Assessment Of Serum Resistin Relation To Hepatocellular Carcinoma In Patient With Liver Cirrhosis

Mahmoud Abdou Ashour*, Fady Maher Wadea*, Nader Mohamad M. Hussein, Abd-Elhalim Mohamed A. Elnagar***.**

*** Internal Medicine department, Faculty of Medicine - Zagazig University**

**** Clinical Pathology department, Faculty of Medicine - Zagazig University**

***** Internal Medicine department, Zagazig General Hospital**

Abstract

Background: Hepatocellular carcinoma in the most prevalent primary liver cancer and the third leading cause of cancer related mortalities worldwide. Increased serum resistin level was suspected to influence the growth and proliferation of malignant cells possibly HCC in patients with liver cirrhosis.

Aim of the work: The aim of this study was to assess the possible relation between serum levels of resistin and HCC in patients suffering of liver cirrhosis.***Methods:*** This case-control study was conducted at the gastroenterology and hepatology unit of the Internal Medicine Department of Zagazig University Hospitals for 6 months in the period from January 2021 to January 2022 on 80 patients divided into two matched groups for age and sex; cases group included 40 cirrhotic patients with HCC (their median ages were 62 years and the range was from 18 – 75 years) and a control group that included 40 cirrhotic patients without HCC (their median ages were 59 years and the range was from 48 – 72 years).

Results: Regarding serum resistin level, our results showed that serum resistin level was significantly higher in cases group than in control group (19.4 vs 3.4 ng/mL) with p-value: < 0.001. There was significant positive correlation between serum resistin and total cholesterol and LDL with p-value: < 0.001. While, there was no significant correlation between serum resistin and other variables. Resistin at cutoff >13.7 with AUC of 0.942 was able to diagnose HCC with a sensitivity of 90% and a specificity of 95%.

Conclusion: serum resistin level may serve as a new diagnostic marker for HCC patients.

Keywords: Liver cirrhosis, Hepatocellular carcinoma, Insulin resistanca, Resistin

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Introduction

Hepatocellular carcinoma "HCC" is the most common primary liver cancer and the second most common cause of cancer-related mortality globally (**1**). Importantly, HCC usually develops in patients with underlying liver cirrhosis (**2**) and it is the most common cause of death in those people (**3**).

Hepatocellular carcinoma (HCC) is a complex disorderly state involving multiple events and etiologies, typically viral hepatitis and metabolic syndrome. The majority of cases occur against a background of chronic inflammation, and this has been confirmed by several clinical and epidemiological studies. The occurrence of HCC is often associated with multiple risk factors such as persistent infection with hepatitis virus, chronic alcohol consumption and aflatoxin B1 exposure. Additionally, metabolic disorders such as diabetes and obesity are also considered risk factors for liver cancer (**4, 5**).

Insulin resistance is a likely cofactor in chronic liver disease which is aggravated by inflammation associated with the underlying liver disease and which potentially contributes to hepatocarcinogenesis. Although HCC is a very

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heterogeneous disease with differences in the genetic and biological background, improving insulin sensitivity in patients with chronic liver disease could have a beneficial effect on the outcome of treatment (**6**).

Resistin also known as adipose tissue-specific secretory factor (ADSF) or C/EBP-epsilon-regulated myeloid-specific secreted cysteine-rich protein (XCP1) is a cysteine-rich adipose-derived peptide hormone that in humans is encoded by the RETN gene. It was originally discovered in mice in 2001 and named for its ability to resist (interfere with) insulin action; at that time, it was proposed as a link between obesity and diabetes. Its activity is implicated in inflammatory processes including: atherosclerosis, rheumatic diseases, nonalcoholic fatty liver disease, and malignancies (**7**).

Resistin acts as intrahepatic cytokine exerting pro-inflammatory actions. Several studies have indicated that resistin may significantly influence the growth and proliferation of malignant cells (**8**) including breast, gastric, and colorectal cancers as well as lymphoma. It has also been suggested that the expression of resistin in cancer cells is associated with more malignant clinic-pathological processes. However, there is still a lack of information about the precise mechanisms of resistin on HCC development.

Aim of the work

The aim of this study was to assess the possible relation between serum levels of resistin and HCC in patients suffering of liver cirrhosis.

Patients and Methods

This was a case control study and patients were recruited from Gastroenterology and Hepatology unit, ICU and outpatients clinic of Internal Medicine department of Zagazig University Hospitals from January 2021 to January 2022.

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

This study included (80) patients matched according to their child's class, age, sex and BMI. They were divided into 2 groups: ***Group (I):*** Included 40 cirrhotic patients with HCC as the cases group. They were 17 females and 23 males. Their ages were in the range between18 – 75 years with median value: 62 years. ***Group (II):*** Included 40 cirrhotic patients without HCC as the control group. They were 15 females and 25 males. Their ages were in the range between 48 – 72 years with median value: 59 years.

Patients with Other malignancies "e.g. breast, kidney, prostate, colon, bladder and skin cancer, patients treated with corticosteroids or any medications known to affect glucose tolerance or insulin secretion, patients with other causes of insulin resistance affecting level of resistin as obesity, acromegaly, Cushing, D.M and PCO and those complaining of HCC on top of NASH were excluded.

After full medical history was taken, all subjects underwent a thorough physical examination and BMI was calculated for all patients.

Laboratory Investigations: including

Complete blood count (CBC), Fasting blood glucose and HA1C, Kidney function & liver function, Lipid profile including HDL, LDL, total cholesterol and TG3, Coagulation profile, and Alpha-fetoprotein (AFP) were done for all patients.

Serum level of Resistin was measured using the Quantikine Human Resistin Immunoassay ELISA kit (Cat. No: E033811a, Bioassay tech. Lab., China). Patient samples were stored at −80◦C at time of collection and

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remained freezed up to the time of resistin measurement.

Radiological examination: included

Abdominal ultrasound, Triphasic CT for diagnosis of site, size, extent and number of focal lesions and Enhanced MRI (in some cases only to confirm diagnosis of HCC).

Statistical analysis:

All data were collected, tabulated, and statistically analyzed using SPSS 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and MedCalc 13 for Windows (MedCalc Software BVBA, Ostend, Belgium). Continuous data were described as the mean ± standard deviation, mean, range and the categorical data were described as a percentage. An independent student t-test was used to compare two groups that have normally distributed data. Percent of categorical variables were compared with the Chi-square (χ^2) test. Correlations between variables were done by using the Pearson correlation coefficient. P< 0.05 was considered to be statistically significant, P< 0.01 was considered to be highly statistically significant.

Results

Regarding demographic characteristics, there was no statistical significant difference between both groups regarding age, gender distribution and smoking history. Regarding Body weight and BMI, patients in HCC group had significantly lower body weight (67 vs 73 Kg) and significantly lower BMI (23.6 vs 24.9 Kg/m2) compared to control group with p-value: 0.006 and 0.029 respectively. Regarding child score, 55.0% of patient in the control group were of class A, 27.5% were of class B and 17.5% were of class C. while in cases group 72.5% of patients were of class B and 27.5% were of class C as shown in table (1).

Regarding laboratory findings, our results showed that patients with HCC had significantly lower Hb concentration, WBCs count, Platelets count, total plasma proteins, serum albumin, Total cholesterol, HDL and LDL. While they had higher levels FBS, ALT, AST, total bilirubin, INR, TG3 and AFP than those without HCC. Also, patients with HCC had significantly higher level of FBS compared to control, however HBA1c level was not significantly differ between the 2 groups as shown in table (2).

Regarding serum resistin level, our results showed that serum resistin level was significantly higher in cases group than in control group (19.4 vs 3.4 ng/mL) with p-value: < 0.001 as shown in figure (1)

Regarding HCC group characteristics; our results showed that 97.5% had < 3 lesions and only 2.5% had > 3 lesions. The size of lesions in 57.5% of cases were > 5cm, and in 40.0% were 3 – 5 cm and in 2.5% were < 3 cm. Regarding child score, 72.5% of cases had class B and 27.5% of cases had class C liver cirrhosis. Portal vein thrombosis was detected in only 35.0% of cases. Regarding HCC stage, our findings showed that stage A, B, D were found in 27.5% for each while stage C were found in 17.5% of cases as shown in table (3).

Regarding correlations of serum resistin with other variables in in HCC group, our results showed that there was significant positive correlation between serum resistin and total cholesterol and LDL with p-value: < 0.001. While, there was no significant correlation between serum resistin and other variables as shown in table (4).

Resistin levels were not significantly differ in relation to size, site, number of focal lesions nor stage of HCC according to BCLC staging as shown in figure (2 & 3).

There was no significant difference in the range of Resistin, ng/mL in BOTH group as regard Child class; In Case: Class C vs B, P= 0.392 across the control as showen in figure (4).

Resistin at cutoff >13.7 with AUC of 0.942 (95% CI:0.867 to 0.982) was able to diagnose HCC with a sensitivity of 90% (95% CI:76.3 -

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97.2%) and a specificity of 95% (95% CI:83.1 - 99.4%). The PPV was94.7 % (95% CI:82.3 - 98.6%) and the NPV was 90.5% (95% CI:78.9 - 96.0%); P= <0.001 as shown in figure (5).

Table (1): Clinico-demographic data in both groups

		Group				Total N=80		Test	P
		Control N=40		Case N=40					
Age		59	48-72	62	18-75	61	18-75	-1.7	0.098
Gender	F	15	37.5%	17	42.5%	32	40.0%	0.2	0.648
	M	25	62.5%	23	57.5%	48	60.0%		
Smoking	No	29	72.5%	21	52.5%	50	62.5%	3.4	0.065
	Yes	11	27.5%	19	47.5%	30	37.5%		
BW		73	53-92	67	56-81	71	53-92	-2.7	0.006
BMI		24.9	19.5-41.8	23.6	16.9-29.1	24.4	16.9-41.8	-2.2	0.029
Child	Class A	22	55.0%	0	0.0%	22	27.5%	30.9	<0.001
	Class B	11	27.5%	29	72.5%	40	50.0%		
	Class C	7	17.5%	11	27.5%	18	22.5%		

Table (2): Laboratory data in both groups

	Group				Total N=80		MW Test	P
	Control N=40		Case N=40					
	Median	Range	Median	Range	Median	Range		
HB	14.6	12.4-17.1	11.7	10.7-14.7	12.7	10.7-17.1	-7.1	<0.001
WBCs	7.8	7.0-8.4	5.3	4.5-6.2	6.6	4.5-8.4	-7.7	<0.001
PLTs	300	270-390	112	82-202	236	82-390	-7.7	<0.001
FBS	100	90-130	117	107-147	110	90-147	-6.6	<0.001
HbA1c	6.0	5.2-6.6	6.0	5.2-6.9	6.0	5.2-6.9	-0.1	0.942
Urea	26	20-32	27	20-32	26	20-32	-0.3	0.786
Creatinine	0.8	0.5-1.0	0.8	0.5-1.0	0.8	0.5-1.0	0.0	>0.999
ALT	19.5	10.0-31.0	73.5	64.0-85.0	47.5	10.0-85.0	-7.7	<0.001
AST	18.0	10.0-35.0	57.6	32.0-112.0	34.5	10.0-112.0	-7.7	<0.001
Alb	4.3	3.5-4.9	2.7	2.1-3.1	3.3	2.1-4.9	-7.7	<0.001
T. Proteins	7.6	6.5-8.9	6.6	6.0-7.0	6.9	6.0-8.9	-6.8	<0.001
T. Bilirubin	1.2	0.4-1.8	4.0	3.4-4.4	2.6	0.4-4.4	-7.7	<0.001
INR	1.1	0.5-1.9	2.3	1.7-2.7	1.8	0.5-2.7	-7.6	<0.001
T, Cholesterol	155	135-181	139	118-169	146	118-181	-4.8	<0.001
LDL	95	82-130	84	71-124	90	71-130	-4.2	<0.001

eISSN 1303-5150

HDL	50	41-63	39	30-52	45	30-63	-6.1	<0.001
TG3	99	65-125	110	78-138	104	65-138	-2.9	0.004
α-FP	4.0	3.4-4.8	308.8	283.2-505.6	144.0	3.4-505.6	-7.7	<0.001

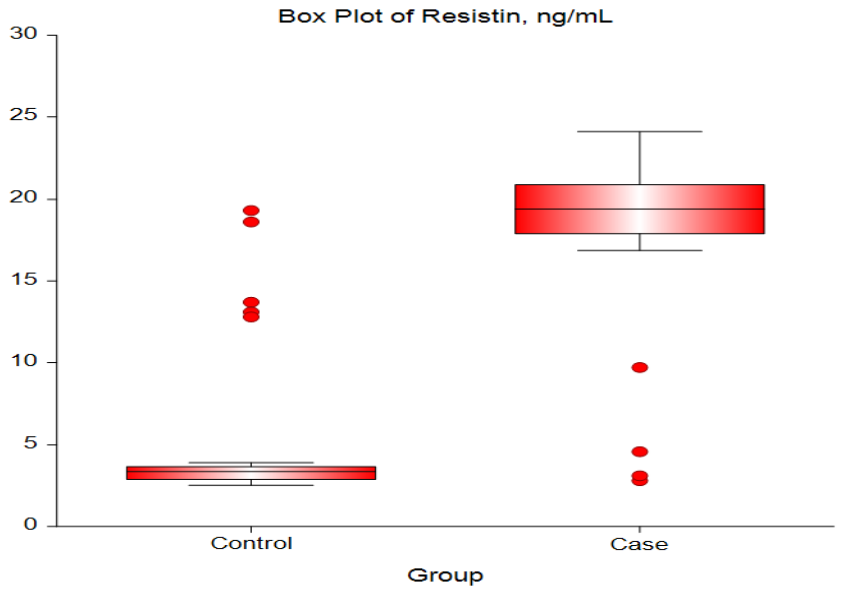


Figure (1): serum resistin level in control and cases groups.

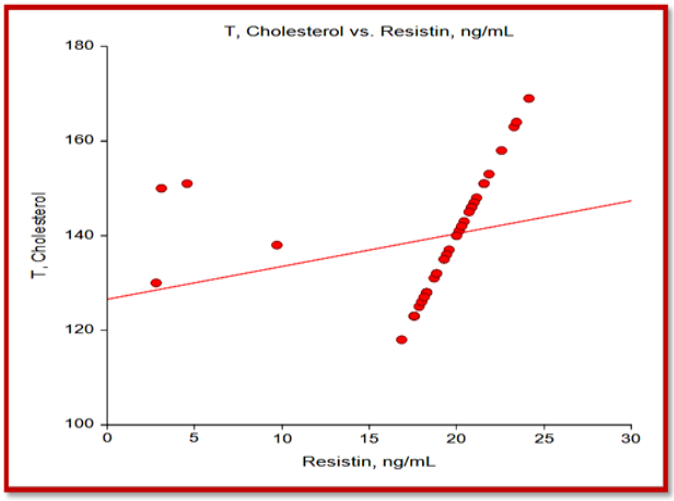
Table (3): Characteristics of the HCC group:

HCC GROUP		N	%
Size of lesions	<3 Cm	1	2.5%
	3-5 Cm	16	40.0%
	> 5 Cm	23	57.5%
Child	Class B	29	72.5%
	Class C	11	27.5%
N. of lesions	<3	39	97.5%
	>3	1	2.5%
PVT	No	26	65.0%
	Yes	14	35.0%
HCC stage	stage A	11	27.5%
	stage B	11	27.5%
	stage C	7	17.5%
	stage D	11	27.5%

eISSN 1303-5150

Table (4): Resistin, ng/mL values in lesions of HCC group:

		Resistin, ng/mL		Test	P
		Median	Range		
PVT	No	19.4	4.6-23.4	-0.2	0.820
	Yes	19.3	2.8-24.1		
No	<3	19.4	2.8-24.1	-1.1	0.260
	>3	17.6	17.6-17.6		
size	<3 Cm	17.9	17.9-17.9	1.7*	0.431
	3-5 Cm	20.1	3.1-24.1		
	> 5 Cm	19.3	2.8-23.4		
HCC stage	stage A	19.3	4.6-23.3	0.74*	0.925
	stage B	19.3	9.7-23.4		
	stage C	17.6	2.8-24.1		
	stage D	20.0	17.6-21.9		



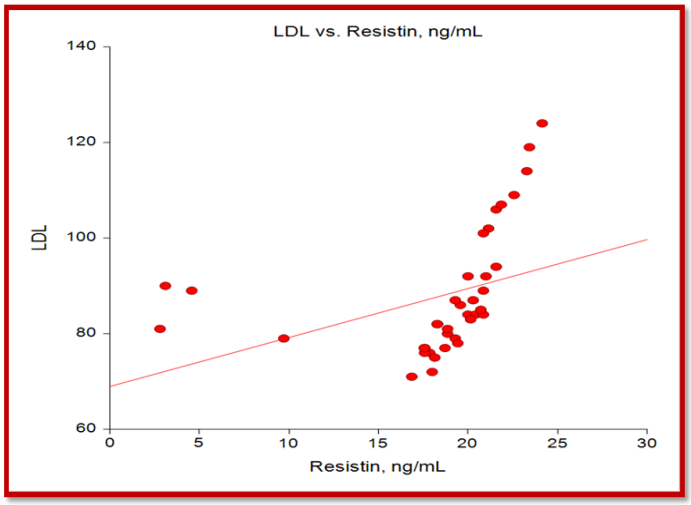


Figure (2 and 3): Correlations of Resistin, ng/mL with TC and LDL in HCC group.

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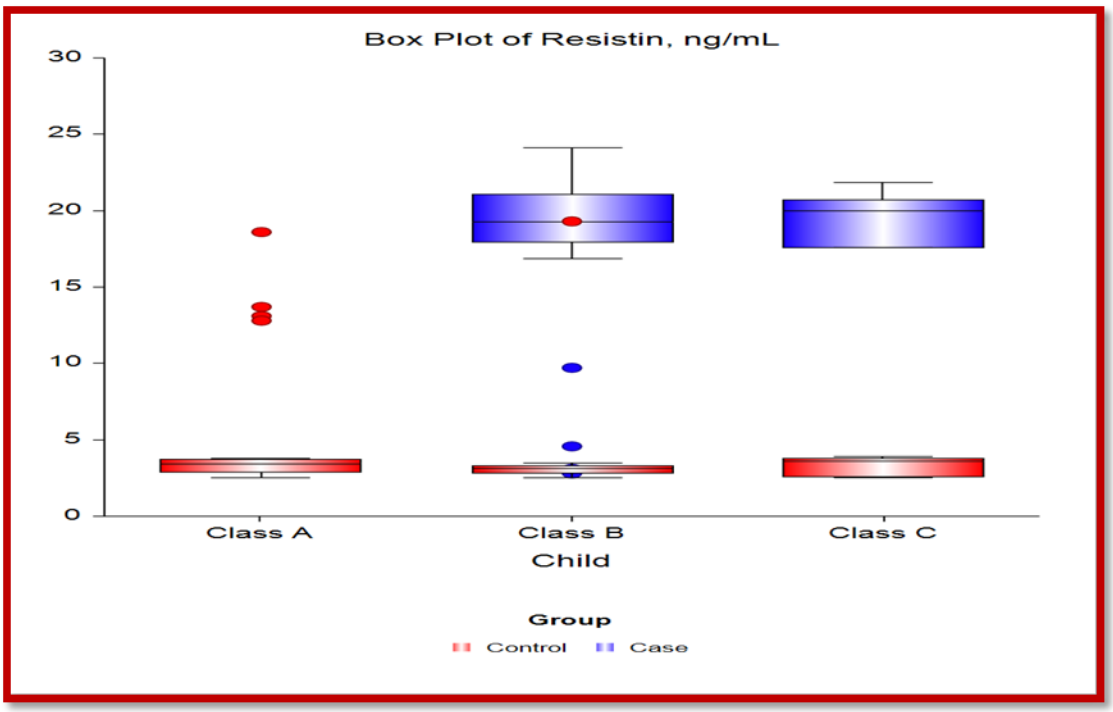

Figure (4): Box-plot diagram represents the range of Resistin, ng/mL in BOTH group as regard Child class

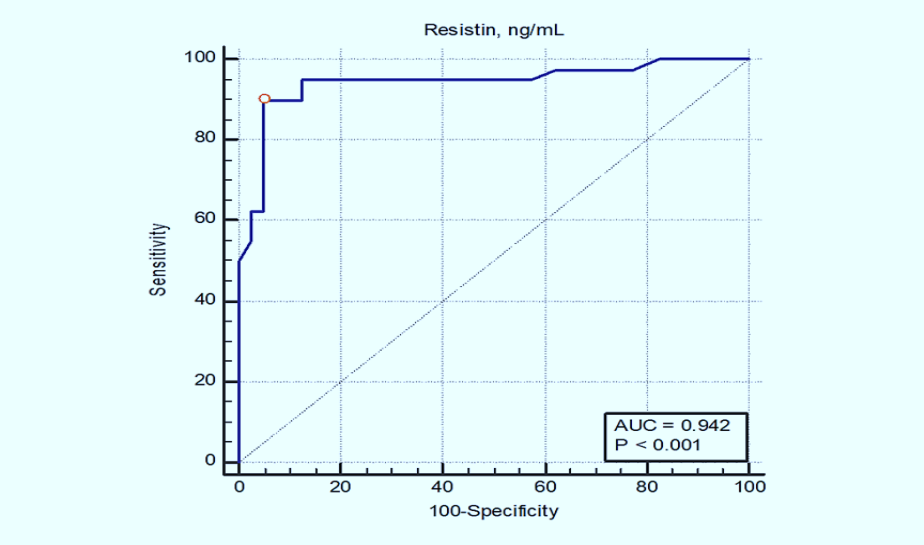

Figure (5): The Area under the ROC curve (AUC) of Resistin as a diagnostic marker for HCC

Discussion

In the present study; HCC patients had a higher male: female ratio (1.6:1) regarding male to female ratio. In the study, done by **Mohamed et al., (9)** patients with HCC had a higher male to female ratio (2.3:1). Their finding was in agreement with **Mohamed et al. (10)**, who reported also a male to female ratio of 2.8: 1 in a study performed on 403 HCC cases at the National Cancer Institute (NCI), Egypt. Moreover, **El-Zayadi et al. (11)** documented the same results.

This may be related to sex-specific differences in exposure to risk factors. Men are more likely to be infected with HBV and HCV, consume alcohol, smoke cigarettes, have higher BMI, and have increased iron stores. A possible

eISSN 1303-5150

role of sex hormones in the development of HCC has also been suggested (**12**).

Regarding laboratory findings, our results showed that there was a statistically significant difference between both groups, patients with HCC had significantly lower Hb concentration, WBCs count, Platelets count, total plasma proteins, serum albumin, total cholesterol, HDL, and LDL. While they had higher levels of FBS, ALT, AST, total bilirubin, INR, TG3, and AFP than those without HCC.

Our results were not in accordance with **Elsayed et al., (8)** study which reported that there was no statistically significant difference between those with HCC and those with LC regarding liver function tests and lipid profile while this study was in agreement with our findings regarding FBS and AFP as well as in **Elbedewy et al., (13)** and **Arrieta et al., (14)** studies.

Insulin resistance plays a critical role in fibrosis progression and increases the risk of HCC regardless of the presence of diabetes (**15**). IR leads to increased hepatocyte lipogenesis, decreased hepatic secretion of very-low-density lipoproteins, and increased hepatic uptake of circulating free fatty acids (FFA) that come from peripheral lipolysis. The resulting liver phenotype is characterized by increased hepatic triglyceride accumulation and macrovesicular steatosis, with varying degrees of necroinflammation and fibrosis (**16**).

Hyperinsulinemia may play a crucial role as an important factor in the onset or progression of HCC through the up-regulation of insulin signal cascades. This could promote fibrogenesis by stimulating the release of connective tissue growth factor, a fibrogenic growth factor from hepatic stellate cells (**17**).

Moreover, the secretion of various adipokines, such as tumor necrosis factor α (TNFα), interleukin-6 (IL-6), and adiponectin may play a role in the relation between insulin resistance and the development of HCC. Increased production of pro-inflammatory cytokines such as TNFα and IL-6 has been reported to be associated with insulin resistance (**18**).

Regarding serum resistin level, our results showed that serum resistin level was significantly higher in the cases group than in the control group (19.4 vs 3.4 ng/mL) with a p-value: of < 0.001.

These findings were in agreement with **Elsayed et al., (8)** who reported that HCC patients showed significantly higher mean values of resistin than cirrhotic patients and the control subjects (p<0.01). Also, **Mohamed et al., (9)** found that serum resistin was significantly higher in cirrhotic patients with HCC than in those without HCC with a mean value of 17.6 and 9.8 ng/ml, respectively (p-value: <0.001). **Elbedewy et al., (13)**, found similar findings regarding serum resistin in HCC patients compared with those without.

The resistin expression in the human liver is increased in various liver diseases and the positive correlation between resistin and inflammation and hepatic fibrosis, which suggests the involvement of this adipokine in the pathophysiology of liver fibrosis (**19**).

Reports suggest resistin induces angiogenesis by regulating various pathways. Evidence indicates in chondrosarcoma cells, it induces VEGF-A expression through PI3K and Akt signaling pathway and downregulates microRNA expression (miR)−16–5p resulting in increased angiogenesis (**20**).

The study done by **Mohamed et al., (9)** reported that serum resistin level was significantly higher among multiple hepatic focal lesions, larger size (>3 cm) hepatic focal lesions as well as patients with portal vein invasion than patients with single, smaller size (below 3 cm) hepatic focal lesions and without portal invasion, with P value less than 0.001.

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While there was no significant difference between them regarding Child score and presence of abdomen ascites.

However in our study, we couldn't document any significant relation of serum resistin to tumor size, number, or portal vein invasion, this is probably due to different populations studied and few cases presented with multiple focal lesions in the current study, so future studies involving a large number of those patients characteristics need to be explored.

Regarding correlations of serum resistin with other variables in the HCC group, our results showed that there was a significant positive correlation between serum resistin and total cholesterol and LDL with a p-value: < 0.001. There was no significant correlation between serum resistin and other variables such as liver function tests or alpha fetoprotein.

Similar to our findings was **Elbedewy et al., (13)**, there was no significant correlation between serum resistin and other variables in their study including liver function.

In addition in **Mohamed et al., (9)** study, there was no significant correlation between serum resistin and ALT, AST, total bilirubin, direct bilirubin, platelets count, and WBCs count.

However, in the study done by **Elsayed et al., (8)** they reported that there was a significant correlation between serum resistin and AFP, child score, tumor number, and tumor size. While there was no significant correlation between serum resistin and total cholesterol, HDL, LDL, and triglycerides and this was not in accordance with our results.

Also, **Elbedewy et al., (13)** reported in their study that there was a significant positive correlation between resistin, and both fasting insulin and AFP.

Regarding the sensitivity and specificity of serum resistin as a marker for HCC, our results showed that at cutoff point > 13.7 ng/ml serum resistin had 90% sensitivity, 95% specificity, 94.7% positive predictive value, and 90.5% negative predictive value for the diagnosis of HCC cases.

Similar to our findings were **Mohamed et al., (9)** who reported that serum resistin levels at a cut-off value greater than 12 ng/ml had 100% sensitivity and 92.3% specificity for detection of HCC (with an overall accuracy of 93.6%).

Also, **Elsayed et al., (8)** reported that patients with serum resistin level greater than 12 ng/ml being 1.6 times more likely to have HCC. And concluded that HOMA and resistin were considered independent risk factors in development of HCC, those patients with resistin > 12 ng/ml and HOMA > 4 being 1.6 times more likely to have HCC.

In conclusion, serum resistin level may serve as a new diagnostic marker for HCC patients, however, its accuracy in detection of early focal lesions and prognosis of these patients should be assessed in further larger studies.

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