Importance of genetic polymorphisms in liver transplantation outcomes

Kelava, Tomislav; Turčić, Petra; Markotić, Antonio; Ostojić, Ana; Šisl, Dino; Mrzljak, Anna

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Importance of genetic polymorphisms in liver transplantation outcomes

Tomislav Kelava, Petra Turcic, Antonio Markotic, Ana Ostojic, Dino Sisl, Anna Mrzljak

ORCID number: Tomislav Kelava (0000-0002-6665-116X); Petra Turcic (0000-0002-2621-8257); Antonio Markotic (0000-0002-0410-542X); Ana Ostojic (0000-0003-4234-4461); Dino Sisl (0000-0002-9993-8191); Anna Mrzljak (0000-0001-6270-2305).

Tomislav Kelava, Dino Sisl, Laboratory for Molecular Immunology, Croatian Institute for Brain Research, University of Zagreb, School of Medicine, Zagreb 10000, Croatia

Petra Turcic, Department of Pharmacology, Faculty of Pharmacy and Biochemistry of University of Zagreb, Zagreb 10000, Croatia

Antonio Markotic, Center for Clinical Pharmacology, University Clinical Hospital Mostar, Mostar 88000, Bosnia and Herzegovina

Ana Ostojic, Department of Medicine, Merkur University Hospital, Zagreb 10000, Croatia

Anna Mrzljak, Department of Medicine, Merkur University Hospital; School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Corresponding author: Anna Mrzljak, MD, PhD, Associate Professor, Department of Medicine, Merkur University Hospital; School of Medicine, University of Zagreb, Zajceva 19, Zagreb 10000, Croatia. anna.mrzljak@mef.hr

Abstract

Although, liver transplantation serves as the only curative treatment for patients with end-stage liver diseases, it is burdened with complications, which affect survival rates. In addition to clinical risk factors, contribution of recipient and donor genetic prognostic markers has been extensively studied in order to reduce the burden and improve the outcomes. Determination of single nucleotide polymorphisms (SNPs) is one of the most important tools in development of personalized transplant approach. To provide a better insight in recent developments, we review the studies published in the last three years that investigated an association of recipient or donor SNPs with most common issues in liver transplantation: Acute cellular rejection, development of new-onset diabetes mellitus and non-alcoholic fatty liver disease, hepatocellular carcinoma recurrence, and tacrolimus concentration variability. Reviewed studies confirmed previously established SNP prognostic factors, such as PNPLA3 rs738409 for non-alcoholic fatty liver disease development, or the role of CYP3A5 rs776746 in tacrolimus concentration variability. They also identified several novel SNPs, with a reasonably strong association, which have the potential to become useful predictors of post-transplant complications. However, as the studies were typically conducted in one center on relatively low-to-moderate number of patients, verification of the results in other centers is warranted to resolve these limitations. Furthermore, of 29 reviewed studies, 28 used gene candidate approach and only one implemented a genome wide association approach. Genome wide association multicentric studies are needed to facilitate the

development of personalized transplant medicine.

Key words: Single nucleotide polymorphisms; Liver transplantation; Acute rejection; Non-alcoholic fatty liver disease; New-onset diabetes mellitus; Hepatocellular carcinoma; Tacrolimus

Core tip: Better stratification of risk before transplantation and/or selection of appropriate donor are crucial to reduce post-transplant complications and improve outcomes. The contribution of genetic risk associated with single nucleotide polymorphisms for the most common complications along with the immunosuppression after liver transplantation is briefly summarized in this review.

INTRODUCTION

Liver transplantation (LT) is the only effective treatment for the end-stage liver failure regardless of its etiology. Although patients' survival following transplantation has markedly improved during the last decades, LT is still burdened with various complications, such as acute cellular rejection (ACR), development of metabolic disorders: New-onset diabetes mellitus (NODM), non-alcoholic fatty liver disease (NAFLD) and/or the recurrence of primary disease like hepatocellular carcinoma (HCC)[1]. Better stratification of risk before transplantation, selection of appropriate donor, and appropriate immunosuppressive therapy might be of crucial importance to reduce these complications and improve the outcomes[2].

The contribution of genetic risk associated with single nucleotide polymorphisms (SNPs) has been extensively investigated. In the present review, we briefly summarize the findings of older investigations for each of the most common complications after LT and give a detailed analysis of discoveries of the studies published in the last three years.

LITERATURE SEARCH

We searched PubMed for articles published after 2017 using a predefined search strategy. For acute cellular rejection we searched PubMed for: "Liver transplantation", rejection and polymorphism. For new-onset diabetes mellitus we searched PubMed for: "Liver transplantation", diabetes, and polymorphism. For NAFLD we searched PubMed for: "Liver transplantation", (NAFLD or steatosis), polymorphism. For HCC recurrence we searched PubMed for: "Liver transplantation", hepatocellular carcinoma, recurrence, and polymorphism. Finally for tacrolimus pharmacokinetic we searched PubMed for: "Liver transplantation", tacrolimus, and polymorphism. Similar search for everolimus and sirolimus returned no relevant studies. Books, dissertations, review articles, meta-analyses, non English articles, and unpublished reports were excluded. Studies non-relevant for the topic, as well as studies with data inconsistency, as assessed by the review of the abstracts or full text, were also excluded.

ACUTE CELLULAR REJECTION AFTER LIVER TRANSPLANTATION

ACR is a common complication after LT with the incidence of 10%-30%. A recently conducted large study showed that ACR is a clinically significant event, associated

with an increased risk of graft failure and death. Clinical risk factors for ACR development include younger recipient age, lack of renal impairment, higher AST levels before LT, longer cold ischemic times and older donors. However, genetic risk factors might play a contributory role[3,4]. ACR is a T-cell mediated reaction, therefore, majority of SNP studies are focused on molecules that participate in T-cell activation, signaling and trafficking.

Although positive association was reported for a relatively high number of SNPs, none of them was firmly and consistently associated with ACR. Studies typically report relatively wide 95% confidence interval (CI) for odds ratio (OR) with a limit close to 1 and lack a confirmation from studies conducted in other centers. The role of TNFa-308 and IL10-1082 SNPs remains controversial even after conducted meta-analyses and might depend on ethnicity[5-7].

Our search identified eight novel studies which are summarized in Table 1. All studies were on genes related to the immune system; seven studies were solely on recipients, while the study by Thude *et al*[8], investigated both donors and recipients. This study reported an association of ACR with incompatibility in human platelet antigen 3 (HPA-3) SNP between the donor and recipient, although on a relatively low number of patients (53 non-rejectors and 43 rejectors). One study investigated SNP (IL28B rs12979860) for which a previous study reported an association with ACR[9], but found no difference[10]. Valero-Hervás *et al*[11] found the association with complement C3 genotype (95%CI for OR 0.09-0.77) on large number of patients and confirmed independency by multivariate analysis. SNP for IL17 (rs2275913) was associated with risk for ACR, and also with IL-17 plasma concentration and cyclosporine metabolism[12]. Yu *et al*[13] found a weak association between ACR and CD276 polymorphism, with CI limits close to 1. The remaining studies found either no association or the association was present only in subgroup analysis[14-16].

Although reviewed studies provide some insight into genetic risk for ACR occurrence, no reliable association has been identified. The approach by Thude *et al*[8], who investigated the recipient-donor relationship, seems to be more promising and should be conducted on larger scale.

NEW-ONSET DIABETES MELLITUS AFTER LIVER TRANSPLANTATION

NODM is a common metabolic complication after liver transplantation with a reported prevalence of 17%-36% despite the improvements in immunosuppressive regimens[17-19]. NODM has a negative effect on recipient and graft survival, and it is associated with cardiovascular complications, infections, chronic rejection and renal failure[17-20]. So far, clinical parameters such as advanced age, ethnicity, family history, body mass index, hepatitis C virus and immunosuppressive drugs have been reported as risk factors for NODM after LT[21-23].

Identifying patients at high risk of developing NODM is rather necessary for preventing the disease, individualization of immunosuppressive protocols and improving the long-term outcomes after LT. The pathophysiology of NODM resembles that of type 2 diabetes mellitus (T2DM) and it is characterized by impaired insulin secretion and insulin resistance. Thus, the numerous genetic polymorphisms that are involved in T2DM may also be associated with the development of NODM[24]. However, these associations in the post-transplantation setting are only starting to be elucidated.

We reviewed four studies that were published in the last three years (Table 2). With the exception of the study by Husen *et al*[25], all were conducted on SNPs previously shown to be associated with T2DM in non-transplant patients. Cen *et al*[26] investigated twelve different recipient's SNPs and found an association with two different SNPs for adiponectin gene rs1501299 and rs82239, and further confirmed rs1501299 (minor allele frequency, MAF 24%) to be an independent risk factor by multivariate regression. For rs82239, MAF (4.7%) was too low for firmer conclusions[26]. Interestingly, they found no association for KCNJ11 rs5219 SNP for which Parvizi *et al*[27] previously reported significant association with NODM. Similarly, the lack of association for nine other SNPs previously associated with DM in non-transplant patients was reported in this study[26]. Zhang *et al*[28] investigated both donor's and recipient's SNPs for small ubiquitin-like modifier 4 (SUMO4) rs237025 and found both of them to be associated with NODM. A recent meta-analysis confirmed that this SNP contributes to DM risk in non-transplant patients[29]. The angiotensin gene polymorphism rs699 is well known to be associated with a risk for various cardiovascular conditions. Moreover, its association with insulin sensitivity has also been reported[30]. Mottaghi *et al*[31] found this SNP to be associated with NODM in liver

Table 1 Genes and their single nucleotide polymorphisms investigated in association with acute cellular rejection after liver transplantation

Ref.	Etiology/Population N (non-ACR/ACR)	Genes and best 95%CI OR	Key points
Yu *et al*[13]	Various Eastern Asian 334/54	Recipient CD276: rs2127015 (0.05-0.93); NS for: rs11072431, rs11574495, rs12593558, rs12594627, rs3816661 rs7176654; Recipient TREML2: rs4714431, rs6915083, rs7754593, rs9394767 NS[1]	Recipient's CD276 (rs2127015) T allele is weakly associated with ACR and with CD276 mRNA expression
Ostojic *et al*[14]	Alcoholic European 156/59	Recipient CXCL9: rs10336 NS; Recipient CXCL10: rs3921 NS	No association found. CXCL9 (rs10336) is associated with earlier ACR occurrence and higher plasma CXCL9 concentrations
Sun *et al*[12]	Various Eastern Asian 66/40	Recipient IL-17: rs2275913 (0.07-0.77)[2]	Associated with increased IL-17 plasma concentration and with cyclosporine metabolism (CYP3A4 and CYP3A5 expression)
Verma *et al*[16]	Various Asian 86/16	Recipient FOXP3: rs3761547, rs3761548, and rs2232365 NS	Association found only in a very small subgroup of steroid resistant ACR patients (*N* = 5) for rs3761548 Associated with the degree of mixed lymphocyte reaction
Thude *et al*[15]	Various European 163/178	Recipient KLRB1: rs1135816 NS	No association found
Thude *et al*[8]	Various European 53/43	Recipient HPA-3 a/b: rs5910 (1.749–41.8); Recipient/donor incompatibility: rs5910 (1.78–7.39); HPA-1, -2, -3, -5, -15 NS for all	HPA-3 incompatibility and HPA-3 b/b genotype were associated with higher incidence of ACR There was no difference in the time of ACR occurrence
Fereidooni *et al*[10]	Various Western Asian 101/39	Recipient IL28B: rs12979860 NS	No association found
Valero-Hervás *et al*[11]	Various European 277/185	Recipient C3 complement rs2230199 (0.09-0.77)	C3FF genotype is associated with lower incidence of ACR, independently after multivariate analysis for sex, HCV infection, therapy and donor type

[1]Although a statistical significance for rs6915083 and rs7754593 of TREML2 is noted in the manuscript, the 95% ORs include 1 and should not be considered a significant association.
[2]Calculated from study data by authors of this review. ACR: Acute cellular rejection; C3: Complement component 3; CD: Cluster of differentiation; CXCL: Chemokine (CXC motif) ligand; CYP: Cytochrome P450; FOXP3: Forkhead box P3; HCV: Hepatitis C virus; HPA: Human platelet antigen; IL: Interleukin; KLRB1: Killer cell lectin-like receptor B1; mRNA: messenger ribonucleic acid; N: Number; NS: Not significant; TREML2: Triggering receptor expressed on myeloid celllike transcript 2; 95%CI OR: 95% confidence interval for odds ratio.

recipients. Finally, Husen *et al*[25] found the recipient's mammalian target of rapamycin mTOR rs2295080 to be associated with NODM in everolimus-treated patients. However, considering that the NODM risk was not a primary study objective and that the number of NODM patients was very low, this result needs further verification.

NON-ALCOHOLIC FATTY LIVER DISEASE AFTER LIVER TRANSPLANTATION

NAFLD is now recognized as the most common etiology of chronic liver disease[32,33], and one of the most common indications for LT, with increasing trends[34,35]. The genetic background of NAFLD is well established and the strongest evidence is provided for PNPLA3 rs738409, which became a major genetic determinant of hepatic fat content[33]. Following liver transplantation NAFLD/non-alcoholic steatohepatitis (NASH) may reoccur or develop *de novo*, with almost 50% of recipients showing evidence of steatosis after 10 years[36].

Recurrent and/or *de novo* allograft steatosis could also be genetically driven, and

Table 2 Genes and their single nucleotide polymorphisms investigated in association with new-onset of diabetes mellitus after liver transplantation

Ref.	Etiology/Population N (non-NODM/NODM)	Genes and best 95%CI OR	Key points
Mottaghi *et al*[31]	Various Iran 62/53	Recipient AGT: rs699 - 7.326 (2.0-26.8), rs4762 – NS	The presence of AGT rs699 T allele may significantly increase the NODM risk
Husen *et al*[25]	Various European 115/12[1]	Recipient Mtor: rs2295080 (1.48-23.4); rs12139042, rs2536 – NS	rs2295080 CC genotype is associated with a risk of DM on everolimus-based IS DM was a secondary objective, with a very low N of DM patients
Cen *et al*[26]	Hepatitis C, HCC China 181/75	Recipient ADIPOQ: rs1501299 (0.05-0.61)[2], rs822396 (0.13-0.70)[3]; NS for recipient SNPs: ADIPOR2 rs767870, TLR4 rs1927907, CCL5 rs2107538 and rs2280789, CYP3A5 rs776746, PPARA rs4823613, ACE rs4291, HSD11B1 rs4844880, KCNJ11 rs5219, KCNQ1 rs2237892	ADIPOQ rs1501299 and rs822396 are associated with a risk of NODM rs1501299 is an independent risk factor
Zhang *et al*[28]	Various China 102/24	Recipients SUMO4: rs237025 (1.42-5.91); Donors SUMO4: rs237025 (1.542–9.007)	Donor and recipient rs237025 G allele and their combination were independent predictive factors for NODM

[1]In the cited article the N of non-diabetic patients is wrongly stated to be 127, which is a total N.
[2]Calculated from study data for codominant model by authors of this review.
[3]Calculated from study data for dominant model by authors of this review. ACE: Angiotensin I converting enzyme; ADIPOQ: Adiponectin, C1Q and collagen domain containing; ADIPOR2: Adiponectin receptor 2; AGT: Angiotensinogen; CCL5: Chemokine (C-C motif) ligand 5; CYP: Cytochrome P450; DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HSD11B1: Hydroxysteroid 11-beta dehydrogenase 1; IS: Immunosuppression; KCNJ11: Potassium inwardly-rectifying channel, subfamily J, member 11; KCNQ1: Potassium voltage-gated channel, KQT: Like subfamily, member 1; mTOR: Mammalian target of rapamycin; N: Number; NODM: New-onset diabetes mellitus; NS: Not significant; PPARA: Peroxisome proliferator-activated receptor alpha; SNP: Single nucleotide polymorphism; SUMO4: Small ubiquitin like modifier 4; TLR4: Toll like receptor 4; 95%CI OR: 95% confidence interval for odds ratio.

our search identified 4 novel studies, summarized in Table 3, which had analyzed the association between donor and recipient SNPs with steatosis occurrence after LT. The donor PNPLA3 G allele was independently associated with steatosis occurrence in two studies from the same group of authors[37,38]. Míková *et al*[37] further reported that donor TM6SF2 rs58542926 A allele is associated with higher odds for steatosis development. Additionally, the strongest association was observed when both PNPLA3 G and TM6SF2 A alleles were present in the donor liver (95%CI for OR 2.01-13.0). However, it should be noted that two studies also reported a weak association between recipient PNPLA3 G allele and steatosis in the univariate model[38,39]. Furthermore, Kim *et al*[39] found that there are higher odds for steatosis development when donor and recipient have PNPLA3 G allele. However, the evidence is weak and CI limits extremely wide, mainly due to a small number of patients. Finally, recipient adiponectin gene SNPs were reported to be weakly associated with *de novo* steatosis in patients transplanted due to chronic hepatitis C virus (HCV) infection[40].

In summary, despite the small number of studies and a relatively small number of patients included, PNPLA3 rs738409 seems to be associated with post-LT steatosis, with novel studies providing stronger evidence for the donor rather than recipient polymorphism. However, based on previous "seed and soil" theory[41] and observations from studies shown in Table 3, we find that it would be of scientific interest to examine the possible interaction effect of donor and recipient genotypes on steatosis occurrence in an adequately powered study. Furthermore, the additive effect of TM6SF2 rs58542926 seems to increase the genetic risk for post-transplant steatosis further.

HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION

HCC is the most common type of primary liver cancer and the second leading cause of tumor-related deaths worldwide[42]. Several HCC risk factors including alcohol

Table 3 Genes and their single nucleotide polymorphisms investigated in association with non-alcoholic fatty liver disease after liver transplantation

Ref.	Etiology/Population N (no steatosis/steatosis)	Genes and best 95%CI OR	Key points
Míková *et al*[37]	Various European 139/129	Donor TM6SF2: rs58542926 (1.28-4.42); Donor PNPLA3: rs738409 (1.28-3.27); Additive: TM6SF2 + PNPLA3 (2.01-13.0); Recipient NS for all	Donor TM6SF2 A allele and PNPLA3 G allele are associated with steatosis in both univariate and multivariate adjusted analyses The additive effect of donor TM6SF2 A allele and donor PNPLA3 G allele is strongly associated with steatosis No association when recipients SNPs were analyzed
John *et al*[40]	HCV North American 72/39	Recipient adiponectin: rs1501299 (1.09-5.5), rs266729 (0.14-0.75); rs2241766, rs17300539 – NS; Donor – NS for all	Recipient but not donor adiponectin rs1501299 GG genotype is significantly, but weakly associated with *de novo* steatosis after adjustment for race and HCV genotype
Kim *et al*[39]	Various Eastern Asian 23/9	Recipient PNPLA3: rs738409 (1.00-9.34)[1]; Donor – NS; Additive donor + recipient: (1.32-117.0)[2]	If both, donor and recipient have G allele, the recipient has higher risk for steatosis weak association, small number of patients
Trunečka *et al*[38]	Various European 89/87	Donor PNPLA3: rs738409 (1.05-1.75); Recipient PNPLA3: rs738409 (1.02-1.57)	PNPLA3 G allele in donors [OR (95%CI) = 1.62 (1.12-2.33)], but not in recipients is independently associated with steatosis after adjustment for age, disease etiology, BMI, diabetes, hypertension, therapy and lipids

[1]Calculated from study data for log-additive model by authors of this review.
[2]Calculated from study data by authors of this review. BMI: Body mass index; HCV: Hepatitis C virus; N-number; NS: Not significant; OR: Odds ratio; PNPLA3: Patatin-like phospholipase domain-containing 3; SNP: Single nucleotide polymorphism; TM6SF2: Transmembrane 6 superfamily member 2; 95%CI OR: 95% confidence interval for odds ratio.

consumption, HCV, hepatitis B virus (HBV), obesity and T2DM can be addressed through a variety of prevention and treatment methods[43]. Nevertheless HCC is an increasing indication for liver transplantation (LT) worldwide, regardless of the etiology[44,45]. LT provides a highly effective treatment option in selected patients, whereas the post-transplant HCC recurrence still remains a negative predictor of post-transplant survival in a substantial part of recipients[46,47]. Significant efforts have been made to identify risk factors for the HCC recurrence, and some of them as tumor size and number of lesions are implemented in selection criteria and prognostic models[48,49]. Mechanisms involved in the HCC development and recurrence are being extensively investigated, but our current knowledge is still limited, restricting our diagnostic and therapeutic options.

Genetic risk factors play an important role in HCC development. Recent investigations indicate an important role of PNPLA3, EGF and TM6SF2 SNPs in HCC susceptibility[50]. A recently conducted genome-wide association study (GWAS) identified rs2431 SNP for fibronectin type III domain containing 3b (FNDC3B) to be associated with the overall survival of HCC patients who underwent liver resection[51]. However, data on HCC recurrence in patients treated with liver transplantation, where both donor and recipient SNPs might contribute to the genetic risk of HCC reoccurrence are scarce. Our search identified three novel studies (Table 4). All three studies were conducted on genes associated with immune system activity. Zhang *et al*[52] found the recipient's SNP for IL-15 (rs10519613) to be associated with the risk of post-transplant HCC recurrence in a cohort of HBV infected patients. Two different studies on toll-like receptor- (TLR) related genes have reported an increased risk of HCC recurrence for donor's TLR4 (rs1927914) and recipient's TLR9 (rs187084) polymorphism, respectively[53,54]. Noteworthy, for TLR4 (rs1927914) polymorphism, previous case-control study reported an association with the HCC development[55]. These studies further emphasize the important role of innate immunity activation in liver carcinogenesis[56].

Table 4 Genes and their single nucleotide polymorphisms investigated in association with hepatocellular carcinoma recurrence after liver transplantation

Ref.	Etiology/Population / N (non HCC/HCC)	Genes and best 95%CI OR	Key points
Shi *et al*[53]	Various / Eastern Asian / 49/34	Donor TLR 4: rs1927914 (1.886-12.5)[1]; Recipient TLR 4: rs1927914 NS	Donor TLR4 TT variant is an independent risk factor for HCC recurrence [OR 95%CI = 6.499 (1.799-23.481), after correction], and is associated with shorter recurrence free survival and overall survival
Zhang *et al*[52]	HBV / Eastern Asian / 74/38	Recipient IL-15: rs10519613 (1.636–16.168), rs13122930 NS; Donor IL-15: rs10519613 NS; rs13122930 NS	Recipient IL-15 rs10519613 CA/AA genotype is an independent risk factor for shorter tumor free survival and overall survival after correcting for histologic grade, tumor thrombus, tumor stage and UCSF criteria / OR 95 CI for tumor free survival = 2.214 (1.041–4.708), for overall survival = 3.152 (1.358–7.315)
de la Fuente *et al*[54]	Various / European / 139/20	Recipient TLR9: rs187084 (0.01–0.87); rs5743836 – NS	TLR9 rs187084 TT genotype was associated with a decreased risk of HCC recurrence

[1]Calculated from study data by authors of this review for dominant model. HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; IL: Interleukin; N: Number; NS: Not significant; OR: Odds ratio; TLR: Toll like receptor; UCSF: University of California San Francisco; 95%CI OR: 95% confidence interval for odds ratio.

TACROLIMUS PHARMACOGENOMICS

One of the most important aspects in patient and graft survival is adequate immunosuppressive therapy. Introduction of calcineurin inhibitors to immunosuppressive regimen has greatly improved the outcomes after liver transplantation, even more so with tacrolimus[57,58]. However, this is a drug with a narrow therapeutic window and many factors may influence its pharmacokinetic and pharmacodynamic profile. For adequate graft and patient survival it is of crucial importance to avoid both, under and over immunosuppression[59,60]. Tacrolimus is metabolized in liver by cytochrome P450 (CYP) isoforms CYP3A4 and CYP3A5[61]. The most important SNP in estimating the achieved tacrolimus plasma concentration is rs776746, also known as 6986A > G. Patients with GG genotype (also known as CYP3A5*3) are CYP3A5 non-expressors and achieve greater tacrolimus concentration than patients with A allele – CYP3A5 expressors (also known as CYP3A5*1)[62,63]. As CYP3A5 is not expressed only in the liver, but also in the intestine and kidney, both donor and recipient genotypes may influence tacrolimus metabolism and subsequently alter the drug dose-normalized concentration[59,63,64]. Recipient genotype appears to be more important in the early post-transplant period, and donor genotype in later post-transplant period[65].

Our search identified ten novel studies (Table 5). All studies determined the CYP3A5 6986A>G (rs776746) SNP confirming its key role and tried to determine contributory SNPs or to provide additional insight into CYP3A5 6986A>G effects. Liu *et al*[66] conducted GWAS study on 115 patients and identified several novel SNPs associated with tacrolimus concentration. In early post-transplant period the tacrolimus concentration was associated with donor FAM26F (rs1057192) and rs1927321 SNPs. These two SNPs together with preoperative creatinine concentration explained 22% of variation in tacrolimus concentration. In later post-transplant period the tacrolimus concentration was associated with donor CYP3A5 (rs776746), TELO2 (rs266762), ESYT1 (rs7980521), rs4903096, and also with recipient CYP3A5 (rs776746) and rs7828796. These six SNPs explained 47.8% of variation. Kato *et al*[67] showed that the variability of tacrolimus concentration caused by CYP3A5 6986A>G (rs776746) genotype can be diminished if the drug is applied intravenously instead of orally. Three studies aimed to identify other important CYPs polymorphisms. The first investigated 29 various SNPs and found two additional SNPs for CYP3A5 (rs4646450 CC genotype and rs15524 TT genotype) to be associated with increased tacrolimus concentration[65], while the second study indicated that rare CYP3A4 SNPs (CYP3A4*20 and CYP3A4*22) may additionally increase tacrolimus concentration[68]. The third study developed a population pharmacokinetic model and found recipient

ABCB1 rsl045642 (C3435T), but not CYP3A5 rs776746 (6986A>G) to be independently associated with tacrolimus metabolism. However, as data on donor CYP3A5 SNPs were not included into the model, conclusion should be taken cautiously[69].

CYP non-related SNPs may affect tacrolimus concentration indirectly by changing CYP expression. This was demonstrated by Ou *et al*[70] who showed that lower levels of tacrolimus in TLR9 rs352139 G allele patients were associated with higher CYP3A5 mRNA expression in the liver. Similarly, SUMO4 rs237025 AA genotype was shown to be independently associated with decreased tacrolimus concentration and also with higher CYP3A5 mRNA expression[71]. The association with decreased tacrolimus concentration independent on CYP3A5 genotype was found for the donor FMO3 SNPs (rs1800822 allele T and rs909530 allele T)[72] and also for the sixth complement component (recipient C6 rs9200 G allele and donor rs10052999 CC/TT genotype), but the exact mechanism remains to be investigated[73]. Deng *et al*[74] analyzed association between tacrolimus metabolism related SNPs and early renal injury and found that CYP3A5*3 was associated with the risk of early glomerular lesion, while CYP2C8*3 was associated with the risk of tubulointerstitial injury.

In summary the reviewed studies confirmed the dominant role of CYP3A5 rs776746, (6986A>G) polymorphism, but also identified few novel SNPs involved in tacrolimus metabolism which might be a promising tool to reduce variability in tacrolimus concentration.

CONCLUSION

Reviewed studies confirmed previously established SNP prognostic factors such as the PNPLA3 rs738409 for NAFLD development and the role of CYP3A5 rs776746 in tacrolimus metabolism. They also identified several novel SNPs, which have the potential to become useful predictors of ACR, NODM, NAFLD, HCC recurrence, and post-transplant tacrolimus concentration variability. However, as the studies were typically conducted in one center on relatively low-to-moderate number of patients, verification of the results in other centers is warranted to resolve these limitations. Furthermore, of 29 reviewed studies, 28 used gene candidate approach and only one implemented a GWAS approach. GWAS multicentric studies are needed to facilitate the development of personalized transplant medicine.

Table 5 Genes and their single nucleotide polymorphisms investigated in association with tacrolimus metabolism after liver transplantation

Ref.	Etiology/Population/N	Genes	Key points
Liu *et al*[66]	Various Eastern Asian 115	Recipient, donor GWAS, association found for: CYP3A5 (rs776746), TELO2 (rs266762), ESYT1 (rs7980521), FAM26F (rs1057192), chr14: 39860228 (rs4903096) chr9: 118304139 (rs1927321), chr8: 83368297 (rs7828796)	Donor FAM26F (rs1057192) and rs1927321 were associated with Tac concentration in recovery phase (first 2 wk) Donor CYP3A5 (rs776746), TELO2 (rs266762), ESYT1 (rs7980521) and rs4903096 were associated with Tac concentration in stabilizing phase (third to fourth post-transplantation week) Recipient CYP3A5 (rs776746) and rs7828796 were associated with Tac concentration in stabilizing phase (third to fourth post-transplantation week)
Ou *et al*[70]	Various Eastern Asian 297	Recipient, donor: CYP3A5 (rs776746)[1], TLR 1 (rs574361, rs4833095), TLR2 (rs4696480), TLR3 (rs5743316, rs3775291), TLR4 (rs1927907), TLR7 (rs3853839), TLR9 (rs187084, rs352139, rs5743836)	Donor and recipient CYP3A5*3 genotype were associated with increased Tac concentration Donor TLR9 rs352139 AA genotype and TLR4 rs1927907 GG genotype were associated with increased Tac concentration Patients with donor TLR9 rs352139 G allele had increased CYP3A5 mRNA expression in transplanted liver tissue No significant association was found for other eight SNPs
Deng *et al*[74]	Not stated Eastern Asian 136	Recipient: CYP3A5 (rs776746)[1], CYP2C8 (rs11572080), ABCB1 (rs1045642, rs1128503)	Association with early renal injury was monitored CYP3A5*3 was associated with the risk of early renal glomerular lesion CYP2C8*3 was associated with the risk of the tubulointerstitial injury No association between ABCB1 SNPs and renal injury
Kato *et al*[67]	Various Eastern Asian 61	Recipient, donor: CYP3A5 (rs776746)[1]	Differences between administration routes of Tac were investigated CYP3A5 genotype influenced Tac concentration when Tac was applied orally, but not when applied intravenously
Gómez-Bravo *et al*[68]	Not stated European 90	Recipient, donor: CYP3A4 [rs67666821 (CYP3A4*20), rs35599367 (CYP3A4*22)], CYP3A5 (rs776746)[1]	CYP3A5*3 genotype was associated with increased Tac concentration The presence of rare CYP3A4 SNPs (CYP3A4*20 and CYP3A4*22) in donor liver increases Tac plasma concentrations Recipient CYP3A4*22 is also associated with increased Tac concentration
Liu *et al*[65]	Not stated Eastern Asian 373	Recipient, donor: CYP2B6 (rs3745274), CYP3A4 (rs4646437), CYP3A5 (rs776746, rs15524, rs4646450, rs3800959)[1]	CYP3A5 rs776746 GG (CYP3A5*3), rs4646450 CC and rs15524 TT genotypes were associated with higher Tac concentrations In the short term both donor and recipient CYP3A5 genotype contributed equally, but later the donor genotype had greater effect No significant association for the remaining 5 SNPs was found, 13 other SNPs were determined, but excluded from analysis because of low MAF

Zhang *et al*[71]	Various	Recipient, donor: CYP3A5 (rs776746)[1], SUMO4 (rs237025)	Donor and recipient CYP3A5*3 genotype are associated with increased Tac concentration
	Eastern Asian 297		Donor SUMO4 rs237025 AA genotype was independently associated with decreased Tac concentration and with higher CYP3A5 mRNA expression
Chen *et al*[69]	Not stated Eastern Asian	Recipient: CYP3A5 (rs776746), ABCB1 (rs1128503, rs2032582, rsl045642)	In a population pharmacokinetic model recipient ABCB1 rsl045642 (C3435T) was independently associated with Tac pharmacokinetic
	125		As data on donor CYP3A5 (rs776746) were not included into the model conclusion should be taken cautiously
Ren *et al*[72]	Not stated	Recipient, donor: CYP3A5 (rs776746)[1], FMO3 (rs1800822, rs2266782, rs1736557, rs909530, rs2266780)	Donor and recipient CYP3A5*3 genotype were associated with increased Tac concentration
	Eastern Asian 110		Donor FMO3 rs1800822 allele T and rs909530 allele T were associated with decreased Tac concentration, independently on CYP3A5 genotype
Liao *et al*[73]	HCC	Recipient, donor: CYP3A5 (rs776746)[1], C6 (rs9200, rs10052999)	Donor and recipient CYP3A5*3 genotype were confirmed to be associated with greater Tac concentration
	Eastern Asian 135		Recipient C6 rs9200 G allele and donor rs10052999 CC/TT genotype were associated with decreased Tac concentration

[1]for CYP3A5 (rs776746) CYP3A5*3 denotes GG genotype, patients with that genotype are CYP3A5 non-expressors. ABCB1: ATP binding cassette subfamily B member 1; C6: Complement C6; CYP: Cytochrome P450; ESYT1: Extended synaptotagmin 1; FAM26F: Gene family with sequence similarity 26, member F; FMO3: Flavin containing monooxygenase 3; MAF: Minor allele frequency; SUMO4: Small ubiquitin like modifier 4; Tac: Tacrolimus; TELO2: Telomere maintenance 2; TLR: Toll like receptor.

REFERENCES

1   **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol* 2016; **64**: 433-485 [PMID: 26597456 DOI: 10.1016/j.jhep.2015.10.006]
2   **Neuberger JM**, Bechstein WO, Kuypers DR, Burra P, Citterio F, De Geest S, Duvoux C, Jardine AG, Kamar N, Krämer BK, Metselaar HJ, Nevens F, Pirenne J, Rodríguez-Perálvarez ML, Samuel D, Schneeberger S, Serón D, Trunečka P, Tisone G, van Gelder T. Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation* 2017; **101**: S1-S56 [PMID: 28328734 DOI: 10.1097/TP.0000000000001651]
3   **Levitsky J**, Goldberg D, Smith AR, Mansfield SA, Gillespie BW, Merion RM, Lok AS, Levy G, Kulik L, Abecassis M, Shaked A. Acute Rejection Increases Risk of Graft Failure and Death in Recent Liver Transplant Recipients. *Clin Gastroenterol Hepatol* 2017; **15**: 584-593.e2 [PMID: 27567694 DOI: 10.1016/j.cgh.2016.07.035]
4   **Wiesner RH**, Demetris AJ, Belle SH, Seaberg EC, Lake JR, Zetterman RK, Everhart J, Detre KM. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. *Hepatology* 1998; **28**: 638-645 [PMID: 9731552 DOI: 10.1002/hep.510280306]
5   **Rattanasiri S**, McDaniel DO, McEvoy M, Anothaisintawee T, Sobhonslidsuk A, Attia J, Thakkinstian A. The association between cytokine gene polymorphisms and graft rejection in liver transplantation: a systematic review and meta-analysis. *Transpl Immunol* 2013; **28**: 62-70 [PMID: 23104141 DOI: 10.1016/j.trim.2012.10.003]
6   **Zhang XX**, Bian RJ, Wang J, Zhang QY. Relationship between cytokine gene polymorphisms and acute rejection following liver transplantation. *Genet Mol Res* 2016; **15** [PMID: 27173241 DOI: 10.4238/gmr.15027599]
7   **Liu F**, Li B, Wang WT, Wei YG, Yan LN, Wen TF, Xu MQ, Yang JY. Interleukin-10-1082G/A polymorphism and acute liver graft rejection: a meta-analysis. *World J Gastroenterol* 2012; **18**: 847-854 [PMID: 22371646 DOI: 10.3748/wjg.v18.i8.847]
8   **Thude H**, Bischoff W, Sterneck M, Marget M, Nashan B, Koch M. Polymorphisms of the human platelet antigen-1, -2, -3, -5, and -15 systems and acute cellular liver transplant rejection. *Hum Immunol* 2017; **78**: 534-539 [PMID: 28705752 DOI: 10.1016/j.humimm.2017.07.004]
9   **Bitetto D**, Fabris C, Falleti E, Fornasiere E, Avellini C, Cmet S, Cussigh A, Fontanini E, Pirisi M, Corradini SG, Merli M, Molinaro A, Toniutto P. Recipient interleukin-28B Rs12979860 C/T polymorphism and acute cellular rejection after liver transplantation: role of the calcineurin inhibitor used. *Transplantation* 2012; **93**: 1038-1044 [PMID: 22495472 DOI: 10.1097/TP.0b013e31824df7f3]
10   **Fereidooni H**, Azarpira N, Yaghobi R, Vahdati A, Malek-Hoseini SA. Interleukin-28B rs12979860 C/T Polymorphism and Acute Cellular Rejection after Liver Transplantation. *Int J Organ Transplant Med*

2017; **8**: 28-33 [PMID: 28299025]

11   **Valero-Hervás DM**, Sánchez-Zapardiel E, Castro MJ, Gallego-Bustos F, Cambra F, Justo I, Laguna-Goya R, Jiménez-Romero C, Moreno E, López-Medrano F, San Juan R, Fernández-Ruiz M, Aguado JM, Paz-Artal E. Complement C3F allotype synthesized by liver recipient modifies transplantation outcome independently from donor hepatic C3. *Clin Transplant* 2017; **31** [PMID: 27801525 DOI: 10.1111/ctr.12866]

12   **Sun B**, Gao J, Shi W, Guo Y, Fan J, Zhang J, Li X, Liu G. The interleukin-17 G-197A polymorphism is associated with cyclosporine metabolism and transplant rejection in liver transplant recipients. *Pharmacogenomics* 2019; **20**: 447-456 [PMID: 30799725 DOI: 10.2217/pgs-2018-0198]

13   **Yu X**, Wei B, Su R, Yao J, Feng X, Jiang G, Xie H, Wu J, Xu X, Zhang M, Zheng S, Zhou L. A risk assessment model of acute liver allograft rejection by genetic polymorphism of CD276. *Mol Genet Genomic Med* 2019; **7**: e689 [PMID: 31044564 DOI: 10.1002/mgg3.689]

14   **Ostojic A**, Markotic A, Kelava T, Mrzljak A. Association between CXCL9/10 polymorphisms and acute rejection of liver allograft. *Medicine (Baltimore)* 2019; **98**: e14612 [PMID: 30813187 DOI: 10.1097/MD.0000000000014612]

15   **Thude H**, Rother S, Sterneck M, Klempnauer J, Nashan B, Schwinzer R, Koch M. The killer cell lectin-like receptor B1 (KLRB1) 503T>C polymorphism (rs1135816) and acute rejection after liver transplantation. *HLA* 2018; **91**: 52-55 [PMID: 29111570 DOI: 10.1111/tan.13172]

16   **Verma S**, Tanaka Y, Shimizu S, Tanimine N, Ohdan H. Significant association between *FOXP3* gene polymorphism and steroid-resistant acute rejection in living donor liver transplantation. *Hepatol Commun* 2017; **1**: 406-420 [PMID: 29404469 DOI: 10.1002/hep4.1052]

17   **Xu X**, Ling Q, He ZL, Gao F, Zheng SS. Post-transplant diabetes mellitus in liver transplantation: Hangzhou experience. *Hepatobiliary Pancreat Dis Int* 2008; **7**: 465-470 [PMID: 18842490]

18   **Samuelson AL**, Lee M, Kamal A, Keeffe EB, Ahmed A. Diabetes mellitus increases the risk of mortality following liver transplantation independent of MELD score. *Dig Dis Sci* 2010; **55**: 2089-2094 [PMID: 20467898 DOI: 10.1007/s10620-010-1267-5]

19   **Moon JI**, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG. Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: Long-term follow up. *Transplantation* 2006; **82**: 1625-1628 [PMID: 17198248 DOI: 10.1097/01.tp.0000250361.60415.96]

20   **Pageaux GP**, Faure S, Bouyabrine H, Bismuth M, Assenat E. Long-term outcomes of liver transplantation: diabetes mellitus. *Liver Transpl* 2009; **15** Suppl 2: S79-S82 [PMID: 19877023 DOI: 10.1002/lt.21913]

21   **Saliba F**, Lakehal M, Pageaux GP, Roche B, Vanlemmens C, Duvoux C, Dumortier J, Salamé E, Calmus Y, Maugendre D; Diapason Study Group. Risk factors for new-onset diabetes mellitus following liver transplantation and impact of hepatitis C infection: an observational multicenter study. *Liver Transpl* 2007; **13**: 136-144 [PMID: 17192854 DOI: 10.1002/lt.21010]

22   **Kuo HT**, Lum E, Martin P, Bunnapradist S. Effect of diabetes and acute rejection on liver transplant outcomes: An analysis of the organ procurement and transplantation network/united network for organ sharing database. *Liver Transpl* 2016; **22**: 796-804 [PMID: 26850091 DOI: 10.1002/lt.24414]

23   **Ling Q**, Xie H, Lu D, Wei X, Gao F, Zhou L, Xu X, Zheng S. Association between donor and recipient TCF7L2 gene polymorphisms and the risk of new-onset diabetes mellitus after liver transplantation in a Han Chinese population. *J Hepatol* 2013; **58**: 271-277 [PMID: 23041303 DOI: 10.1016/j.jhep.2012.09.025]

24   **Davidson J**, Wilkinson A, Dantal J, Dotta F, Haller H, Hernández D, Kasiske BL, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell M, van der Woude FJ, Wheeler DC; International Expert Panel. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation* 2003; **75**: SS3-S24 [PMID: 12775942 DOI: 10.1097/01.TP.0000069952.49242.3E]

25   **Husen P**, Straub K, Willuweit K, Hagemann A, Wedemeyer H, Bachmann HS, Herzer K. SNPs Within the MTOR Gene Are Associated With an Increased Risk of Developing De Novo Diabetes Mellitus Following the Administration of Everolimus in Liver Transplant Recipients. *Transplant Proc* 2019; **51**: 1962-1971 [PMID: 31303410 DOI: 10.1016/j.transproceed.2019.03.027]

26   **Cen C**, Fang HX, Yu SF, Liu JM, Liu YX, Zhou L, Yu J, Zheng SS. Association between ADIPOQ gene polymorphisms and the risk of new-onset diabetes mellitus after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2017; **16**: 602-609 [PMID: 29291779 DOI: 10.1016/S1499-3872(17)60069-9]

27   **Parvizi Z**, Azarpira N, Kohan L, Darai M, Kazemi K, Parvizi MM. Association between E23K variant in KCNJ11 gene and new-onset diabetes after liver transplantation. *Mol Biol Rep* 2014; **41**: 6063-6069 [PMID: 24996284 DOI: 10.1007/s11033-014-3483-0]

28   **Zhang T**, Liu Y, Hu Y, Zhang X, Zhong L, Fan J, Peng Z. Association of donor and recipient SUMO4 rs237025 genetic variant with new-onset diabetes mellitus after liver transplantation in a Chinese population. *Gene* 2017; **627**: 428-433 [PMID: 28689037 DOI: 10.1016/j.gene.2017.06.060]

29   **Li YY**, Wang H, Yang XX, Geng HY, Gong G, Kim HJ, Zhou YH, Wu JJ. *Small Ubiquitin-Like Modifier 4 (SUMO4)* Gene M55V Polymorphism and Type 2 Diabetes Mellitus: A Meta-analysis Including 6,823 Subjects. *Front Endocrinol (Lausanne)* 2017; **8**: 303 [PMID: 29163370 DOI: 10.3389/fendo.2017.00303]

30   **Underwood PC**, Sun B, Williams JS, Pojoga LH, Raby B, Lasky-Su J, Hunt S, Hopkins PN, Jeunemaitre X, Adler GK, Williams GH. The association of the angiotensinogen gene with insulin sensitivity in humans: a tagging single nucleotide polymorphism and haplotype approach. *Metabolism* 2011; **60**: 1150-1157 [PMID: 21306748 DOI: 10.1016/j.metabol.2010.12.009]

31   **Mottaghi S**, Azarpira N, Dehshahri A, Khalvati B, Namazi S. Evaluation of Angiotensinogen M235T and T174M Polymorphisms, Demographic and Clinical Factors in New-Onset Diabetes after Liver Transplantation in Iranian Patients. *Int J Organ Transplant Med* 2019; **10**: 137-147 [PMID: 31497276]

32   **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]

33   **Eslam M**, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. *J Hepatol* 2018; **68**: 268-279 [PMID: 29122391 DOI: 10.1016/j.jhep.2017.09.003]

34   **Kim WR**, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2016 Annual Data Report: Liver. *Am J Transplant* 2018; **18** Suppl 1: 172-253 [PMID: 29292603 DOI: 10.1111/ajt.14559]

35   **Goldberg D**, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, Charlton M. Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease

Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver Transplantation. *Gastroenterology* 2017; **152**: 1090-1099.e1 [PMID: 28088461 DOI: 10.1053/j.gastro.2017.01.003]

36 **Narayanan P**, Mara K, Izzy M, Dierkhising R, Heimbach J, Allen AM, Watt KD. Recurrent or De Novo Allograft Steatosis and Long-term Outcomes After Liver Transplantation. *Transplantation* 2019; **103**: e14-e21 [PMID: 29994981 DOI: 10.1097/TP.0000000000002317]

37 **Míková I**, Neřoldová M, Hubáček JA, Dlouhá D, Jirsa M, Honsová E, Sticová E, Lánská V, Špičák J, Trunečka P. Donor PNPLA3 and TM6SF2 Variant Alleles Confer Additive Risks for Graft Steatosis After Liver Transplantation. *Transplantation* 2020; **104**: 526-534 [PMID: 31356578 DOI: 10.1097/TP.0000000000002876]

38 **Trunečka P**, Míková I, Dlouhá D, Hubáček JA, Honsová E, Kolesár L, Lánská V, Fraňková S, Šperl J, Jirsa M, Poledne R. Donor PNPLA3 rs738409 genotype is a risk factor for graft steatosis. A post-transplant biopsy-based study. *Dig Liver Dis* 2018; **50**: 490-495 [PMID: 29396131 DOI: 10.1016/j.dld.2017.12.030]

39 **Kim H**, Lee KW, Lee K, Seo S, Park MY, Ahn SW, Hong SK, Yoon KC, Kim HS, Choi Y, Lee HW, Yi NJ, Suh KS. Effect of PNPLA3 I148M polymorphism on histologically proven non-alcoholic fatty liver disease in liver transplant recipients. *Hepatol Res* 2018; **48**: E162-E171 [PMID: 28718984 DOI: 10.1111/hepr.12940]

40 **John BV**, Aiken T, Garber A, Thomas D, Lopez R, Patil D, Konjeti VR, Fung JJ, McCollough AJ, Askar M. Recipient But Not Donor Adiponectin Polymorphisms Are Associated With Early Posttransplant Hepatic Steatosis in Patients Transplanted for Non-Nonalcoholic Fatty Liver Disease Indications. *Exp Clin Transplant* 2018; **16**: 439-445 [PMID: 29863454 DOI: 10.6002/ect.2018.0070]

41 **Dumortier J**, Giostra E, Belbouab S, Morard I, Guillaud O, Spahr L, Boillot O, Rubbia-Brandt L, Scoazec JY, Hadengue A. Non-alcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil". *Am J Gastroenterol* 2010; **105**: 613-620 [PMID: 20040915 DOI: 10.1038/ajg.2009.717]

42 **Global Burden of Disease Liver Cancer Collaboration**, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, Al-Raddadi R, Alvis-Guzman N, Amoako Y, Artaman A, Ayele TA, Barac A, Bensenor I, Berhane A, Bhutta Z, Castillo-Rivas J, Chitheer A, Choi JY, Cowie B, Dandona L, Dandona R, Dey S, Dicker D, Phuc H, Ekwueme DU, Zaki MS, Fischer F, Fürst T, Hancock J, Hay SI, Hotez P, Jee SH, Kasaeian A, Khader Y, Khang YH, Kumar A, Kutz M, Larson H, Lopez A, Lunevicius R, Malekzadeh R, McAlinden C, Meier T, Mendoza W, Mokdad A, Moradi-Lakeh M, Nagel G, Nguyen Q, Nguyen G, Ogbo F, Patton G, Pereira DM, Pourmalek F, Qorbani M, Radfar A, Roshandel G, Salomon JA, Sanabria J, Sartorius B, Satpathy M, Sawhney M, Sepanlou S, Shackelford K, Shore H, Sun J, Mengistu DT, Topór-Mądry R, Tran B, Ukwaja KN, Vlassov V, Vollset SE, Vos T, Wakayo T, Weiderpass E, Werdecker A, Yonemoto N, Younis M, Yu C, Zaidi Z, Zhu L, Murray CJL, Naghavi M, Fitzmaurice C. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. *JAMA Oncol* 2017; **3**: 1683-1691 [PMID: 28983565 DOI: 10.1001/jamaoncol.2017.3055]

43 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

44 **Yang JD**, Larson JJ, Watt KD, Allen AM, Wiesner RH, Gores GJ, Roberts LR, Heimbach JA, Leise MD. Hepatocellular Carcinoma Is the Most Common Indication for Liver Transplantation and Placement on the Waitlist in the United States. *Clin Gastroenterol Hepatol* 2017; **15**: 767-775.e3 [PMID: 28013117 DOI: 10.1016/j.cgh.2016.11.034]

45 **Verna EC**, Patel YA, Aggarwal A, Desai AP, Frenette C, Pillai AA, Salgia R, Seetharam A, Sharma P, Sherman C, Tsoulfas G, Yao FY. Liver transplantation for hepatocellular carcinoma: Management after the transplant. *Am J Transplant* 2020; **20**: 333-347 [PMID: 31710773 DOI: 10.1111/ajt.15697]

46 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

47 **Escartin A**, Sapisochin G, Bilbao I, Vilallonga R, Bueno J, Castells L, Dopazo C, Castro E, Caralt M, Balsells J. Recurrence of hepatocellular carcinoma after liver transplantation. *Transplant Proc* 2007; **39**: 2308-2310 [PMID: 17889173 DOI: 10.1016/j.transproceed.2007.06.042]

48 **Mazzaferro V**, Chun YS, Poon RT, Schwartz ME, Yao FY, Marsh JW, Bhoori S, Lee SG. Liver transplantation for hepatocellular carcinoma. *Ann Surg Oncol* 2008; **15**: 1001-1007 [PMID: 18236119 DOI: 10.1245/s10434-007-9559-5]

49 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]

50 **Fujiwara N**, Hoshida Y. Hepatocellular Carcinoma Risk Stratification by Genetic Profiling in Patients with Cirrhosis. *Semin Liver Dis* 2019; **39**: 153-162 [PMID: 30912093 DOI: 10.1055/s-0039-1681031]

51 **Wei J**, Sheng Y, Li J, Gao X, Ren N, Dong Q, Qin L. Genome-Wide Association Study Identifies a Genetic Prediction Model for Postoperative Survival in Patients with Hepatocellular Carcinoma. *Med Sci Monit* 2019; **25**: 2452-2478 [PMID: 30945699 DOI: 10.12659/MSM.915511]

52 **Zhang T**, Liu Y, Peng X, Fan J, Peng Z. Association between Recipient IL-15 Genetic Variant and the Prognosis of HBV-Related Hepatocellular Carcinoma after Liver Transplantation. *Dis Markers* 2017; **2017**: 1754696 [PMID: 29162948 DOI: 10.1155/2017/1754696]

53 **Shi G**, Wang C, Zhang P, Ji L, Xu S, Tan X, Li H. Donor Polymorphisms of Toll-like Receptor 4 rs1927914 Associated with the Risk of Hepatocellular Carcinoma Recurrence Following Liver Transplantation. *Arch Med Res* 2017; **48**: 553-560 [PMID: 29221801 DOI: 10.1016/j.arcmed.2017.11.011]

54 **de la Fuente S**, Citores MJ, Lucena JL, Muñoz P, Cuervas-Mons V. *TLR9*-1486C/T polymorphism is associated with hepatocellular carcinoma recurrence after liver transplantation. *Biomark Med* 2019; **13**: 995-1004 [PMID: 31317790 DOI: 10.2217/bmm-2019-0030]

55 **Minmin S**, Xiaoqian X, Hao C, Baiyong S, Xiaxing D, Junjie X, Xi Z, Jianquan Z, Songyao J. Single nucleotide polymorphisms of Toll-like receptor 4 decrease the risk of development of hepatocellular carcinoma. *PLoS One* 2011; **6**: e19466 [PMID: 21559380 DOI: 10.1371/journal.pone.0019466]

56 **Aravalli RN**. Role of innate immunity in the development of hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 7500-7514 [PMID: 24282342 DOI: 10.3748/wjg.v19.i43.7500]

57 **Moini M**, Schilsky ML, Tichy EM. Review on immunosuppression in liver transplantation. *World J Hepatol* 2015; **7**: 1355-1368 [PMID: 26052381 DOI: 10.4254/wjh.v7.i10.1355]

58   **Haddad EM**, McAlister VC, Renouf E, Malthaner R, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus for liver transplanted patients. *Cochrane Database Syst Rev* 2006; CD005161 [PMID: 17054241 DOI: 10.1002/14651858.CD005161.pub2]

59   **Staatz CE**, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet* 2004; **43**: 623-653 [PMID: 15244495 DOI: 10.2165/00003088-200443100-00001]

60   **de Jonge H**, Naesens M, Kuypers DR. New insights into the pharmacokinetics and pharmacodynamics of the calcineurin inhibitors and mycophenolic acid: possible consequences for therapeutic drug monitoring in solid organ transplantation. *Ther Drug Monit* 2009; **31**: 416-435 [PMID: 19536049 DOI: 10.1097/FTD.0b013e3181aa36cd]

61   **Hebert MF**. Contributions of hepatic and intestinal metabolism and P-glycoprotein to cyclosporine and tacrolimus oral drug delivery. *Adv Drug Deliv Rev* 1997; **27**: 201-214 [PMID: 10837558 DOI: 10.1016/s0169-409x(97)00043-4]

62   **Mourad M**, Wallemacq P, De Meyer M, Malaise J, De Pauw L, Eddour DC, Goffin E, Lerut J, Haufroid V. Biotransformation enzymes and drug transporters pharmacogenetics in relation to immunosuppressive drugs: impact on pharmacokinetics and clinical outcome. *Transplantation* 2008; **85**: S19-S24 [PMID: 18401258 DOI: 10.1097/TP.0b013e318169c380]

63   **Provenzani A**, Santeusanio A, Mathis E, Notarbartolo M, Labbozzetta M, Poma P, Provenzani A, Polidori C, Vizzini G, Polidori P, D'Alessandro N. Pharmacogenetic considerations for optimizing tacrolimus dosing in liver and kidney transplant patients. *World J Gastroenterol* 2013; **19**: 9156-9173 [PMID: 24409044 DOI: 10.3748/wjg.v19.i48.9156]

64   **Koch I**, Weil R, Wolbold R, Brockmöller J, Hustert E, Burk O, Nuessler A, Neuhaus P, Eichelbaum M, Zanger U, Wojnowski L. Interindividual variability and tissue-specificity in the expression of cytochrome P450 3A mRNA. *Drug Metab Dispos* 2002; **30**: 1108-1114 [PMID: 12228187 DOI: 10.1124/dmd.30.10.1108]

65   **Liu J**, Ouyang Y, Chen D, Yao B, Lin D, Li Z, Zang Y, Liu H, Fu X. Donor and recipient P450 gene polymorphisms influence individual pharmacological effects of tacrolimus in Chinese liver transplantation patients. *Int Immunopharmacol* 2018; **57**: 18-24 [PMID: 29454235 DOI: 10.1016/j.intimp.2018.02.005]

66   **Liu Y**, Zhang C, Li L, Ou B, Yuan L, Zhang T, Fan J, Peng Z. Genome-Wide Association Study of Tacrolimus Pharmacokinetics Identifies Novel Single Nucleotide Polymorphisms in the Convalescence and Stabilization Periods of Post-transplant Liver Function. *Front Genet* 2019; **10**: 528 [PMID: 31214251 DOI: 10.3389/fgene.2019.00528]

67   **Kato H**, Usui M, Muraki Y, Okuda M, Nakatani K, Hayasaki A, Ito T, Iizawa Y, Murata Y, Tanemura A, Kuriyama N, Azumi Y, Kishiwada M, Mizuno S, Sakurai H, Isaji S. Intravenous Administration of Tacrolimus Stabilizes Control of Blood Concentration Regardless of CYP3A5 Polymorphism in Living Donor Liver Transplantation: Comparison of Intravenous Infusion and Oral Administration in Early Postoperative Period. *Transplant Proc* 2018; **50**: 2684-2689 [PMID: 30401377 DOI: 10.1016/j.transproceed.2018.03.049]

68   **Gómez-Bravo MA**, Apellaniz-Ruiz M, Salcedo M, Fondevila C, Suarez F, Castellote J, Rufian S, Pons JA, Bilbao I, Alamo JM, Millán O, Brunet M, Rodríguez-Antona C. Influence of donor liver CYP3A4*20 loss-of-function genotype on tacrolimus pharmacokinetics in transplanted patients. *Pharmacogenet Genomics* 2018; **28**: 41-48 [PMID: 29256966 DOI: 10.1097/FPC.0000000000000321]

69   **Chen B**, Shi HQ, Liu XX, Zhang WX, Lu JQ, Xu BM, Chen H. Population pharmacokinetics and Bayesian estimation of tacrolimus exposure in Chinese liver transplant patients. *J Clin Pharm Ther* 2017; **42**: 679-688 [PMID: 28833329 DOI: 10.1111/jcpt.12599]

70   **Ou B**, Liu Y, Zhang T, Sun Y, Chen J, Peng Z. TLR9 rs352139 Genetic Variant Promotes Tacrolimus Elimination in Chinese Liver Transplant Patients During the Early Posttransplantation Period. *Pharmacotherapy* 2019; **39**: 67-76 [PMID: 30537010 DOI: 10.1002/phar.2204]

71   **Zhang T**, Liu Y, Zeng R, Ling Q, Wen P, Fan J, Peng Z. Association of donor small ubiquitin-like modifier 4 rs237025 genetic variant with tacrolimus elimination in the early period after liver transplantation. *Liver Int* 2018; **38**: 724-732 [PMID: 28941036 DOI: 10.1111/liv.13597]

72   **Ren L**, Teng M, Zhang T, Zhang X, Sun B, Qin S, Zhong L, Peng Z, Fan J. Donors FMO3 polymorphisms affect tacrolimus elimination in Chinese liver transplant patients. *Pharmacogenomics* 2017; **18**: 265-275 [PMID: 28084894 DOI: 10.2217/pgs-2016-0098]

73   **Liao JH**, Li CC, Wu SH, Fan JW, Gu HT, Wang ZW. Gene Variations of Sixth Complement Component Affecting Tacrolimus Metabolism in Patients with Liver Transplantation for Hepatocellular Carcinoma. *Chin Med J (Engl)* 2017; **130**: 1670-1676 [PMID: 28685716 DOI: 10.4103/0366-6999.209886]

74   **Deng R**, Liao Y, Li Y, Tang J. Association of CYP3A5, CYP2C8, and ABCB1 Polymorphisms With Early Renal Injury in Chinese Liver Transplant Recipients Receiving Tacrolimus. *Transplant Proc* 2018; **50**: 3258-3265 [PMID: 30577195 DOI: 10.1016/j.transproceed.2018.06.040]