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Original Research

Sex differences in inflammatory biomarkers during long-term evolocumab therapy

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KEYWORDS
PCSK9 inhibitor;
Evolocumab;
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Sex-specific effects

BACKGROUND: Atherosclerotic cardiovascular disease remains a predominant cause of morbidity and mortality worldwide, driven by complex interactions between lipid metabolism and chronic inflammation. While evolocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, is established in lowering low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk, its long-term effects on inflammatory biomarkers—and potential sex-specific responses—are not fully understood.

OBJECTIVE: This study aimed to elucidate the impact of prolonged evolocumab therapy on inflammation markers in a routine clinical setting, focusing on sex-related differences.

METHODS: We analyzed data from 202 hypercholesterolemic patients (111 men, 91 women) treated with evolocumab for at least 36 months. Key inflammatory indices, including the monocyte-to-high-density lipoprotein cholesterol ratio (MHR) and platelet-to-monocyte ratio (PMR), were assessed longitudinally alongside traditional lipid parameters.

RESULTS: Significant sex-related differences emerged in inflammatory profiles: men exhibited consistently higher MHR levels at baseline ($P = .010$) and throughout follow-up ($P < .001$), whereas women showed persistently elevated PMR values ($P < .001$). Intriguingly, a strong inverse correlation was observed between lymphocyte count and lipoprotein(a) levels in women ($r_s = -0.885$, $P < .001$), a pattern absent in men, suggesting distinct immunometabolic mechanisms.

CONCLUSION: Our findings reveal pronounced biological sex differences in inflammatory responses to long-term evolocumab therapy, highlighting the need to incorporate sex-specific considerations in cardiovascular risk management and treatment monitoring. These novel insights pave the way for personalized therapeutic strategies and call for further investigation into the clinical significance of inflammation in lipid-lowering treatment outcomes.

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality worldwide, driven by the interplay of dysregulated lipid metabolism and chronic, low-grade inflammation.[1] Among the available lipid-lowering therapies, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), such as evolocumab, have emerged as highly effective agents capable of profoundly reducing low-density lipoprotein cholesterol (LDL-C) levels and, consequently, lowering cardiovascular risk.[2]

Emerging evidence highlights a bidirectional relationship between lipid metabolism and inflammation, in which inflammatory processes not only accelerate atherogenesis but may also modulate the response to lipid-lowering interventions.[3] While the LDL-C lowering efficacy of PCSK9i is well established, their effects on systemic inflammation remain less clear and are an area of active investigation.[4,5]

A recent meta-analysis reported that PCSK9i do not significantly reduce high-sensitivity C-reactive protein (hs-CRP) levels, regardless of inhibitor type, dosage, or degree of LDL-C reduction.[6] However, this finding should be interpreted cautiously, as most patients included in these studies were receiving background statin therapy, which independently lowers hs-CRP.[7] Consequently, the true impact of PCSK9 inhibition on inflammatory pathways that are not modulated by statins remains uncertain and warrants further exploration.[8]

Novel composite indices, such as the monocyte-to-high-density lipoprotein cholesterol ratio (MHR) and the platelet-to-monocyte ratio (PMR), have recently gained attention as promising markers of systemic inflammation and cardiovascular risk.[9,10] These ratios capture the complex interactions between immune and lipid pathways, providing a more integrated reflection of both ASCVD progression and therapeutic response.[9,10] Although prior research has examined the role of inflammatory biomarkers in ASCVD,[11,12] evidence regarding their modulation by PCSK9i—particularly in real-world clinical settings—remains scarce.

In addition, sex-based biological differences have emerged as key determinants of both lipid metabolism and inflammatory regulation, with growing recognition as men and women may experience different responses to lipid-lowering therapies.[13,14] Understanding these sex-specific variations is crucial to developing more precise, personalized strategies for cardiovascular risk reduction.[15]

Against this background, the present study aimed to evaluate the long-term effects of evolocumab on inflammatory biomarkers in routine clinical practice, with particular attention to sex-related differences. By longitudinally assessing changes in MHR and PMR, we sought to provide novel insights into the intersection of PCSK9 inhibition, inflammation, and cardiovascular risk, ultimately informing more individualized therapeutic approaches and improving the clinical utility of these emerging biomarkers.

Methods

Study design and participants

This study is part of an ongoing lipid clinic audit program conducted by the Department of Medical and Surgical Sciences (DIMEC) at the University of Bologna (Bologna, Italy), aimed at characterizing the clinical profile of patients with dyslipidemia and assessing the effectiveness of lipid-lowering therapies. The study protocol was approved by the relevant Ethics Committee (Approval Code: LLD-RP2018), and previous analyses from this program have already been published.[14,16,17]

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, and written informed consent was obtained from all participants.

For the present analysis, data were collected from all patients with hypercholesterolemia who received evolocumab at the Lipid Clinic of the IRCCS Azienda Ospedaliero-Universitaria di Bologna (Bologna, Italy) between December 2017 and November 2023.

Patients were eligible for treatment according to the recommendations of the European Society of Cardiology, the European Atherosclerosis Society,[18] and the criteria established by the Italian Regulatory Agency (AIFA).[17,19] Additional inclusion criteria were age $\geq$18 years and ongoing treatment with maximum tolerated oral lipid-lowering therapy for at least 6 months prior to evolocumab initiation, without planned dose modification. Patients receiving PCSK9i for $<$36 months or exhibiting noncompliance were excluded. No further exclusion criteria were applied beyond clinical eligibility and treatment stability.

During the study period, both evolocumab and alirocumab were available in our clinic; however, for this analysis, only patients treated with evolocumab were included. This choice ensured treatment homogeneity and minimized potential confounding from differences in dosing regimens, pharmacokinetics, or clinical management between the 2 PCSK9i. By focusing on a single agent, we specifically aimed to evaluate the long-term effects of evolocumab on inflammatory biomarkers, while acknowledging the potential for selection bias, which is addressed in the study limitations.

Patients were clinically evaluated at baseline, after 3 months and 6 months of treatment, and subsequently every 6 months thereafter (Fig. 1).

Assessments

Clinical data and physical assessments

Patients' clinical history was meticulously reviewed, with specific attention to the presence of ASCVD, smoking habits, and ongoing pharmacological treatments. In accordance with the classification system established by the American College of Cardiology and the American Heart Association, background-statin therapy was stratified into 3 categories based on intensity.[20] High-intensity

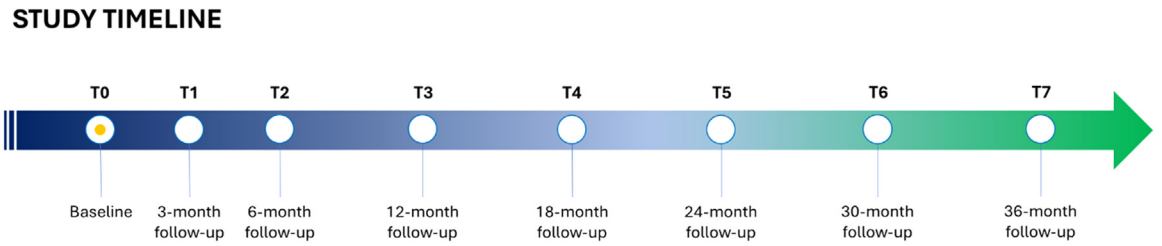

Figure 1. Study timeline.

statin therapy was defined as atorvastatin ≥40 mg or rosuvastatin ≥20 mg daily; moderate-intensity therapy included atorvastatin ≤20 mg, rosuvastatin ≤10 mg, simvastatin ≥20 mg, pravastatin ≥40 mg, lovastatin ≥40 mg, or fluvastatin 80 mg; low-intensity therapy was defined as simvastatin 10 mg, pravastatin ≤20 mg, lovastatin ≤20 mg, or fluvastatin ≤40 mg daily.

Genetic screening for pathogenic variants associated with familial hypercholesterolemia (FH) was performed in cases with clinical features suggestive of the disorder. Anthropometric measurements were collected using standardized procedures: height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, with patients standing upright, barefoot, wearing light clothing, and gazing straight ahead. Body mass index (BMI) was then calculated as weight in kilograms divided by height in meters squared (kg/m²).[21]

Laboratory analyses

Laboratory analyses were conducted to assess a comprehensive panel of biochemical and hematological parameters. Venous blood samples were collected from each participant after an overnight fast. Biochemical measurements included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), lipoprotein(a) [Lp(a)], apolipoprotein B (Apo-B), apolipoprotein A1 (Apo-A1), fasting plasma glucose, serum uric acid, creatinine (Cr), total and fractionated bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), creatine phosphokinase (CPK), and thyroid-stimulating hormone (TSH). Lp(a) concentrations were determined using an immunoturbidimetric assay, while LDL-C was calculated using the Friedewald equation.[22] Renal function was estimated via the glomerular filtration rate (eGFR), applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[23]

Complete blood count (CBC) parameters were also evaluated, including white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), as well as differential leukocyte counts (lymphocytes [LY], monocytes [MO], neutrophils [NE], eosinophils [EO], and basophils [BA]).

Among these, 2 composite indices were derived and used as markers of systemic inflammation: the MHR and the PMR, both of which have been increasingly recognized as surrogate markers of vascular inflammation and predictors of cardiovascular risk.

Statistical analysis

Data normality was assessed by histograms, q-q plots, and Shapiro–Wilk's test. Continuous variables were summarized using medians and IQRs. To identify the main and interaction effects of sex and time points, the nonparametric analysis of longitudinal data in factorial experiments (nparLD; F1-LD-F1 design) was applied for lymphocyte, MHR, and PMR variables.[24] To control for potential confounders, models were adjusted for baseline values of Lp(a), LDL-C, monocyte and PLT, age, and statin use. Experimental results were summarized with Wald statistic, degrees of freedom, and *P*-values. The Mann–Whitney U test was applied for sex comparisons separately at each time point. The Friedman test was used to compare the change over time. Using the time-dependent changes of each variable, area under the curve (AUC) values were also calculated and compared between sexes using the Mann–Whitney U test. Spearman correlation coefficients were calculated using median values of lymphocyte count and lipid parameters at the corresponding time points to examine the relationship between changes over time. A *P*-value <5% was considered as statistically significant. All analyses were conducted using base and nparLD libraries of R 4.3.1 (www.r-project.org) software.[25]

Finally, a posthoc power analysis was conducted to evaluate whether the sample size was sufficient to detect sex-related differences in the primary inflammatory biomarkers (MHR and PMR) at each visit. Given the nonparametric distribution of the data, Cliff's δ was calculated as the effect size, which was subsequently converted to Cohen's d for the power calculations. These analyses were conducted using the effsize package in R and the G*Power 3.1 software.[26]

Results

Baseline characteristics

A total of 202 patients treated with evolocumab for at least 36 months as of November 2023 were included in the analysis (men: $n = 111$; women: $n = 91$). Baseline characteristics are detailed in Table 1.

Table 1. Baseline characteristics of the patients enrolled in the study.

Characteristics	All patients ($n = 202$)	Men ($n = 111$)	Women ($n = 91$)	*P*-value
Age (years)	65.5 (56.25-72)	64 (55-70)	68 (60-73)	**.008**
History of ASCVD (*n*; %)	113 (60.8)	54 (53.5)	59 (69.4)	**.027**
Type 2 diabetes mellitus (*n*; %)	29 (14.7)	20 (18.3)	9 (10.2)	.110
Background lipid-lowering therapy				
Statin				.484
High-intensity dosage (*n*; %)	48 (57.1)	30 (60)	18 (52.9)	
Moderate-intensity dosage (*n*; %)	35 (41.7)	20 (40)	15 (44.1)	
Low-intensity dosage (*n*; %)	1 (1.2)	0 (0)	1 (2.9)	
Ezetimibe (*n*; %)	136 (75.1)	83 (83)	53 (65.4)	**.007**
BMI (kg/m^2)	26.9 ± 4.09	27.44 ± 4.03	26.26 ± 4.09	**.045**
Laboratory analyses				
TC (mg/dL)	214.5 (190-253.75)	204 (181-235)	226 (198.25-269.5)	**<.001**
HDL-C (mg/dL)	54.67 ± 13.07	49.78 ± 10.89	60.42 ± 13.11	**<.001**
TG (mg/dL)	132 (92.5-174.5)	131.5 (92.25-176.25)	134.00 (88.75-173.75)	.890
LDL-C (mg/dL)	131.6 (110.95-168.6)	126.2 (103.1-156.3)	141.1 (115.4-183.05)	**.010**
Lp(a) (mg/dL)	40.8 (11.9-106.75)	44.8 (11.43-113.7)	23.7 (10.7-87.05)	.358
eGFR (mL/min)	82 (68-93)	88 (70-94)	78 (66.5-88.5)	**.049**
AST (U/L)	25 (20-30)	27 (22-34)	22 (19-28.25)	**<.001**
ALT (U/L)	23 (16-32.5)	28 (20-38.5)	19 (14-27)	**<.001**
γ-GT (U/L)	24 (17-33)	28 (21-42)	19 (15-25)	**<.001**
CPK (U/L)	140.5 (85-241)	188.5 (107.25-271)	102 (68.5-148)	**<.001**
Blood cell parameters				
WBC (10^9/L)	6.32 (5.47-7.54)	6.50 (5.53-7.71)	6.23 (5.22-7.3)	.356
RBC (10^{12}/L)	4.8 ± 0.51	4.96 ± 0.51	4.6 ± 0.45	**<.001**
HGB (g/dL)	14.3 (13.5-15)	14.8 (14.1-15.55)	13.55 (12.7-14.3)	**<.001**
HCT (%)	42.5 ±4.01	44.16 ± 3.54	40.49 ± 3.65	**<.001**
MCV (fL)	88.85 ± 5.7	89.3 ± 5.05	88.31 ± 6.44	.284
MCH (pg)	30 (28.5-31)	30.2 (28.5-31.5)	29.8 (28.6-30.55)	.074
MCHC (g/dL)	33.38 ± 1.23	33.62 ± 1.27	33.07 ± 1.1	**.005**
RDW (%)	13.2 (12.5-14)	13.2 (12.6-14.1)	13.2 (12.4-13.8)	.859
PLT (10^9/L)	247 (214-285)	233 (199-260)	268 (235-310)	**<.001**
MPV (fL)	10.91 ± 0.94	10.96 ± 0.98	10.82 ± 0.9	.389
LY (10^9/L)	2.59 ± 3.26	2.18 ± 0.76	3.1 ± 4.76	.118
MO (10^9/L)	0.45 (0.37-0.54)	0.47 (0.39-0.55)	0.42 (0.33-0.56)	.105
NE (10^9/L)	3.54 (2.80-4.25)	3.64 (2.93-4.41)	3.31 (2.71-3.96)	.101
EO (10^9/L)	0.18 (0.11-0.27)	0.2 (0.13-0.3)	0.16 (0.1-0.22)	**.021**
BA (10^9/L)	0.05 (0.03-0.06)	0.05 (0.03-0.06)	0.04 (0.03-0.06)	.376
Inflammatory profile				
MHR	0.33 (0.25-0.44)	0.36 (0.27-0.44)	0.28 (0.19-0.4)	**.004**
PMR	541.67 (445.6-695.26)	622.41 (494.72-820)	484.05 (433.38-633.45)	**<.001**

Abbreviations: ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate transaminase; BA, basophil count; BMI, body mass index; CPK, creatinine phosphokinase; eGFR, estimated glomerular filtration rate; EO, eosinophil count; γ-GT, gamma glutamyl transferase; HCT, hematocrit; HDL-C, high-density lipoprotein cholesterol; HGB, hemoglobin; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LY, lymphocyte count; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MHR, monocyte-to-HDL cholesterol ratio; MO, monocyte count; MPV, mean platelet volume; N, number of patients; NE, neutrophil count; PLT, platelet count; PMR, platelet-to-monocyte ratio; RBC, red blood cell count; RDW, red blood cell distribution width; TC, total cholesterol; TG, triglycerides; WBC, white blood cell count.

Values are expressed as mean ± SD, median (1st/3rd quartiles), and *n* (%).

Bold values indicate statistically significant *P*-values.

Women were older than men (mean age: 68 vs 64 years, $P < .05$), and had a significantly higher prevalence of ASCVD. In contrast, men more frequently used ezetimibe and had a higher BMI compared to women ($P < .05$).

Regarding laboratory parameters, women showed higher levels of TC, HDL-C, and LDL-C, whereas men exhibited significantly higher values of eGFR, AST, ALT, and γ-GT ($P < .05$). In the CBC, men had higher values of RBC, HGB,

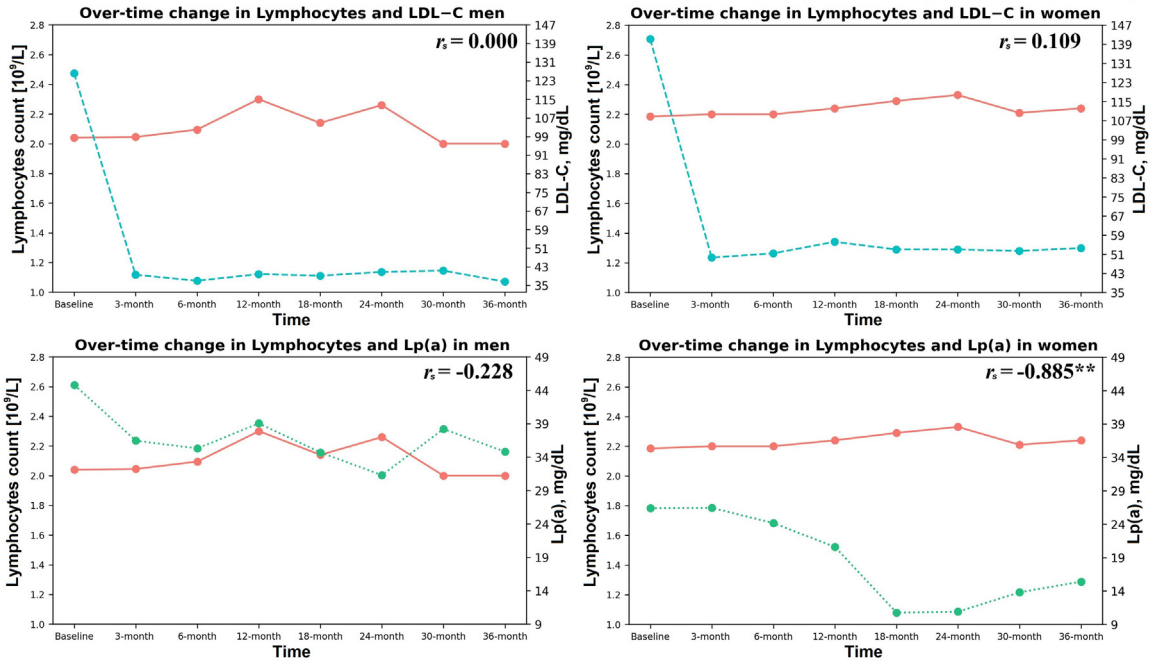

Figure 2. Longitudinal trends of lymphocyte related LDL-C and Lp(a) in plasma concentrations. Abbreviations: LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).
Dashed blue line: LDL-C; Dotted green line: Lp(a); Solid red line: Lymphocyte; r_s: Spearman correlation coefficient; *: $P < .05$; **: $P < .001$. Each data point represents the median value at the corresponding time point. The correlation coefficients (r_s) were calculated using the median values of lymphocyte count and lipid parameters across all time points to assess overall temporal association.

HCT, MCHC, and EO, while PLT were significantly higher in women ($P < .05$).

With respect to inflammatory markers, baseline levels of MHR and PMR were significantly higher in men and women, respectively ($P < .05$). When baseline characteristics were compared according to ezetimibe use, no significant differences were observed in most lipid, hematologic, or inflammatory parameters ($P > .05$). However, patients not receiving ezetimibe showed slightly higher TC values ($P = .042$) and a marginal trend toward higher LDL-C levels ($P = .051$), as reported in Supplementary Table 1. In the overall cohort, γ-GT, CPK, and MCHC also showed statistical differences, but none of these findings — including TC — were confirmed in sex-stratified analyses. Specifically, in men none of the parameters differed significantly, whereas in women only CPK levels were slightly higher among those receiving ezetimibe (Supplementary Table 1).

Longitudinal trends in LY and lipid parameters

Longitudinal changes in lymphocyte counts and corresponding LDL-C and Lp(a) plasma concentrations are presented in Figure 2.

In men, LDL-C levels declined markedly within the first 3 months and then stabilized. Lymphocyte counts fluctuated over time without a clear pattern. No correlation was observed between lymphocyte count and LDL-C ($r_s = 0.000$, $P = 1.000$), nor between lymphocyte count and Lp(a) ($r_s = -.228$, $P = .588$).

In women, LDL-C followed a similar early decline. Lymphocyte counts remained relatively stable. The correlation between lymphocyte count and LDL-C was not significant ($r_s = 0.109$, $P = .797$), whereas a strong and statistically significant inverse correlation was observed between lymphocyte count and Lp(a) ($r_s = –0.885$, $P = .007$).

Trends in MHR and PMR over time

Figure 3 illustrates longitudinal trends in MHR relative to LDL-C and Lp(a), stratified by sex.

In men, MHR fluctuated without a clear trend. Correlations with LDL-C ($r_s = –.024$, $P = .955$) and Lp(a) ($r_s = –0.333$, $P = .420$) were not statistically significant. In women, MHR also showed moderate fluctuations. The correlations with LDL-C ($r_s = –0.180$, $P = .670$) and Lp(a) ($r_s = –0.619$, $P = .102$) were also likewise negligible. Notably, Lp(a) levels declined until 18 months, followed by a slight rebound, while MHR peaked between months 12 and 24, declining thereafter.

Figure 4 shows the trends in PMR over time.

In men, PMR remained relatively stable, showing no meaningful correlation with LDL-C ($r_s = 0.000$, $P = 1.000$) or Lp(a) ($r_s = 0.357$, $P = .385$). In contrast, women displayed persistently higher PMR values with greater variability. The correlation with LDL-C was not statistically signficant ($r_s = –0.192$, $P = .649$), while a trend toward a moderate positive association with Lp(a) was observed ($r_s = 0.643$, $P = .086$).

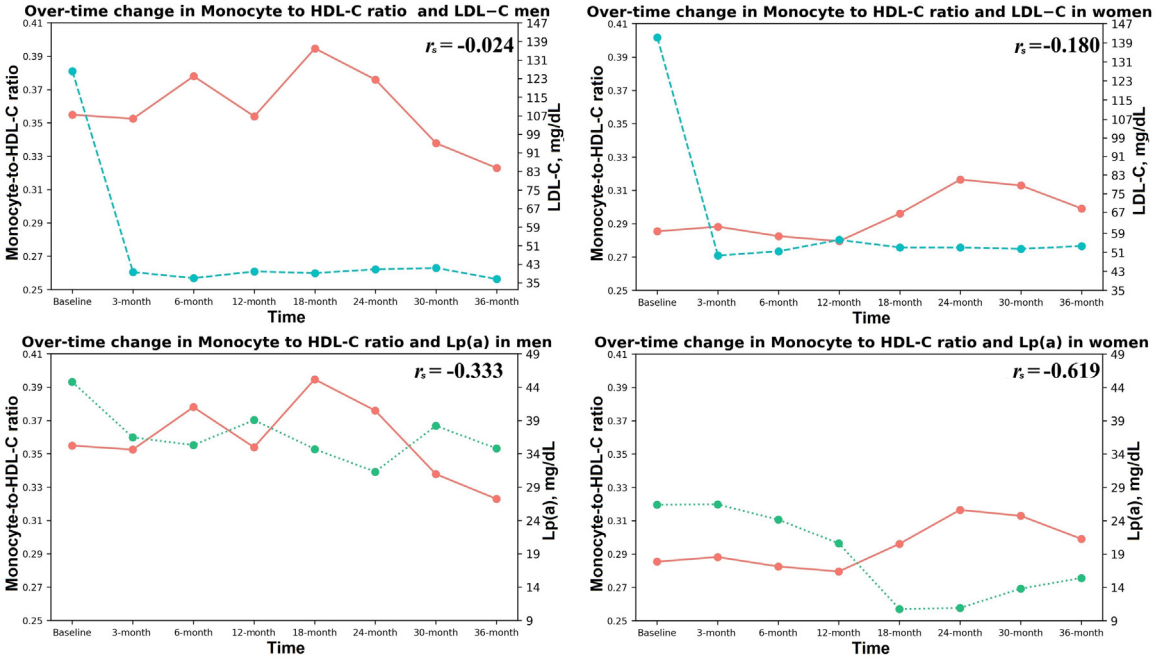

Figure 3. Longitudinal trends of monocyte-to-HDL-C ratio related LDL-C and Lp(a) in plasma concentrations.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MHR, monocyte-to-HDL-C ratio. Dashed blue line: LDL-C; Dotted green line: Lp(a); Solid red line: MHR; r_s: Spearman correlation coefficient; *: $P < .05$; **: $P < .001$. Each data point represents the median value at the corresponding time point. The correlation coefficients (r_s) were calculated using the median values of MHR and lipid parameters across all time points to assess overall temporal association.

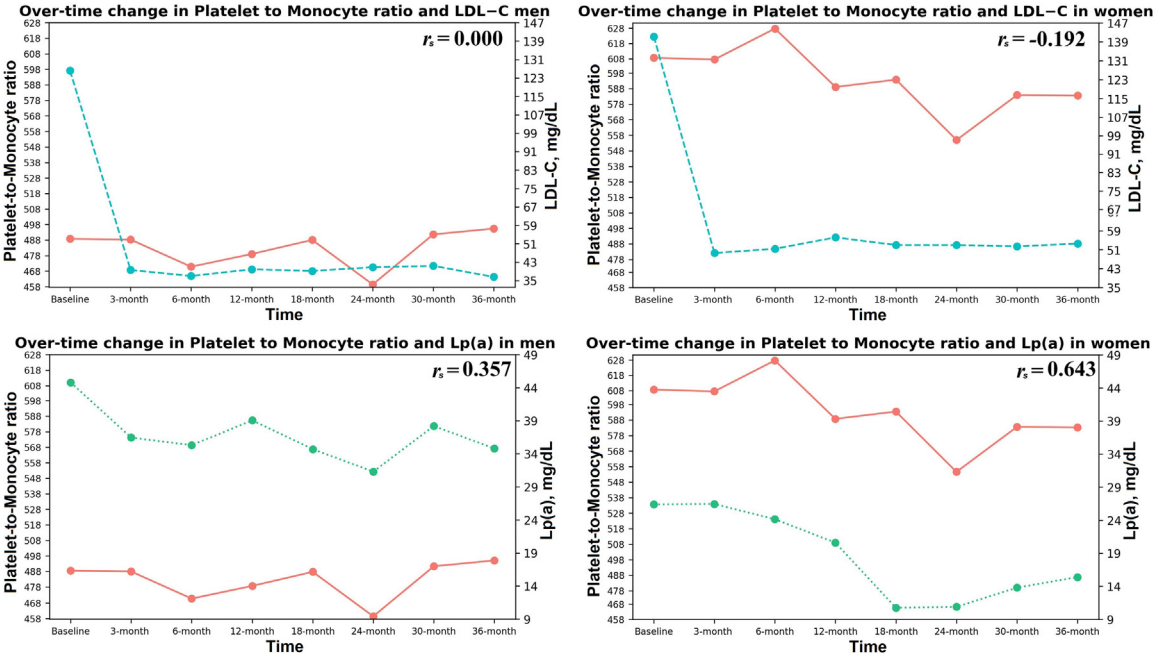

Figure 4. Longitudinal trends of platelet-to-monocyte ratio related LDL-C and Lp(a) in plasma concentrations.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PMR, platelet-to-monocyte ratio.
Dashed blue line: LDL-C; Dotted green line: Lp(a); Solid red line: PMR; r_s: Spearman correlation coefficient; *: $P < .05$; **: $P < .001$. Each data point represents the median value at the corresponding time point. The correlation coefficients (r_s) were calculated using the median values of PMR and lipid parameters across all time points to assess overall temporal association.

Table 2. Nonparametric analysis of longitudinal data in factorial experiments for changes in plasma concentrations in lymphocytes, MHR, and PMR.

Source of variation	df	Wald	*P*-value	*adj. P*-value
Lymphocytes count (10^9/L)				
Sex	1	1.463	.198	**.002**
Time	7	12.012	.095	.196
Sex x Time	7	3.071	.872	**.026**
Monocyte-to-HDL-C ratio				
Sex	1	16.590	**<.001**	**.007**
Time	7	9.787	.201	.222
Sex x Time	7	7.398	.388	**.022**
Platelet-to-monocyte ratio				
Sex	1	26.212	**<.001**	**.001**
Time	7	5.656	.580	.976
Sex x Time	7	2.407	.933	.995

Abbreviations: df, degrees of freedom; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MHR, monocyte-to-HDL-C ratio; PMR, platelet-to-monocyte ratio.
adj. *P*-value: adjusted for baseline values of Lp(a), LDL-C, monocytes, platelets, age, and statin treatment.

Modeling the ınteraction between sex and time on ınflammation

Given the non-normal distribution of variables (assessed via histograms, Q–Q plots, and the Shapiro–Wilk test; see Supplementary Figs 1 and 2), we applied a nonparametric analysis of longitudinal data in factorial experiments to evaluate lymphocyte count, MHR, and PMR across time (Table 2).

Lymphocyte counts did not differ significantly by sex ($P = .198$), time ($P = .095$), or their interaction ($P = .872$). However, after adjusting for baseline Lp(a), LDL-C, monocyte and PLT, age, and statin therapy, significant effects emerged for sex (adjusted $P = .002$) and for the interaction term (adjusted $P = .026$), suggesting a sex-related and time-dependent modulation.

MHR values were significantly higher in men both before ($P < .001$) and after adjustment (adjusted $P = .07$). No significant time effect was observed (adjusted $P = .222$), but the sex–time interaction remained significant (adjusted $P = .022$).

PMR values were consistently higher in women across all time points ($P < .001$; adjusted $P = .001$). Neither time (adjusted $P = .976$) nor sex–time interaction (adjusted $P = .995$) was significant.

Timepoint comparisons and AUC analyses

Lymphocyte counts did not differ significantly between men and women at any specific time point, and no differences were observed in the AUC values ($P = 1.000$; Table 3).

MHR was significantly higher in men at baseline ($P = .010$) and remained significantly elevated at most follow-up points (T1-T4: $P < .001$; T5: $P = .004$; T6: $P = .042$). At T7, the difference approached but did not reach statistical significance ($P = .053$). AUC analysis confirmed significantly higher MHR in men ($P = .043$).

PMR was consistently and significantly higher in women at all time points ($P < .001$), including baseline. AUC for PMR was also significantly greater in women ($P = .002$), indicating a robust sex-related influence. However, within-group comparisons did not show significant temporal trends for lymphocyte counts, MHR, or PMR.

Posthoc power analyses

Posthoc power analyses at $\alpha = 0.05$ were subsequently performed to evaluate sex differences in MHR and PMR at each visit, and the results are presented in Supplementary Table 2. For MHR, Cliff's δ values ranged from 0.22 to 0.43, indicating small to medium effects. Cohen's d values ranged from 0.31 to 0.71, with the highest effects observed at visits T2-T3. For PMR, Cliff's δ values ranged between 0.33 and 0.42, indicating medium and consistent effects. Cohen's d values were observed to range between 0.36 and 0.44, with the largest effects noted at visits T2–T6. Overall, posthoc power values for MHR and PMR tended to be moderate to high, with corresponding effect sizes indicating medium-level differences between sexes.

Discussion

This study aimed to investigate the long-term effects of evolocumab on inflammatory biomarkers in a routine clinical setting, with particular focus on sex-related differences. Our findings show that while overall inflammatory markers—including lymphocyte counts, MHR, and PMR—remained stable over time, distinct and consistent sex-specific differences in MHR and PMR were observed. These results suggest that men and women may exhibit different inflammatory responses to evolocumab, potentially reflecting underlying biological differences in immune regulation and lipid metabolism.[27]

Table 3. Between-sex changes in lymphocyte concentrations, MHR, and PMR over time.

Time points	All patients ($n = 202$)	Men ($n = 111$)	Women ($n = 91$)	*P*-value[b]
Lymphocytes count (10^9/L)				
Baseline (T0)	2.16 (1.78-2.72)	2.08 (1.78-2.45)	2.19 (1.86-2.82)	.188
3 mo (T1)	2.12 (1.75-2.58)	2.05 (1.68-2.523)	2.19 (1.9-2.63)	.190
6 mo (T2)	2.19 (1.79-2.76)	2.1 (1.79-2.83)	2.2 (1.84-2.72)	.647
12 mo (T3)	2.27 (1.88-2.8)	2.32 (1.812-2.82)	2.24 (1.94-2.66)	.982
18 mo (T4)	2.21 (1.87-2.73)	2.16 (1.79-2.68)	2.28 (1.97-2.77)	.273
24 mo (T5)	2.26 (1.84-2.66)	2.26 (1.68-2.67)	2.31 (2-2.64)	.262
30 mo (T6)	2.07 (1.67-2.72)	2.03 (1.58-2.72)	2.22 (1.83-2.69)	.315
36 mo (T7)	2.22 (1.84-2.72)	2.07 (1.74-2.69)	2.27 (1.95-2.72)	.208
AUC	86.76 (70.64-98.37)	87.93 (69.67-105)	85.28 (74.48-96.07)	1.000
***P*-value[a]**	.837	.184	.985	
Monocyte-to-HDL-C ratio				
Baseline (T0)	0.32 (0.24-0.43)	0.36 (0.26-0.44)	0.28 (0.19-0.39)	**.010**
3 mo (T1)	0.32 (0.26-0.42)	0.36 (0.28-0.45)	0.29 (0.23-0.35)	**<.001**
6 mo (T2)	0.32 (0.26-0.48)	0.38 (0.28-0.53)	0.28 (0.23-0.37)	**<.001**
12 mo (T3)	0.33 (0.26-0.46)	0.36 (0.31-0.51)	0.28 (0.22-0.37)	**<.001**
18 mo (T4)	0.34 (0.24-0.45)	0.39 (0.29-0.48)	0.29 (0.21-0.39)	**<.001**
24 mo (T5)	0.35 (0.25-0.46)	0.38 (0.27-0.5)	0.32 (0.21-0.38)	**.004**
30 mo (T6)	0.33 (0.26-0.43)	0.34 (0.29-0.44)	0.31 (0.2-0.4)	**.042**
36 mo (T7)	0.31 (0.23-0.42)	0.33 (0.26-0.46)	0.3 (0.21-0.37)	.053
AUC	13.16 (10.53-17.47)	16.95 (11.59-18.04)	11.47 (10.29-13.72)	**.043**
***P*-value[a]**	.131	.073	.492	
Platelet-to-monocyte ratio				
Baseline (T0)	541.67 (446.51-687.5)	484.1 (436.1-625.7)	622.41 (498.28-816.67)	**<.001**
3 mo (T1)	531.31 (426.71-683.66)	478.2 (385.5-604.9)	611.25 (507.76-759.37)	**<.001**
6 mo (T2)	513.56 (430.43-690.18)	468.63 (386-579.28)	645.83 (493.75-739.17)	**<.001**
12 mo (T3)	532.44 (437.17-657.3)	479 (402-584.5)	589.47 (504.88-740.54)	**<.001**
18 mo (T4)	535.08 (432.14-657.51)	488.1 (400-595.6)	595.24 (474.36-744.44)	**<.001**
24 mo (T5)	513.81 (424.45-663.35)	469.4 (399.6-585.1)	601.19 (475.41-736.88)	**<.001**
30 mo (T6)	518.71 (433.59-645.36)	490.8 (385.6-564.2)	590.02 (491.67-700.05)	**<.001**
36 mo (T7)	522.12 (421.94-689.02)	488.7 (390.9-582.4)	583.89 (475.84-737.01)	**.003**
AUC	18,069 (15,954-22,183)	16,713 (15,546-18,633)	20,806 (18,670-28,065)	**.002**
***P*-value[a]**	.573	.415	.655	

Abbreviations: AUC, area under the curve; HDL-C, high-density lipoprotein cholesterol; MHR, monocyte-to-HDL-C ratio; n, number of patients; PMR, platelet-to-monocyte ratio.
Values are expressed as median (1st/3rd quartiles).
[a]Within-group comparison.
[b]Between-group comparisons.

In addition to these inflammatory disparities, baseline clinical characteristics differed markedly between the sexes in ways that could influence inflammatory status. Women presented with significantly higher baseline levels of TC, LDL-C, and HDL-C, in parallel with comparable statin use but lower ezetimibe utilization. In this regard, minor baseline differences in TC and LDL-C levels were also observed between patients receiving and those not receiving ezetimibe. However, these variations were modest, not confirmed in sex-stratified analyses, and are unlikely to have influenced the longitudinal changes in inflammatory biomarkers during evolocumab therapy. Women also had a significantly lower BMI than men—a factor associated with reduced systemic inflammation and decreased monocytic and platelet activation.[28] Together, these differences suggest that both lipid burden and body composition may contribute to the sex-specific inflammatory profiles observed at treatment initiation.

The combination of elevated LDL-C and reduced ezetimibe use among women likely reflects a lower overall intensity of lipid-lowering therapy.[29] This aligns with previous evidence showing that women with ASCVD are less frequently treated with combination regimens or therapy escalation compared with men.[30] Such disparities may arise from under-recognition of cardiovascular risk in women and sex-related differences in care delivery.[31] The significantly higher prevalence of ASCVD in our female cohort further suggests that PCSK9i therapy was often initiated at a more advanced stage of disease in women.

Given the mean age of 68 years among women in our cohort, these lipid differences are unlikely to be solely attributable to menopausal status. Instead, they likely reflect

a combination of factors, including clinical inertia, underrecognition of risk, and inherent biological variations in lipid metabolism. This pattern highlights the urgent need for timely and aggressive lipid-lowering strategies in high-risk women and illustrates how sex-specific disease trajectories can influence treatment outcomes.[32]

A key finding was the persistently elevated baseline MHR in men compared with women – a difference that remained stable throughout follow-up. This is consistent with prior studies documenting sex-related variations in inflammatory biomarkers, particularly in cardiovascular disease and during lipid-lowering treatment.[33] Elevated MHR in men may indicate a more pronounced proinflammatory milieu, which could affect therapeutic responsiveness. Considering the established interplay between inflammation, lipid metabolism, and ASCVD pathogenesis,[34] such differences may have important implications for personalized risk assessment and treatment strategies.[35] Conversely, PMR values were consistently higher in women, suggesting distinct inflammatory or thrombotic phenotype during evolocumab therapy. This supports the concept that sex-related differences in immune function and platelet activity contribute to different cardiovascular risk profiles and treatment responses.[27]

Although lymphocyte counts did not differ between the sexes or change significantly over time, a sex-specific association with lipid biomarkers was identified. In women, lymphocyte counts were strongly and inversely correlated with Lp(a) levels, suggesting that reductions in Lp(a) may be linked to immunomodulatory effects of evolocumab, particularly in female patients.[36] However, since Lp(a) levels were similar between sexes, we no longer consider this marker to be the primary explanation for the observed sex differences in inflammatory responses. The absence of this association in men points to distinct mechanisms of lipid-immune interactions, warranting further research to determine their implications for long-term cardiovascular outcomes.

The lack of significant temporal changes in inflammatory biomarkers, together with the clear sex differences we observed, raises questions about their utility as dynamic predictors of cardiovascular events, especially given the clear sex differences we observed. While evolocumab may not induce major systemic inflammatory shifts, the persistent sex-specific disparities in MHR and PMR highlight their potential as markers of underlying biological processes influencing treatment efficacy and further support the consideration of sex in the evaluation of lipid-lowering therapies and their effects on inflammation.[37]

The role of sex hormones must be interpreted cautiously, particularly in postmenopausal women, in whom the sharp decline in estrogen levels is accompanied by lifelong hormonal exposure and residual receptor activity that may continue to influence immune function and lipid metabolism.[38] Supporting this, the Brisighella Heart Study reported higher circulating PCSK9 levels in postmenopausal women compared with both premenopausal women and men.[39] Similarly, a large multicenter European cohort of 3673 individuals (47.9% men, 52.1% women) aged 54–79 years—an age range in which nearly all women are postmenopausal—confirmed that PCSK9 levels were significantly higher in women.[40] Moreover, this study revealed sex-specific differences in PCSK9 determinants, such as lipid-lowering therapy, latitude, and metabolic factors.

Collectively, these findings identify postmenopause as a critical biological context in which PCSK9 regulation diverges between the sexes, potentially explaining differences in PCSK9i efficacy and vascular effects. This highlights the need to consider hormonal changes and residual immunometabolic differences when tailoring treatment strategies in this population. In this context, the persistent sex differences in MHR and PMR observed in our study likely reflect complex immunometabolic interactions influenced by both hormonal and nonhormonal factors, including BMI and treatment intensity. Estrogens are known to reduce monocyte activation, enhance endothelial nitric oxide bioavailability, and favorably modulate HDL metabolism, which may underlie the lower MHR in women.[41] Conversely, testosterone has been associated with a proinflammatory immune profile, characterized by increased monocyte activation and endothelial dysfunction, potentially explaining the higher MHR in men.[42] In parallel, platelet reactivity, generally higher in women, especially under proinflammatory or prothrombotic conditions, may account for the elevated PMR in female patients.[43] These mechanistic insights underscore the central role of sex hormones and immune regulation in shaping inflammatory responses to lipid-lowering therapies.[44]

Notably, the persistence of these differences even after adjusting for baseline lipid and inflammatory factors suggests the involvement of intrinsic biological determinants beyond measurable baseline imbalances. Lower BMI in women and differences in treatment exposure may also contribute. These observations are consistent with growing evidence that estrogens exert systemic anti-inflammatory effects by modulating immune cell activity, monocyte recruitment, and lipid metabolism, whereas men typically exhibit a more proinflammatory phenotype, consistent with higher MHR values.[13] Women's enhanced platelet reactivity and unique platelet–monocyte interactions may further contribute to elevated PMR.[45] Together, these findings reflect sex-specific immunometabolic networks influencing both inflammatory dynamics and therapeutic responses, reinforcing the need to integrate sex-based considerations into cardiovascular risk stratification and personalized treatment.[46]

Our findings further characterize sex differences in response to lipid-lowering therapy, and underscore the importance of incorporating sex-specific analyses into clinical evaluation and trial design. The higher baseline inflammatory markers observed in men support the use of individualized treatment approaches, particularly in patients with elevated inflammatory burden,[47,48] whereas the persistently higher PMR in women suggests that monitoring this parameter could provide valuable insights into treatment response and residual risk. Even though temporal changes were absent, the consistent sex differences in these ratios underscore

the importance of incorporating sex-specific analyses into clinical evaluation and trial design. Future research should explore whether sex-tailored therapeutic strategies could optimize PCSK9i efficacy.

Although MHR and PMR are not yet standard clinical biomarkers, their robust, reproducible sex-specific differences suggest they merit further study as adjunctive tools for assessing inflammatory burden and guiding therapeutic decisions. Large-scale, prospective studies are needed to define sex-specific reference intervals, determine whether these markers predict long-term cardiovascular outcomes, and clarify their role in identifying residual inflammatory risk in PCSK9i-treated patients.

This study has several limitations. Its relatively small sample size and single-center design may limit generalizability, underscoring the need for larger, sex-balanced, multicenter cohorts to validate these findings. In addition, the restricted panel of inflammatory biomarkers, focused on easily obtainable hematologic ratios, precluded comprehensive characterization of inflammatory pathways, as key mediators such as hs-CRP, interleukin-6, and tumor necrosis factor-α were not measured. Future studies incorporating a broader range of inflammatory biomarkers will be essential to fully define the anti-inflammatory effects of PCSK9 inhibition. Finally, the observational nature of our study limits causal inference, and randomized controlled trials are needed to confirm these associations. Moreover, only patients treated with evolocumab were included, even though alirocumab was also used in our practice. While this ensured a homogeneous treatment group, it may limit generalizability to the broader PCSK9i class.

In conclusion, this study provides novel evidence of sex-specific inflammatory responses to long-term evolocumab therapy, highlighting persistent differences in MHR and PMR between men and women. These results underscore the importance of integrating sex as a biological variable in the assessment of lipid-lowering efficacy and cardiovascular risk. Building on our finidings and previous evidence, MHR and PMR may serve as simple, cost-effective tools to complement standard inflammatory markers and risk stratification in clinical practice.

CRediT authorship contribution statement

Federica Fogacci: Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Serra İlayda Yerlitaş Taştan:** Writing – review & editing, Visualization, Software, Methodology, Investigation, Formal analysis. **Marina Giovannini:** Writing – review & editing, Methodology, Investigation, Data curation. **Egidio Imbalzano:** Writing – original draft, Methodology, Formal analysis. **Dmitri Mitselman:** Writing – review & editing, Methodology, Investigation, Data curation. **Claudio Borghi:** Writing – review & editing, Validation, Supervision, Conceptualization. **Gökmen Zararsız:** Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Arrigo F.G. Cicero:** Writing – original draft, Visualization, Supervision, Resources, Methodology, Investigation, Data curation, Conceptualization.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University of Bologna (Code: LLD-RP2018).

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Declaration of generative AI and AI-assisted technologies in the writing process

The authors used ChatGPT to assist with spelling and grammar checks during the preparation of this work. All content was subsequently reviewed and edited by the authors, who take full responsibility for the final version of the manuscript. No AI tools were used to generate or analyze the scientific content of this work.

Declarations of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2025.11.011.

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