



Impact of SLC01B3 Polymorphisms on Clinical Outcomes in Lung Allograft Recipients Receiving Mycophenolic Acid

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Abstract

Single nucleotide polymorphisms (SNPs) in genes involved in mycophenolic acid (MPA) metabolism have been shown to contribute to variable MPA exposure, but their clinical effects are unclear. We aimed to determine if SNPs in key genes in MPA metabolism affect outcomes after lung transplantation. We performed a retrospective cohort study of 275 lung transplant recipients, 228 receiving mycophenolic acid and a control group of 47 receiving azathioprine. Six SNPs known to regulate MPA exposure from the SLCO, UGT and MRP2 families were genotyped. Primary outcome was one-year survival. Secondary outcomes were 3-year survival, nonminimal (A2 or B2) acute rejection, and chronic lung allograft dysfunction (CLAD). Statistical analyses included time-to-event Kaplan Meier with log-rank test and Cox regression modeling. We found that SLC01B3 SNPs rs4149117 and rs7311358 were associated with decreased one-year survival [rs7311358 HR 7.76 (1.37–44.04), p=0.021; rs4149117 HR 7.28 (1.27–41.78), p=0.026], increased risk for nonminimal acute rejection [rs4149117 TT334/T334G: OR 2.01(1.06–3.81), p=0.031; rs7311358 GG699/G699A: OR 2.18(1.13–4.21) p=0.019] and lower survival through three years for MPA patients but not for azathioprine patients. MPA carriers of either SLC01B3

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CONFLICT OF INTEREST

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SNP had shorter survival after CLAD diagnosis (rs4149117 $p=0.048$, rs7311358 $p=0.023$). For the MPA patients, Cox regression modelling demonstrated that both SNPs remained independent risk factors for death. We conclude that hypofunctional SNPs in the SLCO1B3 gene are associated with an increased risk for acute rejection and allograft failure in lung transplant recipients treated with MPA.

INTRODUCTION

Lung transplantation has become the definitive treatment for select patients with a variety of end-stage lung diseases. However, compared to other solid organ transplant recipients, lung transplantation portends a shorter life expectancy with a median survival between 5.5–6 years¹. Despite advances in surgical technique and medical management, this overall survival has only slightly improved in the past 10 years. The limiting factor in survival continues to be the development of chronic lung allograft dysfunction (CLAD), which include bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). The current immunosuppression strategy is a three-drug regimen consisting of a calcineurin inhibitor (CNI), an anti-proliferative agent and glucocorticoids. Mycophenolic acid (MPA) has largely replaced azathioprine (AZA) as the anti-proliferative drug of choice with two-thirds of lung recipients receiving as part of maintenance immunosuppression following transplant¹. This occurred primarily due to studies demonstrating a decreased incidence of acute rejection and bronchiolitis obliterans as well as a potential survival benefit^{2, 3}. MPA inhibits inosine monophosphate dehydrogenases (IMPDH1 and IMPDH2), which controls the rate limiting step for guanine monophosphate synthesis in the *de novo* pathway of purine synthesis used to drive lymphocyte proliferation⁴. It is given in one of two forms: the prodrug mycophenolate mofetil and mycophenolate sodium. Currently, patients receive a predetermined starting dose of mycophenolate mofetil that varies by institution, though usually between 2 to 3 grams per day. However, it is unknown whether variations in mycophenolate metabolism affect outcomes of lung transplant recipients.

Mycophenolic acid dose adjustments are primarily made in reaction to changes in clinical status such as leukopenia or infection with no therapeutic drug monitoring. Although MPA therapeutic drug monitoring is not currently routine in the clinical setting, several studies have evaluated MPA exposure by determining the area under the curve from 0–12 hours (AUC_{0-12}) for non-lung solid organ transplant recipients^{5, 6}. These studies and others have demonstrated that MPA levels vary widely between individuals⁷. The importance of this variability is underscored by studies in renal and cardiac transplantation that demonstrate an association between lower MPA levels and rejection, indicating a deleterious effect of suboptimal dosing on post-transplant outcomes^{8–10}.

MPA exposure is regulated by two main pathways (Figure 1). Gut esterases initialize metabolism of the prodrug mycophenolate mofetil or mycophenolate sodium into MPA, accounting for approximately 60% of the total MPA accumulation in the peripheral blood. The remaining amount of MPA is converted by the Uridine 5'-diphospho-glucuronosyltransferase (UGT) family of proteins (UGT1A8, 1A9, 1A10, 2B7) into an inactive metabolite, mycophenolic acid glucuronide (MPAG), and a minor metabolite, acyl-

mycophenolic acid glucuronide (Ac-MPAG). Ac-MPAG is biologically active¹¹, but is produced in such small quantities that it has a minor impact on overall MPA effect, mainly in relation to adverse drug effects^{12–14}. MPAG is the substrate for the remaining bulk of MPA exposure. This is regulated by MPAG uptake into the liver by the family of solute carrier organic anion (SLCO) transporters, where it is incorporated into the bile, excreted back into the intestines via the multidrug resistance associated protein 2 (MRP2, formerly ATP Binding Cassette Subfamily C Member or ABCC2) and converted back to MPA through metabolism by gut bacteria¹⁵. This second-pass enterohepatic recirculation is responsible for up to 40% of overall MPA exposure^{16–18}.

Several SNPs have been linked to variations in the transport and metabolism of MPA^{19, 20}. In renal transplantation, SNPs in the UGT family and the SLCO family of membrane transporters have been shown to correlate with MPA exposure^{21–23}. In lung transplantation, one study demonstrated an association between hypofunctional SNPs and a decrease in the measured MPA AUC but clinical outcomes were not examined²⁴. A different group found an association between hypofunctional SNPs in the MRP2 gene and persistent acute rejection but did not correlate this with MPA levels, nor with long-term outcomes²⁵. Here, we evaluated how the presence of SNPs leading to functional variants of the UGT, SLCO and ABCC2 proteins impacted clinical outcomes post-lung transplantation.

PATIENTS AND METHODS

Study Design, Patient Selection and Data Collection

We conducted a single-center retrospective cohort study of adult primary lung transplant recipients between 2008 and 2013 who had been previously enrolled in our recipient genetic database. Patients were excluded based on death within 30 days of lung transplantation, multi-organ recipients, age <18years at time of transplantation, transplantation at a different center and subsequent transfer of care, or if they were unable to provide a DNA sample. The cohort was divided into two groups based on the anti-metabolite agent they received for immunosuppression during the first post-transplant year, ‘Mycophenolate’ or ‘Azathioprine’. The primary outcome was survival at one-year post-transplant. Secondary outcomes were development of nonminimal (A2 or B2) acute cellular rejection (ACR) or lymphocytic bronchiolitis (LB), development of CLAD and 3-year survival. CLAD was defined, as previously described, as a drop of 20% or more in either forced expiratory volume in one second (FEV1) or Forced Vital Capacity (FVC) measured on two separate occasions at least three weeks apart in the absence of acute rejection or infection²⁶.

Data collected in the retrospective genetic database included recipient and donor demographic variables, transplant surgery details, including ischemic time and use of cardiopulmonary bypass, immunosuppression through the first post-transplant year, episodes of acute rejection and date and cause of death. Data were collected through December 2016 and maintained in a secure REDCap database. Informed consent was obtained from each patient prior to enrollment in the study. The study protocol was approved with waiver of informed consent by the Institutional Review Board of Washington University in Saint Louis (IRB #201105421).

Immunosuppression Regimen

During the study period, all patients were maintained on a 3-drug immunosuppression regimen consisting of a calcineurin inhibitor, an anti-proliferative and a corticosteroid. Induction immunosuppression consisted of a single dose of 20mg of intravenous basiliximab on days 0 and 4 post-transplant and 1 gram of intravenous methylprednisolone given intraoperatively. The calcineurin inhibitor of choice was tacrolimus. Patients were maintained on tacrolimus with a trough goal of 7–10mcg/ml in the initial year following transplantation and 4–7mcg/ml subsequently. Patients with renal dysfunction had a trough goal of 3–5mcg/ml. Patients were started on their anti-proliferative agent on post-operative day 0, with it being administered intravenously until the patient was capable of taking oral medications. The study period spans a time during which the antiproliferative agent of choice transitioned from azathioprine to mycophenolate owing to studies indicating potentially improved outcomes with mycophenolate compared to azathioprine in the late 2000s^{2, 3}. The standard starting dose of mycophenolate mofetil, the anti-proliferative agent of choice at our institution during most of the study period, was 1 gram twice daily, with adjustments made at the discretion of the treating transplant pulmonologist. Corticosteroid dosing was determined according to protocol which consisted of initial dose of 0.5mg/kg of methylprednisolone twice daily x6 doses after which patients were switched to prednisone 0.5mg/kg daily (maximum of 40mg) with a preset taper down to 5mg by six months post-transplant. Immunosuppression changes due to changes in clinical status or adverse drug effects were made at the discretion of the treating transplant pulmonologist.

DNA Collection and Identification of SNPs

Saliva samples from each lung transplant recipient were collected using the OGR-500 collection kit (DNA Genotek, Ottawa, ON, Canada). The median time to DNA collection was 144 days (range 9–1417 days) after transplantation. Genotyping was accomplished using a TaqMan® single tube genotyping assay using allelic specific primers (Life Technologies, Foster City, CA) for indicated SNPs. Allelic PCR results were analyzed using Taqman Genotyper v1.0.1 (Life Technologies) reported by DNA Genotek and entered into the REDCap database at Washington University.

Statistical Analysis

Baseline demographic and clinical variables are expressed as means with standard deviations or medians with interquartile for normal and nonnormally distributed continuous variables, respectively, and as percentages for categorical variables. Comparison of continuous demographic and clinical variables were made using the student's t test or Wilcoxon test, depending on the results of tests of normality. Categorical variables were analyzed using the Pearson chi-square test. Survival analysis was conducted using the Kaplan-Meier curve with the log-rank test for equality of survivors. Multivariable survival modelling was performed using a backwards stepwise Cox regression analysis with inclusion of all baseline clinical and demographic variables with $p < 0.25$ or those deemed clinically significant based on prior knowledge. Diagnostics were performed to ensure proportional hazards assumptions were met. Results were considered significant with a two-sided p-value < 0.05 . All statistical

analyses were performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY.).

RESULTS

Patient Population and SNP Genotypes

Of the 504 patients transplanted during the study period, 278 patients participated in the DNA database and were eligible for enrollment in this study (Figure 2). 228 (82.0%) of these patients were maintained on MPA through at least the first post-transplant year and 47 (16.9%) were maintained on azathioprine. SNPs in genes with known relevance to MPA metabolism were analyzed, including, UGT1A8, UGT1A9, MRP2, SLCO1B1 and SLCO1B3. The genotype frequencies of these SNPs within our cohort are outlined in Table 1. All SNPs were found to be in Hardy-Weinberg equilibrium with a p-value >0.05 for observed vs. predicted frequencies.

SNPs in the UGT superfamily and MRP2 gene were not significantly associated with primary or secondary endpoints in either the Mycophenolate or Azathioprine group. The two SNPs in the SLCO1B3 gene, rs4149117 and rs7311358, were found to be significant among the Mycophenolate group, but not among the Azathioprine group. Tables 2 and 3 show baseline demographic and clinical variables for these SNPs among the respective groups. For both SNPs, a significantly larger number of patients with the variant allele in the Mycophenolate group were female and non-white. Additionally, for the Mycophenolate group, there was no difference in administered MPA dose between groups at 1, 6- and 12-months post-transplant. SNPs for both rs4149117 and rs7311358 were more common in the azathioprine group than in the mycophenolate group, but this did not reach statistical significance (rs 7311358: 33.3% vs. 24.5%, $p=0.167$; rs4149117: 33.3% vs. 24.8%, $p=0.235$)

Survival

The primary outcome of one-year survival was significantly decreased in Mycophenolate patients carrying at least one copy of the SNP in both rs4149117 (334TT/TG, Figure 3A, $p=0.040$) and rs7311358 (699GG/GA, figure 3B, $p=0.030$). This difference persisted through two years, although it was no longer statistically significant at three years for either rs4149117 ($p=0.14$) or rs7311358 ($p=0.08$). This difference was not identified in Azathioprine patients (1yr: $p=0.163$; 2yr: $p=0.235$; 3yr: $p=0.366$, K-M curves not shown). For the Mycophenolate group, Cox regression modelling demonstrated that rs4149117 remained an independent risk factor for death through two years, while rs7311358 remained an independent risk factor through three years (Table 4). Additionally, having had no episodes of acute rejection within the first year was protective against death at one year. Finally, use of cyclosporine appeared to be associated with increased risk of death at one year when compared to tacrolimus, although limited sampling size calls for caution in interpreting this result.

Acute Rejection

Overall, there was no significant difference in acute cellular rejection in patients in Mycophenolate vs. Azathioprine groups (62% vs. 71%, OR 0.64(0.33–1.24), $p=0.183$). We did find a significantly increased incidence of nonminimal acute rejection within the first post-transplant year for Mycophenolate patients with at least one copy of either SNP. Patients with the rs4149117 SNP were at a 2-fold increased risk of developing nonminimal acute rejection (OR 2.01, 1.06–3.81, $p=0.031$). Likewise, patients with the rs7311358 SNP were at similar increased risk (OR 2.18, 1.13–4.21, $p=0.019$). Azathioprine patients had no significant difference in nonminimal acute rejection for either rs4149117 or rs7311358 genotypes ($p=0.429$). Additionally, the time to first episode of nonminimal acute rejection was shorter for Mycophenolate group with at least one copy of either rs4149117 or rs7311358 SNPs (Figure 4). It was not significantly different for the Azathioprine group (data not shown).

CLAD

In total, 131 of 228 (57.5%) Mycophenolate patients and 23 of 47 (48.9%) Azathioprine patients developed CLAD during the follow up period. Overall, the median time to diagnosis of CLAD was 30.4 months (IQR 14.9–64.3). Interestingly, Mycophenolate patients without the SNPs had a higher rate of CLAD during the study follow up period for both rs4149117 (64% vs 48.1%, $p=0.039$) and rs7311358 (63.3% vs 49%, $p=0.070$). However, of the Mycophenolate patients diagnosed with CLAD, those with at least one copy of either SNP had a shorter survival after diagnosis of CLAD (Figure 5). In addition, of those Mycophenolate patients diagnosed with CLAD at any point, overall post-transplant survival was significantly decreased in patients who carried either of the SNPs (Figure 6). Among Azathioprine patients, there was no difference in either development of CLAD or survival after CLAD based on SNP genotype.

Influence of Calcineurin Inhibitor Use

Given that the type of calcineurin inhibitor used was associated with measured outcomes both in our cohort and that the small sample size precludes subgroup analysis based on calcineurin inhibitor type, we performed sensitivity analyses excluding those patients not maintained on tacrolimus. We found consistent survival outcomes with both SNPs as previously noted. Mycophenolate patients with the SNPs demonstrated decreased survival (Supplemental Figure S1, Supplemental Table S1) and Azathioprine patients with SNPs demonstrated no significant difference in survival when compared to patients without the SNPs. Additionally, we found that the difference in time to first episode of nonminimal ACR remained significant for Mycophenolate patients (Supplemental Figure S2) and insignificant for Azathioprine patients.

DISCUSSION

Our data demonstrate that SNPs in the *SLCO1B3* gene are significantly associated with nonminimal acute rejection and graft survival in lung transplant recipients receiving mycophenolic acid, but not azathioprine for immunosuppression. Specifically, we found that patients with the wildtype (334GG and 699AA) genotypes in the *SLCO1B3* gene had

significantly better graft survival than patients with at least one copy of either SNP (TT334/T334G or GG699/G699A). This was most pronounced during the first post-transplant year but persisted through three years of follow up. The difference in early post-transplant survival has a potentially profound impact on overall survival post-transplant since we know from prior data that while the median survival for lung transplant patients overall is about 6 years, it is significantly longer in patients who survive the first year¹.

This study is, to our knowledge, the first to provide evidence of a link between hypofunctional polymorphisms in the *SLCO1B3* gene and both acute rejection and graft failure in lung transplant recipients receiving mycophenolic acid. Although it may not be surprising that patients with hypofunctional SNPs are at an increased risk of high grade acute rejection, research into which specific mutations are linked to poor outcomes remains limited²⁵. It has previously been demonstrated that inadequate immunosuppression is independently associated with development of nonminimal acute cellular rejection^{27, 28}. Furthermore, many prior studies have demonstrated that nonminimal acute rejection is associated both with the development of BOS and with graft survival^{29–33}. Therefore, the increased rates of nonminimal acute rejection among patients who carry the SNPs is one plausible explanation for their decreased graft survival.

An interesting finding was that patients who did not carry the SNPs actually had an increased rate of development of CLAD, despite having better survival. One explanation for this finding is that nonminimal acute cellular rejection is usually treated with augmented immunosuppression, i.e. high-dose systemic steroids, increased maintenance immunosuppression and, possibly, antithymocyte globulin therapy. This augmentation in immunosuppression can decrease the risk of further rejection and might explain why patients with nonminimal acute rejection had lower rates of CLAD^{34–36}. Another consideration is that MPA-induced airway damage might depend on SNP-related differences in cellular MPA metabolism. Indeed, a recent study demonstrated that MPA can be toxic and lead to loss of integrity in airway epithelial cells in a dose-dependent manner³⁷. Patients with these hypofunctional *SLCO1B3* SNPs may be protected from this MPA-induced airway injury due to lower MPA serum levels. Further investigation regarding the impact of these SNPs on epithelial biology, including recipient versus donor tissues, are needed.

The *SLCO1B3* gene is part of a family of soluble organic anion transporters. Its influence on MPA pharmacokinetics has been previously examined in renal transplantation. In a pharmacokinetic analysis of 70 renal transplant recipients receiving MPA with either tacrolimus or sirolimus, Picard et al found that 334GG patients had lower exposure to MPA when compared to TT334 or T334G patients, but similar exposure to MPAG. It was concluded that the 334GG patients had decreased exposure to MPA because of decreased uptake of MPAG and subsequent decreased enterohepatic circulation³⁸. However, MPAG serum levels were no different between the two groups, which makes their conclusions questionable. Conversely, in a study of 87 renal transplant recipients, Miura et al found that patients with the 334GG and 699AA genotype had significantly higher MPA AUC_{6–12} compared with TT334/GG699 and T334G/G699A patients²². Those 334GG/699AA patients also tended to have higher MPA AUC_{0–12}, although this did not reach statistical significance. This means 334GG/699AA patients had higher measured levels of MPA over the course of

12 hours, leading to an increased exposure to MPA. They concluded that this increased late MPA exposure is indicative of increased MPAG uptake and increased enterohepatic circulation in those with 334GG/699AA. This conclusion is also supported by a study showing that the 334GG and 699AA genotypes were associated with increased SLCO1B3 activity³⁹. Unfortunately, neither of these studies put their findings in context of clinical outcomes. The current study attempts to fill that gap in knowledge by evaluating the clinical consequences of these SNPs. Indeed, our findings that TT334/GG699 and T334G/G699A patients have decreased survival and higher rates of acute rejection are supportive of the aforementioned pharmacokinetic studies demonstrating these patients have decreased exposure to MPA given the same dose as those without the polymorphisms.

The current study has several limitations. The first is the retrospective nature of the study. There is an inherent selection bias for patients who survived long enough to provide DNA samples, sometimes months or even years after transplant. However, this might have served to diminish the observed impact of these SNPs in patients who developed graft failure before enrollment into the study. Additionally, nuanced changes in some clinical variables, such as alterations to immunosuppression agent selection beyond the first year or initiation of azithromycin for attenuation of CLAD, were not available in the database. Although the retrospective nature of the study precluded the collection of and direct correlation with pharmacokinetic data in this cohort, we were able to demonstrate that MPA dose at several time points in the first post-transplant year were not significantly different among the groups ruling out the possibility that the differences we observed were due to actual differences in MPA dose. Finally, the pharmacodynamics of MPA must be considered given the variable activity of its target, inosine monophosphate dehydrogenase (IMPDH). Earlier reports have shown that IMPDH activity varies among transplant recipients⁴⁰⁻⁴³ and polymorphisms in IMPDH can alter MPA effectiveness⁴⁴⁻⁴⁸. There is also some evidence that MPA exposure itself can alter IMPDH expression^{49, 50}. We did not account for these pharmacodynamics differences in the current study. Despite these limitations, this study provides new evidence to suggest a critical link between a gene involved in MPA pharmacokinetics and early graft failure.

Overall MPA exposure and effectiveness is likely regulated by the complex interplay of genetic, pharmacokinetic and pharmacodynamic factors. Nevertheless, the current study provides evidence that the interplay of these factors has a significant impact on clinical outcomes. Further study is needed to further elucidate the role of pharmacogenetics in MPA metabolism and translate those findings into better clinical practice, more individualized medication regimens and, hopefully, improved outcomes in lung transplant patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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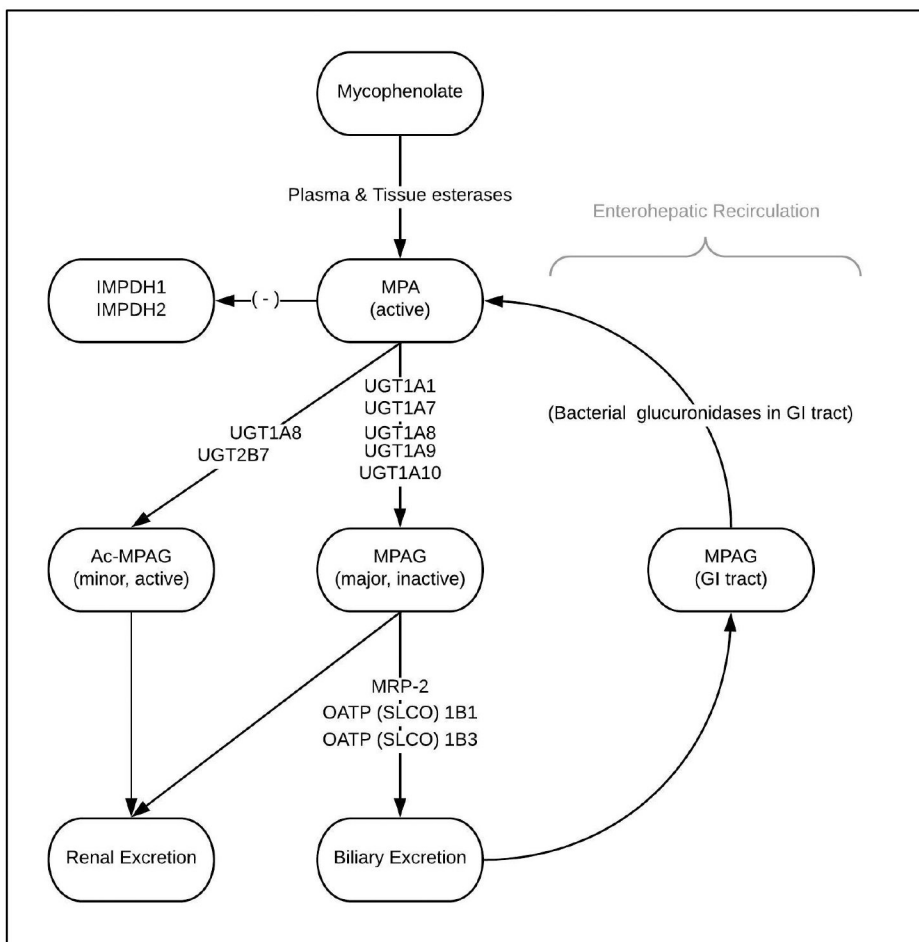


Figure 1: Metabolic pathway of MPA. The salt mycophenolate mofetil is rapidly hydrolyzed by plasma and tissue esterases into the active form MPA. The UGT superfamily then converts MPA to either AcMPAG, an active minor metabolite, or MPAG, an inactive major metabolite. SLCO1B1/1B3 family of transporters help incorporate MPAG into bile where it is excreted into the intestines and gut bacteria hydrolyze it back to MPA for the enterohepatic circulation. A more detailed explanation of each protein is contained in the text. MPA: mycophenolic acid, UGT: uridine glucuronidase transferases, OATP: organic anion transporter protein, SLCO: soluble organic anion transporter, MRP-2: membrane resistance protein-2, IMPDH: inosine monophosphate dehydrogenase.

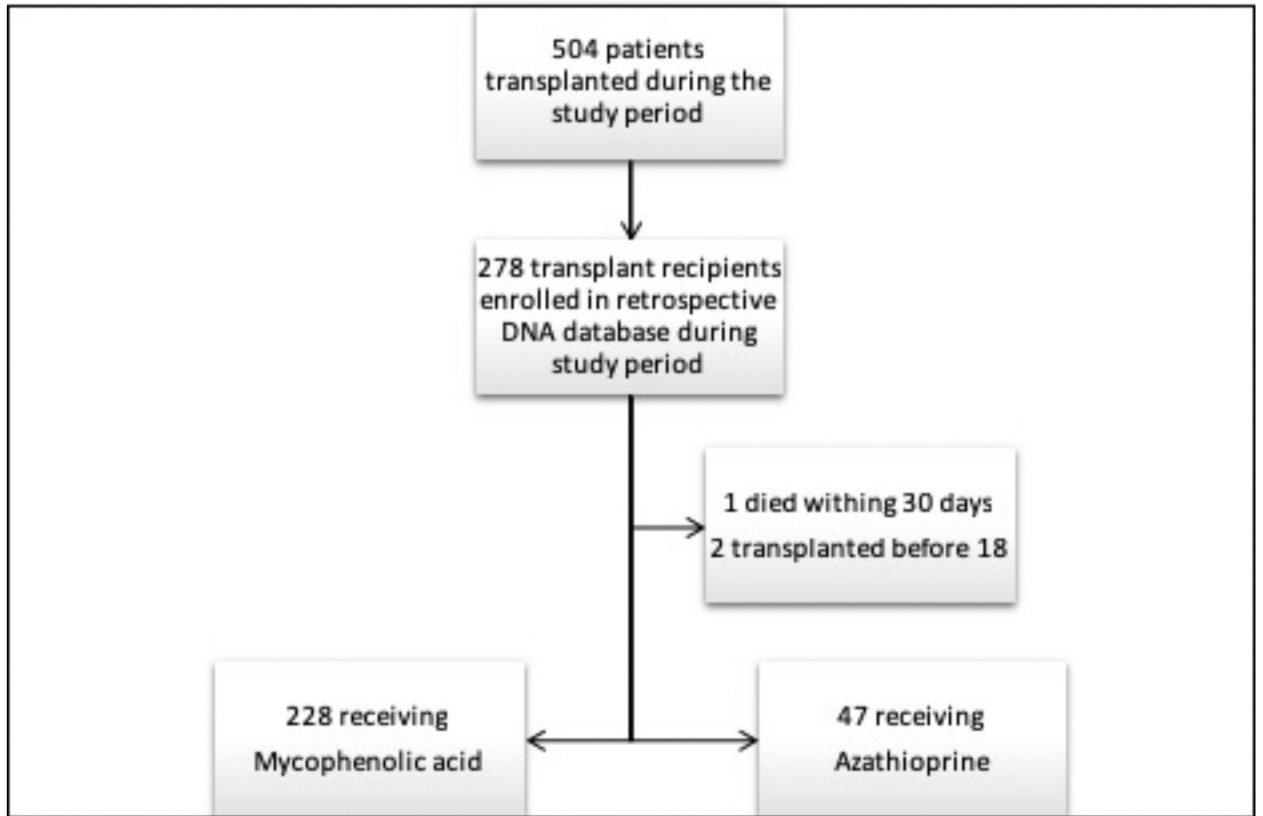


Figure 2: Flowchart of Patient Selection. During the study period, a total of 504 patients were transplanted. Of those, 278 were captured in the DNA lung transplant database and eligible for enrollment in the study. 3 eligible patients were excluded for reasons indicated.

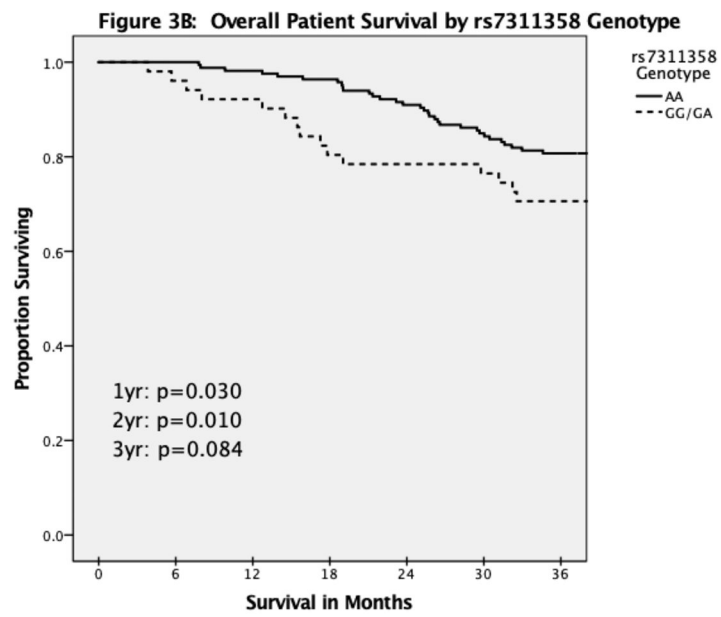
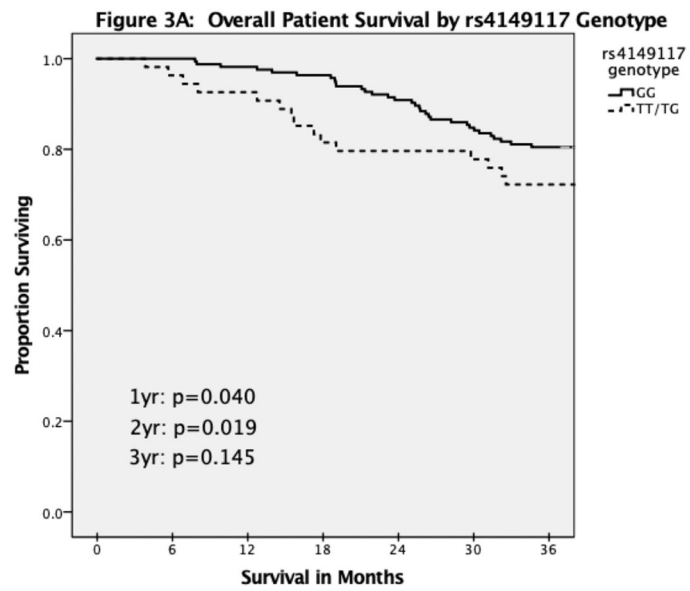


Figure 3: Kaplan Meier survival curves of overall patient survival stratified by genotype. A: Survival based on rs4149117 genotype. B: Survival based on rs7311358 genotype.

Figure 4A: Time to First Episode of Nonminimal Acute Cellular Rejection for Mycophenolate Patients

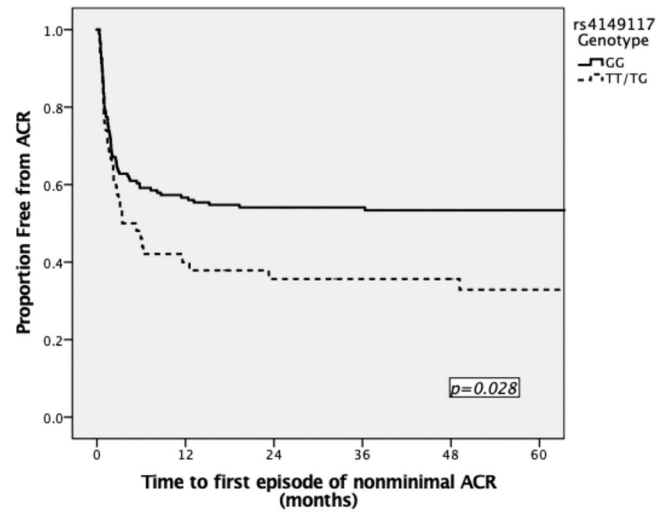


Figure 4B: Time to First Episode of Nonminimal Acute Cellular Rejection for Mycophenolate Patients

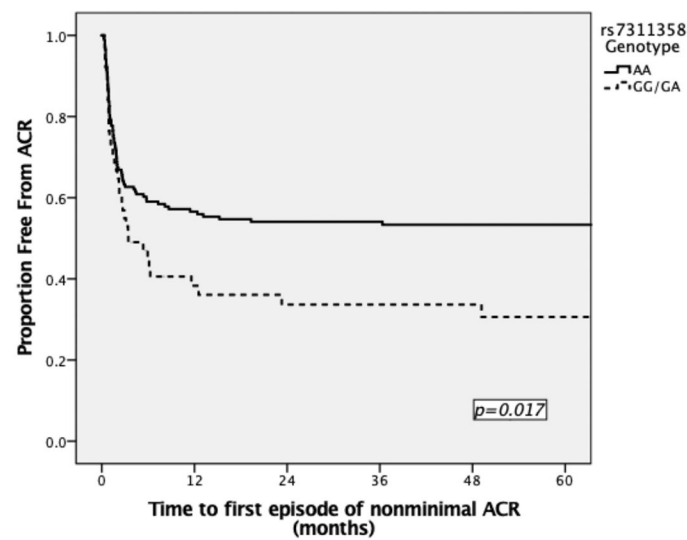


Figure 4:
Time to First Episode of Nonminimal Acute Cellular Rejection for Patients Receiving Mycophenolate by A) rs4149117 genotype and B) rs7311358 genotype.

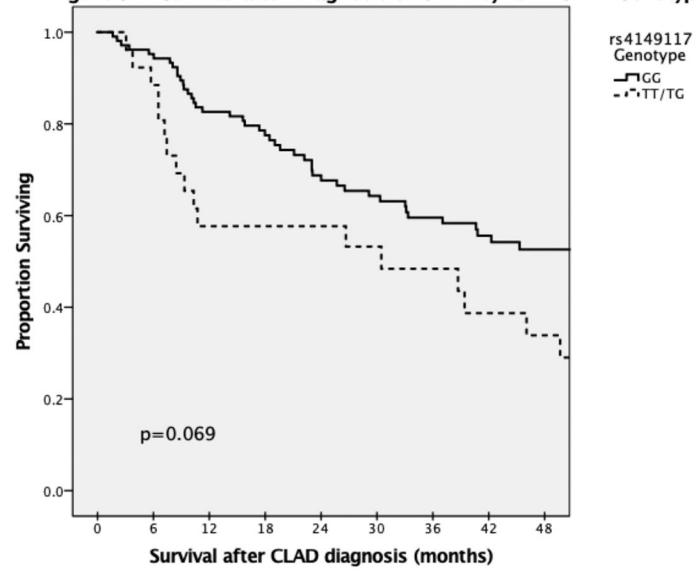
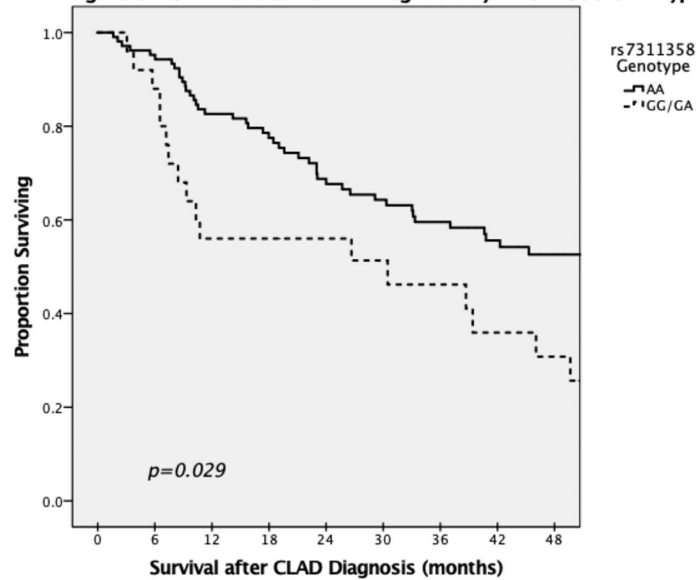
Figure 5A: Survival after Diagnosis of CLAD by rs4149117 Genotype**Figure 5B: Survival after CLAD Diagnosis by rs7311358 Genotype**

Figure 5: Survival after Diagnosis of CLAD by genotype. Time 0 along the x-axis indicates time of diagnosis of CLAD and not time of transplantation. A: stratified by rs4149117 genotype. B: stratified by rs7311358 genotype.

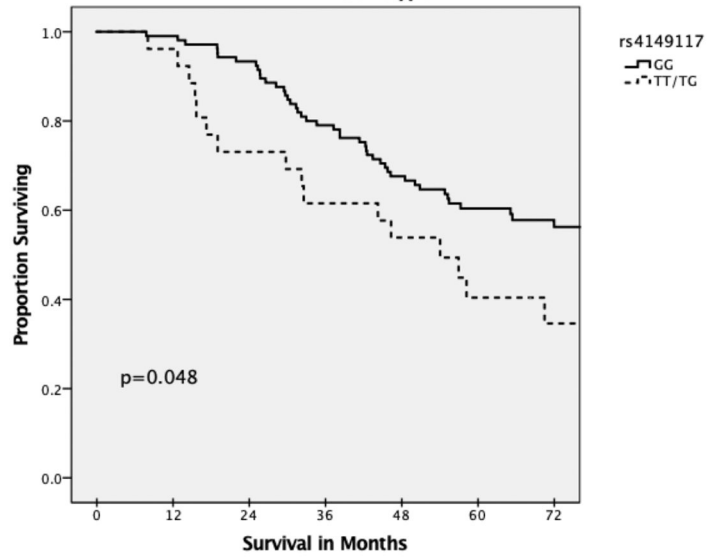
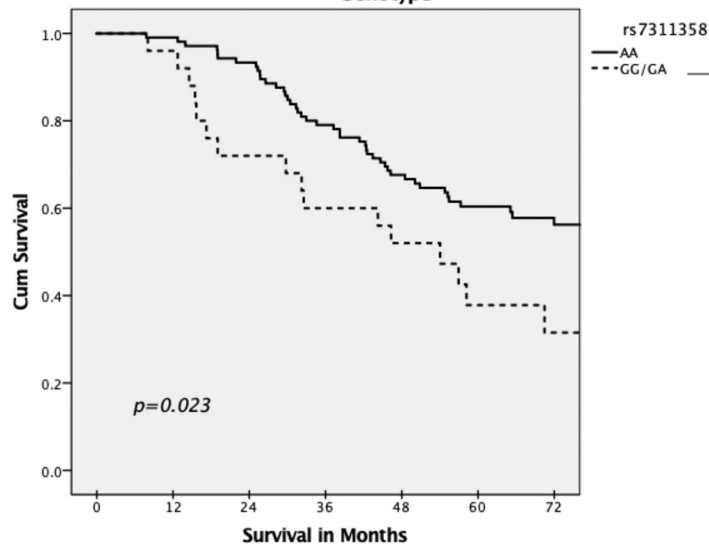
Figure 6A: Overall Survival of Patients Diagnosed with CLAD by 4149117 Genotype**Figure 6B: Overall Survival of Patients Diagnosed with CLAD by rs7311358 Genotype**

Figure 6: Overall survival of patients diagnosed with CLAD. Time 0 on the x-axis indicates time of transplantation. A: stratified by rs4149117 genotype. B: stratified by rs7311358 genotype

Table 1:**SNP Genotype Frequencies ***

GENE	SNP	GENOTYPE	FREQUENCIES, <i>n</i> (%)	
			Mycophenolate	Azathioprine
UGT1A8	rs1042597	GG	26 (11.9)	4 (8.9)
		CC	110 (50.2)	28 (62.2)
		GC	83 (37.9)	13 (28.9)
UGT1A9	rs2741049	CC	85 (39.9)	19 (43.2)
		TT	39 (18.3)	7 (15.9)
		CT	89 (41.8)	18 (40.9)
ABCC2 (MRP2)	rs3740066	CC	81 (37)	15 (33.3)
		TT	27 (12.3)	2 (4.4)
		CT	111 (50.7)	28 (62.2)
SLCO1B1	rs2306283	AA	73 (34)	12 (26.7)
		GG	37 (17.2)	8 (17.8)
		AG	105 (48.8)	25 (55.6)
SLCO1B3	rs4149117	GG	164 (75.2)	30 (66.7)
		TT	4 (1.8)	1 (2.2)
		GT	50 (22.9)	14 (31.1)
SLCO1B3	rs7311358	AA	166 (76.5)	30 (66.7)
		GG	3 (1.4)	1 (2.2)
		AG	48 (22.1)	14 (31.1)

* Total *n* varies due to DNA sample quality

Table 2:

Demographic and Clinical Factors for Mycophenolate Patient Group

Genotype		rs4149117			rs7311358		
		GG (n=164)	TT/GT (n=54)	p	AA (n=166)	GG/AG (n=51)	p
Recipient Factors	Age (years, mean ±SD)	53.2±13.7	53.2±12.4	0.978	53.2±13.7	53.4±12.4	0.932
	Female Gender, n (%)	61 (37.2)	28 (51.9)	0.057	62 (37.3)	27 (52.9)	0.048
	Race, n (%)						0.026
	White	158 (96.3)	47 (87)	0.012	160 (96.4)	45 (88.2)	
	Non-White	6(3.7)	7(13)		6(3.6)	6 (11.8)	
Diagnosis, n (%)	Diagnosis, n (%)			0.310			0.448
	ILD	81 (49.4)	23 (42.6)		81 (48.8)	23 (45.1)	
	COPD	35 (21.3)	15 (27.8)		36 (21.7)	14 (27.5)	
	Cystic Fibrosis	27 (16.5)	9 (16.7)		28 (16.9)	8 (15.7)	
	A1AT	7(4.3)	0 (0)		7 (4.2)	0 (0)	
	Sarcoidosis	3 (1.8)	3 (5.6)		3 (1.8)	2 (3.9)	
	Other	10 (6)	3(5.6)		10 (6)	3 (5.9)	
	LAS	48.4±19.6	49.3±20.4	0.779	48.3±19.5	49.9±20.7	0.601
Donor Factors	Age, years (mean ±SD)	37.0±14.2	37.1±16.1	0.968	36.9±14.2	37.1±16.3	0.931
	Female Gender, n (%)	59 (36)	20 (37)	0.888	60 (36.1)	18 (35.3)	0.912
	Race, n (%)			0.238			0.335
	White	124 (75.6)	45 (83.3)		126 (75.9)	42 (82.4)	
	Non-White	40 (24.4)	9 (16.7)		40 (24.1)	9 (17.6)	
Transplant Factors	Transplant Type			0.255			0.279
	Bilateral	156 (95.1)	54 (100)		158 (95.2)	51 (100)	
	Single	8 (4.8)	0 (0)		8 (4.9)	0 (0)	
	Cardiopulmonary Bypass	81 (49.4)	33 (61.1)	0.135	81 (48.8)	32 (62.7)	0.081
	Ischemic Time, min (mean ± SD)	275.6±68.1	283.6±72.5	0.466	276.4±68	279.2±71.8	0.793
	PGD at 72 hours			0.440			0.624
	0	30 (19.1)	14 (26.9)		32 (20.1)	12 (24.5)	
	1	108 (68.8)	32 (61.5)		108 (67.9)	31 (63.3)	
	2	11 (7.0)	5 (9.6)		11 (6.9)	5 (10.2)	
	3	8 (5.1)	1 (1.9)		8 (5.0)	1 (2.0)	
Calcineurin Inhibitor	Calcineurin Inhibitor			0.956			0.885
	Tacrolimus	159 (96.9)	54 (100%)		161 (97)	51 (100)	
	Cyclosporine	5 (3.1)	0		5 (3)	0	
	Any Acute Rejection at 1 Year, n (%)	126 (76.8)	36 (66.7)	0.138	127 (76.5)	35 (68.6)	0.258
MPA Dose, g [median(range)]	MPA Dose, g [median(range)]						
	Month 1	1 (0–3)	1.25 (0–2.5)	0.167	1 (0–3)	750 (0–1.5)	0.134
	Month 6	1 (0–3)	1 (0–2)	0.171	1 (0–3)	1 (0–2)	0.287

Genotype		rs4149117			rs7311358		
		GG (n=164)	TT/GT (n=54)	p	AA (n=166)	GG/AG (n=51)	p
	Month 12	1 (0–3)	1 (0–2)	0.345	1 (0–3)	1 (0–3)	0.549

ILD: Interstitial lung disease, COPD: chronic obstructive pulmonary disease, A1AT: alpha-1 antitrypsin, LAS: lung allocation score, PGD: primary graft dysfunction

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Table 3:
Demographic and Clinical Factors for Azathioprine Patient Group *

		rs4149117		
Genotype		GG (n=30)	TT/GT (n=15)	p-value
Recipient Factors	Age (years, mean \pm SD)	48.6 \pm 16.2	49.4 \pm 13.9	0.971
	Female Gender, n (%)	13 (43.3)	8 (53.3)	0.526
	Race, n (%)			0.041
	White	30 (100)	13 (86.7)	
	Non-White	0 (0)	2 (13.3)	
	Diagnosis, n (%)			0.701
	ILD	7 (23.3)	5 (33.3)	
	COPD	8 (26.7)	5 (33.3)	
	Cystic Fibrosis	9 (30.0)	2 (13.3)	
	A1AT	2 (6.7)	1 (6.7)	
	Other	4 (13.3)	1 (6.7)	
	LAS, median (IQR)	43.67 (33.17–50.13)	38.67 (35.39–48.33)	0.246
Donor Factors	Age, years (mean \pm SD)	35.1 \pm 14.4	33.1 \pm 13.2	0.782
	Female Gender, n (%)	15 (50)	5 (33.3)	0.289
	Race, n (%)			0.612
	White	24 (80)	11 (73.3)	
	Non-White	6 (20)	4 (26.7)	
Transplant Factors	Transplant Type			0.153
	Bilateral	30 (10)	14 (93.3)	
	Single	0 (0)	1 (6.7)	
	Cardiopulmonary Bypass	9 (30)	5 (33.3)	0.820
	Ischemic Time, min (mean \pm SD)	280.77 \pm 66.03	282.20 \pm 62.96	0.754
	PGD at 72 hours			0.205
	0	8 (26.7)	3 (20)	
	1	21 (70)	9 (60)	
	2	1 (3.3)	1 (6.7)	
	3	0 (0)	2 (13.3)	
	Calcineurin Inhibitor			0.041
	Tacrolimus	30 (100)	13 (86.6)	
	Cyclosporine	0 (0)	2 (13.3)	
	Any Acute Rejection at 1 Year, n (%)	20 (66.7)	8 (53.3)	0.384

* rs4149117 and rs7311358 demonstrated complete linkage disequilibrium in the Azathioprine group, therefore, demographics are only reported for rs4149117.

ILD: Interstitial lung disease, COPD: chronic obstructive pulmonary disease, A1AT: alpha-1 antitrypsin, LAS: lung allocation score, PGD: primary graft dysfunction

Table 4:

Cox Regression Analysis for Risk of Death by Genotype in Patients Receiving Mycophenolic Acid

<i>rs7311358</i>						
	Risk of Death at One Year			Risk of Death at Three Years		
Overall Model	<i>Chi-square 22.082</i> <i>p=0.002</i>			<i>Chi-square 11.298</i> <i>p=0.080</i>		
Variable	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Recipient Gender	1.74	0.30–9.97	0.535	1.38	0.75–2.55	0.303
Recipient Race, Nonwhite	2.74	0.27–27.34	0.391	2.02	0.71–5.75	0.190
Donor Race, Nonwhite	3.72	0.69–20.10	0.127	1.53	0.80–2.90	0.197
Cardiopulmonary Bypass	0.62	0.11–3.42	0.583	0.63	0.35–1.14	0.129
No Acute Rejection at 1 year	0.17	0.03–0.90	0.037	--	--	--
rs7311358: GG or GA	7.76	1.37–44.04	0.021	1.97	1.04–3.72	0.036
CNI: Cyclosporine vs. tacrolimus	12.73	0.83–19.49	0.068	2.41	0.56–10.48	0.239
<i>rs4149117</i>						
	Risk of Death at One Year			Risk of Death at Three Years		
Overall Model	<i>Chi-square 20.993</i> <i>p=0.004</i>			<i>Chi-square 8.564</i> <i>p=0.128</i>		
Variable	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Recipient Gender	1.63	0.29–9.12	0.586	1.36	0.74–2.51	0.318
Recipient Race, Nonwhite	2.22	0.22–22.26	0.498	--	--	--
Donor Race, Nonwhite	4.08	0.75–22.17	0.103	1.51	0.79–2.87	0.205
Cardiopulmonary Bypass	0.62	0.11–3.38	0.576	0.67	0.38–1.20	0.181
No Acute Rejection at 1 year	0.18	0.04–0.96	0.045	--	--	--
rs4149117: TT or TG	7.28	1.27–41.78	0.026	1.86	0.99–3.48	0.054
CNI: Cyclosporine vs. tacrolimus	12.28	0.83–182.69	0.069	2.23	0.53–9.95	0.265