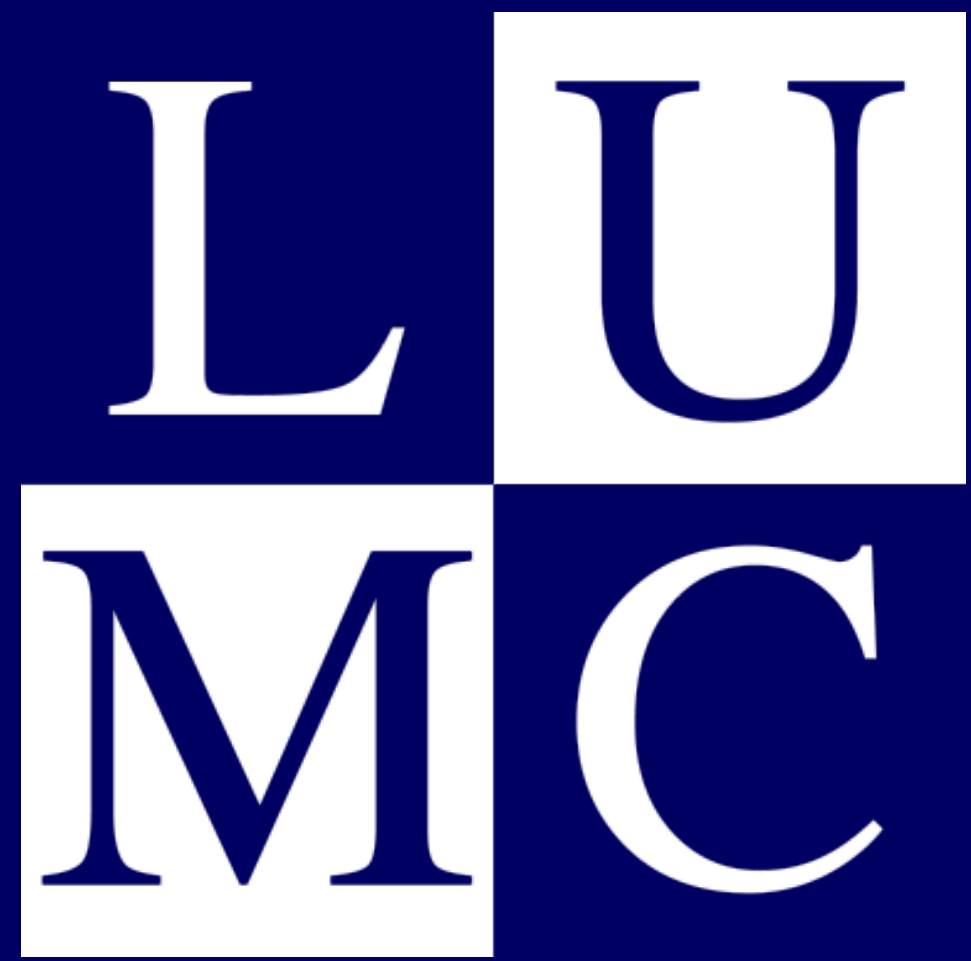




Exploring risk factors for everolimus discontinuation and serious side effects in renal transplant recipients on everolimus and prednisolone dual therapy.

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Introduction

The mTOR inhibitor everolimus is a emergent non-nephrotoxic alternative for calcineurin inhibitors (CNIs) in renal transplantation which slowly finds its way into new immunosuppressive regimens. Despite its proven efficacy and close therapeutic drug monitoring everolimus is also known for high discontinuation rates and serious side effects.

Objectives

The aim of this study was to find risk factors for discontinuation and serious side effects to optimize everolimus immunosuppressive therapy and to improve patient outcome.

Materials & Methods

- 99 stable renal transplant recipients converted from cyclosporine, mycophenolate mofetil and prednisolone triple therapy to everolimus and prednisolone dual therapy were followed up to 18 monts after conversion. Initial everolimus dose of 3 mg b.i.d.
- The dataset consisted out of an extensive amount of demographic, transplant related, pharmacogenetic and pharmacokinetic data derived from a previously published pharmacokinetic model (1).

- A parametric survival model was used to describe the time to discontinuation and the most hazardous side effects pneumonitis, infection and new onset diabetes mellitus by means of nonlinear mixed-effects modelling.

- Analysis was performed using NONMEM 7.3, R-Statistics and Pirana (2)

The development of the different time-to-event models was the in two steps: first a base model without any explanatory factors was constructed; thereafter the base model was used to explore potential covariates. In order to describe the time-to-first event a parametric survival function was used as presented below:

$$S(t) = e^{-\int_0^t h(t)dt}$$

The hazard is h(t), and the ‘survival’ S(t) is a function of the cumulative hazard within the time interval between start of the study (time zero) and the time t of the event describing the probability of not experiencing an event within this interval. The covariates were included into functions (λ_{cov}) that were factors modifying the base hazard (h_0).

$$h(t) = h_0(t) * \lambda_{cov1} * \lambda_{cov2} * \dots * \lambda_{covn}$$

Results

Table 1: Clinical characteristics			
	Number (%)	Mean ± SD	Median (Range)
Demographical			
Male	65 (66)		
Female	34 (34)		
Caucasian	84 (85)		
Age (years)		52 (13)	54 (22-71)
Weight (kg)		79 (15)	78 (50 -129)
Ideal Body Weight (kg)		67 (8)	67 (49-83)
Height (cm)		174 (10)	174 (152 -194)
Creatinine (mmol/L)		118 (34)	113 (61 - 251)
Diabetes Mellitus at start	11 (11)		
Hematocrit (L/L)		0.38 (0.04)	0.37 (0.29-0.5)
Exposure			
Everolimus dose (mg)		2.5 (0.8)	3 (0.75 -5.25)
Everolimus AUC (µg* ^h /L)		156 (60)	148 (54 - 488)
Everolimus C _{max} (µg/L)		24 (9.5)	23.5 (6.2 - 66.6)
Everolimus C _{min} (µg/L)		9.5 (4.3)	8.5 (3.3 -32.2)
Transplantation related			
Delayed graft function	15 (15.2)		
Cold Ischemic Time (h)		9.4 (7.8)	8.5 (2 -28)
Donor Age		49 (13)	51 (18 - 72)
Renal Function			
Week 32 (ml/min)		70 (25)	71 (23 - 120)
Week 52 (ml/min)		71 (24)	70 (23-120)
Week 104 (ml/min)		71 (25)	76 (23 -120)
Efficacy and safety responses			
Completion of study	58 (59)		
Freedom from acute rejection	96 (97)		
Interstitial Pneumonia	11 (11)		
Serious infections (airway, gastrointestinal, urinary tract)	35 (35)		
New onset Diabetes Mellitus	14 (14)		

Table 2: Objective function value and number of parameters of different tested survival functions		
Survival function	Number of parameters	OFV
Discontinuation		
Weibull	2	632.9
Exponential	1	642
Gompertz	2	623.3
Log logistic	2	630.2
Log normal	2	627.2
Pneumonia		
Weibull	2	197.6
Exponential	1	200.7
Gompertz	2	194
Log logistic	2	198
Log normal	2	196
Infection		
Weibull	2	545.7
Exponential	1	555
Gompertz	2	540.3
Log logistic	2	543.5
Log normal	2	540.3
New onset DM		
Weibull	2	243.892
Exponential	1	244.012
Gompertz	2	243.974
Log logistic	2	249.912
Log normal	2	243.501

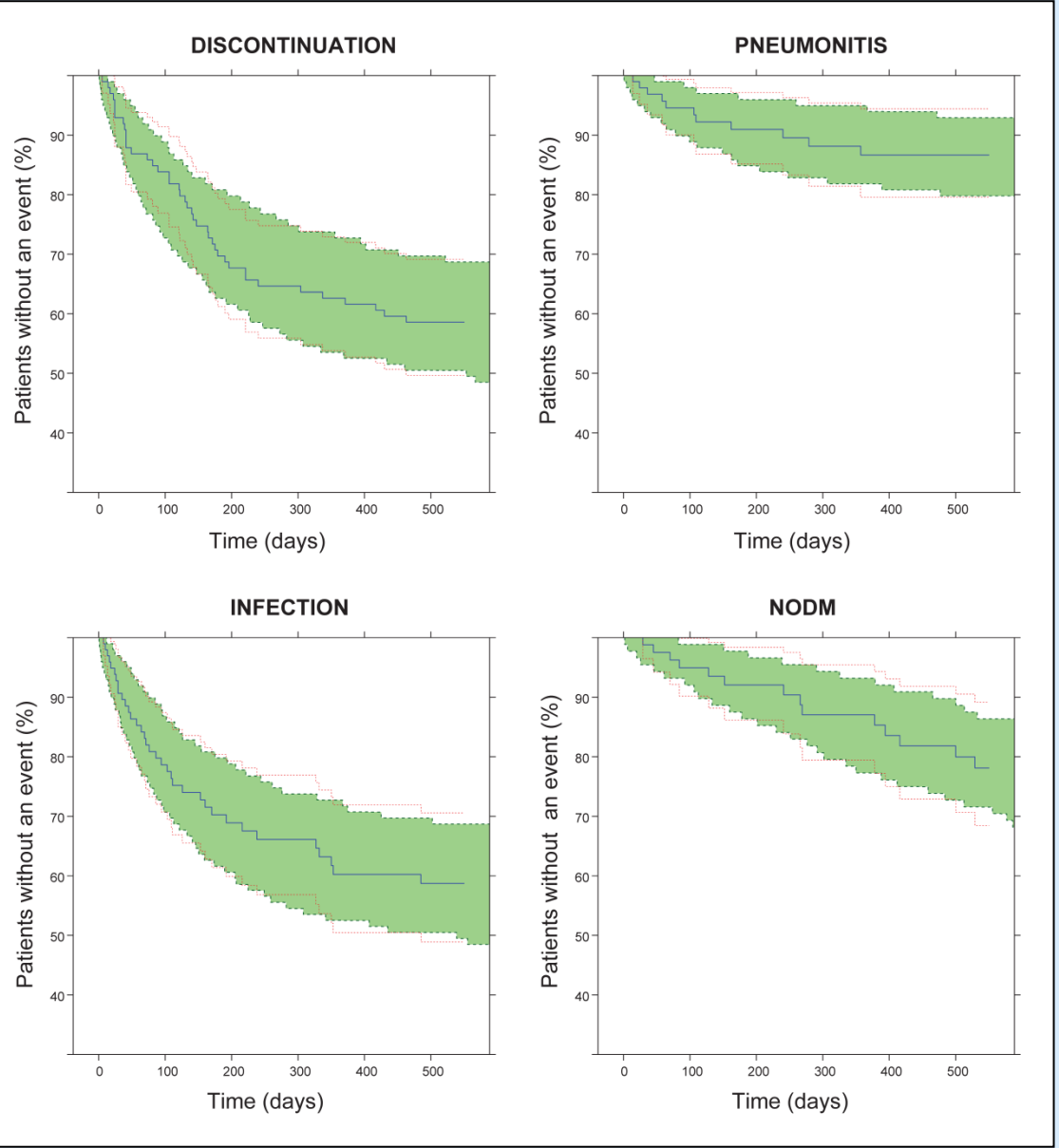


Figure 1: Kaplan-Meier Plots of the percentage of patients without an event (Discontinuation, Pneumonitis, Infection, NODM) vs Time after everolimus initiation. The shaded area represents the 95% prediction intervals for the simulated data. The continuous line represents the real data, the dashed red lines represent the 90% confidence interval of the real data.

Table 3: Results of the univariate covariate analysis for each endpoint								
	Dropout		Pneumonitis		Infection		New Onset DM	
Model	Δ OFV	P value	Δ OFV	P value	Δ OFV	P value	Δ OFV	P value
Base model	0	-	0	-	0	-	0	-
Continuous								
Age	8.484	0.0036	3.172	0.0749	1.200	0.2732	6.544	0.0105
Weight	4.684	0.0304	0.572	0.4494	0.001	0.9791	2.537	0.1112
AUC	0.017	0.8975	3.489	0.0618	0.763	0.3822	0.308	0.5788
C _{min}	1.469	0.2255	3.056	0.0805	1.430	0.2317	0.444	0.5050
C _{max}	0.804	0.3698	3.098	0.0784	1.338	0.2473	0.358	0.5496
AUC _{min}	19.432	0.0000	13.663	0.0002	2.620	0.1055	1.401	0.2365
Leukocytes	-	-	-	-	4.143	0.0418	-	-
Cholesterol	-	-	-	-	0.393	0.5310	-	-
Triglycerides	-	-	-	-	0.716	0.3976	-	-
Dichotomous								
Recipient Race	3.666	0.0555	0.005	0.9421	2.911	0.0880	0.012	0.9112
Diabetes Mellitus at start	0.789	0.3744	2.716	0.0993	0.444	0.5052	-	-
Sex	1.398	0.2371	0.355	0.5513	1.003	0.3167	1.116	0.2908
CYP3ACOMBINED	1.012	0.3144	0.704	0.4014	-	-	-	-
PXR (NR1J2) -24113G>A	6.513	0.0107	5.612	0.0178	2.028	0.1545	4.377	0.0364
PXR (NR1J2) 7635A>G	0.149	0.6996	0.291	0.5894	1.202	0.2729	0.874	0.3498
ABCB1								
ABCB1 3435C>T	5.604	0.0179	0.520	0.4707	0.033	0.8562	2.799	0.0943
ABCB1 1236C>T	2.173	0.1405	1.406	0.2358	0.023	0.8788	0.549	0.4587
ABCB1 2677T>G	0.002	0.9633	0.214	0.6438	0.345	0.5568	1.687	0.1940
ABCB1 -129T>C	0.036	0.8495	0.951	0.3294	2.588	0.1077	0.017	0.8961
ABCB1 haplo CCG	5.053	0.0246	0.171	0.6789	0.008	0.9272	2.181	0.1398
ABCB1 haplo TTT	1.918	0.1661	0.328	0.5666	0.122	0.7264	0.294	0.5877
ABCB1 haplo TCG	1.980	1.9800	0.366	0.5450	1.341	0.2469	0.295	0.5869
Donor Type								
Donor Type	-	-	-	-	-	-	5.822	0.0158
Avg daily CsA AUC till week 6 after Tx	-	-	-	-	-	-	3.286	0.0699
Avg daily CsA AUC from week 6 till conv to EVR	-	-	-	-	-	-	0.187	0.6654
# AUC (AUC above 156 µg*hr/L (30% above target)	4.147	0.0417	6.063	0.0138	-	-	-	-
# AUC (AUC above 180 µg*hr/L (50% above target)	0.189	0.6637	13.084	0.0003	-	-	-	-
Δ OFV: difference in objective function value between covariate and base model #, not used for the SCM.								

Table 4: Results of the multivariate covariate analysis for each endpoint			
MODEL	absolute OFV	ΔOFV	P-value
Discontinuation			
forward inclusion			
BASE-model	623.276		
Step 1: AND effect AUCmin	603.844	-19.432	0.00001
Step 2: AND effect Age	595.580	-8.264	0.00404
Step 3: AND effect Race	589.757	-5.823	0.01581
Step 4: AND effect PXR (NR1J2) -24113G>A	584.079	-5.678	0.01718
backward deletion			
FULL-model	584.079		
Step 1: MINUS effect PXR (NR1J2) -24113G>A	589.757	5.678	0.01718 *
Step 2: MINUS effect Race	595.580	5.823	0.01581 *
Step 3: MINUS effect Age	603.844	8.264	0.00404
Step 3: MINUS effect AUCmin	614.792	19.212	0.00001
Pneumonitis			
forward inclusion			
BASE-model	194.028		
Step 1: AND effect AUCmin non-linear	173.901	-20.127	0.00001
Step 2: AND effect PXR (NR1J2) -24113G>A	165.396	-8.505	0.00354
backward deletion			
FULL-model	165.396		
Step 1: MINUS effect P227	173.901	7.406	0.00650
Step 1: MINUS effect AUCmin non-linear	194.028	20.127	0.00454
Infection			
forward inclusion			
BASE-model	521.936		
Step 1: AND effect Leukocytes	517.793	-4.143	0.04181
backward deletion			
FULL-model	517.793		
Step 1: MINUS effect Leukocytes	521.936	4.143	0.04181 *
New Onset Diabetes Mellitus			
forward inclusion			
BASE-model	244.012		
Step 1: AND effect Age	237.468	-6.54369	0.01053
backward deletion			
FULL-model	237.468		
Step 1: MINUS effect Age	244.012	-6.54369	0.01053 *
ΔOFV >3.84 (P<0.05) forward inclusion and >6.64 (P<0.01) for backward deletion. * left out of the final model. ΔOFV difference of OFV			

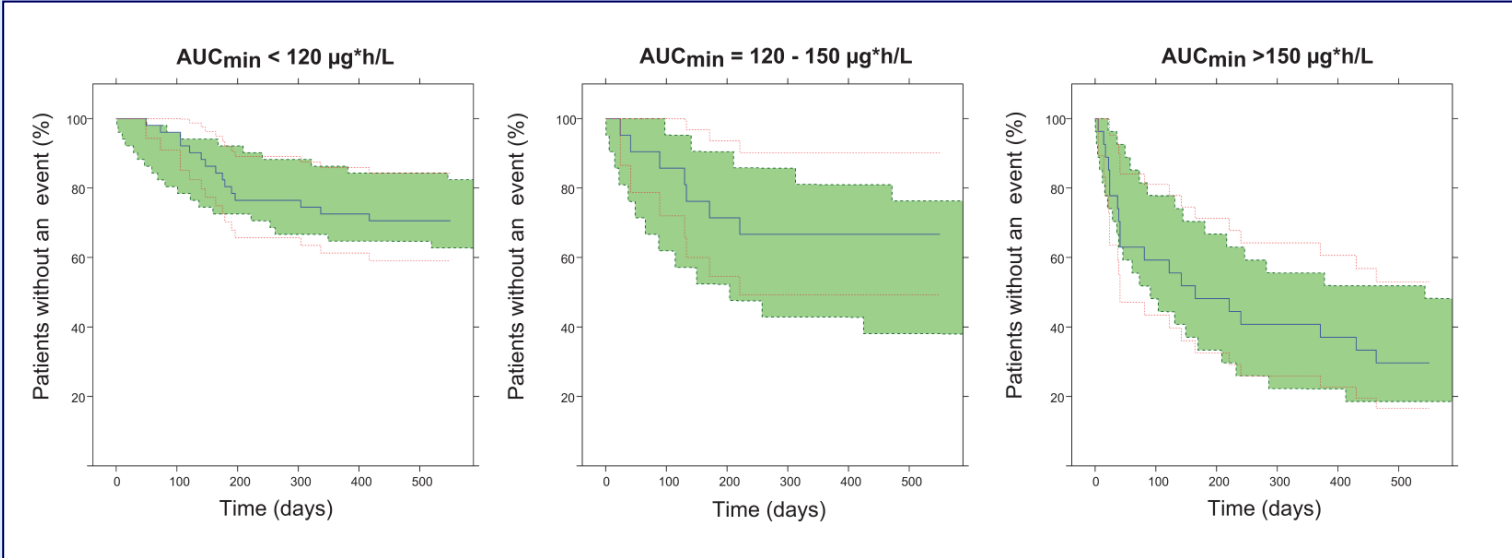


Figure 2: Kaplan-Meier VPC of final time to event model stratified by AUC_{min} groups. The shaded area represents the 95% prediction intervals for the simulated data. The continuous line represents the real data, the dashed red lines represent the 90% confidence interval of the real data.

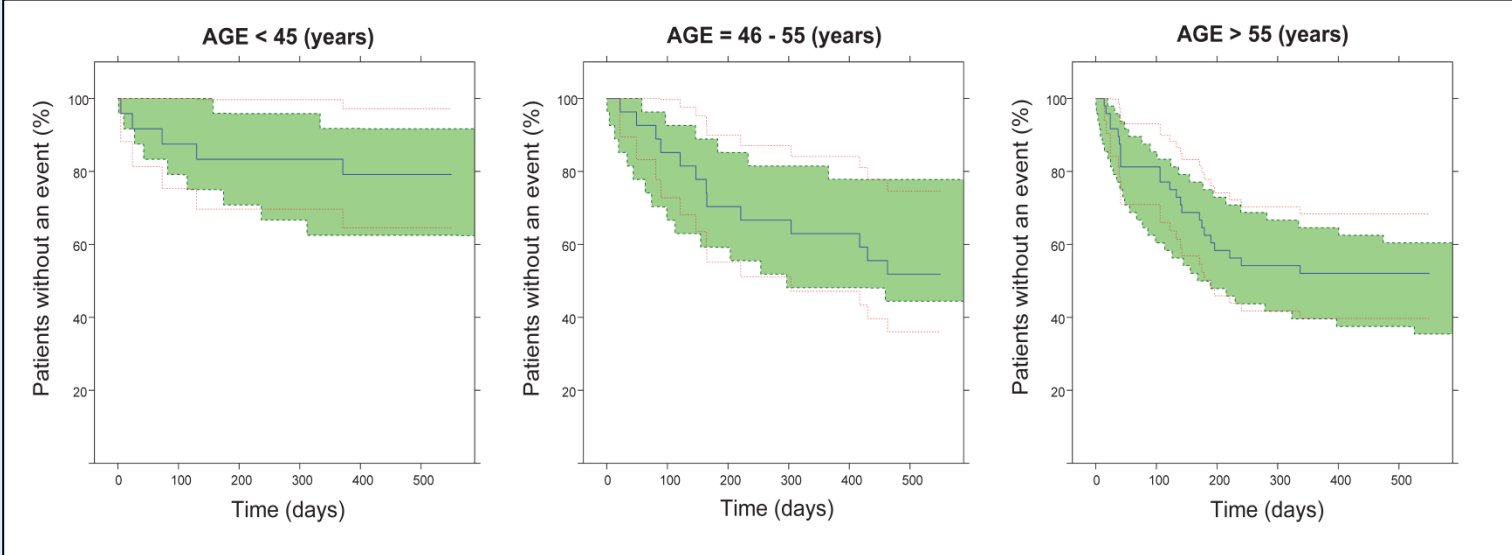


Figure 3: Kaplan-Meier VPC of final time to event model stratified by age group. The shaded area represents the 95% prediction intervals for the simulated data. The continuous line represents the real data, the dashed red lines represent the 90% confidence interval of the real data.

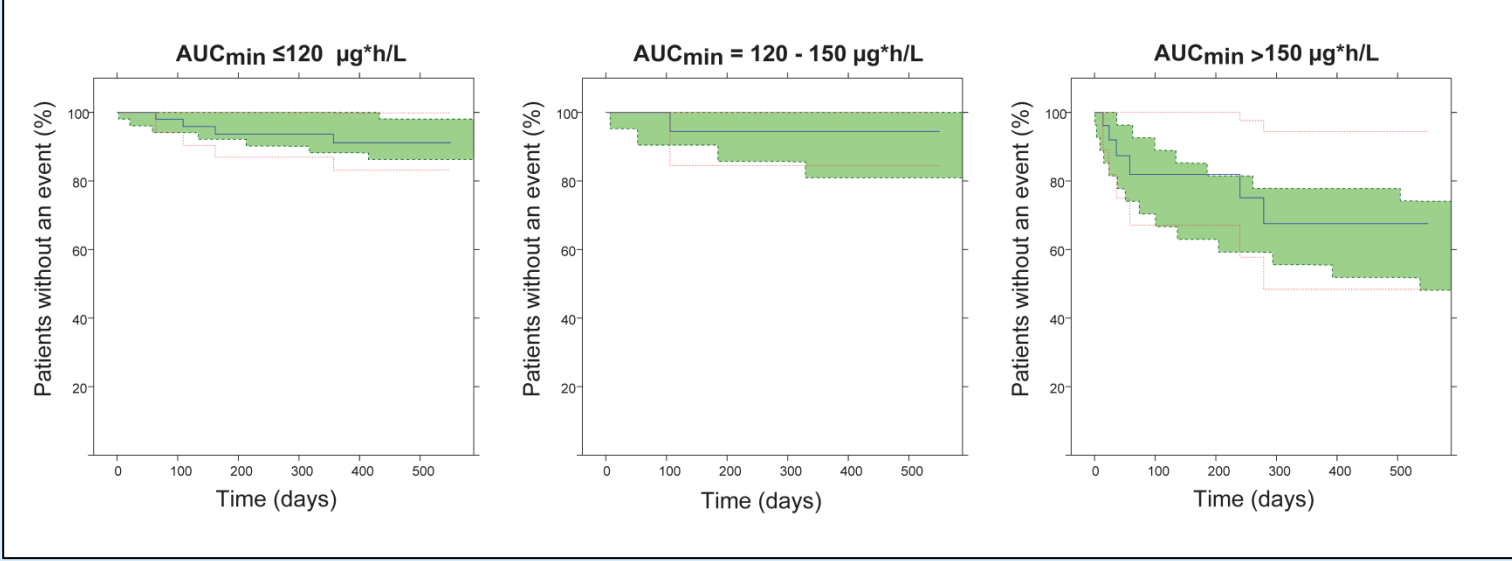


Figure 4: Kaplan-Meier VPC of final time to event model stratified by AUC_{min} groups. The shaded area represents the 95% prediction intervals for the simulated data. The continuous line represents the real data, the dashed red lines represent the 90% confidence interval of the real data.

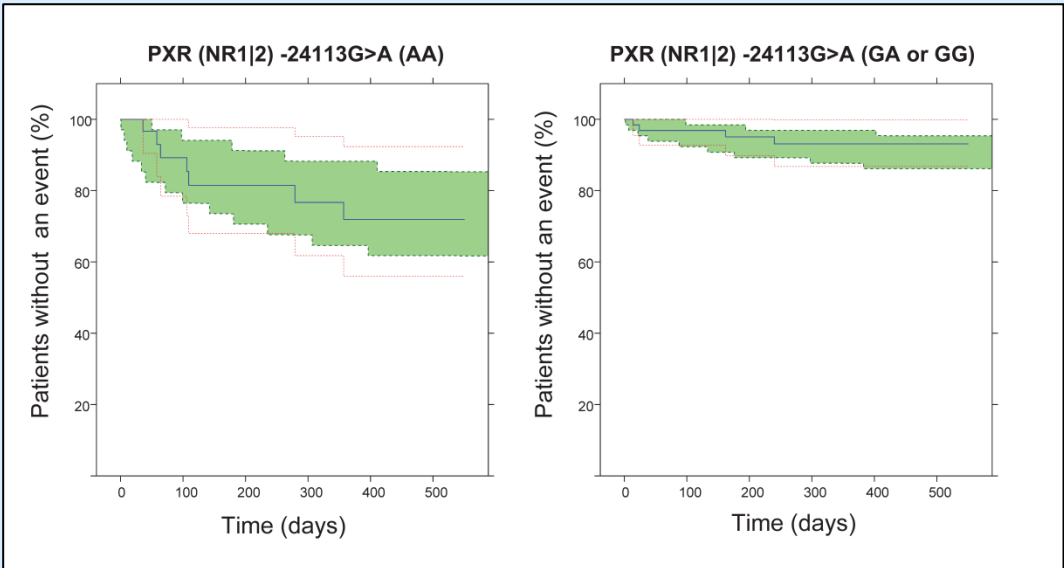


Figure 5: Kaplan-Meier VPC of final time to event model stratified by PXR (NR1J2) -24113G>A groups. The shaded area represents the 95% prediction intervals for the simulated data. The continuous line represents the real data, the dashed red lines represent the 90% confidence interval of the real data.

Conclusions

- High discontinuation rates and low acute rejection rates in this study: 2 mg as initial dose might be a better option.
- Discontinuation was associated with high everolimus exposure and increasing age.
- Non infectious interstitial pneumonitis associated with high everolimus exposure and PXR (NR1J2) (-24113G>A) AA genotype.
- No risk factors identified for new onset diabetes mellitus and infection.

References

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