Journal of Cardiology 64 (2014) 32–36

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

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

Hiroshi Takahashi (BSc)[a,b], Yasuhiko Ito (MD, PhD)[c,d,*], Hideki Ishii (MD, PhD)[e], Toru Aoyama (MD, PhD)[a], Daisuke Kamoi (MD, PhD)[a], Hirotake Kasuga (MD, PhD)[f], Kaoru Yasuda (MD, PhD)[d], Shoichi Maruyama (MD, PhD)[d], Seiichi Matsuo (MD, PhD)[d], Toyoaki Murohara (MD, PhD)[e], Yukio Yuzawa (MD, PhD)[b]

[a] Cardiovascular Center, Nagoya Kyoritsu Hospital, Nagoya, Japan
[b] Department of Nephrology, Fujita Health University School of Medicine, Toyoake, Japan
[c] Department of Renal Replacement Therapy, Nagoya University Graduate School of Medicine, Nagoya, Japan
[d] Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[e] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[f] Department of Nephrology, Nagoya Kyoritsu Hospital, Nagoya, Japan

ARTICLE INFO

*Article history:*
Received 24 August 2013
Received in revised form 21 October 2013
Accepted 29 October 2013
Available online 22 December 2013

*Keywords:*
GNRI
Cardiovascular mortality
Hemodialysis
Albumin
BMI

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

* Corresponding author at: Department of Nephrology and Renal Replacement Therapy, Nagoya University, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Tel.: +81 52 744 2192; fax: +81 52 744 2209.
*E-mail addresses:* yasuito@med.nagoya-u.ac.jp, yasuito57@gmail.com, yasuhiko@synnet.or.jp (Y. Ito).

0914-5087/$ – see front matter © 2013 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jjcc.2013.10.018

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