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**Purpose:** Sulfur dioxide (SO\(_2\)) is a novel gaseous signaling molecule that plays an important role in inflammation, which contributes to the pathogenesis of acute kidney injury (AKI). The aim of this study was to explore the predictive value of plasma SO\(_2\) for AKI in high-risk patients.

**Patients and Methods:** A prospective cohort of 167 patients who underwent major noncardiac surgery was enrolled in the study. Plasma SO\(_2\), urine neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinase-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7) levels were detected immediately after the operation. The primary endpoint was new-onset AKI within 72 h after admission. The ability of biomarkers including SO\(_2\) and a clinical risk model to predict AKI was compared by receiver operator characteristic (ROC) curve analysis and decision curve analysis (DCA), additional contributions were evaluated by integrated discrimination improvement (IDI) and net reclassification improvement (NRI) analyses.

**Results:** A total of 61 (36.5\%) patients developed AKI within 72 h of surgery. Compared to NGAL and [TIMP-2]·[IGFBP7], SO\(_2\) showed better predictive ability for new-onset AKI with an area under the ROC curve of 0.771 (95\% confidence interval: 0.700–0.832, \(p<0.001\)). The improvement in predictive value by including SO\(_2\) in the clinical risk model was supported by NRI (0.28; \(P=0.04\)) and IDI (0.15; \(P=0.001\)) analyses. The net benefit of the combination of SO\(_2\) and clinical variables was the max in DCA.

**Conclusion:** Plasma SO\(_2\) shows a useful value for predicting new-onset AKI, and improved AKI prediction based on clinical variables, which can guide the implementation of preventive measures for high-risk patients.

**Keywords:** gasotransmitter, AKI, predictive modelling, intensive care unit

**Introduction**

Acute kidney injury (AKI) is a major public health burden—occurring in more than half of critical ill patients and is associated with increased risk of both in-hospital mortality and long-term chronic kidney disease.\(^{1,2}\) Given the low efficacy of interventions for AKI, identification of high-risk patients and implementation of preventive strategies are critical to assure a good clinical outcome. Diagnosis of AKI is currently based on oliguria or/and elevated serum creatinine.\(^{3}\) However, the former is closely related to the patient’s overall fluid volume whereas the latter is a late marker that may not be detected even when glomerular filtration rate has decreased by half.\(^{4}\) Thus, these 2 functional markers are neither sensitive nor
specific, which could delay diagnosis and treatment.\textsuperscript{5,6} Numerous studies have investigated potential biomarkers for identifying high-risk patients and facilitating the diagnosis of AKI.\textsuperscript{7} However, most biomarkers have disadvantages and limited utility in clinical practice.\textsuperscript{8,9} Sulfur dioxide (SO\textsubscript{2}), which was previously regarded as a toxic gas,\textsuperscript{10,11} is now recognized as a novel gasotransmitter.\textsuperscript{12} SO\textsubscript{2} is endogenously produced by the metabolism of the sulfur-containing amino acid L-cysteine\textsuperscript{13} and plays important physiological and pathophysiological roles.\textsuperscript{14-16} SO\textsubscript{2} levels are elevated in patients with acute pneumonia, chronic renal failure, and pediatric acute lymphoblastic leukemia with bacterial infection.\textsuperscript{17-19} We speculated that as an indicator of inflammation, SO\textsubscript{2} may predict the development of AKI in high-risk patients. To test this hypothesis, in this study we used SO\textsubscript{2} to develop an AKI prediction model and compared its performance with that of established markers of AKI in a prospective cohort of postoperative critically ill patients.

**Materials and Methods**

**Study Setting and Population**

The present study was carried out in a 20-bed surgical intensive care unit (ICU) of Beijing Chao-Yang Hospital from January 1, 2020 to October 31, 2020. The study was designed and conducted and is reported according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement.\textsuperscript{20} The study was approved by the human ethics committee of Beijing Chao-Yang hospital, Capital Medical University (Beijing, China) (no. 2020-ke-236). Informed consent from patients or their next of kin was obtained before consecutive patients were prospectively enrolled in the study. We included patients who underwent major noncardiac surgery and stayed in the ICU longer than 48 h. The exclusion criteria were age <18 years; development of AKI before ICU admission; insufficient data or blood samples; chronic kidney disease (CKD); operated by nephrectomy or kidney transplantation; and not transferred to the ICU immediately after the operation.

**Definitions and Clinical Endpoints**

The definition and classification of AKI were based on serum creatinine and urine output criteria proposed by Kidney Disease: Improving Global Outcomes.\textsuperscript{3} New-onset AKI was defined as AKI occurring within 72 h after the operation. CKD was defined according to National Kidney Foundation criteria as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m\textsuperscript{2} for at least 3 months irrespective of the cause. GFR was estimated with the Cockcroft–Gault formula.\textsuperscript{21} If at least 5 values for serum creatinine were available, the median of all values available from 6 months to 6 days prior to enrollment was used as the baseline; otherwise, the lowest value in the 5 days prior to enrollment was used. If no pre-enrollment creatinine was available or the emergency patient’s serum creatinine was abnormal at the time of admission, baseline creatinine was estimated using the Modification of Diet in Renal Disease equation assuming that baseline eGFR was 75 mL/min per 1.73 m\textsuperscript{2}.\textsuperscript{22} Sepsis and septic shock were diagnosed according to the Sepsis 3.0 definition of the American College of Chest Physicians/Society of Critical Care Medicine.\textsuperscript{23}

The primary endpoint was the development of AKI within 72 h after enrollment. Secondary endpoints for the purpose of characterizing the patient population included ICU and hospital mortality and length of ICU and hospital stays.

**Data Collection**

Demographic information and clinical data such as chronic illnesses, pre-ICU medications (including nephrotoxic drugs), surgical procedure, laboratory blood tests, duration of mechanical ventilation, and length of ICU and hospital stays were prospectively collected during the hospital stay and recorded in case report forms. Baseline serum creatinine, everyday creatinine, and hourly urine output on ICU admission and thereafter were measured and recorded. The severity of illness was estimated with Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment (SOFA) scores.

**Sample and Laboratory Analysis**

Paired blood and urine samples were collected immediately after the operation. After 30 min, the samples were centrifuged at 3000 rpm at 4°C for 10 min, and the supernatant (plasma) was stored at −80°C. SO\textsubscript{2} concentration were analyzed by high-performance liquid chromatography analysis (HPLC) (Series number:USKH127476, produce year: 2020).\textsuperscript{15} A 100 µL volume of plasma was mixed with 70 µL of sodium borohydride and 10 µL of methyl 2-bromopropionate (both from Sigma-Aldrich, St. Louis, MO, USA), followed by incubation for 10 min at 42°C. Perchloric acid (40 µL) was added and the mixture was centrifuged at 12,400 rpm for 10 min at 23°C to
remove precipitated proteins; 10 µL Tris-HCl (pH=3.0) was then added to the supernatant for neutralization before HPLC analysis. The mobile phases were a methanol: acetic acid: water buffer (5.00:0.25:94.75 by volume, pH=3.4) and pure methanol. All measurements were performed at an excitation wavelength of 392 nm and absorption wavelength of 479 nm. Quantification analysis was done by the standardization of sodium sulfate. According to previous research, we set up 7 sets of standard samples with different concentrations of sulfite, and measured their peak areas respectively using HPLC, and then obtained the standard curve (Figure S1). The R² of the standard curve is 0.9986, which proves that the determination accuracy is excellent. Commercially available enzyme-linked immunosorbent assay kits were used to measure urine concentrations of neutrophil gelatinase-associated lipocalin (NGAL) (CSB-E09408h; Cusabio, Wuhan, China), tissue inhibitor of metalloproteinase-2 (TIMP-2) (DTM200; R&D Systems, Minneapolis, MN, USA), and insulin-like growth factor-binding protein 7 (IGFBP7) (ARG81498; argo Biolaboratories, Shanghai, China). The assays were performed by technicians who were blinded to clinical data, and the supervising physicians were blinded to the biomarker test results.

Statistical Analysis
Continuous variables are presented as a median with 25th and 75th percentiles (interquartile range [IQR]), and categorical variables are presented as percentages. Continuous data were compared between groups with the Student’s t-test or Mann–Whitney U-test, and categorical variables were compared with the chi-squared test or Fisher’s exact test. Receiver operator characteristic (ROC) curve analysis was performed to assess the predictive value of biomarkers for AKI during follow-up. The cutoff point was the value with the highest sensitivity and specificity. Clinical parameters with p<0.10 in the univariate analyses were included in the multivariate logistic regression model. The calibration of the model was assessed with the Hosmer–Lemeshow test. Bootstrapping with repeated sampling was performed to confirm the stability of the model. We compared the predictive performance of the clinical risk model before and after adding different biomarkers by calculating the statistical significance of differences between area under the ROC curve (AUC) values which were defined as follows: 0.90–1.0, excellent; 0.80–0.89, good; 0.70–0.79, useful; 0.60–0.69, poor; and 0.50–0.59, not useful. Improvement in the predictive accuracy of the models was evaluated by calculating the relative integrated discrimination improvement (IDI) and net reclassification improvement (NRI). We also estimated the clinical utility and net benefit of the new predictive models by decision curve analysis (DCA), which identifies patients who are at risk of AKI based on the clinic prediction model with and without biomarkers. The x axis shows threshold values for AKI while the y axis represents the net benefit for the different threshold values of AKI; a higher net benefit is provided by prediction models that are farthest away from the slanted dashed gray line (assuming all adverse events) and horizontal black line (assuming no adverse event). For all analyses, statistical significance was taken as a 2-sided p value <0.05. Statistical analyses were performed using SPSS v25 (SPSS Inc, Chicago, IL, USA), MedCalc v.16.4.3 (MedCalc, Ostend, Belgium), and R 4.0.3 (R Project for Statistical Computing, Vienna, Austria).

Results
Subject Characteristics and Event Rates
We screened 282 subjects who were admitted to the ICU after major noncardiac surgery and typically had at least 1 recognized risk factor for AKI. A total of 115 patients were excluded for the following reasons: age <18 years (n=1); developed AKI before ICU admission (n=56); CKD (n=28); operated by nephrectomy or kidney transplantation (n=20); not transferred to the ICU immediately after the operation (n=8); and invalid or missing test results (n=2). Thus, 167 subjects were ultimately included in the prospective cohort; their demographic information is shown in Table 1.

In total, 61 patients (36.5%) met the primary endpoint of new-onset AKI. Each AKI case was diagnosed based on elevated creatinine (34.4%), oliguria (41.0%), or both (24.6%). Of these cases, 57.4% (n=35) were stage I, 32.8% (n=20) were stage II, and 9.8% (n=6) were stage III. The median (IQR) length of stay in the ICU was 2 (2–4) days for patients with AKI and 6 (3–8) days for those without AKI (Table 2).

Predictive Performance of SO2 Compared to Established AKI Biomarkers
Plasma SO2 was higher in patients with new-onset AKI (Table 3) and increased with AKI severity (Figure 1). Plasma SO2, urine NGAL, and [TIMP-2]–[IGFBP7] were associated with the incidence of AKI in the univariate
Table 1 Baseline Characteristics of Patients Stratified by New-Onset Acute Kidney Injury

| Variables                      | All Patients | Non-AKI     | New-Onset AKI | P value |
|--------------------------------|--------------|-------------|---------------|---------|
|                                | N=167        | N=106       | N=61          |         |
| Male n (%)                     | 97 (58.1)    | 64 (60.4)   | 33 (54.1)     | 0.428   |
| Age (years)                    | 66 (57–74)   | 65 (56–72)  | 69 (59–78)    | 0.024   |
| BMI (kg/m²)                    | 24.0 (21.0–26.1) | 23.7 (20.8–26.0) | 24.7 (22.4–26.3) | 0.053   |
| Chronic comorbidities n (%)    |              |             |               |         |
| Hypertension                   | 98 (58.7)    | 53 (50.0)   | 45 (73.8)     | 0.003   |
| Diabetes                       | 46 (27.5)    | 25 (23.6)   | 21 (34.4)     | 0.131   |
| Coronary heart disease         | 33 (19.8)    | 20 (18.9)   | 13 (21.3)     | 0.703   |
| COPD/asthma                    | 10 (6.0)     | 7 (6.6)     | 3 (4.9)       | 0.658   |
| Chronic liver disease          | 8 (4.8)      | 7 (6.6)     | 1 (1.6)       | 0.148   |
| Surgical specialty n (%)       |              |             |               |         |
| General                        | 127 (76.0)   | 86 (81.1)   | 41 (67.2)     | 0.042   |
| Orthopedic                     | 8 (4.8)      | 3 (2.8)     | 5 (8.2)       | 0.118   |
| Thoracic                       | 13 (7.8)     | 9 (8.5)     | 4 (6.6)       | 0.653   |
| Gynecology                     | 8 (4.8)      | 3 (2.8)     | 5 (8.2)       | 0.118   |
| Others                         | 11 (6.6)     | 5 (4.7)     | 6 (9.8)       | 0.199   |
| ASA classification n (%)       |              |             |               |         |
| 1–2                            | 46 (27.4)    | 32 (30.2)   | 14 (23.0)     | 0.313   |
| 3                              | 101 (60.5)   | 67 (63.2)   | 34 (5.7)      | 0.342   |
| 4–5                            | 20 (12.0)    | 7 (6.6)     | 13 (21.3)     | 0.010   |
| Operation time (hours)         |              |             |               |         |
| 4.1 (2.3–7.2)                  | 3.6 (2.3–6.3) | 5.0 (2.6–7.9) | 0.257   |
| Estimated blood loss (mL)      | 200 (100–600) | 100 (50–400) | 200 (100–800) | 0.010   |
| Fluid balance in operation (mL/h) | 505 (358–850) | 478 (357–820) | 521 (360–913) | 0.492   |
| APACHE II                      | 13 (9–18)    | 12 (9–16)   | 16 (10–19)    | 0.064   |
| SOFA                           | 3 (1–5)      | 2 (1–4)     | 4 (1–5)       | 0.015   |
| Sepsis n (%)                   | 11 (6.6)     | 5 (4.7)     | 6 (9.8)       | 0.199   |
| Lactate (mmol/L)               | 1.2 (0.9–1.9) | 1.2 (0.9–1.6) | 1.5 (1.0–2.2) | 0.078   |
| Mechanical ventilation n (%)   | 124 (74.3)   | 78 (73.6)   | 46 (75.4)     | 0.795   |
| Use of vasopressors n (%)      | 70 (41.9)    | 36 (34.0)   | 34 (55.7)     | 0.006   |
| Baseline creatinine (µmol/L)   | 59.1 (48.8–69.1) | 57.3 (47.0–66.0) | 64.5 (53.0–79.2) | 0.009   |
| Use of nephrotoxic drugs n (%) | 17 (10.2)    | 10 (9.4)    | 7 (11.5)      | 0.674   |

Note: Continuous variables are presented as median and interquartile range.

Abbreviations: AKI, acute kidney injury; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; APACHE II, acute physiologic and chronic health evaluation II; SOFA, sequential organ failure assessment.

Analysis (Table S1). Figure 2 shows the AUCs for plasma SO₂ and established AKI biomarkers. Plasma SO₂ had an AUC of 0.771 (95% confidence interval [CI]: 0.700–0.832, p<0.001) for predicting AKI, with an optimal cutoff value of 15.0 µmol/l. In contrast, NGAL and [TIMP-2]-[IGFBP7] showed lower performance in predicting AKI, with AUCs of 0.648 (95% CI: 0.570–0.720, p=0.001) and 0.655 (95% CI: 0.578–0.727, p<0.001), respectively. The statistical significance of the differences between the AUCs of SO₂ and AKI biomarkers was confirmed with the DeLong method (p=0.045 for plasma SO₂ and NGAL; p=0.036 for plasma SO₂ and [TIMP-2]-[IGFBP7]).

Predictive Superiority of Plasma SO₂ Over Other Biomarkers in the AKI Risk Model

In the univariate analysis, hypertension, estimated blood loss, baseline creatinine, SOFA score, and use of vasopressors were associated with the occurrence of AKI. Of these variables, hypertension, estimated blood loss, and baseline
creatinine were retained for the final model (Table S2). The calibration of the model was confirmed with the Hosmer–Lemeshow goodness-of-fit test (p>0.05). This clinical model predicted AKI with an AUC of 0.782 (95% CI: 0.712–0.843, p<0.001).

The inclusion of SO₂ significantly improved the predictive ability of the clinical model for AKI, supported by NRI [0.282 (0.043–0.583), p=0.038] and IDI [0.145 (0.088–0.202), p<0.001] analyses and Delong’s test (p=0.013) (Table 4). In contrast, the model was not improved by including NGAL and [TIMP-2]-[IGFBP7]. In the multivariate logistic regression analysis, the risk of AKI based on the clinical–plasma SO₂ risk prediction model was 1/(1 + e−z), z=0.005 +1.171×plasma SO₂ +3.256×hypertension +1.001×estimated blood loss. The optimal cutoff probability was 0.395; patients with a probability higher than this value were at risk of developing AKI after major noncardiac surgery.

Figure 3 shows the decision curves of 4 models (clinical, clinical–SO₂, clinical–NGAL, and clinical–[TIMP-2]-[IGFBP7]) for predicting AKI. The clinical–SO₂ model had the highest net benefit at 10%–60% of the probability threshold; that is, if a patient with a risk of AKI between 10% and 60% warranted further therapy (such as hemodynamic monitoring or preventive interventions), AKI screening using clinical–SO₂ would have the most benefit for study participants after taking into account cost, adverse effects, and other negative factors in the screening tests. Although the net benefit of the 4 models tended to be similar with increasing probability threshold, they diverged significantly at low probability threshold.

**Sensitivity Analysis**

As SO₂ is produced by neutrophils, the risk prediction analysis was repeated after excluding patients with white blood count <4×10⁹/l (n=7). The predictive value of SO₂ was enhanced when it was incorporated into the model with clinical variables (AUC=0.780 and 0.855, respectively; p<0.001).

**Discussion**

This is the first study to investigate the predictive utility of endogenous SO₂ for AKI in critically ill patients. We found that plasma concentration of SO₂ was significantly higher in patients who developed AKI after major noncardiac surgery than in those who did not, and was independently associated with the risk of AKI. Our results are novel because they show the plasma SO₂ profile of critically ill patients and

### Table 2 Outcomes Between Patients with and without New-Onset AKI

| Variables                  | All Patients | Non-AKI | New Onset AKI | P value |
|----------------------------|--------------|---------|---------------|---------|
| MV (hours)                 | N=167        | N=106   | N=61          |         |
| LOS in ICU (days)          | 14.8 (4.0–37.4) | 14.0 (3.5–34.0) | 17.6 (10.6–46) | 0.040   |
| LOS in hospital (days)     | 3 (2–6)      | 2 (2–4) | 6 (3–8)       | <0.001  |
| ICU mortality              | 20 (13–30)   | 19 (13–30) | 20 (14–31) | 0.656   |
| Hospital mortality         | 3 (1.8)      | 0 (0)   | 3 (4.9)       | 0.021   |
|                           | 4 (2.4)      | 0 (0)   | 4 (6.6)       | 0.008   |

**Note:** Continuous variables are presented as median and interquartile range.

**Abbreviations:** MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit.

### Table 3 Levels of Plasma SO₂ and Urine Biomarkers in New-Onset AKI and Non-AKI Patients

| Variables                  | All Patients | Non-AKI | New Onset AKI | P value |
|----------------------------|--------------|---------|---------------|---------|
| Plasma SO₂ (µmol/l)        | N=167        | N=106   | N=61          |         |
|                           | 11.9 (6.9–15.6) | 8.9 (3.4–14.2) | 15.5 (11.9–18.9) | <0.001  |
| Urine NGAL (ng/mL)         | 23.4 (13.0–60.7) | 18.0 (12.4–37.4) | 45.7 (15.5–87.8) | 0.002   |
| Urine TIMP-2 (ng/mL)       | 3.3 (2.2–4.5) | 3.1 (2.2–4.2) | 3.6 (2.5–4.9) | 0.024   |
| Urine IGFBP7 (ng/mL)       | 86.1 (70.0–106.0) | 82.4 (65.7–97.2) | 99.0 (82.8–115.5) | 0.001   |
| [TIMP-2]-[IGFBP7] (ng/mL)/ |
| [1000]                     | 0.33 (0.2–0.4) | 0.3 (0.2–0.4) | 0.4 (0.3–0.5) | 0.001   |

**Note:** Continuous variables are presented as median and interquartile range.

**Abbreviations:** SO₂, Sulfur dioxide; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7.
demonstrate its predictive capacity for AKI, which was superior to that of urine NGAL and [TIMP-2]-[IGFBP7] and enhanced that of a conventional clinical model, as supported by IDI and NRI analyses and DCA.

AKI is a common postoperative complication that is independently associated with poor prognosis in critically ill patients who have undergone surgery. However, early identification of high-risk patients can lead to initiation of preventive measures (eg, avoiding nephrotoxins, volume management, and individualized hemodynamic resuscitation) before renal damage occurs, which can reduce mortality and improve clinical outcomes. The predictive ability of plasma SO$_2$ was compared to that of other AKI biomarkers. The most widely used biomarkers are TIMP-2 and IGFBP7, which are expressed in tubular cells in response to DNA damage and are markers for G1 arrest. However, this has not been validated in different populations, which is important as AKI can be caused by different factors. NGAL, the most extensively studied AKI biomarker, is expressed in many tissues and the level in urine is elevated as early as 3 h after tubular injury. However, NGAL expression lacks specificity as a biomarker because it increases with age and infection and is higher in females. In the present study, both [TIMP-2]-[IGFBP7] and NGAL showed limit predictive value for AKI, possibly because in our cohort of postoperative patients, only a minority had sepsis; meanwhile, AKI-induced elevation in urinary TIMP-2/IGFBP7 level is

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**Figure 1** Discrimination of plasma SO$_2$ between non-AKI and AKI of different severities. ***Comparison between non-AKI and AKI of different severities (p<0.001).**

**Figure 2** Predictive value of plasma SO$_2$ and urine biomarkers for new-onset AKI. **Abbreviations:** AKI, acute kidney injury; SO$_2$, Sulfur dioxide; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7.
associated with increased kidney filtration, which is more commonly associated with sepsis than with hemorrhage.\textsuperscript{38} Our multivariate logistic regression analysis suggested that estimated blood loss but not sepsis was a risk factor for new-onset AKI; thus, AKI in our cohort was mostly caused by ischemia, which is expected to affect TIMP-2 and GFDP7 levels. The upregulation of NGAL in AKI is positively correlated with the severity of kidney injury,\textsuperscript{34} however, most AKI patients in our cohort had only mild injury and therefore, the increase in NGAL expression was relatively insignificant. In our study, plasma SO\(_2\) showed better predictive performance than urine [TIMP-2]-[IGFBP7] and NGAL for the development of AKI in postoperative critically ill patients.

**Figure 3** Decision curve for prediction of new-onset AKI using different prediction models.

**Abbreviations:** AKI, acute kidney injury; SO\(_2\), Sulfur dioxide; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7.

SO\(_2\) has recently been identified as a gasotransmitter in the cardiovascular system. Previously studies reported endogenous SO\(_2\) synthesis pathways in the heart, stomach, lung, kidney, spleen, liver, and retina in mammals that play an important role in systemic homeostasis.\textsuperscript{12} SO\(_2\) was identified as a key regulator of inflammation in the pathogenesis of cardiovascular, ophthalmologic, and neurologic diseases\textsuperscript{39–41} that acts by attenuating tumor necrosis factor (TNF)-\(\alpha\)-induced inhibitor of nuclear factor (NF)-kappaB (I\(\kappa\)B) phosphorylation and degradation and NF-\(\kappa\)B p65 phosphorylation.\textsuperscript{42,43} Elevated levels of endogenous SO\(_2\) were detected in patients with acute early edge infection and postural tachycardia syndrome, suggesting that it is an early and sensitive indicator of inflammation.\textsuperscript{19,44} In the pathophysiology of AKI, inflammation induces endothelial and tubular cell injury;\textsuperscript{45} we therefore speculated that SO\(_2\) could be a biomarker of AKI, although the plasma level of SO\(_2\) in critical care patients and its relationship to AKI has not been previously reported. In the present study, we firstly revealed the existence of the plasma endogenous SO\(_2\) in critical ill patients and the elevation of SO\(_2\) demonstrated a good predictive performance in detecting new-onset AKI. Studies on AKI based on predictive analytics\textsuperscript{46–49} have used only conventional biomarkers or clinical variables, the novelty of our study is not only demonstrate a promising biomarker but also contribute to the pathophysiologic mechanisms of AKI.

Our study had some limitations. Firstly, it was a single-center study involving noncardiac postoperative patients, which limits the external validity of our findings.

**Table 4** Comparison of the ROC Curves, NRI and IDI of Combination vs Clinic Models in Predicting AKI

| Combination          | DeLong | NRI   | \(p\) for NRI | IDI   | \(p\) for IDI |
|---------------------|--------|-------|---------------|-------|---------------|
| Clinic - SO\(_2\) vs Clinic | 0.014  | 0.282 | 0.039         | 0.145 | <0.001        |
| Clinic - NGAL vs Clinic | 0.266  | 0.219 | 0.065         | 0.060 | 0.004         |
| Clinic - [TIMP-2] - [IGFBP7] vs Clinic | 0.158  | 0.066 | 0.510         | 0.025 | 0.035         |

**Abbreviations:** ROC, receiver operator characteristic; NRI, net reclassification improvement; IDI, integrated discrimination improvement; SO\(_2\), Sulfur dioxide; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7.
Secondly, we did not conduct a sample size analysis because of the absence of relevant data. Thirdly, we did not have a validation cohort and as the predictive model was evaluated in the same cohort as that used for model training, the possibility of overfitting cannot be excluded. Finally, we did not analyze time-dependent variables or include dynamic predictions of AKI after the operation, which should be addressed in future studies.

**Conclusion**

In summary, plasma SO2 level was significantly higher in patients who developed new-onset AKI within 72 h of ICU admission after major noncardiac surgery than in those who did not develop AKI. Additionally, plasma SO2 was a better predictor of AKI in our cohort than established AKI biomarkers such as urine [TIMP-2]-[IGFBP7] and NGAL. The predictive ability of SO2 was enhanced in combination with clinical variables. These findings provide a basis for further investigations on the role of SO2 in the pathogenesis of AKI in critically ill patients.

**Abbreviations**

SO2, Sulfur dioxide; AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7; ROC, receiver operator characteristic; DCA, decision curve analysis; IDI, integrated discrimination improvement; NRI, net reclassification improvement; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CKD, chronic kidney disease; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CRF, case report forms; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment. HPLC, high-performance liquid chromatography analysis.

**Data Sharing Statement**

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

**Ethics Approval and Informed Consent**

The study was approved by the human ethics committee of Beijing Chao-Yang hospital, Capital Medical University (Beijing, China). The chief ethics number was 2020-ke-236. Informed consent from patients or their next of kin was obtained before patients joined in the study. The study followed the ethical principles of the Declaration of Helsinki 1964.

**Consent for Publication**

The manuscript does not contain any individual person’s data in any form.

**Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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**Disclosure**

The authors declare that they have no competing interests.

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