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Serum PCSK9 and MYLIP/IDOL Levels in Familial Hypercholesterolemia: Relationship with Lipid Profile

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Abstract

Background: Familial Hypercholesterolemia (FH), which is defined as a genetic disorder that causes a person to have high levels of LDL-C for their entire life, and therefore increases the risk of heart disease. Both PCSK9 and MYLIP/IDOL are proteins involved in regulating the amount of LDL receptors present on cell surfaces, but use different mechanisms.
Objective: To compare the levels of serum PCSK9 and MYLIP/IDOL along with other lipid-profile parameters between healthy individuals, untreated FH patients, and treated FH patients.
Methods: A cross-sectional study comparing three groups of individuals with different types of hypercholesterolemia was conducted among 90 subjects from Baghdad, Iraq (age 20-50 years): 30 normal control group members; 30 untreated familial hypercholesterolemia (FH) patients; and 30 treated FH patients. The serum PCSK9 and MYLIP/IDOL levels were determined via sandwich ELISA, while the concentrations of TC, TG, HDL-C, and LDL-C were evaluated through the use of a Roche Cobas Integra 400 analyzer.
Results: There were differences among groups in all parameters measured ($P<0.0001$). The untreated FH group exhibited higher TC, TG, LDL-C, PCSK9, and MYLIP/IDOL than the control group; however, the untreated FH group also exhibited lower HDL-C than the control group. When compared to the untreated FH group, the treated FH group exhibited lower TC, LDL-C, and MYLIP/IDOL; conversely, the treated FH group also exhibited higher HDL-C and PCSK9 than the untreated FH group. After multiplicity adjustment, there were no differences between groups in terms of TG. The untreated FH group exhibited a positive correlation between MYLIP/IDOL and TC ($r=0.607$; adjusted $P=0.0034$). ROC analyses demonstrated that the highest area under curves (AUCs) were observed for LDL-C (1.000), TC (0.983), MYLIP/IDOL (0.982), and PCSK9 (0.921).
Conclusion: There were significant lipid alterations in FH patients, which were accompanied by differences in PCSK9 and MYLIP/IDOL levels. Although treated FH patients had higher PCSK9 levels than untreated FH patients, their MYLIP/IDOL levels were lower. This may reflect different regulatory mechanisms for the LDL receptor pathway after treatment.

Keywords: Familial Hypercholesterolemia (FH); PCSK9; MYLIP; IDOL; LDL-C, ELISA.

1. Introduction

The most prevalent genetic disorder of LDL clearance, FH, results in high levels of LDL-C beginning in childhood and continuing throughout the individual's life, creating an enormous cumulative load of cholesterol and significantly elevating the probability of developing ASCVD at a relatively young age [1,2]. Current international guidelines continue to stress that FH is largely undiagnosed and untreated, even though there is compelling data supporting the fact that early detection, cascade testing, and aggressive treatment of LDL-C can greatly decrease cardiovascular risk [3]. FH can be caused by pathogenic variants in LDLR, APOB, or PCSK9; however, the severity of the disease will depend upon how much damage is being done by the variant, the person's polygenic background, metabolic comorbidities, and environmental factors [4]. The genetic makeup of people with FH from the Middle East may differ from those with FH from Europe. A study using data from the Qatar Biobank showed that there was a high rate of individuals who were likely or definitely diagnosed with FH and that it would be beneficial to use ancestry-specific screening methods [4]. Guidance from the region also emphasizes early diagnosis and continued use of lipid-lowering drugs to prevent long-term cardiovascular risks [5]. A variety of molecular processes regulate the amount of low-

density lipoprotein receptors (LDLR) present, for example, PCSK9 can bind to LDLR and then direct the receptor to be degraded by lysosomes; as a result, PCSK9 reduces the ability to clear LDL from blood, on the other hand, the inducible degrader of LDLR (IDOL), which is an E3 ubiquitin ligase produced by MYLIP, adds ubiquitin to LDLR and causes it to be degraded via a separate post-translational pathway [6-8]. Both of these ways that LDLR levels are controlled are important in medicine since most currently used medications that lower LDL-cholesterol levels will either increase the number of LDLRs or the activity of those receptors on the liver [7].The association between lipid-lowering drugs and the two regulatory proteins is of special interest, Chan et al. [6] showed that untreated FH patients had higher circulating IDOL and PCSK9 levels than controls; however, when those same FH patients started taking statins, their IDOL levels decreased and PCSK9 levels increased. The different responses of the two proteins provide a possible explanation for why there are differences in the effects of untreated vs. treated FH, nevertheless, such results should not be used as generalizations for all types of lipid-lowering drugs since PCSK9-targeted therapies and other non-LDLR dependent treatments can have different biological responses [9–11]. Despite growing interest in FH within the region, there is still very little data available regarding FH in Iraq. A 2024 study conducted in Duhok indicated that there was a lack of improvement in lipid-lowering therapies and managing cardiovascular risk factors for those individuals who had dyslipidemia [12]. Furthermore, regional Middle East and North Africa (MENA) studies have shown that there are many issues related to identifying and treating individuals with severe FH [13,14]. There are currently few studies that evaluate circulating PCSK9 and MYLIP/IDOL along with traditional lipid parameters across untreated and treated FH populations in Iraq. Therefore, the purpose of this study was to compare serum PCSK9, MYLIP/IDOL, and lipid profiles of healthy control subjects, untreated FH patients, and treated FH patients in Baghdad, Iraq; additionally, we were interested in examining relationships between these variables and determining if they could be used as diagnostic tools.

2. Materials and Methods

2.1 Study Design, Setting, and Participants

A cross-sectional comparative study was performed in Baghdad, Iraq. Study participants were selected from private medical laboratories and out-patient clinics during the period of June-September 2026. This study was composed of 90 individuals between the ages of 20 and 50 years old, who were divided into three groups of equal size (n=30): healthy controls, untreated FH patients and treated FH patients. The classification for participants who have been diagnosed with familial hypercholesterolemia (FH) was made based upon the clinical diagnosis of FH which each participant had received prior to their enrollment in the study. All participants with FH were classified based upon their current use of lipid-lowering therapies when they provided blood samples. Participants with FH that were not taking any lipid-lowering therapies were classified as being in the "untreated" FH category. Participants with FH that were taking a physician prescribed lipid-lowering therapy were classified as being in the "treated" FH category.

2.2 Sample Collection

For each participant, a 5-mL sample of venous blood was drawn into a gel separator tube. All samples were allowed to sit at room temperature to allow the blood to clot. After clotting had occurred, the samples were centrifuged at 3000 revolutions per minute (rpm) for five minutes. Following centrifugation, the separated serum was collected and frozen at –20 degrees Celsius until biochemical and biomarker analysis could be performed.

2.3 Lipid Profile Measurements

Serum total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were determined using an automated chemistry analyzer (Roche Cobas Integra 400, Roche Diagnostics).

2.4 Serum PCSK9 and MYLIP/IDOL Assays

The level of serum PCSK9 concentration was measured by means of a human PCSK9 sandwich enzyme-linked immunosorbent assay (ELISA) kit (ELK Biotechnology, Cat. No. ELK10569). According to the manufacturer, the assay has a detection range of 1.57-100 ng/mL; it has a sensitivity of 0.49 ng/mL; it has an intra-assay coefficient of variation (CV) less than 8%; and it has an inter-assay CV less than 10%. The assay uses a pre-coated anti-PCSK9

microplate, biotin-conjugated detection antibody, HRP-conjugate, and TMB substrate, and the absorbance is read at 450 nm.

The MYLIP/IDOL levels in the blood samples were measured by an ELISA sandwich method (MYLIP, BT LAB, Cat. No. E5215Hu). The manufacturer reports that this ELISA can detect MYLIP/IDOL from 10 to 2000 ng/L and its sensitivity is 5.24 ng/L. This ELISA uses a microplate that has been pre-coated with anti-MYLIP antibodies; it also uses a biotin-labeled detection antibody, a streptavidin-HRP conjugate, a substrate solution and a stop solution, with absorbance read at 450 nm.

2.5 Statistical Analysis

Continuous variables were reported as Mean ± Standard Deviation (SD). The Shapiro-Wilk and Levene's Tests were used to assess the normality and homogeneity of variance of each continuous variable. On the basis of those assessments, TC and LDL-C were analyzed using the Kruskal-Wallis Test, followed by the Holm-Adjusted Mann-Whitney U Post-Hoc Comparison; TG, HDL-C, and PCSK9 were analyzed using One-Way ANOVA, followed by the Tukey Post-Hoc Test; and MYLIP/IDOL were analyzed using Welch ANOVA, followed by the Holm-Adjusted Pairwise Welch t-Test. Pearson correlations were analyzed separately in untreated and treated FH populations for biomarkers that were pre-specified as possible markers of disease. The Holm method was applied to control the number of false positive results. To determine if there was a difference in how well each biomarker could differentiate between those who had untreated FH and those who did not have FH (i.e. healthy controls), receiver operating characteristic (ROC) curves were created. Optimal thresholds were identified based on the Youden index. The 95% confidence intervals for the area under the curve (AUC) were calculated based upon 3,000 stratified bootstrap samples. All statistical tests were conducted at a level of significance of $P < 0.05$. Graphs show data points for each subject along with the average value and standard deviation of those values. Additionally, graphs illustrate the statistically significant differences between all possible pairs after adjusting for multiple comparisons.

3. Results

The six parameters that we tested for were significantly different across all three of the groups we studied ($P<0.0001$). As compared to healthy controls, untreated FH patients demonstrated significantly increased levels of TC, TG, LDL-C, PCSK9, and MYLIP/IDOL; as well as significantly decreased levels of HDL-C. Untreated FH patients exhibited the highest TC (313.25 ± 31.79 mg/dL), TG (155.82 ± 26.48 mg/dL), LDL-C (239.88 ± 25.92 mg/dL), and MYLIP/IDOL (705.67 ± 126.14 ng/L); while PCSK9 was found to be the highest in the treated FH group (42.23 ± 5.83 ng/mL). When comparing treated FH patients to untreated FH patients, treated FH patients displayed significantly reduced levels of TC, LDL-C, and MYLIP/IDOL and significantly elevated levels of HDL-C and PCSK9. While treated FH patients had lower levels of TG as compared to untreated FH patients (145.01 ± 23.44 vs. 155.82 ± 26.48 mg/dL), there was no statistically significant difference in TG levels between treated FH patients and untreated FH patients after accounting for multiple comparisons (P=0.2042).

Table 1: Descriptive statistics and overall group comparison

Parameter	Healthy Control Mean ± SD	Untreated FH Mean ± SD	Treated FH Mean ± SD	Overall P
TC (mg/dL)	179.38 ± 19.20	313.25 ± 31.79	222.68 ± 30.23	<0.0001
TG (mg/dL)	118.94 ± 22.98	155.82 ± 26.48	145.01 ± 23.44	<0.0001
HDL-C (mg/dL)	52.07 ± 5.78	41.69 ± 5.27	47.05 ± 5.57	<0.0001
LDL-C (mg/dL)	106.26 ± 17.32	239.88 ± 25.92	145.94 ± 28.51	<0.0001
PCSK9 (ng/mL)	19.82 ± 4.23	30.22 ± 5.55	42.23 ± 5.83	<0.0001
MYLIP/IDOL (ng/L)	344.74 ± 63.71	705.67 ± 126.14	473.25 ± 70.42	<0.0001

Table 2: Pairwise post-hoc comparisons (multiplicity-adjusted P values)

Parameter	Healthy vs Untreated FH	Healthy vs Treated FH	Untreated vs Treated FH
TC	<0.0001	<0.0001	<0.0001
TG	<0.0001	0.0002	0.2042
HDL-C	<0.0001	0.0021	0.0009
LDL-C	<0.0001	<0.0001	<0.0001
PCSK9	<0.0001	<0.0001	<0.0001
MYLIP/IDOL	<0.0001	<0.0001	<0.0001

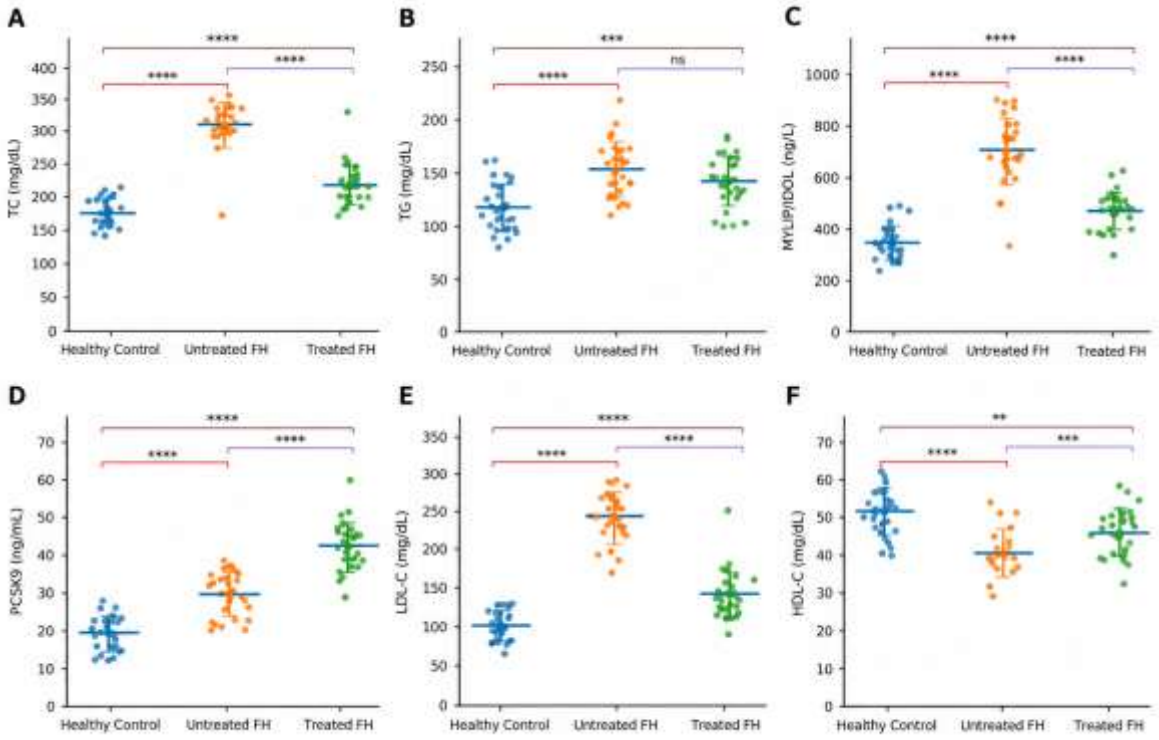

Figure 1. *Comparative distribution of lipid profile parameters, PCSK9, and MYLIP/IDOL levels across healthy controls, untreated familial hypercholesterolemia, and treated familial hypercholesterolemia groups.*

Pearson Correlation Analysis in FH Patients

MYLIP/IDOL demonstrated a moderately positive relationship with TC (r=0.607, P=0.0004) in the absence of treatment for FH. This relationship remained statistically relevant even after applying the Holm correction method to account for multiple comparisons (adjusted P=0.0034). Although there was a nominal relationship between MYLIP/IDOL and LDL-C (r=0.455, P=0.0116), it lost statistical relevance after using the Holm correction method (adjusted P=0.0928). All other pre-specified correlations were no longer statistically relevant once the multiplicity adjustments had been applied. None of the pre-specified correlations achieved statistical relevance in patients with treated FH.

Table 3: Pearson correlation analysis in untreated and treated FH patients

Variable pair	Untreated FH	Treated FH
PCSK9 vs TC	r=0.196; P=0.2988	r=-0.335; P=0.0706
PCSK9 vs TG	r=0.333; P=0.0719	r=-0.157; P=0.4074
PCSK9 vs HDL-C	r=0.190; P=0.3143	r=-0.316; P=0.0885
PCSK9 vs LDL-C	r=-0.026; P=0.8923	r=-0.293; P=0.1158
MYLIP/IDOL vs TC	r=0.607; P=0.0004	r=0.155; P=0.4143
MYLIP/IDOL vs TG	r=0.089; P=0.6404	r=-0.043; P=0.8205
MYLIP/IDOL vs HDL-C	r=0.196; P=0.3001	r=-0.316; P=0.0892
MYLIP/IDOL vs LDL-C	r=0.455; P=0.0116	r=0.175; P=0.3555
PCSK9 vs MYLIP/IDOL	r=0.210; P=0.2645	r=0.143; P=0.4494

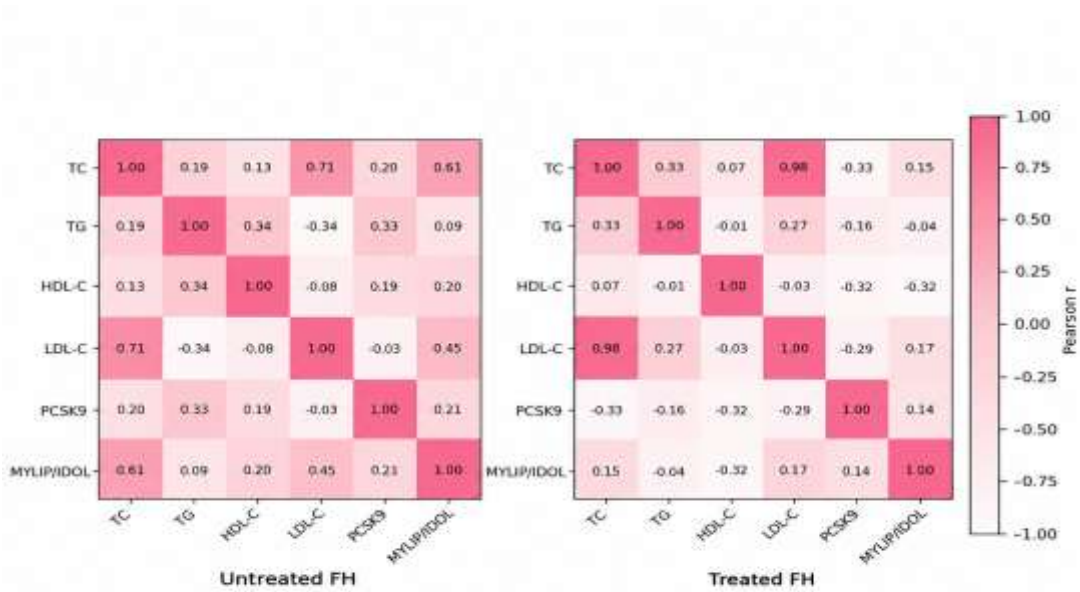

Figure 2. *Pearson correlation matrices of lipid profile parameters, PCSK9, and MYLIP/IDOL in untreated and treated familial hypercholesterolemia patients*.

ROC Curve Analysis

The ROC analysis was used to compare the group of untreated FH patients (n = 30) to the healthy control group (n = 30). In terms of separation within the dataset, LDL-C demonstrated complete separation (AUC = 1.000). TC and MYLIP/IDOL both had extremely high AUC values (0.983 and 0.982, respectively) as well; these were then followed by PCSK9 (0.921), HDL-C (0.909), and TG (0.858). As noted earlier, these estimates are exploratory and do not provide evidence for an independent diagnostic validation. This is primarily due to the case-control study design employed, and the clinical selection process used to identify individuals with FH which may falsely inflate the apparent discriminatory power of each biomarker.

Table 4: Exploratory diagnostic performance for untreated FH versus healthy controls

Marker	AUC	95% CI	Direction	Cutoff	Sensitivity %	Specificity %
TC (mg/dL)	0.983	0.943–1.000	Higher	281.00	96.7	100.0
TG (mg/dL)	0.858	0.759–0.936	Higher	128.10	86.7	70.0
HDL-C (mg/dL)	0.909	0.828–0.971	Lower	47.00	86.7	83.3
LDL-C (mg/dL)	1.000	1.000–1.000	Higher	177.00	100.0	100.0
PCSK9 (ng/mL)	0.921	0.849–0.973	Higher	26.52	73.3	96.7
MYLIP/IDOL (ng/L)	0.982	0.938–1.000	Higher	500.00	96.7	100.0

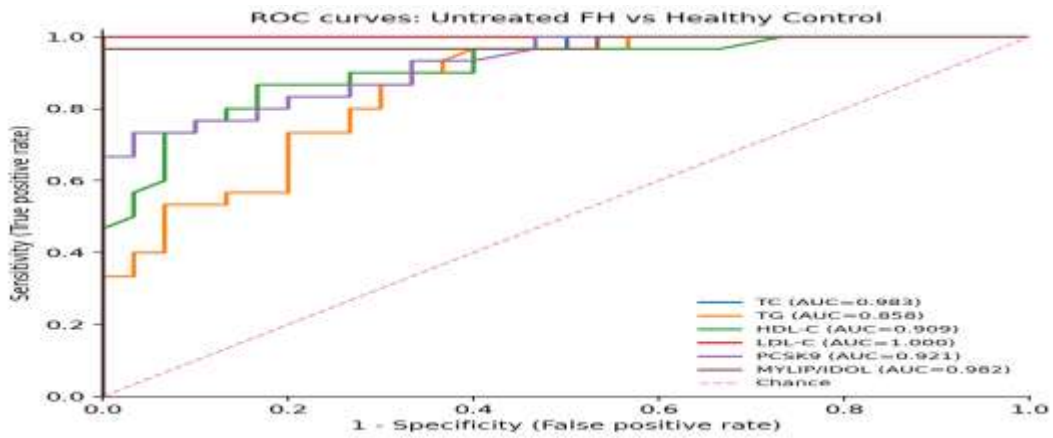

Figure 3: *Combined ROC curves for discrimination of untreated familial hypercholesterolemia from healthy controls.*

4. Discussion

The current study on Iraqis has clearly demonstrated biochemical differences among healthy individuals, those with untreated familial hypercholesterolemia (FH), and those with treated FH. The untreated FH group had the classic clinical presentation of severely elevated total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), and decreased high-density lipoprotein-cholesterol (HDL-C); all of these are consistent with the long-term exposure to elevated LDL-C that characterizes FH and results in early onset atherosclerotic cardiovascular disease [1–3]. Additionally, the degree of LDL-C elevation observed within the untreated group is consistent with recent review articles and consensus statements which describe the typical clinical presentation of FH [2,9,15]. Finally, the fact that treated patients continue to exhibit elevated levels of LDL-C after treatment highlights one of the major issues associated with providing quality health care to individuals suffering from FH; although treatment can significantly improve an individual's lipid profile, it does not guarantee that they will reach their recommended LDL-C targets [1,16,17]. The Canadian, German, Malaysian, Japanese, Dutch and Norwegian cohorts are real world studies that clearly indicate a large percentage of treated FH patients are unable to reach the guideline recommended LDL-C levels, even with lipid lowering medication [16–20]. Additionally, sex-specific analysis indicates there may be significant differences in treatment intensity and target achievement among different types of patients and/or healthcare delivery systems [21,22]. Therefore, the findings of this Iraqi study should be considered part of an overall global trend where partial biochemical response does not necessarily equate to adequate long-term risk reduction. TG was different than TC and LDL-C. TG was significantly different between each of the three groups, but there were no differences between treated and untreated FH patients once we controlled for multiple comparisons. This is what you would expect to see, since FH is primarily an issue with LDL being removed from the body, whereas TG is related to metabolism and lifestyle [15]. Therefore, the current way to manage this condition is to focus on lowering LDL-C levels, and reducing the total amount of LDL someone has accumulated over time [9]. PCSK9 increased progressively from controls to untreated FH and was greatest in treated FH. PCSK9 decreases LDLR recycling and inhibits the ability of the liver to clear LDL [7, 8]. Statins activate SREBP2 which may enhance the expression of both LDLR and PCSK9, thus providing a potential mechanism for why patients receiving treatment have greater PCSK9 levels [6, 8, 10]. However, since this was a cross-sectional study and there was no standardized treatment protocol, the observed pattern cannot be attributed to a particular drug. The opposite pattern was shown by MYLIP/IDOL; it was at its highest level in untreated FH patients, while it decreased in FH patients receiving treatment. This is consistent with what Chan et al. [6] found when they reported a decrease in serum IDOL and an increase in PCSK9 after initiating statin therapy, MYLIP/IDOL causes ubiquitination of LDLR, leading to its degradation. Therefore, MYLIP/IDOL is another pathway of regulation, which is different from PCSK9, yet complements it [7,8]. In addition, there are reports that show metabolic effects on the expression of IDOL [23].

The correlation results also indicate that circulating PCSK9 and MYLIP/IDOL may not always be in agreement with traditional lipid parameters, this was to be anticipated as the levels of each in the bloodstream are affected by the function of LDLR, genetic make-up, metabolic state and past treatments [23,24]. As such, these biomarkers should be viewed as part of a larger LDLR regulatory pathway, not just as indicators of specific lipid levels. The excellent ROC performance of both PCSK9 and MYLIP/IDOL could indicate some clinical utility, however, caution is required in interpreting the findings, Case-control studies have a tendency to overestimate the ability of a marker to discriminate between cases and controls if the groups are clearly defined (clinically), especially if the primary means used for case

definition is LDL-C [2]. Therefore, these biomarkers should be viewed as preliminary tests to help guide further research and evaluation, rather than established diagnostic markers that can be relied upon without verification through prospective studies [25]. The results of this study are also of regional significance, studies on Arab and Middle East/North Africa (MENA) populations show that there are still significant deficiencies in the identification of FH, achievement of LDL-C targets, and availability of advanced lipid-lowering drugs [26]. Similarly, international data indicate that early case identification, cascade screening, and greater availability of specialized lipid-related services can lead to better outcomes for patients with FH [27,28]. To advance FH research in Iraq, we need to implement standardized clinical scoring systems, screen families of individuals who test positive for FH, and selectively use genetic testing.

5. Conclusion

This study identified that there were distinct patterns of PCSK9 and MYLIP/IDOL in individuals diagnosed with familial hypercholesterolemia, as well as a correlation between the individuals' treatment status and how both of these pathways that regulate LDLR responded. These results demonstrate that evaluating PCSK9 and MYLIP/IDOL along with traditional lipid profiles is biologically relevant and provides additional insight into the mechanisms involved in regulating cholesterol in individuals with FH. While the diagnostic value and clinical applications of these proteins require further validation, the current results provide a strong foundation for future prospective studies. Additional large multi-center studies within the Iraqi population will be necessary to confirm the relationship between PCSK9 and MYLIP/IDOL and FH, and to determine whether they can be used as tools to help assess and manage FH.

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