A predictive nomogram for choosing tacrolimus or cyclosporine as immunosuppression drugs for pediatric recipients after liver transplantation

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Abstract

Background: Tacrolimus (TAC) is the first choice of calcineurin inhibitors (CNIs) for recipients after pediatric LT. But there are some special pediatric recipients present an unsatisfied prognosis with the therapy of TAC. We aimed to construct a simple clinical model to predict the effectiveness of TAC in recipients after pediatric LT and help clinicians to choose CsA for an alternative quickly. Methods: Patients who received pediatric LT from 2006 to 2019 at RenJi Hospital, Shanghai Jiaotong University School of Medicine were included in this study. Retrospective data, including demographics, comorbidities, pre-operative lab values, outcome based on post-transplantation events were collected. A nomogram estimating the risk of poor curative effects of those recipients who receive an IS protocol based on TAC was constructed using multivariate logist regression analysis. Results: A total of 2032 recipients were included in this study. Seven parameters (recipient CYP type, cholangitis before LT, GRWR, spleen long diameter, serum albumin, graft volume reduction, donor CYP type) were used to construct the nomogram. The nomogram showed good discriminative performance with the area under receiver operating characteristic (ROC) curve (AUC) of 74.5%, and good calibration. Decision curve analysis demonstrated that the model had a high clinical application potential. Conclusions: A simple clinical model with well performance in predicting the risk of poor curative effects of those recipients who receive an IS protocol based on TAC was constructed. The nomogram can help clinicians quickly choose CsA as an alternative if there are high risks.

Introduction

The routine and widespread use of immunosuppression (IS) drugs have resulted in step-wise improvements in post-transplant survival rates[1]. That may be reflected in the decreased rates of early severe acute rejection and rejection-related graft loss, and more than 63% of late mortality after liver transplantation (LT) is non-hepatic cause[2]. Calcineurin inhibitors [CNIs, tacrolimus (TAC) or cyclosporine (CsA)], corticosteroids and antimetabolites [most often mycophenolic acid (MPA)] are currently among the most common choice for LT immunosuppression[3]. CNIs, particularly TAC, is the primary choice in IS drugs, and more than 80% of recipients are treated with the basis of TAC after pediatric LT[4]. However, long-term utilization of CNIs presents significant side effects, such as malignancy, infection metabolic disorders, and organ toxicities[5, 6]. Therefore, individual therapy should be performed to minimize the side effects.

Because of a much higher potent and a better post-transplant survival rate than CsA, TAC is the first line CNIs drugs in pediatric LT, and CsA has been used less frequently[4]. Although the side effects are similar between TAC and CsA, including hypertension, nephrotoxicity, neurotoxicity and lipid metabolic disorders, they have different immunological mechanisms and pharmacokinetics[7]. Recipients may develop different benefit and harm profiles with the therapy of TAC or CsA. Clinicians usually consider switching TAC to CsA when recipients develop severe side effects or present an unsatisfied efficacy during therapy of TAC (Table 1).

It is more beneficial for the special recipient population to receive CsA over alternative TAC.

Therefore, it is significant that if we are able to choose IS drugs with respect to patient's pretransplant and/or intraoperative risk factors[8]. We designed a retrospective study in pediatric liver transplantation with a large sample size. In this study, we analyzed risk factors of switching IS drugs after pediatric LT. This study aimed to construct a simple clinical model using common clinical features for the early evaluation and prediction of the effectiveness of TAC in recipients after pediatric LT and help clinicians to choose CsA for an alternative quickly.

Methods:

Patients and study design

Patients who received pediatric LT from 2006 to 2019 at RenJi Hospital, Shanghai Jiaotong University School of Medicine were included in this study. Patients with loss of follow-up or death within the first month after operation were excluded from this study. All the patients were follow-up until the study end date of December 2019. All pediatric LT in this study received approval from Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics Committee. No organs from executed prisoners were transplanted and reported in this study. This retrospective study was performed following the declaration of Helsinki guidelines.

To analyzed risk factors of switching IS drugs after pediatric LT, patients were divided into two groups: patients with switching IS drugs and patients without switching IS drugs. Data of recipients were collected from our maintained database of liver transplantation. Patient characteristics including demographics, co-morbidities, pre-operative lab values, outcome based on post-transplantation events were compared between the two groups.

Variables collected

Clinic-pathological variables included in this study are as follows: recipient's/ donor's age and body weight at liver transplantation, sex, type of cytochrome P450 (CYP), recipients' growth situation, spleen long diameter, primary disease of the recipient, complications before transplantation, child pugh score of the recipient, pediatric end-stage liver disease (PELD) score of the recipient, graft recipient body ratio (GRWR), surgical type. Pre-operative laboratory assessments included serum albumin, bilirubin, international normalized ratio (INR), prothrombin time (PT). Post-transplantation events included acute rejection in 3 months after pediatric LT, protocols of IS drugs, complications and death.

Follow-up

In the first 3 months after discharge, the patients were followed up weekly, and then every two weeks from the fourth month to the sixth month and monthly after 6 months. Liver function, viral infection and serum immunosuppressant (TAC or CsA) concentration were tested routinely. Liver ultrasound was performed at least once every three months.

Immunosuppression protocol after pediatric LT

TAC, CsA, corticosteroids, and mycophenolate mofetil (MMF) were the principal scheme of IS drugs. Steroids were given intravenously with a gradually decreasing dosage and then gradually reduced to oral glucocorticoid during the first week after LT. The initial dose of TAC was 0.1-0.15 mg[?]kg-1[?]d-1 and the target blood concentration was 8-12 ng/mL at the first month, 7-10 ng/mL between the 2nd and 6th month, 5-8 ng/ mL between the 7th and 12th month and maintained 5 ng/mL according to the liver function after 1 year. The dosage of TAC was modified based on liver function and serum concentration of TAC. Adding MMF or switching TAC to CsA would be considered if the serum concentration of TAC was low and the target concentration could not be reached after increasing the dose of TAC or severe side effects occurred.

Statistical analysis

The variables gathered from our maintained database were compared between patients with switching IS drugs and patients without switching IS drugs. Categorical variables were analyzed using a χ^2 test and were expressed using numbers and proportion (%). Continuous variables were analyzed using a t-test or a Wilcoxon signed rank test. Continuous normal distribution was expressed as mean ± standard deviation and non-continuous normal distribution was expressed as median and interquartile (IQR). SPSS (IBM, version 26) and R (R Foundation for Statistics Computing) were used to perform the analyses.

Variables that were identified as statistically significantly ($p< 0.05$) were selected using the univariate logistic regression analysis, and were retained as candidate predictors for prediction modeling. After a stepwise selection process, risk factors were identified in the multivariate logistic analysis. Finally, a nomogram was constructed using these determined risk factors to predict the risk of poor curative effects of those recipients who receive an IS protocol based on TAC, and then may switch TAC to CsA. The established nomogram was further evaluated by using calibration curves. In addition, the discriminative performance of the nomogram was evaluated using the area under receiver operating characteristic (ROC) curve (AUC) and the clinical usefulness of the nomogram was assessed using decision curve analysis (DCA).

Results:

Patient characteristics and outcomes

A total of 2032 recipients were included in this study. 1687 recipients received a protocol of IS all the time after pediatric LT and did not switch IS drugs. 345 recipients switched IS drugs midway after pediatric LT under the guidance of clinicians. The demographics and clinical characteristics of patients with switching IS drugs and patients without switching IS drugs are shown in Table 2. There were significant differences in recipient CYP type ($p<0.001$), cholangitis before LT ($p=0.029$), serum albumin ($p=0.044$), surgical type ($p=0.018$), graft volume reduction in the operation ($p=0.008$), kinds of IS drugs ($p<0.001$), addition of MMF ($p<0.001$), donor CYP type ($p<0.001$), and donor age at LT ($p=0.021$) between the two groups. Patients in switching IS drugs group had a higher rate of acute rejection in 3 months after LT, a higher rate of developing mental, neurological, and urinary complications after LT but a lower mortality rate and a lower rate of developing portal vein complications and post-transplant lymphoproliferative disorder (PTLD) than patients in no switching IS drugs group (Table 3).

Selection of predicting factors associated with switching IS drugs

Univariate logistic analysis showed that recipient CYP type, cholangitis before LT, GRWR, INR, serum albumin, graft volume reduction, addition of MMF, donor age at LT, donor CYP type, acute rejection in 3 months after LT, portal vein complications, urinary complications, mental and neurological complications, PTLD after LT were significantly associated with risks of switching IS drugs (Table 4). In multivariate logist analysis, seven potential predictors were identified, including recipient CYP type, cholangitis before LT, GRWR, spleen long diameter, serum albumin, graft volume reduction, donor CYP type.

Prediction nomogram construction

A nomogram incorporating the above seven independent predictive factors was built (Figure 1). The length of the variable axis represents visually the relative contribution of each predictor. Recipient CYP type of AA and low serum albumin contributed the most points to the model if present. The nomogram assigned the probability of switching IS drugs by accumulating the scores of every risk factor detected on the points scale. The bottom scale showed the risk of poor curative effects of those recipients who receive an IS protocol based on TAC by the total score. Higher scores indicated worse prognosis and clinicians may choose CsA instead of TAC for protocol of IS initially.

Validation of nomogram performance

ROC curve was conducted to evaluate the prediction ability (Figure 2). The AUC of this nomogram was 74.5% and the cut-off value for risk probability in this model was 1.3, with a specificity and sensitivity of 75.3% and 63.2%, respectively. The calibration curve of this nomogram for the risk between the actual

and predicted probability was consistent (Figure 3A). The DCA analysis evaluated the clinical value of the nomogram (Figure 3B), which indicated that recipients with the threshold risk of about 20 to 50% were recommended to using this nomogram.

Discussion:

In this study, we constructed a nomogram to predict the risk of poor curative effects of those recipients who receive an IS protocol based on TAC. ROC curve, calibration curve and DCA were employed to identify the model's predicted reliability, which showed a well prediction ability with AUC values over 0.7. The nomogram showed that recipients with CYP type of AA or AG, low serum level of albumin, high GRWR and not receiving volume reduction had a significant higher risk of switching IS drugs. Donor CYP type of AA or AG also contributed medium points to this model. No cholangitis and spleen long diameter above 86 cm did not make much contribution.

Recipients who express CYP3A5 are more difficult to reach the target blood concentration of TAC than those not[14], which may increase the risk of toxicity of TAC because of overexposure. Similar to this, both recipient and donor CYP type are predictors in our model. However, it seems that recipient CYP type has no correlation with the oral clearance of TAC[15] as it mainly metabolizes in the donor liver and intestine[16]. The relationship between recipient CYP type and TAC dosing are still not clearly defined in pediatric liver transplantation[17]. Research showed that recipient CYP type has no significant contribution on metabolism of TAC[18] while other authors found that recipient CYP type plays a more prominent role than donor CYP type[19]. The discrepancy may be due to the expression of CYP are associate with the length of time after pediatric LT and recipient age[20, 21].

The patients who were initially treated with TAC but later switched to CsA had a higher rate of acute rejection, urinary complications and mental and neurological complications, which was quite possible that severe complications were the reason to consider switching TAC to CsA. Lower mortality and incidence of portal vein complications and PTLD may indicate that this part of recipients benefited from the protocol of switching IS drugs. To achieve individual therapy for minimizing the side effect of IS drugs, CsA is an alternative when TAC-based therapy receiving a poor prognosis.

The inherent limitations of a single-center retrospective study are the limitations in our study. The definite reason clinicians chose a therapeutic regimen of switching IS drugs for each recipient is not available now. Additionally, a small part of the recipient had switched CsA to TAC latterly and did not report in our study. More prospective studies are required to validate the nomogram.

In conclusion, some recipients may benefit from switching IS drugs timely after pediatric LT. We constructed a simple model including recipient CYP type, cholangitis before LT, GRWR, spleen long diameter, serum albumin, graft volume reduction and donor CYP type to predict the risk of poor curative effects of those recipients who receive an IS protocol based on TAC. The nomogram can help clinicians quickly choose CsA as an alternative if there are high risks.

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Table 1. Comparison between CsA and TAC

CNIs options	Superiority compared to TAC/ CsA	Conditions may consider switching TAC to CsA
CsA	Lower rate of new-onset diabetes after transplant (NODAT)[9] May have lower neurotoxicity[10] Reduced the risks after liver transplantation of death, graft loss, acute rejection and steroid-resistant rejection[9, 11]	The serum concentration of TAC is low and unable to reach the target serum concentration after increasing the dose of TAC. Severe complications developed such as posterior reversible encephalopathy syndrome (PRES), seizures and some other CNS symptoms.[12, 13]
TAC	Easier to achieve the balance between efficacy and side effects[9]	

CNIs: Calcineurin inhibitors, CsA: cyclosporine, TAC: tacrolimus, CNS: central nervous system

Table 2. Characteristics of the switching IS drugs patients and no switching IS drugs patients.

Factor	No switching IS drugs group	Switching IS drugs group	P v
Number	1687	345	
Recipient age at LT, median (IQR), months	8.00 [6.00, 17.00]	9.00 [6.00, 17.00]	0.16
Recipient sex, Female	917 (54.4)	174 (50.4)	0.20
Recipient weight at LT, median (IQR), kg	7.70 [6.50, 10.00]	7.80 [6.90, 10.00]	0.20
Growth retardation	1067 (63.2)	225 (65.2)	0.52
Recipient CYP type			<0.
AA AG GG	108 (6.4) 555 (32.9) 1024 (60.7)	71 (20.6) 181 (52.5) 93 (27.0)	
Primary disease at transplantation			0.32
Acute liver failure	8 (0.5)	5 (1.4)	
Cholestatic liver disease	1502 (89.0)	299 (86.7)	
Metabolic liver disease	124 (7.4)	30 (8.7)	
Neoplastic disease	24 (1.4)	4 (1.2)	
Re-transplantation	20 (1.2)	4 (1.2)	
Vascular disease	9 (0.5)	3 (0.9)	
Complications before transplantation			
History of heart disease	221 (13.1)	43 (12.5)	0.81
Portal hypertension	732 (43.4)	136 (39.4)	0.19
Gastrointestinal bleeding	258 (15.3)	57 (16.5)	0.62
Cholangitis	590 (35.0)	99 (28.7)	0.02
Ascites	1057 (62.7)	225 (65.2)	0.40
GRWR, median (IQR)	3.14 [2.50, 3.83]	3.28 [2.57, 3.93]	0.06
Spleen long diameter (IQR), millimeter	90.00 [76.00, 107.00]	93.00 [80.00, 105.00]	0.14
INR, median (IQR)	1.30 [1.10, 1.67]	1.29 [1.12, 1.62]	0.91
Albumin, median (IQR), g/dL	3.49 [3.10, 3.92]	3.43 [3.05, 3.84]	0.04
TB, median (IQR)	12.90 [3.50, 20.30]	12.60 [3.30, 19.20]	0.66
PT, median (IQR)	14.70 [12.50, 19.00]	14.60 [12.70, 18.50]	0.90
Child pugh score at transplantation, median (IQR)	9.00 [7.00, 10.00]	9.00 [7.00, 10.00]	0.57
PELD score, median (IQR)	18.00 [11.00, 27.00]	19.00 [12.00, 26.00]	0.67

Factor	No switching IS drugs group	Switching IS drugs group	P v
Surgical type			0.01
SLT	86 (5.1)	14 (4.1)	
OLT	213 (12.6)	63 (18.3)	
LDLT	1388 (82.3)	268 (77.7)	
Graft volume reduction	81 (4.8)	5 (1.4)	0.00
IS drugs			<0.
TAC	1679 (99.5)	71 (20.6)	
CsA	8 (0.5)	274 (79.4)	
Addition of MMF	994 (58.9)	293 (84.9)	<0.
Donor CYP type			<0.
AA	217 (12.9)	83 (24.1)	
AG	699 (41.4)	198 (57.4)	
GG	771 (45.7)	64 (18.6)	
Donor sex (Female)	917 (54.4)	174 (50.4)	0.20
Donor age at LT, median (IQR), years	29.00 [25.00, 34.00]	28.00 [23.00, 33.00]	0.02
Donor BMI, median (IQR)	21.90 [19.40, 24.20]	21.20 [18.90, 24.10]	0.06

Data are presented as n (%) unless otherwise indicated. BMI: body mass index; IQR: interquartile range; INR: international normalized ratio; TB: total bilirubin; PT: prothrombin time; PELD: pediatric end-stage liver disease; LT: liver transplantation; SLT: split liver transplantation; OLT: orthotopic liver transplantation; LDLT: living donor liver transplantation; IS: immunosuppression; MMF: mycophenolate mofetil

Table 3. Outcomes of switching IS drugs patients and no switching IS drugs patients.

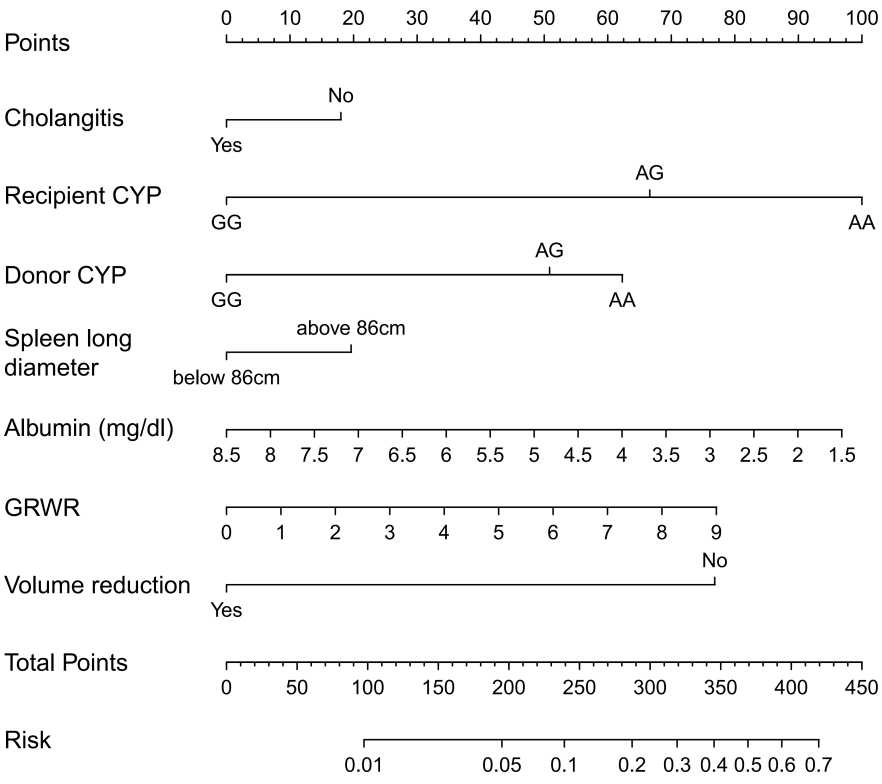
	No switching IS drugs group	Switching IS drugs group	P value
Number	1687	345	
Death	139 (8.2)	11 (3.2)	0.005
Viral infection status (positive)			
EBV	911 (54.0)	182 (52.8)	0.716
CMV	463 (27.4)	112 (32.5)	0.069
HBV	91 (5.4)	13 (3.8)	0.265
Acute rejection in 3 months after LT	385 (22.8)	171 (49.6)	<0.001
Vascular Complications			
Portal vein	88 (5.2)	8 (2.3)	0.03
Hepatic artery	31 (1.8)	3 (0.9)	0.295
Respiratory complications	455 (27.0)	87 (25.2)	0.546
Digestive complications	366 (21.7)	58 (16.8)	0.257
Urinary complications	98 (5.8)	31 (9.0)	0.037
Mental and neurological complications	33 (2.0)	16 (4.6)	0.006
Hematological complications	189 (11.2)	47 (13.6)	0.236
Skeletal complications	38 (2.3)	7 (2.0)	0.955
Allergy or urticaria	398 (23.6)	65 (18.8)	0.065
PTLD	84 (5.0)	8 (2.3)	0.043

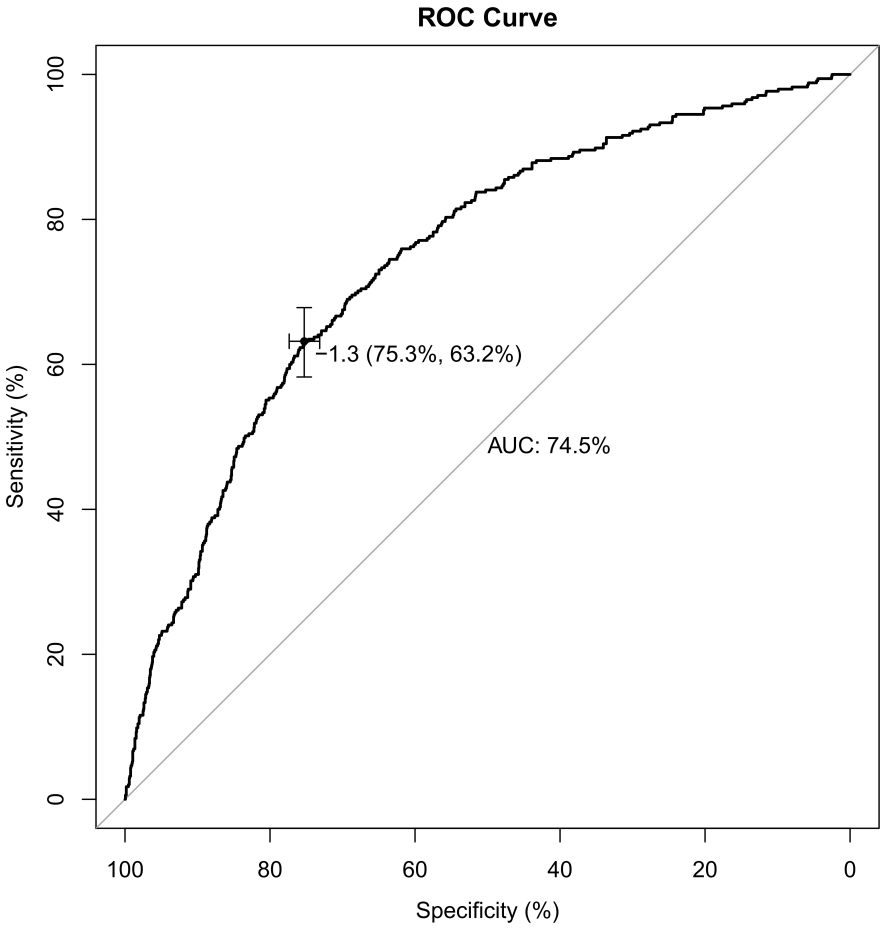
EBV: Epstein-Barr virus; CMV: cytomegalovirus; HBV: hepatitis B virus; PTLD: post-transplant lymphoproliferative disorder

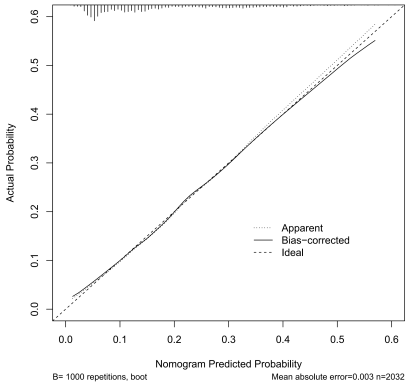
Table 4. Risk factors associated with switching IS drugs.

	Univariate analysis	**Univariate analysis**	**Univariate analysi**
	HR	**CI**	**p-value**
Recipient sex	1.1366	0.9015 - 1.4332	0.2787
Recipient age at LT	0.9997	0.9959 - 1.0033	0.8886
Recipient CYP type			
AA	REF		
AG	0.4961	0.3524 - 0.7008	< 0.001
GG	0.1381	0.0957 - 0.1995	< 0.001
Complications before transplantation			
History of heart disease	0.9445	0.6586 - 1.3268	0.7487
Portal hypertension	0.849	0.6692 - 1.0741	0.1746
Gastrointestinal bleeding	1.0962	0.7951 - 1.4901	0.5658
Cholangitis	0.7483	0.5785 - 0.9616	0.0251
Ascites	1.1175	0.8785 - 1.4274	0.3691
GRWR	1.1222	1.0067 - 1.2495	0.0363
Spleen long diameter (IQR), millimeter	1.0006	0.9965 - 1.0046	0.7561
INR, median (IQR)	0.9892	0.9504 - 1.0241	0.0442
Albumin, median (IQR)	0.8294	0.6901 - 0.9935	0.0442
TB, median (IQR)	0.9982	0.9873 - 1.0089	0.7451
PT, median (IQR)	0.9993	0.9949 - 1.0031	0.7315
Child pugh score at transplantation, median (IQR)	1.0157	0.9618 - 1.0729	0.5757
PELD score, median (IQR)	0.9996	0.9912 - 1.0078	0.9257
Surgical type			
SLT	REF		
OLT	1.8169	0.9916 - 3.5323	0.0636
LDLT	1.1861	0.686 - 2.2065	0.564
Graft volume reduction	0.2916	0.102 - 0.6552	0.008
Addition of MMF	3.9284	2.9046 - 5.411	< 0.001
Donor sex	1.1704	0.9281 - 1.4758	0.1834
Donor age at LT	0.9876	0.9781 - 0.9975	0.0131
Donor BMI	0.9764	0.9495 - 1.0041	0.0943
Donor CYP type			
AA	REF		
AG	0.7406	0.551 - 1.0009	0.0483
GG	0.217	0.1511 - 0.3103	< 0.001

NA: not available; REF:reference







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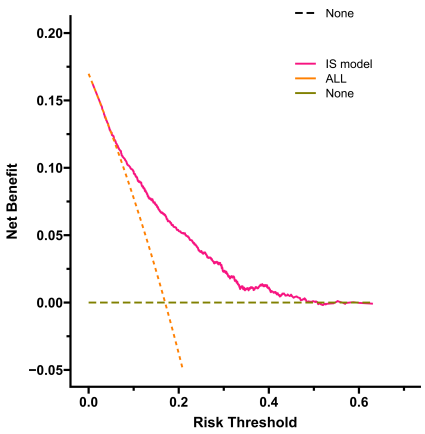

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