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ORIGINAL RESEARCH

Risk Stratification in Acute Coronary Syndrome by Comprehensive Morphofunctional Assessment With Optical Coherence Tomography

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ABSTRACT

BACKGROUND Artificial intelligence enables simultaneous evaluation of plaque morphology and computational physiology from optical coherence tomography (OCT).

OBJECTIVES This study sought to appraise the predictive value of major adverse cardiovascular events (MACE) by combined plaque morphology and computational physiology.

METHODS A total of 604 patients with acute coronary syndrome who underwent OCT imaging in ≥1 nonculprit vessel during index coronary angiography were retrospectively enrolled. A novel morphologic index, named the lipid-to-cap ratio (LCR), and a functional parameter to evaluate the physiologic significance of coronary stenosis from OCT, namely, the optical flow ratio (OFR), were calculated from OCT, together with classical morphologic parameters, like thin-cap fibroatheroma (TCFA) and minimal lumen area.

RESULTS The 2-year cumulative incidence of a composite of nonculprit vessel-related cardiac death, cardiac arrest, acute myocardial infarction, and ischemia-driven revascularization (NCV-MACE) at 2 years was 4.3%. Both LCR (area under the curve [AUC]: 0.826; 95% CI: 0.793-0.855) and OFR (AUC: 0.838; 95% CI: 0.806-0.866) were superior to minimal lumen area (AUC: 0.618; 95% CI: 0.578-0.657) in predicting NCV-MACE at 2 years. Patients with both an LCR of >0.33 and an OFR of ≤0.84 had significantly higher risk of NCV-MACE at 2 years than patients in whom at least 1 of these 2 parameters was normal (HR: 42.73; 95% CI: 12.80-142.60; $P < 0.001$). The combination of thin-cap fibroatheroma and OFR also identified patients at higher risk of future events (HR: 6.58; 95% CI: 2.83-15.33; $P < 0.001$).

CONCLUSIONS The combination of LCR with OFR permits the identification of a subgroup of patients with 43-fold higher risk of recurrent cardiovascular events in the nonculprit vessels after acute coronary syndrome.
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Acute coronary syndromes (ACSs) are still one of the major causes of morbidity and mortality worldwide.[1] Because atherosclerosis is a systemic vascular disease,[2] up to 53% of patients experiencing ACS present with multivessel coronary atheroma,[3,4] and the presence of obstructive nonculprit lesions is associated with poor clinical outcome.[3] Furthermore, a high proportion of patients will experience recurrent ACS after the first episode,[5,6] often depending on nonculprit lesions, some of them initially appearing as angiographically mild and inconspicuous at the index procedure.[7-10] Diagnostic methods enabling refinement of the risk stratification of these nonculprit lesions in ACS might be instrumental to tailor prevention strategies and ultimately to reduce the incidence of future recurrent events in high-risk patients.

The PROSPECT[11] (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) and CLIMA[12] (Relationship Between OCT Coronary Plaque Morphology and Clinical Outcome) studies have highlighted that specific lesion features—namely, large plaque burden, small luminal area, the presence of thin-cap fibroatheromas (TCFAs), and the infiltration of macrophages—can predict future cardiovascular events associated with nonculprit lesions in high-risk patients. Nonetheless, this strategy of detecting vulnerable plaques is unlikely to pervade the clinical practice because of the low a priori likelihood of events per plaque,[2] the low predictive values of each individual feature,[11,12] and the poor reproducibility of manual plaque characterization.[13]

Novel computational algorithms have been recently developed and validated for accurate calculation of coronary physiology and for morphologic plaque characterization in intravascular optical coherence tomography (OCT), based on artificial intelligence (AI).[14,15] These novel approaches enable a fully automatic, comprehensive morphofunctional evaluation of the coronary plaque in vivo, thus improving the reproducibility and reducing the subjectivity of the assessment. Based on these technological improvements, a novel morphologic OCT index that integrates the most prognostic relevant plaque features, named the lipid-to-cap ratio (LCR), is hereby proposed. Its prognostic value to predict future coronary events related to untreated nonculprit lesions after ACS is evaluated, in combination with the optical flow ratio (OFR), a functional parameter of coronary physiology derived from OCT that has been showed to have good agreement with pressure wire-based fractional flow reserve (FFR).[14,16]

METHODS

STUDY PATIENTS AND PROTOCOL. This study is a substudy of a prospective OCT registry (NCT03084991). All patients with ACS who underwent coronary angiography and OCT examinations at the Second Affiliated Hospital of Harbin Medical University between 2017 and 2018 and who had completed a 2-year clinical follow-up at the time of the present analysis were screened. Inclusion criteria for the present study were as follows: 1) diagnosis of ACS at the patient's discharge from the hospital, encompassing ST- and non-ST-segment elevation myocardial infarction and unstable angina; 2) patients who had successful revascularization of the culprit vessel; and 3) OCT imaging acquired in ≥1 untreated nonculprit vessels (planned staged percutaneous coronary intervention [PCI] was regarded as treated nonculprit vessels). Exclusion criteria were: 1) poor OCT image quality; 2) OCT pull back in the nonculprit vessel shorter than 30 mm; 3) any sign pointing out possible iatrogenia linked to OCT acquisition (dissection, staining); and 4) severe valvulopathy.

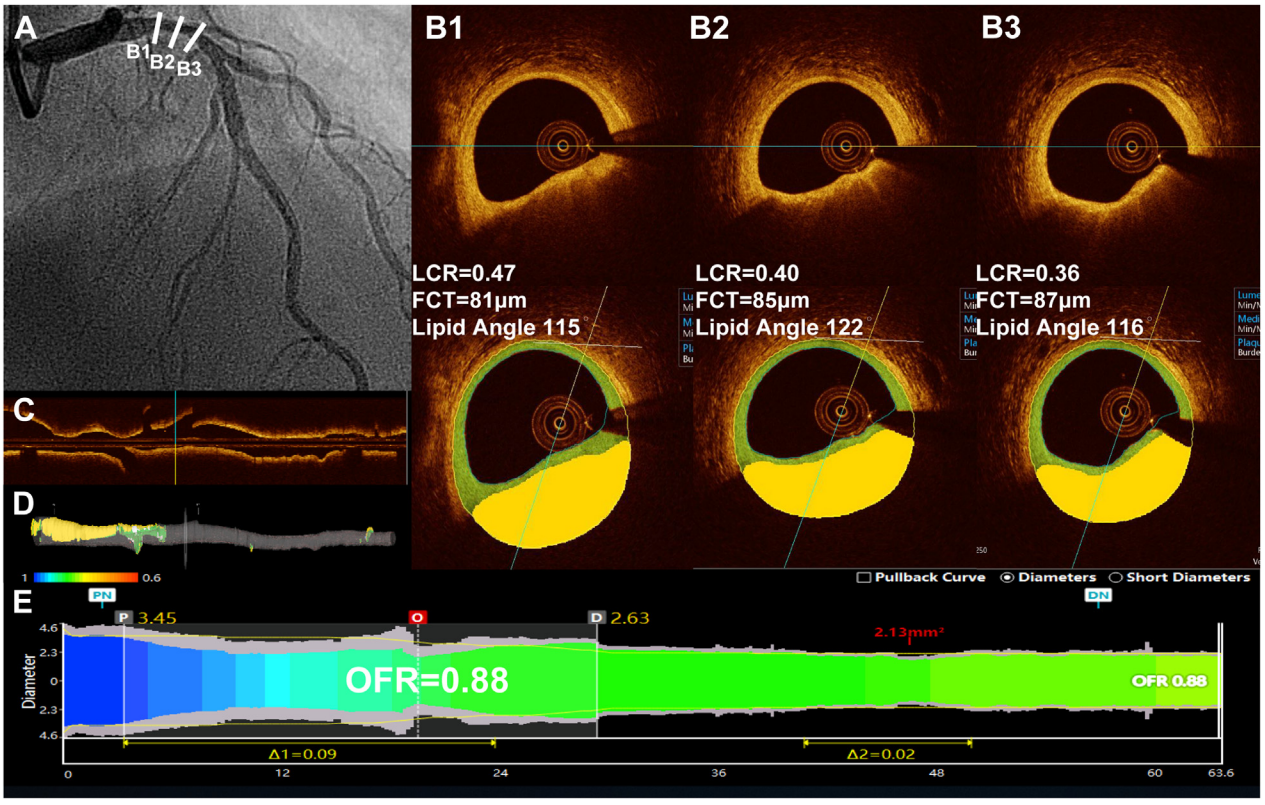
At the study hospital, OCT was frequently used in patients with ACS for assessing lesion morphology in culprit as well as in nonculprit vessels to guide the treatment strategy except the following conditions: 1) hemodynamic instability; 2) severe anatomic tortuosity; 3) acute or chronic renal insufficiency; and 4) left main disease. The therapeutic strategy of the nonculprit artery was determined by the interventional cardiologist according to local practice. The treatment strategy for nonculprit lesions was based on stenosis severity if functional assessment was not available. A nonculprit lesion with angiographic stenosis of >70% or ischemic evidence related to the nonculprit lesion was usually treated with stent implantation. However, the final decision of the treatment strategy was decided by the operator. Analysis of the clinical data was performed at the iMcorelab (Second Affiliated Hospital of Harbin Medical University) before any OCT analysis and entered into an unmodifiable auditable database. Imaging data were analyzed at a different core laboratory (CardHemo, Med-X Research Institute, Shanghai Jiao Tong University) by independent analysts, who were blinded to the clinical data and follow-up results.

The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Harbin

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
AI = artificial intelligence
AUC = area under the curve
FCT = fibrous cap thickness
FFR = fractional flow reserve
iFR = instantaneous wave-free ratio
LAD = left anterior descending
LCR = lipid-to-cap ratio
MACE = major adverse cardiovascular events
MI = myocardial infarction
MLA = minimal lumen area
NCV-MACE = nonculprit vessel–related major adverse cardiovascular events
OCT = optical coherence tomography
OFR = optical flow ratio
PCI = percutaneous coronary intervention
ROC = receiver-operating characteristic
TCFA = thin-cap fibroatheroma

FIGURE 1 **Representative Example of Simultaneous Morphofunctional Assessment of Nonculprit Lesion**



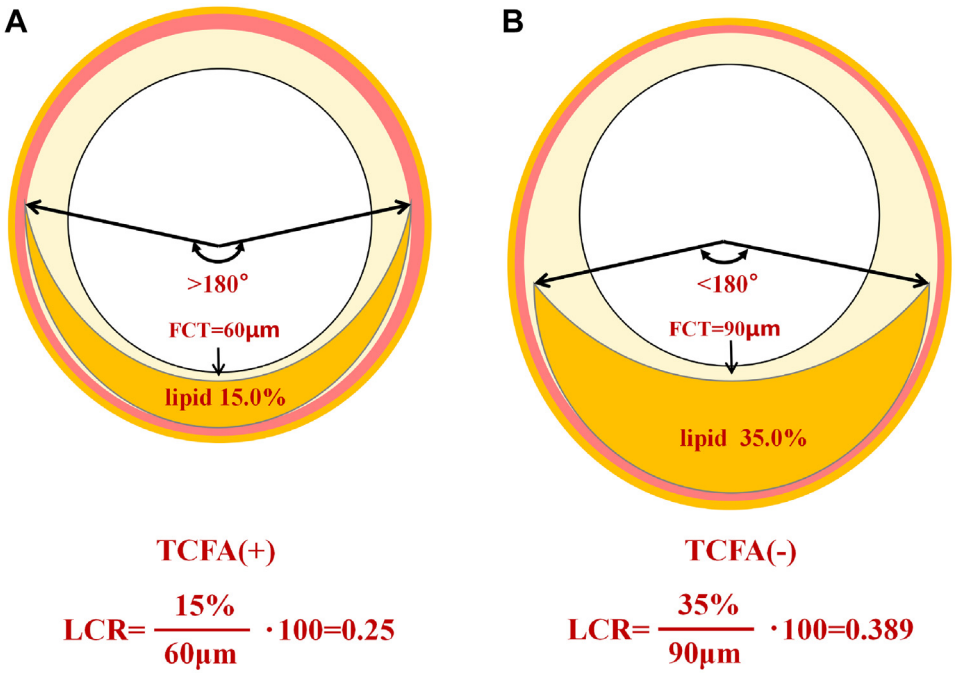
(A) Coronary angiography at the index procedure shows an intermediate lesion in the proximal LAD (nonculprit). **(B)** Optical coherence tomography showed a lipidic plaque (B1-B3) located in the proximal LAD. Automatic computed values of LCR, FCT, and lipid arc are shown on the corresponding cross sections (B1-B3). The plaque composition can be also presented **(C)** in the longitudinal view and **(D)** as a 3-dimensional reconstruction of the lumen with plaque composition superimposed. **(E)** The computed OFR measurements are color-coded and displayed on the lumen-media diameter profiles. OFR at the most distal position is 0.88. FCT = fibrous cap thickness; LAD = left anterior descending artery; LCR = lipid-to-cap ratio; OFR = optical flow ratio.

Medical University and was conducted in accordance with the Declaration of Helsinki. All patients provided informed consent for enrollment into the institutional database, authorizing the use of their anonymized data and information in future studies for investigational or quality-control purposes.

IMAGE ACQUISITION AND QUANTITATIVE ANALYSIS. The invasive procedure was performed within 72 hours from the onset of symptoms, depending on the patient's risk, by a radial or femoral approach, with a 6-F or 7-F guiding catheter, according to the standard procedure. Coronary angiographies were acquired on a flat panel system at 15 frames/s. The culprit vessel was identified by the operator according to electrocardiogram changes; regional wall motion abnormalities; and angiographic features of instability, like ulceration, contrast staining, flow limitation, or intraluminal filling defects. The optimal therapy to restore antegrade flow in the culprit lesion was left at the operator's discretion and might include PCI with or without stenting, thrombus aspiration, or intravenous thrombolysis.

After successful treatment of the culprit lesion, OCT images of the nonculprit vessels were obtained with frequency-domain OCT systems, C7-XR or OPTIS (Abbott Vascular), at a frame rate of 100 or 180 MHz, respectively, and a pull back speed of 20 to 40 mm/s. Anonymized OCT images were analyzed at an independent core laboratory (CardHemo, Med-X Research Institute, Shanghai Jiao Tong University) by experienced analysts using dedicated quantitative analysis software (OctPlus, version 2.0, Pulse Medical Imaging Technology).[15,16] The methodology for automatic plaque characterization and OFR computation, using AI-aided software, has been previously described (Figure 1).[14,15] Briefly, lumen and internal elastic

FIGURE 2 **Calculation of LCR and TCFA**



Plaque A meets the criteria for TCFA (angle of >180° and cap thickness of ≤65 μm), but the LCR is below 0.33. However, plaque B does not strictly meet criteria for the diagnosis of TCFA, but the LCR is above 0.33 (high risk). TCFA = thin-cap fibroatheroma; other abbreviations as in Figure 1.

lamina contours were automatically delineated on all OCT cross sections. Plaque composition, including lipidic, fibrous, and calcific tissues, was subsequently detected by the software and quantified. For long vessels that were imaged with 2 or more OCT pull backs, the OFR was computed in each pull back and combined to generate the final OFR value at the most distal position.[14,17] A novel index, the LCR), was then automatically calculated based on the AI model, taking into account the lipidic burden of the plaque and the cap thickness over the diseased segment (Supplemental Methods).

The lesion with the maximum LCR was defined as the region of interest of the nonculprit vessel. If the patient had more than 1 lesion in the nonculprit vessels, the maximum LCR was defined as the patient's LCR for the patient-level analysis. Finally, other classical morphologic parameters of the lesion with potential prognostic value, like the presence of TCFA, defined as maximal lipid angle of >180° and fibrous cap thickness (FCT) of ≤65 μm, were also automatically determined by measuring the arc of the lipid core and the FCT (Figure 2).

CLINICAL OUTCOMES. All patients enrolled in the registry were prospectively followed up by clinical visit or phone call at 1 month, 6 months, and 12 months within the first year after discharge and every 12 months after 1 year. Major adverse cardiovascular events (MACE) were defined as the composite of cardiac death, nonfatal acute myocardial infarction (MI), and ischemia-driven revascularization. MACE was further classified as culprit vessel-related or nonculprit vessel-related MACE (NCV-MACE) by the clinical event committee of the study at iMcorelab, depending on electrocardiogram changes, wall motion abnormalities, or angiographic findings at the recurrent event. If these criteria were deemed insufficient to adjudicate the event to a specific vessel (eg, attributable to sudden death without autopsy), then MACE was classified as indeterminate. NCV-MACE was the primary endpoint of the study. For analytic purposes, all clinical events were considered NCV-MACE unless they could be clearly adjudicated to the culprit vessel. Planned staged PCI for nonculprit vessels within 30 days was not considered NCV-MACE.

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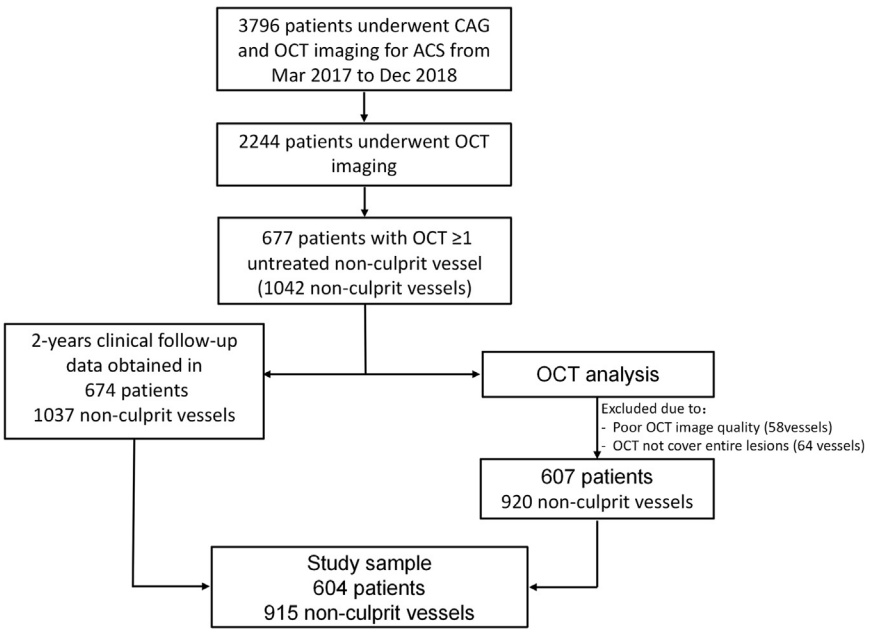
FIGURE 3 Study Flow Chart



A total of 915 nonculprit vessels in 604 patients were included for the final analysis. ACS = acute coronary syndrome; CAG = coronary angiography; OCT = optical coherence tomography.

STATISTICAL ANALYSIS. Categorical variables were reported as counts (percentages) and compared by the Fisher exact test. Continuous variables with normal or skewed distributions were reported as mean ± SD or median (IQR), respectively, and compared using Student's *t*-test or the Mann-Whitney *U*-test, respectively. The cutoff values of OCT parameters were determined by the receiver-operating characteristic (ROC) curve, area under the curve (AUC), and maximal Youden index (J). Incidence rates of NCV-MACE for the dichotomous categories defined by the different OCT parameters were calculated by the Kaplan-Meier method at the patient level, assuming the condition of proportional hazards, and compared by the log-rank test. The univariate relationship between variables (clinical characteristics and OCT parameters) with NCV-MACE was determined by the Cox proportional hazards model with fixed univariate entry. Variables that showed significant univariate relationships with NCV-MACE in the Cox proportional hazards model were entered into multivariate regression to calculate adjusted HRs, and nonsignificant variables were dropped by means of forward selection. Statistical analyses were performed both at the patient level and vessel level. The software package MedCalc, version 19 (MedCalc Software) was used for statistical analysis. All comparative tests were 2-tailed, and a *P* value of ≤0.05 was considered statistically significant.

RESULTS

STUDY POPULATION. From March 2017 to December 2018, 3,796 patients with ACS were admitted to the study center, of whom 2,244 (59.1%) underwent OCT imaging. Altogether 677 patients with 1,042 untreated nonculprit vessels met the inclusion criteria and were found to be potentially eligible for the study. However, 122 vessels were excluded because of poor OCT quality and incomplete OCT imaging of the lesion, and 5 vessels were missing follow-up data, thus finally resulting in 604 patients (915 vessels) included and suitable for analysis (Figure 3). No patient had to be excluded because of OCT-related iatrogenia. Clinical follow-up was completed in 674 of the 677 eligible patients (99.6%) at 2 years, including all 604 patients who were included in the final statistical analysis. Table 1 shows the patients' and procedural characteristics of the study sample. Mean age was 57.2 ± 11.2 years, most patients were male (76%), and 17.5% were diabetic. The most common clinical presentation was ST-segment elevation MI (67.7%), and only 304

patients were treated with stenting of the culprit lesion (50.3%), whereas the remainder were treated with thrombus aspiration, intravenous thrombolysis, drug-coated balloon, or alternative therapies. Patients were categorized as the stent group and no-stent group, accordingly. During the follow-up period, patients received antiplatelet medications and statins (Supplemental Table 1), according to guideline-recommended standards of care.

OCT FINDINGS. A total of 915 nonculprit vessels were automatically analyzed. The highest LCR per patient was found most frequently in the left anterior descending artery (LAD) (36.6%), followed by the right coronary artery (33.3%) and left circumflex coronary artery (30.1%). The lowest OFR value per patient was also most frequently found in the LAD (39.4%), followed by the right coronary artery (31.0%) and left circumflex coronary artery (29.6%). In nonculprit plaques, the mean value for LCR was 0.261 ± 0.160, for minimal lumen area (MLA) was 4.17 ± 2.11 mm^2, and for OFR was 0.86 ± 0.11 (Supplemental Table 2). TCFA was detected in nonculprit vessels of 69 patients (11.4%). Patients with NCV-MACE had higher percent diameter stenosis (44 [34-50] vs 34 [26-42]; $P < 0.001$), higher LCR (0.440 ± 0.144 vs 0.253 ± 0.156; $P < 0.001$), lower OFR (0.69 ± 0.20 vs 0.87 ± 0.10; $P < 0.001$), and higher prevalence of TCFA (34.6% vs 10.4%; $P = 0.068$) than NCV-MACE-free patients. **Figure 1** shows a representative case of the automatic calculation of LCR, OFR, MLA, and TCFA in a nonculprit vessel.

ADVERSE EVENTS. During the 2-year follow-up, 51 patients (8.4%) experienced clinical events. The cumulative incidences of culprit vessel MACE and NCV-MACE at 2 years were 4.1% (n = 25) and 4.3% (n = 26), the latter including 8 cardiac deaths or cardiac arrest, 2 MIs (Supplemental Figure 1), and 16 revascularizations (**Table 2**). The 2-year cumulative incidence of NCV-MACE was 3.0% (n = 9) in the stent group vs 5.7% (n = 17) in the no-stent group ($P = 0.102$).

CUTOFF VALUE OF OCT PREDICTORS FOR NCV-MACE. The optimal cutoff values of the different OCT parameters for the prediction of NCV-MACE were determined by the ROC curve and maximal Youden index. The following cutoff values were found to provide the optimal balance between

TABLE 1 Baseline Demographic Characteristics (N = 604)

Patient characteristics	
Age, y	57.2 ± 11.2
Men	459 (76.0)
Diabetes mellitus	106 (17.5)
Insulin-requiring diabetes	36 (6.0)
Hypertension	273 (45.2)
Hyperlipidemia	264 (43.7)
Hypertension needing drugs	260 (43.0)
Smoking	347 (57.4)
Positive family history	150 (24.8)
Previous MI	41 (6.8)
Previous PCI	35 (5.8)
Previous CABG	0 (0)
Previous stroke	27 (4.5)
History of renal insufficiency	7 (1.2)
History of heart failure	6 (1.0)
Procedural characteristics	
Indication for angiography	
STEMI	409 (67.7)
NSTEMI	131 (21.7)
Unstable angina	64 (10.6)
Coronary artery disease	
2-vessel disease	293 (48.5)
3-vessel disease	311 (51.5)
Stent performed	304 (50.3)
Lesion parameters for region of interest (n = 915)	
Diameter stenosis, %	34 (26-42)
Minimal lumen area, mm^2	3.76 (2.63-5.24)
Lesion length	15.3 (10.0-25.0)
Presence of macrophages	450 (49.2)
Vessel optical flow ratio	0.86 ± 0.11
Lip-to-cap ratio	0.261 ± 0.160
Minimum FCT, μm	83 (68-107)
Maximum lipid angle, °	137 (96-195)
Plaque burden, %	50 (45-56)

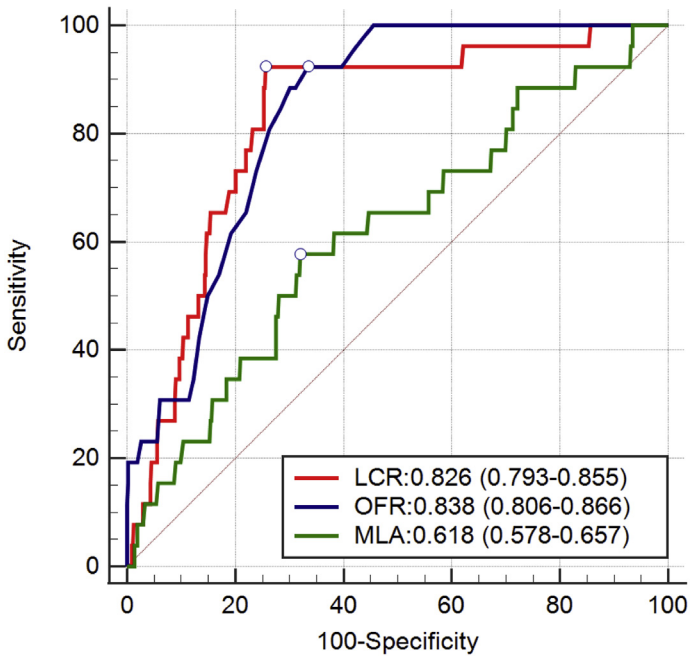
Values are mean ± SD, n (%), or median (IQR).

CABG = coronary artery bypass graft; FCT = fibrous cap thickness; MI = myocardial infarction; PCI = percutaneous coronary intervention; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 2-Year Clinical Events

	All Nonculprit Vessel-Related Major Adverse Cardiovascular Events	Stent Group (n = 304)		No-Stent Group (n = 300)	
		Nonculprit Vessel Related	Indeterminate Vessel Related	Nonculprit Vessel Related	Indeterminate Vessel Related
Cardiac death	8	0	2	0	6
Acute myocardial infarction	2	1	0	1	0
Ischemia-driven revascularization	16	6	0	10	0

FIGURE 4 Receiver-Operating Characteristic Curve Analysis and Predictive Value of Optical Coherence Tomography Variables for Nonculprit Vessel Related Major Adverse Cardiovascular Events



The areas under the curve are marked in the lower right corner of the graph with 95% CIs. MLA = minimal lumen area; other abbreviations as in Figure 1.

sensitivity and specificity for the prediction of NCV-MACE during a 2-year follow-up: LCR of >0.33 (AUC: 0.826; 95% CI: 0.793-0.855; $P < 0.001$), MLA of ≤2.95 mm^2 (AUC: 0.618; 95% CI: 0.578-0.657; $P = 0.045$), and OFR of ≤0.84 (AUC: 0.838; 95% CI: 0.806-0.866; $P < 0.001$) (Figure 4). There were 2 cases of NCV-MACE in the subgroup of patients with an LCR of ≤0.33 vs 24 patients with an LCR of >0.33 and 2 cases of NCV-MACE in the subgroup with OFR of >0.84 vs 24 patients with OFR of ≤0.84. The AUC for the prediction of NCV-MACE was significantly higher for both LCR (difference: 0.208; 95% CI: 0.082-0.334; $P = 0.001$) and OFR (difference: 0.220; 95% CI: 0.115-0.325; $P < 0.001$) compared with MLA, while there was no significant difference between LCR and OFR (difference: 0.012; 95% CI: -0.069 to 0.093; $P = 0.776$). The ROC curves of percent diameter stenosis, plaque burden, lesion length, macrophages, lipid angle, and FCT are shown in Supplemental Figure 2.

TABLE 3 Prognostic Performance of OCT Parameters

Predictors	LCR	OFR	MLA (mm^2)	TCFA	LCR + OFR	TCFA + OFR
Optimal cutoff (mm^2)	>0.33	≤0.84	≤2.95	NA	>0.33/≤0.84	NA/≤0.84
Sensitivity, %	92.3	92.3	57.7	34.6	88.5	33.6
Specificity, %	74.4	66.6	70.0	89.5	87.4	95.3
PPV, %	14.0	11.1	7.5	12.9	24.0	25.0
NPV, %	99.5	99.5	97.3	96.8	99.4	97.0

LCR = lipid-to-cap ratio; MLA = minimal luminal area; NA = not applicable; NPV = negative predictive value; OFR = optical flow ratio; PPV = positive predictive value; TCFA = thin-cap fibroatheroma.

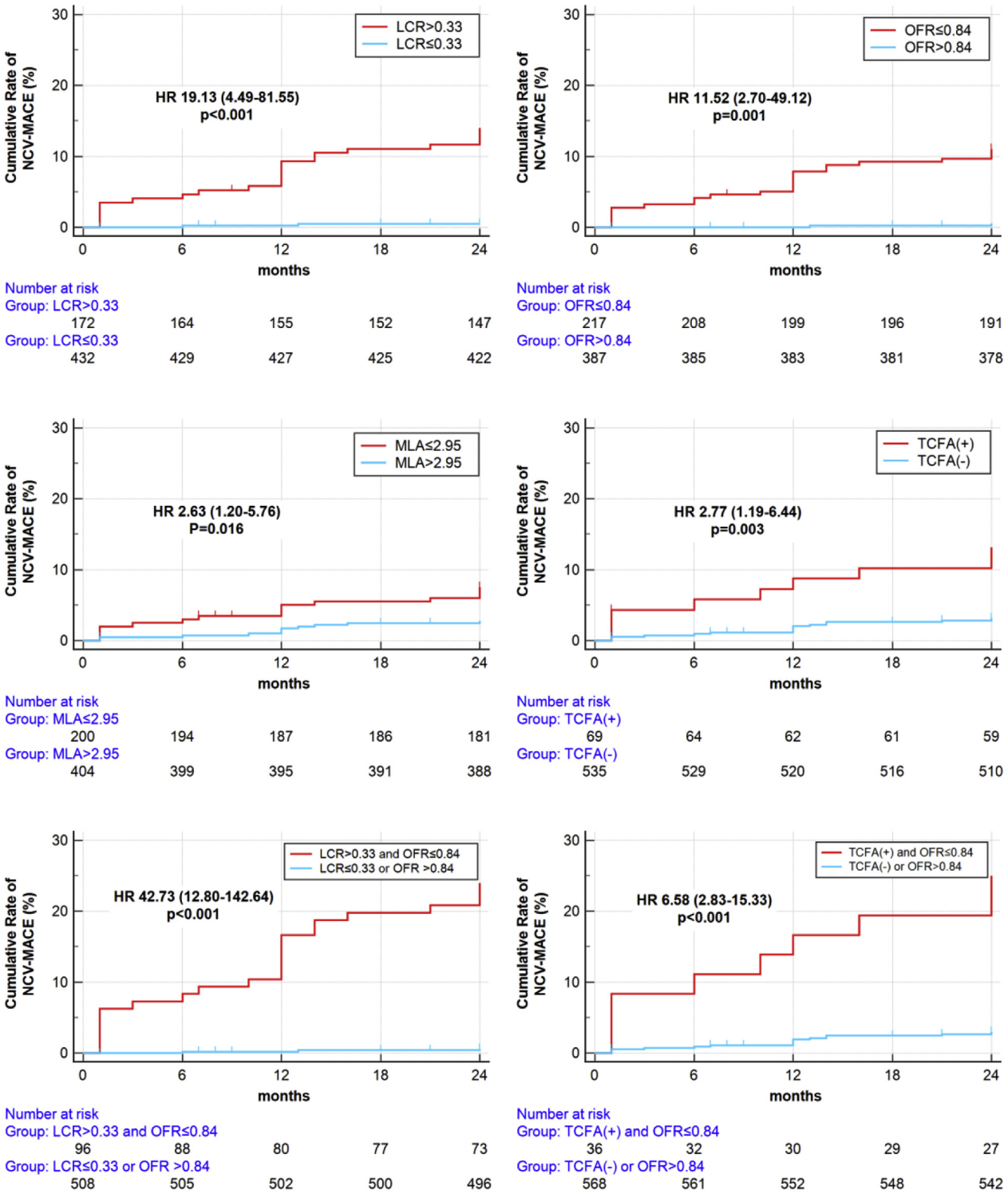
PROGNOSTIC PERFORMANCE OF THE DIFFERENT OCT PREDICTORS AND THEIR COMBINATION. The prognostic performance of the different OCT predictors, alone and in combination, according to the optimal cutoff value defined in the ROC analysis, is presented in Table 3. Separately, both LCR and OFR were the most sensitive methods to predict future events in the nonculprit vessels. Classical TCFA, however, remained the most specific method. Although all parameters showed very high negative predictive value, the positive predictive value remained very low for each method alone, ranging from 7.5% for MLA to 14% for LCR. The combination of a morphologic feature, like LCR or TCFA, with a functional parameter of physiology, like OFR, substantially improved the positive predictive value for future cardiovascular events (LCR + OFR: 24%; TCFA + OFR: 25%).

The prognostic performance of the different predictors, using the standard diagnostic OFR cutoff of ≤0.80, confirms the robustness of the analysis (Supplemental Table 3, Supplemental Figures 3 and 4).

In the event-free survival analysis, all OCT predictors could identify a subgroup of patients with higher NCV-MACE at 2 years, according to the cutoff values previously defined: LCR of >0.33 (HR: 19.13; 95% CI: 4.49-81.55; $P < 0.001$), OFR of ≤0.84 (HR: 11.52; 95% CI: 2.70-49.12; $P = 0.001$), MLA of ≤2.95 mm^2 (HR: 2.63; 95% CI: 1.20-5.76; $P = 0.016$), and TCFA (HR: 2.77; 95% CI: 1.19-6.44; $P = 0.018$). The combination of LCR of >0.33 and OFR of ≤0.84 provided the strongest discriminative power (HR: 42.73; 95% CI: 12.8-142.6; $P < 0.001$), superior to the combination of TCFA and OFR of ≤0.84 (HR: 6.58; 95% CI: 2.83-15.33; $P < 0.001$) (Figure 5, Central Illustration, Supplemental Tables 4 and 5).

INDEPENDENT PREDICTORS OF CLINICAL EVENTS RELATED TO NONCULPRIT VESSELS. The patient-level and vessel-level independent correlates of NCV-MACE and acute MI/revascularization are given in Table 4. The insulin-requiring diabetes was a significant predictor of NCV-MACE (Supplemental Table 6). A baseline LCR of >0.33 and OFR of ≤0.84 were both significant independent predictors of

FIGURE 5 **Kaplan-Meier Curves of Event Rates for Different OCT Predictors and Their Combinations**



NVC-MACE = nonculprit vessel major adverse cardiovascular events; other abbreviations as in Figures 1 to 4.

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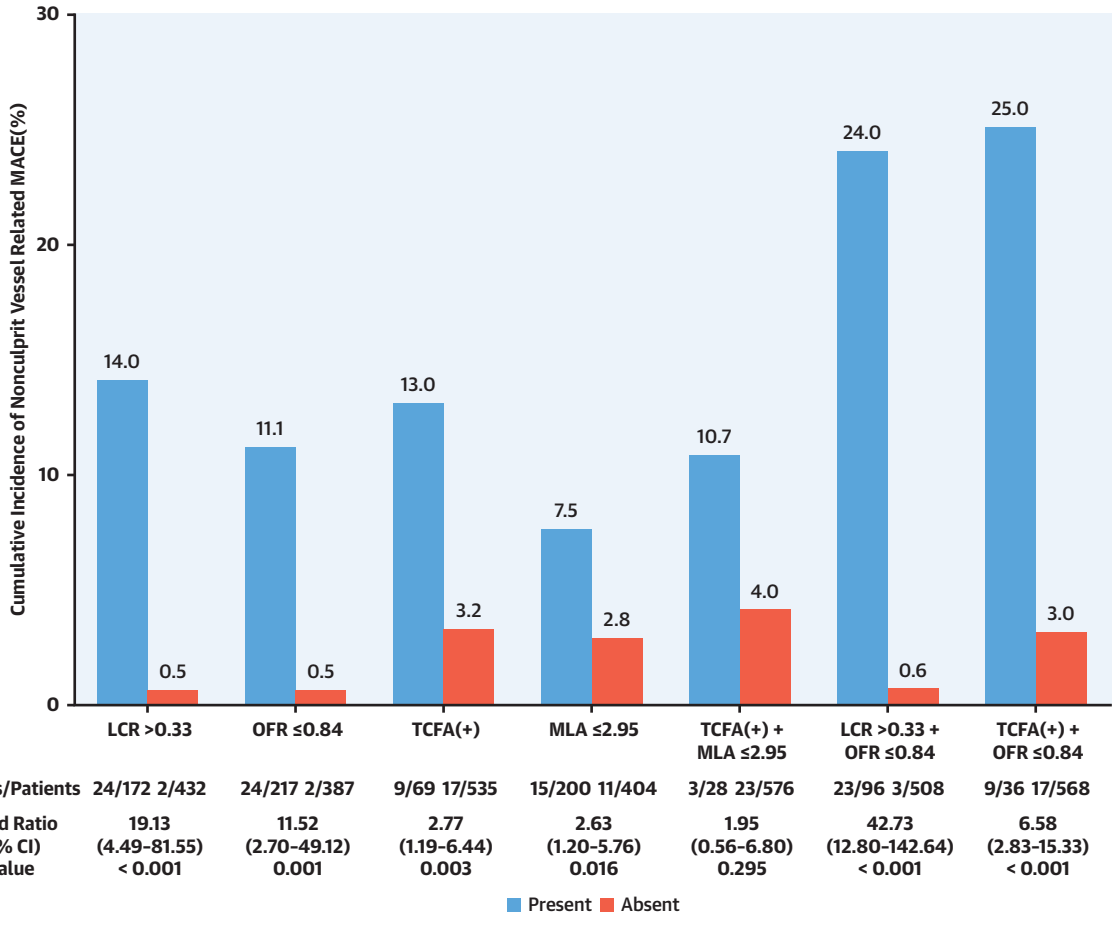
CENTRAL ILLUSTRATION **2-Year Cumulative Incidence of Nonculprit Vessel Related Major Adverse Cardiovascular Events for Patients With and Without Optical Coherence Tomography-Defined High-Risk Criteria**



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LCR = lipid-to-cap ratio; MACE = major adverse cardiovascular events; MLA = minimal lumen area; OFR = optical flow ratio; TCFA = thin-cap fibroatheroma.

NCV-MACE (Supplemental Tables 7 and 8) and acute MI/revascularization (Supplemental Tables 9 and 10).

DISCUSSION

The main findings of this study are as follows. 1) A simultaneous evaluation of plaque morphology and coronary physiology is feasible using a single OCT pull back with AI-aided software. 2) The hereby proposed LCR integrates most of the morphologic features reported as prognostically relevant by previous studies and has superior prognostic performance to any single morphologic feature alone. 3) Comprehensive morphofunctional evaluation of nonculprit vessels is significantly associated with the risk of NCV-MACE, a composite of cardiac death, MI, and ischemia-driven revascularization. The combination of LCR of >0.33 and OFR of ≤0.84 rendered the highest prognostic performance, detecting a subgroup of patients with 43-fold higher risk of recurrent events at the 2-year follow-up.

The evaluation and treatment of nonculprit lesions in the setting of ACS is still an open question.[2,4] Functional approaches using FFR in nonculprit lesions have proven to be superior to a strategy of culprit-only treatment[18,19]; however, deferral of lesions based on FFR or instantaneous wave-free ratio (iFR) assessment is associated with higher long-term

risk of future cardiovascular events in ACS, as compared with deferral in patients with stable coronary heart disease,[20-22] thus suggesting that pressure-based indexes alone do not consistently identify stenosis for which revascularization can be safely deferred.[4] The mechanism underneath this phenomenon is unclear but might be likely related to transient microvascular dysfunction during the acute phase of ACS, resulting in submaximal hyperemia during the infusion of adenosine or other vasodilators and, thereafter, in falsely negative FFR values.[23-25] Hyperemia-independent indexes, like iFR, have tried to overcome this limitation, with incomplete success. Although FFR underestimates the severity of nonculprit lesions in ACS, iFR overestimates it.[22,26] The accuracy of wire-based physiology improves, however, 5 to 6 days after the onset of the acute phase.[27]

OFR has been advocated to circumvent the intrinsic fluctuations in microvascular function during ACS[17,28] because they are independent of microvascular conditions. However, the severity of epicardial stenosis is also exaggerated during the acute phase of ACS,[29] but this effect might be minimized by following a strict protocol, with appropriate administration of vasodilators before the assessment.

The use of intracoronary imaging to detect the vulnerable plaque in nonculprit vessels has succeeded in identifying some morphologic predictors of future events. The PROSPECT study, using intravascular ultrasound, in both grayscale and radiofrequency analysis, identified plaque burden, MLA, and radiofrequency-defined TCFA as predictors of future cardiovascular events.[11] More recently, the CLIMA (Relationship Between OCT Coronary Plaque Morphology and Clinical Outcome) study used OCT to identify MLA, cap thickness, lipid arc circumferential extension, and the presence of macrophages as predictors of a composite of cardiac death and MI at 1 year of follow-up.[12] Patients with the concurrence of all 4 predictors had 7.5-fold higher risk of the composite endpoint.[12] Most recently, the PROSPECT II study assessed nonculprit lesions with a combination of near-infrared spectroscopy and intravascular ultrasonography, finding that patients with ≥1 lesion presenting high plaque burden and high lipid content had a 2.6-fold higher risk of events than the other patients.[30] Nonetheless, these studies demonstrated that the incidence of events per plaque was indeed very low, thus resulting in very low predictive values of any morphologic parameter, alone or combined,[11,12,30] thereby discouraging a strategy of preventive interventions on the vulnerable plaque.[2] The positive predictive value of LCR is low, and without significant difference with TCFA, it may be attributed to a low event rate at a short follow-up time, aggressive drug therapy, and low prevalence of vulnerable plaque.

TABLE 4 Independent Predictors of Clinical Events Related to Nonculprit Vessels During Follow-Up

Predictors	HR (95% CI)	*P* Value
Nonculprit vessel–related major adverse cardiovascular events		
Predictors of patient-level events		
Insulin-requiring diabetes	2.71 (1.12-6.54)	0.027
LCR >0.33	19.13 (4.49-81.55)	<0.001
OFR ≤0.84	11.52 (2.70-49.12)	0.001
LCR >0.33 and OFR ≤0.84	42.73 (12.8-142.6)	<0.001
Predictors of vessel-level events		
LCR >0.33	10.72 (3.67-31.33)	<0.001
OFR ≤0.84	6.81 (2.55-18.14)	<0.001
LCR >0.33 and OFR ≤0.84	22.45 (9.60-52.53)	<0.001
AMI and revascularization		
Predictors of vessel-level events		
LCR >0.33	9.74 (2.79-34.04)	<0.001
OFR ≤0.84	5.30 (1.73-16.22)	0.003
LCR >0.33 and OFR ≤0.84	15.19 (5.82-39-63)	<0.001

AMI = acute myocardial infarction; other abbreviations as in Table 3.

Our current study follows the path defined by CLIMA, further refining its methodology in some aspects. The LCR integrates cap thickness and the specific lipidic content of the plaque, which might improve the specificity of simply quantifying plaque burden and might be more meaningful from a mechanistic point of view, as suggested by the recent results of the PROSPECT II study.[30] Furthermore, the current study combines for the first time, to our knowledge, this morphologic assessment with a functional evaluation, incorporating a computational method of physiology that is independent of microvascular function and more accurate than angiography-based methods.[17,14] This simultaneous evaluation with the same OCT pull back was possible with AI-aided software, which provides an objective estimation in a timely fashion. The average analysis time for 1 OCT pull back is <1 minute.[15] This enables the implementation of the method in the daily routine and minimizes possible iatrogenia caused by multiple rewiring with different devices.[18] Of note, in patients with ACS with OCT imaging already performed in the culprit vessel, the same OCT catheter can be used to image the nonculprit vessels for analysis of OFR and LCR, which might represent the early application for OFR and LCR.

The combination of morphology and physiology seems instrumental to enhance the prognostic performance of intracoronary assessment of nonculprit lesions. The combination of a morphologic parameter with OFR substantially increased the positive

predictive value of the approach, notwithstanding the low incidence of events. This is a significant step forward as compared with previous imaging studies.[11,12] The most efficient combination was LCR plus OFR: patients with LCR of >0.33 and with OFR of ≤0.84 had a 43-fold higher risk of events, which was much higher than previous studies. The association between TCFA and the severity of stenosis in nonculprit vessels had been previously reported,[31] thus suggesting a synergistic interplay between classical features of vulnerability and functional repercussions. MLA had been indeed consistently reported as a predictor in all previous morphologic studies,[11,12] but OFR is more accurate for functional assessment than MLA,[14,17] and our results are strongly reassuring of this interplay between morphology and function (Supplemental Figures 5 and 6). Whether OFR can also provide a stable cutoff value for prognostic purposes, unlike the variable cutoffs reported for MLA, is a question that should be answered in future studies.

STUDY LIMITATIONS. This was a retrospective study, with the intrinsic limitations to this kind of design. Selection bias cannot be completely ruled out, but it was prevented by means of a systematic search in the institutional database with strictly predefined inclusion and exclusion criteria at both core labs. The use of OCT-guided PCI to discern between plaque rupture and erosion in the culprit lesion, and tailor the treatment accordingly, might explain the relatively low proportion of stented culprit lesions in the study. Although there is supporting evidence for this therapeutic approach,[32] it is, however, not the standard of care in all centers. Clinical outcomes might be partially influenced by the different therapeutic approaches, although this study minimized that effect by focusing on nonculprit vessels. In addition, the follow-up OCT images for events related to the nonculprit vessel were incomplete. Therefore, the lesion-level analysis is not available.

Our study analyzed multiple nonculprit vessels and multiple lesions in most cases, and the results were reported at both the patient and vessel levels, which may be more meaningful for patient-oriented preventive actions (vulnerable patients).[2] Nonetheless, lesion-specific results would be more interesting for preventive interventions on the lesion (vulnerable plaque), but current evidence seems to discourage such a strategy to date.

The strong signal attenuation caused by lipid plaque precludes the visibility of the external lamina layer, which is an inherent limitation of OCT images. No method can determine the deep boundaries of the lipid core and the external elastic lamina behind the lipid from OCT images. However, the AI model integrated information from adjacent proximal and distal image frames to make a plausible prediction. Although the previously developed AI model has been thoroughly validated using expert consensus as standard reference,[15] pathologic validation is lacking. The accuracy of the expert and AI in measuring lipid and plaque volumes in plaques with a large lipid core remains for further investigation. Future improvement of the AI model might further improve the accuracy of plaque characterization and, thus, increase the prognostic value of LCR. Although previous OCT studies on nonculprit vessels had identified macrophages as an important predictor of future events,[12] they showed an insignificant relationship with NCV-MACE in multivariate Cox regression analysis. This may be because the performance of AI software is still insufficient for a reliable detection of macrophages.[15] Future versions of the convolutional model used for plaque analysis should improve for macrophage detection.

CONCLUSIONS

The combination of morphologic and functional assessment of nonculprit lesions in ACS is superior to classical morphologic features of vulnerability or physiology alone for the prediction of future cardiovascular events. The combination of LCR and OFR physiology in nonculprit lesions can be automatically done with a single AI-aided OCT pull back and permits the identification of a subset of patients with a 43-fold higher risk of adverse clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: LCR is a novel OCT-based index that integrates the most relevant morphologic features reported as prognostically relevant for nonculprit lesions in ACS. LCR has a higher prognostic performance than any morphologic parameter alone.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Simultaneous morphofunctional evaluation of nonculprit vessels has superior predictive value for future coronary events as compared with purely morphologic or purely functional assessment, thus suggesting a synergistic interplay between plaque morphology and physiology in the clinical outcome of patients with ACS.

COMPETENCY IN MEDICAL KNOWLEDGE 3: The combination of LCR (morphologic parameter) and OFR (functional parameter) can be currently done with a single OCT pull back and enables the detection of a subgroup of patients with 43-fold higher risk of future coronary events.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Preventive actions should be intensified and the health monitoring should be tightened in patients with ACS who present an LCR of >0.33 and an OFR of ≤ 0.84 in nonculprit vessels.

TRANSLATIONAL OUTLOOK: The prognostic value of this comprehensive morphofunctional assessment performed onsite by trained analysts, instead of centrally analyzed in a core-lab, should be appraised in future studies.

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APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.