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Original Article

SERUM FERRITIN; A STRONG NON-INVASIVE PREDICTOR FOR NAFLD PROGRESSION

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ABSTRACT

Objective: To determine and compare serum ferritin in non-alcoholic fatty liver disease (NAFLD) patients of our ethnicity and to find a predictive value of serum ferritin in designating the progression of the disease.
Study Design: Cross-sectional diagnostic study
Place and Duration of Study: Shalamar Hospital and Combined Military Hospital Lahore Pakistan, from Mar to Jul 2019.
Methodology: On abdominal ultrasonography and raised LFTs, age, gender and BMI matched 129 subjects were classified as cases and controls. After that NAFLD fibrosis score (NFS) was calculated in the cases who had hyper-echoic liver margins and later subjects were divided into 43 healthy controls (group A), 66 subject with steatosis (group B) and 20 subjects with steatohepatitis (group C). Fasting serum ferritin, insulin, glucose levels were measured and HOMA-IR was calculated using {Glucose (mg/dl) × insulin (µlU/ml) / 405} formula. Data was entered and analysed on SPSS version 21. For group comparison, diagnostic performance and to declare ferritin as independent predictor we applied, one way ANOVA, ROC curve and binary logistic regression analysis respectively. A *p*-value of ≤0.05 was taken as statistically significant.
Results: There was a significant difference between the serum ferritin among all the groups. Area under the curve of serum ferritin for group B and group C were 0.603 and 0.885 and serum ferritin levels of ≥40.75 ng/ml with sensitivity of 94% and specificity of 69% were declared to be of the best diagnostic value. While the value of ≥67.55ng/ml of serum ferritin is the best predictor for presence of fibrosis with 95% sensitivity and 42% specificity. In this study the positive and negative predictive value of serum ferritin in determining the fibrosis were 96% and 33% respectively.
Conclusion: Serum ferritin has a good positive predictive value.

Keywords: serum ferritin, predictor, NAFLD, NFS.

How to Cite This Article: *Qamar M, Tauseef T, Naqvi QA, Ehsan K, Anwar R, Fatima SA. Serum Ferritin; A Strong Non-Invasive Predictor For NAFLD Progression. Pak Armed Forces Med J 2023; 73(Suppl-I): S462-467. DOI: https://doi.org/10.51253/pafmj.v73iSUPPL-1.11365*

INTRODUCTION

Since the eve of the new era filled with gadgets and technology, the lifestyle of human beings has drastically changed leading to obesity, metabolic syndrome and multiple chronic disorders. According to WHO in 2016, 39% of the adult population is either overweight or obese.[1] With a continuum rise in BMI so are the diseases related to it. The prevalence of non-alcoholic fatty liver disease (NAFLD) since its discovery in 1990 has been increasing at such a fast pace that it has become one of the most common liver diseases.[2] Highest being in South America and lowest in Africa the global prevalence has reached 25.24% for NAFLD.[3,4] In Pakistan too, the prevalence of NAFLD has reached a level of 15% with the highest prevalence in pathans.[5]

NAFLD does not only comprise fat deposits in the liver rather it can progress to three stages that are hepatitis, fibrosis and cirrhosis. Biopsy of the liver is the most reliable and accurate test for the assessment and grading of the extent of hepatic tissue injury. Researchers are busy finding more accurate and reliable means for non-invasive prognostic testing of NAFLD. Methods like NAFLD Score, fibrosis-4 (FIB-4) and some biomarkers have proved to be promising methods though not the gold standard.[2]

According to the 'two-hit theory' of NAFLD, insulin resistance causing fat accumulation in the liver is the first cunt leading to the absence of the inhibition of hormone-sensitive lipase, free fatty acid gets accumulated in the liver. Then oxidative stress and inflammation especially due to iron, give the second blow leading to inflammation of the steatotic lesion. Increased deposition of iron acts through the Fenton reaction, as a catalyst to oxidative stress and by increasing lipid peroxidation in the fatty liver. Ferritin has a positive correlation with iron load, it explains the increase in ferritin levels during NAFLD. Ferritin also acts as pro-inflammatory cytokine which causes the progression of the disease from non-alcoholic fatty liver (NAFL) to

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Received: 29 Oct 2022; revision received: 01 Feb 2023; accepted: 22 Feb 2023

non-alcoholic steatohepatitis (NASH) by activating the hepatic stellate cells.[6,7]

There have been controversial results regarding predictive value of ferritin in diagnosing the extent of the lesion. Keeping in consideration the pathogenesis and linkage of iron for oxidative stress in the progression of NAFLD, the objective was to explore the fact that it, can ferritin act as a predictive biomarker of NAFLD and its stages.

METHODOLOGY

After the approval from Ethical Review Committee Postgraduate Medical Institute Lahore, an observational study was conducted at the departments of medicine and radiology of CMH and Shalamar Hospital Lahore. All the subjects were recruited after a written informed consent.

Inclusion Criteria: The subjects with bright or hyperechoic liver patterns on ultrasonography and ALT of <30u/l for males and >19u/l for females were all declared as NAFLD subjects.

Exclusion Criteria: All the subjects having liver cirrhosis and other liver diseases, diabetes mellitus (type 1), renal failure, endocrine disorders, thrombotic disorders, pregnancy, carcinoma or usage of any drug with the purpose of weight loss in the past 6 months.

After abdominal ultrasonography age, gender and BMI matched a total number of 129 subjects were classified as cases and controls were recognized. After that NAFLD fibrosis score (NFS) was calculated in the cases that had hyper-echoic liver margins, by using the following formula

$$(-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{diabetes (yes=1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (}\times 10^9/\text{l)} - 0.66 \times \text{albumin (g/dl)}.)$$

A total number of 129 subjects were divided into following groups. Group A (43) were healthy controls. Group B (66) were having simple steatosis with NFS <-1.455. Group B (20) had intermediate or advanced fibrosis with a score ≥-1.455.

A detailed personal, past, drug and socioeconomic history was taken. A detailed general physical examination was conducted and BMI was calculated by the formula; body weight (kg)/ height^2 (m^2).

Lipid profile, complete blood picture and liver function tests were obtained from the available hospital data. At a speed of 3,000 rpm, the serum was segregated. Serum ferritin and insulin were measured by enzyme-linked immunoassay technique and fasting serum glucose was measured by its oxidase method. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by using {Glucose (mg/dl) × insulin (µlU/ml) / 405} formula.

Data was entered and analyzed using SPSS 21. To check the normality of the data Shipharo Wilk test was applied and all the parameters were normally distributed hence the data was presented in Mean ± SD along with frequencies and percentages. To find the relationship of the categorical data Chi-square was applied. One-way ANOVA was used to find the difference between quantitative variables. Pearson's correlation was used to find an association between the serum ferritin and other quantitative variables in disea-sed subjects, for the diagnostic performance of biochemical variables receiver operating characteristic (ROC) curve was applied. Binary logistic regression analysis was further carried out to declare significant predictors of NAFLD and fibrosis in the studied patients. Less than 0.05 was declared as statistically significant *p*-value while <0.01 was considered as highly significant *p*-value.

RESULTS

The mean ages of the three groups were 47 ±12.54 years, 44.3 ± 12.29 and 55.8 ± 8.53 in groups A, B and C respectively as the NAFLD subjects and controls were age-matched hence no significant difference was noted although a highly significant difference was noted in the group B and C with a *p*-value <0.01. On the categorical demographic data, chi-square was applied which showed a significant association between hypertension and the presence of diabetes mellitus II as the disease progresses with the highest frequencies of 90% obese and 60% diabetics in a fibrotic group compared to the other two groups while hypertension was more common among the steatotic group with a percentage of 40%. In the fibrotic group, 80% of the patients had mild to moderate fibrosis while rest of them had advance fibrosis. (Table-I & II).

A statistically highly significant difference was seen among all the biochemical markers except HOMA-IR where (*p*-value=0.163) with more insulin resistance in steatosis (Group B) compared to fibrosis (Group C) although the difference is not statistically significant. Age, platelet count, albumin and serum ferritin had a statistically significant difference among the steatotic and fibrotic groups. (Table-II)

In group B subjects a positive significant correlation of serum ferritin with age, BMI, ALT, AST and insulin was noted while among the group C patients, ferritin had a positive correlation with age only. (Table-III)

Table-I: Frequency distribution of general characteristics among the groups and their association using Chi-square.

Variables		Group A n=43, n (%)	Group B n=66, n (%)	Group C n=20, n (%)	*p*-value
Gender	Male	21	34	10	0.963
	Female	22	32	10	
Body Mass Index	Normal (18-22.99)	4	6	0	0.198
	Over weight (23-24.99)	8	16	2	
	Obese (>25)	31	44	18	
Hyper-tension	Yes	6	26	4	0.011*
	No	37	40	16	
Diabetes Mellitus II	Yes	1	10	12	<0.01**
	No	42	56	8	

**Less than 0.05 p-value (statistically significant), **Less than 0.01 p-value (highly significant)*

Table-II: Group comparison of biochemical markers using one-way ANOVA

Variables	Groups			ANOVA	*p*-value	Post hoc Test
	Group A	Group B	Group C			
Age (years)	47±12.6	44.4±12.3	56.8±8.7	8.248	<0.01**	(A,C) , (B,C)
Alanine aminotransferase	18.3±6.0	68.9±61.4	50.9±23.7	16.403	<0.01**	(A,B), (A,C)
Aspartate transaminase	22.3±7.0	53.8±29.5	64.9±28.8	29.720	<0.01**	(A,B), (A,C)
Platelet count	268.7±61.0	258.3±52.8	29.6±41.3	8.520	<0.01**	(A,C) , (B,C)
Albumin	42.8±4.4	45.1±3.8	42.8±5.5	4.875	<0.01**	(A,B) , (B,C)
Serum glucose	63.8±25.6	84.6±32.4	98.6±29.3	11.025	<0.01**	(A,B) , (A,C)
Serum insulin	9.4±4.6	21.7±27.8	21.7±9.1	5.232	<0.01**	(A,B) , (A,C)
HOMA-IR	1.5±1.0	6.1±17.3	5.2±2.3	1.839	0.163	
Serum ferritin	41.3±27.9	81.1±32.4	120.7±	42.263	<0.01**	(A,B) , (A,C) , (B,C)

*Less than 0.05 *p*-value (statistically significant), **Less than 0.01 *p*-value (highly significant)

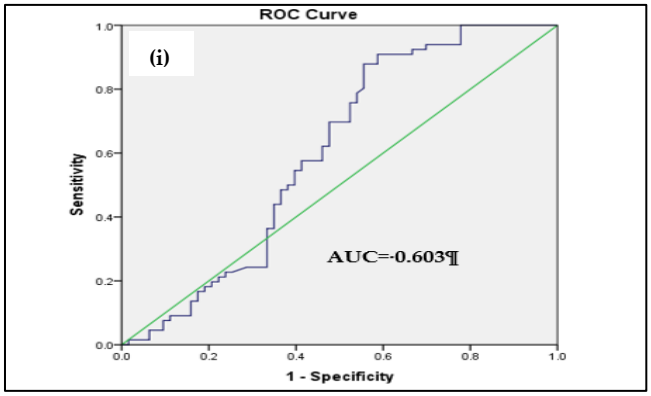
Table-III: Correlation of serum ferritin with other variables in groups B and C using Pearson's correlation.

Variables	Group B		Group C	
	Pearson correlation	Significance	Pearson correlation	Significance
Age	0.232	0.061	0.451	0.045*
Body mass index	0.481	0.000**	0.138	0.562
Alanine aminotransferase	0.388	0.001**	0.142	0.549
Aspartate transaminase	0.309	0.012*	-0.131	0.581
Platelet count	0.186	0.135	0.066	0.782
Albumin	0.112	0.369	0.095	0.690
Serum glucose	-0.104	0.408	0.289	0.217
Serum insulin	0.008	0.032*	0.190	0.423
HOMA-IR	-0.027	0.832	0.267	0.255

**Less than 0.05 p-value (statistically significant), **Less than 0.01 p-value (highly significant)*

In steatosis and fibrosis area under the curve for serum ferritin is 0.603 and 0.885 respectively. After the ROC curve analysis for prediction of NAFLD, serum ferritin levels of ≥ 40.75 ng/ml with sensitivity of 94% and specificity of 69% should be the best diagnostic value (Figure-1). While the value of ≥67.55ng/ml of serum ferritin is the best predictor for the presence of fibrosis with 95% sensitivity and 42% specificity. In this study, the positive and negative predictive values of serum ferritin in determining fibrosis were 33% and 96% respectively.

Binary logistic analysis was conducted to find out the independent predictors for fibrosis. Increased levels of serum ferritin and AST were found to be independent predictors for fibrosis in the patients suffering from NAFLD. While decrease in the levels of serum insulin, ALT and platelet count can predict the presence of fibrosis leading from NAFLD. (Table-IV).



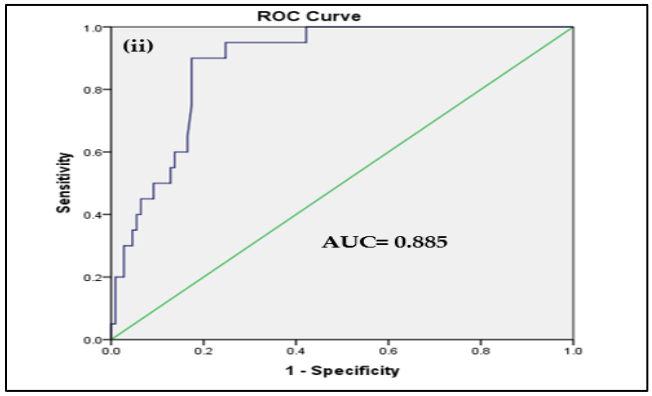


Figure-1: Receivers operating curves between serum ferritin levels and (i) NAFLD and (ii) fibrosis in predicting the occurrence of the two outcomes.

AUC: area under the ROC curve.

steatosis. Which is contrary to some studies where increase in platelet count had been reported in subjects with NAFLD and fibrosis.[15] While researchers advocated association of thrombocytopenia with progression of the disease as the liver functions deteriorate and the platelet growth factors released from the liver decrease hence leading to decreased platelet count with advanced disease.[16]

Serum albumin levels were found to be significantly decreased in fibrotic patients compared to steatotic patients, this is incoherent with the study conducted by Kawaguchi and colleagues.[17] Due to the decreased blood flow or decreased liver functioning in fibrotic state the albumin-production may have decreased.[17]

The glycemic factors, that is serum fasting glucose

Table-IV: Binary logistic regression analysis for prediction of independent variables in the patients of NAFLD.

Variables	B	SE	Wald	Significance	Exp (B)
Serum ferritin	0.107	0.037	8.498	0.004*	1.113
Serum glucose	0.042	0.028	2.271	0.132	1.043
Serum insulin	-0.086	0.104	0.684	0.048*	0.918
HOMA-IR	0.074	0.211	0.124	0.725	0.917
Alanine aminotransferase	-0.087	0.034	6.469	0.011*	0.917
Aspartate transaminase	0.098	0.046	4.604	0.032*	1.103
Platelet count	-0.051	0.018	8.179	0.004**	0.958
Albumin	-0.043	0.135	0.102	0.705	1.077

**Less than 0.05 p-value (statistically significant), **Less than 0.01 p-value (highly significant)*

DISCUSSION

In the present study a highly significant increase in age and diabetes mellitus was noted among the NAFLD subjects with fibrosis compared to steatosis except of hypertension which was more common in steatotic group. Nakeeb *et al*[7] and Angulo *et al*[9] and Sagnetha *et al* [10] reported that age, BMI and DM were significantly raised for fibrosis and while Angulo et al 9 stated that hypertension was not associated with the progression of the disease. Wong and his colleagues[11] reported association of obesity with NASH but no involvement of ethnicity in the progression. While two Indian studies[12,13] showed no association of diabetes with progression of NAFLD.

Statistically significant difference of AST and ALT levels were noted among controls and NAFLD subjects. With AST raised in fibrosis compared to steatosis while vice versa was noted in ALT. Nakeeb *et al*[7] also reported raised AST levels though no significant difference was noted on ALT levels in any of the groups of their study. While Sanyal *et al*[14] stated that ALT >40 had a 91.42% positive predictive value for NAFLD diagnosis.

Platelet count was significantly decreased in fibrotic subjects when compared with controls and simple

and insulin levels except HOMA-IR had a significant variation between healthy and diseased groups. Though neither of the two had any statistically significant difference in fibrotic and steatotic phases. This is not in accord with some early and few latest studies[18,19] stating that all serum glucose, insulin and HOMA-IR all increase as the disease progresses from steatosis to fibrosis. However, Singh[12] who studied histological changes in NAFLD subjects with and without diabetes reported no significant difference in histology among both the groups. Another Indian study[12] showed no association of glycemic factor with progression.

Raised levels of serum ferritin but within the normal rage had been noted with a significant difference among all the groups. Similar results were reproduced by El Nakeeb, Qamar and Ployzos.[7,19,20] Meanwhile Kowdely *et al*[8], and few other studies[21] reported hyperferritinemia only in the NASH patients while Parikh in 2015[22] showed hyperferritinemia with significant difference among all the groups.

Statistically serum ferritin is directly associated with ALT, AST and insulin in steatotic patients while in the fibrotic subject the association is absent with BMI, ALT, AST and glycemic factors. A statistically non-

significant negative association of ferritin with AST is present among the subjects with progressed disease. Yan[23] stated a negative association of age with ferritin in NAFLD patients, although they found a strong association of ferritin with HOMA-IR, ALT and AST with no correlation with BMI. A study conducted by Galarrequi[24] reported a strong correlation of ferritin with AST, ALT and HOMA-IR along with lipid profile components among the patients suffering with NAFLD.

Recently researchers are busy in finding non-invasive markers/methods that can correctly identifying advanced stages of NAFLD so that liver biopsy can be replaced. As iron is metabolized in the liver hence some new studies have suggested that its metabolic parameters may prove to be a good biomarker for the prediction of the disease and its outcome.[10,24] We hypothesized that NAFLD can be a good diagnostic predictor for fibrosis. The cutoff value of ≥40.75ng/ml and ≥67.55ng/ml for serum ferritin in simple steatosis and NAFLD with fibrosis respectively was found to be best for predicting the occurrence of fibrosis in NAFLD subjects with AUC 0.885. Similarly, some researchers like Al Nakeeb, Parikh and Seyedain declared cut-off values 48 ng/mL, <72.5 ng/mL and 51.95 ng/mL respectively for NAFLD and fibrosis.[7,22] On the other hand some researchers proved higher cut of values for the prediction of fibrosis.[6,25]

In this study, we can declare that serum ferritin alone can be an independent predictor for fibrosis. Other biochemical markers like insulin, ALT, AST and platelet count all can be good predictors too.

CONCLUSION

Serum ferritin has a good positive predictive value.

RECOMMENDATIONS

We would like to suggest that the study should have be performed on a larger sample and instead of NFS liver biopsy should be used to categorise the fibrosis.

ACKNOWLEDGEMENT

We acknowledge the support and guidance of Dr Sajjid Nisar, Dr Karman Aziz and Dr Saqib Javeed All the authors declare that there are no relevant financial or non-financial conflicts of interest to be disclosed.

Conflict of Interest: None.

Author's Contributions

MQ: Idea/ conceptualization, Statistical analysis, discussion and drafting of the manuscript.

AT & QAN: Final approval of the manuscript and critical review, KE: Proof reading, reference writing and critical review, RA & SAF: sample collection and proof reading.

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