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Prognostic performance of interleukin-10 in patients with chest pain and mild to moderate coronary artery lesions—an 8-year follow-up study

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Abstract

Background Interleukin (IL)-10, IL-6 and their ratio (IL-6/IL-10) play an important role in the risk of developing coronary artery disease, and may correlate with its outcomes. Few clinical trials have investigated the prognostic impact of these factors on long-term cardiovascular events in patients presented with chest pain. **Methods** A prospective study was performed on 566 patients admitted with chest pain and identified mild to moderate coronary artery lesions. IL-10, IL-6 and IL-6/IL-10 were measured. **Results** A total of 511 patients completed the follow-up. The median follow-up time was 74 months. Kaplan-Meier analysis demonstrated a clear increase of the incidence of major adverse cardiac events during the follow-up period in patients with below-median levels of IL-10 ($P = 0.006$) and above-median levels of IL-6/IL-10 ($P = 0.012$). Multivariate Cox proportional hazards analysis indicated the IL-10 levels to be strong independent predictors after adjustment for underlying confounders. **Conclusions** Elevated IL-10 levels are associated with a more favorable long-term prognosis in patients with chest pain and mild to moderate coronary artery lesions. IL-10 could be used for early risk assessment of long-term prognosis.

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Keywords: Chest pain; Coronary artery disease; Interleukin-6; Interleukin-10; Prognosis

1 Introduction

Inflammation is a major driving force underlying the initiation of coronary plaques, their unstable progression, and eventual rupture. Inflammation biomarkers have been extensively investigated in the case of coronary artery disease (CAD). Current evidence supports that inflammation markers, including cytokines [such as interleukin (IL)-10, IL-6] may play an important role in the risk of developing coronary artery disease, and may correlate with its outcomes.

IL-10 is an immunoregulatory cytokine secreted by activated monocytes/macrophages and lymphocytes.[1,2] It has multifaceted anti-inflammatory properties which have been shown to play a protective role for atherosclerotic lesion development and progression in animal studies.[1,3] In the c7E3 Anti Platelet Therapy in Unstable Refractory angina (CAPTURE) study, patients with elevated IL-10 levels had a decreased risk of death and nonfatal myocardial infarction during a 6-month follow-up.[4] These data suggest that IL-10 may be protective against pro-inflammatory mediators in CAD. IL-6 can drive production of reactant proteins, including C-reactive protein (CRP), and may increase plaque instability by driving expression of matrix metalloproteinases (MMPs), tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1).[5] In the Fragmin and Fast Revascularization During Instability in Coronary Artery Disease II (FRISC II) trial, elevated IL-6 (> 5 ng/L) was associated with higher 6- and 12-month mortality, independent of troponin and high-sensitivity CRP (hs-CRP).[6] However, few clinical researches have evaluated the prognostic performance of IL-10 or IL-6 levels, in particular, the IL-6/IL-10 complex on long-term cardiovascular outcomes in patients presented with chest pain.

Most patients with acute coronary syndrome (ACS) exhibit mild to moderate stenosis, which is associated with vulnerable plaques.[7] Abrupt rupture of plaques resulting intracoronary thrombosis are the principal etiology of ACS. Therefore, the present study investigate whether IL-10 and IL-6 concentrations or the IL-6/IL-10 ratio have prog-

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nostic impact in predicting future cardiovascular events in patients presented with chest pain and mild to moderate stenosis of the coronary artery.

2 Methods

2.1 Patient population

Patients aged 18–80 years hospitalized in Beijing An Zhen Hospital for chest pain from February 2007 to May 2009 and who showed segmental stenosis resulting in > 20% and < 70% lumen diameter reduction in at least one major coronary arteries on coronary angiography (CAG) and quantitative coronary angiography (QCA) were enrolled in the study. Exclusion criteria in this study were cardiac shock, valvular heart disease, history of coronary revascularization, main coronary branch diameter > 2.25 mm, lumen diameter stenosis ≥ 70%, left ventricular ejection fraction < 30%, systemic inflammatory diseases, known immune system or connective tissue diseases, baseline creatinine > 2.5 mg/dL (if male) or > 2.0 mg/dL (if female), baseline alanine aminotrasferase or aspartate aminotransferase three times that of normal, heart transplant recipients, patients whose life expectancy was less than three years, and patients who could not comply with our research program. Written informed consents for all procedures were obtained from each patient. The present study complied with the Declaration of Helsinki and was approved by the institutional review board of Beijing An Zhen Hospital, Capital Medical University, and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China.

2.2 Baseline characteristics

After evaluating the lesion with CAG and QCA, demographic features and clinical characteristics were recorded. Fasting blood samples were drawn from the ulnar vein on the morning after the CAG procedure and were filled in tubes with ethylene diamine tetraacetic acid (EDTA) as anticoagulation. The blood samples were centrifuged at 1500 r/min for 10 min. Plasma samples were immediately separated into multiple aliquots and stored at –80°C within 30 min. Triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum creatinine and other routine blood biochemical examination were measured in a biochemical analyzer (Hitachi 7600, Tokyo). Plasma hs-CRP was determined using an enzyme-linked immunosorbent assay. The concentrations of the plasma IL-10 and IL-6 were determined using commercially available protein arrays (Raybiotech, Norcross, GA, USA) following the manufacturer's instructions.

2.3 Endpoints and follow-up

All the patients were followed-up by telephone interviews at 1, 3, 6, 12, 18, 24, 36, 48, 60, 72, 84, and 96 months after CAG. The primary endpoint [major adverse cardiac events (MACEs)] was a composite of all cause death, nonfatal acute myocardial infarction, revascularization, and angina pectoris requiring rehospitalization. Nonfatal myocardial infarction was defined according to the universal definition of myocardial infarction. Revascularization was defined as any surgical or percutaneous reintervention. Angina pectoris requiring rehospitalization was defined as a recurrent episode of ischemic chest pain requiring inpatient hospital admission for further evaluation, according to the symptoms of chest pain, electrocardiographic changes in ischemia, and levels of cardiac enzymes. All endpoints were centrally adjudicated by the independent clinical events committee that had no knowledge of patient data. In the cumulative analysis of endpoints, events were counted only once, whichever occurred first.

2.4 Statistical analyses

Statistical analyses were performed on SPSS Version 17.0 (SPSS, Chicago, Ill., USA). Normally-distributed continuous variables were presented as mean ± SD, variables with a skewed distribution as the median together with interquartile range (IQR). Categorical variables are expressed as percentages.

The relationship between IL-10, IL-6 and the baseline cardiovascular risk factors was investigated using Spearman's rank correlation statistic. The Kaplan-Meier method was used to illustrate the timing of events during follow-up in relation to IL-10, IL-6 and IL-6/IL-10 and statistical assessment was performed with the log-rank test. The prognostic value of IL-10, IL-6 and IL-6/IL-10 was assessed by investigating its relation with the composite outcome in Cox proportional-hazards analyses. Various Cox regression models were performed to evaluate the predictive values of IL-10, IL-6 and IL-6/IL-10 on the risk of cardiovascular events. The first model was adjusted for traditional risk factors [including age, gender, body mass index (BMI), hypertension, diabetes, smoking status and LDL-C]. The second model was additionally adjusted for discharge diagnosis. Further adjustment was performed for the hs-CRP and white blood count levels (Model 3). Patients who lost to follow-up were analyzed as censored data. The proportional-hazards assumptions of all Cox proportional-hazards analyses were assessed with Schoenfeld's tests, and no relevant violations were observed. Hazard ratios (HRs) and 95% CI are reported. $P < 0.05$ was deemed to be statistically significant.

3 Results

3.1 Patient characteristics

A total of 566 patients were recruited between February 2007 and May 2009. Of these subjects, 511 (90.3%) patients finished follow-up by February 2015. A flow chart was performed (Figure 1). Median length of follow-up was 74 (range 1–96) months. Seven patients reached the endpoint within one month. During the follow-up, 201 events occurred: 31 patients died, 14 patients suffered a nonfatal myocardial infarction, 57 patients underwent revascularization and 99 patients were readmitted for angina pectoris. As shown in Table 1, the median age was 59.1 years and 68.7% of the patients were men. Discharge diagnosis of the study population included four types as follows: coronary atherosclerosis in 269 patients, stable angina pectoris in 82 patients, unstable angina pectoris in 193 patients, and acute myocardial infarction in 22 patients. Baseline characteristics of the population are listed in Table 1.

3.2 IL-10, IL-6 and IL-6/IL-10

IL-10 levels were skewed distributed, with a median of 60.02 ng/L (IQR: 35.14–96.28 ng/L). However, no significant differences were found in the IL-10 concentrations among the different diagnosis groups (P = 0.595). The minimum level was 2.17 ng/L in the coronary arteriosclerosis group, and the maximum was 1309.12 ng/L in those with unstable angina pectoris. The IL-6 levels were also skewed distributed, with a median of 168.49 ng/L (IQR: 94.09–310.75 ng/L). Although all subjects in the study population had mild to moderate coronary artery lesions, there were significant differences in the IL-6 concentrations among the different diagnosis groups (P < 0.001). The minimum level was 0.49 ng/L in the group with coronary arteriosclerosis and the maximum was 5819.77 ng/L in those with acute myocardial infarction. Details of the serum levels of IL-10, IL-6 and IL-6/IL-10 of the patients according to the diagnosis groups are shown in Table 2.

Patients who experienced adverse clinical events during

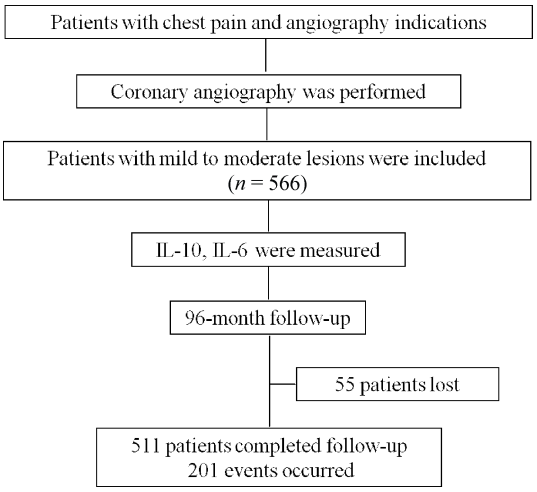

Figure 1. Flow chart of the study. IL: interleukin.

Table 1. Baseline characteristics of included patients.

Characteristic	Overall cohort (n = 566)
Age, yrs	59.1 (51.9–66.8)
Male gender	68.7%
BMI, kg/m^2	25.7 (24.1–27.3)
Hypertension	61.8%
Diabetes mellitus	19.4%
Dyslipidaemia	20.2%
Current smoking	38.2%
White blood count, ×10^9/L	6.4 (5.4–7.4)
Platelet count, ×10^9/L	202.0 (166.8–227.0)
CKMB, mmol/L	9.0 (5.0–13.0)
Creatinine, μmol/L	80.0 (68.8–92.0)
TG, mmol/L	1.55 (1.11–2.06)
TC, mmol/L	4.45 (3.85–5.14)
HDL-C, mmol/L	1.01 (0.86–1.15)
LDL-C, mmol/L	2.76 (2.22–3.43)
Minimal lumen diameter, mm	2.07 (1.73–2.46)
Percent diameter stenosis	39.37 (31.64–47.08)
Lesion length, mm	15.42 (11.18–22.01)
Minimal lumen area, mm^2	3.36 (2.34–4.77)
Percent area stenosis	62.18 (52.10–71.11)
Plaque area, mm^2	8.64 (5.34–13.52)
IL-10, ng/L	60.02 (35.14–96.28)
IL-6, ng/L	168.49 (94.09–310.75)
HsCRP, mg/L	4.57 (1.87–12.12)

Continuous variables are given as means ± SD or medians (IQR) unless other indicated. BMI: body mass index; CKMB: creatine kinase MB; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.

Table 2. Levles of IL-10, IL-6, and IL-6/IL-10 of the patients according to the diagnosis groups.

Variable	AS (n = 269)	SAP (n = 82)	UAP (n = 193)	AMI (n = 22)
IL-10, ng/L	58.09 (34.09–99.93)	60.28 (32.27–84.88)	63.78 (38.04–96.81)	59.45 (33.01–88.84)
IL-6, ng/L	160.85 (94.09–258.88)	167.81 (83.60–420.30)	180.25 (96.86–370.71)	188.81 (96.87–472.51)
IL-6/ IL-10	2.71 (0.90–6.65)	3.64 (1.93–8.05)	3.14 (1.69–6.85)	4.38 (2.59–13.83)

The data are given as means ± SD or medians (IQR). AMI: acute myocardial infarction; AS: coronary arteriosclerosis; IL: interleukin; IQR: interquartile range; SAP: stable angina pectoris; UAP: unstable angina pectoris.

follow-up showed lower IL-10 [53.72 (IQR: 26.96–80.48) ng/L *vs*. 63.73 (IQR: 39.33–105.74) ng/L, $P < 0.001$] and higher IL-6 [178.83 (IQR: 104.52–348.44) ng/L vs. 166.36 (87.85–282.79) ng/L, $P = 0.015$] than those who did not have any adverse events.

Using Spearman's correlation analysis, a significant correlation was found between the levels of IL-10 and IL-6 ($r = –0.327$, $P < 0.001$). We evaluated the relationship between IL-10 and baseline characteristics, which indicate that the levels of IL-10 were weakly correlated with the creatinine concentrations ($r = –0.106$, $P = 0.015$). No other correlations were observed (Table 3). The plasma levels of IL-6 showed weak correlations with discharge diagnosis ($r = 0.094$, $P = 0.038$) and diabetes mellitus ($r = 0.090$, $P = 0.047$). No association was found with other conventional cardiovascular risk factors, such as age, gender, hypertension, TC, LDL-C or smoking status (Table 4). No significant relationship was found between IL-10 and the severity of coronary disease ($P > 0.05$).

As shown in the Kaplan-Meier survival curves, patients with below-median levels of IL-10 (log-rank $P = 0.006$) and above-median levels of IL-6/IL-10 (log-rank $P = 0.012$) had a much higher rate of MACEs during follow-up, whereas IL-6 did not demonstrate this association (long-rank $P = 0.076$) (Figures 2–4).

Table 5 shows the unadjusted HRs of IL-10, IL-6 and IL-6/IL-10 for outcomes (HR = 0.668, 95% CI: 0.501–0.892, $P = 0.006$; HR = 1.311, 95% CI: 0.970–1.773, $P = 0.078$; HR = 1.483, 95% CI: 1.086–2.025, $P = 0.013$, respectively).

Table 3. Correlation between IL-10 and baseline characteristics.

Variables	Correlation coefficient	*P* value
IL-6	–0.327	< 0.001
Creatinine	–0.106	0.015
Current smoking	–0.077	0.076
TC	–0.071	0.103
Diabetes mellitus	–0.059	0.177
LDL-C	–0.055	0.211
BMI	–0.040	0.354
Male gender	–0.039	0.377
CKMB	0.037	0.394
Age	–0.025	0.567
Discharge diagnosis	0.024	0.578
HDL-C	0.021	0.625
Hs-CRP	0.009	0.840
Hypertension	–0.006	0.897

BMI: body mass index; CKMB: creatine kinase MB; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.

Table 4. Correlation between IL-6 and baseline characteristics.

Variables	Correlation coefficient	*P* value
IL-10	–0.327	< 0.001
Discharge diagnosis	0.094	0.038
Diabetes mellitus	0.090	0.047
Creatinine	0.074	0.102
Male gender	0.060	0.186
BMI	0.051	0.260
TC	0.041	0.368
Hypertension	0.038	0.403
CKMB	0.029	0.523
Age	0.024	0.601
Current smoking	0.022	0.626
HDL-C	–0.018	0.693
LDL-C	0.017	0.706
Hs-CRP	–0.007	0.885

BMI: body mass index; CKMB: creatine kinase MB; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.

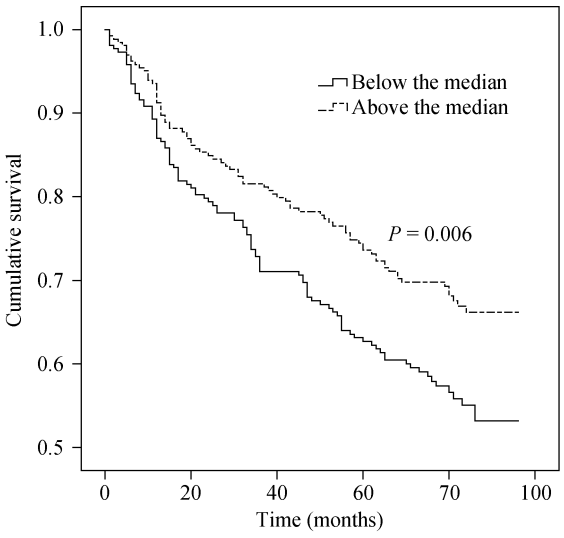

Figure 2. Kaplan-Meier curves for event-free survival according to baseline IL-10 values stratified by the median of 60.02 ng/L. IL: interleukin.

Even after adjustment for age, gender, BMI, hypertension, diabetes, smoking status and LDL-C in Model 1, associations between IL-10, IL-6/IL-10 and long-term MACEs remained significant (Table 5). Moreover, in the models including discharge diagnosis (Table 5, Model 2) and even the value of hs-CRP and WBC (Table 5, Model 3), IL-10 remained a strong independent predictor of adverse outcomes ($P = 0.013$ and 0.046, respectively). However, IL-6 showed no statistically significant association with the out-

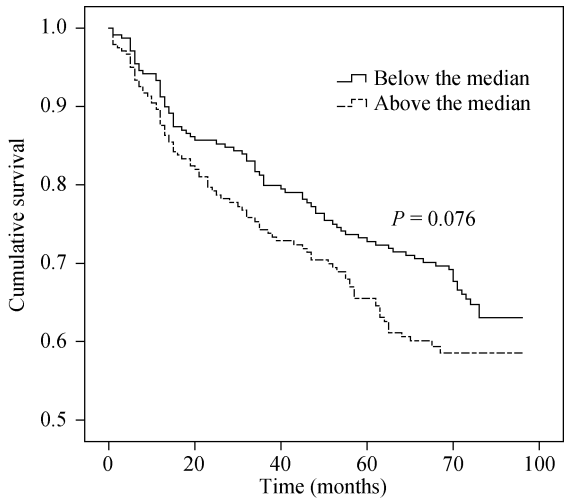

Figure 3. Kaplan-Meier curves for event-free survival according to baseline IL-6 values stratified by the median of 168.49 ng/L. IL: interleukin.

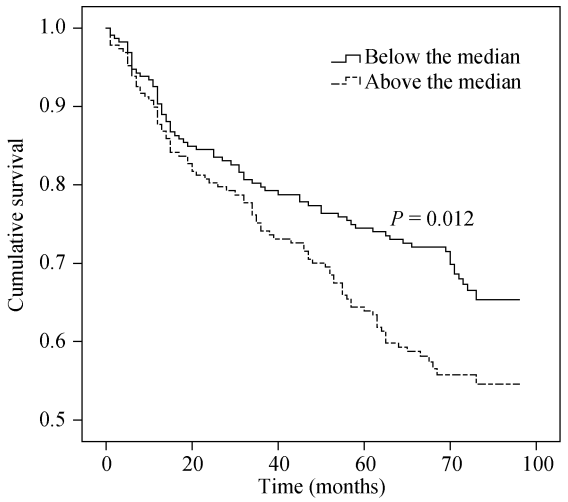

Figure 4. Kaplan-Meier curves for event-free survival according to baseline IL-6/IL-10 values stratified by the median of 3.06. IL: interleukin.

Table 5. Association of IL-10, IL-6 and IL-6/IL-10 at baseline with MACEs during follow-up.

	IL-10		IL-6		IL-6/IL-10	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Unadjusted	0.668 (0.501–0.892)	0.006	1.311 (0.970–1.773)	0.078	1.483 (1.086–2.025)	0.013
Model 1						
IL-10/IL-6	0.698 (0.521–0.935)	0.016	1.274 (0.941–1.725)	0.118	1.395 (1.018–1.910)	0.038
Age	1.007 (0.991–1.023)	0.395	1.012 (0.996–1.030)	0.148	1.014 (0.997–1.032)	0.113
Gender	1.183 (0.819–1.708)	0.371	1.326 (0.897–1.959)	0.157	1.218 (0.815–1.819)	0.337
BMI	0.989 (0.938–1.042)	0.683	0.991 (0.940–1.045)	0.742	1.001 (0.947–1.058)	0.977
Hypertension	1.273 (0.922–1.757)	0.143	1.278 (0.912–1.792)	0.155	1.252 (0.886–1.769)	0.202
Diabetes	1.337 (0.953–1.877)	0.093	1.295 (0.908–1.848)	0.154	1.216 (0.837–1.767)	0.305
Smoking status	1.316 (0.946–1.832)	0.103	1.347 (0.944–1.921)	0.101	1.395 (0.970–2.005)	0.072
LDL-C	1.019 (0.861–1.206)	0.827	1.082 (0.905–1.293)	0.389	1.076 (0.898–1.289)	0.428
Model 2						
IL-10/IL-6	0.692 (0.517–0.926)	0.013	1.231 (0.909–1.667)	0.179	1.300 (0.948–1.781)	0.103
Age	1.004 (0.989–1.021)	0.586	1.010 (0.993–1.027)	0.243	1.011 (0.994–1.029)	0.206
Gender	1.160 (0.806–1.671)	0.425	1.285 (0.871–1.896)	0.206	1.193 (0.800–1.779)	0.386
BMI	0.985 (0.935–1.038)	0.575	0.989 (0.938–1.043)	0.688	0.995 (0.941–1.052)	0.854
Hypertension	1.314 (0.949–1.821)	0.100	1.313 (0.933–1.848)	0.118	1.311 (0.924–1.861)	0.130
Diabetes	1.264 (0.897–1.782)	0.180	1.272 (0.890–1.818)	0.187	1.162 (0.797–1.693)	0.435
Smoking status	1.308 (0.939–1.823)	0.112	1.364 (0.955–1.949)	0.088	1.416 (0.983–2.041)	0.062
LDL-C	1.059 (0.893–1.256)	0.509	1.119 (0.935–1.340)	0.221	1.120 (0.934–1.345)	0.222
Discharge diagnosis	1.338 (1.157–1.547)	< 0.001	1.328 (1.143–1.544)	0.000	1.362 (1.164–1.593)	0.000
Model 3						
IL-10/IL-6	0.734 (0.542–0.994)	0.046	1.215 (0.887–1.664)	0.226	1.244 (0.897–1.726)	0.191
Age	1.006 (0.989–1.023)	0.495	1.010 (0.992-1.028)	0.261	1.012 (0.994–1.030)	0.198
Gender	1.186 (0.805–1.748)	0.388	1.244 (0.823–1.882)	0.300	1.136 (0.741–1.743)	0.558
BMI	0.990 (0.937–1.046)	0.720	0.995 (0.941–1.053)	0.873	1.000 (0.943–1.060)	0.995
Hypertension	1.249 (0.891–1.752)	0.196	1.225 (0.861–1.744)	0.259	1.225 (0.853–1.760)	0.271
Diabetes	1.183 (0.823–1.700)	0.364	1.221 (0.842–1.769)	0.293	1.094 (0.738–1.622)	0.655
Smoking status	1.348 (0.951–1.911)	0.093	1.437 (0.988–2.091)	0.058	1.506 (1.024–2.214)	0.037
LDL-C	1.081 (0.905–1.292)	0.391	1.129 (0.935–1.363)	0.208	1.129 (0.933–1.365)	0.212
Discharge diagnosis	1.390 (1.193–1.619)	< 0.001	1.387 (1.185–1.624)	0.000	1.433 (1.215–1.690)	0.000
hs-CRP	0.998 (0.988–1.008)	0.662	1.000 (0.990–1.010)	0.983	0.998 (0.988–1.009)	0.769
White blood count	0.987 (0.901–1.082)	0.783	1.001 (0.914–1.096)	0.990	1.009 (0.918–1.110)	0.852

Model 1 adjusted for age, gender, BMI, hypertension, diabetes, smoking status and LDL-C; Model 2 was additionally adjusted for discharge diagnosis; Model 3 further adjusted for traditional risk factors hs-CRP and white blood count. BMI: body mass index; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; LDL-C: low-density lipoprotein cholesterol; MACEs: major adverse cardiovascular events.

come (the *P* values for IL-6 were 0.118, 0.179 and 0.226 in the three models, respectively) (Table 5). Additionally, receiver operating characteristic curve analyses were performed. The best cutoff of IL-10 was 22.88 ng/L.

4 Discussion

The present study demonstrates that elevated IL-10 levels are associated with a more favorable long-term prognosis in Chinese patients with chest pain and mild to moderate coronary artery lesions. When we combined markers as IL-6 to IL-10 ratios, we observed a strong relationship between them and the development of MACEs even after adjustment of traditional risk factors. As far as our knowledge, this is the first study demonstrating the role of IL-10 levels in Chinese patients presented with chest pain and mild to moderate lesions.

Understanding of the pathophysiology of atherosclerosis has changed markedly over the past few decades. It is now widely accepted that inflammation plays a fundamental role in the genesis and development of atherosclerosis. In recent years, multiple scientific studies have emphasized the role of pro-inflammatory cytokines in the development of atherosclerosis. Nevertheless, there is little evidence available on the potential role of anti-inflammatory cytokines in this process.

IL-10, which is produced by various inflammatory cells, especially macrophages,[2] has multifaceted anti-inflammatory properties. *In vitro* and *in vivo* studies in animals have shown a protective role for IL-10 in both atherosclerotic lesion formation and stability.[3,8] Indeed, numerous recent experimental studies have shown that either systemic or local IL-10 gene transfer not only attenuates atherogenesis,[1,9] but also affects processes associated with lesion progression.[10] Additionally, IL-10 expression has also been identified within human atherosclerotic plaques.[11] IL-6 is a well- known cytokine with potent pro-inflammatory properties.

A previous study demonstrated that elevated levels of IL-6 were associated with increased risk of future myocardial infarction in apparently healthy men,[12] which support a role for cytokine-mediated inflammation in the early stages of atherogenesis. Hu, *et al*.[13] found that myocardial infarction patients had significantly higher levels of IL-10 and IL-6 than healthy controls. However, Smith, *et al*.[14] demonstrated serum IL-10 concentrations were lower in unstable angina patients compared with those who had chronic stable angina (28.4 *vs*. 14.0 pg/mL, 95% CI: 9.8–19.0, $P < 0.0001$) even after adjustment for confounding variables, while IL-6 concentrations were higher in the unstable angina group (29.0 *vs*. 11.4 pg/mL; 95% CI: 1.0–12.6, $P = 0.04$). Moreover, Jha, *et al*.[15] evaluated plasma circulatory markers in patients with CAD and lower levels were found for IL-10 in CAD patients compared with healthy controls. George, *et al*.[16] compared the IL-6 and IL-10 levels between vulnerable and stable patients, which indicated IL-10 may discriminate them and have a protective role against plaque rupture in patients with coronary atherosclerosis. Results from the European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis-Intravascular Ultrasound (ATHEROREMO-IVUS) study showed lower circulating IL-10 was associated with higher plaque burden and large virtual histology-thin cap fibroadenoma lesions, which suggesting a protective role for the cytokine in extent and vulnerability of atherosclerosis.[17]

Previous studies on the prognostic utility of IL-10 in patients with ACS have provided conflicting results. Malarstig, *et al*.[18] evaluated the concentrations of IL-10 and found IL-10 reflected a pro-inflammatory state in patients with ACS. Cavusoglu, *et al*.[19] measured baseline plasma IL-10 levels in 193 well-characterized male patients with ACS and followed for 5 years for the development of major adverse cardiovascular events. After controlling for a variety of baseline variables, elevated plasma IL-10 levels were proved to be a strong and independent predictor of the composite outcome of death or non-fatal myocardial infarction.

However, more evidences are available supporting the protective effect of IL-10 on future outcomes. In the c7E3 Anti Platelet Therapy in Unstable Refractory angina (CAPTURE) study, elevated IL-10 levels are associated with a decreased risk of death and nonfatal myocardial infarction in patients with ACS during a 6-month follow-up.[4] One data show a highly significant inverse independent relationship between IL-10 levels and the composite endpoint of all-cause mortality, reinfarction and cerebrovascular events during a 4-year follow-up in patients with an acute myocardial infarction. The results indicate about a 6-fold increased risk of suffering a future event when being below the median level of IL-10 in the study population.[20] Lower levels of IL-10 were observed on admission in patients with unstable angina who subsequently had cardiovascular events during a 3 months follow-up period.[21] A study including 80 patients with Non-ST Elevation Acute Coronary Syndrome (NSTEACS) demonstrated that IL-6/IL-10 ratio was the most important predictor for coronary events during the 12 months follow-up period ($P = 0.006$).[22]

Our findings are in keeping with data from animal model studies that suggest IL-10 has a protective role in atherosclerosis. Although we have not found any significant rela-

tionship between IL-6 concentrations and adverse outcomes, IL-6 concentrations were higher in patients who had events. These results suggest that the risk for development of MACEs is higher in patients with higher IL-6 and lower IL-10 concentrations. In particular, the IL-10 was the most powerful predictor of the development of MACEs during the 8-year follow-up period. This finding suggests that anti-inflammatory cytokine IL-10 can be used for early risk assessment in patients presented with chest pain and mild to moderate coronary artery lesions.

4.1 Limitations

Although IL-10 is proved to be a good marker for long-term outcomes, it is not routinely available in the clinical practice. Undoubtedly, the association between inflammation, coronary plaque instability, and clinical outcomes is extremely complex. Although strict inclusion and exclusion criteria have been set, many potential variables can modulate interleukin values which could not be adjusted. Apart from the above, almost ten percent of the patients lost to follow-up during the 8-year study period, which could have influenced the results. The outcomes and conclusions should be interpreted with these limitations in mind. Large-scale studies with long-term follow-up information are needed.

4.2 Conclusions

Elevated IL-10 levels are associated with a more favorable long-term prognosis in patients with chest pain and mild to moderate coronary artery lesions. IL-10 could be used for early risk assessment of long-term prognosis.

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