**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 87798

**Manuscript Type:** MINIREVIEWS

**Dynamic changes and clinical value of lipocalin 2 in liver diseases caused by microbial infections**

Chen F *et al*. Clinical value of LCN2 in liver diseases

Feng Chen, Shan-Shan Wu, Chao Chen, Cheng Zhou

**Feng Chen, Shan-Shan Wu, Chao Chen, Cheng Zhou,** State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang Province, China

**Co-first authors:** Feng Chen and Shan-Shan Wu.

**Author contributions:** Chen F and Zhou C contributed to the concept and design of the whole study; Chen F prepared the draft; Chen F and Zhou C wrote and revised the manuscript; Chen C contributed to drawing the figure; All authors contributed to preparing, reading, and approving the ﬁnal manuscript; Chen F and Wu SS have been working together on the research of LCN2; Wu SS participated in the conception of the paper and was instrumental and responsible for the comprehensive literature search, figure plotting, preparation and submission of the current version of the manuscript; Chen F and Wu SS have made crucial and indispensable contributions to the publication of this manuscripts as the co-first authors.

**Corresponding author: Cheng Zhou, MD, Associate Professor,** State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, No. 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China. zhoucheng0113@zju.edu.cn

**Received:** August 28, 2023

**Revised:** December 4, 2023

**Accepted:** January 9, 2024

**Published online:**

**Abstract**

Lipocalin 2 (LCN2) plays a pivotal role in iron metabolism, particularly in the context of microbial infection resistance (*e.g.*, viruses, bacteria, parasites, *etc.*). LCN2 combats microbial infection by directly assisting the body in competing with microorganisms for iron, inducing immune cells to secrete various cytokines to enhance systemic immune responses, or recruiting neutrophils to infectious sites. The liver serves as the primary organ for LCN2 secretion during microbial infections. This review encapsulates recent advances in dynamic changes, clinical values, and the effects of LCN2 in infectious liver diseases caused by various microbial microorganisms.

**Key Words:** Lipocalin 2; Microbial infection; Immunity; Liver diseases

Chen F, Wu SS, Chen C, Zhou C. Dynamic changes and clinical value of lipocalin 2 in liver diseases caused by microbial infections. *World J Hepatol* 2024; In press

**Core Tip:** Lipocalin 2 (LCN2) is a sensitive marker for infections because its change can be detected at the very early stage of various pathogenic microorganism infections. Infection with a variety of pathogens can cause liver damage, and it is well established that LCN2 is expressed differently in different clinical conditions. By observing the level of LCN2, doctors can evaluate the progression of the disease and the treatment efficacy. LCN2 is also a predictor marker in some end-stage liver diseases and is promising as a new diagnostic marker. Due to its strong binding with iron, targeting LCN2 also shows great potential in the treatment of infectious diseases.

**INTRODUCTION**

Lipocalin 2 (LCN2) is a secreted protein from the Lipocalin family with a molecular weight of 25 kDa, consisting of 178 amino acid residues[1]. It is widely expressed across various cell types, including neutrophils, macrophages, activated leukocytes, adipocytes, hepatocytes, tumor cells, stromal cells, and osteoblasts. The LCN2 mRNA was initially isolated from a kidney cell cDNA library infected with SV40 in 1989 by Hraba-Renevey *et al*[2], and it was named 24p3. Subsequently, in 1993, Kjeldsen *et al*[3] successfully purified LCN2 from human neutrophils. LCN2’s diverse functions were discovered in different cell types, resulting in several names inspired by its various roles. In addition to the original designation as 24p3[2], it was referred to as 25 kDa protein for its molecular weight[3], neutrophil gelatinase-associated lipocalin (NGAL or HNL) for its aggravating inflammatory response *via* recruitment of neutrophils[4], oncogenic lipocalin for its promotion of tumor growth[5], superinducible protein (or SIP24)[6] for its heightened expression in response to fibroblast growth factor in BALB/c 3T3 cells, uterocalin for its elevated level around parturition in the uterus[7], and siderocalin for its function in sequestering iron[8]. In 2004, Flo TH published a paper in Nature officially named it LCN2, following the nomenclature of the lipocalin family, a gene group evolutionarily conserved and found in all kingdoms of life. In the Flo TH paper, LCN2 was demonstrated to play an important role in innate immunity against iron-dependent bacterial infections. Over time, the name LCN2 gained widespread acceptance and standardization[9,10].

Similar to other members of the Lipocalins family, LCN2 has a highly conserved core structure, characterized by an eight-stranded, antiparallel β-barrel with the calyx, or ligand-binding site. Compared with other members, LCN2 exhibits a calyx that is unusually shallower and broader, featuring a lining of positively charged residues. Consequently, LCN2 does not directly bind positively charged ions but rather sequesters irons by binding the negatively charged ferric siderophore with a sub-nanomolar dissociation constant[11]. The ligands housed in the calyx suggests that LCN2’s primary function is intricately linked to iron metabolism.

LCN2 has been reported to be expressed in many organs, including the liver[12-15], kidney[16-18], lungs[19,20], brain[21,22], heart[23,24], bone marrow[25], and spleen[26], bronchus[27], stomach[28], small intestine[29], pancreas[30], prostate gland[31], thymus[32]. Despite its presence in numerous organs, the liver emerges as the major site of LCN2 generation. During the body’s response to harmful microorganisms, 90% of the LCN2 upregulation originates from the liver. It has been reported that in mice, upon bacterial infection, the mRNA level of LCN increased by 30-40-fold in the liver, in contrast to an approximately 1.5-fold elevation in the spleen and lung[33]. Physiologically, hepatocytes take up iron majorly by transferrin-mediated pathway, and LCN2 was demonstrated to be not essential in hereditary hemochromatosis (HH)[34]. However, when the body with HH was infected by microorganisms, such as Salmonella Typhimurium, iron-capturing LCN2 was inducted to confer the host resistance to systemic infection with Salmonella and improve control of bacterial replication[35]. Therefore, LCN2 is proposed to play an important role in microbial infection-induced hepatitis.

**In viral infectious liver diseases**

As a key organ of detoxification, the liver assumes a crucial role in the body’s defense mechanisms. Viral infections, including hepatitis B virus (HBV) and hepatitis C virus (HCV), can induce a series of inflammatory pathological changes in the liver, leading to varying degrees of hepatitis. This progression may result in fibrosis, cirrhosis, liver failure, and ultimately, liver cancer. Individuals at different stages of HBV-related liver diseases manifest varying degrees of iron metabolic disorders[36]. Following viral infection, LCN2 levels begin to rise and exhibit variation during different phases of liver disease, underscoring the potential of LCN2 in the diagnosis and treatment of viral hepatitis. Due to the lack of suitable mouse models for viral hepatitis, studies on LCN2 in viral liver diseases mainly focus on disease diagnosis.

LCN2 is mainly related to the degree of inflammation in the body during viral liver disease and can serve as an indicator of various complications, such as cirrhosis, ascites, peritonitis, hepatorenal syndrome, nephritis, *etc.* Our previous study showed that the serum LCN2 levels in patients with chronic hepatitis B were significantly higher than those in normal controls[37]. Lu *et al*[38] examined the serum of patients with HBV-associated acute-on-chronic liver failure (ACLF) and found that LCN2 levels were significantly higher than that of patients without ACLF. Moreover, the serum LCN2 levels significantly correlated with the total bilirubin, international normalized ratio, and model for end-stage liver disease model (MELD). The MELD score was independently associated with the overall survival in patients with HBV-ACLF, and serum LCN2 is also an independent risk factor for hepatorenal syndrome. Thus, the above data showed significant value in predicting the prognosis of HBV-ACLF.

In patients with liver cirrhosis, Gungor *et al*[39] reported that in patients with stable cirrhosis, serum LCN2 levels were not significantly different when compared with controls, while LCN2 levels in plasma and urine were significantly higher in cirrhosis patients with hepatorenal syndrome. Cox regression analysis revealed that plasma LCN2 and MELD-Na scores independent predicted of mortality. Nevertheless, conflicting perspectives exist, Borkham-Kamphorst *et al*[40] found that there was no difference in LCN2 between cirrhosis and non-cirrhosis patients, with compensatory cirrhosis patients exhibiting similar LCN2 levels to end-stage liver disease patients.

Concerning the relationship between LCN2 and viral load, studies in the patients infected with HCV showed no correlation between LCN2 levels and HCV viral load[41]. The diagnostic value of LCN2 in HCV infection-associated renal glomerular injury remains unclear. Strazzulla *et al*[42] observed significant increase in urine LCN2 levels in HCV-infected patients after one year of treatment with direct antiviral drugs, whereas Nada *et al*[43] reported a descrease in urine LCN2. Both studies, however, showed unchanging glomerular filtration rate. The disparate results may stem from individual differences in patient samples, systemic inflammation, and drug toxicity, necessitating further investigation (Table 1).

Because of its small molecular weight, LCN2 may directly leak from the kidney into the urine, allowing it to be clinically detected through noninvasive methods. Urinary LCN2 levels can be used to assess kidney injury in chronic liver disease complications or renal toxicity after antiviral drug administration[16,17,44]. To evaluate the efficacy of urinary LCN2 as a diagnostic biomarker for different etiology of acute kidney injury (AKI) in cirrhosis and its role as a prognostic marker, Hamdy *et al*[44] studied 83 patients with liver cirrhotic AKI due to HCV or combined with HBV infections, and they revealed that different urine LCN2 levels matched different types of kidney dysfunction in cirrhotic patients, thus providing suggestions for management decisions in the diagnostic process. It needs to be pointed out that, in addition to a systemic inflammatory reaction, the kidneys themselves are also damaged in the virus-induced hepatorenal syndrome[45], resulting in a significant increase of LCN2.

**In bacterial infectious liver diseases**

Bacterial infections pose an escalating global health challenge, and the LCN2 has been repetitively found to play an important role in the body's defense against bacterial infections (Figure 1).

LCN2 inhibits bacterial growth primarily by sequestering iron, an essential nutrient for life. Bacterial invasion, growth, and reproduction rely on iron, creating a natural competition with the body’s iron-dependent activities. Mechanistically, bacteria acquire iron by synthesizing siderophores and forming siderophore-Fe complexes. The host employs LCN2 to directly bind the siderophores-Fe complex, thereby controlling bacterial growth. Therefore, LCN2 is an important component of the innate immune system in defense against bacterial infection [46]. In LCN2 deficient mice, a challenge with a sublethal dose of Escherichia coli intraperitoneally resulted in a substantially higher amount of bacteremia and bacterial burden in the liver compared to the control mice. However, no significant differences in other components of the immune response, including leukocyte numbers, neutrophil infiltration, and various cytokines, such as TLR-induced tumor-necrosis factor, interleukin (IL)-12, IL-6 and MIP-2 were found between wild-type and lipocalin-2-deficient mice[9].

*In vivo,* LCN2 may also act as an antioxidant by regulating iron homeostasis to combat bacteria. Studies in LCN2 deficient mice revealed decreased levels of tissue redox state indicators cysteine and glutathione in the liver and plasma, elevated indices of liver damage such as transaminasemia, lactate dehydrogenase, and increased mortality. Moreover, the application of an iron chelator, Desferoxamine, was able to protect LCN2-deficient mice from LPS-induced toxicity and reduce mortality[47].

As a constituent of innate immunity, the antibacterial effects of LCN2 are intricately regulated by the immune system. During the early phase of infection, the innate immunocytes, such as neutrophils and macrophages, are activated, leading to the secretion of substantial quantities of LCN2. LCN2 then stimulates these immunocytes to produce a variety of cytokines and chemokines (IL-6, IL-10, TNF-α, MCP-1, *etc.*), thereby enhancing the migration and phagocytosis of macrophages to bolster antibacterial function. Deletion of the LCN2 gene results in impaired functions of immune cells, including compromised homeostasis and morphological development of neutrophils, decreased migration ability and exudation, as well as reduced secretions of cytokines and chemokines, such as TNF-α, IL-6, IL-1β, MCP-1, and MIP-2[48]. LCN2 knockout mice exhibit higher expression of Th17 cell polarization markers, with transcription factor RORγt and cytokines IL-17A and IL-21 significantly up-regulated[49].

LCN2 itself also interacts with other immune factors in various types of cells, such as toll-like receptor ligands (*e.g.*, TollLike Receptor 4 ligands), cytokines (*e.g.*, IL-6, IL-1, IL-22, TNF-α, IFN-γ), and growth factors (*e.g.*, insulin-like growth factor)[33,50,51]. It was reported that IL-6 treatment stimulated hepatocytes to produce more LCN2 *in vitro* and in vivo, and the elevation of LCN2 was abrogated in the IL-6R Hep−/−, IL-6 −/−mice, and Stat3 Hep−/− mice. Hepatocyte-specific LCN2 knockout mice showed increased susceptibility to infection with Klebsiella pneumoniae or Escherichia coli, leading to increased bacterial translocation from the gut to mesenteric lymph nodes and reduced liver regeneration after partial hepatectomy. These findings suggest that the production of hepatocyte-specific LCN2 depends on IL-6 activation of the signal transducers and activators of the transcriptions 3 (STAT3) signaling pathway. Hepatocyte-derived LCN2 protects against bacterial infection and promotes liver regeneration[33]. Another study demonstrated that rIL-22-induced antimicrobial activity mediated by IL-22Ra1 and STAT3 signaling is partially dependent on LCN2[51].

During bacterial infection, elevated levels of LCN2 expression are detected in both hepatocytes and neutrophils. The LCN2 from these distinct sources coordinates to combat bacteria, albeit with differing roles. While extracellular LCN2, secreted by liver cells, serves to restrict systemic bacterial infection, neutrophils transported LCN2 are carried in specific granules of neutrophils to local sites, contributing to the resistance against local bacterial infection through a network of neutrophil extracellular traps (NETs). The recently discovered mechanism, NETs, describes the process by which neutrophils kill bacteria through both cell-death-dependent and cell-death-independent pathways. Among the more than 80 proteins identified as components of NETs, LCN2 emerges as one of the crucial proteins. Notably, LCN2 in NETs is exclusively derived from neutrophils and not from hepatocytes or other cells. Complete or specific genetic deletion of the LCN2 gene in neutrophils does not impact NETs formation but does reduce the bactericidal effect of NETs *in vitro*[52].

LCN2 also resists bacterial invasion by maintaining intestinal microecological stability. It plays an important role in maintaining the species and abundance of intestinal flora and contributes to the gastrointestinal antibacterial barrier. Studies have shown that in the gut of LCN2 knockout mice, there is a significant and dramatic alteration in the species and abundance of intestinal flora change. Notably, iron-dependent strains expand significantly, leading to dysbiosis and continuous colonization by segmented filamentous bacteria (SFB). SFB is a special symbiotic intestinal bacterium within the firmicutes, fundamental for the production of innate and acquired immunity in the gastrointestinal and respiratory tracts and necessary for the maturation of the host intestinal immune barrier[53]. Deletion of LCN2 may provide a favorable environment for SFB colonization by inhibiting the antibacterial response of epithelial cells, altering the mucous composition, or establishing the antibacterial barrier. The increased SFB, in turn, can upregulate the level of LCN2. A study reported a significant increase in LCN2 levels in the liver and serum of SFB-colonized mice, accompanied by upregulation of the pro-inflammatory TH17 and TH1 cells in the liver-draining lymph nodes[54].

The dynamic changes in LCN2 levels during bacterial infection present potential applications for the early diagnosis of complications in liver diseases. Behairy *et al*[55] demonstrated that the level of LCN2 was significantly elevated in the patients with chronic liver diseases complicated with bacterial infection compared with those without bacterial infection. This finding suggests that LCN2 is an early diagnostic indicator for chronic liver disease with bacterial infection. Similarly, Liu *et al*[56] found that the level of LCN2 in ascites from decompensated liver cirrhosis with spontaneous bacterial peritonitis (SBP) was significantly higher than that in the non-SBP group, and the LCN2 level was positively correlated with ascitic polymorphonuclear leukocyte and negatively correlated with ascitic albumin. Furthermore, the dynamic changes of ascitic LCN2 were able to predict the clinical prognosis of SBP patients. Another study by Cullaro *et al*[57] showed a close relationship between ascitic LCN2 level and patient mortality, indicating that LCN2 serves as a molecular diagnostic biomarker of peritonitis in liver cirrhotic patients and an independent predictor of short-term hospitalization mortality. In addition, a study in the sepsis animal model of cecal ligation and puncture showed the LCN2 Levels in mouse liver and lung increased significantly during the early hyper-inflammatory phase, despite the dysfunction of innate immunity characterized by a severely decreased expression of most inflammatory mediators. This highlights the potential importance of LCN2 in the diagnosis of sepsis[58]. Thus, LCN2 is suggested to be an important clinical biomarker for early diagnosis of sepsis.

As a siderophore-binding protein, LCN2 provides wide application in the treatment of bacterial infections. Due to its multidrug resistance and the lack of effective antimicrobial drugs, carbapenem-resistant Acinetobacter baumannii (A. baumannii) has been designated by the World Health Organization as a priority critical pathogen for the development of novel therapeutics. Sheldon *et al*[59] observed the transcriptional profile in the A. baumannii-infected mice and revealed that the expression of LCN2 gene was the most highly upregulated during A. baumannii bacteremia. *In vitro* studies have also shown that LCN2 inhibits iron-dependent growth of A. baumannii and induces iron-regulated gene expression. In an LCN2 knockout mouse model, although LCN2 gene deletion did not alter the number of microflora in A. baumannii-infected tissues, it significantly aggravated the severity of infection and increased mortality.

Similarly, in a sepsis animal model induced by the infection of A. baumannii, the injection of recombinant mouse LCN2 prolonged the survival time of mice by decreasing the number of bacteria in macrophages and multiple organs, including the liver, spleen, and lungs[60]. LCN2 has been regarded as novel therapeutics to combat A. baumannii infection.

**In parasitic infectious liver diseases**

Infection caused by a variety of parasites, such as Schistosoma, Leishmania, and Plasmodium, can lead to liver damage. Iron, being an essential trace element for parasite survival, is acquired by intracellular pathogens from multiple sources within host cells, such as heme, ferlactoferrin or ferrictransferin. This ability may contribute to parasites' survival in different environmental conditions within the host[61]. As a metabolic enzyme and a cofactor in oxidative transport, iron plays a crucial role in immune surveillance. Therefore, controlling iron homeostasis is one of the central battlegrounds in combating pathogen infection.

LCN2's robust iron-binding ability assumes a crucial role in the body's resistance to parasitic infections[62]. Dighal *et al*[63] studied the intramonocytic labile iron pool (LIP) in Indian post Kala-azar dermal Leishmaniasis and found enhanced gene expressions of the iron influx gateways, including LCN2, possibly contributing to the heightened LIP. Therefore, restricting the availability of iron for parasites is regarded as a potential therapeutic strategy against parasitic infections.

Emerging evidence has shown that macrophage polarization plays a critical role in the initiation and progression of liver diseases. The underlying molecular mechanisms are intricate and involve various signaling pathways, including TollLike Receptor 4/nuclear factor kappa-B (NF-κB), janus kinase/STATs, transforming growth factor-β/smads, peroxisome proliferators-activated receptor, Notch, and miRNA signaling pathways[64]. Various factors, such as microorganisms, hypoxia, metabolism, *etc.*, can influence the macrophage polarization. As an iron-related protein involved in innate immune response, LCN2 is modulated by the host’s immune system and interacts with macrophages. Studies have reported that LCN2 promotes M1 polarization of macrophages under *S. japonicum* soluble worm antigens (SWA) treatment. In addition, during the early infection stage in mice treated with *schistoma japonicum*, the expression of LCN2 significantly increased in the liver, mainly located in macrophages *via* the upregulation of NF-kb signaling. This study highlighted the importance of NF-κB/LCN2 in migration and phagocytosis of M1 macrophages stimulated by SWA, emphasizing the essential role of NF-κB/LCN2 in early innate immune responses to infection[65]. Recently, it has been reported that GATA3 is a master regulator for macrophage polarization and infiltration[66,67]. Therefore, investigating the relationship between LCN2 and GATA3 in macrophage polarization of various liver diseases may provide valuable insights.

Besides, Oxidative stress can also lead to an increase in LCN2. In *in vitro* experiments, the up-regulation of LCN2 expression after H2O2 treatment was found to be offset by the addition of antioxidants, dimethyl sulfoxide or cysteamine[68]. Al-Shaebi *et al*[69] found that in the mouse model of malaria induced by Plasmodium chabaudi infection, the expression of the LCN2 gene reduced significantly after treatment with a plant antioxidant, Indigofera oblongifolia leaf extracts (ILE). ILE demonstrated a protective effect on mouse liver injury infected with Plasmodium chabaudi by enhancing the antioxidant capacity of the liver and significantly reducing the red blood cell count and hemoglobin content in mice caused by infection.

**CONCLUSION**

In summary, LCN2 emerges as a sensitive marker for infections, as its changes can be detected at the very early stage of various pathogenic microorganism infections, even preceding the detection of the commonly used clinical acute phase protein α2 macroglobulin. Infection with a variety of pathogens can lead to liver damage, Monitoring the level of LCN2 allows doctors to evaluate disease progression and treatment efficacy. LCN2 also serves as a predictive marker in certain end-stage liver diseases, holding promise as a novel diagnostic marker. Additionally, due to its robust iron-binding capacity, targeting LCN2 presents great potential in the treatment of infectious diseases.

Indeed, the application of LCN2 in clinical setting is not without challenges. First, given that LCN2 is expressed at different levels in different organs, plasma, and urine, it is crucial to determine the appropriate situations to test specific samples and develop standardized sample-handling protocols*.* Second, the variability in LCN2 data across studies is attributed to different methods of detection. Addressing this issue would entail standardizing the detection methods and establishing specific thresholds for diagnosis, necessitating future work with large sample verification. Third, LCN2, being a very sensitive indicator of inflammation, is also sensitive to various other factors. Therefore, evaluating and mitigating the impact of confounding factors on LCN2 reading is essential. Finally, despite promising results in drug studies targeting LCN2, extensive experiments are required to confirm whether regulating iron metabolism *via* LCN2 may lead to unexpected side effects, as iron involves many aspects of the body’s functions.

**REFERENCES**

1 **Xiao X**, Yeoh BS, Vijay-Kumar M. Lipocalin 2: An Emerging Player in Iron Homeostasis and Inflammation. *Annu Rev Nutr* 2017; **37**: 103-130 [PMID: 28628361 DOI: 10.1146/annurev-nutr-071816-064559]

2 **Hraba-Renevey S**, Türler H, Kress M, Salomon C, Weil R. SV40-induced expression of mouse gene 24p3 involves a post-transcriptional mechanism. *Oncogene* 1989; **4**: 601-608 [PMID: 2542864]

3 **Kjeldsen L**, Johnsen AH, Sengeløv H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. *J Biol Chem* 1993; **268**: 10425-10432 [PMID: 7683678]

4 **Xu SY**, Carlson M, Engström A, Garcia R, Peterson CG, Venge P. Purification and characterization of a human neutrophil lipocalin (HNL) from the secondary granules of human neutrophils. *Scand J Clin Lab Invest* 1994; **54**: 365-376 [PMID: 7997842 DOI: 10.3109/00365519409088436]

5 **Reilly PT**, Teo WL, Low MJ, Amoyo-Brion AA, Dominguez-Brauer C, Elia AJ, Berger T, Greicius G, Pettersson S, Mak TW. Lipocalin 2 performs contrasting, location-dependent roles in APCmin tumor initiation and progression. *Oncogene* 2013; **32**: 1233-1239 [PMID: 22614012 DOI: 10.1038/onc.2012.159]

6 **Davis TR**, Tabatabai L, Bruns K, Hamilton RT, Nilsen-Hamilton M. Basic fibroblast growth factor induces 3T3 fibroblasts to synthesize and secrete a cyclophilin-like protein and beta 2-microglobulin. *Biochim Biophys Acta* 1991; **1095**: 145-152 [PMID: 1932134 DOI: 10.1016/0167-4889(91)90077-b]

7 **Liu Q**, Ryon J, Nilsen-Hamilton M. Uterocalin: a mouse acute phase protein expressed in the uterus around birth. *Mol Reprod Dev* 1997; **46**: 507-514 [PMID: 9094098 DOI: 10.1002/(sici)1098-2795(199704)46:4<507::Aid-mrd9>3.0.Co;2-s]

8 **Holmes MA**, Paulsene W, Jide X, Ratledge C, Strong RK. Siderocalin (Lcn 2) also binds carboxymycobactins, potentially defending against mycobacterial infections through iron sequestration. *Structure* 2005; **13**: 29-41 [PMID: 15642259 DOI: 10.1016/j.str.2004.10.009]

9 **Flo TH**, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, Akira S, Aderem A. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. *Nature* 2004; **432**: 917-921 [PMID: 15531878 DOI: 10.1038/nature03104]

10 **Charkoftaki G**, Wang Y, McAndrews M, Bruford EA, Thompson DC, Vasiliou V, Nebert DW. Update on the human and mouse lipocalin (LCN) gene family, including evidence the mouse Mup cluster is result of an "evolutionary bloom". *Hum Genomics* 2019; **13**: 11 [PMID: 30782214 DOI: 10.1186/s40246-019-0191-9]

11 **Goetz DH**, Holmes MA, Borregaard N, Bluhm ME, Raymond KN, Strong RK. The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Mol Cell* 2002; **10**: 1033-1043 [PMID: 12453412 DOI: 10.1016/s1097-2765(02)00708-6]

12 **Borkham-Kamphorst E**, Drews F, Weiskirchen R. Induction of lipocalin-2 expression in acute and chronic experimental liver injury moderated by pro-inflammatory cytokines interleukin-1β through nuclear factor-κB activation. *Liver Int* 2011; **31**: 656-665 [PMID: 21457438 DOI: 10.1111/j.1478-3231.2011.02495.x]

13 **Asimakopoulou A**, Vucur M, Luedde T, Schneiders S, Kalampoka S, Weiss TS, Weiskirchen R. Perilipin 5 and Lipocalin 2 Expression in Hepatocellular Carcinoma. *Cancers (Basel)* 2019; **11** [PMID: 30893876 DOI: 10.3390/cancers11030385]

14 **Sultan S**, Cameron S, Ahmad S, Malik IA, Schultze FC, Hielscher R, Rave-Fränk M, Hess CF, Ramadori G, Christiansen H. Serum Lipocalin2 is a potential biomarker of liver irradiation damage. *Liver Int* 2013; **33**: 459-468 [PMID: 23331620 DOI: 10.1111/liv.12073]

15 **Xu G**, Wang YM, Ying MM, Chen SD, Li ZR, Ma HL, Zheng MH, Wu J, Ding C. Serum lipocalin-2 is a potential biomarker for the clinical diagnosis of nonalcoholic steatohepatitis. *Clin Mol Hepatol* 2021; **27**: 329-345 [PMID: 33465844 DOI: 10.3350/cmh.2020.0261]

16 **Shang W**, Wang Z. The Update of NGAL in Acute Kidney Injury. *Curr Protein Pept Sci* 2017; **18**: 1211-1217 [PMID: 27634444 DOI: 10.2174/1389203717666160909125004]

17 **Wasung ME**, Chawla LS, Madero M. Biomarkers of renal function, which and when? *Clin Chim Acta* 2015; **438**: 350-357 [PMID: 25195004 DOI: 10.1016/j.cca.2014.08.039]

18 **Soni SS**, Cruz D, Bobek I, Chionh CY, Nalesso F, Lentini P, de Cal M, Corradi V, Virzi G, Ronco C. NGAL: a biomarker of acute kidney injury and other systemic conditions. *Int Urol Nephrol* 2010; **42**: 141-150 [PMID: 19582588 DOI: 10.1007/s11255-009-9608-z]

19 **Chen XR**, Wang DX. Serum MCP-1 and NGAL Play an Important Role in the Acute Inflammatory Event of Chronic Obstructive Pulmonary Disease. *COPD* 2021; **18**: 425-431 [PMID: 34325599 DOI: 10.1080/15412555.2021.1954151]

20 **Wang XR**, Li YP, Gao S, Xia W, Gao K, Kong QH, Qi H, Wu L, Zhang J, Qu JM, Bai CX. Increased serum levels of lipocalin-1 and -2 in patients with stable chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2014; **9**: 543-549 [PMID: 24920892 DOI: 10.2147/COPD.S62700]

21 **Llorens F**, Hermann P, Villar-Piqué A, Diaz-Lucena D, Nägga K, Hansson O, Santana I, Schmitz M, Schmidt C, Varges D, Goebel S, Dumurgier J, Zetterberg H, Blennow K, Paquet C, Baldeiras I, Ferrer I, Zerr I. Cerebrospinal fluid lipocalin 2 as a novel biomarker for the differential diagnosis of vascular dementia. *Nat Commun* 2020; **11**: 619 [PMID: 32001681 DOI: 10.1038/s41467-020-14373-2]

22 **Naudé PJW**, Ramakers IHGB, van der Flier WM, Jiskoot LC, Reesink FE, Claassen JAHR, Koek HL, Eisel ULM, De Deyn PP. Serum and cerebrospinal fluid Neutrophil gelatinase-associated lipocalin (NGAL) levels as biomarkers for the conversion from mild cognitive impairment to Alzheimer's disease dementia. *Neurobiol Aging* 2021; **107**: 1-10 [PMID: 34365256 DOI: 10.1016/j.neurobiolaging.2021.07.001]

23 **Bolignano D**, Coppolino G, Lacquaniti A, Buemi M. From kidney to cardiovascular diseases: NGAL as a biomarker beyond the confines of nephrology. *Eur J Clin Invest* 2010; **40**: 273-276 [PMID: 20415702 DOI: 10.1111/j.1365-2362.2010.02258.x]

24 **Taub PR**, Gabbai-Saldate P, Maisel A. Biomarkers of heart failure. *Congest Heart Fail* 2010; **16 Suppl 1**: S19-S24 [PMID: 20653707 DOI: 10.1111/j.1751-7133.2010.00168.x]

25 **Cho CH**, Cha J, Chang EA, Nam MH, Park SJ, Sung HJ, Lee SR. Analysis of bone marrow supernatant neutrophil gelatinase-associated lipocalin and hematological parameters in hematological malignancy. *J Clin Lab Anal* 2020; **34**: e23253 [PMID: 32091174 DOI: 10.1002/jcla.23253]

26 **Aoyama T**, Kuwahara-Arai K, Uchiyama A, Kon K, Okubo H, Yamashina S, Ikejima K, Kokubu S, Miyazaki A, Watanabe S. Spleen-derived lipocalin-2 in the portal vein regulates Kupffer cells activation and attenuates the development of liver fibrosis in mice. *Lab Invest* 2017; **97**: 890-902 [PMID: 28504685 DOI: 10.1038/labinvest.2017.44]

27 **Chan YR**, Liu JS, Pociask DA, Zheng M, Mietzner TA, Berger T, Mak TW, Clifton MC, Strong RK, Ray P, Kolls JK. Lipocalin 2 is required for pulmonary host defense against Klebsiella infection. *J Immunol* 2009; **182**: 4947-4956 [PMID: 19342674 DOI: 10.4049/jimmunol.0803282]

28 **Alpízar-Alpízar W**, Laerum OD, Illemann M, Ramírez JA, Arias A, Malespín-Bendaña W, Ramírez V, Lund LR, Borregaard N, Nielsen BS. Neutrophil gelatinase-associated lipocalin (NGAL/Lcn2) is upregulated in gastric mucosa infected with Helicobacter pylori. *Virchows Arch* 2009; **455**: 225-233 [PMID: 19727808 DOI: 10.1007/s00428-009-0825-8]

29 **Zollner A**, Schmiderer A, Reider SJ, Oberhuber G, Pfister A, Texler B, Watschinger C, Koch R, Effenberger M, Raine T, Tilg H, Moschen AR. Faecal Biomarkers in Inflammatory Bowel Diseases: Calprotectin Versus Lipocalin-2-a Comparative Study. *J Crohns Colitis* 2021; **15**: 43-54 [PMID: 32556317 DOI: 10.1093/ecco-jcc/jjaa124]

30 **Gleeson FC**, Levy MJ, Jackson RA, Murphy SJ, Halling KC, Kipp BR, Graham RP, Zhang L. Lipocalin-2 Expression in Pancreas Adenocarcinoma Tumor Microenvironment Via Endoscopic Ultrasound Fine Needle Biopsy Is Feasible and May Reveal a Therapeutic Target. *Pancreas* 2020; **49**: e98-e99 [PMID: 33122534 DOI: 10.1097/MPA.0000000000001669]

31 **Tung MC**, Hsieh SC, Yang SF, Cheng CW, Tsai RT, Wang SC, Huang MH, Hsieh YH. Knockdown of lipocalin-2 suppresses the growth and invasion of prostate cancer cells. *Prostate* 2013; **73**: 1281-1290 [PMID: 23775308 DOI: 10.1002/pros.22670]

32 **Jaberi SA**, Cohen A, D'Souza C, Abdulrazzaq YM, Ojha S, Bastaki S, Adeghate EA. Lipocalin-2: Structure, function, distribution and role in metabolic disorders. *Biomed Pharmacother* 2021; **142**: 112002 [PMID: 34463264 DOI: 10.1016/j.biopha.2021.112002]

33 **Xu MJ**, Feng D, Wu H, Wang H, Chan Y, Kolls J, Borregaard N, Porse B, Berger T, Mak TW, Cowland JB, Kong X, Gao B. Liver is the major source of elevated serum lipocalin-2 levels after bacterial infection or partial hepatectomy: a critical role for IL-6/STAT3. *Hepatology* 2015; **61**: 692-702 [PMID: 25234944 DOI: 10.1002/hep.27447]

34 **Huang H**, Akira S, Santos MM. Is the iron donor lipocalin 2 implicated in the pathophysiology of hereditary hemochromatosis? *Hepatology* 2009; **49:** 1012-1016 [PMID: 19152427 DOI: 10.1002/hep.22699]

35 **Nairz M**, Theurl I, Schroll A, Theurl M, Fritsche G, Lindner E, Seifert M, Crouch ML, Hantke K, Akira S, Fang FC, Weiss G. Absence of functional Hfe protects mice from invasive Salmonella enterica serovar Typhimurium infection via induction of lipocalin-2. *Blood* 2009; **114:** 3642-3651 [PMID: 19700664 DOI: 10.1182/blood-2009-05-223354]

36 **Gao YH**, Wang JY, Liu PY, Sun J, Wang XM, Wu RH, He XT, Tu ZK, Wang CG, Xu HQ, Niu JQ. Iron metabolism disorders in patients with hepatitis B-related liver diseases. *World J Clin Cases* 2018; **6**: 600-610 [PMID: 30430115 DOI: 10.12998/wjcc.v6.i13.600]

37**Chen F**, He JL, Zheng M, Zhu HH, Li SP, Wang K, Zhang XX, Zhao YR, Wu SS, Chen Z. Complementary laboratory indices for predicting the disease status of patients with hepatitis B virus infection. *J Viral Hepat* 2013; **20**: 566-574 [PMID: 23808995 DOI: 10.1111/jvh.12067]

38 **Lu J**, Lin L, Ye C, Tao Q, Cui M, Zheng S, Zhu D, Liu L, Xue Y. Serum NGAL Is Superior to Cystatin C in Predicting the Prognosis of Acute-on-Chronic Liver Failure. *Ann Hepatol* 2019; **18**: 155-164 [PMID: 31113585 DOI: 10.5604/01.3001.0012.7907]

39 **Gungor G**, Ataseven H, Demir A, Solak Y, Gaipov A, Biyik M, Ozturk B, Polat I, Kiyici A, Cakir OO, Polat H. Neutrophil gelatinase-associated lipocalin in prediction of mortality in patients with hepatorenal syndrome: a prospective observational study. *Liver Int* 2014; **34**: 49-57 [PMID: 23799980 DOI: 10.1111/liv.12232]

40 **Borkham-Kamphorst E**, van de Leur E, Zimmermann HW, Karlmark KR, Tihaa L, Haas U, Tacke F, Berger T, Mak TW, Weiskirchen R. Protective effects of lipocalin-2 (LCN2) in acute liver injury suggest a novel function in liver homeostasis. *Biochim Biophys Acta* 2013; **1832**: 660-673 [PMID: 23376114 DOI: 10.1016/j.bbadis.2013.01.014]

41 **Strazzulla A**, Coppolino G, Di Fatta C, Giancotti F, D'Onofrio G, Postorino MC, Mazzitelli M, Mammone SV, Gentile I, Rivoli L, Palella E, Gravina T, Costa C, Pisani V, De Maria V, Barreca GS, Marascio N, Focà A, Fuiano G, Gulletta E, Torti C. Is neutrophil gelatinase associated lipocalin useful in hepatitis C virus infection? *World J Hepatol* 2016; **8**: 815-824 [PMID: 27429717 DOI: 10.4254/wjh.v8.i19.815]

42 **Strazzulla A**, Coppolino G, Barreca GS, Gentile I, Rivoli L, Postorino MC, Mazzitelli M, Greco G, Costa C, Pisani V, Marascio N, Simeoni M, Focà A, Fuiano G, Foti D, Gulletta E, Torti C. Evolution of glomerular filtration rates and neutrophil gelatinase-associated lipocalin during treatment with direct acting antivirals. *Clin Mol Hepatol* 2018; **24**: 151-162 [PMID: 29684978 DOI: 10.3350/cmh.2017.0059]

43 **Nada A**, Abbasy M, Sabry A, Abdu Allah AM, Shehab-Eldeen S, Elnaidany N, Elimam H, Mohamed Ibraheem KI, Essa A. Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) in HCV-Positive Egyptian Patients Treated with Sofosbuvir. *Can J Gastroenterol Hepatol* 2020; **2020**: 1632959 [PMID: 32083035 DOI: 10.1155/2020/1632959]

44 **Hamdy HS**, El-Ray A, Salaheldin M, Lasheen M, Aboul-Ezz M, Abdel-Moaty AS, Abdel-Rahim A. Urinary Neutrophil Gelatinase-Associated Lipocalin in Cirrhotic Patients with Acute Kidney Injury. *Ann Hepatol* 2018; **17**: 624-630 [PMID: 29893703 DOI: 10.5604/01.3001.0012.0931]

45 **Ginès P**, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. *Nat Rev Dis Primers* 2018; **4**: 23 [PMID: 30213943 DOI: 10.1038/s41572-018-0022-7]

46 **Wilson BR**, Bogdan AR, Miyazawa M, Hashimoto K, Tsuji Y. Siderophores in Iron Metabolism: From Mechanism to Therapy Potential. *Trends Mol Med* 2016; **22**: 1077-1090 [PMID: 27825668 DOI: 10.1016/j.molmed.2016.10.005]

47 **Srinivasan G**, Aitken JD, Zhang B, Carvalho FA, Chassaing B, Shashidharamurthy R, Borregaard N, Jones DP, Gewirtz AT, Vijay-Kumar M. Lipocalin 2 deficiency dysregulates iron homeostasis and exacerbates endotoxin-induced sepsis. *J Immunol* 2012; **189**: 1911-1919 [PMID: 22786765 DOI: 10.4049/jimmunol.1200892]

48 **Wang Q**, Li S, Tang X, Liang L, Wang F, Du H. Lipocalin 2 Protects Against Escherichia coli Infection by Modulating Neutrophil and Macrophage Function. *Front Immunol* 2019; **10**: 2594 [PMID: 31781104 DOI: 10.3389/fimmu.2019.02594]

49 **Klüber P**, Meurer SK, Lambertz J, Schwarz R, Zechel-Gran S, Braunschweig T, Hurka S, Domann E, Weiskirchen R. Depletion of Lipocalin 2 (LCN2) in Mice Leads to Dysbiosis and Persistent Colonization with Segmented Filamentous Bacteria. *Int J Mol Sci* 2021; **22** [PMID: 34884961 DOI: 10.3390/ijms222313156]

50 **Zhao P**, Stephens JM. STAT1, NF-κB and ERKs play a role in the induction of lipocalin-2 expression in adipocytes. *Mol Metab* 2013; **2**: 161-170 [PMID: 24049731 DOI: 10.1016/j.molmet.2013.04.003]

51 **Zheng M**, Horne W, McAleer JP, Pociask D, Eddens T, Good M, Gao B, Kolls JK. Therapeutic Role of Interleukin 22 in Experimental Intra-abdominal Klebsiella pneumoniae Infection in Mice. *Infect Immun* 2016; **84**: 782-789 [PMID: 26729763 DOI: 10.1128/IAI.01268-15]

52 **Li H**, Feng D, Cai Y, Liu Y, Xu M, Xiang X, Zhou Z, Xia Q, Kaplan MJ, Kong X, Gao B. Hepatocytes and neutrophils cooperatively suppress bacterial infection by differentially regulating lipocalin-2 and neutrophil extracellular traps. *Hepatology* 2018; **68**: 1604-1620 [PMID: 29633303 DOI: 10.1002/hep.29919]

53 **Ericsson AC**, Hagan CE, Davis DJ, Franklin CL. Segmented filamentous bacteria: commensal microbes with potential effects on research. *Comp Med* 2014; **64**: 90-98 [PMID: 24674582]

54 **Hathaway-Schrader JD**, Poulides NA, Carson MD, Kirkpatrick JE, Warner AJ, Swanson BA, Taylor EV, Chew ME, Reddy SV, Liu B, Westwater C, Novince CM. Specific Commensal Bacterium Critically Regulates Gut Microbiota Osteoimmunomodulatory Actions During Normal Postpubertal Skeletal Growth and Maturation. *JBMR Plus* 2020; **4**: e10338 [PMID: 32161843 DOI: 10.1002/jbm4.10338]

55 **Behairy Bel-S**, Salama EI, Allam AA, Ali MA, Elaziz AM. Lipocalin-2 as a marker of bacterial infections in chronic liver disease: a study in Egyptian children. *Egypt J Immunol* 2011; **18**: 31-36 [PMID: 23082468]

56 **Liu H**, Zhu P, Nie C, Ye Q, Gao Y, Liu H, Pang G, Han T. The value of ascitic neutrophil gelatinase-associated lipocalin in decompensated liver cirrhosis with spontaneous bacterial peritonitis. *J Clin Lab Anal* 2020; **34**: e23247 [PMID: 32100329 DOI: 10.1002/jcla.23247]

57 **Cullaro G**, Kim G, Pereira MR, Brown RS Jr, Verna EC. Ascites Neutrophil Gelatinase-Associated Lipocalin Identifies Spontaneous Bacterial Peritonitis and Predicts Mortality in Hospitalized Patients with Cirrhosis. *Dig Dis Sci* 2017; **62**: 3487-3494 [PMID: 29098551 DOI: 10.1007/s10620-017-4804-7]

58 **Vazquez DE**, Niño DF, De Maio A, Cauvi DM. Sustained expression of lipocalin-2 during polymicrobial sepsis. *Innate Immun* 2015; **21**: 477-489 [PMID: 25227123 DOI: 10.1177/1753425914548491]

59 **Sheldon JR**, Himmel LE, Kunkle DE, Monteith AJ, Maloney KN, Skaar EP. Lipocalin-2 is an essential component of the innate immune response to Acinetobacter baumannii infection. *PLoS Pathog* 2022; **18**: e1010809 [PMID: 36054235 DOI: 10.1371/journal.ppat.1010809]

60 **Lim D**, Park SJ, Kim HY, Shin M, Song M. Lipocalin2 as a potential antibacterial drug against Acinetobacter baumannii infection. *J Microbiol* 2022; **60**: 444-449 [PMID: 35344190 DOI: 10.1007/s12275-022-2007-1]

61 **Wilson ME**, Vorhies RW, Andersen KA, Britigan BE. Acquisition of iron from transferrin and lactoferrin by the protozoan Leishmania chagasi. *Infect Immun* 1994; **62**: 3262-3269 [PMID: 8039896 DOI: 10.1128/iai.62.8.3262-3269.1994]

62 **Weiss G**. Iron and immunity: a double-edged sword. *Eur J Clin Invest* 2002; **32 Suppl 1**: 70-78 [PMID: 11886435 DOI: 10.1046/j.1365-2362.2002.0320s1070.x]

63 **Dighal A**, Mukhopadhyay D, Sengupta R, Moulik S, Mukherjee S, Roy S, Chaudhuri SJ, Das NK, Chatterjee M. Iron trafficking in patients with Indian Post kala-azar dermal leishmaniasis. *PLoS Negl Trop Dis* 2020; **14**: e0007991 [PMID: 32023254 DOI: 10.1371/journal.pntd.0007991]

64 **Wang C**, Ma C, Gong L, Guo Y, Fu K, Zhang Y, Zhou H, Li Y. Macrophage Polarization and Its Role in Liver Disease. *Front Immunol* 2021; **12**: 803037 [PMID: 34970275 DOI: 10.3389/fimmu.2021.803037]

65 **Shen H**, Wang Z, Huang A, Zhu D, Sun P, Duan Y. Lipocalin 2 Is a Regulator During Macrophage Polarization Induced by Soluble Worm Antigens. *Front Cell Infect Microbiol* 2021; **11**: 747135 [PMID: 34616693 DOI: 10.3389/fcimb.2021.747135]

66 **El-Arabey AA**, Abdalla M. GATA3 as an immunomodulator in obesity-related metabolic dysfunction associated with fatty liver disease, insulin resistance, and type 2 diabetes. *Chem Biol Interact* 2022; **366**: 110141 [PMID: 36058260 DOI: 10.1016/j.cbi.2022.110141]

67 **El-Arabey AA**, Denizli M, Kanlikilicer P, Bayraktar R, Ivan C, Rashed M, Kabil N, Ozpolat B, Calin GA, Salama SA, Abd-Allah AR, Sood AK, Lopez-Berestein G. GATA3 as a master regulator for interactions of tumor-associated macrophages with high-grade serous ovarian carcinoma. *Cell Signal* 2020; **68**: 109539 [PMID: 31935430 DOI: 10.1016/j.cellsig.2020.109539]

68 **Roudkenar MH**, Kuwahara Y, Baba T, Roushandeh AM, Ebishima S, Abe S, Ohkubo Y, Fukumoto M. Oxidative stress induced lipocalin 2 gene expression: addressing its expression under the harmful conditions. *J Radiat Res* 2007; **48**: 39-44 [PMID: 17229997 DOI: 10.1269/jrr.06057]

69 **Al-Shaebi EA**, Dkhil MA, Al-Quraishy S. Indigofera oblongifolia regulates the hepatic gene expression profile induced by blood stage malaria. *Microb Pathog* 2018; **119**: 170-182 [PMID: 29630927 DOI: 10.1016/j.micpath.2018.04.009]

**Footnotes**

**Conflict-of-interest statement:** All authors declare that they have no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** August 28, 2023

**First decision:** November 20, 2023

**Article in press:**

**Specialty type:** Infectious diseases

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** El-Arabey AA, Egypt; Perazzo JC, Argentina **S-Editor:** Liu JH **L-Editor:** A **P-Editor:**

**Figure Legends**



**Figure 1 Schematic outline of lipocalin 2 antibacterial effects.** During bacterial infections, most lipocalin 2 (LCN2) is secreted by liver cells, while some are derived from immune cells such as macrophages and neutrophils. LCN2 exerts an antibacterial effect mainly in two ways. One, it chelates LCN2-sensitive siderophores to form the LCN2-siderophores-Fe complex, which prevents the bacteria from absorbing iron and inhibits bacterial growth. Two, it stimulates the antibacterial immune response through stimulating immunocytes, which secrete various inflammatory cytokines and chemokines, promoting the migration and phagocytosis of macrophages. The cytokines and chemokines from immunocytes then further stimulate immunocytes and hepatocytes to produce more LCN2, forming a positive feedback loop to enhance the antibacterial immune response. LCN2 derived from hepatocytes and macrophages enters the systemic circulation to fight bacteria, and LCN2 is a component of NETs from neutrophils, which plays an important role in local inflammation. LCN2: Lipocalin 2; LPS: Lipopolysaccharide; IL: Interleukin; CXCL: Chemokines; IFN: Interferon; TNF: Tumor necrosis factor.

**Table 1 Expression of lipocalin 2 in different viral hepatitis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Sample** | **Cases** | **LCN2 level** | **Ref.** |
| Blood  | 675 mild chronic hepatitis B, 178 moderate chronic hepatitis B, 199 severe chronic hepatitis B and 317 fulminant hepatitis B, 246 healthy volunteers | Chronic hepatitis, fulminant hepatitis significantly higher than control | [37] |
| Blood | 54 patients with HBV-ACLF and 49 patients with CHB | HBV-ACLF higher than CHB | [38] |
| Blood and urine | 64 patients with cirrhosis and 23 control subjects | Cirrhosis with hepatorenal syndrome patients is significantly higher than controls, no difference between stable cirrhosis and control | [39] |
| Blood | 192 patients with chronic liver diseases of variable etiology and clinical severity in comparison to 91 healthy controls. | Chronic liver diseases were higher than healthy controlsNo significant differences between cirrhotic and non-cirrhotic patients. | [40] |
| Blood  | 48 patients with chronic HCV | Not correlated with HCV viral load  | [41] |
| Blood | 87 Egyptian patients with chronic hepatitis C infection | Significantly decrease after HCV treatment with DAA  | [42] |
| Blood | 102 chronic hepatitis C virus infection | Significantly increase after HCV treatment with DAA  | [43] |

LCN2: Lipocalin 2; HBV-ACLF: Hepatitis B virus –related acute-on-chronic liver failure; CHB: Chronic hepatitis B; HCV: Hepatitis C virus; DAA: Direct-acting antivirals.