71935_Auto_Edited.docx

Name of Journal: *World Journal of Hepatology*

Manuscript NO: 71935

Manuscript Type: ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors and Prediction of Acute Kidney Injury After Liver Transplantation: Logistic Regression and Artificial Neural Network Approaches

ACUTE KIDNEY INJURY AFTER LIVER TRANSPLANTATION

Luis Cesar Bredt, Luis Alberto Batista Peres, Michel Risso, Leandro Cavalcanti de Albuquerque Leite Barros

Abstract

BACKGROUND

The acute kidney injury (AKI) has serious consequences on the prognosis of patients undergoing liver transplantation (LT). Recently, artificial neural network (ANN) was reported to have better predictive ability than the classical logistic regression (LR) for this postoperative outcome.

AIM

Identify the risk factors of AKI after deceased-donor liver transplantation (DDLT) and compare the prediction performance of ANN with that of LR for this complication.

METHODS

Adult patients with no evidence of end-stage kidney disfunction (KD) who underwent the first DDLT according to model for end-stage liver disease (MELD) score allocation system was evaluated. AKI was defined according to the International Club of Ascites (ICA) criteria, and potential predictors of postoperative AKI were identified by LR. Both ANN and LR prediction performance were tested.

RESULTS

The incidence of AKI was 60.6% (n = 88/145) and the following predictors were identified: MELD score >25 (OR=1.999), preoperative kidney dysfunction (KD) (OR= 1.279), extended criteria donors (ECD) (OR=1.191), intraoperative arterial hypotension (IOAH) (OR=1.935), intraoperative massive blood transfusion (MBT) (OR=1.830), and postoperative serum lactate (SL) (OR=2.001) by LR. The AUROC was best in ANN (0.81, 95%CI = 0.75–0.83) than LR (0.71 (95%CI 0.67–0.76). RMSE (root-mean-square error) and MAE (mean absolute error) in ANN model were 0.47 and 0.38, respectively.

CONCLUSION

The severity of liver disease, pre-existing KD, marginal grafts, hemodynamic instability, MBT and SL were predictors of postoperative AKI, and ANN had better prediction performance than LR in this scenario.

Key Words: logistic regression; liver transplantation; acute kidney injury; machine learning; artificial neural network

Bredt LC, Peres LAB, Risso M, Barros LCAL. Risk factors and Prediction of Acute Kidney Injury After Liver Transplantation: Logistic Regression and Artificial Neural Network Approaches . *World J Hepatol* 2021; In press

Core Tip: This study aims to identify the risk factors and compare the performance of artificial neural network (ANN) with that of logistic regression (LR) analysis to predict AKI after deceased-donor liver transplantation (DDLT). LR analysis revealed the following predictors of AKI: previous kidney dysfunction (KD), marginal grafts, intra-operative arterial hypotension (IOAH), massive blood transfusion (MBT), and serum lactate (SL). ANN prediction had better performance than LR in this scenario.

INTRODUCTION

Among the possible complications of complex abdominal and liver procedures, acute kidney injury (AKI) should be considered a major cause of postoperative morbidity and mortality[1-6]. Updated data report a 0.9-17.9% incidence of AKI after liver resection,[7-9] and 4% up to 94% after LT[10,11], either living-donor (LDLT) and deceased-donor LT (DDLT). Although there is a lack of a reported standard definition of postoperative AKI [12] after DDLT, it is of fundamental importance to identify patients at risk for AKI after LT, ideally by the set of preoperative clinical evaluation, as well as by the complementary information of the intraoperative period, thus enabling the adoption of preventive measures or early therapies for AKI in the postoperative period.

There are many studies available based on deep learning models for different clinical purposes in distinct fields of medicine, such as for complex imaging acquisition and processing [13-17], and artificial neural network (ANN) as a deep learning modality is commonly used to solve complex problems, where the behavior of variables is not rigorously known. In the specific field of AKI after LT, along with other machine learning techniques (gradient boosting machine, random forest, decision tree, support vector machine, naïve Bayes, and deep belief network) ANN have already been compared to multivariable logistic regression (LR) regarding their prediction performance.[18] We hypothesized that ANN would be a feasible alternative with higher performance than the classic LR model, reinforcing the wide applicability of ANN and its ability to learn from input data with or without supervision.

The multifactorial origin of AKI after LT makes it complex to predict which candidate for the procedure has an increased risk of this complication, and in the face of this complexity, along with the classical LR, ANN would be a very reliable prognostic tool for AKI risk assessment, where the relative risk term is parameterized by an ANN instead of regression, enabling the application of deep learning, whereas comparative studies evaluating such a promising tool for predicting AKI following LT are scarce. [19-20]

In face of this serious postoperative complication, this retrospective cohort of patients that undergone only-first DDLT aimed to identify the risk factors of postoperative AKI and compare the prediction performance of ANN with that of LR for this complication.

MATERIALS AND METHODS

Study Design

A retrospective audit of a tertiary referral hospital was conducted for patients of both sexes, aged > 18 years, with diagnosis of liver cirrhosis and portal hypertension (platelets <100.000/mm^3, splenomegaly and/or esophageal varices), eventually associated with hepatocellular carcinoma (HCC), undergoing the first DDLT between

September 2017 and June 2021, allocated according to Model for End-Stage Liver Disease (MELD) score, with no evidence of end-stage kidney disease. The MELD score was dichotomized at 25 points for statistical purposes according to Xu *et al*[21], and the minimum hospital stay was 7 days according to Wong *et al*[22] and ICA definitions for the onset of AKI.[23]

Renal Dysfunction Definitions

Kidney dysfunction (KD) subtypes were defined according to Wong *et al* (Table 1)[22] and the International Club of Ascites (ICA) definitions (Table 2)[23], and both the acute deterioration in renal function and the background CKD could be structural or functional in nature, including HRS types 1 and 2 (Table 3).[23] Estimated glomerular filtration rate (eGFR) were calculated by the Modified Diet in Renal Disease 6 (MDRD6) formula: eGFR = 198 × [serum creatinine (mg/dL)$^{-0.858}$ × age$^{-0.167}$ × 0.822 if patient is female × 1.178 if patient is black] × [serum urea nitrogen concentration (mg/dL)]$^{-0.293}$ × [urine urea nitrogen excretion (g/d)]$^{0.249}$. [29]

Graft Definitions

Marginal liver grafts of extended criteria donor (ECD) were defined as a graft with 3 or more of the following donor features: >60 years, BMI >27-30 kg/m^2, macrovesicular steatosis >30%, intensive care unit (ICU) stay >4 days, sustained arterial hypotension >1 h, cold ischemia times (CIT) >8 h, warm ischemia times (WIT) >40-45 minutes, controlled sepsis, history of alcoholism, sCr >1,2 mg/dL, arterial hypotensive episodes <60 mmHg >1 h, bilirubin >2.0 mg/dL, alanino transaminase (ALT) >170 U/L, and aspartate transaminase (AST) >140 U/L, the use of dopamine doses >10 microg/kg per min and peak serum sodium >155 mEq/L[24-26].

Routine biopsy was performed on the donor allograft for all patients included in the study. Liver specimens were evaluated with hematoxylin and eosin staining as either frozen and permanent section. Macrovesicular steatosis was defined as a single vacuole larger than the nucleus, replacing most of the hepatocytes cytoplasm and displacing the nucleus to the cell membrane.[27] Macrosteatosis was categorized as no steatosis (<5%), mild steatosis (10%-29%), moderate steatosis (30%-60%), and severe steatosis (>60%).[28]

Hemodynamic Status and Monitoring

Fluid administration consisted of a baseline infusion of a balanced crystalloid (Plasmalyte®, Baxter, Belgium) with or without 4% albumin (depending on patient conditions). Rapid infusers, perfusion heaters, and a Cell Saver® (Haemonetics, Massachusetts, EUA) for blood recovery were ready for use prior to induction, In accordance to American Society of Anaesthesiologists (ASA) guidelines, Cell Saver® has effectiveness in reducing the volume of allogeneic blood transfused.[30]

A Flow Trac/EV1000 System® (Edwards Lifesciences, Irvine, USA) was inserted and hemodynamic interventions were guided using continuous cardiac index (CCI), stroke volume index (SVI), mixed venous oxygen saturation (SvO_2), central venous pressure (CVP), and mean arterial pressure (MAP). Fluids were administered if SVI was <30 mL/m^2 and/or CCI <2 L/min/m^2 for compensation for blood loss *via* 250-500 mL fluid boluses of either Plasmalyte®, to strictly maintain MAP >65 mmHg, avoiding hemodynamic instability as described elsewhere[31,32].

Blood loss monitoring consists of visual assessment of the surgical field, including the extent of blood present, presence of microvascular bleeding, surgical sponges, clot size and shape, and volume in suction canister. In case of active haemorrhage, blood products administration were guided by using rotational thromboelastometry monitoring *via* ROTEM® (Tem Innovations GmbH, Munich, Germany), hemoglobin/hematocrit monitoring, coagulation tests (international normalized ratio [INR], activated partial thromboplastin time [aPTT], fibrinogen concentration [normal range:200 to 400 mg/dL], and platelet count.[30] Whereas there's no clear evidence that ROTEM® improved survival in LT patients, it was effective in reducing bleeding and fewer patients required both platelets and fresh frozen plasma (FFP) transfusion.[33] Monitoring for perfusion of vital organs includes standard ASA monitoring, renal monitoring (urine output), and analysis of arterial blood gasses and serum (SL) level (cutoff of 2.0 mmol/L).[30]

Massive blood transfusion (MBT) protocol for avoidance of dilutional coagulopathy were activated when hemorrhage were expected to be massive (antecipaded need to replace 50% or more of blood volume within 2 h), or bleeding continued after the transfusion of 4 units of packed red blood cells (PRBC) within a short period of time (1-2 h), or systolic blood pressure (SBP) were below 90 mmHg and heart rate is above 120 beats per minute in the presence of uncontrolled bleeding.[34] According to the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study group recommendations, blood transfusion of RBC, fresh frozen plasma (FFP) and platelets were on a 1:1:1 ratio.[35]

Postreperfusion (PRS) was defined as a decrease in MAP >30% below the baseline value, for at least 1 minute, occurring during the first 5 minutes after reperfusion of the liver graft, asystole, or hemodynamically significant arrhythmias, or the need to start the infusion of vasopressors during the postreperfusion period.[36] Intraoperative arterial hypotension (IOAH) was defined as MAP less than 65-60 mmHg for at least 5 minutes, or any exposure to MAP less than 55-50 mmHg[32], irrespective of the cause: prolonged surgery time, massive bleeding, RPS and/or hemodynamic instability because of end-stage liver disease.

Statistical Analysis

The baseline characteristics of the patients were expressed in absolute values, the average ± standard deviation and percentage, when appropriate. The comparison between groups was performed for continuous variables using the Kruskal-Wallis test and the Mann-Whitney test. The assumptions were made to perform or not the parametric tests, and the categorical variables were compared using the chi-square test. Independent variables with significance in the univariate model was selected for the bootstrap classical LR model to assess the effect of bivariate independent variables (graft quality, patients characteristics and intraoperative events) on the incidence of postoperative AKI. The results of the model were expressed by odds ratio (OR), together with the corresponding 95% confidence intervals, Nagelkerke R2 statistic, and Hosmer and Lemeshow goodness of fit test. The p values < 0.05 were considered significant. A relationship map between the significant variables in the LR model was also constructed.

The explanatory variables selected in LR model were used for the ANN machine learning. Before developing prediction models, our collected data were divided into 70% of training dataset cases and 30% of test dataset cases. The cases in the training dataset were used for developing machine learning models. The ANN method had its own hyperparameters (number of layers in multilayer perceptron ANN), with a 10-fold cross-validation. This cross-validation process was used for developing the model, and performance was evaluated. The activation function of hidden layer was made by hyperbolic tangent activation function, and Softmax for the output layer. All possible combinations of hyperparameters were investigated, and the hyperparameters with the highest average validation AUROC were considered as optimal hyperparameters, and after that, the final model was tested for performance by root-mean-square error (RMSE) and mean absolute error (MAE) calculation. The importance of variables for the model were calculated. ANN structural model was constructed according to Haykin (2001)[37].

Our primary analysis attempted to analysis the prediction ability of machine learning and LR model in terms of AUROC. Accuracy was defined as the sum of the number of cases with true positive and true negative results divided by total number of test set. Statistical calculations were performed using the SPSS 28.0® software for Windows®.

RESULTS

During the period from September 2017 to June 2021, 145 DDLT were included in the statistics. Of the total, 88 (60.6%) patients presented any further stage of postoperative AKI during the 7 days follow-up, 22 (15.1%) patients developed stage 1 AKI, 36 (24.8%) patients developed stage 2, and 30 (20.6%) patients developed stage 3 AKI (Table 4), and renal replacement therapy (RRT) being required in 12 patients (8,7%) of the total of patients. All patients preoperative baseline information, donors, and grafts characteristics according to the occurrence of AKI are shown in Table 5 and 6. The intraoperative data related to IOAH, blood derivatives transfusion, and piggy-back clamping, and laboratorial tests until the seventh postoperative (PO) day are shown in Table 7.

In the LR analysis, Nagelkerke R2 statistic was 0.147. Hosmer and Lemeshow goodness of fit test was not significant at 5% (P = 0.247). The six following factors were confirmed as predictors (Table 8): biological (not adjusted) MELD score ≥25 (OR=1.999, 95%CI=1.586-2.503, p <0.001), pre-existing KD (OR= 1.279, 95%CI= 0.916-1.686, p <0.001), ECD (OR= 1.191, 95%CI= 0.711-1.787, P = 0.002), IOAH (OR= 1.935, 95%CI= 1.505-2.344, p<0.001), MBT (OR= 1.830, 95%CI= 1.428-2.241, p<0.001), serum lactate at the end of LT (OR= 2.001, 95%CI= 1.616-2.421, p<0.001), and the relationships between the significant variables were explored by a relationship map detailed on figure 1.

Data of the two models respective to area under receiver-operating characteristic curve (AUROC) to predict AKI of all stages are detailed on figure 2. ANN had largest test AUROC (0.81, 95%CI 0.75–0.83) and highest accuracy (0.68) than LR analysis [(AUROC (0.71, 95%CI 0.67 to 0.76), accuracy = 0.68].

Importance plot for ANN is shown in figure 3 (KD and MELD score ranked first and second. Multilayer perceptron ANN presented 1 hidden layer by hyperbolic tangent activation function with 4 nodes in the layer, as presented in the ANN structural model diagram (figure 4), and the prediction RMSE was 0.47 and the prediction MAE was 0.38.

DISCUSSION

As described elsewhere[37], the findings in the present study demonstrated a high incidence of postoperative AKI, and the predictive ability of ANN and LR models for this complication. An important point in this research, is that AKI prediction was focused on the identification of significant risk factors at the end of the procedure, thus enabling the adoption of preventive measures or early therapies for AKI in the postoperative period.

In the present study, the severity of the chronic liver disease, pre-existing KD, marginal grafts, hemodynamic instability with MBT and consequent inadequate tissue perfusion during LT, were predictors of AKI after DDLT, and the relationship map illustrated through a visual pattern, the relationship between the variables, although it is important to understand that a visual relationship does not always mean statistical causation. As demonstrated in our study, in the case of machine learning-based techniques, the importance of each variable in the dataset can be indicated by the characteristic importance measure, which can improve the transparency of the algorithm according to He *et al*[20]

According to our results, ANN had larger AUROC and higher accuracy to predict AKI after DDLT than LR, which is consistent with the previous study with different machine learning tools, whereas the performance of the ANN were inferior to those of all other machine learning techniques in prediction of AKI after LT[19]. Multilayer perceptron has already been associated to a good performance in predicting in-hospital mortality, reinforcing the good performance of ANN to predict clinical outcomes, although there have been some reports that performance of the machine learning techniques are not superior LR model to predict mortality[38].

Regarding the risk factors identified in the present research, several other authors have already described that higher MELD scores[39] were associated with AKI after LT.[20,40] Xu *et al*[21] showed that MELD score >25 was predictor of AKI, and in patients with MELD scores >30, the most required RRT.[41,42] Moreover, in the cirrhosis scenario, the functional renal disorders can be added as risk factors for AKI, such as recipient HRS[23,42,43]. Donor marginal liver grafts of ECD were identified elsewhere as strong predictors of PGD[24-26] and post-LT AKI.[20] Patients undergoing LT can experience IOAH and consequent AKI because of multiple factors, including the duration of surgery, massive bleeding[16,42,44], the severity of the PRS[36,45.46] and the severity of the end-stage liver disease[47–52], in addition, MBT may be an additional risk factor for postoperative AKI.[35,53,54]

The present retrospective study has important limitations, regarding sample size and moreover, the lack of evaluation of clinical outcomes of patients according to the occurrence of post-LT AKI, either for short as long-term evolution. Despite these limitations, the high incidence of AKI reported highlights the importance of this issue, and the predictors identified may provide a focus for further research. ANN methods may provide feasible tools for forecasting AKI after LT, and perhaps provide a high-performance predictive model that may ultimately improve perioperative management of these patients at risk for this serious complication.

CONCLUSION

According to our results, the severity of the chronic liver disease, pre-existing KD, marginal grafts, hemodynamic instability, MBT and inadequate tissue perfusion during LT were predictors of AKI after DDLT, and ANN had better prediction performance than LR in this scenario

ARTICLE HIGHLIGHTS

Research background

Development of a risk score of AKI after DDLT according to these identified predictors

Research motivation

The severity of liver disease, preexisting KD, marginal grafts, hemodynamic instability, MBT and SL were predictors of postoperative AKI, and ANN had better prediction performance than LR

Research objectives

According to the predictors identified by LR, ANN had better performance (AUROC) than the classical LR for AKI prediction

Research methods

LR analysis for predictors identification, and comparative analysis of ANN and LR prediction performance

Research results

Identify the risk factors of AKI after DDLT and validate a prediction tool for this complication

Research conclusions

Improvement of perioperative management of patients candidates for LT

Research perspectives

AKI post-LT is a serious complication, and its prediction by validated tools is crucial

71935_Auto_Edited.docx

ORIGINALITY REPORT

12%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.wjgnet.com Internet	127 words — 4%
2	www.gavinpublishers.com Internet	81 words — 3%
3	www.mdpi.com Internet	60 words — 2%
4	Luis Cesar Bredt, Luis Alberto Batista Peres. "Artificial neural network for prediction of acute kidney injury after liver transplantation for cirrhosis and hepatocellular carcinoma", WArtificial Intelligence in Cancer, 2021 Crossref	30 words — 1%
5	Zeng-Lei He, Jun-Bin Zhou, Zhi-Kun Liu, Si-Yi Dong, Yun-Tao Zhang, Tian Shen, Shu-Sen Zheng, Xiao Xu. "Application of machine learning models for predicting acute kidney injury following donation after cardiac death liver transplantation", Hepatobiliary & Pancreatic Diseases International, 2021 Crossref	24 words — 1%
6	f6publishing.blob.core.windows.net Internet	19 words — 1%

7 Joanna Baron-Stefaniak, Judith Schiefer, Paul Lichtenegger, Edmund J. Miller et al. "D-dopachrome tautomerase predicts outcome but not the development of acute kidney injury after orthotopic liver transplantation", HPB, 2019
Crossref

15 words — < 1%

8 doi.org
Internet

14 words — < 1%

9 Sibel Ozler, Efser Oztas, Basak Gumus Guler, Ali Turhan Caglar. "Increased levels of serum IL-33 is associated with adverse maternal outcomes in placenta previa accreta", The Journal of Maternal-Fetal & Neonatal Medicine, 2019
Crossref

13 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE MATCHES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	OFF		