DOI: 10.15825/1995-1191-2025-4-138-145

ASSOCIATION BETWEEN *TGFB1* RS1800469 POLYMORPHISM AND POST-TRANSPLANT COMPLICATIONS IN PEDIATRIC LIVER RECIPIENTS

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Objective: to evaluate the association between carriage of the rs1800469 polymorphism of the *TGFB1* gene and the risk of post-transplant complications, rejection episodes, and infectious diseases in pediatric liver recipients. **Materials and methods.** The study included 219 pediatric liver recipients (92 boys, 127 girls), aged 2.4 to 204 months (median 8 months). Indications for liver transplantation (LT) were end-stage liver failure resulting from congenital or acquired liver diseases. Genotyping of the *TGFB1* rs1800469 polymorphism was performed using real-time polymerase chain reaction (PCR) with TaqMan probes. **Results.** A comparative analysis of the allele frequency of rs1800469 of the *TGFB1* gene was performed in three groups of pediatric liver recipients: (1) with versus without post-transplant complications, (2) with versus without rejection episodes, and (3) with versus without infectious complications. In all groups, allele frequencies conformed to Hardy–Weinberg equilibrium ($p > 0.05$). No significant differences in rs1800469 variant distribution were observed between recipients with and without overall complications or between those with and without rejection episodes. However, marked differences emerged between recipients with and without infectious complications: the C/C genotype was 1.9 times less frequent ($p = 0.0102$), the C allele was 1.3 times less frequent ($p = 0.0175$), and the T allele was 1.4 times more frequent ($p = 0.0175$) in the infection group. Under a dominant inheritance model, carriers of the T allele (C/T + T/T) had 2.53-fold higher odds of infection compared with those with the homozygous C/C genotype in the group of recipients with infections than in those without ($p = 0.0077$). **Conclusion.** In pediatric liver transplant recipients, the *TGFB1* polymorphic variant rs1800469 is not associated with either a complicated post-transplant course or the occurrence of graft rejection episodes. However, carriers of the T allele appear to have an increased risk of infectious complications compared with those with the homozygous C/C genotype. These findings suggest that the rs1800469 T allele may serve as a genetic marker for increased susceptibility to infections and could be considered in strategies for prevention of complications and individualized adjustment of immunosuppressive therapy.

Keywords: congenital liver diseases, liver transplantation, TGFB1 rs1800469, infectious complications.

INTRODUCTION

Liver transplantation remains the only definitive treatment for young children with end-stage liver failure resulting from congenital or acquired liver disease. However, post-transplantation, a range of complications may occur, arising either from immunosuppressive therapy or the underlying disease. The occurrence and severity of these complications may, in many cases, depend on the recipient's genetic profile. Thus, identification of genetic markers that reflect individual patient characteristics could facilitate the prediction, prevention, and management of post-transplant complications.

Several studies, including our own, have demonstrated that in pediatric liver transplant (LT) recipients, blood levels of transforming growth factor-β1 (TGF-β1), a pleiotropic cytokine with profibrogenic and immunosuppressive properties, may be associated with graft status, particularly with the development of rejection or transplant dysfunction [1–3]. These observations suggest that TGF-β1 may serve as a potential prognostic biomarker for post-transplant complications. Nevertheless, the causal relationship between protein levels and complications remains unclear: high levels of the cytokine may represent both a cause and a consequence of fibrotic processes [4, 5]. Given the multifactorial regulation of TGF-β1 expression, it is plausible that individual genetic determinants influencing cytokine production contribute to the pathogenesis of post-transplant complications [6, 7].

In patients with various pathological conditions, including liver diseases, an association has been established between circulating levels of TGF-β1 and carriage of the polymorphic variant rs1800469 in the *TGFB1* gene

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[8, 9]. This single-nucleotide polymorphism (SNP), also known as C(–509)T, represents a cytosine-to-thymine substitution in the gene's promoter region and is thought to influence transcription factor binding affinity [10]. Reporter gene assays have demonstrated that promoter constructs containing cytosine at position –509 exhibit significantly higher transcriptional activity than those carrying thymine [8].

Several studies have suggested that the carriage of specific *TGFB1* polymorphic alleles may contribute to the development of post-transplant complications, including acute rejection, graft fibrosis, and renal dysfunction [11–13]. Furthermore, the role of TGFB1 gene polymorphisms has been investigated in the pathogenesis of infectious diseases such as hepatitis B and C, human papillomavirus (HPV), and COVID-19 [14–16].

In adult patients with liver cirrhosis secondary to hepatitis B or C infection, significant differences have been observed in the frequencies of rs1800469 and rs1800470 variants compared to healthy controls, suggesting that these polymorphisms may influence both susceptibility to viral infection and predisposition to cirrhosis [17–19]. However, the direction of association varies across studies: while the T allele at position –509 (rs1800469) is most frequently linked to increased risk [18–20], other reports have implicated the C allele [8, 17] or found no significant associations at all [21].

No studies investigating the role of *TGFB1* gene polymorphisms in the development of post-LT complications among pediatric liver recipients were found in the available literature. Our previous research demonstrated that in children who underwent liver transplantation for various congenital and acquired liver diseases, the frequencies of individual variants rs1800469, rs1800470, and rs1800471 did not differ significantly from those in healthy controls. However, rare haplotypes of these polymorphic loci were significantly more common in recipients [22]. Analysis of *TGFB1* polymorphic loci and their haplotypes in specific subgroups, such as patients with biliary atresia or histologically confirmed fibrosis of the explanted liver, revealed significant differences compared to healthy individuals [23, 24]. The high prevalence of rare allelic variants and haplotypes of the *TGFB1* gene in children with liver disease suggests their potential association not only with progression to liver failure but also with development of post-transplant complications.

The present study aims to evaluate the risk of post-transplant complications, including rejection episodes and infectious diseases, in pediatric LT recipients carrying the rs1800469 polymorphic variant of the TGFB1 gene.

MATERIALS AND METHODS

The study included 219 pediatric LT recipients aged 2.4 to 204 months (median age, 8 months), comprising 92 boys and 127 girls. The investigation was conducted in accordance with a protocol approved by the Local Ethics Committee, Shumakov National Medical Research Center of Transplantology and Artificial Organs (Moscow, Russia).

Indications for liver transplantation were end-stage liver failure resulting from liver diseases, such as biliary atresia (BA), biliary hypoplasia (BH), Alagille syndrome, Caroli syndrome, and Byler disease, as well as rarer disorders such as Crigler–Najjar syndrome, Gierke disease, alpha-1 antitrypsin deficiency, tyrosinemia, fulminant and autoimmune hepatitis, cryptogenic cirrhosis, and others.

After transplantation, patients received double- or triple-drug immunosuppressive therapy, which included tacrolimus, corticosteroids, and mycophenolate mofetil. Routine follow-up and management of recipients were performed in accordance with the clinical guidelines of the Russian Transplant Society and the institutional protocols at Shumakov National Medical Research Center of Transplantology and Artificial Organs.

During the first year following transplantation, recipients developed various complications, including immune, infectious, vascular, biliary, surgical, and other postoperative disorders. Immune complications comprised episodes of acute cellular and antibody-mediated rejection, diagnosed based on a combination of laboratory parameters (elevated serum transaminases and/or bilirubin levels) and clinical manifestations such as jaundice, acholic or hypocholic stools, and occasionally skin itching.

Infectious complications included bacterial intestinal infections leading to cholangitis, bacterial pneumonia, generalized sepsis with systemic inflammatory response syndrome (SIRS), peritonitis secondary to intestinal perforation or obstruction, and cytomegalovirus (CMV) infection.

Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Mini Kit on an automated QIAcube™ platform (Qiagen, Germany), following the manufacturer's instructions.

Genotyping of the TGFB1 rs1800469 polymorphism was performed by real-time polymerase chain reaction (PCR) using TaqMan® probes (Applied Biosystems, USA) on a CFX96™ real-time PCR detection system (Bio-Rad, USA), according to the manufacturer's instructions.

The TaqMan assay (Assay ID: C_8708473_10) identifies allelic variants at the G/A locus of rs1800469, which are complementary to the C/T nucleotides on the other DNA strand.

Data collection and statistical evaluation were performed using Microsoft Excel. Analysis of genotype and allele frequencies for the studied SNP, as well as assessment of the potential influence of genotype on clinical traits, were carried out using the SNPstats software [22].

The odds ratio (OR) and its 95% confidence interval (CI) were calculated to estimate the strength of associations.

Genotype frequencies were expressed as a percentage of individuals in the cohort, while allele frequencies were expressed as a percentage of chromosomes, according to the formula:

$$\text{Allele frequency} = \frac{(2 \times \text{number of homozygotes}) + \text{number of heterozygotes}}{2 \times \text{total number of individuals}}$$

A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1 presents the demographic and clinical characteristics of the pediatric LT recipients included in the study.

The majority of patients in the study cohort were children with congenital cholestatic liver diseases, the most common diagnosis being BA, which accounted for 48% of all cases. Three groups of LT recipients were analyzed: (1) with versus without post-transplant complications, (2) with versus without rejection episodes, and (3) with versus without infectious complications. In all examined groups, the distribution of rs1800469 alleles of the *TGFB1* gene was consistent with the Hardy–Weinberg equilibrium (p > 0.05).

To evaluate the potential association between post-transplant complications and the rs1800469 polymorphism of the *TGFB1* gene, a comparative analysis of genotype and allele frequencies was performed in pediatric LT recipients with complicated and uncomplicated postoperative courses (Fig. 1).

Table 1

Clinical and demographic characteristics of pediatric liver recipients

Characteristic	Value
Number of recipients, n	219
Age, median (range), months	8.4 (2.4–204)
Sex, number (%)	Male: 92 (42) Female: 127 (58)
Underlying disease, n (%)	219 (100)
BA	105 (48)
BH	24 (11)
Caroli syndrome	11 (5)
Alagille syndrome	10 (4.5)
Byler's disease	10 (4.5)
Others	59 (27)
Post-LT complications, n (%)	
Complication / No complication	131 (60) / 88 (40)
Rejection / No rejection	28 (13) / 191 (87)
Infections / No infections	52 (24) / 167 (76)

Abbreviations: BA, biliary atresia; BH, biliary hypoplasia; LT, liver transplant.

The analysis presented in Fig. 1 did not reveal any statistically significant differences in the frequencies of genotypes or alleles of the rs1800469 locus between pediatric LT recipients who developed complications and those who had an uneventful postoperative course during the first year after transplantation.

Fig. 2 shows the results of a comparative analysis of genotype and allele frequencies of the same locus in groups of recipients with and without graft rejections (labeled as "Rejection" and "No rejection" in the figure) during the first year following liver transplantation.

The results presented in Fig. 2 also showed no statistically significant differences in the frequencies of genotypes or alleles at the rs1800469 locus between recipients who experienced rejection episodes and those who did not.

A comparative analysis of genotype and allele frequencies at the rs1800469 polymorphic locus was further performed between groups of recipients with and without infectious complications that developed during the first year ppost-transplant (Fig. 3).

As shown in Fig. 3, statistically significant differences were observed in the distribution of genotypes and alleles of the rs1800469 locus between these two groups.

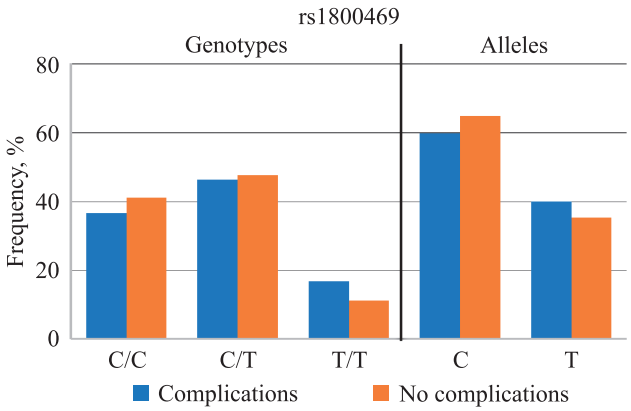

Fig. 1. Frequency of rs1800469 genotypes and alleles among recipients with and without complications

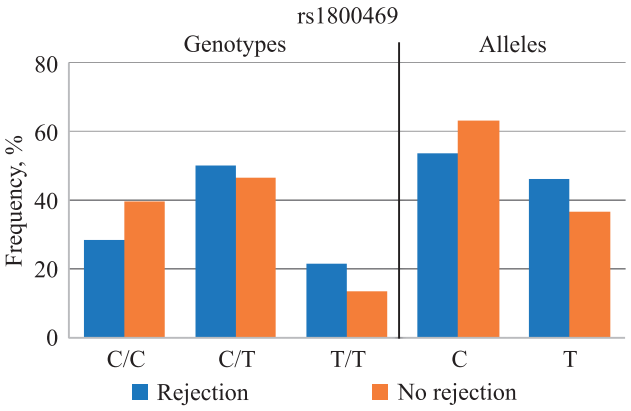

Fig. 2. Frequency of TGFB1 rs1800469 genotypes and alleles among recipients with and without graft rejection

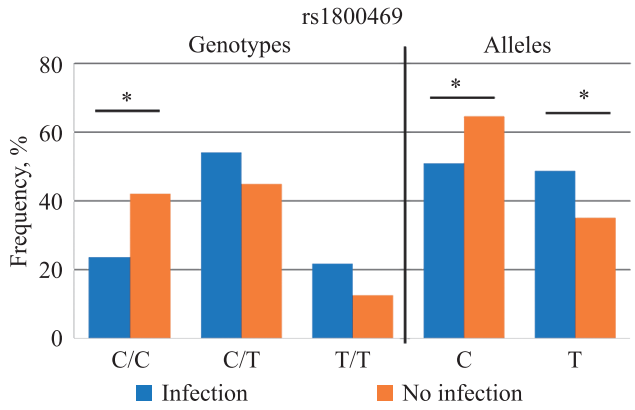

Fig. 3. Frequency of rs1800469 genotypes and alleles among recipients with and without infectious complications. * – $p < 0.05$

Table 2

Distribution of TGFB1 rs1800469 genotypes in gene–gene interaction models among liver recipients with infectious complications

Model	Genotype	Frequency, %		OR (95% CI)	p-value
		With infections	Without infections		
Codominant	C/C	23	43	Comparison group	0.028*
	C/T	58	44	**2.47 (1.17–5.19)**	
	T/T	19	13	**2.73 (1.04–7.16)**	
Dominant	C/C	23	43	Comparison group	0.0077*
	C/T + T/T	77	57	**2.53 (1.24–5.16)**	
Recessive	C/C + C/T	81	87	Comparison group	0.29
	T/T	19	13	1.57 (0.69–3.57)	
Overdominant	C/C + T/T	42	56	Comparison group	0.078
	C/T	58	44	1.76 (0.94–3.29)	

* – $p < 0.05$.

Among recipients with infectious complications, carriers of the homozygous C/C genotype were 1.9 times less frequent ($p = 0.0102$), the C allele was 1.3 times less frequent ($p = 0.0175$), and the T allele was 1.4 times more frequent ($p = 0.0175$) compared to recipients without infectious complications.

For a more detailed statistical assessment, the distribution of rs1800469 genotypes in recipients with and without infectious complications was analyzed under various models of allelic interaction (codominant, dominant, recessive, and overdominant). The corresponding genotype frequencies, odds ratios (ORs), and 95% confidence intervals (CIs) are summarized in Table 2.

As shown in Table 2, statistically significant differences were observed between groups with and without infectious complications under two genetic models. In the codominant model, the carrier frequency of the heterozygous C/T genotype was 2.47 times higher, and that of the homozygous T/T genotype was 2.73 times higher compared to the homozygous C/C variant. In the dominant model, carriers of the T allele (C/T + T/T) were 2.53 times more frequent than those with the C/C genotype in the compared recipient groups.

DISCUSSION

The development of post-transplant complications depends to a certain extent on the individual characteristics of the recipient's immune system. It is possible that the rs1800469 polymorphic locus of the *TGFB1* gene may serve as a potential genetic marker of predisposition to such complications.

In this study, we analyzed the distribution of genotypes at SNP rs1800469 among pediatric liver recipients with various types of post-transplant complications, identified a statistically significant association with infectious complications, and calculated the relative chance of their development in carriers of different variants of the *TGFB1* gene.

In the group of pediatric LT recipients who developed serious complications within the first year after transplantation, the frequencies of genotypes and alleles of the rs1800469 polymorphism of the *TGFB1* gene did not differ significantly from those observed in recipients with a favorable postoperative course. Some of the complications recorded – such as surgical, biliary, or vascular – are unlikely to be associated with immune mechanisms or with the activity of the cytokine TGF-β1. Therefore, the absence of a general association between the carriage of *TGFB1* polymorphic variants and the overall incidence of complications appears reasonable. Nonetheless, several studies have reported associations between *TGFB1* polymorphisms and broader clinical outcomes, including post-transplant survival after heart transplantation [25] and overall survival in hematopoietic stem cell recipients [26]. It is possible that in these cases, the observed relationships reflect, at least in part, the influence of cytokine TGF-β1 levels on the studied outcomes.

In the subgroup of pediatric liver recipients who developed acute rejection episodes, no statistically significant differences were found in the distribution of *TGFB1* polymorphic alleles compared with recipients without rejection. As noted in the introduction, there are currently no published data on the role of *TGFB1* polymorphism in the development of rejection following liver transplantation in children. However, in adult solid-organ recipients, several studies have demonstrated an association

between polymorphic variants of this cytokine gene and the incidence of rejection [11, 25]. Our previous study similarly found no significant association between circulating TGF-β1 levels and rejection episodes in pediatric liver recipients [3]. It is known that rejection occurs less frequently in pediatric liver recipients than in adults; therefore, the relatively small number of recipients with rejection episodes in this study (n = 28) may have limited the statistical power to detect genetic differences. It is also possible that the role of *TGFB1* polymorphic loci in the development of rejection may depend on factors such as the type of transplanted organ, recipient age, and ethnic background.

This study revealed a link between *TGFB1* polymorphism and the risk of developing post-LT infectious complications in children. Specifically, carriers of the T allele (C/T + T/T) of rs1800469 were found to develop infectious complications 2.5 times more frequently than recipients with the C/C genotype. Notably, in our previous study, no significant association was observed between circulating TGF-β1 levels measured before transplantation, and at one month and one year post-transplant, and the frequency of post-transplant infectious complications [3]. This finding may suggest that the genetic marker provides a more stable and sensitive indicator of susceptibility than the protein marker, whose concentration can be influenced by numerous environmental factors.

To our knowledge, no previous studies have investigated the role of TGFB1 genetic polymorphism in the development of infectious complications after liver transplantation in either pediatric or adult recipients. However, studies in adult patients with liver cirrhosis resulting from hepatitis B or C virus infection have shown that the presence of the T allele of rs1800469 is associated with an increased risk of infection in several populations [8, 18, 19]. In addition, these studies show that infected patients had higher levels of cytokine in their blood. Thus, our data, showing a higher incidence of infectious complications in carriers of the T allele, are broadly consistent with previous findings. Nevertheless, some reports have failed to identify significant differences in TGFB1 rs1800469 distribution between patients with infectious hepatitis and healthy controls [21, 27], which may be due to differences in study design and ethnic origin of the cohorts.

The findings of this study indicate that the rs1800469 polymorphism in the *TGFB1* gene in pediatric LT recipients is not associated with an unfavorable post-transplant course or an increased risk of graft rejection. However, carriage of this variant may be linked to the risk of developing infectious complications after liver transplantation. These results suggest that the rs1800469 locus could serve as a potential genetic marker for predicting post-transplant infectious complications in children and for optimizing immunosuppressive therapy to prevent infectious diseases. Further research is warranted to assess the prognostic value of the *TGFB1* rs1800469 polymorphism as a marker of infection risk and its possible relationship with individualized immunosuppressant requirements.

CONCLUSION

The risk of post-transplant complications may be influenced by both the expression level of the cytokine TGF-β1 and its genetic polymorphism. Analysis of the rs1800469 locus in the TGFB1 gene in pediatric liver recipients revealed no association between this variant and an overall complicated postoperative course or episodes of graft rejection. However, the odds ratio for carriers of the T allele (C/T + T/T genotypes) was 2.5 times higher than for carriers of the homozygous C/C genotype among recipients who developed infectious complications compared to those without infections. These findings suggest that carriage of the T allele of rs1800469 may increase susceptibility to post-transplant infections. This locus may therefore serve as a potential genetic marker for identifying patients at increased risk of infectious complications and for guiding individualized immunosuppressive therapy.

The authors declare no conflict of interest.

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The article was submitted to the journal on 29.07.2025