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1 **A machine learning approach to estimate the Glomerular Filtration Rate in Intensive Care Unit patients**
2 **based on plasma iohexol concentrations and covariates**

3

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6

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31 **Abstract**

32 Introduction: This work aims to evaluate whether a machine learning approach is appropriate to estimate the
33 glomerular filtration rate (GFR) in intensive care unit (ICU) patients based on sparse iohexol pharmacokinetic
34 data and a limited number of predictors.

35 Methods: Eighty-six unstable patients received 3250 mg of iohexol IV and had 9 blood samples collected 5, 30,
36 60, 180, 360, 540, 720, 1080 and 1440 min thereafter. Data splitting was performed to obtain a training (75%)
37 and a test set (25%). To estimate GFR, 37 candidate potential predictors were considered and the best machine
38 learning approach among multivariate-adaptive regression spline and extreme gradient boosting (Xgboost) was
39 selected based on the root mean square error (RMSE). The approach associated with the best results in a 10-fold
40 cross-validation experiment was then used to select the best limited combination of predictors in the training set,
41 which was finally evaluated in the test set.

42 Results: The Xgboost approach yielded the best performance in the training set. The best combination of covari-
43 ates was made up of; iohexol concentrations at times 180 and 720 min; the relative deviation from these theoret-
44 ical times; the difference between these 2 concentrations; the simplified acute physiology score II; serum
45 creatinine; and the fluid balance. It resulted in RMSE=6.2 mL/min and $r^2=0.866$ in the test set. Interestingly, the
46 8 patients in the test set with a GFR<30 mL/min were all predicted accordingly.

47 Conclusions: Xgboost provided accurate GFR estimation in ICU patients based on 2 timed blood concentrations
48 after iohexol IV administration and 3 additional predictors.

49 **Keywords:** machine learning; iohexol; Xgboost; glomerular filtration rate; critical care; acute circulatory failure.

50

51 **Key Points**

- 52 • Development of a machine learning model to estimate glomerular filtration rate through iohexol clearance in
53 ICU patients.
- 54 • This opens the way to the development of machine learning models to estimate drug exposure.
- 55 • This approach can be implemented through web interfaces for treatment individualization using therapeutic
56 drug monitoring.

57

58 1. Introduction

59 Accurate estimation of the glomerular filtration rate (GFR) in intensive care unit (ICU) patients is very im-
60 portant, not only because it has a high prognostic value but also because it helps to adjust care in order to avoid
61 potential renal failure and also adjusts the dose of low therapeutic index drugs with renal elimination (aminogly-
62 cosides, beta-lactams...). Currently, in routine care, GFR is estimated using serum creatinine, an endogenous
63 compound (produced by muscle catabolism) filtered by the kidneys [1]. However, patients hospitalized in the
64 ICU may not have steady-state production and elimination of creatinine (due to fever, liver failure, change in
65 fluid balance, rhabdomyolysis, increase in creatinine secretion...) rendering formulas based on serum creatinine
66 inaccurate [2].

67 Iohexol has been initially marketed in France as a radiographic contrast medium. It is mainly indicated for CT-
68 scans, urography or angiography in children, adolescents and adults (Summary of Product Characteristics).
69 Iohexol exhibits interesting pharmacokinetic characteristics which makes it a good candidate for the estimation
70 of GFR [3]. Several abbreviated formulas have been proposed to estimate GFR using only a few blood samples
71 drawn during the elimination phase after IV administration of iohexol, the most popular being the Bröchner-
72 Mortensen formula [4]. However, the characteristics of ICU patients, presenting altered drug distribution pat-
73 terns, render these formulas inappropriate. Thus, the best way to calculate iohexol pharmacokinetic parameters
74 in these patients is to obtain a full pharmacokinetics (PK) profile. Some studies have developed population
75 pharmacokinetics (POPPK) models for iohexol in specific populations (kidney transplant recipients, elderly
76 patients) using different structural models (2 or 3 compartments) [5–8]. However, estimating the pharmacokinet-
77 ics of a compound requires drawing many blood samples, which is not easy to apply in routine care. In a recent
78 work, we showed that POPPK modeling and Bayesian estimation of iohexol clearance allows accurate assess-
79 ment of GFR in ICU patients [9]. However, these tools require population pharmacokinetic modeling skills and
80 software that may not be readily available in ICUs. Furthermore, in the context of unstable renal function as
81 observed in patients with acute circulatory failure, assumptions on the structural model may be inaccurate or too
82 simplistic, due to some degree of erratic variability of concentrations over the sampling period.

83 Rather than defining a structural model to describe observed data, machine-learning approaches use algorithmic
84 modeling of free parameters linked with complex interactions [10]. In the context of pharmacokinetics, these
85 methods could be used to estimate clearance from a number of patient features, i.e. demographic characteristics,
86 laboratory test results, disease history, or associated medications. Extreme gradient boosting is a machine-
87 learning approach based on boosting. In brief, simple regression trees are iteratively built by finding split values
88 among all input variables that minimize prediction error. The iterative process constructs an additional regres-
89 sion tree of the same structure, but which minimizes the residual errors of the first regression tree [11]. Multivar-
90 iate adaptive regression splines (MARS) capture the nonlinear relationships in the data. This method assesses
91 cut points (knots) for each predictor, converts continuous features into ordered categorical variables, and then
92 creates a linear regression model with the candidate feature(s). The exact form of the nonlinearity is not specified
93 before the train of the model and the approach investigates nonlinearities and interactions in the data that help to
94 maximize accuracy [12].

95 These non-linear methods are meant to make estimations with the highest accuracy. Once constructed, these
96 predictive models can be used in clinical practice using web-interfaces or applications. This work aims to use
97 machine learning to estimate ICU patients' GFR at the time of sampling using a limited number of Iohexol blood
98 concentrations and other predictors, and to compare its performance to that of the Bröchner-Mortensen formula
99 and of a population pharmacokinetics model.

101 **2. Material & methods**

103 *2.1. Patients and pharmacokinetic study*

104 This is a post-hoc analysis of the database of the "IOXREA" study (NCT0205026). This clinical study was set
105 up by the intensive care units at the University Hospitals of Tours, Strasbourg and Orleans and aimed at describ-
106 ing pharmacokinetic profiles of iohexol in unstable ICU patients with acute circulatory failure of any cause.
107 Details of the protocol and patient characteristics are available in a recent article reporting the iohexol population
108 pharmacokinetic model developed [9]. In brief, at most 12h after admission to ICU patients received a unique
109 iohexol dose of 3235 mg by intravenous bolus injection and had 9 blood samples collected at 5, 30, 60, 180, 360,
110 540, 720, 1080 and 1440 min after. Body weight, body mass index, serum creatinine at admission and during
111 iohexol sampling, plasma protein and albumin, blood urea, the fluid balance, simplified acute physiology score
112 II (SAPSII) [13], nephrotoxic drugs administered, hematocrit and plasma sodium were recorded. Iohexol plasma
113 concentration measurement was performed using a High-Performance Liquid Chromatography with Diode-
114 Array Detection (HPLC-DAD) method in the laboratory of biochemistry at Tours University Hospital [14].

116 *2.2. Principle of the machine learning analysis*

117 The present study used supervised learning to estimate iohexol clearance (as a surrogate marker of GFR), a con-
118 tinuous outcome (regression problem), the reference value of which was set using a reference method (CL_{Ref}).
119 The reference iohexol clearance values were obtained using the population pharmacokinetic model previously
120 developed in these patients, all the concentration-time points available [9] and maximum a posteriori bayesian
121 estimation. A training set was used to build and tune the model parameters (through iterations by minimizing an
122 objective function, i.e. the algorithm "learns" how to predict reference clearance) and once the best model was
123 defined, it was evaluated on an independent test set that has not been used to develop the model (by measuring
124 the accuracy of clearance estimation).

126 *2.3. Data preparation and feature engineering*

127 The potential predictors investigated in the present study included pharmacokinetic data (iohexol concentrations,
128 sampling times, and differences between theoretical and actual sampling times), demographic data (age, sex,
129 weight, height, body mass index, body surface area), laboratory test results (creatinine at inclusion and during
130 iohexol sampling, urea, albumin, hematocrit, proteinemia, natremia) and clinical data (fluid balance during
131 pharmacokinetic assessment, SAPSII, main admission diagnostic and administration of nephrotoxic drugs the
132 day before inclusion). The iohexol sampling was gathered into 9 theoretical time classes (bins), leading to 9
133 columns per patient for iohexol concentrations (ESM_1). To account for the deviation of true vs. theoretical
134 sampling times, a new variable was created, corresponding to the relative deviation with respect to the theoreti-

135 cal time within each bin. For example, if the sample time was 185 min and the corresponding theoretical time
136 was 180 min, the relative time difference was $(185 - 180)/180 = 0.028$.

137

138 *2.4. Exploratory data analyses*

139 Exploration of the data was performed by means of the GGally R package ([https://CRAN.R-](https://CRAN.R-project.org/package=GGally)
140 [project.org/package=GGally](https://CRAN.R-project.org/package=GGally)) using scatterplots, boxplots and density distribution plots. This analysis allows
141 exploring correlations between variables, because some machine learning methods (including MARS) exhibit
142 poor performance with highly correlated features. Additionally, it was used to explore the correlation between
143 the reference clearance and the predictors.

144

145 *2.5. Pre-processing of the data*

146 A pre-processing step is needed before the development of machine-learning models. Most machine-learning
147 methods cannot deal with missing data (including MARS) and thus require an imputation step. We used the k
148 nearest neighbor imputation (5 nearest neighbors) to impute missing data [15]. Additionally, MARS requires a
149 normalization step (centering and scaling) and the exclusion of predictors characterized by a null variance (mon-
150 otonic predictors that often make the model crash), which we applied.

151 Validation of the algorithms and evaluation of their predictive performances in an independent dataset is a cru-
152 cial step to evaluate the merits of the model. Data splitting was performed by random selection of patients in a
153 training (75%) and a test set (25%). Estimations obtained in the validation set were compared to CL_{Ref} .

154

155 *2.6. Selection of a first machine-learning approach*

156 First, Xgboost and MARS were run using all features in the training set. The models were tuned by searching the
157 parameter combination associated with the lowest root mean squared error (RMSE) and highest r^2 with reference
158 GFR values, using a 10-fold cross-validation for which the training dataset was randomly split into 10 parts. The
159 best combination of parameters was investigated in 90% of the training dataset (analysis set) and evaluated in the
160 10% remaining (assessment) dataset, and this process was repeated 10 times. For Xgboost, the parameters, tuned
161 among a grid of fifty random combinations, were: the number of predictors randomly sampled at each split
162 (mtry, between 1 and the number of predictors), the minimum number of data points in a node required for the
163 node to be split further (min_n, between 1 and 40), the maximum depth of the tree (tree_depth, between 1 and
164 15) and the rate at which the boosting algorithm adapts from iteration-to-iteration (learn_rate, between 0 and
165 0.08). For MARS the parameters, tuned among a grid of fifty random combinations, were the number of terms in
166 the model (between 1 and 37) and the highest possible degree of interaction between features (1 or 2). Secondly,
167 once the best parameter combination was found, the models were evaluated using additional 10-fold cross-
168 validations to assess the mean RMSE and r^2 and their standard deviations.

169

170 *2.7. Features selection*

171 We calculated the maximal information coefficient (MIC), which measures the strength of the linear or non-
172 linear association between two variables X and Y, and selected the 4 variables best associated with iohexol
173 clearance, in addition to iohexol concentrations and corresponding relative time differences. Then, combinations

174 of limited numbers of predictors were investigated in terms of mean RMSE and r^2 using 10-fold cross-validation
175 in the training set, with the best approach selected at the previous step (Xgboost or MARS).
176 Finally, the model with the best performances was selected to predict iohexol clearance values in the independ-
177 ent test set. The relative importance of the estimators was evaluated by random permutations and a variable
178 importance plot was drawn. The estimation performance was evaluated using scatter plots of estimated vs. CL_{Ref}
179 and Bland-Altman plots. Reference and estimated iohexol clearance values were secondarily categorized into
180 groups according to the Kidney Disease Improving Global Outcome (KDIGO) acute kidney injury working
181 group recommendations, as follows: <30 mL/min, ≥ 30 to 60 mL/min, ≥ 60 to 90 mL/min, ≥ 90 to 130 mL/min
182 and ≥ 130 mL/min and a confusion matrix was drawn.

183

184 *2.8. Robustness evaluation*

185 To evaluate the influence of iohexol concentration and sampling time uncertainty, 10% noise was randomly
186 added to the test set using the addNoise function of the sdcMicro R package [16] and the resulting performances
187 were compared to those of the best model. The individual predicted clearances were compared using a paired t-
188 test.

189

190 *2.9. Comparison with other approaches*

191 Results obtained in the test dataset using the best machine-learning approach were compared to those obtained
192 using the standard Bröchner Mortensen formula using 4 blood samples drawn during the elimination phase (180,
193 360, 540 and 720 min or 180, 360, 540 and 1440 min after iohexol administration) [4]. They were also compared
194 to those from a Maximum a posteriori Bayesian estimator using 3 iohexol samples (0.1, 1 and 9h post infusion)
195 and a non-linear mixed effect population pharmacokinetic model developed in Monolix (Monolix version
196 2019R1. Antony, France: Lixoft SAS, 2019. <http://lixoft.com/products/monolix/>). For each method, the relative
197 mean prediction error (MPE) and the relative RMSE were calculated. A linear mixed effect model was built with
198 random effect on “subject” to assess the differences in the approaches to approximate CL_{Ref} (comparison of
199 MPE).

200

201 **3. Results**

202

203 *3.1. Patients*

204 Eighty-six patients were included and randomly assigned to the training or the test set (Table 1). No difference
205 was observed for characteristics between the training and test sets. Among these patients, 4 had hyperfiltration
206 ($GFR > 130$ ml/min), 3 had a GFR between 90 and 130 ml/min and 62 (72%) had acute kidney injury according
207 to the KDIGO classification. Thirty one patients had a previous chronic kidney disease ($GFR < 90$ ml/min).
208 Twenty three patients died during the ICU stay.

209

210 *3.2. Exploratory data analyses*

211 Strong correlations were observed at the individual level between the iohexol concentrations measured at the
212 different sampling times, but the more distant the times the lower the correlation (ESM_2). The SAPSII, serum
213 creatinine and urea were the predictors best associated with the reference clearance ($r > 0.4$).

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3.3. Xgboost and MARS with all predictors

The performances obtained for Xgboost after 10-fold cross-validation were: mean \pm SD RMSE = 10.4 \pm 1.7mL/min and $r^2 = 0.925 \pm 0.017$. The best tuned parameters values were mtry = 8, min_n = 6, tree_depth = 6 and learning rate = 0.003. For MARS, the mean \pm SD RMSE = 11 \pm 2.4mL/min and $r^2 = 0.902 \pm 0.035$ and the best tuned parameters values were num_terms = 4 and prod_degree = 2. Based on these results, the Xgboost approach was retained for the next steps.

3.4. Feature selection

The most important features as regards the maximal information coefficient (ESM_1) were serum creatinine, blood urea, SAPSII and fluid balance. Combinations of these predictors, together with iohexol concentrations and relative time differences were then investigated using Xgboost. Their respective performances are presented in Table 2. The best model was #14 (Table 2). In this model, 16/65 “720 min” times (24.6%) had to be imputed in the training set, while no data was missing in the test set. The variable importance plot of this model is presented in ESM_2, showing that concentrations at time 720 and 180 min were the variables of highest importance.

3.5. Evaluation in the test set

Model #14 was investigated in the test set and exhibited RMSE = 6.2 mL/min and $r^2 = 0.866$. The predicted vs. reference clearance scatter-plot is presented in Figure 1 and the corresponding Bland-Altman plot in Figure 2. The individual predicted and reference clearance values in the test set were not statistically different, with or without random noise ($p = 0.1517$) (Table 3). Eighteen predicted clearance values out of 21 (86%) could be correctly classified according to the GFR KDIGO classification (Figure 3). There was no patient at all in the normal or hyperfiltration group. Interestingly, the 8 patients with GFR < 30 mL/min were all predicted accordingly.

3.6. Comparison with other approaches

Relative MPE and its 95% confidence interval, relative RMSE, bias standard deviation, and the number of profiles with MPE out of the $\pm 10\%$ or $\pm 30\%$ intervals obtained with the different iohexol clearance estimation approaches as compared to the reference values, are presented in Table 4. The machine learning and the population pharmacokinetics model had a significantly lower bias than the Bröchner Mortensen approach, while there was no difference between the first two (Table 4). Precision was similar whatever the approach used (no statistical test was performed as only one value per approach was available). No significant difference with the CL_{ref} was observed for the Xgboost ($\beta \pm SD$; pvalue: 0.27 ± 1.09 ; 0.804), Xgboost with noise (1.48 ± 1.09 ; 0.177) or MAP-BE with the 3 sample LSS (-0.91 ± 1.09 ; 0.405) while a significant difference was observed for both Bröchner Mortensen formulae (3.77 ± 1.11 ; 0.001 and 6.23 ± 1.09 ; <0.0001 for BM with samples at 24 and 12h respectively). The predicted clearance values using each method for each patient are presented in Figure 4.

4. Discussion

254 In this work, we developed an extreme gradient boosting model relying on iohexol concentration at times 180
255 and 720 min, SAPSII, serum creatinine and fluid balance over the iohexol sampling period for iohexol clearance
256 estimation. Contrary to pharmacokinetic-based approaches, whose goal is to describe the underlying physiologi-
257 cal phenomena, the goal of a machine-learning model is to make accurate predictions (or estimations), with
258 whatever variables are necessary. It is thus a different concept aiming to increase the predictive performance,
259 with the trade-off on interpretability.

260 One advantage of our model is that the number of samples needed to predict GFR is decreased in comparison to
261 Bayesian models, which require at least 3 samples or to the Bröchner-Mortensen formulae, which requires 3 or
262 4. Furthermore, in ICU patients whose renal function may fluctuate over short periods of time, a method using as
263 few iohexol concentrations as possible may limit GFR estimation errors due to erratic deviations of concentra-
264 tions from their theoretical exponential decay. The model developed uses various features, not only pharmaco-
265 netic data, to describe iohexol clearance, making the model less dependent on possible measurement errors. We
266 checked this by adding 10% noise to iohexol concentrations in the test set, showing that the estimations were not
267 significantly affected. It is very important to note that, at least in ICU patients, our approach provides better
268 predictive performances than the classical BM method. The availability of a tool that is less dependent on
269 iohexol concentrations may be particularly useful in such unstable patients.

270
271 Interestingly, during the selection of predictors, we observed that correlation between very close iohexol concen-
272 trations caused an increase in RMSE, even if the individual predictors were all important. To illustrate that, the
273 RMSE of the model including all the concentrations available was 10.4 ml/min vs. 9.55 ml/min for the final
274 model. This led us to select only two time points, one close to (180 min) and the other distant from (720 min)
275 iohexol administration. Similarly, sampling times close to the end of the infusion were not considered, first be-
276 cause small variations in sampling times can lead to high variations in concentrations and secondly, because they
277 correspond to the distribution phase and may not reflect the clearance of the tracer. Most of the GFR measure-
278 ment methods based on iohexol pharmacokinetics use samples drawn during the first few hours following infu-
279 sion. This is particularly relevant for outpatients in whom it is important to decrease the time spent at hospital.
280 The BM method and most of the POPPK models previously published were built using such time constraints. As
281 such, Asberg et al developed a non-parametric population pharmacokinetic model in pediatric and adult patients
282 from 4 samples in the 5 hours after iohexol administration [8]. Similarly, Riff et al proposed a three-point LSS
283 using a parametric model with samples up to 270 min in adult kidney transplant patients [7]. However, in ICU,
284 expanding the sampling period is not problematic as patients stay longer at hospital.

285
286 The model evaluated here, whether or not 10% noise was introduced, yielded quite similar MPE and RMSE to
287 the Bayesian approach (non-significant differences in MPE), but performed far better than the BM formulae
288 which exhibited significant differences with the reference clearance (Table 4). Using our model, GFR was not
289 well estimated in some patients (with up to 10 mL/min differences), but there was no systematic bias (Figure 4).
290 The Bland-Altman plot showed that one patient's clearance was very poorly predicted with a difference out of
291 the confidence interval of bias. In routine care, the acceptable value of bias is variable according to the context.
292 Special attention paid to the patient's data did not allow us to detect specific issues (his iohexol concentrations
293 were around the 25th percentile of the distribution of concentrations at times 180 and 720 min and its CL_{ref} was

294 calculated from 9 samples). However, it cannot be excluded that inaccuracy in the reference clearance assess-
295 ment participated in this discrepancy. The estimations obtained using the Xgboost approach were accurate
296 enough to satisfactorily classify new patients in its GFR category [1], especially those with severely impaired
297 renal function. Indeed, all the patients with $GFR < 30$ mL/min were predicted accordingly. Two patients had a
298 predicted value < 30 mL/min while their reference value was actually in the 30-60 mL/min class, but the error
299 made remained under 5 mL/min (they were at the limits of the class). The patient with the large bias in clearance
300 estimation (discussed above) was also misclassified (predicted > 60 mL/min but in the 30-60 mL/min class).

301
302 The present results were developed in a rather small population and have to be investigated in other patients
303 before considering the model for use for routine care. The performance of our model is probably not good
304 enough to make it suitable for routine clinical use. There are several reasons for this. First, all the sampling times
305 included in the analysis were binned to reference times, leading to uncertainty in the concentrations observed.
306 Indeed, a very strict sampling protocol would have been necessary to avoid this uncertainty. However, as shown
307 by our sensitivity analysis, the model was quite robust with regards to noise introduced in the concentration data,
308 as well as to small variations in sampling times. This robustness can be explained by the addition of new predic-
309 tors to counteract this uncertainty (relative deviation to theoretical time). Secondly, as stated before for the outli-
310 er patient, another source of “noise” is the uncertainty in the reference clearance. Indeed, in this study, reference
311 clearance was assessed using a previously developed population pharmacokinetic model [9] with all the availa-
312 ble iohexol concentrations. However, only 3 and 4 concentration-time points were available in 4 and 7 patients,
313 respectively. As machine-learning methods optimize accuracy, uncertainty in the reference may lead to flawed
314 models and decreasing estimation accuracy. In our analysis, missing observations had to be imputed for the
315 selection of the best approach, as MARS cannot cope with missing data. In contrast, Xgboost allows for missing
316 data and we made the analysis with and without imputations in the training set and obtained better performances
317 with data imputation for missing values (data not shown). One can be surprised by the inclusion in our model of
318 creatinine, a worse estimator of GFR than iohexol clearance. We evaluated the final model without creatinine
319 and found that the performances were slightly poorer (increase in RMSE from 9.55 to 9.87 ml/min). As our
320 judgment criterion was the RMSE, we kept this variable in the final model. However, its importance is rather
321 low in comparison to iohexol concentrations, as shown in the variable importance plot (supplemental Figure 5 in
322 ESM_2).

323 In a population of unstable ICU patients with acute circulatory failure one could expect more severe renal failure
324 than what can be inferred from creatinine values (Table 1). However, it has been demonstrated using iohexol
325 clearance in the IOXREA study [9] that despite low plasma creatinine values, GFR was rather low on average
326 while the individual GFR values varied in a wide range (3 to 170 ml/min). This emphasizes that creatinine is not
327 suited to estimate GFR in unstable critically ill patients, because creatinine rise in case of AKI is slow and acute
328 changes in the volume of distribution (due to fluid load) may artificially decrease serum creatinine.

329
330 To the best of our knowledge, up until now, these machine-learning approaches have rarely been used in phar-
331 macology and never in pharmacokinetics. Examples of pharmacological applications, recently reviewed by
332 Badillo et al [10], focused mainly on the prediction of drug-drug or drug-food interactions using large public
333 databases [17], on the prediction of quantitative structure-activity relationships [18], or on safety personalization

334 [19]. The present work is the first of its kind and demonstrates that machine-learning analysis can be successful-
335 ly applied to a rather small dataset of pharmacokinetic nature, in essence. This opens the way to the development
336 of models of treatment individualization through therapeutic drug monitoring, as well as to the function assess-
337 ment using demographic data and laboratory test results.

338
339 The Bröchner-Mortensen formula is quite easy to implement on a simple spreadsheet as it relies on a regression
340 equation, while the implementation of population pharmacokinetics or Xgboost models is more difficult. Indeed,
341 while some simple machine learning models can be easily explained (e.g., if they rely on linear regression), more
342 complex ones such as Xgboost, allow to highly improve accuracy but work as black boxes. A solution is to de-
343 velop user-friendly interfaces allowing physicians to calculate patient GFR on their own. Our team has devel-
344 oped such tools in the Immunosuppressant Bayesian Adaptation (for the ISBA) website, in order to estimate
345 exposure to immunosuppressive drugs (<https://pharmaco.chu-limoges.fr/>) and Asberg et al. provided a shiny
346 application for a non-parametric iohexol clearance calculation in renal transplant patients [8]. We also developed
347 an interactive R shiny application to use the model developed here (<https://jbwoillard.shinyapps.io/App-3/>). In
348 conclusion, once improved and validated on a larger number of patients, this tool could represent a simple means
349 to estimate GFR in ICU patients.

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351

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356 Armelle Mathonnet, Pierre Marquet and Chantal Barin-Le Guellec declare that they have no potential conflicts
357 of interest that might be relevant to the contents of this manuscript.

358 AVAILABILITY OF DATA AND MATERIAL: The data that support the findings of this study are
359 available from Charlotte Salmon Gandonnière upon reasonable request (char-
360 lotte.salmon.gandonniere@gmail.com), code is available under request (Rmarkdown html file).

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413 Table 1: Patient characteristics in the development and the validation datasets

Variable	Training set	Test set	P value
N	65	21	
Iohexol clearance* (mL/min) (mean (SD))	45.9 (38.1)	35.9 (16.9)	0.245
Iohexol concentration at 5 min (mg/L) (median [IQR])	319.6 [225.2, 430.3]	363.7 [277.9, 460.9]	0.394
Iohexol concentration at 30 min (mg/L) (median [IQR])	169.9 [144.1, 202.6]	186.2 [147.1, 235.7]	0.221
Iohexol concentration at time 60 min (mg/L) (median [IQR])	134.9 [109.0, 169.3]	157.4 [121.8, 205.2]	0.128
Iohexol concentration at time 180 min (mg/L) (median [IQR])	91.3 [64.8, 129.6]	99.8 [80.3, 125.8]	0.194
Iohexol concentration at time 360 min (mg/L) (median [IQR])	58.5 [35.2, 99.4]	70.5 [57.4, 97.3]	0.177
Iohexol concentration at time 540 min (mg/L) (median [IQR])	36.6 [21.8, 82.4]	49.3 [33.8, 63.2]	0.414
Iohexol concentration at time 720 min (mg/L) (median [IQR])	27.5 [15.3, 72.8]	37.6 [20.1, 49.5]	0.649
Iohexol concentration at time 1080 min (mg/L) (median [IQR])	19.5 [6.5, 50.6]	22.8 [15.8, 31.2]	0.668
Iohexol concentration at time 1440 min (mg/L) (median [IQR])	10.9 [4.3, 40.0]	12.1 [6.2, 22.0]	0.686
Baseline serum creatinine (μM) (mean (SD))	75.0 (25.7)	74.5 (16.3)	0.940
Weight (Kg) (mean (SD))	83.7 (21.2)	78.6 (19.9)	0.334
Height (cm) (mean (SD))	169.0 (8.6)	169.9 (9.2)	0.656
Body Mass Index (Kg/m ²) (mean (SD))	29.3 (7.3)	27.2 (6.6)	0.238
Body surface area (m ²) (mean (SD))	2.0 (0.3)	1.9 (0.3)	0.365
Age (years) (mean (SD))	65.3 (14.3)	64.1 (10.4)	0.715
Sex Female (%)	22 (35.5)	9 (42.9)	0.732
SAPS II (mean (SD))	61.5 (22.0)	56.5 (14.9)	0.334
Nephrotoxic drugs the days before inclusion = Yes (%)	50 (80.6)	19 (90.5)	0.482
Hematocrit (%) (mean (SD))	31.8 (5.9)	31.8 (7.0)	0.984
Proteinemia (g/L) (mean (SD))	53.1 (7.4)	52.8 (8.9)	0.866
Albuminemia (g/L) (mean (SD))	28.5 (5.6)	28.9 (6.4)	0.811
Blood sodium (mmol/l) (mean (SD))	137.2 (5.7)	136.4 (3.7)	0.522
Serum creatinine during iohexol sampling (μM) (median	122.0 [74.0,	99.0 [79.0,	0.608

[IQR]	190.0]	186.0]	
Blood urea during iohexol sampling (median [IQR])	11.2 [7.4, 17.0]	10.4 [7.2, 14.5]	0.287
Rapid fluid infusion between ICU admission and study inclusion (mL) (median [IQR])	1105 [0, 3000]	1000 [500, 2000]	0.387
Rapid fluid infusion during iohexol-pharmacokinetic sampling (mL) (median [IQR])	500 [0, 2000]	895 [500, 1000]	0.882
Fluid balance during iohexol-pharmacokinetic sampling (mL) (mean (SD))	1668 (2857)	1297 (2079)	0.584
Main admission diagnosis (%)			
1 : cardiogenic shock	2 (3.2)	1 (4.8)	
2 : septic shock	31 (50.0)	12 (57.1)	
3 : hemorrhagic shock	1 (1.6)	1 (4.8)	
4 : other shock	4 (6.5)	1 (4.8)	
5 : de novo acute respiratory failure	4 (6.5)	1 (4.8)	
6 : acute respiratory failure on chronic respiratory insufficiency	6 (9.7)	1 (4.8)	
7 : Coma	5 (8.1)	0 (0.0)	
8: Acute kidney injury	1 (1.6)	0 (0.0)	
10 : cardiac arrest	4 (6.5)	1 (4.8)	
13 : other	4 (6.5)	3 (14.3)	

414 *measured using all available Iohexol samples and a population pharmacokinetic model

415 Table 2 Comparison of different Xgboost models based on reduced numbers of predictors. Performances are the
 416 mean \pm SD after 10-fold cross-validation of the training set.

#Model	Models investigated	RMSE \pm SD	R ² \pm SD
1	Iohexol concentration at time 180, 360 & 540 min, relative deviation to theoretical time 180, 360 & 540, Serum creatinine during iohexol sampling (μ M), Blood urea, SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	11.8 \pm 1.28	0.912 \pm 0.020
2	Iohexol concentration at time 60, 360 & 720 min, relative deviation to theoretical time 60, 360 & 720, Serum creatinine during iohexol sampling (μ M), Blood urea, SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	11.7 \pm 1.68	0.878 \pm 0.029
3	Iohexol concentration at time 60, 360, 540 & 720 min, relative deviation to theoretical time 60, 360, 540 & 720, Serum creatinine during iohexol sampling (μ M), Blood urea, SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	12.4 \pm 1.68	0.869 \pm 0.033
4	Iohexol concentration at time 180 & 540 min, relative deviation to theoretical time 180 & 540, Serum creatinine during iohexol sampling (μ M), Blood urea, SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	12.9 \pm 1.37	0.895 \pm 0.034
5	Iohexol concentration at time 540 min, relative deviation to theoretical time 540, Serum creatinine during iohexol sampling (μ M), Blood urea, SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	15.2 \pm 1.43	0.851 \pm 0.032
6	Iohexol concentration at time 360 min, relative deviation to theoretical time 360, Serum creatinine during iohexol sampling (μ M), Blood urea, SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	14.4 \pm 1.70	0.847 \pm 0.036
7	Iohexol concentration at time 60 & 540 min, relative deviation to theoretical time 60 & 540, Blood urea, SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	13.8 \pm 1.66	0.866 \pm 0.035
8	Iohexol concentration at time 180 & 540 min, relative deviation to theoretical time 180 & 540, Serum creatinine during iohexol sampling (μ M), SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	11.2 \pm 1.43	0.901 \pm 0.032
9	Iohexol concentration at time 360 & 540 min, relative deviation to theoretical time 360 & 540, Serum creatinine during iohexol sampling (μ M), SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	11.4 \pm 1.47	0.897 \pm 0.027
10	Iohexol concentration at time 540 & 720 min, relative deviation to theoretical time 540 & 720, Serum creatinine during iohexol sampling (μ M), SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	14.6 \pm 1.87	0.822 \pm 0.058

11	Iohexol concentration at time 360 & 720 min, relative deviation to theoretical time 360 & 720, Serum creatinine during iohexol sampling (μM), SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	12.9 \pm 1.24	0.864 \pm 0.031
12	Iohexol concentration at time 180 & 720 min, relative deviation to theoretical time 180 & 720, Serum creatinine during iohexol sampling (μM), SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	10.2 \pm 1.32	0.930 \pm 0.023
13	Iohexol concentration at time 180 & 360 min, relative deviation to theoretical time 180 & 360, Serum creatinine during iohexol sampling (μM), SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL)	11.6 \pm 1.61	0.893 \pm 0.043
14	Iohexol concentration at time 180 & 720 min, relative deviation to theoretical time 180 & 720, Serum creatinine during iohexol sampling (μM), SAPS II, Fluid balance during iohexol pharmacokinetic sampling (mL), time_diff = iohexol concentration at time 180 min - iohexol concentration at time 720 min)	9.55\pm 1.22	0.948 \pm 0.019

417 Parameters used were mtry = number of predictors - 1, trees = 1000, min_n = 5, tree_depth = 5, learn_rate =
418 0.01 from the results of 10 folds cross validation, RMSE is root mean square error in mL/min, r^2 is the coeffi-
419 cient of determination. The model retained is in bold.

Table 3: Individual predicted iohexol clearance using the best model (#14), without and with 10% random noise added, and reference iohexol clearance for all the patients of the test set (n=21). Discrepancies with the categories of Glomerular Filtration categorized by stages, as recommended by the Kidney Disease Improving Global Outcome (KDIGO) AKI work group are highlighted in bold

Patient number	Predicted iohexol clearance (mL/min)	Predicted iohexol clearance with a 10% random noise (mL/min)	Reference iohexol clearance (mL/min)
1	8.2	8.33	5.5
2	15.5	15.7	16.5
3	17.9	18.2	18.9
4	27.0	27.0	22.2
5	22.2	22.8	22.3
6	26.4	32.1	24.4
7	24.2	23.5	24.8
8	25.5	25.3	25.1
9	28.5	28.0	30.8
10	33.7	33.9	31.4
11	28.4	26.3	32.7
12	35.0	37.1	37.6
13	46.3	38.3	39.2
14	30.7	29.8	40.2
15	38.4	39.0	41.7
16	58.0	63.6	47.7
17	41.7	42.9	47.9
18	52.4	52.8	48.0
19	70.8	73.9	53.5
20	67.2	75.5	71.4
21	61.5	70.8	71.9

Table 4: Mean prediction errors (MPE) and Root mean square errors (RMSE) for (1) the 2-sample Xgboost model without or with random noise, (2) the 3-samples limited sampling strategy and maximum a posteriori Bayesian estimation (0.1, 1 and 9h) and (3) the 4-samples Bröchner-Mortensen (BM) formula (samples at 3, 6, 9 and 12 or 24h post administration).

Model	MPE (mL/min) [95% confidence interval]	RMSE (mL/min)/Standard deviation	Percentage of relative MPE out of the ±10% interval (%)	Percentage of relative MPE out of the ±30% interval (%)
XGboost	0.3 [-12.2, 12.8]	6.2/6.4	43	9.5
XGboost with 10% noise	1.5 [-12.1, 15.1]	6.9/6.9	43	19
Limited sampling strategy, MAP- Bayesian estimator	- 0.9 [-12.2, 10.37]	5.7/5.7	38	4.8
BM 3, 6, 9, 12h	*6.2 [-4.5, 16.9]	8.2/5.4	57	24
BM 3, 6, 9, 24h	*3.7 [-5, 12.4]	6.6/4.4	45	5.0

* Significant differences from the other values (linear mixed effect model with random effect on subject).

Figure legends

Figure 1- Iohexol clearance estimated using the Xgboost model vs. reference clearance in the test set.

Figure 2- Bland-Altman plot for Xgboost estimated and reference clearance values in the test set. Differences = reference - Xgboost clearance and Means is the average of reference and Xgboost clearance in each individual.

Figure 3 Confusion matrix for patients of the test set, depending on the glomerular filtration rate categories.

Figure 4- Comparison of the different methods for estimation of CL in the test set. BM is Bröchner-Mortensen formula, MAP-BE is maximum a posteriori Bayesian estimation based on the 0.1, 1 and 9h limited sampling strategy and the parametric POPPK model developed using Monolix.