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Original article

Association of geriatric nutritional risk index with infection-related mortality in patients undergoing hemodialysis: The Q-Cohort Study

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SUMMARY

Background & aims: The geriatric nutritional risk index (GNRI) is a simple but useful nutritional marker for all-cause mortality and cardiovascular mortality in patients undergoing hemodialysis (HD). However, whether the GNRI can predict infection-related mortality in patients undergoing HD remains unclear, and there is insufficient evidence regarding whether the GNRI improves the predictive value for risk assessment beyond the existing conventional nutritional markers. Here, we investigated the association between the GNRI and infection-related mortality in patients undergoing HD and evaluated the predictive value of GNRI.

Methods: A prospective cohort study was performed on a total of 3436 Japanese HD patients aged ≥18 years. Patients were divided into four groups by quartiles of GNRI: (Quartile 1 [Q1], >100.2; Q2, 95.9–100.2; Q3, 90.8–95.8; Q4, <90.8). We estimated the relationship between GNRI and all-cause mortality and infection-related mortality using a Cox proportional hazards model. To assess the additional predictive value of the GNRI in risk assessment, we compared the c-statistic, net reclassification improvement, and integrated discrimination improvement among serum albumin, serum creatinine, and the GNRI.

Results: During follow-up period (median, 4.0 years), a total of 564 patients died; 120 of these patients died of infectious disease. All-cause mortality and infection-related mortality increased linearly with lower GNRI levels. After adjusting for confounding risk factors, the GNRI was an independent predictor of infection-related mortality as well as all-cause mortality (hazard ratio [HR], 5.89; 95% confidence interval [CI], 2.85–13.8; $P < 0.001$ for Q4 vs. Q1, HR, 2.62; 95% CI, 1.23–6.24; $P = 0.01$ for Q3 vs. Q1). Additionally, when the GNRI was incorporated into a model with potential risk factors instead of serum albumin, the c-statistic increased significantly (0.811 vs. 0.821, $P = 0.03$), and the net reclassification improvement and integrated discrimination improvement was 0.26 ($P = 0.005$) and 0.005 ($P = 0.01$). This association was more apparent in the older patients (0.739 vs. 0.760, $P = 0.02$) than in the younger patients (0.916 vs. 0.912, $P = 0.35$). Similar results were observed between serum creatinine and the GNRI, but the difference did not reach statistical significance.

Conclusions: Lower GNRI levels are an independent risk factor for infection-related mortality in patients undergoing HD. Moreover, addition of the GNRI to models with standard risk factors significantly improves the predictive ability of infection-related mortality, especially in older patients.

1. Introduction

Infectious disease is often a life-threatening condition and the second leading cause of death in patients undergoing hemodialysis

Abbreviations: GNRI, geriatric nutritional risk index; BMI, body mass index; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

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(HD) [1,2]. Malnutrition is highly prevalent in patients undergoing HD and closely associated with an increased risk of infection-related mortality [3,4], all-cause mortality [5,6], and cardiovascular mortality [4,7]. Therefore, nutritional management is of great importance for patients undergoing HD. Some currently available nutritional screening tools include serum albumin [5], body mass index (BMI) [8,9], serum creatinine, [10] subjective global assessment [11], and the malnutrition-inflammation score (MIS) [10]. The MIS is generally considered to be a better nutritional indicator than other tools for patients undergoing HD, but it is a complicated procedure requiring a subjective assessment.

The geriatric nutritional risk index (GNRI), which is calculated from both serum albumin and BMI, is a relatively new assessment tool for evaluating older patients [12–15]. Previous research has revealed that the GNRI is a simple and accurate risk assessment tool for identifying patients who are at nutritional risk among those undergoing HD, and it is therefore expected to serve as an alternative method to the MIS [16]. However, the clinical utility of the GNRI in the prediction of infection-related mortality among patients undergoing HD remains unclear, and there is insufficient evidence regarding whether the GNRI improves the predictive value for risk assessment beyond the existing conventional nutritional markers.

The aim of the present study was to investigate the relationship between the GNRI and all-cause and infection-related mortality in a prospective cohort of Japanese patients undergoing HD. In addition, we evaluated whether the GNRI can provide alternative clinical value for predicting the incidence of unfavorable outcomes using the net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

2. Materials and methods

2.1. Study design and population

The Q-Cohort Study is a multicenter, prospective, longitudinal, observational cohort study conducted in Japanese patients undergoing HD, and a detailed description of the survey in this study has been previously published [17,18]. Briefly, a total of 3598 patients aged ≥18 years who received HD treatment at 39 dialysis facilities in Fukuoka and Saga prefectures on Kyushu Island, Japan, in December 2006 and December 2007 consented to participate in the present study. After excluding 97 patients whose clinical outcome information was lacking and 65 patients whose demographic data were lacking, the final cohort comprised 3436 patients. The patients were followed up prospectively from each patient's date of study registration to December 2010. This study was approved from the Kyushu University Institutional Review Board for Clinical Research (Approval Number 20-31). All participants provided written informed consent for the use of their clinical data for research. The study was registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN ID: 000000556). This study was performed in adherence with the guidelines of the Declaration of Helsinki.

2.2. Definition of GNRI and poor nutritional status

The GNRI was calculated by modifying the nutritional risk index for elderly patients as previously reported [16]:

$$\mathrm{GNRI} = [14.89 \times \text{serum albumin (g/dL)}] + [41.7 \times \text{body weight/ideal body weight}]$$

Body weight/ideal body weight was set to 1 when the body weight exceeded the ideal body weight. Instead of using the Lorentz formula in the original GNRI equation [12], the ideal body weight in the present study was defined as the value calculated from the height and a BMI of 22 kg/m^2, as previously described [16].

Next, the patients were divided into quartiles according to the GNRI: quartile 1 [Q1], >100.2; Q2, 95.9–100.2; Q3, 90.8–95.8; Q4, <90.8.

A poor nutritional status was defined as a GNRI of <90, as previously reported [18].

2.3. Clinical parameters

We collected the following demographic information and baseline clinical data from the medical records: age, sex, time on dialysis therapy, hemoglobin, serum albumin, serum creatinine, serum calcium, serum phosphate, serum total cholesterol, serum C-reactive protein (CRP), serum ferritin, BMI, Kt/V, and normalized protein catabolic rate. The physicians at each dialysis facility collected the information regarding the current use of antihypertensive agents and history of diabetes or cardiovascular disease in each patient. Body height and weight were measured with the patient in light clothing without shoes, and the BMI (kg/m^2) was then calculated. Blood samples were collected from a vascular access before starting dialysis. Serum CRP and serum ferritin were transformed logarithmically. The ESAs used in this study were epoetin α, epoetin β, and darbepoetin α. The ESA dosage for darbepoetin α administration was obtained by multiplying the dosage (μg) of darbepoetin α by 200. If serum albumin was <4.0 g/dL, the corrected serum Ca concentration was calculated using the following formula: corrected Ca (mg/dL) = observed total Ca (mg/dL) + (4.0 − serum albumin concentration [g/dL]). Adequacy of dialysis were measured by single-pool Kt/V by the Daugirdas method [20].

2.4. Outcomes

The outcomes were the all-cause mortality rate and infection-related mortality rate. The local physicians at each dialysis facility checked the health status of the studied patients annually, and checked by mail or telephone for any patients who moved to other dialysis facilities where no collaborator of this study existed. These outcomes were determined on the basis of the patients' medical records.

2.5. Statistical analyses

The baseline data of the study patients according to GNRI levels are presented as mean (standard deviation [SD]), median (interquartile range), or percentage for categorical measures. Trends in continuous and categorical values across GNRI levels were examined by the Jonckheere–Terpstra and Cochran–Armitage tests, respectively. Kaplan–Meier curves and a log-rank test were used to evaluate the survival probabilities for all-cause mortality and infection-related mortality according to GNRI levels. The Cox proportional hazards model was also used to estimate the age-, sex-, and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality and infection-related mortality according to GNRI levels. We also performed subgroup analyses to estimate the impact of a poor nutritional status on mortality according to subgroups of risk factors. To investigate whether the accuracy of predicting these outcomes improve after addition of the GNRI into a basic model with potential risk factors (age, sex, predialysis systolic blood pressure, dialysis duration, history of cardiovascular disease, diabetes, hemoglobin, cardiothoracic ratio, serum calcium, serum phosphate, serum total cholesterol, log-CRP, log-ferritin, Kt/V, and normalized protein catabolic rate), we calculated the c-statistic using a receiver operating characteristic

curve, NRI, and IDI. Moreover, the differences in predictive values among a basic model with the GNRI, a basic model with serum albumin and a basic model with serum creatinine were further examined. All statistical analyses were performed using the SAS software package version 9.3 (SAS Institute, Cary, NC, USA) or R software package (version 3.2.3; R Development Core Team). Two-sided P values of <0.05 were considered statistically significant in all analyses.

3. Results

3.1. Study participants and baseline characteristics

The clinical characteristics of the patients according to the GNRI quartile are provided in Table 1. The patients with lower GNRI levels had a greater mean age, higher proportion of women, and shorter dialysis duration. The mean systolic and diastolic blood pressures, hemoglobin, serum albumin, serum creatinine, serum phosphate, serum cholesterol, BMI, and normalized protein catabolic rate decreased with lower GNRI levels. On the other hand, the mean cardiothoracic ratio, serum calcium, and Kt/V; the median serum CRP; and the frequency of a history of cardiovascular disease were significantly higher in patients with lower GNRI levels.

3.2. Effects of GNRI on clinical outcomes

During the 4-year follow-up period, 564 patients (16.4%) died of all causes and 120 patients (3.5%) died of infection. The survival rates according to GNRI levels are shown in Fig. 1. The 4-year event-free survival probabilities for all-cause mortality decreased with lower GNRI levels (log rank = 250.4, $P < 0.001$), and infection-related mortality decreased with lower GNRI levels (log rank = 102.0, $P < 0.001$).

As shown in Table 2, all-cause mortality and infection-related mortality decreased linearly with lower GNRI levels. The age- and sex-adjusted HR of all-cause mortality and infection-related mortality increased significantly with lower GNRI levels. Compared with Q1, all-cause mortality was significantly higher in Q2 (age- and sex-adjusted HR, 1.21; 95% CI, 0.89–1.66; $P = 0.23$), Q3 (age- and sex-adjusted HR, 1.63; 95% CI, 1.22–2.19; $P < 0.001$), and Q4 (age- and sex-adjusted HR, 3.23; 95% CI, 2.46–4.29; $P < 0.001$) and infection-related mortality was significantly higher in Q2 (age- and sex-adjusted HR, 1.89; 95% CI, 0.84–4.65; $P = 0.13$), Q3 (age- and sex-adjusted HR, 2.72; 95% CI, 1.29–6.43; $P = 0.008$) and Q4 (age- and sex-adjusted HR, 7.13; 95% CI, 3.56–16.3; $P < 0.001$). As shown, the associations of the GNRI with all-cause mortality and infection-related mortality were significant even after adjustment for confounding factors. In the subgroup analysis, the association between a poor nutritional status and infection-related mortality was stronger in patients with a longer than shorter dialysis duration (P for interaction = 0.04) (Fig. 2).

3.3. Prognostic value of GNRI

To evaluate the prognostic value of the GNRI, we compared the discriminatory abilities among a basic model, a basic model with serum albumin, a basic model with serum creatinine and a basic model with the GNRI (Table 3, Fig. 3). The c-statistic for infection-related mortality was significantly greater in the basic model with the GNRI than in the basic model (0.802 vs. 0.821, $P = 0.02$); it was also significantly greater in the basic model with the GNRI than in the basic model with serum albumin (0.811 vs. 0.821, $P = 0.03$). Furthermore, both the NRI and IDI significantly increased in the basic model with the GNRI than in the basic model with serum albumin (0.26, $P = 0.005$; 0.005, $P = 0.01$). Next, we compared the predictive performance between the GNRI and serum creatinine. The c-statistic, NRI, and IDI for infection-related mortality showed slightly better predictive performance in the basic model with the GNRI than in the basic model with serum creatinine (Table 3). However, the difference did not reach statistical significance

Table 1
Baseline characteristics according to geriatric nutritional risk index levels.

	GNRI levels				
	Q1 (>100.2) ($n = 870$)	Q2 (95.9–100.2) ($n = 838$)	Q3 (90.8–95.8) ($n = 902$)	Q4 (<90.8) ($n = 826$)	P for trend
Age, years	58.6 (12.5)	62.5 (11.7)	64.9 (12.4)	68.9 (12.3)	<0.001
Women, %	28.3	38.9	46.1	50.5	<0.001
Dialysis duration, years	5.9 (2.7–10.6)	5.8 (2.2–11.9)	5.3 (2.0–12.3)	4.9 (1.7–11.5)	0.08
Predialysis systolic blood pressure, mmHg	156.1 (22.3)	154.1 (22.3)	152.4 (23.2)	149.3 (25.3)	<0.001
Predialysis diastolic blood pressure, mmHg	78.5 (11.8)	77.2 (12.2)	75.9 (12.4)	73.9 (13.5)	<0.001
Antihypertensive agent use, %	62.4	61.7	64.6	61.6	0.92
RAS-blocker use, %	40.6	41.8	46.7	44.2	0.03
VDRA use, %	75.4	72.9	71.5	60.1	<0.001
Dosage of ESA, U/week	4000 (3000–4500)	3000 (2188–4500)	4500 (3000–6000)	4500 (3000–8000)	0.004
Iron use, %	38.6	35.2	38.7	30.0	0.003
Diabetes, %	29.5	29.7	29.5	26.9	0.25
History of cardiovascular disease, %	29.4	32.5	31.9	41.3	<0.001
Cardiothoracic ratio, %	49.6 (5.1)	50.0 (5.4)	50.6 (5.3)	51.9 (5.9)	<0.001
Hemoglobin, g/dL	10.8 (1)	10.6 (1.1)	10.5 (1.1)	10.2 (1.3)	<0.001
Serum albumin, g/dL	4.2 (0.3)	3.9 (0.2)	3.7 (0.2)	3.3 (0.4)	<0.001
Serum creatinine, mg/dL	11.4 (2.6)	10.7 (2.6)	10.0 (2.5)	8.7 (2.3)	<0.001
Serum calcium,[a] mg/dL	9.3 (0.7)	9.3 (0.7)	9.4 (0.7)	9.6 (0.9)	<0.001
Serum phosphate, mg/dL	5.2 (1.1)	5.0 (1.1)	4.9 (1.2)	4.6 (1.3)	<0.001
Serum total cholesterol, mg/dL	159.9 (35.1)	157.8 (36.2)	155.3 (33.8)	149.8 (40.7)	<0.001
Serum C-reactive protein, mg/dL	0.11 (0.05–0.22)	0.13 (0.05–0.25)	0.13 (0.07–0.32)	0.20 (0.08–0.67)	<0.001
Serum ferritin, ng/mL	178 (83–337)	161 (60–264)	163 (64–281)	164 (73–317)	0.86
Body mass index, kg/m^2	22.7 (2.7)	22.0 (2.9)	21.0 (2.9)	18.8 (2.5)	<0.001
Kt/V, single pool	1.51 (0.24)	1.58 (0.26)	1.61 (0.29)	1.61 (0.30)	<0.001
nPCR, g/kg/day	0.97 (0.17)	0.98 (0.19)	0.97 (0.20)	0.92 (0.20)	<0.001

The data are presented as mean (standard deviation), median (interquartile range), or percentage for categorical measures.
Abbreviations: VDRA, vitamin D receptor activators; ESA, erythropoiesis-stimulating agent; nPCR, normalized protein catabolic rate.
[a] Corrected by serum albumin.

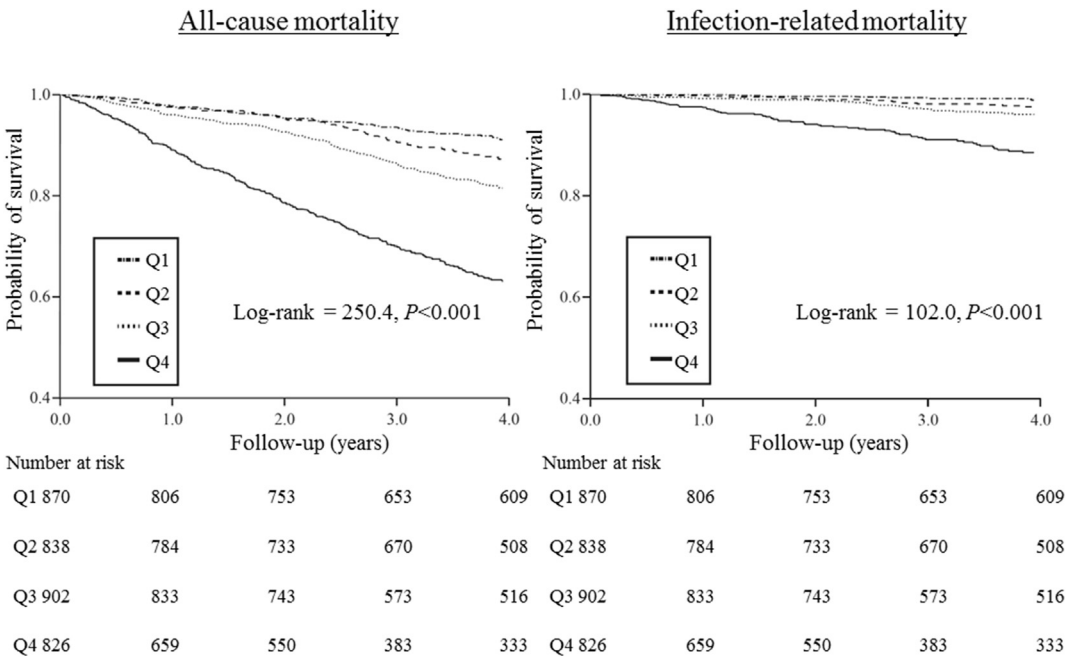

Fig. 1. Survival rates for all-cause mortality and infection-related mortality according to geriatric nutritional risk index levels during the 4-year follow-up period.

Table 2
Associations between geriatric nutritional risk index levels and risks of all-cause mortality and infection-related mortality.

	No. of events/patients	Age- and sex-adjusted			Multivariable-adjusted[a]		
		HR (95% CI)	*P*-value	*P* for trend	HR (95% CI)	*P*-value	*P* for trend
All-cause mortality							
GNRI (per 1 decrement)		1.06 (1.06–1.08)	<0.001		1.07 (1.06–1.08)	<0.001	
Q1	69/870	1.00 (reference)		<0.001	1.00 (reference)		<0.001
Q2	93/838	1.21 (0.89–1.66)	0.23		1.17 (0.86–1.61)	0.32	
Q3	143/902	1.63 (1.22–2.19)	<0.001		1.58 (1.18–2.14)	0.002	
Q4	259/826	3.23 (2.46–4.29)	<0.001		2.66 (2.00–3.59)	<0.001	
Infection-related mortality							
GNRI (per 1 decrement)		1.10 (1.08–1.12)	<0.001		1.09 (1.05–1.11)	<0.001	
Q1	8/870	1.00 (reference)		<0.001	1.00 (reference)		<0.001
Q2	17/838	1.89 (0.84–4.65)	0.13		1.74 (0.77–4.29)	0.19	
Q3	28/902	2.72 (1.29–6.43)	0.008		2.62 (1.23–6.24)	0.01	
Q4	67/826	7.13 (3.56–16.3)	<0.001		5.89 (2.85–13.8)	<0.001	

Abbreviations: HR, hazard ratio; CI, confidence interval; GRNI, geriatric nutritional risk index.
[a] Adjusted for age, sex, predialysis systolic blood pressure, dialysis duration, diabetes, history of cardiovascular disease, hemoglobin, cardiothoracic ratio, serum calcium, serum phosphate, serum total cholesterol, log-serum C-reactive protein, log-serum ferritin, Kt/V, and normalized protein catabolic rate.

between these two models, suggesting that the predictive performance of the GNRI is almost equal to that of serum creatinine. Similar results were observed for all-cause mortality, and the predictive performance improved more steeply for infection-related mortality than for all-cause mortality.

3.4. Stratified analysis

Finally, we performed a stratified analysis to estimate whether the predictive performance differed between the younger and older patients (Table 4, Fig. 4). Interestingly, the association between the GNRI and infection-related mortality became clearer in the older patients, but the association became weaker in the younger patients. In the older patients, the c-statistic for infection-related mortality was significantly greater in the basic model with the GNRI than in the basic model with serum albumin (0.760 vs. 0.739, $P = 0.02$), and both the NRI and IDI significantly increased (0.35, $P < 0.001$; 0.006, $P = 0.02$). In the younger patients, however, there was no significant difference between the basic model with the GNRI and the basic model with serum albumin (0.912 vs. 0.916, $P = 0.35$), and both the NRI and IDI were not significant (−0.32, $P = 0.13$; −0.003, $P = 0.75$). On the other hand, the difference didn't reach statistically significance between the basic model with serum creatinine and the basic model with the GNRI.

4. Discussion

The present study clearly demonstrates that the GNRI is useful for predicting both infection-related mortality and all-cause mortality in Japanese patients undergoing HD. Importantly, our results show that the GNRI can serve as an alternative to serum albumin and serum creatinine, which are standard nutritional markers, in terms of clinical parameters that predict the incidence of unfavorable outcomes, especially in older patients. We believe that our findings highlight the clinical utility of the GNRI to predict the risk of infection-related mortality in patients undergoing HD.

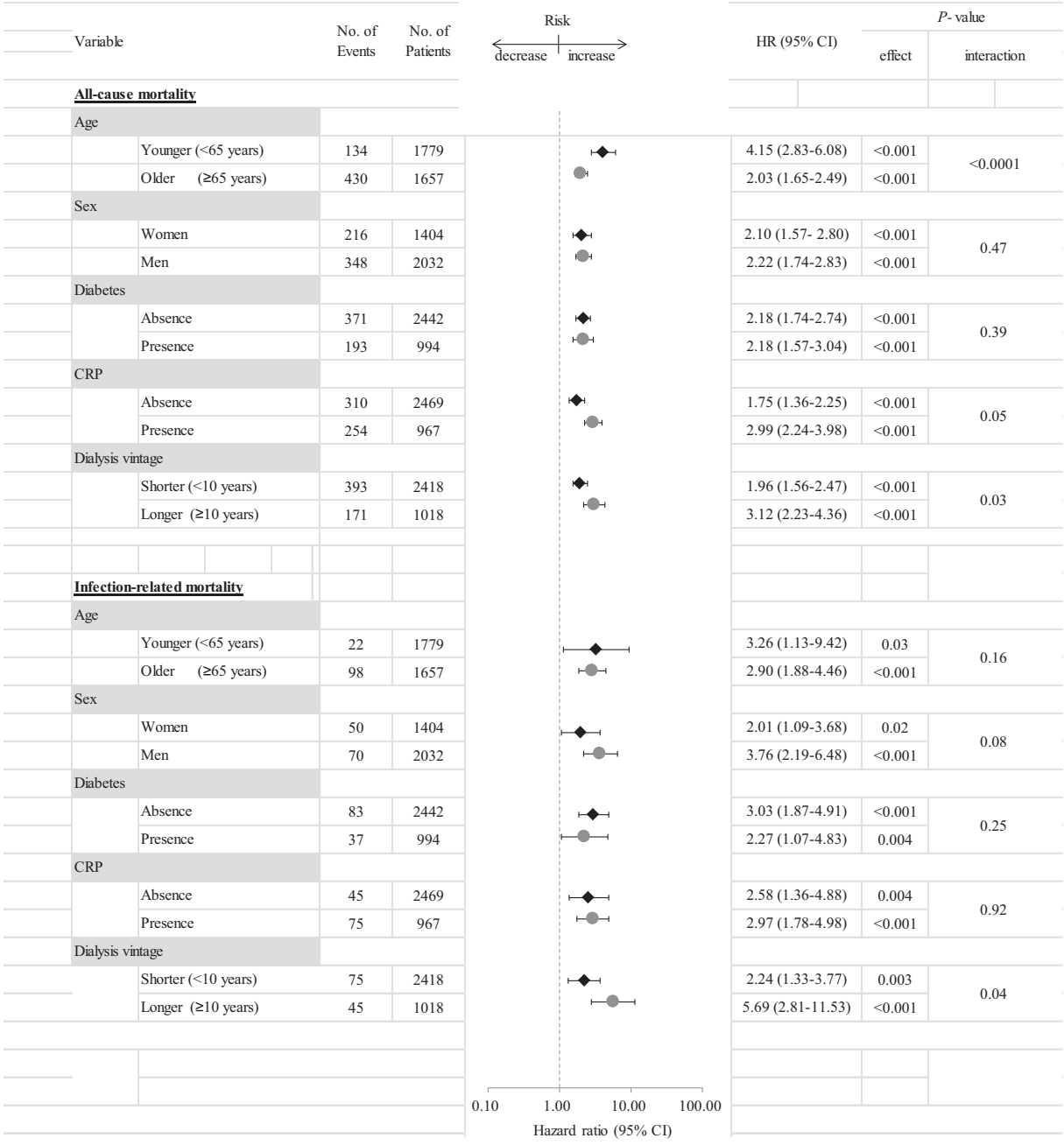

Fig. 2. Multivariable-adjusted hazard ratios of poor nutritional status for all-cause mortality and infection-related mortality according to subgroups of baseline characteristics. For the multivariable-adjusted model, adjustments were made for age, sex, predialysis systolic blood pressure, dialysis duration, diabetes, history of cardiovascular disease, hemoglobin, cardiothoracic ratio, serum calcium, serum phosphate, serum total cholesterol, log-serum C-reactive protein, log-serum ferritin, Kt/V, and normalized protein catabolic rate.

Table 3
Predictive value of each model for all-cause mortality and infection-related mortality using c-statistic, net reclassification improvement, and integrated discrimination improvement.

Predictive models	C-statistic	*P*-value	NRI	*P*-value	IDI	*P*-value
All-cause mortality						
Basic model	0.787 (0.767–0.806)	Reference	Reference		Reference	
Basic model + albumin	0.794 (0.774–0.813)	0.04	0.22	<0.001	0.01	<0.001
Basic model + creatinine	0.798 (0.776–0.816)	0.003	0.31	<0.001	0.02	<0.001
Basic model + GNRI	0.798 (0.778–0.816)	0.005	0.25	<0.001	0.02	<0.001
+GNRI vs. +albumin[a]	0.004 (0.000–0.007)	0.05	0.15	<0.001	0.006	<0.001
+GNRI vs. +creatinine[a]	0.000 (−0.008 to 0.009)	0.96	0.01	0.80	0.001	0.84
Infection-related mortality						
Basic model	0.802 (0.760–0.835)	Reference	Reference		Reference	
Basic model + albumin	0.811 (0.773–0.844)	0.08	0.28	0.002	0.004	0.06
Basic model + creatinine	0.817 (0.779–0.850)	0.05	0.31	<0.001	0.02	<0.001
Basic model + GNRI	0.821 (0.783–0.853)	0.02	0.26	0.005	0.01	0.006
+GNRI vs. +albumin[a]	0.010 (0.008–0.019)	0.03	0.26	0.005	0.005	0.01
+GNRI vs. +creatinine[a]	0.004 (−0.016 to 0.024)	0.72	0.01	0.92	0.003	0.53

Basic model included age, sex, predialysis systolic blood pressure, dialysis duration, diabetes, history of cardiovascular disease, hemoglobin, cardiothoracic ratio, serum calcium, serum phosphate, serum total cholesterol, log-serum C-reactive protein, log-serum ferritin, Kt/V, and normalized protein catabolic rate.
Abbreviations: NRI, net reclassification improvement; IDI, integrated discrimination improvement; GNRI, geriatric nutritional risk index.
[a] Difference between two models.

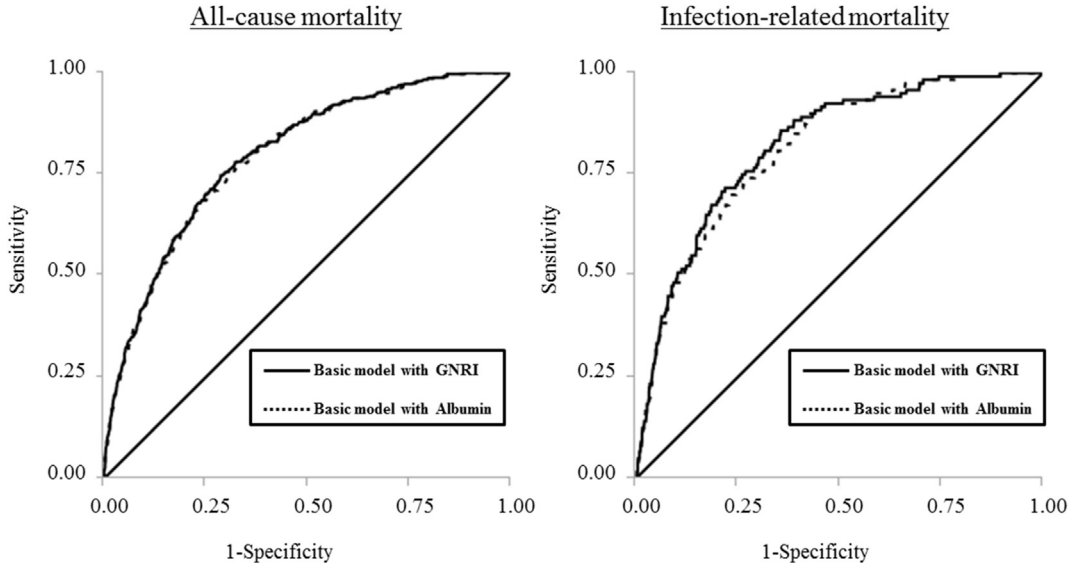

Fig. 3. Comparison of the accuracy of the risk assessment for all-cause mortality and infection-related mortality between the basic model with serum albumin and that with the geriatric nutritional risk index. The basic model included age, sex, predialysis systolic blood pressure, dialysis duration, diabetes, history of cardiovascular disease, hemoglobin, cardiothoracic ratio, serum calcium, serum phosphate, serum total cholesterol, log-serum C-reactive protein, log-serum ferritin, Kt/V, and normalized protein catabolic rate.

It has been well established that malnutrition is associated with all-cause mortality [5,6], cardiovascular mortality [4,7], and infection-related mortality [3,4] in patients undergoing HD. The GNRI is widely accepted as a screening method with which to clinically detect malnutrition in patients undergoing HD. To the best of our knowledge, the present study is the first investigation to reveal that the GNRI is independently associated with an increased risk of infection-related mortality and highlight its clinical usefulness in the risk assessment of infection-related death in the clinical treatment of patients undergoing HD.

Another important finding in our study is that addition of the GNRI to a model involving potential risk factors is significantly superior to addition of serum albumin to the same model in terms of predicting infection-related death, especially in older patients. The GNRI has been reported as a predictive nutritional marker in patients undergoing HD [16,19,20], but there is insufficient evidence regarding whether the predictive value of the GNRI is more effective than those of the existing conventional nutritional markers in risk assessment. Recently, it was reported that studies of novel risk markers should evaluate whether incorporation of a new marker improves the risk assessment provided by established risk markers [22]. Although the predictive value of serum albumin for risk assessment of infection-related death is well established [3,4], our findings clearly show that the GNRI is superior to serum albumin for predicting infection-related death using the c-statistic, NRI, and IDI.

The strong association between malnutrition and clinical outcomes may be explained by the complicated synergistic effects of malnutrition, inflammation, and atherosclerosis (MIA syndrome). Our subgroup analysis showed that the association between the GNRI and infection-related mortality was stronger among patients with a long than short dialysis duration. Chronic inflammation and atherosclerosis are reportedly more common among patients with a long dialysis duration [23], which might provide supporting

Table 4
Stratified analysis of predictive value of each model by separating age for all-cause mortality and infection-related mortality using c-statistic, net reclassification improvement, and integrated discrimination improvement.

Predictive models	C-statistic	*P*-value	NRI	*P*-value	IDI	*P*-value
All-cause mortality						
Younger patients						
Basic model	0.766 (0.724–0.804)	Reference	Reference		Reference	
Basic model + albumin	0.797 (0.758–0.832)	0.03	0.34	<0.001	0.03	<0.001
Basic model + creatinine	0.778 (0.734–0.812)	0.34	0.37	<0.001	0.02	<0.001
Basic model + GNRI	0.794 (0.754–0.828)	0.04	0.36	<0.001	0.02	<0.001
+GNRI vs. +albumin[a]	−0.004 (−0.006 to 0.014)	0.44	−0.18	0.04	−0.006	0.12
+GNRI vs. +creatinine[a]	0.013 (−0.007 to 0.043)	0.17	0.08	0.39	0.005	0.39
Older patients						
Basic model	0.724 (0.696–0.750)	Reference	Reference		Reference	
Basic model + albumin	0.729 (0.701–0.755)	0.21	0.14	0.01	0.008	<0.001
Basic model + creatinine	0.738 (0.710–0.764)	0.02	0.29	<0.001	0.02	<0.001
Basic model + GNRI	0.735 (0.707–0.761)	0.04	0.24	<0.001	0.02	<0.001
+GNRI vs. +albumin[a]	0.006 (0.001–0.012)	0.03	0.22	<0.001	0.009	<0.001
+GNRI vs. +creatinine[a]	−0.002 (−0.015 to 0.011)	0.73	−0.03	0.61	−0.003	0.50
Infection-related mortality						
Younger patients						
Basic model	0.911 (0.818–0.959)	Reference	Reference		Reference	
Basic model + albumin	0.916 (0.825–0.962)	0.62	0.67	<0.001	0.03	0.07
Basic model + creatinine	0.918 (0.844–0.958)	0.46	0.21	0.32	0.02	0.19
Basic model + GNRI	0.912 (0.820–0.960)	0.86	0.13	0.54	0.02	0.08
+GNRI vs. +albumin[a]	−0.004 (−0.012 to 0.004)	0.35	−0.32	0.13	−0.003	0.75
+GNRI vs. +creatinine[a]	−0.005 (−0.024 to 0.013)	0.58	−0.36	0.07	0.02	0.11
Older patients						
Basic model	0.730 (0.679–0.775)	Reference	Reference		Reference	
Basic model + albumin	0.739 (0.689–0.783)	0.27	0.16	0.12	0.004	0.14
Basic model + creatinine	0.756 (0.708–0.798)	0.07	0.37	<0.001	0.02	0.001
Basic model + GNRI	0.760 (0.714–0.801)	0.03	0.32	0.002	0.009	0.02
+GNRI vs. +albumin[a]	0.022 (0.004–0.039)	0.02	0.35	<0.001	0.006	0.02
+GNRI vs. +creatinine[a]	0.005 (−0.03 to 0.04)	0.79	0.004	0.97	0.003	0.71

Basic model included age, sex, predialysis systolic blood pressure, dialysis duration, diabetes, history of cardiovascular disease, hemoglobin, cardiothoracic ratio, serum calcium, serum phosphate, serum total cholesterol, log-serum C-reactive protein, log-serum ferritin, Kt/V, and normalized protein catabolic rate.
Abbreviations: NRI, net reclassification improvement; IDI, integrated discrimination improvement; GNRI, geriatric nutritional risk index.
[a] Difference between two models.

evidence that the unfavorable impact of malnutrition synergistically increases in patients with a long dialysis duration.

The subgroup analysis revealed a difference in the predictive value of the GNRI between the younger and older patients. This discrepancy may derive from the fact that the BMI, which is a factor constituting the GNRI, impacts mortality differently between younger and older patients [24]. In older patients, a high serum albumin and high BMI are linearly associated with a reduced risk of infection-related death; thus, the predictive value of the GNRI tended to be synergistically higher than that of serum albumin in this study. In younger patients, however, the association between the BMI and mortality is "U-shaped," so the predictive value of the GNRI may decrease; there is no evidence of a difference in the predictive value between the GNRI and serum albumin. Therefore, clinicians should note that the clinical usefulness of the GNRI may differ among patients.

Some previous studies compared the predictive value of the GNRI and serum albumin for clinical outcomes, including all-cause mortality. In a study of a Japanese cohort, the prognostic value of the GNRI for all-cause mortality and cardiovascular-related mortality was superior to that of serum albumin [21]. In contrast, a study of an Israeli cohort showed that the performance of the GNRI is not better and is even slightly worse than that of serum albumin [25]. We speculate that the discrepancies between the results of these studies may have been caused by differences in the distribution of the baseline characteristics of the studied patients, especially the BMI and dialysis duration. In the above-mentioned Israeli cohort, which comprised relatively "healthy" people, the mean BMI was 27.5 kg/m^2 and the median dialysis duration was 23.0 months [25]. In our study, which comprised relatively "sicker" people, the mean BMI was 21.1 kg/m^2 and the median dialysis duration was 66.5 months. The difference in race may have partly contributed to this discrepancy. The clinical utility of the GNRI may differ according to various patient-related factors, and further studies are needed.

Several limitations in this study should be noted. First, a single measurement of the GNRI at baseline was used for the analyses. This single measurement may have failed to capture the intra-individual variability over time and resulted in misclassification of the patients into different GNRI level categories. Moreover, the predictive value of the GNRI changes over time, giving more detailed information about causative effects. However, our data do not reflect the changes in the GNRI over time. Further studies are needed to determine the impact of the changes in the GNRI over time on all-cause mortality and infection-related mortality. Second, all patients were Japanese. The mortality of Japanese patients undergoing HD is reportedly better than that of patients in the US and Europe undergoing HD [26]. Furthermore, the causes of death differ among these races. In our cohort, the percentage of infection-related death was relatively lower than that in the US and Europe. The relationship between the malnutrition status and mortality in patients undergoing HD differs according to race [27]. Therefore, clinicians should apply the results of the present study to other ethnic groups with care, and note that the generalizability of our findings may be limited. Third, we could not obtain information about the use of a catheter as vascular access. A higher risk of mortality has been reported for patients undergoing HD with a catheter than with a native arteriovenous fistula [28]. Additionally, a national survey in Japan revealed that catheters were associated with a 3.5-fold higher 1-year survival risk than arteriovenous fistulas [29]. Patients with malnutrition tend to be introduced to the use of catheters in clinical practice. Thus, information regarding

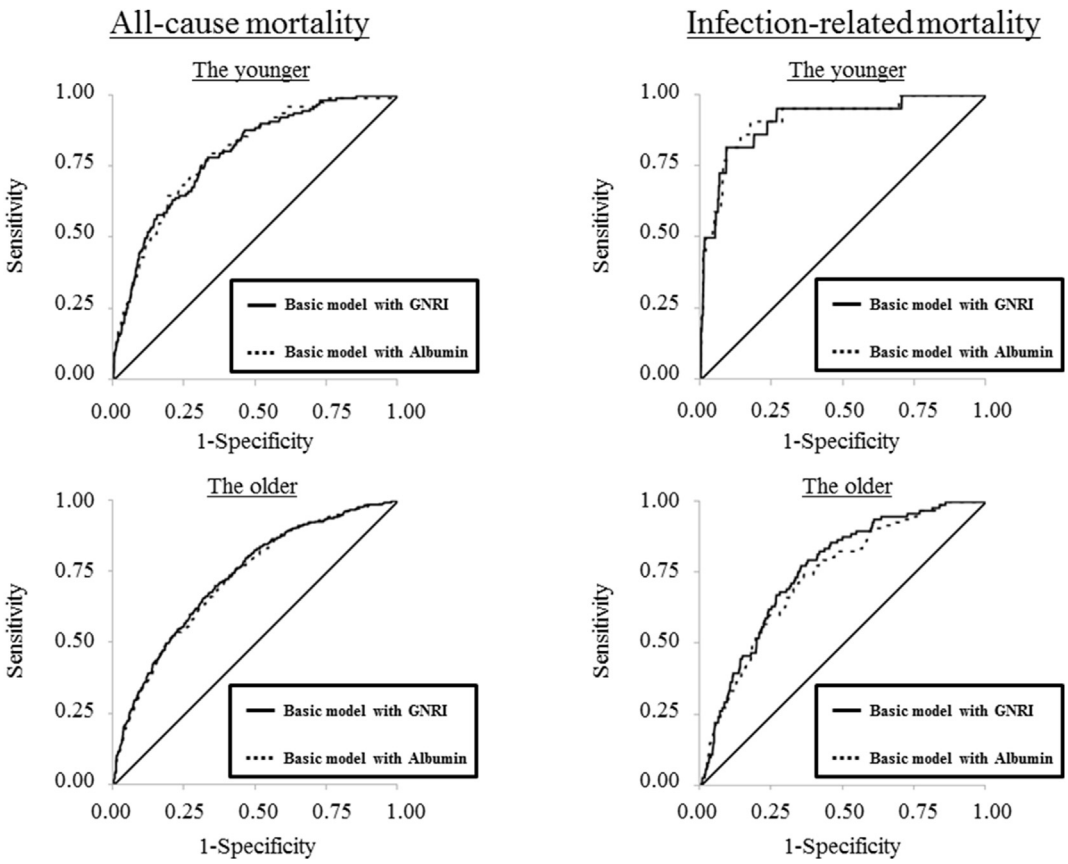

Fig. 4. Stratified analysis to estimate whether the predicting value for all-cause mortality and infection-related mortality differed between young and old patients.

catheter use is of great importance, especially with respect to infection-related mortality. Further research is required to examine the relationship between malnutrition and infection-related mortality considering the influence of catheter use.

In conclusion, a lower GNRI is strongly associated with infection-related mortality in patients undergoing HD. Our findings suggest that the predictive value of the GNRI for predicting infection-related mortality is superior to that of serum albumin, especially in older patients.

Statement of authorship

The authors declare to have no conflict of interest. Contributions are as follows: study design: YM, ST, TN; data acquisition: MT, ST, TN, HH, KT; data interpretation: YM, ST, KT; statistical analysis: YM, ST; supervision: TN, KM, HH, TK. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KT takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors provided critical reviews of the draft and approved the final version.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Masakane I, Nakai S, Ogata S, Kimata N, Hanafusa N, Hamano T, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2013). Ther Apher Dial 2015;19:540–74.
[2] Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, et al. US renal data system 2015 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2016;67(Suppl. 1):A7–8.
[3] Mehrotra R, Duong U, Jiwakanon S, Kovesdy CP, Moran J, Kopple JD, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. Am J Kidney Dis 2011;58:418–28.
[4] Lukowsky LR, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K. Patterns and predictors of early mortality in incident hemodialysis patients: new insights. Am J Nephrol 2012;35:548–58.
[5] Iseki K, Kawazoe N, Fukiyama K. Serum albumin is a strong predictor of death in chronic dialysis patients. Kidney Int 1993;44:115–9.
[6] Chertow GM, Goldstein-Fuchs DJ, Lazarus JM, Kaysen GA. Prealbumin, mortality, and cause-specific hospitalization in hemodialysis patients. Kidney Int 2005;68:2794–800.
[7] Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn Jr H, Kopple JD, et al. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. Nephrol Dial Transplant 2005;20:1880–8.
[8] Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. Am J Clin Nutr 2005;81:543–54.
[9] Chazot C, Gassia JP, Di Benedetto A, Cesare S, Ponce P, Marcelli D. Is there any survival advantage of obesity in Southern European haemodialysis patients? Nephrol Dial Transplant 2009;24:2871–6.
[10] 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.
[11] Enia G, Sicuso C, Alati G, Zoccali C. Subjective global assessment of nutrition in dialysis patients. Nephrol Dial Transplant 1993;8:1094–8.
[12] Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005;82:777–83.
[13] 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.
[14] Cereda E, Klersy C, Pedrolli C, Klersy C, Cassani E, Caccialanza R, et al. The Geriatric Nutritional Risk Index predicts hospital length of stay and in-hospital weight loss in elderly patients. Clin Nutr 2015;34:74–8.
[15] Gärtnet S, Kraft M, Kruger J, Schmekel S, Gärtner S, Krüger J, et al. Geriatric nutritional risk index correlates with length of hospital stay and inflammatory markers in older inpatients. Clin Nutr 2017;36:1048–53.
[16] Yamada K, Furuya R, Takita T, Maruyama Y, Yamaguchi Y, Ohkawa S, et al. Simplified nutritional screening tools for patients on maintenance hemodialysis. Am J Clin Nutr 2008;87:106–13.
[17] Taniguchi M, Yamada S, Tokumoto M, Tsuruya K, Hirakata H, Fujimi S, et al. Does cinacalcet improve the prognosis of dialysis patients? Ther Apher Dial 2009;13(Suppl. 1):S15–9.
[18] Eriguchi R, Taniguchi M, Ninomiya T, Hirakata H, Fujimi S, Tsuruya K, et al. Hyporesponsiveness to erythropoiesis-stimulating agent as a prognostic factor in Japanese hemodialysis patients: the Q-Cohort study. J Nephrol 2015;28:217–25.
[19] Kobayashi I, Ishimura E, Kato Y, Okuno S, Yamamoto T, Yamakawa T, 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.
[20] Daugirdas JT. The post: pre dialysis plasma urea nitrogen ratio to estimate K.t/V and NPCR: validation. Int J Artif Organs 1989;12:420–7.
[21] Takahashi H, Ito Y, Ishii H, Aoyama T, Kamoi D, Kasuga H, et al. Geriatric nutritional risk index accurately predicts cardiovascular mortality in incident hemodialysis patients. J Cardiol 2014;64:32–6.
[22] Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:2408–16.
[23] Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int 1999;55:1899–911.
[24] Hoogeveen EK, Halbesma N, Rothman KJ, de Mutsert R, Halbesma N, Dekker FWR, et al. Obesity and mortality risk among younger dialysis patients. Clin J Am Soc Nephrol 2012;7:280–8.
[25] Beberashvili I, Azar A, Sinuani I, Shapiro G, Feldman L, Sandbank J, et al. Geriatric nutritional risk index, muscle function, quality of life and clinical outcome in hemodialysis patients. Clin Nutr 2016;35:1522–9.
[26] Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, 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.
[27] Wong JS, Port FK, Hulbert-Shearon TE, Carroll CE, Wolfe RA, Agodoa LY, et al. Survival advantage in Asian American end-stage renal disease patients. Kidney Int 1999;55:2515–23.
[28] Pisoni RL, Arrington CJ, Albert JM, Ethier J, Kimata N, Krishnan M, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: an instrumental variable analysis. Am J Kidney Dis 2009;53:475–91.
[29] Kukita K, Ohira S, Amano I, Naito H, Azuma N, Ikeda K, et al. 2011 update Japanese society for dialysis therapy guidelines of vascular access construction and repair for chronic hemodialysis. Ther Apher Dial 2015;19(Suppl. 1):1–39.