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Characteristics and risk factors for renal recovery after acute kidney injury in critically ill patients in cohorts of elderly and non-elderly: a multicenter retrospective cohort study

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ABSTRACT

Background: The purpose of this study was to explore the risk factors for renal nonrecovery among elderly and nonelderly patients with acute kidney injury (AKI) in critically ill patients.

Methods: A multicenter retrospective cohort of 583 critically ill patients with AKI was examined. We found the best cutoff value for predicting renal recovery by age was 63 years old through logistic regression. All patients were divided into two cohorts, age <63 and age ≥63-years old; on the basis of renal recovery at 30 days after AKI, the two patient cohorts were further divided into a renal recovery group and a renal nonrecovery group. Multivariate logistic regression was used to analyze the risk factors affecting renal recovery in the two cohorts.

Results: The 30-day renal recovery rate of patients aged <63 years was 70.0% (198/283), multivariate analysis showed that the independent risk factors affecting renal nonrecovery in age <63 years old included AKI stage, blood lactate level and hemoglobin level. The 30-day renal recovery rate of patients aged ≥63 years was 28.7% (86/300), multivariate analysis showed that the independent risk factors for renal nonrecovery in age ≥63-years old included diabetes mellitus, surgery with general anesthesia, AKI stage, APACHE II score, eGFR, and hemoglobin level.

Conclusions: The renal nonrecovery after AKI in critically ill patients in patients aged ≥63 years was more strongly affected by multiple risk factors, such as diabetes mellitus, surgery with general anesthesia, eGFR, and APACHE II score, in addition to hemoglobin and AKI stage.

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Introduction

Acute kidney injury (AKI) occurs in 7–25% of hospitalized patients [1–3], and the incidence of AKI among critically ill patients is as high as 30–60% [4,5]. AKI increases the risk of chronic kidney disease (CKD) and mortality and leads to an enormous medical cost burden [4,5]. Renal recovery after AKI is an independent factor that is associated with the survival of patients. Renal nonrecovery in the hospital or after discharge was found to be related to an increase in long-term mortality [6,7]. Previous studies have suggested that age is an influencing factor for renal recovery, and advanced age is related to renal nonrecovery [8,9]. However, the characteristics of AKI renal recovery in elderly and nonelderly patients are not clear. To present, there is lack of data on the incidence and risk factors of renal recovery in the elderly and nonelderly patients with AKI in critically ill patients. In this study, we first calculated the cutoff value of age predicting renal recovery among all patients. According to this cutoff value, the patients were divided into two age cohorts, and we investigated the risk factors for renal nonrecovery after AKI in the elderly and nonelderly cohorts.

Materials and methods

Study design and population

This multicenter retrospective cohort study was conducted for the duration of 31 months (January 2017 to

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August 2019) at four tertiary centers in China (Peking University People's Hospital, Gansu Provincial Hospital, The First Affiliated Hospital of Hunan University of Medicine and Handan First Hospital). The study was approved by the institutional review boards of Peking University People's Hospital (approval No. 2019PHB042-01). Informed consent was not required because no treatment interventions were provided and protected health information was not collected or analyzed. All data were processed anonymously before analysis. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [10].

This study enrolled critically ill adult patients diagnosed with AKI in the intensive care units (ICUs) of four tertiary hospitals. The exclusion criteria were patients with CKD stage 5 (estimated glomerular filtration rate [eGFR] <15 mL/min per 1.73 m^2, chronic dialysis, prior kidney transplant) at baseline, pregnant or lactating women, and patients with incomplete data. Kidney function was determined by eGFR based on the Chronic Kidney Disease Epidemiology Collaboration equation [11]. AKI definition was based on RIFLE GFR criteria [12]: reduction of $>25\%$ of the eGFR than the baseline level that was known or presumed to have occurred within the previous 7 days. The stage of AKI according to eGFR was as follows [12,13]: stage 1 referred to 25–49% reduction in eGFR compared with baseline; stage 2 referred to $50-74\%$ reduction in eGFR; stage 3 referred to $\geq 75\%$ reduction in eGFR or initiation of renal replacement therapy.

Data collection

The data were collected retrospectively. All the data were obtained from electronic medical records. The data input was completed by trained doctors and research nurses. They were not aware of the study and did not participate in the management or care of the patients. Data quality was assessed by reviewing a random sample of 10% of all medical records. All reported events were confirmed by looking at the hospital chart or by telephone interview. The data was first accessed on 9 April 2019.

We retrieved all the demographic and clinical data of all subjects in this study, including age, sex, past medical history (hypertension, coronary heart disease, diabetes mellitus, chronic kidney disease), and the cause of AKI (sepsis, hypovolemia, heart failure, nephrotoxic drugs, and retrorenal obstruction), laboratory values (hemoglobin level, lactate level, creatinine level, eGFR, albumin level, D-dimer level, C-reactive protein level, and PO_2/FiO_2 ratio) at the same time of AKI diagnosis and ICU admission and surgery under general anesthesia and vasopressor drugs (epinephrine, norepinephrine, vasopressin, dopamine, and phenylephrine) used before AKI occurred. The Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score within 24 h after AKI diagnosis were also recorded.

A history of hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or treatment with antihypertensive drugs. The definition of a history of coronary heart disease was as follows: (1) patients with stable angina pectoris or other symptoms related to coronary heart disease; (2) those who had known infarct or non-infarct coronary heart disease symptoms in the past and had no symptoms after treatment; and (3) those with a history of an acute coronary syndrome (including ST-segment elevation acute myocardial infarction, non-ST segment elevation acute myocardial infarction, and unstable angina pectoris) but no acute coronary event within 12 months. A history of diabetes mellitus was defined as previous diabetes dietary control, oral antidiabetic drugs or insulin treatment, or glycosylated hemoglobin greater than 6.5%. Chronic kidney disease was defined as an eGFR <60 and >15 mL/min/1.73 m^2 or albuminuria (albumin excretion rate >30 mg/24 h; albumin-to-creatinine ratio >30 mg/g) present for >3 months [14]. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (sepsis-3) [15].

Outcomes

The outcome was renal recovery 30 days after AKI. Renal recovery after AKI was defined as no longer fulfilled the criteria for stage 1 AKI, but their eGFR might not have yet returned to baseline (defined as eGFR at 30 days $\geq 90\%$ of baseline eGFR) [16]. Patients who experienced recurrence after renal recovery or died during the follow-up period were considered to have no renal recovery. Baseline eGFR was defined as mean eGFR before 3 months of this admission or the maximum eGFR measured before ICU admission after this hospitalization or an estimation using the Modification of Diet in Renal Disease (MDRD) study equation (assuming a patient's eGFR of 75 mL/min/1.73 m^2) [17]. Information on renal recovery 30 days after AKI was collected from the electronic medical record or by telephone interview.

Statistical analyses

The NCSS-PASS 11 sample size estimation software was used to calculate the sample size of the logistic

regression model. This study mainly investigated the relationship between AKI stage and renal nonrecovery after AKI. We expected a sample size large enough to detect an odds ratio (OR) of 3.0, with 85% power at the 0.05 significance level using a two-sided test. After the calculation, the required sample size was 156.

Normally distributed continuous variables are described with the mean ± standard deviation, and an independent sample *t* test was used for analysis; nonnormally distributed continuous variables are described with the median (25th percentile, 75th percentile), and the nonparametric Mann–Whitney *U* test was used for analysis. Categorical variables are described with the percentage, and the Pearson χ^2 test was used for analysis. The missing data rate of all variables was <1%, missing continuous variables were inferred as the median of nonmissing values, and missing categorical covariates were inferred as the most frequent categorical values.

We performed logistic regression analysis on all patients to find out whether age was an independent risk factor for renal nonrecovery after AKI. The Receiver operating characteristic (ROC) curve was used to analyze the value of predicting renal nonrecovery with age. The maximal Youden's index was used to estimate the optimal cutoff values for predicting renal recovery by age. According to this cutoff value, all patients were divided into two cohorts. Univariate analysis was used to screen out meaningful risk factors in each cohort, and all risk factors were evaluated by collinearity diagnostics. If any conditional index was greater than or equal to 30, a bivariate correlation matrix was constructed to evaluate the pairwise correlation. The variables with a pairwise correlation greater than or equal to 0.70 were considered to show a high level of collinearity, which was resolved by one of two options: merging the two variables into one variable or deleting one of the two variables from the model. The remaining variables entered the logistic regression model to identify the meaningful independent risk factors for renal nonrecovery after AKI. The logistic regression model was constructed using a forward stepwise selection procedure. On the basis of univariate analysis ($p < 0.05$) and collinearity between variables (conditional index > 30), the independent variables were selected to establish the logistic regression model. ORs and 95% confidence intervals were calculated. The calibration of the logistic regression model was assessed by the Hosmer-Lemeshow goodness-of-fit statistic. The area under the ROC curve (AUC) was used to evaluate the discrimination ability of the prediction models.

For all analyses, a 2-sided *p* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 26.0 for Windows (SPSS, Chicago, IL).

Results

Among 667 critically ill patients diagnosed with AKI, 84 patients (24 who had CKD stage 5, 34 who were pregnant or lactating, 5 who had incomplete data and 21 who dropped out during the follow-up) were excluded. A total of 583 patients were included in the final analysis. Among 583 patients with AKI, 515 (88.3%) patients had baseline eGFR, and 68(11.7%) patients used MDRD study equation to calculate baseline eGFR. 212 (36.4%) patients had baseline eGFR before this hospitalization, the median eGFR was 79.1 (68.8–91.5) mL/min/1.73 m^2, and the time from this admission was 9 (3.5–24.0) months. The median time before ICU in this hospitalization was 7.0 (4.0–13.0) days, 148 (25.4%) patients had less than 7 days before admission to the ICU, the baseline eGFR was 88.2 (72.8–96.4) mL/min/1.73 m^2, 155 (26.6%) patients had more than 7 days before admission to the ICU, and the baseline eGFR was 78.6 (63.1–92.7) mL/min/1.73 m^2, there was no significant difference between the two groups ($p = 0.36$).

Among all the 583 patients with AKI, 284 patients with renal recovery and 299 patients with renal nonrecovery were identified. There were 15 risk factors associated with renal nonrecovery: age, a history of diabetes mellitus, a history of hypertension, a history of chronic kidney disease, surgery under general anesthesia, sepsis, PO_2/FiO_2 ratio, lactate level, hemoglobin level, albumin level, C-reactive protein level, D-dimer level, eGFR, AKI stage and APACHE II score. Logistic regression analysis found that the independent risk factors of renal nonrecovery in AKI patients included age, a history of diabetes mellitus, a history of hypertension, surgery under general anesthesia, sepsis, hemoglobin level, eGFR, AKI stage and APACHE II score. The AUC of age assessing renal nonrecovery was 0.709(95% CI, 0.667–0.751), with an optimal cutoff value of 63, a sensitivity of 71.6% and a specificity of 70.1%. According to this cutoff value, all patients were divided into two cohorts: age <63-years old and age ≥63-years old. There were 283 patients in the age <63 years cohort and 300 patients in the age ≥63 years cohort. 92 patients died within 30 days after AKI in 583 patients, including 32 dead patients in the age <63 years cohort and 60 dead patients in the age ≥63 years cohort, 92 dead patients all in the renal nonrecovery group. 432 of 491 surviving AKI patients were transferred to the ICU, the renal recovery rate of AKI was 58.2% in 177 patients

with ICU stay ≥7 days, and 63.5% in 255 patients with ICU stay <7 days. The flow chart of selected patients is shown in Figure 1.

Among the age <63 years cohort, the 30-day renal recovery rate of AKI was 70.0% (198/283). The proportion of participants with a surgery under general anesthesia, lactate level, C-reactive protein level, D-dimer level, AKI stage and APACHE II score in the renal nonrecovery group were higher than those in the renal recovery group. The hemoglobin level in the renal nonrecovery group were lower than those in the renal recovery group, and the difference was statistically significant ($p < 0.05$) (see Table 1).

In the age ≥63 years cohort, the 30-day renal recovery rate of AKI was 28.7% (86/300). The proportion of participants with a history of diabetes mellitus, history of hypertension, sepsis, hypovolemia, surgery under general anesthesia, use of vasopressor drugs, D-dimer level, C-reactive protein level, AKI stage, and APACHE II score in the renal nonrecovery group were higher than those in the renal recovery group. The eGFR, hemoglobin level and albumin level in the renal nonrecovery group were lower than those in the renal recovery group, and the difference was statistically significant ($p < 0.05$) (see Table 1).

Multivariate logistic regression analysis showed that the independent risk factors affecting the renal nonrecovery after AKI in the age <63 years cohort included AKI stage, lactate level, and hemoglobin level. AKI stage and lactate level were negatively correlated with renal recovery, and hemoglobin was positively correlated with renal recovery (Table 2). In the age <63 years cohort, The AUC for prediction of renal nonrecovery was 0.709 (95% CI, 0.643–0.776) for AKI stage, 0.662 (95% CI, 0.582–0.742) for lactate, and the AUC for prediction of renal recovery was 0.723 (95% CI, 0.659–0.788) for hemoglobin (Figure (2(A,B))). and the regression model showed a good calibration (Hosmer-Lemeshow $\chi^2 = 10.881$; $p = 0.209$).

Multivariate logistic regression analysis showed that the independent risk factors affecting renal nonrecovery in the ≥63 years cohort included a history of diabetes mellitus, surgery under general anesthesia, AKI stage, APACHE II score, eGFR, and hemoglobin at the time of AKI diagnosis. The APACHE II score, AKI stage, and surgery under general anesthesia were negatively correlated with renal recovery, and hemoglobin and eGFR were positively correlated with renal recovery (Table 2). In the age ≥63 years cohort, The AUC for prediction of renal nonrecovery was 0.592 (95% CI, 0.523–0.660) for diabetes mellitus, 0.581 (95% CI, 0.512–0.650) for surgery under general anesthesia, 0.779 (95% CI, 0.724–0.835) for AKI stage, 0.614 (95% CI, 0.545–0.683) for APACHE II score, and the AUC for prediction of renal recovery was 0.718 (95% CI, 0.650–0.787) for eGFR and 0.713 (95% CI, 0.651–0.775) for hemoglobin (Figure (2(C,D))). and the regression model showed a good calibration (Hosmer-Lemeshow $\chi^2 = 4.906$; $p = 0.768$).

Considering that the APACHEII score includes age, in order to avoid the impact of age on APACHEII score, the relationship between APACHEII score and AKI renal recovery was analyzed again after removing age. In the age ≥63 years cohort, APACHEII of nonage in AKI renal nonrecovery group was higher than that in the renal recovery group (13.0 (11.0, 16.0) vs. 12.0 (10.0, 14.0), $p = 0.018$). Logistic regression analysis showed that APACHEII of non-age was still an independent risk factor for AKI renal nonrecovery (OR 1.13, 95% CI 1.01–1.25, $p = 0.028$), the AUC for prediction of renal nonrecovery was 0.587 (95% CI, 0.519–0.654) for APACHEII of nonage. In the age <63 years cohort, although APACHEII of nonage in the AKI renal nonrecovery group was higher than that in the renal recovery group (14.0 (11.0, 19.0) vs 12.0 (10.0, 16.0), $p = 0.005$), logistic regression analysis showed that APACHEII of nonage

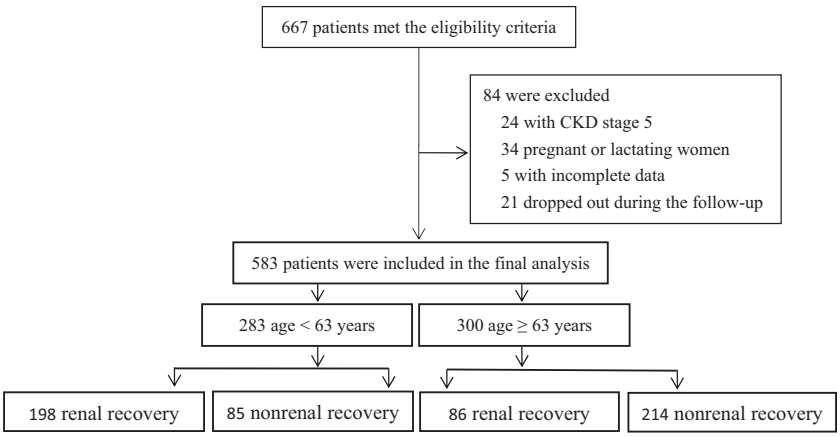

Figure 1. Flow chart of selected patients.

Table 1. Comparison of demographic and clinical characteristics for the study population.

	Age < 63-year cohort			Age ≥ 63-year cohort		
	Renal recovery $n = 198$	No renal recovery $n = 85$	p Value	Renal recovery $n = 86$	Non renal recovery $n = 214$	p Value
Age (years, M[P_{25}–P_{75}])	51.0 (44.0, 56.0)	52.0 (46.0, 55.0)	0.853	69.0 (66.3, 77.0)	70.0 (66.0, 77.0)	0.894
Male sex (n[%])	116 (58.6)	56 (65.9)	0.249	63 (73.3)	146 (68.2)	0.391
Past medical history [n (%)]						
Hypertension	28 (14.1)	20 (23.5)	0.054	20 (23.3)	90 (42.1)	0.002
Diabetes mellitus	19 (9.6)	10 (11.8)	0.581	14 (16.3)	74 (34.6)	0.002
Coronary heart disease	20 (10.1)	13 (15.3)	0.212	29 (33.7)	68 (31.8)	0.745
Chronic kidney disease	37 (18.7)	9 (10.6)	0.087	15 (17.4)	47 (22.0)	0.370
Cause of AKI (n[%])						
Sepsis	38 (19.2)	25 (29.4)	0.058	15 (17.4)	65 (30.4)	0.022
Hypovolemia	98 (49.5)	34 (40.0)	0.142	46 (53.5)	84 (39.3)	0.024
Heart failure	39 (19.7)	12 (14.1)	0.263	17 (19.8)	49 (22.9)	0.554
Nephrotoxic drugs	12 (6.1)	4 (4.7)	0.651	6 (7.0)	15 (7.0)	0.992
Retrorenal obstruction	11 (5.6)	10 (11.8)	0.402	2 (2.3)	1 (0.5)	
Vasopressor drugs (n[%])	47 (23.7)	26 (30.6)	0.227	23 (26.7)	97 (45.3)	0.011
Surgery under general anesthesia (n[%])	49 (24.7)	34 (40.0)	0.010	19 (22.1)	82 (38.3)	0.007
AKI stage (n[%])						
1	82 (41.4)	13 (15.3)	<0.001	59 (68.6)	47 (22.0)	<0.001
2	77 (38.9)	25 (29.4)		21 (244)	67 (31.3)	
3	39 (19.7)	47 (55.3)		6 (7.0)	100 (46.7)	
APACHE II score (M[P_{25}–P_{75}])	14.0 (12.0, 18.0)	16.0 (12.0, 20.5)	0.003	17.5 (15.0, 19.0)	18.0 (17.0, 21.0)	0.016
Laboratory data						
PO_2/FiO_2 ratio (M[P_{25}–P_{75}])	254.0 (189.0, 315.3)	230.0 (199.7, 281.8)	0.174	220.0 (172.9, 247.0)	198.0 (165.8, 245.0)	0.171
Lactate (mmol/L, M[P_{25}–P_{75}])	1.8 (1.3, 2.3)	2.3 (1.2, 3.4)	0.023	2.4 (1.8, 3.1)	2.7 (1.9, 3.6)	0.077
Hemoglobin (g/L, M[P_{25}–P_{75}])	108.0 (89.0, 123.0)	83.0 (77.0, 100.0)	<0.001	97.0 (86.0, 107.8)	77.0 (68.0, 97.0)	<0.001
Albumin (g/L, M[P_{25}–P_{75}])	28.6 (25.7, 32.6)	27.6 (26.0, 29.8)	0.068	27.4 (25.2, 31.0)	26.0 (24.0, 28.4)	0.015
eGFR(mL/min/1.73 m^2, M[P_{25}–P_{75}])	39.2 (24.7, 51.0)	32.9 (22.9, 50.6)	0.222	38.4 (29.8, 51.1)	27.2 (21.5, 35.5)	<0.001
D-Dimer (ng/L, M[P_{25}–P_{75}])	1420.0 (495.3, 3230.5)	2360.0 (925.0, 3935.0)	0.025	1248.5 (657.8.0, 2560.0)	1970.0 (961.0, 3945.0)	0.002
C-reactive protein (mg/L, M[P_{25}–P_{75}])	96.8 (45.9, 177.9)	174.9 (66.7, 187.9)	0.006	59.6 (23.6, 120.5)	112.6 (44.6, 182.1)	<0.001

AKI: acute kidney injury; APACHE II: acute physiologic assessment and chronic health evaluation II; eGFR: estimated glomerular filtration rate.

Table 2. Multivariate logistic regression analysis for nonrenal recovery in AKI cohorts of different ages.

	Age < 63 year cohort		Age ≥ 63 year cohort	
	OR (95% CI)	p value	OR (95% CI)	p Value
AKI stage	2.54 (1.72–3.73)	<0.001	3.50 (2.20–5.56)	<0.001
Hemoglobin (g/L)	0.97 (0.96–0.98)	<0.001	0.98 (0.96–0.99)	0.003
Lactate (mmol/L)	1.32 (1.09–1.59)	0.004		
Diabetes mellitus			2.85 (1.29–6.33)	0.010
eGFR (mL/min/1.73 m^2)			0.95 (0.93–0.97)	<0.001
Surgery under general anesthesia			2.72 (1.24–5.96)	0.012
APACHE II score			1.15 (1.03–1.28)	0.012

AKI: acute kidney injury; eGFR: estimated glomerular filtration rate; APACHE II: acute physiologic assessment and chronic health evaluation II.

was still not an independent risk factor for AKI renal nonrecovery.

Discussion

The main findings of this study included a higher rate of the 30-day renal nonrecovery in the age ≥63 years cohort, a history of diabetes mellitus, surgery under general anesthesia, AKI stage, APACHE II score, eGFR, and hemoglobin were independent risk factors for renal nonrecovery in the age ≥63 years cohort, and the AKI stage, lactate, and hemoglobin were independent risk factors for renal nonrecovery in the age <63 years cohort. This study found for the first time that the optimal cutoff value of age related to renal nonrecovery after AKI was 63-years old, the rate of renal nonrecovery in patients older than 63 years with AKI was significantly increased, and renal nonrecovery after AKI was associated with more risk factors among older patients than among younger patients.

Previous studies have reported that the renal recovery rate after AKI is between 33% and 90% [18]. In this study, the overall renal recovery rate of all patients was 48.7%. The difference in renal recovery was related to the different recruited cohorts, diagnostic criteria for AKI, the definition of renal recovery, and follow-up

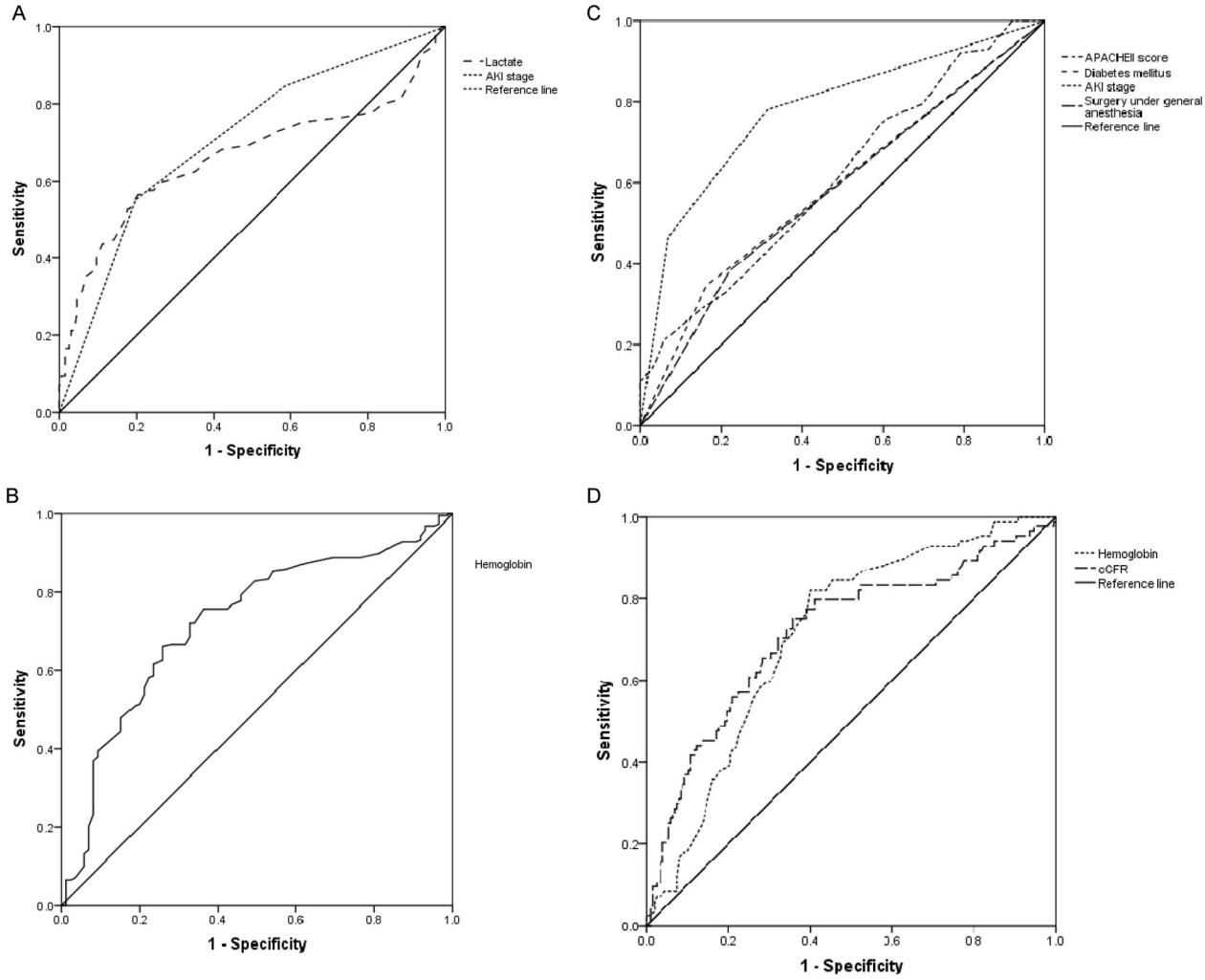

Figure 2. The ROC curve of risk factors for the prediction of the nonrenal recovery (A) and renal recovery (B) of AKI in the age $<$ 63 years cohort, and the risk factors for the prediction of the nonrenal recovery (C) and renal recovery (D) of AKI in the age $\geq$ 63 year cohort.

time. At present, there is no unified consensus on the definition of renal recovery and the duration of follow-up. Most previous studies used creatinine-based AKI criteria and definition of renal recovery. Long et al. [19] used serum creatinine as the research index to contrast the effect of the definition of four different degrees of renal recovery on the progression to CKD and survival. Their study showed that the optimal definition of renal recovery to predict survival was a reduction in blood creatinine to within 1.5 times baseline within 30 days. Patients whose serum creatinine decreased to 1.5 baseline had significantly better 1-year survival than patients with no renal recovery within 30 days; the risk of developing and progressing to CKD within 5 years was significantly increased if the patient's renal recovery was limited to serum creatinine falling to 1.25–1.5 times the baseline within 30 days. Since creatinine was influenced by age, sex, weight, race, etc., and muscle mass and fluid status also affect creatinine value, eGFR was used to define AKI, AKI stage, and renal recovery in this study, which can more accurately evaluate renal function and its changes.

Previous studies have suggested that advanced age was an unfavorable factor for renal recovery [8,9]. To elaborate on the characteristics of renal recovery in elderly and nonelderly cohorts, we used the Youden index to find the cutoff value of age affecting renal recovery at 63 years, which was used to divide all patients into two cohorts, elderly and nonelderly. These two cohorts were analyzed separately for risk factors influencing renal nonrecovery after AKI, which had not been reported in previous studies. We found that AKI stage and hemoglobin were common risk factors in both cohorts. Forni et al. [18] reviewed previous studies and found that the AKI stage was negatively correlated with renal recovery, and the higher the stage of AKI was, the

lower the rate of renal recovery. A total of 284 patients had renal recovery in this study, including 49.6% of patients with stage 1 AKI, 34.5% of patients with stage 2 AKI, and 15.8% of patients with stage 3 AKI, which suggested that patients with higher AKI stages had a lower rate of renal recovery. Dividing all renal recovery patients into two groups with 63 years as the cutoff point, the proportion of patients in AKI stage 3 was significantly lower than that in AKI stage 1 and stage 2 in both groups, with 19.7% of AKI stage 3 patients in the age $<$63 years cohort and 7.0% of AKI stage 3 patients in the age $\geq$63 years cohort. Few studies have evaluated the role of anemia in renal recovery after AKI. Our study found that among all patients, the level of hemoglobin was a risk factor associated with renal nonrecovery. In a retrospective single-center study [20] that enrolled 41 patients with AKI requiring renal replacement therapy, anemia was associated with renal recovery at discharge. Another retrospective study [21] that included 211 patients with AKI suggested that the effects of anemia may be more pronounced in severe cases of AKI, in which case the effects of prolonged hypoxia may interfere with the extent and rate of renal recovery.

The APACHE II score was currently in widespread clinical use to predict outcomes in critically ill patients. To avoid the influence of age on APACHE II score, we calculated APACHE II of non age. In this study, we used these two scores as possible risk factors associated with renal nonrecovery, and we found that these two scores in the age $<$63 years cohort were significantly different in univariate analysis, but neither score was a risk factor for renal nonrecovery in multivariate analysis. However, it was different in the age $\geq$63 years cohort, and the APACHE II and APACHE II of non age scores were independent risk factor for renal nonrecovery. Mehta et al. [22] suggested that higher APACHE III scores were associated with a lower rate of renal recovery in acute renal failure patients. This illustrated that older patients aged $\geq$63 years may have lower rates of renal recovery with greater disease severity.

Past medical history was also considered an important factor associated with renal recovery, and the most common factors were hypertension, diabetes mellitus, and coronary heart disease [18]. Univariate analysis in this study found that diabetes mellitus was a risk factor for renal nonrecovery in all patients, but the multivariate analysis was performed and showed that diabetes mellitus was independently associated with renal recovery only in the elderly cohort. This suggested that diabetes mellitus caused more damage than other chronic diseases. Some studies [23] suggested that once diabetes mellitus occurs, most patients continue to manifest progressive renal damage even if glycemia is tightly controlled. This suggested that key pathogenic mechanisms involved in the induction and progression of diabetic nephropathy remain active, and no effective treatment is currently available. Studies have suggested that the reason diabetes mellitus emerges as an independent risk factor among patients of advanced age is because there was a positive correlation between the damage to the kidneys caused by diabetes mellitus and the length of the disease course [24].

eGFR has been widely used for the evaluation of renal recovery after AKI, and most studies chose to use the eGFR before AKI as the baseline; however, individual studies varied in their choice of time point before AKI considered to be the baseline. This study used the eGFR at the time of AKI diagnosis as the observation index. Univariate analysis found higher eGFR in the renal recovery group than in the nonrenal recovery group in the age $\geq$63 years cohort, and multivariate analysis found that eGFR was a predictor of renal recovery after AKI in the age $\geq$63 years cohort.

It is well known that surgery under general anesthesia increases the burden on renal function, but we do not know whether undergoing surgery under general anesthesia before AKI affects renal recovery. Our study found that among all patients, the proportion of surgery in the nonrenal recovery group was significantly higher than that in the renal recovery group, but multivariate analysis suggested that surgery under general anesthesia was associated with renal recovery only in patients aged $\geq$63 years, which may be related to decreased organ function reserve leading to decreased tolerance to surgery under general anesthesia in elderly patients.

There are certain limitations of this study. First, we included more independent variables, but our sample size was relatively small after grouping, although it basically satisfied the requirement of ten times the number of independent variables. Due to the relatively small sample size, sensitivity analysis and subgroup analysis were not conducted to further exclude the influence of some confounding factors. Second, this was a retrospective observational study, which may have generated selection bias, although we included patients from multiple centers and employed multivariate regression analysis to correct for confounders. Third, we had a shorter follow-up of our patients, and there are studies that considered a follow-up of three months to be more appropriate. These factors all may generate bias, which still needs further validation by large-scale prospective studies in the future.

Conclusions

This study found that elderly patients had lower rates of renal nonrecovery after AKI than younger patients. AKI stage and hemoglobin were common risk factors among all patients, and renal nonrecovery after AKI was associated with more risk factors among older patients than among younger patients. Maintenance of higher hemoglobin levels in clinical practice contributes to renal recovery among all patients. In the future, large-scale prospective studies are needed to further clarify the risk factors, therapy, and prognosis of renal recovery after AKI in the elderly and nonelderly cohorts..

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Ethical approval

Our protocols were approved by the institutional review boards of Peking University People's Hospital (approval No. 2019PHB042-01) and performed according to the recommendations of the Declaration of Helsinki for Biomedical Research involving human subjects. The institutional review boards of Peking University People's Hospital approved to waive of the need for an informed consent and to use the opt-out approach in the study, because the data were retrospectively and anonymously analyzed.

Author contributions

XZ and CL substantially contributed to the conception and design of the study and were major contributors in writing the original manuscript. FZ and SL also substantially contributed to the conception and design of the study and were contributors to the revision of the manuscript. YL, FG, HX, YJ, SL, MC, TD and ZW substantially contributed to the acquisition and analysis of the data. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s)

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Data Availability statement

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

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