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Combined Prognostic Value of Pre-Procedural Protein-Energy Wasting and Inflammation Status for Amputation and/or Mortality after Lower Extremity Revascularization in Hemodialysis Patients with Peripheral Arterial Disease

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Abstract: Background: Although lower extremity revascularization is commonly performed in hemodialysis patients, poor prognosis remains a major problem. Protein-energy wasting is reportedly associated with chronic inflammation and advanced atherosclerosis in hemodialysis patients. We investigated the association between the geriatric nutritional risk index (GNRI) as a surrogate marker of protein-energy wasting, C-reactive protein (CRP), and their joint roles in the prediction of amputation and/or mortality. **Methods:** We enrolled 800 patients successfully underwent lower extremity revascularization. Patients were divided into low, middle and high tertile (T1, T2 and T3) according to GNRI and CRP levels, respectively. **Results:** Amputation-free survival rates for 8 years were 47.0%, 56.9%, and 69.5% in T1, T2, and T3 of the GNRI, and 65.8%, 58.7%, and 33.2% for T1, T2, and T3 of CRP, respectively ($p<0.0001$ for both). Declined GNRI [adjusted hazard ratio (aHR) 1.78, 95% confidence interval (CI) 1.24-2.59, $p=0.0016$ for T1 vs. T3] and elevated CRP (aHR 1.86, 95%CI 1.30-2.70, $p=0.0007$ for T3 vs. T1) were independent predictors of amputation and/or mortality. In the combined setting of both variables, the risk was 3.77-fold higher (95% CI 1.97-7.69, $p<0.0001$) in the T1 of GNRI with T3 of CRP than in the T3 of GNRI with T1 of CRP. **Conclusions:** Patients with pre-procedural decreased GNRI and elevated CRP levels frequently experienced amputation and/or mortality, and a combination of both variables could more accurately stratify the risk.

Keywords: lower extremity revascularization; peripheral artery disease; hemodialysis; geriatric nutritional risk index; C-reactive protein

Introduction

Chronic kidney disease (CKD) patients requiring maintenance hemodialysis (HD) therapy have been widely recognized as the highest-risk population for cardiovascular disease, including peripheral artery disease (PAD).[1–3] Although lower limb revascularization has been commonly performed to treat PAD, poorer prognosis such as higher amputation or mortality rate remains a major clinical problem compared to those without CKD after revascularization regardless of bypass surgery[4,5] or endovascular therapy (EVT).[6,7] In addition, these situations have not improved although the advances in the medical management of HD patients in the last decade yet.[8,9] On the other hand, protein-energy wasting (PEW),[10] a state of decreased body protein mass and energy fuel, is reportedly prevalent in patients with CKD.[11,12] PEW can result not only from a poor diet but also be induced by inflammatory processes,[13,14] and inflammatory status itself is associated

with higher cardiovascular and all-cause mortality in this population.[15] Moreover, we previously reported that presence of PEW and inflammatory status was independently associated with lowering ankle brachial index (ABI), and that patients with these factors had a lower chance of survival.[16] In these contexts, we investigated the association of pre-procedural geriatric nutritional risk index (GNRI),[17,18] a surrogate marker of PEW, and C-reactive protein (CRP) levels with limb amputation and/or mortality after lower extremity revascularization in patients with CKD undergoing HD.

Methods

Patients

This is a retrospective study. From January 2009 to April 2018, 800 consecutive HD patients who underwent successful lower extremity revascularization (535 with endovascular therapy [EVT] and 265 with bypass surgery) with measurement of preprocedural GNRI and CRP levels at Matsunami General Hospital (Kasamatsu, Japan) and Nagoya Kyoritsu Hospital (Nagoya, Japan) were enrolled in this study. Patients with acute limb ischemia were excluded. Clinical information such as established risk factors, indications for revascularization, and target lesions was obtained from medical records.

GNRI and CRP Measurements

Blood samples were collected before the procedural day to measure serum albumin and CRP levels. The GNRI was calculated from individually obtained serum albumin levels and body weights, as reported by Yamada et al.[19]:

$$GNRI = [14.89 \times albumin\ (g/dl)] + [41.7 \times (body\ weight/ideal\ body\ weight)]$$

The body weight/ideal body weight ratio was set to one when the patient's body weight exceeded the ideal body weight. Ideal body weight was defined as the value calculated from the height and body mass index of 22.[19] All patients underwent HD therapy one day prior to the procedure, and body weight after HD therapy was used to calculate the GNRI. Serum CRP levels were measured using a latex-enhanced, highly sensitive CRP immunoassay. Then, patients were divided into tertiles according to their GNRI and CRP levels.

Follow-up

Patients were routinely followed up after discharge at 1, 3, and 6 months during 1 year, thereafter, followed up at yearly intervals using duplex scanning. If patients did not attend a hospital follow-up, they were interviewed by a telephone as possible, and the follow-up ended on the last visit day if we could not contact the patient. The follow-up period ended in January 2019. The primary outcome was amputation-free survival (AFS), officially defined as freedom from above-ankle amputation of the index limb or death from any cause.[20] The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Matsunami General Hospital (code: 573) and Nagoya Kyoritsu Hospital (code: K132－02), respectively. Written informed consent was waived to be obtained with Information regarding opt-out of this study on the website in each hospital due to the retrospective manor of this study.

Statistical Analyses

Normal distributed variables were expressed as mean ± SD, and asymmetrically distributed data were given as the median and interquartile range. Differences between the groups were evaluated using one-way analysis of variance or the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. The AFS rates among the groups were expressed using the Kaplan–Meier method and the difference was compared using a log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for each factor using the Cox proportional hazards models. All baseline variables with P < 0.05 by univariable analysis were entered into a multivariate

model to determine independent predictors of the outcome. To clarify whether the predictability for amputation and/or mortality would improve after the addition of GNRI alone, CRP alone, and both into a baseline model with established risk factors, we calculated the C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The C-index is defined as the area under receiver-operating characteristic curves between individual predictive probabilities for the endpoints and the incidence of the endpoints, and was compared among each predicting model.[21] The NRI indicates how many rate of patients improved their predicted probabilities for the endpoints, and the IDI expressed the average improvement in predicted probabilities for the endpoints after addition of variables into the baseline model.[22] Differences were set to be statistically significant at a two-sided P value less than 0.05. All statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

The clinical characteristics of the patients are shown in **Table 1**.

Table 1. Patient clinical characteristics.

	All patients (n = 800)	GNRI < 88.1 (n = 269)	GNRI 88.1-96.7 (n = 264)	GNRI > 96.7 (n = 267)	P value
Male gender (%)	66.9	62.5	67.4	70.7	0.12
Age (years)	67±10	69±10	67±9	66±10	0.0024
Diabetes (%)	63.3	63.2	64.7	61.8	0.78
Hypertension (%)	62.1	58.0	61.7	66.7	0.12
Dyslipidemia (%)	24.5	18.2	25.8	29.6	0.0076
Smoking (%)	25.7	18.6	31.4	27.2	0.0078
Body mass index (Kg/m^2)	21.2±3.3	19.2±2.9	21.0±2.6	23.3±3.0	<0.0001
Coronary artery disease (%)	63.5	58.7	63.9	67.8	0.092
Stroke (%)	16.9	18.6	15.5	16.5	0.63
Indications (%)					<0.0001
Claudication	47.1	36.8	43.9	60.4	
Rest pain	12.3	13.6	11.5	11.9	
Ulcer / gangrene	40.6	49.6	44.6	27.7	
GNRI	92.0±9.8	81.4±5.8	92.3±2.4	102.4±5.3	<0.0001
CRP (mg/l)	5.1 (2.0-20.0)	11.3 (2.9-44.5)	4.0 (1.0-14.0)	3.0 (1.0-12.0)	<0.0001
Pre-procedural ABI	0.62 (0.45-0.79)	0.65 (0.41-0.87)	0.57 (0.44-0.79)	0.64 (0.49-0.77)	0.35
Procedure (%)					<0.0001
Bypass surgery	33.1	38.7	39.8	21.0	
Endovascular therapy	66.9	61.3	60.2	79.0	
Number of lesions	825	282	271	272	
Target artery (%)					<0.0001
Iliac	18.1	22.7	17.6	14.3	
Femoropopliteal	62.1	52.8	59.1	72.8	
Below-knee	21.3	24.5	23.3	12.9	

GNRI, geriatric nutritional risk index; CRP, C-reactive protein; ABI, ankle-brachial index.

Table 1. Clinical characteristics (continued).

	Serum CRP < 2.0 mg/l (n = 270)	Serum CRP 2.0–12.6 mg/l (n = 266)	Serum CRP > 12.6 mg/l (n = 264)	P value
Male gender (%)	62.6	69.2	68.9	0.19
Age (years)	66±10	67±10	69±10	0.046
Diabetes (%)	60.4	60.9	63.3	0.091

|				
Hypertension (%)	63.7	61.7	61.0	0.80
Dyslipidemia (%)	25.9	24.8	22.7	0.68
Smoking (%)	27.5	24.8	24.9	0.75
Body mass index (Kg/m²)	20.9±3.1	21.2±3.0	21.5±3.7	0.15
Coronary artery disease (%	63.2	65.0	63.5	0.78
Stroke (%)	18.6	18.4	13.6	0.22
Indications (%)				<0.0001
Claudication	61.9	49.6	29.6	
Rest pain	14.6	15.9	6.5	
Ulcer / gangrene	23.5	34.5	63.9	
GNRI	94.3±9.4	93.1±9.7	89.1±10.1	<0.0001
CRP (mg/l)	1.0 (1.0-2.0)	5.9 (3.9-8.0)	39.5 (20.0-70.0)	<0.0001
Pre-procedural ABI	0.65 (0.47-0.79)	0.63 (0.44-0.82)	0.57 (0.43-0.76)	0.23
Procedure (%)				<0.0001
Bypass surgery	22.2	30.5	47.0	
Endovascular therapy	77.8	69.5	53.0	
Number of lesions	274	271	280	
Target artery (%)				<0.0001
Iliac	22.3	18.5	13.6	
Femoropopliteal	69.7	64.6	52.1	
Below-knee	8.0	17.0	34.3	

GNRI, geriatric nutritional risk index; CRP, C-reactive protein; ABI, ankle-brachial index.

Patients were divided into tertiles according to GNRI levels; tertile 1 (T1): <88.1, T2:88.1-96.7and T3: >96.7, and CRP levels; T1: <2.0 mg/l, T2:2.0-12.6 mg/l and T3: >12.6 mg/l. Patients with lower GNRI had higher CRP levels [11.3 (2.9-44.5) mg/l, 4.0 (1.0-14.0) mg/l and 3.0 (1.0-12.0) mg/l in T1, T2, and T3, respectively; p<0.0001], and a higher prevalence of ulcer/gangrene (49.6%, 44.6%, and 27.7% in T1, T2, and T3, respectively; p<0.0001). Similarly, patients with higher CRP also had lower GNRI (94.3±9.4, 93.1±9.7 and 89.1±10.1 in T1, T2 and T3, respectively, p<0.0001) and higher prevalence of ulcer/gangrene (23.5%, 34.5% and 63.9% in T1, T2 and T3, respectively, p<0.0001).

Predictive value of the GNRI and CRP

During the follow-up period (median, 43 months), 56 (7.0%) patients required major amputation, and 183 (22.9%) patients died. Kaplan-Meier analysis showed that the AFS rates for 8 years were 47.0%, 56.9%, and 69.5% in T1, T2, and T3 of the GNRI, and 65.8%, 58.7%, and 33.2% in T1, T2, and T3 of CRP, respectively (p<0.0001 for both) (**Figure 1**).

Fig. 1 Amputation-free survival rates in tertiles of GNRI (left panel) and CRP (right panel)
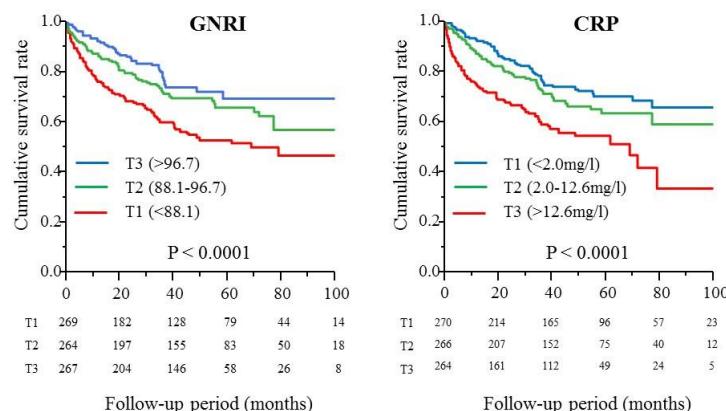
After adjustment for male sex, age, previous coronary artery disease, procedure (EVT vs. bypass surgery), below-knee artery disease, and ulcer/gangrene as covariates with p<0.05 by univariate analysis, decreased GNRI [adjusted HR 1.78, 95% CI 1.24-2.59, p=0.0016 for T1 vs. T3], and elevated CRP (adjusted HR 1.86, 95%CI 1.30-2.70, p=0.0007 for T3 vs. T1) were identified as independent predictors of amputation and/or mortality (**Table 2**). Similar results were obtained for the amputation and mortality rates.

Table 2. Predictive value of GNRI and CRP for amputation and mortality.

	Non-Adjusted		Adjusted**	
	HR (95%CI)	P value	HR (95%CI)	P value
Amputation or death				
GNRI (vs. T3)		<0.0001*		0.0070*
T2	1.46 (1.03-2.09)	0.031	1.42 (0.97-2.09)	0.070
T1	2.18 (1.57-3.07)	<0.0001	1.78 (1.24-2.59)	0.0016
CRP (vs. T1)		<0.0001*		0.0026*
T2	1.32 (0.93-1.89)	0.11	130 (0.90-1.91)	0.15
T3	2.33 (1.67-3.27)	<0.0001	1.86 (1.30-2.70)	0.0007
Amputation				
GNRI (vs. T3)		<0.0001*		0.032*
T2	1.11 (0.78-2.44)	0.79	1.05 (0.46-2.39)	0.89
T1	3.17 (1.70-6.37)	0.0002	2.01 (1.04-4.12)	0.034
CRP (vs. T1)		0.0003*		0.045*
T2	1.26 (0.58-2.79)	0.54	1.01 (0.45-2.23)	0.98
T3	3.35 (1.75-6.85)	0.0001	2.02 (1.02-4.25)	0.042
Mortality				
GNRI (vs. T3)		0.0002*		0.0083*
T2	1.51 (1.03-2.23)	0.032	1.51 (0.99-2.33)	0.052
T1	2.12 (1.48-3.09)	<0.0001	1.87 (1.25-2.84)	0.0020
CRP (vs. T1)		0.0004*		0.043*
T2	1.30 (0.89-1.90)	0.17	1.29 (0.86-1.94)	0.20
T3	2.03 (1.42-2.93)	<0.0001	1.64 (1.11-2.45)	0.012

*: p for trend; **; adjusted for male, age, previous coronary artery disease, endovascular therapy (vs. bypass surgery), below-knee artery disease and ulcer/gangrene as covariates with p<0.05 by univariate analysis.

Combined predictive value of the GNRI and CRP

The combined setting of both variables could stratify the risk of amputation and/or mortality, and the risk was 3.77-fold higher (95% CI 1.97-7.69, p<0.0001) in GNRI T1 with CRP T3 than in GNRI T3 with CRP T1 (**Figure 2**).

Fig. 2 Adjusted hazard ratio (HR) for amputation and/or mortality in combined settings of tertiles of GNRI and CRP
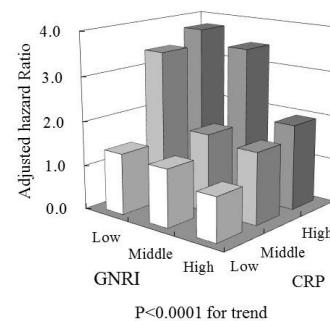
P<0.0001 for trend

The adjusted HR was 3.77 (95% CI 1.97-7.69) for patients with lower GNRI and higher CRP vs. those with higher GNRI and lower CRP.

Similar results were also obtained for amputation and mortality (adjusted HR 3.64, 95% CI 1.32-12.8, p=0.0018 for amputation, and adjusted HR 3.68, 95% CI 1.76-8.39, p<0.0001 for mortality for GNRI T1 with CRP T3 vs. GNRI T3 with CRP T1, respectively) (**Figure 3**).

Fig. 3 Adjusted hazard ratio (HR) for amputation (left panel) and mortality (right panel) in combined settings of tertiles of GNRI and CRP

P=0.0018 for trend   P=0.0001 for trend
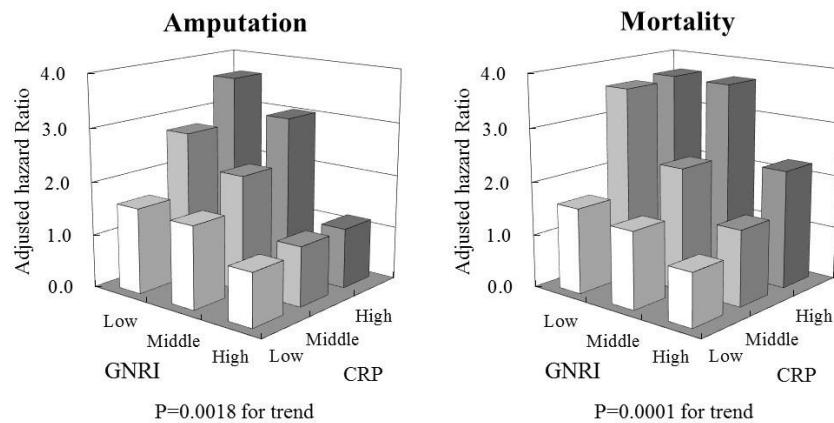
The adjusted HR for patients with lower GNRI and higher CRP vs. those with higher GNRI and lower CRP was 3.64 (95% CI 1.32-12.8) for amputation, and 3.68 (95%CI 1.76-8.39) for mortality.

For model discrimination, the addition of both GNRI and CRP in a predicting model with established risk factors improved the C-statistics (from 0.661 to 0.716, p=0.0021), NRI (0.508, p<0.0001), and IDI (0.042, p<0.0001), even greater than that of each individual (NRI 0.145, p=0.047 and IDI 0.006, p=0.035 vs. GNRI alone, and NRI 0.427, P<0.0001 and IDI 0.029, p<0.0001 vs. CRP alone, respectively) (**Table 3**).

Table 3. Discrimination of each prediction model for amputation or mortality using the C-index, net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

	C-index (95%CI)	P value	NRI	P value	IDI	P value
Established risk factors*	0.661	reference		reference		reference
+GNRI	0.710	0.0060	0.456	<0.0001	0.037	<0.0001
+CRP	0.681	0.0034	0.217	0.0063	0.014	0.0001
+GNRI and CRP	0.716	0.0021	0.508	<0.0001	0.042	<0.0001
+GNRI and CRP vs. +GNRI	0.006**	0.047	0.145	0.047	0.006	0.035
+GNRI and CRP vs. +CRP	0.035**	0.038	0.427	<0.0001	0.029	<0.0001

* Model includes male sex, age, previous coronary artery disease, endovascular therapy (vs. bypass surgery), below-knee artery disease, and ulcer/gangrene. **; estimated difference.

Discussion

Our results clearly demonstrate that a preprocedural decline in GNRI and elevated CRP levels, which reflect PEW and chronic inflammation status, affect poor AFS after lower limb revascularization in patients undergoing HD, and that the combination of both variables could not only stratify the risk of poor AFS but also improve predictability.

Numerous studies have reported consistently poorer prognosis after lower limb revascularization in patients undergoing HD compared to the general population in spite of advances in medical management of HD.[4–9] In previous studies, we have reported the following findings: 1) severe/moderate nutritional risk (GNRI<92) was higher in patients undergoing HD (53%) than in the elderly general population (21%-43%) despite HD patients (average of 64 years) being younger than the elderly general population (80-85 years).[12] 2) In patients who underwent bypass surgery, pre-procedural CRP levels was markedly higher in HD patients than in non-HD patients (median of 11

mg/l vs. 4 mg/l).[23] 3) Interestingly, pre-procedural elevated CRP levels could predict poor AFS in only HD patients but not non-HD patients who underwent infrapopliteal bypass surgery.[24] Thus, our results in the present study might be reasonably explained, and the PEW and chronic inflammation status, a CKD-specific morbidity, might be considered to be one of cause of poor AFS after lower limb revascularization in this population.

In addition, we previously reported that the limb salvage rate after bypass surgery was comparable between HD and non-HD patients when performing propensity score matching with unfavorable factors, including pre-procedural CRP levels.[24] This suggests the possibility of improved prognosis if inflammation status is adequately managed even in patients undergoing HD. In this context, the recently developed Wound, Ischemia, and foot infection (WIfI) scoring system is considered important for assessing the risk of poor AFS. Unfortunately, WIfI scores were not measured in the present study. The association between WIfI score and prognosis in this high-risk population should be clarified in the future.

The condition of PEW was previously referred to as malnutrition, inflammation, and atherosclerosis (MIA) syndrome before it was officially defined by the International Society of Renal Nutrition and Metabolism (ISRNM).[13,14] We have previously reported the close association of both declined GNRI and elevated CRP with abnormal ABI.[16] Abnormal ABI also reportedly reflects not only PAD but also systemic atherosclerosis,[25,26] thus, these previous findings might manifest as MIA syndrome. In this context, patients with decreased preprocedural GNRI and elevated CRP levels were considered to have advanced atherosclerosis and poor prognosis in the present study. Thus, physicians should pay more attention to these unfavorable conditions in this population.

Finally, the addition of both preprocedural GNRI and CRP levels in a predictive model with established risk factors such as age, infrapopliteal disease, or ulcer/gangrene significantly improved the predictability for poor AFS after revascularization to a greater extent than the addition of GNRI and CRP alone. Thus, measurement of both variables before procedures might be clinically beneficial to predict prognosis more accurately because these variables are also easily obtained in daily practice.

The present study has several limitations. First, all the study participants were Japanese, who reportedly have a lower atherosclerotic risk compared to patients in the United States and Europe.[27] Second, the study participants were from two centers only. Third, we could not assess the WIfI scores. The lack of data regarding wound or infection status in the limbs might be the most important limitation of this study.

Conclusions

A preprocedural decline in GNRI and elevated CRP level, which reflect PEW and chronic inflammation status, are closely associated with poor AFS after lower limb revascularization in chronic HD patients. Furthermore, the combination of both variables could not only stratify the risk of amputation and/or mortality, but also improve predictability when added to established risk factors.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Matsunami General Hospital (code: 573) and Nagoya Kyoritsu Hospital (code: K132－02), respectively.

Informed Consent Statement: Written informed consent was waived to be obtained with Information regarding opt-out of this study on the website in each hospital due to the retrospective manor of this study.

Data Availability Statements: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: No found was available in the present study.

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