Impact of Nutritional and Inflammation Status on Long-Term Bleeding in Patients Undergoing Percutaneous Coronary Intervention with an Oral Anticoagulant

Ruka Yoshida[1, 2], Hideki Ishii[3], Itsuro Morishima[2], Akihito Tanaka[1], Yasuhiro Morita[2], Kensuke Takagi[2], Naoki Yoshioka[2], Kenshi Hirayama[3], Naoki Iwakawa[3], Hiroshi Tashiro[1], Hiroki Kojima[1], Takayuki Mitsuda[1], Yusuke Hitora[3], Kenji Furusawa[1], Hideyuki Tsuboi[2] and Toyoaki Murohara[3]

[1] Department of Cardiology, Nagoya University Hospital, Nagoya, Japan
[2] Department of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan
[3] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Aim: Patients undergoing percutaneous coronary intervention (PCI) who require both oral anticoagulant (OAC) and antiplatelet therapy (APT) are exposed to a serious risk of bleeding. The aim of this study was to clarify the relationship among nutritional and inflammation status and long-term bleeding in patients requiring both OACs and APT after PCI.

Methods: We performed PCI in 3,718 consecutive patients between April 2011 and March 2017, 302 of whom were treated with both OACs and APT. Patients were followed for up to 3 years for bleeding events, defined as the Bleeding Academic Research Consortium (BARC) class ≥ 3 bleeding. We retrospectively evaluated the ability of the Geriatric Nutritional Risk Index (GNRI) and high-sensitivity C-reactive protein (hs-CRP) to detect bleeding events.

Results: During a median follow-up of 1,080 days, bleeding events were observed in 53 (17.5%) patients. Bleeding events were associated with a low GNRI (≤ 98) (hazard ratio [HR], 3.16; 95% confidence interval [CI], 1.84−5.45; $p < 0.0001$) and hs-CRP level ≥ 2.5 mg/L (HR, 2.75; 95% CI, 1.61−4.78; $p = 0.0003$). A low GNRI + high hs-CRP showed a 5.12-fold increase in the incidence of BARC class ≥ 3 bleeding (95% CI, 2.68−9.91; $p < 0.0001$) compared with a normal GNRI + low hs-CRP. The addition of the GNRI and hs-CRP to the PRECISE-DAPT score improved C-statistics from 0.67 to 0.71 and enhanced the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (NRI, 0.36, $p < 0.0001$; IDI, 0.066, $p < 0.0001$).

Conclusions: The GNRI and hs-CRP were novel predictors of the long-term bleeding risk in patients requiring both OACs and APT after PCI.

Key words: Antiplatelet therapy, Oral anticoagulant, Percutaneous coronary intervention, Bleeding events, Geriatric nutritional risk index

Introduction

Approximately 5%−10% of patients undergoing percutaneous coronary intervention (PCI) require long-term oral anticoagulant (OAC) use because of atrial fibrillation, mechanical heart valves, and other conditions[1]. In such patients, both antiplatelet therapy (APT) and OACs are indicated; however, great concern regarding bleeding complications (4%−16% of cases) has been raised[2, 3]. Various prediction scores for bleeding events have been proposed for patients who are taking antithrombotic agents[4, 5], and recently the PRECISE-DAPT score has been developed[6]. However, the performance of these risk scores to detect bleeding events

is moderate in patients who require both OACs and APT after PCI[7, 8].

Several studies have indicated a relationship between hypoalbuminemia and bleeding events in various conditions[9-11]. Recently, comprehensive nutritional assessment scores, such as the Geriatric Nutritional Risk Index (GNRI)[12] or controlling nutritional status (CONUT) score[13], have emerged, and these scores and inflammation markers were reported to be associated with long-term adverse events[14-16]. However, little is known about the relationship between nutritional status, inflammation, and long-term bleeding events in patients who are taking both OACs and antiplatelet agents after PCI.

Aim

The aim of this study was to investigate the relationship between the GNRI, C-reactive protein (CRP), and long-term bleeding events in patients undergoing PCI who required both OACs and APT.

Methods

Patient Population

The study population was first collected at single Japanese tertiary hospital to evaluate the predictive performance of various bleeding risk scores, and has been described previously[8]. In brief, among 3,718 patients who underwent PCI from April 2011 to March 2017, patients with indications for long-term OAC treatment were enrolled. Exclusion criteria were as follows: history of intracranial bleeding, cardiogenic shock, patients who did not take antiplatelet agents, peptic ulcer in the previous 6 months, thrombocytopenia (platelet count, $< 50 \times 10^9$/L), major bleeding (according to the Thrombolysis in Myocardial Infarction criteria[17]) in the previous 12 months, and a life expectancy of less than 12 months. The indication for PCI was based on established European[18], American[19], and Japanese[20] guidelines. This study was approved by the research review board of our hospital. Moreover, this study was conducted according to the tenets of the Helsinki Declaration. All patients provided consent for participation in this study.

Antithrombotic Treatment

The details of the antithrombotic treatment also have been described previously[8]. All patients received at least one antiplatelet agent (thienopyridine [200 mg ticlopidine, 75 mg clopidogrel, or 3.75 mg prasugrel daily] and/or 81–100 mg aspirin daily) and an OAC (vitamin K antagonist or a direct OAC [DOAC]). The type and timing of discontinuing antiplatelet agents,

and the selection of the OAC were at the discretion of each attending physician. In the periprocedural period, OACs were continued if possible.

GNRI and High-Sensitivity CRP

The patient's serum albumin level, body weight (BW), and height were measured before PCI. The GNRI was calculated by modifying the GNRI as follows[21]:

GNRI = (14.89 × albumin [g/dL] + 41.7 × BW/ideal BW [iBW]).

The BW/iBW was set to 1 when the patient's BW exceeded the iBW. The iBW in the present study was calculated from a body mass index (BMI) of 22, which is associated with the lowest mortality[22]. Then, patients were divided into two groups based on previous studies as follows: GNRI ≤ 98 (low GNRI) and > 98 (normal GNRI)[12].

Serum high-sensitivity CRP (hs-CRP) levels were determined using a latex immune-nephelometry method (NITTOBO MEDICAL, Tokyo, Japan). Receiver operating characteristic curve analyses were carried out to examine the optimal cutoff value of hs-CRP to predict bleeding events. Subsequently, patients were divided into two groups based on the best cutoff value: low hs-CRP and high hs-CRP.

To estimate the combined effects of the GNRI with hs-CRP on predicting bleeding events, patients were divided into four groups: normal GNRI + low hs-CRP; normal GNRI + high hs-CRP; low GNRI + low hs-CRP; and low GNRI + high hs-CRP.

Assessments and Follow-Up

Demographic, angiographic, and procedural data were collected from hospital charts or hospital databases. Follow-up data were obtained from hospital charts or by contacting patients telephonically for up to 3 years. All patient follow-up data were obtained by March 2018.

The primary outcome of this study was out-of-hospital bleeding defined as the Bleeding Academic Research Consortium (BARC)[23] class ≥ 3 and occurring 7 days or later after the index PCI; bleeding that occurred earlier was censored. We selected 7 days as a conservative time frame based on the current trend in the length of hospital stay for patients with acute coronary syndrome and to exclude events related to the index PCI procedure.

Anemia was classified as a hemoglobin level < 12 g/dL in men and < 11 g/dL in women[24]. The estimated glomerular filtration rate (eGFR) was calculated using the following equation for Japanese patients recommended by the Japanese Society of Nephrology:
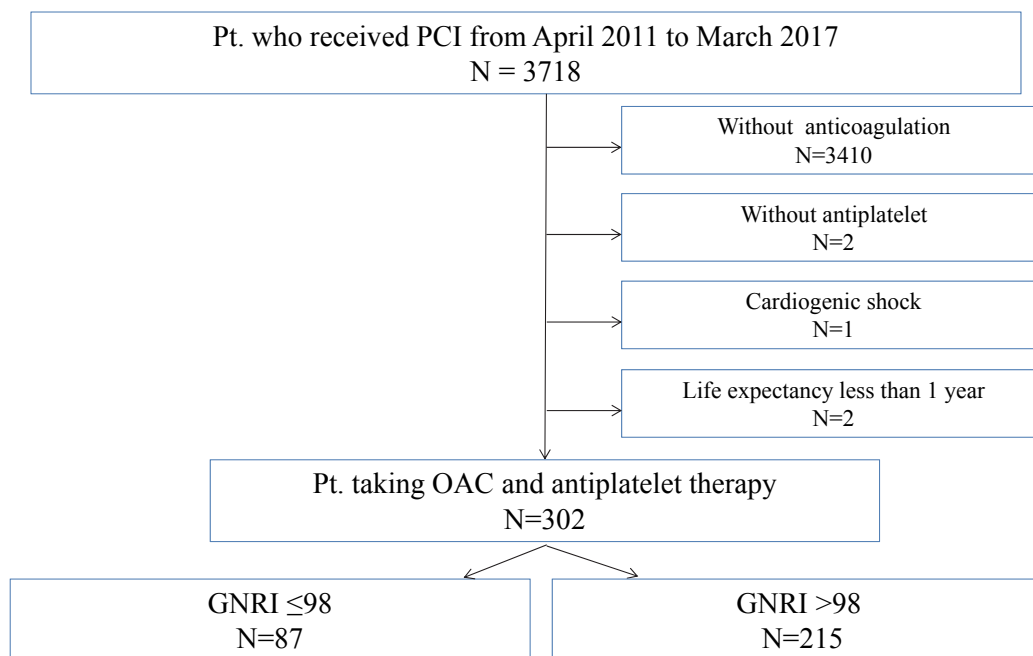
Fig. 1. Flowchart detailing the study design.

Pt., patient; PCI, percutaneous coronary intervention; OAC, oral anticoagulant; GNRI, Geriatric Nutritional Risk Index.

eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (× 0.739 if female) [25].

Statistical Analyses

Continuous variables were summarized as the mean and standard deviation (SD) or the median and interquartile range (IQR), and categorical variables are shown as numbers and proportions. Continuous variables were compared using Student's *t*-test or the Wilcoxon rank-sum test based on their distributions. Categorical variables were compared using chi-squared tests.

Bleeding event rates at 3 years were calculated using the Kaplan−Meier method and compared using the log-rank test. Since the PRECISE-DAPT score was best able to stratify bleeding events of patients who required both OACs and APT after PCI among four famous bleeding risk scores (HAS-BLED, ORBIT, PRECISE-DAPT, and PARIS scores) [8], we adopted it as the reference bleeding score. Thus, a Cox proportional hazards model was used to estimate the contribution of the PRECISE-DAPT score, GNRI, and continuous values of hs-CRP levels to predict bleeding events.

Model discrimination was assessed using the C-statistic. Improvements in predictive accuracy were determined by calculating the net reclassification improvement and the integrated discrimination improvement [26].

All statistical analyses were performed using JMP software version 13.1 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). A *p*-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 3,718 patients who underwent PCI during the study period, we identified 302 eligible patients who took both OACs and antiplatelet agents. Of these 302 patients, 87 had a low GNRI and 215 had a normal GNRI (**Fig. 1**). The clinical characteristics of the recruited patients are summarized in **Table 1**. The overall follow-up rate was 92.1%. The median length of follow-up was 787 (IQR = 424−1,080) days for the low GNRI group and 1,080 (IQR = 671−1,080) days for the normal GNRI group. Advanced age, female sex, and a high prevalence of heart failure were significantly more frequent in the low GNRI group. A low GNRI was also associated with decreased total cholesterol, low-density lipoprotein cholesterol, triglyceride levels, and eGFR, and increased glycated hemoglobin, hs-CRP, and brain natriuretic peptide levels.

The mean PRECISE-DAPT score was significantly higher in the low GNRI group than in the normal GNRI group (PRECISE-DAPT: low GNRI, 35.6 [SD =

Table 1. Patient's clinical characteristics, medication, and procedural characteristics at baseline

Patients: n	low GNRI (n=87)	normal GNRI (n=215)	p value
Clinical baseline characteristics			
Mean (SD) age (years)	76.9 (9.0)	70.2 (8.6)	<0.0001
Male sex	57 (65.5%)	178 (82.8%)	0.001
Mean (SD) BMI (kg/m²)	21.0 (3.5)	24.4 (3.5)	<0.0001
Diabetes mellitus	47 (54.0%)	90 (41.9%)	0.05
Hypertension	62 (71.3%)	162 (75.4%)	0.47
Dislipidemia	42 (48.3%)	148 (68.8%)	0.001
Smoking history	57 (65.5%)	134 (62.3%)	0.60
Prior myocardial infarction	18 (20.7%)	60 (27.9%)	0.19
Prior heart failure	65 (74.7%)	76 (35.4%)	<0.0001
Prior stroke	15 (17.2%)	27 (12.6%)	0.30
Prior PCI	31 (35.6%)	85 (39.5%)	0.53
Prior CABG	16 (18.4%)	42 (19.5%)	0.82
Serum albumin (g/dl)	3.6 (0.3)	4.3 (0.3)	<0.0001
Total cholesterol (mg/dl)	152.8 (34.4)	172.4 (41.0)	0.0001
LDL-cholesterol (mg/dl)	89.5 (29.2)	104.1 (35.0)	0.001
HDL-cholesterol (mg/dl)	40.3 (12.8)	42.7 (10.6)	0.09
Triglyceride (mg/dl)	90 [60, 128]	117 [74, 171]	0.003
Glycated hemoglobin (%)	6.0 (1.3)	5.7 (0.9)	0.03
hs-CRP (mg/dl)	0.27 [0.13, 0.51]	0.1 [0.05, 0.24]	<0.0001
BNP (pg/ml)	291.6 [155.1, 606.2]	81.6 [39.7, 180.2]	<0.0001
eGFR (ml/min/1.73 m²)	53.3 (24.7)	65.2 (19.8)	<0.0001
PRECISE-DAPT score	35.6 (16.3)	24.9 (11.3)	<0.0001
Medication at discharge			
Aspirin	74 (85.1%)	195 (90.7%)	0.17
Thienopyridine	84 (96.6%)	197 (91.6%)	0.10
DAPT	73 (83.9%)	177 (82.3%)	0.74
PPI	83 (95.4%)	197 (91.6%)	0.23
Type of OAC			0.27
VKA	55 (63.2%)	121 (56.3%)	
DOAC	32 (36.7%)	94 (43.7%)	
Indication for OAC			0.87
Atrial fibrillation	58 (66.7%)	150 (69.7%)	
Post cardiac surgery	15 (17.2%)	34 (15.8%)	
Other (apical aneurysm, pulmonary embolism, PAD)	14 (16.1%)	31 (14.4%)	
DAPT continuation (continue number/survivor, %)			
At 1 month	77/87 (88.5%)	180/214 (84.1%)	0.42
At 3months	55/85 (64.7%)	139/212 (65.6%)	0.89
At 6 months	46/84 (54.8%)	106/211 (50.2%)	0.52
At 12 months	24/76 (31.6%)	75/207 (36.2%)	0.49
Procedural characteristics			
DES	66 (75.9%)	141 (65.6%)	0.08
Indication of PCI			0.34
STEMI	27 (31.0%)	66 (30.7%)	
NSTEMI	3 (3.5%)	4 (1.9%)	
Unstable AP	13 (14.9%)	19 (8.8%)	
Stable AP	44 (50.6%)	126 (58.6%)	

Values are the mean ± standard deviation (SD), n (%), or median (interquartile range) as appropriate. GNRI, geriatric nutritional risk index; BMI, body-mass index; PCI, pertcutaneous coronary intervention; CABG, coronary artery bypass graft; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CR, high-sensitivity C-reactive protein; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; DAPT, dual antiplatelet therapy; PPI, proton-pump inhibitor; OAC, oral anticoagulant; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; PAD, peripheral artery disease; DES, drug eluting stent; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; AP, angina pectoris.
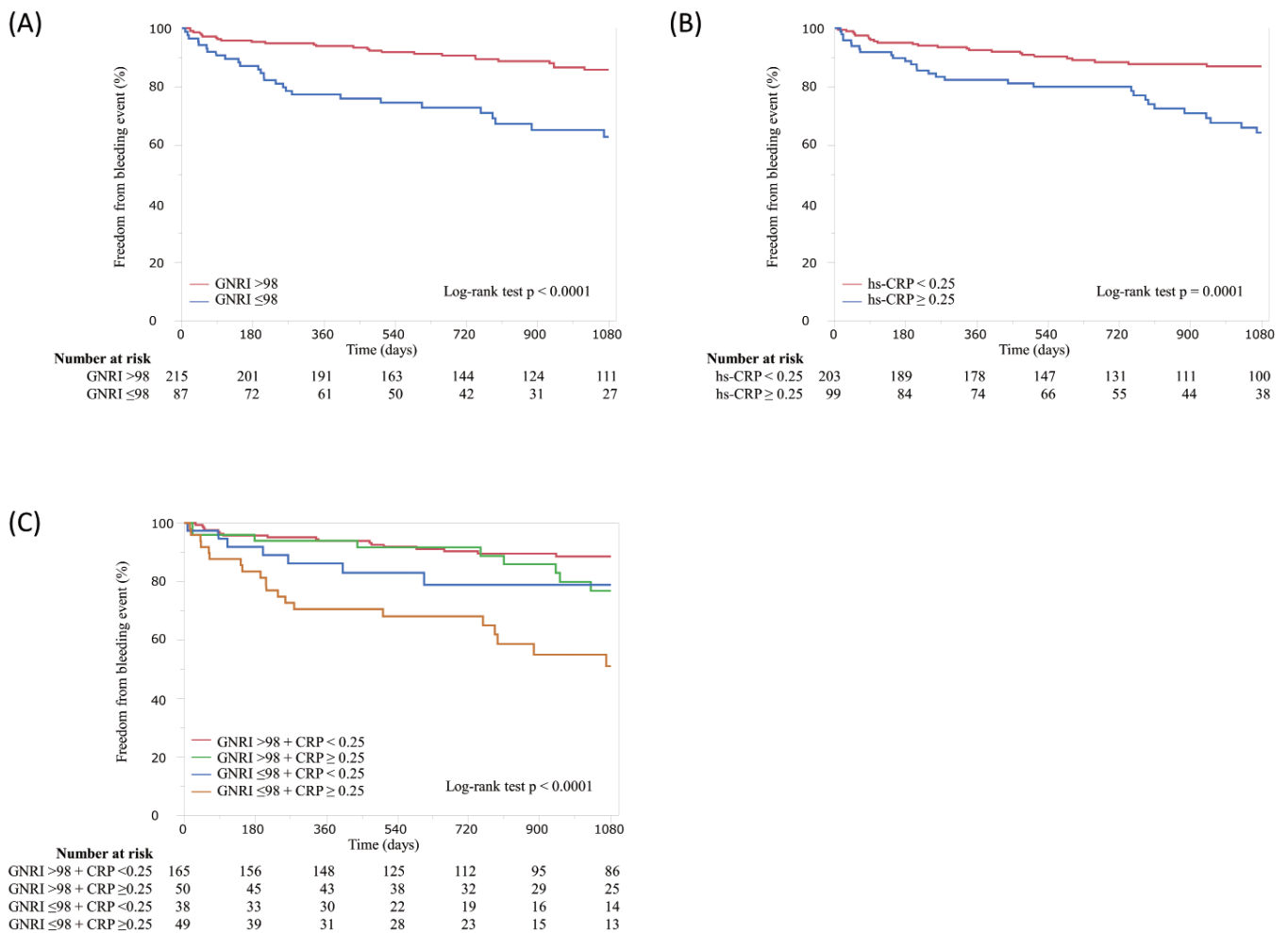
(A)

(B)

(C)

Fig. 2. Cumulative incidence of the Bleeding Academic Research Consortium class ≥3 bleeding.

Panel A shows the freedom from adverse bleeding events in patients stratified by the GNRI. Panel B shows the freedom from adverse bleeding events in patients stratified by hs-CRP. Panel C shows the freedom from adverse bleeding events in patients stratified by a combination of the GNRI and hs-CRP.

16.3]; normal GNRI, 24.9 [SD=11.3]; *p*<0.0001).

The DAPT continuation rate was comparable between the two groups at 1, 3, 6, and 12 months (**Table 1**).

Bleeding Events and Predictive Performance of GNRI and hs-CRP

During the entire follow-up period, the primary outcome (BARC class ≥3 bleeding) occurred in 27 patients (31.0%) in the low GNRI group and 26 patients (12.1%) in the normal GNRI group. The median time to the first occurrence of BARC class ≥3 bleeding was 237 (IQR=76−636) days.

Fig. 2 shows the 3-year risk estimates comparing the groups in terms of BARC class ≥3 bleeding. BARC class ≥3 bleeding for the low and normal GNRI groups occurred in 37.1% and 14.3% of patients, respectively

(hazard ratio [HR], 3.16; 95% confidence interval [CI], 1.84−5.45; *p*<0.0001) (**Fig. 2A**).

hs-CRP levels were divided using an optimal cut-off value of 2.5 mg/L (area under the curve=0.64; *p*=0.001). Results for the low hs-CRP (<2.5 mg/L) and high hs-CRP (≥2.5 mg/L) groups were BARC class ≥3 bleeding in 35.7% and 13.2% of patients, respectively (HR, 2.75; 95% CI, 1.61−4.78; *p*=0.0003) (**Fig. 2B**). Regarding the combined effects of GNRI and hs-CRP, low GNRI + high hs-CRP showed a 5.12-fold increase in the incidence of BARC class ≥3 bleeding (95% CI, 2.68−9.91; *p*<0.0001) compared with normal GNRI + low hs-CRP. In contrast, no significant increase was observed in the incidence of bleeding events for normal GNRI + high hs-CRP or low GNRI + low hs-CRP compared with normal GNRI + low hs-CRP (**Fig. 2C**).

Table 2. Predictive value for Adverse Bleeding Events (BARC class ≥3 bleeding) by Cox analysis

Variables	Univariate		Multivariate (Model 1)		Multivariate (Model 2)		Multivariate (Model 3)	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
PRECISE-DAPT	1.04 (1.02−1.06)	<0.0001	1.03 (1.01−1.05)	0.001	1.04 (1.02−1.06)	<0.0001	1.03 (1.02−1.05)	0.0004
Low GNRI	3.16 (1.84−5.45)	<0.0001	2.13 (1.17−3.87)	0.01			1.75 (0.96−3.20)	0.07
hs-CRP	1.08 (1.04−1.12)	0.001			1.09 (1.04−1.13)	0.001	1.08 (1.03−1.12)	0.004

PRECISE-DAPT, PRECISE-DAPT score; GNRI, geriatric nutritional risk index; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; 95% CI, 95% confidence interval.

Cox proportional hazards modeling is shown in **Table 2**. After adjustment for the PRECISE-DAPT score, a low GNRI independently predicted adverse bleeding events (HR, 2.13; 95% CI, 1.17−3.87; $p=$ 0.01); after adjustment for both the PRECISE-DAPT score and hs-CRP, a low GNRI tended to be associated with the increased incidence of bleeding events. (HR, 1.75; 95% CI, 0.96−3.20; $p=$0.07). In contrast, hs-CRP independently predicted bleeding events after adjustment for the PRECISE-DAPT score and GNRI.

The C-statistic for BARC class ≥3 bleeding was 0.67 (95% CI, 0.52−0.64, $p=$0.001) for the PRECISE-DAPT score alone. Adding the GNRI and hs-CRP to the PRECISE-DAPT score increased the predictive accuracy of bleeding events (**Table 3**).

Discussion

In this study, we assessed the comprehensive nutritional assessment score and inflammation marker as risk factors for long-term bleeding events in patients treated with PCI who required both OACs and APT. The main findings of the present study were as follows:

1) The GNRI was able to discriminate bleeding risk in patients who underwent PCI and required both OACs and APT.

2) hs-CRP was an independent predictor of long-term bleeding events by Cox proportional hazards analysis.

3) The combination of the GNRI and hs-CRP could detect the patients with the highest risk of bleeding events.

4) The addition of the GNRI and hs-CRP to the PRECIS-DAPT score, which is an established bleeding risk score, significantly improved the ability to stratify bleeding risk in these patients.

Our study highlighted the clinical impact of nutritional status and inflammation on long-term bleeding events in those who required both OACs and APT after PCI. Bleeding complications are associated with an increased risk of subsequent adverse outcomes, such as death, myocardial infarction, stroke, and stent thrombosis[27]. Therefore, it is very important to identify high risk patients; however, it is difficult to predict bleeding events[4, 6], particularly in patients who require both OACs and APT[7]. In the present study, the GNRI and hs-CRP could discriminate the bleeding risk in this subset of patients. Moreover, adding the GNRI and hs-CRP increased the accuracy to discriminate bleeding events of the established bleeding risk score (PRECISE-DAPT score). In this regard, the result of the present study offered information of importance.

In previous studies, the GNRI has been recognized as a nutrition-related risk index that makes it possible to stratify the risk of morbidity and mortality in relation to pathologies in elderly patients, which are often associated with malnutrition[12]. The GNRI appraises the BMI as well as serum albumin levels. In the present study, the addition of BMI alone to the PRECISE-DAPT score did not improve its ability to predict bleeding events compared with the GNRI. There could be various reasons for this. Previous epidemiologic studies have found that underweight patients were associated with a greater incidence of bleeding complications than normal-weight patients[4]. However, the relationship between BMI and bleeding events was a reverse J-shape or a U-shape, which demonstrated the lowest risk in patients with a normal BMI compared with underweight or overweight patients. Moreover, BMI alone may not distinguish sarcopenic obesity, an expression of the loss of lean body mass and increased fat mass, which has been recognized as a risk for multimorbidity in some populations[28]. Therefore, it might be important to assess BMI together with nutritional status, and the GNRI was appropriate for this purpose.

There are several other nutritional screening tools, and each has its advantages and disadvantages. Some are based on subjective data, such as the Subjective Global Assessment[29] and Mini-Nutritional Assessment[30]. Other tools are based on objective biochemical and clinical data, such as the GNRI[12] and the CONUT score[13]. To assess nutritional status correctly,

Table 3. Discrimination of each predictive model of Adverse Bleeding Events (BARC class ≥ 3 bleeding)

Variables	C-statistic	*p* value	NRI	*p* value	IDI	*p* value
PRECISE-DAPT	0.67	< 0.0001	Reference		Reference	
+ BMI	0.68	< 0.0001	0.01	0.51	0.001	0.45
+ Alb	0.67	< 0.0001	0.06	0.44	0.005	0.26
+ low GNRI	0.69	< 0.0001	0.30	0.02	0.028	0.04
+ hs-CRP	0.70	< 0.0001	0.28	0.01	0.051	< 0.0001
+ low GNRI and hs-CRP	0.71	< 0.0001	0.36	0.02	0.066	< 0.0001

PRECISE-DAPT, PRECISE-DAPT score; GNRI, geriatric nutritional risk index; hs-CRP, high-sensitivity C-reactive protein; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

combining both subjective and objective tools is important[31]. However, for daily clinical practice, an objective and simple tool that uses routinely measured data is desirable. Furthermore, subjective indices require the training and experience of medical practitioners, and it might be affected by the questioner's opinions. The GNRI, which uses only serum albumin level and BMI, is an easy and efficient screening tool to assess the nutritional status of patients undergoing PCI.

It has been suggested that a large proportion of patients at high risk for atherosclerosis also had a high bleeding risk, reflecting an overlap of the risk predictors for thrombosis and bleeding[32]. A sub-analysis of the DAPT study revealed that polyvascular disease was a strong predictor of bleeding events as well as a predictor of ischemic events[33]. Inflammation is also known to play an important role in the initiation and progression of atherosclerosis[34]. In the present study, hs-CRP, which is a popular marker of inflammation, was revealed to be useful for predicting bleeding events after PCI. It is very difficult to show the mechanism underlying the effect of inflammation on the bleeding risks from the results of this observational study. However, several studies have demonstrated that systemic inflammation is correlated with advanced age and sarcopenia[35]. In the present study, patients with a low GNRI were significantly older and had higher hs-CRP levels than patients with a normal GNRI. When considered comprehensively, bleeding events might be involved in the context of a malnutrition−inflammation−atherosclerosis syndrome, which is a malignant cycle propounded in patients with chronic kidney disease, formed by malnutrition and inflammation[36]. Therefore, it was suggested that assessing both nutritional and inflammation status as well as established risk factors was required to improve the identification of patients at high risk for bleeding among those who underwent PCI and required both OACs and APT.

The role of bleeding risk scores should be to identify high risk patients for a more careful review and follow-up, as well as to draw attention to reversible factors[37]. From this perspective, the GNRI is simple, practical, and reversible; until now, data on interventions in nutritional status that improve the risk for long-term bleeding events have been limited. Thus, future studies should investigate if nutritional intervention will improve the risk for bleeding events in patients taking both OACs and antiplatelet agents after PCI.

Study Limitations

This study had several limitations. First, it was performed at a single medical center and followed a non-randomized, retrospective study design. Accordingly, only a limited number of patients were enrolled. Moreover, by the nature of the retrospective observational design, regimens of APT and the duration of the DAPT were at the discretion of the treating physicians. Second, the association among nutritional and inflammation status, and long-term bleeding risks might differ by race. The results of our study might not be generalizable to patients other than Japanese patients. Third, the nutritional status and inflammation marker was measured only at the time of the index PCI. Therefore, these conditions might change during the follow-up period. Fourth, patients taking a DOAC tended to be included more in recent years. Therefore, DOACs were used more frequently in patients on the SAPT and OAC regimen, although this regimen was employed in less than one-sixth of the patients. Furthermore, we did not examine the comorbidity or frailty scores. Most patients in this study may have been affected to some degree by frailty or comorbidity rather than their nutritional status alone. However, such a bias might be reduced because other factors were taken into account; considering that patients in this study underwent invasive procedures probably reflects patient frailty and comorbidity. Additional studies with large sample sizes are needed to investigate the effect of intervention on nutritional status for patients taking an OAC treated with PCI.

Conclusion

The GNRI and hs-CRP are novel predictors of long-term bleeding risk in patients taking both OACs and antiplatelet agents after PCI. Adding the GNRI and hs-CRP to the PRECISE-DAPT score improved the ability to stratify bleeding risk in these patients.

Conflict of Interest

Research Funding

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