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The utility of pentraxin 3 and platelet-derived growth factor receptor beta as non-invasive biomarkers for prediction of cardiovascular risk in MAFLD patients

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Abstract

Background Metabolic-associated fatty liver disease (MAFLD) has emerged as the predominant form of chronic liver disease globally linked with heightened cardiovascular disease (CVD) risk, the leading cause of mortality among affected individuals.

Aim This study aims to assess serum PTX3 (pentraxin 3) and platelet-derived growth factor receptor beta (PDGFRβ) as potential non-invasive biomarkers for predicting cardiovascular risk (CVR) in MAFLD patients.

Method A case–control investigation encompassing 84 MAFLD patients without prior CVD history and 30 age- and gender-matched healthy controls was conducted. Both cohorts underwent comprehensive laboratory and radiological evaluations. CVR was evaluated through common carotid artery intima-media thickness (IMT), Framingham risk score, and QRISK 2 score. The efficacy of two ELISA biomarkers PTX3 and PDGFRβ was examined for correlation with CVR in MAFLD patients.

Results MAFLD patients displayed significantly heightened levels of PTX3 and PDGFβ compared to healthy controls ($P<0.001$, $P=0.016$, respectively). PDGFβ exhibited a notably positive correlation with the Framingham score ($P=0.016$), while no significant correlation was observed with pentraxin 3 ($P=0.061$). Univariate and multivariate analyses identified diabetes mellitus (DM) ($P<0.001$*), hypertension ($P=0.005$), visceral fat ($P<0.001$*), waist/hip circumference ($P=0.04$), and PDGFβ ($P=0.03$) as robust predictors of CVR, with PTX3 demonstrating limited prognostic utility.

Conclusion PDGFβ emerged as a promising early non-invasive predictor of CVR in MAFLD patients, highlighting its potential role in guiding tailored preventive interventions, while PTX3 exhibited a modest impact warranting further investigation.

Keywords MAFLD, PDGFβ, Pentraxin 3, Cardiovascular risk, High-sensitivity C-reactive protein, Framingham risk score

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Introduction

The escalating prevalence of NAFLD is intimately connected to the rising occurrence of metabolic disorders [1]. This intricate relationship not only imposes a significant strain on public health systems but also heightens the susceptibility to cardiovascular complications, thereby exacerbating both morbidity and mortality [2]. Recently, the term "Metabolic-Associated Steatotic Liver Disease" (MAFLD) has been proposed within the context of NAFLD to better encapsulate the multifaceted nature of this condition [3]. Beyond its hepatic manifestations, MAFLD is acknowledged as a systemic ailment with profound implications, particularly regarding cardiovascular risk (CVR) [2]. Individuals afflicted with MAFLD face an augmented likelihood of cardiovascular events, emphasizing the urgency for effective risk assessment tools [3].

Pentraxin-3 (PTX3) is a member of the pentraxin superfamily akin to acute-phase reactants like C-reactive protein (CRP) [4]. It serves as a versatile soluble recognition receptor, exerting influence on the immunoinflammatory response [5]. Its production is induced by pro-inflammatory stimuli such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and lipopolysaccharides (LPS), all recognized as pivotal factors in the development of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [6]. Notably, PTX3 has been implicated in the pathogenesis of atherosclerosis progression and cardiovascular events, suggesting a possible role in cardiovascular risk assessment [7]. Furthermore, elevated PTX3 levels have been linked to impaired endothelial function, contributing to cardiovascular risk across various clinical scenarios. Numerous studies have proposed that heightened PTX3 may serve as a biomarker for predicting cardiovascular risk and prognosis in patients with diverse cardiovascular conditions [4, 8, 9].

Hepatic stellate cell activation has been associated with platelet-derived growth factor receptor beta (PDGFRβ), which has been the focus of numerous therapeutic investigations, particularly in MAFLD patients [10]. PDGFβ has been implicated in the pathogenesis of atherosclerosis, vascular remodeling, and endothelial dysfunction [11–13]. While existing studies offer insights into the potential roles of PTX3 and PDGFβ in cardiovascular risk, further research is warranted to specifically explore the relationship between PDGFβ levels and cardiovascular outcomes in MAFLD patients. Unraveling the mechanisms by which PDGF-BB contributes to cardiovascular risk in this population could unveil novel therapeutic targets for averting cardiovascular complications in MAFLD patients.

This clinical study aims to address the pressing need for non-invasive biomarkers capable of robustly predicting CVR in MAFLD patients. PTX3 and PDGFβ have emerged as promising candidates, reflecting the intricate interplay between hepatic dysfunction, chronic inflammation, and cardiovascular complications.

Patients and methods

Study design

This prospective case–control study aimed to investigate the utility of PTX3 and platelet-derived growth factor receptor beta (PDGFβ) as non-invasive biomarkers for predicting CVR in patients diagnosed with MAFLD [2]. The study adheres to ethical guidelines and has received approval from the Institutional Review Board (IRB).

Study participants

The study population comprised two groups

Group I includes individuals diagnosed with MAFLD, while Group II consists of healthy controls without MAFLD. Participants in Group I were recruited from hepatology and gastroenterology clinics, National Liver Institute Hospital (NLI), Menoufia University, Egypt. Institutional review board of NLI approval and written informed patients' consent are prerequisites for enrolment in this study. Inclusion criteria encompass age (18–70 years) with a confirmed diagnosis of MAFLD [2]. Group II participants were with matched age and sex.

Exclusion criteria

The exclusion criteria were as follows:

- Age less than 18
- Other causes of liver chronic diseases (viral, autoimmune, and metabolic)
- Alcohol consumption
- $\geq$10% weight loss within 6 months
- Patients with a previous history of cardiovascular events (angina, myocardial infarction, transient ischemic attack, and stroke)
- Patients receiving drugs that cause fatty liver such as amiodarone, diltiazem, tamoxifen, and steroids
- Patients who use statins
- Patients with liver decompensation, hepatic encephalopathy, ascites, and variceal bleeding
- Patients with chronic kidney diseases, systemic autoimmune diseases, and sepsis
- Patients suggested to have urinary tract infections (UTI), gynecological disorders, or neurological disorders as PTX3 is overexpressed in these disorders

Sample size and sampling

The sample size calculation was based on the prevalence of MAFLD and the anticipated effect size for the

biomarkers. A total of 114 participants were included: 84 MAFLD patients (Group I) and 30 healthy controls (Group II). The participants were selected using a convenience sampling method from the hepatology and gastroenterology clinics at the National Liver Institute Hospital (NLI), Menoufia University, Egypt.

Clinical and laboratory assessment

All participants underwent a thorough clinical evaluation, including a detailed medical history and physical examination. Anthropometric measurements, including weight, height, waist circumference, and hip circumference, were recorded. Laboratory assessments included liver function tests, lipid profiles, fasting blood glucose, and insulin levels. Inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) were also measured.

Abdominal ultrasonography to confirm the diagnosis of MAFLD and to assess liver steatosis.

Biomarker measurement

Plasma PTX3 was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Quantikine) (R&D Systems, Inc. 614 McKinley Place NE Minneapolis, MN 55413, USA) [14].

Plasma PDGFβ was measured with a commercially available ELISA kit (ThermoFisher Scientific), according to the manufacturer's instructions.

All plasma samples were diluted 1/10 with diluent provided by the manufacturer. Absorbance values were obtained with an iMark™ microplate absorbance reader (Bio-Rad) [15]. Blood samples were collected after an overnight fast, centrifuged, and stored at − 80 °C until analysis. The ELISA procedures were performed according to the manufacturer's instructions.

Cardiovascular risk parameters

Common carotid artery intima-media thickness (IMT) was measured using B-mode ultrasonography as a surrogate marker for subclinical atherosclerosis and cardiovascular risk (CVR) [16], non-invasive scores (Framingham risk score, which is based on age, sex, total cholesterol, smoking, HDL, systolic blood pressure, BP being treated with antihypertensive) [17], all were defined as CVD risk predictors at 10 years. Individuals with low risk have 10% or less CHD risk at 10 years, with intermediate risk 10–20%, and with high risk 20% or more.

Statistical analysis

Data were analyzed using SPSS software version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as frequencies and percentages. Independent *t*-tests and chi-square tests were used to compare continuous and categorical variables, respectively, between the two groups. Pearson's correlation coefficient was employed to assess the relationship between PTX3, PDGFβ, and CVR parameters. Multivariate regression analysis was conducted to identify independent predictors of CVR. A P value of < 0.05 was considered statistically significant.

Results

There is no significant difference in demographics between the two groups. Clinically, fatty liver patients (Group I) show a significantly higher prevalence of diabetes (DM) and hypertension (HTN) compared to healthy controls (Group II) (Table 1). Pentraxin 3 and PDGFβ exhibited statistically significant differences between the two groups (Table 2). Pentraxin 3 and PDGFβ show significant correlations with various parameters such as age, intimal thickness (IMT), waist/hip ratio, and BMI. Some correlations are positive (e.g., with age), while others are negative (e.g., with HDL) (Table 3). According to a Framingham score of more than 10, univariate analysis revealed that age, DM, HTN, waist/hip ratio, and PDGFβ are identified as significant factors affecting CVR in NAFLD patients, and the results of multivariate analysis highlight the importance of considering age, diabetes, visceral fat level, and PDGFβ in assessing cardiovascular risk in MAFLD patients (Table 4). ROC curves of PTX3 and in predicting CVR are illustrated in Fig. 1 with higher accuracy of PDGFβ. Univariate and multivariate Logistic regression analysis for cardiovascular risk predictors in MAFLD patients had defined age, DM, and PDGFβ with OR 1.148, 1.929, and 1.263, respectively (Table 5).

Discussion

Understanding the role of PTX3 and PDGFβ in predicting cardiovascular risk in MAFLD patients is crucial, not only for refining risk assessment strategies but also for facilitating targeted interventions.

Examining pentraxin 3 levels in MAFLD patients compared to healthy controls revealed significant differences, with implications for understanding potential cardiovascular risk in this vulnerable population. Pentraxin 3 levels ranged from 0.50 to 12.20, with a mean of 2.92 ± 2.45, while in controls, the range was narrower, varying from 0.50 to 6.0, with a mean of 1.73 ± 1.18 ($P < 0.001$). Previous research has associated PTX3 as an inflammatory marker with elevated levels in NAFLD patients, especially in those with advanced fibrosis [7, 18, 19]. These findings, combined with our study, highlight the potential role of PTX3 as a non-invasive marker in MAFLD patients.

Pentraxin 3 (PTX3) belongs to the pentraxin family of proteins involved in the inflammatory response and has implications in cardiovascular diseases [20]. Remarkably,

Table 1 Comparison between the two studied groups according to all study variables

		Group I (MASLD) ($n=84$)		Group II (control) ($n=30$)		*P* value
		Number	Percentage	Number	Percentage	
Demographic	Sex					
	Female	60	71.4	19	63.3	
	Age (years)					
	Min.–max	39.0–60.0		38.0–60.0		0.612
	Mean ± SD	50.27 ± 7.71		49.13 ± 7.98		
Clinical characteristics	DM					
	No	34	40.5	30	100.0	< 0.001*
	Prediabetic	11	13.1	0	0.0	
	Yes	39	46.4	0	0.0	
	HTN					
	No	52	61.9	30	100.0	< 0.001*
	Yes	32	38.1	0	0.0	
	T. cholesterol	241.96 ± 59.90		201.40 ± 32.06		< 0.001*
	HDL	46.89 ± 10.25		54.37 ± 8.13		0.001*
	LDL	145.12 ± 38.05		127.80 ± 31.70		0.024*
	Triglycerides	149.69 ± 55.69		111.37 ± 39.48		0.001*
	HOMA IR	4.26 ± 2.79		1.95 ± 0.65		< 0.001*
	QUIKI	0.32 ± 0.03		0.36 ± 0.12		< 0.001*
	IMT	0.09 ± 0.07		0.07 ± 0.01		< 0.001*
	QR risk	10.98 ± 9.37		5.42 ± 9.81		< 0.001*
	Framng (%)	14.67 ± 10.10		4.72 ± 4.82		< 0.001*

SD standard deviation, χ^2 chi-square test, *t* Student *t*-test, *P P* value for comparing between the studied groups, *U* Mann–Whitney test, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *SBP* systolic blood pressure, *IMT* intimal thickness, *HTN* hypertension, *QR risk* quantitative risk of stroke, *QUIKI* Quantitative Insulin Sensitivity Check Index, *HOMA* Homeostatic Model Assessment, *PDGFβ* platelet-derived growth factor, *DM* diabetes mellitus

*statistically significant at $P \leq 0.05$

Table 2 Comparison between the two studied groups according to pentraxin 3 and PDGFRB

	Group I ($n=84$)	Group II ($n=30$)	*U*	*P*
Pentraxin 3				
Min.–max	0.50–12.20	0.50–6.0	752.0*	0.001*
Mean ± SD	2.92 ± 2.45	1.73 ± 1.18		
Median (IQR)	1.96 (1.40–3.03)	1.47 (1.20–1.70)		
PDGFRB				
Min.–max	1.07–8.0	1.18–6.18	886.50*	0.016*
Mean ± SD	2.26 ± 1.46	1.71 ± 1.04		
Median (IQR)	1.64 (1.41–2.50)	1.45 (1.34–1.60)		

PDGF platelet-derived growth factor, *SD* standard deviation, *U* Mann–Whitney test, *P P* value for comparing between the studied groups

*statistically significant at $P \leq 0.05$

in the current study, correlation studies revealed significant associations of PTX3 with cardiovascular risk factors and scores, including waist/hip circumference, and intimal thickening by echocardiography.

Literature reports suggest that in patients with NAFLD, PTX3 levels are linked to visceral fat accumulation and

Table 3 Correlation between pentraxin 3 and PDGFβ with different praters in MAFLD patients

	Pentraxin 3		PDGFβ	
	r_s	*P*	r_s	*P*
Age	0.088	0.427	0.296	0.006*
IMT	0.240	0.028*	0.358	0.001*
Waist/hip	0.224	0.040*	0.092	0.404
BMI	0.201	0.067	0.237	0.030*
Total cholesterol	0.034	0.758	0.177	0.107
HDL	−0.067	0.548	−0.128	0.246
LDL	0.141	0.200	0.125	0.258
Triglycerides	0.021	0.853	0.074	0.501
HOMA.IR	0.010	0.929	−0.018	0.869
QUIKI	−0.007	0.951	0.016	0.888
Framng	0.206	0.061	0.261	0.016*
SBP	0.176	0.109	0.296	0.006*
QR risk	0.160	0.147	0.321	0.084

P P value for comparing between the studied groups, *PDGF* platelet-derived growth factor, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *SBP* systolic blood pressure, *IMT* intimal thickness

*statistically significant at $P \leq 0.05$

Table 4 Validity (AUC, sensitivity, specificity) for pentraxin 3 and HC CRP to discriminate risk Framng (≥ 10) (*n* = 49 vs. 35)

	AUC	*P*	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Pentraxin 3	0.546	0.474	0.414–0.678	> 1.72	63.27	51.43	64.6	50.0
PDGFRB	0.627	0.049*	0.508–0.746	> 1.48	69.39	45.71	64.2	51.6

AUC area under a curve, *P* value probability value, *C.I* confidence intervals, *NPV* negative predictive value, *PPV* positive predictive value

*statistically significant at $P \leq 0.05$

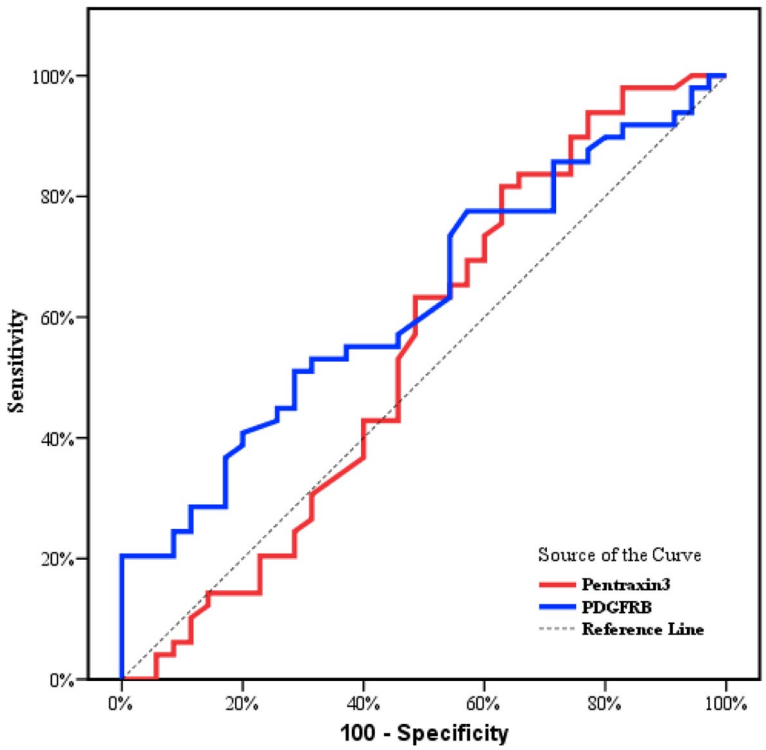

Fig. 1 ROC curve for pentraxin 3 and HC CRP to discriminate risk Framng (≥ 10) (*n* = 49 vs. 35)

Table 5 Univariate and multivariate Logistic regression analysis for cardiovascular risk predictors in MAFLD patients

	Univariate		#Multivariate	
	P	OR (LL–UL 95% C.I)	*P*	OR (LL–UL 95% C.I)
Sex (female)	1.000	1.0 (0.383–2.612)		
Age (years)	< 0.001*	1.200 (1.112–1.294)	0.002*	1.148 (1.051–1.255)
Pentraxin 3	0.638	0.958 (0.803–1.144)		
DM	0.001*	5.218 (2.027–13.432)	0.006*	1.929 (1.209–3.077)
HTN	0.005*	4.167 (1.533–11.324)	0.339	2.047 (0.472–8.886)
Waist/hip	0.049*	1.975 (1.0–3.899)	0.823	1.121 (0.410–3.066)
BMI	0.059	1.071 (0.997–1.151)		
PDGFβ	0.038*	1.579 (1.025–2.433)	0.302	1.355 (0.761–2.415)

OR odd's ratio, *C.I* confidence interval, *LL* lower limit, *UL* upper Limit, #all variables with $P < 0.05$ were included in the multivariate

*statistically significant at $P \leq 0.05$

cardiovascular risk. Studies have shown that PTX3 levels are significantly elevated in NAFLD patients with visceral obesity, often reflected by increased waist circumference, compared to those without visceral obesity [21]. Additionally, higher PTX3 levels are associated with an increased risk of developing cardiovascular complications in these patients [22]. Moreover, PTX3 levels correlate positively with visceral fat accumulation and insulin resistance in patients with NAFLD, indicating a relationship between waist/hip circumference, PTX3 levels, and cardiovascular risk in NAFLD patients [23].

Investigating PDGFβ in our study revealed elevated levels in MAFLD patients compared to healthy controls (*P* 0.016). Previous research suggests a role for PDGFβ in NAFLD-related fibrosis, with further validation of fibrosis scores containing PDGFβ, such as the PRTA score, demonstrating efficiency in grading fibrosis in NAFLD cases [10].

Our study established a positive correlation of PDGFβ with age, BMI, intimal thickening by echocardiography, systolic blood pressure, and Framingham score. Age, BMI, and elevated systolic blood pressure are well-established risk factors for cardiovascular disease, and their associations with PDGFβ further support its potential role in predicting cardiovascular risk in MAFLD patients [24].

Notably, the correlation between both biomarkers in our study and various clinical and metabolic cardiovascular risk factors highlights their potential as cardiovascular risk predictors in NAFLD patients. PDGFβ appears to be a more efficient predictor of cardiovascular risk due to its intimate relationship with high-risk predictors compared to PTX3.

Regression analysis negated any role for PTX3 in predicting cardiovascular risk, while PDGFβ showed significance (*P* 0.03). Additionally, DM, hypertension, visceral fat, and waist/hip circumference proved efficacy in predicting cardiovascular risk in MAFLD cases.

Despite these findings, analysis of the ROC curves revealed slightly higher sensitivity for PDGFβ (69.39%) compared to PTX3 (63.27%), with relatively similar positive predictive values. These results emphasize the complex nature of predicting Framingham risk using inflammatory markers, highlighting the need for comprehensive risk assessment in individuals with diabetes and high BMI [25].

Endorsing PDGFβ in cardiovascular risk scores could be valuable in MAFLD cases, necessitating further research for enhanced prediction capabilities. Further studies in larger and more diverse populations are necessary to validate these findings.

Conclusion

Our study underscores the potential of PDGFβ as a non-invasive biomarker for predicting cardiovascular risk in MAFLD patients while highlighting the limited role of PTX3 in this context. Integrating PDGFβ, along with traditional risk factors, could improve risk stratification and inform targeted interventions for managing cardiovascular risk in MAFLD. Further validation studies in diverse populations are warranted to establish the clinical significance of these biomarkers in routine practice.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CRP	C-reactive protein
FB	Fasting blood sugar
PTX3	Pentraxin 3
HSCRP	High-sensitivity C-reactive protein
IMT	Intima-media thickness
CVR	Cardiovascular risk
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
NAFLD	Non-alcoholic fatty liver disease
MAFLD	Metabolic-associated fatty liver disease
MASLD	Metabolic-associated steatotic liver disease
PPBG	Postprandial blood glucose
TG	Triglycerides
IMT	Intimal thickness
HTN	Hypertension
QR risk	Quantitative risk of stroke
QUIKI	Quantitative Insulin Sensitivity Check Index
HOMA	Homeostatic Model Assessment
PDGFβ	Platelet-derived growth factor
DM	Diabetes mellitus

Authors' contributions

BH, team leader and supervision and conceptualization; EM, formal analysis, writing original draft, editing and publication; MM, data curation, formal analysis; GS, methodology; SM, methodology; TM, methodology; ST, data curation, formal analysis.

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Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the National Liver Institute, Menoufia University (NLI 00003413). Written informed consent was obtained from all participants.

Consent for publication

Written informed consent was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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