Original Article

The Geriatric Nutritional Risk Index Predicts Long-Term Survival and Cardiovascular or Limb Events in Peripheral Arterial Disease

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Aim: The Geriatric Nutritional Risk Index (GNRI) was developed to assess the nutritional risk and is associated with mortality. However, there are limited reports on the relationship between the GNRI and overall survival (OS) in peripheral artery disease (PAD). Therefore, the purpose of this study was to examine the relationship between GNRI and OS and cardiovascular or limb events in patients with PAD.

Methods: A prospective cohort study was performed on 1,219 patients with PAD. The baseline GNRI was calculated from the serum albumin level and body mass index obtained at the first visit. The patients were divided into four groups according to the GNRI: G0 (>98), G1 (92–98), G2 (82–91), and G3 (<82). The endpoints were OS and freedom from major adverse cardiovascular events (MACE) and MACE plus limb events (MACLE).

Results: The median follow-up period was 73 months. There were 626 deaths (51.4%) during the follow-up. The rate of cardiovascular death was 51.3%. OS clearly depended on the GNRI ($p<0.01$), with five-year OS rates of 80.8% for G0, 62.0% for G1, 40.0% for G2, and 23.3% for G3. In multivariate analyses, the GNRI, age, ankle–brachial pressure index (ABPI), critical limb ischemia, estimated glomerular filtration rate (eGFR), and C-reactive protein (CRP) were independent factors associated with OS, and GNRI, age, ABPI, coronary artery disease, diabetes mellitus, eGFR, and CRP were associated with MACE and MACLE (all $p<0.05$). Statins were found to improve OS, MACE, and MACLE ($p<0.01$).

Conclusions: GNRI is an independent predictor for OS, MACE, and MACLE in patients with PAD.

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Introduction

Patients with peripheral artery disease (PAD) are complicated with diabetes mellitus (DM), chronic kidney disease (CKD), or other risk factors and may experience extensive and severe systemic atherosclerosis that causes mortality due to coronary artery disease (CAD) and ischemic stroke[1-4]. We previously reported that a low body mass index (BMI) is an independent predictor for all-cause mortality in patients with PAD[3]. The mortality rates for different levels of BMI follow a J-shaped curve, with cardiovascular mortality showing a tendency for a bimodal distribution with peaks at lower and higher BMI.

Malnutrition is common and is associated with increased mortality in cardiovascular disease (CVD), such as CAD and stroke[5, 6], and nutritional indicators such as BMI, serum albumin, and total cholesterol are predictors of survival in patients with CVD[5-7]. The geriatric nutritional risk index (GNRI) is calculated from serum albumin and components of BMI and was developed as a screening tool to assess nutritional risk[8]. This index is a simple and established nutritional assessment in subjects who have CVD and those on hemodialysis, as well as other elderly patients[8-11]. However, long-term life expectancy, including cardiovascular events and the fate of the leg, according to the GNRI in diverse patients with PAD,

has not been defined. Thus, the purpose of this study was to evaluate the clinical significance of GNRI for these events in patients with PAD.

Patients and Methods

Patients

The subjects were patients with PAD who were referred to the Cardiovascular Hospital of Central Japan (Kitakanto Cardiovascular Hospital) between January 1, 2001, and November 31, 2018. Prior to the start of the study, the patients received a full explanation of the examination methods and provided written informed consent. The study protocol was approved by the Medical Ethical Committee of the Cardiovascular Hospital of Central Japan. All patients had an ankle–brachial pressure index (ABPI) of <0.90 at their first visit. The final diagnosis of PAD was based on clinical symptoms and iliac or femoropopliteal artery stenosis of $\geq 70\%$ on angiography or ultrasound. The clinical stages of PAD were classified using the criteria of the Inter-Society Consensus for the Management of Peripheral Arterial Disease[1].

Clinical and Laboratory Analysis

Clinical data were obtained by review of primary data for age, ABPI, BMI, DM, smoking history, and hypertension. Blood was collected during fasting in order to determine the albumin, creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, glucose, D-dimer, and C-reactive protein (CRP) levels. Hypertension was defined as blood pressure of $\geq 140/90$ mmHg recorded at least twice or intake of antihypertensive agents. DM was defined as a fasting plasma glucose level of >126 mg/dL for at least two measurements or a requirement for antidiabetic therapy[12]. The estimated glomerular filtration rate (eGFR) was obtained using the Modification of Diet in Renal Disease equation for creatinine, as modified by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) $= 194 \times (serum\ creatinine)^{-1.094} \times (age)^{-0.287}$ ($\times 0.739$ if female)[13]. In patients on hemodialysis, the serum creatinine level just before the hemodialysis was used to obtain the eGFR. An electrocardiogram and echocardiography were recorded in all patients. CAD was defined as a treatment history or a positive sign in coronary angiography or stress/rest myocardial perfusion scintigraphy.

Assessment of GNRI

Baseline GNRI was calculated from serum albumin and BMI obtained at the first hospital visit, using the following formula[8]: GNRI $= 14.89 \times$ serum albu-

min (g/dL) $+ 41.7 \times$ (present body weight/ideal body weight). If the patient's body weight exceeded the ideal body weight, the present body weight/ideal body weight was set to 1. The ideal body weight was defined as the value calculated from height and a BMI of 22 kg/m^2, instead of the value calculated using the Lorentz formula in the original GNRI equation[9, 14]. The patients were divided into four groups according to the GNRI: G0 (no risk, >98), G1 (low risk, 92–98), G2 (moderate risk, 82–91), and G3 (high risk, <82)[8, 15].

Drug Administration and Treatments

All patients took at least one antiplatelet agent, and those with intermittent claudication initially received exercise rehabilitation and medication for more than three months. Oral aspirin, clopidogrel, or ticlopidine was administered, and an oral drug for the treatment of claudication (cilostazol, beraprost, or sarpogrelate) was added to exercise therapy. Drugs for other conditions were added as needed. Medications that continued for over three months or administered for more than three months before death were classified as drug treatment.

Data Analysis and Endpoints

Patients were followed up at one, three, and six months after treatment and evaluated at four- or six-month intervals at hospital visits. Vital signs and medication regimens were assessed using medical records and written questionnaires for quality of life completed at the Foot Care Club in our hospital or in response to an invitation letter[3, 7, 16]. An invitation to the meeting and a questionnaire were sent to each patient once a year. Through this club, we organized educational meetings to provide lectures on exercise programs, foot care, and new medical trends.

Myocardial infarction was defined as described previously[16, 17]. Ischemic stroke was defined as the presence of a new focal neurological deficit lasting 24 h or more. Brain magnetic resonance imaging/computed tomography was required to confirm stroke. Transient ischemic attack (TIA) was defined as the presence of a new focal neurological deficit lasting less than 24 h. Limb revascularization was performed in cases with worsening symptoms and progression or restenosis of the lesion. Restenosis after revascularization was defined as a decrease in ABPI of ≥ 0.15 and $\geq 50\%$ stenosis on angiography or duplex ultrasonography[16, 18]. Major amputation was defined as "above-the-ankle amputation."

The endpoints were overall survival (OS), freedom from major adverse cardiovascular events (MACE: all-cause death, nonfatal myocardial infarc-

tion, stroke, or TIA), and freedom from MACE plus limb events (MACLE: MACE, any repeat revascularization for a limb, and major amputation).

Statistical Analysis

Continuous variables were expressed as a median (interquartile range) and were compared by Wilcoxon's test. Categorical variables were expressed as a number (%) and were compared using the chi-squared test. The Kaplan–Meier method was used to determine the OS, MACE, and MACLE in the follow-up period. The hazard ratio (HR) and 95% confidence interval (CI) were calculated for individual factors in the Cox univariate analysis. Factors with $p < 0.05$ in this analysis were used in multivariate Cox regression models to determine factors associated with endpoints. The C-index and Net Reclassification Index (NRI) were calculated to assess whether the accuracy of predicting these events would improve after adding the BMI, serum albumin level, or GNRI to a baseline model with established risk factors. Simple Pearson's correlations were calculated between the GNRI and risk factors other than the BMI and serum albumin level. Factors with $p < 0.05$ in the analysis were evaluated using stepwise forward linear multiple regression analysis to examine the relationships among the risk factors and the GNRI. Statistical analyses were carried out using IBM SPSS Statistics ver. 25.0 (IBM Corp., Armonk, NY, USA) and Microsoft R Open version 3.5.1 with additional packages, including Rcmdr, Epi, pROC, and PredictABEL (https://mran.revolutionanalytics.com/; Microsoft Corporation, Redmond, WA, USA). Individual differences were considered to be significant at $p < 0.05$.

Results

Patient Characteristics and Causes of Death

Follow-up was possible for 1,219 out of the 1,234 subjects. The median and mean ages of the 1,219 patients were 73 (67–79) and 72.6 ± 9.9 (range: 38 to 98) years, respectively. The median and mean follow-up periods were 58 (19–105) and 72.4 ± 60.1 months, respectively. There were 626 deaths (51.4%) during the follow-up due to cardiac or major vascular disease ($n = 224$, 35.8%), cerebrovascular disease ($n = 97$, 15.5%), malignancy ($n = 125$, 20.0%), pneumonia ($n = 91$, 14.5%), and other causes ($n = 89$, 14.2%). The prevalence of CVD-related deaths was 51.3% ($n = 321$).

The baseline characteristics and comorbidities of patients according to the GNRI are shown in **Table 1**. A total of 537 patients had GNRI of ≤ 98: G1, $n = 308$; G2, $n = 164$; and G3, $n = 65$. Patients with lower GNRI were older and had lower levels of ABPI, BMI, albumin, eGFR, total cholesterol, LDL-C, and triglyceride and higher levels of CRP and D-dimer. In patients with normal GNRI (>98), the prevalence of critical limb ischemia (CLI), stroke, TIA, and hemodialysis was lower, and that for CAD and the revascularization rate were higher.

All-Cause Mortality

The cumulative three-, five-, and ten-year OS rates in all patients were 78.8, 67.9, and 43.9%, respectively. These OS rates showed significant differences among GNRI levels (all $p < 0.001$) (**Fig. 1**). The cumulative five-year OS rates were 80.8% for G0, 62.0% for G1, 40.0% for G2, and 23.3% for G3. In univariate analyses, age, ABPI, GNRI, lower eGFR, higher CRP and D-dimer, history of stroke or TIA, and CLI were significantly associated with OS (**Table 2**). Revascularization or treatment with statins or aspirin improved mortality. In multivariate analyses, age, ABPI, GNRI, levels of eGFR and CRP, and prevalence of CLI were significantly related to OS, and statins also improved OS.

MACE and MACLE

MACE and MACLE showed significant differences between the patients with normal and lower GNRI (**Fig. 2**). In multivariate analyses, age, ABPI, CAD, DM, GNRI, and levels of eGFR and CRP were independent factors associated with MACE (**Table 3**), and age, ABPI, CAD, DM, GNRI, and levels of eGFR and CRP were independent factors associated with MACLE (**Table 4**). Statins were found to reduce MACE and MACLE.

GNRI as a Predictor of Life Expectancy and Cardiovascular or Limb Events

Differences of the C-index and NRI of the baseline models with or without GNRI, albumin level, or BMI for OS, MACE, and MACLE are shown in **Table 5**. GNRI was a significant risk factor improving the C-index for OS, MACE, and MACLE. NRI improved significantly after adding the GNRI to the baseline model, beyond the baseline model plus BMI or albumin level in OS, MACE, and MACLE.

Correlations among GNRI and Other Risk Factors

Correlations among GNRI and other risk factors were analyzed with stepwise forward multiple regression analysis, besides BMI and albumin level. These correlations are shown in **Table 6**. GNRI had significant correlations with CLI, age, total cholesterol, ABPI, triglyceride, sex (male), CRP, eGFR, and hypertension.

Table 1. Baseline clinical characteristics of patients with peripheral arterial disease with normal (>98) and low (≤ 98) geriatric nutritional risk indexes (GNRI)

Factor	All patients $n = 1219$	G0 GNRI >98 $n = 682$ (55.9%)	G1-3 GNRI ≤ 98 $n = 537$ (44.1%)	p-value
Age (year)	73 (67-79)	71 (65-77)	76 (70-82)	<0.001
Gender (male)	923 (75.7%)	528 (77.4%)	395 (73.6%)	0.122
Ankle brachial pressure index	0.70 (0.50-0.81)	0.71 (0.56-0.83)	0.63 (0.43-0.80)	<0.001
Critical limb ischemia	248 (20.3%)	73 (10.7%)	175 (32.6%)	<0.001
Body mass index (kg/m^2)	22.0 (19.8-24.3)	23.4 (21.7-25.1)	19.7 (18.0-21.7)	<0.001
Risk factors				
History of stroke or TIA	224 (18.4%)	109 (16.0%)	115 (21.4%)	0.017
Coronary artery disease	346 (35.8%)	223 (40.1%)	123 (30.0%)	0.001
Hypertension	800 (65.6%)	460 (67.4%)	340 (63.3%)	0.145
Diabetes mellitus	464 (38.1%)	274 (40.2%)	190 (35.4%)	0.096
Smoking	874 (71.7%)	502 (73.6%)	372 (69.3%)	0.096
Hemodialysis	134 (11.0%)	47 (6.9%)	87 (16.2%)	<0.001
Laboratory data				
Albumin (g/dL)	4.0 (3.7-4.2)	4.1 (4.0-4.5)	3.7 (3.3-4.0)	<0.001
eGFR (mL/min/1.73 m^2)	55.0 (41.7-67.4)	57.1 (46.1-68.7)	50.7 (35.3-65.1)	<0.001
C-reactive protein (mg/dL)	0.19 (0.08-0.51)	0.15 (0.08-0.34)	0.26 (0.10- 0.86)	<0.001
Total cholesterol (mg/dL)	185 (159-214)	192 (167-219)	176 (149-205)	<0.001
LDL-C (mg/dL)	113 (91-135)	118 (95-139)	107 (83-130)	<0.001
HDL-C (mg/dL)	48 (39-58)	47 (39-57)	48 (39-58)	0.486
Triglyceride (mg/dL)	121 (83-169)	139 (100-192)	100 (71-140)	<0.001
D-dimer (μg/dL)	0.9 (0.5-2.1)	0.7 (0.5-1.5)	1.3 (0.8-2.8)	<0.001
Drugs				
Statin	635 (52.1%)	371 (54.4%)	264 (49.2%)	0.069
Aspirin	670 (55.0%)	385 (56.5%)	285 (53.1%)	0.239
Thienopyridines	556 (45.6%)	325 (47.7%)	231 (43.0%)	0.107
Cilostazol	575 (47.2%)	318 (46.6 %)	257 (47.9%)	0.669
Beraprost	424 (34.8%)	227 (33.3%)	197 (36.7%)	0.226
Sarpogrelate	95 (7.8%)	53 (7.8%)	42 (7.8%)	1.000
ACE inhibitor	128 (10.5%)	79 (11.6%)	49 (9.1%)	0.188
ARB	360 (29.5%)	213 (31.2%)	147 (27.4%)	0.146
β-blocker	194 (15.8%)	112 (16.4%)	80 (14.9%)	0.477
Ca antagonist	613 (50.3%)	358 (52.5%)	255 (47.5%)	0.083
Warfarin	139 (11.4%)	77 (11.3%)	62 (11.6%)	0.928
Direct oral anticoagulant	25 (2.1%)	15 (2.2%)	10 (1.9%)	0.839
Revascularization	695 (57.0%)	419 (61.4%)	276 (51.4%)	<0.001
Endovascular treatment	524 (43.0%)	315 (46.2%)	209 (38.9%)	0.011
Bypass surgery	171 (14.0%)	104 (15.2%)	67 (12.5%)	0.021

TIA: transient ischemic attack, eGFR: estimated glomerular filtration rate, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker

Discussion

All-Cause Mortality

This is the first report on the relationships between GNRI and all-cause mortality in diverse patients with PAD. Yokoyama *et al.* reported that GNRI is an independent predictor of MACE and MACLE in patients with PAD following endovascular therapy[19]. However, they did not report a relationship between GNRI and all-cause mortality. GNRI is an independent predictor for OS, and mortality is strongly correlated with ABPI, CLI, eGFR, CRP level, and GNRI. CLI and low ABPI are related to a higher five-year risk of a cardiovascular event[3, 20], based on
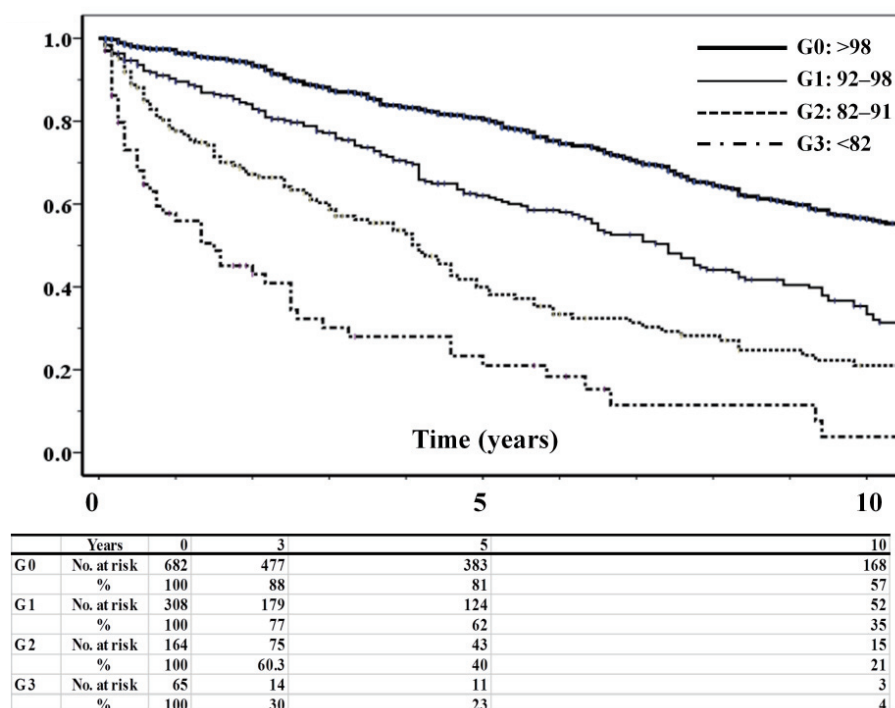
	Years	0	3	5	10
G0	No. at risk	682	477	383	168
	%	100	88	81	57
G1	No. at risk	308	179	124	52
	%	100	77	62	35
G2	No. at risk	164	75	43	15
	%	100	60.3	40	21
G3	No. at risk	65	14	11	3
	%	100	30	23	4

Fig. 1. Kaplan–Meier estimates of OS according to the GNRI. There were significant differences among each GNRI level (all $p < 0.001$).

Table 2. Predicted risk factors for overall survival in Cox univariate and multivariate analyses

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (year)	1.065	1.055-1.075	< 0.001	1.043	1.030-1.055	< 0.001
Sex (male)	1.051	0.863-1.280	0.623			
Ankle brachial pressure index	0.388	0.294-0.513	< 0.001	0.644	0.420-0.985	0.043
Critical limb ischemia	2.708	2.268-3.233	< 0.001	1.374	1.025-1.843	0.034
History of stroke or TIA	1.743	1.441-2.108	< 0.001	1.126	0.867-1.463	0.374
GNRI	0.935	0.927-0.944	< 0.001	0.961	0.948-0.974	< 0.001
eGFR (mL/min/1.73m²)	0.984	0.980-0.988	< 0.001	0.988	0.983-0.993	< 0.001
C-reactive protein (mg/dL)	1.202	1.159-1.247	< 0.001	1.169	1.109-1.233	< 0.001
D-dimer (μg/dL)	1.019	1.011-1.027	< 0.001	1.006	0.994-1.019	0.290
Statin	0.255	0.206-0.316	< 0.001	0.351	0.267-0.462	< 0.001
Aspirin	0.638	0.544-0.748	< 0.001	0.862	0.693-1.071	0.181
Revascularization	0.640	0.545-0.751	< 0.001	0.780	0.551-1.105	0.162

HR: hazard ratio, CI: confidence interval, GNRI: geriatric nutritional risk index, eGFR: estimated glomerular filtration rate.

severe systemic atherosclerosis. Several studies suggested that CKD is a prognostic indicator of CVD[21, 22], and cardiovascular mortality is 10–30 times higher in patients treated with hemodialysis than in the general population[21]. Malnutrition is also an independent risk factor for mortality, with several reports showing a correlation between malnutrition and mortality in patients with CVD[5, 6, 23]. GNRI was developed as a simplified tool to assess the nutritional risk[8] and was also found to be an independent predictor of OS in patients with PAD in the current study. These consistent results suggest that patients with severe PAD and lower GNRI or lower eGFR have severe systemic atherosclerosis that leads to higher mortality.
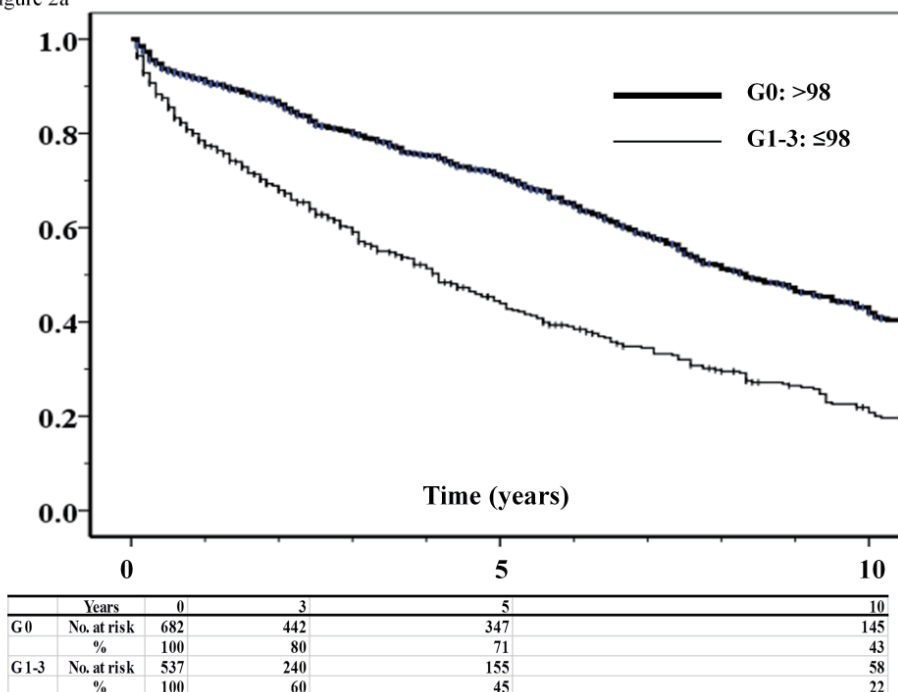
Figure 2a

	Years	0	3	5	10
G 0	No. at risk	682	442	347	145
	%	100	80	71	43
G 1-3	No. at risk	537	240	155	58
	%	100	60	45	22

Figure 2b

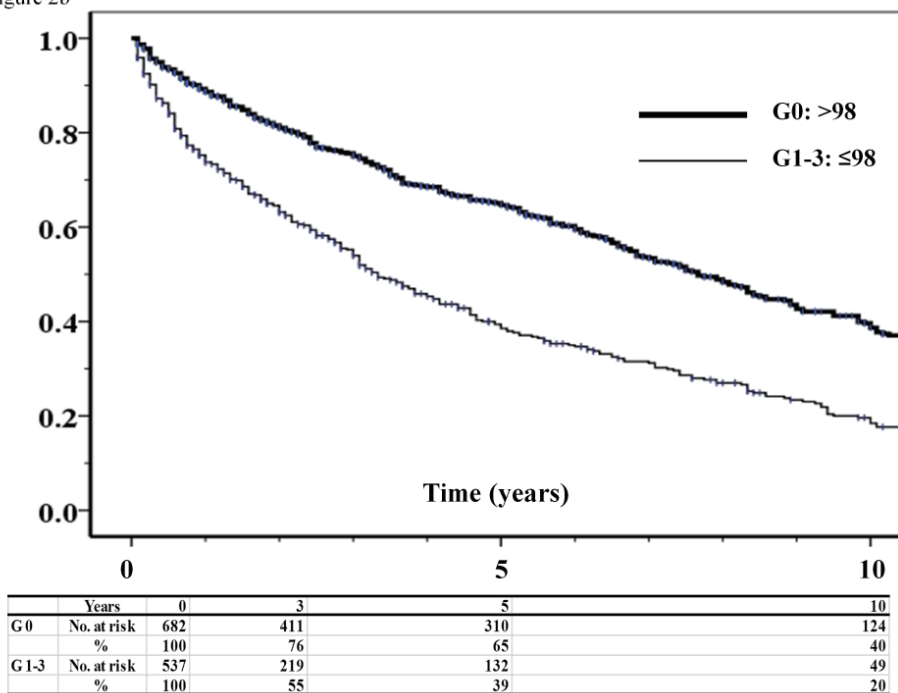|	Years	0	3	5	10
G 0	No. at risk	682	411	310	124
	%	100	76	65	40
G 1-3	No. at risk	537	219	132	49
	%	100	55	39	20

Fig. 2. Kaplan–Meier estimates of freedom from MACE (a) and freedom from MACLE (b) in patients with normal and lower GNRI

There was a significant difference between groups G0 (GNRI>98) and G1–G3 (GNRI ≤ 98) ($p < 0.001$).

MACE and MACLE

Lower ABPI, CAD, DM, lower eGFR, and lower GNRI are independent factors associated with MACE and MACLE in multivariate analyses. The prevalence of CLI and lower ABPI are related to a higher rate of cardiovascular events due to severe systemic athero-

Table 3. Risk factors for major adverse cardiovascular events (MACE) in Cox univariate and multivariate analyses

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (year)	1.045	1.036-1.054	<0.001	1.031	1.020-1.042	<0.001
Sex (male)	1.149	0.956-1.381	0.138			
Ankle brachial pressure index	0.428	0.331-0.553	<0.001	0.642	0.437-0.943	0.024
Critical limb ischemia	2.337	1.973-2.769	<0.001	1.276	0.971-1.676	0.080
History of stroke or TIA	1.498	1.250-1.796	<0.001	0.988	0.775-1.260	0.923
Coronary heart disease	1.306	1.124-1.517	<0.001	1.542	1.252-1.898	<0.001
Diabetes	1.283	1.102-1.493	0.001	1.422	1.161-1.741	0.001
GNRI	0.950	0.941-0.958	<0.001	0.974	0.962-0.987	<0.001
eGFR (mL/min/1.73 m^2)	0.987	0.984-0.991	<0.001	0.994	0.990-0.998	0.005
C-reactive protein (mg/dL)	1.161	1.121-1.202	<0.001	1.129	1.074-1.186	<0.001
D-dimer (µg/dL)	1.015	1.007-1.024	<0.001	1.004	0.991-1.018	0.525
Statin	0.330	0.276-0.394	<0.001	0.384	0.306-0.482	<0.001
Aspirin	0.858	0.741-0.993	0.040	0.974	0.793-1.196	0.802
Revascularization	0.725	0.624-0.842	<0.001	0.985	0.945-1.027	0.469

HR: hazard ratio, CI: confidence interval, GNRI: geriatric nutritional risk index, eGFR: estimated glomerular filtration rate

Table 4. Risk factors for major adverse cardiovascular and limb events (MACLE) in Cox univariate and multivariate analyses

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (year)	1.036	1.028-1.045	<0.001	1.019	1.009-1.030	<0.001
Ankle brachial pressure index	0.417	0.326-0.534	<0.001	0.598	0.417-0.858	0.005
Critical limb ischemia	2.186	1.841-2.588	<0.001	1.194	0.910-1.567	0.201
History of stroke or TIA	1.497	1.251-1.791	<0.001	1.069	0.843-1.357	0.581
Coronary heart disease	1.227	1.048-1.436	0.011	1.353	1.082-1.693	0.008
Diabetes	1.199	1.032-1.395	0.018	1.284	1.051-1.569	0.015
GNRI	0.954	0.946-0.962	<0.001	0.974	0.962-0.986	<0.001
eGFR (mL/min/1.73 m^2)	0.989	0.986-0.992	<0.001	0.993	0.989-0.997	<0.001
C-reactive protein (mg/dL)	1.145	1.105-1.187	<0.001	1.101	1.047-1.157	<0.001
D-dimer (µg/dL)	1.013	1.004-1.021	0.004	1.001	0.987-1.015	0.910
Statin	0.329	0.277-0.391	<0.001	0.381	0.305-0.475	<0.001
Aspirin	0.852	0.737-0.986	0.031	0.929	0.764-1.130	0.461
Revascularization	0.848	0.731-0.984	0.030	0.876	0.687-1.118	0.288

HR: hazard ratio, CI: confidence interval, GNRI: geriatric nutritional risk index, eGFR: estimated glomerular filtration rate

sclerosis[3, 20]. We reported that DM is an independent risk factor for the progression of Fontaine stages[24] and MACE and MACLE in patients with PAD[7, 25]. In this study, a lower GNRI was also found to be an independent predictor for MACE or MACLE in diverse patients with PAD. CVDs are a major cause of MACE or MACLE, and malnutrition reflected by a lower GNRI might be responsible for MACE and MACLE. A recent study also showed that underweight patients with CLI have an extremely poor prognosis[26], and GNRI was found to be a reliable predictive marker for amputation-free survival in patients with CLI[15].

Therefore, our results suggest that screening for GNRI is important for nutritional management of patients with PAD.

GNRI as a Risk Predictor

Several nutritional indicators, including BMI, serum albumin, and total cholesterol, have been reported to predict survival in patients with CVD[5-7]. Comparisons of the validity of several nutritional tools suggested that GNRI is as useful as others for the assessment of nutritional risk[9, 19]. GNRI is also an established nutritional assessment tool for subjects

Table 5. Discrimination of each predictive model for all-cause death, major adverse cardiovascular events (MACE), and MACE plus limb events (MACLE) using the C-index and net reclassification index (NRI)

	C-index (95%CI)	*p*-value	NRI (95%CI)	*p*-value
All-cause death				
Established risk factors	0.8118 (0.7871-0.8366)	Reference		Reference
Established risk factors + BMI	0.8161 (0.7917-0.8405)	0.302	0.1940 (0.0822-0.3058)	0.001
Established risk factors + albumin	0.8171 (0.7929-0.8414)	0.181	0.2185 (0.1076-0.3294)	0.000
Established risk factors + GNRI	0.8218 (0.7980-0.8456)	0.042	0.2485 (0.1380-0.3591)	0.000
MACE				
Established risk factors	0.8011 (0.7745-0.8278)	Reference		Reference
Established risk factors + BMI	0.8022 (0.7758-0.8285)	0.698	0.0950 (-0.0194-0.2094)	0.104
Established risk factors + albumin	0.8072 (0.7811-0.8334)	0.073	0.1394 (0.0264-0.2525)	0.016
Established risk factors + GNRI	0.8091 (0.7834-0.8348)	0.043	0.1668 (0.0537-0.2799)	0.004
MACLE				
Established risk factors	0.7854 (0.7584-0.8123)	Reference		Reference
Established risk factors + BMI	0.7893 (0.7628-0.8159)	0.390	0.1344 (0.0195-0.2492)	0.022
Established risk factors + albumin	0.7934 (0.7666-0.8201)	0.110	0.1381 (0.0244-0.2518)	0.017
Established risk factors + GNRI	0.7984 (0.7723-0.8245)	0.034	0.1992 (0.0859-0.3121)	0.001

Established risk factors included age, ankle brachial pressure index, critical limb ischemia, coronary heart disease, diabetes mellitus, estimated glomerular filtration rate, C-reactive protein, and use of statins.
CI: confidence interval, BMI: body mass index, GNRI: geriatric nutrition risk index

Table 6. Correlations between geriatric nutritional risk index and other risk factors in stepwise forward multiple regression analysis

Factor	β	B	95% CI	*p*-value
Critical limb ischemia	-0.232	-4.760	-6.037 to -3.482	<0.001
Age (year)	-0.183	-0.161	-0.209 to -0.113	<0.001
Total Cholesterol (mg/dL)	0.161	0.28	0.016 to 0.041	<0.001
Ankle brachial pressure index index	0.115	3.558	1.826 to 5.289	<0.001
Triglyceride (mg/dL)	0.100	0.10	0.005 to 0.016	0.001
Sex (male)	0.100	1.705	0.619 to 2.792	0.001
C-reactive protein (mg/dL)	-0.098	-0.452	-0.691 to -0.213	0.001
eGFR (mL/min/1.73 m^2)	0.083	0.028	0.009 to 0.046	0.005
Hypertension	0.073	1.074	0.101 to 2.046	0.013

$R^2 = 0.270$, F for change in $R^2 = 6.258$, $P < 0.001$
β: standardized coefficient, B: non- standardized coefficient, CI: confidence interval for B, eGFR: estimated glomerular filtration rate
Factors with $p < 0.05$ in Pearson correlation analysis: age, sex, critical limb ischemia, ankle brachial pressure index, history of stroke or transient ischemic attack, coronary artery disease, diabetes mellitus, hypertension, smoking, eGFR, C-reactive protein, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, D-dimer

with CVD and those on hemodialysis[8-11, 14]. Our study suggests that GNRI with dual evaluation of BMI and serum albumin may improve the diagnostic accuracy by overcoming the limitations of each parameter alone and may accurately predict OS, MACE, and MACLE in patients with PAD.

Other than BMI and albumin level, GNRI has significant correlations with CLI, age, total cholesterol, ABPI, triglyceride, CRP, eGFR, and hypertension. These results showed that GNRI has correlations with the severity of PAD, inflammation, and CKD in addition to nutritional factors. The present study lacked data regarding serial changes in the nutritional status, so we could not determine any effect of this on the clinical outcome in patients with PAD. Nutritional intervention is usually difficult to perform strictly. In addition, the effectiveness of nutritional therapy for patients with PAD remains unclear. We showed that malnutrition and inflammation are common and are a risk factor for poor clinical outcomes in patients with PAD, suggesting the nutritional intervention to be a novel therapeutic target in the man-

agement of patients with PAD.

Limitations

The limitations of this study were as follows. First, the sample sizes were relatively small and the study was performed at a single facility. Second, the prescription rate of statins was relatively low according to the guidelines at the time of treatment; this rate increased over time. Third, the life expectancy of patients with PAD was poor and the numbers in G3 and G2 were not enough to show full-length Kaplan–Meier curves. Therefore, we showed Kaplan–Meier estimates of OS, MACE, and MACLE according to the GNRI only for 10 years. Fourth, changes in lifestyle, including the nutritional status, during follow-up were not accounted for in this study. Therefore, we were unable to clarify the changes in BMI and serum albumin during the follow-up period. These issues require examination in further studies on life expectancy and fate of the leg in patients with PAD.

Conclusion

GNRI was found to be an independent predictor of OS, MACE, and MACLE in patients with PAD. This suggests that a simple and practical assessment of GNRI might be useful for predicting long-term outcomes in these patients.

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