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Predicting perioperative acute Kidney injury in liver surgery

L. Coeman, P. Wyffels, J. Van Limmen, P. Wouters

Abstract: *Introduction:* During the perioperative period, acute kidney injury (AKI) is a serious complication with increased short- and long-term mortality (1, 2, 3). In former studies, the incidence of AKI following hepatobiliary surgery varied between 5.1 and 15.5% (10, 11, 13-15). The aim of the study is to examine the perioperative risk factors for development of AKI in patients undergoing liver surgery and to compare predictive models made by supervised decision tree models.
Methods: In this retrospective cohort study, patients who had undergone liver surgery between March 2010 and December 2017 in Ghent University Hospital were screened after ethical committee approval. A set of preoperative and postoperative laboratory results, surgery and patient characteristics were collected. To create a predictive model, the dataset was randomly divided into a training set (60%) to train the model and a test set (40%) to analyze the accuracy of the model. To train the model, tree-based models were used in the form of a simple tree, pruned tree, bagging trees, random forests and boosting trees.
Results: 1162 patients were analyzed and because of missing data, 602 patients had to be excluded from the dataset. The misclassification error of the different decision tree models varied between 3.12% and 4.02%. Random forests is the prediction model with the lowest misclassification error of 3.12%. The difference in serum creatinine immediately after surgery is ranked as the highest predictor with a relative influence of 50% in the boosting trees model. This predictor is followed by postoperative serum creatinine with a relative influence of 13%. At the third place is preoperative hemoglobin with a relative influence of 9.2%.
Conclusion: Decision tree models can predict AKI after hepatobiliary surgery in this study. Of all the predictive models, random forests had the lowest misclassification rate and this model should be explored more often in future research trials.

Keywords: Acute Kidney Injury; decision tree models; liver surgery; prediction model.

Introduction

During the perioperative period, acute kidney injury (AKI) is a serious complication with increased short- and long-term mortality (1, 2, 3). AKI can develop in patients with and without comorbidities and it is a syndrome that can be reversed (4). Major surgery is the second leading cause of AKI but still it remains underdiagnosed in the perioperative period (5). To have an accurate diagnosis and prognostication of AKI, a consistent and standardized definition of AKI is crucial. On top of that, a uniform definition allows the comparison of studies and is therefore important both in the clinical and research settings. These definitions have started in 2004 with the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) definition and classification criteria ref. This was followed by the Acute Kidney Injury Network (AKIN) criteria in 2007 ref . Finally the Kidney Disease: Improving Global Outcomes (KDIGO) classification system, published in 2012, combined the 2. This classification system is globally used as the uniform definition for AKI.

Over the last 2 decades, the incidence of acute kidney injury (AKI) has grown due to this new definition (4). But other factors such as an increasingly aging population, increased prevalence of diabetes, increasing number of comorbidities of the hospitalized population and the liberal use of intravenous contrast agents for imaging and intervention procedures contribute to the higher incidence of AKI (6, 7).

Nevertheless, major surgery remains a prominent cause of AKI in hospitalized patients, responsible for up to 40% of in-hospital AKI cases (5, 7, 8). The incidence of AKI in this group of

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patients is variable though, depending on the surgical setting and the definition that was used for AKI (9). Post-operative development of AKI has especially been studied in cardiovascular surgery. However, these results can't be extrapolated automatically to abdominal surgery because of the absence of the cardiopulmonary pump (10). Liver surgery also may cause important fluid shifts and blood loss (11). It has a high risk of postoperative AKI with unique features due to the underlying diseases of the patients as well as surgical and anesthetic management considerations (12). In former studies, the incidence of AKI following hepatobiliary surgery varied between 5.1 and 15.5%. The majority of these patients in all studies were placed in the less severe stage of AKI (Stage 1) (10, 11, 13-15).

Previous studies have shown that AKI is a serious perioperative complication and is associated with increased costs, prolonged hospital stay, and both short- and long-term mortality (1, 2, 3, 10, 16).

Functional markers such as serum creatinine and urine output are essential in the KDIGO definition of AKI but these markers only become abnormal later on in the course of the syndrome (18). Earlier detection of AKI may improve patient outcomes and the prevention of further renal harm. A method that detects AKI early on could potentially lead to improved patient outcomes and decreased costs (4, 17, 19). Risk scores could be useful because they combine information available at a moment where decisions might be taken. These scores have the purpose to get an adequate preoperative evaluation of the postoperative risk for AKI. It is of specific importance because the kidney function can be influenced by some modifiable factors in the interdisciplinary perioperative management process (21). There is increasing knowledge about the pathophysiology of AKI but specific treatments remain scarce. Interventions are generally started when there is an elevation of serum creatinine or decrease in urine output. These are only addressing already existing kidney damage but not ongoing kidney injury. Thus there should be more focus and increasing efforts on the early detection and prevention of AKI. Newly established biomarkers could help predict AKI after major surgery (20, 24). Various predicting scoring systems already have been created but the predictive accuracy of these models remain suboptimal (9, 22, 23).

The aim of the study is to examine the perioperative risk factors for development of AKI in patients undergoing liver surgery. Furthermore, the additional goal is to compare predictive models made by decision tree models. Decision trees are a class of machine learning models that represent information in a clear way. This study will use different kinds of tree models and it will determine which model has the best predicting power for developing perioperative AKI.

Methods

Patients and study design

This study has gotten the approval of the ethics committee of the University Hospital Ghent to start his retrospective cohort study. This study was registered with the local code EC/2016/0803and with number B670201628986 for Belgium. Individual informed consent was waived because of the retrospective nature of this study. Patients who had undergone liver surgery between March 2010 and December 2017 in Ghent university hospital were screened. The researchers collected the data out of the electronic patient records from the hospital. A set of preoperative and postoperative laboratory results, type of surgery, type of resection, duration of the surgery and patient characteristics were collected. Preoperative hemoglobin (g/dl), hematocrit (%), thrombocytes ($x10^9$/L), prothrombin (%), fibrinogen (g/L), creatinine (mg/dl) and liver transaminases (U/L) were analyzed in the blood samples and the same laboratory results were screened each day until day 7 postoperatively. The method of surgery was divided into laparoscopy and laparotomy. The type of resection was divided into 10 categories. Diabetes, arterial hypertension, ischemic cardiomyopathy, chronic obstructive pulmonary disease and peripheral vascular disease belonged to the patient characteristics that were determined, according to the study of Kheterpal et al (23). Furthermore, the changes of serum creatinine and hemoglobin were calculated immediately after surgery. The diagnosis of postoperative AKI was done according to the previously mentioned KDIGO criteria, solely based on serum creatinine over a period of 7 days.

Statistics

Training and test data sets

The prediction process to classify patients into having a form of AKI or not has a learning step and a prediction step. In the learning step, the model is developed based on given training data. In the prediction step, the model is used to predict the response for given data. As depicted in the flowchart

below (Fig. 1), the raw dataset was narrowed down to a complete dataset without missing data. To create a predictive model, the dataset was randomly divided into a training set (60%) to train the model and a test set (40%) to analyze the accuracy of the model.

Tree based models

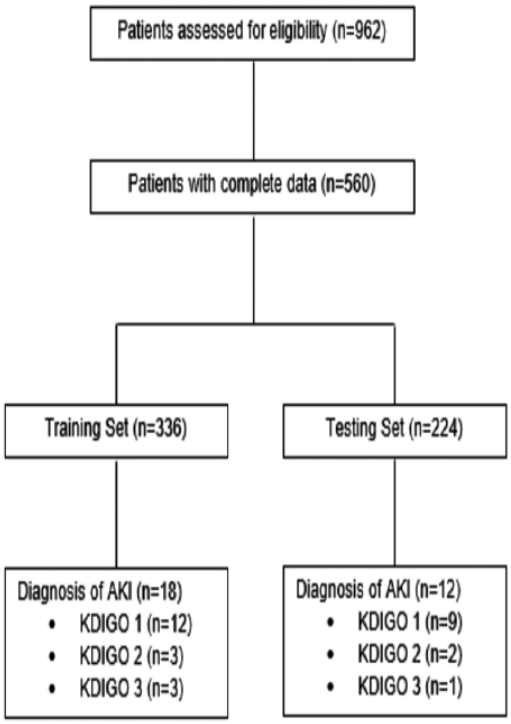
To train the model, decision trees were used. To split the data, specific predictor selection measures are being used to select the best predictor. With more than one predictor taking part in the decision-making process, it is necessary to decide the relevance and importance of each of the predictors, thus placing the most relevant at the root node and further traversing down by splitting the nodes. As we move further down the tree, the level of uncertainty decreases, thus leading to a better classification or best split at every node. To decide these, splitting measures such as the misclassification error rate and the Gini coefficient were used. However even after pruning the tree to correct for overfitting, it is often not competitive with other methods in terms of prediction accuracy. A large bias for simple trees and a large variance for complex trees will be present. Methods where groups of trees are used, have a better prediction performance than utilizing a single decision tree. These ensemble methods are based on the hypothesis that combining multiple models together can often produce a much more powerful predicting model (Figure 2). In the generated models there are 2 classifications: true or false. True means the occurrence of AKI and false means the absence of AKI.

Software

Statistical analysis was done using R version 3.6.1. The specific packages used were 'trees' (v.1.0-40), Random forests (v. 4.6-14), 'gbm' (v.2.1.5) and 'caret'(v 6.0-85) for modeling and testing the specific tree based algorithms.

Results

Because of missing data, 602 patients had to be excluded from the dataset. 560 patients with complete data remained. The final predictors that were used to create the predicting models were preoperative laboratory results, preoperative known patient characteristics, method of surgery, type of resection and immediately postoperative laboratory results. Of these 560 patients with complete data, 30 patients developed some kind of AKI postoperatively. 21 of these developed an AKI in KDIGO stage 1, 5 patients developed KDIGO stage 2 and 4 patients developed KDIGO stage 3. Following the data management flowchart as depicted in figure 1, these 560 patients were randomized in a training set with 336 patients and a testing set with 224 patients. In the training set, 18 patients developed a form of AKI. 12 patients developed KDIGO stage 1, 3 patients developed KDIGO stage 2 and 3 patients developed KDIGO stage 3. In the testing set to evaluate the models, 12 of 224 patients developed a form of AKI. 9 patients acquired KDIGO stage 1, 2 patients acquired KDIGO stage 2 and 1 patient acquired KDIGO stage 3.



Flow diagram

Simple Tree

Based on the training dataset, a simple tree with 6 terminal nodes can be made (Fig. 2). In the root node of this tree, the dataset is split by the difference in serum creatinine immediately after surgery and preoperatively. The threshold of the difference is set at 0.205 mg/dl. This split generates two internal nodes which have preoperative hemoglobin as the predictor for the next split. The thresholds for these are different: 11.75 g/dl when DeltaCreat is lower than 0.205 mg/dl and 14.55 g/dl when DeltaCreat is higher than 0.205 mg/dl. If the preoperative

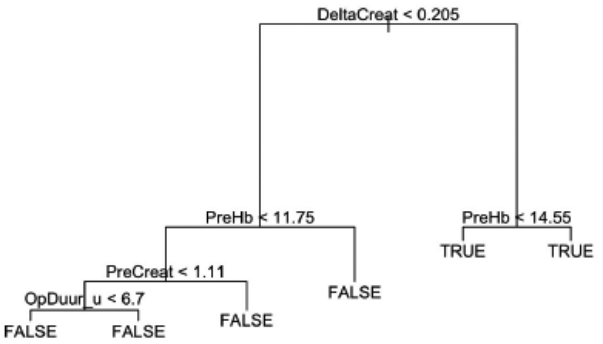


Fig. 1. — Simple decision tree generated by using training set. DeltaCreat = The difference in serum creatinine immediately postoperative and preoperative; PreHb = Preoperative hemoglobin; PreCreat = Preoperative serum creatinine; OpDuur_u = Length of surgery in hours.

hemoglobin is lower than 11.75 g/dl, another internal node is made with preoperative creatinine as the predictor. When the preoperative hemoglobin is higher than 11.75 g/dl, the terminal node with classification false occurs. If the preoperative serum creatinine is lower than 1.11 mg/dl, another internal node is made with the length of surgery as predictor. When the preoperative serum creatinine is higher than 1.11 mg/dl, the terminal node with classification false occurs. The threshold of length of surgery is at 6.7 hours. Both outcome classifications of this predictor are the same: false. The results of applying the simple tree model to the testing dataset can be found in table 1. Here, 12 patients developed a form of AKI and 212 patients did not develop AKI. The model predicted 9 out of 224 patients to develop AKI. Thus 3 patients were wrongly classified. In total, there were 9 mispredictions in 224 cases of the testing data. The model predicted 6 patients to not have an AKI, but they actually did and it predicted 3 patients to have an AKI but they actually did not. There were 6 correct predictions of patients developing AKI. The misclassification rate of this predicting model is 4%.

Pruned Tree

Using a 10-fold cross-validation, a subtree is formed with only 1 root node and two terminal nodes. If the difference in serum creatinine immediately after surgery is lower than 0.205 mg/dl, there is no prediction of AKI. If the difference is higher than 0.205 mg/dl, the classification of AKI occurs. The results of applying the pruned tree model to the testing dataset can be found in table 1.

Bagging Trees

As depicted in figure 2, the misclassification error is outlined next to how many trees are used

Table 1

Contingency tables of decision tree models

	Testing data AKI			
		False	True	Total Prediction
Simple Tree Model AKI	False	209	6	215
	True	3	6	9
	Total Testing	212	12	
Pruned Tree Model AKI	False	211	7	218
	True	1	5	6
	Total Testing	212	12	
Bagging Tree Model AKI (n=125 trees)	False	211	7	218
	True	1	5	6
	Total Testing	212	12	
Random Forests Model AKI (n=125 trees)	False	212	7	219
	True	0	5	5
	Total Testing	212	12	
Boosting Trees Model AKI (n=510 trees)	False	210	6	216
	True	2	6	8
	Total Testing	212	12	

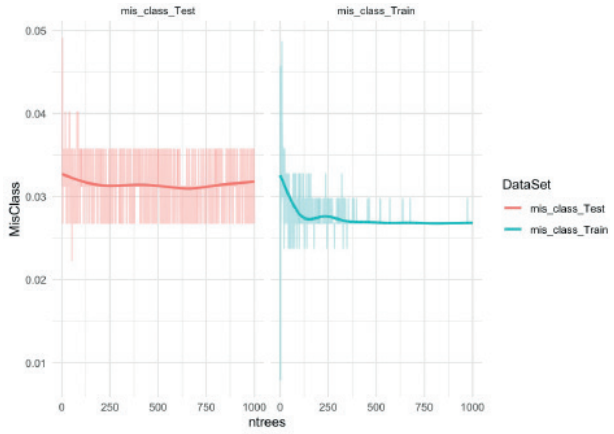


Fig. 2. — Bagging Trees showing the trend of misclassification in relation to the number of trees that were used.

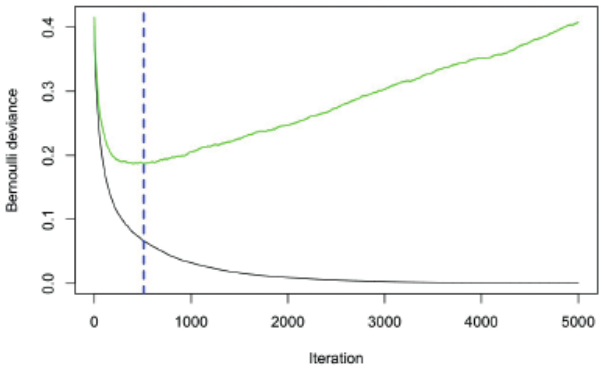


Fig. 3. — Boosting trees showing the trend of misclassification in relation to the number of trees that were used. The black line is the trend for the training dataset and the green line is the trend for the testing dataset.

and thus how many bootstrap samples are used to generate the prediction value. Because of the deep decline at the beginning, a bagging tree model is made with 125 bootstrap samples. The results of applying the bagging trees model to the testing dataset can be found in table 1.

Random Forests

In the random forests model, the misclassification error shows a deep decline for the first 100 trees for both the training and the testing dataset. A Random Forests model is made with 125 bootstrap samples. The results of applying the random forests model to the testing dataset can be found in table 1.

Boosting trees

Represented in figure 4 above, the Bernoulli deviance (= a measure for misclassification error for boosting) takes a deep dive for the first 250 trees for both the training and testing dataset. For the training dataset, the Bernoulli deviance becomes smaller as the number of trees accumulate. For the testing dataset however, after 510 trees, the Bernoulli deviance rises again. The results of applying the boosting trees model to the testing dataset can be found in table 1.

In table 2, the different predictors are shown with their relative influence in the boosting trees model. The difference in serum creatinine immediately after surgery and preoperatively is ranked highest with a relative influence of 50%. This predictor is followed by postoperative serum creatinine with a relative influence of 13%. At the third place is preoperative hemoglobin with a relative influence of 9.2%.

Table 2

Representation of the relative influence of the different predictors in percentage

Predictor	Relative Influence
DeltaCreat	50.01
Postoperative serum creatinine	13.03
Preoperative hemoglobin	9.22
Postoperative INR	9.13
Preoperative serum creatinine	4.13
DeltaHb	2.98
Postoperative hemoglobin	2.67
Preoperative INR	2.56
Left hepatectomy	1.45
Age	1.09
Preoperatively trombocytes	1.07
Postoperatively trombocytes	1.06
Ischemic cardiomyopathy	0.90
Length of surgery	0.35
Gender	0.15
Type of resection	0.10
Diabetes mellitus	0.08

In table 3, a summary of the different tree based prediction models can be found. The misclassification error, sensitivity and specificity is depicted for each model. The misclassification error of the different decision tree models varied between 3.12% and 4.02%. Random forests is the prediction model with the lowest misclassification error of 3.12%. The pruned tree model, bagging trees model and the boosting trees model have the same misclassification error of 3.57%. The model

Table 3

Summary of the accuracy of decision tree models

Prediction model	Sensitivity	Specificity	Misclassification Error
Single Tree	0.50	0.98	0.0402
Pruned Tree	0.42	0.99	0.0357
Bagging Trees	0.42	0.99	0.0357
Random Forests	0.42	1.00	0.0312
Boosting Trees	0.50	0.99	0.0357

with the highest value is the single tree model which has a misclassification error of 4.02%.

Discussion

In this study, 5 different types of tree-based models were tested to predict AKI after liver surgery. The misclassification error of the different decision tree models varied between 3.12% and 4.02%. These trees try to keep the error as low as possible and based on this, random forests was the most accurate prediction model with the lowest error rate of 3.12%. We have found that the difference in serum creatinine, postoperative serum creatinine and preoperative hemoglobin are the predictors with the most influence for the prediction of AKI. This means our models are making their predictions mainly based on these parameters. In contrast with the Kheterpal et al. predictive study, the preoperative patient characteristics were not as important in our study and had no big influence in the prediction of AKI (23).

It isn't a surprise that the single tree model has the highest misclassification error because of the large bias and large variance that is characteristic for a single decision tree. Though it is remarkable that the pruned tree model, bagging trees model and the boosting trees models have the same misclassification error whilst the specificity of boosting trees is higher than the other two. This conveys that the same misclassification error does not necessarily have the same sensitivity and specificity. This is because the misclassification error does not take the type of misprediction into account though it can be very important. The specificity of the decision tree models is very high, always above 98% and for random forests even 100%. However, the sensitivity is 50% at its maximum for single tree and boosting trees. It lies at only 42% for pruned tree, bagging trees and even random forests, which scored good for specificity and misclassification error. This means that for random forests, our best predicting model, a negative likelihood ratio of 0.58 can be calculated. A high amount of false negatives is not a good characteristic for a predicting tool. In clinical practice, it is important to optimize the sensitivity and specificity for conditions that have a wide range of prevalence. When a patient is wrongly classified as false positive, some preventive strategies can be less harmful than when a patient is wrongly classified as false negative and no interventions are done.

It can be interesting to compare predictive models made by decision tree models because of their clarity of representing information. A decision tree can convey a lot by the way it is built. In the models, there are 2 classifications: true or false. For the simple tree, 2 major regions can be visualized: non-AKI on the left and the development of AKI on the right. These regions are more clearly visualized in the pruned tree, where only 2 leaf nodes are remaining: false on the left and true on the right. Furthermore in the simple tree, the length of the branches are long at the first split made by the DeltaCreat predictor and are smaller further down. This means a great decrease in impurity at the first split of the dataset. This also represents itself when the relative influence of the different predictors is calculated. DeltaCreat is the one with the most influence for the prediction of AKI with a relative percentage of 50. It emphasizes that a kidney function test with serum creatinine immediately after surgery is very important in our prediction for AKI. This can be done when the patient arrives on intensive care or the post anesthesia care unit.

Despite several interesting findings, this study has some limitations. Because these prediction models present a retrospective study, no strong conclusions can be drawn about the performance in a live clinical setting. The retrospective aspect led to incomplete data and information bias because of rudimentary registration of parameters. Furthermore, the absence of several possible predictors could have delayed our prediction of AKI in the perioperative period. The predictive accuracy of the models may also be different in prospective settings if they are implemented on patient populations which vary considerably from the population in this study. It can be said that the purpose of a predictive model is to predict the outcome of AKI with an accurate probability at an early stage. This way, effective preventive interventions can be undertaken. In this study however, our most important parameter is the difference in serum creatinine immediately after surgery and this can only be measured late in the perioperative period. In future prospective research,

more intraoperative predictors such as urine output, blood loss, blood transfusion and vein clamping can be taken into account as well as more patient characteristics.

Because of the missing observations of urine output, only a part of the KDIGO criteria could be used to make the classification of AKI. The classification of AKI in this study was only binary so there was no further classification in the different stages of AKI. However, in recent studies, the KDIGO definition can be criticized (27). The perioperative period has shown to be a unique environment with its diagnostic challenges. Studies have shown that urine output frequently is decreased in the intraoperative and postoperative period because of the release of aldosterone and vasopressin from stress, hypovolemia and surgical considerations (27-29). Serum creatinine is also a diagnostic tool that is an inaccurate marker for glomerular filtration rate. From injury to the necessary diagnostic rise, serum creatinine has a temporal delay. It will only begin to rise after the glomerular filtration rate is decreased by 50% (30). To diagnose the early stages of AKI, novel biologic biomarkers have been the focus of ongoing research (24, 31, 32). In future prospective research, it would be interesting to use predicting tree models with panels of biomarkers to see if they can accurately predict kidney damage in an early stage.

In conclusion, decision tree models can predict AKI after hepatobiliary surgery in this study though more research is needed with a prospective approach. The rise in serum creatinine immediately after surgery, compared with the preoperative value, stood out as the most important perioperative risk factor so obtaining the serum creatinine postoperatively is very important in the risk stratification of developing AKI. Of all the predictive models, random forests had the lowest misclassification rate and this model should be explored more often in future research trials. Supervised models such as decision trees can be an useful tool for clinicians in the future when large amounts of data need to be adequately processed and converted so they are suitable for daily clinical use.

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