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# Value of Neutrophil Counts in Predicting Surgery-Related Acute Kidney Injury and the Interaction of These Counts With Diabetes in Chronic Kidney Disease Patients With Hypertension

## A Cohort Study

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**Abstract:** As a component of routine blood cell analyses, the quantity of neutrophils present is a proven predictor of morbidity and mortality in several clinical settings. However, whether episodes of acute kidney injury (AKI) are associated with higher neutrophil counts in vulnerable groups, such as chronic kidney disease (CKD) patients with hypertension, are unknown. This study was conducted to investigate the relationship between neutrophil counts and the incidence of surgery-related AKI in CKD patients with hypertension.

This was a retrospective cohort study of the relationship between neutrophils and surgery-related AKI. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression models.

In total, 119 (11.9%) of 998 patients experienced surgery-related AKI during hospitalization from October 2008 to February 2013. We divided patients into 4 quartiles according to their neutrophil counts. After adjusting for multiple covariates, the patients in the 4th quartile of neutrophil counts had greater ORs for AKI compared to those in the 1st quartile. The incidence of AKI increased 1.59-fold for those patients with neutrophil counts  $\geq 6.30 \times 10^9/L$ . There was a positive linear association between the neutrophil count upon admission and the

predicted probability of AKI. The cross-validation revealed a statistically significant predictive accuracy for AKI (area under the curve (AUC) = 0.68, 95% CI, 0.67–0.69). The interaction analyses revealed that higher neutrophil counts are associated with a heightened risk of AKI in the presence of diabetes (OR = 3.38, 95% CI, 1.06–10.80). There were no interactions between neutrophil counts and age ( $P=0.371$ ), sex ( $P=0.335$ ), estimated glomerular filtration rate ( $P=0.487$ ), systolic blood pressure ( $P=0.950$ ), diastolic blood pressure ( $P=0.977$ ), the presence of chronic heart failure ( $P=0.226$ ), or sepsis ( $P=0.796$ ).

The neutrophil count upon admission, an index that is easily and rapidly measured, is valuable for the prediction of surgery-related AKI in CKD patients with hypertension, especially in those with diabetes.

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**Abbreviations:** AKI = acute kidney injury, AUC = area under the curve, BMI = body mass index, BP = blood pressure, CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein cholesterol, IQR = interquartile range, KDIGO = Kidney Disease Improving Global Outcomes, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, Scr = serum creatinine, SD = standard deviation.

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## INTRODUCTION

Acute kidney injury (AKI) is a serious complication after surgery because AKI is a convincing predictor of various long-term outcomes,<sup>1–6</sup> including chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular disease (heart failure, myocardial infarction), and increased mortality (30–50% of all patients with AKI die despite appropriate treatment).<sup>1,7</sup> Although preventative measures have improved, AKI is frequently experienced after surgery, and the rate ranges from 3% to 43%.<sup>2,3,8,9</sup>

Patients with CKD have an increased risk for AKI. CKD is major risk factor for the progression of AKI, and CKD is significantly associated with the causes and consequences of AKI. In a recent meta-analysis<sup>10</sup> that included 1,285,045 participants, 0.2% to 6% of the individuals among the general cohort developed AKI, while 2% to 25% of CKD patients developed AKI. When adjusted for covariates, a 2- to 8-fold progressive increase in the frequency of AKI occurs in CKD patients. Furthermore, hypertension was also found to be an independent risk factor of AKI.<sup>9,11</sup> For these reasons, it is

essential to monitor and diminish the factors contributing to AKI in vulnerable patients, such as patients with CKD and hypertension.

The quantity of neutrophils is a component of routine blood cell counts. The neutrophil, which is a granular leukocyte with a 3- to 5-lobed nucleus, plays an important role in the first line of the innate immune defense against infectious diseases<sup>12,13</sup> and may be an independent predictor of mortality risk,<sup>14</sup> cardiovascular risk,<sup>15</sup> and cancer prognosis.<sup>16</sup> Although a few studies have demonstrated that neutrophil measurements provide substantial prognostic information regarding AKI, correlations between AKI and mortality have not been extensively studied in patients with CKD and hypertension. To address this knowledge gap, this study was conducted to investigate whether surgery-related AKI in CKD patients is associated with the level of neutrophils in the blood.

## METHODS

### Data Source

We conducted a single-center, retrospective cohort study of hospitalized adults. All of the deidentified data were obtained from the hospital information system (HIS) of the 3rd Xiangya Hospital (Changsha, China), which serves as the sole portal of clinical data entry for all public inpatient settings across different regions of China and provides the complete health records of patients, including age, sex, race, body mass index (BMI), blood pressure (BP), hospital service type (medical, surgical, or other), clinical diagnosis in the form of the International Classification of Disease (ICD-10), surgery date, surgical sites, and laboratory data. Comorbidities, including cardiovascular risk factors and medical conditions, such as “sepsis,” “diabetes,” “coronary disease,” and “chronic heart failure,” were extracted from the system, as indicated by the ICD-10 codes. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was not necessary because all subjects were anonymized. The institutional review board approved this study (No. 2015-S139). The reporting of the study conforms to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>17</sup>

### Patients

Patients who underwent only 1 elective surgery during hospitalization with a discharge diagnosis of “chronic kidney disease” and “hypertension” between October 2008 and February 2013 were considered potential candidates (n = 1035). All the patients were adults (aged  $\geq 18$  years) who were hospitalized for the first time and were discharged alive and whose electronic medical records before surgery did not contain the relevant field of “signs of infection.” We excluded patients with missing data, such as pre- or postoperative blood creatinine (n = 5), patients with secondary hypertension except renal hypertension (n = 2), patients who underwent 2 or more surgeries (n = 14), and patients whose final diagnoses included acute cardio-cerebrovascular diseases (acute coronary heart disease, acute heart failure, acute stroke, or acute cerebral hemorrhage), hematologic diseases, or malignant tumors (n = 16). In total, 998 eligible patients were included in this study (Figure 1).

### Outcome Variables and Covariates

All the patients were followed up until the development of hospital-acquired AKI based on the KDIGO (Kidney Disease: Improving Global Outcomes) AKI classification system<sup>18</sup>

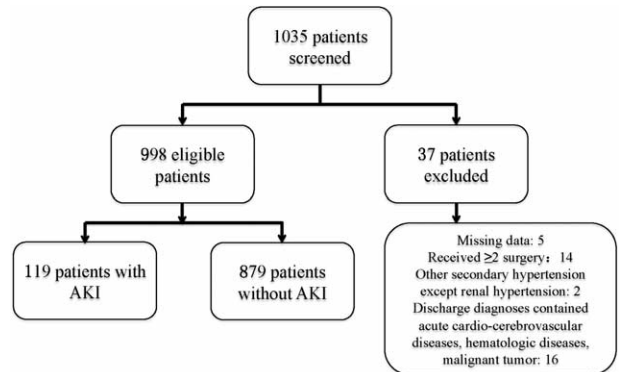


FIGURE 1. Flow chart of patient selection.

(a serum creatinine (Scr) increase of greater than 0.3 mg/dL within 48 hours or a 1.5-fold Scr increase within 7 days after surgery) using the peak-to-nadir Scr difference. In brief, the nadir Scr level was defined as the lowest value recorded during the first 3 days of hospitalization. The peak Scr level was defined as the highest value recorded during the week (7 days) after surgery.

The estimated glomerular filtration rate (eGFR) was derived from the nadir Scr level recorded during hospitalization using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.<sup>19</sup> The baseline neutrophil counts were measured with an automated hematology analyzer (Beckman Coulter LH750, America), and the normal reference range was  $1.80$  to  $6.30 \times 10^9/L$ . Additional covariates of interest recorded during hospitalization were selected according to the reported AKI risk factors,<sup>2,9</sup> such as age, gender, BP, plasma biomedical markers (routine blood tests, glucose, and blood lipid levels), final diagnoses (diabetes mellitus, coronary disease, CKD, or sepsis), the use of vasoactive (norepinephrine, epinephrine, dopamine, metaraminol, isoproterenol, phentolamine, nitroprusside, etc.) or anti-arrhythmic drugs (amiodarone, lidocaine, propafenone, quinidine, mexiletine, etc.), and surgery sites.

### Statistical Analysis

All of the analyses were performed using IBM SPSS Version 22.0 (SPSS, Inc., Chicago, IL) and R (version 2.12.0). Continuous variables were presented as means  $\pm$  standard deviations (SDs), or the median interquartile range (IQR) when the data exhibited a skewed distribution. The analysis of variance (ANOVA) or a post hoc analysis of the least significant difference (LSD) were used to compare the means of the normally distributed continuous variables, otherwise, the Kruskal–Wallis test was used. Categorical variables were expressed as proportions and tested using the Chi-squared test. The entire study population was divided into 4 groups according to the baseline neutrophil quartiles: quartile 1 (neutrophils  $< 3.4 \times 10^9/L$ ), quartile 2 (neutrophils  $\geq 3.4 \times 10^9/L$  and  $< 4.4 \times 10^9/L$ ), quartile 3 (neutrophils  $\geq 4.4 \times 10^9/L$  and  $< 6.13 \times 10^9/L$ ), and quartile 4 (neutrophils  $\geq 6.13 \times 10^9/L$ ), and the parameters were compared between these 4 subgroups. Next, the logistic predictive values, the odds ratios (ORs) and 95% confidence intervals (CIs) for AKI were calculated using the logistic regression model after adjustment for multiple confounders. Model 1 was the crude model. In model 2, the

analysis was adjusted for age and sex. In model 3, we adjusted for age, sex, BMI, baseline eGFR, BP, heart rate, and surgery sites. In addition to the independent parameters analyzed in model 3, model 4 included admission fasting blood concentrations of lymphocytes, eosinophils, red blood cells, hemoglobin, blood platelets, glucose, blood urea nitrogen, triglycerides, and low-density lipoprotein cholesterol (LDL-C) as well as complication status (heart failure, sepsis, diabetes) in the list of independent parameters. We then estimated the risk of AKI associated with neutrophil counts  $\geq 6.30 \times 10^9/L$  in all the models. A 10-fold cross-validation was used to test and verify the predictive accuracy of the model.

Finally, we analyzed the joint effects of neutrophil counts ( $<6.30$  and  $\geq 6.30 \times 10^9/L$ ) and the presence of diabetes mellitus. Other interaction product terms were also examined to assess how neutrophil counts ( $<6.30$  and  $\geq 6.30 \times 10^9/L$ ) interacted with age, eGFR, systolic blood pressure (SBP), and diastolic blood pressure (DBP), which were treated as continuous parameters, as well as sex, the presence of heart failure, and sepsis. All interactions were analyzed using the final logistic model (model 4). A *P*-value of 0.05 (2-tailed) was established as the threshold for statistical significance.

## RESULTS

During hospitalization, surgery-related AKI developed in 119 patients (11.9%). We divided these patients into 4 quartile groups according to their neutrophil counts and referenced the 1st quartile during all analyses. The baseline characteristics of the patients are presented and compared among each neutrophil-count quartile (Table 1). For the 998 subjects, the mean age was 51.70 years. All of the subjects were of Asian descent. The median length of stay in the hospital was 21 days (IQR, 12–32 days). The median neutrophil count was  $5.08 \times 10^9/L$ . Compared to the 1st quartile, patients in the 4th quartile were more likely to be older and female with a higher incidence of metabolic disorders (high BP, high heart rate, high cholesterol, and high glucose), higher levels of hemoglobin, red blood cells, blood platelets, and creatinine, and a greater use of vasoactive and anti-arrhythmic drugs.

Table 2 illustrates the AKI risk according to the quartile groups based on neutrophil counts. From the lowest neutrophil quartile to the highest, the incidence rate of AKI increased from 8.00% to 17.70%. In all 4 models of the statistical analysis, the ORs for AKI increased with increasing neutrophil-count quartile. Whether using the unadjusted or adjusted analysis, the 4th quartile group had a higher OR for AKI than the 1st quartile (all *P* values  $<0.05$ ). A neutrophil count  $\geq 6.30 \times 10^9/L$  was associated with a mean 59% in the incidence of AKI. Based on the above observations, we explored the relationship between neutrophils and AKI. Figure 2 shows the linear relationship between the neutrophil count and the predicted probability of AKI, and this relationship had a positive linear correlation after adjusting for multiple covariates. The cross-validation of model 4 revealed a statistically significant predictive accuracy for AKI (area under the curve (AUC) = 0.68, 95% CI, 0.67–0.69) (Figure 3).

The presence of diabetes alone had no independent predictive value (OR = 0.99, 95% CI, 0.52–1.90), neither harm nor benefit, regarding the endpoint evaluated. However, the interaction analyses indicated that higher neutrophil counts are associated with a heightened risk of AKI in the presence of diabetes (OR = 3.38, 95% CI, 1.06–10.80). Figure 4 presents the joint effects of neutrophil counts and diabetes for the

incidence of AKI. There were no interactions between neutrophil counts and age (*P* = 0.371), sex (*P* = 0.335), eGFR (*P* = 0.487), SBP (*P* = 0.950), DBP (*P* = 0.977), the presence of chronic heart failure (*P* = 0.226), and sepsis (*P* = 0.796).

## DISCUSSION

Although many other factors are associated with heightened risks for AKI, low eGFRs, and high BP remain powerful prognostic markers.<sup>10,11</sup> In addition, mortality and cardiovascular morbidity in CKD with hypertension are extremely high,<sup>20,21</sup> and AKI worsens these outcomes. AKI is a serious complication that is frequently observed after surgery. To date, there has been no specific therapeutic regimen.<sup>22,23</sup> Thus, it is essential to identify risk factors and prevent postoperative AKI in CKD patients with hypertension.

Numerous biomarkers may predict AKI.<sup>24–33</sup> Andrea et al<sup>25</sup> found that a neutrophil gelatinase-associated lipocalin (NGAL) level greater than 155 ng/mL at 6 hours after cardiac surgery was associated with an OR of 7.1 (95% CI, 2.7–18) for postoperative AKI in CKD. Additionally, kidney injury molecule-1 (KIM-1) and liver fatty acid-binding protein (L-FABP)<sup>29,31,32</sup> were also early postoperative predictors of AKI. A retrospective cohort study that involved 616 patients<sup>30</sup> revealed that preoperative serum cystatin C and heavy proteinuria (OR 3.14, 95% CI, 1.26–7.77) were associated with an increased risk of AKI, independent of advanced age, hypertension, and combined surgery. The combination of these risk factors could improve the prediction of AKI among patients who underwent cardiac surgery.

Among these markers, neutrophil counts are easily accessible and commonly examined, and they are a component of routine blood analyses. The presence of neutrophils has proven to be a predictor of morbidity and mortality in several clinical settings.<sup>15</sup> However, few studies have determined the correlation between neutrophil counts and AKI, and the linear relationship observed between neutrophil counts and AKI is consistent with a previous report,<sup>28</sup> which found a U-shaped relationship between white blood cells (WBCs) and AKI in critically ill patients. When these authors analyzed the relationships between subtypes of WBCs and AKI, the adjusted ORs associated with a quartile increase in neutrophils (and no other WBC subtype) were 0.99 (95% CI, 0.71–1.40), 0.83 (95% CI, 0.59–1.16), 1 (Reference), 1.23 (95% CI, 0.87–1.75), and 1.69 (95% CI, 1.41–2.51).

The present study is the first report of a positive linear relationship between preoperative neutrophil counts and surgery-related AKI in CKD patients with hypertension, who underwent 1 surgery during hospitalization. This association was maintained after accounting for potential confounders. This finding suggests that neutrophil counts are associated with the development of surgery-related AKI, and neutrophil counts may be used as an additional clinical indicator of an increased AKI risk in CKD with hypertension.

In addition, we provided new information regarding the association between neutrophils and AKI in both the presence and absence of common conditions. Sepsis, which is a generalized inflammatory syndrome and the leading cause of AKI in clinical practice,<sup>34,35</sup> affects the kidney, lung, heart, brain, and immune system.<sup>36</sup> Chronic heart failure and diabetes are also independent risk factors for developing AKI.<sup>9</sup> Our results demonstrated that the predictive value of neutrophil counts regarding the development of AKI was highly affected by the presence of diabetes (but independent of chronic heart

**TABLE 1.** Baseline Characteristics, Stratified by Neutrophil-Count Quartile

	Neutrophil-Count Quartiles				Total
	Q1 ( $<3.40 \times 10^9/L$ )	Q2 ( $3.40-4.40 \times 10^9/L$ )	Q3 ( $4.40-6.13 \times 10^9/L$ )	Q4 ( $\geq 6.13 \times 10^9/L$ )	
N	251	248	251	248	998
Age, y*	50.11 ± 15.27	51.49 ± 15.29	50.44 ± 15.00	54.81 ± 15.54	51.70 ± 15.37
Male sex (%)*	57.37	65.32	63.75	54.84	60.5
BMI, kg/m <sup>2</sup> *	21.96 ± 3.07	22.48 ± 2.89	23.02 ± 3.20	22.75 ± 2.97	22.55 ± 3.06
eGFR, mL/min/1.72 m <sup>2</sup>	11.43 ± 17.13	12.13 ± 18.31	12.09 ± 21.59	13.58 ± 19.14	12.30 ± 19.10
SBP, mm Hg	155.32 ± 21.52	157.16 ± 22.70	157.96 ± 23.41	160.52 ± 25.96	157.74 ± 23.49
DBP, mm Hg	92.00 ± 14.44	92.01 ± 14.31	92.18 ± 15.25	95.01 ± 17.89	92.80 ± 15.57
Heart rate, beats/min*	81.58 ± 11.11	83.04 ± 12.61	85.05 ± 13.22	89.88 ± 15.46	84.88 ± 13.53
Use of drugs					
Anti-arrhythmic drugs, %*	1.99	7.66	6.77	11.69	7.01
Vasoactive drugs, %*	5.98	10.71	9.68	13.71	9.92
Admission fasting blood concentrations of					
Lymphocytes, $\times 10^9/L$ *	1.30 ± 0.57	1.26 ± 0.46	1.42 ± 0.56	1.30 ± 0.61	1.32 ± 0.65
Eosinophils, $\times 10^9/L$ *	0.19 ± 0.18	0.22 ± 0.22	0.22 ± 0.17	0.14 ± 0.14	0.19 ± 0.18
Basophils, $\times 10^9/L$	0.03 ± 0.03	0.02 ± 0.02	0.03 ± 0.03	0.03 ± 0.03	0.03 ± 0.03
Red blood cells, $\times 10^{12}/L$ *	2.87 ± 0.81	2.95 ± 0.87	3.09 ± 0.86	3.09 ± 0.91	3.00 ± 0.87
Hemoglobin, g/L*	82.53 ± 23.68	87.86 ± 26.24	89.84 ± 25.65	89.42 ± 26.13	87.41 ± 25.51
Blood platelets, $\times 10^9/L$ *	145.61 ± 58.51	151.08 ± 53.00	172.62 ± 67.62	186.45 ± 83.62	164.34 ± 68.73
Glucose, mmol/L*	4.73 ± 1.16	4.94 ± 1.61	5.09 ± 2.24	5.14 ± 1.43	4.97 ± 1.67
Uric acid, $\mu\text{mol}/L$	425.96 ± 128.70	431.61 ± 140.83	437.26 ± 147.24	435.24 ± 161.67	432.51 ± 144.90
Blood urea nitrogen, mmol/L	21.16 ± 10.63	21.62 ± 11.30	21.90 ± 10.68	21.39 ± 12.17	21.62 ± 11.29
HDL, mmol/L	1.25 ± 0.37	1.21 ± 0.33	1.24 ± 0.37	1.18 ± 0.38	1.22 ± 0.36
LDL-C, mmol/L*	2.20 ± 0.64	2.30 ± 0.59	2.35 ± 0.71	2.39 ± 0.89	2.31 ± 0.72
Triglycerides, mmol/L*	1.42 ± 1.12	1.46 ± 0.97	1.47 ± 0.88	1.69 ± 1.54	1.51 ± 1.16
Total cholesterol, mmol/L	4.11 ± 0.95	4.19 ± 0.90	4.28 ± 1.02	4.39 ± 1.42	4.24 ± 1.10
Discharge diagnoses					
Diabetes, %*	6.37	12.5	17.13	18.55	13.6
Chronic heart failure, %*	9.16	9.68	10.76	15.73	11.30
Coronary heart disease, %	4.78	4.84	3.98	6.05	4.9
Sepsis, %*	10.36	10.08	11.16	25.00	14.13
Surgery sites					
Cardiovascular surgery, %	6.77	9.68	11.55	14.11	10.5
Blood and lymphatic system surgery, %	7.17	8.47	9.56	9.27	8.6
Urogenital surgery, %	77.29	72.58	70.12	61.69	70.4
Digestive surgery, %	1.59	1.61	3.19	4.44	2.7
Musculoskeletal surgery, %	1.20	0.80	0.40	2.01	1.1
Other sites, %	5.98	6.85	5.18	8.47	6.6

BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate HDL = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure. Comparisons were performed using the chi-squared test for the categorical variables, the ANOVA test was used for normally distributed continuous variables (post hoc analysis of LSD between 2 groups), and the Kruskal–Wallis test was used for nonnormally distributed continuous variables (Mann–Whitney *U*-test between 2 groups).

\**P* < 0.05.

failure and sepsis). Although only 23.15% (231/998) of the subjects exhibited elevated neutrophil levels, the high neutrophil and diabetes product term was independently associated with an increased risk for AKI. Thus, neutrophil counts remain a powerful prognostic marker for AKI in the presence of diabetes.

Although clinical studies have been relatively insufficient, the role of neutrophils in the mechanism of AKI has been extensively investigated in experimental studies. It is well known that neutrophils are clear, independent markers of inflammation and play an important role in the pathogenesis

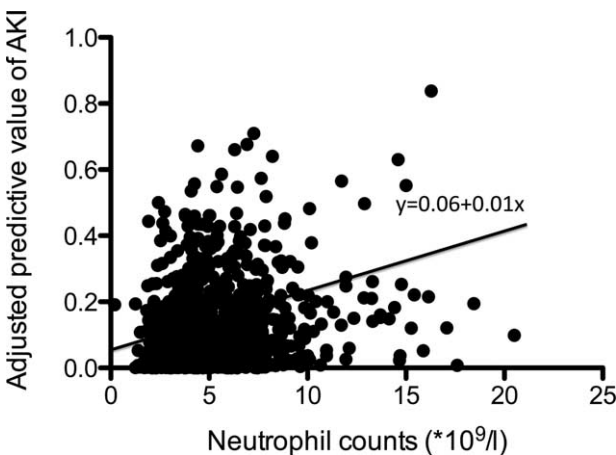
of renal damage, particularly in the presence of CKD, hypertension, and diabetes.<sup>37–41</sup> Several studies in AKI models have demonstrated an association between AKI and an increase of infiltrating neutrophils in the kidney.<sup>42–45</sup> Neutrophils are recruited rapidly to sites of inflammation<sup>46</sup> through inflammatory mediators, including IL-17 (interleukin 17), SLP-76 (SH2 domain-containing leukocyte phosphoprotein of 76 kDa), ADAP (adhesion and degranulation promoting adaptor protein), adhesion molecules, TLR2 (toll-like receptor-2), TLR4 (toll-like receptor-4), and MYD88 (myeloid differentiation factor



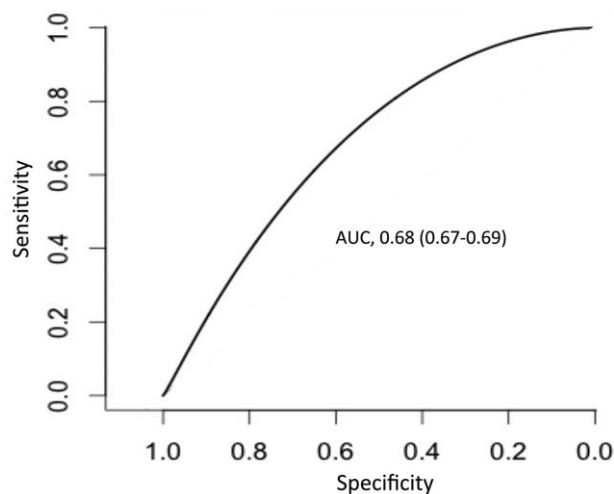
**TABLE 2.** ORs (95% CIs) for the Incidence of AKI Stratified According to the 4 Neutrophil-Count Quartiles Upon Admission

	Neutrophil-Count Quartile				Neutrophil Counts $\geq 6.30 \times 10^9/L$
	Q1 ( $<3.40 \times 10^9/L$ )	Q2 ( $3.40-4.40 \times 10^9/L$ )	Q3 ( $4.40-6.13 \times 10^9/L$ )	Q4 ( $\geq 6.13 \times 10^9/L$ )	
N	251	248	251	248	231
AKI incidence	8.00%	10.90%	11.20%	17.70%	17.75%
Model 1	1 (Reference)	1.41 (0.77-2.59)	1.45 (0.79-2.65)	2.49 (1.42-4.37)*	1.91 (1.26-2.87)*
Model 2	1 (Reference)	1.36 (0.77-2.59)	1.42 (0.77-2.59)	2.40 (1.37-4.23)*	1.87 (1.23-2.83)*
Model 3	1 (Reference)	1.36 (0.74-2.52)	1.36 (0.74-2.51)	2.12 (1.17-3.84)*	1.65 (1.06-2.56)*
Model 4	1 (Reference)	1.29 (0.69-2.40)	1.34 (0.72-2.51)	2.04 (1.11-3.77)*	1.59 (1.01-2.50)*

AKI = acute kidney injury. Model 1, unadjusted. Model 2, adjusted for age and sex. Model 3, adjusted for age, sex, BMI, baseline eGFR, BP, heart rate, and surgery sites. Model 4, adjusted for the same independent parameters as Model 3 and admission fasting blood concentrations of lymphocytes, eosinophils, red blood cells, hemoglobin, blood platelets, glucose, blood urea nitrogen, triglycerides, LDL-C, and complication status (heart failure, sepsis, diabetes).  
\* $P < 0.05$ .



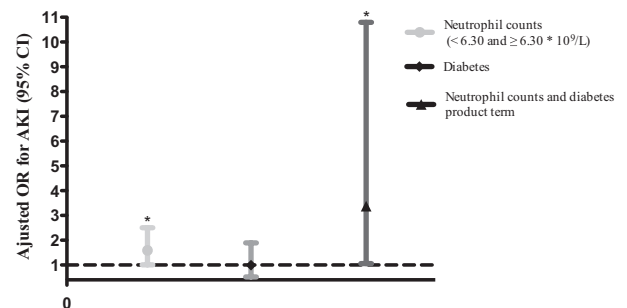
**FIGURE 2.** Linear relationships between WBC counts and ORs for AKI after adjustment for multiple confounders.



**FIGURE 3.** Cross-validated receiver-operating characteristic curves for predicting AKI using model 4.

88), and contribute to the innate immune responses of vascular permeability, hypoxia, ischemia-reperfusion, and apoptosis of tubular cells.

The potential limitations of our study should be mentioned. First, we used discharge diagnoses, which have low sensitivity but high specificity for patients with CKD and hypertension, to identify diseases. As a result, our findings are likely to be representative of the risk for patients with severe CKD; these findings may not be generalizable to all forms of CKD and hypertensive patients, including mild renal impairment defined by smaller changes in creatinine levels. Second, several valuable variables that may be predictors of patient outcomes, including intra-operative information (operation time and intraoperative urine output) and levels of inflammatory markers other than neutrophils (such as cytokines, among others), were not assessed in the present study.<sup>47</sup> However, neutrophil counts are a relatively clinically accessible biomarker before surgery; thus, the use of these counts in this study may be consistent with actual clinical practice. Third, the comprehensiveness of the statistical analysis presented in this paper was limited due to the small number of patients examined in this study and the correspondingly small number of events observed in diabetes patients with high neutrophil counts, a more comprehensive statistical analysis was not possible; therefore, the results presented in this investigation should be reviewed with caution and confirmed in larger cohorts. Moreover, the interaction analysis with diabetes may have been affected by selection bias because



**FIGURE 4.** The joint effects of neutrophil counts ( $<6.30$  and  $\geq 6.30 \times 10^9/L$ ) and diabetes on the likelihood of AKI, after adjusting for multiple confounders, \* $P < 0.05$ .

patients with diabetes could potentially have had higher neutrophil counts. Thus, the results relating to the differential prognostic significance of high neutrophil counts with respect to diabetes should be regarded as suggestive at best rather than as conclusive findings; these results should be confirmed in other prospective studies. Finally, although our study provides an easily and rapidly measured index as a predictor, there is still a lack of general use in clinical practice. Future studies addressing these limitations are necessary.

In summary, the present study indicates that a positive linear relationship exists between neutrophil counts and AKI. Neutrophil counts (an easy, rapid, measurable index) are valuable for the prediction of surgery-related AKI in CKD patients with hypertension, especially in those with diabetes.

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