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# Genetic variants of innate immune receptors and infections after liver transplantation

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**Core tip:** After liver transplantation, immunosuppressive therapy is needed to avoid allograft rejection that is mainly mediated through adaptive immunological responses. In the setting, the existence of genetic variants of innate immunity receptors may increase the risk of post-transplant infections in comparison with patients carrying wild-type alleles. This manuscript reviews the published studies analyzing the influence of innate immunity gene variants on the development of post-transplant infections and other complications.

## Abstract

Infection is the leading cause of complication after liver transplantation, causing morbidity and mortality in the first months after surgery. Allograft rejection is mediated through adaptive immunological responses, and thus immunosuppressive therapy is necessary after transplantation. In this setting, the presence of genetic variants of innate immunity receptors may increase the risk of post-transplant infection, in comparison with patients carrying wild-type alleles. Numerous studies have investigated the role of genetic variants of innate immune receptors and the risk of complication after liver transplantation, but their results are discordant. Toll-like receptors and mannose-binding lectin are arguably the most important studied molecules; however, many other receptors could increase the risk of infection after transplantation. In this article, we review the published studies analyzing the impact of genetic variants in the innate immune system on the development of infectious complications after liver transplantation.

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## INTRODUCTION

Liver transplantation is the treatment of choice for end-stage liver disease. New developments in surgical techniques, medical care, and immunosuppressant therapies have improved both graft and patient survival<sup>[1,2]</sup>. However, infections are still among the main complications after liver transplantation; it has been estimated that up to 80% of liver recipients will develop at least one episode of infection during the first year after transplantation<sup>[3,4]</sup>. Although several identifiable clinical risk factors are clearly associated with higher risk of post-transplant infection<sup>[5]</sup>, variations in the receptors of the innate immune system could play an important role in its incidence and severity.

Bacteria are the leading cause of early infection after liver transplantation. Both the sources and etiology of infection change over time, according to the degree of immunosuppression and the presence of clinical risk factors. In the first month after transplantation, bacterial infections typically arise from the abdominal cavity, surgical wound, intravenous catheters, and the respiratory tract. Between the first and the sixth month after transplantation, the risk of opportunistic infections is increased because of the higher degree of immunosuppression. After the sixth month, infections are usually community acquired and predominantly respiratory and urinary, although cholangitis can occur if there are strictures in the biliary tree<sup>[3,6-8]</sup>.

Viral infections after liver transplantation are frequent. Herpes simplex virus reactivation can occur early post-transplantation, typically with orolabial or genital ulcers appearing 2-3 wk after transplantation<sup>[9]</sup>. Herpes zoster virus reactivation occurs in around 10% of solid organ transplant recipients, but is mostly limited to dermal manifestations. The first year after transplantation poses the greatest risk of Epstein-Barr virus (EBV), which may be associated with lymphoproliferative disease<sup>[10]</sup>. Cytomegalovirus (CMV) can cause direct disease, manifested as fever, bone marrow suppression, and organ invasion. In addition, due to its ability to induce immunomodulation, CMV can cause indirect effects; these include favoring the development of opportunistic infections and hepatitis C virus (HCV) recurrence, EBV-associated lymphoproliferative disease, acute rejection, chronic allograft dysfunction, vascular and hepatic artery thrombosis, and ultimately, allograft failure and death<sup>[11-15]</sup>. Although several risk factors for CMV infection have been described, the most important is donor-recipient serology mismatch (donor positive/recipient negative) at the time of transplantation. Also, certain immunosuppressive therapies (lymphocyte-depleting drugs such as anti-thymocyte globulin) and acute allograft rejection are associated with a higher risk of CMV infection<sup>[11,16]</sup>. Other viral infections after transplantation, such as human herpesvirus 6 and 7, are less frequent and usually asymptomatic. However, they can also produce pneumonitis, encephalitis, hepatitis, and bone marrow suppression. Human herpesvirus 8 is also associated with Kaposi sarcoma<sup>[17]</sup>.

Fungal infections represent one of the most life-threatening complications after liver transplantation. Although its incidence has declined (5%-30% depending on the series), they continue to be associated with high mortality. *Candida* species are the most frequent invasive fungi, followed by *Aspergillus* species<sup>[18]</sup>. Most invasive fungal infections (IFIs) occur early after transplantation, mainly during the first 3 mo. Multiple risk factors exist for IFI, such as pre-transplant comorbidity, surgical complications, and morbid post-transplant course<sup>[18-21]</sup>. Pre-transplant comorbidity includes a high Model for End-Stage Liver Disease score, acute hepatic insufficiency, pretransplant renal insufficiency, prolonged preoperative hospitalization, previous use of broad-spectrum antibiotics, fungal colo-

nization, and re-transplantation<sup>[18-21]</sup>. Surgical complications include long surgical time, high intraoperative use of blood products, and choledochojejunostomy anastomosis, while a morbid post-transplant course involves dialysis requirement, acute rejection, CMV infection, early graft failure, and reoperation after transplantation<sup>[18-21]</sup>.

The correct integrity and functionality of the host's immune system is a key pathogenic factor for the occurrence and severity of post-transplant infection. The innate immune system is the first line of defence against invasion by pathogens. It comprises cellular components [neutrophils, macrophages, dendritic cells, and natural killer (NK) cells] and molecular mediators (cell receptors, complement system, cytokines, and chemokines). Innate immune responses occur rapidly, with limited specificity and an inability to generate immunological memory. Innate immune receptors, also named pattern-recognition receptors (PRRs), are expressed by effector immune cells as either soluble or membrane-bound proteins. They recognize conserved structures, named pathogen-associated molecular patterns (PAMPs), which are broadly distributed among different types of microbes but absent from host cells, and are essential for microbial survival and pathogenicity. The binding of microorganisms by PRRs triggers intracellular signal pathways that culminate in the synthesis of cytokines and chemokines. This then causes inflammation, and induces the maturation and migration of antigen-presenting cells to secondary lymphoid tissues, where they activate adaptive responses. In contrast to the innate immune system, the adaptive immune system is slower to activate, but achieves highly specific immune responses based on immunological memory. Adaptive immunity is mainly mediated by T and B lymphocytes, which express antigen-specific receptors generated by genetic recombination during lymphocyte development. The repertoire of lymphocyte receptors is broad enough to recognize virtually any antigen. After the first exposure to an antigen, it takes up to 3-5 d to produce sufficient numbers of antigen-specific T and B cell clones, while the innate immune system generates a protective inflammatory response within minutes of pathogen exposure<sup>[22-26]</sup>.

Acute cellular and humoral allograft rejection is mediated by T and B cells respectively<sup>[27-29]</sup>. Patients undergoing solid organ transplantation must receive immunosuppressive therapy, which predominantly alters the adaptive immune response by blocking lymphocyte activation signaling pathways, depleting lymphocytes, or diverting lymphocyte traffic<sup>[25,30,31]</sup>. In these circumstances, the innate immune response predominates in the defence against infection.

Gene polymorphisms, typically single nucleotide polymorphisms (SNPs), are common, occurring in > 1% of the general population. SNPs may alter the amino acid sequence, affect promoter characteristics, or may be completely "silent". Several SNPs have been described in relation to the genes encoding immune recognition<sup>[32]</sup>. Indeed, previous studies have found higher infection

rates in populations with SNPs in genes encoding innate immunity components<sup>[32-36]</sup>. Table 1 summarizes the most relevant studies about innate immunity gene variants and risk of post-transplant liver infections.

## INNATE IMMUNITY AND POST-TRANSPLANT LIVER INFECTION

### Toll-like receptors

**Biology:** Toll-like receptors (TLRs) are a family of transmembrane proteins composed of a leucine-rich extracellular domain (the ligand binding site), a transmembrane domain, and a cytoplasmic domain [referred to as the TLR and interleukin (IL)-1 receptor (TIR) domain]. Binding of a PAMP to a TLR triggers a signaling cascade that ultimately induces the production of proinflammatory cytokines and type I interferons (IFNs). To date, 11 TLRs are described in mammals. Each TLR recognizes different pathogenic structures, and are expressed on the cell surface (*e.g.*, TLR1, TLR2, TLR4-6 and TLR10) or in endosomal compartments (*e.g.*, TLR3 and TLR7-9). When PAMPs are detected, TLR dimerization and recruitment of intracellular adaptor proteins and kinases occur. Most TLRs use myeloid differentiation primary response protein (MyD88) as the signal adapter, while TLR3 uses TIR-domain-containing adapter-inducing IFN- $\beta$  (TRIF)<sup>[23,24,37]</sup>.

TLR1 is associated with TLR2, and both recognize the microbial lipopeptides present in a wide variety of bacteria, fungi, parasites and viruses. To date, 17 polymorphisms have been described in the coding region, of which ten are non-synonymous, that is, they produce an amino acid change<sup>[38]</sup>. Some of these variants cause an inability of TLR1 to bind its agonist without diminishing its expression<sup>[39]</sup>, while others result in reduced protein expression in the cell wall without reducing intracellular levels, suggesting an alteration of receptor trafficking<sup>[40]</sup>. In other cases, the polymorphism is associated with an excessive response that is partially mediated by increased cell surface expression of TLR1<sup>[41]</sup>.

TLR2 recognizes microbial membrane constituents such as lipoteichoic acid, peptidoglycan, and lipoproteins of Gram-positive bacteria, lipoarabinomannan of *Mycobacteria*, and zymosan of *Candida*, among others. TLR2 needs to form heterodimers with TLR1 or TLR6 to be able to initiate cell activation. TLR2 sequencing has revealed multiple SNPs, although only a few are functionally relevant. The most frequently studied are Arg753Gln, Pro631His and Arg677Trp. The prevalence of these polymorphisms varies by ethnicity<sup>[42]</sup>. The Arg753Gln polymorphism limits antigen recognition through deficient tyrosine phosphorylation rather than reducing protein expression, which impairs MyD88 recruitment, compromising TLR2-TLR6 assembly, and resulting in hyporesponsiveness to the antigen<sup>[43-48]</sup>. Defective membrane internalization and functional gain of the receptor has been observed with the Pro631His polymorphism, leading to increased immune activation<sup>[49]</sup>.

TLR3 is an intracellular receptor located in the endoplasmic reticulum that typically recognizes double-stranded RNA of viral origin. After recognition of its ligand, TLR3 interacts with UNC-93B, a protein required for TLR3 trafficking from endoplasmic reticulum to the endosomal compartment<sup>[50]</sup>. At least 136 SNPs exist in the *TLR3*, of which only four exist in the protein-coding region and result in amino acid changes (N284I, Y307D, L412F and S737T). L412F is the most prevalent variant and reduces the receptor activity to near 30%, while Y307D and S737T have similar activity levels to the wild-type alleles, and N284I reduces the activity to background levels. These variants do not lead to a reduction in the intracellular protein expression or in vesicles, but do appear to alter the receptor trafficking to the cell surface<sup>[51,52]</sup>.

TLR4 binds Gram-negative bacteria lipopolysaccharide (LPS), fungal mannans, and certain viral glycoproteins. First, LPS is bound by circulating LPS-binding protein (LBP), which functions as an opsonin for CD14, which in turn acts as a catalyst for the binding of LPS to MD-2, a co-receptor that is physically associated with TLR4. Finally, LPS binding to the TLR4/MD-2 complex activates intracellular signals that lead to the production of proinflammatory cytokines. Although various non-synonymous polymorphisms exist, only Asp299Gly and Thr399Ile are present at a frequency higher than 5%. They are located in the extracellular domain and, in Europe, frequently co-segregate<sup>[53]</sup>. Reduced responsiveness to LPS is higher in patients carrying the Asp299Gly polymorphism than in those with Thr399Ile. Some authors have demonstrated that hyporesponsiveness of *TLR4* variants is associated with a structural change in the ligand-binding receptor and a deficient recruitment of MyD88 and TRIF signalling adapters, but not with either decreased TLR4 expression or the interaction with MD-2 co-receptor<sup>[54,55]</sup>.

TLR5 recognizes the flagellin of flagellated bacteria; of the 18 SNPs described, 13 are non-synonymous, and three reduce the functional response to bacterial flagellin. These variants are Asp694Gly, Leu822Phe and Arg392stop, but only the latter is present in > 10% of individuals. Arg392stop causes the loss of the transmembrane domain and the signaling of the entire cytoplasmic tail. TLR5 polymorphisms are associated with *Legionella pneumophila* infection and Crohn's disease<sup>[56,57]</sup>.

TLR6 has a high sequence similarity to TLR1, and acts as a co-receptor with TLR2 that recognizes diacylated lipopeptides. However, information on *TLR6* polymorphisms is limited. Although 53 SNPs have been described, only 11 encode for changes in amino acid sequences, and only one has an allelic frequency > 5% (Ser249Pro)<sup>[58]</sup>. The Ser249Pro polymorphism is associated with reduced IL-6 production in response to lipopeptide and mycobacterial stimulation. Although the mechanism by which this variant impairs IL-6 production is unknown, it seems that it is not associated with a reduction in protein expression levels<sup>[59]</sup>.

TLR7 and TLR8, which share a high degree of struc-

tural similarity, are located in the endosomal compartment membranes, and recognize single-stranded RNA. TLR7 is mostly expressed in plasmacytoid dendritic cells, while TLR8 expresses predominantly in monocytes, macrophages, and myeloid dendritic cells. They facilitate the production of type I IFN and other cytokines. Little is known about *TLR7* and *TLR8* polymorphisms. The Leu11Gln variant of *TLR7* is the most prevalent, and impairs the signaling sequence. It has been associated with HIV, a higher susceptibility to HCV infection, and a lower response to IFN treatment<sup>[60-62]</sup>. The Met1Val polymorphism of *TLR8* leads to the formation of a truncated form of TLR8 that alters transcriptional activity. This variant has been associated with HIV and tuberculosis, and recent studies have shown an association of *TLR8* polymorphisms with HCV infection<sup>[63]</sup>.

TLR9 is located in the endoplasmic reticulum where it detects bacterial and viral nucleic acids containing CpG motifs. At least 50 SNPs have been described, but most occur infrequently. Some of these variants are associated with noninfectious diseases such as lymphoma, asthma, and Crohn's disease<sup>[64,65]</sup>, as well as infections such as HIV, malaria, bacterial meningitis, and tuberculosis<sup>[66-70]</sup>.

TLR 10 and 11 have not been studied in depth. TLR10 is a member of the TLR1/2/6/10 cluster, and is hypothesized to have a similar function to TLR1 and TLR6, although the literature is scarce<sup>[49]</sup>. TLR11, which binds and recognizes uropathogenic bacteria, is probably nonfunctional in humans owing to a premature stop codon<sup>[53]</sup>.

**TLR polymorphisms and bacterial infection after liver transplantation:** In a recent study that analyzed the genetic variants of a broad number of innate immune receptors in liver transplant recipients, including all TLR members, the authors found no association between genetic variants and clinically significant bacterial infections during the first 3 mo after transplantation<sup>[71]</sup>.

The authors of a study of 706 liver recipients with *TLR4* polymorphisms failed to find an association between the Asp299Gly and Thr399Ile variants and either the incidence or outcome of Gram-negative infection; additionally, they noted that none of patients with *TLR4* variants developed septic shock<sup>[72]</sup>. Furthermore, *TLR4* variants were not associated with bacterial infections after either kidney or simultaneous kidney and pancreas transplantation<sup>[73]</sup>. These results contrast with previous published studies in immunosuppressed and immunocompetent patients. Lorenz *et al.*<sup>[74]</sup> reported that patients admitted to intensive care units (ICUs) with septic shock, who carried the Asp299Gly *TLR4* polymorphism, were more likely to have Gram-negative infections and more severe disease. Agnese *et al.*<sup>[75]</sup> also observed that, in patients admitted to a surgical ICU, those with *TLR4* polymorphisms had a higher incidence of Gram-negative infections. In the transplantation setting, Ducloux *et al.*<sup>[76]</sup> reported a higher incidence of bacterial infection in kidney transplant recipients carrying the *TLR4* variant. Thus,

there are discordant results on the influence of *TLR4* variants on Gram-negative bacterial infections. This is a research topic that warrants future investigation with larger cohort of patients.

Infections caused by Gram-positive bacteria are also important after liver transplantation<sup>[4]</sup>. Structural components of Gram-positive microorganisms are predominantly recognized by TLR2. Polymorphism of *TLR2* was first described following the observation of an increased risk of Gram-positive septic shock in patients admitted to the ICU with the genetic variant<sup>[77]</sup>. A study performed in 755 liver transplant recipients demonstrated that the Arg-753Gln *TLR2* polymorphism was not associated with an increased incidence of Gram-positive bacterial infections, although patients carrying the variant gene did present more frequently with septic shock and higher recurrence rates<sup>[78]</sup>. Despite this, the 90-d mortality was similar between patients carrying the variant and wild-type alleles.

Other studies have also reported that TLR polymorphisms are associated not with a higher incidence of infectious disease but with a more severe presentation. Specifically, individuals with sepsis and septic shock carrying *TLR1* variants have greater acute lung injury, organ dysfunction, and mortality, as well as a higher susceptibility to Gram-positive infection<sup>[41,79]</sup>.

Solid organ transplant recipients are at higher risk of developing tuberculosis after transplantation, mostly by the reactivation of latent infection<sup>[80]</sup>. TLRs, specifically TLR2 (associated with TLR1 and TLR6), TLR4, and TLR9 play critical roles in recognizing mycobacteria<sup>[81]</sup>. Some studies have described an association between some of these polymorphisms and tuberculosis, although none are reported in liver transplant recipients. It is important to note that some TLR variants can be protective against mycobacterial infection<sup>[82]</sup>.

**TLR polymorphisms and viral infection after liver transplantation:** The TLR2/TLR1 complex recognizes CMV envelope glycoproteins B and H, and associations between CMV infection and specific TLR SNPs have been described<sup>[46,83,84]</sup>. Kijpittayarit *et al.*<sup>[85]</sup> studied the Arg-753Gln *TLR2* polymorphism in 92 HCV-infected liver transplant recipients, and observed that recipients carrying the variant allele had higher CMV DNA levels in their peripheral blood when compared with recipients carrying the wild-type allele. Regardless of the higher CMV replication in patients carrying the *TLR2* variant allele, only homozygous patients presented CMV disease more frequently. In a later study of 737 liver recipients published by the same group, an analysis of the association between *TLR2* polymorphisms and CMV infection revealed that homozygous Arg753Gln was significantly associated with an increased risk of CMV disease, particularly tissue-invasive forms<sup>[86]</sup>.

Other viral infections have also been related to deficiencies of innate immunity, but no studies were performed in liver transplant recipients. The herpes viruses are known to be recognized by TLR2, TLR9 and TLR3.



**Table 1** Main published findings in the association of innate immune gene variants with the development of infections after liver transplantation

Innate immune receptor polymorphism		Results	Ref.
Bacterial infections	Donor MBL	Incidence of CSI was 3.8-fold higher in the recipients of MBL variant livers Mutation in the donor MBL2 was associated with CSI (HR = 2.8, $P = 0.02$ ) Mutation in donor MBL2 was associated to CSI (HR = 2.58, 95%CI: 1.62-4.10) Higher incidence of septic shock in recipients of a MBL2 variant liver (HR = 9.64, 95%CI: 2.59-36)	Bowman <i>et al</i> <sup>[123]</sup> Worthley <i>et al</i> <sup>[124]</sup> de Rooij <i>et al</i> <sup>[126]</sup> Cervera <i>et al</i> <sup>[127]</sup>
	Donor ficolin	Mutation of donor ficolin was associated to CSI (HR = 2.33, 95%CI: 1.36-4)	de Rooij <i>et al</i> <sup>[126]</sup>
	NOD2	NOD2 polymorphism was associated to CSI (HR = 2.0, $P = 0.04$ )	Janse <i>et al</i> <sup>[145]</sup>
	Donor MASP	Wild-type allele of MASP2 in the donor was associated to CSI (HR = 2.65, 95%CI: 1.22-5.73)	de Rooij <i>et al</i> <sup>[126]</sup>
Viral infections	TLR2	Patients with TLR2 polymorphism presented higher rates of Gram positive infection recurrence (27.8% <i>vs</i> 11.8%, $P = 0.07$ ) and gram positive septic shock (11.1% <i>vs</i> 1.2%, $P = 0.047$ )	Lee <i>et al</i> <sup>[78]</sup>
	TLR2	CMV load was higher in patients with TLR2 polymorphism ( $P = 0.03$ ) CMV disease was higher in patients homozygous for the TLR2 polymorphism (HR = 1.91, 95%CI: 0.91-3.4)	Kijpittayarit <i>et al</i> <sup>[85]</sup>
	TLR2	TLR2 polymorphism homozygosity was associated to tissue-invasive CMV disease (HR = 3.40, 95%CI: 1.51-7.64)	Kang <i>et al</i> <sup>[86]</sup>
	MBL	MBL wild-type genotype was associated to a higher incidence of CMV invasive disease in SOT (OR = 6.0, 95%CI: 1.1-32.5)	Cervera <i>et al</i> <sup>[129]</sup>
Fungal infections	Ficolin	MBL deficient donor is associated to CMV infection (54% <i>vs</i> 32%, $P = 0.02$ ) 44% CMV infection in patients receiving a FNC2 wild-type liver <i>vs</i> 27% in patients receiving a variant FCN2 liver ( $P < 0.02$ )	de Rooij <i>et al</i> <sup>[130]</sup> de Rooij <i>et al</i> <sup>[130]</sup>
	TLR2	Homozygous TLR2 mutation is associated with allograft failure and mortality in HCV-infected recipients (RR = 5.2, 95%CI: 1.65-13.9)	No studies in liver transplantation Eid <i>et al</i> <sup>[155]</sup>
	TLR3	Higher rate of allograft failure and mortality in patients with TLR3 polymorphism (44.3% <i>vs</i> 30.8%, $P = 0.09$ )	Lee <i>et al</i> <sup>[156]</sup>
	NK cells	HCV patients with rapid fibrosis progression had impaired TLR7/8-induced interferon response compared with patients with slow fibrosis progression ( $P = 0.039$ ) and impaired TLR3 and TLR9 cytokine production ( $P = 0.008$ )	Howell <i>et al</i> <sup>[157]</sup>
HCV recurrence	IL28B	Lack to antiviral response to HCV therapy associated to the absence of the activating NK receptor haplotype KIR2DS2 ( $P = 0.008$ ). KIR2L3 haplotype has been correlated to recurrent allograft hepatitis ( $P = 0.04$ )	Nellore <i>et al</i> <sup>[151]</sup>
	IL28B	No difference in the frequencies of IL28B polymorphisms in patients with and without fibrosing cholestatic hepatitis	Duarte-Rojo <i>et al</i> <sup>[168]</sup>
	IL28B	Recipients with CC genotype or CT genotype had delayed time to HCV recurrence compared to TT (10.4 <i>vs</i> 6.7 mo, $P = 0.002$ ). Recipients with TT genotype had worse graft survival (42% <i>vs</i> 62%, $P = 0.02$ )	Allam <i>et al</i> <sup>[162]</sup>
	IL28B	Higher response to antiviral therapy for CC genotype compared to CT or TT (59% <i>vs</i> 25%, $P = 0.002$ ). Higher sustained virological response in patients with favorable donor and recipient genotypes ( $P < 0.01$ )	Coto-Llerena <i>et al</i> <sup>[161]</sup>
No association	TLR	Higher progression to cirrhosis (HR = 5.96, 95%CI: 1.29-27.6), liver-related death or re-transplantation among recipients with a CC genotype donor.	Duarte-Rojo <i>et al</i> <sup>[167]</sup>
	TLR	IL28B genotype in the recipient is associated to severe HCV recurrence (OR = 4.27, $P = 0.014$ ). Allele IL28B T in the donor tend to have lower incidence of severe HCV recurrence (OR = 0.46, $P = 0.19$ )	Cisneros <i>et al</i> <sup>[166]</sup>
	TLR	Sustained viral response to HCV therapy was 100% if both donor and recipient were CC genotype, while it was only 25% if neither donor nor recipient had CC genotype ( $P = 0.025$ )	Firpi <i>et al</i> <sup>[163]</sup>
	TLR	IL28B non-CC in the recipient had a higher risk of severe recurrent HCV (OR = 1.57, $P < 0.05$ ). IL28B CC in the donor was associated to higher risk of severe recurrent HCV (OR = 7.02, $P < 0.001$ )	Biggins <i>et al</i> <sup>[164]</sup>
No association	TLR	None of a broad range of genetic variants in recipient and donor innate immunity receptors was associated to bacterial or fungal infections after liver transplantation.	de Mare-Bredemeijer <i>et al</i> <sup>[71]</sup>
	MBL	The presence of donor MBL2 variant is not associated to a higher incidence of CSI (47% <i>vs</i> 36%, $P = 0.19$ )	Curvelo <i>et al</i> <sup>[125]</sup>
	TLR4	Incidence of Gram-negative infection was not higher in patients with TLR4 mutations (13.5% <i>vs</i> 19.3% in patients with wild-type allele, $P = 0.39$ )	Lee <i>et al</i> <sup>[72]</sup>
	TLR2	Incidence of Gram-positive bacterial infection was not different related to TLR2 polymorphism (31.6% <i>vs</i> 31.6%)	Lee <i>et al</i> <sup>[78]</sup>

NOD: Nucleotide-binding and oligomerization domain; TLR: Toll-like receptor; MBL: Mannose-binding lectin; CSI: Clinically significant infections; SOT: Solid organ transplant; MASP: MBL-associated serine proteases; NK: Natural killer; IL: Interleukin.

TLR2 polymorphisms have been associated with a higher recurrence rate of herpes simplex virus (HSV) type 2 genital ulcers, and greater viral shedding in healthy individuals<sup>[87]</sup>. Recurrent herpes labialis also appears more frequent in individuals with a deficient TLR3 response, which is probably related to the *L412F* polymorphism<sup>[88]</sup>. In contrast, Svensson *et al*<sup>[89]</sup> observed that individuals with the same SNP had lower HSV2 infection rates. Varicella-zoster virus is also recognized by TLR2<sup>[90]</sup>.

**TLR polymorphisms and fungal infection after liver transplantation:** TLR2, TLR4 and TLR9 reportedly mediate some aspects of fungal recognition<sup>[91]</sup>.

**Invasive candidiasis:** A study in mice observed that cytokine production in response to candidal infection was determined by TLR2, but that TLR4 also participated in the host defense by modulating chemokine synthesis and neutrophil recruitment<sup>[92]</sup>. Specifically, TLR2 has been observed to recognize phospholipomannan, while TLR4 recognizes O-linked mannan. TLR9 recognizes *Candida albicans* DNA and induces cytokine production, but the role of TLR9 in invasive candidiasis might only be secondary<sup>[93]</sup>. In a study performed in non-neutropenic patients, Van der Graaf *et al*<sup>[94]</sup> described that the presence of the Asp299Gly and Thr399Ile *TLR4* polymorphisms was associated with increased risk for candidal septicemia. Woehrle *et al*<sup>[95]</sup> studied the cytokine response in critically ill patients with septic shock and its relationship with *TLR2* polymorphisms. The authors found that patients with candidal septicemia in the presence of the Arg753Gln *TLR2* SNP had an attenuated cytokine production when compared with patients with the wild-type allele. More recently, Plantinga *et al*<sup>[96]</sup> analyzed the SNPs related to TLR1, TLR2, TLR4, TLR6, TLR9, MyD88 and another adaptor protein named TIRAP (Toll-interleukin 1 receptor domain containing adaptor protein) in patients with candidal septicemia, and they only observed an increased susceptibility to candidemia in patients with *TLR1* polymorphisms. No information exists about the risk of candida infection and TLR polymorphisms following liver transplantation.

**Invasive aspergillosis:** Initial *in vitro* studies observed TLR2 to be the critical receptor for *Aspergillus* spp. recognition by the innate immune system<sup>[97]</sup>, and that this was mediated by CD14. Subsequent studies have determined that TLR4 can also detect *Aspergillus*, but that this only induces cytokine production in response to *Aspergillus* conidia, and not to the hyphae that are responsible for tissue invasion<sup>[98-100]</sup>. More recently, TLR9 has been observed to recognize *Aspergillus* DNA<sup>[101]</sup>. Studies in stem cell recipients have described an association between TLR polymorphisms and invasive aspergillosis. For example, Bochud *et al*<sup>[102]</sup> analyzed TLR2, TLR3, TLR4 and TLR9 polymorphisms in 336 patients undergoing allogeneic hematopoietic stem-cell transplantation; of whom, 33 developed invasive aspergillosis. The authors found an association between donor *TLR4* polymorphisms and a higher risk of invasive aspergillosis. Recently, de Boer *et*

*al*<sup>[103]</sup> described similar results in patients receiving allogeneic stem cell transplantation from donors with *TLR4* polymorphisms. TLR2 can recognize *Aspergillus*, and TLR2 ligand recognition usually occurs through heterodimeric association with TLR1 or TLR6. Therefore, Kesh *et al*<sup>[104]</sup> analyzed the association between *TLR1* or *TLR6* polymorphisms and the incidence of invasive aspergillosis in stem cell transplantation recipients, and identified that either the Arg80Thr *TLR1* polymorphism or the combination of *TLR1* Asn248Ser and *TLR6* Ser249Pro polymorphisms in the recipients were associated with invasive aspergillosis. In the setting of liver transplantation, no studies have analyzed the association of TLR polymorphisms with the incidence of invasive aspergillosis.

**Other invasive fungal infections:** *Pneumocystis jirovecii* pneumonia is a potentially life-threatening pulmonary infection in immunocompromised patients. Its incidence has declined substantially with the use of universal prophylaxis<sup>[105]</sup>. The major host defense system against *Pneumocystis* infection is adaptive immunity, in which CD4<sup>+</sup> T cells are the most important. In *TLR4*-deficient mice infected with *Pneumocystis*, the authors observed that the number of lung cysts did not differ between *TLR4*-deficient and wild-type mice, but they did observe that the former had more lung destruction<sup>[106]</sup>. The authors concluded that TLR4 signaling was not protective against *Pneumocystis* infection, but was responsible for regulating inflammation after infection. Zhang *et al*<sup>[107]</sup> analyzed the role of TLRs in the recognition of *Pneumocystis* in a mouse model, revealing that cytokine production in alveolar macrophages was activated through recognition by TLR2, but not TLR4. In a subsequent study, they also reported that TLR2 was not involved in the phagocytosis of *Pneumocystis*, but that *TLR2* deficient mice had increased microbial burden when compared with wild-type mice<sup>[108]</sup>. A recent study in mice found that cytokine production in response to *Pneumocystis* infection was dependent on MyD88, but that it was independent of both TLR2 and TLR4<sup>[109]</sup>. In conclusion, it is not clear which receptors are involved in the recognition of *Pneumocystis*.

The incidence of cryptococcal infection after liver transplantation is low, and usually occurs in the late post-transplant period because of reactivation of latent infection. Mortality increases when the central nervous system is involved. Additionally, liver transplantation is associated with a more severe presentation, higher risk of dissemination, and a poorer outcome than other transplant types<sup>[110]</sup>. Host defence against *Cryptococcus neoformans* is mainly mediated by CD4<sup>+</sup> T lymphocytes, while the MyD88 adaptor plays a critical role in the innate immune response against *Cryptococcus*. Recent studies demonstrate that TLR9 recognizes the DNA of this fungal pathogen<sup>[111,112]</sup>. Previous studies have reported that, although glucuronoxylomannan is a ligand for TLR2 and TLR4, it seems that these receptors are dispensable for the defence against *Cryptococcus*. van der Graaf *et al*<sup>[113]</sup> and Yauch *et al*<sup>[114]</sup> analyzed mononuclear cells from volunteers, and observed that individuals carrying the Asp299Gly *TLR4*

polymorphism did not develop increased tumor necrosis factor- $\alpha$  or IL-10 levels when their mononuclear cells were stimulated by *Cr. neoformans*.

### Mannose-binding lectin

Mannose-binding lectin (MBL) is a soluble C-type lectin that recognizes carbohydrates on the surface of numerous microorganisms, including *N*-acetylglucosamine *D*-mannose, *N*-acetyl mannosamine, and *L*-fucose. Although it is primarily synthesized by the liver, small levels of extrahepatic production have been described in the small intestine and testes, which represent about 1% of the total produced. MBL circulates as a serum protein, although an intracellular pool of MBL exists. It consists of a structural subunit composed of three identical polypeptide chains forming a triple helix. Circulating MBL consists of oligomers of this subunit, with higher order oligomers (tetramers to hexamers) being the effective forms. Additionally, MBL-associated serine proteases (MASPs) are present in the serum, of which only MASP-2 effectively activates the complement cascade. MBL can facilitate microorganism phagocytosis through direct opsonization or triggering complement activation, but also cooperates with other PRRs<sup>[115,116]</sup>. The MBL gene (*MBL2*) is located at chromosome 10q11.2-21. There are five known polymorphic sites within the *MBL2* gene, all of which decrease the amount of circulating MBL. Two SNPs are situated in the *MBL2* promoter region (H or L at -550 and Y or X at -221), and three are in exon 1, at codons 52 (allele D), 54 (allele B) and 57 (allele C). These SNPs interfere with the formation of higher-order oligomers and cause decreased serum levels of MBL. Variant alleles of both codon 54 and 57 reduce the levels of functionally viable MBL in the serum to approximately one-eighth that of the wild-type phenotype. The variant allele at codon 52 encodes intermediate levels of MBL, and the polymorphism in the promoter region also reduces the MBL levels<sup>[34,117]</sup>.

The presence of MBL variant alleles is associated with bacterial and viral infection in both immunosuppressed and immunocompetent patients. In some studies, variant alleles have resulted in more severe clinical infections. In contrast, intracellular infection appears to be more frequent in individuals with high MBL levels, because of the increased opsonization and phagocytosis. Low levels of MBL might mitigate the excessive complement-mediated damage found in inflammatory conditions that cause tissue destruction<sup>[33,118-122]</sup>.

In the liver transplantation setting, because MBL is mainly produced by the liver, serum MBL levels depend on the donor genotype after transplantation. Thus, reduced serum MBL levels are seen in recipients with the wild-type *MBL2* genotype who receive a liver with an *MBL2* variant genotype. Conversely, patients with an *MBL2* variant genotype receiving a liver from a wild-type donor, experience increased serum MBL levels after transplantation. These changes occur during the first 2 d after transplantation<sup>[123,124]</sup>.

***MBL2* polymorphisms and bacterial infection after liver transplantation:** Although a recent study did not observe a higher incidence of bacterial infection in recipients of *MBL2* variant livers<sup>[125]</sup>, several studies have described a higher frequency of clinically significant bacterial infections in patients receiving livers from *MBL2* variant donors compared to patients receiving wild-type livers<sup>[123,124,126]</sup>. In addition, these studies observed that *MBL2* polymorphisms in the recipient were not associated with increase rates of infection. A study by our group found no association between *MBL2*-deficient livers and the incidence of bacterial infection, but we did observe that recipients of an *MBL2* variant allograft had more severe infection (more frequent septic shock, higher levels of C-reactive protein, and higher creatinine levels)<sup>[127]</sup>.

***MBL2* polymorphisms and viral infection after liver transplantation:** The first study relating CMV infection to MBL deficiency in transplantation involved 16 kidney recipients at high risk of developing CMV infection (donor positive/recipient negative). The authors observed that patients with low serum MBL levels had a higher incidence of CMV infection<sup>[128]</sup>. The same results were obtained in a study of kidney and pancreas recipients<sup>[86]</sup>. More recently, we determined that the presence of a wild-type genotype was associated with a higher incidence of invasive CMV disease in recipients with positive CMV serology pre-transplantation. These results could be explained by the facilitation of CMV phagocytosis in patients with higher serum MBL levels<sup>[129]</sup>. In liver transplantation, de Rooij *et al.*<sup>[130]</sup> described that patients receiving livers from *MBL2* deficient donors had an increased risk of CMV infection compared with those receiving a wild-type liver.

MBL does not neutralize HSV1 and HSV2, which block the activation of both the classical and alternative complement pathways through glycoprotein C<sup>[131]</sup>. Despite this, Seppänen *et al.*<sup>[132]</sup> described that individuals with recurrent HSV2 infection presented the *MBL2* variant genotype more frequently.

***MBL2* polymorphisms and fungal infection after liver transplantation:** MBL binds to *Aspergillus fumigatus*, *C. albicans*, and *Cr. neoformans*<sup>[133]</sup>. There are no studies relating *MBL2* polymorphisms with the incidence of fungal infection in liver transplant recipients, but some studies have described associations in other immunosuppressed patients. For example, Granell *et al.*<sup>[134]</sup> observed that donor with an MBL-low genotype resulted in more invasive fungal infections in HLA-identical allogeneic stem cell transplantation recipients. Lambourne *et al.*<sup>[135]</sup> reported that immunocompromised patients with lower MBL levels had a higher incidence of invasive aspergillosis. Ou *et al.*<sup>[136]</sup> reported a higher incidence of cryptococcal meningitis in non-HIV patients with *MBL2* polymorphisms. Additionally, in nonimmunosuppressed patients with secondary peritonitis, candidal infection was more frequent in those with low MBL levels<sup>[137]</sup>.



As stated, MBL is associated with MASPs. When MBL recognizes a ligand, one of three MASPs is activated. Of these, MASP-2 plays a predominant role in complement activation. The *MASP2* gene is located on chromosome 1p36.23-31, where nine polymorphisms have been identified<sup>[138-140]</sup>. de Rooij *et al.*<sup>[126]</sup> observed that *MASP2* polymorphism homozygosity in the donor was associated with an increased incidence of clinically significant bacterial infections in liver transplant recipients. In stem cell transplantation, Granell *et al.*<sup>[134]</sup> described that *MASP2* mutations in the recipient were associated with higher incidences of invasive fungal infection.

### Other PRRs

L-ficolin binds to carbohydrate present in lipoteichoic acid, a constituent of Gram-positive bacteria<sup>[141]</sup>. Similar to MBL, the liver synthesizes ficolin, and polymorphisms in the promoter region of the *FCN2* gene are associated with differences in ficolin-2 serum levels. Patients receiving a donor liver with *FCN2* polymorphisms had demonstrated an increased incidence of clinically significant bacterial infection<sup>[126]</sup>. Liver recipients of donors without the minor T-allele of the *FCN2* gene present a higher incidence of CMV infection compared with patients receiving a liver with at least one copy of the minor T allele. The presence of an *FCN2* variant in the recipient does not increase the incidence of CMV infection<sup>[130]</sup>. Recently ficolin-A has been demonstrated to bind *Aspergillus* conidia, but there are no studies relating ficolin deficiency with invasive fungal infections in liver transplant recipients<sup>[142]</sup>.

Nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) are a family of intracellular receptors that recognize bacterial peptidoglycans. They are expressed by macrophages, dendritic cells and certain intestinal epithelial cells. NLR subfamilies include the NOD receptors (NOD1 and NOD2). Three *NOD2* SNPs have been described, and the variants have been associated with inflammatory disease such as arthritis, asthma, and Crohn's disease<sup>[143,144]</sup>. Furthermore, a recent study has described a higher incidence of bacterial infection in liver transplant recipients carrying the R720W polymorphism<sup>[145]</sup>. The authors also observed that homozygous recipients for this polymorphism developed earlier infection than heterozygous or wild type. However, this result has to be interpreted with caution given the small number of patients.

Dectin-1 is a C-type lectin receptor expressed predominantly in the lungs and intestine by dendritic cells, monocytes, macrophages, neutrophils, a subset of T cells, B cells, eosinophils, and mast cells. It is the main receptor involved in the recognition of  $\beta$ -glucans, major structural components of the fungal cell wall, and interacts with *Candida*, *Aspergillus*, *Pneumocystis*, *Coccidioides*, *Penicillium*, and *Saccharomyces*<sup>[98,146,147]</sup>. Ferwerda *et al.*<sup>[148]</sup> first described an association between the Dectin-1 polymorphism and a higher incidence of mucocutaneous fungal infection. In a recent study with hematology patients, a Dectin-1 poly-

morphism was associated with increased risk of invasive aspergillosis and higher levels of galactomannan<sup>[149]</sup>. In contrast, Rosentul *et al.*<sup>[150]</sup> found no association between Dectin-1 polymorphisms and higher incidences of candidemia or worse clinical outcomes.

## INNATE IMMUNITY AND HCV RECURRENCE

HCV infection is the most frequent cause of end-stage liver failure requiring transplantation. After transplantation, HCV recurrence occurs in nearly all patients and the progression to cirrhosis and allograft failure is often accelerated. Between 10% and 30% of liver recipients develop allograft cirrhosis within 5 years of transplantation<sup>[151,152]</sup>. Risk factors associated with an accelerated progression to cirrhosis include: high HCV RNA load, genotypes 1b and 4 (probably related to the lower response to antiviral treatment), female gender, older donor age, steatosis of the graft, the degree of HLA matching, the immunosuppressive drugs used, and CMV and human herpesvirus 6 infection after transplantation<sup>[153,154]</sup>. However, genetic factors may also play an important role in HCV recurrence and subsequent graft loss.

In a study performed in 92 HCV-infected, liver transplant recipients, the authors analyzed the relationship of *TLR2* Arg753Gln, *TLR4* Asp299Gly and Thr399Ile polymorphisms with HCV recurrence, liver fibrosis, and mortality. They described a higher incidence of allograft failure and mortality due to recurrence of HCV infection in individuals homozygous for the *TLR2* polymorphism, but not in either the *TLR2* heterozygous patients or those with *TLR4* variants<sup>[155]</sup>. The same team recently described that *TLR2*-deficient cells were unable to respond to HCV core and NS3 proteins *in vitro*, because the interaction between *TLR2* and the intracellular MyD88 adapter was defective<sup>[47]</sup>.

In a study analyzing the relationship between the Phe412Leu *TLR3* polymorphism and HCV infection in liver transplant recipients, the *TLR3* polymorphism occurred more frequently in HCV-infected liver transplant recipients than in recipients for other indications. Univariate analysis uncovered a higher incidence of allograft loss and mortality in HCV-infected patients with the *TLR3* polymorphism when compared with the wild-type genotype, although this association was lost following multivariate analysis<sup>[156]</sup>. Howell *et al.*<sup>[157]</sup> recently analyzed several *TLR* polymorphisms and their relation with rapid fibrosis after liver transplantation in HCV infected patients. They concluded that patients who developed fibrosis earlier after transplantation were more likely to have deficient *TLR7/8* and *TLR3* responses.

Variants in NK cell receptors are also associated with the risk of HCV recurrence after liver transplantation. Serum NK cell levels prior to transplantation may predict the severity of HCV recurrence<sup>[151]</sup>.

Although previous studies have described associations between HCV recurrence and distinct innate recep-



tors, most have found a clear relation with the IL-28B polymorphism. IL-28 comprises a family of cytokines (type III IFN) including IL-28A, IL-28B and IL-29. The IL-28B gene (*IL28B*) is located on chromosome 19, is composed of six exons, and produces IFN- $\lambda$ 3, which regulates T regulatory cells and enhances cellular adaptive immunity<sup>[158,159]</sup>. Polymorphisms in this gene do not affect serum IL-28B transcript levels, and their impact on IL-28B function remains unknown. IL-28B is produced by both bone-marrow-derived cells and hepatocytes. Thus, the interplay between donor and recipient genotypes is complex after liver transplantation. In nontransplanted patients infected with HCV, *IL28B* polymorphisms have been associated with a sustained virological response after antiviral treatment; predominantly in those patients infected with viral genotype 1. In addition, the existence of CC genotype in the rs12979860 locus has been associated to spontaneous HCV clearance<sup>[160]</sup>.

In the liver transplantation setting, various studies have analyzed *IL28B* polymorphisms, mainly rs12979860 (alleles T and C) and rs8099917 (alleles T and G). Recipients with the *IL28B* rs12979860 TT genotype typically have early and more severe HCV recurrence, and a higher incidence of graft loss. Non-CC recipients who received a liver from a CC donor had the highest risk of developing severe HCV recurrence. Patients with CC genotype not only had less severe HCV recurrence, but also presented higher rates of sustained viral response after antiviral treatment when compared with recipients with a different genotype. Although patients who received a liver from a CC donor have more risk of severe HCV recurrence, they also have higher virological response rates than patients receiving a liver from a non-CC donor<sup>[8,161-167]</sup>. The rs8099917 *IL28B* polymorphism has also been studied in patients with liver transplantation, revealing that non-TT recipients receiving a liver from TT donors had the highest risk for severe recurrence. The *IL28B* genotype had no effect on graft survival in liver recipients without HCV infection<sup>[164]</sup>.

Some authors have tried to analyze the relation between *IL28B* polymorphisms and the development of fibrosing cholestatic hepatitis (a severe manifestation of recurrent HCV infection after liver transplantation). As this is an infrequent complication, the results must be interpreted with caution. However, it seems that recipients with an unfavorable *IL28B* genotype tend to have more fibrosing cholestatic hepatitis, and that this complication is more frequent when the donor has a favourable *IL28B* genotype<sup>[168]</sup>.

## CONCLUSION

The innate immune system could play an important role in liver transplantation. The majority of studies have demonstrated that SNPs of the innate receptors are associated with higher infection rates after transplantation. The importance of these results is in the possibility of establishing individualized risk profiles for each patient

prior to transplantation and the development of prophylactic strategies after transplantation. Furthermore, if specific deficiencies can be proven to be associated with higher infection rates, it may be possible to use recombinant molecules (*i.e.*, recombinant MBL) as therapeutic agents. Future studies on the association between innate immunity variations and the risk of infection after liver transplantation are warranted.

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