

Association Between Polymorphisms in Cytokine Gene and Viral Infections in Renal and Liver Transplant Recipients: A Systematic Review

Prashant Sakharkar¹, Subrata Deb² and Nina Mashayekhi¹

¹ Roosevelt University College of Pharmacy, Schaumburg, IL, USA. ² Larkin University College of Pharmacy, Miami, FL, USA.

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ABSTRACT - Purpose: Although transplantations are associated with an increased risk of post-transplantation infections, they greatly improve life expectancy and patients' quality of life. Cytokine genes play an important role in the success of transplants due to their immunological functions. A systematic review was conducted to evaluate cytokine gene polymorphisms and risk of cytomegalovirus (CMV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in kidney and liver transplant recipients. **Methods:** A systematic search was conducted using PubMed, EMBASE, Medline and Google Scholar from their inception until January 28, 2019 using appropriate key words. Review articles, case reports or series, studies conducted on non-human subjects and published in languages other than English were excluded. Data were abstracted using a standardized form. The quality of the studies included was assessed using "Risk of Bias Assessment tool for Non-randomized Studies (RoBANS)". **Results:** Thirty-one studies met our inclusion criteria; populations studied were diverse with a sample ranging from 20 to 1,671. Nineteen studies evaluated Interleukin (IL)-28B polymorphism, while six studies evaluated interferon lambda (IFN- λ) gene polymorphisms and their impact on CMV, HCV, and HBV progression. Polymorphisms in IL-10 gene were investigated in six studies. Polymorphisms in IL-12B and IL-1B gene were associated with a higher risk of developing CMV infections while polymorphisms in IL-28B were associated with a lower incidence of CMV infection in renal transplant recipients. Similarly, polymorphisms in IL-28B were associated with higher liver dysfunction from HBV infection in liver transplant recipients. Studies included had low risk of bias. **Conclusions:** Cytokine gene polymorphisms IL-12B and IL-1B were found to be associated with an increased risk of infection in kidney transplants and IL-28B in liver transplant recipients. However, the small number and heterogeneity of studies limits the generalization of our results. Further research may lead to finding these associations in larger studies which perhaps improve the use of genetic testing and targeted antiviral therapy. This will further reduce the risk of viral infections associated with cytokine gene polymorphisms in post renal and liver transplant recipients.

Keywords: Cytokines; gene polymorphism; cytomegalovirus; hepatitis C; hepatitis B; CMV infection; renal transplant; liver transplant; solid organ transplant.

INTRODUCTION

Solid organ transplants remain the last possible recourse for some patients with organ failure. Transplants represent improvement in the quality of life for dialysis patients and those with other chronic disease states by offering them a second opportunity at life. Over 135,000 solid organ transplants were performed worldwide in 2016; over 34,000 of these were performed in the United States and there are more than 114,000 people on the waiting list as of April 2018 (1, 2). The most common solid organ transplants are renal transplants followed by liver transplants. Unfortunately, transplants pose a high risk for infections which can be a major cause of

morbidity and mortality among patients after transplantation. In fact, it is the second leading cause of death in patients with renal transplants (3). Those who undergo transplantation are highly susceptible to both bacterial and viral infections due to the immunosuppressive therapy which is used to prevent transplant rejection. Post-transplantation infections include those caused by *Streptococcus pneumoniae*, cytomegalovirus (CMV), Hepatitis C virus (HCV)

Address for Correspondence: Prashant Sakharkar, PharmD, MPH, Associate Professor, Clinical and Administrative Sciences, Roosevelt University College of Pharmacy, 1400 N Roosevelt Blvd, Schaumburg, IL, (USA); Email: psakharkar@roosevelt.edu

and BK polyomavirus. Renal and hepatic transplant graft survival is severely complicated by these infectious pathogens.

CMV infection is the most common opportunistic infection and is a major cause of post-transplant infection (4). CMV is a double stranded deoxyribonucleic acid (DNA) virus and mostly presents as a latent virus that can be reactivated post-transplantation. CMV occurs in 8-32% of renal transplant recipients. CMV disease was associated with an increased risk of graft rejection or loss (5). There are several risk factors that contribute to the development of CMV infection such as age, concomitant infections, immunosuppression, and genetic polymorphisms (4). The infection typically does not cause symptoms in its latent phase but may present flu-like symptoms in the host when reactivated and can affect many organs. Elevated liver enzymes, thrombocytopenia and leukopenia can occur in the host (4).

Similar to renal transplants, liver transplants are also susceptible to viral infection and subsequent allograft rejection. Viral hepatitis is characterized by inflammation of the liver, and its pathogenesis, disease progression, and treatment are influenced by cytokines. In the three major stages of hepatitis infection - namely acute, chronic, and cirrhosis - cytokines play a prominent role in the first two stages when the disease is in the development and maintenance stage (6). Among the five types of hepatitis virus (A, B, C, D, E), the main focus of cytokines is on HCV and HBV pathogenesis, graft survival or rejection, and treatment outcome. In patients who receive liver transplants with HCV recurrence, 10-20% of them develop cirrhosis within five years, compared to the general population who develop cirrhosis within twenty to thirty years (7). HBV can also cause liver cirrhosis and is a major public health concern due to risk of death. According to the World Health Organization, around 650,000 people will pass away due to complications associated with HBV (7).

Cytokines are a large class of proteins and are essential elements in both the adaptive and innate immune system and can affect cells in the body which mobilize and induce inflammation during infection (7). Interestingly, cytokines can have dual roles in the development and progression of viral infection in liver and kidney transplant patients. Certain proteins demonstrate anti-viral properties compared to others which facilitate immune-mediated inflammatory effects. Similar to most viral

infections, subsequent to HCV and HBV infections, the body attempts to clear the viral load through an immune response via cytokines such as interleukin (IL), tumor necrosis factor-alpha (TNF- α) and interferon (IFN) (8). In the absence of appropriate cytokine functions, the HCV or HBV infections eventually lead to fibrogenesis of the liver and require a liver transplant. The success of a liver transplant is considerably dependent on the status of cytokine functions (8). Cytokines play an important role in CMV, HBV, and HCV infections, as well as triggering the induction of these cytokines during infection (9). There is evidence that cytokines have a protective role in CMV infections, as they produce IFN- λ and IL, but cytokines also induce T-cells that cause chronic inflammation-related tissue damage if unregulated (9).

Different forms of cytokine genes arising from the variation in the DNA sequence or polymorphism can lead to altered functionality of cytokines, which in turn can differentially affect the development, progression, and treatment of viral infections (10). Single-nucleotide polymorphisms (SNP) in cytokines, which occur from changes in a single nucleotide base leading to altered protein and function, may be associated with a susceptibility to and an increased risk of infection and response to antiviral treatments (10). The role of cytokine gene polymorphisms and their associations with CMV infection have yet to be fully studied. The presence of these SNPs may predict a patient's outcome during post-transplantation. Further research is needed and exploration into these polymorphisms is essential in order to improve health outcomes in patients with solid organ transplants, such as renal and liver transplants, and other disease conditions. This is crucial in order to guide therapy and tailor drugs to a patient's genetic makeup in order to prevent complications from infections and to ensure graft and patient survival.

Several studies have broadly investigated the association of cytokine gene polymorphisms and different types of infections post solid organ transplant. However, there are limited studies that have systematically assessed the impact of cytokine polymorphisms on CMV infection in renal transplant recipients and HBV and HCV infection among liver transplant recipients. The aim of this study is to explore whether in renal and liver transplant recipients (population), are cytokine gene polymorphisms (Exposure/Non-exposure) associated with risk of CMV, HBV and HCV

infections (Outcomes) by using the Patient or Population, Intervention or Exposure, Comparison and Outcomes (PICO) framework. This review primarily focuses on systematically organizing and analyzing the association between cytokine gene polymorphism and CMV in renal transplant recipients and HBV and HCV in liver transplant recipients.

METHODS

Data sources, search terms and inclusion criteria:

A search was performed through Medline (up to January 2019), EMBASE (up to January, 2019), PubMed (up to January, 2019) and Google Scholar (up to January, 2019) to identify studies that examined the associations between cytokine gene polymorphisms and CMV in renal transplant and HBV and HCV in liver transplant recipients. The following keywords were used in the search - “cytokine”, “cytokine gene”, “polymorphism”, “polymorphism, genetic”, “Cytomegalovirus”, “Hepatitis B”, “Hepatitis C”, “Hepatitis”, “viral infections”, “renal transplantation”, “kidney transplantation”, “renal transplant”, “liver transplantation”, “liver transplant”, “solid organ transplantation”, “solid organ transplant” (Appendix S1). The last search was performed on January 28, 2019. At first, titles and abstracts were screened for their inclusion, followed by a screening of the full texts. Review articles, case reports or studies, studies conducted in other than human subjects, performed in other than renal and liver transplant recipients, and articles published in other than the English language were excluded.

Data extraction

Electronic database searches were performed by all authors. The two investigators (SB and PS) assessed the eligibility and quality of all studies included according to the predetermined selection criteria. Information was extracted independently by all authors from eligible publications using a data abstraction form which included the following: Authors, year of publication, country of origin, study design, sample size, genotype, polymorphisms and its impact on transplant outcome (post-transplant

infection) (Appendix S2). Discrepancies between the investigators were discussed and resolved by consensus.

Quality of publications

The quality of publications was assessed using Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS). The RoBANS tool contains six domains, including the selection of participants, confounding variables, measurement of the intervention (exposure), blinding of the outcome assessment, incomplete outcome data, and selective outcome reporting (11). RoBANS is a validated tool that is reliable and feasible for the assessment of the methodological quality of non-randomized studies. Review Manager version 5.3.3 was used to generate a summary of the RoBANS results (12). Our review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (13) (Appendix S3).

RESULTS

Study characteristics:

Our screening identified 73 potentially relevant articles. A total of 31 studies were included that met our inclusion criteria (Figure 1).

Nine studies explored the association of cytokine gene polymorphism and post-transplant CMV infection in renal transplant recipients, six studies assessed the association with HBV and 16 studies looked at its association with HCV infection post liver transplantation. Fourteen studies were from a European population, six studies were from Asian populations, and 11 studies were performed in a mixed population. Nineteen studies were performed to evaluate IL-28B polymorphism in renal and hepatic transplant patients, while 6 studies evaluated the association between IFN- λ gene polymorphism and its impact on the progression of CMV, HCV, and HBV. Polymorphisms in IL-10 were investigated in six studies. The characteristics of the studies included are presented in Table 1. The quality assessment of included non-randomized studies based on RoBANS tool is presented in Table 2.

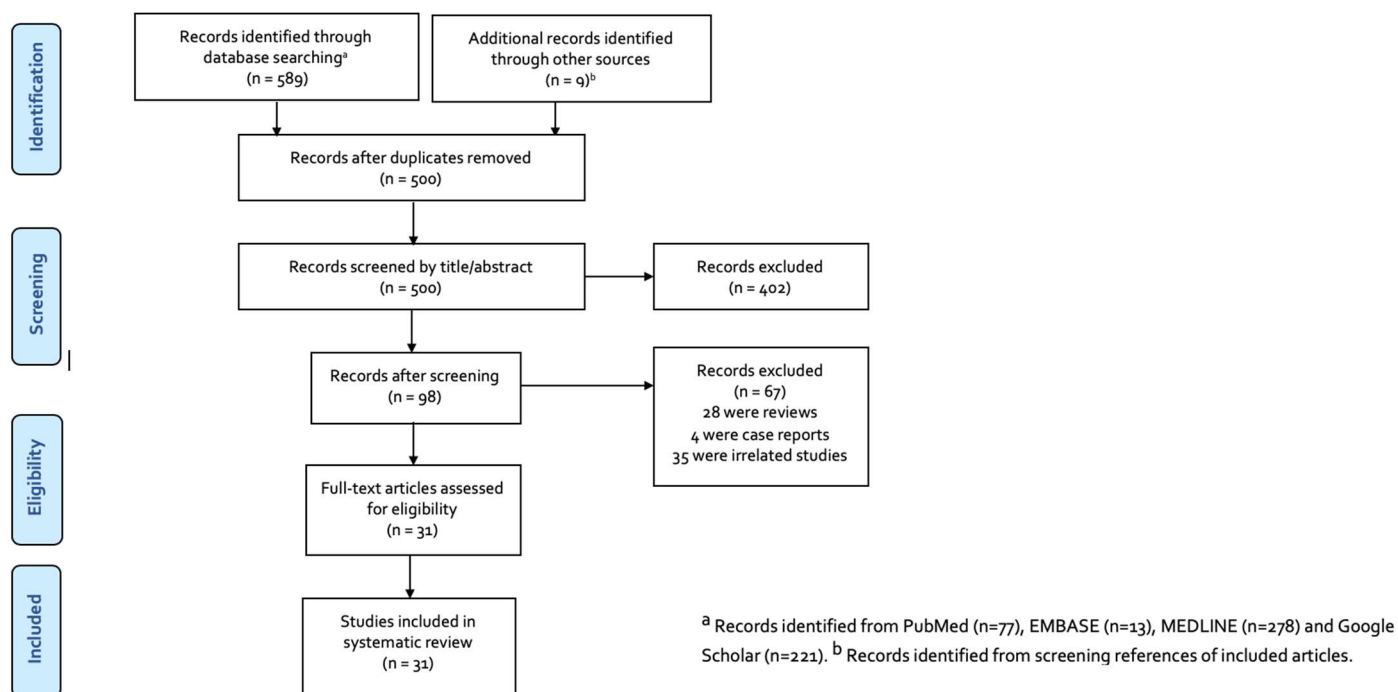


Figure 1. Flow diagram of identification, screening and inclusion of studies

Table 2. Quality assessment of included non-randomized studies based on RoBANS tool

Authors, Year	Selection of Participants	Confounding Variables	Intervention Measurement	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting
Fernandez-Ruiz M et al, 2015	+		+	+	+	+
Manuel O et al, 2015	+		+	+	+	+
Santiago JL et al, 2018	+	+	+	+		+
Hoffmann T et al, 2008	+		+	+	+	+
Hoffmann T et al, 2010	+		+	+	+	+
Rodrigo E et al, 2007	+	+		+	+	+
Alakulppi N et al, 2006	-		+	+	+	+
Aguado et al, 2018	+	+	+	+	+	+
Vu et al, 2014	+	+	+	+	+	+
Allam et al, 2013	+	+	+	+	+	+
Lange et al, 2011	-	+	+	+		+

Table 2. Quality assessment of included non-randomized studies based on RoBANS tool

Authors, Year	Selection of Participants	Confounding Variables	Intervention Measurement	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting
Mueller JL et al, 2016	+	+	+	+	+	+
Fernandez-Carrillo C et al, 2014	+	+	+	+	+	+
Barbera F et al, 2015	+	+	+	+	+	+
Firpi RJ et al., 2013	+	+	+	+	+	+
Monaghan KG et al, 2015	-	+	+	+	+	+
Cisneros E et al, 2013	+	+	+	+	+	+
El Awady MK et al, 2014	+	+	+	+	+	+
Kawaoka T et al, 2012	+	+	+	+	+	+
Harada N et al, 2014	+	+	+	+	+	+
Coto-Llerena M et al, 2011	+	+	+	+	+	+
Charlton MR et al, 2011	+	+	+	+	+	+
Duarte-Rojo A et al, 2012	+	+	+	+	+	+
Świątek-Kościelna B et al, 2017	+	+	+	+	+	+
Ge D et al, 2009	+	+	+	+	+	+
Li W et al, 2012	+	+	+	+	+	+
Li W et al, 2011	+	+	+	+	+	+
Li Y et al, 2017	+	+	+	+	+	+
Abbott et al, 2007	-	+	+	+	+	+
Ben-Ari Z et al, 2003	-	+	+	+	+	+
Chen et al, 2016	+	+	+	+	+	+

In this table, + sign denotes a low risk of bias, blank denotes an unclear risk of bias, and – sign denotes a high risk of bias.

The studies included showed low risk of bias for both blinding for outcome assessment and selective outcome reporting domain of the tool in all of the studies, high risk of bias for selection of the

participants and confounding variables domain in five studies and unsure risk of bias for intervention measurement and incomplete outcome data domain in two studies (Figure 2).

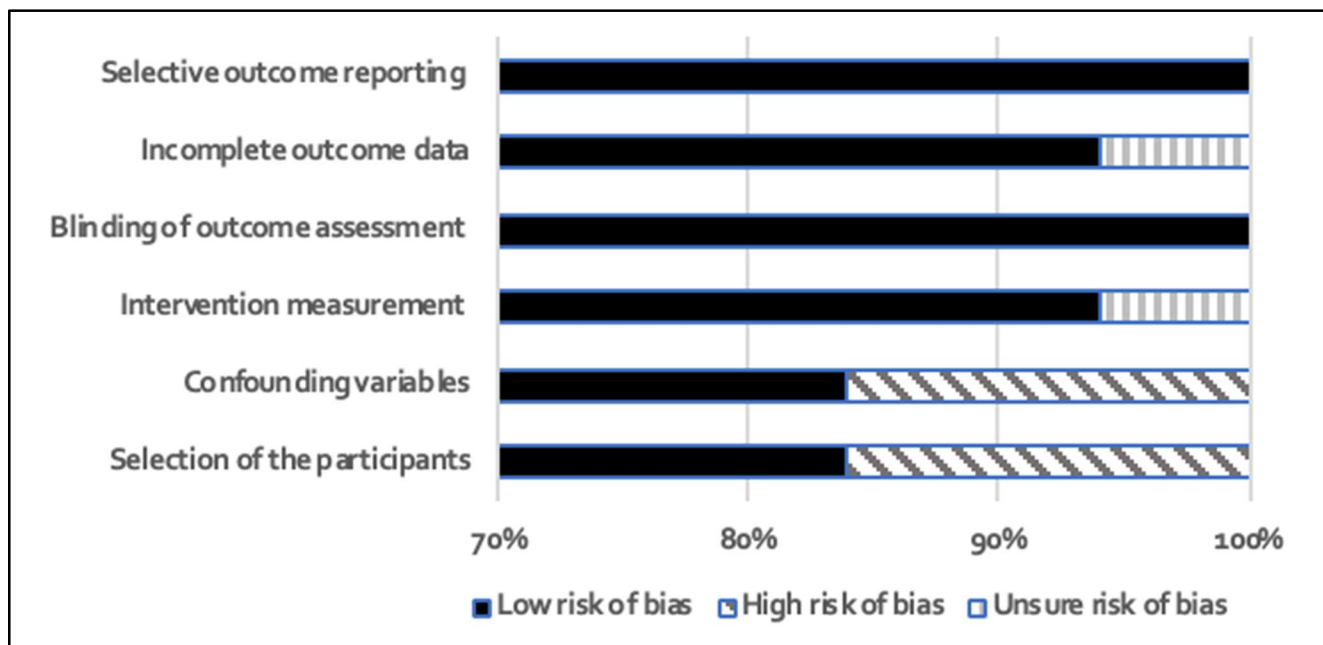


Figure 2. Summary of the methodological quality of all enrolled studies

Role of Cytokines in Renal Transplant

A lower incidence of CMV infection was found in patients with A-allele genotypes of toll like receptor 2 (TLR-2) and T-allele genotypes of IL-28B. Patients with the A-allele were less susceptible to CMV infection compared to patients with the GG genotype (14). The 12-month CMV infection free survival rate was 85%, compared to 53% in patients with the GG genotype. The survival rate was also higher among patients with the TT genotype of TLR-9 compared to those with the AA/AG genotypes of dendritic cell-specific ICAM 3-grabbing nonintegrin (DC-SIGN) SNP, 54% compared to 40%, respectively. This effect was found to be more pronounced in patients not on prophylaxis therapy and was also associated with a lower risk of CMV infection. This study concluded a significant relationship between the number of unfavorable SNP genotypes and the overall risk of CMV infection, specifically, SNPs in IL-28B, TLR-9, and DC-SIGN genes may have modulated the susceptibility to CMV infection in these patients (14).

In another study, the incidence of CMV replication emerged to be higher among recipients who were homozygous for the minor allele of rs368234815 (-G/-G carriers) compared with other patients (TT/TT or TT/-G carriers). The results of

this study indicated that IFN- λ rs368234815 polymorphism might be a risk factor for developing CMV associated complications post-renal transplantation (15). In a retrospective study conducted in Spain, 205 patients developed CMV infection and the median time to onset was 2.7 months (15). However, Santiago and colleagues found no association of IFN- λ -874 A/T polymorphism as a predictive marker of CMV infection in their analyses (16). Previously, the C-allele was found to be an independent risk factor for CMV infection on a multifactorial Cox regression analysis. This risk was estimated to be even higher in patients with a positive CMV serological status before the transplantation and who did not receive prophylaxis (17). Programmed cell death protein (PD)-1 is known to inhibit IFN- λ production and has been reported to be clinically relevant in immune disorders. Forty six percent of those that were carriers of the A-allele acquired CMV infection. It has been hypothesized that the A-allele could affect PD-1 inhibition and increase inflammatory mediators post kidney transplantation (18). Hoffman and colleagues in this study further concluded that the A-allele was associated with risk of CMV infection in those who did not receive prophylaxis. In patients with PD-1.3, the A-allele had a much

higher risk of CMV infection and prophylaxis based on genetic markers, which needs to be further researched (18).

Cytokine polymorphisms (IL-10, transforming growth factor beta (TGF- β), TNF- α , IFN- λ , IL-6, IL-4, IL-2, IL-4R, IL-12, IL-4RA, IL-1RA, IL-1R, IL-1B, and IL-1A) were studied to determine the relationship between cytokine polymorphisms and infection in kidney transplant recipients (19). A total of 122 patients developed at least one instance of infection within the first year. Female patients developed infections more than their male counterparts. Recipients with -511 IL-1B CC genotype or with -1188 IL-12 CA and CC genotypes were at higher risk of developing infections in the first year. These genotypes predicted the risk of post-transplantation infection in the first year after transplantation (19).

Seventy-one CMV seronegative recipients of grafts from CMV seropositive donors were studied in Finland where IL-10, IL-6, and IFN- λ gene polymorphisms were explored for the links between these genes and infection. The donor IL-10 (-1082 AA) genotype reduced the incidence of CMV infection, suggesting that gene polymorphism may impact the likelihood of CMV infection in high risk patients (20). A lower risk of CMV reactivation in those with AA genotypes compared to AT genotypes of the IFN- λ gene was predicted in a large sample in this Spanish study. No genotypes conferred a protective effect among polymorphisms in IL-28B. The authors found no differences between IFN- λ levels in those with and without CMV replication and no differences between peak viral load, duration, or onset of replication due to a small sample size (21).

Patients with donor-positive/recipient-negative (D+/R-) serostatus were found to be associated with a high risk of CMV infection among Hispanic renal transplant recipients in this study by Vu et al (22). A significant association was found between IFN- γ +874 A>T polymorphism and the risk of CMV infection. The IFN- γ +874 AA genotype was associated with a 3.4-fold increased risk for the CMV-infected group compared to the non-CMV group. Individuals with IFN- γ +874 AT and AA genotypes exhibited a higher risk of allograft loss. The results of this study suggested that renal transplant recipients with the variant homozygous IFN- γ AA genotype were at risk of CMV infection, whereas the high producer IFN- γ +874 TT genotype

appears to be associated with a lower risk of CMV infection (22).

Cytokine Polymorphism and Hepatitis C Virus

An investigation by Allum and colleagues indicated that liver transplant patients with a CC or CT genotype of IL-28B had a lesser chance of graft rejection compared to the TT genotype (62% versus 48%) (23). Interestingly, the positive influence of the CC/CT genotype on reappearance of HCV and the potential of graft rejection were not reliant on antiviral treatment. The authors concluded that unlike the popular notion that donor IL-28B is a predictor of liver transplant success, the recipient's IL-28B status is actually more important in assessing the final outcome of graft survival (23). Similarly, the effect of IL-28B polymorphisms was evaluated in donor and recipient on graft survival during liver transplant. In a cohort of 91 patients with HCV reinfection after liver transplant, genotype rs12979860 CT/TT was identified as a predictor of HCV infection (24).

Allograft cirrhosis was developed in 20% of the patients. Recipients who received a liver from those with epidermal growth factor (EGF) non-AA alleles had an increased graft cirrhosis progression compared to those with an AA allele donor liver (25). An increased rate of sustained virologic response (SVR) was seen in the CC allele of IL-28B compared to non-CC alleles. However, no association was found between the recipient or donor IL-28B and patatin like phospholipase domain containing 3 (PNPLA3) genotype and adverse clinical outcomes (25). In another study, polymorphisms in the IFN- λ 4 rs368234815 strongly influenced antiviral treatment response. After transplantation, recipient IFN- λ 4 genotype TT/TT was associated with a higher SVR rate (26). SVR occurred more in patients receiving a liver from a donor with a favorable genotype, however this result was found to be not statistically significant (26).

HCV RNA clearance induced by antiviral treatment was associated with the cytokine alleles. rs12979860 CC and rs12980275 AA genotype was associated with both end of therapy response (EOTR) and SVR while rs8099917 TT genotype was not associated with SVR but was significantly associated with EOTR (27). Homozygosity of the rs12979860 CC genotype was associated with a positive response to antiviral treatment, suggesting that analyzing IL-28B genotypes might be helpful in order to optimize HCV therapy (27). Patients who

did not have the CC genotype of IL-28B but received an IL-28B CC donor liver were found to have a higher chance of achieving SVR than those who obtained a non-CC donor liver. Only 25% of patients achieved SVR if they did not have the CC allele from donor or recipient. Patients also had less fibrosis than recipients with CT and TT genotypes, however, this difference was found not statistically significant. Patient survival did not alter due to IL-28B polymorphism and only 3 patients had graft failures in this study (28). The donor or recipient with rs12979860 CC was also found associated with an increased SVR who were undergoing antiviral treatment (29).

In a study with a Spanish patient cohort, post-transplantation HCV infection was influenced in recipients carrying IL-28B rs12979860 genotype. Forty patients developed severe HCV recurrence while 49 patients did not. It was statistically significant that more patients who had severe HCV recurrence had the TT allele and the T allele was associated with poor outcomes (30). The presence of the T allele in the liver donor had a lower risk of severe HCV recurrence, suggesting its more protective effect concluding that this genetic polymorphism can be a highly reliable predictive indicator of HCV reinfection (30). The authors suggested that the patients who have susceptible genotypes receive prophylactic antiviral treatment in order to improve health outcomes. In one small Egyptian study, IL-28B SNP and preoperative HCV titer predicted post-transplant HCV recurrence and disease-free survival (DFS) while genes in oligoadenylate synthase (OAS) and IL-1B had no association with DFS (30). Those with the CC genotype of IL-18B had higher rates of DFS after transplantation. Patients who had the IL-28B CT and TT alleles were more likely to develop HCV infection recurrence than those with the CC genotype. IL-1B polymorphism was not associated with HCV recurrence post transplantation (31).

The SVR rate was higher in donor grafts who had the TT genotype (73.3%) compared to TG+ GG group (20%) in this small Japanese study (32). Similar results were observed in another larger Japanese study where presence of the major allele (TT) in either the recipient or the donor was found to be associated with an SVR of 53% and 48%, respectively. The minor allele (TG or GG) was found to be associated with an SVR of 26% and 32%, respectively (33). On the other hand, SVR was determined to be higher in recipients with CC

genotypes and when receiving grafts from CC genotype donors (34). Recipients with the TT and CT genotype had a shorter time to HCV recurrence within 5 years compared to the CC genotype, 100%, 87%, and 78%, respectively in this study (35). Donor genotype was not found associated with time to recurrence. The rate of SVR was associated with the recipient and donor IL-28B genotype. Recipients with the CC or CT genotype had a higher SVR rate than those with the TT genotype, 58%, 47%, 0%, respectively. Donors with the CC or CT genotype had similar rates. Rates were highest in those who had both matching donor and recipient CC genotype. Patients with the TT genotype or those who received a donor liver from a TT genotype did not attain SVR. Polymorphisms in IL-28B were predictive of fibrosis. Recipients with the TT genotype (32%) had faster fibrosis formation after one year of transplantation (35). These results were also confirmed in a cohort study done in the United States among 255 patients that underwent liver transplantation with HCV. Both recipient and donor CC genotype favored SVR (36).

Polymorphisms of IL-10 and their association with disease progression were investigated in a Polish patient cohort of 196 individuals (37). SNPs such as 1082(A/G) rs1800896, 819(C/T) rs1800871, 592(C/A) rs1800872 and +4529(A/G) rs3024498 in the promoter region of IL-10 gene were investigated. The abundance of ACCA, ATAA, GCCA and GCCG haplotypes were recognized in >5% of individuals. The C allele of 592(C/A) SNP was related to liver inflammation and appeared to be protective, whereas ACCA and ACC haplotype were related to SVR and had lower potential to relapse (37). Genetic variations in the IL-28B gene were related to up to two-fold change in the treatment outcome in individuals with European ancestry and African-Americans. The formation and level of IFN- λ s were measured to be higher in hepatocytes of HCV-inflicted patients and were associated with a positive IL-28B genotype and treatment outcome. For the rs12979860 genotypes, patients with two favorable response alleles (CC) had a higher probability of SVR to peginterferon alpha (PEG-IFN- α) and ribavirin (RBV) (38).

Cytokine Polymorphism and Hepatitis B Virus

In a cohort of 200 HBV individuals, the SNPs of IL-18 gene (rs187238 and rs1946518) and IL-28B (rs8099917) were studied in the Chinese Han population (39). The abundance of IL-18 SNPs was

similar between recipient and donor in relapsing or non-relapsing HBV individuals. The authors found that the circulating IFN- λ levels were lower in HBV patients with relapse history compared to the non-relapsing patients (39). Interestingly, the IL-28B rs8099917 was associated with elevated alanine transaminase (ALT) and aspartate transaminase (AST) in HBV liver transplant individuals. Similarly, graft recipient individuals with allele G, and both the GG and GT genotypes, experienced elevated ALT and AST levels. The patients with genetic variants of IL-28B eventually had more hepatic dysfunction from HBV infection (39). The presence of SNPs of IL-28B (rs12979860, rs12980275, rs8099917) had a direct influence on serum ALT activity and the viral load in HBV-infected patients in the authors' previous investigation. There is strong evidence to suggest that rs8099917 G allele is a predictor of hepatic injury after liver transplantation and that patients with this variant should be observed for potential future relapse (40).

Lower platelet counts may be beneficial to HBV-related recipients as it plays a role in liver recovery. Genetic variants of IL-28B may influence liver function recovery as the rs12979860 T allele and rs8099917 C allele have higher peripheral platelet counts after transplantation in the third and fourth day (41). IL-28B protective genotypes, rs12979860 CC allele and rs8099917 AA allele, had significantly lower platelet levels in the first 4 days after transplantation. Abbott and colleagues reported two polymorphisms, namely, a microsatellite change in the +875 IFN- γ CA Allele and a SNP in the +A874T, in the intron 1 of the IFN- γ gene. Both of the variants have been attributed to elevated IFN- γ formation which can lead to different clinical characteristics. In a study involving Polynesian women, the microsatellite and the SNP variants had a strong effect on unfolding innate immune responses in HBV patients (42). Similarly, a remarkable distinction was identified in the abundance of IFN- γ polymorphisms between HBV-infected versus healthy patients (43). The authors did not observe any significant dissimilarity in the HBV infection outcomes due to TNF- α , IL-6 and IL-10 polymorphisms (42). IL-6 gene polymorphism is another potential predictor of HBV prognosis, including hepatocellular carcinoma (HCC) (43). Chen and colleagues suggested that liver donors with rs2069852 AA variants are associated with HCC relapse and the reference SNP could work as a strong

predictor of HCC relapse and shorter life expectancy following transplantation in the Chinese Han population (44).

DISCUSSION

Solid organ transplantations are a lifesaving procedure for those with chronic and end stage diseases and it can improve the quality of life of the recipient. However, there can be complications associated with transplants that further increase the risk of graft rejection, morbidity, and mortality for the patient. Risk factors such as age, immunosuppression and genetic composition can further complicate the development and progression of viral infection. In this review, we have investigated thirty-one studies related to various cytokine gene polymorphisms to determine if they influence CMV, HBV, and HCV infection risk in renal and liver transplant recipients. The results were consistent in demonstrating a relationship between cytokine gene polymorphisms and risk of viral infection. The findings of this systematic review suggest that gene polymorphism may be associated with a higher risk of viral infections, except in one instance when the cytokine variant form afforded lower risk of infection, in renal and liver transplant patients.

While eliciting the immune response, the cytokines can exert pro-inflammatory or anti-inflammatory functions in organ recipients (7). In the context of the current work, IL-1B, IL-6, IL-12 and IL-18 have pro-inflammatory actions, whereas IFN- λ -based genes (IL-28B) and IL-10 are anti-inflammatory in nature. The IL-1B and IL-18 cytokines are involved in generating complex cytotoxic actions through inflammation. IL-10 is a master regulator of anti-inflammatory and immunosuppressive actions and provides a protective role in hepatic viral infections and post-transplant infections (19, 20). Whereas IL-28B is part of the cluster of genes known as type III interferons or IFN- λ 3, which is associated with comprehensive antiviral and cytotoxic actions (45).

In the patients who have undergone renal transplants, polymorphisms in IL-12, IL-1B, IFN- λ , and PD1 were associated with a higher risk of CMV infection. Individuals with G/-G allele in the IFN- λ cytokine were more prone to developing CMV-associated complications post-transplant. The C allele in the p40 gene of IL-12B was considered to be an independent risk factor for CMV infection in

one study, especially in carriers who did not receive antiviral prevention therapy. The A allele was also associated with a higher risk of CMV in those who did not receive prophylaxis therapy. Patients who had the T-allele of IL-28B and carriers of TLR-9 SNP had lower incidences of CMV infection. Polymorphisms in IFN- λ was also studied but it did not prove to be a predictive marker of CMV infection.

Polymorphisms in IL-28B were associated with both the risk of HCV disease pathogenesis and hepatic dysfunction from HBV infection in patients that underwent hepatic transplants. Three studies concluded that the CC genotype in IL-28B was associated with a greater rate of SVR compared to the TT genotype. The -592 C allele in IL-10 cytokine was associated with mild hepatic inflammation when compared to the A allele. Pharmacogenomics is an important aspect of HCV treatment where the genomic polymorphisms of cytokines dominate if an individual is a candidate for PEG-IFN- α and RBV treatment or not. Although, with the advent of newer small molecules drugs for HCV, the PEG-IFN and RBV are losing their place in the clinic. Nevertheless, a large number of HCV patients worldwide are still being treated with the interferon-based regimens.

Similar to HCV, the HBV virus can cause acute and chronic liver issues that can eventually require a liver transplant. Although the discussion on IL-10 started lately, there are few interesting observations about the role of this cytokine in HCV infections. IL-18 is known to be a dominant inflammatory cytokine, which can fight with the HBV and remove it from the host (human) body. IL-18 is one of the cytokines that induces IFN- λ and as a result IL-18 can provide protection from HBV infection. In addition, similar to HCV, IL-28B has a key role in the HBV disease development, progression and graft survival outcomes. Similarly, IFN- λ is a protective cytokine and exerts a strong function on the treatment of HBV infection; the genetic variants of the IFN- λ gene could be a crucial factor in the HBV disease timeline.

The carriers of cytokine polymorphisms demonstrate differential susceptibility to viral infection as well as response from antiviral treatment following liver or kidney transplants. Among the cytokine genes discussed in this study, polymorphisms of IL-28B have reached conclusive implications in the disease pathogenesis and clinical management of viral hepatitis. For the rs12979860

polymorphism of the IL-28B gene, the individuals with the CC genotype had a better prognosis compared to CT or TT genotypes, which essentially drive the organ transplant recipients towards hepatic fibrosis (27, 28). It is plausible that CT or TT genotype carriers express IL-28B protein isoforms that are unable to activate the phosphorylation pathways, leading to removal of the protective effects of IL-28B. According to the guidelines of the Clinical Pharmacogenetics Implementation Consortium, patients with the CC genotype, compared to CT or TT genotypes, have a higher probability of positive treatment outcome from a shorter treatment regimen (24-28 weeks versus 48 weeks) with PEG-IFN- α and RBV (46). Similarly, though the mechanism of this effect is not clear, for the rs8099917 of the IL-28B gene, the TT genotype is hepatoprotective and is considered more desirable for the antiviral treatment (29). Thus, IL-28B genotypes can serve as a robust indicator of therapeutic success in IFN-RBV based treatments of hepatic viral infection. Similarly, the carriers of IL-10 polymorphisms (-592A or -819T) demonstrated improved response to the IFN-RBV regimen (47). It is noteworthy to mention that the basal functions of both IL-28B and IL-10 are anti-inflammatory in nature. In comparison, the polymorphisms of pro-inflammatory cytokines such as IL-1B (-511 CC) or IL-12 (-1188 CA and CC) actually increased the risk of developing infection in kidney transplant patients (19). We postulate that the variants of IL-1B or IL-12 downregulate the NK cell activation and dampen T cell mediated cytotoxicity, which make the transplant patients more susceptible to viral infection.

Further studies are needed to determine a direct association between CMV, HBV and HCV infections and cytokine polymorphisms. Additional analysis may improve patients' health outcomes and reduce further complications. In the future, immunosuppressive and antiviral therapy can be specifically tailored to patients undergoing transplantation based on cytokine polymorphisms to limit their infection risk. Since cytokines have dual roles of defense and inflammation in the viral infections, the use of antiviral and immunosuppressant medications or the type of medications in transplant patients can be heavily determined by the polymorphic status of their cytokines. The therapeutic outcome or adverse effect landscape of antivirals and immunosuppressants could be affected by the cytokine variant status of a

particular patient. The new generation anti-HCV small molecules have become part of the routine treatment in the last five years and the studies on the effect of these cytokine polymorphisms on their small molecule treatment outcome is warranted.

The current study has several limitations. Several studies examined a small sample population and many did not establish statistical significance due to this. Another drawback was that multiple studies primarily examined Caucasian patients despite the genetic variance among different races. Only a handful of studies were multicenter, multinational, or both, thereby limiting the scope of their application. Heterogeneity of studies, a handful of studies with small sample size, and variability in clinical settings all limited our ability to perform a meta-analysis to assess the summary effect of association between cytokine gene polymorphisms and post-transplant CMV, HBV and HCV infection.

CONCLUSIONS

In conclusion, our systematic review has demonstrated that cytokine gene polymorphisms, especially IL-12B and IL-1B, were found to be associated with an increased risk of infection in kidney transplant recipients and IL-28B in liver transplant recipients. These results further confirm the role of cytokine variants in assessing susceptibility to infections, treatment efficacy, and outcomes in renal and liver transplant recipients. It is important for researchers to continue exploring cytokine gene polymorphisms to better inform healthcare providers about their possible role and impact on health outcomes, especially in renal and liver transplant patients, as well as in patients with other disease conditions, to guide their treatment options. The presence of unfavorable SNPs in donor and recipient genotypes may predict a recipient's susceptibility to post-transplant complications. It is important to conduct genetic testing and analyze a patient's cytokine genetic makeup prior to transplantation of an organ from a donor to ensure a favorable genotype which may lead to optimized drug therapy, reduced costs, and better health outcomes.

CONFLICT OF INTEREST

Authors have no financial or any other conflict of interest to declare.

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APPENDIX

S1: Search strategy used for PubMed

#1 - Cytokine [tiab] OR cytokine gene [tiab] OR "Cytokines" [MeSH]

#2 - polymorphism [tiab] OR genetic polymorphism*[tiab] OR "Polymorphism, genetic" [MeSH]

#3 - 1 AND 2

#4 - viral infection*[tiab] OR cytomegalovirus*[tiab] OR "cytomegalovirus"[MeSH] OR hepatitis [tiab] OR hepatitis virus*[tiab] OR "hepatitis c"[MeSH] OR "hepatitis b"[MeSH]

#5- solid organ transplant*[tiab] OR solid organ transplantation*[tiab] OR renal transplant*[tiab] OR renal transplantation*[tiab] OR "kidney transplantation"[MeSH] OR liver transplant*[tiab] OR liver transplantation*[tiab] OR "liver transplantation"[MeSH]

#6 - #3 AND #4 AND #5

S2: Content of data abstraction form used

1. Title
2. Author(s)
3. Year of publication
4. Citation
5. Publication type
6. Country of origin
7. Study type
8. Selection of Participant
9. Blinding
10. Sample size, number in control/intervention group
11. Ethnicity
12. Cytokine gene explored
13. Allele/Polymorphism/SNPs reported
14. Intervention
15. Comparison
16. Post-transplant outcomes (CMV, HBV, HCV infection)
17. Measures of association and statistical significance reported (OR, HR, SVR, p-value etc.)
18. Study limitations stated
19. Comments/Remarks if any

Table 1. Characteristics of the studies included and association of cytokine gene polymorphisms and viral infections in renal and liver transplant recipients

Authors and Year of Publication	Country of Origin	Study Design	Sample Size	Ethnicity	Cytokine Gene	Allele/Polymorphism/ SNPs	Intervention/ Comparison	Impact on Post-transplant Outcome (Infection)
Fernandez-Ruiz M et al., 2015	Spain	Cohort	315	93% Caucasian 6% African 1% Asian	IL-10, CCR-5, TLR-2, TLR-9, DC-SIGN, MCP-1, IL-28B	A-allele, T-allele, GG, TT, AA, AG, CT, TT	12-month cumulative incidence of laboratory-confirmed CMV infection (either asymptomatic infection or CMV disease) was assessed.	IL-28B, TLR-9, and DC-SIGN genes might modulate the susceptibility to CMV infection. Patients with T-allele genotypes of IL-28B SNP had lower incidence of CMV infection (aHR: 0.66). Carriers of TLR-9 SNP also had lower incidence of infection (aHR: 0.61) in renal transplant patients.
Manuel O et al., 2015	Switzerland	Cohort	840	Caucasian	IFN-λ	-G/-G, TT/TT, TT/-G carriers	Patients with -G/-G allele vs other patients (TT/TT or TT/-G)	IFN-λ rs368234815 (-G/-G) polymorphism might be a risk factor for developing CMV-associated complications post renal transplantation.
Santiago JL et al., 2018	Spain	Retrospective cohort	600	Spanish	IFN-γ	+874 A/T	Patients with AT allele vs AA or TT	Found no association of IFN-γ 874 A/T polymorphism as a predictive marker of CMV infection in the analyses (HR: 1.30, p value: 0.81) in renal transplant patients.
Hoffmann T et al., 2008	Switzerland	Retrospective cohort	469	Caucasian	IL-12B	p40 gene	C allele carriers vs A/A allele carriers	The C allele was an independent risk factor for CMV infection (OR: 1.52, p: 0.043) especially in patients who did not receive prophylaxis and had a positive CMV serological status before renal transplantation (OR: 1.88, p: 0.028)
Hoffmann T et al., 2010	Switzerland	Retrospective cohort	469	Caucasian	PD-1	Intron 4 gene (PD-1.3)	A allele carriers vs G/G allele carriers	A allele was associated with a higher risk of CMV in seropositive patients who did not receive prophylaxis

Table 1. Characteristics of the studies included and association of cytokine gene polymorphisms and viral infections in renal and liver transplant recipients

Authors and Year of Publication	Country of Origin	Study Design	Sample Size	Ethnicity	Cytokine Gene	Allele/Polymorphism/ SNPs	Intervention/ Comparison	Impact on Post-transplant Outcome (Infection)
Rodrigo E et al., 2007	Spain	Retrospective cohort	255	Spanish	IL-10, TGF-B, TNF- α , IFN- γ , IL-6, IL-4, IL-2, IL-4R, IL-12, IL-4RA, IL-1RA, IL-1R, IL-1B, and IL-1A	CC, CT, TT alleles of IL-1B, AA, CA, CC alleles of IL-12, C, CT, TT alleles of TGF-B 10, CC, GC, GG alleles of TGF-B 25, AA, GA, GG alleles of TNF- α , GG, GT, TT alleles of IL-4	Appearance and number of infections within the first year after transplantat ion were identified	therapy (OR: 2.60, p: 0.006) in renal transplant patients. Recipients with -511 IL-1B CC genotype or with -1188 IL-12 CA and CC genotypes were at higher risk of developing CMV infections in the first year (RR: 2.67, p: 0.007 and RR: 2.57, p: 0.012, respectively) in renal transplant recipients.
Alakulppi N et al., 2006	Finland	Cohort	71	Finnish	IL-10, IL-6, and IFN- γ	Alleles of IL-10, IL-6, and IFN- γ	AA genotype vs other alleles	Recipient polymorphisms did not reduce CMV infection incidences. Donor IL-10 (-1082 AA) genotype reduced the incidence of CMV infection in renal transplant patients. (HR: 0.3, p: 0.043) Polymorphisms did not have any impact on the risk of CMV replication after renal, lung and liver transplantation. They observed a lower risk of CMV reactivation in those with AA genotype compared to AT genotypes of the IFN-gamma gene IFN- γ (OR: 0.42, p: 0.051).
Aguado et al., 2018	Spain	Retrospective cohort	184	Spanish	IFN- γ , IL-28B	T & A allele of IFN- γ and C & T allele of IL-28B	IFN- γ : TT vs AT, AA vs AT IL-28B: CC vs CT, TT vs CT	A statistically significant correlation was found to be associated with a high risk of CMV infection in those with the IFN- γ A>T polymorphism
Vu et al., 2014	United States	Retrospective Cohort	247	Hispanic	IL-10, TNF- α , IFN- γ	IL-10 -1082 A>G, -592 A>C, TNF- α -308 A>G, IFN- γ +874 A>T	Role of IL-10 -1082 A>G, -592 A>C; TNF- α -308 A>G; and IFN- γ +874 A>T gene	A statistically significant correlation was found to be associated with a high risk of CMV infection in those with the IFN- γ A>T polymorphism

Table 1. Characteristics of the studies included and association of cytokine gene polymorphisms and viral infections in renal and liver transplant recipients

Authors and Year of Publication	Country of Origin	Study Design	Sample Size	Ethnicity	Cytokine Gene	Allele/Polymorphism/ SNPs	Intervention/ Comparison	Impact on Post-transplant Outcome (Infection)
Allam et al. 2013	United States	Retrospective cohort	1060	Mostly Caucasian	IL-28B	CC, CT, TT	polymorphisms was studied in Hispanic renal transplant recipients (RTRs) with CMV and without CMV infection CC vs CT vs TT	(OR: 3.4, p: 0.01) in renal transplant recipients.
Lange et al., 2011	Germany, Switzerland	Cohort	91	German, Swiss nationals	IL-28B	CT/TT, CC	CC vs CT/TT genotypes	Recipient IL-28B status is important in assessing the final outcome of graft survival (HR for TT genotype: 3.27, p<0.001) Genotype rs12979860 CT/TT was identified as a predictor of liver transplant in HCV patients (p: 0.046)
Mueller JL et al. 2016	United States	Cohort	264	84% Caucasians, 6% African Americans, 7% Hispanic, 3% Asian	IL-28B	CC, CT, TT	CC vs CT vs TT	In patients with HCV, the CC IL-28B variant in both recipients and donors is associated with increased rate of SVR (54% vs 36% for non-CC genotype) in liver transplantation.
Fernandez-Carrillo C et al., 2014	Spain	Cohort	86	Spanish	IFN- λ 4 IL-28B	rs368234815 genotypes were defined as TT/TT, TT/G or G/G. IL-28B rs12979860 (CC, CT, TT) and rs8099917 (TT, GT, GG)	Association between recipient IFN- λ 4 favorable genotype (TT/TT) and SVR compared to unfavorable genotypes (TT/G and G/G)	Recipient TT/TT genotype is associated with a higher SVR after liver transplantation.
Barbera F et al. 2015	Italy	Retrospective cohort	57	Europeans	IL-28B	Rs12980275 AA, AG-GG, rs12979860 CC,	Rs12980275 AA vs AG vs GG,	Homozygous allele of rs12979860 was associated

Table 1. Characteristics of the studies included and association of cytokine gene polymorphisms and viral infections in renal and liver transplant recipients

Authors and Year of Publication	Country of Origin	Study Design	Sample Size	Ethnicity	Cytokine Gene	Allele/Polymorphism/ SNPs	Intervention/ Comparison	Impact on Post-transplant Outcome (Infection)
Firpi RJ et al., 2013	United States	Retrospective cohort	135	Caucasian	IL-28B	CT-TT, rs8099917 TT, TG-GG CC, CT, TT	rs12979860 CC vs CT vs TT, rs8099917 TT vs TG vs GG CC vs CT vs TT	with SVR independent of the donor's genotype in patients with HCV in liver transplant patients. The CC genotype had less fibrosis, but it was not statistically significant. No statistically significant difference in patient survival was determined in HCV patients (CC aHR: 1.12 (p: 0.73), non-CC: 1.30 (p: 0.41))
Monaghan KG et al., 2015	United States	Retrospective cohort	22	White Caucasian, African American and Hispanics	IFN- λ 3	rs12979860 (C/T) and rs8099917 (T/G)	recipient and donor genotype associations between each SNP (rs12979860 C and rs8099917 T) and SVR status CC vs CT vs TT	Transplantation of a rs12979860 CC graft has a more favorable post-transplant antiviral response among those who are HCV-positive and in those post-transplantation is more likely to achieve SVR.
Cisneros E et al., 2012	Spain	Retrospective Cohort	90	Spanish	IL-28B	CC, CT, TT	CC vs CT vs TT	More patients with the allele rs12979860-T had severe HCV recurrence than those without it (82.9% vs 53.1%, OR: 4.30, p: 0.0028) in liver transplant patients.
El Awady MK et al., 2014	Egypt	Cohort	50	Egyptians	IL-28B, IL-1B	CC, CT, TT of IL-1B, CC, CT, TT of IL-28B	CC vs CT vs TT	In patients with chronic HCV infection, the CC genotype of the IL-28B gene had a correlation with higher rates of disease-free survival at 62.5% (p: 0.025) in liver transplant recipients.
Kawaoka T et al., 2012	Japan	Cohort	20	Japanese	IL-28B	TG+GG, TT	TG+GG vs TT	In patients with HCV who completed IFN therapy, the SVR rate of donors TT group

Table 1. Characteristics of the studies included and association of cytokine gene polymorphisms and viral infections in renal and liver transplant recipients

Authors and Year of Publication	Country of Origin	Study Design	Sample Size	Ethnicity	Cytokine Gene	Allele/Polymorphism/ SNPs	Intervention/ Comparison	Impact on Post-transplant Outcome (Infection)
Harada N et al., 2014	Japan	Cohort	96	Japanese	IL-28B	TT, GG, TG	TT vs TG+GG	was higher than the TG+GG group (73% vs 20%) while the recipient's alleles were similar among liver transplant recipients. Presence of the TT allele in the recipient or donor corresponded to SVR of 53% and 48%, respectively in patients with HCV. Difference of SVR between TT and TG/GG in recipient was statistically significant in liver transplant recipients.
Coto-Llerena M et al. 2011	Spain	Cohort	128	Spanish	IL-28B	Rs12989860, CC, CT, TT, rs8099917 TT, GT, GG	CC vs CT vs TT in rs1298960, TT, GT, GG in rs8099917	Antiviral therapy response rate was higher for recipient genotype CC compared to CT/TT before and after liver transplantation in HCV-infected patients (100% vs 48%, p:0.013)
Charlton MR et al., 2011	United States	Retrospective cohort	189	N/R	IL-28B	CC, CT, TT	CC vs CT vs TT	The TT genotype was associated with more rapid fibrosis (p: 0.024). Donor and recipient CC variant were associated with increased rate of sustained virologic response (59% and 58%, respectively) in liver transplant patients.
Duarte-Rojo A et al., 2012	United States	Cohort	255	N/R	IL-28B	CC, CT, TT	CC vs non-CC genotype	In liver transplant recipients with HCV, the CC genotype from the donor showed a higher rate of cirrhosis progression (HR: 5.96), liver-related death or re-transplantation. Donor CC genotype favored

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Świątek-Kościelna B et al., 2017	Poland	Cohort	196	Polish nationals of Caucasian ethnicity	IL-10	-1082(A/G) rs1800896, -819(C/T) rs1800871, -592(C/A) rs1800872 and +4529(A/G) rs3024498.	A, G, C, T alleles	inflammation and fibrosis. Only after antiviral therapy does the donor CC genotype become favorable IL-10 SNPs are associated with disease severity. -592C allele is associated with mild hepatic inflammation and is protective against tissue inflammation vs A allele (OR: 0.592, p: 0.035). -819C allele might be associated with SVR (OR: 0.570, p: 0.028) in liver transplant patients.
Ge D et al., 2009	United States	Cohort	1671	European Americans, Hispanics, African Americans	IL-28B	rs12979860	CC vs TT, CC vs CT	In patients with European ancestry, and Hispanic and African American patients, the CC genotype is associated with a greater rate of SVR than the TT genotype (OR: 7.3, 6.1, 5.6, respectively) in liver transplant recipients.
Li W et al., 2012	China	Cohort	200	Chinese Han population	IL-18, IL-28B	alleles of IL-18, IL-28B	GG, GT, TT	Patients with genetic variants of IL-28B had more hepatic dysfunction from HBV infection. G allele recipients was associated with higher ALT & AST levels (p <0.05) in liver transplant.
Li W et al., 2011	China	Cohort	648	Chinese Han population	IL-28B	rs12979860, rs12980275 and rs8099917	rs12979860, rs12980275 vs rs8099917	IL 28-B G allele is a predictor of hepatic injury after liver transplantation.
Li Y et al. 2017	China	Retrospective cohort	231	Chinese	IL-28B	TT genotype, CC genotype, GG genotype	TT vs CC vs GG	Recipients with CC genotype of rs12979860 and AA genotype of rs8099917 in IL-28B had lower peripheral platelet count after liver

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Abbott et al., 2007	New Zealand	Cohort	126	Polynesian women	IFN- γ	Intron 1	Homozygous 12/12, heterozygous 12/non-12, homozygous non-12/non-12	transplantation in the first 4 days. They concluded no differences in ALT and AST between recipients with different genotypes after transplantation. The IFN- γ CA genotype was associated with the risk of chronic HBV infection because of a dominant effect of the 12 CA-repeat allele on developing natural immunity in homozygotes (OR: 5.8, p: 0.003) and heterozygotes (OR: 2.7, p: 0.01) in liver transplant patients.
Ben-Ari Z et al. 2003	Israel	Cohort	77	Israeli nationals	TNF- α , IL-6, IL-10, IFN- γ	A/A genotype of IFN- γ	Control group vs patients with chronic HBV infection	Authors did not observe any significant dissimilarity in the HBV infection outcomes due to TNF- α , IL-6 and IL-10 polymorphisms. 65.2% of patients exhibited potential to produce IFN- γ in low levels (A/A genotype) compared to 37.5% in the control group (p: 0.003) in liver transplant patients
Chen et al. 2016	China	Cohort	110	Chinese Han population	IL-6	Rs2069852 AA variants	AA vs AG and GG genotypes	Liver donors with rs2069852 AA variants correlate with HCC relapse and shorter life expectancy following liver transplantation (p: 0.010)

IL=Interleukin; CCR= Chemokine (C-C motif) Receptor; TLR=Toll Like Receptor; DC-SIGN= Dendritic Cell-specific ICAM 3-Grabbing Nonintegrin; MCP= Monocyte Chemoattractant Protein; IFN- λ =interferon lambda; TNF- α =Tumor Necrosis Factor Alpha; TGF-B=Transforming Growth Factor Beta; OR= Odds Ratio; HR: Hazard Ratio; aHR: Adjusted Hazard Ratio; CMV = Cytomegalovirus; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; SVR = Sustained Virologic Response; p = p-value; HCC=Hepatocellular Carcinoma; IFN- γ =Interferon Gamma; ALT=Alanine Transaminase; AST= Aspartate Transaminase; SNP=Single Nucleotide Protein; N/R=Not Reported

S3: 2009 PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4, Fig.1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3, 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-4, Appendix S2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3-4, Appendix S2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3-4, Fig. 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4, Fig. 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3-4, Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-12, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-15, Table 2, Fig. 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-15, Table 2, Fig. 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20