialysate flow was fixed at 500 mL/min, which was supplied by a central provider. Blood flow was between 160 and 250 mL/min. No patient reused the dialyzer.

In 273 HD patients, 109 died, 139 survived, and 25 moved or changed the clinic during 7 years. CV events, which are called as major adverse cardiovascular events (MACE), were defined by a

composite of CV death, non-fatal myocardial infarction, unstable angina, heart failure, stroke, peripheral arterial disease, and sudden death. CV death was shown in 51 patients: 22 (cardiac failure), 17 (stroke), 7 (sudden death), 3 (peripheral arterial disease), and 2 (aortic dissection and aneurysm). The rest was defined non-CV death.

Blood samples and GNRI measurement

Blood samples were collected just before the dialysis session on Monday or Tuesday. Blood cells were counted using an automated analyzer and serum concentration of albumin (Alb), phosphate and C-reactive protein (CRP) was measured by a standard method. These values were a mean of three measurements within 3 months at the beginning of the study period. GNRI was calculated by the formula [18]:

GNRI = 14.89× (serum Albumin level) + 41.7× (DW/IBW)

DW; dry weight

IBW; ideal body weight

DW/IBW=1, if DW>IBW

Baseline characteristics of the patients were presented in Table 1. In an original study, subjects with GNRI<92 were of high mortality [18]. Thus, in this study, the participants were classified into 2 groups by GNRI to follow the survival and CV events for 7 years.

Statistics

All data were shown as mean ± standard deviation of the mean. An unpaired *t*-test or a Mann-Whitney U-test was performed in comparison between two groups. A chi-square test was also performed to determine the statistical significance. In analysis for mortality and CV events, Kaplan-Meyer curve was depicted and log-rank test was performed, followed by univariate and multivariate Cox proportional hazard analysis. Shapiro-Wilk normality test was conducted using the software R (Ver. 2.12.1), and showed that GNRI in our population was normally distributed. All analysis except Shapiro-Wilk normality test was performed using the statistical computer program StatView (Abacus Concepts, Berkely, CA). A p value <0.05 was considered statistically significant.

RESULTS

Stratification by GNRI

Patients were distributed in 17 patients with GNRI<82, 85 patients with 82-92, 100 patients with 92-98, and 71 patients with ≧98. The distribution was statistically normal by Shapiro-Wilk normality test. GNRI<92 is reported to be high risk of mortality in the original study [18]. In addition, HD patients with GNRI<91.2 showed high mortality [27]. Thus, we classified patients into 2 groups (<92 and ≧92) by GNRI to analyze all-cause mortality, CV and non-CV mortalities, and CV events.

All-cause mortality

In 273 HD patients, 46 patients (45.1%) died in those with GNRI<92, whereas 63 patients (36.8%) died in those with GNRI ≧92. The Kaplan-Meyer curve showed that the survival rate of a 7-years follow-up tends to be lower in those with GNRI<92 than in those with GNRI ≧92 with p=0.131 by log-rank test (Fig. 1). In univariate Cox proportional hazard analysis, age, short HD duration, the presence of DM, not taking active vitamin D analogs and non-calcium-containing phosphate binders, high CRP, and low GNRI were associated with all-cause mortality (Table 2). In multivariate Cox proportional hazard analysis, age, not taking non-calcium-containing phosphate binders, high CRP, and low GNRI were independent predictors of all-cause mortality after adjustment with covariates, suggesting that GNRI is a good marker for mortality of

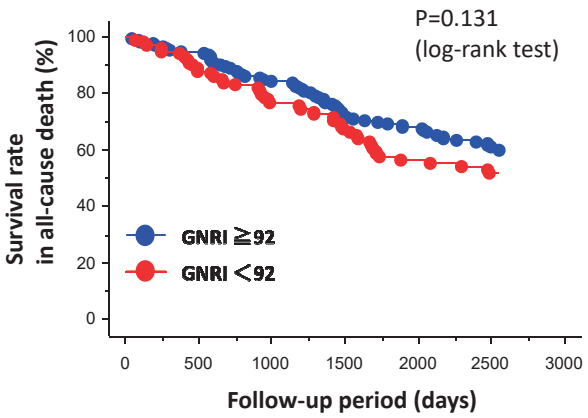

Fig. 1. Kaplan-Meier estimates of cumulative survival in all-cause mortality according to GNRI above and below 92.

Table 1. Baseline data in maintenance HD patients in 2006

	Total	GNRI		p value
		<92	≧ 92	
N	273	102	171	
Age（year）	61.3±13.0	65.6±11.1	58.7±13.4	<0.001
HD duration（month）	87.5±80.3	101.2±91.1	79.4±72.3	<0.05
Blood access AV fistula / graft	256/17	Jun-96	160/11	n.s.*
Male/Female	157/116	49 /53	108 / 63	n.s.*
DM -/+	195 /78	73/ 29	122/ 49	n.s.*
Active vitamin D analog -/+	106 /167	40/62	66 /105	n.s.*
Non-calcium-containing phosphate binder -/+	181 /92	67/35	114 /57	n.s.*
Ca（mg/dL）	9.2±0.9	9.0±0.9	9.3±0.8	<0.05
P（mg/dL）	5.5±1.3	5.3±1.3	5.6±1.4	n.s.
ALP（U/L）	272.6±105.1	282.9±105.9	266.5±104.5	n.s.
Intact PTH（pg/mL）	232.0±237.0	192.4±186.3	255.6±260.1	n.s.
CRP（mg/dL）	0.2±0.38	0.25±0.5	0.17±0.3	n.s.
Alb（g/dL）	3.8±0.4	3.5±0.4	4.0±0.3	<0.001
BMI（kg/m^2）	20.2±3.0	18.3±2.1	21.4±2.7	<0.001
GNRI	93.4±7.1	86.3±5.4	97.6±3.8	<0.001

*: chi-square test

Table 2. Univariate and multivariate Cox proportional Hazards for all-cause mortality

	Univariate		Multivariate	
	HR（95%CI）	p value	HR（95%CI）	p value
Age	1.051（1.035-1.069）	<0.001	1.039（1.019-1.059）	<0.001
HD duration	0.996（0.993-0.999）	<0.01	0.998（0.994-1.001）	n.s.
Graft[#1]	0.891（0.434-1.830）	n.s.	0.761（0.336-1.727）	n.s.
Gender[#2]	1.15（0.790-1.674）	n.s.	1.066（0.701-1.620）	n.s.
DM[#3]	1.618（1.094-2.392）	<0.05	0.811（0.515-1.309）	n.s.
Active vitamin D analog[#4]	0.607（0.417-0.883）	<0.01	0.76（0.499-1.16）	n.s.
Non-calcium-containing phosphate binder[#5]	0.361（0.222-0.587）	<0.001	0.449（0.249-0.810）	<0.01
Ca	0.896（0.719-1.116）	n.s.	1.34（0.996-1.803）	n.s.
P	0.934（0.807-1.080）	n.s.	1.069（0.898-1.273）	n.s.
ALP	1（0.998-1.002）	n.s.	0.999（0.997-1.001）	n.s.
Log（PTH）	0.67（0.413-1.086）	n.s.	1.526（0.831-2.801）	n.s.
Log（CRP）	2.78（1.940-3.982）	<0.001	1.998（1.306-3.057）	<0.01
GNRI	0.955（0.930-0.980）	<0.001	0.96（0.928-0.993）	<0.05

#1 Graft（arteriovenous fistula: 0, graft: 1）
#2 Gender（female: 0, male: 1）
#3 DM（-: 0, +: 1）
#4 Active vitamin D analog（-: 0, +: 1）
#5 Non-calcium-containing phosphate binders（-: 0, +: 1）

maintenance HD patients (Table 2). This finding is compatible with previous studies [21, 28].

CV and non-CV mortalities

The causes of death in 109 patients were shown in Table 3. In the Kaplan-Meyer curve and Log-rank test, the CV mortality rate for 7 years was not significantly different between patients with GNRI<92 and those with GNRI ≧92 (Fig. 2). On the other hand, non-CV mortality was significantly lower in GNRI<92, compared to GNRI ≧92 (Fig. 3). In univariate Cox proportional hazard analysis, age, not taking active vitamin D analogs and non-calcium-containing phosphate binders, low PTH, high CRP, and low GNRI were associated with non-CV mortality (Table 4). In multivariate Cox proportional hazard analysis, age, not taking non-calcium-containing phosphate binders, high CRP, and low GNRI were independent predictors of non-CV mortality after adjustment with covariates (Table 4). These findings suggest that poor nutritional status is intensively associated with non-CV mortality in our population. It is of note that 12 patients (11.8%) and 9 patients (5.3%) died from infection

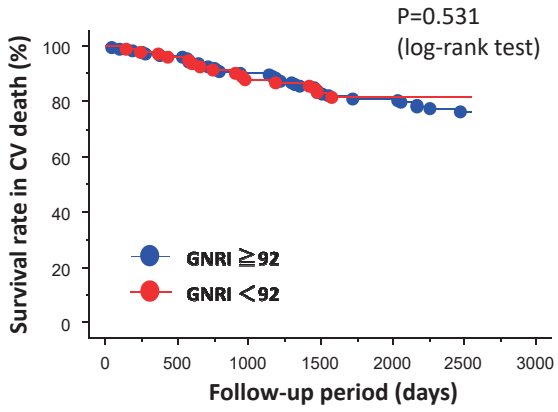

Fig. 2. Kaplan-Meier estimates of cumulative survival in CV mortality according to GNRI above and below 92.

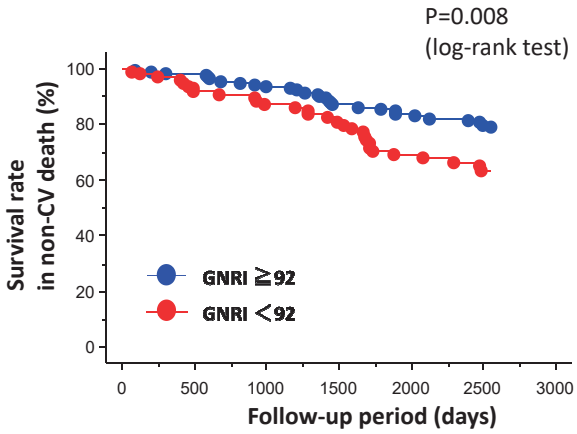

Fig. 3. Kaplan-Meier estimates of cumulative survival in non-CV mortality according to GNRI above and below 92.

Table 3. The causes of death and the number of maintenance HD patients

Causes of death	Total (N)	GNRI <92	GNRI ≧ 92
Cardiovascular events	51	16	35
Heart failure	22	7	15
Stroke	17	4	13
Sudden death	7	3	4
Peripheral arterial disease	3	2	1
Aortic disease	2	0	2
Infection	21	12	9
Cancer	12	5	7
Unknown	11	4	7
Cachexia	4	1	3
Liver cirrhosis	2	2	0
Gastrointestinal hemorrhage	2	2	0
Others	6	4	2
Total	109	46	63

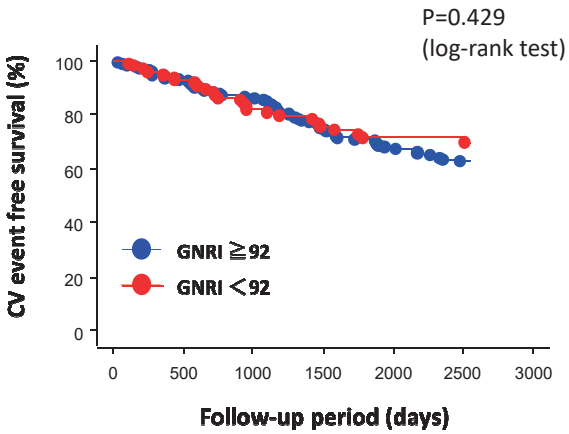

Fig. 4. Time to the first CV events according to GNRI above and below 92.

in GNRI<92 and GNRI ≧92, respectively, whereas cancer casused death in 5 patients (4.9%) and 7 patients (4.1%) of each group (Table 3).

CV events and GNRI

Next, we analyzed 82 CV events, which firstly occurred during the study period: 26 occurred in GNRI<92 whereas 56 occurred in GNRI ≧92. As for causes of the CV events, stroke including transient ischemic attack (TIA), heart failure with hospitalization, peripheral arterial disease, myocardial infarction, unstable angina, sudden death, and others occurred in 27, 20, 11, 7, 6, 5 and 6 patients, respectively. We depicted the time to the first CV event in patients with GNRI<92 and those with GNRI ≧92 (Fig. 4). Similar to the CV mortality, the GNRI was not significantly associated with all CV events in our population.

Taken together, in our historical cohort, the nutritional index GNRI was not statistically associated with future CV events and CV mortality but with non-CV mortality.

DISCUSSION

The present study firstly demonstrated an intensive association between the nutritional status and non-CV death in maintenance HD patients. CV events and CV death were not associated with the nutritional status, suggesting that the nutritional status was significantly associated with survival of maintenance HD patients mainly due to non-CV events.

Growing body of evidence suggests that high nutritional risk is a strong predictor of mortality and hospitalization in aged frail people, acute ill patients, and patients undergoing dialysis therapy [6-11]. In CKD patients, especially in HD patients, 2-year and 5-year survivals are as low as about 90% and 60%, respectively [25,29]. Indeed, our data showed that about a half of our patients died in 7 years, indicating that the subjects of this study were most likely general dialysis population of our country. In the previous studies of dialysis patients, age, DM, inflammation, hyperphosphatemia, non-calcium based phosphate binders, vitamin D deficiency and poor nutritional status were reported to be an independent

Table 4. Univariate and multivariate Cox proportional Hazards for non-CV mortality

	Univariate		Multivariate	
	HR (95%CI)	p value	HR (95%CI)	p value
Age	1.066 (1.042-1.090)	<0.001	1.043 (1.016-1.070)	<0.01
HD duration	0.997 (0.997-0.993)	n.s.	0.999 (0.994-1.004)	n.s.
Graft[#1]	0.943 (0.342-2.603)	n.s.	0.677 (0.224-2.046)	n.s.
Gender[#2]	1.094 (0.654-1.829)	n.s.	0.991 (0.556-1.765)	n.s.
DM[#3]	1.326 (0.761-2.309)	n.s.	0.955 (0.507-1.799)	n.s.
Active vitamin D analog[#4]	0.535 (0.320-0.892)	<0.05	0.657 (0.366-1.181)	n.s.
Non-calcium-containing phosphate binder[#5]	0.281 (0.138-0.573)	<0.001	0.364 (0.157-0.845)	<0.05
Ca	0.784 (0.576-1.066)	n.s.	1.273 (0.844-1.921)	n.s.
P	0.830 (0.673-1.022)	n.s.	0.999 (0.779-1.281)	n.s.
ALP	0.999 (0.996-1.001)	n.s.	0.997 (0.994-1.000)	n.s.
Log (PTH)	0.511 (0.271-0.965)	<0.05	1.350 (0.589-3.096)	n.s.
Log (CRP)	3.099 (1.897-5.062)	<0.001	2.245 (1.257-4.009)	<0.01
GNRI	0.926 (0.896-0.957)	<0.001	0.938 (0.897-0.980)	<0.01

#1 Graft (arteriovenous fistula: 0, graft: 1)
#2 Gender (female: 0, male: 1)
#3 DM (-: 0, +: 1)
#4 Active vitamin D analog (-: 0, +: 1)
#5 Non-calcium-containing phosphate binders (-: 0, +: 1)

determinant of the mortality [1, 2, 4, 14, 21, 30-32]. These findings are consistent with our results, where age, HD duration, high CRP, the presence of DM, and low GNRI were associated with higher mortality, whereas using active vitamin D analog and non-calcium-containing phosphate binders were associated with lower mortality. In multivariate Cox proportional hazard analysis, low GNRI was an independent risk factor for mortality after adjustment with the covariates, which is consistent with the previous reports [21, 28, 33].

According to the recent report of the Japanese Dialysis Registry, CV death was shown in 37.7% of 29,525 HD patients who died in 2014 in Japan (26.3% in heart failure, 7.1% in cerebrovascular accident, and 4.3% in ischemic heart disease) [34]. Infection and cancer, which were the second and third leading cause of death, were observed in 20.9% and 9.0%, respectively [34]. Our data were almost compatible with these data (46.8% in CV death, 19.3% in infection, and 11.0% in cancer), although the rate of stroke (15.6%) was relatively high. In our analysis, GNRI does not predict CV death and CV events but may predict non-CV death in maintenance HD patients. These findings are inconsistent with a recent study showing a significant association between poor nutritional status and CV death in incident HD patients [26]. Although the reason of this discrepancy is uncertain, their study population shows older, higher ratio of DM, and lower serum Alb levels, suggesting lower nutritional status and higher risk of CV events, compared to our study population. In addition, among patients starting HD therapy, CV event risk as well as CV mortality may be increased because of instability of blood pressure and body fluid, and because of fragility in those of poor nutrition. Thus, nutritional status differently affects CV events and the prognosis in incident and maintenance HD patients.

We demonstrated that low GNRI was significantly associated with non-CV death in maintenance HD patients. The mechanisms might be explained primarily by altered immune function and the susceptibility to various infectious diseases described below. Indeed, GNRI was demonstrated to be associated with serum inflammatory markers and to be a significant predictor of PEW status for the elderly patients [35]. Inflammatory cytokines stimulate protein degeneration and suppress protein synthesis, leading to malnourished status [36], which, in turn, leads to impaired immune function, anemia, and skeletal muscle loss as well as bone loss. Then, anorexia, malaise, impaired physical performance and malnutrition may further develop. In this condition, pneumonia, sepsis, decubitus, bone fractures may occur, which affect mortality. Malnutrition greatly increases susceptibility to infectious diseases including HIV/AIDS, tuberculosis, and malaria in low-income countries, particularly in children [37]. Malnutrition is thought to be a major risk factor in the onset of active tuberculosis [38]. A large controlled inpatient study demonstrated that malnutrition showed an independent risk factor for nosocomical infections, which account for 6-10% of all in-hospital deaths worldwide [39]. In addition, even in apparent healthy subjects, malnutrition is related to dysfunctional immune responses, which may contribute to increased susceptibility and severity to infectious diseases [40]. Therefore, malnutrition is related directly to non-CV death but not to the incidence of CV event or CV death.

Another aspect we may concern is the method evaluating the nutritional status. The nutritional status of HD patients was evaluated using SGA, MIS, MNA, NRS, MUST, MST, and GNRI [14, 27, 35, 36]. Although MIS is reliable enough and associated with mortality among this population [37], subjective assessment such as dietary intake and digestive symptoms is necessary to complete. On the other hand, GNRI was developed as a simple nutritional assessment tool for aged people. In dialysis patients, GNRI was highly correlated with other nutritional indices including MIS, and reported to be useful for mortality prediction [21, 28]. Higher mortality of dialysis patients was reported in patients with GNRI<91.2 [27] and with GNRI<90 [21, 28]. In the present study, we found that patients with GNRI<92 had significantly lower survival rate in non-CV death, and that low GNRI was an independent predictor of all-cause mortality. Since serum Alb and BMI were associated with all-cause (HR: 0.431, 95%CI: 0.265-0.702, and HR: 0.961, 95%CI: 0.896-1.030) and non-CV mortalities (HR: 0.291, 95%CI: 0.154-0.550, and HR: 0.883,

95%CI: 0.796-0.981) in univariate Cox proportional hazard analysis, GNRI, which is composed of these indices, might be a better predictor for survival.

In the present study, we longitudinally followed HD patients for 7 years. Because our dialysis centers/ hospitals were located in the countryside, there were a few cases dropped-out from the observation. Shortcomings of this study were small number of patients and a historical cohort study. However, our study population was typical chronic HD patients in our country, based on the baseline characteristics and, causes of death, and CV events. Therefore, a multicenter large-scale prospective study should be needed to make findings of this study more certain.

In conclusion, we firstly demonstrated a strong relationship of poor nutritional status with non-CV death but not with CV-death and CV events in maintenance HD patients. GNRI may be a good predictor for survival, especially for non-CV mortality, in maintenance HD patients.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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REFERENCES

1) de Mutsert R, Snijder MB, van der Sman-de Beer F, *et al*. Association between body mass index and mortality is similar in the hemodialysis population and the general population at high age and equal duration of follow-up. *J Am Soc Nephrol* 2007;18:967-74.

2) Stenvinkel P, Heimburger O, Lindholm B, Kaysen GA, Bergstrom J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol Dial Transplant* 2000;15:953-60.

3) Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis* 2003;42:864-81.

4) de Mutsert R, Grootendorst DC, Axelsson J, *et al*. Excess mortality due to interaction between protein-energy wasting, inflammation and cardiovascular disease in chronic dialysis patients. *Nephrol Dial Transplant* 2008;23:2957-64.

5) Lopes AA, Bragg-Gresham JL, Elder SJ, *et al*. Independent and joint associations of nutritional status indicators with mortality risk among chronic hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Ren Nutr* 2010;20:224-34.

6) Kagansky N, Berner Y, Koren-Morag N, Perelman L, Knobler H, Levy S. Poor nutritional habits are predictors of poor outcome in very old hospitalized patients. *Am J Clin Nutr* 2005;82:784-91.

7) Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med* 2012;172:1071-7.

8) McAdams-DeMarco MA, Suresh S, Law A, *et al*. Frailty and falls among adult patients undergoing chronic hemodialysis: a prospective cohort study. *BMC Nephrol* 2013;14:224.

9) Auais M, Morin S, Nadeau L, Finch L, Mayo N. Changes in frailty-related characteristics of the hip fracture population and their implications for healthcare services: evidence from Quebec, Canada. *Osteoporos Int* 2013;24:2713-24.

10) Farid K, Zhang Y, Bachelier D, *et al*. Cognitive impairment and malnutrition, predictors of all-cause mortality in hospitalized elderly subjects with cardiovascular disease. *Arch Cardiovasc Dis* 2013;106:188-95.

11) Conroy S, Dowsing T. The ability of frailty to predict outcomes in older people attending an acute medical unit. *Acute Med* 2013;12:74-6.

12) Kim JC, Kalantar-Zadeh K, Kopple JD. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J Am Soc Nephrol* 2013;24:337-51.

13) Fouque D, Kalantar-Zadeh K, Kopple J, *et al*. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008;73:391-8.

14) Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 2001;38:1251-63.
15) Ho LC, Wang HH, Peng YS, *et al*. Clinical utility of malnutrition-inflammation score in maintenance hemodialysis patients: focus on identifying the best cut-off point. *Am J Nephrol* 2008;28:840-6.
16) Dessi M, Noce A, Agnoli A, *et al*. The usefulness of the prognostic inflammatory and nutritional index (PINI) in a haemodialysis population. *Nutr Metab Cardiovasc Dis* 2009;19:811-5.
17) Ibrahim S, El Salamony O. Depression, quality of life and malnutrition-inflammation scores in hemodialysis patients. *Am J Nephrol* 2008;28:784-91.
18) Bouillanne O, Morineau G, Dupont C, *et al*. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr* 2005;82:777-83.
19) Cereda E, Vanotti A. The new Geriatric Nutritional Risk Index is a good predictor of muscle dysfunction in institutionalized older patients. *Clin Nutr* 2007;26:78-83.
20) Cereda E, Zagami A, Vanotti A, Piffer S, Pedrolli C. Geriatric Nutritional Risk Index and overall-cause mortality prediction in institutionalised elderly: a 3-year survival analysis. *Clin Nutr* 2008;27:717-23.
21) Kobayashi I, Ishimura E, Kato Y, *et al*. Geriatric Nutritional Risk Index, a simplified nutritional screening index, is a significant predictor of mortality in chronic dialysis patients. *Nephrol Dial Transplant* 2010;25:3361-5.
22) Chan M, Kelly J, Batterham M, Tapsell L. Malnutrition (subjective global assessment) scores and serum albumin levels, but not body mass index values, at initiation of dialysis are independent predictors of mortality: a 10-year clinical cohort study. *J Ren Nutr* 2012;22:547-57.
23) Beberashvili I, Azar A, Sinuani I, *et al*. Comparison analysis of nutritional scores for serial monitoring of nutritional status in hemodialysis patients. *Clin J Am Soc Nephrol* 2013;8:443-51.
24) Abd-El-Gawad WM, Abou-Hashem RM, El Maraghy MO, Amin GE. The validity of Geriatric Nutrition Risk Index: simple tool for prediction of nutritional-related complication of hospitalized elderly patients. Comparison with Mini Nutritional Assessment. *Clin Nutr* 2014;33:1108-16.
25) Nakai S, Watanabe Y, Masakane I, *et al*. Overview of regular dialysis treatment in Japan (as of 31 December 2011). *Ther Apher Dial* 2013;17:567-611.
26) Takahashi H, Ito Y, Ishii H, *et al*. Geriatric nutritional risk index accurately predicts cardiovascular mortality in incident hemodialysis patients. *J Cardiol* 2014;64:32-6.
27) Yamada K, Furuya R, Takita T, *et al*. Simplified nutritional screening tools for patients on maintenance hemodialysis. *Am J Clin Nutr* 2008;87:106-13.
28) Park JH, Kim SB, Shin HS, Jung YS, Rim H. Geriatric nutritional risk index may be a significant predictor of mortality in Korean hemodialysis patients: a single center study. *Ther Apher Dial* 2012;16:121-6.
29) Goodkin DA, Bragg-Gresham JL, Koenig KG, *et al*. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003;14:3270-7.
30) Kestenbaum B, Sampson JN, Rudser KD, *et al*. Serum Phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005;16:520-8.
31) Fiedler R, Dorligjav O, Seibert E, Ulrich C, Markau S, Girndt M. Vitamin D deficiency, mortality, and hospitalization in hemodialysis patients with or without protein-energy wasting. *Nephron Clin Pract* 2011;119:c220-6.
32) Jamal SA, Vandermeer B, Raggi P, *et al*. Effect of calcium-based versus non-calcium based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet* 2013;382:1268-77.
33) Panichi V, Cupisti A, Rosati A, *et al*. Geriatric nutritional risk index is a strong predictor of mortality in hemodialysis patients: data from the riscavid cohort. *J Nephrol* 2014;27:193-201.

34) The Japanese Society for Dialysis Therapy statistical survey committee. An overview of regular dialysis treatment in Japan (As of December 31, 2014) *Nippon Touseki Kaishi* 2016;49:1-34. (Eng Abstr)

35) Tsai MT, Hu FH, Lien TJ, Chen PJ, Huang TP, Tarng DC. Interaction between geriatric nutritional risk index and decoy receptor 3 predicts mortality in chronic hemodialysis patients. *Am J Nephrol* 2014;40:191-9.

36) Han HQ, Zhou X, Mitch WE, Goldberg AL. Myostatin/activin pathway antagonism: molecular basis and therapeutic potential. *Int J Biochem Cell Biol* 2013;45:2333-47.

37) Schaible UE, Kaufmann SH. Malnutrition and infection: complex mechanisms and global impacts. *PLoS Med* 2007;4:e115.doi:10.1371/journal.pmed.0040115.

38) Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. *Int J Tuberc Lung Dis* 2004;8:286-98.

39) Schneider SM, Veyres P, Pivot X, *et al*. Malnutrition is an independent factor associated with nosocomial infections. *Br J Nutr* 2004;92:105-11.

40) Takele Y, Adem E, Getahun M, *et al*. Malnutrition in healthy individuals results in increased mixed cytokine profiles, altered neutrophil subsets and function. *PLoS One* 2016;11:e0157919. doi:10.1371/journal.pone.0157919.

41) Kalantar-Zadeh K, Kleiner M, Dunne E, Lee GH, Luft FC. A modified quantitative subjective global assessment of nutrition for dialysis patients. *Nephrol Dial Transplant* 1999;14:1732-8.

42) de Mutsert R, Grootendorst DC, Boeschoten EW, *et al*. Subjective global assessment of nutritional status is strongly associated with mortality in chronic dialysis patients. *Am J Clin Nutr* 2009;89:787-93.

43) Rambod M, Bross R, Zitterkoph J, *et al*. Association of Malnutrition-Inflammation Score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. *Am J Kidney Dis* 2009;53:298-309.