Biomarkers for prediction of acute kidney injury after Cardiac and Non-cardiac Elective Surgeries: A comparative observational study

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Abstract

Background: Acute kidney injury (AKI) is a frequent postoperative (PO) complication for cardiac surgery; however, its co-incidence after non-cardiac surgery (NCS) is indefinite.

Objectives: To determine the predictors for postoperative (PO-AKI) among patients undergoing NCS.

Patients and methods: 413 patients aged >40-y underwent NCS procedures requiring longer than 1h and 205 patients underwent CABG surgery as a control group for AKI incidence only. Blood samples were obtained for the estimation of serum creatinine and calculation of the neutrophil/lymphocyte ratio (NLR). All patients received general inhalational anesthesia according to the surgical procedure. PO-AKI was diagnosed according to the guidelines of the European Renal Best Practice. Study outcomes included the incidence of PO-AKI and its relation to patient's data.

Results: The incidence of PO-AKI was 10.4% and AKI patients were significantly older, obese and had lower preoperative hemoglobin concentration (HBC). Seven patients (1.7%) required packed RBCs transfusion and 32 patients (7.7%) developed intraoperative hypotension (IOH) with significantly lower frequencies among No-AKI patients. The NLR was significantly higher in samples of AKI than in No-AKI patients. Regression analysis defined NLR and IOH as significant predictors for PO-AKI. Paired-Sample analysis showed a significant (P=0.01) difference between the area under the curve in favor of NLR.

Conclusion: AKI after is more frequent among older obese patients with low HBC. Excessive blood loss, IOH and long operative time increased the risk of PO-AKI. Preoperative NLR showed high predictive performance for PO-AKI and might be considered ~~as~~ promising routine, cheap and feasible test for distinguishing patients vulnerable to develop AKI.

Keywords: Postoperative acute kidney injury; Non-cardiac surgery; Neutrophil/lymphocyte ratio; Intraoperative hypotension; Preoperative prediction .

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Introduction

Acute kidney injury (AKI) is a common complication of cardiac surgeries **(He et al., 2022)**, burns **(Kim et al., 2019)**, sepsis, and with contrast-requiring diagnostic or therapeutic interventions especially percutaneous coronary interventions **(Ma et al., 2022)**. However, AKI was reported after major non-cardiac surgeries (NCS), especially thoracic, orthopedic and urological surgeries with similar risk factors and outcome associations across surgery types **(Grams et al., 2016)**.

Sun et al., (2023) observed 21 risk factors for perioperative AKI, but the most important factors are the presence of a history of kidney disease, operation time >180 min, and preoperative estimated glomerular filtration rate (eGFR). Postoperative AKI (PO-AKI) may occur before or after 48-h PO and so categorized as early or late PO-AKI **(Ishikawa et al., 2022)**.

The pathophysiology of AKI is multifactorial, damage of the resident immune and intrinsic renal cells by the insult as ischemia, hypoxia, drugs or toxins initiates a mortal cascade for renal tubular cells through recursion of immune cells through the release of chemokines **(Deng et al., 2022)**, these cells infiltrate the renal tissue, promote macrophage polarity conversion, and various programmed deaths, phenotypic conversion and cycle arrest of the intrinsic **(Chen et al., 2022)**.

This inflammatory cascade aggravates injury to tubular epithelial cells and reduces the GFR during the extension phase, which is the most promising phase for successful treatment and intervention of AKI **(Gerhardt & McMahon, 2022)**. The relevant ratios of different cell types in peripheral blood can reflect the inflammation **(Ilonzo et al., 2021)** and neutrophil-to-lymphocyte ratio (NLR), a readily available marker of inflammation and physiologic stress showed strong associations with early onset, progression or recovery of AKI **(Schiffl & Lang, 2023)**. This work tried to evaluate the predictors for the possibility of the development of postoperative AKI (PO-AKI) among patients older than 40-y old and undergoing long-duration NCS.

Patients and methods

Design: Prospective non-randomized comparative multicenter study

Setting: Departments of Anesthesia & ICU, Medical Biochemistry, Faculty of Medicine, Benha & Tanta Universities in conjunction with multiple private hospitals.

Patients: All patients assigned for non-cardiac surgical procedures were evaluated clinically and using routine lab investigations for legibility for inclusion in the study.

Inclusion criteria: Patients older than 40-y, assigned for NCS procedures requiring operative time longer than 1h, free of exclusion criteria were enrolled in the study (NCS-Group). For comparative purposes and considering the established high prevalence of PO-AKI after cardiac surgeries **(Zakkar et al., 2016; Oprea et al., 2018; Wang et al., 2020)**, 205 patients assigned for coronary artery bypass grafting (CABG) surgery with cardiopulmonary pump (CBP) and fulfilling the inclusion criteria were included as a positive control group (CABG-Group) for comparison for incidence of PO-AKI only.

Exclusion criteria: Age younger than 40-y, indications for a surgical procedure requiring <1h operative time, emergency surgery, inflammatory disorders, autoimmune diseases, maintenance on immunosuppressant therapy, maintenance on drugs inducing bone marrow depression, endocrinopathy, coagulopathy, and refusal to participate in the study are the exclusion criteria **Ethical Considerations:** The study protocol was approved to be started in Jan 2021 and the final approval was obtained after completing the case collection in July 2022.

Anesthetic procedure

A) NCS-Group

Midazolam (0.03–0.05 mg/kg) was used for premedication and non-invasive monitors for heart rate (HR), systolic and diastolic blood pressure (SBP, DBP) and oxygen saturation (Sp_{O2}). Patients were pre-oxygenated for 3-5 min with 100% O_2, anesthesia was induced by thiopental sodium (3-5 mg/kg), fentanyl (3-5 µg/kg) and pancuronium (0.1 mg/kg), then tracheal intubation was aided by gentle tracheal pressure and endotracheal tube measuring 6.5 mm was inserted. Tidal volume was set at 8 ml/kg, respiratory rate at 12 breath/min. Anesthesia was maintained with sevoflurane in a mixture of oxygen/air (1:1) and fentanyl and pancuronium were provided as boluses according to the requirements. Muscle relaxant was reversed using neostigmine 0.05 mg/kg with atropine 0.01 mg/kg.

B) CABG-Group

On arrival to the theater, patients were pre-medicated using midazolam (0.03–0.05 mg/kg), central venous catheter and arterial cannula were inserted in the internal jugular vein and radial artery under local anesthesia. Standard invasive monitors were attached for continuous monitoring of HR, SBP, DBP and central venous pressure (CVP). Induction of anesthesia carried out using thiopental sodium (3-5 mg/kg), fentanyl (3-5 µg/kg) and pancuronium (0.1 mg/kg) and controlled mechanical ventilation was applied to keep $PaCO_2$ at a range of 35-45 mmHg. Maintenance anesthesia was provided as sevoflurane with a mixture of oxygen/air (1:1), atracurium (5-10 µg/kg/minute) and fentanyl was provided as boluses according to the requirements. Initial dose of anticoagulant was provided as heparin sulphate (4 mg/kg) with supplemental dose to keep the activated clotting time >400 seconds and then CPB was established using membrane oxygenator, roller pump and non-pulsatile flow with a flow rate of 2.4 L/min/m^2. Anesthesia was maintained on CPB by propofol 3-4 mg/kg/h, systemic temperature was maintained in the range of 34-35°C. Blood cardioplegia, consisted of 1:1 volume of normal saline and blood and composed of potassium chloride 30 mEq/L, lidocaine 120 mg/L and sodium bicarbonate 26 mEq/L was started as 10 ml/kg with boluses of 5 ml/kg every 20-30 minutes. If inotropics were indicated it was provided as dobutamine (3-5 µg/kg/minute).

Intraoperative monitoring

- As previously defined by **Cheung et al., (2015)** intraoperative hypotension (IOH) was defined as systolic blood pressure <90 mm Hg for >5 minutes or decreased MAP by 35% of the preoperative measures and intraoperative bradycardia was defined as HR of <60 beats/min for >5 minutes.
- IOH was treated with the rapid infusion of lactated Ringer’s solution and intravenous boluses of ephedrine and IO bradycardia was managed in a hemodynamically unstable patient by intravenous atropine 0.5 mg

that was repeated up to a total dose of 3mg, while in hemodynamically stable patient by glycopyrrolate 0.2 mg that was repeated up to a total of 1 mg.

- Intraoperative packed RBC transfusion was provided if blood loss was in the range of 750-1500 ml with compensatory tachycardia and pre-existing anemia or concomitant cardiac or pulmonary disease **(British Committee for Standards in Hematology, 2006)**.

Laboratory workup

Blood samples were obtained under complete aseptic conditions from the antecubital vein and were divided into two parts:

- One part was put in a tube containing tri-potassium ethylenediaminetetraacetate (K3-EDTA) for determination of hemoglobin concentration (HBC), complete blood count (CBC) and differential leucocytic count for calculation of the neutrophil/lymphocyte ratio (NLR) **(Jo et al., 2011)**. CBC was repeated immediately at the end of surgery (Immediate PO), 12-h and 72-h PO for calculation of NLR
- Another part was centrifuged to obtain serum for estimation of serum creatinine (Cr) using the Jaffe-based creatinine-picrate formation in an alkaline medium **(Jaffe, 1886; Peake & Whiting, 2006)** to determine baseline serum Cr that was re-estimated immediate, 12-h and 72-h PO.

Diagnostic criteria for AKI

According to the European Renal Best Practice for diagnosis and severity staging of AKI **(ERBP, 2012)** AKI Stage I was diagnosed if serum Cr level was increased by 1.5-1.9 times the baseline level or by >0.3 mg/dl above the baseline levels; Stage II if serum Cr level was increased by 2-2.9 times the baseline level and Stage III if there was increased serum Cr level by >3 times the baseline level.

Study outcomes

1. The primary outcome is the incidence of PO-AKI among patients undergoing NCS or CABG surgery
2. The secondary outcomes include
   - The relation between PO-AKI in NCS patients and patients' demographic, clinical and lab data
   - The predictors for PO-AKI among variate showed significant relation to its incidence

Statistical analysis

The incidence of PO-AKI was compared between patients undergoing NCS and CABG only. Then, the data of patients undergoing NCS were categorized according to development of PO-AKI as AKI and No-AKI groups. Results were analyzed using t-test for independent means, paired t-test for dependent means and Chi-square test (X^2 test). Pearson's correlation analysis was used to determine the variate correlated with the AKI incidence and these variates were evaluated as predictors for AKI using Univariate and Multivariate Regression analyses. The significance of these predictors was assured using the Receiver Operating Characteristic (ROC) curve as judged by area under ROC curve (AUROC) and the difference between the AUROCs was assessed using the paired-analysis of difference between AUROC using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA). Significance was determined at the cutoff point of P<0.05.

Results

During the study duration, 413 patients underwent NCS and 205 underwent CABG and PO-AKI was detected in 90 patients, 43 NCS patients (10.4%) and 47 CABG patients (22.9%) with significant (P<0.001) higher incidence of PO-AKI among CABG patients (**Fig. 1 & 2**).

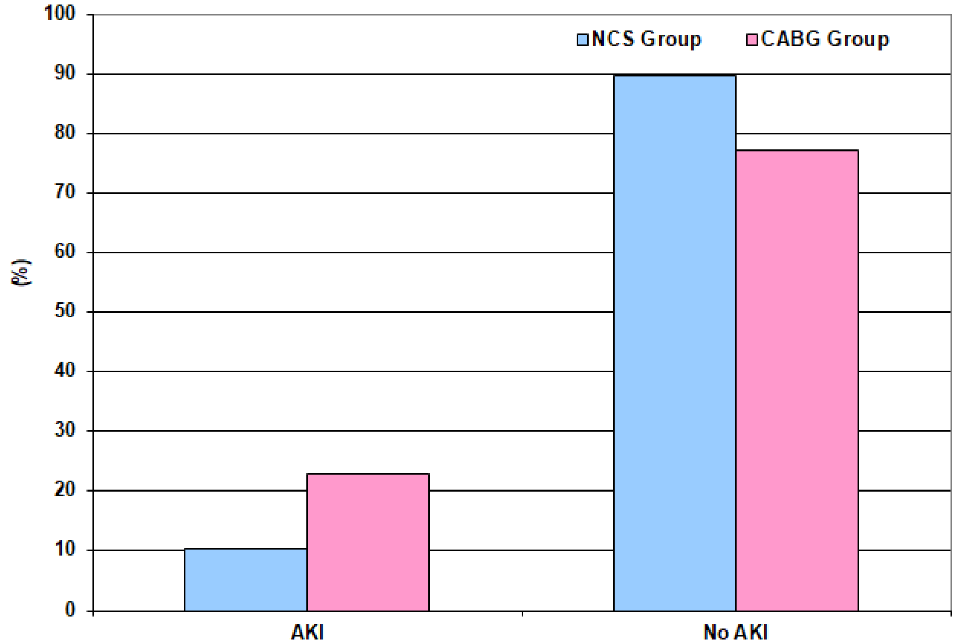

Fig.1. The incidence of PO-AKI among studied patients

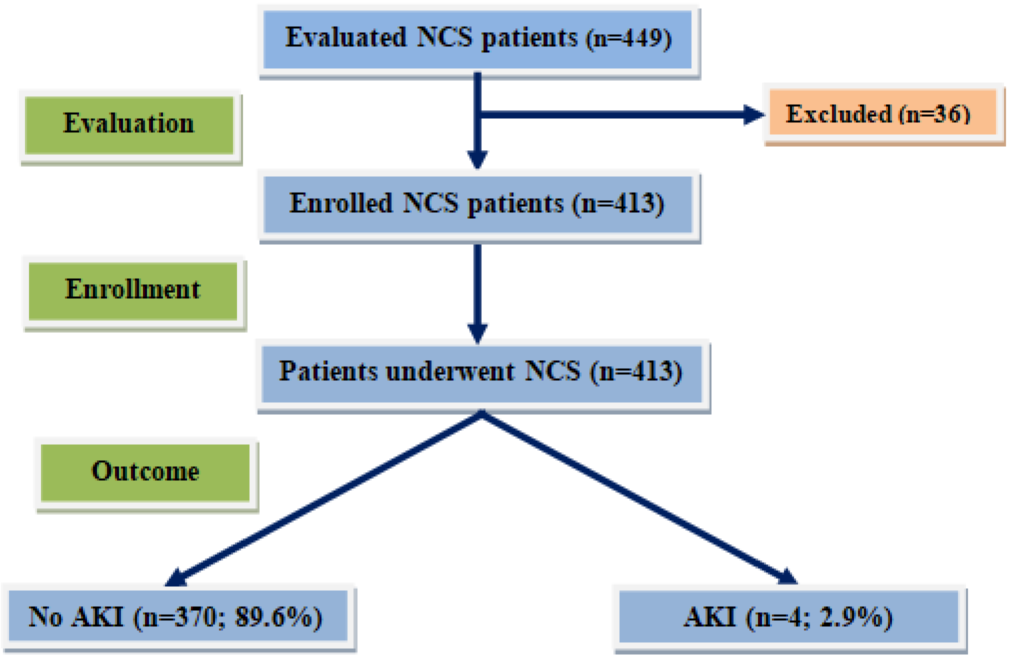

Fig.2. Study Flow Chart

Serum Cr levels showed significantly progressive increases in immediate, 12-h and 72-h PO in comparison to preoperative levels and to each preceding measure in all patients underwent NCS with significantly (P<0.001) higher serum Cr levels estimated in samples of AKI than in NO-AKI patients (**Table 1, Fig. 3**).

Table 1. Serum Cr (mg/ml) levels estimated during 72-h PO period

Data	No-AKI patients (n=370)	AKI patients (n=43)	P-value
Preoperative	0.73±0.21	0.79±0.2	0.058
Immediate PO	0.8±0.2	1±0.36	<0.001
12-h PO	0.84±0.21	1.25±0.53	<0.001
72-h PO	0.88±0.22	1.59±0.56	<0.001

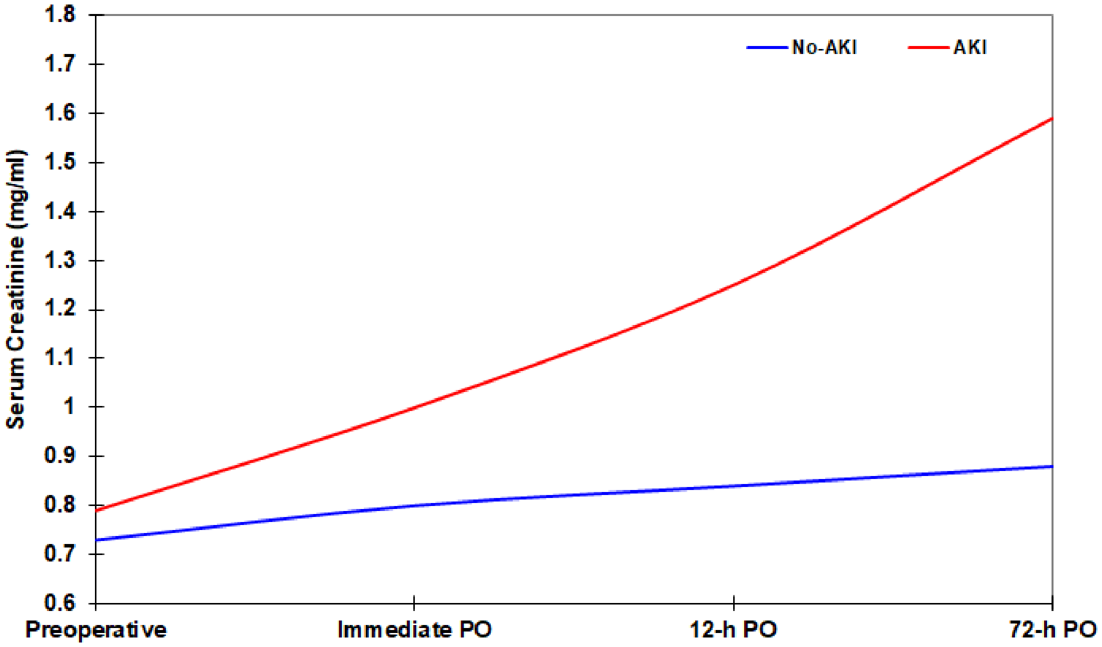

Fig.3. Mean serum creatinine levels estimated in patients categorized according to development of AKI

Estimated serum Cr in immediate PO samples of AKI patients defined one patient (2.3%) of AKI grade II and 42 patients of stage-I with median increase of serum Cr of 1.2 [IQR=1.08-1.34]. At 12-h PO, 5 patients (11.6%) progressed to AKI stage-II with median increase of serum Cr of 1.46 [IQR= 1.22-1.84] and at 72-h, one patient progressed to AKI stage-III and 21 patients to AKI stage-II with a median increase of serum Cr of 2.02 [IQR= 1.7-2.21] as shown in (**Fig.4**).

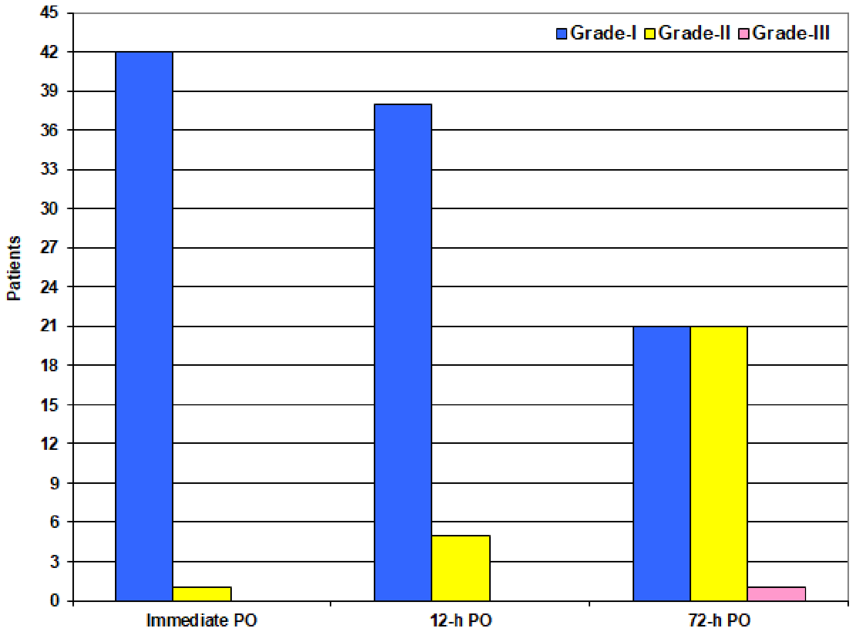

Fig.4. Distribution of AKI patients according to AKI grade during 72-h PO

AKI patients were significantly older and showed higher BMI and lower HBC in comparison to No-AKI patients, while other patients' data showed non-significant differences between AKI and No-AKI patients as shown in (**Table 2**).

Table 2. Enrolment data of NCS patients categorized according to development of AKI

Data		**No AKI patients (n=370)**	**AKI patients (n=43)**	**P-value**
Age (years)		60±8.7	64±8.2	0.002
Gender	**Males**	257 (69.5%)	35 (81.4%)	0.104
	Females	113 (30.5%)	8 (18.6%)	
Body mass index (kg/m^2)	**<30**	244 (65.9%)	22 (51.2%)	0.071
	>30	126 (34.1%)	21 (48.8%)	
	Average	29.5±2.3	30.3±2.8	0.017
ASA grade	**I**	224 (60.5%)	27 (72.8%)	0.795
	II	119 (32.2%)	12 (27.9%)	
	III	27 (7.3%)	4 (9.3%)	
Surgical procedure	**Abdominal**	161 (43.5%)	22 (51.1%)	0.504
	Vascular	63 (17%)	10 (23.3%)	
	Orthopedic	64 (17.3%)	5 (11.6%)	
	Plastic	44 (11.9%)	3 (7%)	
	ENT	38 (10.3%)	3 (7%)	
Preoperative HBC (g/dl)		11.8±1.5	10.9±1.3	0.0008

P-value <0.05 indicates significant inter-group differences

All operative data showed significant differences in favor of No-AKI patients. Only 7 patients (1.7%) required transfusion of packed RBCs and 32 patients (7.7%) developed IOH with significantly lower frequencies among No-AKI patients (**Table 3).**

Table 3. Operative data of patients who had NCS categorized according to AKI development

Data	No-AKI patients (n=370)	AKI patients (n=43)	P-value
Operative time (min)	152.2±26.8	165.3±22.5	0.0011
Anesthesia time (min)	171.4±30	183±24	0.0072
Operative blood loss (ml)	561±85	592±137	0.019
Patients required RBCs transfusion	4 (1.1%)	3 (7%)	0.0045
Number of patients developed IOH	20 (5.4%)	12 (27.9%)	<0.001

The calculated NLR showed time-course progressive increase during the 72-h PO period in samples of all patients in comparison to preoperative ratio with significantly higher ratios in samples of AKI than No-AKI patients (**Table 4, Fig. 5**).

Table 4. Time-course change of the calculated NLR in samples of patients had NCS and were categorized according to development of AKI

Data	No AKI patients (n=370)	AKI patients (n=43)	P-value
Preoperative	1.02±0.18	1.2±0.27	<0.001
Immediate PO	1.29±0.21	1.81±0.24	<0.001
12-h PO	1.5±0.25	2.26±0.26	<0.001
72-h PO	1.68±0.27	2.44±0.22	<0.001

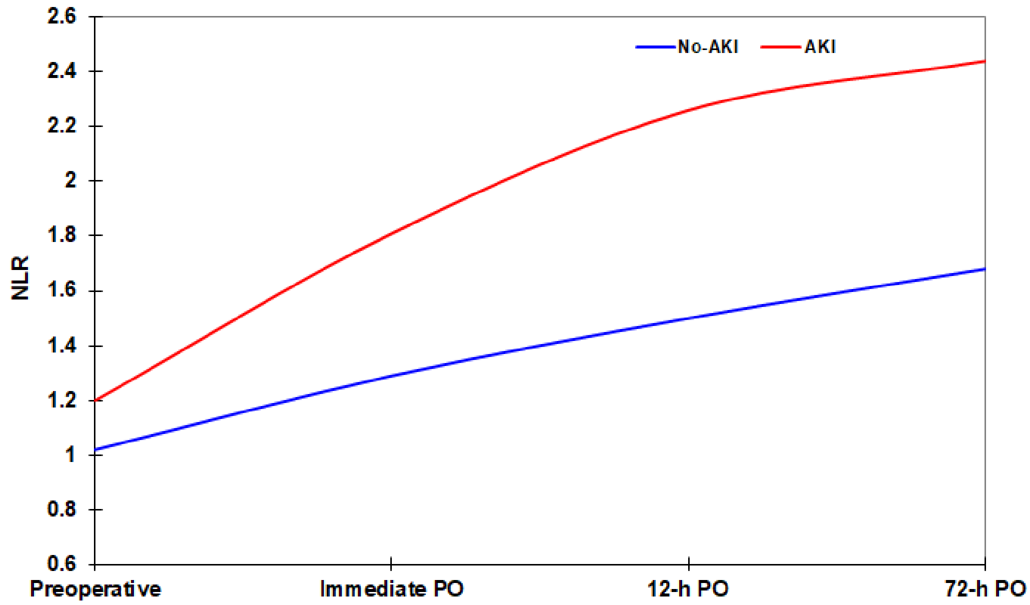

Fig.5. Mean NLR calculated for patients categorized according to development of AKI

The incidence of PO-AKI showed positive significant correlation with old age, male gender, high BMI and NLR, long operative and anesthesia times, development of IOH and excessive blood loss with subsequent need for transfusion of packed RBC, while the relation between the incidence of PO-AKI and low HBC was negative significant. Regression analysis of the correlated variate excluded anesthesia time, intraoperative blood loss, preoperative HBC and male gender as predictors for PO-AKI, while stratified the other variate according to the significance of the coefficient in descending order of significance as follows: high preoperative NLR, IOH, need for transfusion, long operative time, old age and high BMI as predictors for PO-AKI (**Table 5**).

Table 5. Statistical analyses of preoperative and intraoperative variate as predictors for PO-AKI

Preoperative data			**Intraoperative data**		
Pearson's Correlation analysis					
Variate	"r"	P	Variate	"r"	P
Age	0.141	0.004	Operative time	0.150	0.002
Male gender	0.112	0.023	Anesthesia time	0.120	0.015
BMI	0.104	0.034	IO hypotension	0.257	<0.001
Hemoglobin	-0.134	0.006	IO blood loss	0.102	0.038
NLR	0.284	<0.001	Need for transfusion	0.139	0.005
Univariate Regression analysis					
Variate	β	P	Variate	β	P
Age	0.129	0.004	Operative time	0.148	0.001
Male gender	0.080	0.073	Anesthesia time	0.005	0.985
BMI	0.095	0.032	IO hypotension	0.251	<0.001
Hemoglobin	0.077	0.087	IO blood loss	0.015	0.777
NLR	0.306	<0.001	Need for transfusion	0.184	<0.001

Multivariate regression analysis defined NLR (β=0.282, P<0.001) and IOH (β=0.255, P<0.001) as the significant predictors for the development of PO-AKI, while excluded old age, high BMI and long operative time as predictors for PO-AKI. ROC curve analysis assured these results with AUROC= 0.768±0.049 (P<0.001; 95%CI: 0.672-863) for NLR and AUROC=0.613±0.051 (P=0.016; 95%CI: 0.513-0.712) for IOH (**Fig. 6**). Paired-Sample analysis of difference between AUROC for NLR and IOH showed significant (P=0.01) difference between AUROC for both variate in favor of NLR with AUROC difference of 0.155±0.290 (95%CI: 0.037-0.273).

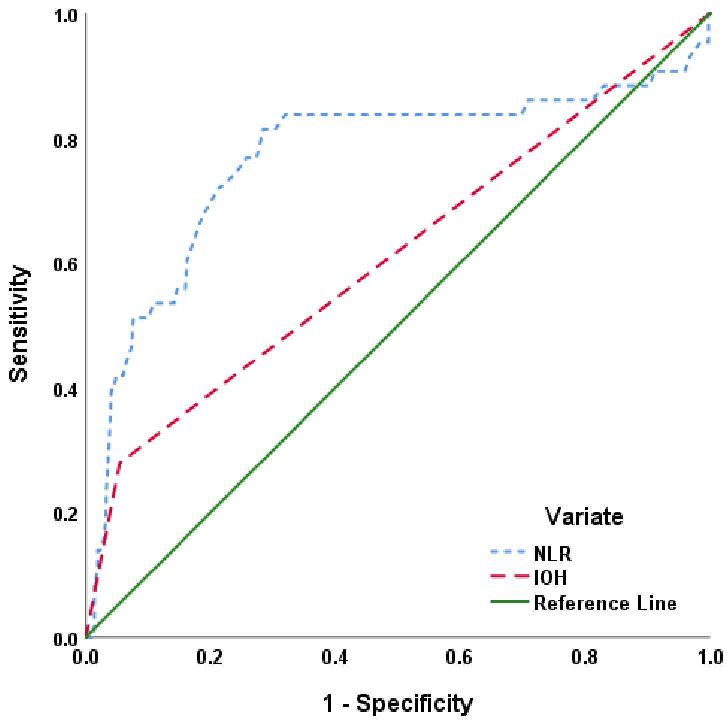

Fig. 6. ROC curve analysis for predictors of AKI after NCS

Discussion

During the study period, 90 patients (14.6%) developed AKI; with significantly higher incidence among patients had CABG (22.9%) than patients had NCS (10.4%). The reported incidence of AKI among patients had NCS go in hand with **Brenton French et al., (2022)** and **Yang et al., (2022)** who reported incidence of AKI of 7.3% and 8.5%, respectively in patients undergoing NCS. Recently, **Sun et al., (2023)** detected an overall prevalence of AKI among patients undergoing NCS of 6.57%.

The calculated NLR showed significantly progressing values during 72-h PO but was higher in AKI than in No-AKI patients. Further, high preoperative NLR using statistical analyses was found to predict AKI development among NCS patients. In line with these findings, **Lu et al., (2021)** in a meta-analysis to evaluate the predictive value of NLR for AKI found high NLR had a significant (P<0.000 01 & 0.000 3) predictive value for AKI in studies with a sample size of ≤ 300 and >300 cases, respectively, irrespective for type of surgery or cases. Thereafter, **Tang et al., (2022)** found preoperative high NLR (NLR≥3.555) was an independent risk factor associated with PO-AKI in patients for NCS under general anesthesia with sensitivity and specificity; 86.4% and 51.9%, respectively. Recently, **Feng et al., (2023)** found that in patients with liver cancer and low NLR the 3-year recurrence-free and overall survival rates were significantly better after postoperative adjuvant trans-catheter arterial chemoembolization and concluded that NLR can provide a reference for patients' selection for such procedure. Further, **Wang et al., (2023)** reported a prevalence of AKI of 5.62% after NCS and NLR ≥ 5 was independently associated with the development of PO-AKI.

Among patients had NCS, the incidence of AKI showed positive significant correlation with IOH, which occurred in 7.7% of NCS patients and

1.7% of total patients required packed RBCs transfusion. In line with these data, **Smischney et al., (2020)** found development of AKI of stage II/III was related to development of PO hypotension down to MAP ≤55 mmHg and MAP of ≤65 mmHg was associated with increased risk of 30-day major adverse cardiac or cerebrovascular events in patients admitted to ICU after NCS. Also, **Milder et al., (2022)** out of a systematic review and meta-analysis demonstrated a significant relation between intraoperative oliguria and the risk of AKI after NCS. However, statistical analyses found preoperative high NLR had higher predictive performance for PO-AKI than IO hypotension and this finding go in hand with **Makevičius et al., (2022)** who found IO hypotension and NLR are associated with PO-AKI, but an NLR>3.5 is the most important predictive factor of PO-AKI.

Further, the incidence of PO-AKI showed positive significant correlation with patients' age, male gender, BMI, type of NCS especially abdominal surgeries and with preoperative hemoglobin concentration with subsequent need for transfusion of packed RBCs. Similarly, **Joshi et al., (2021)** found older age; higher BMI and need for PO ventilation were independent predictors of AKI after elective hepatic resection. Further, **Wilson et al., (2021)** showed that decreased preoperative glomerular filtration rate, perioperative anemia, total number of blood transfusions, re-interventions, and postoperative respiratory complications are the predictors for AKI after NCS.

Thereafter, **Zhou & Liu (2022)** reported non-linearity between IO hemoglobin drop and PO-AKI and found a relationship between creatinine level and development of AKI and both preoperative and perioperative drop of hemoglobin in patients undergoing NCS. Further, **Xie et al., (2022)** using Multivariate logistic regression analysis found older age, chronic diseases, high white blood cells count, serum creatinine, NLR and prognostic nutrition index were independent prognostic factors for sepsis-induced AKI, but high NLR showed higher significance as predictor. Recently, **Privratsky et al., (2023)** in analysis of incidence of AKI in a multicenter retrospective study reported a total incidence rate of 6.6% and found the odds ratios of AKI were 2.06, 1.9, 1.51 and 1 for males older, younger than 50 and females older, younger than 50 years, respectively.

However, statistical analyses found the predictive performance of these predictors for PO-AKI was inferior to the performance of IOH and higher preoperative NLR with a significant difference between AUROC in favor of NLR than IOH. Similarly, **Makevičius et al., (2022)** found IOH and NLR are associated with PO-AKI, but an NLR>3.5 is the most important predictive factor of PO-AKI.

The previously documented diagnostic variates for PO-AKI are the estimated urine output and serum Cr **(ERBP, 2012)**, however, determination of these variate is time consuming **(Silverton et al., 2021)** and serum Cr to achieve the diagnostic levels for AKI, there must be decrease of estimated glomerular filtration rate by about 50% **(Ronco et al., 2017)**, thus causing a significant delay in the diagnosis and treatment **(Delanaye et al., 2017)**. Furthermore, estimation of biomarkers that could predict kidney injury such as urine interleukin-18 and plasma neutrophil gelatinase-associated lipocalin **(Ronco et al., 2019)** is expensive, tedious and requires the availability of ELISA technique, while estimation of NLR is more convenient, cheap and is a routine test performed for all patients. These data in conjunction with the detected high predictive performance of preoperative NLR allow consider it as promising test for distinguishing patients vulnerable to develop AKI.

Conclusion

Postoperative AKI was reported by an incidence of 10.7% among patients undergoing NCS which is high enough to be taken into consideration especially among patients with high-risk factors. However, the predictive performance of these risk factors is inferior to that of the development of IOH, excessive blood loss and long operative time, but the estimation of differential leucocytic count and calculation of NLR before surgery showed higher performance characteristics allowing to distinguish patients liable to develop PO-AKI especially if associated with other preoperative risk factors or with the development of IOH.

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