

The Prevalence, Risk Factors and Prognosis of Acute Kidney Injury after Lung Transplantation: A Single-center Cohort Study in China

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Abstract

Background

To evaluate the incidence, risk factors, and prognosis of acute kidney injury (AKI) after lung transplantation (LTx).

Methods

Records of patients who underwent LTx in a single center were retrospectively reviewed. The prevalence of post-transplant AKI, the use of continuous renal replacement therapy (CRRT), and the risk factors for AKI were investigated. The impact of AKI and CRRT on short-term outcomes and long-term survival was measured.

Results

148 patients were included with 67 cases developed post-operative AKI. 31 patients underwent CRRT; the percentage of CRRT was 6.2%, 0%, 10% and 86.2% in no-AKI, and stage 1, 2 and 3 AKI, respectively. Patients with AKI had significantly higher ICU mortality and in-hospital mortality. The 1-year post-LTx survival rate of patients with AKI was 47.8%, significantly lower than those without (74.1%). There was no difference in the 1-year survival rate of those with stage 1 and stage 2 AKI, but patients with stage 3 AKI showed the worst survival. Patients who underwent CRRT had an inferior survival outcome (9.7% vs. 76.1%, $P < 0.05$). We found that higher APACHE II score (OR 1.082, $P = 0.009$), and higher intraoperative fluid balance (OR 1.001, $P = 0.012$) were independent risk factors, and female (OR 2.539) and pulmonary hypertension (OR 2.869) were potential risk factors for post-LTx AKI. A prediction model integration of the above factors showed a good concordance with actual risks and had a C-index of 0.76 (95% CI, 0.66–0.87).

Conclusion

Severe AKI which needed CRRT had a negative impact on the short-term and long-term outcomes.

Introduction

Lung transplantation (LTx) is an established therapy for end-stage lung disease, the number and survival rate of LTx has increased gradually in the last decade (1, 2). However, many factors may have a negative impact on these patient's outcome and currently the primary graft dysfunction (PGD) has been the leading cause of morbidity and mortality after LTx (3).

Acute kidney injury (AKI) is very common in the critically ill and may compromise patient prognosis. In recent years, some research has indicated that AKI after LTx is common and severe AKI, which requires continuous renal replacement therapy (CRRT), may increase the patient's mortality, even free of PGD (4–7). Research on this issue is sparse in China. Thus we conducted this single-center, retrospective cohort study to evaluate the incidence, risk factors and outcome of AKI after LTx.

Methods

Patients

We retrospectively reviewed the records of all adult patients (>18 years) who underwent LTx from January 2015 to May 2019 at the First Affiliated Hospital of Guangzhou Medical University, which is the largest LTx center in Southern China. The Local Ethics Committee approved the study and individual consent was waived due to the nature of the retrospective study. All LTx have been performed according to the standard technique, and the patient's data were prospectively collected from our database. Individual medical records were then retrospectively reviewed and analyzed with respect to patient demographics; main indications for LTx; single or bilateral LTx; operative time; surgical outcome; postoperative morbidity and mortality.

Definition and management of AKI and CRRT

AKI definition was according to the KIDGO classification (8). Post LTx AKI was defined as AKI occurring within 1 week after the operation. The management of AKI and CRRT was in line with the guidelines (8) and depended on the opinion of attending physicians.

Outcomes

The prevalence of post-transplant AKI and CRRT use, and the risk factors for AKI were investigated. We also measured the impact of AKI and CRRT on short-term outcomes [in-hospital mortality, ICU mortality, length of stay (LOS) of ICU, LOS of hospital, ventilator-free days (VFD) at 28 days]; and long-term survival. In addition, to predict the risk for developing AKI, we aimed to build a multivariate model integrating important risk factors.

Statistical analysis

Descriptive statistics are presented as mean, median, standard deviation, and ranges for the continuous variables, and as counts and percentages for categorical variables. Comparisons between groups were performed using a χ^2 test with Fisher's exact test or ANOVA test as appropriate. Kaplan-Meier curves were used to evaluate event-free survival according to categorical variables, compared by the life-table method. Significant variables at univariate analysis were included in a Cox regression multivariate analysis with a stepwise forward conditional method. The prediction model (nomogram) was developed according to the methods previously described (9). The Bootstrapping method was used for internal validation. The

Calibration plot was drawn to evaluate the match level between the predicted probabilities from the nomogram and the actual probabilities. The predictive accuracy (discrimination) of the model was measured via a concordance index (c-index). Bootstraps resample methods with 100 repetitions were used for these activities. All analyses were carried out using SPSS version 20 (IBM Corp, Armonk, NY) and R 2.14.1 software with Package Hmisc version 3.4-2. A two-sided P value of 0.05 was considered to be significant.

Results

Patient Characteristics

A total of 148 patients with complete data were included, 125 of whom were male (84.5%); mean age was 55.7 ± 13.6 years; 94 patients underwent single lung transplant (63.5%) and the rest (36.5%) underwent bilateral lung transplant. The main indications for LTx were chronic obstructive pulmonary disease (COPD) (39.9%), idiopathic pulmonary fibrosis (IPF) (27.7%) and connective tissue disease-lung disease (CTD-LD) (16.2%). The mean acute physiologic assessment and chronic health evaluation (APACHE) II score of these patients, when admitted to ICU, was 16.9 ± 6.9 . Table 1 summarized all baseline characteristics.

Prevalence of AKI and CRRT use

Among the 148 cases, 67 (45.3%) patients developed post-LTx AKI, 28 (18.9%), 10 (6.8%) and 29 (19.6%) patients at stage 1, 2 and 3, respectively. A total of 31 cases (20.9%) underwent CRRT; the percentage of CRRT was 6.2%, 0%, 10% and 86.2% in no-AKI, stage 1, 2 and 3 AKI respectively (Fig 1).

The impact of AKI on post-LTx outcomes

Patients with AKI had significantly higher ICU mortality and in-hospital mortality, especially stage 3 patients. Consistently, patients with more severe AKI had longer ICU and hospital stays, and shorter ventilation-free days. The results were summarized in table 2.

The impact of post-transplant AKI and CRRT on survival

The 1-year post-LTx survival rate of those with AKI was 47.8%, significantly lower than those without (74.1%). There was no difference in the 1-year survival rate of those with stage 1 (67.9%) and stage 2 (80.0%) AKI, but patients with stage 3 AKI showed worst survival (17.2%). Patients that underwent CRRT were associated with inferior survival outcomes (9.7% vs. 76.1%, $P < 0.05$). In the multivariate Cox model, we found that CRRT (HR 8.92, 95% CI 3.52-22.60; $P < 0.001$), rather than any AKI stage, was the only independent prognosis factor. (Fig 2)

Risk factors for AKI and a prediction model

By comparing baseline features, we observed some variables were significantly different between patients without AKI and with AKI at different stages. Using logistic regression, we found that higher APACHE II score (OR 1.082, 95% CI 1.020-1.148, $P=0.009$), and higher intraoperative fluid balance (OR 1.001, 95% CI 1.000-1.002, $P=0.012$) were independent risk factors, and female (OR 2.539, 95% CI 0.909-7.095, $P=0.075$) and pulmonary hypertension (OR 2.869, 95% CI 0.952-8.650, $P=0.061$) were potential risk factors for post-transplant AKI.

We then integrated the APACHE II score, intraoperative fluid balance, gender, and pulmonary hypertension to build a nomogram. The C-index for post-transplant AKI prediction was 0.76 (95% CI, 0.66–0.87) in this nomogram. The calibration plot for the probability of AKI showed an optimal agreement between the prediction by nomogram and actual observation (Fig3-4).

Discussion

To our knowledge, this is the first study to investigate the current state of post-LTx AKI in China. In our cohort, the incidences of AKI, AKI-3, and RRT were 45.3%, 19.6%, and 20.9%, respectively; we also demonstrated that the independent risk factors for post-LTx AKI included higher APACHE II score, PH, female, and positive intraoperative fluid balance. It was shown that patients with post-LTx AKI had poorer short-term and long-term outcomes. However, CRRT, rather than AKI, was an independent prognostic factor for survival.

AKI is a frequent complication after LTx. In our study, the incidence of post-LTx AKI(45.3%) was similar to a recently published meta-analysis(52.5%, 95% CI: 45.8–59.1%) (7). Some risk factors may contribute to the post-LTx AKI such as hypoxia, hypercapnia, altered renal function prior to LTx, hypotension during surgery and use of CPB during surgery (10–13). However, according to our center's protocol, we seldom listed patients with renal dysfunction, and we always use ECMO instead of CPB during surgery. In our study, the positive intraoperative fluid balance was an independent risk factor for the post-LTx AKI, which seemed to be in contrast to the Balci's study (14). However, the patients with more positive fluid balance during surgery was also always accompanied by more intraoperative hemorrhage, these patients would receive more intraoperative transfusion and vasopressors; this condition of uncontrolled hemodynamic has been proved to have a great negative impact on the development of AKI (12). Furthermore, fluid overload has been demonstrated to be associated with adverse kidney events in critically ill patients (15, 16). The relationship between hypotension and AKI is well known (14, 17), however, when patients with hypotension during surgery need fluid resuscitation, we must manage the amount of fluid more accurately to avoid overcorrection.

PH was very common in end-stage lung disease. Due to a pathophysiological process involving right ventricular dysfunction and venous congestion, PH made a great contribution to AKI (18, 19). And some previous studies have suggested that PH is a predictor for post-LTx AKI (20, 21). Our study also demonstrated that a higher APACHE II score when a patient was admitted to ICU was another independent risk factor to predict post-LTx AKI, the APACHE II score was widely used to predicted patient's

in-hospital mortality (22). However, few studies focus on the predictive effect of this score on the development of AKI after LTx. Another interesting finding in our study was that females seemed to be more susceptible to post LTx AKI. This was in direct contrast to Bennett's study (23), which indicated that males may more likely to suffer from post-LTx AKI. It is very difficult to explain the reasons for this difference, but one possible explanation could be our relatively small population which would decrease the statistical power. While some research had focused on the impact of gender distribution on the development of AKI in selected patients (24–26), the results of the research remained controversial.

In accordance with previous studies (7, 18, 19, 27). AKI, especially severe AKI, requiring RRT was associated with poorer short-term and long-term prognosis. However, RRT, other than AKI-stage 3, was associated with poorer long-term outcomes independently in our study. The initiation of RRT could be influenced by many factors such as resource, patient factors, and physician's experience. The main indication for this population was oliguria in our ICU due to the nature of LTx which requires negative fluid balance in the postoperative period, therefore 5 patients without AKI also received RRT in 2015 for the purpose of progressive fluid management. However, the optimal timing of RRT in AKI was still controversial and progressively earlier initiation of RRT was potentially harmful (28, 29). Second, although a randomized controlled trial (RCT) directly comparing outcomes of severe AKI patients with and without RRT was not available, we could get some inspiration from the AKIKI trial (30) which performed a subgroup analysis focusing on the outcome difference between AKI patients with and without RRT. The AKIKI trial found that the 60-day mortality was 37%, 49% and 62% among those patients who never had RRT, those who had early RRT and those who had delayed RRT, respectively, after adjustment for baseline severity of illness. Due to the relatively small sample size which might affect the statistical power, large prospective study trials are needed to conclude the role of RRT in the post-LTx patients.

The major limitations of this study were: 1) the nature of a retrospective and monocentric study; 2) a relatively small population; 3) a long period of observation and the changes to the population and technology. Large prospective studies are called for to better identify the risk factors associated with the post-LTx AKI and successful preventive strategies.

In conclusion, this is the first study in China to confirm the importance of renal function in the early postoperative phase after LTx. Great attention should be paid to the hemodynamics and fluid balance. Severe AKI requiring RRT proved to have an absolutely negative impact on the short-term and long-term outcomes.

Abbreviations

AKI
acute kidney injury;
LTx
lung transplantation;

CRRT
continuous renal replacement therapy;
APACHE
acute physiologic assessment and chronic health evaluation;
PGD
primary graft dysfunction;
LOS
length of stay;
VFD
ventilator-free days;
C-index
concordance index;
COPD
chronic obstructive pulmonary disease;
IPF
idiopathic pulmonary fibrosis;
CTD-LD
connective tissue disease-lung disease;
RCT
randomized controlled trial.

Declarations

Ethics approval and consent to participate

Our research was performed in accordance with the Declaration of Helsinki and approved by the Ethics committee of the First Affiliated Hospital of Guangzhou Medical University. Individual consent was waived due to the nature of the retrospective study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Authors' contributions

LS, XL, YL performed the conception and design of the study. XL, YL supplied the administrative support. LS, XL, YL provided study materials. LS, SC, LN, YX, WL collected and assembled the data. LS, HZ, LZ, HS, JH analyzed and interpreted the data. All authors wrote and approved the manuscript.

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Tables

Table 1. Patient demographic, intra and post-operative characteristics regarding post-LTx AKI

characteristics	non-AKI	AKI stage 1	AKI stage 2	AKI stage 3	P value
No.	n=81	n=28	n=10	n=29	
Percentage	54.7%	18.9%	6.8%	19.6%	
Age(years)	54.5±14.4	57.6±12.2	56.8±14.5	57.0±12.9	0.786
Gender(F/M)	8/73	6/22	2/8	7/22	
Singe/Bilateral LTx	57/24	20/8	6/4	11/18	0.015
Indication for LTx					0.855
COPD	33(40.7%)	10(35.7%)	5(50.0%)	11(37.9%)	
IPF	21(25.9%)	9(32.1%)	1(10.0%)	10(34.5%)	
CTD-LD	10(12.3%)	6(21.4%)	2(20.0%)	6(20.7%)	
Others	17(20.9%)	3(10.7%)	2(20.0%)	2(6.9%)	
APACHE II score	15.0±5.9	17.3±6.4	20.0±8.2	20.8±7.9	<0.001
Underlying disease					
Hypertension	12(14.8%)	4(14.3%)	4(40%)	7(24.1%)	0.177
Diabetes mellitus	11(13.6%)	1(3.6%)	0(0%)	9(31%)	0.017
Chronic kidney disease	4(5.0%)	0(0%)	0(0%)	0(0%)	0.609
Pulmonary hypertension	65(80.2%)	26(92.9%)	9(90.0%)	24(82.8%)	0.472
Others	40(49.4%)	10(35.7%)	4(40%)	18(62.1%)	0.287
Baseline Scr(md/dl)	0.76±0.24	0.72±0.16	0.66±0.26	0.73±0.21	0.615
Baseline eGFR	131.6±63.8	130.7±65.7	192.5±209.1	130.4±44.0	0.112
Pre-transplant mechanical ventilation	1	2	4	3	<0.001
Pre-transplant ECMO	0	2	1	2	0.038
Intra-operative ECMO	23(28.4%)	7(25.0%)	3(30.0%)	16(45.2%)	0.110
VV-ECMO	5(6.2%)	3(10.7%)	0(0%)	4(13.8%)	

VA-ECMO	18(22.2%)	4(14.3%)	3(30.0%)	12(41.4%)	
Post-operative ECMO	8(9.8%)	4(14.2%)	1(10.0%)	10(34.5%)	0.038
VV-ECMO	1(1.2%)	2(7.1%)	0(0%)	4(13.8%)	
VA-ECMO	7(8.6%)	2(7.1%)	1(10.0%)	6(20.7%)	
Post-operative ECMO duration(day)	0.31±1.07	0.68±1.66	0.60±1.90	1.38±2.82	
Operation time(min)	358.7±157.7	330.5±128.6	305.0±149.7	452.8±159.9	0.007
Intra-operative hemorrhage(ml)	1603.7±1898.1	1593.9±1496.7	1121.0±957.8	5436.2±5778.6	<0.001
Intra-operative transfusion(ml)					
RBC	1077.5±876.9	1066.8±846.4	1092.0±608.1	2762.9±2338.0	<0.001
Plasma	972.2±665.5	998.2±611.4	990.0±395.7	2079.3±1496.9	<0.001
PLT	278.6±704.5	192.9±201.8	52.1±109.6	276.0±240.1	0.590
Intra-operative fluid balance(ml)	116.4±475.9	146.4±311.4	136.0±321.2	1230.0±1051.1	<0.001
Post-operative pneumonia within 1week	58(71.6%)	21(75%)	6(60%)	25(86.2%)	0.299

Table 2. post-LTx outcomes for patients with non-AKI and AKI

Outcomes	non-AKI n=81	AKI stage 1n=28	AKI stage 2n=10	AKI stage 3n=29	P value
ICU mortality	4.9%	7.1%	10%	44.8%	<0.001
In-hospital mortality	7.4%	10.7%	20%	62.1%	<0.001
LOS of ICU (days)	16.1±20.6	21.7±21.2	35.4±51.3	40.6±35.8	<0.001
LOS of hospital (days)	49.4±27.9	44.6±23.9	74.4±46.2	58.7±34.5	0.029
Require CRRT	6.2%	0	10%	86.2%	<0.001
VFD at 28 days(days)	17.0±9.1	15.6±6.8	14.4±9.2	7.6±9.8	<0.001

Figures

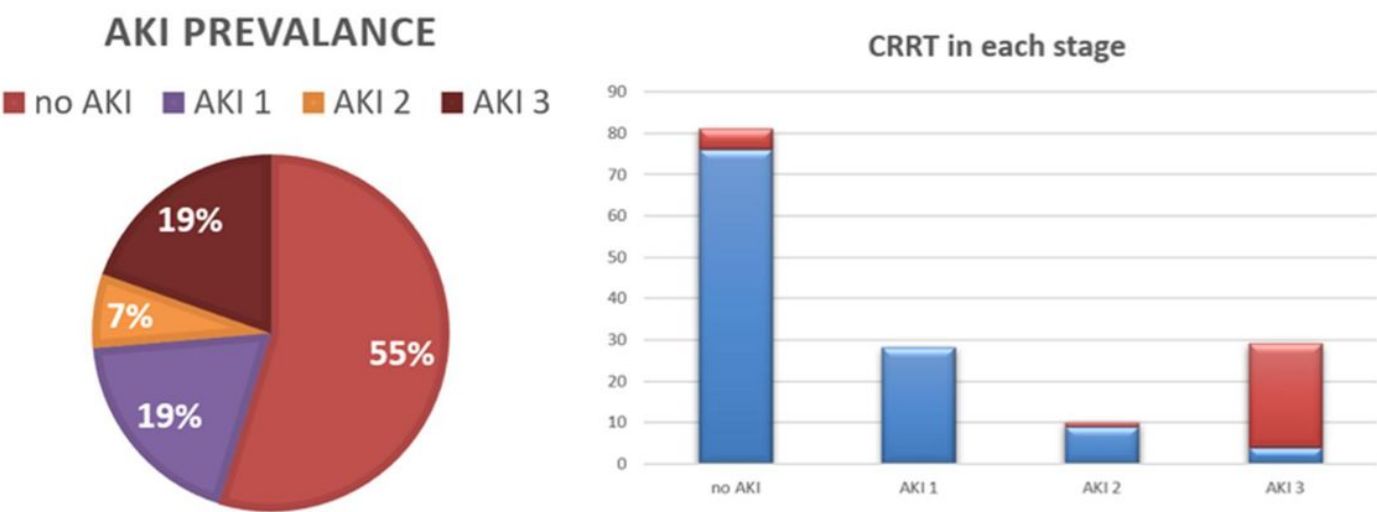


Figure 1

The prevalence of post-LTx AKI and CRRT

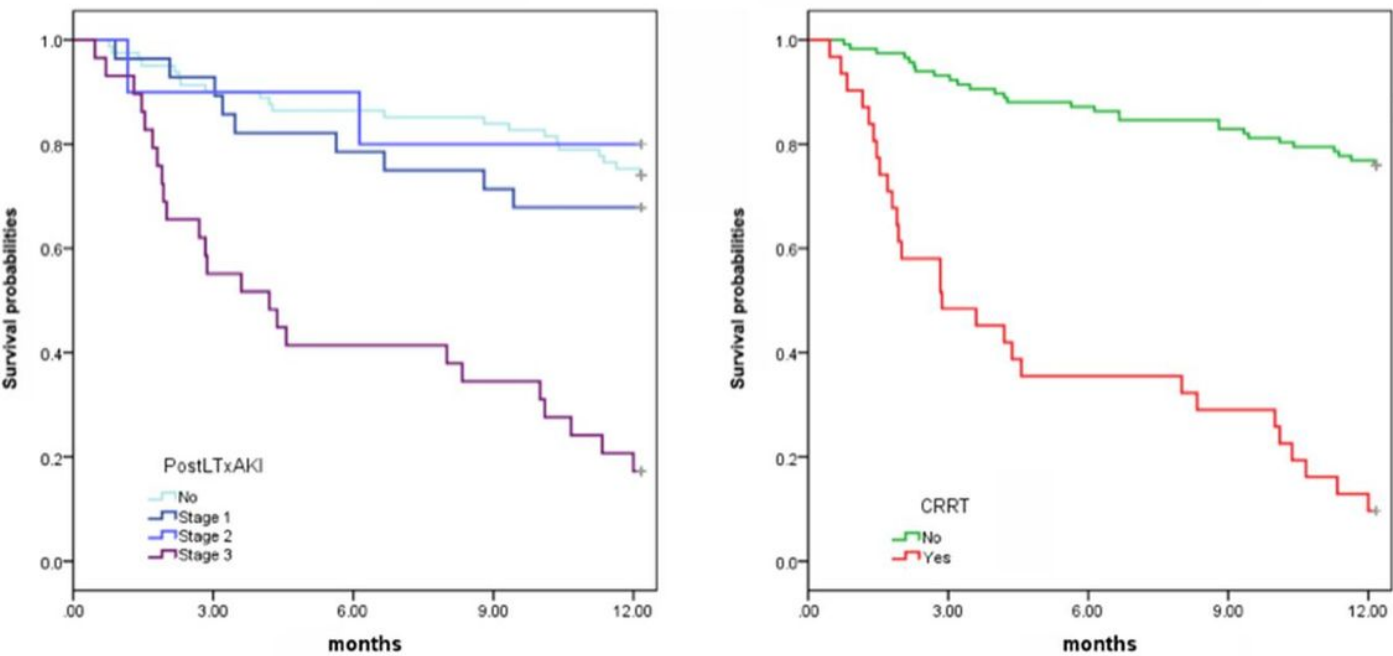


Figure 2

Survival analyses of post-transplant AKI (A) and CRRT (B)

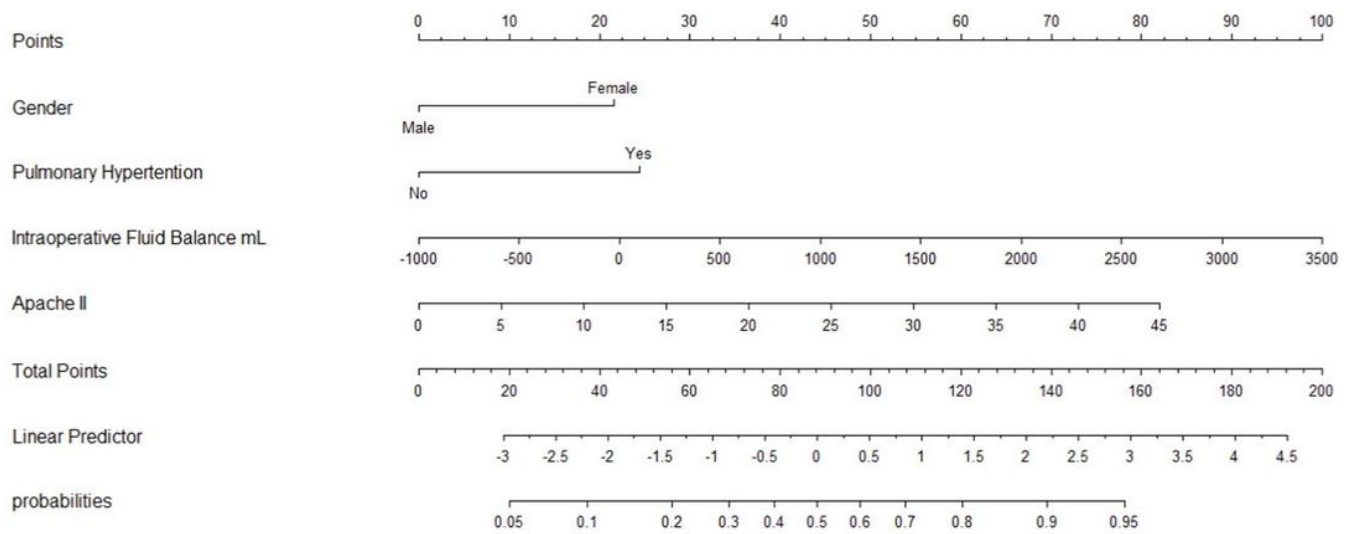


Figure 3

The probability of AKI predicted by nomogram

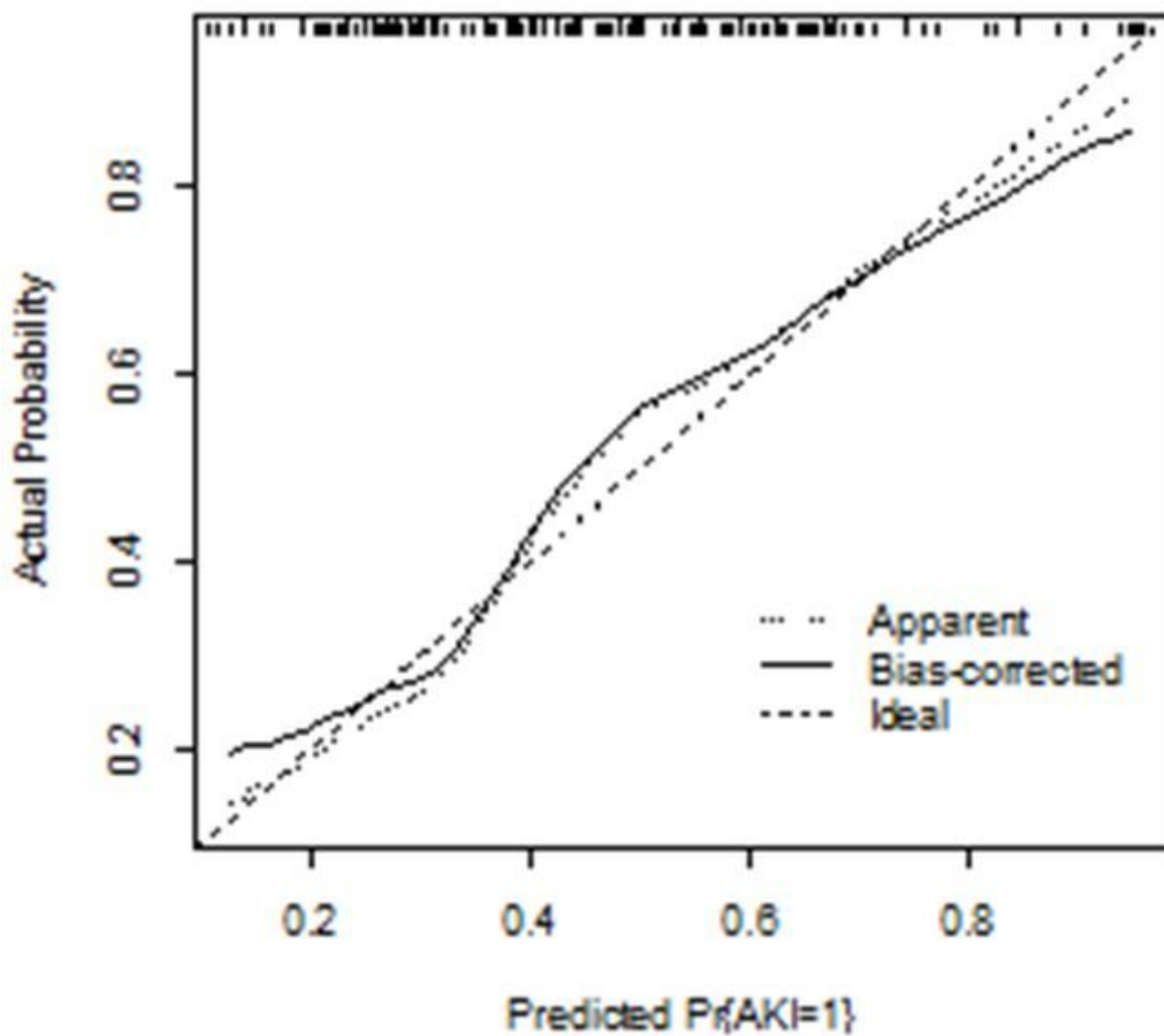


Figure 4

The probability of AKI predicted by actual observation