

Study of Serum Pentraxin-3 Level in Non-alcoholic Fatty Liver Disease and Its Affection by Concomitant Chronic Hepatitis B Virus Infection in Egyptian Patients

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Background and study aim: Non-alcoholic fatty liver disease (NAFLD) is similar to alcoholic fatty liver disease, in which there is excessive fat in the liver but no excess alcohol use. It has emerged as one of the most common liver disorders worldwide. Many attempts were made to rename NAFLD. Recently, an international expert panel agreed on a new definition that is more linked to metabolic dysfunction. NAFLD was replaced with the term "metabolic associated fatty liver disease (MAFLD)" with a set of easy "positive" diagnostic criteria. When exposed to pro-inflammatory stimuli that are linked to the pathogenesis of NAFLD, dendritic cells, macrophages, fibroblasts, and activated endothelial cells produce PTX3. We aimed to evaluate PTX3 levels in NAFLD and their association with concomitant chronic HBV.

Patients and Methods: This study included 100 subjects: 40 with NAFLD, 40 with NAFLD and concomitant chronic

hepatitis B, and 20 healthy subjects. Serum PTX 3 was measured by ELISA.

Results: Our study revealed that PTX 3 was higher in patients with NAFLD and those with concomitant HBV infection than control.

Conclusion: We concluded that PTX-3 levels were higher in patients with NAFLD with or without concomitant HBV than in controls. PTX 3 may help identify those who are at risk of developing metabolic syndrome, as its level in patients with concurrent NAFLD and HBV is higher than the level in NAFLD patients alone, but this difference is not statistically significant. This reflects an inflammatory response caused by changes in metabolic profile rather than an infection-related response.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a liver disorder defined by the buildup of macrovesicular hepatic lipids in people who drink little or no alcohol [1]. NAFLD has rapidly emerged as one of the most frequent liver illnesses in both the developed and developing worlds, with a global prevalence of roughly 25% [2]. In the past, NAFLD has been linked to metabolic dysregulation as the main theory in the pathogenesis of the disease. As the prevalence of the disease increases, several ideas have been raised about the term "NAFLD" [3–5].

Several attempts have been made to rename NAFLD; each attempt has different theories and different degrees of visualization. An international expert team consensus was recently reached by 32 distinguished experts from 22 countries to discover a more suitable and general redefinition of fatty liver disease associated with metabolic dysfunction. This includes a more suitable name, "metabolic (dysfunction) associated fatty liver disease (MAFLD)" to replace NAFLD [6] and an easily applicable set of "positive" diagnostic criteria.

The diagnosis of MAFLD can be entertained in the presence of hepatic steatosis, in addition to at least one of the following three criteria: 1) overweight/obesity [body mass index in Caucasians (BMI) ≥ 25 kg/m²], 2) presence of type 2 diabetes mellitus, or 3) evidence of metabolic dysregulation defined by the presence of at least two of the seven metabolic at-risk criteria; Waist circumference of $\geq 94/80$ cm in men or women • Blood pressure $\geq 130/85$ mmHg; • Plasma triglycerides ≥ 150 mg/dL; • HDL-cholesterol $< 40/50$ mg/dL for men and women • pre-diabetes; • HOMA-insulin resistance score ≥ 2.5 ; • plasma highly sensitive CRP > 2 mg/d [6, 7].

Pentraxin 3 (PTX3) is a long pentraxin of the pentraxin superfamily (PTX3), also known as tumor necrosis factor-stimulated gene 14 (TSG-14), a class of versatile and evolutionary conserved proteins [8, 9]. In terms of structure, PTX3 has a pentraxin-like C-terminal domain connected to an unrelated N-terminal domain [10, 11]. Innate immunity, inflammation, tissue healing, and cancer are all interconnected by PTX3, which plays essential non-redundant roles in humoral innate immunity in microbial infections [8, 12–15].

The primary innate immune system cells that produce PTX3 in response to pro-inflammatory stimuli like tumor necrosis factor- α (TNF), interleukin-1 (IL-1), and lipopolysaccharides (LPS) are dendritic cells, macrophages, fibroblasts, and activated endothelial cells. These stimuli were all thought to be significant contributors to the pathogenesis of NAFLD and non-alcoholic steatohepatitis (NASH) [16, 17].

In this study, we aimed to evaluate serum PTX3 levels in non-alcoholic fatty liver disease and their association with concomitant chronic hepatitis B infection in Egyptian patients.

PATIENTS AND METHODS

This cross-sectional study included 100 subjects attending the Tanta Tropical Medicine Department, Faculty of Medicine. From July 2022 until cases were collected

Male or female patients older than 18 years and patients with chronic HBV infection were enrolled in the study. In addition to hepatic steatosis, the diagnosis of MAFLD was considered when at least one of the following

three criteria was met: 1) Type 2 diabetes mellitus, 2) overweight/obesity (body mass index in Caucasians: BMI ≥ 25 kg/m²), or 3) evidence of metabolic dysregulation, as defined by the presence of at least two of the seven metabolic at-risk criteria; 94 or 80 cm around the waist in men and women • HDL cholesterol $< 40/50$ mg/dL for men and women; • blood pressure $\geq 130/85$ mmHg; • plasma triglycerides ≥ 150 mg/dL; • Insulin resistance score of 2.5 on the HOMA • a plasma high-sensitive CRP of more than 2 mg/dl, while patients under the age of eighteen, those who consume large amounts of alcohol (more than 21 drinks for men and 14 for women per week), those on medications that cause fatty liver (amiodarone, diltiazem, tamoxifen, steroids), those taking statins (because they lower plasma PTX3), those with hepatic decompensation, hepatic encephalopathy, ascites, variceal bleeding, elevated serum bilirubin level, chronic kidney diseases, autoimmune diseases, and sepsis were not included in the current study.

The study participants were divided into: group I, which consisted of 40 patients with NAFLD identified by diffuse hyperechoic echo texture in abdominal ultrasound and verified by fibroscan examination after ruling out other causes of fatty liver; group II, which comprised those with NAFLD and laboratory evidence of chronic hepatitis B viral infection (hepatitis B s ag and PCR); and group III, which included 20 healthy control subjects with a negative medical history, a normal physical examination, normal laboratory results, and abdominal ultrasound. All of the patients underwent a thorough history, anthropometric measurements of their weight, height, waist circumference, and body mass index (BMI), as well as radiological examination, including ultrasound on the abdomen and pelvis for evaluation of the liver condition, splenic size, and presence of ascites, and fibroscan.

Laboratory investigations:

After an overnight fast, 6 mL of venous blood was drawn under aseptic conditions into two serum tubes containing a clot activator and one Na-citrate tube between 8:00 and 10:00 am. After that, the blood was centrifuged for fifteen minutes at 3000g. On the same day of collection, blood glucose levels, lipid profiles (total cholesterol, triglycerides, HDL, and LDL), INR, and liver function tests (ALT, AST, albumin, and

total protein) were all estimated. Until pentraxin 3 testing, the second serum sample was kept at -20 degrees Celsius.

KONELAB PRIME 60i was used to detect serum ALT, AST, albumin, total protein, total cholesterol, triglycerides, HDL, and blood glucose levels using reagents from Thermo Fisher Scientific Oy-Finland (catalog numbers: TR71121, TR70121, TR36026, TR34026, TR13421, TR22421, EEA012, EEA014, and 981304, respectively).

Stago STA compact was used to measure PT, activity, and INR with kits from DIAGNOSTICA STAGO (Neoptimal 10 catalog no. 01164).

Serum Pentraxin 3 (PTX3) was measured using the Sun Red Human PTX3 ELISA kit (Catalogue No. 201-12-1939). The kit measured the amount of human pentraxin 3 (PTX3) in samples using an enzyme-linked immunosorbent assay (ELISA) double-antibody sandwich method. Pentraxin 3 (PTX3) was added to a monoclonal antibody enzyme well that had previously been coated with a human pentraxin 3 (PTX3) monoclonal antibody and allowed to incubate. Subsequently, biotin-labeled pentraxin 3 (PTX3) antibodies were added and mixed with streptavidin-HRP to create an immune complex. Finally, further incubation was performed and the enzyme was removed by repeat washing. After adding Chromogen Solutions A and B, the liquid's color turned blue. After adding acid, the color eventually turned yellow. There was a positive correlation found between the color chroma and the amount of the human drug pentraxin 3 (PTX3) in the sample.

Statistical analysis:

The computer was fed data, and IBM SPSS software package version 20.0 was used for analysis. New York, Armonk: IBM Corp. The continuous variables were presented as medians with ranges or means \pm standard deviations. Numbers and percentages were used to represent categorical variables. Chi-squared tests were used for categorical variables and independent sample t-tests for continuous variables to evaluate differences between groups. The odds ratios (OR) and 95% confidence intervals (CI) for tumor response were calculated using the Roc curve and logistic regression tests. The results' significance was assessed at the 5% level.

RESULTS

The study population included 100 subjects, and the sex distribution among the studied groups is demonstrated in Table 1.

Anthropometric assessments revealed a statistically significant difference ($p < 0.001$) in body weight (kg/m²), body mass index (BMI), and waist circumference (cm) among the three groups. These measurements showed significant variance between groups I and II and group III, as well as between groups I and II. Additionally, a statistically significant difference ($p < 0.001$) was seen in the levels of ALT (U/L), AST (U/L), and fasting blood sugar (mg/dL) among the three groups. Compared to group III, ALT and AST were significantly higher in groups I and II. Groups I and II had significantly more fasting blood sugar than group III, and group I had higher fasting blood sugar than group II as demonstrated in Table 2.

Regarding the lipid profile, triglycerides (mg/dL), HDL (mg/dL), LDL (mg/dL), and total cholesterol (mg/dL) were statistically significantly different among the three study groups. HDL levels were lower in groups I and II than in group III, but triglycerides were significantly higher in groups I and II than in group III, and they were higher in group I than II. Compared to group III, groups I and II had greater levels of LDL (mg/dL) and total cholesterol (mg/dL), as seen in Table 2.

On the other hand, concerning serum pentraxin 3, we found a statistically significant difference between the three studied groups; it was higher in groups I and II than in group III, while no significant difference was found between groups I and II, as demonstrated in Table 2.

We also found a statistically significant difference between group I and group II regarding metabolic syndrome and DM (P-value < 0.001). They were significantly higher in Group I. There was no statistically significant difference found between group I and group II regarding fibrosis score and steatosis score, as demonstrated in Table 3.

There was a statistically significant difference in plasma PTX3 in patients with metabolic syndrome and patients without metabolic syndrome in groups I and II; the level was high in patients with metabolic syndrome, as demonstrated in Table 4.

As regards the correlation of serum pentraxin 3 and different parameters, there was a significant positive correlation between pentraxin-3 level and body weight (kg), body mass index (kg/m²), waist circumference (cm), ALT (U/L), AST (U/L), fasting blood sugar (mg/dL), LDL (mg/dL), total cholesterol (mg/dL), and CAP. There was a significant negative correlation between pentraxin-3 level and HDL (mg/dL),

while no statistically significant correlation was found between pentraxin-3 and the other studied parameters, as demonstrated in *Table 5*.

The receiver operating characteristic curve (ROC) was constructed to assess the accuracy of pentraxin-3 levels in patients with and without metabolic syndrome. It shows that the cutoff point was >11 with a sensitivity of 60.0% and a specificity of 82.86 (*Table 6 and Figure 1*).

Table (1): Sex distribution of the studied groups.

Sex	Male	Group I		Group II		Group III		Chi-Square
		N	%	N	%	N	%	P-value
		26	65	31	77	11	55	0.185
	Female	14	35	9	22	9	45	

Table (2): Characteristics and investigations of studied groups.

		Group I		Group II		Group III		ANOVA
								P-value
Age (Years)	Range	38	- 65	33	- 66	33	- 71	0.247
	Mean ±SD	50.425 ±	7.111	49.850 ±	9.082	46.600 ±	9.955	
Body weight (Kg)	Range	75	- 114	69	- 99	64	- 78	<0.001*
	Mean ±SD	92.2 ±	11.49	85.275 ±	6.66	68.25 ±	4.315	
Height (cm)	Range	153	- 183	154	- 183	158	- 188	0.092
	Mean ±SD	167.35 ±	9.393	169.5 ±	7.239	172.35 ±	8.093	
Body mass index (Kg/m ²)	Range	25.1	- 48.1	24.7	- 36.6	20.5	- 26.4	<0.001*
	Mean ±SD	33.378 ±	6.860	29.833 ±	3.463	23.040 ±	1.661	
Waist circumference (cm)	Range	82	- 135	81	- 120	73	- 91	<0.001*
	Mean ±SD	109.075 ±	14.682	99.550 ±	9.282	82.450 ±	5.395	
ALT (U/L)	Range	13	- 143	22	- 85	11	- 20	<0.001*
	Mean ±SD	41.630 ±	33.634	48.078 ±	17.398	14.600 ±	2.186	
AST (U/L)	Range	11	- 93	18	- 73	10	- 18	<0.001*
	Mean ±SD	36.438 ±	25.133	41.760 ±	16.435	12.800 ±	2.016	
Albumin (g/dL)	Range	3.2	- 5.9	3.8	- 5.8	4.3	- 5.5	0.007*
	Mean ±SD	4.800 ±	0.672	4.530 ±	0.488	4.988 ±	0.329	
Total bilirubin (mg/dL)	Range	0.3	- 1.2	0.2	- 1.2	0.2	- 1.3	0.133
	Mean ±SD	0.696 ±	0.305	0.795 ±	0.288	0.640 ±	0.320	
INR	Range	1	- 1.4	1	- 1.46	0.7	- 1.1	<0.001*
	Mean ±SD	1.108 ±	0.114	1.177 ±	0.131	0.890 ±	0.141	
Fasting blood sugar (mg/dL)	Range	77	- 131	74	- 115	65	- 88	<0.001*
	Mean ±SD	105.375 ±	17.041	89.925 ±	12.624	73.250 ±	6.980	
Triglyceride (mg/dL)	Range	105	- 222	120	- 200.6	90	- 124	<0.001*
	Mean ±SD	178.150 ±	29.788	161.190 ±	19.962	109.200 ±	9.578	
HDL (mg/dL)	Range	25	- 52	28	- 50	39	- 56	<0.001*
	Mean ±SD	38.175 ±	8.515	36.625 ±	5.960	45.650 ±	5.528	
LDL (mg/dL)	Range	70	- 183	80	- 175	60	- 92	<0.001*
	Mean ±SD	141.275 ±	27.422	130.050 ±	24.105	73.750 ±	10.366	
Total Cholesterol (mg/dL)	Range	118	- 249	160	- 265	135	- 168	<0.001*
	Mean ±SD	215.000 ±	36.813	202.625 ±	22.601	150.350 ±	8.911	
Plasma PTX3 (ng/mL)	Range	5.5	- 15.5	3.8	- 16.5	1.3	- 5.7	<0.001*
	Mean ±SD	9.983 ±	2.484	11.160 ±	3.215	3.603 ±	1.386	

ALT alanine aminotransferase, AST aspartate aminotransferase, INR international normalized ratio, HDL high-density lipoprotein, LDL low-density lipoprotein, PTX3 pentraxin-3

Table (3): Comparison between group I and group II as regards some parameters.

		Group I		Group II		P-value
		N	%	N	%	
Metabolic syndrome	Patients with metabolic syndrome	31	77.50	14	35.00	<0.001*
	Patients without metabolic syndrome	9	22.50	26	65.00	
HTN	Yes	16	40.00	14	35.00	0.644
	No	24	60.00	26	65.00	
DM	Yes	38	95.00	10	25.00	<0.001*
	No	2	5.00	30	75.00	
CAP	S1	8	20.00	9	22.50	0.901
	S2	7	17.50	8	20.00	
	S3	25	62.50	23	57.50	
Fibro scan	F0-F1	32	80.00	29	72.50	0.332
	F2	8	20.00	9	22.50	
	F3	0	0.00	2	5.00	
T-Test						P-value
CAP	Range	240 - 398		240 - 389		0.439
	Mean ±SD	306.200 ± 46.446		298.550 ± 41.334		
Fibro scan	Range	3.5 - 9.6		4 - 12.3		0.113
	Mean ±SD	6.263 ± 1.612		6.875 ± 1.800		

HTN hypertension, DM diabetes mellitus, CAP controlled attenuation parameter

Table (4): Plasma PTX3 levels in patients with metabolic syndrome and patients without metabolic syndrome.

	Plasma PTX3 (ng/mL)	Patients with metabolic syndrome		Patients without metabolic syndrome		P-value
Group I	Range	5.5 - 15.5		6 - 11		0.036*
	Mean ±SD	10.423 ± 2.513		8.467 ± 1.753		
Group II	Range	11.5 - 16.5		3.8 - 14.03		<0.001*
	Mean ±SD	14.091 ± 1.400		9.581 ± 2.774		
All Patient	Range	5.5 - 16.5		3.8 - 14.03		<0.001*
	Mean ±SD	11.564 ± 2.799		2.799 ± 2.799		

Table (5): Correlation of pentraxin-3 level with the other studied parameters in all studied cases:

Correlations						
	Plasma PTX3 (ng/mL)					
	Group I		Group II		All Patient	
	R	P-value	R	P-value	R	P-value
Age (Years)	-0.016	0.922	0.197	0.224	0.107	0.346
Body weight (Kg)	0.382	0.015*	0.521	0.001*	0.304	0.006*
Height (cm)	-0.332	0.036*	-0.081	0.619	-0.168	0.136
Body mass index (Kg/m ²)	0.422	0.007*	0.397	0.011*	0.282	0.011*
Waist circumference (cm)	0.303	0.057	0.520	0.001*	0.269	0.016*
ALT (U/L)	0.496	0.001*	0.030	0.852	0.297	0.007*
AST (U/L)	0.477	0.002*	0.137	0.400	0.320	0.004*
Albumin (g/dL)	0.094	0.564	0.120	0.459	0.052	0.649
Total bilirubin (mg/dL)	-0.064	0.696	-0.330	0.038*	-0.166	0.140
INR	0.202	0.211	-0.012	0.942	0.125	0.268
Fasting blood sugar (mg/dL)	0.272	0.089	0.507	0.001*	0.229	0.041*
Triglyceride (mg/dL)	0.187	0.248	0.459	0.003*	0.211	0.061
HDL (mg/dL)	-0.384	0.014*	-0.169	0.298	-0.283	0.011*
LDL (mg/dL)	0.341	0.031*	0.451	0.004*	0.331	0.003*
Total Cholesterol (mg/dL)	0.178	0.272	0.587	<0.001*	0.281	0.012*
CAP	0.768	<0.001*	0.563	<0.001*	0.613	<0.001*
Fibro scan	0.154	0.343	0.140	0.389	0.176	0.118

Table (6): Sensitivity, specificity, and cutoff value of pentraxin-3 in patients with metabolic syndrome and patients without metabolic syndrome.

	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Plasma PTX3 (ng/mL)	>11	60.0	82.86	81.8	61.7	72.9%

PPV= positive predictive value, NPV= negative predictive value.

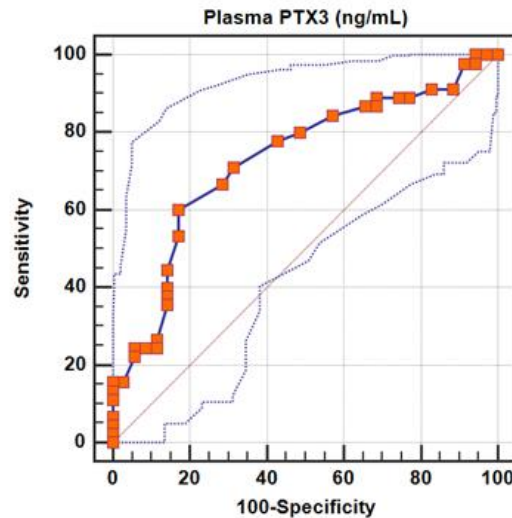


Figure (1). Sensitivity, specificity, and cutoff value of pentraxin-3 in Patients with metabolic syndrome and Patients without metabolic syndrome

Discussion

NAFLD, which is also a symptom of metabolic syndrome, is one of the chronic liver diseases that affect mostly obese people [18]. Its distinguishing characteristic is the large lipid droplets that accumulate inside the liver cells [19].

After 6 to 8 hours of any inflammatory situation, serum PTX3 levels reach their maximum levels due to the fast release of stored PTX3 by active neutrophils [20, 21].

The liver produces the short pentraxins in response to local inflammation, whereas the injured tissues cause the long pentraxin (PTX3) to be expressed [22].

In response to pro-inflammatory stimuli like TNF-alpha, IL-1, and lipopolysaccharide (LPS), which are all said to be crucial elements in the development and evolution of NASH, a range of cell types, including monocytes, macrophages, and endothelial cells, release PTX3 [23].

The goal of the current study was to compare the plasma PTX3 levels of patients with NAFLD and those with concurrent chronic hepatitis B virus infection and hepatic steatosis.

We discovered that patients with NAFLD had significantly greater plasma levels of PTX3 than controls. Our findings were in agreement with Yoneda et al. (2008). It showed that the PTX3 levels in NAFLD patients were significantly higher than those in the healthy control group [24]. Independent of the elements of the metabolic syndrome, Ozturk et al. (2016) showed that PTX3 levels in NAFLD patients with fibrosis were greater than those in NAFLD patients without fibrosis and healthy people [25]. In contrast, Maleki et al. (2014) reported no significant variations in plasma PTX3 levels between NAFLD and healthy control patients [26].

In our study, there was no significant difference between NAFLD patients with and without chronic HBV regarding plasma PTX3. PTX3 is directly produced by damaged tissues, and a rapid increase indicates inflammation. Elevated PTX3 concentrations are related to liver-associated pathological conditions such as liver infections, NAFLD, NASH, and hepatic tumors [27].

In the current research, there were significant positive correlations between serum PTX3 levels and BMI, waist circumference, fasting blood sugar (FBS), TG, ALT, and AST, but a negative

correlation between PTX3 levels and HDL. Additionally, with a cut-off value for PTX3 > 11 ng/ml, those who had metabolic syndrome in the current study had greater levels of PTX3 than those without metabolic syndrome. Similar findings were made by Kardas F et al. in 2015, who discovered that obese children and adolescents with metabolic syndrome and higher triglyceride levels had significantly higher plasma PTX3 concentrations and that PTX3 levels in their study had a negative correlation with HDL cholesterol [28]. However, the research conducted by Witasp A. et al. (2014) and Slusher A. et al. (2017) discovered that PTX3 is inversely correlated with obesity and that it elevates with exercise and weight loss [29, 30].

Many studies revealed significantly higher ALT and AST levels in NAFLD with or without HBV infection than control subjects. Increased hepatic enzyme levels are indicators of hepatocellular necrosis [30, 31, 32]. This is in agreement with our study.

The present study revealed that NAFLD patients with or without chronic HBV infection, in comparison to healthy controls, had significantly higher levels of FBS, triglycerides, total cholesterol, and LDL, and significantly lower levels of HDL. This agreed with Nakahara T. et al., 2014 [32]. Because both NAFLD and type 2 diabetes mellitus (T2DM) share the risk factors of excessive adiposity, increased lipids, and insulin resistance, they frequently coexist.

In our study, there was also a statistically significant difference in plasma PTX3 between patients with metabolic syndrome and patients without metabolic syndrome in groups I and II. The level was high in patients with metabolic syndrome, which agrees with Makhlof M. 2019 [33].

The study by Han Q et al. (2021) showed that increased serum PTX3 levels were associated with a poor prognosis of HBV-related HCC, and a high PTX3 level was an independent factor associated with a reduced survival time of HCC patients [34].

This study had some limitations. First, fatty liver disease was diagnosed by ultrasound and fibroscan. Second, the sample size in our study is relatively small. Finally, the study population was from one hospital and cannot represent the general population. Therefore, findings need to

be validated using more sophisticated techniques, such as liver biopsies, and a more representative population.

Conclusion

We concluded that patients with NAFLD, whether or not they also had concurrent HBV infection, had greater serum levels of PTX-3 than healthy individuals. Furthermore, although this difference is not statistically significant, serum PTX3 level is higher in patients with concurrent NAFLD and HBV infection than in individuals with NAFLD alone, suggesting that serum PTX3 may be useful in identifying people who are at risk of developing metabolic syndrome. This reflects an inflammatory response caused by changes in metabolic profile rather than an infection-related response. It needs more research to confirm this study's conclusions.

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Conflict of interest; None.

Ethics approval and consent to participate:

The study received ethical approval from the Faculty of Medicine at Tanta University, with approval code 35592/7/22, and participants gave their agreement.

All patients agreed to collect this data by signing a written informed consent.

Abbreviation:

NAFLD: Non-alcoholic fatty liver disease
 MAFLD: "metabolic (dysfunction) associated fatty liver disease.
 PTX3: Pentraxin 3.
 TSG-14: tumor necrosis factor-stimulated gene 14.
 TNF-alpha: Tumor necrosis factor alpha,
 IL-1: interleukin-1
 LPS: lipopolysaccharides
 NASH: nonalcoholic steatohepatitis.
 HBV: hepatitis B virus
 INR: international normalization ratio.
 LDL: low-density lipoprotein.
 HDL: high-density lipoprotein.
 CAP: controlled attenuation parameter
 TG: triglycerides
 FBS: fasting blood sugar.

HIGHLIGHTS

- NAFLD has quickly emerged as one of the most common liver disorders in both developed and developing countries
- Serum PTX 3 levels were higher in patients with NAFLD and NAFLD with concomitant chronic hepatitis b than in healthy subjects.
- Serum PTX 3 may help identify those who are at risk of developing metabolic syndrome.

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