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Quantitative Validation of the Coronary Angioscopic Yellow Plaque with Lipid Core Burden Index Assessed by Intracoronary Near-Infrared Spectroscopy

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Aim: We aimed to validate the subjective and qualitative angioscopic findings by the objective and quantitative near-infrared spectroscopic (NIRS) assessment to compensate each other's drawbacks.

Methods: This is a single-center prospective observational study. Patients undergoing a planned follow-up coronary angiography after percutaneous coronary intervention were prospectively enrolled from January 2018 to April 2019. The major three vessels were examined by NIRS-intravascular ultrasound, followed by coronary angioscopic evaluation. Yellow color grade on angioscopy was classified into four grades (0, white; 1, slight yellow; 2, yellow; and 3, intensive yellow) at a location of maximal lipid core burden index over 4 mm [LCBI (4)] on NIRS in each vessel.

Results: A total of 95 lesions in 44 patients (72.6±6.7 years, 75% male) were analyzed. LCBI (4) was significantly different among different yellow color grades by coronary angioscopy (ANOVA, $p<0.001$). Positive correlation was found between angioscopic yellow color grade and LCBI (4) (beta coefficient 164.8, 95% confidence interval 122.9–206.7; $p<0.001$). The best cutoff value of LCBI (4) to predict the presence of yellow plaque (yellow color grade ≥ 2) was 448 (sensitivity 79.3%, specificity 69.7%, C-statistic 0.800, 95% confidence interval 0.713–0.887, $p<0.001$).

Conclusion: The qualitative angioscopic assessment was objectively validated by the quantitative NIRS evaluation, which would be helpful for the reinterpretation of the existing evidences of both imaging modalities.

Key words: Coronary angioscopy, Near-infrared spectroscopy, Vulnerable plaque

Clinical Investigation
Introduction

Cholesterol-rich lipid core atheromas are associated with myocardial infarction and cardiac death[1]. This so-called vulnerable plaque can be identified by various intracoronary imaging modalities, such as optical coherence tomography, intravascular ultrasound (IVUS), coronary angioscopy, near-infrared spectroscopy (NIRS), etc[2-5].

Coronary angioscopy has provided substantial information of the coronary atherosclerosis as yellow plaques. Coronary lesions with high-grade yellow color have been regarded as high-risk plaques and demonstrated to be associated with future coronary events[6]. However, albeit its relatively high and acceptable reproducibility[3], the subjectivity of its visual assessment may be one of the drawbacks of the coronary angioscopy. On the other hand, NIRS can more objectively and quantitatively detect lipid-rich plaques than the other imaging modalities. The recent prospective cohort study, the Lipid-Rich Plaque (LRP)

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study, has demonstrated the significant relationship between lipid core burden index (LCBI) by NIRS and future clinical events[5]. Binary cutoff value of 400 maximal LCBI over any 4 mm segment [max LCBI (4)] may be a reasonable predictor for subsequent events at patient and plaque levels.

Both imaging modalities showed their ability to detect the high-risk plaque and its clinical association. The angioscopy has a long history of clinical evidence but with less subjectivity and limited availability only in Japan[3, 7, 8], whereas the NIRS has relatively less clinical evidence but with robust subjectivity[9, 10]. If there is a strong scientific correlation between yellow plaque on angioscopy and LCBI on NIRS, clinical significance of both imaging modalities will synergistically increase.

Aim

We aimed to validate the subjective and qualitative angioscopic findings by the objective and quantitative NIRS assessment to compensate each other's drawbacks.

Methods

Study Design and Population

This is a single-center prospective observational study. Patients undergoing a planned follow-up coronary angiography after percutaneous coronary intervention (PCI) were prospectively enrolled from January 2018 to April 2019 in our institution. Coronary angiography was performed by radial artery approach using a 6 Fr sheath and catheters. The major three vessels, namely, left anterior descending artery, left circumflex artery, and right coronary artery, were examined by NIRS-IVUS, followed by coronary angioscopic evaluation. All arteries were scanned irrespective of the presence of coronary stenosis. Lesions that either NIRS or angioscopy cannot evaluate due to any reasons (e.g., incomplete blood flush, tortuous vessel, severe stenosis, etc.) were excluded from the final analysis. This study was approved by the Osaka Police Hospital Ethics Committee (reference number: 1193) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all enrolled patients.

NIRS-Intravascular Ultrasound

NIRS-IVUS was used to detect lipids in the walls of the coronary vessels (Infraredx, Inc., Burlington, Massachusetts). The NIRS-IVUS system can generate a map of coronary artery lipid core. During the pullback, the NIRS-IVUS performs approximately 30,000 measurements per 100 mm of artery scanned. Results of the measurement are displayed in an image called a "chemogram," in which the base represents mm of pullback and the height represents rotation from zero to 360 degrees. Areas with a prominent lipid core are displayed as yellow, and areas without a prominent lipid core are displayed as red. A quantitative image metric is automatically reported as a numerical LCBI that represents the fraction of the chemogram yellow pixels times 1,000. Maximal LCBI over any 4 mm segment [max LCBI (4)] was automatically calculated by the imaging console.

Coronary Angioscopy

The nonocclusion type of angioscopy, VISIBLE™ (FiberTech Co., Ltd., Tokyo, Japan), was used. Angioscopic observation of the whole vessel was done while blood was cleared away from the viewing area by the injection of 3% dextran-40 [3, 4, 8]. Cases with good image quality were included in this analysis. Yellow color grade was classified into four grades (0, white; 1, slight yellow; 2, yellow; and 3, intensive yellow) compared with the standard colors[3, 8, 11]. **Fig. 1** illustrates image examples of yellow color grades. Presence of yellow plaque was defined as the yellow color grade ≥ 2 [3, 4, 8]. Three analysts of coronary angioscopy (T. Omatsu, T. Kobayashi, and Y. Hamanaka) who were blinded to patients' characteristics evaluated the angioscopic images. The inter-observer and intra-observer reproducibility (percent agreement) for the interpretation of angioscopic images in our institution was 85% and 95% for plaque color[3, 4, 8].

Matching Methodology of NIRS-IVUS and Coronary Angioscopy

Fig. 2 illustrates a case example of matching methodology for coronary angioscopy and NIRS-IVUS. First, a coronary artery was assessed by NIRS-IVUS. According to the obtained chemogram, the location of max LCBI (4) was angiographically recorded. Second, the vessel wall of the recorded location was assessed by coronary angioscopy as described above. The LCBI (4) value was matched with the corresponding yellow plaque color grade.

Statistical Analysis

Data are expressed as mean ± standard deviation or median and interquartile range with differences (95% confidence interval). Group means for continuous variables with normal and non-normal distributions were compared using Student's *t*-tests and Mann–Whitney *U* tests, respectively. Normality

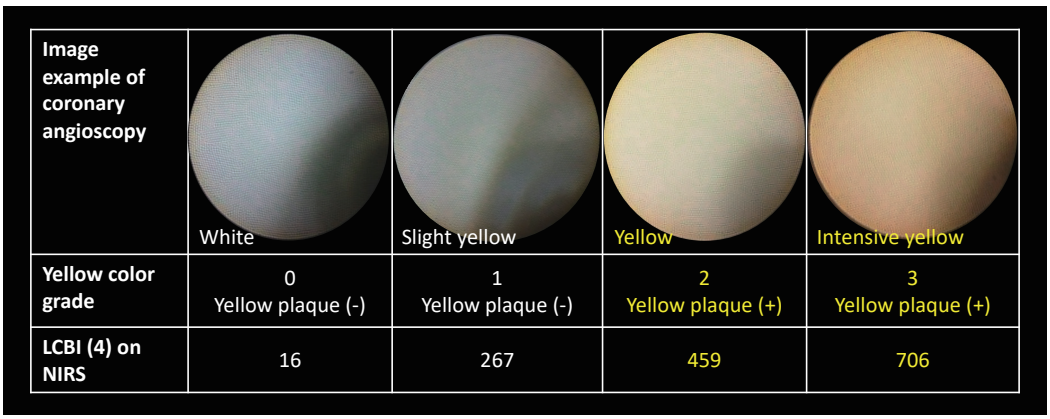


Fig. 1. Image examples of yellow plaque color grades on coronary angioscopy

Image examples of yellow color grades on coronary angioscopy are summarized with corresponding LCBI (4) on NIRS. Presence of yellow plaque was defined as the yellow color grade ≥ 2. Abbreviations: NIRS, near-infrared spectroscopy; LCBI (4), lipid core burden index over 4 mm

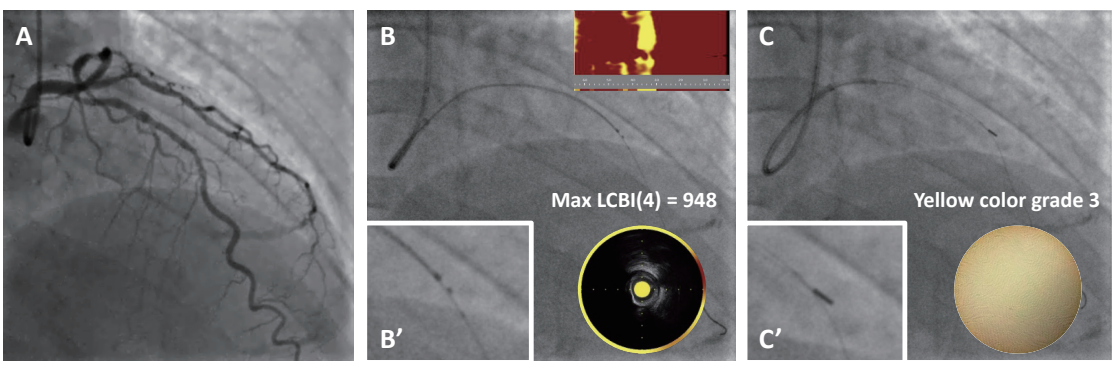


Fig. 2. Case example of matching methodology for coronary angioscopy and NIRS-IVUS

A: Left anterior descending artery was assessed by coronary angioscopy and NIRS-IVUS. B: The position of max LCBI (4) was angiographically recorded (magnified view in B'). Chemogram of the NIRS-IVUS is shown on the upper-right corner. The cross-sectional IVUS image is indicated on the right-bottom corner. This vessel had a max LCBI (4) of 948. C: Vessel wall of the angiographically recorded position was assessed by coronary angioscopy (magnified view in C'). The yellow plaque color grade observed was grade 3. Angioscopic image is shown on the right-bottom corner. Abbreviations: NIRS-IVUS, near-infrared spectroscopy-intravascular ultrasound; max LCBI (4), maximal lipid core burden index over any 4 mm segment

of data distribution was tested by the Kolmogorov–Smirnov test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. One-way analysis of variance (ANOVA) with Tukey's post hoc test was used for comparisons of continuous variables. Receiver operating characteristic (ROC) curves were generated to obtain area under the curve values with 95% confidence intervals (C-statistic) and also sensitivity and specificity for each LCBI (4) value as a predictor of yellow plaque defined as yellow plaque color grade ≥ 2. The Youden index (sensitivity + specificity − 1) was calculated, and the corresponding cutoff value for the highest Youden index was considered as the optimal cutoff value of LCBI (4) for predicting yellow plaque. Linear regression model was used for the assessment of the linear correlation between yellow color grade on coronary angioscopy and LCBI (4) values on NIRS-IVUS. This analysis was further stratified by stented or non-stented lesions. Generalized linear regression model with yellow color grade as a variable of interest and stented segment as a covariate was employed to assess the impact of stents on the LCBI (4) values considering the clustered nature of >1 lesion analyzed from the same patients, which might result in unknown correlations among measurements within the clusters. All statistical analyses were performed with SPSS (version 23.0.0, IBM, New York).

Data Availability

The deidentified participant data will not be shared.

Results

Study Population

Tables 1 and 2 summarize patient and lesion characteristics, respectively. A total of 95 lesions in 44 patients (72.6 ± 6.7 years, 73% male) were analyzed. The majority of the patients had hypertension (95%) and dyslipidemia (100%). Almost all patients (98%) used statin, while ezetimibe was used in 25 patients (57%). One third of the lesions assessed (28/95) was a stented segment. Percent area stenosis was 56.4 ± 10.5%. No complication occurred during both imaging procedures.

Correlation between Max LCBI (4) by NIRS and Yellow Plaque Color Grade by Coronary Angioscopy

Fig. 3 illustrates the relationship between LCBI (4) by NIRS and yellow plaque color grade by coronary angioscopy. LCBI (4) was significantly different among different yellow color grades by coronary angioscopy (ANOVA, $p<0.001$). Positive correlation was found between angioscopic yellow color grade and LCBI (4) (beta coefficient 164.8, 95% confidence interval 122.9–206.7; $p<0.001$). ROC analysis indicated that the best cutoff value of LCBI (4) to predict the presence of yellow plaque (grade ≥ 2) was 448 (sensitivity 79.3%, specificity 69.7%) [C-statistic 0.800, 95% confidence interval 0.713–0.887, $P<0.001$]. Fig. 4 shows the similar linear correlation between LCBI (4) and yellow color grade regardless of stented or non-stented lesions. Generalized linear model showed that metallic stent struts did not have a significant impact on the LCBI (4) values (beta coefficient −8.2, 95% confidence interval −84.3–67.8; $p=0.832$), whereas yellow color grade had a positive correlation with LCBI (4) values (beta coefficient 164.9, 95% confidence interval 123.9–205.8; $p<0.001$).

Discussion

The main findings of this study can be summarized as follows: (1) LCBI (4) was significantly different among different yellow color grades by coronary angioscopy; (2) positive correlation was found between angioscopic yellow color grades and LCBI (4); and (3) the best cutoff value of LCBI (4) by NIRS to predict the presence of yellow plaque on coronary angioscopy was 448.

Quantitative Validation of Yellow Plaque on Coronary Angioscopy by NIRS-IVUS

Over the past two decades, angioscopic studies have demonstrated that vulnerable plaque identified as

Table 1. Patient characteristics

	n=44
Age, years	72.6 ± 6.7
Male sex	32 (73)
Body mass index	24 ± 3.4
Diabetes mellitus	22 (50)
HbA1c, %	6.4 ± 0.9
Hypertension	42 (95)
Current smoker	4 (9)
Dyslipidemia	44 (100)
History of myocardial infarction	32 (73)
Serum lipid profile, mg/dl	
Total cholesterol	142.2 ± 32.9
High-density lipoprotein cholesterol	46.1 ± 13.2
Low-density lipoprotein cholesterol	72.5 ± 24.3
Triglycerides	134.0 ± 91.0
Creatinine, mg/dL	0.9 ± 0.2
eGFR, mL/min/1.73 m^2	64.6 ± 14.2
C-reactive protein, mg/dL	1.0 ± 2.0
Medication	
Statin	43 (98)
Ezetimibe	25 (57)
Aspirin	43 (98)
Clopidogrel	4 (9)
Prasugrel	25 (57)
ACE inhibitor/ARB	37 (84)
β-blocker	28 (64)
Ca-blocker	14 (32)

Data are expressed as number (%) or mean ± standard deviation. Abbreviation: eGFR = glomerular filtration rate; ACE inhibitor = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

Table 2. Lesion characteristics

	n=95
Vessel assessed	
Right coronary artery	32 (33.7)
Left anterior descending artery	37 (38.9)
Left circumflex artery	24 (25.3)
Left main trunk	2 (2.1)
NIRS- IVUS parameters	
Max LCBI (4)	429.5 ± 223.0, 414 [246 – 583]
Max LCBI (4) at stented segment	28 (29.5)
Lumen area, mm^2	7.78 ± 2.93, 7.20 [5.40 – 9.70]
Vessel area, mm^2	13.78 ± 4.45, 13.20 [10.90 –16.80]
Plaque area, mm^2	6.00 ± 2.40, 5.70 [4.30 – 7.80]
Percent area stenosis, %	43.6 ± 10.5, 42.6 [36.5 – 51.8]

Data are expressed as number (%) or mean ± standard deviation or median [interquartile range]. Abbreviations: NIRS-IVUS = near infrared spectroscopy-intravascular ultrasound; Max LCBI (4) = maximal lipid core burden index over any 4 mm.

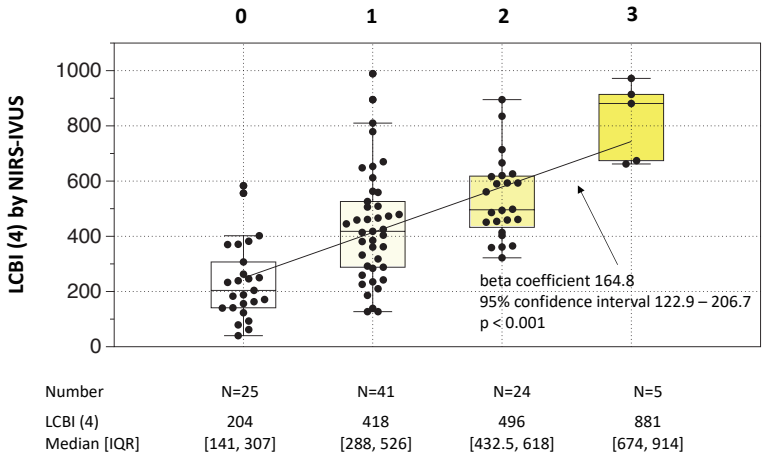
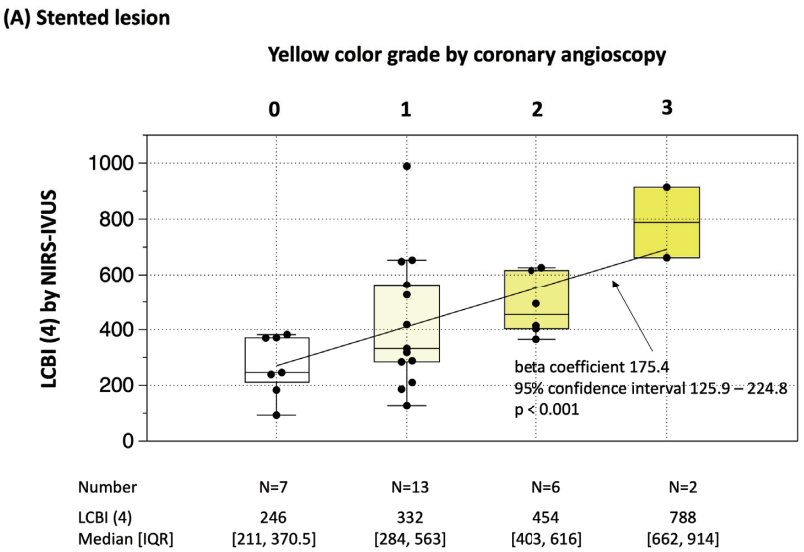


Fig. 3. Correlation between yellow plaque color grade by coronary angioscopy and LCBI (4) by NIRS

Figure 3 illustrates the relationship between LCBI (4) by NIRS and yellow plaque color grade by coronary angioscopy. LCBI (4) was significantly different among different yellow color grades by coronary angioscopy (ANOVA, $p<0.001$). All pairwise comparisons other than a comparison between grades 1 and 2 ($p=0.131$) presented a significant difference ($p<0.01$). Abbreviations: NIRS-IVUS, near-infrared spectroscopy-intravascular ultrasound; LCBI (4), lipid core burden index over 4 mm; IQR, interquartile range



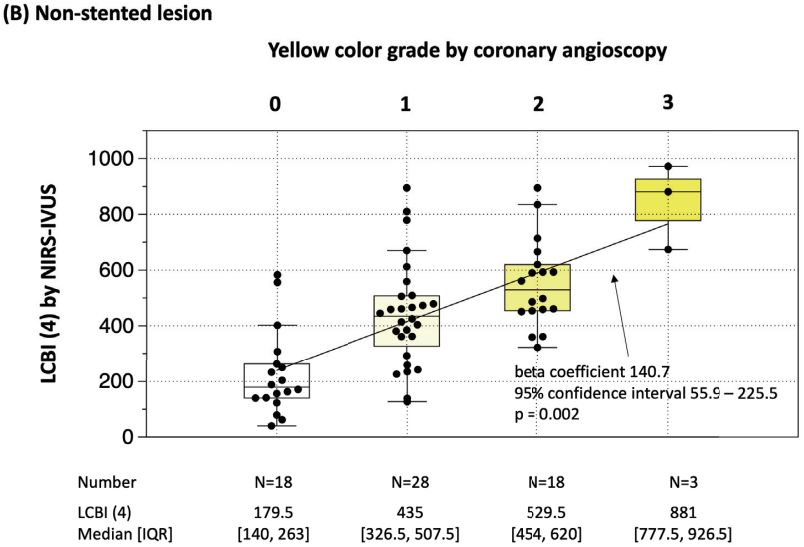


Fig. 4. Correlation between yellow plaque color grade by coronary angioscopy and LCBI (4) by NIRS stratified by stented and non-stented lesions

Figure 4 shows the linear relationship between LCBI (4) by NIRS and yellow plaque color grade by coronary angioscopy in stented (A) and non-stented lesions (B). Abbreviations: same as Fig. 3

yellow plaque on angioscopy is associated with subsequent clinical events[3, 8, 12, 13]. A prospective cohort study (N=552) demonstrated that patients with multiple yellow plaque have a higher risk of future acute coronary syndrome events than those without (adjusted hazard ratio 1.23, 95% confidence interval 1.03–1.45; p=0.02)[12]. The study design of this cohort study seems similar to that of the LRP study but was published 13 years ago. The angioscopy has a long history and a plenty of evidences on the assessment of coronary atherosclerosis. Nevertheless, there were several drawbacks of angioscopy, e.g., limited field of view, subjective and qualitative evaluation, limited use in Japan, technical complexity, technical difficulty in tortuous and small vessels, and superficial assessment of coronary plaque. Especially as to the reproducibility of the analysis, the semi-quantitative assessment of yellow plaque is always suffering the criticism of its limited reproducibility, although previous reports provided the acceptable reproducibility of coronary angioscopy for assessing yellow color grade[3, 7, 8, 12]. There were several attempts to quantify the yellow color grade subjectively[14]. It is, however so far, not realized. This study used a new technology NIRS that enables quantification of LRP. Different yellow color grades had different ranges of LCBI on NIRS. The higher the yellow color grade on angioscopy was, the higher the LCBI (4) on NIRS was. The semi-quantitative yellow color assessment was for the first time successfully validated by the fully automatic quantitative evaluation on NIRS.

Optimal Cutoff Value of LCBI (4) for Prediction of Future Clinical Events

Previous small studies have consistently shown the significant association of the max LCBI (4) on NIRS with major adverse cardiovascular events[15-17]. The cutoff value of max LCBI (4) for prediction of future clinical events, however, varied in different reports. The ATHEROREMO-NIRS substudy (N=203) reported that coronary artery disease patients with an LCBI equal to or above 43.0 in a non-culprit coronary artery had a fourfold risk of adverse cardiovascular events during 1-year follow-up (adjusted hazard ratio: 4.04; 95% confidence interval: 1.33–12.29; p=0.01)[17]. The ORACLE-NIRS registry (N=239) showed that the adjusted hazard ratio for non-target vessel LCBI ≥ 77 was 14.05 (95% confidence interval 2.47–133.51, p=0.002)[15]. The Spectrum NIRS-IVUS registry (N=121) reported that a max LCBI (4) ≥ 400 in a non-stented segment at baseline was significantly associated with major adverse cardiovascular and cerebrovascular events during a follow-up duration of 603 ± 145 days (hazard ratio 10.2, 95% confidence interval 3.4–30.6, p< 0.001)[16]. Based on the previous findings, a cutoff point of 400 max LCBI (4) was prespecified in the LRP study[18]. The LRP study (N=1,563) is the first study to prospectively demonstrate the cutoff value of 400 max LCBI (4) works quite well to identify the high-risk population[5]. Patients with a max LCBI (4) more than 400 had an adjusted hazard ratio for non-culprit major cardiovascular event of 1.89 (1.26–2.83; p=0.0021). This study showed that a cutoff value of 448 was correlated with the presence of high-risk yellow plaque. Considering these previous NIRS evidences and the present finding, a cutoff 400 may be reasonable. Similarity between 448 in the present study and 400 in the LRP study would also support the robustness of the cutoff point. Yellow plaque on coronary angioscopy and a max LCBI (4) ≥ 400 on NIRS are similarly useful findings for prediction of future clinical events. Moreover, this cutoff value may be applicable regardless of stented or non-stented lesions. The present analysis showed the limited impact of stent struts on LCBI values. The similar correlation between yellow color grade on angioscopy and LCBI (4) on NIRS-IVUS was found in both stented and non-stented lesions **(Fig. 4)**. A previous study evaluating neoatherosclerosis by NIRS-IVUS also indicated the limited influence of stent struts on the assessment of LCBI by NIRS-IVUS[19].

Although LCBI (4) by NIRS-IVUS showed excellent discriminative performance (C-statistic 0.800) with the best cutoff value of 448, specificity was not so high (69.7%). Not only lipid plaque burden represented by LCBI (4) but also cap thickness over the lipid plaque would influence on plaque vulnerability. On angioscopy, thick cap fibroatheroma is relatively white, while thin cap fibroatheroma looks yellow. NIRS-IVUS can detect lipid plaque underlying fibrous cap irrespective of its cap thickness. Therefore, NIRS-IVUS might potentially overestimate the vulnerability of some plaques (i.e., thick cap fibroatheroma). The limited resolution of IVUS did not allow us to evaluate the impact of cap thickness on the LCBI values and angioscopic yellow color grade in the present study. Higher resolution of optical coherence tomography than IVUS would enable this analysis. Further prospective investigations would be warranted to evaluate the clinical significance of the current findings.

Study Limitations

This study has several limitations. First, this was a single-center observational study, and its sample size was relatively small, resulting in the limited statistical power and impaired generalizability of the current

findings. Second, patients with tortuous or small vessels not suitable for angioscopic examination were excluded, resulting in a selection bias. Third, coronary angioscopy sometimes could not acquire the images of whole vessel wall due to insufficient blood elimination and, in such cases, might have missed some yellow plaques. Finally, matching segments between NIRS-IVUS and angioscopy was challenging. Although we used the predetermined systematic methodology for matching, the accuracy for matching segments might be limited.

Conclusions

This study demonstrated a strong positive correlation between yellow plaque color grade by coronary angioscopy and LCBI (4) by NIRS. The qualitative angioscopic assessment was objectively validated by the quantitative NIRS evaluation, which would be helpful for the reinterpretation of the existing evidences of both imaging modalities. Yellow plaque on coronary angioscopy and a max LCBI (4) ≥ 400 on NIRS are similarly useful findings for prediction of future clinical events.

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Notice of Grant Support

None.

Conflict of Interest

Y. Sotomi received speaker honoraria from Abbott Vascular Japan and Boston Scientific Japan. A. Hirata received speaker honoraria from Bristole-Myers Squibb. Y. Ueda received speaker honoraria from Sanofi and Daiichi-Sankyo and received research grant from Abbott Vascular, Bayer, Nihon Kohden, and AstraZeneca. A. Hirayama received speaker honoraria from Bayer, Takeda, Daiichi-Sankyo and received donations scholarship funds from Boston Scientific Japan, Abbott Vascular Japan, Medtronic, Japan Lifeline, Hokushin Medical, Active Medical. Y. Sakata received speaker honoraria from AstraZeneca, Otsuka Pharmaceutical Ono Pharmaceutial, Daiichi-Sankyo, Bayer, and Boehringer Ingelheim. Y. Higuchi received speaker honoraria from Daiichi-Sankyo. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

IRB Information

Research ethics committee of Osaka Police Hospital, Reference number 1193

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