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Prediction Role Of Some Cytokines, Hormones Parameters In Chronic Of Liver Diseases

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Abstract

Background: *There are several different liver disorders and illnesses. Some are brought on by viruses, such as hepatitis. Others may be brought on by using drugs or consuming excessive alcohol. Cirrhosis may result from chronic liver damage or scar tissue. One indication of liver illness is jaundice, or yellowing of the skin.*

Aim: *study to determine the predictive role of IL-12, TNF-a, erythropoietin, vitamin D3 and insulin markers in chronic liver diseases in Iraqi patients.*

Methods: *Diyala's Khanaqin Teaching Hospital conducted the study from January to March 2023. Khanaqin Teaching Hospital's advising unit consultant doctor diagnosed 50 liver failure patients' blood samples. Healthy people gave 30 blood samples as controls. ELISA (Diaclone Research, Besancon, France) measured serum IL-12, TNF-a, Erythropoietin, and Insulin. I-chroma equipment for human serum vitamin D3 fluorescence immune-assay. We evaluated our data with SPSS 24.0 and Graph Pad Prism 10.*

Results: *The study found higher disease prevalence in males (66.0%) compared to females (34.0%), higher rates in 51-60 and 61-70 age groups (24.0% and 32.0%), and lower prevalence in non-obese liver patients (24.0%) compared to obese patients (76.0%), with significant differences ($p<0.05$) among gender, Patients had significantly greater levels of IL-12, TNF-a, Erythropoietin, and Insulin indicators compared to healthy persons ($p<0.05$).In contrast, people with liver failure had considerably lower vitamin D3 levels ($p<0.05$) than healthy individuals. Above markers were unaffected by age, weight, or gender. The ROC curve concluded that liver disease indicators are sensitive and specific. Liver failure risk variables included gender, age, and obesity. Due to high sensitivity and specificity in diagnosing chronic liver disorders, IL-12, TNF-a, erythropoietin, vitamin D3, and insulin indicators are involved in pathogenesis.*

Keywords. *Chronic liver diseases, IL-12, TNF-a, erythropoietin, vitamin D3 and insulin.*

INTRODUCTION

Chronic liver disease (CLD) is a progressive degradation that impacts the liver's activities over a period of over six months [1]. These processes comprise the production of coagulation factors as well as additional proteins, the detoxification of toxic metabolic byproducts, and the removal of bile. Cirrhosis and fibrosis are the results of CLD, which is a chronic disorder characterized by inflammation, liver parenchymal damage, and repair [2]. Chronic liver disease has a wide range of etiologies, including toxins, long-term alcohol consumption, infection, autoimmune illnesses, genetic abnormalities, and metabolic problems. The last phase of chronic liver disease, known as cirrhosis, is characterized by disturbance of the liver's construction, the development of many nodules, vascular rearrangement, neo-angiogenesis, and the deposition of an extracellular matrix [3]. The contributing factors of CLD among those aged 15 to 29 have changed over the past ten years. Viral hepatitis continues to be the leading cause of CLD-related mortality, but the prevalence of HBV is declining globally, and NAFLD is the

primary factor driving a rise in CLD occurrence [4]. Immune cell development, maturing, and operational stimulation are all significantly influenced by cytokines. Numerous kinds of cell, including NK cells, macrophages, CD4+T cells, and CD8+T cells, generate cytokines [5]. Interleukin-12 (IL-12) constitutes one of the most significant proinflammatory molecules that is primarily produced by antigen-presenting cells in reaction to IFN-activation and provided with the onset of the immune system's reaction [6]. As a consequence, IL-12 is frequently regarded as a single of the most precisely defined variables determining Th1 and Th2 distinction. According to a new study, IL-12 has a significant impact in non obeese patients with liver illness, indicating its participation in the process of inflammation that results in such illnesses [7]. Another study is required for relation IL-12 with obese patients with liver inflammation. Tumor necrosis factor-α (TNFα) is a pleiotropic cytokine generated by a number of immune system cells, particularly macrophages and monocytes [8]. TNF may activate a number of pathways of signaling associated with apoptosis, proliferating, and inflammatory. The function of TNF in fibrosis of the liver has not yet been thoroughly described, despite the fact that it has been linked to the etiology of persistent inflammation of the liver that results in hepatic fibrosis, and subsequently its role liver diseases not clear [9]. According to [10], vitamin D has been scientifically linked to the etiology of several illnesses, such as malignancies, inflammatory reactions, autoimmune disorders, heart disease, and disorders of the liver. Although the cause of the relationship between NAFLD and decreased levels of vitamin D is yet unknown, vitamin D can safeguard against fibrosis and inflammation in the stellate cells of the liver [11]. Therefore, more researches required for showed correlation between vitamin D and liver diseases. Insulin reduces gluconeogenesis and increases the production of glycogen in the liver's cells via increasing glucose absorption. Thus, hyperglycemia in the context of elevated insulin dosages results in a surplus of glycogen formation and retention in the organ of liver. Glycogenosis can increase blood enzyme levels, but it doesn't appear to harm hepatocytes and isn't linked to fibrosis or irreversible liver damage. When insulin and glucose are stopped, glycogenosis quickly reverses. Additionally, large dosages of corticosteroids can promote hyperglycemia, which can lead to glycogenesis [12].

Erythropoietin (EPO), a glycoprotein hormone mostly generated by the kidneys, encourages erythrocyte precursor cells to multiply and specialization. EPO works to safeguard the kidneys. The erythropoietin receptor (EPOR), which is present in various systems besides the kidneys, suggests that EPO also has a role in neuroprotection, anti-inflammation, anti-oxidation, and apoptosis [13]. According to a recent investigation, end-stage cirrhosis patients' possible inadequate EPO response may be explained by weak, poor hepatic synthesis capability, a declining cofactors leveled and proinflammatory mechanism of feedback [14]. That refer to importance of this hormone in liver diseases. So the present study come due to the lack of studies in Diyala province on the roles of IL-12, TNF-a, erythropoietin, vitamin D3 and insulin markers in the pathophysiology of obese patients with chronic liver failure, the current study aims to identify the roles of these markers in those patients in this area.

MATERIAL AND METHODS

SAMPLES COLLECTION

The current study was applied in Khanaqin Teaching Hospital /Diyala province within period from January into March 2023. Fifty samples blood were taken from liver failure patients who came to the Khanaqin Teaching Hospital and those examination and diagnosis by the consultant doctor in the advisory units/ Khanaqin Teaching Hospital. Thirty samples blood were taken from healthy individuals and labeled as a control group. The age's groups of patients and healthy individuals ranged from 35 into 80 years. The collected blood taken from two groups (patients and healthy) were putted in centrifuge (4000 rpm for 5 minutes) for separate serum from plasma. Serum quantities of IL-12, TNF-a, Erythropoietin, and Insulin markers within samples were measured by Enzyme-linked immune-sorbent assay (ELISA) (Diaclone Research, Besancon, France). I-chroma machine utilized to determine levels of vitamin D3 in serum of human using fluorescence immune-assay (FIA).

STATISTICAL ANALYSIS

IL-12, TNF-a, Erythropoietin, Vitamin D3 and Insulin markers were showed as Mean±SD, with student t-test used to determine the differences significance (comparison 2 groups) or F test (comparison more than 2 groups). Another parameters (gender, age periods, and obesity) were noticed as frequencies and percentages, and Pearson-Chi-square test was used to reveal significant different within frequencies. Receiver operating characteristic (ROC) curve was used to detect area under the curve (AUC), specificity and sensitivity of L-12, TNF-a, Erythropoietin, Vitamin D3 and Insulin markers. P≤0.05 was detected significant. Present data were programmed by SPSS v. 24.0 and Graph pad prism v.10 statistical software program.

RESULTS

Outcomes of current study showed significant variations (p<0.05) among gender, age groups, and obesity in patients with liver failure. Where it is found this diseases is more incidence in males (66.0%) versus females (34.0%). 51-60 and 61-70 years groups showed high percent (24.0% and 32.0%) than ≤40 and >70 (10.0% and 14.0%) respectively. Finally, non-obese liver patients showed low prevalence (24.0%) versus obese patients (76.0%) (Table 1).

TABLE 1. Baseline of demographic features of liver failure patients

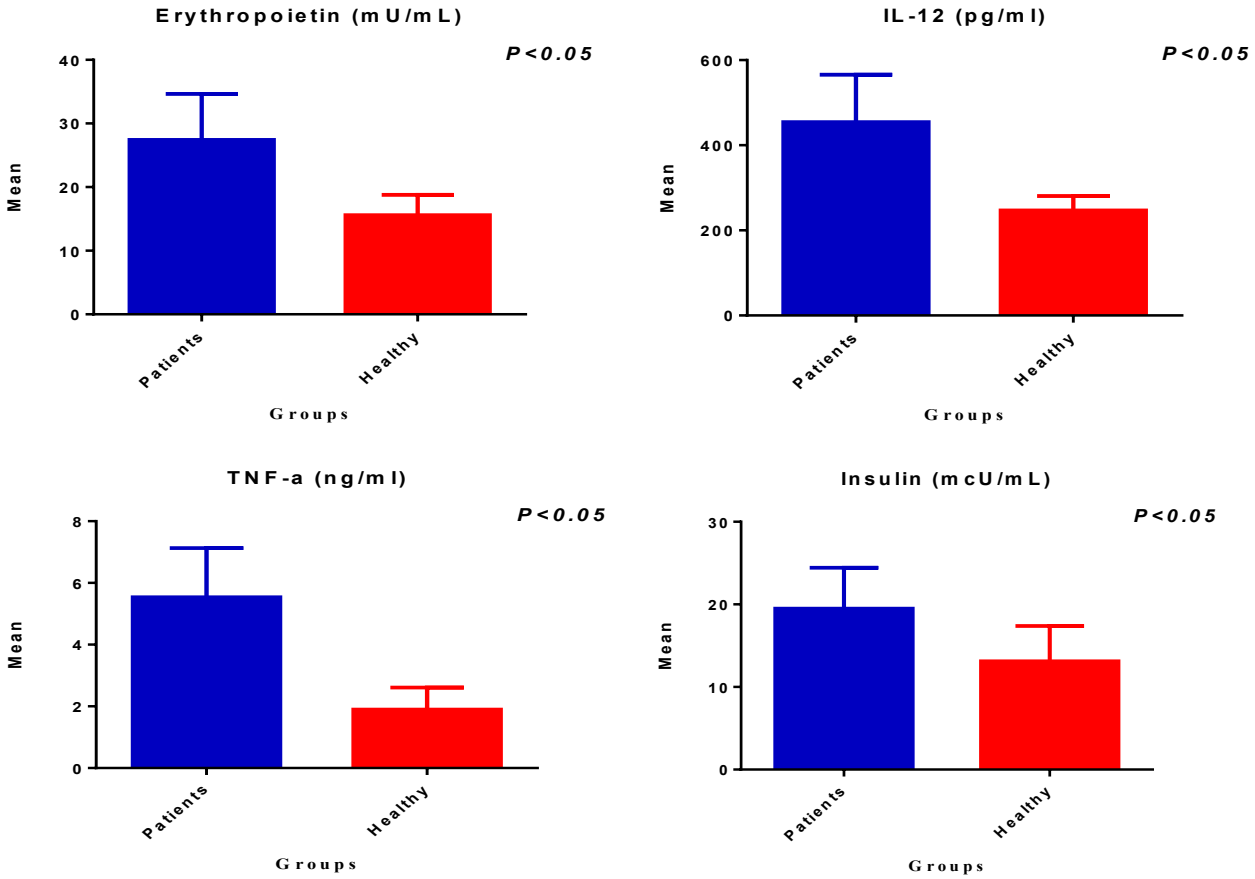
		Count	Percent	P value
Gender	Males	33	66.0%	p<0.05*
	Females	17	34.0%	
Age groups (years)	≤40	5	10.0%	p<0.05*
	41-50	10	20.0%	
	51-60	12	24.0%	
	61-70	16	32.0%	
	>70	7	14.0%	
Obesity	Non-obese	12	24.0%	p<0.001***
	Obese	38	76.0%	

Present outcomes noticed the levels of IL-12, TNF-a, Erythropoietin, and Insulin markers were significantly highest (p<0.05) in patients (27.42±7.23, 454.28±111.63, 5.54±1.59, and 19.48±4.97) versus healthy (15.57±3.20, 246.73±34.01, 1.90±0.71, and 13.10±4.28) respectively. In opposite, patients with liver failure show significantly lowest levels (p<0.05) of vitamin D3 in patients (14.22±5.93) versus healthy (30.47±6.00) (table 2 and figure 1).

TABLE2. Comparison average levels of clinical markers between study groups

groups		N	Mean	SD	P value
Erythropoietin (mU/mL)	Patients	50	27.42	7.23	P<0.001***
	Healthy	30	15.57	3.20	
IL-12 (pg/ml)	Patients	50	454.28	111.63	P<0.001***
	Healthy	30	246.73	34.01	
TNF-a (ng/ml)	Patients	50	5.54	1.59	P<0.001***

	Healthy	30	1.90	0.71	
Insulin (mcU/mL)	Patients	50	19.48	4.97	P<0.001***
	Healthy	30	13.10	4.28	
Vitamin D3 (ng/ml)	Patients	50	14.22	5.93	P<0.001***
	Healthy	30	30.47	6.00	



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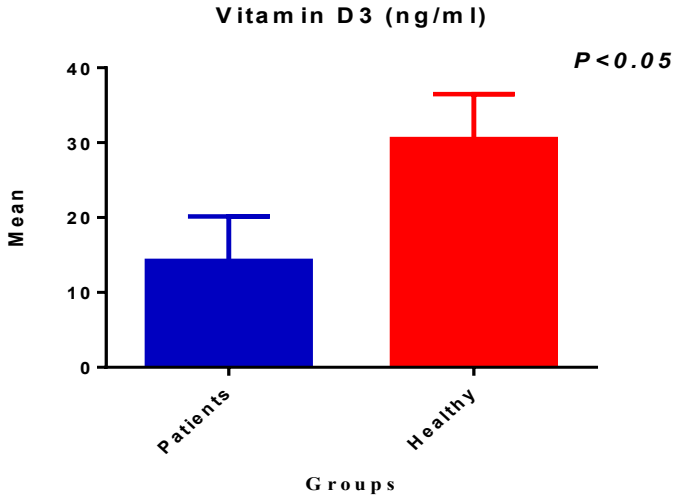


IGURE 1. Comparison average levels of clinical markers between study groups

Findings of present research don't showed effect of gender and age on IL-12, TNF-a, Erythropoietin, vitamin D3 and Insulin markers in patients with liver damage (Table 3 and 4).

TABLE 3. Comparison average levels of clinical markers between males versus females of liver failure patients

Gender		N	Mean	SD	P value
Erythropoietin (mU/mL)	Males	33	28.55	7.14	P>0.05
	Females	17	25.24	7.09	
IL-12 (pg/ml)	Males	33	443.73	115.15	P>0.05
	Females	17	474.76	104.73	
TNF-a (ng/ml)	Males	33	5.27	1.86	P>0.05
	Females	17	6.06	0.66	
Insulin (mcU/mL)	Males	33	20.97	4.20	P>0.05
	Females	17	18.59	5.17	
Vitamin D3 (ng/ml)	Males	33	13.33	6.03	P>0.05
	Females	17	15.94	5.48	

TABLE 4. Comparison average levels of clinical markers among age groups of liver failure patients

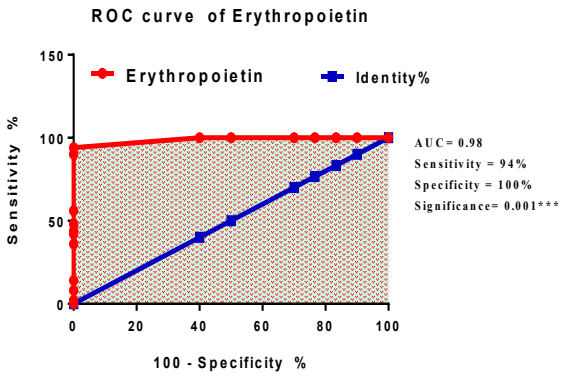
Age groups	N	Erythropoietin (mU/mL)		IL-12 (pg/ml)		TNF-a (ng/ml)		Insulin (mcU/mL)		Vitamin D3 (ng/ml)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
≤40	5	30.00	10.27	339.60	12.54	7.00	0.71	21.20	2.59	14.20	3.96
41-50	10	28.40	5.56	424.10	78.13	4.30	1.49	19.80	2.74	11.40	6.82

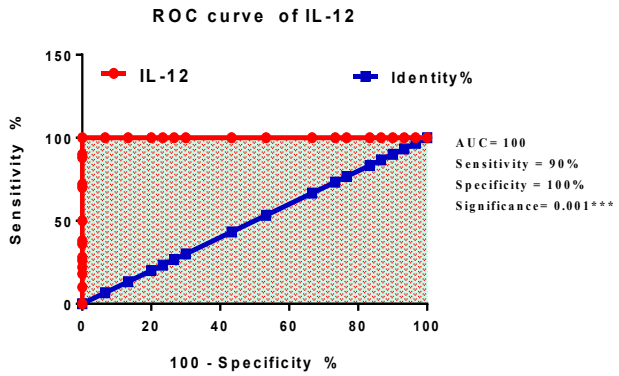
51-60	12	26.83	6.94	470.92	113.88	5.33	1.37	22.75	4.61	14.42	7.45
61-70	16	27.69	6.63	476.69	128.63	6.13	0.72	19.06	5.84	13.81	4.93
>70	7	24.57	9.71	499.57	102.98	6.29	0.49	20.00	2.45	18.86	2.27
P value		p>0.05		p>0.05		p>0.05		p>0.05		p>0.05	

Findings of present study don't showed effect of obesity on TNF-a, Erythropoietin, vitamin D3 and Insulin markers in patients with liver damage. In contrast, we found the obesity is significantly impact ($p<0.05$) on IL-12 marker, where it is found high levels of IL-12 was high in obese patients (472.42±117.27) versus non-obese (396.83±67.18) (Table 5). Based on ROC curve results, present study showed the IL-12, TNF-a, Erythropoietin, vitamin D3 and Insulin markers scored high sensitivity (99%, 92%, 94%, 93%, and 80%) and specificity (100%, 80%, 100%, 90%, and 80%) in screening patients with liver failure (figure 2).

TABLE 5. Comparison average levels of clinical markers between obese and non-obese of patients with liver failure

Obesity		N	Mean	SD	P value
Erythropoietin (mU/mL)	Non-obese	12	28.00	7.70	P>0.05
	Obese	38	27.24	7.17	
IL-12 (pg/ml)	Non-obese	12	396.83	67.18	P<0.05*
	Obese	38	472.42	117.27	
TNF-a (ng/ml)	Non-obese	12	6.17	1.85	P>0.05
	Obese	38	5.34	1.48	
Insulin (mcU/mL)	Non-obese	12	20.67	2.87	P>0.05
	Obese	38	19.11	5.44	
Vitamin D3 (ng/ml)	Non-obese	12	14.00	5.56	P>0.05
	Obese	38	14.29	6.11	





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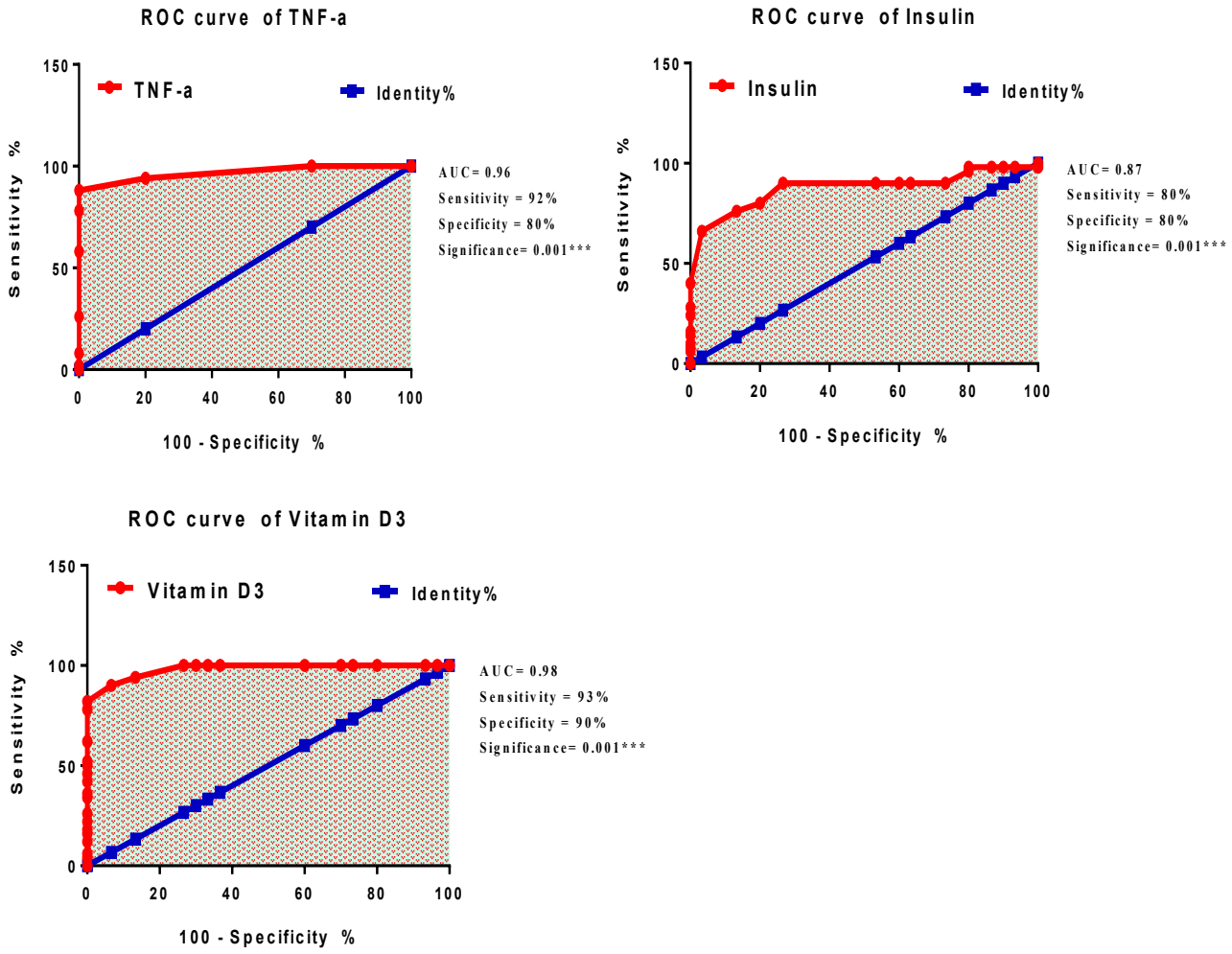

FIGURE 2. Receiver operating characteristic (ROC) curve of clinical markers

DISCUSSION

The outcome of the current investigation revealed a higher frequency of liver failure in men than in women, and these results were consistent with those from the USA[15] .The higher incidence of chronic illnesses and alcohol intake in men than in women, as well as sample size, are all associated with a greater incidence of liver failure in men than in women [16] .Women are more likely than males to suffer advanced fibrosis, especially beyond the age of 50, according to a meta-analytic and systematic review[17].The doctor must be aware of gender differences since they might affect a patient's chances of receiving a certain diagnosis and their chance of developing a liver condition [18] .Additional research is necessary to evaluate the function of sexual hormones as well as gender-based differences in health habits and medical choices. Across all categories of age, the current study's findings demonstrated a rise in the probability of liver failure with aging, particularly beyond forty years of age, and our results concurred with those of [19] .The liver is the body's primary metabolic tissue, and research has shown that it has a higher potential for regeneration and aged more gradually than other parts of the body [20] . It has been demonstrated that elderly people experience a quicker progression of liver conditions, which can occasionally result in end-stage liver disease requiring transplantation [19]. An older transplanted liver will have a lower tolerance for further harm [21].

With regard to obesity, the current observations demonstrated a significant incidence of liver damage in obese individuals, and these outcomes were consistent with those of [22]. An earlier study found that although it is not a standalone prognostic indicator, overweight and obesity are only weakly related to longevity in individuals with cirrhosis. The short-term prognosis of individuals with cirrhosis and acute gastrointestinal bleeding (AGIB) is not significantly affected by overweight or obesity [23]. The leading cause of liver illness in the world is now understood to be metabolism liver illness, which is linked to obesity. It is necessary to develop strategies to combat obesity-related liver disease through behavior change initiatives that encourage people to lead healthier lifestyles. To have the greatest benefits on lifestyle modifications, such initiatives should be combined with societal-level government initiatives [24]. In individuals suffering from liver failure, [25] found elevated levels of IL-12, and these findings corroborated those of the current research. Lipid buildup in the hepatocytes is the primary cause of non-alcoholic fatty liver disease (NAFLD). According to [26] , lipid buildup raises the levels of fatty acids and adipokines, which stimulate Kupffer cells. The natural killer cells in the hepatocytes get triggered by stimulated Kupffer cells, which also cause the synthesis of IL-12. In addition to triggering natural killer cells, IL-12 boosts interferon- synthesis. An investigation suggested that a diet high in fat could promote Kupffer cell engagement. Kupffer cell removal would lower IL-12 expression respectively, according to a different research by [27] Zhan et al., (2010). Tumor necrosis factor-a, IL-6, IL-1, IL-1, and IL-18 are additional cytokines generated from the inflammation process that contribute to the etiology of NAFLD [28]. Due to the BARD scores and NAFLD fibrosis rating, serum IL-12 production was also linked to the degree of severity of NAFLD. At a precision cut-off of more than 49.5 pg/mL, a moderately favorable connection between serum IL-12 concentration and BARD score was shown to reliably forecast high BARD scores [29] . In cases of chronic liver disease, IL-12 protects the liver from damage. The activation of T-helper (Th)-1 cells and the inhibition of Th-2 cells both include the pro-inflammatory cytokine IL-12. A hyperactive inflammatory reaction and excessive IL-12 release harm the liver as well amongst additional organs [30]. Further investigation revealed that those with NAFLD had higher levels of cytokines, such as IL-12, which are pro-inflammatory. Mice with hepatosteatosis generate higher IL-12, in accordance with a study [29]. According to prior research, IL-6 and IL-10 may contribute to ongoing inflammation and resistance to insulin, whilst IL-12 and TNF may encourage liver damage and the advancement of NAFLD. These compounds' plasma concentration analyses and associations with clinical indicators can be employed as novel indicators to track the evolution of NAFLD and reveal the emergence of nonalcoholic steatohepatitis (NASH) [31]. According to a new investigation, IL-12 and CXCL-10 play a significant role in alcohol-induced liver disease, verifying their function in irritation and being present in the later stages of the illness by encouraging immune cells to migrate towards the places where inflammation occurs [32]. The current study's findings, which corroborated those of [33], indicated that patients had greater amounts of TNF-a than individuals in good health did. TNF, which is overproduced in fat tissue and triggers the expulsion of the pro-inflammatory lipokine leptin from fat cells, is a modulator of insulin resistance in adiposity. Increased blood levels of TNF and accessible TNFR1 were previously found in non-alcoholic steatohepatitis (NASH) individuals, and these levels were linked to illness worsening. Additionally, elevated hepatic TNFR1 transcripts as well as higher TNF levels in both adipose and liver tissue were found in NASH individuals, again related with progressing disease [34].

An earlier study found that therapy with anti-TNFR1 dramatically reduced liver fibrosis, apoptotic damage, NAFLD activity, and alanine aminotransferase (ALT) levels. Therefore, our findings point to specific TNFR1 suppression as a potentially effective strategy for treating NAFLD [35] .The current investigation found that patients had higher erythropoietin (EPO) rates than individuals in good health, and these findings were consistent with those of [36]. Erythropoietin (EPO), which is primarily responsible for maintaining red blood cell bulk, may also play other biological roles unrelated to erythropoiesis, such as angiogenesis and protecting tissue [37]. While a fetus, EPO is created in the hepatic; however, following being born, the kidney becomes the primary site of creation. In normal subjects, the liver can sustain production levels of up to 10% of the total EPO syntheses,

although this level can be increased to 90–100% [38]. Nonetheless is being demonstrated that in the dearth of renally generated EPO, liver EPO production is insufficient to treat anemia. Numerous disorders have been associated with increased circulation EPO, however information on people with cirrhotic conditions are few, and the amount of plasma EPO in cirrhotic patients is debatable [39]. According to [40], arterial low blood pressure, hepato kidney damage, and anemia are all symptoms of cirrhosis and are caused by liver fibrosis, malfunction of the liver, and the production of cytokines that are pro-inflammatory. According to [41], a rise in EPO might be caused by renal a lack of oxygen hypoxia, hemorrhaging or an EPO-mediated hepato-protective and regenerative pathway. However, a possible inadequate EPO reaction in end-stage cirrhosis may be explained by low liver synthesis capability, a declining co-factor level, and inflammation feedback systems [42]. According to earlier research, EPO has a novel role in promoting KCs' multiplication and internalization as well as in drawing in monocytes in response to liver damage [43]. Another set of findings point to the significance of EPO as a defense mechanism in the liver's defense toward lipopolysaccharide (LPS), leading to sepsis in the hepatocytes, by reducing liver and mitochondrial harm brought on by lipopolysaccharide (LPS), perhaps through inhibition of NLR family pyrin domain containing 3 (NLRP3) communication44. Comparable to how EPO therapy might prevent damage to the liver and kidneys brought on by ischemia reperfusion (IR), research findings revealed this [45].

Erythropoietin (EPO) boosts total regulatory T cell (Treg) among individuals with autoimmune hepatitis (AIH), especially those who display the elevated functional indicator HLA-DR, according to [46]. These findings support further research examining the claim that erythropoietin (EPO) or erythropoietin (EPO) analogues enhance Treg to enhance prognosis in AIH sufferers. Hepatogenous diabetic results in higher resistant to insulin, which is a pathophysiology aspect of chronic liver failure. Hepatogenous diabetes and insulin resistance are caused by specific causes such as liver parenchymal cell destruction, portal-systemic shunting, and hepatitis C virus. However, retinopathy and heart disease risk are inadequate, and the primary causes for mortality in cirrhotic individuals who have diabetes are liver disease, hepatocellular cancer, and gastrointestinal bleeding [47]. It is still unknown if the production of insulin from pancreatic beta cells fails, as it is in diabetes type 2 [47]. It has been disclosed that individuals with long-term liver disease have impaired production of insulin. Nevertheless, these individuals also exhibit insulin resistance/hyperinsulinemia, so it is not clear if the underlying cause of hepatogenous DM is identical with that of type 2 DM [48]. In laparoscopic biopsy tissues from individuals with cirrhosis of the liver, there is evidence of pancreatic islet hypertrophy. According to scientists, cirrhosis patients' islets exhibit stronger multiplication and lesser apoptosis than individuals without a history of persistent liver disease. These results imply that increasing the resistance to insulin may have forced the pancreatic beta cells to change, leading to hyperinsulinemia in cirrhotic individuals [49]. A limited number of clinical trials have examined the long-term benefits and safety of insulin, despite the fact that it is the therapy of choice for those with T2DM and cirrhosis of the liver. An earlier prospective cohort research found that using insulin increased the incidence of low blood sugar, heart attacks, liver-related problems, and death compared to not using insulin in persons with T2DM with compensatory cirrhosis. As a result, the usage of insulin in people with healed liver cirrhosis may need additional consideration [50]. Previous research demonstrated that fructose from food intake significantly increases hepatic resistant to insulin through the intricate interaction of numerous metabolic processes, perhaps a few of which are unrelated to greater consumption of calories and weight gain. The prior research refutes the idea that fructose is only a source of appealing calories that causes more weight gain and elevated insulin levels by demonstrating that fructose, not glucose, is the metabolically problematic part of sugar in diets [51] and observed the serum 25 (OH) D was substantially lower in the NAFLD group than in the healthy reference group; these findings were consistent with the current investigation. Vitamin D insufficiency affected more than two thirds of NAFLD patients, whereas only a single third of those in the control group [52]. The link involving vitamin D level and NAFLD/NASH was examined in 45 papers as part of a comprehensive systematic analysis by [53] . Of these, 16 research refuted the adverse relationship involving vitamin D level and NAFLD

that was observed in 29 investigations. According to [54], significant vitamin D insufficiency is highly correlated with liver damage and the seriousness of the illness in fibrosis and hepatic failure individuals. Vitamin D insufficiency is common in individuals with persistent infection with HBV. On the contrary hand, a meta-analysis on the link between blood levels of vitamin D and NAFLD individuals' histologic intensity revealed no correlation between it as measured by NAS and fibrosis score [55].

According to a previous investigation, acute vitamin D insufficiency is a biomarker for prediction in autoimmune hepatitis (AIH) and is linked to therapy non-response, cirrhosis advancement, liver-related mortality, or the necessity for an organ transplant [56]. Recent research revealed that patients taking immunosuppressive medication with steroids to avoid rejections or those in their initial post-transplant year had a significant risk of 25(OH) D3 insufficiency. As a result, patients should have their blood 25(OH) D3 levels periodically checked following a transplanted liver [57]. In a different research, it was discovered that preoperative Vitamin D levels are connected to the degree of severity of the illness and have a strong association with persistent infection in the initial 28 days following surgery (DFS). Furthermore, measurements on DFS 28 demonstrated a significant correlation with the function of the graft following orthotopic liver transplantation (OLT) [57]. Present study showed not effect of gender , age, and obesity on erythropoietin, IL-12, TNF-a, insulin, and vitamin D3 in patients with renal failure, in except, IL-12 scored high levels in obese liver failure patients than non-obese due to high inflammation in patients with obesity. Results of present study showed high sensitivity and specificity of IL-12, TNF-a, Erythropoietin, Vitamin D3 and Insulin markers in screening patients with liver failure due to these markers play important roles in pathophysiology of liver diseases [55].

CONCLUSIONS

We came to the conclusion that obesity, age, and gender were indicators of risk for hepatic failure. Due to their high sensitivity and specificity in the identification of chronic liver disorders, IL-12, TNF-a, erythropoietin, vitamin D3, and insulin indicators have assumed significant parts in the pathogenesis of chronic liver conditions.

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DECLARATIONS

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AUTHOR CONTRIBUTIONS

Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing, Visualization, Supervision, Project Administration, and Funding Acquisition all done by the author.

DATA AVAILABILITY

All data analysed during this paper are included in this article.

ETHICS APPROVAL

The study was conducted in accordance with the Declaration of Helsinki, and Ethical Committee ohf University of Baghdad -Iraq/ College of Nursing/ Basic Science Department, Vietnam as number: 6811/QD-DHYHN.

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