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## **Mycophenolic acid exposure prediction using machine learning**

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## Abstract

Therapeutic drug monitoring of mycophenolic acid (MPA) based on area under the curve (AUC) is well established and machine learning (ML) approaches could help to estimate AUC. The aim of this work is to estimate the AUC of MPA in organ transplant patients using Xgboost ML models.

A total of 12,877 MPA AUC<sub>0-12h</sub> requests from 6884 patients sent to our ISBA expert system ([www.pharmaco.chu-limoges.fr/](http://www.pharmaco.chu-limoges.fr/)) for AUC estimation and dose recommendation based on MPA concentrations measured at least at 3 sampling times (approx. 20min, 1 and 3h after dosing) were used to develop 2 ML models based on 2 or 3 concentrations. Data were split into a training set (75%) and a test set (25%) and the Xgboost models in the training set with the lowest RMSE in a ten-fold cross-validation experiment were evaluated in the test set and in 4 independent full-pk datasets from renal or heart transplant patients.

ML models based on 2 or 3 concentrations, differences between these concentrations, relative deviations from theoretical times of sampling, presence of a delayed absorption peak and 5 covariates (dose, type of transplantation, associated immunosuppressant, age and time between transplantation and sampling) yielded accurate AUC estimation performances in the test datasets (relative bias<5% and relative RMSE<20%) and better performance than MAP Bayesian estimation in the 4 independent full-pk datasets.

The Xgboost ML models described allow accurate estimation of MPA AUC<sub>0-12h</sub> and can be used for routine exposure estimation and dose adjustment and will soon be implemented in a dedicated web interface.

## Introduction

Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid (MPA), an immunosuppressive drug inhibiting inosine monophosphate dehydrogenase which is an enzyme involved in the de novo pathway for purine biosynthesis<sup>1</sup>. Although, MMF was initially marketed as a fixed dose drug, it exhibits a large inter-individual pharmacokinetic variability, poor relationships between dose vs. mycophenolic acid (MPA) area-under-the-curve (AUC) or through blood level (C<sub>0</sub>) vs. AUC; and a better correlation between MPA AUC and patient outcome than any single concentration-time point or dose . While the last conference consensus recommended MPA therapeutic drug monitoring (TDM) based on the AUC as the best exposure marker <sup>2</sup>, TDM is still not performed everywhere or for all patients. This is probably due to the poor predictive value of the C<sub>0</sub> and the difficulty to estimate MPA AUC without the use of population pharmacokinetic models and maximum a posteriori Bayesian estimators based on limited sampling strategies. Indeed, this approach is not easy to implement in routine practice and needs some pharmacokinetic background and computer skills.

This led us to launch in 2005 the Immunosuppressant Bayesian Dose Adjustment (ISBA) expert system and website <sup>3</sup> to share tools able to estimate the inter-dose AUC of immunosuppressants using population pharmacokinetics (POPPK) models and maximum a posteriori Bayesian estimation (MAP-BE) on the basis of 3 blood samples and patient characteristics (type of graft, age, post transplantation period, drug measurement assay) and the expertise required to interpret the data and make dose recommendations. On this website, each request posted is validated in less than 48h by a trained pharmacologist, representing a huge workload due to the large number of requests received from transplant centers worldwide (>120,000 since 2005). The POPPK models used in the ISBA back-office for MMF have all been developed using an in-house PK modelling package (ITSIM) that employs the iterative two-stage Bayesian estimation method (ITSB), as previously reported<sup>4</sup>. To describe the complex MPA profiles, we used one-compartment models with linear elimination and absorption modeled using two gamma distributions<sup>5</sup>. No covariate is used in the models but several

priors (“models”) have been built based on a few characteristics: cyclosporine co-treatment, adult/children, type of transplantation, drug assay and post-transplantation period. These models have been largely and successfully used, as reported in several papers<sup>6-11</sup>.

Machine learning is widely used in numerous application including pharmacology (Pubmed Entry “Machine learning” & “Pharmacology”= 600 in 2018, 846 in 2019) especially in structure/activity predictions<sup>12,13</sup> or drug discovery<sup>14</sup> but only a few applications to predict drug exposure, PK parameters or optimal dose exist<sup>15-19</sup>. Recently, we successfully applied a machine learning approach for tacrolimus AUC estimation that yielded better performance in terms of relative bias or imprecision vs reference trapezoidal rule AUC than maximum a posteriori Bayesian estimation (MAP-BE), even with only 2 samples<sup>19</sup>. We used extreme gradient boosting (Xgboost R package) where simple regression trees are iteratively built by finding among all the input variables, split values that minimize the prediction error. The iterative process constructs an additional regression tree of the same structure that minimizes the residual errors of the previous regression tree<sup>20</sup>.

A major difference between the population pharmacokinetics approach and machine learning is that POPPK involves results from specifying a mechanistic model, physiologically interpretable to describe the observed data while ML aims to find the best algorithmic model that minimizes prediction errors based on the data and results. ML exhibits excellent performances while losing in interpretability (“black box” phenomenon). The more the algorithm used to predict a result is complex, the more the performances are improved but the interpretability decreases<sup>21</sup>. Currently, the algorithms associated with the highest number of wins in the Kaggle competition are deep neural networks and Xgboost methods<sup>22</sup>.

The objective of this study was to develop Xgboost models to estimate mycophenolic acid (MPA) inter-dose AUC<sub>0-12h</sub>, based on a limited number of blood concentrations (2 or 3) and predictors, and to compare their performance to that of MAP-BE in external validation datasets.

## Methods

### Patients and data

The MPA AUC<sub>0-12</sub> estimation and dose recommendation requests received on our ISBA website since 2007, whatever the type of transplantation, were extracted and cleaned using the tidyverse framework<sup>23</sup>. We selected the requests with: an interdose of 12h; MPA plasma levels measured using HPLC; and at least 3 sampling time points at approximately 20 min (10 to 30 min, C20), 60 min (45 to 75 min, C1) and 180 min (160 to 200 min, C3) after drug intake. The 20, 60, 180 min limited sampling strategy (LSS) was previously reported as the optimal sampling schedule in most situations for MMF AUC<sub>0-12</sub> estimation based on samples taken in the 4h post dosing<sup>2</sup>. The other predictors available were the morning dose of MMF, the time elapsed between transplantation and sampling, the indication of MMF (in decreasing order: kidney, heart transplantation, nephrotic syndrome, liver, lung transplantation, lupus in adult patients, lupus in pediatric patients, hematopoietic stem cell transplantation and all the remaining cases gathered as “others”), the associated immunosuppressant (cyclosporine, tacrolimus, sirolimus/everolimus or none of these) and patients' age.

### Plan of the study

In this study, supervised learning was used to predict AUC<sub>0-12h</sub>, whose reference value had been obtained by our ISBA expert system using MAP-BE and at least 3 concentrations. Two machine learning (ML) models were developed in parallel, one including only 2 concentrations and the other including 3. The data were split into a training set, used to build the model, tune the hyperparameters and evaluate model performance by cross-validation and a test set used to evaluate the performance of the models in an independent set of data. The performances were evaluated in the test set only after the best model had been optimized in the training set, by calculating the root mean square error (RMSE, expressed in mg\*h/L) between the estimated and reference AUCs. Because the reference (MAP BE) AUC<sub>0-12h</sub> can be considered as an imprecise and

potentially biased estimate of the “true” AUC, the results of our Xgboost models based on 2 or 3 concentrations to the “true” AUCs obtained from full PK profiles using MAP BE applied to all the samples available were also compared. For that, we used 4 different datasets from adult renal transplant patients (i) on MMF + tacrolimus; PCCP<sup>24</sup>, (ii) on MMF + cyclosporine (Stablocine<sup>25</sup>) and (iii) on MMF + cyclosporine or sirolimus (CONCEPT<sup>26</sup>) and one from adult heart transplant patients on MPA + cyclosporine or tacrolimus (PIGREC<sup>10</sup>). The performances of the Xgboost models in these confirmation datasets were also compared to that of the MAP-BE based on the 3 time-points limited sampling strategies available on ISBA.

## Feature engineering

The MPA concentrations were binned into 3 theoretical time classes (concentrations at 20min (C20 sampled between 10 and 30min), at 1h (C1 sampled between 45 and 75 min) and at 3h (C3 sampled between 160 and 200 min)), leading to 3 predictors per patient. The relative deviation with respect to the theoretical times was also considered. For instance, if the actual sampling time was 1.06h for the theoretical time 1h, the relative time difference was  $(1.06 - 1)/1 = 0.06$ . The differences between the concentrations C1 – C20, C1 – C3 and C3 – C20 were also considered as potential predictors and, to add information about potentially delayed absorption peaks, 3 dummy variables corresponding to C3>C1, C3>C20 and C3>C20&C1 were created. Finally, the set of features used to predict AUC0-12h were: the categorized indication of MMF, the categorized associated immunosuppressant, patient age, time elapsed between transplantation and MPA plasma sampling, MMF morning dose, MPA concentrations at times 20min, 1h and 3h, relative deviation from the theoretical times, differences between concentrations, and dummy variables for delayed absorption peak. For the models based on 2 concentrations (C1 and C3), the relative time difference for C20 and the concentration differences or dummy delayed absorption including C20 were removed.

## Exploratory data analyses

A correlation matrix and scatterplots were drawn to explore the correlation between AUC0-12h and predictors using the GGally package<sup>27</sup>. Boxplots were also built to investigate AUC0-12h/dose in the subgroup with cyclosporine vs other immunosuppressants, split by MMF indications. Indeed, cyclosporine is known to be associated with lower AUC/dose values due to inhibition of MPA enterohepatic recycling<sup>28</sup>.

## Pre-processing of the data

For all the ML analyses, the tidymodels framework was used<sup>29</sup>. The two categorical variables “indication for MMF” and “associated immunosuppressants” were one hot encoded (i.e., transformed in 0/1 dummy variables). No other pre-processing was applied to the data, as Xgboost does not require normalization. There was no missing data in the predictors. Data splitting was performed by random selection of patients in a training (75%) and a test set (25%).

## Development of the Xgboost models

A tuning step was done by searching, in a 40X40 grid, the parameter combination associated with the lowest RMSE and highest  $r^2$  between estimated and reference AUC0-12 values, using a 10-fold cross-validation (for which the training dataset was randomly split into 10 parts). In brief, the best combination of parameters was investigated in 90% of the training set (called the analysis subset) and evaluated in the remaining 10% (called the assessment subset) and this process was repeated 10 times by circular permutation. The parameters tuned were: the number of predictors randomly sampled at each split (mtry, between 1 and 28), the minimum number of data points in a node required for the node to be split further (min\_n between 1 and 40), the maximum depth of the tree (tree\_depth, between 1 and 15), the rate at which the boosting algorithm adapts from iteration-to-iteration (learn\_rate, between 0 and 0.08) and the amount of data randomly exposed to the fitting routine at each tree (sample\_size, between 0.1 and 1). The relative importance of the predictors was then evaluated by random permutations and variable importance plots were drawn. Once the best



parameter combinations had been selected, the model was evaluated using 10-fold cross-validations to assess the mean RMSE and  $r^2$  and their standard deviations in the training set and scatter plots of estimated and residuals vs. reference AUC0-12 were drawn. In a last step, the AUC0-12 prediction was performed in the test set and the performances were evaluated by calculation of the RMSE,  $r^2$ , the relative mean prediction error (MPE), relative RMSE (imprecision) and the number and proportion of estimations with an MPE value out of the  $\pm 20\%$  interval. Scatter plots of predicted vs. reference AUC0-12, and of residuals vs. reference AUC0-12 were also drawn.

### External evaluation vs full PK profiles and comparison with POPPK

Concentrations at 20min, 1h and 3h as well as dose, sampling times and time elapsed between transplantation and MPA plasma sampling were extracted from the PK databases to predict the AUC0-12 using the ML models and the MAP-BE based on 3 concentrations, as used in ISBA. The full concentration profiles were also used to calculate the “true” AUC0-12 using MAP-BE with all the available samples.

Performances of the ML models using 2 or 3 concentrations and of MAP-BE based on 3 concentrations were compared to the reference AUC0-12 in terms of the relative MPE and relative RMSE and the proportion of MPE out of the  $\pm 10\%$  or the  $\pm 20\%$  interval. Additionally, scatter plots of predicted AUCs or residuals vs. the reference AUC0-12 were drawn to compare the different approaches.

The PCCP study<sup>24</sup> included 128 PK profiles of 11 samples (0, 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 12h post dosing) collected at 7 and 14 days, 1, 3 and 6 months after renal transplantation. The Stablocine study<sup>25</sup> included 20 PK profiles of 10 or 11 samples (0, 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 9h and (not present in every profile) 12h post dosing) in stable renal transplant patients. The CONCEPT study<sup>26</sup> included 67 PK profiles of 10 or 11 samples (0, 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 9h and (not present in every profile) 12h post dosing) collected at weeks 12, 16 and 26 after renal transplantation. The

PIGREC study<sup>10</sup> included 75 PK profiles of 10 samples (0, 0.33, 0.66, 1, 1.5, 2, 3, 4, 6 and 9h post dosing) collected between day 7 and day 14, and at 1,3 and 12 months after transplantation.

## Results

### Patients and data

A total of 12,877 MPA AUC<sub>0-12h</sub> requests from 6884 patients fulfilling the inclusion criteria were available in the cleaned datasets extracted from ISBA (out of 12,890 requests before cleaning). The characteristics of the training and test sets are reported in Table 1. The AUC<sub>0-12</sub> ranged between 1 and 181 mg\*h/L and 3 and 164 mg\*h/L in the training and test sets, respectively. Boxplots of AUC<sub>0-12</sub>/dose in the different subgroups defined by cyclosporine vs other immunosuppressants and indication of MMF are presented in Figure S1.

### Exploratory data analyses

The correlation matrix between AUC<sub>0-12</sub> and individual predictors is presented in Figure S2 and shows rather poor correlation in general, the best being with C1h ( $r=0.7$ ) and C3h ( $r=0.66$ ).

### Xgboost model

The best-tuned parameter values for each model are presented in Supplemental Table S1. Excellent validation results were obtained in the training set (using 10-fold cross-validation) and in the test set (Table 2). Interestingly, there was no difference between the two validation steps, suggesting that there was no overfitting in the training set, thanks to the cross-validation. AUC<sub>0-12</sub> ML estimation was approximately twice better when using 3 concentrations rather than 2. The relative MPE was close to 0 and the relative RMSE <20% in both the training and test sets. The scatter plots and residual plots obtained in the test sets are presented in Figure 1. The variable importance plot of each model is presented in Figure S3 and shows that concentrations at time 3 and 1h were the most important variables.

## External evaluation vs the reference AUC0-12 and comparison with POPPK estimates

The results of external validation in full-PK databases are presented in Table 3 and show that only the Xgboost model with 3 concentrations led to better results than with 2 points or the 3-point MAP-BE, in comparison to the reference AUC. The prediction performance in the early period post-transplantation (<1 month) was similar to that in the whole validation datasets.

Figure 2 presents the scatter plots and residual plots of estimated vs. reference AUC0-12 in these final validation studies. Figure 3 presents for each individual the MPA AUC0-12 estimated using ML with 2 or 3 samples, MAP-BE with 3 samples and the reference AUC0-12.

## Discussion

In this work, we developed Xgboost ML models based on 2 or 3 samples to estimate the AUC0-12h of MPA in transplant or auto-immune indications. The models were developed using the standard ML procedure with a development in a training set using cross-validation for tuning of the parameters and estimation of the performances and once the best model was selected, validation in the test set. The results were then compared on an external dataset with those obtained by extensive-sampling AUC0-12 estimated using MAP-BE using all the available samples (reference AUC0-12) and to MAP-BE estimates based on a 3-point LSS, as employed by the ISBA expert system<sup>3</sup> in renal and heart transplant patients. The performances of the ML were excellent as compared to the reference AUC0-12 when using 3 concentrations, and numerically better than those of MAP-BE based on the 3-point LSS.

The performances obtained with the 3-point ML model were better in all the external validation datasets, in terms of imprecision and number of profiles out of the  $\pm 20\%$  acceptability interval, than the 3-point MAP-BE. Additionally, the MAP-BEs available in ISBA and used in the present study for comparison to ML were initially developed using the datasets used here for validation, probably

advantaging them. However, in line with our previous results for tacrolimus, ML yields better results. The ML model using only 2 samples showed acceptable bias values but imprecision around 25%, which is not so high in comparison to literature results but very close to the threshold of 25% considered as the limit for accurate estimation in the last MPA consensus<sup>2</sup>. This 2-point ML estimator might still be used in cases where only 2 samples are available, but the prescriber has to be informed of the degraded performance in comparison to the 3-point model.

In addition to better performances than the 3 samples MAP-BE used in ISBA, the ML approach has the advantage of practicability, as our single ML model can accommodate all associated immunosuppressants or MMF indications, when different MAP-BEs are necessary for each subgroup in ISBA.

There are some differences between this study and our previous one with tacrolimus<sup>19</sup>. Indeed, tacrolimus POPPK is not easy to model, but it has obvious associations with covariates that explain part of the inter-individual variability, the dose-exposure relationship is good and the AUC is fairly correlated with single time-points (the first being the trough level, used in routine practice)<sup>30</sup>. All these elements may explain why our first ML algorithms were successful. The situation is very different with MMF, which can be regarded as the worst-case scenario: MPA exhibits very complex pharmacokinetics, the very diverse (and sometimes chaotic) individual profiles are much more difficult to model and there is only a weak correlation between the dose and the AUC (as shown here), and between the AUC and any single time point<sup>2</sup>. Therefore, it was much more challenging to develop accurate ML algorithms for MPA, and this achievement suggests it should be possible for all the other drugs for which TDM is performed. The progress when compared to MAP-BE looks less impressive than with tacrolimus, but this highlights the fact that learning from a less precise reference (here MAP-BE imprecision is ~20% for MMF) results in somewhat less precise prediction. If the ML models were trained in a large, full-profile dataset they would have been more accurate, but we did not have such a database. In our hands, trading rich profiles for a lower number of patients

(i.e. training the ML algorithms in the validation datasets) did not result in a better performance either.

The principle of ML is to build algorithms that estimate individual values with the lowest imprecision, which is perfectly adapted to TDM. However, ML algorithms cannot study the determinants of inter- or intra-individual variability or perform simulations to estimate a priori the first dose, or calculate the probability of target attainment for different dosing regimens, for instance. Therefore, we think that ML may replace POPPK for individual exposure estimation but that POPPK will remain very useful for other purposes. Additionally, although being very accurate, ML algorithms are not as flexible as POPPK models. For instance, our ML models cannot take into account more than 3 samples per patient and the sampling times have to be in the same ranges as those of the training set (since the validation for times outside these ranges has not yet been done).

Imprecision values observed in the present study (19%, 14.7%, 22.5%, in renal and 14.6 % in heart transplantation) are slightly better than those reported in the literature, in the range of 20%-25%<sup>5,10,31-35</sup>. These values are higher in comparison to other immunosuppressants (e.g. tacrolimus, with imprecision ~10%) but they reflect the complexity of MPA pharmacokinetics. Some papers reported slightly better precision, but these POPPK models were either not validated in independent datasets<sup>7,9,36</sup> or they compared 3-points MAP-BE AUCs to reference AUCs obtained using 6 samples and the same POPPK model, leading probably to overestimation of the MAP-BE results<sup>11</sup>.

The randomized, comparative APOMYGRE study in 137 adult kidney transplant recipients on CsA showed that concentration-controlled MMF dosing using the MAP-BE implemented in ISBA had a significant lower incidence of acute rejection than patients with standard-dose MMF<sup>37</sup>. In their meta-analysis, Metz et al.<sup>38</sup> concluded that when concentration-controlled dosing is performed based on pharmacokinetic calculation to a target concentration, MPA exposure is well controlled and clinical outcomes are improved, which has been stressed in the very recent consensus conference paper<sup>2</sup>.

Based on the better performance of our ML estimator in comparison to ISBA MAP-BEs (among which those used in the APOMYGRE study), we propose to use it for routine calculation of MPA AUC and will make it available to the medical community through a web-interface. In the meantime, a temporary shiny application ([https://jbwoillard.shinyapps.io/App-7\\_mmf\\_ml/](https://jbwoillard.shinyapps.io/App-7_mmf_ml/)) has been built to test the model (for research purposes only).

The added value of AUC-based dose adjustment of MMF has currently been demonstrated for the very early post-transplant phase (especially the first weeks after transplantation)<sup>2</sup>. The performances of our ML models in patients transplanted for less than 1 month (only one study in kidney and one in heart transplant patients had data collected within the 1st month) were very similar to those in the whole validation population.

The use of our ML estimator is submitted to some restrictions, due to the datasets used to design it: it was developed using MPA concentrations measured using HPLC and in which the inter-dose was 12h. Additionally, the external dataset used for external validation comprised only renal and heart transplant recipients. It's performances in the other MMF indications for which the model was developed (nephrotic syndrome, liver or lung transplantation, lupus, pediatric lupus, hematopoietic stem cell transplantation and "other" mostly corresponding to auto-immune disease) are still to be evaluated.

We believe that the ML models we developed are insensitive to the achievement of the pharmacokinetic steady-state, because they do not rely on a pharmacokinetic model and they gave excellent results in the very large training and validation datasets, where part of the profiles were certainly not at steady-state (e.g., profiles collected on day 7 post-transplantation where the dose had already been adjusted based on adverse effects).

However, these ML models have some limitations. To cope with deviations from the theoretical times, we included them as new features in the model but we have no idea about the accuracy of the algorithms when samples are drawn outside the ranges actually observed in our datasets. This has to

be investigated in further studies. In the meantime, we do not recommend using the algorithms when samples are collected outside the pre-defined ranges (20 min: from 10 to 30 min; 60 min: from 45 to 75 min; and 180 min: from 160 to 200 min). Also, our ML models are less flexible than MAP-BE and cannot manage more than 3 samples. These ML models are perfectly adapted for routine use but not really for research projects or specific cases in which more than 3 samples are available.

In conclusion, an Xgboost ML model providing accurate estimation of mycophenolic acid AUC0-12h has been developed for many MMF indications, and validated in independent groups of kidney and heart transplant recipients. It will soon be implemented in a dedicated web interface for these two indications. A patent has been filed.

## Study Highlights

- What is the current knowledge on the topic? Mycophenolic acid (MPA) AUC0-12h for individual dose adjustment is difficult to estimate in routine patient care.
- What question did this study address? We investigated whether machine learning models could estimate MPA AUC0-12h using a limited number of blood concentrations, as well as or even better than deterministic pharmacokinetic models with Bayesian estimation.
- What does this study add to our knowledge? We developed and validated in kidney or heart transplants Xgboost machine learning models allowing accurate estimation of MPA AUC0-12h based on 3 blood concentrations with better performances than that of the pharmacokinetic approach previously employed.
- How might this change clinical pharmacology or translational science? These models will be soon implemented in an expert system made available to the transplant community through a dedicated website.

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## Author Contributions

Jean-Baptiste WOILLARD designed the research, Jean-Baptiste Woillard, Marc Labriffe, Jean Debord and Pierre Marquet performed the research and analyzed the data, Jean-Baptiste Woillard and Pierre Marquet wrote the manuscript.



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Table 1: Characteristics of the ISBA requests used for the development and validation of the models

	<b>Train (n=9658)</b>	<b>Test (n=3219)</b>
<b>Time between transplantation and MPA blood concentrations (years)</b>	1.07 [0.25, 5.42]	1.06 [0.25, 5.73]
<b>AUC0-12h (mg*h/L)</b>	39.30 [29.11, 51.20]	39.24 [28.96, 50.88]
<b>Patient age (year)</b>	53.74 [38.58, 64.45]	52.85 [39.01, 64.10]
<b>Morning dose (mg)</b>	750 [500, 1000]	750 [500, 1000]
<b>Deviation from the 20m theoretical time</b>	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
<b>Deviation from the 1h theoretical time</b>	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
<b>Deviation from the 3h theoretical time</b>	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
<b>Concentration difference between C1h and C20m</b>	1.70 [-1.44, 5.61]	1.70 [-1.58, 5.50]
<b>Concentration difference between C1h and C3h</b>	5.20 [2.03, 9.20]	5.39 [2.10, 9.30]
<b>Concentration difference between C20m and C3h</b>	2.10 [-0.90, 8.00]	2.30 [-0.80, 8.38]
<b>Delayed absorption (C3&gt;C1)</b>	1293 (13.4)	409 (12.7)
<b>Delayed absorption (C3&gt;C20)</b>	3228 (33.4)	1035 (32.2)
<b>Delayed absorption (C3&gt;C20 &amp; C3&gt;C1)</b>	1145 (11.9)	379 (11.8)
<b>Associated immunosuppressant</b>		
<b>Tacrolimus</b>	5265 (54.5)	1811 (56.3)
<b>Ciclosporine</b>	2580 (26.7)	830 (25.8)
<b>None</b>	1542 (16.0)	483 (15.0)
<b>Sirolimus/everolimus</b>	271 ( 2.8)	95 ( 3.0)
<b>Transplant type</b>		
<b>Kidney</b>	7398 (76.6)	2470 (76.7)
<b>Heart</b>	782 (8.1)	246 (7.6)
<b>Nephrotic syndrome</b>	524 (5.4)	187 (5.8)
<b>Liver</b>	296 (3.1)	100 (3.1)
<b>Lung</b>	202 (2.1)	79 (2.5)
<b>Lupus</b>	97 (1.0)	30 (0.9)
<b>Pediatric lupus</b>	45 (0.5)	9 (0.3)

<b>Bone marrow</b>	34 (0.4)	13 (0.4)
<b>Other</b>	280 (2.9)	85 (2.6)

(median [IQR]) are presented for continuous data and n(%) for categorical data.

Table 2: Performances of the models in the training and testing datasets to estimate AUC0-12 obtained from 3 samples MAP-BE from ISBA

		<b>MPA 2 samples</b>	<b>MPA 3 samples</b>
<b>training</b>	<b>*RMSE <math>\pm</math> SD (mg*h/L)</b>	6.78 $\pm$ 0.08	5.59 $\pm$ 0.07
	<b>*R<sup>2</sup> <math>\pm</math> SD</b>	0.864 $\pm$ 0.004	0.908 $\pm$ 0.002
	<b>Relative MPE (%)</b>	2.7	1.8
	<b>Relative RMSE (%)</b>	18.6	14.5
<b>testing</b>	<b>RMSE (<math>\mu</math>g*h/L)</b>	6.41	5.34
	<b>R<sup>2</sup></b>	0.876	0.914
	<b>Relative MPE (%)</b>	2.1	1.4
	<b>Relative RMSE (%)</b>	17.0	13.2
	<b>Number of MPE out of the <math>\pm</math>20% interval n(%)</b>	560 (17.4%)	306 (9.5%)

\*Values and standard deviations obtained after 10 fold cross-validation,

Table 3: Performances of ML models and MAP-BE based on 3 samples LSS to estimate reference AUC0-12s obtained from full PK profiles using the trapezoidal rule.

Study	Method	All patients				Patients in the first month post transplantation			
		Relative MPE (%)	Relative RMSE (%)	Bias out of $\pm 20\%$ n (%)	Bias out of $\pm 10\%$ n (%)	Relative MPE (%)	Relative RMSE (%)	Bias out of $\pm 20\%$ n (%)	Bias out of $\pm 10\%$ n (%)
PCCP study (n=128 / n 1 <sup>st</sup> month = 49)	Xgboost 2 concentrations	-1.2	24.2	46 (35.9)	80 (62.5)	-1.1	24.1	20 (40.8)	67.3 (33)
	Xgboost 3 concentrations	-4.0	19.0	39 (30.5)	76 (59.4)	-4.9	19.2	15 (30.6)	57.1 (28)
	MAP-BE 3 concentrations	1.0	19.9	37 (28.9)	81 (63.3)	2.4	20.0	15 (30.6)	61.1 (30)
Stablocine (n=20)	Xgboost 2 concentrations	1.5	17.8	4 (20)	10 (50)	NA	NA	NA	NA
	Xgboost 3 concentrations	2.8	14.7	2 (10)	8 (40)	NA	NA	NA	NA
	MAP-BE 3 concentrations	9.3	20.5	7 (35)	9 (45)	NA	NA	NA	NA
CONCEPT (n=67)	Xgboost 2 concentrations	-0.8	26.3	27 (40)	42 (63)	NA	NA	NA	NA
	Xgboost 3 concentrations	-1.1	22.5	14 (21)	43 (64)	NA	NA	NA	NA
	MAP-BE 3 concentrations	2.1	25.1	18 (27)	40 (60)	NA	NA	NA	NA
PIGREC (n=75/ n 1 <sup>st</sup> month = 20)	Xgboost 2 concentrations	2.5	23.1	31 (41)	44 (59)	7.7	20.4	7 (35)	12 (60)
	Xgboost 3 concentrations	-1.2	15.6	17 (23)	41 (55)	3.5	14.3	6 (30)	10 (50)
	MAP-BE 3 concentrations	3.5	17.3	17 (23)	47 (63)	4.6	19.1	5 (25)	11 (55)

Figure 1: Scatter plots and residual plots of predicted vs reference interdose AUC0-12s in the test set, for MPA using 2 or 3 MPA plasma concentrations.

Figure 2: Scatter plots and residual plots of predicted vs reference interdose AUC0-12s in the external validation studies split into renal and heart transplantation. The MPA AUC0-12 is estimated using the Xgboost model from 2 or 3 MPA plasma concentrations and MAP-BE is the maximum a posteriori Bayesian estimation based on 3 samples and the parametric POPPK models available on ISBA.

Figure 3: Comparison of the different methods of MPA AUC0-12 estimation in the external validation studies. MAP-BE is maximum a posteriori Bayesian estimation based on the 20min, 1 and 3h limited sampling strategy and the parametric POPPK models available in ISBA. The colour blue refers to kidney transplant patients and red, heart transplant patients.