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Elevated Ferritin/CRP Ratio: A Predictor of Liver Damage in Alcoholic Liver Disease Patients

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ABSTRACT:

Background: Alcoholic liver diseases are becoming a new threat for the middle age people which is affecting the socioeconomical standards of developing country like India. Due to chronic consumption of alcohol multiple problems associated with overall liver health can lead to pathological conditions like liver (steatosis) to alcoholic hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. The pathogenesis of ALD is an interplay of factors associated with oxidative stress and inflammation. The present study aimed to evaluate the association between ferritin and CRP in ALD and its severity.

Materials and methods: The study included total 190 subjects. Out of which 90 patients diagnosed with ALD and 100 were healthy controls. The current study evaluated serum levels of ferritin and CRP were measured, and the ratio was calculated for each subject.

Results: This study investigated the Ferritin/C-Reactive Protein (CRP) ratio in patients with alcoholic liver disease (ALD) and compared it among ALD subgroups according to the severity of the disease. Statistical analysis showed significantly higher ferritin levels and CRP levels in the ALD group compared to controls. The Ferritin/CRP ratio was found to be a potential biomarker for the early detection of inflammation and iron overload in patients with ALD, providing insight into the pathophysiology of the disease. The circulatory levels of serum ferritin and group than healthy controls (550.4 ± 210.6/ 108.2 ± 56.4) and Serum CRP levels were high in ALD as compared to control (12.7 ± 6.9/ 3.1 ± 1.7) respectively. Further it was observed that the ferritin /CRP ratio was well correlated with severity of ALD (r=0.95). These results suggest that the Ferritin/CRP ratio could be a useful adjunct in the clinical management of ALD.

Conclusion: The present study concluded that oxidative stress marker serum ferritin and inflammatory marker CRP levels were elevated in ALD and Ferritin /CRP ratio also showed its statistically significant correlation severity of ALD. Hence the present study like to indicate the role of oxidative stress in liver damage in ALD and provide an insight about the diagnosis, staging as well base for therapeutic approach towards ALD.

INTRODUCTION

Alcoholic liver disease (ALD) is increasing day by day due to changing social status of use of alcohol in daily life. As the generations changes there is a lot of changes occurs on overall lifestyle of an individual which is based on his surrounding, social status, work profile, mental health. In 2024, the burden of Alcoholic Liver Disease (ALD) in India continues to rise due to increasing alcohol consumption, with the country remaining one of the highest contributors to global alcohol-related liver disease cases. ALD significantly impacts public health, with high prevalence and mortality rates. Factors such as poor awareness, lack of early interventions, and limited healthcare infrastructure

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worsen the scenario. India reported over 69,000 incident cases of alcohol-induced cirrhosis annually, with ongoing trends indicating further increases in disease burden [1,2]. This condition spans a spectrum from fatty liver (steatosis) to cirrhosis and hepatocellular carcinoma. Alcoholic Liver Disease (ALD) often progresses through stages, with cirrhosis and hepatocellular carcinoma (HCC) being severe outcomes. Chronic alcohol consumption leads to fibrosis and scarring of liver tissue, culminating in cirrhosis. It is characterized by irreversible liver damage, portal hypertension, and liver dysfunction. ALD is one of the leading causes of cirrhosis worldwide. Medically unattended cases of Liver Cirrhosis may continuous the excess use of alcohol and this alcohol insult with subclinical oxidative stress and inflammation increases the risk of HCC. Chronic inflammation, oxidative stress, and genetic mutations caused by alcohol contribute to cancer development. Hence timely diagnosis and management are essential to reduce these further complications [3]. A crucial role of oxidative stress may initiate multiple signalling pathways which show their detrimental effects in the pathogenesis of ALD as well as in its progression.

Ferritin, is an iron storage protein and stores iron in mainly liver, spleen, bone marrow, skeletal muscle and macrophages. Ferritin is typically found in cytoplasmic fractions, lysosomes and mitochondria. The elevated levels of ferritin in serum results in multifaced complex mechanism which is associated with multiple processes [4-6]. High ferritin suggests the disturbance in iron metabolism and storage. Its high concentrations initiate oxidative stress as well inflammation. In Alcoholic Liver Disease (ALD), ferritin levels are often elevated due to a combination of factors linked to liver damage and iron metabolism. One of the reasons for iron overload in chronic alcohol consumption is due to increased intestinal iron absorption, leading to iron overload in the liver. Excessive iron aggravates, oxidative stress and hepatocellular damage and inflammatory environment further enhances ferritin release into blood stream and contribute elevating serum ferritin levels. ALD is also associated with systemic inflammation due to which the pro-inflammatory cytokines concentrations will be high. These proinflammatory cytokines further work towards progressing the inflammatory cascade by stimulating ferritin synthesis as part of the acute-phase response. All these features ultimately result in damage to hepatocyte. Due to injury and necrosis, these damage hepatocytes release intracellular ferritin into the bloodstream, contributing to increased serum ferritin levels.

The C-Reactive Protein (CRP), an acute-phase reactant, is produced by the liver in response to systemic inflammation. Hence CRP is considered as one of the reliable markers of systemic inflammation. For multiple inflammatory diseases CRP levels provides the inflammatory status such as rheumatoid arthritis, sepsis, and chronic liver disease [7-9]. Chronic alcohol consumption leads to hepatocellular injury and activation of immune pathways, causing increased production of CRP. Elevated levels are often observed in alcoholic hepatitis, a severe form of ALD. Higher CRP levels was associated with severe inflammation and poor outcomes in ALD, such as progression to cirrhosis or multi-organ dysfunction. CRP levels can help distinguish between alcohol-induced liver inflammation and superimposed bacterial infections, a common complication in ALD. Monitoring CRP in patients with ALD can guide clinicians in assessing the inflammatory burden and tailoring management strategies. However, it should be interpreted alongside other clinical and laboratory findings. In ALD, CRP levels are generally elevated due to the underlying hepatic inflammation. Previous studies have shown a direct correlation between CRP levels and liver damage in patients with ALD [7-9].

The ferritin/CRP ratio provides the iron overload status, risk due of oxidative damages and inflammation. At the same time CRP provides the degree of inflammation. Very limited literature is available on ferritin CRP ration in ALD and its severity. The ferritin/CRP ratio has the capacity to emerge as a potential marker to assess the balance and imbalance in iron overload, oxidative stress and inflammation. High serum ferritin/CRP ratio reflects excess iron storage, damage to hepatocytes and chances of oxidative damage [10]. However, its application in alcoholic liver disease remains underexplored.

The present study aimed to evaluate the Ferritin/CRP ratio in patients with ALD and compare it to a control group to explore its diagnostic and prognostic potential.

MATERIALS AND METHODS

The present study was conducted at a tertiary care hospital and included 90 ALD patients and 100 age- and sex-matched healthy controls without any history of alcohol use or any disorders related to liver any chronic inflammatory condition.

Inclusion Criteria: ALD group: Subjects/ Cases diagnosed with ALD aged between 30-65 years, with liver function tests, imaging (ultrasound/CT),

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and medical history. Control group: Healthy individuals without any history of alcohol use or any disorders related to liver or any chronic inflammatory condition. **Exclusion Criteria:** Non-alcoholic liver diseases, such as viral hepatitis, autoimmune liver disease, or metabolic disorders. Any acute infections or inflammatory conditions that could affect CRP levels.

Blood Sampling and Analysis

Venous blood samples were collected from all participants after an overnight fast. Serum was separated and stored at -20°C for later analysis. Serum ferritin levels were measured using an immunoassay method. Serum CRP levels were measured using a high-sensitivity CRP assay. The ratio was calculated by dividing the serum ferritin level by the CRP level for each participant.

Statistical Analysis

Data were analyzed using SPSS version 23. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. The independent t-test was used to compare the means between the ALD and control groups. A p-value of < 0.01 was considered statistically significant.

OBSERVATIONS AND RESULTS

Table No.1: Demographic Data of all study participants

The demographic characteristics of the study participants are summarized in Table 1.

Characteristic	ALD Group (n=90)	Control Group (n=100)
Age (years)	45.6 ± 10.3	46.2 ± 9.7
BMI (kg/m²)	27.4 ± 4.5	24.8 ± 3.2
Alcohol Consumption	20.2 ± 5.1 years	N/A

Table No.2: Comparison of Serum Ferritin and CRP Levels between ALD and Controls

The mean and S.D. of serum ferritin and CRP levels in the ALD and control groups are shown in Table 2.

Parameter	ALD Group (n=90)	Control Group (n=100)	p-value
Ferritin (ng/mL)	550.4 ± 210.6	108.2 ± 56.4	<0.001
CRP (mg/L)	12.7 ± 6.9	3.1 ± 1.7	<0.001
Ferritin/CRP Ratio	43.4 ± 28.9	35.0 ± 16.3	0.032

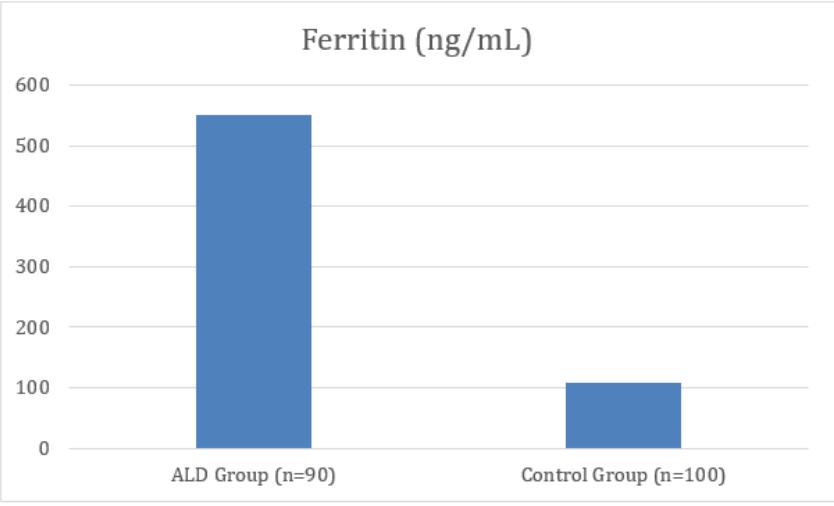

Figure No.1: Ferritin Levels in ALD and Control Groups

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The above bar graph illustrated significantly higher ferritin levels in the ALD group compared to the control group.

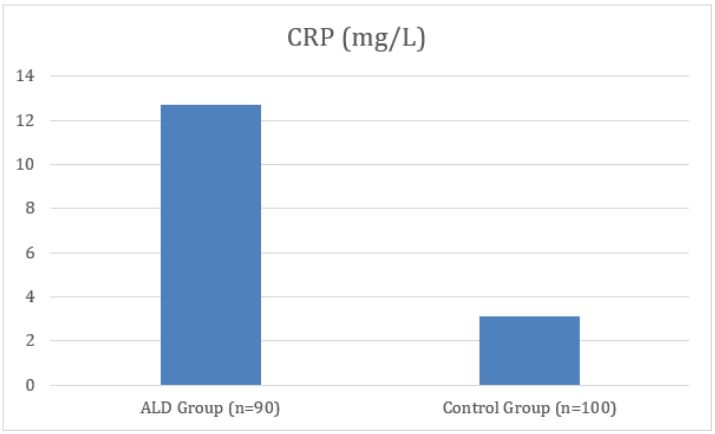

Figure 2: CRP Levels in ALD and Control Groups

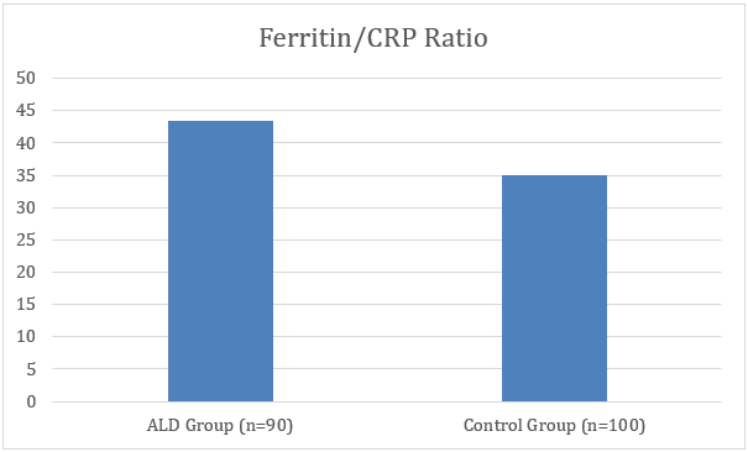

Figure No.3: Comparison of Ferritin/CRP Ratio

The Ferritin/CRP ratio was higher in the ALD group compared to the control group, with a statistically significant difference ($p = 0.032$).

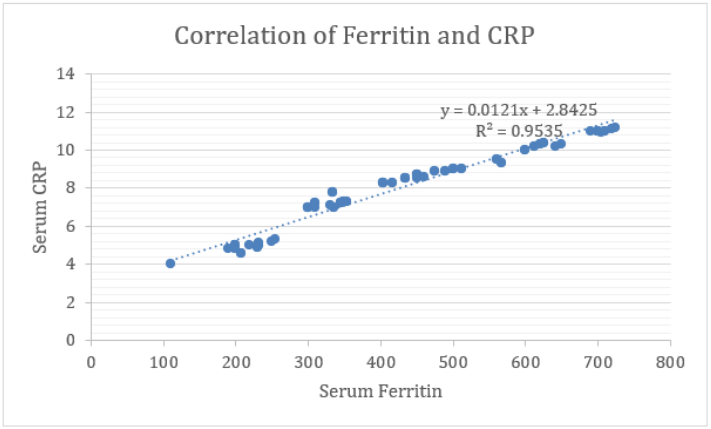

Figure No.4: Correlation of serum Ferritin and CRP in ALD patients

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The correlation among serum Ferritin and CRP was statistically significant (r=0.95). and further it was observed that it was also associated with the degree of severity of ALD.

Table No. 3: Comparison of Serum Ferritin and CRP Levels between ALD subgroups according to severity of the disease

Parameter	**Mild ALD (n=37)**	**Moderate ALD (n=40)**	**Severe ALD** (n=13)
Ferritin (ng/mL)	370.4 ± 110.6	408.2 ± 176.8	634± 346.9
CRP (mg/L)	5.7 ± 1.9	7.1 ± 2.7	11.1 ± 3.6
Ferritin/CRP Ratio	40.4 ± 12.9	45.0 ± 15.8	52.0 ± 26.3

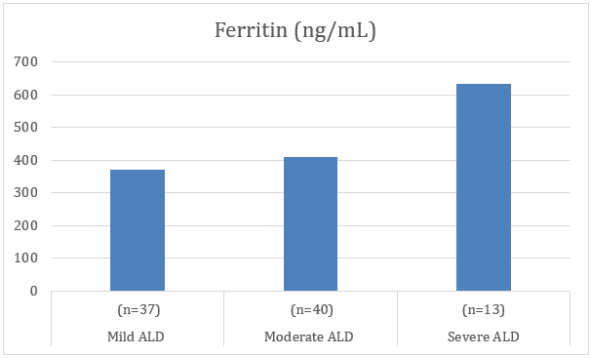

Figure No.5: Comparison of Serum Ferritin among ALD subgroups

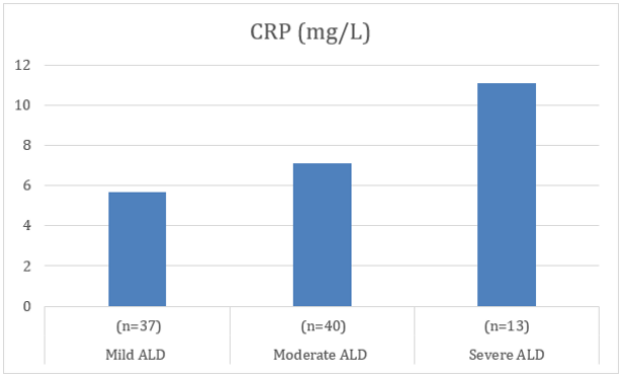

Figure No.6: Comparison of Serum CRP among ALD subgroups

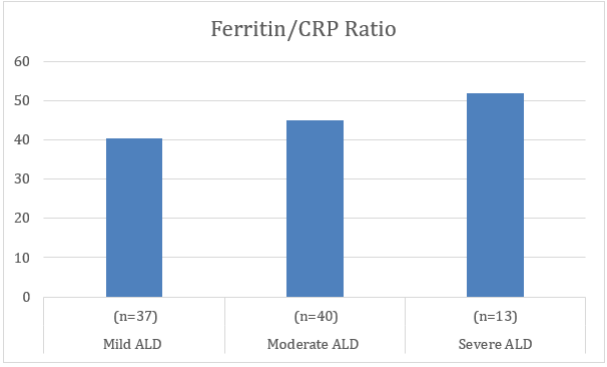

Figure No.7: Comparison of Serum Ferritin/ CRP ratio among ALD subgroups

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DISCUSSION

This study demonstrates that the Ferritin/CRP ratio is significantly elevated in patients with alcoholic liver disease (ALD) compared to healthy controls. The increase in both ferritin and CRP levels in ALD patients reflects the underlying pathophysiology of the disease, which involves both inflammation and iron overload. Ferritin, as an acute-phase reactant, is elevated in response to inflammation, while chronic alcohol consumption leads to hepatic iron accumulation, exacerbating liver damage. Ferritin, an intracellular protein complex responsible for iron storage, plays a critical role in regulating iron homeostasis and preventing oxidative damage in cells. However, in the context of alcoholic liver disease (ALD), elevated serum ferritin levels can contribute to the exacerbation of oxidative stress and liver injury. The mechanism by which ferritin mediates oxidative stress in ALD involves several key pathways. Ferritin stores iron in a non-toxic, ferric (Fe^{3+}) form, but when ferritin is released into the circulation or when its storage capacity is exceeded (as seen in ALD), free iron can accumulate. This free iron is highly reactive and can participate in the Fenton reaction, where ferrous iron (Fe^{2+}) catalyses the production of hydroxyl radicals (OH•) from hydrogen peroxide (H_2O_2). These reactive oxygen species (ROS) cause lipid peroxidation, protein damage, and DNA strand breaks, which contribute to hepatocellular injury and inflammation in ALD [11,12].

Ferritin itself can act as a pro-inflammatory mediator. Elevated ferritin levels in ALD reflect both iron overload and an acute-phase response. Ferritin is an acute-phase reactant, meaning its levels increase in response to inflammation.

In chronic alcoholism the sub clinical inflammation releases various cytokines like TNF Alpha (TNF-α), Interleukin-6 (IL -6) and Interleukin-1β (IL-1β). These cytokines stimulate the synthesis of ferritin in hepatocytes and macrophages. The increase concentration of ferritin in hepatocyte further initiates inflammation and oxidative stress which initiates a never-ending vicious cycle of oxidative damage and inflammatory changes in hepatocytes. These further work towards the development of scar tissue and hepatocyte damage, resulting in release of ferritin in blood. The increased ferritin levels then further amplify inflammation, creating a vicious cycle that exacerbates liver damage in ALD [14, 16]. Iron accumulation in the form of ferritin exerts its effects via multiple ways. As ferritin is also stored on mitochondria, its excessive accumulation and detrimental oxidative damage effects results in mitochondrial dysfunction. Excessive iron load in ferritin may lead to generation of reactive oxygen species (ROS) within mitochondria damages mitochondria and affects its functions. ROS further disturbs various cellular signalling pathways, leading to hepatocyte apoptosis and necrosis, contributing to the progression of ALD [15].

In a review article Najma et al reported that in the presence of excessive iron concentration hepatocytes activates the Kupffer cell activation which secretes proinflammatory and profibrotic factors and finally results in activation of hepatic stellate cell. Thes activated hepatic stellate cells for a longer time results into promoting liver fibrosis, which is a classical feature of ALD progression. In the previous literature various studies based on this theory have shown that ferritin levels are significantly higher in patients with ALD, and this correlates with disease severity and liver dysfunction [17].

The current study observed that elevated serum levels of ferritin in ALD initiates stimulation of multiple pathways via oxidative stress through increased iron availability, mitochondrial dysfunction, and the amplification of inflammation. This oxidative stress drives hepatocellular damage and disease progression, making ferritin a key player in the pathogenesis of alcoholic liver disease [12-14].

CRP plays a critical role in the inflammatory processes in ALD. The inflammatory pathways set by CPR further damage the hepatocytes and develop liver injury and plays a crucial role in ALD disease progression. The mechanisms by which CRP mediates inflammation in ALD is much a complex process which involves several interconnected cascade mechanisms [8,9].

The hepatocellular injury and hepatic damage resulted due to the hepatotoxic effects of metabolites produced after alcohol metabolism. The activation of various immune responses due to chronic usage of alcohol also leads to liver injury. An alcohol metabolite acetaldehyde, stimulate the release of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β from activated macrophages and Kupffer cells in the liver. These cytokines, further stimulates the synthesis of CRP in hepatocytes. CRP is an acute-phase protein and also acts as a sensitive marker of systemic inflammatory response. It elevated concentration in blood reflects the extent of liver injury and the inflammatory burden in ALD [17,18]. CRP activates the classical pathway of the complement system when it binds to apoptotic cells, damaged tissue, or pathogens. In ALD, this activation amplifies the inflammatory response. The

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binding of CRP to liver cells and other damaged tissue surfaces triggers complement activation, leading to the recruitment of inflammatory cells like neutrophils and macrophages. These cells release additional pro-inflammatory cytokines and reactive oxygen species (ROS), perpetuating the inflammatory cycle in the liver.[19] The cascade of inflammatory events started in hepatocytes initiates the insult by progressive hepatic injury, fibrosis which leads to hepatic cirrhosis in ALD.

Recruitment and activation of neutrophils is facilitated CRP in ALD. When CRP attaches itself to pathogens, injured tissue, or apoptotic cells, it can trigger the classical route of the complement system. This activation increases the inflammatory response in ALD. Complement is activated when CRP binds to the surface of liver cells and other injured tissue, which attracts inflammatory cells such as neutrophils and macrophages. The inflammatory cycle in the liver is sustained by these cells' secretion of more pro-inflammatory cytokines and reactive oxygen species (ROS) [19]. In ALD, this series of inflammatory events leads to liver damage, fibrosis, and eventually cirrhosis.
The resident macrophages in the liver, play a crucial role in the initiation and progression of liver inflammation. CRP, through its binding to damaged hepatocytes and the subsequent activation of the complement system, contributes to the activation of Kupffer cells. These cells then release pro-inflammatory cytokines (such as TNF-α) and chemokines which further amplify the inflammatory cascade. The activation of Kupffer cells by CRP work towards the progression of chronic inflammation cascade which is a characteristic feature of ALD [20, 21].
In chronic inflammation in ALD, activation of Hepatic Stellate Cells (HSCs), also stimulates collagen production and results in fibrosis. In this manner chronic inflammatory environment, contributes to the fibrogenic process in liver via CRP in ALD. In another mechanism the fibrogenic effect has been shown by CRP by enhancing the secretion of profibrotic cytokines and growth factors, such as TGF-β, which promote HSC activation which results in liver fibrosis. By the multiple mechanisms CRP-driven inflammation work towards the development of liver injury which results in cirrhosis in ALD. Further, targeting of the TGF-β signalling pathway can be one step towards the therapeutic approach of inhibiting the progression of liver disease [22].
So beyond its role in complement activation and neutrophil recruitment, CRP itself may have direct pro-inflammatory effects. CRP can interact with cell surface receptors on liver cells, endothelial cells, and immune cells, triggering the release of cytokines and promoting a pro-inflammatory state. In ALD, these direct interactions contribute to the exacerbation of hepatic inflammation, driving the progression of the disease from steatosis to more severe forms like alcoholic hepatitis and cirrhosis [23].

Multiple mechanisms operate for development of hepatic injury due to chronic alcoholic exposure of hepatocytes. Through the activation of the complement system, recruitment of neutrophils, activation of Kupffer cells, and promotion of fibrogenesis, innate immune responses, liver sinusoidal endothelial cell dysfunction and hepatic stellate cell activation, and gut-liver and adipose-liver cross talk in response to alcohol [24].

Hence the Ferritin/CRP ratio has the potential to serve as a useful biomarker for iron overload and inflammation together in ALD patients. Due to multifaced ferritin and CRP in setting of liver injury and its progression the ratio could also help in monitoring disease progression and therapeutic efficacy in ALD management. Further studies in this regard with larger sample sizes and longitudinal data will be suggested to validate and support the above-mentioned study findings which can provide the evidence-based support to explore the clinical utility of the Ferritin/CRP ratio in ALD.

CONCLUSION

The Ferritin/CRP ratio is a promising biomarker for assessing iron overload and inflammatory milieu in ALD. Elevated levels of both ferritin and CRP in ALD patients suggest the multifaced burden of systemic inflammation, iron dysregulation, oxidative damage and liver injury. This ratio could offer a useful adjunct in clinical settings for early detection and monitoring of ALD, assisting in patient management and treatment approaches.

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