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Wenjing Li

Binzhou People's Hospital

Hongyan Zhou

Binzhou People's Hospital

Nan Meng

Binzhou People's Hospital

Xiaoyan Liang

15734084426@163.com

Binzhou People's Hospital

Article

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Clinical Study on NAFLD Intervening in the Progression of Coronary Atherosclerosis by Affecting TREM2-Related Inflammatory Pathways Regulated by Adipose Tissue

Wenjing Li¹, Hongyan Zhou², Nan Meng¹, Xiaoyan Liang^{3,4*}

1. Department of Cardiology, Binzhou People's Hospital, 256600, Binzhou, Shandong Province, China

2. Department of Laboratory Medicine, Binzhou People's Hospital, 256600, Binzhou, Shandong, China

3. Department of Central Laboratory, Binzhou People's Hospital, 256600, Binzhou, Shandong, China

4. Shandong Provincial Key Laboratory for Diagnosis and Treatment of Infectious Diseases in Medical and Health Sciences, Binzhou People's Hospital, Shandong, 256600, China

*Corresponding author:

Xiaoyan Liang, Department of Central Laboratory, Binzhou People's Hospital, No. 707 Huanghe 15th Road, Bincheng District, 256600, Binzhou, Shandong Province of China. E-mail: 15734084426@163.com.

Running Title: Intervention of NAFLD against atherosclerosis

Conflict of interest

The authors acknowledge that they have no conflict of interest.

Authors' contributions

Xiaoyan Liang designed the study and supervised the overall project. Wenjing Li drafted the article and critical revision. Hongyan Zhou collected data; Nan Meng participated in data analysis.

Abstract

Objective : To investigate the effect of non-alcoholic fatty liver disease (NAFLD) on the progression of coronary atherosclerotic heart disease (CCS) and its association with TREM2-related inflammatory pathways. **Methods:** A total of 56 CCS inpatients were divided into the NAFLD+CCS group (n=33) and CCS group (n=23) based on NAFLD diagnostic criteria. Basic clinical and biochemical indicators, liver/visceral fat content, and coronary atherosclerosis severity (GS score) were detected. Monocyte subsets (classical CD14⁺⁺CD16⁻, intermediate CD14⁺⁺CD16⁺, non-classical CD14⁺CD16⁺⁺) were analyzed by flow cytometry. Serum sTREM2, IL-6, and IL-10 concentrations were measured by ELISA or enzyme-linked immunosorbent assay. **Results** Compared with the CCS group, the NAFLD+CCS group had significantly higher absolute monocyte count (MO), hs-CRP, GS score, and sTREM2 concentration (all $P<0.05$). Regarding monocyte subsets, the proportion of classical monocytes (CM) was lower ($80.12\pm4.38\%$ vs. $83.93\pm5.35\%$, $P=0.005$), while intermediate (IM: $4.83\pm1.48\%$ vs. $3.25\pm1.53\%$, $P=0.000$) and non-classical monocytes (NCM: $8.53\pm3.26\%$ vs. $6.50\pm3.17\%$, $P=0.024$) were higher in the NAFLD+CCS group. Levels of IL-6 and IL-10 were also significantly elevated in the NAFLD+CCS group (both $P<0.001$). **Conclusion :** NAFLD

exacerbates systemic inflammation and coronary atherosclerosis in CCS patients, accompanied by abnormal monocyte subset distribution and increased sTREM2. It is speculated that TREM2 may regulate macrophage polarization via the PI3K/AKT/NF- κ B pathway, thereby mediating adipose tissue inflammation and participating in NAFLD-related atherosclerosis progression.

Keywords

Non-alcoholic fatty liver disease (NAFLD); Coronary atherosclerotic heart disease (CCS); TREM2; Monocyte subsets; Inflammatory pathways

1. Research Background

1.1 Relationship between NAFLD and Atherosclerosis

Non-alcoholic fatty liver disease (NAFLD) refers to the accumulation of excess fat in the liver not caused by heavy alcohol intake^[1]. Its understanding has expanded from an extrahepatic manifestation of metabolic syndrome (Mets) to a key driver of atherosclerosis, ultimately leading to atherosclerotic cardiovascular diseases (ASCVD) such as coronary artery disease (CAD) and ischemic stroke (IS)^[2]. Despite 10%-25% of NAFLD patients developing non-alcoholic steatohepatitis (NASH), cirrhosis, or liver failure, ASCVD remains the leading cause of death in this population^[3]. The latest scientific statement from the American Heart Association (AHA) explicitly identifies NAFLD as an emerging risk factor for ASCVD^[3].

1.2 Mechanism of Adipose Tissue Inflammation in NAFLD-Related Atherosclerosis

NAFLD-driven mechanisms, including insulin resistance (IR), dyslipidemia, systemic inflammation, and oxidative stress, promote endothelial damage, inflammatory cell activation, foam cell formation, and smooth muscle cell proliferation in arteries, accelerating atherosclerosis^[4]. Insulin resistance in adipose tissue induces triglyceride breakdown and free fatty acid (FFA) release^[5]. FFAs are transported to the liver, stabilizing apolipoprotein B (apoB) production and inhibiting its degradation, thereby increasing very low-density lipoprotein (VLDL) synthesis. VLDL remnants penetrate the arterial wall, inducing endothelial dysfunction and uptake by inflammatory monocytes, leading to foam cell accumulation^[6]. Additionally, adipose tissue IR triggers the release of tumor necrosis factor- α (TNF- α)^[7], which activates the hepatic nuclear factor- κ B (NF- κ B) pathway, secreting pro-inflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP). Single-nucleotide polymorphisms (SNPs) in the TNF- α gene further promote NASH progression by regulating inflammation, steatosis, and fibrosis^[8]. TNF- α also induces hepatocellular expression of proprotein convertase subtilisin/kexin type 9 (PCSK9), which inhibits LDL uptake by degrading LDL receptors. High IL-6 levels are associated with endothelial dysfunction and arterial stiffness^[9], while CRP promotes atherosclerosis by upregulating plasminogen activator inhibitor-1 (PAI-1) and adhesion molecules, inhibiting nitric oxide (NO) formation, and enhancing LDL uptake^[10].

1.3 Relationship between TREM2-Related Pathways and Adipose Tissue Inflammation

Triggering receptor expressed on myeloid cells-2 (TREM2) is an innate immune receptor of the lectin-like immunoglobulin superfamily, primarily expressed on myeloid cells such as macrophages^[11, 12]. As a signaling hub for inflammation and lipid metabolism [13], TREM2 is cleaved by proteases ADAM17 and ADAM10 at the stalk region H157-S158 to produce soluble TREM2 (sTREM2). Circulating monocytes are heterogeneous: in mice, Ly-6Chi and Ly-6Cmid monocytes are inflammatory subsets^[14]; in humans, monocytes are classified into classical CD14++CD16- (85%, high phagocytic capacity), intermediate CD14++CD16+ (5%,

pro-inflammatory), and non-classical CD14⁺CD16⁺⁺ (10%, pro-inflammatory with high migration)^[15]. Studies have shown higher proportions of intermediate and non-classical monocytes in Cockayne syndrome (CS) patients and healthy elderly individuals^[16, 17]. TREM2 has been reported to promote macrophage M1-to-M2 polarization via NF-κB-related metabolism, inhibiting osteoarthritis^[18]. However, its mechanism in regulating NAFLD-related adipose tissue inflammation and atherosclerosis remains unclear. This study hypothesizes that sTREM2 may affect visceral adipose tissue inflammation and coronary atherosclerosis progression by regulating NAFLD-related pathways.

2. Experimental Design

2.1 Study Subjects

A total of 56 inpatients in the Department of Cardiology, Binzhou People's Hospital, from January 1 to May 1, 2024, were enrolled. Grouping was based on the 2019 ESC CCS diagnostic criteria and 2023 AASLD NAFLD diagnostic criteria:

- Experimental group (NAFLD+CCS): 33 cases (liver fat content $\geq 5\%$ by QCT)
- Control group (CCS): 23 cases (liver fat content $< 5\%$ by QCT)

2.2 Detection Indicators and Methods

2.2.1 Basic Indicators

- Biochemical indicators: Liver/kidney function, blood glucose, lipids, and inflammatory markers (hs-CRP) were detected by standard laboratory methods.
- Imaging examinations: Chest/abdominal CT (QCT for liver/visceral fat content), cardiac color Doppler ultrasound (LVEF measurement), and coronary angiography (GS scoring for atherosclerosis severity).

2.2.2 Inflammatory and Cellular Indicators

- Monocyte subsets: Peripheral blood was stained with FITC-conjugated anti-CD16, PE-conjugated anti-CD14, and APC-conjugated anti-CD45, then analyzed by BD FACSCanto flow cytometry.
- Cytokines and sTREM2: Serum IL-6 and IL-10 levels were detected by flow cytometry; serum sTREM2 concentration was measured by AIDISHENG human sTREM-2 ELISA kit using a Caretium KC-100 microplate reader.

2.2.3 Statistical Methods

SPSS 27.0 software was used for analysis. Measurement data were expressed as mean $\pm$ SD (normal distribution, independent samples t-test) or M(P25, P75) (non-normal distribution, non-parametric test). Categorical data were compared by the χ^2 test. $P < 0.05$ was considered statistically significant.

2.2.4 Ethics approval and consent to participate

This clinical study has confirmed that all experiments were conducted strictly in accordance with relevant guidelines and regulations. The Medical Ethics Committee of Binzhou People's Hospital has approved and supported this research. Informed consent was obtained from all individual participants included in the study. The ethical number is: Lun Shen (2023) No. 514.

2.3 Experimental Materials and Equipment

- Reagents: PE anti-human CD14, APC anti-human CD45, FITC anti-human CD16 (BioLegend), human sTREM-2 ELISA kit (AIDISHENG), lysing solution, PBS, etc.
- Equipment: BD FACSCanto flow cytometer, Caretium KC-100 microplate reader, low-temperature centrifuge, vortex oscillator, constant temperature incubator, 5mL flow

tubes, and pipettes.

3. Experimental Results

3.1 Clinical Data Characteristics

Statistically significant differences were observed in the following indicators between the two groups (Table 1):

- Higher absolute monocyte count (MO), hs-CRP, GS score, and sTREM2 concentration in the NAFLD+CCS group (all $P < 0.05$).
- No significant differences in gender, age, BMI, hypertension/diabetes prevalence, smoking/drinking status, lipids (TG, TC, LDL-C), liver function (ALT, AST), LVEF, or visceral fat area (all $P > 0.05$).
- FIB-4 and FLI indices suggested more severe liver fibrosis and higher NAFLD risk in the experimental group.

Table 1 Clinical Data Characteristics of the Two Groups

Indicators	CCS+NAFLD Group (n=33)	CCS (n=23)	Group	P Value
Male gender, n (%)	20 (60.6)	12 (52.2)		0.362
Hypertension, n (%)	24 (72.7)	13 (56.5)		0.165
Diabetes mellitus, n (%)	17 (51.5)	8 (34.8)		0.167
Smoking, n (%)	5 (15.2)	1 (4.3)		0.202
Alcohol consumption, n (%)	5 (15.2)	1 (4.3)		0.202
Age (years)	66 (60,70.5)	62 (54,68)		0.070
Height (cm)	165 (160,170)	160 (160,170)		0.289
Body weight (kg)	74.9±12.17	72.87±11.03		0.526
BMI (kg/m ²)	26.96±3.07	26.74±2.61		0.778
Visceral fat area (cm ²)	219.5 (141.0,264.6)	183.5 (151.5,236.8)		0.479
Medication use, n (%)				
ACEI/ARB	15 (45.5)	12 (52.2)		0.412

Indicators		CCS+NAFLD Group (n=33)	CCS (n=23)	Group	P Value
β -receptor blocker		16 (48.5)	16 (69.6)		0.097
Calcium blocker	channel	5 (15.2)	4 (17.4)		0.551
Statin		28 (84.8)	23 (100.0)		0.062
Diuretic		2 (6.0)	0 (0.0)		0.343
Nitrate		22 (66.7)	17 (73.9)		0.391
Hematological parameters					
WBC ($\times 10^9/L$)		6.47 (5.55,7.70)	5.78 (4.67,7.13)		0.091
NEU ($\times 10^9/L$)		3.92 (3.46,4.69)	3.59 (2.38,4.30)		0.066
LY (%)		27.69 $\pm$ 8.59	31.51 $\pm$ 6.55		0.078
MO (%)		7.60 (5.85,8.65)	7.30 (6.30,8.00)		0.538
Absolute MO count ($\times 10^9/L$)		0.52 (0.38,0.62)	0.42 (0.32,0.51)		0.037
MPV (fL)		10.2 (9.15,10.6)	10.8 (10.1,11.2)		0.008
PLT ($\times 10^9/L$)		220 (202,257)	206 (182,249)		0.326
Hb (g/L)		134 (124,151)	140 (131,154)		0.758
Inflammatory & hepatic function indices					
hs-CRP (mg/L)		1.75 (0.87,5.01)	0.50 (0.50,0.87)		0.000
ALB (g/L)		44.00 $\pm$ 3.71	44.58 $\pm$ 3.29		0.551

Indicators	CCS+NAFLD Group (n=33)	CCS (n=23)	Group	P Value
ALT (U/L)	16 (13,27)	21 (16,29)		0.275
AST (U/L)	16 (14,22)	19 (16,23)		0.137
BILT (μmol/L)	10.4 (8.39,14.55)	10.9 (8.5,15.4)		0.714
BILD (μmol/L)	4.61 (3.84,6.90)	4.80 (3.71,7.40)		0.940
UnBiL (μmol/L)	5.8 (4.04,7.8)	6.1 (4.40,8.11)		0.647
FIB-4	1.231 (0.907,1.590)	1.262 (0.910,1.570)		0.927
FLI	2.0638 (0.7897,5.6712)	1.8497 (1.0561,3.7271)		0.745
Thyroid function				
FT3	4.56±0.63	4.77±0.68		0.240
FT4	15.61±2.55	15.66±2.46		0.936
TSH	2.02 (1.18,2.65)	2.00 (1.20,2.87)		1.000
Glucose & lipid metabolism				
FBG (mmol/L)	5.86 (5.14,7.46)	5.55 (4.59,7.16)		0.244
TG (mmol/L)	1.56 (1.37,2.52)	1.37 (1.10,1.94)		0.127
TC (mmol/L)	4.60±1.05	4.62±1.08		0.951
LDL-C (mmol/L)	2.73±0.93	2.89±1.07		0.556
HDL-C (mmol/L)	1.14±0.24	1.21±0.25		0.268

Indicators	CCS+NAFLD Group (n=33)	CCS (n=23)	Group	P Value
Remnant cholesterol (mmol/L)	0.57 (0.39,0.82)	0.46 (0.30,0.60)		0.159
ApoA1 (g/L)	1.2106 (1.06,1.40)	1.23 (1.12,1.33)		0.726
ApoB (g/L)	0.90±0.21	0.93±0.05		0.681
Myocardial injury & cardiac function				
CK (U/L)	82 (61.5,96.5)	83 (65,114)		0.469
CK-MB (U/L)	13 (11.5,15)	14 (11,20)		0.384
cTnT (pg/mL)	7.89 (5.61,12.6)	6.20 (4.63,12.5)		0.516
NT-proBNP	73.7 (37.3,134.5)	46.6 (23.3,100)		0.247
LVEF (%)	60 (58.5,65)	65 (57,68)		0.245
Coronary status & core biomarker				
Coronary stenosis score (GS)	34.5 (23,53.75)	25 (22.5,37)		0.040
sTREM2 (pg/mL)	516.38 (312.17,699.15)	94.10 (31.95,757.46)		0.048

3.2 Monocyte Subset Distribution

The NAFLD+CCS group showed significantly altered monocyte subset proportions compared with the CCS group (Table 2, Figures 1-4):

- Lower classical monocytes (CM): 80.12%±4.38% vs. 83.93%±5.35% (P=0.005)
- Higher intermediate monocytes (IM): 4.83%±1.48% vs. 3.25%±1.53% (P=0.000)
- Higher non-classical monocytes (NCM): 8.53%±3.26% vs. 6.50%±3.17% (P=0.024)

Table 2 Monocyte Subset Distribution of the Two Groups (% , Mean±SD)

Groups	n	CM	IM	NCM
CCS+NAFLD	33	80.115±4.378	4.8291±1.480	8.5306±3.2631
CCS	23	83.926±5.347	3.2487±1.534	6.5000±3.1665
P Value	-	0.005	0.000	0.024

Note: CM=Classical Monocytes, IM=Intermediate Monocytes, NCM=Non-Classical Monocytes

Figure Legends

- **Figure 1** Representative flow cytometry plots of monocyte subsets in the NAFLD+CCS group. Peripheral blood cells were stained with FITC-conjugated anti-CD16, PE-conjugated anti-CD14, and APC-conjugated anti-CD45. Classical monocytes (CD14++CD16-), intermediate monocytes (CD14++CD16+), and non-classical monocytes (CD14+CD16++) were gated and analyzed.
- **Figure 2** Representative flow cytometry plots of monocyte subsets in the CCS group. Gating strategy and staining reagents were consistent with Figure 1.
- **Figure 3** Statistical analysis of monocyte subset proportions between the two groups. *P<0.05 indicates a statistically significant difference compared with the CCS group.*

3.3 Inflammatory Factor Levels

Serum IL-6 and IL-10 levels were significantly higher in the NAFLD+CCS group (Table 3, Figure 5):

- IL-6: 12.57 (8.46, 20.65) pg/mL vs. 0.85 (0.39, 2.79) pg/mL (*P<0.001*)
- IL-10: 1.82 (0.95, 3.60) pg/mL vs. 0.6 (0.43, 2.14) pg/mL (*P<0.001*)

Table 3 IL-6 and IL-10 Levels of the Two Groups (M(P25,P75), pg/mL)

Groups	n	IL-6	IL-10
NAFLD+CCS	33	12.57 (8.46, 20.65)	1.82 (0.95, 3.60)
CCS	23	0.85 (0.39, 2.79)	0.6 (0.43, 2.14)
P Value	-	< 0.001	< 0.001

Figure Legends

- **Figure 4** Boxplot analysis of IL-6 and IL-10 levels in the two groups. The box represents the interquartile range (P25-P75), the horizontal line inside the box is the median, and the whiskers represent the minimum and maximum values. *P<0.001 indicates a statistically significant difference compared with the CCS group.*
- **Figure 5** Boxplot analysis of serum sTREM2 concentration in the two groups. The box represents the interquartile range (P25-P75), the horizontal line inside the box is the median, and the whiskers represent the minimum and maximum values. *P=0.048*

indicates a statistically significant difference compared with the CCS group.

4. Discussion

This study demonstrates that NAFLD exacerbates systemic inflammation and coronary atherosclerosis in CCS patients, characterized by elevated hs-CRP, IL-6, IL-10, and GS scores. The abnormal distribution of monocyte subsets (increased pro-inflammatory IM and NCM, decreased CM) and elevated sTREM2 concentration suggest that TREM2-related pathways may be involved in this process.

Mechanistically, TREM2 is known to regulate macrophage polarization and inflammation via the PI3K/AKT/NF- κ B pathway. In mouse microglia, TREM2 inhibits LPS-induced pro-inflammatory mediators (IL-1 β , TNF- α) and enhances anti-inflammatory factors (IL-10, TGF- β) through PI3K/AKT signaling^[19]. Pinocembrin suppresses TNF- α and IL- β production by inhibiting PI3K/AKT phosphorylation and NF- κ B activation^[20], while TREM2 mediates macrophage polarization via PI3K/AKT to protect against *Pseudomonas aeruginosa* keratitis^[21]. NF- κ B is a key transcription factor in macrophage polarization, linking inflammatory signaling to metabolic regulation^[22, 23].

We speculate that NAFLD may upregulate sTREM2, which modulates macrophage polarization via the PI3K/AKT/NF- κ B pathway, exacerbating adipose tissue inflammation. This cascade promotes monocyte subset abnormalities and pro-inflammatory cytokine release, accelerating coronary atherosclerosis. However, this mechanism requires validation in basic research, including in vitro macrophage polarization assays and in vivo NAFLD-atherosclerosis models.

5. Conclusions

NAFLD exacerbates systemic inflammation and coronary atherosclerosis in CCS patients, accompanied by abnormal monocyte subset distribution and increased serum sTREM2 concentration. TREM2 may regulate macrophage polarization via the PI3K/AKT/NF- κ B pathway, mediating adipose tissue inflammation and participating in NAFLD-related atherosclerosis progression. These findings provide new insights into the pathological link between NAFLD and ASCVD, identifying TREM2 as a potential therapeutic target.

Consent for publication

Not applicable. This study does not involve human participants.

Availability of data and materials

The data of this study can be obtained from the corresponding author according to reasonable requirements.

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Not applicable.

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Figures

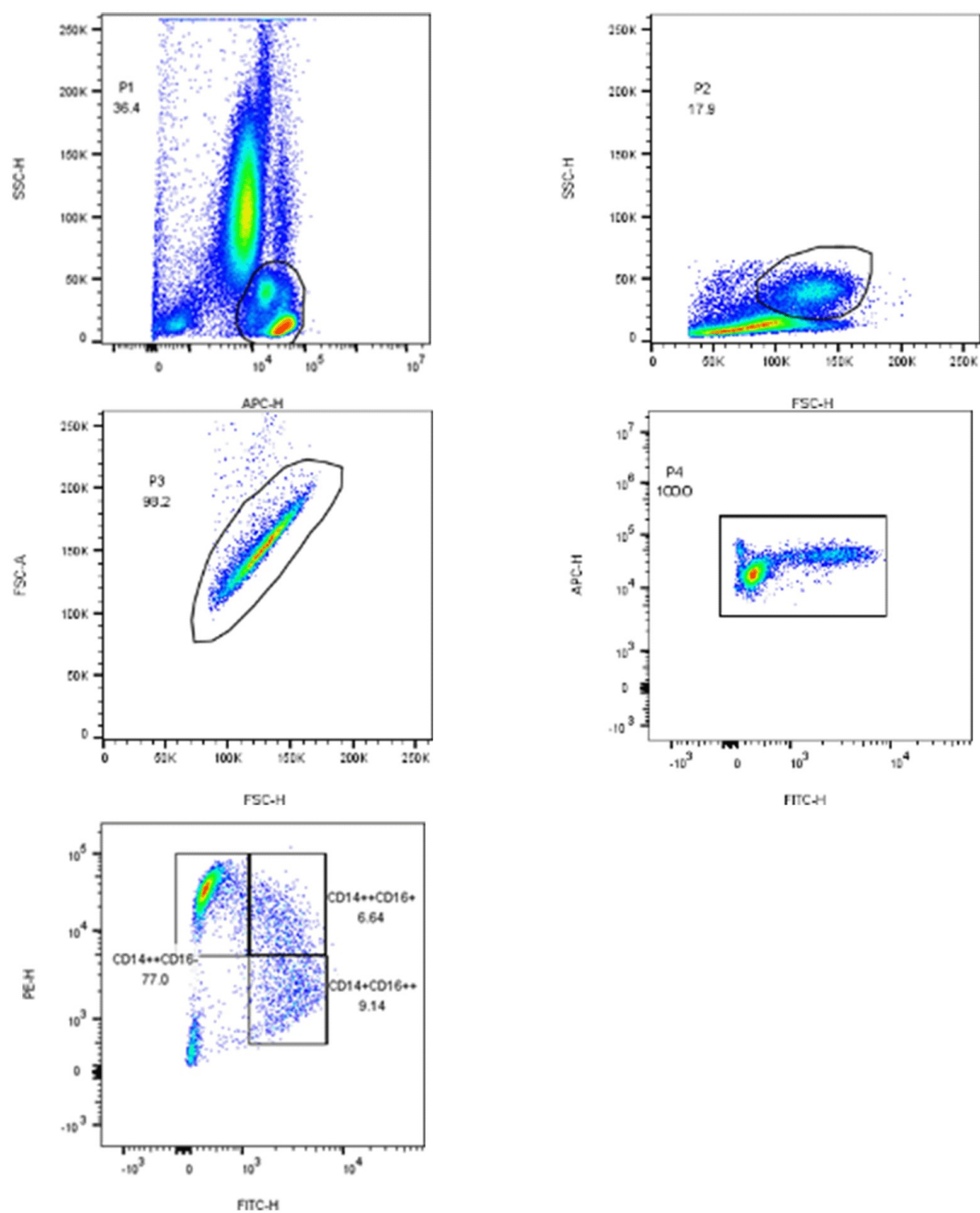


Figure 1

Representative flow cytometry plots of monocyte subsets in the NAFLD+CCS group. Peripheral blood cells were stained with FITC-conjugated anti-CD16, PE-conjugated anti-CD14, and APC-conjugated anti-CD45. Classical monocytes (CD14++CD16-), intermediate monocytes (CD14++CD16+), and non-classical monocytes (CD14+CD16++) were gated and analyzed.

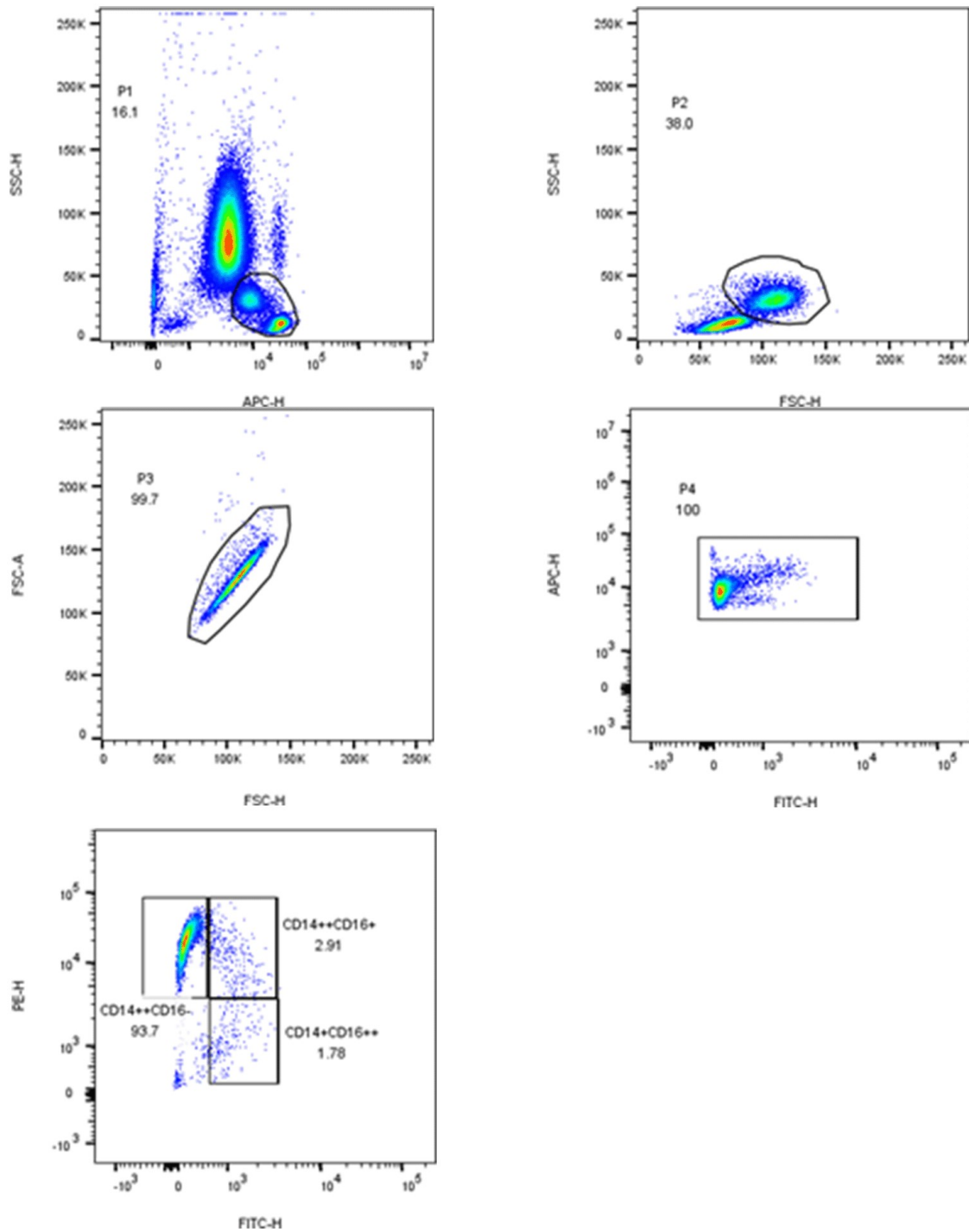


Figure 2

Representative flow cytometry plots of monocyte subsets in the CCS group. Gating strategy and staining reagents were consistent with Figure 1.

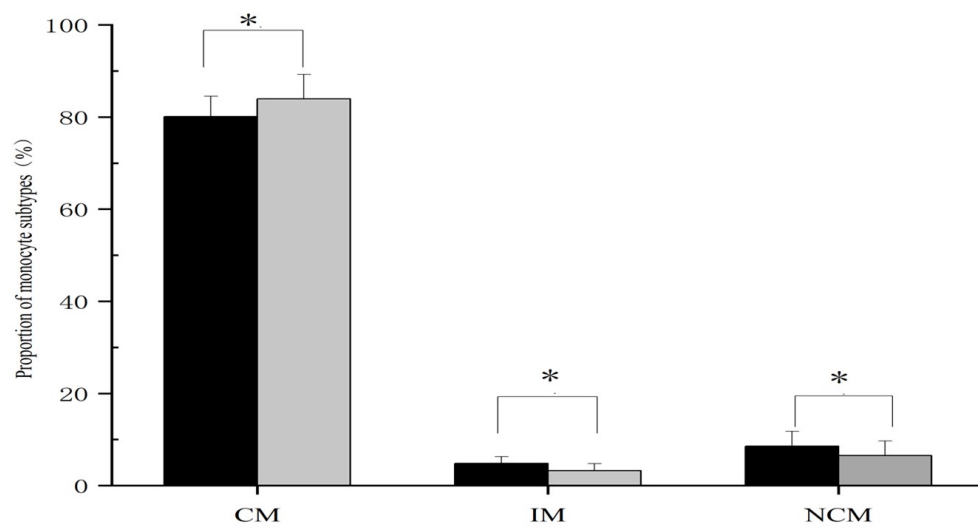


Figure 3

Statistical analysis of monocyte subset proportions between the two groups. $P < 0.05$ indicates a statistically significant difference compared with the CCS group.



Figure 4

Boxplot analysis of IL-6 and IL-10 levels in the two groups. The box represents the interquartile range (P25-P75), the horizontal line inside the box is the median, and the whiskers represent the minimum and maximum values. $P < 0.001$ indicates a statistically significant difference compared with the CCS group.

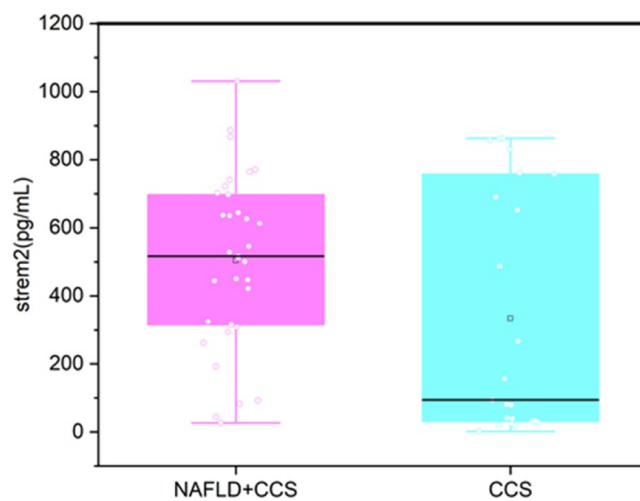


Figure 5

Boxplot analysis of serum sTREM2 concentration in the two groups. The box represents the interquartile range (P25-P75), the horizontal line inside the box is the median, and the whiskers represent the minimum and maximum values. $P=0.048$ indicates a statistically significant difference compared with the CCS group.