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Geriatric Nutritional Risk Index as a Simple Predictor of Mortality in Maintenance Hemodialysis Patients: A Single Center Study

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Abstract

Background: Malnutrition is associated with higher risk of mortality in maintenance hemodialysis (MHD) patients. The geriatric nutritional risk index (GNRI) has been developed as a tool to assess the nutritional risk. Objectives: The purpose of the present study was to examine the significance of the GNRI as a mortality predictor in MHD patients. Methods: We retrospectively examined the GNRI of 259 MHD patients aged 59.2 ± 12.8 years, and followed up for 36 months. The patients were divided into two groups according to GNRI values of 91.0. Predictors for all-cause mortality were examined using Kaplan-Meier and Cox proportional-hazards analyses. Results: During the follow-up period of 36 months, a total of 76 patients died. Kaplan-Meier survival analysis showed that the subjects with a GNRI < 91 (n = 29) had a lower survival rate than those with a GNRI > 91 (n = 230) (Log-rank test, p < 0.0001). Multivariate Cox proportional-hazards analysis demonstrated that the GNRI was a significant predictor of adjusted all-cause mortality (hazard ratio 0.927; confidence interval 0.870 - 0.984, p = 0.013). Conclusion: The results of the present study demonstrate that the GNRI is a strong predictor of all-cause mortality in MHD patients.

Keywords

Hemodialysis, Malnutrition, Geriatric Nutritional Risk Index, Mortality

1. Introduction

Protein-energy wasting (PEW) is an important issue in hemodialysis (HD) patients, with a reported prevalence

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ranging from about 20% to 78% [1]. Nutritional risk factor is one of the strong predictors of mortality in HD patients [2] [3]. Thus, evaluation of nutritional status is essential clinical procedure for managing these patients.

Multiple mechanisms have been reported to explain the link between PEW and mortality in HD patients, including derangements in muscle, adipose tissue, gastrointestinal, hematopoietic and immune systems, abnormal activation of the inflammatory process [4]. A clinical assessment of nutritional status is mandatory in HD patients, but there is no single gold-standard method, easily performed in a reproducible manner and not affected by other confounding conditions. Therefore, it is necessary to screen patients for the presence of PEW with a variety of measures and to perform this investigation on a regular clinical practice [5].

The geriatric nutritional risk index (GNRI) is a very simple method based on body weight, height and serum albumin levels to assess nutritional status in various pathological conditions. Previous studies have investigated the reliability of GNRI in assessing malnutrition [6] and in predicting all-cause mortality in chronic HD patients [7] [8]. All the reported studies in uremic patients were performed, however, in Asian cohorts and data from European, or Caucasian, populations are lacking.

The purpose of the present study was to evaluate the GNRI as a nutritional tool for predicting mortality in a Japanese MHD population.

2. Methods

2.1. Study Subjects and Procedures

This was a retrospective cohort study conducted at a single center in Japan. The subjects were recruited from among patients who had been routinely treated through an arteriovenous fistula in the dialysis unit of the Shinjuku Ishikawa Clinic for at least 6 months. The Institutional Review Board of the Shinjuku Ishikawa Clinic approved all study protocols, and they were performed in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects. Informed consent was obtained from all of the subjects.

HD patients with malignancy, active inflammation, liver cirrhosis, gastrointestinal bleeding, or severe illness were excluded from participation. The patients who were enrolled as subjects (n = 259) underwent stable regular HD with a bicarbonate dialysate. Their underlying diseases were chronic glomerulonephritis (n = 98), diabetic nephropathy (n = 76), hypertensive nephrosclerosis (n = 52), polycystic kidney disease (n = 18), and chronic pyeonephritis (n = 9), or unknown origin (n = 6).

All patients were on thrice-weekly HD and no further selection was performed in patients. Blood pressure (BP) was measured with a mercury sphygmomanometer with the patient in the supine position after resting for 10 to 15 minutes, and mean values for the 1-month period preceding enrollment were used in the statistical analysis. Dry weight was targeted to achieve a normotensive edema-free state. Previous cardiovascular disease and smoking status were collected from medical records. Diabetes was defined as a history or presence of diabetes and/or a fasting plasma glucose concentration > 126 mg/dl or HbA1c concentration > 6.5% or prescription of glucose-lowering agents.

2.2. Laboratory and Nutritional Parameters

Blood sampling was performed before the mid-week dialysis session day after an overnight fast. Serum urea nitrogen, creatinine, calcium, phosphorous, albumin, total cholesterol, high-density lipoprotein (HDL)-cholesterol and C-reactive protein (CRP) levels and the hemoglobin concentration were measured with an autoanalyzer (Hitachi Co., Tokyo, Japan) by standard laboratory methods. Total calcium was corrected by the patient's albumin level. Intact parathyroid hormone (iPTH) was measured by an immunoradiometric assay (Nichol's Institute, San Juan Capistrano, CA, USA). The body mass index (BMI) was expressed in kg/m^2. Urea kinetics were assessed by measuring a blood-based dialysis parameter, Kt/V [9], and the mean value of the 3 measurements during each of the 3 months before the start of the study was used in the analysis. The normalized protein catabolism rate (nPCR) was used as an indirect indicator of protein intake and was obtained using the following formula as previously described [10].

The GNRI was calculated by modifying the Nutritional risk index for elderly patients, as reported by Yamada *et al.* [6] as follows: GNRI = [14.89 × albumin (g/dl)] + [41.7 × (body weight/ideal body weight)]. As body weight we considered the value at the end of the dialysis session, and it was used also for BMI calculation. Body

weight/ideal body weight was set to 1 when the patient's body weight exceeded the ideal body weight [6]. The ideal body weight in the present study was calculated using height and a BMI of 22, which is reportedly associated with the lowest morbidity rate in the Asian population [11].

2.3. Study Outcome

Data for endpoints were obtained from hospital charts. Primary endpoint of the study was all-cause mortality during the follow-up period from January 1, 2011, to December 31, 2014. The vital status of the subjects was assessed by searching the electronic dialysis records. Patients were censored if they were alive on December 31, 2014.

2.4. Statistical Analysis

Normally distributed, unpaired continuous values were expressed as means ± SD and compared by performing an analysis of variance. Nonparametric values were expressed as median values and compared by performing the Kruskal-Wallis test. Categorical values were expressed as percentages and compared by performing the Fisher's exact test. Logistic regression analysis was used in a model to determine how independent variables predicted the GNRI value. We considered some variables that possess P-value < 0.10 in univariate logistic regression analyses, gender, dialysis vintage, and presence of diabetes as independent variables for multivariate logistic regression analyses. The area under the receiver operating curve (ROC) analysis was performed to calculate the cut-off values of GNRI.

The survival analysis was based on the Kaplan-Meier curve with subjects censored for death. A log-rank test was used to compare the survival rates of two groups. A multivariate Cox proportional hazards model with adjustment for multivariate factors was used to evaluate mortality risk. Results were expressed as a hazard ratio (HR) with 95% confidence intervals (CIs). A P-value < 0.05 was considered to be statistically significant. All statistical analyses were performed by using the SAS version 9.2 software program (SAS Institute Inc., Cary, NC, USA) for Windows personal computers.

3. Results

The baseline characteristics of the study population are shown in **Table 1**. The mean age of the 259 subjects was 59.2 ± 12.8 years, and the mean dialysis vintage was 131.3.2 ± 92.0 years months. The prevalence of diabetes 68.0% in all subjects. The study population included 70 women and 189 men. To determine a possible cut-off value of GNRI for survival, the sensitivity and specificity were examined by ROC analysis. A GNRI value of 91 was shown to indicate the highest value for sensitivity and specificity (**Figure 1**). The AUC for GNRI from ROC analysis was 0.673 (95% CI, 0.545 - 0.781) and the positive likelihood for GNRI was 4.719.

The clinical characteristics of the 259 subjects according to GNRI are shown in **Table 2**. The mean GNRI value of the subjects with a GNRI < 91 was 87.6 ± 3.3, and that of the subjects with a GNRI > 91 was 101.8 ± 7.4. Subjects with a GNRI < 91 exhibited significantly older age, lower body weight and BMI, lower serum albumin and creatinine compared with those with a GNRI > 91. As shown in **Figure 2**, there was a significant correlation between age and GNRI ($r = -0.3515$, $P < 0.0001$).

During the follow-up period of 36 months, a total of 26 patients died. The Kaplan-Meier analysis revealed that subjects with a GNRI < 91 (n = 29) had a significant lower survival rate compared with that of those with a GNRI > 91 (n = 230) (P < 0.0001, **Figure 3**). Univariate Cox proportional hazards analysis for mortality showed that age (HR 1.079, 95% CI 1.042 - 1.119, P < 0.0001), serum levels of albumin (HR 0.185, 95% CI 0.065 - 0.580, P = 0.0043), creatinine (HR 0.720, 95% CI 0.612 - 0.846, P < 0.0001) and calcium (HR 1.979, 95% CI 1.091 - 3.577, P = 0.0245) were significant predictor of mortality (**Table 3**). Multivariate Cox proportional hazards analysis demonstrated that GNRI was a significant predictor of mortality (HR 0.927, 95% CI 0.870 - 0.984, P = 0.0130) (**Table 4**). In addition, age (HR 1.063, 95% CI 1.023 - 1.107, P = 0.0016), Kt/V (HR 0.058, 95% CI 0.005 - 0.682, P = 0.0233) and serum calcium levels (HR 1.819, 95% CI 1.090 - 3.004, P = 0.0226) were also significant predictors of mortality.

4. Discussion

We investigated the GNRI as a nutritional tool for predicting mortality in a Japanese MHD population. We used

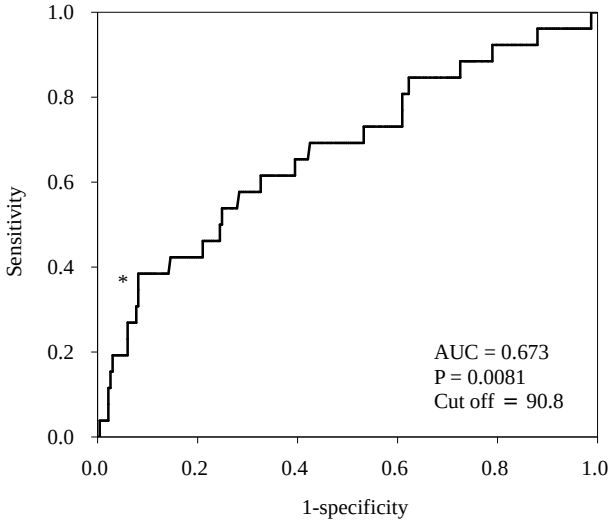

Figure 1. Receiver operating curve analysis to examine a cut-off value of GNRI for all-cause mortality.

Table 1. Baseline characteristics of the study population.

Variable	N = 259
Age (years)	59.2 ± 12.8
Men/women	189/70
Dialysis vintage (months)	131.3 ± 92.0
Diabetes (−/+)	176/83
Body weight (kg)	60.2 ± 13.5
Body mass index	22.3 ± 3.7
Albumin (g/dl)	3.9 ± 0.3
Blood urea nitrogen (mg/dl)	68.0 ± 14.9
Creatinine (mg/dl)	11.9 ± 2.4
C-reactive protein (mg/dl)	0.30 ± 0.44
GNRI	100.2 ± 8.4
Kt/V	1.45 ± 0.24
Systolic blood pressure (mmHg)	152.1 ± 22.6
Diastolic blood pressure (mmHg)	82.4 ± 14.6
Normalized PCR	0.93 ± 0.17
Hemoglobin (g/dl)	10.6 ± 0.9
Ferritin (ng/ml)	72.7 ± 75.6
Calcium (mg/dl)	9.0 ± 0.7
Phosphorus (mg/dl)	5.4 ± 1.2
Intact PTH (pg/ml)	76.2 ± 66.8
Uric acid	7.5 ± 1.1
Total cholesterol (mg/dl)	158.9 ± 31.8
HDL-cholesterol (mg/dl)	47.3 ± 14.9
Non-HDL-cholesterol (mg/dl)	111.6 ± 31.7

GNRI, geriatric nutritional risk index; PCR, protein catabolic rate; PTH, parathyroid hormone.

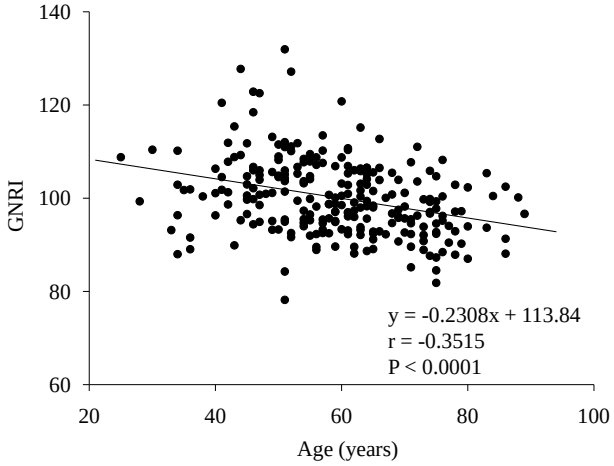

Figure 2. Relationship between age and GNRI.

Table 2. Clinical characteristics of 259 study subjects according to geriatric nutritional risk index (GNRI).

	GNRI < 91	GNRI ≥ 91	P
Age (years)	65.8 ± 13.4	58.4 ± 12.5	0.0029
Men/women	16/13	173/57	0.0274
Dialysis vintage (months)	147.0 ± 95.2	129.3 ± 91.6	0.3303
Diabetes (−/+)	21/8	155/75	0.6762
Body weight (kg)	46.9 ± 8.5	61.9 ± 13.0	<0.0001
Body mass index	18.2 ± 1.8	22.9 ± 3.6	<0.0001
Albumin (g/dl)	3.6 ± 0.3	3.9 ± 0.3	<.0001
Blood urea nitrogen (mg/dl)	64.6 ± 15.3	68.5 ± 14.8	0.1843
Creatinine (mg/dl)	9.8 ± 2.3	12.1 ± 2.3	<0.0001
C-reactive protein (mg/dl)	0.32 ± 0.44	0.30 ± 0.45	0.8314
GNRI	87.6 ± 3.3	101.8 ± 7.4	<0.0001
Kt/V	1.6 ± 0.3	1.4 ± 0.2	0.0194
Systolic blood pressure (mmHg)	147.0 ± 28.3	152.7 ± 21.7	0.2018
Diastolic blood pressure (mmHg)	78.7 ± 14.7	82.9 ± 14.6	0.1497
Normalized PCR	0.92 ± 0.18	0.93 ± 0.17	0.5988
Hemoglobin (g/dl)	10.4 ± 1.2	10.6 ± 0.8	0.1935
Ferritin (ng/ml)	95.1 ± 83.2	69.9 ± 74.3	0.0966
Calcium (mg/dl)	8.9 ± 0.9	9.0 ± 0.6	0.5181
Phosphorus (mg/dl)	5.1 ± 1.5	5.5 ± 1.2	0.1140
Intact PTH (pg/ml)	86.9 ± 75.2	74.8 ± 65.7	0.3590
Uric acid (mg/dl)	7.2 ± 1.0	7.5 ± 1.1	0.1583
Total cholesterol (mg/dl)	157.2 ± 34.7	159.2 ± 31.5	0.7522
HDL-cholesterol (mg/dl)	49.6 ± 17.1	47.1 ± 14.7	0.3849
Non-HDL-cholesterol (mg/dl)	107.6 ± 34.5	112.1 ± 31.4	0.4680

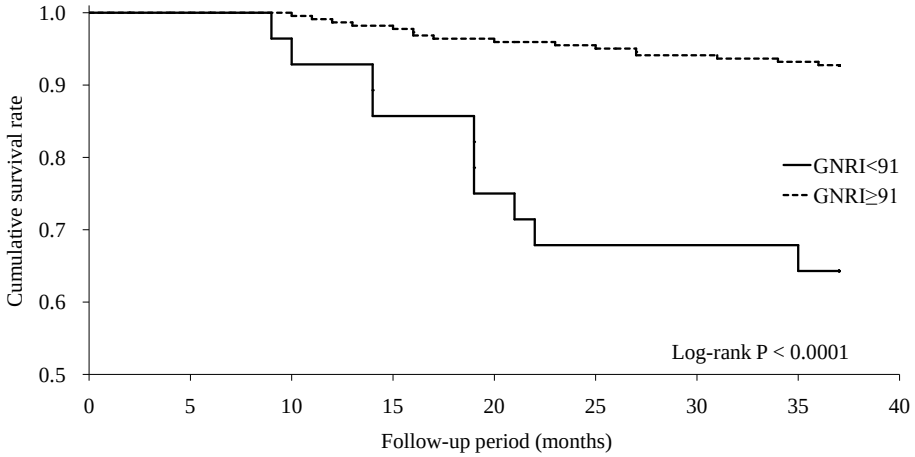

Figure 3. Kaplan-Meier survival curves for all-cause mortality according to geriatric nutritional risk index values.

Table 3. Univariate Cox proportional hazards analysis of mortality.

	HR	95%CI	P
Age (/years)	1.079	1.042 - 1.119	<0.0001
Men (vs. women)	1.534	0.625 - 4.595	0.3697
Dialysis vintage (/months)	1.003	0.999 - 1.006	0.1855
Diabetes (vs. No)	1.187	0.506 - 2.603	0.6806
Body weight (/kg)	0.978	0.945 - 1.008	0.1585
Body mass index (/1)	0.922	0.814 - 1.031	0.1629
Albumin (g/dl)	0.185	0.065 - 0.580	0.0043
Blood urea nitrogen (/mg/dl)	0.984	0.958 - 1.010	0.2339
Creatinine (/mg/dl)	0.720	0.612 - 0.846	<0.0001
C-reactive protein (/mg/dl)	1.416	0.655 - 2.378	0.3246
GNRI (/1)	0.928	0.880 - 0.977	0.0037
Kt/V (/1)	0.225	0.040 - 1.227	0.0854
Systolic blood pressure (/mmHg)	1.011	0.993 - 1.028	0.2326
Diastolic blood pressure (/mmHg)	0.991	0.965 - 1.017	0.4789
Normalized PCR (/1)	0.145	0.013 - 1.473	0.1035
Hemoglobin (/g/dl)	1.126	0.728 - 1.814	0.6100
Ferritin (/ng/ml)	1.003	0.999 - 1.006	0.1488
Calcium (/mg/dl)	1.979	1.091 - 3.577	0.0245
Phosphorus (/mg/dl)	0.765	0.539 - 1.063	0.1135
Intact PTH (/pg/ml)	1.004	0.999 - 1.008	0.1307
Uric acid (/mg/dl)	0.885	0.610 - 1.253	0.5009
Total cholesterol (/mg/dl)	0.997	0.985 - 1.009	0.6601
HDL-cholesterol (/mg/dl)	0.973	0.942 - 1.001	0.0571
Non-HDL-cholesterol (/mg/dl)	1.002	0.990 - 1.014	0.6795

Table 4. Multivariate Cox proportional hazards analysis of mortality.

	HR	95%CI	P
Age (/years)	1.063	1.023 - 1.107	0.0016
Men (vs. women)	1.228	0.425 - 4.186	0.7175
Dialysis vintage (/months)	1.003	0.998 - 1.007	0.2143
Diabetes (vs. No)	1.181	0.479 - 2.774	0.7081
GNRI (/1)	0.927	0.870 - 0.984	0.0130
Kt/V (/1)	0.058	0.005 - 0.682	0.0233
Calcium (/mg/dl)	1.819	1.090 - 3.004	0.0226

a cut-off value of GNRI of 91 to identify subjects with the highest risk according to ROC analysis. Subjects with a GNRI < 91 had a significant lower survival rate compared with that of those with a GNRI > 91. The results of the present study clearly showed that the GNRI value represents a strong predictor for all-cause mortality in Japanese HD patients.

Assessment of nutritional status is essential to prevent, diagnose and treat uremic malnutrition in uremic patients [5]. Biochemistry, anthropometry, body composition analysis, and interviews are variably used together with scores and indexes to obtain a comprehensive assessment of the nutritional status in uremic patients [5]. Many nutritional screening tools have been reported in the elderly, hospitalized patients, community patients, or patients with cancer or infections. Some of them may be safely and easily applied to MHD patients as well [12]. The Subjective Global Nutritional Assessment is a well validated clinical tool for screening malnutrition [2] and the malnutrition-inflammation score (MIS) is able to predict mortality and hospitalization in MHD patients [13]. However, both require subjective assessment and judgment by a skilled investigator.

In the present study, GNRI was one of the parameters as a predictor of all-cause mortality. The GNRI consists of few objective components, including serum albumin and BMI and represents a simple nutritional screening tool [6]. The GNRI score has been shown able to predict increased healthcare costs and higher risk of hospitalization in independent-living older adults; so it may be a low-cost tool that might be routinely used in population-based settings [14].

Yamada *et al.* [6] suggested that the most accurate GNRI cut-off value to identify malnourished HD patients was < 91.2, based on the MIS. Kobayashi *et al.* [7] reported that HD patients with GNRI < 90 exhibited a poorer nutritional status in terms of a lower BMI, serum levels of albumin and creatinine compared with GNRI > 90. Park *et al.* [8] confirmed in Korean HD patients that GNRI may be a significant predictor of mortality. More recently, Panichi *et al.* [15] have shown that values lower than 92 may represent a strong indicator of unfavorable outcome in Caucasian HD patients.

Takahashi *et al.* have recently indicated that GNRI at initiation of HD therapy could predict cardiovascular mortality with incremental value of the predictability compared to serum albumin and body mass index in HD patients [16]. Although the lowest GNRI quartile (<92) is strongly associated with malnutrition signs and with increased risk of all-cause mortality, no predictive value emerged regarding non-fatal cardiovascular events in HD patients. This apparent discrepancy may be explained considering that malnourished patients have lower survival and so less chance to develop a cardiovascular event, but when a cardiovascular event does occur, a malnourished patient has less chance to recover and more chance to die. Our data also clearly confirmed the reliability of GNRI as a tool for the diagnosis of malnutrition in a longitudinal observation [17].

Various mechanisms may explain the link between PEM and mortality in renal failure, including derangements in muscle, adipose tissue, gastrointestinal, hematopoietic and immune systems, and abnormal activation of the inflammatory process [18], as well as co-morbidities. Low albumin, cholesterol, and BMI are indicators of PEM, but they may not be causally responsible for the negative outcome. The reduction in muscle mass, namely sarcopenia, observed in PEM may be due to uremic toxins or procatabolic conditions (metabolic, hormonal, or neuropathic derangements, including inactivity).

There are some limitations in this study that should be considered. First, this study is based on a relatively small sample size of HD patients from a single center, limiting the ability of our findings to be generalized.

Second, this study used only a retrospective approach, without manipulation of confounding factors. We could not rule out a recalling bias. Randomized, controlled trials are needed to explore the role of GNRI value on mortality risk in chronic HD patients. Third, we did not show the prescription of renin-angiotensin system inhibitors, statins, and vitamin D. These agents may affect the mortality risk of GNRI. Fourth, other confounding factors may be neglected because the GNRI was calculated from the formula including serum albumin and BMI.

5. Conclusion

The results of the present study clearly show that GNRI values are significantly associated with all-cause mortality in Japanese HD patients. We conclude that the GNRI may be a very simple tool to use that may be considered as a reliable predictor for all-cause mortality risk in the HD population.

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Disclosure

The authors have no conflicts of interest to declare.

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