Machine Learning to Predict Post-Operative Acute Kidney Injury Stage 3 After Heart Transplantation

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Abstract

Background

Acute kidney injury (AKI) stage 3, one of the most severe complications in patients with heart transplantation (HT), is associated with substantial morbidity and mortality. We aimed to develop a machine learning (ML) model to predict post-transplant AKI stage 3 based on preoperative and perioperative features.

Methods

Data from 107 consecutive HT recipients in the provincial center between 2018 and 2020 were included for analysis. Logistic regression with L2 regularization was used for the ML model building. The predictive performance of the ML model was assessed using the area under the curve (AUC) in 10-fold stratified cross-validation and was compared with that of the existing clinical metrics.

Results

Post-transplant AKI occurred in 71 (66.3%) patients including 13 (12.1%) stage 1, 13 (12.1%) stage 2, and 45 (42.1%) stage 3 cases. The top four features selected for the ML model to predicate AKI stage 3 were serum cystatin C, estimated glomerular filtration rate (eGFR), right atrial long-axis dimension, and serum creatinine (SCr). The predictive performance of the ML model (AUC: 0.828; 95% confidence interval [CI]: 0.745–0.913) was significantly higher compared with that of the existing clinical metrics including eGFR (AUC: 0.694; 95%[CI]: 0.594–0.795, $p < 0.05$) and SCr (AUC: 0.525; 95%[CI]: 0.411–0.636), $p < 0.001$).

Conclusions

The ML model, which achieved an effective predictive performance for post-transplant AKI stage 3, may be helpful for timely intervention to improve the patient's prognosis.

Background

Heart transplantation (HT) remains a life-sustaining treatment decision for numerous end-stage heart disease patients[1]. Despite the advancement of various immunosuppressive therapies and treatment programs, the incidences of acute kidney injury (AKI) and of severe AKI requiring renal replacement therapy (RRT) in patients with HT remains high in recent years[2]. AKI most commonly occurs in the first week after HT, with the incidence of 22-76%, and is associated with high rates of morbidity and mortality[3-6].

Early AKI detection following HT is meaningful for interventions that prevent future kidney damage and preserve kidney function because AKI is associated with mortality more than 60% during intensive care unit stay among hospitalized postsurgical patients[7]. Moreover, AKI, especially stage 3, is correlated with subsequent progressive chronic kidney disease (CKD) along with decreased survival rates of HT recipients. Various features associated with AKI stage 3, such as drugs, immunosuppression therapies, hemodynamics, and some anesthesia- and surgery-related factors have been identified by traditional models in previous studies[6,8]. However, their predictive performance is relatively limited on account of the limited amount of patient information extracted and some of the features having a conflicting effect. Due to these reasons, it is indispensable to develop a novel and efficient model to predict AKI stage 3.

As a powerful tool for intelligent data analysis, machine learning (ML) can be utilized to model medical data. Computational algorithms are constructed to develop a model to associate a spectrum of features of the given datasets with the outcome. ML has been commonly used in medical data analysis for diagnosis and prognosis of a variety of tumors, such as in breast[9] and prostate cancers[10]. Furthermore, there is clear evidence that ML can be used for analysis in other medical fields as well. For instance, a recent study on predicting 5-year all-cause mortality in patients with suspected coronary artery disease showed that ML had superior predictive performance compared with traditional clinical or coronary computed tomography angiography metrics alone[11]. We hypothesize that ML adds incremental value to the prediction of adverse events. Therefore, the objective of this study was to evaluate the feasibility and accuracy of ML to predict AKI stage 3 in HT patients and then to compare the performance to that of existing clinical metrics.

Methods

Data collection

Data of all HT patients in Guangdong Provincial People's Hospital were collected and analyzed from January 2018 through September 2020. All patients had undergone primary orthotopic deceased-donor heart transplantation due to various causes. Exclusion criteria were recipient age < 18 years at the time of transplantation, retransplantation, or RRT prior to heart transplantation (Figure 1). Patient data were obtained from the hospital database or electronic records. This retrospective study was approved by the Institutional Review Board of the Guangdong Provincial People's Hospital and was conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived given the retrospective nature of the study.

Study features

We reviewed the medical records of the patients retrospectively and collected clinical data including: demographic features such as age, gender, and body mass index; primary cardiac disease; the history of cardiac surgery, diabetes, hypertension, hyperlipidemia, peripheral vascular disease, and coronary arterial disease; pretransplant heart function features; pretransplant renal function features, such as serum

creatinine (SCr), estimated glomerular filtration rate (eGFR), CKD, urine N-acetyl-beta-D-glucosaminidase, serum cystatin C (CysC)[12]; liver function features; the use of any of the following preoccupation support measures: intra-aortic balloon pump and extracorporeal membrane oxygenation; echocardiography features; donor characteristics such as age, gender, weight, cause of death, and ischemia time of donor heart; aortic occlusion time; cardiopulmonary bypass time; blood transfusion. All features were divided into three subsets: preoperative, perioperative, and donor characteristics.

Study outcomes

The study outcome was post-transplant AKI defined based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria[13]: an increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 umol/L) within 48h or to > 1.5 times baseline within the first 7 postoperative days. AKI was classified into 3 stages depending on the level of SCr: stage 1, SCr increase by ≥ 0.3 mg/dl (≥ 26.5 umol/L) within 48 h or 1.5–1.9-fold increase from the baseline; stage 2, 2–2.9-fold increase from the baseline; stage 3, ≥ 3-fold increase from the baseline, increase in SCr by ≥ 4.0 mg/dl (≥ 354 umol/L) or the start of RRT. The baseline SCr was referred to as the average of all values available from 3 months to one day prior to heart transplantation. Then, we obtained the eGFR, which was calculated by the Chronic Kidney Disease-Epidemiology Collaboration Group equation[14].

Machine learning

The ML system consisted of three parts: feature selection, model building, and model evaluation (Figure 2). It was implemented in WEKA 3.8.

To evaluate the worth of a feature, Pearson's correlation between the feature and the class was calculated. The correlations of the features included were ranked in descending order (Figure 3), and the features highly correlated with postoperative AKI stage 3 were selected. The details of feature selection are shown in the supplementary material (Supplementary Table 1).

We selected different classifiers (e.g., logistic regression with L2 regularization, logistic regression, random forest, naïve Bayes, and support vector machine) to build classifiers based on the features highly correlated with AKI stage 3. The full details of model selection are shown in the supplementary material (Supplementary Table 2). After the model selection procedure, the logistic regression with L2 regularization was the selected model. L2 regularization is a regularized method that shrinks the regression coefficients towards 0 by placing a penalty on the summation of the estimated coefficients. Although the regularization method may lead to biased regression estimates, it results in a more stable model that produces excellent predictive performance in particular when applied to external datasets (the details of the algorithm are presented in the supplementary materials)[15].

The performance of the ML model was evaluated using 10-fold cross-validation. The dataset was randomly divided into ten folds with approximately the same number of patients. Nine folds were used as

the training set, while the remaining fold was used as the validation set. Every fold was used as a training set nine times and as a validation set once. Therefore, the outcome of every patient was predicted once.

Statistical analysis

Continuous features with normal distribution based upon the Durbin-Watson test were presented as mean ± standard deviation; data with skewed distributions were presented as median and interquartile range (IQR); and categorical features were presented as frequency (percentage). The receiver operator characteristic curves were used to evaluate the performance of the ML model and of the existing clinical metrics (eGFR and SCr) to predict post-transplant AKI stage 3, and the differences between areas under the curves (AUCs) were compared based on Delong et al[16]. The accuracy, sensitivity, and specificity of the model based on the optimum cutoffs were computed. All statistical analyses were performed with SPSS version 22.0 software (SPSS, Chicago, Illinois, USA) and R statistical software (R Foundation, Vienna, Austria) by using RStudio Server version 1.3. The presented statistical significance levels were all two-sided and $p < 0.05$ was considered significant.

Results

Study population

From 141 patients with HT from January 2018 through September 2020, 34 were excluded for the following reasons: younger than 18 years old (n = 15); had preoperative RRT (n = 16); younger than 18 years old and had preoperative RRT (n = 2); and had retransplantation (n = 1). Finally, a sample of 107 patients was analyzed with 71 (66.3%) patients suffering from AKI. Furthermore, the incidences of AKI stages 1, 2, and 3 were 13 (12.1%), 13 (12.1%), and 45 (42.1%), respectively. Of those who met the criteria for AKI stage 3, 40 (88.9%) received RRT, which lasted for a median of 93 (47–243) hours, and 20 (44.4%) deaths were observed (Table 1). Donor, recipient, and surgery-related characteristics are listed in Table 1.

Table 1
Donor, recipient and surgical characteristics in the cohorts

Features	No AKI	AKI stage1	AKI stage2	AKI stage3
	36(34.7)	13(12.1)	13(12.1)	45(42.1)
Preoperative characteristics				
Age, y	47(38–56)	51(44–59)	44(29–52)	52(46–59)
Male, sex	30(83.3)	11(84.6)	10(76.9)	41(91.1)
Height, cm	169(164–172)	169(164–170)	167(163–174)	168(163–172)
Weight, kg	58(55–69)	67(57–70)	58(50–70)	62(55–73)
BMI, kg/m^2	20(19–24)	23(20–24)	22(19–23)	23(20–25)
Primary cardiac disease(yes)				
Dilated cardiomyopathy	21(58.3)	10(76.9)	7(53.8)	20(44.4)
Valvular disease	4(11.1)	0(0.0)	1(7.7)	24(53.3)
Ischemic cardiac disease	6(16.7)	2(15.4)	3(23.1)	7(15.6)
Restrictive cardiomyopathy	2(5.6)	0(0.0)	0(0.0)	12(26.7)
Hypertrophic cardiomyopathy	1(2.7)	1(7.7)	0(0.0)	0(0.0)
Other cardiac disease	1(2.7)	0(0.0)	2(15.4)	2(4.4)
Medical history(yes)				
Prior cardiac surgery	12(33.3)	8(61.5)	7(53.8)	23(51.1)
Diabetes mellitus	8(22.2)	1(7.7)	3(23.1)	10(22.2)
Hypertension	6(17.6)	2(15.4)	2(15.4)	10(22.2)
Hyperlipidemia	3(8.3)	0(0.0)	1(7.7)	2(4.4)

Data displayed as median and interquartile range or n (%).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; Cryo, cryoprecipitation; CVA, cerebrovascular accident; CysC, cystatin C; DBIL, direct bilirubin; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; FFP, fresh freezing plasma; FVII, factor VII; FVIII, factor VIII; HCY, homocysteine; IABP, intra-aortic balloon pump; ICU, intensive care unit; IVSd, interventricular septal end-diastolic thickness; LA-ap, left atrial anteroposterior dimension; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PCC, prothrombin complex concentrate; RA-l, right atrial long-axis dimension; RBC, red blood cell; RRT, renal replacement therapy; RV-l, right ventricular long-axis dimension; SCr, serum creatinine; SPAP, systolic pulmonary artery pressure; TBIL, total bilirubin; UAlb, urine albumin; UCr, urine creatinine; PLT, blood platelet; UNAG, urine N-acetyl-κ-d-glucosaminidas; UPro, urine protein.

Features	No AKI	AKI stage1	AKI stage2	AKI stage3
	36(34.7)	13(12.1)	13(12.1)	45(42.1)
Peripheral vascular disease	9(25.0)	2(15.4)	3(23.1)	6(13.3)
Coronary arterial disease	8(22.2)	3(23.1)	4(30.8)	12(26.7)
Heart function				
NT-proBNP, pg/mL	2207(1076–4085)	4479(1271–6969)	1714(1286–3322)	4307(1239–8302)
HCY, μmol/L	10(7–35)	9(8–10)	12(12–12)	31(10–451)
Renal function				
Baseline SCr, mmol/L	89(75-111)	87(73-97)	92(72-107)	92(110-149)
eGFR, ml/min/1.73m^2	86(65–103)	84(74–94)	87(69–115)	65(47–84)
CKD(eGFR < 60 mL/min per 1.73 m^2)(yes)	9(25.0)	1(7.7)	2(15.4)	22(48.9)
UNAG, U/L	17(10–35)	14(11–25)	14(6–14)	25(10–41)
UNAG/UCr, U/mmol	6(2–18)	2(2–6)	3(2–3)	11(3–26)
CysC, mg/L	1.1(0.8–1.6)	1.4(0.9–1.7)	1.1(0.9–1.2)	1.6(1.4–2.6)

Table 1. **(Continued)**

Features	No AKI	AKI stage1	AKI stage2	AKI stage3
	36(34.7)	13(12.1)	13(12.1)	45(42.1)
UAlb/Ucr, mg/g	143(115-182)	68(35-222)	57(35-80)	122(29-964)

Data displayed as median and interquartile range or n (%).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; Cryo, cryoprecipitation; CVA, cerebrovascular accident; CysC, cystatin C; DBIL, direct bilirubin; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; FFP, fresh freezing plasma; FVII, factor VII; FVIII, factor VIII; HCY, homocysteine; IABP, intra-aortic balloon pump; ICU, intensive care unit; IVSd, interventricular septal end-diastolic thickness; LA-ap, left atrial anteroposterior dimension; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PCC, prothrombin complex concentrate; RA-l, right atrial long-axis dimension; RBC, red blood cell; RRT, renal replacement therapy; RV-l, right ventricular long-axis dimension; SCr, serum creatinine; SPAP, systolic pulmonary artery pressure; TBIL, total bilirubin; UAlb, urine albumin; UCr, urine creatinine; PLT, blood platelet; UNAG, urine N-acetyl-κ-d-glucosaminidas; UPro, urine protein.

Features	No AKI 36(34.7)	AKI stage1 13(12.1)	AKI stage2 13(12.1)	AKI stage3 45(42.1)
Upro/Ucr, mg/g	285(211-401)	111(106-223)	140(100-179)	71(18-216)
Liver function				
TBIL, umol/L	22(16–32)	19(17–21)	21(17–24)	19(15–29)
DBIL, umol/L	5(3–10)	4(3–5)	4(3–6)	5(3–10)
Preoccupative support(yes)				
IABP	4(11.1)	3(23.1)	0(0.0)	7(15.6)
ECMO	4(11.1)	1(7.7)	2(15.4)	4(8.9)
Echocardiography				
LA-ap, mm	48(41–54)	43(42–52)	51(44–53)	52(46–58)
LVIDd, mm	68(60–76)	73(70–84)	69(61–73)	69(63–77)
LVIDs, mm	58(50–65)	69(63–74)	58(52–70)	60(53–69)
LVEF, %	26(20–34)	23(18–28)	28(24–40)	24(20–30)
RV-l, mm	61(56–67)	63(60–66)	60(57–64)	63(58–72)
RA-l, mm	54(47–61)	48(46–54)	52(48–60)	61(51–69)
IVSd, mm	8(7–10)	8(7–9)	9(8–9)	8(8 – 0)
Mitral regurgitation area, cm^2	6(3–12)	8(4–15)	8(3–11)	8(3–10)
Tricuspid regurgitation area, cm^2	4(2–7)	1(0–3)	3(2–8)	5(2–9)
SPAP, mmHg	40(30–58)	44(32–56)	46(39–54)	44(36–60)

Data displayed as median and interquartile range or n (%).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; Cryo, cryoprecipitation; CVA, cerebrovascular accident; CysC, cystatin C; DBIL, direct bilirubin; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; FFP, fresh freezing plasma; FVII, factor VII; FVIII, factor VIII; HCY, homocysteine; IABP, intra-aortic balloon pump; ICU, intensive care unit; IVSd, interventricular septal end-diastolic thickness; LA-ap, left atrial anteroposterior dimension; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PCC, prothrombin complex concentrate; RA-l, right atrial long-axis dimension; RBC, red blood cell; RRT, renal replacement therapy; RV-l, right ventricular long-axis dimension; SCr, serum creatinine; SPAP, systolic pulmonary artery pressure; TBIL, total bilirubin; UAlb, urine albumin; UCr, urine creatinine; PLT, blood platelet; UNAG, urine N-acetyl-κ-d-glucosaminidas; UPro, urine protein.

Features	No AKI	AKI stage1	AKI stage2	AKI stage3
	36(34.7)	13(12.1)	13(12.1)	45(42.1)
Days on waiting list	22(11–26)	30(18–35)	15(10–40)	20(8–32)
Donor characteristics				
Age, y	38(29–46)	38(33–49)	31(28–40	40(29–47)
Male, sex	34(94.4)	12(92.3)	12(92.3)	40(88.9)
Weight, kg	65(60–70)	60(48–70)	60(50–70)	60(49–68)
Cause of death(yes)				
Trauma	26(72.2)	8(61.5)	5(38.5)	30(66.7)
CVA	9(25.0)	3(23.1)	6(46.2)	12(26.7)
Others	1(2.7)	2(15.4)	2(15.4)	3(6.7)
Time of ischemia donor heart, min	202(181–223)	187(159–224)	245(208–300)	208(183–242)
Perioperative characteristics				
Aortic occlusion time, min	132(112-143)	129(118-145)	260(214-298)	238(216-286)
CPB time, min	251(218–312)	267(250–279)	137(119–162)	122(110–136)
Blood transfusion(yes)				

Table 1. **(Continued)**

Features	No AKI	AKI stage1	AKI stage2	AKI stage3
	36(34.7)	13(12.1)	13(12.1)	45(42.1)
FVII	8(22.2)	3(23.1)	1(7.7)	5(11.1)

Data displayed as median and interquartile range or n (%).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; Cryo, cryoprecipitation; CVA, cerebrovascular accident; CysC, cystatin C; DBIL, direct bilirubin; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; FFP, fresh freezing plasma; FVII, factor VII; FVIII, factor VIII; HCY, homocysteine; IABP, intra-aortic balloon pump; ICU, intensive care unit; IVSd, interventricular septal end-diastolic thickness; LA-ap, left atrial anteroposterior dimension; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PCC, prothrombin complex concentrate; RA-l, right atrial long-axis dimension; RBC, red blood cell; RRT, renal replacement therapy; RV-l, right ventricular long-axis dimension; SCr, serum creatinine; SPAP, systolic pulmonary artery pressure; TBIL, total bilirubin; UAlb, urine albumin; UCr, urine creatinine; PLT, blood platelet; UNAG, urine N-acetyl-κ-d-glucosaminidas; UPro, urine protein.

Features	No AKI	AKI stage1	AKI stage2	AKI stage3
	36(34.7)	13(12.1)	13(12.1)	45(42.1)
FVIII	11(30.5)	3(23.1)	1(7.7)	14(31.1)
PCC	10(27.8)	3(23.1)	1(7.7)	17(37.8)
Cryo	12(33.3)	4(30.8)	5(38.5)	13(28.9)
RBC	12(33.3)	3(23.1)	3(23.1)	15(33.3)
PLT	34(94.4)	13(100.0)	13(100.0)	43(95.6)
FFP	19(52.8)	3(23.1)	3(23.1)	23(51.1)
Postoperative characteristics				
Post-operative SCr, umol/L	120(93-145)	153(140-164)	159(146-220)	346(241-457)
RRT(yes)	0(0.0)	0(0.0)	0(0.0)	40(88.9)
RRT time, h	0(0–0)	0(0–0)	0(0–0)	93(47–223)
Days in ICU	6(5–8)	7(6–9)	6(5–11)	10(8–16)
Re-admission to hospital(yes)	4(11.1)	2(15.4)	1(7.7)	11(24.4)
Death(yes)	4(11.1)	2(15.4)	1(7.7)	20(44.4)
Data displayed as median and interquartile range or n (%).				
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; Cryo, cryoprecipitation; CVA, cerebrovascular accident; CysC, cystatin C; DBIL, direct bilirubin; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; FFP, fresh freezing plasma; FVII, factor VII; FVIII, factor VIII; HCY, homocysteine; IABP, intra-aortic balloon pump; ICU, intensive care unit; IVSd, interventricular septal end-diastolic thickness; LA-ap, left atrial anteroposterior dimension; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; NT-proBNP, N-terminal pro brain-type natriuretic peptide; PCC, prothrombin complex concentrate; RA-l, right atrial long-axis dimension; RBC, red blood cell; RRT, renal replacement therapy; RV-l, right ventricular long-axis dimension; SCr, serum creatinine; SPAP, systolic pulmonary artery pressure; TBIL, total bilirubin; UAlb, urine albumin; UCr, urine creatinine; PLT, blood platelet; UNAG, urine N-acetyl-κ-d-glucosaminidas; UPro, urine protein.				

Feature selection

The features were ranked by Pearson correlation in descending order (Fig. 3). The top four features were recognized as the significant features and were selected for the training of the ML model. Those features were as follows: preoperative CysC (r = 0.380), eGFR (r = 0.356), right atrial long-axis dimension (RA-l; r = 0.354), and SCr (r = 0.281).

Prediction of AKI stage 3

The ML model exhibited a significantly higher AUC (0.828; 95%[CI]:0.745–0.913) compared to the existing clinical metrics alone for prediction of AKI stage 3 (eGFR: 0.694, 95%[CI]: 0.594–0.795, $p < 0.05$; SCr: 0.525, 95%[CI]: 0.411–0.636, $p < 0.001$) (Fig. 4). The accuracy, sensitivity, and specificity for the prediction of AKI stage 3 were 75.7%, 91.1%, and 75.8% for the ML model; 66.4%, 62.2%, and 69.4% for eGFR; and 64.2%, 68.9%, and 41.9% for SCr, respectively.

Discussion

The results of the present study suggested that the ML model could be an effective tool for risk stratification and prediction of post-transplant AKI stage 3 for individual patients. The performance of the ML model was superior to that of the existing clinical metrics alone (eGFR or SCr). To the best of our knowledge, this study is the first to evaluate the predictive capability of ML methods for the assessment of severe postoperative AKI in patients undergoing HT.

Early identification and prevention of AKI in patients undergoing HT may play an important role in selecting treatment regimens and thus improving prognosis, given the high short- and long-term mortality risks associated with AKI after HT. If acute renal failure happens, the short-term mortality increases 3.5-fold and 1-year mortality 2.3-fold[1]. However, the ability to accurately identify high-risk patients who may develop AKI is a major challenge in clinical practice. Although traditional risk factors for the prediction of post-transplant AKI have been identified, they are population-based tools [7,12], which are less effective for individual risk evaluations. Furthermore, the traditional features to predict post-transplant AKI from existing models have relatively limited predictive performance[17], highlighting the need for a more precise model for personalized treatment decisions.

Analyzing and integrating the numerous risk features in an individual patient can be a confounding task for the clinician. The increasing number of clinical features influencing risk stratification from various medical checks amplifies the intricacy of assessment and makes it more difficult for clinicians to make a correct decision involving risk stratification in an individual patient. Moreover, the unanticipated aspects of possible interactions between a few weaker risk features in an individual patient are frequently underestimated[11]. Machine learning, both supervised and unsupervised, can overcome these challenges by deep integration of the experimental and clinical datasets to build powerful risk models and reclassify patient groups[18].

Our results demonstrated that by the integration of clinical information, experimental datasets, and ultrasonography-derived metrics, the ML model (AUC:0.828) showed superior risk prediction for AKI stage 3 compared with preoperative eGFR (AUC: 0.694) and SCr (AUC: 0.525) alone. These features had been identified as predictors of AKI by logistic regression analysis in previous studies [12,19,20]. However, the numbers of features included in the analyses of these studies were limited to decrease the interactions between features. In our study, the ML model provided an excellent value in prognostic performance while considering 51 features and potential feature–feature interactions in patients. This characteristic permits

a deep exploration of all available data for non-linear patterns that could predict the risk stratification of a particular individual[15].

As reported in previous studies, the occurrence of AKI is a consequence of multiple multifactorial interactive methods that cannot be interpreted in the context of a single etiologic factor[17,21,22]. In the light of our findings, CysC, eGFR, RA-l, and SCr were all predictive factors included in the ML model for predicting the development of AKI stage 3. In particular, CysC, a biomarker for the quantification of kidney function loss, was the most related predictive factor in patients with AKI stage 3, and it may have the ability to detect AKI one to two days before the rise of SCr with higher accuracy and precision [23]. Furthermore, except for acute renal failure, no other factors were found to alter CysC levels, enhancing its effectiveness as an endogenous marker for predicting AKI. Our findings confirm the predictive value of eGFR ranked after CysC, one explanation of this may be that CysC reflects GFR changes more sensitively compared to SCr, and eGFR, used widely in clinical practice instead of GFR, is calculated with SCr in this study[23].

Cardiac features can reflect the confluence of heart–kidney interactions through hemodynamic dimensions. The difference between arterial perfusion pressure and venous outflow pressures must be adequately large to keep sufficient renal blood flow and glomerular filtration. In the setting of this concept, the inability of impaired left ventricular function makes low forward flow with reduced left ventricular ejection fraction (LVEF), and consequently leading to prerenal hypoperfusion. Interestingly, we found that LVEF had no significant effect on the development of AKI stage 3. This is supported by previous studies as Jin et al.[24] demonstrated that LVEF was not independently and significantly associated with the development of AKI after cardiac operations. This was illustrated by a relative preservation of eGFR derived from efferent arteriolar constriction following on from the renin-angiotensin system to accommodate the reduced LVEF. In patients with markedly reduced renal blood flow exceeding renal autoregulatory capacity, the compensatory increase in eGFR is lost and could evolve into AKI. Alternatively, the elevated central venous pressures, as a result of changes in right heart structure such as an augmented diameter of RA-l, can bring about an increased renal resistance; the kidneys may subsequently become more susceptible to the occurrence of AKI. This mechanism has been presented in clinical researches in patients with cardiac dysfunction using invasive hemodynamic measurements[25,26].

Study Limitations

This study has several limitations. First, our research was a single-center study with a relatively limited sample of patients, which may be subject to selection bias; thus, a multicenter study will be needed to confirm our findings. Second, although we appraised 51 diverse features with the ML algorithm, we did not consider additional features, such as cardiac magnetic resonance due to its retrospective nature, that may contribute to better risk prediction. Third, we did not conduct external validation to verify the robustness of our results using an independent dataset from other centers; this is our future research direction.

Conclusions

In summary, the ML model based on preoperative and perioperative features can serve as an effective tool for the prediction of post-transplant AKI stage 3. Through the model, the risk of an individual patient with potential AKI stage 3 after HT could be identified accurately, enabling a timely intervention.

Abbreviations

AKI: Acute kidney injury; HT: Heart transplantation; ML: Machine learning; AUC: Area under the curve; eGFR: Estimated glomerular filtration rate; SCr: serum creatinine; RRT: Renal replacement therapy; CKD: Chronic kidney disease; CysC: Serum cystatin C;IQR: Interquartile range; LVEF:Left ventricular ejection fraction.

Declarations

Ethics approval and consent to participate

The ethics committee of Guangdong Provincial People's Hospital approved the study (NO: 2019261H). The Helsinki Declaration and the princi-ples of the Committee on Publishing Ethics were considered in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TYL was responsible for the design, data collection, manuscript writing. YYL involved in the study conception, planning, interpretation, writing, and critically revising the manuscript. RC helped in methodology, data collection and data analysis. JSH, YJW and JL provided advice on study design and conception. GSL involved in critically revising the manuscript.MW and HL supervised the conduct of the study and was responsible for the paper as a whole including design, methodology, and full checking of the final draft.

All Authors read and approved the manuscript.

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Not applicable.

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Figures

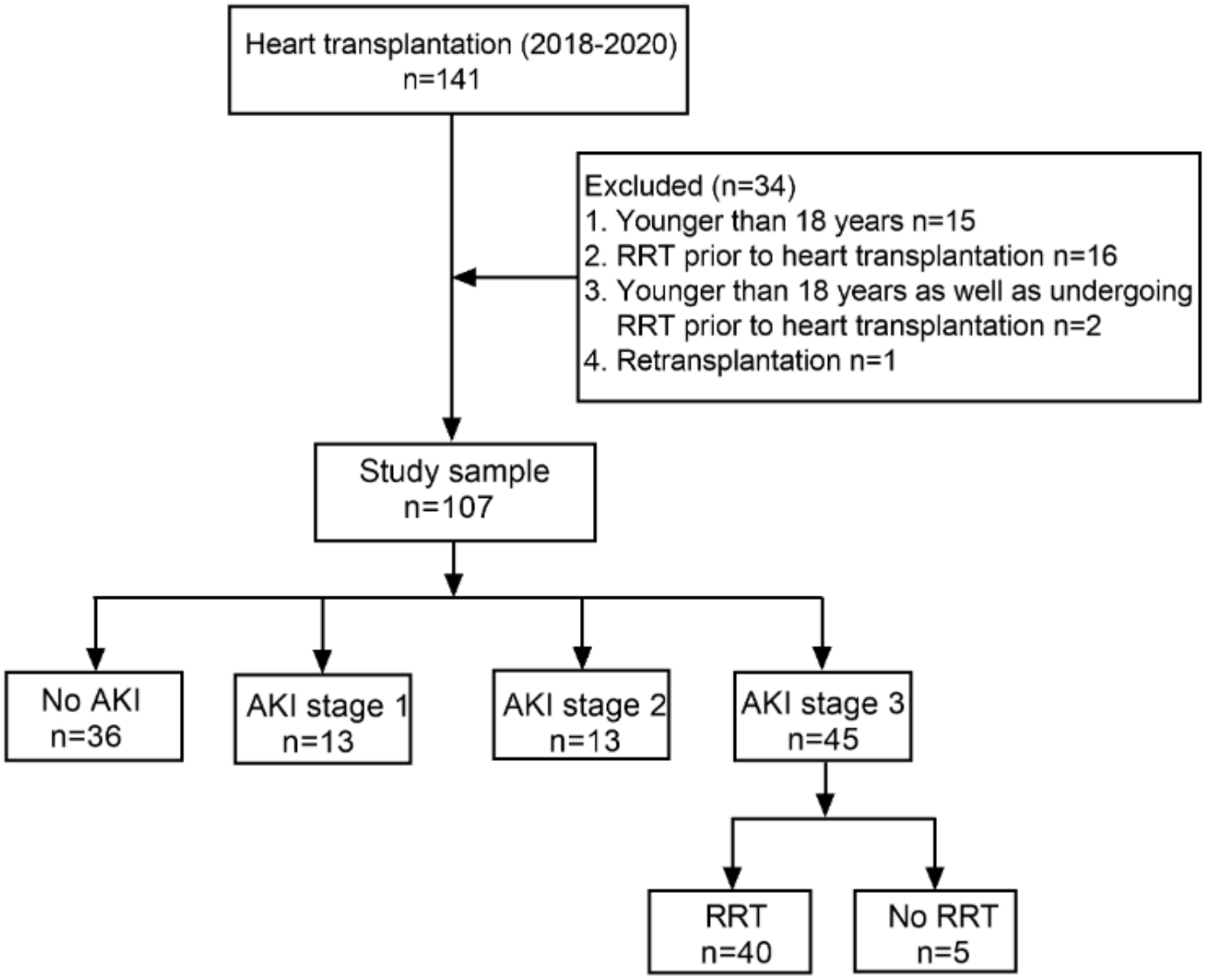

Figure 1

Diagram of study population based on postoperative AKI severity. AKI, acute kidney injury; RRT, renal replacement therapy

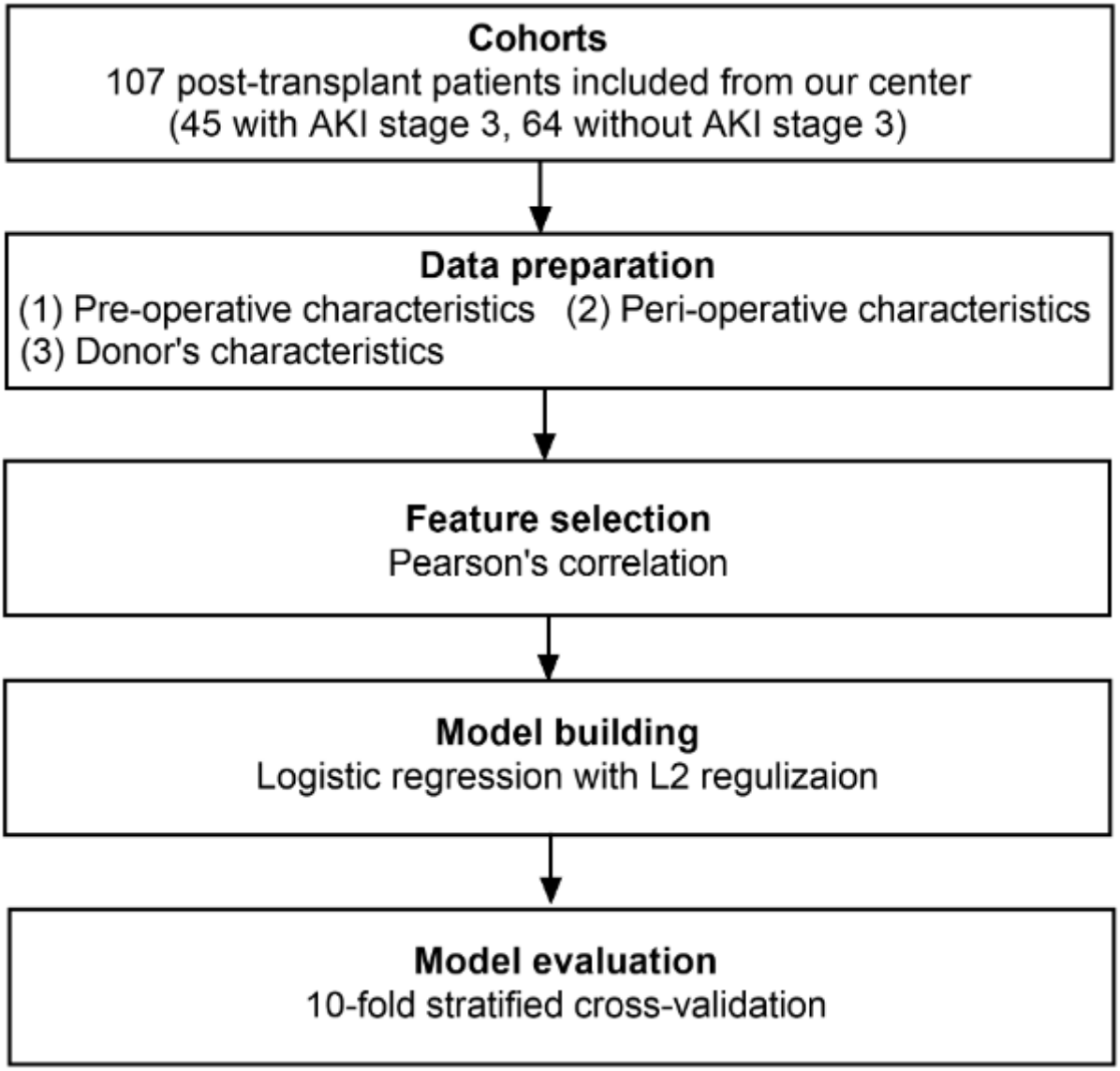

Figure 2

Workflow for the classification of patients undergoing HT with and without post-transplant AKI stage 3 using machine learning. AKI, acute kidney injury

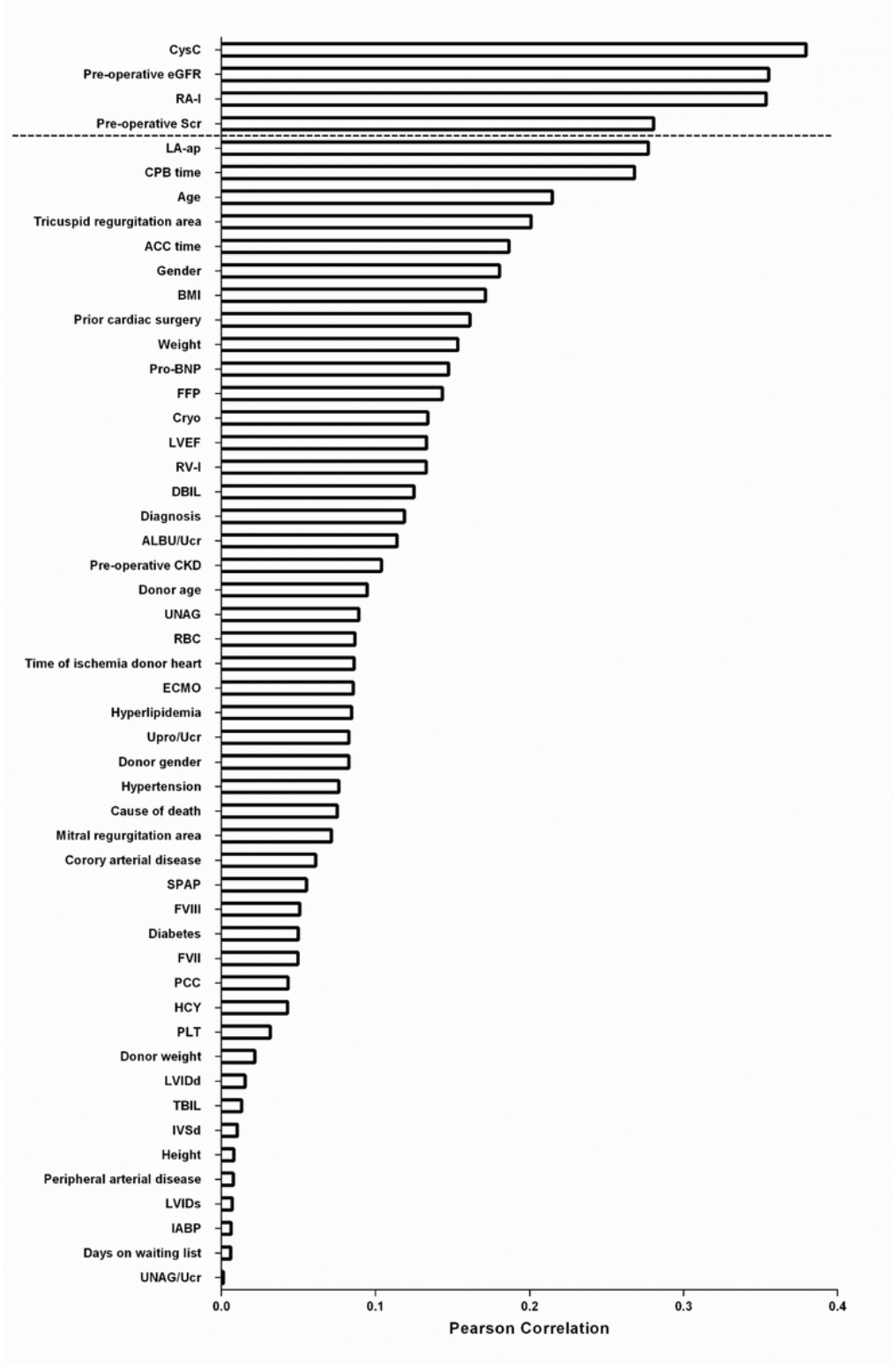

Figure 3

Feature selection. Pearson's correlation was used to evaluate the worth of a feature. The features were ranked in descending order by Pearson's correlation and the top four features were used for model building. Abbreviation as in Table 1

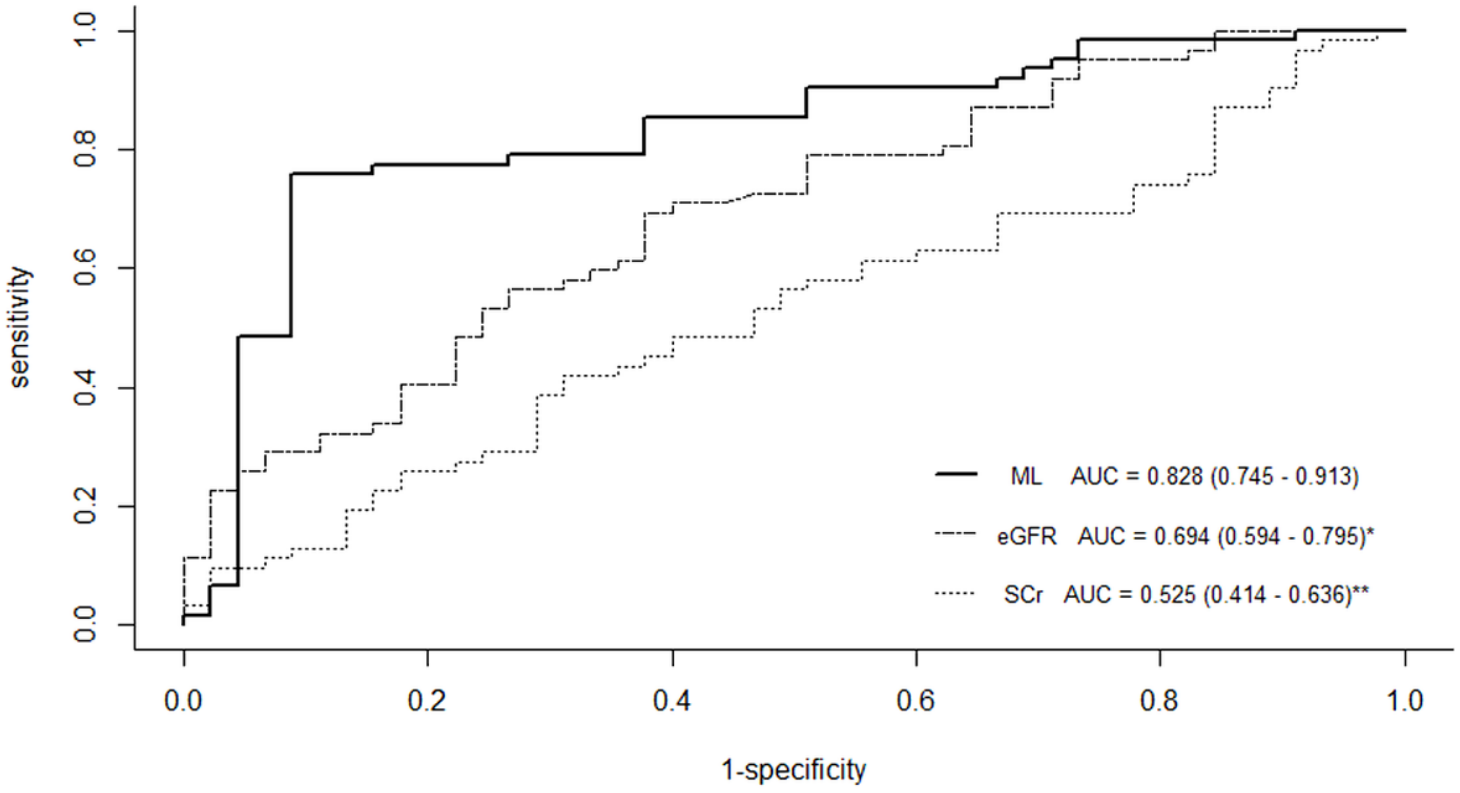

Figure 4

Receiver operating characteristic curves for prediction of post-transplant AKI stage 3. Machine learning using the logistic regression with L2 regularization in 10-fold cross-validation showed a significantly higher area under the curve for AKI stage 3 prediction than all other clinical metrics using DeLong's test (*p < 0.05□**p < 0.001). AUC, area under the curve; eGFR, estimated glomerular filtration rate; ML, machine learning; SCr, serum creatinine

Supplementary Files

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- Supplementarymaterials.docx