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Original Article

The impact of malnutritional status on survival in elderly hemodialysis patients

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Abstract

Background: The number of geriatric patients with end-stage renal disease undergoing maintenance hemodialysis has increased in Taiwan. However, protein-energy wasting is prevalent and associated with poor outcome in this patient population. It is generally well-known that geriatric nutritional risk index (GNRI) is a good survival predictor in general elderly patients. However, the association of GNRI with mortality in geriatric end-stage renal disease patients remains unclear. The present study aimed to assess the predictive ability of GNRI for overall mortality in elderly hemodialysis patients.

Methods: GNRI was measured in a cohort of 104 hemodialysis patients aged ≥65 years. Thereafter, these patients were followed for a median period of 38.5 months. For all cases, all-cause mortality was the primary endpoint.

Results: Patients with baseline GNRI <92 had significantly lower body weight, body mass index, serum albumin, and hemoglobin level, but were administered a higher erythropoietin dose as compared to those with GNRI ≥92. Basal GNRI independently correlated with erythropoietin resistance index ($\beta = -1.97$, $p < 0.001$) and serum high-sensitivity C-reactive protein ($\beta = -0.71$, $p = 0.021$). By the conclusion of the study, 45 patients had died. High GNRI was associated with the lower risk of mortality after adjustment for other potential confounders [hazard ratio = 0.41; 95% confidence interval (CI) = 0.22−0.90; $p = 0.005$].

Conclusion: GNRI is a significant predictor for mortality in elderly hemodialysis patients, and may be adopted to improve assessment of the malnutrition−inflammation status.

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Keywords: elderly; geriatric nutritional risk index; hemodialysis; mortality

1. Introduction

Similar to many other developed countries, the population in Taiwan is rapidly aging. This demographic change will have a major impact on the rise in prevalence of chronic illnesses. Aging is associated with several other risk factors, including hypertension, diabetes mellitus, obesity, and cardiovascular disease, and may contribute to the development and progression of chronic kidney disease.[1,2] Yang and Hwang[3] revealed that the elderly constituted the major proportion of patients with end-stage renal disease (ESRD) in Taiwan. Moreover, protein-energy wasting (PEW), a state of loss of body protein mass and energy fuels, is prevalent and associated with increased mortality in elderly ESRD patients.[4,5] Routine nutritional evaluation is strongly recommended for timely identification, prevention, and treatment of malnutrition in all elderly dialysis patients. Because PEW consists of many causes and clinical manifestations, a gold standard method is currently not available for diagnosis of this entity.[6]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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The geriatric nutritional risk index (GNRI), which is calculated from height, body weight, and serum albumin, was initially proposed to predict nutrition-related complications in hospitalized elderly patients.[7] Due to its simplicity, GNRI is widely applied in various clinical settings.[8,9] Recently, the GNRI was reportedly used to successfully assess the nutritional status and predict long-term outcome in ESRD patients.[10,11] However, the validity of GNRI is examined mainly in adult dialysis patients. Whether the GNRI could predict mortality in geriatric ESRD patients remains unclear. Therefore, we performed a single-center, prospective cohort study to investigate the predictive value of the GNRI for overall mortality among elderly hemodialysis (HD) patients.

2. Methods

2.1. Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Changhua Christian Hospital, Changhua County, Taiwan (CCHIRB-140904). Informed consent was obtained in written form from all participants before enrollment.

2.2. Study design

The study recruited a cohort of patients receiving HD therapy at a single dialysis unit from July 1, 2008 to December 31, 2008. Initially, 119 patients older than 65 years and ongoing dialysis for ≥6 months were screened. The following patients were excluded from the study: (1) those with inadequate dialysis defined as Kt/V urea <1.2 ($n = 2$); (2) those on dialysis for <12 h/wk ($n = 3$); and (3) patients with clinical conditions of infectious disease ($n = 1$), malignancy ($n = 5$), or hepatobiliary disease ($n = 4$). Finally, 104 clinically stable patients (54 men and 50 women; mean age 72 years) were enrolled and followed up until December 31, 2013.

All patients received HD therapy three times weekly with a standard bicarbonate-buffered dialysate bath utilizing disposable biocompatible dialyzers with a membrane surface area of 1.6–1.7 m^2. The mean dialysis duration before study entry was 64 months. No major adjustments were made in terms of dialysis treatments or protocols during this follow-up period. A thorough medical history of all patients was taken at the beginning of study. The presence of cardiovascular disease (CVD) was defined as a medical history, clinical symptoms, or findings of congestive heart failure, arrhythmia, coronary artery, cerebrovascular, and/or peripheral arterial disease. The primary endpoint was all-cause mortality from the time of inclusion.

2.3. GNRI

The GNRI is calculated incorporating serum albumin levels, body weight, and height by modifying the nutritional risk index for elderly patients, as reported by Bouillanne et al.[7] The GNRI equation is as follows:

Table 1
Areas under receiver operating characteristic (ROC) curve and cutoff values of geriatric nutritional risk index (GNRI), serum albumin, body mass index (BMI), and body weight with sensitivity and specificity for prediction of mortality.

Parameters	Area under ROC curve	p	Cutoff value	Sensitivity (%)	Specificity (%)
GNRI	0.603 ± 0.056	0.040	<92	64.4	55.9
Albumin (g/dL)	0.602 ± 0.054	0.073	<3.85	62.2	52.5
BMI (kg/m^2)	0.540 ± 0.060	0.060	<23.2	61.9	40.7
Body weight (kg)	0.449 ± 0.058	0.395	<59.3	51.6	45.8

$$\text{GNRI} = [14.89 \times \text{albumin (g/dL)}] + [41.7 \times (\text{body weight/ideal body weight})] \quad (1)$$

The ideal body weight was calculated from the height and a body mass index (BMI) of 22 kg/m^2 because of its validity and its reported association with the lowest mortality in the Asian population.[12,13] Body weight/ideal body weight was set to 1 when the patient's body weight exceeded the ideal body weight. The cut-off value of GNRI for predicting mortality was derived from creating a receiver operating characteristic (ROC) curve. The area under the ROC curve defined the probability for discriminating risk of mortality. The best cutoff with the highest sensitivity and lowest 1 − specificity for GNRI was 92 (Table 1).

Dietary protein intake was estimated by calculating normalized protein catabolic rate from the urea generation rate by using single-pool urea kinetics.[14] Body weight was determined as *dry weight*, and measured subsequent to each dialysis session. Blood pressure was measured at the beginning of each HD session with a standard sphygmomanometer in the nonaccess arm by dialysis staff while the patient was resting for at least 5 minutes with both feet on the floor. Patient response to erythropoietin treatment was examined using erythropoietin resistance index (ERI), defined as the weekly weight-adjusted erythropoietin dose (U/kg/wk) divided by hemoglobin level (g/dL).

2.4. Laboratory measurements

All blood samples were taken from patients who had fasted overnight before the mid-week dialysis session. Serum levels of high-sensitivity C-reactive protein (hs-CRP) were determined by utilizing an immunoturbidimetric assay and rate nephelometry (Beckman Coulter, Galway, Ireland). Serum creatinine, urea, albumin, calcium, phosphate, iron, and total iron-binding capacity levels were measured by using a model 7600 Autoanalyzer (Hitachi Ltd, Tokyo, Japan). Transferrin saturation was determined by calculating the ratio of serum iron and total iron-binding capacity, multiplied by 100. Serum levels of ferritin were measured with a radioimmunoassay kit (Incstar, Stillwater, MN, USA). The dialysis dose was measured by calculating mid-week Kt/V urea, which was computed by use of the Daugirdas equation.[15]

2.5. Statistical analyses

Data are expressed as the mean values ± standard deviation for continuous variables with a normal distribution, and percentages for categorical variables, respectively. Potential differences between the groups were evaluated by Student *t* test for continuous variables and by Pearson χ^2 test for categorical variables. We further applied areas under ROC curve and cutoff values of GNRI, serum albumin, BMI, and body weight, respectively, with optimal sensitivity and specificity for prediction of overall mortality. To determine the independent factors that correlated with GNRI, a multivariate linear regression analysis was performed. Baseline variables with a *p* value <0.1 by univariate analysis were entered into a multivariate model to determine independent predictors for the endpoint. A Cox proportional hazard analysis was used to calculate hazard ratio (HR) and 95% confidence intervals (CI) for determining the association of baseline variables with all-cause mortality. Survival curves were examined by the Kaplan–Meier method. Differences were considered statistically significant at $p < 0.05$. Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical characteristics of patients

To compare the discriminative ability among GNRI, serum albumin, BMI, and body weight, areas under the ROC curve were calculated (Table 1). The GNRI had a relatively good predictive value. Its cutoff value of 92 was validated by comparing the areas under the ROC curve, and was determined to exhibit better accuracy in assessing the risks of mortality in the geriatric hemodialysis patients.

The clinical characteristics of all patients are shown in Table 2. Patients with baseline GNRI <92 had significantly lower body weight, body mass index, serum albumin, and hemoglobin, and higher erythropoietin doses as compared to those with GNRI ≥92. We further performed a multivariate regression analysis for the contributing factors of GNRI at baseline. No correlation was found between GNRI and traditional risk factors, including age, sex, hypertension, diabetes mellitus, and previous CVD. However, baseline GNRI was negatively correlated with ERI ($\beta = -1.97$, $p < 0.001$) and serum hs-CRP ($\beta = -0.71$, $p = 0.021$; Table 3).

3.2. Association of GNRI with outcome

During the follow-up period (median, 38.5 months), 14 patients were censored at the time they were transferred to other dialysis units ($n = 12$) or shifted to peritoneal dialysis ($n = 2$). Overall, 45 patients (43.3%) had died by the end of the study period. The Kaplan–Meier survival curves showed that patients with baseline GNRI of ≥92 were associated with a lower probability of overall mortality (Fig. 1, solid line).

Table 2
Baseline characteristics and laboratory data of the elderly hemodialysis patients.

Parameters	Geriatric nutritional risk index		
	<92 ($n = 23$)	≥92 ($n = 81$)	*p*
Age (y)	73 ± 7	72 ± 6	0.801[a]
Male sex	10 (43.5)	44 (54.3)	0.363[b]
Hypertension	6 (26.1)	35 (43.2)	0.142[b]
Diabetes mellitus	6 (26.1)	32 (40.0)	0.220[b]
Previous CVD[c]	4 (17.4)	29 (35.8)	0.094[b]
Systolic BP (mmHg)	137 ± 29	138 ± 26	0.811[a]
Diastolic BP (mmHg)	73 ± 13	76 ± 16	0.422[a]
HD duration (mo)	61 ± 50	65 ± 49	0.743[a]
Kt/V urea	1.8 ± 0.7	2.0 ± 0.9	0.214[a]
nPCR (g/kg/d)	1.2 ± 0.6	1.3 ± 0.3	0.341[a]
Body weight (kg)	48 ± 8	59 ± 9	<0.001[a]
Body mass index (kg/m^2)	20 ± 2	23 ± 4	0.001[a]
hs-CRP (mg/L)	5.2 ± 3.0	4.8 ± 3.5	0.063[a]
Albumin (g/dL)	3.3 ± 0.3	3.9 ± 0.3	<0.001[a]
Calcium (mg/dL)	9.2 ± 0.9	9.5 ± 0.6	0.064[a]
Phosphorous (mg/dL)	4.5 ± 1.1	4.5 ± 1.2	0.963[a]
Hemoglobin (g/dL)	8.9 ± 1.3	10.6 ± 1.3	<0.001[a]
Dose of erythropoietin (U/Kg/wk)	100 ± 29	64 ± 45	<0.001[a]
Ferritin (μg/L)	605 ± 539	634 ± 405	0.143[a]
Transferrin saturation (%)	24 ± 13	25 ± 14	0.421[a]

Data are presented as *n* (%) or mean ± standard deviation.
BP = blood pressure; CVD = cardiovascular disease; hs-CRP = high-sensitivity C-reactive protein; nPCR = normalized protein catabolic rate.
[a] Student *t* test.
[b] Pearson χ^2 test.
[c] Previous CVD category consisted of coronary artery disease, cerebrovascular disease, and peripheral arterial disease.

The association between GNRI and all-cause mortality was assessed through Cox proportional hazard analysis (Table 4). Patients with GNRI value of ≥92 were associated with lower risk for overall mortality (HR = 0.41; 95% CI = 0.22–0.90; $p = 0.005$) and the risk of death for each increment in one unit of GNRI was also significantly reduced (HR = 0.91; 95% CI = 0.85–0.91; $p < 0.001$) after adjustment for other potential confounders.

Table 3
Factors are associated with geriatric nutritional risk index at baseline in multivariate regression analysis.[a]

Parameters	β	95% CI	*p*
Age, per 1 y	−0.05	(−0.27–0.18)	0.073
Sex, male	0.16	(0.12–2.88)	0.911
HD duration, per 1 mo	−0.05	(−0.11–0.13)	0.870
Diabetes mellitus, presence	−0.25	(−1.50–1.03)	0.754
Previous CVD, presence	0.11	(−2.98–2.99)	0.914
ERI, per 1 U/Kg/wk per g/dL Hb	−1.97	(−3.55–−1.01)	<0.001
hs-CRP, per 1 mg/L	−0.71	(−1.10–−0.45)	0.021

The adjusted r^2 of the model was 0.36.
CVD = cardiovascular disease; ERI = erythropoietin resistance index; Hb = hemoglobin; HD = hemodialysis; hs-CRP = high-sensitivity C-reactive protein.
[a] The multivariate model included GNRI as a dependent variable, and age, sex, dialysis vintage, diabetes mellitus status, history of cardiovascular disease, ERI, and hs-CRP as independent variables.

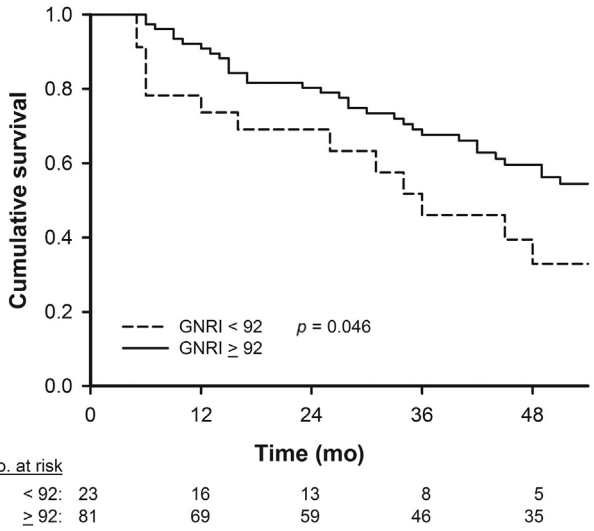

Fig. 1. Kaplan–Meier analysis curves for all-cause mortality among elderly hemodialysis patients in close relationship with the geriatric nutrition risk index (GNRI). Patients were stratified into groups based on the cutoff values 92 of GNRI.

4. Discussion

In this study, we demonstrated the validity of GNRI in predicting overall mortality among elderly HD patients. The risk of all-cause death significantly increased in patients with GNRI <92 at baseline during long-term follow-up. In addition, high ERI and hs-CRP were correlated with low GNRI. Those patients with low GNRI also had low body weight, low body mass index, low serum albumin, low hemoglobin, and high ERI. These components are compatible with syndromes of PEW.

As life expectancy has risen due to improvements in Taiwan's public health and medical care, there has been an increasing number of geriatric patients undergoing renal replacement therapy due to ESRD.[3] These patients are at the risk of frailty and PEW due to various reasons such as reduced food intake due to poor appetite, chronic inflammation, loss of nutrients during dialysis, metabolic acidosis, increased energy expenditure, and hormonal and primary neuromuscular disorders.[16–19] PEW is always underestimated and may lead to serious consequences in geriatric ESRD patients, including impaired physical functioning, poorer quality of life, frequent superimposed illness, and increased mortality.[20,21] Among the available nutritional screening tools, GNRI was the easiest to perform for identifying PEW status in ESRD patients undergoing maintenance dialysis.[10,11,22] In this study, we further confirmed that declining GNRI is closely associated with hypoalbuminemia and reduced BMI. Thus, the GNRI is considered to be a useful diagnostic material for the presence of PEW in elderly patients undergoing HD therapy.

Notably, the presence of PEW is found in 18–75% of ESRD patients in previous studies using different criteria.[4,23] However, there are fewer data concerning the frequency of PEW in elderly ESRD patients. In our study, the prevalence of malnutrition based on a GNRI cutoff value of 92 was ~22%, and no difference was observed between men and women. This prevalence rate was much lower than that (53.4%) in Japanese incident HD patients using the same diagnostic criteria.[24] The causes of the discrepancy in frequency of PEW between these two reports were not clear. Whether the nutritional risk of our patients improves after undergoing maintenance HD therapy needs to be further examined.

As mentioned above, GNRI has been validated as a simpler and more accurate nutritional indicator than other screening tools and was reported to be correlated with mortality, various nutritional parameters, oxidative stress,[25] and inflammation[24,26] in maintenance HD patients. To the best of our knowledge, this is the first recent study demonstrating that patients with low GNRI were associated with anemia and poor response to erythropoietin treatment owing to high ERI (Table 3). Kalantar-Zadeh et al[27] studied 339 maintenance HD patients and found the existence of elements of malnutrition–inflammation complex syndrome as indicated by increased inflammatory markers as well as decreased nutritional status in close relationship with erythropoietin hyporesponsiveness and refractory anemia. Therefore, GNRI may be a reliable method to predict the required doses of erythropoietin in this population based on the degree of malnutrition.

There are some limitations that need to be mentioned. First, we cannot exclude the possibility of residual confounding factors, although most factors have been adjusted in our study. Second, in a prospective cohort study, we cannot prove the causality. Therefore, further studies are needed to confirm this association.

In conclusion, lower GNRI was associated with a higher risk of overall mortality in the elderly ESRD patients undergoing maintenance HD. The clinical practitioners, nephrologists, may use GNRI to assess nutritional status in elderly HD patients since such expensive laboratory tests are not widely available.

Table 4
Multivariate Cox proportional hazard analysis for relative risk of overall mortality calculated by geriatric nutritional risk index (GNRI) levels in a median follow-up of 38.5 months.

	Hazard ratio (95% CI)[a]			Hazard ratio (95% CI)[a]	
	GNRI cutoff value			GNRI	
	<92	≥92	*p*	1 unit increase	*p*
All-cause mortality					
Unadjusted	1	0.54 (0.32–0.99)	0.041	0.93 (0.89–0.97)	<0.002
Multivariate adjustment[b]	1	0.41 (0.22–0.90)	0.005	0.91 (0.85–0.91)	<0.001

CI = confidence interval.

[a] Hazard ratios and 95% CIs were derived from Cox regression analysis based on initial GNRI value at the start of the cohort.

[b] The multivariate model included variables for age, sex, diabetes mellitus, prior cardiovascular disease, systolic blood pressure, hemodialysis duration, urea Kt/V, hemoglobin, calcium, and phosphorus.

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