

# Recognizing Dysfunctional Innate and Adaptive Immune Responses Contributing to Liver Damage in Patients With Cirrhosis



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**The human host immune system wards off attacks by enemies such as viruses by mounting an inflammatory response which may sometimes injure self-tissues. Dysfunctional immune/inflammatory response by the host may affect the functioning of vital organs. The largest number of innate immune cells in the body resides in the liver. On encountering a new insult or injury to the liver, the innate immune system responds quickly to counter it. Acute liver insults may trigger acute liver failure or acute on chronic liver failure; these disorders are associated with a predominant innate immune response. Activation of the reticuloendothelial system (part of the innate immune response) predicts short-term and medium-term survival in patients with acute on chronic liver failure. Liver diseases associated with an aberrant adaptive immune response like autoimmune hepatitis respond well to treatment with steroids and other immunosuppressants, while those associated with innate immune dysfunction like acute on chronic liver failure do not respond well to steroids; recent reports suggest that the latter disorders may respond to therapeutic plasma exchange. How does the immune system in a patient with liver disease respond to SARS CoV2 infection? While commonly used tests in routine clinical practice provide clues to activation of different arms of immune response in patients with cirrhosis, specialized tests may help characterize this further. This review discusses the tests which reflect aberrant immune responses and treatment of patients with cirrhosis. (J CLIN EXP HEPATOL 2022;12:993–1002)**

The host immune system is a vital department of our body and the moment a person dies, this department is disbanded, leaving the physical human body accessible to microbial invasion, destruction, and decay. In times of peace, the presence of defence forces is not obvious in a society; similarly, in the absence of enemy (microbial) invasion, the importance of immune system is often not appreciated in the human body. As with any efficient defence force, immune responses to tackle the con-

stant microbial attack are silent and not discerned by the host.

Similar to a nation's army, navy, and air force, the human body has innate and adaptive immune responses. Skin, gastrointestinal tract, and lungs—where the human body interfaces with the external environment—need constant surveillance to sense enemy attacks. How do these sensors recognize the enemy from their own nation?

In predisposed individuals, the immune response starts to train its ammunition onto host antigens (termed autoimmune disease), resembling a “civil war”. It is important to recognize the tell-tale signs of this civil war and its causative factors and implement interventions to quell this uprising. If a new enemy—never before encountered—attacks, how will the host immune system respond?

In this review, we describe how to recognize dysfunctional innate and adaptive immune responses by clinical features and appropriate investigations in patients with cirrhosis and therapeutic interventions to address these.

## Innate Versus Adaptive Immune Responses

The innate immune response lacks antigen specificity and generally lacks memory, while adaptive immunity is antigen-specific, diverse and has memory.<sup>1</sup>

The innate immune system (“rapid action force”) is present from birth and responds immediately (within minutes) of sensing the enemy (microbe). In contrast, the

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**Abbreviations:** ACLF: acute on chronic liver failure; AIH: autoimmune hepatitis; ANCA: anti-neutrophil cytoplasmic antibodies; APASL: Asia Pacific Association for Study of Liver; CRP: C-reactive protein; COVID-19: coronavirus disease of 2019; DAMPs: damage-associated molecular patterns; EASL: European Association for Study of Liver; HLA: human leukocyte antigen; IgG: immunoglobulin G; IgG4 RD: IgG4 related disease; MELD: Model for End-Stage Liver Disease; NK cells: natural killer cells; PAMPs: pathogen-associated molecular patterns; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; SARS CoV2: severe acute respiratory syndrome coronavirus 2; sMR: soluble mannose receptor; TLR: toll-like receptor; VWF: von Willebrand factor

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adaptive immune system is slow to respond (after days to weeks of exposure) to microbes and comprises responses learned from prior exposure to a microbial antigen; they are not present from birth. Some of the rapid action forces (like neutrophils) move immediately to the site of enemy attack. In contrast, heavyweight guns (“artillery”) like macrophages are difficult to shift rapidly to the scene of attack and are best placed in strategic locations which are constantly vulnerable to enemy attack. Both innate and adaptive immune systems have cells (“soldiers”) and humoral factors (like cytokines and immunoglobulins) to fight the microbial enemy. Effector cells of innate immune response include neutrophils, eosinophils, basophils, macrophages, monocytes, mast cells, natural killer (NK) cells, and NK T cells, while adaptive immune cells are T lymphocytes and B lymphocytes.<sup>2</sup> NK cells—traditionally defined as innate immune cells—help coordinate innate and adaptive immune responses.<sup>3</sup>

Innate immune cells recognize lipopolysaccharide and peptidoglycan components of microbes termed as pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors. To exemplify, toll-like receptor 4 (TLR4) on the surface of macrophages recognizes lipid A/lipopolysaccharide constituents of the cell wall of Gram-negative bacteria. Cytosolic pattern recognition receptors such as NOD-like receptors in innate immune cells recognize PAMPs and endogenous danger-associated molecular patterns (DAMPs) derived from damaged and dying cells. On sensing DAMPs or PAMPs, effector arms of innate immune responses are activated—including cells that phagocytose microbes (ex: neutrophils and macrophages) and cells that release pro-inflammatory chemokines and cytokines (e.g. neutrophils, macrophages, dendritic cells, and NK cells).

Specific receptors on T and B lymphocytes recognize peptide fragments presented along with human leukocyte antigen (HLA) by antigen-presenting cells. Interaction of a T cell receptor with peptide–HLA complex leads to T cell differentiation into T helper cells (which can activate B cells to trigger a humoral immune response) and cytotoxic T cells (which provide cellular immunity).

### Reticuloendothelial System Versus Mononuclear Phagocyte System

In the mid-1960s, the reticuloendothelial system was renamed as the mononuclear phagocyte system.<sup>4</sup> These two terms refer to overlapping, but distinct parts of the immune system. The mononuclear phagocyte system refers to cells like macrophages, monocytes, and dendritic cells while excluding endothelial cells.<sup>5,6</sup>

As they appear net-like on electron microscopy, macrophages are referred to as “reticular” cells. The term reticuloendothelial system emphasizes the anatomical proximity and interlinked functioning of tissue-resident macro-

phages and endothelial cells. Kupffer cells (macrophages) reside next to endothelial cells in liver sinusoids. Both cells share important functions—they participate in innate immune responses and remove waste products from blood traversing the liver sinusoidal filter. Kupffer cells remove insoluble waste by phagocytosis while liver sinusoidal endothelial cells remove soluble macromolecular and colloidal (<100 nm) waste by endocytosis.<sup>7</sup>

### Terminology of Autoimmune Diseases and Immune-mediated Diseases is a Bit Confusing

When do we refer to some liver diseases as “auto” immune? The “auto” in autoimmune diseases may imply two explanations. When the host immune system targets the host itself, we use the term autoimmune diseases. At present, the term ‘autoimmune diseases’ is restricted to those diseases wherein dysfunctional adaptive immune responses (like self-reactive CD4+ and CD8+ T cells) target self-antigen. Continued immune-mediated damage to the host liver initiated by a known trigger such as alcohol and drugs, even after the triggering factor is no longer present in the body, is termed as immune-mediated liver disease and not an autoimmune disease, even though the insulted organ is still one’s own liver.

#### *Immune-mediated Liver Diseases*

When immune response to chronic hepatitis B infection damages the liver or kidneys, we use the term “immune-mediated damage” to the self (this is not termed autoimmune hepatitis or glomerulonephritis, the preferred term is immune-mediated hepatitis or glomerulonephritis due to hepatitis B infection).<sup>8</sup>

Liver diseases caused by viruses and idiosyncratic drug reactions are examples of diseases considered immune-mediated liver diseases.<sup>9,10</sup>

#### *Auto-inflammatory Diseases*

The host response to injury is inflammation. Recently, the term “auto-inflammatory” disease has been coined.<sup>11,12</sup> These inflammatory disorders are characterized by an innate immune response, while the adaptive immune system is not activated (autoantibodies and autoreactive T cells are absent). Hereditary periodic fever syndromes were initial disorders identified to have these peculiar features; however, this term now includes diseases like neonatal-onset multi-system inflammatory disease, linked to mutant cryopyrin. Dysregulated sense-stressing pathways may also be linked to auto-inflammatory diseases.

Auto-inflammatory and autoimmune classification are not watertight compartments as there is a component of both innate and adaptive system activation in most diseases with one compartment predominating over the other.<sup>13</sup> The closely intertwined innate and adaptive immune systems mean that patients with liver diseases due

to dysfunctional adaptive immune responses (e.g. autoimmune hepatitis [AIH]) will also have innate immune responses activated. Similarly, patients with severe alcoholic hepatitis—a disorder of predominant innate immune attack on the liver—also have adaptive immune responses activated.

**IS THE LIVER AN IMMUNE ORGAN (TABLE 1)?**

Adaptive immune cells (T and B lymphocytes) differentiate and mature in primary lymphoid organs (bone marrow and thymus) and secondary lymphoid organs (spleen, lymph nodes, and mucosa-associated lymphoid tissue). The liver mounts a strong innate immune response and a weak adaptive immune response. It is also important in inducing immunological tolerance. Hence, the liver can be considered as a (predominantly innate) immune organ.<sup>7,14</sup>

The dual blood supply to the liver from portal and systemic circulation and fenestrated sinusoids facilitate the rapid exchange of immunogenic metabolites and toxins from the blood into hepatocytes. Hepatocytes and different immune resident cells in the liver co-ordinate phagocytosis of pathogens by pattern recognition receptors and scavenger receptors. Lipopolysaccharides, lipoteichoic acids, and glycopeptides are examples of PAMPs recognized by pattern recognition receptors like TLRs (located on the surface or in the endoplasmic reticulum), NOD-like receptors, and retinoic acid-inducible gene I receptor (located in the cytoplasm).

The liver is enriched with innate immune cells (Table 1). Liver dendritic cells and macrophages mediate effective antigen presentation to stimulate adaptive immune responses.<sup>15</sup> Lymphocytes in the liver are selectively enriched with NK cells and NK T cells.<sup>16</sup>

Liver sinusoids, subendothelial compartments, and space of Disse are home to a variety of tissue-resident

innate immune cells like Kupffer cells, myeloid-derived suppressor cells, and innate lymphocytes including NK cells, NK T cells, and  $\gamma\delta$  T cells.<sup>17</sup>

In a healthy liver, these cells regulate Th1 and Th17 cells by releasing anti-inflammatory cytokines predominantly IL10. Kupffer cells account for about 90% of the fixed macrophages in the body. These innate immune cells clear hepatotropic pathogens and metabolites (DAMPs) while leading to immune tolerance by anti-inflammatory cytokines (IL10, TGF $\beta$ , and IL13). Hepatic endothelial cells also have an innate immune function as suggested by the expression of surface TLRs and secretion of chemokines.<sup>18</sup> The distinctive anti-inflammatory phenotype of liver resident innate cells is due to the differentiation of myeloid and lymphoid progenitors/immature hepatic stellate cells in the liver. Neutrophils, a major innate immune cell, are mostly absent in a healthy liver; in contrast, neutrophilic infiltration surrounding hepatocytes is a typical histological feature in severe alcoholic hepatitis. The signalling by pattern recognition receptors and release of chemokines are responsible for the migration of neutrophils to the inflamed liver. Hepatocytes contribute to the innate immune response by producing most innate immune proteins like complements<sup>7</sup> and also secrete soluble pathogen recognition molecules such as C-reactive protein (CRP).<sup>19</sup> CRP refers to a protein that reacts to the C-polysaccharide of the pneumococcal cell wall.

The liver harbors many antigen-presenting cells which are professional (like dendritic cells and Kupffer cells) and non-professional (like liver sinusoidal endothelial cells and hepatic stellate cells). When antigens are presented by these cells to T cells, the latter can undergo apoptosis, anergy, or differentiate into regulatory T cells. The remarkable tolerance of the liver to many gut-derived antigens is mediated by hepatic dendritic cells and regulatory T cells. The balance between inflammatory and anti-inflammatory cytokine milieu maintains immune tolerance of the liver while retaining the ability to clear gut-derived pathogens and toxic metabolites. It is important for the hepatic immune system to override immune tolerance to respond to pathogens and tumours.

Among the different solid organs transplanted, the liver is the most tolerogenic organ. How liver transplant tolerance occurs is not well understood; the local microenvironment and hepatic immune cells are likely to be important.<sup>20</sup> The use of immunosuppressive drugs to prevent rejection of the transplanted liver is beyond the scope of this review.

Different innate lymphocyte populations like NK cells, CD56 (+) T cells, NK T cells,  $\gamma\delta$  T cells, and mucosa-associated invariant T cells accumulate in the liver. Innate lymphocytes recognize conserved metabolites derived from microorganisms and host cells and kill target cells and/

**Table 1 Immune Cells With Relevance to the Liver.**

	Innate immune cells	Adaptive immune cells
Cells from blood flowing through the liver	Neutrophils Eosinophils Basophils NK cells NK T cells Monocytes <sup>a,b</sup>	T-lymphocytes B-lymphocytes Plasma cells
Cells residing in the liver	Macrophages <sup>a,b</sup> Hepatic dendritic cells <sup>a</sup> Sinusoidal endothelial cells <sup>b</sup> Hepatocytes	

<sup>a</sup>Part of the mononuclear phagocyte system.

<sup>b</sup>Part of the reticuloendothelial system.

or activate other immune cells. Innate lymphocytes can promote the maturation of antigen-presenting cells, leading to immunogenic T cell responses. These cells may override hepatic immune tolerance to autoantigens, leading to the induction of autoreactive T cells targeting the liver, causing autoimmune liver disease.

During inflammation, triggers like alcohol, virus, toxins, and cholesterol lead to metabolic reprogramming of innate and adaptive immune cells altering their phenotype to inflammatory cells. However, the imbalance between the activities of immune regulatory cells and effector T cells may lead to an autoimmune disease.<sup>15</sup>

Apart from innate immune cells, adaptive lymphocytes like MHC restricted CD4+, CD8+ T cells, both activated and memory phenotype, and B cells also enrich the liver. In a healthy liver, these cells undergo apoptosis/deletion (thus the liver is a “graveyard of T cells”) or acquire antigen-specific tolerance due to antigen presentation by tolerogenic hepatic dendritic cells and non-professional APCs in the liver (hepatocytes and endothelial cells).<sup>21,22</sup>

In patients with cirrhosis and more so, in ACLF patients, bacterial overgrowth and inflammation in the intestines and bacterial translocation lead to many PAMPs along with reduced detoxification of bacterial lipopolysaccharides. These are recognized by TLRs and NOD-like receptors on Kupffer cells and result in further activation of innate immune cells like neutrophils and production of pro-inflammatory cytokines (TNF $\alpha$ , IL8, and interferons) and CXCL chemokines. DAMPs like high mobility group box 1 (HMGB1) protein, ATP complexes, uric acid, cholesterol, triglycerides, succinates, and products of liver cell necrosis are increased in decompensated cirrhosis. The DAMPs along with IL1 $\alpha$  and IL33 activate pattern recognition receptors like advanced glycation end product-specific receptors, TLRs 2 and 4, siglec-10, and syndecan-3, resulting in sterile inflammation by activating the innate immune system.<sup>23</sup>

With such a large contingent of innate immune cells located in the liver, it is likely that a dysfunctional innate immune response may cause liver damage. Overwhelming of the scavenging capacity of the reticuloendothelial system located in liver sinusoids as a consequence of acute liver insult in patients with cirrhosis may result in acute on chronic liver failure (ACLF).<sup>23</sup>

## INNATE VERSUS ADAPTIVE IMMUNE SYSTEM IN LIVER DISEASES

How do we recognize the liver diseases associated with innate immune dysfunction and those with adaptive immune dysfunction? Once these syndromes are recognized by appropriate tests, then treatment can be planned, aimed at these dysfunctional immune mechanisms.

## LIVER DISORDERS WITH PREDOMINANT ACTIVATION OF THE ADAPTIVE IMMUNE SYSTEM (AUTOIMMUNE LIVER DISEASES)

### Autoimmune Hepatitis (AIH)

Raised serum immunoglobulin G levels and infiltrates of lymphocytes and plasma cells in liver biopsy—part of criteria to diagnose AIH—point to a dysfunctional adaptive immune response causing AIH.

The postulated self-antigens targeted in AIH are asialoglycoprotein receptors located on the hepatocyte surface in type 1 AIH and CYP 450 2D6 and other antigens in hepatocyte microsomes in type 2 AIH.<sup>24,25</sup> HLA-DR3 and HLA-DR4 increase the risk of type 1 AIH in Caucasians. HLA haplotype DRB1\*0301-DRB3\*0101-DQA1\*0501-DQB1\*0201 is associated with type 1 AIH.<sup>26</sup> Type 1 AIH was associated with HLA DRB1\*04 in northern India and with HLA B27, HLA Cw6, and HLADR\*01,\*14,\*15, and \*07 in western India.<sup>27,28</sup> Dysfunction of innate immune cells like NK T cells, monocytes, Kupffer cells, and dendritic cells also occurs in AIH.<sup>29</sup>

Molecular mimicry (virus or drug mimicking hepatocyte antigens) may confuse host immune sensing mechanisms in AIH. Viruses like hepatitis viruses, Epstein Barr virus, and measles virus and drugs like minocycline, atorvastatin, methyl dopa, nitrofurantoin and pemoline may trigger AIH. The precise definition of these liver diseases is important.<sup>30</sup> It is interesting to note that CYP 450 2D6, the postulated target antigen for type 2 AIH, is a drug-metabolizing enzyme.

### Primary Sclerosing Cholangitis (PSC)

PSC may occur secondary to portal bacteremia, biliary infection, and toxic bile acids. Anti-neutrophil cytoplasmic antibodies (ANCA) exemplify the activation of the humoral arm of the adaptive immune system in PSC.<sup>31</sup> pANCA, anti-PR3 ANCA, and IgA antibodies against glycoprotein-2 indicate poor prognosis in PSC patients.<sup>32</sup> In addition to HLA, other genes close to the HLA region (TNF $\alpha$  and MHC-1 chain-related gene family) are also considered as susceptibility genes for PSC.<sup>32</sup>

### Primary Biliary Cholangitis (PBC)

The loss of tolerance to a ubiquitous mitochondrial antigen which is a residue of pyruvate dehydrogenase complex is postulated to drive PBC. This loss of tolerance may be mediated by molecular mimicry and generation of neoantigen due to modification of self-antigen.<sup>33</sup>

### Overlap Syndromes

The dysfunctional adaptive immune response may attack more than one of the above target antigens in the liver; the resulting clinical phenotype wherein AIH, PSC, and PBC can overlap with each other is termed “overlap syndrome.”

### IgG4 related disease (IgG4 RD)

These are fibro-inflammatory multisystem disorders with an exuberant expansion of IgG4 class-switched cells and plasma cells. Classically described as an autoimmune disorder with varied T-helper cell responses, innate immune activation may also contribute to fibrosis, thus proposing an overlap with an autoinflammatory component.<sup>34-36</sup> Liver involvement in IgG4 RD may be due to AIH, secondary to IgG4 related sclerosing cholangitis or type 1 autoimmune pancreatitis associated hepatopathy.<sup>37,38</sup>

## LIVER DISEASE WITH PREDOMINANT ACTIVATION OF THE INNATE IMMUNE SYSTEM

### Acute on chronic liver failure (ACLF)

Organ failures and high short-term mortality in ACLF patients may be due to an exaggerated systemic inflammatory response. Innate immune responses including reticuloendothelial system activation may drive the clinical syndrome of ACLF.<sup>35</sup> Raised levels of plasma von Willebrand factor (VWF), a marker of endothelial activation, correlate with severity of liver disease and predict outcome in patients with ACLF as defined by the Asia Pacific Association for Study of Liver (APASL).<sup>39</sup> Raised plasma VWF levels and serum soluble CD163 and soluble mannose receptor (sMR) levels correlate with disease severity and predict death in patients with ACLF, as defined by the European Association for Study of Liver (EASL).<sup>40-42</sup> Thus, ACLF diagnosed by criteria proposed by APASL or EASL gives clue to the presence of an overactive innate immune response.

How does innate immune activation worsen liver damage in patients with cirrhosis who develop ACLF? The exact mechanism is not well understood at present. Overwhelmed scavenging capacity of reticuloendothelial cells may lead to inflammatory debris clogging the liver sinusoids, reduce perfusion in liver microcirculation, and aggravate liver failure in these patients.<sup>43</sup>

### Macrophage activation syndrome

Hemophagocytic lymphohistiocytosis is a hyper-inflammatory syndrome due to aberrant activation of macrophages, NK cells, and T cells.<sup>44,45</sup> When this occurs secondary to lymphoproliferative disorder, infections, auto-inflammatory diseases, or autoimmune diseases, it is termed as macrophage activation syndrome.<sup>46,47</sup> The clinical phenotype is usually multi-organ inflammation, predominantly hepatitis, cytopenia, and unremitting fever. The hemophagocytic syndrome can be seen in patients with viral hepatitis, AIH, and drug-induced liver injury<sup>48,49</sup> and maybe associated with adverse outcomes in patients with cirrhosis.<sup>50</sup>

Some of the current criteria to diagnose macrophage activation syndrome exclude patients with certain liver diseases. For example, criteria to diagnose macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis have infectious hepatitis as an exclusion criterion.<sup>51</sup> If pre-existing liver disease is an exclusion criterion to diagnose macrophage activation syndrome,<sup>52</sup> then these criteria cannot be applied to study innate immune activation in ACLF patients, who have pre-existing cirrhosis.

## INDICES OF IMMUNE ACTIVATION IN CIRRHOSIS AND ACLF—DIAGNOSTIC UTILITY (TABLE 2)

The predominant type of immune cells infiltrating the liver seen on liver biopsy, analyzing the peripheral white blood cells on routine tests and by more specialized tests, and study of circulating soluble markers of immune activation can help recognize if any of the arms of the immune system are activated in patients with liver diseases.

### Inflammatory Infiltrate in the Liver

Inflammatory infiltrate, if seen on liver biopsy, reflects the predominant immune system (innate versus adaptive) which is activated and may be contributing to liver disease.

**Table 2 Tests to Recognize Overactive Innate and Adaptive Immune Systems Associated With Liver Diseases.**

Diagnostic marker	Innate immune activation	Adaptive immune activation	Example of clinical condition
Cellular infiltrates on liver biopsy		Lymphocytes Plasma cells	Autoimmune hepatitis
	Neutrophils		Alcoholic hepatitis
Peripheral blood cells	Neutrophil/lymphocyte ratio		ACLF
	Monocyte subsets	B cells	
	NK cells	CD8 T cells	
	Neutrophil subsets	CD4 T cells	
Circulating biomarkers		Immunoglobulin G	Autoimmune hepatitis
	Ferritin		Alcoholic hepatitis
	von Willebrand factor		ACLF
	sCD163		
	soluble mannose receptor		

The immune cells recruited from the bloodstream into the liver parenchyma often start infiltrating at the portal tracts. Neutrophilic infiltrate in liver biopsy is a typical feature of severe alcoholic hepatitis (i.e. over-active innate immune response). Eosinophilic infiltrates on liver biopsy in patients with idiosyncratic drug allergy again suggests an overactive innate immune response in the liver. The presence of lymphocytes and plasma cells infiltrating the portal tracts on liver biopsy in AIH points to an adaptive immune response attacking the liver.

**Immune Cells in Peripheral Blood**

In hospitalized patients with cirrhosis and with ACLF, the ratio of neutrophils (innate immune cells) to lymphocytes (adaptive immune cells)—a marker of immune dysregulation—independently predicted 90-day mortality.<sup>53,54</sup>

Specialized tests can identify which subsets of T or B lymphocytes, neutrophils, or macrophages are turned on or off. For example, pro-inflammatory and anti-inflammatory macrophage phenotypes can be recognized by flow cytometric studies in ACLF patients. Patients with ACLF have leukocytosis, neutrophilia, and lymphopenia. Whole blood RNA expression studies showed neutrophilia, higher proportions of macrophages, M0-like monocytes, and lower proportions of memory lymphocytes, CD8 T cells, and NK cells as the hallmark of ACLF.<sup>55</sup>

**Circulating Soluble Biomarkers**

‘Raised levels of markers of macrophage activation like serum ferritin (typically >500 mcg/L), soluble CD163 (a hemoglobin–haptoglobin scavenger receptor), and sMR indicate activated innate immune system in cirrhosis and ACLF patients.<sup>42</sup> An elevated serum CD25 level indicates T cell activation, which can happen as a downstream stream event in macrophage activation. Raised plasma VWF levels signify endothelial activation in cirrhosis and ACLF patients.<sup>39</sup> Specifically, these markers document reticuloendothelial activation in these liver diseases.

Raised levels of serum IgG in AIH indicate adaptive immune response.

**INDICES OF INNATE IMMUNE (RETICULOENDOTHELIAL) ACTIVATION IN CIRRHOSIS AND ACLF—PROGNOSTIC UTILITY (TABLE 3)**

The blood levels of inflammatory markers are raised in patients with cirrhosis and are even higher in patients with ACLF. Are these inflammatory markers sequelae of liver injury or do they influence the progression of liver disease? Severe alcoholic hepatitis often precipitates ACLF.<sup>56</sup> Markers of reticuloendothelial activation correlate with liver disease severity and predict death,

**Table 3 Innate Immune (ReticuloEndothelial) Activation Markers Predict Survival Independent of MELD Score in ACLF and Severe Alcoholic Hepatitis.**

Study	Liver disease	No. of patients	Markers measured	Outcome assessed	Significance
Vijayalekshmi, et al. <sup>54</sup>	Severe alcoholic hepatitis	50	Plasma VWF antigen	3-month mortality	adjusted HR: 1.002 (95% CI: 1–1.004)
Tiwari, et al. <sup>55</sup>	Severe alcoholic hepatitis	34	Plasma VWF collagen binding activity	In-hospital mortality (hospital stay: 6 days, median)	AUC: 0.72 (95% CI: 0.54–0.89)
Prasanna, et al. <sup>36</sup>	ACLF (as defined by APASL criteria)	50	Plasma VWF collagen binding activity	In-hospital composite poor outcome <sup>a</sup> (hospital stay: 6 days, median)	AUC: 0.68 (95% CI: 0.52–0.84)
Grønbaek, et al. <sup>39</sup>	ACLF (as per EASL criteria)	185	Serum sCD163 Serum sMR	3-month mortality	AUC: 0.66 (0.59–0.73) AUC: (0.66 (0.59–0.72)

ACLF: acute on chronic liver failure, APASL: Asia Pacific Association for Study of Liver, VWF: von Willebrand factor, AUC: Area under the receiver operating curve, EASL: European Association for Study of Liver, sCD163: soluble CD163, sMR: soluble Mannose Receptor.

<sup>a</sup>Composite poor outcome: death/liver transplant/discharge in a moribund state.

independent of Model for End-Stage Liver Disease (MELD) scores, in patients with severe alcoholic hepatitis.<sup>57,58</sup> The prognostic ability of these indices suggest that these inflammatory markers may contribute to the worsening of severity of liver disease in these patients.

In a systematic review of 6 studies including 765 patients (cirrhosis: 715 patients; ACLF: 50 patients), elevated plasma levels of VWF antigen at baseline independently predicted mortality over 25.6 months (23.6–33 months) in patients with cirrhosis (area under the curve: 0.74; 95% confidence interval: 0.7–0.79) with an optimal cutoff of 318% (216–390%), median (range).<sup>59</sup> Plasma VWF levels also predicted short-term (over 7 days) mortality in ACLF patients. Combining VWF levels to the MELD score increases the prognostic value in patients with end-stage liver disease.<sup>40</sup>

In patients with cirrhosis and ACLF, serum levels of CD163 and sMR increased incrementally with worsening disease severity. Both sCD163 and sMR independently predicted mortality at 1–3 months and at 6 months and had equal or better predictive accuracy than the MELD score. Combining these macrophage activation markers to the MELD score also improved the prognostic ability.<sup>42,50</sup>

## DIFFERENTIATING INNATE VERSUS ADAPTIVE IMMUNE DYSFUNCTION IN LIVER DISEASES: THERAPEUTIC IMPLICATIONS

Chronic hepatitis due to AIH is caused by a dysfunctional adaptive immune response and responds well to treatment with prednisolone. In contrast, patients with ACLF due to AIH do not respond so well to steroid treatment.<sup>60,61</sup> Similarly, patients with alcohol-related ACLF tolerate steroids poorly and it is not certain if steroid treatment is beneficial or deleterious in them.<sup>62</sup> Recent evidence suggests that plasma exchange may benefit patients with liver disorders with predominant innate immune dysfunction (like acute liver failure, ACLF).<sup>63</sup>

### Plasma Exchange to Treat Liver Disorders Associated with Innate Immune Dysfunction (Acute Liver Failure, Acute on Chronic Liver Failure)

Depending on the volume of plasma exchanged at each session to treat these liver failure syndromes, plasma exchange can be classified as high volume, standard volume, and low volume.<sup>64–67</sup> Plasma exchange improves transplant-free survival in patients with acute liver failure<sup>64–66</sup> and ACLF.<sup>66–71</sup> The beneficial effect of plasma exchange in these liver disorders with a predominant innate immune response may be by attenuating innate immune activation and removing inflammatory debris including macromolecules like VWF.<sup>43</sup>

## HOW DOES THE HOST IMMUNE SYSTEM RESPOND TO A VIRUS OR A DRUG NOT ENCOUNTERED BEFORE?

The rapidity of the response needed and the lack of prior memory of such an enemy encountered in the past suggest that the innate arm of the immune system will respond to the first exposure to a new enemy (like a new virus) not encountered before.

Acute liver injury/failure is predominantly caused by paracetamol overdose in the West; in contrast, this is mostly caused by hepatitis E in northern India and rodenticide ingestion in southern India.<sup>71–74</sup> Raised plasma VWF levels correlate with disease severity and predict in-hospital survival in patients with rodenticide induced hepatotoxicity, suggesting that innate immune activation may contribute to the pathogenesis of rodenticidal hepatotoxicity.<sup>75</sup>

## COVID-19 and Liver Disease

How does the host immune system respond to severe acute respiratory syndrome coronavirus 2 (SARS CoV2) infection in a patient with cirrhosis?<sup>76</sup> Coronavirus disease of 2019 (COVID-19) is characterized by pulmonary endotheliopathy as the virus invades lung endothelium.<sup>77,78</sup> In a study of reticuloendothelial activation in 143 hospitalized COVID-19 patients, none of whom had liver disease, levels of markers of activation of macrophages (serum CD163 and serum ferritin) and endothelium (plasma VWF) increased with increasing COVID-19 severity. Only baseline VWF levels independently correlated with disease severity and predicted in-hospital mortality.<sup>79</sup> Plasma exchange and low dose steroids may help severe/critical COVID-19 patients, by reducing levels of VWF and other inflammatory debris in circulation.<sup>80</sup>

SARS CoV2 does not appear to be hepatotropic, though the viral entry receptor (angiotensin-converting enzyme-2) has been described in cholangiocytes. Acute hepatitis in COVID-19 patients may also be due to drugs or as part of systemic inflammatory response.

Cirrhosis increases the risk of death in patients with COVID-19.<sup>81</sup>

Can exposure to SARS CoV2 or COVID-19 vaccine trigger autoimmune hepatitis<sup>82,83</sup>? It is unclear from preliminary reports if this association has any causative link.

A study of 110 AIH patients with COVID-19 found new-onset liver injury in 37% of patients. The severity of COVID-19 disease and mortality were similar in AIH patients and in those with chronic liver disease due to other causes. Continued immunosuppressive treatment for AIH did not increase the risk for severe COVID-19 but reduced new-onset liver injury during COVID-19.<sup>84</sup>

Liver disorders due to a dysfunctional adaptive immune response like AIH respond well to steroid treatment. In contrast, those associated with dysfunctional innate

immune responses, like ACLF, respond poorly to steroids. The overwhelmed scavenging function of reticuloendothelial cells in liver sinusoids may contribute to the progression of liver failure in ACLF patients and plasma exchange may help by removing some of the inflammatory debris which clogs the liver microcirculation in these patients. Appropriate tests help us to identify which arm of the immune system is predominantly activated in patients with cirrhosis and select patient for appropriate treatment to ameliorate immune dysfunction.

## CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

RG and CEE: contributed to conceptualizing, writing, review, and editing of this manuscript.

## CONFLICTS OF INTEREST

The authors have none to declare.

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