Association of Circulating IgE and CML levels With in-Stent Restenosis After Drug-Eluting Stent Implantation in Type 2 Diabetic Patients With Stable Coronary Artery Disease

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Abstract

Background: We investigated whether serum levels of immunoglobin (Ig) E and Nε-carboxymethyl-lysine (CML) are related to in-stent restenosis (ISR) in patients with stable coronary artery disease and type 2 diabetes mellitus (T2DM).

Methods: Serum levels of IgE and CML were measured in 416 stable angina patients with T2DM who received angiographic follow-up 12 months after percutaneous coronary intervention (PCI) with third-generation drug-eluting stent (DES) implantation for *de novo* lesions. Multivariate logistic regression analysis was performed to assess the association between IgE or CML and ISR. In mice models, femoral artery injury was induced in mice receiving albumin or glycated albumin injection, and immunofluorescence staining of the injured artery segment was performed 4 weeks later using CML and IgE antibodies.

Results: Both IgE and CML levels were higher in patients with ISR (n=196) compared with non-ISR patients (n=220). The rate of ISR increased stepwise with increasing tertiles of IgE and CML levels, and IgE correlated significantly with CML. After adjusting for potential confounders, IgE and CML levels remained independently associated with ISR. IgE and CML levels improved the predictive capability of traditional risk factors for ISR, and there existed an interaction between IgE and CML in relation to ISR (P for interaction < 0.01). In mice models, glycated albumin induced increased CML and IgE infiltration in the injured femoral artery segment which was associated with a higher degree of neointimal hyperplasia and luminal stenosis.

Conclusion: Elevated circulating IgE and CML levels confer an increased risk for ISR after DES-based PCI in type 2 diabetic patients with stable coronary artery disease.

Background

Despite widespread use of drug-eluting stents (DES), in-stent restenosis (ISR) remains a significant clinical problem after percutaneous coronary intervention (PCI) [1], occurring in 3–20% of patients after DES implantation [2, 3]. The prevalence of ISR is even higher in patients with type 2 diabetes mellitus (T2DM), which causes particular concern since diabetic population is growing and these patients often have more severe and diffuse coronary artery disease requiring DES-based revascularization [4]. The mechanism of ISR in type 2 diabetic patients remains incompletely elucidated, but is likely to be multifactorial. Apart from mechanical and technical factors as well as patient- and operator-related conditions, certain biochemical abnormalities and inflammatory cytokines induced by diabetes have been documented to exaggerate neointimal hyperplasia and to promote ISR [1, 5, 6].

Advanced glycation end products (AGEs), which form more abundantly during T2DM as a consequence of chronic hyperglycemia, are extensively distributed in the diabetic vasculature. Mounting evidence has indicated that AGEs play a key role in cell signal to accelerate vasculopathy in diabetes. For example, they react with receptor for AGEs (RAGE) to increase oxidative stress, expression of transforming factor-β and

extracellular matrix accumulation [7]. Elevated AGEs have been suggested as a risk factor for post-PCI restenosis as well as coronary artery disease progression in type 2 diabetic patients[7, 8]. Nε-carboxymethyl-lysine (CML), a major isoform of AGEs, contributes to endothelial dysfunction in diabetes and is associated with cardiovascular mortality [9–11]. Nevertheless, the relationship between CML and ISR remains unclear.

Immunoglobin (Ig) E, despite its lowest abundance *in vivo*, exerts a crucial effect in mediating type I hypersensitivity both systematically and locally and defending against pathogens as the first line[12]. Previous studies have demonstrated that elevated IgE level is most common in allergy, and interestingly, the risk of cardiovascular diseases such as acute myocardial infarction, heart failure, atrial fibrillation, and peripheral vascular disease is increased in patients with allergic disorders [13–16]. Recent data revealed that IgE promotes coronary atherosclerosis [17], participates in abdominal aortic aneurysm formation[18] and coronary artery spasm, independent of atheromatous disease[19]. Likewise, elevated IgE level in serum has been shown to correlate with multivessel disease and contribute to discriminating coronary artery disease severity [20].

Although formation of AGEs has been reported to correlate with immunological and allergic disorders such as asthma and arthritis[21], the exact role of allergic inflammation in both pathogenesis of coronary artery disease and occurrence of adverse events following stent implantation just starts to be noticed in recent years [22]. In addition, knowledge regarding the interaction between IgE and CML on ISR is still scanty. In this study, we sought to examine if circulating levels of IgE and CML are associated with ISR in patients with T2DM after PCI with DES implantation. We also assayed serum IgE and CML levels and performed immunofluorescence staining of injured femoral artery in a high-fat diet/streptozotocin (STZ)-induced diabetic mouse model.

Methods

This study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical cohort

A total of 606 consecutive patients with T2DM who received follow-up coronary angiography around 12 months after DES-based PCI of *de novo* lesions in native coronary artery from January 2017 to December 2020 were recruited from the database of Shanghai Ruijin Hospital PCI Outcome Program[23]. This program utilizes clinical and angiographic information for various cardiovascular diseases to estimate risk-adjusted outcomes. Data on demographics, clinical characteristics and angiographic features, left ventricular function determined by two-dimensional echocardiography according to modified Simpson's rule, and in-hospital management were collected retrospectively, whereas outcomes during follow-up were identified prospectively. For the purpose of this study and to avoid confounding serum data, we excluded patients with acute coronary syndrome (n=133), familial hypercholesterolemia (n=5), malignant tumor (n

=6), renal failure requiring hemodialysis (n=4) or prior coronary bypass grafting (n=27). Patients with history of asthma (n=5), autoimmune disease (n=4), and rheumatic heart disease (n=6) were also excluded. Thus, the remaining 416 patients were eligible and categorized in the final analysis **(Figure 1).**

The diagnosis of T2DM was made according to the criteria of American Diabetes Association [symptoms of diabetes with casual plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L) or fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), 2h postprandial glucose ≥200mg/dL (11.1 mmol/L) during an oral glucose tolerance test, and currently or previously treated with insulin and/or oral hypoglycemic agents] [24]. Hypertension was diagnosed according to seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7)[25]. Hyperlipidemia was defined according to a guideline on the management of blood cholesterol[26].

Coronary angiography and quantitative analysis

Coronary angiography and PCI were performed through radial or femoral approach using standard methods. All lesions were stented with a normal-to-normal technique, usually including 5-mm- long, angiographically normal segments proximal and distal to the lesion. The third-generation DES was applied to all patients, but the choice of stent type and technique of deployment were left for the discretion of the operators. A plurality of matching angiographic images was obtained after intracoronary nitrate injection for each patient. All patients were encouraged to take guideline-recommended medications after the procedure.

End-diastolic frames from both baseline and follow-up angiograms were selected with identical angulations that best showed the stenosis at its most severe degree with minimal foreshortening and branch overlap[27]. Quantitative coronary analysis (QCA) of baseline and follow-up angiograms was made using the Cardiovascular Measurement System version 3.0 software (Terra, GE, USA) by two experienced cardiologists, who were blinded to patients' clinical information and biochemical measurements[28, 29]. Briefly, the outer diameter of contrast-filled catheter was used for calibration to determine absolute measurements in millimeters. Lesion length was measured as the distance from the proximal to distal shoulder. A value of 0 mm was assigned for minimal lumen diameter in the case of total occlusion at baseline. ISR was defined as recurrence of luminal diameter stenosis of > 50% within the stent or in the 5-mm proximal or distal segments adjacent to the stent at follow-up angiography [28, 29]. For patients with multiple coronary lesions, the most severe restenotic lesion at follow-up was included in the analysis.

Biochemical assessments

Peripheral venous blood samples were obtained at the day of angiography after an overnight fasting. To avoid a diurnal variation in IgE concentration and dramatic fasting interval effects, all blood samples were obtained at 8:00 am. Serum levels of glucose, blood urea nitrogen, uric acid, creatinine, and lipid profiles, including triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, lipoprotein (a), apolipoprotein A-I and apolipoprotein B were measured

using standard laboratory techniques on a HITACHI 912 Analyzer (Roche Diagnostics, Germany). Blood concentration of glycosylated hemoglobin (HbA1c) was measured using ion-exchange high performance liquid chromatography with Bio-rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, USA). Serum levels of high-sensitivity C-reactive protein (hsCRP) were determined by ELISA (Biocheck Laboratories, Toledo, OH, USA). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [30].

Serum levels of IgE and CML were determined by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocols (BMS2097, eBioscience; STA-816, Cell BioLabs). The average inter-assay coefficient of variance (CV) was 6.2% and 5.8% for IgE and CML, respectively, and the average intra-assay CV was 6.6% or 7.2% for IgE or CML, respectively.

Diabetic mouse model

Animal experiments were approved by Hospital Animal Care Committee and complied with Guide for the Care and Use of Laboratory Animals by the National Institutes of Health. 6-8 weeks old C57BL/6J male mice were housed in a pathogen-free environment and received intraperitoneal injections of albumin (A3139, Sigma Aldrich) (100μg each), or glycated albumin (100μg each) every other day for 12 weeks. The glycated albumin was prepared through a glycation process[8]. Then, femoral artery injury was induced with a wire as previously described [31]. Serum was collected for analysis of CML and IgE 4 weeks later using ELISA kit (STA-816, Cell BioLabs; E99-115, Bethyl Laboratories) and injured femoral artery was harvested for hematoxylin and eosin staining and immunofluorescence staining using CML and IgE antibodies (ab27684, Abcam; 553416, BD Biosciences,).

Statistical analysis

All statistical analyses were performed with SPSS 26.0 (IBM, Armonk, New York) and R Programming Language 4.0.2. Continuous variables are expressed as mean ± standard deviation (SD) if data were normally distributed, or as median (25th–75th percentile) otherwise, and categorical variables are summarized as frequencies (percentages). IgE and CML levels were presented both as an original skewedly-distributed variable and a $\log_2$ transformed normally distributed variable. Continuous variables were compared between two groups using student's t-test or Mann–Whitney U test. For categorical variables, differences between groups were evaluated with chi-square test. Pearson's and Spearman's correlation tests were used to assess the relation between IgE and CML. Logistic regression models were applied to detect the relationship between ISR and serum IgE or CML level. IgE or CML was analyzed as a continuous variable with log- transformation, as an ordinal variable, and as a categorical variable divided into tertiles. Odds ratios (OR) were calculated with unadjusted, adjusted for age, sex, body mass index, smoking, dyslipidemia, hypertension (model 1), and further adjusted by adding HbA1c, left ventricular ejection fraction, statin use, number of diseased vessels, B2/C lesion, bifurcation, chronic total occlusion, and stent diameter (model 2). Receiver-operating characteristic (ROC) curves were plotted to determine the power of IgE and CML for detecting ISR, and the C statistics was compared using Delong method.

Category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to assess the added value in reclassification of the patients. The 2-sided P value < 0.05 was considered statistically significant.

Results

Baseline clinical characteristics

In this clinical cohort, ISR and non-ISR were detected in 196 and 220 patients, respectively. Patients with or without ISR did not differ with respect to age, gender distribution, body mass index, risk factors for coronary artery disease and renal function. Blood concentrations of HbA1c and hsCRP were higher whereas left ventricular ejection fraction and statin use were lower in ISR patients. Despite similar degree of coronary stenosis intervened and average number and length of stents implanted, patients with ISR received smaller stents, and had higher percentages of circumflex or right coronary artery lesion, multivessel disease, and complex lesion morphology **(Table 1)**.

IgE and CML levels with ISR

Serum levels of IgE and CML were higher in ISR group compared with non-ISR group [IgE: 187.10 (63.75-489.65) vs 80.25 (30.65-202.50), P<0.001; CML: 203.26 (164.50-266.84) vs 174.26 (130.85-215.56), P<0.001]. There was a stepwise increase in incidence of ISR from the lowest tertile to the highest tertile of Ig E or CML (all P for trend <0.001) **(Figure 2).** Serum IgE correlated positively with CML levels (all patients: r=0.331, P<0.001; ISR group: r=0.433, P<0.001; non-ISR group: r= 0.153, P=0.023), even after adjusting for confounding factors **(Table 2)**. Logistic regression models were constructed to confirm the association between ISR and IgE or CML level in various subgroups **(Figure 3)**. In multivariable analysis, both serum IgE and CML levels remained independent factors for ISR in patients with T2DM after adjusting for age, sex, body mass index, smoking, dyslipidemia, hypertension, HbA1c, left ventricular ejection fraction, stain use, number of diseased vessel, class B2/C lesion, bifurcation, chronic total occlusion, and stent diameter. The result patterns were similar when serum IgE or CML level was used as a standardized continuous variable with log- transformation and as an ordinal or categorical variable **(Table 3)**.

ROC curves showed that addition of IgE or CML to the basic clinical model significantly improved diagnostic performance for ISR in patients with T2DM [area under the curve (AUC): 0.759 (0.713-0.804) or 0.748 (0.701-0.794) vs 0.705 (0.655-0.755), all P<0.01] **(Figure 4)**. Likewise, compared with the basic clinical model, the inclusion IgE or CML had significant improvement in reclassification as assessed by the categorical NRI [0.120 (0.047-0.194); 0.099 (0.034-0.163), respectively] and IDI [0.074 (0.049-0.010); 0.062 (0.038-0.086), respectively] (**Table 4)**. More importantly, there was a significant interaction between IgE and CML in relation to ISR (P for interaction < 0.01). At high tertile of IgE (≥210.7 ng/ml), patients with high tertile of CML (≥215.5 ng/ml) had a significantly increased risk of ISR compared with those with low tertile of CML (≤161.5 ng/ml) (adjusted OR=6.784, 95% CI 2.304–19.969, P=0.001) (**Figure 5**).

Findings in mice models

Mice receiving glycated albumin injection exhibited elevated CML and IgE levels in serum and increased CML and IgE infiltration in the injured femoral artery segment which were associated with a higher degree of neointimal hyperplasia and luminal stenosis **(Figure.6)**.

Discussion

This study is the first to show that in type 2 diabetic patients with stable coronary artery disease, IgE correlated positively with CML. Elevated IgE and CML was associated ISR after DES-based PCI, independent of traditional risk factors.

Role of elevated circulating IgE and CML in ISR

In the bare metal stent era, the stainless-steel struts may act as a foreign body to induce effector cells of hypersensitivity, increasing IgE release and participating in ISR [32, 33]. Our study cohort is unique as all patients had stable angina and received third-generation DES which reflects well the current clinical practice. The technology of new DES has been improved dramatically, often consisting of a cobalt-chromium alloy platform, an antiproliferative drug (such as everolimus or zotarolimus) and a biodegradable polymer-coating with enhanced biocompatibility [34]. Nevertheless, the stent being an exogenous substance may cause several reactions by promoting proliferation of vascular smooth muscle cells, immune responses and neointima hyperplasia after implantation, leading to ISR and late thrombosis.

The major finding of this study is that serum IgE levels were higher in patients with ISR comparted to non-ISR group. Furthermore, the incidence of ISR increased stepwise across the tertiles of serum IgE, and circulating IgE level remained an independent factor for ISR in patients with T2DM after adjusting for potential confounders. These observations jointly support a notion that allergic inflammation to stent contributes, at least partly, to the development of ISR in type 2 diabetic patients after DES-based PCI. Finn et al reported that allergy-mediated inflammation plays a more critical role with DES-related ISR than with bare metal stent–related ISR[35]. Previous studies have shown that IgE is associated with diabetes status and may be an independent risk factor for pre-diabetes and diabetes [36, 37]. IgE induces platelet activation and aggregation [38] and arterial smooth muscle hyperplasia [39], which are essential in the pathophysiology of ISR [40]. More importantly, IgE activates mast cells and basophils by binding to high-affinity receptor FcεRI [41], and induces release of preformed inflammatory mediators and *de novo* synthesis and secretion of cytokines, chemokines, and eicosanoids, which may cause adverse events after stent implantation [22, 42]. Based on these findings and our results, we speculate that in diabetic patients who had elevated serum IgE, vascular injury resulting from balloon dilatation and stent implantation could increase further IgE levels and activate allergic inflammation and relevant effector cells, potentially facilitating the occurrence of ISR.

Another finding of this study is that CML, one of the most typical AGEs that have been implicated in diabetes-related complications [7, 9], was correlated with ISR in patients with T2DM. Abundant evidence has demonstrated that production of AGEs is not only a sign of high blood sugar, but also reflects cumulative metabolic burden, oxidative stress and inflammation[43]. AGEs elicit secretion of inflammatory cytokines in basophils which are thought to play a pivotal role in allergic reactions and abundant expression of high-affinity receptors for IgE[44, 45]. In the study of food allergy, CML acts as an immunogen by inducing activation and proliferation of various immune cells, and participates in the development of chronic inflammation [46, 47]. Our results show that IgE correlated positively with CML and there existed a significant interaction of IgE and CML in relation to ISR, suggesting that elevated circulating CML might contribute to activation of granular cells and amplification of inflammation, mediating more local and systemic IgE release and, at the same time, leading to the pathogenesis of ISR in type 2 diabetic patients.

Potential clinical implications

The findings of the present study are of clinical relevance. Our results imply that measurement of IgE and CML is useful for evaluating the risk of ISR in patients with T2DM undergoing DES-based PCI. More importantly, aggressive glycemic control and anti-allergic and anti-inflammatory therapy might be mandatory to reduce ISR, especially for individuals with high level of IgE or CML[48]. Further prospective studies with large cohorts are warranted to confirm these issues.

Study limitations

The present study has several limitations inherited from its retrospective, cross-sectional design for the point of ISR investigation, thereby allowing us to detect association, not to formulate causal link. The sample size in ISR and non-ISR groups was small and all patients were specially selected. Although baseline clinical characteristics and angiographic features were quite homogenously distributed in patients with and without ISR, certain selection biases and unknown confounding factors possibly impacting on IgE and CML could not be excluded. ISR was determined by interpretation of angiography but not through intracoronary imaging (such as intravascular ultrasound), thus we could not provide the details about the degree of ISR. Finally, the relation of serum IgE and CML levels with ISR will be more precisely characterized by serial biochemical measurements.

Conclusions

This study demonstrates that in patients with T2DM, elevated serum IgE and CML levels confer an increased risk of ISR after DES-based PCI. Novel information as such provides new insight into the pathophysiology of ISR and the management of type 2 diabetic patients with stable coronary artery disease.

Abbreviations

AGEs: advanced glycation end-products; AUC: area under the curve; CML: Nε-carboxymethyl-lysine; DES: drug-eluting stent; HbA1c: glycosylated hemoglobin; IDI: integrated discrimination improvement; Ig: immunoglobin; ISR: in-stent restenosis; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NRI: net reclassification improvement; OR: odds ratio; PCI: percutaneous coronary intervention; QCA: quantitative coronary analysis; RAGE: receptor for AGEs; ROC: receiver-operating characteristic; SD: standard deviation; T2DM: type 2 diabetes mellitus.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent was obtained from all patients, and clinical investigation was conducted according to the principle of the Declaration of Helsinki.

Consent for publication

All authors consent this manuscript for publication.

Availability of data and materials

Data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YD, YS and LQW wrote the article, substantially contributed to discussion of the content, and edited the manuscript. JML, QJC, YYB, TYL, CJL, FHD, XQW performed the experiments and researched data for the article. YD, YS, JML and QJC analyze the data; LL, QJ and WFS substantially contributed to discussion of the content and reviewed the manuscript.

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Tables

Table 1 Baseline characteristics in patients with T2DM

	Non-ISR (n=220)	ISR (n=196)	*P* Value
Male, n (%)	168 (76.4)	143 (73.0)	0.425
Age, y	66.53±9.43	67.59±8.82	0.241
Body mass index, kg/m^2	25.50±3.42	25.10±3.46	0.235
Smoking, n (%)	63 (28.6)	59 (30.1)	0.743
Hypertension, n (%)	169 (76.8)	160 (81.6)	0.228
Systolic blood pressure, mm Hg	137.85±20.40	140.26±22.04	0.248
Diastolic blood pressure, mm Hg	74.41±12.58	75.43±14.69	0.448
Dyslipidemia, n (%)	25 (11.4)	20 (10.2)	0.704
Serum creatinine, μmol/L	80.00 (70.25-93.00)	82.50 (68.00-99.75)	0.518
eGFR, mL/min per 1.73 m^2	80.00±17.26	78.77±33.05	0.640
HbA1c, %	7.33±1.35	7.64±1.35	0.020
Fasting blood glucose, mmol/L	7.15±2.28	7.66±2.94	0.050
Triglyceride, mmol/L	1.75±1.72	1.64±1.16	0.442
Total cholesterol, mmol/L	3.62±1.01	3.59±1.03	0.823
HDL cholesterol, mmol/L	1.09±0.27	1.04±0.26	0.054
LDL cholesterol, mmol/L	2.04±0.80	2.02±0.85	0.877
hsCRP, mg/L	0.94 (0.41-2.24)	1.15 (0.52-4.59)	0.021
IgE, ng/ml	80.25 (30.65-202.50)	187.10 (63.75-489.65)	<0.001
CML, ng/ml	174.26 (130.85-215.56)	203.26 (164.50-266.84)	<0.001
Ejection fraction, %	62.46±8.89	60.34±10.54	0.028
Medication, n (%)			
Dual antiplatelet therapy	209 (95.0)	185 (94.4)	0.781
ACEI/ARB	146 (66.4)	132 (67.3)	0.832
β-Blockers	183 (83.2)	159 (81.1)	0.584
Statins	217 (98.6)	184 (93.9)	0.009
Diseased vessel, n (%)			
Left main	11 (5.0)	19 (9.7)	0.065
Left anterior descending	157 (71.4)	153 (78.1)	0.118

Left circumflex	98 (44.5)	115 (58.7)	0.004
Right coronary artery	108 (49.1)	138 (70.4)	<0.001
Severity of CAD, n (%)			
1-vessel	114 (51.8)	56 (28.6)	<0.001
2-vessel	69 (31.4)	70 (35.7)	0.348
3-vessel	37 (16.8)	70 (35.7)	<0.001
Multivessel disease	106 (48.2)	140 (71.4)	<0.001
Lesion characteristics			
Class B2/C lesion, n (%)	135 (61.4)	145 (74.0)	0.006
Bifurcation lesion, n (%)	54 (24.5)	71 (36.2)	0.009
Chronic total occlusion, n (%)	23 (10.5)	36 (18.4)	0.021
Pre-PCI stenosis, %	85.86±6.29	86.81±8.20	0.189
Average number of stents, n	1.51±0.71	1.63±0.73	0.106
Stent diameter, mm	2.98±0.40	2.84±0.35	<0.001
Stent length, mm	28.52±2.57	28.13±4.94	0.322

T2DM: Type 2 diabetes mellitus; ISR: in-stent restenosis; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hsCRP: high-sensitivity C reactive protein; IgE: immunoglobulin E; CML: Nε-carboxymethyl-lysine; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; PCI: percutaneous coronary intervention

Table 2 Correlation between CML and IgE in patients with T2DM

	Unadjusted r	Unadjusted P	*Adjusted r	*Adjusted P
All	0.331	<0.001	0.324	<0.001
ISR	0.433	<0.001	0.441	<0.001
Non-ISR	0.153	0.023	0.169	0.014

* adjusted for age, sex, body mass index, smoking, dyslipidemia, hypertension, HbA1c, LVEF, statin use, number of diseased vessel, class B2/C lesion, bifurcation lesion, CTO lesion, stent diameter. T2DM: type 2 diabetes mellitus; ISR: in-stent restenosis; HbA1c: glycated hemoglobin A1c; LVEF: left ventricular ejection fraction; CTO: chronic total occlusion.

Table 3 Uni- and multi-variant regression models

	Unadjusted OR	*P*-value	Adjusted for Model 1 OR	*P*-value	Adjusted for Model 2 OR	*P*-value
Log_2 IgE per SD	2.008 (1.613-2.500)	<0.001	2.066 (1.652-2.583)	<0.001	1.989 (1.567-2.526)	<0.001
IgE tertiles	1.831 (1.431-2.344)	<0.001	1.879 (1.461-2.417)	<0.001	1.773 (1.355-2.322)	<0.001
1st	Ref		Ref		Ref	
2st	1.658 (1.019-2.697)	0.042	1.757 (1.070-2.884)	0.026	1.646 (0.971-2.790)	0.064
3st	3.346 (2.043-5.480)	<0.001	3.523 (2.129-5.829)	<0.001	3.137 (1.831-5.374)	<0.001
Log_2 CML per SD	1.818 (1.445-2.287)	<0.001	1.824 (1.444-2.303)	<0.001	1.945 (1.507-2.509)	<0.001
CML tertiles	1.617 (1.268-2.061)	<0.001	1.608 (1.256-2.060)	<0.001	1.744 (1.333-2.282)	<0.001
1st	Ref		Ref		Ref	
2st	1.334 (0.824-2.159)	0.241	1.301 (0.797-2.124)	0.292	1.543 (0.902-2.641)	0.113
3st	2.605 (1.604-4.231)	<0.001	2.574 (1.570-4.221)	<0.001	3.026 (1.768-5.179)	<0.001

IgE and CML is analyzed as a log-transformed continuous variable, an ordinal variable divided according to tertiles of IgE or CML, and a categorical variable using the lowest tertile as reference. Model 1: adjusted for age, sex, body mass index, smoking, dyslipidemia, hypertension. Model 2: adjusted for age, sex, body mass index, smoking, dyslipidemia, hypertension, HbA1c, LVEF, statin use, number of diseased vessel, class B2/C lesion, bifurcation lesion, CTO lesion, stent diameter. As a continuous variable, OR is shown as per 1 SD (standard deviation). OR: odds ratio; HbA1c: glycated hemoglobin A1c; LVEF: left ventricular ejection fraction; CTO: chronic total occlusion

Table 4 The predictive power of models for ISR

C-statistic	P-value	P for comparison	Categorical NRI	P-value	IDI	P-value	
Established risk factors	0.705 (0.655-0.755)	<0.001	Ref	Ref	Ref		
Established risk factors + IgE	0.759 (0.713-0.804)	<0.001	<0.01	0.120 (0.047-0.194)	<0.01	0.074 (0.049-0.010)	<0.01
Established risk factors + CML	0.748 (0.701-0.794)	<0.001	<0.01	0.099 (0.034-0.163)	<0.01	0.062 (0.038-0.086)	<0.01

ISR: in-stent restenosis; NRI: net reclassification improvement; IDI: integrated discrimination improvement

Figures

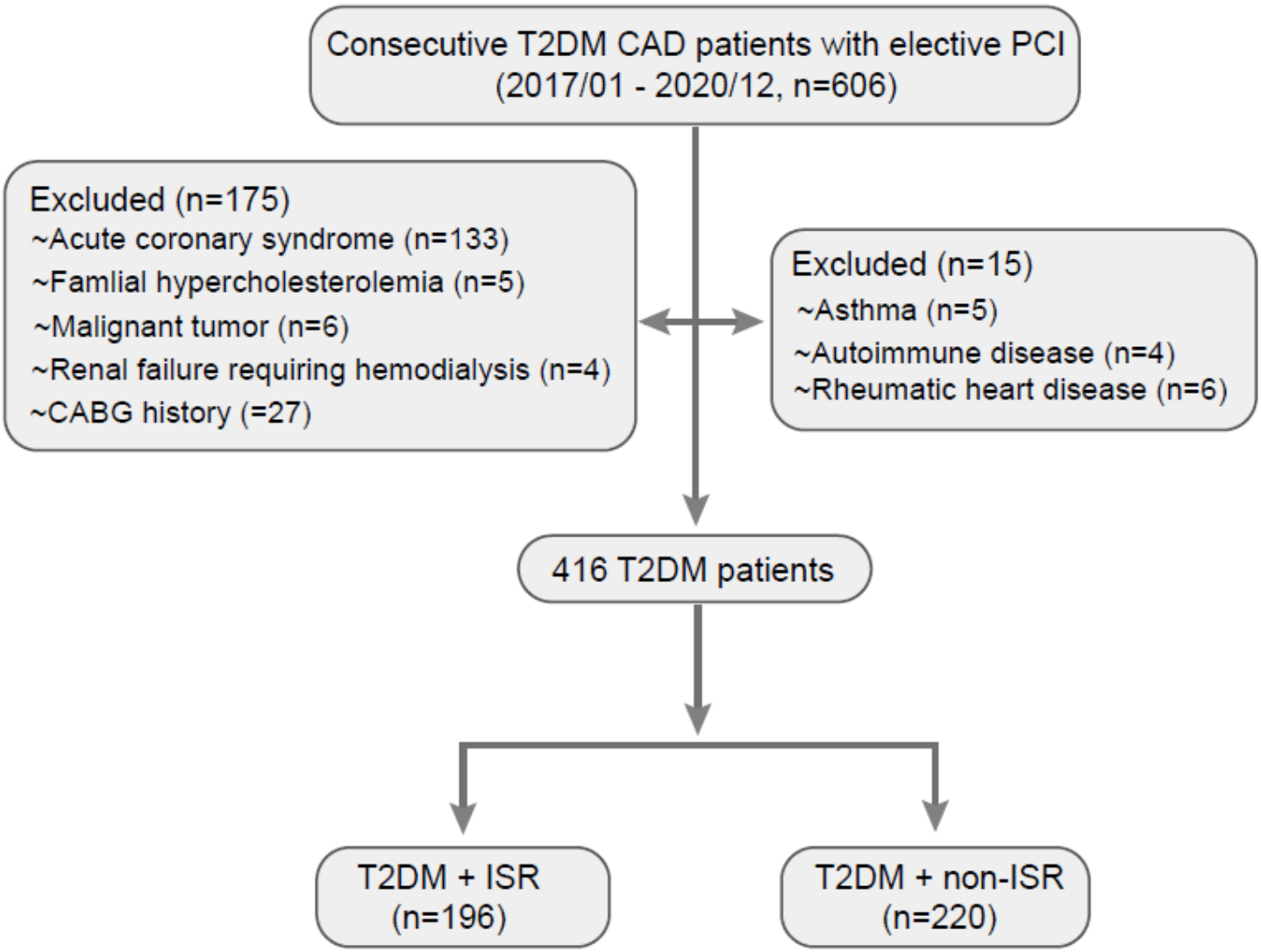

Figure 1

Flow chart of recruitment procedure. T2DM: type 2 diabetes mellitus; CAD: coronary artery disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; ISR: in-stent restenosis

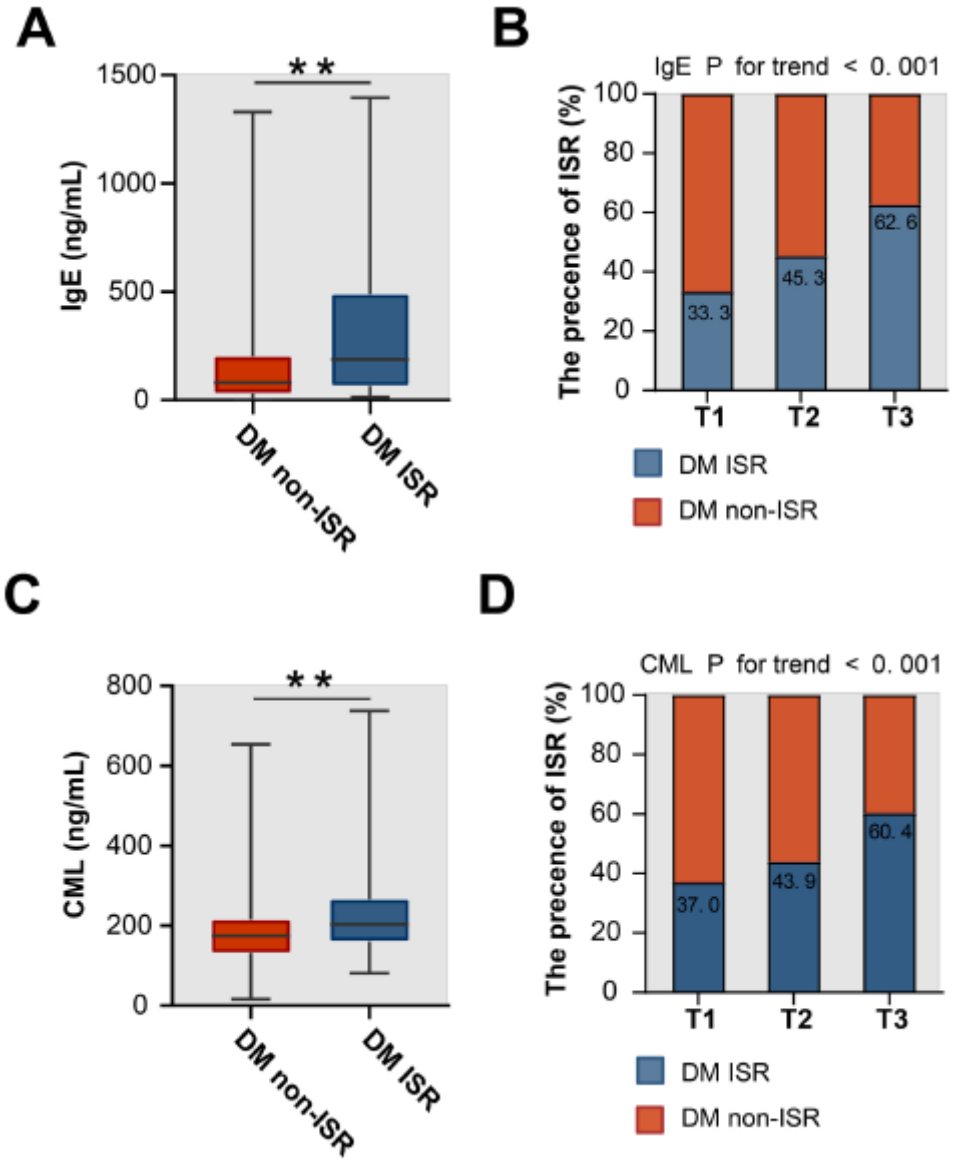

Figure 2

Association of serum IgE and CML levels with ISR in T2DM patients. Comparison of serum IgE (A) and CML (C) levels between patients with and without ISR in T2DM patients. In-stent restenosis across the tertiles of IgE (B) and CML (D). ISR: in-stent restenosis; T2DM: type 2 diabetes mellitus. **P < 0.01

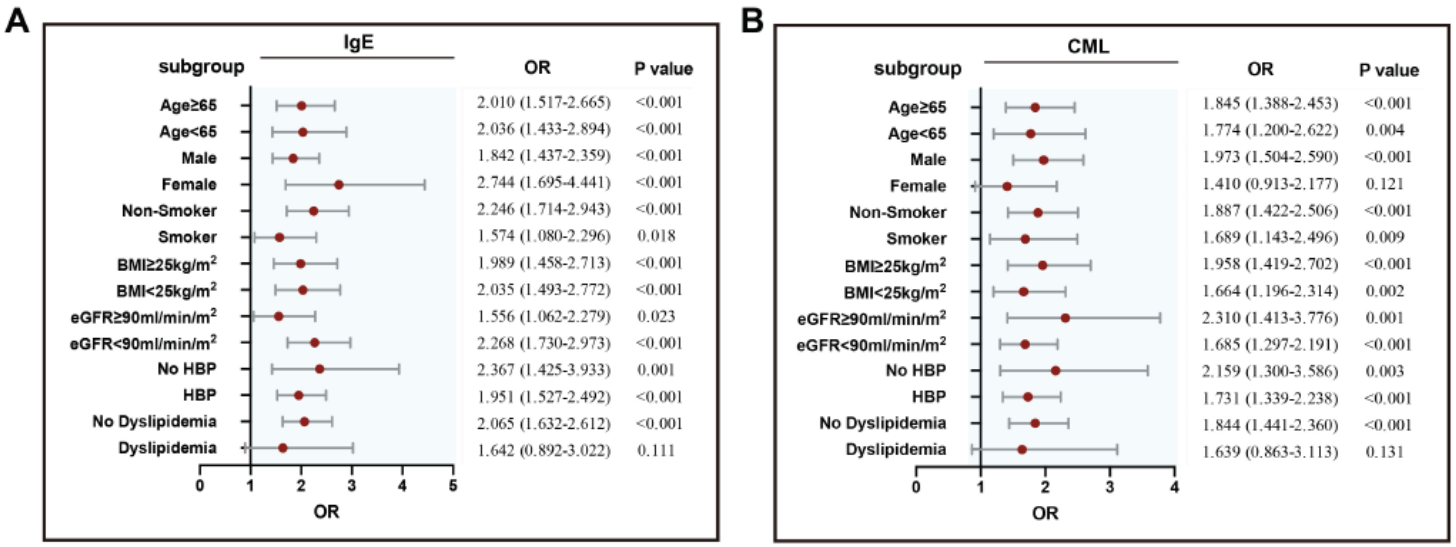

Figure 3

Forrest plots (unadjusted) to analyze the predictive value of IgE (A) or CML (B) for ISR in different subgroups of T2DM patients. IgE or CML was included as a log- transformed continuous variable. BMI: body mass index; eGFR: estimated glomerular filtration rate; HBP: high blood pressure; ISR: in-stent restenosis; T2DM: type 2 diabetes mellitus

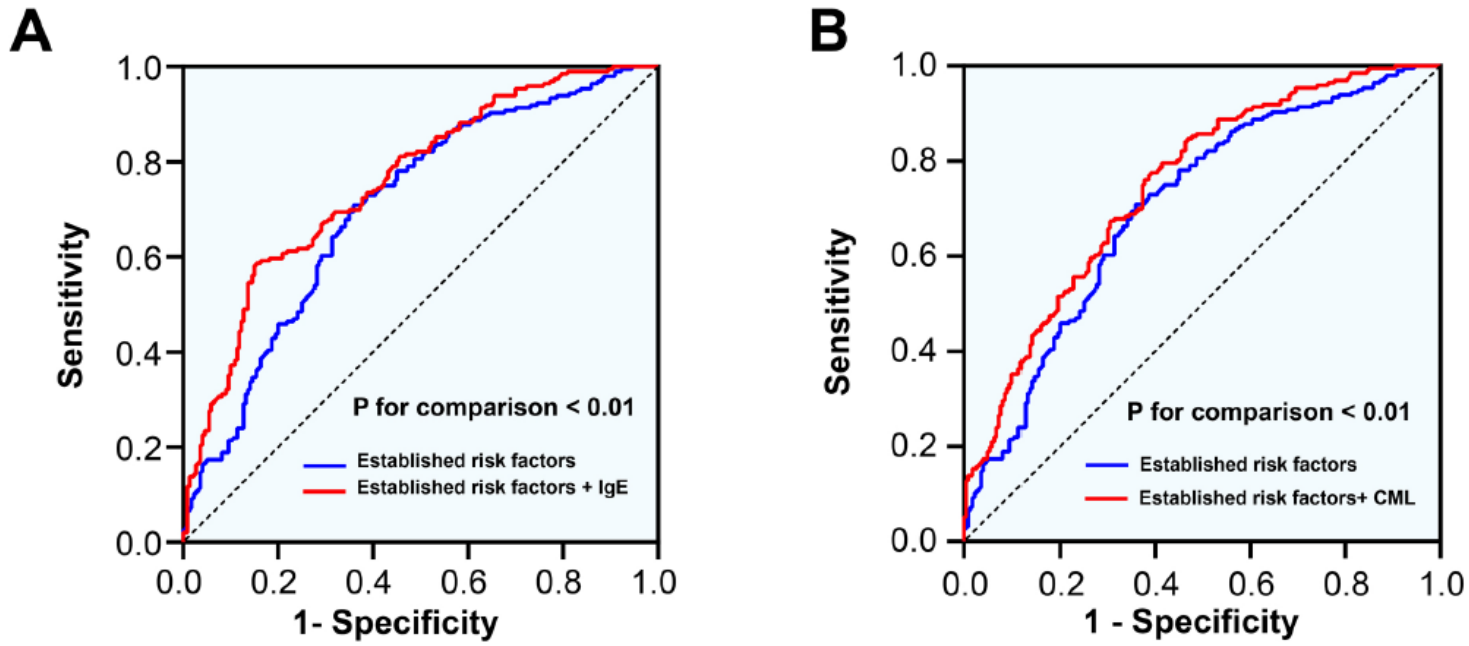

Figure 4

Receiver operating characteristic curve analysis between models to verify the predictive values of IgE (A) and CML (B).

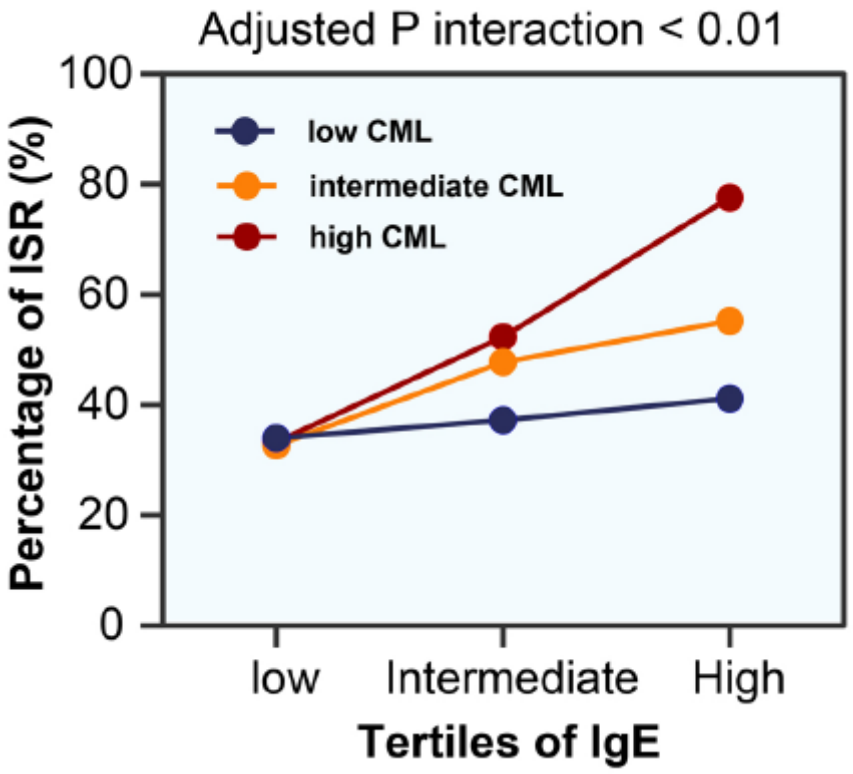

Figure 5

Percentage of ISR in relation to interaction between IgE and CML. ISR: in-stent restenosis.

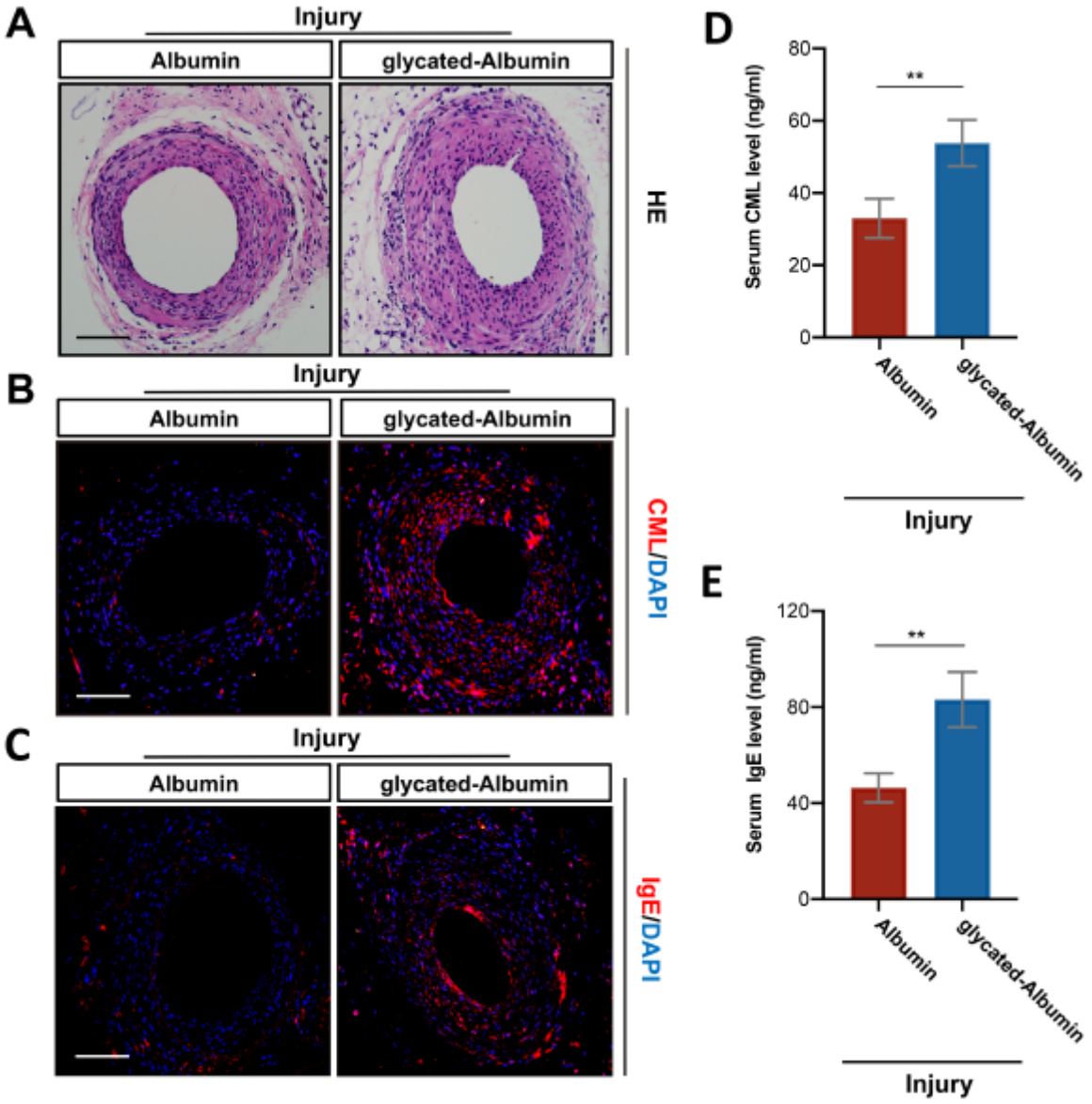

Figure 6

Glycated albumin induced greater neointimal hyperplasia and elevated CML and IgE in mice. The mouse arteries were harvested 28 days after injury. Representative images of H&E staining (A) and immunofluorescent staining for CML (red) (B) and IgE (red) (C) of wire-injured femoral artery sections in mice receiving albumin and glycated albumin injection. Serum CML (D) and IgE (E) levels in mice. **P < 0.01, n=6 each group. Scale bar: 100μm