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Fatty Liver Disease and Its Impaction on Insulin Resistance

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) involves excess liver fat accumulation without specific causes like alcohol or viral infections, categorized into simple steatosis and nonalcoholic steatohepatitis (NASH). While simple steatosis is generally stable, NASH is linked to progressive liver disease. Diagnosis excludes secondary causes, and NAFLD, marked by hepatocyte changes, inflammation, and fibrosis, may lead to severe complications. Strongly correlated with adipose and hepatic tissue insulin resistance (IR). NAFLD disrupts glucose-insulin interplay, compromising insulin's regulatory functions and contributing to metabolic disorders and disease progression.

Objective: This study aimed to investigate fatty liver disease and evaluate its impact on IR.

Patients and Methods: This cross-sectional study, conducted at Ain Shams University, included 98 adult patients with NAFLD patients who had liver disease and impaired glucose tolerance to assess IR. We recorded demographic and anthropometric data, metabolic syndrome assessment, ultrasound grading of steatosis, and laboratory tests for liver function, FIB-4 index, and IR using HOMA-IR. **Results:** In this study, IR was prevalent in 63.3%. The cases, predominantly females (52%), had mean age of 43 years, 50% were hypertensive, and 48% were diabetic. IR was directly related to age, and its prevalence was significantly higher in patients with diabetes and hypertension. IR correlated positively with body weight, BMI, ALT, AST, FIB-4, TG, and cholesterol. Fatty liver grading showed a significant association with IR, particularly in grade 2 cases. The optimal HOMA-IR cutoff for distinguishing between grade I and II fatty liver was >2.56, with high sensitivity (100%) and specificity (88.73%). These findings emphasize the intricate relationship between NAFLD, IR, and associated metabolic factors.

Conclusion: The study established a robust link between IR and NAFLD, noting a 63.3% prevalence of IR in the subjects. Employing HOMA-IR, a cutoff point >2.56 effectively differentiated between NAFLD grades I and II, demonstrating 100% sensitivity, 88.73% specificity, and a remarkable AUC of 98. This underscored HOMA-IR's valuable role in identifying and stratifying NAFLD, especially in individuals with diabetes.

Keywords: NAFLD, NASH, Insulin resistance.

INTRODUCTION

When there is no major alcohol consumption, viral infection, or any identifiable aetiology of liver disease, NAFLD is defined as liver fat accumulation that exceeds 5% of hepatocytes [(1)]. NAFLD is classified into two groups: simple steatosis and NASH. The latter is differentiated from the former by the presence of hepatocellular damage, either with or without fibrosis. While NASH is linked to liver disease that progresses over time, uncomplicated steatosis patients often have stable liver histology [(2)]. When there are no other secondary causes of hepatic steatosis, such as severe alcohol intake, medicines, Wilson's disease, starvation or parenteral nutrition, among other disorders linked to microvesicular steatosis, NAFLD is identified either by histology or imaging [(3)]. Hepatocyte ballooning, lobular inflammation, and/or fibrosis are characteristics of NAFLD, which can result in cirrhosis, hepatocellular carcinoma, and metabolic disorders such IR and DM [(4)].

Reduced whole-body insulin sensitivity and IR in adipose and liver tissue are also substantially correlated with NAFLD. The human body has intricate metabolic pathways that involve molecular interactions between insulin and glucose. IR results from a malfunction in this interaction. Insulin's incapacity to stimulate muscle's absorption of glucose and the liver's inhibition of gluconeogenesis result in a gradual decline in beta cell activity and, eventually, IR [(5)]. Insulin binds to its receptor, which contains 2 alpha and 2 beta chains on the cell surface, and this activates signaling cascade leading to glucose influx into cells, glycogen synthesis, lipogenesis and cell proliferation. On the other hand this cascade leads to down regulation of gluconeogenesis and lipolysis [(6)].

Insulin sensitivity is decreased in insulin-resistant people with NAFLD, not just in muscle but also in liver and adipose tissue. Adipose tissue becomes resistant to insulin's antilipolytic function in insulin-resistant situations, leading to an increase in fatty acid release. Increased insulin levels associated with IR lead to an increase in hepatic triglyceride production when combined with increased lipolysis and/or fat consumption [(7)]. This study aimed to investigate fatty liver disease and evaluate its impact on IR.

PATIENTS AND METHODS

This cross-sectional study, conducted at Internal Medicine Department, Ain Shams University, focused on adults with NAFLD to assess IR.

Inclusion criteria: Adult patients above the age of 18 years, patients with fatty liver disease based upon the results of pelvic abdominal ultrasound, patients with impaired glucose intolerance as evaluated by a 75-g OGTT (i.e., a fasting plasma glucose concentration >7 mmol/l and a 2-hour postglucose plasma glucose concentration >7.8 mmol/l), and patients who are able to provide informed consent.

Exclusion criteria: Alcohol intake, either viral or chronic hepatitis, liver damage brought on by drugs, obstructive disorders of the liver, complete parenteral nourishment, inflammatory hepatitis, Wilson's disease, patients with a

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histological diagnosis of cirrhosis, presence of cancer, pregnancy and declined informed consent.

Study procedure: Demographic data were collected from all patients as age, sex, comorbidities (hypertension, diabetes, metabolic syndrome and drug/herb intake, measurements of waist circumference, body weight, and height are examples of anthropometric testing). The formula for calculating BMI was weight (kg) divided by height (m) squared. The waist circumference was measured using a tape measure placed horizontally around the entire body at a point halfway between the lower rib border and iliac crest. Any three of the following conditions are considered to be indicators of metabolic syndrome: (1) Central obesity (waist circumference of P85 cm in men and P80 cm in women), (2) Triglycerides >1.7 mmol/L, (3) Reduced high-density lipoprotein–cholesterol (<1.0 mmol/L in men and <1.3 mmol/L in women), (4) blood pressure of P130/85 mm Hg and (5) fasting plasma glucose of P5.6 mmol/L. Treatment for the aforementioned metabolic abnormalities is also considered metabolic syndrome [(8)].

Ultrasonography examination: The patient was placed in a supine posture, with his forearm beneath his head and his right arm abducted, to undergo imaging. In order to inspect the liver, the right side of the body was exposed and slightly lifted. The ultrasonic gel-coated probe tip was positioned above the right liver lobe in the intercostal region. A section of the liver devoid of any significant vascular structure and measuring at least 6 cm in thickness was found by the operator. The operator then pressed the probe button to begin capturing images. The measuring depth ranged between 25 and 45 mm. Steatosis is graded by US according to hepatic echogenicity. Grade 0: "being normal;" Grade 1: minor steatosis of the liver; "a slight increase in hepatic parenchymal echogenicity with normal visualisation of diaphragm and intrahepatic vessel margin;" Grade 2: mild to severe steatosis; "moderate increase of echogenicity and slightly impaired visualisation of intrahepatic vessels and diaphragm;" Grade 3 is described as "a marked increase of echogenicity with poor or no visualisation of intrahepatic vessel borders, diaphragm, an,d posterior portion of the right lobe of the liver." [(9)].

Laboratory tests: A complete blood cell count, hemoglobin level, Plt. count, ALT, AST, GGT, ALP and bilirubin was done, The FIB-4 index was assessed as: age (year) × AST (U/L)/(Plt count (10^9/L) × √ALT (U/L)) [(10)], IR was calculated using HOMA-IR according to the following formula: HOMA-IR = fasting insulin (IU/mL) × plasma glucose (mg/dL)/405 [(11)].

Ethical approval: The Ethics Committee of Faculty of Medicine, Ain Shams University approved the study. Following a detailed description of the study's aims, all participants completed an informed consent forms. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis: Data were gathered, checked, coded, and added to SPSS V. 23.0. The quantitative data were expressed as median, inter-quartile range (IQR), and mean ± SD, and ranges where the data were determined to be parametric and non-parametric. Numbers and percentages were also used to represent qualitative characteristics. When a cell's predicted count was less than five, the Chi-square test or the Fisher Exact test were used to compare the qualitative data across the groups. The Mann-Whitney test was used to compare two independent groups with non-parametric distributions, while the independent t-test was used to compare groups with quantitative data and parametric distributions. The correlation between the two quantitative factors within the same group was evaluated using Spearman correlation coefficients. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. When the p-value ≤ 0.05, it was deemed significant.

RESULTS

The studied cases were 98 patients, their mean age was about 43 year, 52 cases were females and 46 cases were males, 50 % of cases were hypertensive, 48 % of cases were diabetic (Table 1).

Table (1): Demographic data and characteristics of the studied patients

		Total no. = 98
Age	Mean± SD	43.21 ± 8.48
	Range	28 – 66
Sex	Female	52 (53.1%)
	Male	46 (46.9%)
HTN	Not	49 (50.0%)
	Present	49 (50.0%)
DM	Not present	51 (52.0%)
	Present and controlled	33 (33.7%)
	Present and not controlled	14 (14.3%)

All studied cases had fatty liver by US, Their mean ALT was 43 IU/l and AST was 39 IU/l, the mean platelets was about 242,000/ml and FIB-4 was about 0.99, their mean TG was 139 mg/dl and cholesterol was about 210 mg/dl, the mean HOMA-IR was 2.34, IR was found in 62 cases (Table 2).

Table (2): US results, ALT, AST, platelets count, FIB-4, TG, Cholesterol, HOMA-IR and IR among the studied patients

		Total no. = 98
US	Fatty liver	98 (100.0%)
ALT (IU /l)	Mean± SD	43.28 ± 10.79
AST (IU /l)	Mean± SD	39.37 ± 9.58
Platelets (mcL)	Mean± SD	242.93 ± 50.30
FIB-4	Mean± SD	0.99 ±0.22
TG (mg/dl)	Mean± SD	139.99 ± 33.98
Cholesterol (mg/dl)	Mean± SD	209.78 ± 50.18
HOMA-IR	Mean± SD	2.34 ± 0.48
Insulin resistance	No IR	36 (36.7%)
	IR	62 (63.3%)

Table (3) showed that IR was directly related to age in the study group, while there was no statistically significant difference in gender between cases with IR and cases without IR.

Table (3): Comparison between cases with insulin resistance and cases without insulin resistance regarding demographic data and characteristics of the studied patients

		No IR	IR	Test value	P-value	Sig.
		No. = 36	No. = 62			
Age	Mean ± SD	37.08 ± 4.88	46.77 ± 8.10	-6.516•	<0.001	HS
	Range	28 – 50	33 – 66			
Sex	Female	15 (41.7%)	37 (59.7%)	2.966*	0.085	NS
	Male	21 (58.3%)	25 (40.3%)			

*: Chi-square test; •: Independent t-test, HS: Highly significant.

Table (4) showed that prevalence of DM and HTN was statistically higher in cases with IR than cases without IR.

Table (4): Comparison between cases with insulin resistance and cases without insulin resistance regarding HTN and DM of the studied patients

		No IR	IR	Test value	P-value	Sig.
		No. = 36	No. = 62			
HTN	Not	26 (72.2%)	23 (37.1%)	11.240*	0.001	HS
	Present	10 (27.8%)	39 (62.9%)			
DM	Not present	32 (88.9%)	19 (30.6%)	31.578*	0.000	HS
	Present and controlled	4 (11.1%)	29 (46.8%)			
	Present and not controlled	0 (0.0%)	14 (22.6%)			

*: Chi-square test, HS: Highly significant

Table (5) showed that IR is directly related to body weight and BMI in the study group.

Table (5): Comparison between cases with insulin resistance and cases without insulin resistance regarding body weight and BMI of the studied patients

		No IR	IR	Test value	P-value	Sig.
		No. = 36	No. = 62			
Body Weight (kg)	Mean ± SD	68.94 ± 1.79	76.81 ± 4.68	-9.656•	<0.001	HS
	Range	65 – 72	68 – 89			
BMI (kg/m^2)	Mean ± SD	23.66 ± 1.05	25.95 ± 1.21	-9.500•	<0.001	HS
	Range	21 – 24.9	23 – 28.2			

•: Independent t-test, HS: Highly significant

Table (6) showed that there was a statistically significant difference between the two groups for ALT, AST, FIB-4, TG, and cholesterol. They were found to be greater in instances with IR than in cases without IR, although there was no statistically significant difference between cases with and without IR in terms of platelets.

Table (6): Comparison between cases with IR and cases without IR regarding laboratory data of the studied patients

		No IR	IR	Test value	P-value	Sig.
		No. = 36	No. = 62			
ALT (IU /l)	Mean ± SD	36.14 ± 5.88	47.42 ± 11.69	-3.658•	0.000	HS
AST (IU /l)	Mean ± SD	29.47 ± 5.92	45.11 ± 11.14	-5.650•	0.000	HS
Platelets (mcL)	Mean ± SD	246.75 ± 36.54	240.71 ± 56.95	0.571•	0.569	NS
FIB-4	Median (IQR) Range	0.76 (0.69 – 0.84) 0.43 – 0.99	1.27 (1.03 – 1.58) 0.43 – 3.01	-6.604≠	0.000	HS
TG (mg/dl)	Mean ± SD	77.67 ± 19.38	176.18 ± 9.03	-32.685•	0.000	HS
Cholesterol (mg/dl)	Mean ± SD	146.75 ± 28.68	246.37 ± 20.59	-19.927•	0.000	HS

Median, IQR and Range: non parametric test •: Independent t-test; ≠: Mann-Whitney test, HS: Highly significant

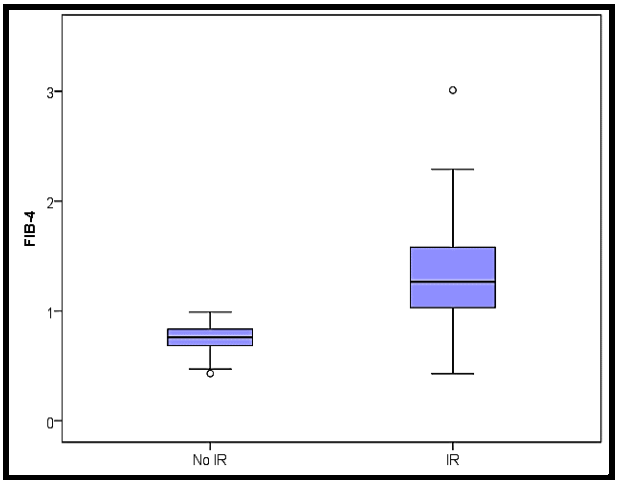

Figure (1): Comparison between cases with IR and cases without IR regarding FIB-4.

Table (7) showed that there was statistically positive correlation between HOMA-IR and age, body weight, BMI, ALT, AST, FIB-4, TG and cholesterol, while HOMA-IR was not statistically correlated to platelets count.

Table (7): Correlation of HOMA-IR and other studied parameters

	HOMA-IR	
	r	**P-value**
Age (years)	**0.608****	**< 0.001**
Body Weight (kg)	**0.777****	**< 0.001**
BMI (kg/m^2)	**0.895****	**< 0.001**
ALT (IU /l)	**0.603****	**< 0.001**
AST (IU /l)	**0.713****	**< 0.001**
Platelets (mcL)	**-0.214***	**0.035**
FIB-4	**0.833****	**< 0.001**
TG (mg/dl)	**0.849****	**< 0.001**
Cholesterol (mg/dl)	**0.924****	**< 0.001**

Spearman correlation coefficient, **: Highly significant

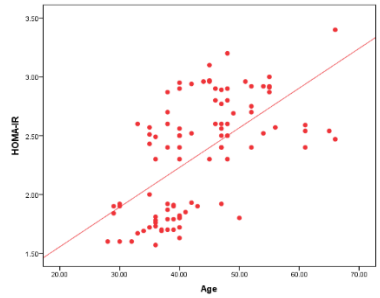

Figure (2): Correlation between HOMA-IR and age

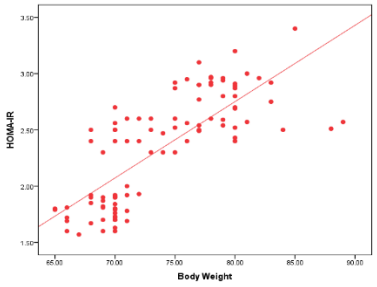

Figure (3): Correlation between HOMA-IR and body weight

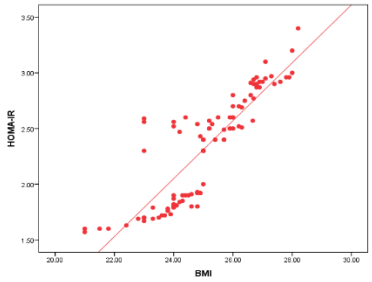

Figure (4): Correlation between HOMA-IR and BMI

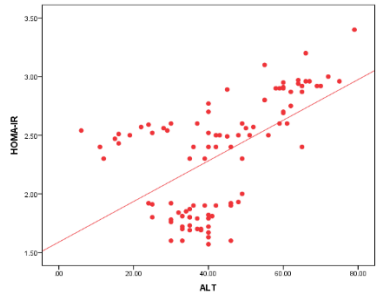

Figure (5): Correlation between HOMA-IR and ALT

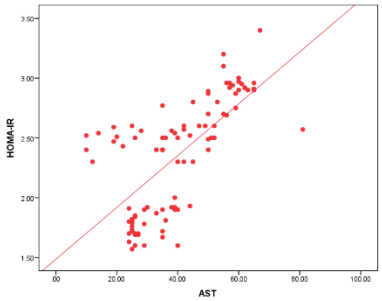

Figure (6): Correlation between HOMA-IR and AST

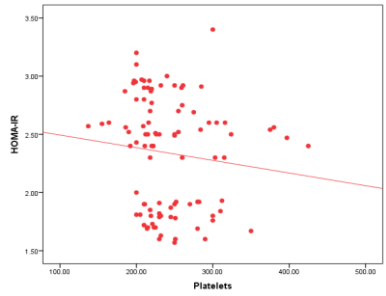

Figure (7): Correlation between HOMA-IR and platelets

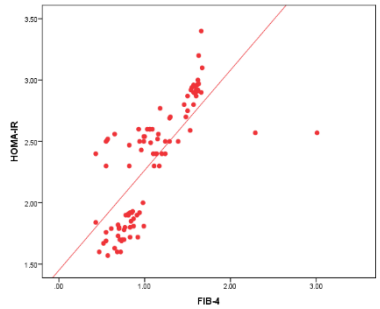

Figure (8): Correlation between HOMA-IR and FIB-4

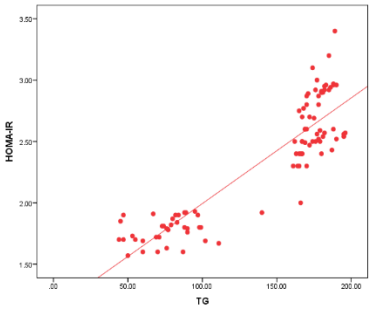

Figure (9): Correlation between HOMA-IR and TG

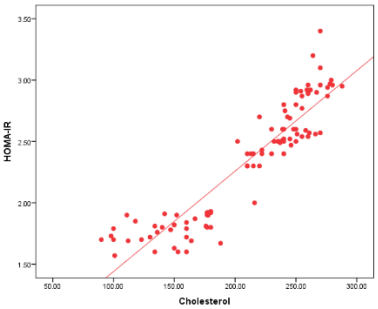

Figure (10): Correlation between HOMA-IR and total cholesterol

Table (8) showed that there was statistically significant relation between fatty liver grading by US and incidence of insulin resistance showing that all grade 2 cases have insulin resistance and only 49.3% of grade 1 case had insulin resistance.

Table (8): Relation between fatty liver grade and incidence of insulin resistance among the studied patients

		Fatty liver		Test value	P-value	Sig.
		Grade 1	Grade 2			
		No. = 71	No. = 27			
Insulin resistance	No IR	36 (50.7%)	0 (0.0%)	21.639*	<0.001	HS
	IR	35 (49.3%)	27 (100.0%)			

*: Chi-square test, **: Highly significant

This ROC curve showed that the best cut off point for HOMA-IR to differentiate between fatty liver grade I and grade II was found > 2.56 with sensitivity of 100%, specificity of 88.73% and AUC curve of 98.6% (figure 11).

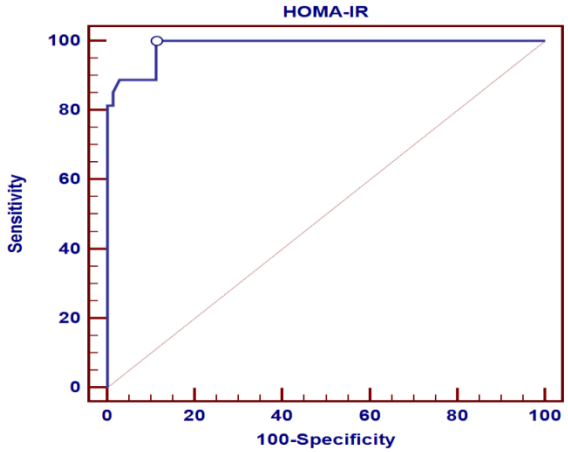

Figure (11): ROC curve for HOMA-IR to differentiate between fatty liver grade 1 and fatty liver grade II.

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
> 2.56	0.986	100.00	88.73	77.1	100.0

DISCUSSION

The studied cases were 98 patients, their mean age was about 43 year, 52 cases were females, 50 % of cases were hypertensive, and 48 % of cases were diabetic. These cases were collected from the Hepatology Clinic and the inpatient Internal Medicine Department, at Faculty of Medicine, Ain Shams University within 5 months. All studied cases had fatty liver by US, their mean ALT was 43 IU /l, and AST was 39 IU/l. The mean platelets was about 242,000/ml and FIB-4 was about 0.99, their mean TG was 139 mg/dl and cholesterol was about 210 mg/dl ,the mean HOMA-IR was 2.34 .

The findings of this investigation showed that IR, determined by HOMA-IR, was found in 62 cases (63.3 %) of the studied cases. This result is consistent with **Saleh *et al.*** [12], which included 40 NAFLD patients and showed that 62.5 % of NAFLD patients have IR.

IR, determined by HOMA-IR, was directly related to age in the study group with a p value < 0.001. These results are compatible with those of **Musso *et al.*** [13] who found a correlation between HOMA-IR and age in NAFLD patients. A reduction in insulin-mediated glucose absorption by peripheral tissues and a delay in insulin-induced inhibition of hepatic glucose output are two possible explanations for these observations [14].

There was no statistically significant difference in gender between cases with IR, determined by HOMA-IR, and cases without IR. This contrasts with the study of **Nagral *et al.*** [15], who reported that NAFLD and IR are more in males than females before menopause but both males and females become near to each other in postmenopausal period.

The prevalence of DM and HTN was statistically higher in cases with IR, determined by HOMA-IR, than cases without IR with a p value = 0.000 and 0.001 respectively. This concurs with **Zhao *et al.*** [16], who said that IR is essential to the onset, course, and advancement of DM, HTN, and other disorders of the metabolism.

IR, determined by HOMA-IR, was positively correlated with body weight and BMI in the study group with a p value < 0.001. These findings are consistent with those from a previous research by **Sagun *et al.*** [17]. Furthermore, the rise in body weight and BMI in NAFLD patients with IR was statistically significant,

which contradicts **Marchesini *et al.* [18],** who indicated that IR was related to NAFLD regardless of BMI.

There was statistically significant difference between IR and non IR groups regarding ALT, AST with a p value =0.000. They were found to be higher in cases with IR, determined by HOMA-IR, than cases without IR. This supports a research by **Gómez-Sámano *et al.* [19]** who found that ALT levels were a reliable indicator of hepatic IR. ALT was the focus of the investigation since it is a liver enzyme that is higher in NASH than AST. They proposed that an excess of free fatty acids to the liver causes hepatic lipotoxicity, which leads to an excess of TG synthesis in the liver and an intracellular build-up of toxic lipid molecules that disrupt insulin signaling and trigger inflammatory pathways. Hepatic IR, dyslipidemia, steatohepatitis with mitochondrial dysfunction, endoplasmic reticulum stress, reactive oxygen species production, and eventually hepatocellular damage are all involved in the response to this metabolic load [19].

Triglycerides (TG) and cholesterol were found to be higher in cases with IR, determined by HOMA-IR, than cases without IR with a p value =0.000. This result is in line with that of **Choi and Ginsberg [20]** who discovered that IR is linked to elevated hepatic steatosis, increased plasma TG, and enhanced hepatic assembly and secretion of VLDL.

IR, determined by HOMA-IR, was positively correlated to FIB-4 with a p value =0.000. This agrees with the study conducted by **Fujita *et al.* [21]**, which recommended that using FIB-4 as a biomarker for evaluation of NAFLD severity and evaluation of risk for IR and incident DM is required. It is also suggested that NAFLD could be diagnosed early in order to prevent IR and DM.

Between patients with IR, there was no statistically significant difference, determined by HOMA-IR, and cases without IR regarding platelets. This is consistent with the research carried out by **Tomassetti *et al.* [22],** which reported that NAFLD was not associated with thrombocytopenia. In contrast, a study that was conducted by **Lopez-Trujilo *et al.* [23]** showed that thrombocytopenia was present in about one quarter of patients with NAFLD.

There was statistically significant relation between fatty liver grading by US and incidence of IR where all grade 2 cases had IR and only 49.3% of grade 1 cases had IR with a p value < 0.001. This is consistent with the research done by **Cetin *et al.* [24],** which reported that IR in NAFLD patients statistically significantly increases as fatty liver grade progresses.

The ROC curve showed that the best cut off point for HOMA-IR to differentiate between fatty liver grade I and grade II was found > 2.56 with sensitivity of 100%, specificity of 88.73% and AUC curve of 98.6%. This is supported with the study conducted by **Ryoo *et al.* [25]**, which reported that IR, determined with HOMA-IR, increased according to the degree of NAFLD in their study, and the cut off point for HOMA-IR of the mild steatosis (grade 1) is about 2.73 (2.55-2.93).

LIMITATIONS: There are limited number of patients. Fibroscan was not used for diagnosis of NAFLD patients. Liver biopsy was not used to diagnose NAFLD and assess its grades.

CONCLUSION

IR and NAFLD are closely associated. Persons with diabetes have a 5-fold greater frequency of NAFLD than do those without the disease. Both the aetiology of NAFLD and the evolution of the condition from steatosis to NASH are linked to IR. The study established a robust link between IR and NAFLD, noting a 63.3% prevalence of IR in the subjects. Employing HOMA-IR, a cutoff point > 2.56 effectively differentiated between NAFLD grades I and II, demonstrating 100% sensitivity, 88.73% specificity, and a remarkable AUC of 98. This underscores HOMA-IR's valuable role in identifying and stratifying NAFLD, especially in individuals with diabetes.

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Conflict of Interest: Nil.

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