Kurdish Studies
Feb 2024
Volume: 12, No: 2, pp.2170-2180
ISSN: 2051-4883 (Print) | ISSN 2051-4891 (Online)
www.KurdishStudies.net

Received: December 2023 Accepted: January 2024
DOI: https://doi.org/10.58262/ks.v12i2.156

Evaluating the Relationship between the Levels of Inflammatory Proteins (Crp, Tnf-α, Il-1β) in Patients with Cirrhosis and the Severity of the Disease

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Abstract

Chronic liver damage leads to the development of cirrhosis, a multisystem illness when damaged tissue gradually replaces healthy tissue. Cirrhosis's effects are not limited to the loss of hepatocytes but it also suffers from ongoing systemic and local inflammation, which exacerbates liver damage it increases the chance of organ loss, increases sensitivity to infection, and prolongs liver damage. This research was carried out in the governorate of Al-Diwaniyah. Samples were taken at Al-Diwaniyah Teaching Hospital between August 9th, 2023 and January 8th, 2024. It included 50 male participants (Abuser of alcoholic beverages). 25 of the subjects had just been diagnosed with cirrhosis, whereas the other 25 had been suffering from it for at least 5 years, the condition was diagnosed by measuring enzyme levels GOT, GPT, total protein and albumin. The research also included measuring the levels of some inflammatory indicators in patients with cirrhosis who were newly infected with the disease and others who had been suffering from it for at least 5 years. These indicators included measuring the level of CRP, TNF-a, IL-1β. The results showed that there is a statistically significant difference in CRP concentration between Group A and Group B below the 5% significance level, with a t-test value of 11.499 and a significant value sig. Equal to zero, which is less than the 5% significance level. We also observe a statistically significant difference in TNF concentration between Group A and Group B that is less than the 5% significance limit, with a t-test value of -41.842 and a significant value sig. Equal to zero, which is less than the 5% significance level. The t-test value of -1.941 with a significant value of 0.058 indicates a statistically significant difference between Group A and Group B in terms of IL-1β concentration, falling below the 10% significance level. Our research found a correlation between serums TNF-a and IL-1β levels and disease development and prognosis. The study compared TNF-a and IL-1β concentrations in two groups of cirrhosis patients. It was observed that the IL-1β and TNF-a were lower in group A than in group B. Based on the high quantities in group B, we may deduce that they are connected with the growth and development of liver cirrhosis. The goal of this study is to analyze the link between the levels of inflammatory proteins and the severity of the illness in persons with liver cirrhosis and following its progression.

Keywords: *Inflammation, CRP, TNF-a, IL-1β, Cirrhosis*

Introduction

Cirrhosis of the liver is common worldwide.1 And has a significant economic impact on many nations.2,3 Treatment of the underlying a etiology and liver transplantation are the primary options for changing the course and development of cirrhosis.1,4 Alcohol-related liver disease (ALD) and nonalcoholic fatty liver disease, also known as (NAFLD/NASH) can both cause

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fibrosis and cirrhosis, as well as raise the risk of hepatocellular carcinoma.5

Most chronic liver illnesses result in the reactivation of inflammation in the circulatory system and liver, which is triggered by innate immune cells.6 The coordinated process by that the liver responds to local damages in an effort to repair the liver's structure and function is known as the inflammatory response. Continuous and/or severe local damage results in a gradual substitution of normal liver tissue with scar tissue due to the continuing inflammatory response. Globally, liver infections and cirrhosis are significant public health issues. The key determinants of systemic inflammation are cytokines, which are generated and released by immune cells as a reaction to damage and stressful stimuli. 7 In a feedback loop, circulating immune cells, particularly neutrophils and macrophages, create and react to these inflammatory substances, favoring a proinflammatory milieu and amplifying the process of inflammation.8 Inflammation, which is mediated by many inflammatory proteins such as (CRP, TNF-α, IL-1β), is one of the key factors linked with the development of liver cirrhosis. CRP, the prototypical human acute phase protein, is a well-known inflammatory marker and one of the most routinely measured molecules in clinical medicine.9 CRP is mainly produced in the liver. During the acute phase of disease, CRP is generated by the majority of parenchymal tissues throughout the body.10 the liver macrophages produce IL-1β and TNF-α in the chronic hepatic.11,12 The innate immune have role in the liver cirrhosis occurrence and development 13

In individuals with cirrhosis, inflammatory protein levels such as (CRP, TNF-α, IL-1β) are key indications of inflammation and disease severity. The purpose of this study is to: (1) determine the levels of inflammatory proteins in patients with cirrhosis; (2) compare the levels of inflammatory proteins in patients newly diagnosed with the disease and patients who have had the disease for five years; and (3) assess the relationship between the levels of inflammatory proteins and the severity of the disease in individuals with liver cirrhosis and tracking its development.

An Overview of Inflammation

As the body's natural host defense mechanism, inflammation starts the pathogenic killing and tissue mending processes and helps restore homeostasis to injured or diseased areas 14. Numerous things might set off an inflammation. These triggers include things like the presence of microbiological contaminants, tissue damage, and metabolic stress (Fig. 1). Following exposure to the trigger, typical immunological tolerance may not be present or there may be a breakdown in barrier functioning. A common set of pathways inside cells is triggered, regardless of the kind of trigger 15. These pathways include nuclear factor (NF)-kB and Toll-like receptor signaling, activation, the establishment of the inflammasome—which releases a variety of inflammatory cytokines—and endoplasmic reticulum stressors (Fig. 1). 15. The ensuing inflammatory response comprises interactions between several cell types as well as the production and response to a wide range of chemical mediators. It is marked by redness, swelling, heat, pain, and loss of function. The exact amount of cells and molecules engaged in the inflammatory response, as well as its exact timing and intensity, are determined by the kind, size, and location of the triggering. These constituents mold and maintain the inflammatory reaction. In order to prevent further damage to the host, systems that cease inflammation and start tissue repair take over after the infection or other trigger is eliminated, or at least controlled. The term "resolution of inflammation" describes the activation of negative feedback mechanisms, such as the generation of anti-inflammatory cytokines, the suppression of pro-inflammatory signaling cascades, the elimination of inflammatory mediator receptors, and the activation of cells involved in self-regulation. Maintaining health and balance requires

effective management of inflammation, but inflammation that involves a loss of tolerance or regulatory mechanisms may become pathogenic 14.

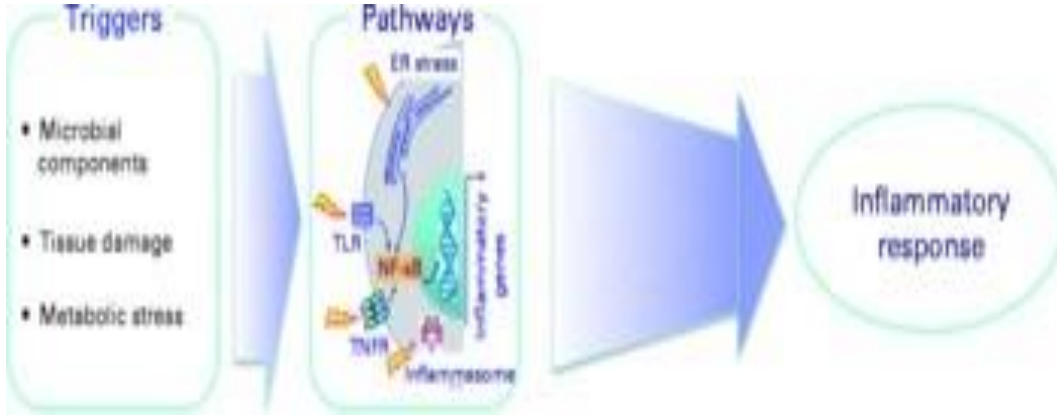

Figure 1: Diagrammatic Representation of the Typical Inflammatory Reaction Brought on by Various Stimulants. The Things that have the Direct Ability to Start an Inflammatory Reaction are Known as Triggers. Toll-like Receptors (Tlrs); Endoplasmic Reticulum (Er); and Tnf Receptors (Tnfrs).

Acute or persistent inflammation is possible (Table 1). Acute inflammation is a first reaction to an infection or another inflammatory trigger, such as tissue damage from radiation or wounds. It is characterized by an increase in plasma and leucocytes, especially granulocytes, moving from the bloodstream into the area of the injury or infection. Numerous cells within the injured tissue, the immune system, and the local vascular system all participate in the biochemical processes that cause inflammation to develop and spread. When the main cause of the response is contained or eliminated, acute inflammation often resolves on its own. Resolution is an active process involving pro-resolving lipid mediators, certain cell types, and anti-inflammatory cytokines 16.17, 18 Prolonged infection is defined by the inflammatory process's simultaneous destruction and repairing of tissue, as well as a progressive change in the kind of cells that are present at the site of inflammation. When tolerance and/or regulatory mechanisms like resolution are compromised, inflammation may become pathological. When this becomes too much, it may cause disease and irreparable damage to the host's tissues.14 These conditions are identified by noticeably elevated levels for inflammatory biomarkers and activated inflammatory cells in the systemic circulation and at the site of tissue damage; this kind of inflammation is known as "high grade." A "low grade" of chronic inflammation can also have limited or no overt clinical symptoms; in this case, the circulatory system's levels of inflammatory cell types and markers of inflammation are not elevated to the same degree as in the aforementioned frank chronic inflammatory diseases. Low-grade subclinical inflammation within adipose tissue may be brought on by obesity.19 Under these circumstances, the adipocyte represents a source of adipokines linked to inflammation; moreover, phagocytes and T cells also infiltrate adipose tissue, which greatly amplifies the inflammatory outcomes from adipose tissue.20 It is believed that the adipokines and cytokines generated have a role in the insulin resistance associated with obesity.21 Elderly people also often have low-grade chronic inflammation, which may exacerbate their frailty based on parameters such as IL-6 and TNF plasma levels.

Table 1: Characteristics of Low-Grade Chronic, Chronic, and Acute Inflammation.

	Acute inflammation	Chronic inflammation	Low-grade chronic inflammation
Trigger	Pathogens, injured tissues	Failure to resolve acute inflammation due to non-degradable pathogens, persistent foreign bodies or autoimmune reactions	Metabolic disturbance; some chronic infections
Major cells involved	Neutrophils and other granulocytes, mononuclear cells (monocytes, macrophages); T cells later	Mononuclear cells (monocytes, macrophages, T cells, B cells), neutrophils, fibroblasts	Mononuclear cells (monocytes, macrophages, T cells, B cells), neutrophils, adipocytes (if adipose tissue involved)
Primary mediators	Vasoactive amines, eicosanoids; chemokines and cytokines later	Cytokines, chemokines, eicosanoids, growth factors, reactive oxygen species, hydrolytic enzymes	Cytokines, chemokines, adipokines (if adipose tissue involved), eicosanoids, reactive oxygen species, hydrolytic enzymes
Onset	Immediate	Delayed	Delayed
Duration	A few days	Unlimited	Unlimited
Outcomes	Resolution, abscess formation, chronic inflammation	Tissue destruction, fibrosis, necrosis	No overt pathology, tissue (vascular) damage, increased insulin resistance, intracellular lipid accumulation

Many of the cells, processes, and substances involved in a genuine inflammatory response are quite similar, despite the differences in the origins, locations, and clinical manifestations. Increases in leucocyte counts and the production and appearance of IL-1, TNF, INF-γ and IL-6 chemokines in the bloodstream are hallmarks of most, if not all, of the chronic inflammatory diseases discussed here. Increased levels of these mediators contribute to tissue death, elicit systemic effects (such as hepatic CRP production), and, in many cases, are the actual cause of the observed clinical signs and symptoms. They enhance the inflammatory process. Many inflammatory illnesses that affect diverse parts of the body have led to the identification of a set of "common" or "generic" signs of inflammation that assessed in the bloodstream.

Some Common Inflammatory Proteins Used in the Diagnosis of Cirrhosis

The level of inflammatory proteins in the blood can be used to quantify inflammation. The following inflammatory proteins are commonly tested in the diagnosis of cirrhosis:

- C-Reactive Protein

CRP is stable protein, it is an inflammatory protein. CRP is an inflammatory indicator, that increase in bacteria infection 22,23. CRP is increased with onocytic mediators such IL-6 and IL-1. CRP gene stimulation occurs in the liver response in high concentration of the inflammatory cytokines 24. CRP increased with rheumatoid arthritis, heart and vessels diseases 25. CRP is an acute-phase protein, departs from normal plasma concentrations by at least 25% with inflammatory diseases.26 CRP concentrations are greatest in serum, with certain infections caused by bacteria increased to one thousand fold 27. If the stimuli are removed, CRP decreased after 18-20 h 28. During (1-3) days of the infection, CRP increase from (1) to (500) g/mL 29. The life style have role in CRP level such as smoking, cholesterol, habits, age, weight, and blood pressure 30. CRP levels that are elevated are often linked with illness, however liver failure is one situation that has been seen to decrease CRP production. CRP production is primarily stimulated in response to pro-inflammatory cytokines, most notably IL-6, and to a lesser extent IL-1 and tumor necrosis factor alpha (TNF-α).31.

- Tumor Necrosis Factor-Alpha

TNF-α is a multifaceted cytokine that belongs to the TNF family. It is implicated in a variety of the inflammatory processes 32,33. While necessary for a well-balanced immune response, overproduction may be detrimental 32. TNF-α is an essential modulator of inflammation, and

under certain circumstances, it may result in apoptosis and necroptosis in cells 34,35,36 TNF-α is regulate the inflammation in the human body 36. It is generated by innate immune system cells like macrophages and NK cells, adaptive immune system cells such as activated T cells 37, 38. TNF-α plays have role in the illnesses, and pharmaceutical TNF-α targeting 34, 39. TNF-α role is complicated and pleiotropic, and blocking it can have unforeseen biological consequences.40

- Interleukin-1beta

IL-1 Beta known as IL-1β or IL-1F2, is a 30.7 kDa pro-inflammatory cytokine that is mostly produced by activated macrophages and monocytes. It plays a crucial role in regulating the host's defensive mechanism against tissue damage and infection.41 IL-1β promotes the synthesis of IL-2, B-cell maturation and proliferation, and fibroblast growth factor activity, all of which in turn promote thymocyte proliferation. Aging and wound healing are only two of the many biological processes that IL-1β is engaged in. Similar to IFN-γ, IL-6, and TNF-α, IL-1 is a pyrogenic cytokine that promotes prostaglandin synthesis, the main mediator of fever induction.

Patients and Methods

Study Design

This research was carried out in the governorate of Al-Diwaniyah. Samples were taken at Al-Diwaniyah Teaching Hospital between August 9th, 2023 and January 8th, 2024. It included 50 male participants (Abuser of alcoholic beverages). 25 of the subjects had just been diagnosed with cirrhosis, whereas the other 25 had been suffering from it for at least 5 years. The research included individuals ranging in age from (40 to 60) years. Every participant's CRP, TNF-α, and IL-1β levels, as well as GOT, GPT, total protein and albumin levels, checked.

Patients

The research groups are as follows:

- Group A: it included 25 patients newly diagnosed with liver cirrhosis.
- Group B: consisted of 25 individuals who had cirrhosis for at least 5 years.

Statistical Analyses

Processing of statistical data was performed using used of applied statistical program "SPSS vr.24" and evidence-based medicine practices. The t-test for independent samples was used to determine the extent of the difference between the two research groups.

Results and Discussion

The current study evaluated the levels of inflammatory proteins in the blood serum of the selected samples and the study has two groups: Group A contained patients newly diagnosed with liver cirrhosis, whereas Group B consisted of individuals who had cirrhosis for at least 5 years, the concentrations of CRP, TNF-α, and IL-1β were estimated in the blood serum of the groups under studies and the following table shows some general statistics about the concentrations recorded for the two groups.

Table 2: General Statistics for the Variables of the Two Groups.

Group Statistics					
	group	N	Mean	SD	SE
CRP	Group A	25	55.356	10.0687	2.0137
	Group B	25	31.392	2.6816	.5363
TNF-α	Group A	25	32.772	2.5167	.5033
	Group B	25	84.160	5.6013	1.1203
IL-1β	Group A	25	20.324	1.7479	.3496
	Group B	25	21.240	1.5853	.3171

The following graph shows the values of the arithmetic means for the three variables studied for the two research groups:

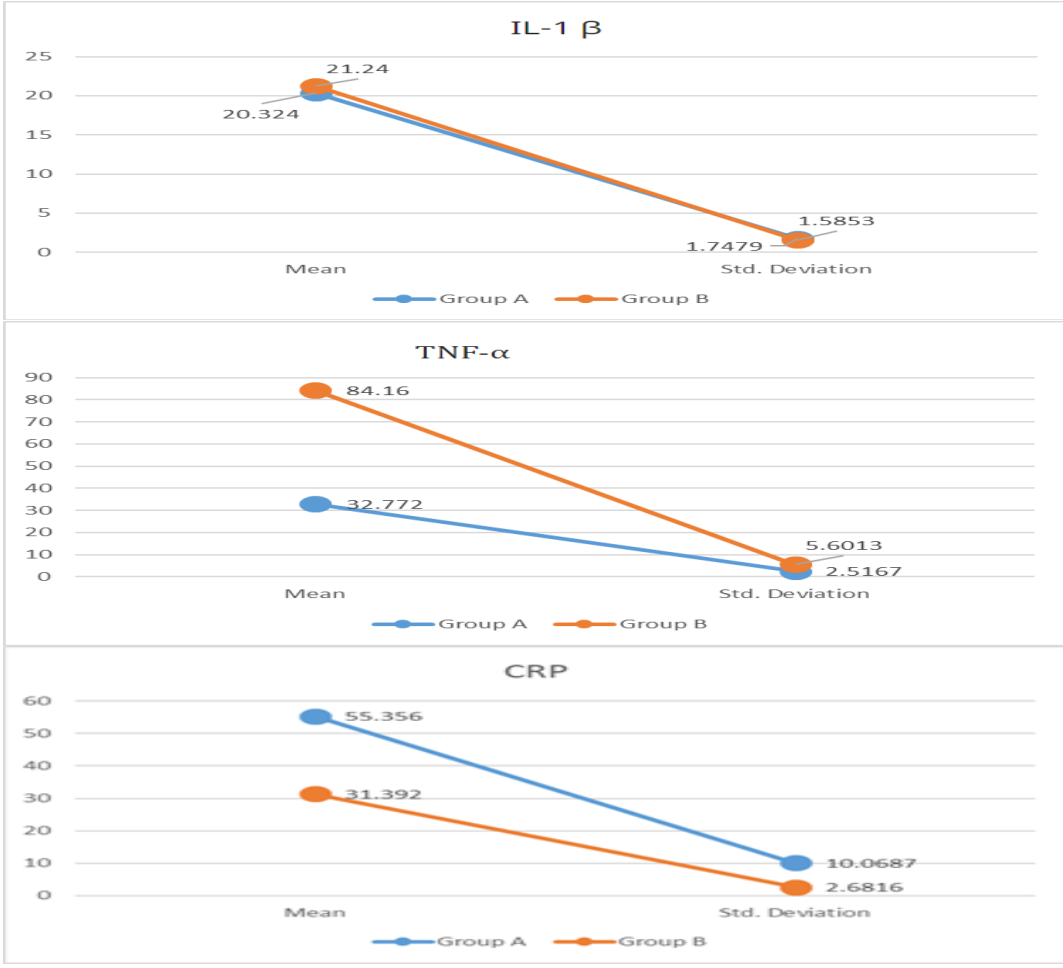

Figure 2: The Values of the Arithmetic Means for the Three Variables Studied for the Two Research Groups.

It is clear from the table and figure above that the arithmetic mean and standard deviation of the CRP concentration for group A was greater than that of group B, while we notice the opposite in the behavior of the arithmetic mean and standard deviation of the TNF-α concentration, as group B was greater than that of group A. And the arithmetic mean and standard deviation of the IL-1β concentration for group B it was greater than that of group A.

For the purpose of determining the difference in IL-1β, TNF-α, and CRP levels between groups A and B, we used the t-test for independent samples for this purpose, where the results were found and included in the following table:

Table 3: T-Test Values for Independent Samples.

Independent Samples Test								
		t-test for Equality of Means						
		T	DF	Sig. (2-tailed)	Mean Difference	SE Difference	95% Confidence Interval of the Difference	
							Lower	Upper
CRP	Equal variances assumed	11.499	48	.000	23.9640	2.0839	19.7740	28.1540
TNF-α	Equal variances assumed	-41.842	48	.000	-51.3880	1.2281	-53.8574	-48.9186
IL-1β	Equal variances assumed	-1.941	48	.058	-.9160	.4720	-1.8649	.0329

The above results show significant difference under 5% significance level between Group A and Group B regarding the CRP concentration, where the t-test value reached 11.499 with a significant value sig. it is equal to zero, which is less than the specified significance level of 5%. From this, we conclude that there is a difference between the two groups, as the CRP concentration value for group A was greater than that of group B, and this is evident when observing the arithmetic means for the two groups.

We also note that there is a statistically significant difference below the 5% significance level between Group A and Group B regarding the TNF-α concentration, where the t-test value reached -41.842 with a significant value sig. it is equal to zero, which is less than the specified significance level of 5%. From this, we conclude that there is a difference between the two groups, as the TNF-α level value for group B was greater than that of group A, and this is clearly evident when observing the arithmetic means for the two groups.

It is clear that there is a statistically significant difference below the 5% significance level between Group A and Group B with regard to the IL-1β concentration, as the t-test value reached -1.941 with a significant value sig. it is equal to 0.058, which is less than the specified significance level of 10%. From this, we conclude that there is a difference between the two groups, as the value of the IL-1β concentration for group B was greater than that of group A, and this is clearly evident when observing the arithmetic means for the two groups.

The following chart shows plotting the absolute values of the t-test for the three variables:

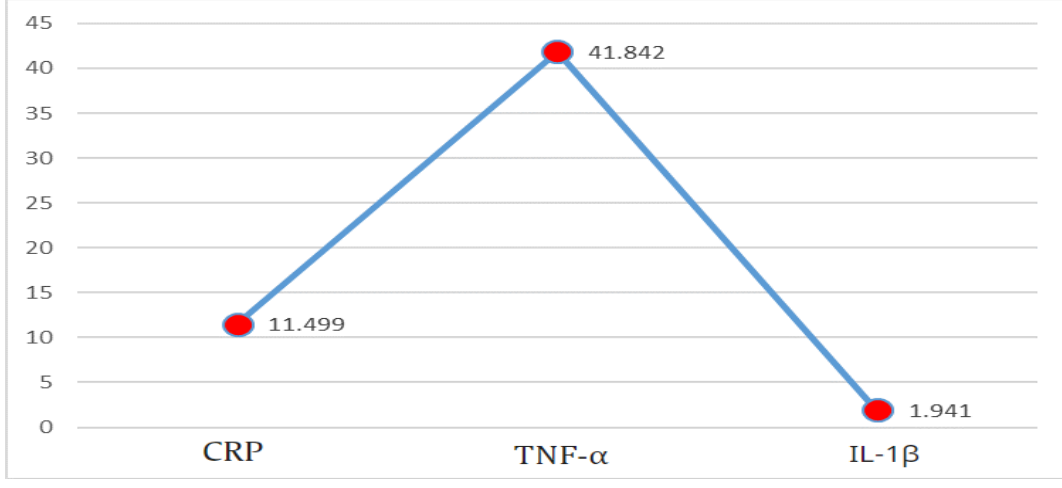

Figure 3: T-Test Values for the Three Variables.

From the figure 3 and table 3, it is clear that the strongest difference between the two groups was in the TNF-α concentration, which had a value of 41.842. Second came the CRP concentration, which had a value of 11.499, and finally came the IL-1β concentration, which had a value of 1.941.

After examining the results, we arrived at a series of conclusions, the most important of which are:

1- The arithmetic mean and standard deviation of CRP concentration for group A was greater than that for group B.
2- We notice the opposite in the behavior of the arithmetic mean and standard deviation of the TNF-α concentration, as group B was greater than group A.
3- The arithmetic mean and standard deviation of the IL-1β concentration for group A were similar to group B.
4- There is a difference between the two groups with regard to the CRP concentration, as the CRP concentration value for group A was greater than that for group B, and this is clearly evident when observing the arithmetic means for the two groups.
5- We conclude that there is a difference between the two groups with regard to the TNF-α concentration, as the TNF-α concentration value for group B was greater than that for group A, and this is clearly evident when observing the arithmetic means for the two groups.
6- There is a difference between the two groups, as the IL-1β concentration value for group B was greater than that for group A, and this is clearly evident when observing the arithmetic means for the two groups.
7- The strongest difference between the two groups was when the TNF-α concentration came second, the CRP concentration and lastly the IL-1β concentration.

Cytokines have a significant role in both acute and chronic inflammation and autoimmune disorders 42. Group A showed a considerable rise in CRP levels, but less so in TNF-α and IL-1β. Group B had significantly higher levels of TNF-α and IL-1β, but lower levels of CRP.

CRP One of the proteins that the liver makes in reaction to inflammation. If there is inflammation in the body, the liver begins to create large amounts of it in order to clear harmful microorganisms, this makes it a benchmark for diagnosing markers of inflammation that are assessed in the blood. CRP has been identified as an inflammatory factor; however, it is not specific and cannot be used to distinguish between inflammatory and non-inflammatory gland illnesses. Still, a spike in its level above 1 mg/L indicates the presence of inflammation 43. These findings indicate that inflammation plays a significant role in the development of liver fibrosis, and that high levels of inflammatory proteins may be linked to an increased risk of the illness advancing to more severe stages.

Our research found a correlation between TNF-α and IL-1β levels and disease development and prognosis. The study compared TNF-α and IL-1β concentrations in two groups of cirrhosis patients. It was observed that the amounts of inflammatory proteins (TNF-α, and IL-1β) were lower in group A than in group B. Based on the high quantities in group B, we may deduce that they are connected with the growth and development of liver cirrhosis.

There are several plausible reasons why this relationship exists. One among these reasons is that inflammation can cause liver cell destruction, cirrhosis advances as a result of this. There

is another opinion that the immune system is likely to be weakened by inflammation, as a result, the body becomes increasingly prone to illness and cirrhosis of the liver is a possible condition.

These results show that measuring inflammatory protein concentrations can be a good method of estimating a patient's risk of developing liver cirrhosis. This may allow the identification of patients who need additional care.

However, the following has to be considered when evaluating the study's findings. First, the research sample size wasn't large at all. Second, all the patients were an adult male. With women, the outcome can be different. These findings should be validated in further research with bigger and more thorough sample sizes.

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