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Original article

Geriatric nutritional risk index accurately predicts cardiovascular mortality in incident hemodialysis patients

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ABSTRACT

Background: Cardiovascular disease (CVD) is a leading cause of death in end-stage renal disease (ESRD) patients. Protein-energy wasting (PEW) or malnutrition is common in this population, and is associated with increasing risk of mortality. The geriatric nutritional risk index (GNRI) has been developed as a tool to assess the nutritional risk, and is associated with mortality not only in elderly patients but also in ESRD patients. However, whether the GNRI could predict the mortality due to CVD remains unclear in this population. We investigated the prognostic value of GNRI at initiation of hemodialysis (HD) therapy for CVD mortality in a large cohort of ESRD patients.

Methods: Serum albumin, body weight, and height for calculating GNRI were measured in 1568 ESRD patients. Thereafter, the patients were divided into quartiles according to GNRI levels [quartile 1 (Q1): <84.9; Q2: 85.0–91.1; Q3: 91.2–97.2; and Q4: >97.3], and were followed up for up to 10 years.

Results: GNRI levels independently correlated with serum C-reactive-protein levels ($\beta = -0.126$, $p < 0.0001$). Rates of freedom from CVD mortality for 10 years were 57.9%, 73.3%, 80.8%, and 89.2% in Q1, Q2, Q3, and Q4, respectively ($p < 0.0001$). The GNRI was an independent predictor of CVD mortality (hazard ratio 3.42, 95% confidence interval 2.05–5.70, $p < 0.0001$ for Q1 vs. Q4). C-index was also greater in an established CVD risk model with GNRI (0.749) compared to that with albumin (0.730), body mass index (0.732), and alone (0.710). Similar results were observed for all-cause mortality.

Conclusion: GNRI at initiation of HD therapy could predict CVD mortality with incremental value of the predictability compared to serum albumin and body mass index in ESRD patients.

Introduction

End-stage renal disease (ESRD) patients have been widely recognized as a highest risk group for cardiovascular disease (CVD) [1,2]. Mortality risk due to CVD in ESRD patients is 10–30 times higher than that in the general population [1], making it a leading cause of death [3]. Thus, risk stratification for CVD mortality is clinically important for improving survival in such subjects.

Protein-energy wasting (PEW) is a state of decreased body protein mass and energy fuels [4] that is reportedly prevalent in ESRD patients [5,6]. PEW also can result not only from a simply inadequate diet, but can also be induced by various factors, especially inflammatory processes [4,7,8]. To assess PEW, serum albumin levels and body mass index (BMI) have been commonly used, and hypoalbuminemia [9–12] and reduced BMI [12–14] are reported to be strongly associated with increased risk of CVD morbidity and mortality in this population. Geriatric nutritional risk index (GNRI), which is calculated from both serum albumin and the components of BMI (height and body weight), was developed as a simplified screening tool to assess the nutritional risk [15], and has

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been associated with mortality not only in elderly patients in various health-care settings [16,17], but also in ESRD patients [18]. Recently, the GNRI was also reported to predict CVD events including CVD mortality in patients with heart failure [19,20]. However, whether the GNRI could predict mortality due to CVD, which is a leading cause of death, remains unclear in ESRD patients. We retrospectively investigated the predictive value of the GNRI for CVD mortality in a large cohort of ESRD patients who had just began hemodialysis (HD) therapy.

Methods

Study population

This study consisted of 1568 consecutive ESRD patients who electively began HD therapy in Nagoya Kyoritsu Hospital (Nagoya, Japan), Kaikokai Central Clinic (Nagoya, Japan), Meiko Kyoritsu Clinic (Nagoya, Japan), Ama Kyoritsu Clinic (Yatomi, Japan) and Anjou Kyoritsu Clinic (Anjou, Japan) between January 1998 and December 2009. Patients with acute renal failure, active inflammatory diseases, or malignancies at the initiation of HD therapy were excluded. Diabetes was defined as a history or presence of diabetes and/or a fasting plasma glucose concentration >126 mg/dl, glycosylated hemoglobin (HbA1c) concentration >6.5%, or the presence of diabetic retinopathy. Hypertension was defined as systolic blood pressure >160 mmHg and/or diastolic blood pressure >90 mmHg before dialysis session, or a history of anti-hypertensive treatment. Smoking habit was defined either as a current habit or as having discontinued cigarette use within 6 months prior to starting HD.

Geriatric nutritional risk index

All clinical data were obtained from individual medical records. Hematocrit, albumin, creatinine, lipid profiles, and C-reactive protein (CRP) were measured using blood samples, which were taken before HD sessions after 2-day interval (Monday or Tuesday) at 2 weeks after initiation of HD therapy. Body mass index (BMI) was calculated from height and body weight data at 2 weeks after initiation of HD, because the state of overhydration in most patients was controlled by this period [12]. Body weight was defined as 'dry weight', measured after each HD session.

The GNRI was calculated from individually obtained serum albumin levels and body weight 2 weeks after initiation of HD therapy, as follows [21]:

$$\mathrm{GNRI} = [14.89 \times \mathrm{albumin}\ \ (\mathrm{g/dl}) + \left[41.7 \times \left(\frac{\mathrm{body\ \ weight}}{\mathrm{ideal\ \ body\ \ weight}}\right)\right]$$

Body weight/ideal body weight was set to 1 when the patient's body weight exceeded the ideal body weight. The ideal body weight in the present study was defined as the value calculated from the height and a BMI of 22 [21], instead of the value calculated using the Lorentz formula in the original GNRI equation. Thereafter, the patients were divided into quartiles according to GNRI levels as quartile 1 (Q1): GNRI < 84.9, Q2: 85.0–91.1, Q3: 91.2–97.2, and Q4: GNRI > 97.3.

Follow-up study

Follow-up was concluded in June 2010. The time point of entry was defined as the initiation of HD therapy. Primary endpoint was CVD death, including those due to heart failure, myocardial infarction, arrhythmia, sudden death, stroke, and other CVD-related deaths. Secondary endpoint was all-cause death. Data for endpoints were obtained from hospital charts and through telephone interviews with patients, conducted by trained reviewers who were blinded to the protocol. In the present study, cases of unwitnessed death were counted as cardiac death.

The study protocol and chart reviews used were approved by the institutional ethics committees of all hospitals, and were conducted in accordance with the Declaration of Helsinki.

Statistical analyses

Statistical analyses were performed using SAS 6.10 software (SAS Institute, Cary, NC, USA). Variables with a normal distribution are expressed as mean values ± SD, and asymmetrically distributed data are given as median and interquartile range (IQR). Differences between the groups were evaluated by one-way analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables and by chi-square test for categorical variables. To determine the factors that correlated with GNRI, multivariate regression analysis was used. Differences in event-free survival among the groups were examined with the Kaplan–Meier method and compared using a log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for each factor by a Cox proportional hazards analysis. All baseline variables with $p < 0.05$ by univariate analysis were entered into a multivariate model to determine independent predictors for the endpoint.

To assess whether the accuracy of predicting mortality would improve after the addition of GNRI into a baseline model with established risk factors, including gender, age, diabetes, hypertension, dyslipidemia, smoking status, hematocrit, creatinine, calcium, phosphate, and CRP, we calculated C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The C-index is defined as the area under receiver-operating characteristic (ROC) curves between individual predictive probabilities for mortality and incidence of mortality, and was compared for the baseline model and enriched models containing the established risk factors plus BMI, serum albumin, and GNRI, respectively [22]. The NRI indicates relatively how many patients improve their predicted probabilities for mortality, while IDI represents the average improvement in predicted probabilities for mortality after adding variables into the baseline model [23]. Differences were considered statistically significant at $p < 0.05$.

Results

Clinical characteristics

Characteristics of the study population are shown in Table 1. These characteristics were similar to those of average HD patients in Japan [2]. On multivariate regression analysis, GNRI levels were independently correlated with male gender ($\beta = -0.060$, $p = 0.045$), age ($\beta = -0.155$, $p < 0.0001$), hematocrit ($\beta = 0.128$, $p < 0.0001$), creatinine ($\beta = 0.287$, $p < 0.0001$), and serum CRP ($\beta = -0.126$, $p < 0.0001$) (Table 2).

Prognostic value of geriatric nutritional risk index

During the follow-up period (mean 63 ± 42 months), 93 patients moved out to other institutes and 19 underwent renal transplantation, and they were censored at the point of moving out. A total of 363 patients (23.1%) died, including 180 deaths (11.5%) due to CVD (56 heart failure, 26 myocardial infarction, 15 fatal arrhythmia, 23 sudden death, 48 stroke, 4 aortic aneurysm, and 8 others). At the 10-year follow-up, Kaplan–Meier survival rates for CVD mortality were 57.9%, 73.3%, 80.8%, and 89.2% in Q1, Q2, Q3, and Q4, respectively ($p < 0.0001$) (Fig. 1). After adjustment for other confounders, GNRI was an independent predictor of CVD mortality [hazard ratio (HR) 1.72, 95% confidence interval (CI) 1.00–2.96, $p = 0.049$ for Q3 vs. Q4, HR 1.99, 95% CI 1.16–3.41, $p = 0.012$ for Q2 vs. Q4, and HR

Table 1
Baseline patient characteristics.

	All patients (n = 1568)	Quartile 1 <84.9 (n = 396)	Quartile 2 ≥84.9 to <91.1 (n = 388)	Quartile 3 ≥91.1 to <97.3 (n = 392)	Quartile 4 ≥97.3 (n = 392)	p-Value
Male (%)	66.9	68.2	62.0	68.6	68.9	0.12
Age (years)	64 ± 13	68 ± 12	65 ± 12	63 ± 12	58 ± 14	<0.0001
Diabetes (%)	52.0	52.0	56.2	52.3	47.7	0.14
Hypertension (%)	74.1	72.0	72.4	76.3	75.8	0.41
Smoking (%)	21.8	21.2	19.4	19.9	26.5	0.12
Body mass index (kg/m^2)	21.1 ± 3.4	18.6 ± 2.5	20.1 ± 2.1	21.4 ± 2.2	24.5 ± 3.4	<0.0001
Hematocrit (%)	29.7 ± 4.3	28.5 ± 4.3	29.6 ± 4.3	30.2 ± 4.1	30.6 ± 4.4	<0.0001
Albumin (g/dl)	3.4 ± 0.5	2.9 ± 0.4	3.4 ± 0.3	3.6 ± 0.3	3.8 ± 0.4	<0.0001
Creatinine (mg/dl)	7.8 ± 3.2	6.6 ± 2.1	7.2 ± 2.2	8.2 ± 2.5	9.3 ± 4.6	<0.0001
Total cholesterol (mg/dl)	164 ± 38	163 ± 40	165 ± 37	165 ± 38	162 ± 35	0.68
LDL-cholesterol (mg/dl)	91 ± 32	90 ± 33	92 ± 32	92 ± 31	90 ± 29	0.67
HDL-cholesterol (mg/dl)	44 ± 14	45 ± 14	46 ± 15	43 ± 12	43 ± 16	0.32
C-reactive protein (mg/l)	1.8 (0.8–5.7)	2.6 (1.0–8.6)	1.7 (0.7–5.8)	1.5 (0.7–4.5)	1.4 (0.6–3.7)	<0.0001

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2
Relationship between geriatric nutritional risk index and baseline variables by multivariate regression analysis.

	β	p-Value
Male	−0.060	0.045
Age	−0.155	<0.0001
Diabetes	0.022	0.46
Hypertension	0.038	0.18
Smoking	−0.035	0.26
Hematocrit	0.128	<0.0001
Creatinine	0.287	<0.0001
Total cholesterol	−0.023	0.82
LDL-cholesterol	0.007	0.80
HDL-cholesterol	−0.061	0.24
Log CRP	−0.126	<0.0001

LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein.

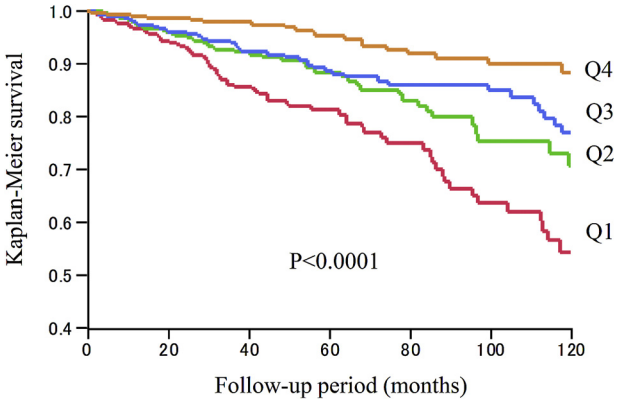

Fig. 1. Kaplan–Meier survival curves for cardiovascular mortality among quartiles (Q) according to geriatric nutritional risk index levels at initiation of hemodialysis therapy.

3.42, 95% CI 2.05–5.70, p < 0.0001 for Q1 vs. Q4] (Table 3). Regarding model discrimination, C-index for CVD mortality was greater in the baseline model plus BMI (0.732, p = 0.036) and plus albumin (0.730, p = 0.0036) as compared to the baseline model alone (0.710), and was much greater in the model plus GNRI (0.749, p = 0.0003), with a statistically significant difference between the model plus BMI (p = 0.034) and plus albumin (p = 0.012) (Table 4). The NRI and IDI for CVD mortality also significantly increased after adding BMI (0.303 and 0.0098), albumin (0.223 and 0.0046), and GNRI (0.385 and 0.0148) into the baseline model. Furthermore, both the NRI and IDI significantly increased in the model plus GNRI, even compared to the model plus BMI (p = 0.046 and p = 0.027) and plus albumin (p = 0.0002 and p < 0.0001), respectively (Table 4). Similar results were observed for all-cause mortality (Supplementary Fig. 1, Tables 1 and 2) as well as the previous report [18].

Discussion

In the present study, we clearly demonstrated that GNRI, originally reported as a tool to assess nutritional status in the elderly,

Table 3
Prognostic value of geriatric nutritional risk index for cardiovascular mortality on Cox analysis.

	Non-adjusted		Adjusted	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value
GNRI (vs. Q4)		<0.0001*		<0.0001*
Q3	1.91 (1.09–3.34)	0.0046	1.72 (1.00–2.96)	0.049
Q2	2.55 (1.47–4.42)	0.0002	1.99 (1.16–3.41)	0.012
Q1	4.41 (2.63–7.39)	<0.0001	3.42 (2.05–5.70)	<0.0001
Male	1.38 (0.99–1.91)	0.054		
Age	1.05 (1.04–1.07)	<0.0001	1.04 (1.03–1.06)	<0.0001
Diabetes	1.76 (1.30–2.38)	0.0002	2.08 (1.48–2.92)	<0.0001
Hypertension	1.41 (1.01–1.95)	0.042	1.24 (0.85–1.80)	0.27
Smoking	1.30 (0.52–1.84)	0.15		
Hematocrit	0.98 (0.95–1.01)	0.17		
Creatinine	0.82 (0.77–0.88)	<0.0001	0.95 (0.87–1.03)	0.18
Total cholesterol	0.99 (0.99–1.00)	0.36		
LDL-cholesterol	1.00 (1.00–1.01)	0.38		
HDL-cholesterol	0.97 (0.92–1.01)	0.14		
C-reactive protein	1.22 (1.13–1.34)	<0.0001	1.09 (1.02–1.16)	0.0075

HR, hazard ratio; CI, confidence interval; Q, quartile; GNRI, geriatric nutritional risk index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
* p for trend. Multivariate model includes all variables at baseline with p < 0.05 by univariate analysis.

Table 4
Discrimination of each predictive model for cardiovascular mortality using C-index, net reclassification improvement and integrated discrimination improvement.

Predictive models	C-index	*p*-Value	NRI	*p*-Value	IDI	*p*-Value
Established risk factors	0.710 (0.670–0.750)	Reference	Reference		Reference	
+BMI	0.732 (0.694–0.769)	0.036	0.303	0.0002	0.0098	<0.0001
+Albumin	0.730 (0.692–0.769)	0.0036	0.223	0.0047	0.0046	0.010
+GNRI	0.749 (0.714–0.785)	0.0003	0.385	<0.0001	0.0148	<0.0001
+GNRI vs. +BMI	0.018 (0.001–0.034)[a]	0.034	0.144	0.046	0.0050	0.027
+ GNRI vs. +albumin	0.019 (0.004–0.034)[a]	0.012	0.309	0.0002	0.0102	<0.0001

Established risk factors included gender, age, diabetes, hypertension, smoking status, hematocrit, creatinine, cholesterols, and C-reactive protein levels.
NRI, net reclassification improvement; IDI, integrated discrimination improvement; BMI, body mass index; GNRI, geriatric nutritional risk index.
[a] Differences between two models.

Table 5
Prevalence of nutritional risk according to geriatric nutritional risk index levels in various populations.

	n	Age	Nutritional risk (%)		
			Severe/moderate <92	Low ≥92 to <98	None ≥98
Rehabilitation-care [15]	2474	83 ± 2	43.6	29.4	27.0
Home-care [16]	241	80 ± 8	20.7	36.1	43.2
Long-term care [17]	358	85 ± 8	37.4	34.9	27.3
ESRD patients at HD therapy initiation (this study)	1568	64 ± 13	53.4	23.3	23.3

ESRD, end-stage renal disease; HD, hemodialysis.

could not only predict CVD mortality, but also improve the predictive accuracy of mortality compared to other predictive models including albumin or BMI, with increasing C-statistics, NRI and IDI, in ESRD patients at the initiation of HD therapy.

Since Stenvinkel et al. reported that malnutrition is closely linked with elevated inflammatory cytokines and carotid intima-media atherosclerosis in ESRD patients [8], so-called malnutrition, inflammation, and atherosclerosis (MIA) syndrome was considered to be an important issue for clinical management in this population. For example, Joki et al. [11] found the association of hypoalbuminemia with advanced coronary artery disease at initiation of HD therapy, and Kaysen et al. [24] also demonstrated that inflammatory responses, such as elevated CRP and interleukin-6, reduce albumin synthesis resulting in hypoalbuminemia. Recently, we reported that both hypoalbuminemia and elevated CRP levels could predict major adverse cardiovascular events after endovascular therapy in chronic HD patients with peripheral artery disease [25]. The PEW is the newly integrated terminology developed from the concept of the MIA syndrome, defined by the expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) [4]. In this regard, our present study confirmed that declining GNRI is closely associated with elevated CRP, thus, the GNRI is suggested to be a useful diagnostic tool for the PEW as a predictor of CVD mortality in ESRD patients.

Furthermore, an important finding of the present study is that the CVD mortality-predicting model using GNRI is superior to that using albumin and BMI alone, with increasing C-statistics, NRI, and IDI as indices of improvement of the predictive ability. Hypoalbuminemia and low BMI are defined as important criteria to diagnose the PEW from the expert panel of the ISRNM [4], because both of them have strong and consistent outcome-predictability of mortality [9–14], even though the former is often associated with severe disease states, and the latter is influenced by fat mass or the state of overhydration [4]. However, the PEW is a complex syndrome consisting of multiple factors. In this regard, because the GNRI is an integrated expression, consisting of albumin and components of BMI (height and body weight), and is regarded as a multiple model itself, it might be practically superior when screening the nutritional risk in this population.

Various studies using different criteria have reported that the prevalence of PEW was approximately 18–75% in ESRD patients [4–7]. In the present study, crudely based on the classification of nutritional risk according to GNRI by Bouillanne et al. [15], at least half of ESRD patients suffer from severe/moderate nutritional risk (GNRI < 92) at the start of HD therapy. Furthermore, this prevalence rate was much higher than in various elderly populations (20.7–43.6%) [15–17], even though ESRD patients were younger than these elderly people (Table 5). This high prevalence should be borne in mind to identify the patients at CVD mortality risk. Whether the nutritional risk improves with HD therapy or not also needs to be investigated.

There are several limitations to the present study. First, all the study subjects were Japanese, who reportedly have a better prognosis as compared to patients in the USA and Europe; further, subclinical atherosclerosis, coronary disease mortality and risk of coronary calcification are lower in Japanese people [26]. Second, we only analyzed the predictive value of GNRI at the start of HD therapy, and did not analyze the impact on mortality of improvements in this value after starting HD therapy.

In conclusion, GNRI values at the start of HD therapy could not only predict CVD mortality, but also improve the accuracy of CVD mortality prediction in ESRD patients. This simple screening tool, using common variables that can be easily obtained in daily clinical practice, might be clinically useful for the assessment of PEW as a CVD mortality risk in this population.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2013.10.018.

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