CD4+/CD8+ ratio positively correlates with coronary plaque instability in unstable angina pectoris patients but fails to predict major adverse cardiovascular events

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Abstract
Background: The association between CD4+/CD8+ ratio and coronary plaque instability in patients with unstable angina pectoris (UAP) has not been investigated. We sought to elucidate the correlation between CD4+/CD8+ ratio and plaque instability in this patient population.

Methods: We enrolled 266 UAP patients who underwent pre-intervention optical coherence tomography (OCT) examination and percutaneous coronary intervention in our center from January 2016 to January 2018. Features of coronary plaques in the culprit arteries were classified as unstable plaque and stable plaque. Primary endpoint was occurrence of a major adverse cardiovascular event (MACE). Receiver operating characteristic (ROC) analyses were used to determine the predictive efficacy of the CD4+/CD8+ ratio for a group of unstable plaque patients, and binary logistic regression analysis was performed to evaluate potential independent predictors of plaque instability. All-cause mortality and MACE between the two groups were analyzed.

Results: UAP patients with unstable plaque had a higher CD4/CD8 ratio compared with stable plaque patients ($p<0.05$). Results of binary logistic regression analyses showed that CD4+/CD8+ ratio $\geq 1.725$ and prior stroke were predictors and risk factors of plaque instability ($p<0.05$). ROC analyses showed that CD4+/CD8+ ratio $\geq 1.725$ was predictive of plaque instability in UAP patients. However, the Kaplan–Meier estimate for MACE and all-cause mortality showed no statistical significance.

Conclusions: Higher CD4+/CD8+ ratio is associated with higher risk of plaque instability in our cohort of UAP patients. However, CD4+/CD8+ ratio was not an independent predictor of 1-year MACE or all-cause mortality.

Keywords: CD4+/CD8+ ratio, MACE, OCT, plaque instability, UAP

Introduction
The rupture and erosion of unstable intravascular coronary plaques and the formation of thrombosis are direct causes of acute coronary syndrome (ACS).1,2 Usually, plaque rupture and secondary thrombosis are considered to be complex pathological events, and typical coronary heart disease risk factors play an important role in the development of ACS.3–6 We know that the occurrence of ACS can be caused by thrombosis or luminal obstruction after the rupture of a coronary plaque in patients with unstable angina pectoris; therefore, early identification and prediction of coronary plaque in unstable angina pectoris (UAP) patients is conducive to the clinical treatment and clinical prognosis of patients.
The immune response theory suggests that T lymphocytes including CD8+ and CD4+ T cells can be observed at various stages of atherosclerosis in both human and non-human primates. This suggests that the immune response plays a part in the progression of the disease. Previous studies have confirmed that fatty macrophages, T lymphocytes (including CD8+ and CD4+), and smooth muscle cells are present mainly in the lipid stripes of atherosclerosis. Therefore, the pathological mechanism suggests that CD4+ and CD8+ T cells are involved in the process of atherosclerotic plaque stability. A recent study showed that the CD4+/CD8+ ratio was correlated positively with the occurrence of ACS. However, the association between the CD4+/CD8+ ratio and the risk of acute coronary events is unclear.

At present, coronary angiography is commonly used to evaluate coronary vascular status, and more accurate data can be obtained. Optical coherence tomography (OCT) can not only detect the vascular morphology of the coronary artery, but also analyze the details of lesions; thus OCT technology can evaluate the components and characteristics of coronary plaques. The use of imaging techniques can therefore better identify unstable plaques.

We investigated the potential association between the CD4+/CD8+ ratio and OCT-confirmed coronary artery instability in patients with UAP. Our results may help predict the risk of plaque rupture and provide an updated clinical basis for the prevention and treatment of coronary atherosclerotic unstable plaques in UAP patients.

Materials and methods

Study population and design
Continuous screening included a total of 266 patients. All participants were selected from UAP patients who were admitted to our center from January 2016 to January 2018 for percutaneous coronary interventional therapy (PCI) and OCT examination (Figure 1). All patients underwent and completed PCI successfully without complications. The diagnosis of UAP was based on pre-established guidelines. Meanwhile, demographic characteristics, clinical features, risk factors for coronary heart disease, blood biochemical data, electrocardiography, echocardiography, coronary angiography (CAG), and OCT results were collected. CAG diagnosed the culprit vessels, while OCT confirmed the vulnerability of plaques at these sites.

Follow up
All patients were subsequently followed for 1 year. Primary endpoint was occurrence of a major adverse cardiovascular event (MACE), including all-cause death, target vessel myocardial infarction (MI), and clinically driven target vessel revascularization.

Definitions of coronary heart disease risk factors
The diagnostic criteria of hyperlipidemia were based on the guidelines for prevention and treatment of dyslipidemia in Chinese adults (2016). Hypertension was diagnosed if the patient had blood pressure of ≥140/90 mmHg during at least three random examinations, or was actively using antihypertensive drugs. Diabetes was diagnosed if the patient’s fasting blood glucose was ≥7.1 mmol/l or ≥11.1 mmol/l 2 h after a meal, or there was a clear history of diabetes and the patient was receiving hypoglycemic drugs. Body mass index (BMI) was calculated by dividing a
patient’s weight in kilograms by the square of their height in meters. Smoking was defined as current or previous smoking with cessation less than 3 months prior.

**Laboratory data**

Blood samples were taken from all patients before procedures and immediately sent to the laboratory for analysis. Routine examination included standard blood work-up, liver function, renal function, blood lipid levels, fasting blood glucose, etc. T lymphocyte counts were expressed as absolute and proportional CD3+ cell numbers and CD4+ and CD8+ cells were counted in all 266 test subjects, from which the CD4+/CD8+ ratio was calculated. Blood tests were conducted using standard methods at the central laboratory.

**PCI procedure and OCT image acquisition**

All patients underwent successful CAG and PCI after admission. After intracoronary nitroglycerine administration, the OCT catheter was advanced distal to the culprit lesion. Imaging of the culprit lesion was then acquired using the frequency-domain OCT C7XR system and the Dragonfly catheter (Lightlab Imaging, St. Jude Medical, Westford, MA).2,16 All treatment strategies were determined by experienced interventional cardiologists. Angiographic images measured reference diameter, minimum lumen diameter, lesion length, and percent diameter stenosis. At the end of the procedure, patients undergoing stent implantation were subjected to final OCT imaging. The images were stored digitally and identified for offline analysis.

**Statistical analysis**

All analyses were performed using SPSS 23.0 for Windows statistical software (SPSS Inc., Chicago, IL, USA). The CD4+/CD8+ ratio was not normally distributed, so non-parametrical testing was used to determine differences. The Spearman correlation coefficient was calculated to assess associations between CD4+/CD8+ ratio and all continuous variables in this study. The Mann–Whitney U test was used to study CD4+/CD8+ ratio as a continuous variable for all risk factors. Normally distributed continuous variables were expressed as means and standard deviations (SDs), whereas categorical variables were presented as percentages. The Chi-square ($\chi^2$) test was used for comparing categorical variables. Significant variables in univariate analysis were

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**Figure 2.** Representative OCT images of normal, TCFA, and plaque rupture (left to right, respectively). OCT, optical coherence tomography; TCFA, thin-cap fibroatheroma.
subsequently included in the multivariate logistic analysis. The cumulative event rate was estimated from Kaplan–Meier curves and compared using the log-rank test. A p value of <0.05 was considered statistically significant.

Results

**CD4+/CD8+ ratio and clinically relevant characteristics**
Baseline clinical characteristics for all patients are described in Table 1. A higher CD4+/CD8+ ratio was observed in patients who smoked (p=0.021), whereas laboratory data showed a positive correlation between CD4+/CD8+ ratio and low density lipoprotein (LDL) levels (r=0.22, p<0.001), and total cholesterol (r=0.191, p=0.002). CD4+/CD8+ ratio was shown to have a negative correlation with high density lipid levels (r=−0.167, p=0.006).

**CAG and OCT findings in relation to CD4+/CD8+ ratio**
CAG and OCT findings in relation to CD4+/CD8+ ratio are presented in Table 2. A higher CD4+/CD8+ ratio was observed in patients with plaque rupture (p=0.019) and TCFA (p=0.027), whereas a lower CD4+/CD8+ ratio was found in patients with calcified plaques (p=0.045). There were no significant differences in other CAG or OCT findings between those with high or low CD4+/CD8+ ratio levels.

**Coronary risk factors and laboratory data in relation to plaque instability**
Coronary risk factors and laboratory data based on plaque instability are shown in Table 3, including the instability (plaque rupture and TCFA patients, n=75), and stable (non-rupture and non-TCFA patients, n=191) groups. CD4+/CD8+ ratio >1.725, prior stroke, hemoglobin, and triglyceride (all p<0.05) were statistically different between the two groups.

**Predictors of plaque vulnerability**
Receiver operating curve (ROC) analysis showed that CD4+/CD8+ ratio was predictive of plaque instability (Figure 3), and the threshold for CD4+/CD8+ ratio was 1.725 with a sensitivity and specificity of 70.7% and 52.4%, respectively (Youden’s index = 0.23). Based on the threshold for the CD4+/CD8+ ratio, the cohort was divided into two groups: a higher CD4+/CD8+ ratio group (CD4+/CD8+ ratio >1.725, n=144) and a lower CD4+/CD8+ ratio group (CD4+/CD8+ ratio ≤1.725, n=122). Significant variables in the univariate analysis were subsequently included in a binary logistic regression analysis, which showed that CD4+/CD8+ ratio >1.725 and prior stroke were predictors of plaque instability (all p<0.05, Table 4). In this study, 53 (70.7%) of the 75 patients with unstable plaques had a CD4+/CD8+ ratio >1.725 (χ²=11.497, p<0.01). Patients with a CD4+/CD8+ ratio >1.725 had an increased risk of plaque instability compared with patients with a CD4+/CD8+ ratio <1.725 [odds ratio (OR) = 2.679, 95% confidence interval (CI): 1.497–4.794].

Outcome
Of 266 patients, 23 suffered from MACE and 7 died during a 1-year follow-up. The Kaplan–Meier estimate for all-cause mortality and MACE showed no significant differences in the lower CD4+/CD8+ ratio group compared with the higher CD4+/CD8+ ratio group (all-cause mortality, 2.5% *versus* 2.8%, p=0.858; MACE, 7.4% *versus* 9.7%, p=0.488; Figures 4 and 5). However, after correcting for smoking in a Cox regression analysis, prior stroke, ruptured plaque, CD4+/CD8+ ratio, and hemoglobin were not predictive (all p>0.05), but levels of LDL were statistically significant for MACE [hazard ratio (HR)=2.26; 95% CI, 1.039–4.915, p=0.04] and all-cause mortality (HR=2.66; 95% CI, 1.068–6.623, p=0.036).

Discussion
In this retrospective study, we found that CD4+/CD8+ ratio correlated with coronary plaque instability in patients with UAP and could predict plaque rupture and TCFA. These findings suggest that CD4+/CD8+ ratio may represent a cost-effective marker for risk stratification in patients with UAP. The current immune response theory of atherosclerotic lesions suggests that T cells exist in atherosclerotic plaques in experimental animals and humans, and there is evidence of different T cell subsets in coronary plaques. Multiple studies have shown that CD4+ T cells are involved in the
Table 1. Baseline characteristics of the patients in relation to ratio of CD4+/CD8+ plasma levels.

|                | [n = 266] | CD4/8 | p value |
|----------------|-----------|-------|---------|
| Age, year      | 65 (24–88)| $r = -0.42$ | 0.490 |
| Male           | 194 (72.9%) | 1.74 [0.77–2.79] | 0.360 |
| Female         | 72 (27.1%) | 1.75 [0.66–2.80] |         |
| BMI, kg/m²     | 24.8 [17.6–37.8] | $r = -0.05$ | 0.450 |
| Hypertension, n (%) |          |       |         |
| Yes            | 183 (68.8) | 1.74 [0.66–2.80] | 0.310 |
| No             | 83 (31.2)  | 1.77 [0.74–2.39] |         |
| Hyperlipidemia, n (%) |        |       |         |
| Yes            | 185 (69.5) | 1.77 [0.66–2.80] | 0.319 |
| No             | 81 (30.5)  | 1.71 [0.74–2.79] |         |
| Diabetes, n (%) |          |       |         |
| Yes            | 81 (30.5)  | 1.75 [0.84–2.63] | 0.980 |
| No             | 185 (69.5) | 1.74 [0.66–2.80] |         |
| Prior or current smoker, n (%) |          |       |         |
| Yes            | 126 (47.4) | 1.80 [0.68–2.80] | 0.021 |
| No             | 140 (52.6) | 1.73 [0.66–2.77] |         |
| Prior stroke, n (%) |         |       |         |
| Yes            | 33 (12.4)  | 1.75 [0.68–2.36] | 0.890 |
| No             | 233 (87.6) | 1.74 [0.66–2.80] |         |
| Prior MI, n (%) |          |       |         |
| Yes            | 27 (10.2)  | 1.71 [0.84–2.80] | 0.606 |
| No             | 239 (89.8) | 1.75 [0.66–2.79] |         |
| Prior peripheral vessel disease, n (%) |        |       |         |
| Yes            | 14 (5.3)   | 1.77 [1.29–2.36] | 0.670 |
| No             | 252 (94.7) | 1.75 [0.66–2.80] |         |
| Prior kidney failure, n (%) |          |       |         |
| Yes            | 5 (1.9)    | 1.59 [1.18–1.99] | 0.681 |
| No             | 261 (98.1) | 1.75 [0.66–2.80] |         |
| Prior COPD, n (%) |          |       |         |
| Yes            | 12 (4.5)   | 1.60 [1.22–1.99] | 0.293 |
| No             | 254 (95.5) | 1.75 [0.66–2.80] |         |
| Prior HF, n (%) |          |       |         |
| Yes            | 31 (11.7)  | 1.73 [1.00–2.37] | 0.518 |
| No             | 235 (88.3) | 1.75 [0.66–2.80] |         |

(Continued)
### Table 1. (Continued)

|                     | CD4/8     | p value |
|---------------------|-----------|---------|
| **Medication:**     |           |         |
| Prior use of statin, n (%) |           |         |
| Yes                 | 113 (42.5)| 1.74 (0.66–2.80) | 0.780 |
| No                  | 153 (57.5)| 1.75 (0.69–2.79) |
| Prior use of β-blockers, n (%) |       |         |
| Yes                 | 65 (24.4)| 1.77 (0.66–2.80) | 0.954 |
| No                  | 201 (75.6)| 1.74 (0.68–2.79)| |
| Prior use of CCB, n (%) |       |         |
| Yes                 | 106 (39.8)| 1.74 (0.68–2.67) | 0.572 |
| No                  | 160 (60.2)| 1.75 (0.66–2.80)| |
| Prior use of ACEI/ARB, n (%) |       |         |
| Yes                 | 90 (33.8)| 1.75 (0.68–2.80) | 0.718 |
| No                  | 176 (66.2)| 1.74 (0.66–2.63)| |
| **Laboratory**      |           |         |
| WBC                 | 6.54 [3.48–15.47] | 0.029 | 0.637 |
| Hemoglobin          | 136 (72–179) | 0.022 | 0.725 |
| PLT                 | 197 [62–539] | -0.03 | 0.623 |
| HDL                 | 1.10 [0.6–2.21] | -0.167 | 0.006** |
| LDL-c               | 1.87 [0.70–4.72] | 0.22 | <0.001** |
| TC                  | 3.49 [1.50–6.19] | 0.191 | 0.002** |
| TG                  | 1.58 [0.43–6.34] | 0.092 | 0.133 |
| Apo A1              | 1.22 [0.76–1.86] | -0.074 | 0.348 |
| Apo B               | 0.73 [0.29–1.43] | 0.128 | 0.105 |
| Lipoprotein a       | 169 [7–1694] | -0.015 | 0.848 |
| Creatinine          | 72 [38–723] | -0.005 | 0.940 |
| Uric acid           | 319 [175–731] | -0.054 | 0.494 |
| AST                 | 21 [9–475] | 0.006 | 0.923 |
| ALT                 | 21.5 [5–404] | -0.009 | 0.881 |
| GLU                 | 5.21 [3.14–19.83] | -0.055 | 0.369 |

**Correlation is significant at the 0.01 level (2-tailed).**

Data are presented as n (%) and median ± [IQR] or r = Spearman’s rank correlation coefficient.

ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; apo-AI, apolipoprotein A1; apo-B, apolipoprotein B; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BMI, body mass index; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; HDL, high density lipoprotein; HF, heart failure; GLU, glucose; IQR, interquartile range; LDL-c, low density lipoprotein-cholesterol; MI, myocardial infarction; PLT, platelet; TC, total cholesterol; TG, total triglycerides; WBC, white blood cell.
Table 2. CD4+/CD8+ ratio according to OCT and angiography findings.

| Target vessel | (n=266) | CD4+/CD8+ | p value |
|---------------|---------|-----------|---------|
| LM            | 5 (1.9) | 1.93 (1.64–2.08) | 0.141   |
| LAD           | 207 (77.8) | 1.73 (0.66–2.80) | 0.611   |
| LCX           | 25 (9.4) | 1.84 (0.89–2.36) | 0.517   |
| RCA           | 39 (14.7) | 1.78 (0.68–2.63) | 0.764   |

| Characteristic of plaque | (n=266) | CD4+/CD8+ | p value |
|--------------------------|---------|-----------|---------|
| Lipid                    | 92 (34.6) | 1.81 (0.68–2.80) | 0.066   |
| Calcified                | 68 (25.6) | 1.68 (0.66–2.40) | 0.045   |
| Fibrotic                 | 106 (39.8) | 1.75 (0.77–2.58) | 0.998   |
| Rupture                  | 9 (3.4) | 1.92 (1.74–2.63) | 0.019   |

| TCFA, n(%)   | (n=266) | CD4+/CD8+ | p value |
|--------------|---------|-----------|---------|
| Ruptured plaque and TCFA | 66 (24.8) | 1.84 (0.91–2.8) | 0.027   |

| Number of vascular lesions | (n=266) | CD4+/CD8+ | p value |
|----------------------------|---------|-----------|---------|
| 1                          | 123 (46.2) | 1.74 (0.68–2.80) | 0.610   |
| 2                          | 79 (29.7) | 1.77 (0.77–2.35) | 0.976   |
| 3                          | 64 (24.1) | 1.74 (0.66–2.63) | 0.530   |
| Bifurcation lesion         | 72 (27.1) | 1.82 (0.89–2.58) | 0.151   |
| CTO                        | 12 (4.5) | 1.57 (0.91–2.80) | 0.208   |

Data are presented as n (%) and median ± [IQR] or p value for Mann–Whitney U test.
CTO, chronic total occlusion; IQR, interquartile range; LAD, left anterior descending artery; LCX, left circumflex; LM, left main; OCT, optical coherence tomography; RCA, right coronary artery; TCFA, thin-cap fibroatheroma.

Table 3. Characteristics of coronary risk factors and laboratory data according to OCT indicated plaque vulnerability.

|                      | Ruptured plaque and TCFA | Nonrupture and non-TCFA | t/χ²  | p value |
|----------------------|--------------------------|--------------------------|-------|---------|
| Male                 | 52 (69.3)                | 142 (74.3)               | 0.147 | 0.701   |
| Age [year]           | 65.38 ± 11.09            | 63.83 ± 10.37            | 1.067 | 0.287   |
| Hypertension         | 54 (72.0)                | 129 (67.5)               | 1.255 | 0.263   |
| Diabetes mellitus    | 22 (29.3)                | 59 (30.9)                | 0.005 | 0.945   |
| Prior or current smoke | 35 (46.7)            | 91 (47.6)                | 0.013 | 0.908   |
| Hyperlipidemia       | 55 (73.3)                | 130 (68.1)               | 1.595 | 0.207   |
| CHF                  | 10 (13.3)                | 21 (11.0)                | 0.408 | 0.523   |
| Family history of CAD | 9 (12.0)                | 27 (14.1)                | 0.125 | 0.724   |

(Continued)
induction and regulation of atherosclerosis, and these studies also confirm that CD4+/CD8+ ratio was significantly correlated with LDL levels. Furthermore, LDL is also an important factor in the progression of coronary atherosclerosis, and the positive correlation between CD4+/CD8+ ratio and LDL was also confirmed in our study. It is undeniable that LDL is related closely to the progression of coronary plaque, but the vulnerability of coronary plaque is not completely dependent on LDL, such as unstable calcification nodules, and there is a high risk of plaque rupture. Many patients with coronary plaque instability are detected by OCT, even if they have no history of smoking, hypertension, diabetes, dyslipidemia or any other traditional coronary heart disease risk, so we sought a new indicator to predict coronary plaque instability.

Recent reports suggest that CD8+ T cells are also important regulatory factors involved in atherosclerosis. Immunohistochemical staining of CD3, CD4, and CD8 showed progressive T cell accumulation during atherosclerosis, the early stages of which were mainly diffuse cytotoxic T cell infiltration, but increasing numbers of T

|                       | Ruptured plaque and TCFA | Nonrupture and non-TCFA | t/χ²  | p value |
|-----------------------|--------------------------|--------------------------|-------|---------|
| Prior MI              | 6 (8.0)                  | 21 (11.0)                | 0.411 | 0.521   |
| Prior stroke          | 35 (46.7)                | 18 (9.4)                 | 5.543 | 0.019   |
| Prior COPD            | 1 (1.3)                  | 11 (5.8)                 | 1.409 | 0.235   |
| BMI                   | 24.92 ± 2.77             | 25.05 ± 3.08             | 0.312 | 0.775   |
| WBC (mmol/l)          | 6.66 ± 1.75              | 6.93 ± 2.05              | 0.982 | 0.326   |
| Hemoglobin (mmol/l)   | 130.34 ± 19.30           | 136.66 ± 15.46           | 6.273 | 0.014   |
| PLT (mmol/l)          | 199.83 ± 56.00           | 203.22 ± 60.75           | 0.41  | 0.682   |
| HDL-c (mmol/l)        | 1.16 ± 0.33              | 1.15 ± 0.27              | 0.315 | 0.753   |
| LDL-c (mmol/l)        | 1.94 ± 0.67              | 1.87 ± 0.62              | 0.747 | 0.455   |
| TC (mmol/l)           | 3.22 ± 0.96              | 3.63 ± 0.96              | 0.835 | 0.393   |
| TG (mmol/l)           | 2.10 ± 1.09              | 1.72 ± 0.88              | 7.305 | 0.008   |
| ApoA1 (g/L)           | 1.21 ± 0.16              | 1.25 ± 0.21              | 1.397 | 0.165   |
| ApoB (g/L)            | 0.74 ± 0.22              | 0.75 ± 0.23              | 2.69  | 0.789   |
| Lipoprotein a (g/L)   | 139 (100,292)            | 202 (98,363)             | 1.319 | 0.189   |
| Creatinine (µmol/L)   | 73 (39,723)              | 72 (39,162)              | 1.225 | 0.225   |
| Uric acid (µmol/L)    | 351.64 ± 98.49           | 326.41 ± 96.70           | 1.501 | 0.135   |
| GLU (mmol/l)          | 5.94 ± 1.92              | 5.92 ± 2.14              | 0.046 | 0.964   |
| CD4+/CD8+ > 1.725     | 53 (70.7)                | 91 (47.6)                | 11.497| 0.001   |

Data are presented as n (%) and mean ± (SD). apo-AI, apolipoprotein A1; apo-B, apolipoprotein B; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GLU, glucose; HDL-c, high density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol; OCT, optical coherence tomography; PLT, platelet; SD, standard deviation; TC, total cholesterol; TCFA, thin-cap fibroatheroma; TG, total triglycerides; WBC, white blood cell.
helper cells were found during disease progression, leading to an elevated CD4+/CD8+ ratio. Previous studies have found that the number of T lymphocytes in the blood and lymph nodes of patients with atherosclerosis and the ratio of CD4+/CD8+ were different. In this study, the ratio of CD4+/CD8+ T cells and coronary plaque instability was detected in the peripheral blood of patients in a predictive manner.34,38

Coronary atherosclerosis is a chronic process of development; we know that UAP is caused mainly by the development of atherosclerotic plaques in coronary arteries, such as ulcers, erosion, rupture, etc., which leads to an inflammatory response in the vascular intima or lumen blockage. Patients with UAP are more likely to have acute MI, and the probability of cardiovascular events is increased. We therefore screened UAP patients with coronary plaque progression for plaque instability or even plaque rupture. In this study, we found that the ratio of CD4+/CD8+ increased with instability of plaques, further validating the above studies.34,38,39

Recently, in one study, Gao and his team confirmed that the Chinese elderly patients with ACS in the peripheral blood CD4+/CD8+ ratio is increased significantly compare to stable angina pectoris patients. ACS patients showed a significantly increased CD4+/CD8+ ratio, which was involved in the progress of coronary artery plaque,11 but only based on the clinical diagnosis of ACS in the study. We know that in the real world, for patients with angina pectoris the situation can be quite different, with many interfering factors making the diagnosis of stable or unstable angina pectoris difficult. We therefore used the most direct and ideal intravascular imaging technique, OCT, to diagnose plaque instability. In our study, the correlation between plaque characteristics confirmed by OCT and the ratio of CD4+/CD8+ cells was then compared. CD4+/CD8+ ratio was found to be an predictor of coronary plaque instability in patients with UAP.

We also followed the all patients for 1 year, with telephone and outpatient follow up being conducted at the 1st, 3rd, 6th and 12th months after the operation. Postoperative anti-platelet aggregation drug therapy was standardized, and CAG review was conducted at the 13th month. It was found that CD4+/CD8+ ratio had no significant statistical significance on patient MACE or death. However, the survival time of the group with a high CD4+/CD8+ ratio was lower than that of the group with a low CD4+/CD8+ ratio, although patients’ prognosis was affected by various other factors. We will await the 3-year follow-up information to further elucidate any role of CD4+/CD8+ ratio in patient survival.

**Figure 3.** ROC analyses for the predictive efficacy of CD4+/CD8+ ratio for plaque instability. ROC, receiver operating curve.

**Table 4.** Association between patient characteristics and the prevalence of plaque vulnerability: results of binary logistic regression analysis.

| independent variables | OR     | 95% CI          | p value |
|-----------------------|--------|-----------------|---------|
| CD4+/CD8+ ratio >1.725| No     | 1               |         |
|                       | Yes    | 2.651 [1.474–4.768] | 0.001   |
| Prior stroke          | No     | 1               |         |
|                       | Yes    | 2.960 [1.380–6.348] | 0.005   |
In our study, most MACE incidences in our higher CD4+/CD8+ ratio group occurred in the first 6 months, and the probability of MACE in months 6–12 was almost identical in both groups. We can assume that PCI can be optimized under precise guidance by OCT, while the early detection of plaque instability may lead to personalized post-operative treatment, such as intensive statin therapy and antithrombotic therapy. After individualized treatment, the prognosis of patients with unstable plaques is not significantly different from that of patients with stable plaques. Therefore, early prediction of coronary plaque instability in patients with UAP is of utmost importance for PCI and post-operative treatment regimens. Our findings further highlight the importance of correctly predicting diagnosis and optimizing treatment. We emphasize the need for early detection and individualized treatment to achieve survival benefits. We know that, in China, some basic hospitals lack OCT devices, even in large medical or cardiology centers because OCT examination is expensive. This examination method has further drawbacks, such as the need for enhanced contrast, specially trained professional technical personnel, limitations of blood vessel lumen diameter, and low penetration. Despite these, OCT examination remains vastly superior to other intravascular examinations. Therefore, when OCT cannot be used because of the limitations detailed above, the CD4+/CD8+ ratio in the peripheral blood can be detected to predict coronary plaque instability, so as to optimize personalized treatment and reduce the MACE rate.

Several limitations should be recognized in this study. First, this study was a single-center retrospective observational study. Secondly, we observed the coronary artery plaques of patients with targeted lesions and did not analyze predictors of the composition of non-target lesions. Furthermore, this study only included UAP patients with successful PCI, so the results could not be extended to all ACS patients. Finally, prognostic survival analysis was based on multi-factor interventions, such as smoking, lifestyle, nutrition, and exercise habits, that might affect mortality, but this information was not available in the data, and the small sample size limited the predicted results.

Despite these limitations, our research also has a number of strengths. Most reports on the prediction of atherosclerotic plaque characteristics by lymphocytes comprise studies of the aorta, carotid and renal arteries, and animal experiments, but there are few studies regarding the direct prediction of coronary plaque. Our study directly predicted the characteristics of coronary plaque in UAP patients by calculating the CD4+/CD8+ T lymphocyte ratio. Extravascular ultrasound, angiography, intravascular ultrasound, pathological biopsy, and other techniques are most commonly used to define the characteristics of plaques; however, studies on
the relationship between the determination of atherosclerotic plaque and CD4+CD8+ T lymphocyte ratio by OCT have not been previously reported. It is of great scientific and clinical significance to predict the instability of coronary atherosclerotic plaques for efficient prevention and treatment. This study is thus both innovative and practical.

Conclusion
Higher CD4+/CD8+ ratio is associated with higher risk of plaque instability, as confirmed by OCT in our cohort of UAP patients. CD4+/CD8+ ratio was not an independent predictor of 1-year MACE and all-cause mortality.

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Author contributions
ZJJ and LS designed the statistical analysis, led the interpretation of research findings, and revised the manuscript. CDY and KXQ participated in design, data collection, dataset generation, statistical analysis, and drafting of the manuscript. All of the authors read and approved the final manuscript.

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Conflict of interest statement
The authors declare that there is no conflict of interest.

Ethics approval and consent to participate
The study was approved by the institutional ethics committee of the First People’s Hospital of Taicang (No.TCYY2019-KY0013) and was carried out in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was formally obtained from all participants.

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