Impact of the Geriatric Nutritional Risk Index on the Long-Term Outcomes of Patients Undergoing Open Bypass for Intermittent Claudication

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Background: Nutritional status has been reported to be a predictor of the outcomes of critical limb ischemia. However, there have been no reports of the association between nutritional status and the prognosis of patients with intermittent claudication (IC). The aim of this study was to examine whether or not the geriatric nutritional risk index (GNRI) is independently associated with the long-term outcomes of elderly patients following open bypass for IC.

Methods and Results: The preoperative nutritional status of patients aged ≥65 years undergoing infrainguinal bypass for IC between 1991 and 2017 was retrospectively evaluated using the GNRI. Patients were divided into 3 groups based on the GNRI: Group I (normal nutritional risk), GNRI >98; Group II (low nutritional risk), GNRI 92 to ≤98; Group III (moderate to high nutritional risk), GNRI <92. The amputation-free survival (AFS), overall survival, and freedom from cardiovascular death up to 5 years were calculated by Kaplan-Meier method and a multivariate analysis was performed to detect independent predictors of each outcome. Group I showed superior outcomes to Group III for each of the 3 outcomes and the multivariate analysis showed that GNRI was an independent predictor of AFS.

Conclusions: The GNRI was independently associated with the AFS of elderly patients who underwent open bypass for IC.

Key Words: Amputation-free survival; Geriatric nutritional risk index; Infrainguinal bypass; Intermittent claudication; Overall survival

The present study was conducted to investigate whether or not significant associations exist between the preoperative nutritional status, estimated using the geriatric nutritional risk index (GNRI), and the long-term prognoses of patients undergoing infrainguinal bypass for IC and to elucidate the preoperative factors that independently predict the postoperative outcome.

Methods

This study was approved by the institutional review boards of Saiseikai Yahata General Hospital and Steel Memorial Yawata Hospital.

Database and Patient Selection

The data on patients aged ≥65 years who underwent infrainguinal bypass for IC because of arteriosclerosis obliterans (ASO) at Steel Memorial Yawata Hospital between January 1991 and March 2015 and at Saiseikai Yahata General Hospital between April 2015 and December 2017 were reviewed. Patients with a history of infrainguinal bypass in either limb but not of EVT or who had a history of EVT or who had a history of EVT were excluded. The association between nutritional status and the prognosis of patients has been gathering attention in various fields of cardiovascular disease research.1–6 Peripheral artery disease (PAD) is no exception and several authors have reported a positive association between nutritional status, estimated using a tool for assessing observational nutritional indices, and the early and late outcomes in patients with PAD.7–9 Most of patients in those studies suffered from critical limb ischemia (CLI), so there are no reports concerning the association between nutritional status and the prognoses of patients with intermittent claudication (IC).

When pharmacologic or exercise therapy fails in IC patients with a functional or life-limiting disability, bypass surgery is recommended for long superficial femoral artery lesions when an autologous vein is available and the life expectancy is >2 years.10 Accordingly, identifying the predictors of the long-term prognoses of patients with IC would be useful for deciding the revascularization strategy, because bypass grafting using an adequate autologous vein generally shows superior durability to endovascular therapy (EVT).11–13

Received January 7, 2019; revised manuscript received March 12, 2019; accepted March 25, 2019; J-STAGE Advance Publication released online April 25, 2019  Time for primary review: 44 days
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of major amputation in the contralateral limb were excluded. When a patient underwent infrainguinal bypass in both limbs simultaneously, the limb with the lower ankle-brachial index (ABI) value was adopted as the ischemic level of the patient.

**Analyzed Variables**

The following variables, together with age and sex, were retrieved from the patients’ clinical charts or electronic medical records: the date of surgery, height, body weight (BW), preoperative laboratory data (serum albumin [Alb], hemoglobin [Hb], ABI), personal history (hypertension [HT], diabetes mellitus [DM], coronary artery disease [CAD], cerebrovascular disease [CVD], dyslipidemia, chronic obstructive pulmonary disease [COPD]), endstage renal disease [ESRD], and current smoking), distal target artery for bypass graft (supragenicular vs. infragenicular), and postoperative antiplatelet medication (aspirin, clopidogrel, ticlopidine, prasugrel, cilostazol, or sarpogrelate) or statin use.

**Evaluation of the Preoperative Nutrition-Related Risks**

The preoperative nutrition-related risk was represented by the GNRI. The GNRI is calculated as: 14.89×Alb (g/dL) +41.7×BW (kg)/ideal BW (kg), where ideal BW (kg)= 22×height (m)×height (m). We used this formula for calculating the ideal BW instead of the Lorentz equation described in the original paper of Bouillanne et al. because knee height was not recorded in the clinical charts of the patients in this study. When the real BW is over the ideal BW, BW/ideal BW is adjusted to 1.

**Grouping of Patients**

The patients were classified into different risk groups based on their GNRI, according to the classification of Bouillanne et al. as follows: GNRI >98, no-risk group; GNRI 92 to ≤98, low nutrition-related risk group; GNRI 82 to <92, moderate nutrition-related risk group; GNRI <82, high nutrition-related risk group. In this study, the patients were divided into 3 groups based on the preoperative GNRI because the number of patients with GNRI values <82 was too few to be analyzed: Group I, no-risk group; Group II, low nutrition-related risk group; Group III, moderate to high nutrition-related risk group.

**Revascularization Strategy for IC and Follow-up**

The revascularization strategy for IC changed over the time period of the study. Open surgery was mainly performed for patients with TASC B–D until 2000. Thereafter, the indication of EVT gradually expanded from TASC A to TASC D. Since the introduction of a stent graft for occlusion of the superficial femoral artery in 2017, the indication of open surgery has been restricted to younger patients or elderly patients with anatomically complicated lesions. Principally, patients undergoing open surgery were observed at an interval of 3–6 months after discharge as outpatients, and the limb and life statuses were verified by phone interviews of patients who could not visit the hospital. A final review was conducted in October to December, 2018 and up to 5 years of data were analyzed.

**Outcome Measures**

Amputation-free survival (AFS) was set as the primary outcome measure and overall survival (OS) and freedom from cardiovascular death (FFCVD) were set as the secondary outcome measures.
Definitions

The boundary of the early and late periods was set between December 2004 and January 2005. IC was defined as Rutherford 1, 2, or 3. HT was defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or both, or ongoing therapy for HT. DM was defined as fasting blood glucose ≥105 mg/dL or ongoing therapy for DM with an oral hypoglycemic agent or insulin injection. CAD was defined as a history of angina pectoris, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. CVD was defined as a history of transient ischemic attack, cerebral infarction, cerebral bleeding, or revascularization of the carotid artery or intracranial artery. COPD was defined as a forced expiratory volume <70% in 1s. ESRD was defined as the need for hemodialysis or peritoneal dialysis. Dyslipidemia was defined as fasting total cholesterol >220 mg/dL, or triglycerides >207 mg/dL (male) or >137 mg/dL (female), or both, or ongoing therapy for dyslipidemia. Patients with a smoking habit who had continued smoking until just before surgery were defined as current smokers. Major amputation was defined as amputation of the leg above the ankle. AFS was defined as survival without major amputation of either limb, even if the limb without any history of infragenicual bypass was amputated.

Statistical Analysis

With the exception of the follow-up period and follow-up index, data are presented as the median (interquartile range) for continuous variables and the number and percentage for categorical variables. The mean follow-up period and the follow-up index are presented as the mean ± standard deviation. In the survival curve, the values at each year are expressed as the survival rate ± standard error.

Comparisons among 3 groups were performed by the Kruskal-Wallis test and Pearson’s chi-squared test for continuous and categorical variables, respectively. Survival curves were calculated by the Kaplan-Meier method, and comparisons among 3 groups were evaluated by a log-rank test. Post-hoc test was performed for variables with P-values <0.05. Continuous variables, categorical variables, and survival curves calculated by the Kaplan-Meier method were compared using the Wilcoxon rank-sum test, Pearson’s chi-squared test, and a log-rank test, respectively. Adjustment was performed for multiplicity with Bonferroni’s correction, and P<0.017 was considered to indicate statistical significance in the multiple comparisons.

A Cox proportional hazards regression analysis that included variables with P<0.1 in the univariate analysis was performed as a multivariate analysis. Death or major amputation, all-cause death, and cardiovascular death were used as the dependent variables in the analysis for AFS, OS, and FFCVD. P<0.05 was considered to indicate statistical significance. The statistical analyses were performed using the JMP software program (version 11.2 for Mac, SAS Institute, Cary, NC, USA).

Results

Flowchart of Patients in the Analysis (Figure 1)

A total of 306 consecutive patients underwent infragenicual bypass for IC for ASO: 66 patients with a history of infragenicual bypass in either limb were excluded; 1 patient was excluded from the analysis because of a history of major amputation of the contralateral limb at the de novo infragenicual bypass; 51 patients <65 years of age were excluded. Consequently, 188 patients were included in the analysis.

A total of 104, 53, and 30 patients were classified by

### Table 1. Patients’ Background Characteristics

| Variable                  | Group I (n=104) | Group II (n=53) | Group III (n=30) | P value |
|---------------------------|----------------|-----------------|-----------------|---------|
| Late time period          | 53, 51%        | 19, 36%         | 8, 27%          | 0.029   |
| Age (years)               | 73.5 (69–78)   | 75 (71.5–79)    | 74.5 (69.8–78.5)| 0.249   |
| Sex, female               | 23, 22%        | 15, 28%         | 9, 30%          | 0.559   |
| BMI                       | 22.9 (21.2–24.1)| 20.3 (18.8–22) | 19.0 (17.8–20.8)| <0.001*|
| Alb (g/dL)                | 4.2 (4.1–4.4)  | 3.8 (3.7–4.1)   | 3.5 (3.3–3.7)   | <0.001* |
| Hb (g/dL)                 | 13.3 (12.5–14.7)| 12.6 (11.3–13.7)| 11.9 (10.9–12.7)| <0.001* |
| ABI                       | 0.51 (0.33–0.62)| 0.51 (0.39–0.59)| 0.49 (0.3–0.59) | 0.621   |
| HT                        | 77, 74%        | 38, 72%         | 19, 63%         | 0.518   |
| DM                        | 44, 42%        | 15, 28%         | 12, 40%         | 0.225   |
| CAD                       | 28, 27%        | 17, 32%         | 13, 43%         | 0.227   |
| CVD                       | 25, 24%        | 9, 17%          | 3, 10%          | 0.196   |
| Dyslipidemia              | 36, 35%        | 11, 21%         | 9, 30%          | 0.200   |
| COPD                      | 4, 4%          | 10, 19%         | 5, 17%          | 0.005*  |
| ESRD                      | 3.3%           | 4.8%            | 4.13%           | 0.084   |
| Current smoking           | 27, 26%        | 19, 37%         | 7, 24%          | 0.352   |
| Target artery, infragenicual| 18, 17%      | 18, 34%         | 7, 23%          | 0.064   |
| Statin                    | 26, 26%        | 11, 22%         | 6, 21%          | 0.763   |
| Antiplatelet agent        | 84, 81%        | 42, 79%         | 21, 70%         | 0.444   |

*1, #2, and #3 were added when the P value in the post-hoc test between Groups I and II, Groups II and III, and Groups III and I was <0.017, respectively. ABI, ankle-brachial pressure; Alb, serum albumin; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; ESRD, endstage renal disease; Hb, hemoglobin; HT, hypertension.
and II, significant differences were observed in BMI, Alb, Hb, and COPD. In the post-hoc analysis of Groups I and II, 0.003 between Groups I and III, and 0.054 between Groups II and III.

5-Year AFS, OS, and FFCVD Rates (Figure 2)
The mean follow-up period was 1,448±536 days and the follow-up index was 0.96±0.12. Neither death nor major amputation occurred within 30 days after surgery. In the

GNRI into Groups I, II, and III, respectively. The GNRI of 1 patient could not be calculated because of a lack of data.

Baseline Characteristics
The characteristics of Groups I, II, and III and the results of the statistical analyses are shown in Table 1.

The variables for which significant differences were observed were late time period, body mass index (BMI), Alb, Hb, and COPD. In the post-hoc analysis of Groups I and II, significant differences were observed in BMI, Alb, Hb, and COPD. In the post-hoc analysis of Groups II and III, Alb was the only factor that showed a significant difference. In the post-hoc analysis of Groups I and III, significant differences were observed in BMI, Alb, and Hb.
GNRI on Prognosis in Claudicants With Bypass

Table 2. (A) Multivariate Analysis of Factors Associated With Amputation-Free Survival, (B) Multivariate Analysis of Factors Associated With Overall Survival, (C) Multivariate Analysis of Factors Associated With Freedom From Cardiovascular Death

|        | Unadjusted | Adjusted  |
|--------|------------|-----------|
|        | HR 95% CI  | P value   |
|        |            |           |
| (A)    |            |           |
| Late time period | 0.51 | 0.25–0.97 | 0.049 |
| GNRI (/10)       | 0.50 | 0.37–0.70 | <0.001 |
| Age (/10 years)  | 2.50 | 1.44–4.33 | 0.001 |
| Sex (female)     | 1.16 | 0.58–2.18 | 0.660 |
| Hb (1 g/dL)      | 0.90 | 0.76–1.11 | 0.204 |
| ABI (/0.1)       | 0.87 | 0.77–1.15 | 0.0497 |
| HT              | 1.04 | 0.56–2.05 | 0.050 |
| DM             | 1.71 | 0.96–3.07 | 0.070 |
| CAD            | 1.85 | 1.01–3.30 | 0.043 |
| CVD            | 0.96 | 0.44–1.91 | 0.920 |
| Dyslipidemia    | 0.70 | 0.34–1.34 | 0.294 |
| COPD           | 2.36 | 1.07–4.70 | 0.035 |
| ESRD           | 2.29 | 0.69–5.68 | 0.156 |
| Current smoking | 1.05 | 0.53–1.96 | 0.872 |
| Infragenicular artery | 1.22 | 0.61–2.30 | 0.555 |
| Statin         | 1.03 | 0.50–1.98 | 0.931 |
| Antiplatelet agent | 1.20 | 0.6–2.65 | 0.618 |

|        | Unadjusted | Adjusted  |
|--------|------------|-----------|
|        | HR 95% CI  | P value   |
|        |            |           |
| (B)    |            |           |
| Late time period | 0.47 | 0.21–0.94 | 0.032 |
| GNRI (/10)       | 0.54 | 0.39–0.79 | 0.002 |
| Age (/10 years)  | 2.40 | 1.35–4.27 | 0.003 |
| Sex (female)     | 0.83 | 0.43–1.74 | 0.608 |
| Hb (1 g/dL)      | 0.89 | 0.75–1.06 | 0.181 |
| ABI (/0.1)       | 0.88 | 0.77–1.02 | 0.094 |
| HT              | 0.89 | 0.47–1.77 | 0.718 |
| DM             | 1.87 | 1.01–3.47 | 0.046 |
| CAD            | 1.85 | 0.98–3.42 | 0.056 |
| CVD            | 0.99 | 0.42–2.03 | 0.973 |
| Dyslipidemia    | 0.62 | 0.28–1.25 | 0.188 |
| COPD           | 2.70 | 1.21–5.45 | 0.017 |
| ESRD           | 2.59 | 0.77–6.47 | 0.111 |
| Current smoking | 0.88 | 0.41–1.74 | 0.730 |
| Infragenicular artery | 1.28 | 0.61–2.47 | 0.498 |
| Statin         | 1.24 | 0.59–2.42 | 0.551 |
| Antiplatelet agent | 1.21 | 0.59–2.82 | 0.620 |

|        | Unadjusted | Adjusted  |
|--------|------------|-----------|
|        | HR 95% CI  | P value   |
|        |            |           |
| (C)    |            |           |
| Late time period | 0.29 | 0.07–0.87 | 0.025 |
| GNRI (/10)       | 0.44 | 0.29–0.73 | 0.002 |
| Age (/10years)  | 2.57 | 1.13–5.87 | 0.025 |
| Sex (female)     | 2.68 | 1.08–6.48 | 0.034 |
| Hb (1 g/dL)      | 0.91 | 0.71–1.18 | 0.488 |
| ABI (/0.1)       | 0.89 | 0.72–1.10 | 0.263 |
| HT              | 0.77 | 0.31–2.04 | 0.577 |
| DM             | 1.45 | 0.58–3.50 | 0.414 |
| CAD            | 3.50 | 1.45–8.93 | 0.006 |
| CVD            | 0.45 | 0.07–1.57 | 0.238 |
| Dyslipidemia    | 0.56 | 0.16–1.52 | 0.266 |
| COPD           | 1.04 | 0.17–3.60 | 0.959 |
| ESRD           | 1.24 | 0.07–6.01 | 0.837 |
| Current smoking | 0.71 | 0.20–1.95 | 0.525 |
| Infragenicular artery | 0.87 | 0.25–2.37 | 0.800 |
| Statin         | 1.12 | 0.36–2.94 | 0.825 |
| Antiplatelet agent | 0.88 | 0.34–2.70 | 0.804 |

GNRI, geriatric nutritional risk index. Other abbreviations as in Table 1.
comparison of Groups I and III, significant differences were observed in the rates of AFS (P<0.001), OS (P=0.003), and FFCVD (P=0.003). There were no significant differences between Groups I and II, or Groups II and III for any of the outcomes.

Discussion

The present study showed that patients with no nutrition risk had significantly better prognoses than those with moderate to high nutrition-related risk following infragenual bypass for IC, which was observed for all outcomes, namely AFS, OS, and FFCVD. Furthermore, the GNRI was independently associated with 5-year AFS.

Multiple predictors of survival-related outcomes in patients with IC have been reported, but no reports have described the association between nutrition and long-term prognosis of patients with IC. Although Alb and BMI seem to be available as surrogate markers for nutrition, the Alb value is easily affected by inflammation or hydration and BW change is affected by fluid status. In particular, the BMI paradox confusing the relationship between BMI as a continuous variable and prognosis. In their review article, Spychalska-Zwolinska et al noted that the prognosis of both malnourished and severely obese patients was worse and that poor outcomes in underweight patients and better results in overweight patients were seen following intervention, but no such a relationship was observed in patients with conservative therapy. The GNRI, which is calculated using both Alb and BMI, is a tool for evaluating nutrition-related risk. Bouillanne et al stressed the difference between nutrition-related risk and nutritional status and stated that nutrition-related risk suggests the risk of events after treatment.

A positive association between the GNRI and the long-term outcomes of patients with PAD was reported by Shiraki et al and Yokoyama et al. Shiraki et al showed that the GNRI was independently associated with all-cause death and freedom from major amputation in patients after EVT for CLI and Yokoyama et al reported that the GNRI was a positive predictor of major adverse cardiovascular limb events (MACLE) in patients with PAD following EVT, most of whom suffered from CLI. In addition, Yokoyama et al indicated that the controlling nutritional (CONUT) score was also an independent predictor of MACLE. The CONUT score is another tool for estimating nutritional status and is widely used, similar to the GNRI. The CONUT score can be simply calculated using blood biomarkers (Alb, total cholesterol, and total lymphocyte count). When analysis of the present study was performed using the CONUT score instead of the GNRI, the CONUT score was not shown to be an independent predictor of any of the outcomes (data not shown).

The goal of treatment for IC is not similar to that for CLI. The first purpose of treatment for IC is to extend the walking distance without pain, which can be followed by the amelioration of quality of life and may lead to an improvement of the life prognosis. Because the prognosis of life and limb in patients with IC is definitely better than that in patients with CLI, the durability of the revascularized artery and preventing deterioration of limb ischemia leading to CLI, even after graft failure, are extremely important. Thus, the correct choice of treatment modality is essential and knowing the predictors of long-term outcome would be useful for deciding the treatment method. The present study showed that >80% of patients ≥65 years of age were still alive without limb loss at 5 years after surgery, suggesting that open bypass using an available autologous vein graft should be actively selected as the revascularization method for long lesions in the femoropopliteal area in patients with no nutritional risk.

Interestingly, the GNRI was not an independent predictor of OS or FFCVD, which was different from the results reported by Shiraki et al. Because the prognosis of limb and life is much better for patients with IC than for patients with CLI, 5 years’ observation may not be sufficient to obtain significant results. In addition to the GNRI, age and COPD were shown to be independent predictors for AFS. When a patient undergoes open bypass, the severity of patients’ comorbidities is taken into consideration and greatly influences the surgical approach, especially for IC. To begin with, surgery is not indicated for patients whose comorbidities are severe enough to restrict walking. For the same reason, frailty, sarcopenia, cognition, or low level of activities of daily living, which have recently come into focus in relation to their association with the late outcomes of patients with CLI, do not become prognostic factors for patients with IC who can undergo open surgery. In the present study, COPD was incidentally found with preoperative pulmonary function testing in patients, most of whom did not have respiratory symptoms that were severe enough to restrict walking. Willey et al also demonstrated that age, COPD, and DM, together with other comorbidities, were predictors of death in a population of more than 175,000 PAD patients, the majority of whom had stable PAD (no history of CLI, amputation, or revascularization at baseline).

Consequently, the present study’s results suggested that even elderly patients, if they are not malnourished and do not have COPD, can be considered as active candidates for open bypass using an autologous vein graft because a long life with freedom from major amputation can be expected.

Study Limitations

First, this was a retrospective study performed by a single vascular surgery team and conducted continuously at 2 hospitals. Second, the study population was relatively small because remarkable advancement in the technology of EVT caused a paradigm shift in revascularization strategies and most patients now undergo EVT for IC caused by femoropopliteal disease. Third, the period of patient enrollment was quite long and the treatment strategy for revascularization changed over that time (as noted earlier). Fourth, the patients’ medication compliance was unclear. Change or discontinuation of medication may have occurred during the follow-up period.

Conclusions

The GNRI was an independent predictor of 5-year AFS in elderly patients who underwent open bypass for IC. Patients with no nutritional risk can be expected to live without limb loss for a longer period after open surgery.
than those with moderate to severe nutrition-related risk.

**Disclosure Statements**

The authors have neither financial nor other potential conflicts to declare.

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