

## Clinical Significance of Interleukin 18 in Chronic Liver Disease: Review Article

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### ABSTRACT

**Background:** The end stage of chronic liver disease (CLD) is cirrhosis, which is characterised by progressive scarring (fibrosis) of the liver due to chronic liver injury and subsequent loss of liver function. Early diagnosis and prevention of complication of liver cirrhosis is challenging, so Interleukin-18 is one of the surrogate serum indicators being investigated for noninvasive evaluation of liver fibrosis. The interferon-gamma inducing factor IL-18 plays a crucial role in the development of chronic liver disease by promoting inflammation. However, its precise role is unclear due to a paucity of data.

**Objective:** Assessment of possible correlation between Interleukin 18 and liver cirrhosis.

**Methods:** Interleukin 18, hepatitis, and liver cirrhosis were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from January 2000 to May 2020 were included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

**Conclusion:** IL-18 plays a pathogenic role in liver cirrhosis as well as portal hypertension development and may represent non-invasive marker for HCV related cirrhosis.

**Keywords:** Interleukin 18, Liver cirrhosis.

### INTRODUCTION

Cirrhosis of the liver is a form of advanced liver disease caused by chronic inflammation and injury that results in the replacement of healthy liver tissue with scar tissue<sup>(1)</sup>.

In poor and medium income nations, viral hepatitis is the primary cause of cirrhosis, while in the West, alcohol and non-alcoholic fatty liver disease are key factors. Cirrhosis strikes more males than women. Cirrhosis has a high economic cost due to human suffering, medical costs, and losing expenses<sup>(2)</sup>.

#### Introduction to Interleukin 18:

Interleukin-18 (IL18) is a member of the IL-1 family of pro-inflammatory cytokines. It is generated as an inactive precursor that must be processed by caspase-1 before it can function. Many different kinds of cells, both hematopoietic and non-hematopoietic, can release IL-18<sup>(3)</sup>. Kupffer cells, which are resident macrophages in the liver, were the first to be identified as producing IL-18. Different from hematopoietic cells, intestine epithelium cells, keratinocytes, and endothelial cells all express IL-18 at steady-state levels. Autoimmune and

inflammatory diseases have been associated to IL-18 dysregulation<sup>(3)</sup>.

#### Processing:

The signal peptide required for cytokine release is present in the vast majority of cytokines. While, the other members of the IL-1 family all have signal peptides, the IL18 gene does not. Much like IL-1 $\beta$ , IL-18 is produced from a biologically inactive precursor. An inactive 24-kilodalton precursor missing a signal peptide and accumulating in the cytoplasm of cells, whose 193-amino-acid sequence is encoded by the IL-18 gene. Similar to IL-1 $\beta$ , the 18kDa mature, The IL-18 caspase 1 in the NLRP3 inflammasome converts the 30 kDa IL-18 precursor into the physiologically active version of IL-18.

Multiple mechanisms control the intracellular production of the biologically active form of IL-18 and its subsequent release into the extracellular environment, control of genes after their initial transcription and again after they've been translated are all examples of the type of gene regulation known as post-transcriptional regulation<sup>(4)</sup>.

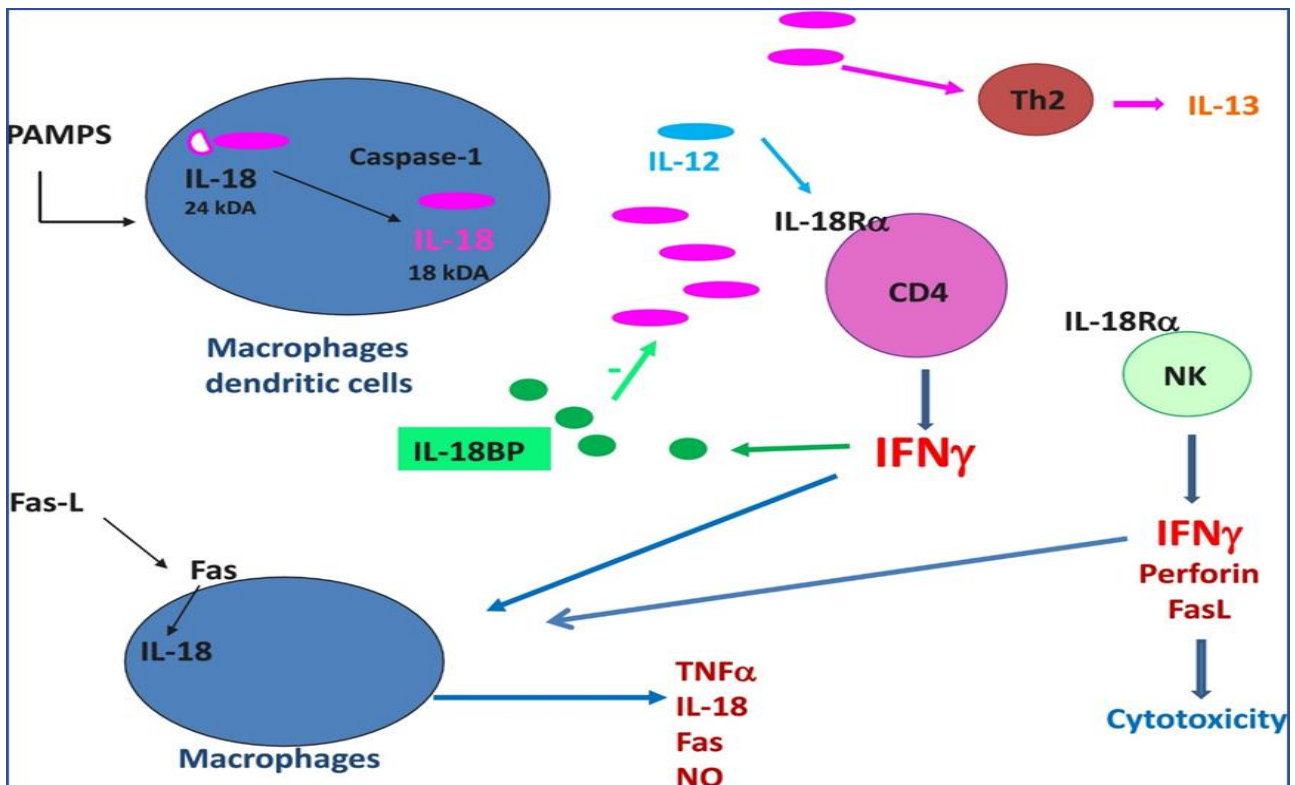


Figure (1): IL-18 biological properties <sup>(5)</sup>.

**Function:**

Macrophages are the primary cells responsible for producing IL-18, but other cell types also produce it. IL-18 has pleiotropic effects and activates multiple cell types. Proinflammatory IL-18 aids in the initiation of type 1 reactions. After infection with lipopolysaccharide (LPS) or other microbial compounds, it works in tandem with interleukin-12 to stimulate cell-mediated immunity. Type II interferon (IFN) production is induced on CD4, CD8 T cells, and NK cells by IL-18 and IL-12. IFN is critical for activating macrophages and other cells <sup>(4)</sup>.

**Clinical significance:**

Inducing IFN-γ, nitric oxide (NO), and reactive oxygen species (ROS) in phagocytes, IL-18 is crucial for host defense against both intracellular and external pathogens. The CD8+ T cells, which are crucial in the process of virus clearance, are also directly activated by IL-18. When IL-12 is not present, IL-18 protects against helminth infection by stimulating the development of Th2 cytokines and granulocytes <sup>(5)</sup>.

Researchers found that intestinal homeostasis necessitated IL-18, which is produced by intestinal epithelial cells. Intestinal barrier function is supported by IL-18. When the barrier is compromised, microbial compounds activate lamina propria macrophages, which in turn triggers inflammation via caspase-1-dependent processing of interleukin-18. In addition, the vascular cell adhesion molecule-1 (VCAM-1) antibody natalizumab blocks the entry of macrophages and other myeloid cells into intestinal and brain tissues in patients with Crohn's disease and multiple sclerosis. Blocking

IL-18 would also limit cell migration across the endothelium and into the intestines since IL-18 promotes VCAM-1 <sup>(6)</sup>.

The most common type of autoimmune hypothyroidism is called Hashimoto's thyroiditis, and it has been linked to IL-18. Also, IL-18 promotes amyloid-beta formation in human neuron cells, a process linked to Alzheimer's disease, and mediates the neuroinflammatory response following brain injury. Besides, it may serve as a marker for monitoring the severity of diabetic nephropathy. Microalbuminuric and macroalbuminuric patients had significantly greater levels of this Interleukin-18 compared to healthy individuals and diabetic patients with normoalbuminuria <sup>(4)</sup>.

Serum concentrations of IL-18 were a significant prognosis factor in patients with IgA nephropathy because they were connected with susceptibility to corticosteroid therapy, and IL-18 was reported to have predictive role for long-term postoperative mortality as an urine biomarker of acute kidney injury (AKI). Furthermore, compared to the overall IgA nephropathy patient population, those with baseline blood IL-18 levels above the median had a renal (four-year) survival rate of 20% <sup>(7-8)</sup>.

Ischemia-induced myocardial dysfunction is prevented by inhibiting caspase-1, which is activated by IL-1b via caspase-1 to produce interleukin-18 <sup>(9)</sup>. It is possible that IL-18, when combined with immune-checkpoint therapy, is an effective treatment for early-stage cancer. That's because it increases the body's supply of T cells, which have been shown to have tumor killing properties <sup>(10)</sup>.

### Interleukin 18 in liver disease and cirrhosis:

While, the precise role of cytokines in the pathophysiology of chronic HCV infection remains unknown, many scientists believe that cytokines play a crucial role in both immunoregulation and immunological dysfunction<sup>(11)</sup>. The levels of IL-18 were found to be indicative of the inflammation and hepatic damage caused by HCV. Its elevated production contributes to chronicity and hastens the progression of chronic hepatitis to cirrhosis. Because T helper 1 (Th1) cells have been linked to the development of hepatitis C virus infection, it follows that interleukin 18 (IL-18) may play a role in the pathogenesis of tissue injury in HCV<sup>(12)</sup>.

Increased vulnerability of liver endothelial cells to apoptosis and increased production of cytokines by type 1 helper cells (Th1) are two key roles IL-18 plays in the progression of liver cirrhosis. The cytotoxicity of both as ligand-mediated Th1 cells and perforin-dependent hepatic natural killer cells are enhanced by IL-18<sup>(13)</sup>.

Increased levels of IL-18 inside the inflammatory infiltrate are characteristic of chronic hepatitis C virus infection (CHC), raising the possibility that this cytokine contributes to the sustained cellular immune response against hepatocytes. In particular, it has been shown that IFN-g therapy exhibits an anti-inflammatory action in vivo via increasing IL-18 binding protein and, in turn, inhibiting IL-18<sup>(14)</sup>.

**Sharma *et al.***<sup>(15)</sup> looked into the role of IL-18 in the development of CHC and found that individuals with CHC and cirrhosis had considerably higher blood levels of IL-18 than those with healed HCV infection. In cirrhotic patients, serum IL-18 levels linked with measures of Child-Pugh status, histological activity, and the extent to which the livers had been necrotized. Patients with CHC have increased amounts of IL-18 transcripts expressed in the liver and increased IL-18 mRNA expression in peripheral blood mononuclear cells, which correlates with the severity and viral load of HCV infection and suggests a role for IL-18 in the development and progression of HCV-related liver disease. These findings suggest that an increase in plasma IL-18 is linked to disease progression and add to the growing body of data implicating IL-18 in the initiation of liver damage. The considerable decrease in plasma IL-18 levels after therapy, as well as the reduction in histological liver damage, are also compatible with this concept<sup>(16)</sup>.

With regards to hepatitis B virus (HBV) infection, IL-18 has therapeutic promise and may aid in the control and spontaneous clearance of HBV infection. Furthermore, the different clinical outcomes and natural histories of HBV infection are significantly impacted by a variation in the promoter region of the IL-18 gene<sup>(17-18)</sup>.

There is a certain hepatotoxic pathway mediated by IL-18 in cholestatic cirrhosis including primary biliary cirrhosis (PBC) and biliary atresia and the mean IL-18 measurement is correlated with disease severity in PBC

as well as autoimmune hepatitis and may have a prognostic and therapeutic value in prevention of cirrhotic changes and regulation of rejection after liver transplantation<sup>(19-20)</sup>.

Hepatic encephalopathy, a result of liver cirrhosis, was also positively correlated with IL-18<sup>(21)</sup>. Studying IL-18 single nucleotide gene polymorphism may be a significant diagnostic for predicting cirrhosis progression in CHC patients, as the probability of developing HCC is 1.17-fold greater in those with the GC or CC genotypes compared to those with the GG genotype<sup>(22)</sup>. Vascular endothelial growth factor, which is involved in sinusoidal remodeling and the formation of portal-systemic collaterals in PH, is activated by IL-18, which plays a crucial role in the development of PH and esophageal varices. That's why they aid in the development of new blood vessels (angiogenesis), vascular malfunction (endothelial dysfunction), and inflammation<sup>(23)</sup>.

### CONCLUSION

IL-18 plays a pathogenic role in liver cirrhosis and portal hypertension development and may represent non-invasive marker for HCV-related cirrhosis.

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### REFERENCES

1. **Mazumder N, Celaj S, Atiemo K *et al.* (2020):** Liver-related mortality is similar among men and women with cirrhosis. *Journal of Hepatology*, 73 (5): 1072-1081.
2. **Sepanlou S, Safiri S, Bisignano C *et al.* (2020):** The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Gastroenterology & Hepatology*, 5 (3): 245-266.
3. **Fabbi M, Carbotti G, Ferrini S (2015):** Context-dependent role of IL-18 in cancer biology and counter-regulation by IL-18BP. *Journal of Leukocyte Biology*, 97 (4): 665-675.
4. **Kaplanski G (2018):** Interleukin-18: Biological properties and role in disease pathogenesis. *Immunological Reviews*, 281 (1): 138-153.
5. **Yasuda K, Nakanishi K, Tsutsui H (2019):** Interleukin-18 in health and disease. *International Journal of Molecular Sciences*, 20 (3): 649-53.
6. **Siegmund B (2010):** Interleukin-18 in intestinal inflammation: friend and foe? *Immunity*, 32 (3): 300–2.
7. **Coca S, Garg A, Thiessen-Philbrook H *et al.* (2014):** Urinary biomarkers of AKI and mortality 3 years after cardiac surgery. *J Am Soc Nephrol.*, 25: 1063–1071.
8. **Shi B, Ni Z, Cao L *et al.* (2012):** Serum IL-18 is closely associated with renal tubulointerstitial injury and

- predicts renal prognosis in IgA nephropathy. *Mediat Inflamm.*, 12: 17-22.
9. **Charles D, Daniela N, Hun K et al. (2013):** Interleukin-18 and IL-18 Binding Protein. *Frontiers in Immunology*, 4: 1664-3224
  10. **Ma Z, Li W, Yoshiya S et al. (2016):** Augmentation of Immune Checkpoint Cancer Immunotherapy with IL18. *Clin Cancer Res.*, 22: 2969–2980.
  11. **Niu Z, Zhang P, Tong Y (2015):** Association of plasma interleukin-18 levels and polymorphisms in interleukin-18 gene with outcomes of hepatitis C virus infections: a meta-analysis. *Journal of Immunoassay and Immunochemistry*, 36 (3): 221-232.
  12. **El-Hendawy G, Salama A, Abd El-Hamid A et al. (2018):** Study of interleukin-18 during antiviral therapy for hepatitis C with sofosbuvir, ribavirin, and interferon in Menoufia hospitals. *Menoufia Medical Journal*, 31 (3): 762-66.
  13. **Selim H, El-Barrawy M, Taha H et al. (2009):** Evaluation of Interleukin-18 as a Non-Invasive Marker of Liver Fibrosis among Chronic Hepatitis C Virus Patients. *The Journal of the Egyptian Public Health Association*, 84: 391-403.
  14. **Vecchiet J, Falasca K, Cacciatore P et al. (2005):** Association between plasma interleukin-18 levels and liver injury in chronic hepatitis C virus infection and non-alcoholic fatty liver disease. *Annals of Clinical & Laboratory Science*, 35 (4): 415-422.
  15. **Sharma A, Chakraborti A, Das A et al. (2009):** Elevation of interleukin-18 in chronic hepatitis C: implications for hepatitis C virus pathogenesis. *Immunology*, 128 (1pt2): 514-522.
  16. **Marín-Serrano E, Rodríguez-Ramos C, Díaz F et al. (2006):** Modulation of the anti-inflammatory interleukin 10 and of proapoptotic IL-18 in patients with chronic hepatitis C treated with interferon alpha and ribavirin. *J Viral Hepat.*, 13 (4): 230-234.
  17. **Zhang P, Wu J, Li Y et al. (2005):** Association of polymorphisms of interleukin-18 gene promoter region with chronic hepatitis B in Chinese Han population. *World J Gastroenterol.*, 11 (11): 1594-1598.
  18. **Kumar K, Kumar G, Chowdhury S et al. (2015):** IL-18 polymorphisms in hepatitis B virus related liver disease. *Cytokine*, 73 (2): 277-282.
  19. **Yagi T, Iwagaki H, Urushihara N et al. (2001):** Participation of IL-18 in human cholestatic cirrhosis and acute rejection: analysis in living donor liver transplantation. *Transplant Proc.*, 33 (1-2): 421-25.
  20. **Yamano T, Higashi T, Nouso K et al. (2000):** Serum interferon-gamma-inducing factor/IL-18 levels in primary biliary cirrhosis. *Clin Exp Immunol.*, 122 (2): 227-231.
  21. **Komala A, Mustika S, Pratomo B (2018):** Overview of Serum Interleukin-18 (IL-18): Levels in Liver Cirrhosis Patients and Their Correlation to Hepatic Encephalopathy. *Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy*, 19 (2): 67-73.
  22. **Eldesoky A, Ahmed N, Zaghloul H et al. (2020):** Interleukin-18 polymorphism as a diagnostic tumor marker for hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. *Egypt Liver Journal*, 10: 51-55.
  23. **Bosch J, Groszmann R, Shah V (2015):** Evolution in the understanding of the pathophysiological basis of portal hypertension: How changes in paradigm are leading to successful new treatments. *J Hepatol.*, 62: 121-130.