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Assessment of Arginase Activity and Antioxidant Markers in Young Liver Cirrhosis Patients in Kirkuk City

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ABSTRACT: Cirrhosis is a condition resulting from chronic liver disease, marked by fibrosis (scar tissue) and nodules (regenerating liver tissue).℧ This study measures serum arginase activity and antioxidant marker parameters in cirrhosis patients in Kirkuk and compares them with healthy controls. The study included 180 people—120 patients and 60 apparently healthy controls—aged 26 to 50 years. Participants were drawn from Kirkuk Teaching Hospital, Azadi Teaching Hospital, and private clinics in Kirkuk, Iraq, between December 2025 and June 2026. Blood samples will be collected from patients and healthy controls, and biochemical parameters will be quantified using appropriate laboratory methods. To find significant difference between the two groups and to check the possible association of arginase activity with the investigated biomarkers, statistical analysis will be done. Serum arginase levels were significantly higher in patients than in controls (99.88 ± 2.59 vs. 59.82 ± 3.38 ng/mL; P = 0.01). Lipid peroxidation was higher in patients than in controls as reflected by the significantly elevated serum MDA (104.36 ± 7.78 vs. 27.85 ± 1.76 nmol/mL; P = 0.01). Nitric oxide (NO) and thioredoxin (Trx) levels were also significantly increased (97.04 ± 3.67 vs. 48.74 ± 2.61 µmol/L and 98.86 ± 1.10 vs. 49.89 ± 1.40 µmol/L, respectively; P = 0.01 for both). The results indicate significant biochemical changes in liver cirrhotic patients, particularly with the elevation of arginase, MDA, NO, and thioredoxin. The changes in these parameters indicate a link between cirrhosis, changes in liver function and oxidative stress.

INTRODUCTION

Chronic liver diseases represent advanced liver damage, and their end stage is called liver cirrhosis, marked by progressive fibrosis, disruption of normal hepatic architecture and regenerative nodule formation due to ongoing liver injury 1. These structural changes obstruct blood flow to the liver and, over time, cause loss of its metabolic, synthetic, detoxification and excretory functions. Compensated cirrhosis may last for years; decompensation is marked by ascites, variceal hemorrhage, hepatic encephalopathy, jaundice, infection and hepatorenal failure 2. Recent clinical guidance holds that cirrhosis is a systemic rather than structural disease, involving abnormalities across the liver, vascular, renal, immune and metabolic systems 3.

Arginase is classified among the arginine amidinohydrolases (EC 3.5.3.1) and functions as the last enzyme of the urea cycle, which is distributed between the mitochondrion and the cytoplasm. This metabolic pathway relies on six enzymatic reactions and two transporters to transform highly toxic ammonia into water-soluble urea, which the kidney then excretes in urine 4. Arginase is a manganese-dependent enzyme that catalyzes the chemical conversion of L-arginine into urea and ornithine. In the catalytic mechanism of arginase, a water molecule positioned between two manganese ions that are also bound within the enzyme's active site is activated into a reactive hydroxide anion. This enables the reactive group to be transferred to the planar guanidino group of the incoming arginine, resulting in the formation of hydrolytic products 5

The distribution pattern of arginase isoenzymes (AI and AII) closely resembles the one seen in normal liver and hepatocellular carcinoma (HCC) 6. In relative terms, though, their activities are altered. In cirrhotic liver, arginase AI accounts for the bulk of total arginase activity (80% of the total), whereas this is not the case in normal liver (>90% of total activity) or

in HCC (roughly 60% of total activity). This drop in arginase AI activity comes with a compensatory increase in arginase AII activity, which in the liver tissue is nearly double that of the controls 7.

Oxidative stress arises when the generation of reactive species rises above the body's capacity to neutralize them 8. Because of its metabolic activity and continuous exposure to endogenous and exogenous substrates requiring biotransformation, the liver is particularly vulnerable. A chronic liver disease characterized by mitochondrial dysfunction, heightened inflammatory signaling, reduced antioxidant capacity and altered ILI may contribute to greater production of ROS and RNS 9.

Thioredoxin (Trx) is an essential redox-regulating protein that participates in controlling cellular thiol homeostasis and in preventing oxidative modification of proteins 10.ↁ Along with thioredoxin reductase and the co-substrate NADPH, the thioredoxin system contributes to reducing oxidized protein thiols and to regulating redox-sensitive signaling pathways. Changes in the thioredoxin pathway may therefore reflect an adaptation to the increased oxidative burden associated with chronic liver disease. Because oxidative stress is closely linked to fibrosis and inflammation, thioredoxin measurement could be added to the classical antioxidants when assessing redox imbalance in cirrhosis11.

Malondialdehyde is a of the major secondary product of polyunsaturated fatty acid peroxidation and also serves as a biochemical marker of oxidative damage to lipids.ↁ The increase in MDA points to damage of circulating and cellular lipids caused by reactive species. In cirrhosis, elevated lipid peroxidation may stem from mitochondrial dysfunction, inflammation, alcohol metabolism, altered iron handling, and weakened antioxidant defenses 12.

Nitric Oxide is a signaling molecule that plays a key role in several physiological functions, including vascular tone, platelet function, inflammation, and hepatic microcirculation. Dysregulation of NO production in cirrhosis leads to an impaired systemic and splanchnic vascular response, as well as to portal hypertension. The relationship between NO and oxidative stress is complex, since NO can combine with superoxide to form reactive nitrogen species such as peroxynitrite, which is a source of nitrosative injury 13.

There is a bidirectional relationship between oxidative stress and hepatic fibrosis. Inflammation and injury of hepatocytes lead to increased generation of ROS/RNS, and oxidative stress promotes activation of stellate cells, deposition of extracellular matrix, and subsequent hepatic damage. This mechanism makes it possible to use both injury markers and antioxidant/redox biomarkers in studies that aim to characterize the biochemical abnormalities of cirrhosis14.

Aimed to the following items:

This study aims to investigate the activity of the arginase enzyme and several antioxidant parameters in young patients with liver cirrhosis in Kirkuk city. It also seeks to investigate the relationship between these biochemical markers and the severity of liver dysfunction, in order to assess whether they could improve the diagnosis and monitoring of liver cirrhosis.

MATERIALS AND METHODS

Subjects:

This study included a total of 180 subjects (120 patients and 60 apparently healthy individuals) ranging from 50 to 26.ↁ

The research was carried out between December 2025 and June 2026 at Kirkuk Teaching Hospital, Azadi Teaching Hospital, and private clinics in Kirkuk, Iraq. They underwent specialized examinations to support their diagnosis.

Samples collection:

Venous blood samples were collected aseptically from the subjects by means of venipuncture.ↁ Of this, 6 ml was collected, divided into two halves, and left at room temperature in a plain tube for 30 minutes. The tube was centrifuged for 10 minutes at 3000 x g. The clear serum is pipetted into clean, dry Eppendorf tubes and stored at (-20)℃ until it is used for various investigations, which are all estimated fresh using an ELISA instrument assay of Chinese origin.

Analysis of Statistics

The mean and standard error of the mean were computed using IBM SPSS software 28.0 (IBM Corp, 2021).ↁ The probability was also analyzed using a student T-test and an ANOVA table. When the data was not parametric, Pearson's chi-square test was used to calculate the probability.

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RESULTS

Comparison of Age and Duration of Disease between Patients with Liver Cirrhosis and Healthy Controls

Table 1 presents a comparison of Age between patients with liver cirrhosis and healthy controls.↻ "The mean age did not differ significantly between patients with liver cirrhosis (37.86 ± 6.06) and the control group (36.13 ± 6.46) (P = 0.06). Regarding the mean duration of disease among patients with liver cirrhosis, it was 2.56 ± 0.74 years.

Table 1: Comparison of Age and Duration of Disease between Patients with Liver Cirrhosis and Healthy Controls

Variable	Patient N=120	Control N=60	P-value
Duration of disease(years)	2.56± 0.74	-----	------
Age.	37.86±6.06	36.13± 6.46	0.06

Liver cirrhosis patients showed elevated levels of arginase, a liver enzyme, compared with the control groups.

As shown in Table 2, the mean Arginase enzyme level in ng/mL was significantly higher among cirrhotic patients (99.88±2.59) than among controls (59.82±3.38) (P = 0.01).

Table 2: Liver enzymes Arginase levels in patients with liver cirrhosis compared to control groups

Liver enzymes levels	**(mean±SD)**		P-value
	Patients with liver cirrhosis	**Control**	
Arginase enzyme ng/mL	99.88±2.59	59.82±3.38	0.01

The blood levels of antioxidant markers in liver cirrhosis patients were compared with those of the control groups.

Malondialdehyde MDA test mean levels in ng/mL were significantly higher in cirrhotic patients (104.36 ± 7.78) than in controls (27.85 ± 1.76) (P = 0.01) (Table 3). Cirrhosis patients had a substantially higher mean nitric oxide (NO) (µ mole/L) level (97.04±3.67) than controls (48.74±2.61) (P = 0). Thioredoxin (Trx) (µ mole/L) was substantially higher in cirrhotic patients (98.86 ±1.10) compared to controls (49.89 ±1.40) (P = 0.01).

Table 3: Malondialdehyde MDA, Nitric oxide (NO) and Thioredoxin (Trx) levels in patients with liver cirrhosis and control groups

Variable	(mean±SD)		P-value
	Patients with liver cirrhosis	**Control**	
Malondialdehyde MDA levels ng /ml	104.36±7.78	27.85±1.76	0.01
Nitric oxide (NO) (µ mole/L)levels	97.04±3.67	48.74±2.61	0. 01
Thioredoxin(Trx) (µ mole/L)levels	98.86 ±1.10	49.89±1.40	0. 01

CHARACTERISTIC ANALYSIS FOR RECEIVER OPERATING

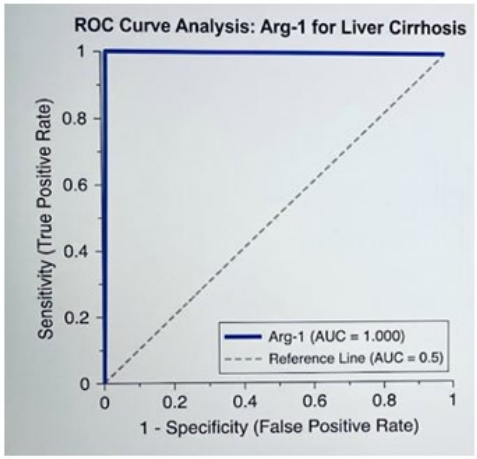
AUC analysis and ROC curve for Patients with liver cirrhosis and healthy subjects

ROC curve analyses were run to determine each biomarker's Area Under the Curve (AUC), Standard Error (SE), 95% Confidence Intervals (95% CI), p-values, optimal cut-off thresholds (via Youden's J statistic), Sensitivity (%), and Specificity

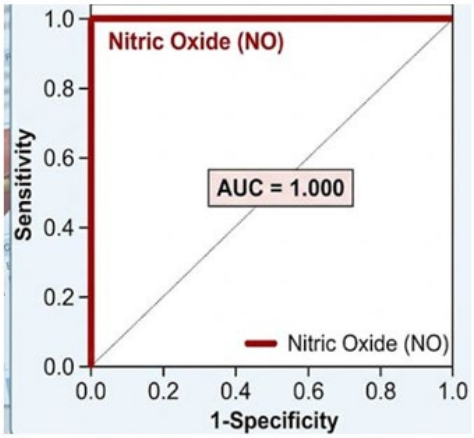
(%).Statistical Significance: Every proposed biomarker showed highly significant diagnostic ability ($p < 0.001$) in distinguishing liver cirrhosis patients from controls.

Table 4: AUC, and proposed markers obtained by the ROC Curves for prediction in Patients with liver cirrhosis compared to the control group

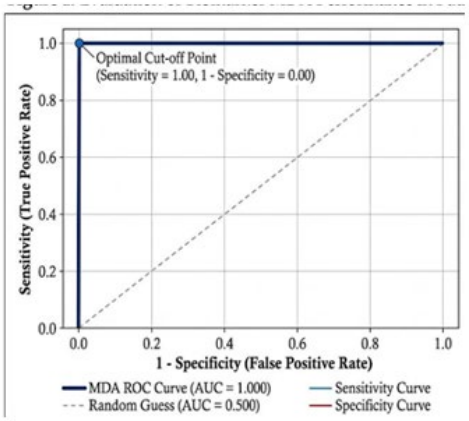
Biomarker Parameter	Patients (Mean ± SD)	Controls (Mean ± SD)	AUC	95% CI	p-value	Cut-off Value	Sensitivity (%)	Specificity (%)
Arg-1 (ng/mL)	99.88 ± 2.59	59.82 ± 3.38	1.000	1.000 – 1.000	< 0.0001	> 94.89	100.0%	100.0%
MDA (nmol/mL)	121.14 ± 130.24	27.85 ± 1.76	1.000	1.000 – 1.000	< 0.0001	> 91.35	100.0%	100.0%
Nitric Oxide - NO (µmol/L)	97.04 ± 3.67	48.74 ± 2.61	1.000	1.000 – 1.000	< 0.0001	> 89.99	100.0%	100.0%
Thioredoxin - Trx (ng/mL)	98.86 ± 1.10	49.89 ± 1.40	1.000	1.000 – 1.000	< 0.0001	> 97.43	100.0%	100.0%



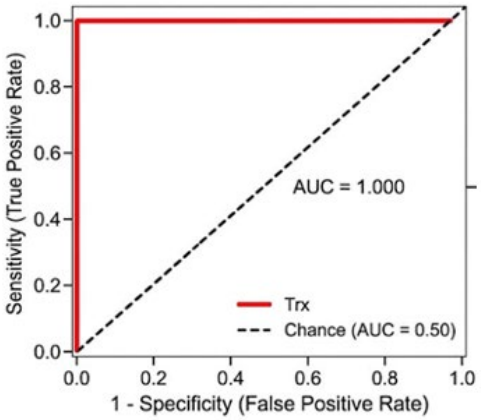
A- Arg-



C- Nitric Oxide – NO



B- MDA



D- Thioredoxin - Trx

Fig.1: ROC Curves for prediction in Patients with liver cirrhosis

DISCUSSION

Serum arginase levels were noticeably higher in the cirrhosis group than in the controls, which suggests disturbed amino acid metabolism and changes in the urea cycle caused by chronic liver damage. Arginase is essential for turning L-arginine into L-ornithine and urea. Arginase I, mostly found in the liver, is central to ammonia detoxification and nitrogen metabolism. Hepatocellular injury can change arginase expression, its release from cells, and enzyme activity, thus altering circulating arginase15 levels.

The raised levels may arise from hepatocyte damage, inflammation, and metabolic shifts as fibrosis advances. The normal architecture and function of the liver are disrupted by structural changes caused by cirrhosis, such as fibrosis and regenerative nodules. In chronic liver disease 16, nitric oxide production, vascular regulation, and inflammation can also be affected by altered arginine metabolism. A possible link between cirrhosis and arginase changes is thus supported by this finding 17.

Duah et al., 18 found most patients had disease lasting through the first years, with symptoms of 8-24 weeks, and most died after a fairly short two-week hospital stay. Such delays suggest managed cases likely had severe or advanced disease, hence rapid progression to death.

Nyarko et al., 19 also documented severe liver disease in the study population, most patients aged 35-40. Duah et al. 106 found most patients in the early years of disease duration. Presenting symptoms matched those in similar studies. Abdominal distension was the commonest symptom, caused by ascites, which is linked to mortality in cirrhotic patients. This study's complication prevalence is similar to reports from other centers and elsewhere

Ogino *et al.*, (2021)study 20 found that more severe somatic symptoms were linked to lower arginase-1 levels. Multiple studies link somatization with chronic liver disease. Fatigue and somatic complaints tied to depression are common and disabling, particularly among cirrhosis patients. Yet no study directly links arginase-1 to physical symptoms, although canè *et al.* (2025) found a negative relationship between workload and arginase-1 in cirrhosis. Mental stress elevates adrenocortical hormone levels and reduces arginase-1 expression. Hepatic encephalopathy is known to influence mental status in cirrhosis patients. 21

Increased oxygenation of lipids during liver cirrhosis could be the cause of this.ↀ The study also found that MDA levels in cirrhotic patients correlate positively with main portal vein width and the degree of esophageal varices. Regression analysis showed that changes in MDA level are linked synchronously with portal hypertension severity 22. Our study examined this because no clinical evidence has yet linked oxidative stress and portal hypertension. In cirrhosis, nitric oxide (NO) is known to play a key role in portal hypertension development and in the high-pressure circulation, meanwhile 23. Plasma nitric oxide may independently predict hepatic venous pressure in cirrhotic patients, given the interaction between nitric oxide and cirrhosis. Also, higher plasma nitric oxide in cirrhotic patients may stem from greater endotoxin translocation from the gut into the bloodstream. Portal vein pressure ultimately rises because endotoxemia raises intrahepatic resistance and boosts nitric oxide release 24. There was a significant increase in serum thioredoxin (Trx) among liver cirrhosis patients when compared with the controls. This rise could be attributed to a heightened oxidant stress and activation of cellular antioxidant defence mechanisms, which are linked to chronic liver injuries. Thioredoxin is a significant redox-regulating protein involved in balancing oxidants and antioxidants by controlling thiol groups of proteins, and by activation of antioxidant systems 25. In liver cirrhosis, the chronic inflammation, hepatocyte damage, and the buildup of reactive oxygen species (ROS) might lead to a compensatory up-regulation and release of thioredoxin as a response to hepatic oxidative injury 26.

In addition, chronic liver inflammation and fibrosis can cause the disruption of the redox balance, resulting in higher concentrations of thioredoxins in the circulation. Thioredoxin has antioxidant and anti-inflammatory properties, but a high serum level of thioredoxin may also represent a higher oxidative stress and persistent tissue damage 27.

CONCLUSIONS

1 The highest mean of patients with liver cirrhosis were in the 37 age group.
2 Liver cirrhosis patients had significantly higher levels of arginase in their blood serum than the control group.
3 Antioxidant responses: An elevation in the serum levels of malondialdehyde (MDA), nitric oxide (NO) and thioredoxin (Trx) indicates that there are disturbances in oxidative balance and redox regulation that may be associated with liver injury, fibrosis and hemodynamic alterations associated with cirrhosis.

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AUTHOR CONTRIBUTIONS

Fatima Sarhad Hassan [1] **Nawal Abdullah Murtadha**[2] Conceptualization, Writing-Original Draft, Writing-Review& Editing. **Nawal Abdullah Murtadha**[2]: Supervision, Validation, Writing-Review & Editing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The data supporting the finding of this study are available from the corresponding author upon reasonable request at ايميل الباحث

Conflicts of Interest

The authors declare no conflict of interest

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