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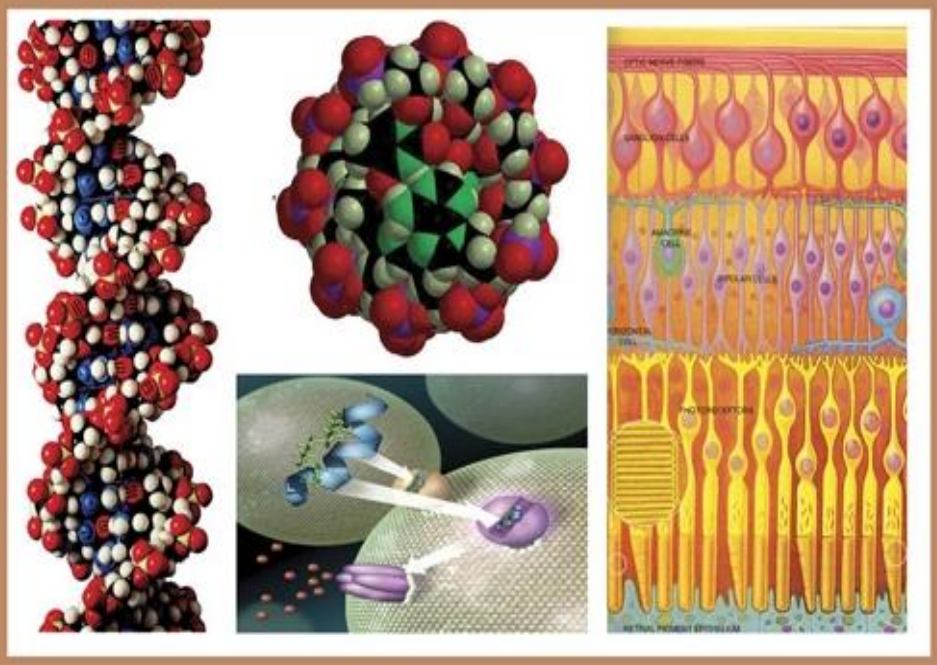

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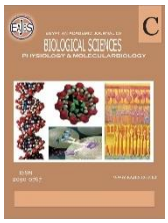

Time To Think of Novel Biomarkers to Detect Perioperative Acute Kidney Injury in Surgical Patients

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ABSTRACT

Background: Perioperative (peri-op) acute kidney injury is impairment of normal baseline renal function during surgery or the immediate postoperative (post-op) period. This study evaluated the incidence of renal tubular damage, severity, and duration of the peri-op period using old and novel biomarkers. **Methods:** This prospective, randomised, and double-blinded clinical study involved 69 patients. Blood and urine samples were collected before and after anaesthesia, and serum creatinine (SCr), cystatin C (SCysC), and urinary N-Acetyl- β-D- glucosaminidase (uNAG) were assayed simultaneously with urea, uric acid, and electrolytes to detect renal tubular damage. Kidney Disease Improving Global Outcomes (KDIGO)-SCr and Translational Research in Biomarker Endpoint (TRIBE) – ScysC criteria used to define AKI. **Results:** The pre-to post-op alterations between SCr (73.50 (62.0-89.50) vs 72.50 (59.25-83.75), p=0.166) and SCysC (51.69 (47.50-62.90) vs 54.84 (51.70-61.82), p=0.100), and the incidence of AKI by KDIGO and TRIBE was 9.4% and 18.8%, respectively. Patients with AKI by KDIGO were all female whereas, for TRIBE, 17.2% females and 1.6% males. The Kaplan-Meier survival curve analysis for AKI based on KDIGO stratified by sex showed that at 63- and 172-minutes post-general anaesthesia (GA), the survival rate against AKI was 97.8% (95% CI: 93.7-100%) and 22.6% (77.4%; 95% CI: 60.5-99.1%) for females and on the contrary no incidence of AKI in male. With TRIBE at 58 minutes post-GA, the survival rate of males was 85.7% (95% CI: 63.3-100.0%) and females at 40 minutes, 72 minutes and 180 minutes were 98.2% (95% CI: 94.8-100.0%), 89.5% (95% CI: 81.1-98.7%) and 52.6% (95% CI: 32.9-84.0%), respectively. **Conclusions:** AKI was common among female adult general surgical patients undergoing GA. SCysC is a more sensitive marker in detecting AKI than SCr in adult general surgical patients.

INTRODUCTION

Acute kidney injury (AKI) is the recent nomenclature of acute renal failure (ARF). William McNider, in 1918, first used the term AKI during a case of mercury poisoning (Makris and Spanou 2016).

However, during the revision of the terminology from ARF to AKI in the study of acute dialysis quality initiative (ADQI), it became evident that AKI does not always progress to renal failure, as previously emphasised. Thus, the term AKI is indicative of the potential reversibility of an acute clinical condition (Meersch *et al*., 2017).

Perioperative (peri-op) acute kidney injury (AKI) depicts a sudden and sustained reduction in baseline renal function during surgery or the immediate postoperative (post-op) period (Goren and Matot 2016). As part of several clinical phenotypes of AKI, peri-op acute kidney injury (P-AKI) describes impairment in a normal baseline renal function during surgery or the immediate post-op period. It is associated with many peri-op events such as haemodynamic instability, anaemia, sepsis, coagulopathy, and mechanical ventilation (Goren and Matot 2016). P-AKI is sometimes designated as surgery-associated AKI (SA-AKI) (Zarbock *et al*., 2018) because it predominantly occurs among patients in surgical settings.

The events of the peri-op period remain the leading cause of AKI among hospitalised patients, with a reported incidence of 18-47 % (Hobson *et al*., 2017). Mortality rates of AKI could be as high as 50- 60% and even higher if therapeutic support is not provided on time (Sharma and Slawski 2012). Additionally, AKI complicates the hospital stay in about 50% of surgical patients seen in prolonged hospital stay and high medical costs (Hobson *et al*., 2015).

For general anaesthesia (GA), isoflurane is a common inhaled anaesthetic. Juxtaposing the absence of an ideal inhalational anaesthetic agent with some reports about isoflurane as an inhalational anaesthetic with improbable renal toxicity (Butterworth *et al*., 2013 & Ong-Sio *et al*., 2017), this is hypothesised that anaesthesia and renal function are highly interconnected and can potentially interfere with one another to alter the human physiological state leading to AKI (Motayagheni *et al*., 2017 & McKinlay *et al*., 2017).

Time-honoured kidney function tests, which are based on the increase in serum creatinine (SCr) and the decrease in urine output (Uo) as validated by Kidney Disease Improving Global Outcomes (KDIGO) (Zhang *et al*., 2017), are considered insensitive pointers of acute changes in perioperative kidney function due to the obligate delay between the onset of AKI and its diagnosis (Romagnoli *et al*., 2018). SCr and Uo can be influenced by nutrition, volume overload, muscle trauma, drugs, and steroids (Goren and Matot 2016). N-Acetyl- β-D-glucosaminidase (uNAG) (Andreucci *et al*., 2017) and cystatin C (SCysC) (Yong *et al*., 2017) are superior markers to evaluate glomerular filtration rate (GFR), promptly screen out AKI, and as well spot the cause than SCr (Goren and Matot 2016). The utility of SCysC and uNAG with existing renal function markers such as SCr is required to mark out AKI to investigate the peri-op flaws of SCr further. SCr is not a real-time marker, and there is a delay between injury and the subsequent rise in SCr. Renal injuries are detected until >50% renal function is lost with delayed reductions in GFR. This lag is observed to occur approximately 48 hours from the time of injury to detection (Awdishu *et al*., 2017). The nephrotoxic effect of the older inhaled anaesthetics are well known (Kaye and Riopelle 2009). However, modern inhalational agents' provision of renal protection is somewhat mixed (McKinlay *et al*., 2017). The present study sought to provide information on the utility of SCysC and uNAG with traditional markers as part of renal function monitoring strategies for patients undergoing isoflurane GA in the general surgical setting. Novel biomarkers can help detect AKI early, identify

aetiology, predict the outcome, and tailor specific early therapies. Unfortunately, no study in Ghana has investigated SCysC and uNAG compared to traditional markers to evaluate renal function and mark out peri-op AKI in the Ghanaian population. Therefore, the present study provides clinical information about using some novel biomarkers in conjunction with the conventional biomarkers among Ghanaian adults undergoing isoflurane GA for elective general surgical procedures.

MATERIALS AND METHODS

Study Objective:

This study aimed to evaluate the incidence and severity of post-op AKI, renal tubular damage, and the time to an acute injury event using old and novel biomarkers.

Study Design:

A prospective, randomised, and double-blind clinical study started after obtaining institutional ethical approval from the Committee on Human Research Publications and Ethics of Kwame Nkrumah University of Science and Technology (no: CHRPE/AP/056/19 dated February 19, 2019) from February 19, 2019, to February 18, 2020. Informed consent was obtained from sixty-nine patients. The study population consisted of the American Society of Anaesthesiologists (ASA) physical status (PS) I and II, male and female adults between 18-60 years scheduled for elective surgical procedures under GA with isoflurane.

Study Setting:

The study was conducted at Komfo Anokye Teaching Hospital (KATH), the second-largest hospital in Ghana, situated in Kumasi, the capital of the Ashanti Region, with a population of 3065000. The only tertiary healthcare facility in the Ashanti Region serves as a referral facility for the northern and adjoining regions of the country. According to the 2018 registry, the hospital has a 1200-bed capacity and approximately 9000–12000 patients undergo surgery each year.

Study Participants:

Inclusion Criteria for the study were the ASA physical status I or II, adults ≥ 18 years of age with normal pre-op renal function. The inferior vena cava (IVC) diameter < 2.1 cm and collapsibility during inspiration >50% without any other signs of dehydration. The eGFR was determined from the most recent pre-op SCr with a modified Cockcroft- Gault (C-G BSA) formula adjusted for the body surface area (1.73 m2 x GFR-Cockcroft-Gault); where the GFR -Cockcroft-Gault is in ml/min, and the body surface area calculated in meters squared using the Dubois-Dubois equation. The Larsson formula for SCysC-based GFR was also used. Larsson formula: eGFR = 77.24 × cystatin C (mg/l)-1.2623. Patients with an eGFR > 80ml/min were recruited. Exclusion Criteria were patients more than 60 years of age, inferior vena cava < 1.7 or collapsibility during inspiration < 50% or presence of other signs of dehydration, known hypersensitivity to isoflurane or other inhalant general anaesthetics, cardiothoracic surgical patients, emergency surgical cases, laparoscopic cases, patients with renal insufficiency or previously verified SCr derangements (> 120 µmol/l). Cases with a massive colloid infusion or blood transfusion, surgical interventions anticipate a major fluid shift were excluded. Patients with difficult venous access (for which sample collection was difficult), those undergoing urologic surgeries (that could compromise renal blood flow), who have received GA in less than a fortnight, pregnancy, received vasopressors, radiocontrast within 24 hours before surgery, and hepatic impairment patients were also excluded from the study.

Study Variables:

1. **Clinical/ Perioperative Variables**: American Society of Anaesthesiology Physical Status (ASA-PS), blood pressure (BP), mean arterial pressure (MAP), inferior vena cava (IVC) size, collapsibility of the IVC, duration of pre-

op fasting, comorbidity, indication for surgery, duration of anaesthesia (including the period of isoflurane use), duration of surgery, surgery performed, type, volume and duration of intravenous fluids infused.

2. **Biochemical Parameters:** Laboratory parameters measured from serum and urine samples before and immediately after anaesthesia from blood SCr, blood urea nitrogen (BUN), SCysC, serum uric acid (SUA), electrolytes (sodium, chloride, potassium, ionised calcium, and magnesium), and urinary- uNAG. SCr and SCysC blood samples were taken before anaesthesia, immediately after anaesthesia, at 24, 48, and 72 hours. Additionally, patients were monitored for any complications or dialysis needed within 30 days after surgery.

Determination of Sample Size and Sampling Techniques:

1. **Sample Size Determination:** Variability in the study population and settings added to the AKI reporting patterns accounts for an estimated AKI prevalence of <1% to 66% (Hoste *et al*., 2018). With no reliable AKI epidemiological estimates across Africa, which is reasoned to be a late presentation or underreporting (Adu *et al*., 2016), a Chronic Kidney Disease Epidemiology (CKD-EPI) evaluated the prevalence of 4.1% is, however, reported among pregnant women with renal compromise in a Kumasi Metro Hospital (Fondjo *et al*., 2018). In the absence of data on AKI prevalence among peri-op patients at KATH, a prevalence of 15% was adopted for the sample size estimation in this study, with reference to the previous studies, and was determined as follows: Required sample size, $n = z^2pq/d^2$ Where; z = z score corresponding to 95% significance level; p = estimated proportion (as referenced from the previous study) = 1 – p; d = precision or the tolerated margin of error.

Therefore, z=1.96, p=0.15, q= (1-0.15), d=0.1

Substituting these values into the above equation/formula:

Required sample size, $n =(1.96)^2 (0.15) (1-0.15) (0.1)^2 = 3.8416 (0.1275)/ 0.01$

Required sample size, n = 49

Considering a 40% dropout rate = 40/100 ×(49) = 19.6

Dropout rate =20

The required sample size [(estimated, 49 + dropout, 20)] n = 69

2. **Determination of the Sampling Technique**: The sampling technique was simple random to give each eligible participant an equal chance of enrolment. To sample 69 participants who met the eligibility criteria were identified each weekday from the registry of the theatre manager's surgical caseloads, a balloting system was used with a total of 150 sheets of papers equally assigned 'Yes' and "No' for them to pick one at the point of recruitment. Those who selected "YES" were enrolled till the sample size of 69 was reached from 305 patients.

Person α was involved in the randomisation process, Person β prepared the drugs, anaesthetised patients, and managed patients in the Intensive Care Unit (ICU), while Person **Ω** was responsible for the patient's intraoperative and ICU records. Person α, **Ω**, and the patient were kept unaware of the drugs used to enable double-blinding.

Conduction of Anaesthesia:

1. **Pre-anaesthetic Assessment and Sample Collection:** On arrival into the preoperative holding unit, confirmation of patient and proposed surgical procedure was done. Data collected included age, gender, and weight. The body mass index (BMI) of each patient was computed as BMI= weight (kg)/ height(m^2). A BMI ≥ 30 kg/ m^2 was considered obese.

As part of the routine pre-anaesthetic evaluation at the pre-op holding area, baseline parameters such as non-invasive blood pressure (NIBP), mean arterial pressure (MAP), electrocardiogram (ECG), pulse oximetry-SpO_2, and pulse were recorded. An ultrasound machine

recorded inferior vena cava (IVC) diameter to calculate the vena cava collapsibility index to assess the hydration status of patients without invasive procedures and increasing patient management costs in a low resource setting. The duration of pre-op fasting, indication for surgery, and the proposed surgical procedure were recorded. A 5ml volume of voided urine specimen was collected in an appropriately labelled urine specimen container. Afterwards, a 16 -18G over-the-needle catheter venous line was inserted into a peripheral vein to collect four millilitres (4 ml) of a venous blood sample into plain sample glass tubes. Samples collected were immediately sent to the research laboratory.

Dictated by the patient's hydration needs, an 0.9% NaCl solution infusion was set up to run using the same venous line where a sample was collected. This type of intravenous infusion was used during and after surgery as it is the standard practice in the study area.

2. **Induction and Maintenance of Anaesthesia:** Preoxygenation of the lungs with 100% oxygen (O_2) for 3 minutes prior to Induction of anaesthesia. The anaesthetic technique was standardised for all patients. Induction of anaesthesia was achieved by Fentanyl 1.5mcg/kg IV, Propofol 2mg/kg IV, and 0.1mg/kg Vecuronium for airway management and neuromuscular block for optimal surgical conditions. All patients were intubated with the appropriate size endotracheal tube. Anaesthesia was maintained with 1-2% minimum alveolar concentration (MAC) of isoflurane in O_2 at a 3L/min rate delivered from isoflurane agent-specific and calibrated vaporiser (Mindray V60) till the end of the surgical procedure evidenced by the last skin suture. Remnant muscle relaxation was counteracted with Atropine 0.02 mg/kg and Neostigmine 0.03- 0.07 mg/kg intravenously. The patient was extubated following clinical evidence of regressed neuromuscular blockade evidenced by adequate spontaneous ventilation. Under continuous monitoring, patients were sent to the post-anaesthesia care unit.

3. **Postoperative Period:** Monitoring vital signs as part of general anaesthetic emergence standard operating protocol (SOP) in the immediate post-op period was ensured and recorded until patients were transferred out of the post-anaesthesia care unit to their respective surgical wards.

Blood SCr and SCysC were sampled immediately after anaesthesia, at 24, 48, and 72 hours after surgery, 4ml of venous blood was collected from each studied subject at a peripheral venous site other than existing the intravenous line together with 5ml of freshly voided urine specimen which was handled as described in the pre-op period above. In addition, patients were monitored for any complications or dialysis needed within 30 days after surgery.

More importantly, because isoflurane was the sole inhalation anaesthetic agent in this study, the conventional expression of anaesthetic gas exposure in MAC- h was determined from the percentage anaesthetic concentration and exposure duration (Singh and Annamalai 2020), which are usually corrected by age. However, the duration (estimated in minutes) of isoflurane administration was quantified in this study.

Data Collection Technique and Patients.

A structured questionnaire was used to collate prespecified demographic, anthropometric, and clinical data from each participant. The data collection tool sought to ascertain 54 variables covering demographic and anthropometric characteristics, anaesthesia, and surgery information in addition to measured laboratory parameters assayed from collected blood and urine samples. Data was collected through communication with study participants, review of clinical charts, and appropriately calibrated measurement scales. Multicomponent Mindray iPM12 patient care monitors

were used for peri-op monitoring of vital signs. GE SonoSite M-turbo ultrasound machine was used to measure IVC size and collapsibility. Selectra Pro S automated chemistry analyser facilitated laboratory assays from ELITech Clinical system, France, Epoc blood analysis system from Siemens Healthineers, and Synergy H1 reader (Bio Tek, USA).

Statistical Methods:

Statistical analysis was performed using the R Language for Statistical Computing version 3.6.0. Categorical data were presented as frequencies and percentages. Binomial logistic regression analysis was performed to determine potential factors associated with the presence of AKI. Normality was checked using Shapiro-Wilk's test and visual inspection with Q-Q plots for continuous data. Normally distributed data were presented as mean ±SD, and the significance of the difference in markers was evaluated between the presence and absence of AKI using paired t-tests. A one-way repeated-measures analysis of variance (repeated measures ANOVA) was used to test for the significance of the difference between groups. Multiple comparisons were adjusted using the Bonferroni correction. Nonparametric data were presented as median (interquartile ranges), and the significance of differences of markers was evaluated using Wilcoxon signed-rank tests with continuity correction.

The level of agreement between the different AKI definitions using SCr and SCysC was evaluated using the Kappa-statistic. Kaplan-Meier survival curve analysis was used to evaluate the times of onset of AKI stratified by sex, and the corresponding cumulative incidences were calculated. Finally, a comparison of survival curves was made using the Log-Rank test. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

RESULTS

Sixty-nine adults were recruited during the study period who received isoflurane anaesthesia for elective general surgical procedures. However, data from 64 (92.75%) patients were analysed. In addition, five patients were omitted from the analysis due to sample attrition.

1. Characteristics of Demographic Data:

The baseline demographic, anthropometric, and clinical characteristics of the study population are shown in Table1. There were more females than males, 87.5% vs 12.5%, respectively. The mean –age, BMI, IVC, duration of fasting, isoflurane use, anaesthesia, and surgery among the entire study population were 39.97 years, 28.3 Kg/m^2, 1.94 cm, 8.0 hours, 91.0 mins, 111.0 mins, and 77.5 mins, respectively.

Table 1: Demographic and clinical characteristics of the study population:

Variables	Mean ± SD Frequency (%)
Age (years)	39.97±14.69
Sex	
Male	8 (12.5%)
Female	56 (87.5%)
Weight (Kg)	72.69±10.53
Height (m^2)	1.61±0.09
BMI (Kg/m^2)	28.31±4.81
IVC diameter (cm)	1.94±0.17
ASA-PS	
1	48 (75.0%)
2	16 (25.0%)
Duration of fasting (hours)	8.0 ±0.42
Duration of isoflurane (mins)	91.0 ± 32.72
Duration of anaesthesia (mins)	111.0 ± 38.48
Duration of surgery (mins)	77.5 ± 28.41
Bubois BSA	1.76±0.14
CGBSA	116.04±30.66
CG Basic	117.97±32.73
Larsson eGFR	0.53 ± 0.04

Data are presented as means ± SD, ratio, and percentages. Isoflurane administered during the procedure was calculated using the formula: consumption of anaesthetic agent in ml/hr = 3 x set concentration % x fresh gas flow L/min (Singh and Annamalai 2020). ASA-American Society of Anaesthesiologists, BSA- body surface area, CG- Cockcroft- Gault, cm-centimetre, DM- diabetes mellitus, GFR- glomerular filtration rate, IVC-inferior vena cava, kg- kilograms, mins- minutes, m-metre, PS-physical status.

2. Comparison of haemodynamic parameters between preoperative, intraoperative, and immediate postoperative periods:

The preoperative (pre-op) systolic blood pressure (SBP) was significantly higher compared to both intraoperative (intra-op) SBP (135.3±19.33 vs 116.86±17.21 mmHg, p<0.0001) and (post-op) SBP (135.3±19.33 vs 120.94±15.42, p<0.0001). There was no statistically significant difference between intra-op and post-op SBP (p>0.05) (Fig.1). Diastolic blood pressure (DBP) showed similar results (Fig.2). The pre-op mean arterial pressure (MAP) was significantly higher compared to both intra-op MAP (98.74±6.91 vs 81.34±4.52 mmHg, p<0.0001) and post-op MAP (98.74±6.91 vs 93.72±5.78, p<0.0001) (Fig.3).

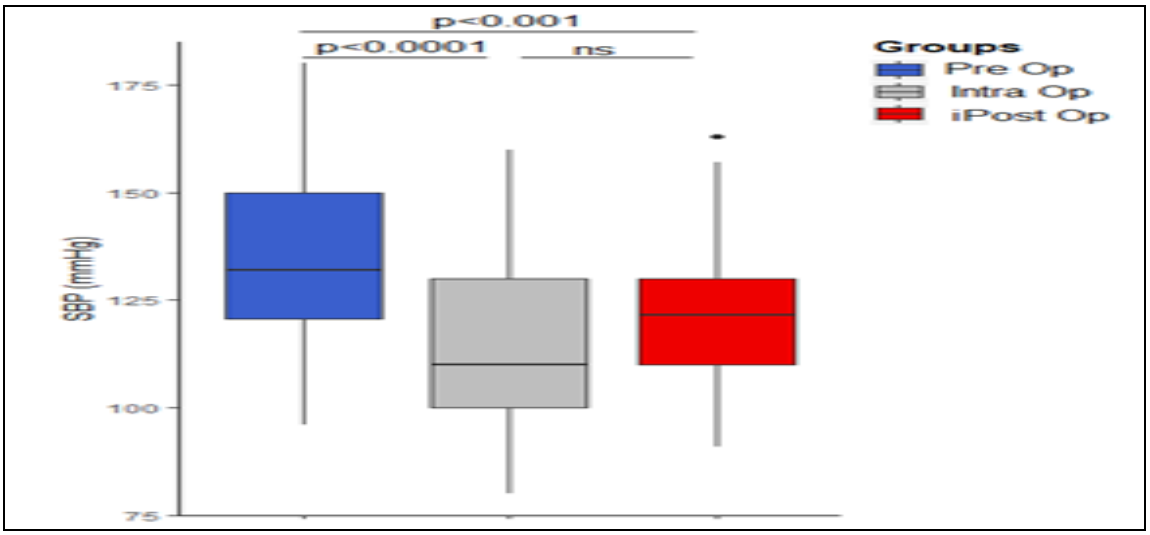

Fig. 1: Comparison of systolic blood pressure (SBP) between preoperative, intraoperative, and immediate postoperative periods.

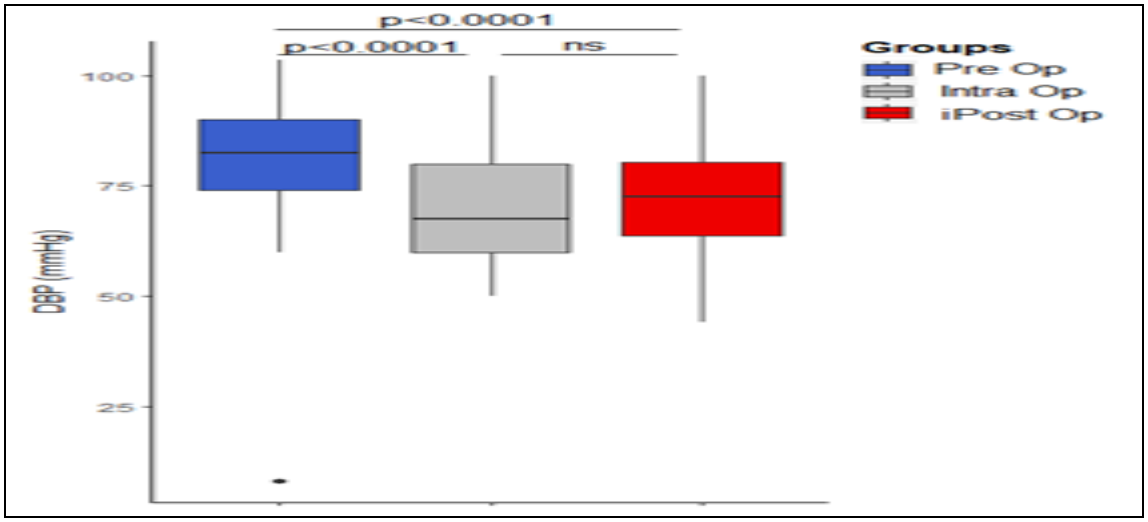

Fig. 2: Comparison of diastolic blood pressure (DBP) between preoperative, intraoperative, and immediate postoperative periods**.**

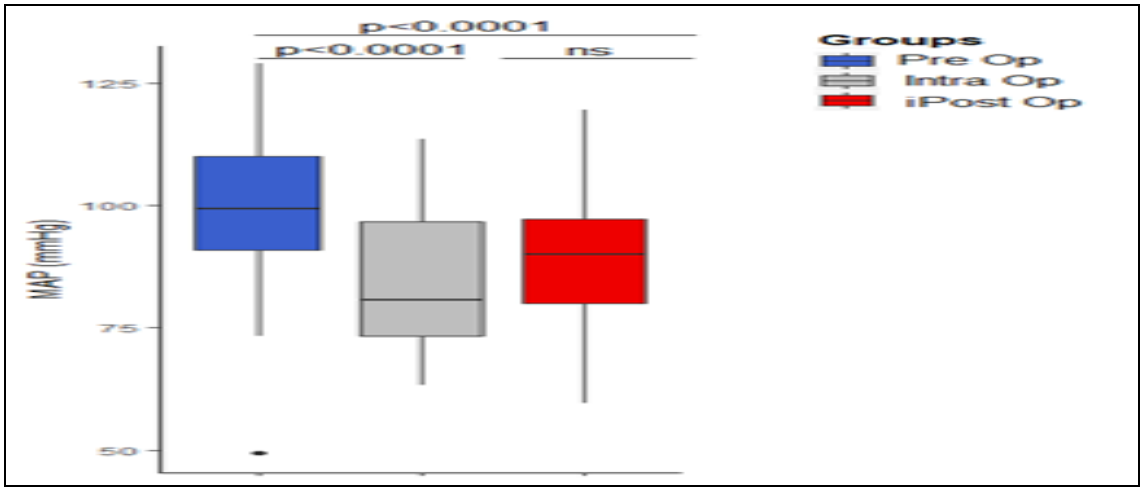

Fig. 3: Comparison of mean arterial pressure (MAP) between preoperative, intraoperative, and immediate postoperative periods.

3. Incidence of Serum Creatinine and Serum Cystatin C AKI:

The demographic and clinical characteristics potentially associated with AKI based on SCysC as shown in Table 2. The female gender odds ratio (OR) = 1.71, 95% confidence interval (CI)-(0.19-15.39), p=0.632), increasing age (31-39 yrs: OR= 1.50, 95% CI (0.19-12.15), p=0.704; 40-49 yrs: OR= 3.60, 95% CI (0.56-23.24), p=0.178; 50-59 yrs: OR= 3.86, 95% CI (0.53-28.24), p=0.184; >60 yrs: OR= 1.80, 95% CI (0.13-24.16), p=0.657), ASA-PS II (OR= 2.67, 95% CI (0.71-10.33), p=0.148), and ≥1 hr Isoflurane duration (OR= 0.54, 95% CI (0.14-2.79), p=0.541) were associated with increased odds of AKI, although not statistically significant. Intraoperative MAP ≥70 (OR= 1.19, 95% CI (0.23-6.31) was statistically significant (p=0.031).

Table 2: Demographic and clinical characteristics potentially associated with SCysC detected AKI.

Variables	AKI absent	AKI present	OR (95% CI)	p-value
Sex				
Male	7 (87.5)	1 (12.5)	1	
Female	45 (80.4)	11 (19.6)	1.71 (0.19-15.39)	0.632
Age (years)				
<31	18 (90.0)	2 (10.0)	1	
31-39	12 (85.7)	2 (14.3)	1.50 (0.19-12.15)	0.704
40-49	10 (71.4)	4 (28.6)	3.60 (0.56-23.24)	0.178
50-59	7 (70.0)	3 (30.0)	3.86 (0.53-28.24)	0.184
≥60	5 (83.3)	1 (16.7)	1.80 (0.13-24.16)	0.657
ASA-PS				
I	41 (85.4)	7 (14.6)	1	
II	11 (68.8)	5 (31.3)	2.67 (0.71-10.33)	0.148
Intra-OP MAP				
<70	10 (66.7)	5 (33.3)	1	
≥70	42 (85.7)	7 (14.3)	1.19 (0.23-6.31)	0.031*
Isoflurane duration				
<1 hr	9 (75.0)	3 (25.0)	1	
≥1 hr	43 (82.7)	9 (17.3)	0.54 (0.14-2.79)	0.541

ASA-PS- American Society of Anaesthesiologists physical status, OR- odds ratio, CI- confidence interval, hr-hour, MAP- mean arterial pressure, OP-operative

Demographic and clinical characteristics potentially associated with AKI based on SCr as shown in Table 3. Increasing age (31-39 yrs: OR= 3.17, 95% CI (0.26-38.85), p=0.367; 50-59 yrs: OR= 4.75, 95% CI (0.38-60.15), p=0.229; >60 yrs: OR= 3.80, 95% CI (0.20-72.00), p=0.374), ASA-PS II (OR= 3.46, 95% CI (0.62-19.24), p=0.156) and ≥70 intra op MAP (OR= 1.17, 95% CI (0.12-11.05), p=0.891) were associated with increased odds of AKI, although not statistically significant (Table 3).

Table 3: Demographic and clinical characteristics potentially associated with AKI based on SCr:

Variables	AKI absent	AKI present	OR (95% CI)	p-value
Sex				
Male	8 (100.0)	0 (0.0)	1	
Female	50 (89.3)	6 (10.7)	na	na
Age (years)				
<31	19 (95.0)	1 (5.0)	1	
31-39	12 (85.7)	2 (14.3)	3.17 (0.26-38.85)	0.367
40-49	14 (100.0)	0 (0.0)	na	na
50-59	8 (80.0)	2 (20.0)	4.75 (0.38-60.15)	0.229
≥60	5 (83.3)	1 (16.7)	3.80 (0.20-72.00)	0.374
ASA-PS				
I	45 (93.8)	3 (6.3)	1	
II	13 (81.3)	3 (18.8)	3.46 (0.62-19.24)	0.156
Intra OP MAP				
<70	10 (91.7)	1 (8.3)	1	
≥70	47 (90.4)	5 (9.6)	1.17 (0.12-11.05)	0.891
Isoflurane duration				
<1 hr	12 (100.0)	0 (0.0)	1	
≥1 hr	46 (88.5)	6 (11.5)	na	na

ASA-PS- American Society of Anaesthesiologists physical status, OR- odds ratio, CI- confidence interval, hr-hour, MAP- mean arterial pressure, OP-operative

The pre-op to post-op alterations between SCr (73.50 (62.0-89.50) vs 72.50 (59.25-83.75), p=0.166) and SCysC (51.69 (47.50-62.90) vs 54.84 (51.70-61.82), p=0.100), did not differ significantly (Fig. 4), the incidence of AKI by Creatinine and TRIBE Cystatin C were 9.4% and 18.8%, respectively. All patients with AKI by KDIGO were females whereas, for TRIBE, there were 11 (17.2%) and 1 (1.6%) females and males, respectively (Fig. 5). Additionally, there were more stage one KDIGO designated AKI than stages two and three, 6.3%, 1.6%, and 1.6%, respectively (Fig. 6).

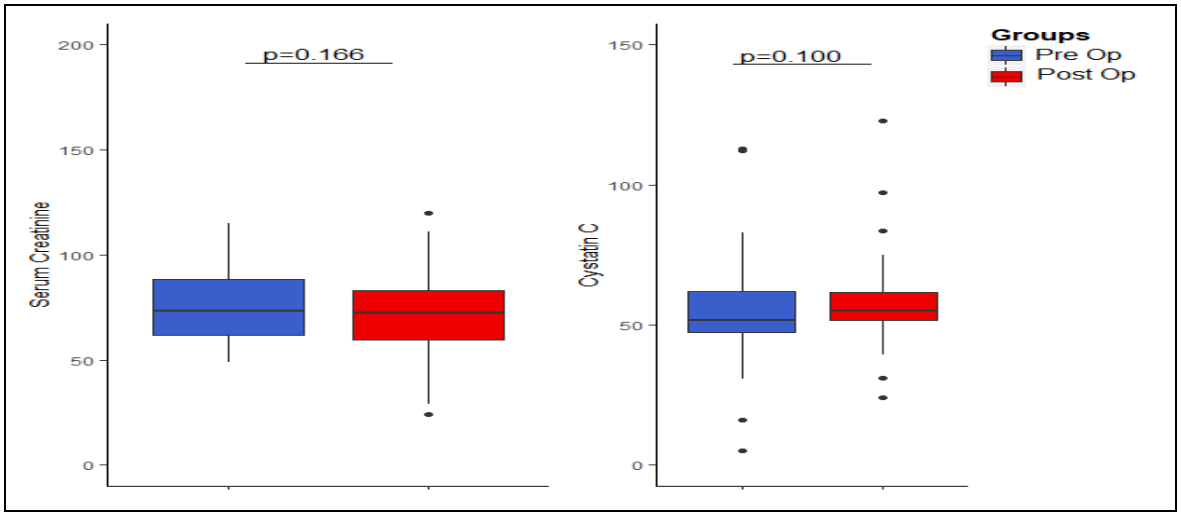

Fig. 4: Comparison of serum creatinine and cystatin C between pre-operation and post-operation periods.

Fig. 5: Incidence of serum creatinine (KDIGO) and serum cystatin C (TRIBE) AKI**.**

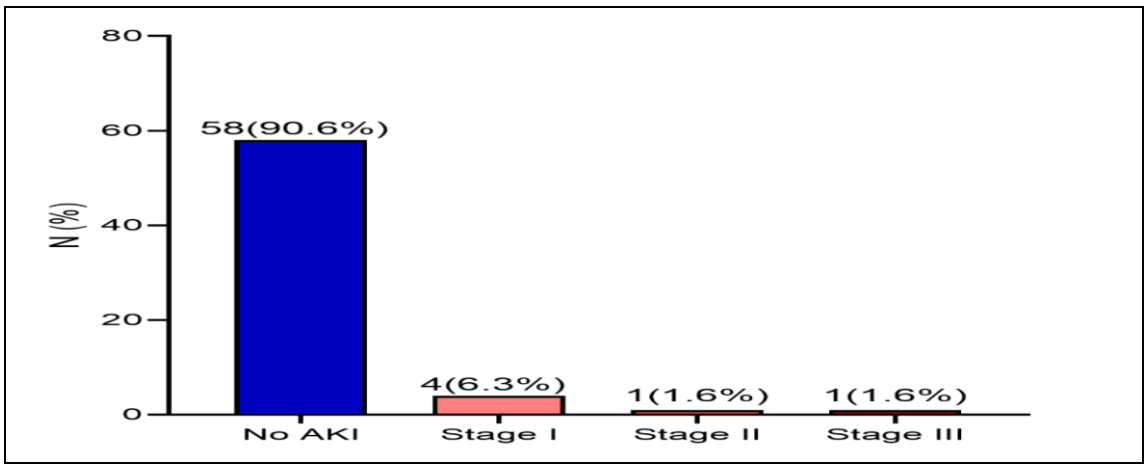

Fig. 6: Acute kidney injury severity staging by KDIGO.

Patients with comorbidities like diabetes, hypertension, chronic obstructive pulmonary disease, and cancer were 6.3%, 23.4%, 1.6%, and 1.6%, respectively. In diabetics and hypertensives, AKI detected were (1.6% and 3.1%), and (3.1% and 7.8%) with SCr and ScysC, respectively. Within 30 days after surgery, 7.8% and 3.1% of patients detected AKI with SCr and ScysC underwent dialysis (Fig. 7). Reduced dialysis cases with ScysC were due to early detection and management.

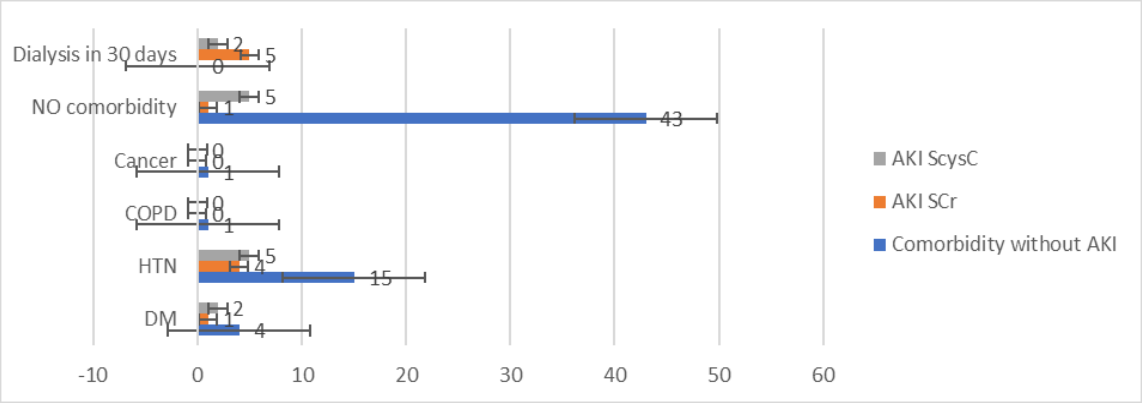

Fig. 7: Comparison of comorbidities in the study groups with AKI

Kaplan-Meier survival curve analysis for AKI based on KDIGO stratified by sex showed that GA with isoflurane administration in males was not associated with AKI development based on KDIGO. Contrarily, at 63 minutes post isoflurane GA administration, the survival rate against AKI based on KDIGO was 97.8% (95% CI: 93.7-100%) for females. However, at 172 minutes after GA with isoflurane administration, 22.6% of the females had developed AKI based on KDIGO (survival rate: 77.4%; 95% CI: 60.5-99.1%). Nonetheless, there was no statistically significant difference between the survival curves for males and females (p=0.370) (Fig. 8).

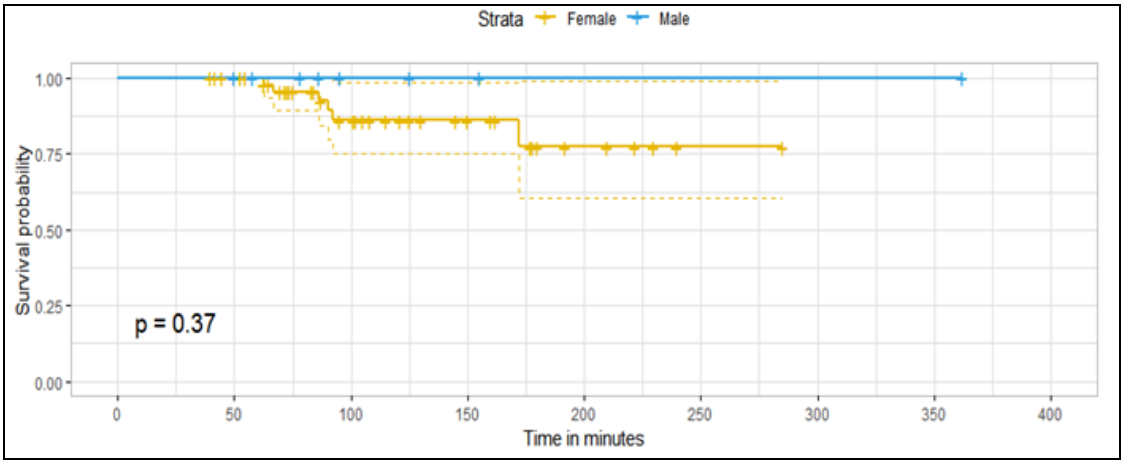

Fig. 8: Kaplan-Meier survival analysis for Creatinine KDIGO defined AKI stratified by sex**.**

Kaplan-Meier survival analysis for Cystatin C TRIBE defined AKI stratified by sex, as shown in figure 8. At 58 minutes post GA with isoflurane administration, the survival rate of males against AKI based on TRIBE was 85.7% (95% CI: 63.3-100.0%). For females, the survival rate against AKI based on TRIBE

at 40 minutes, 72 minutes and 180 minutes post isoflurane administration were 98.2% (95% CI: 94.8-100.0%), 89.5% (95% CI: 81.1-98.7%) and 52.6% (95% CI: 32.9-84.0%), respectively.

Nevertheless, there was no statistically significant difference between the survival curves for males and females (p=0.720) (Fig. 9)

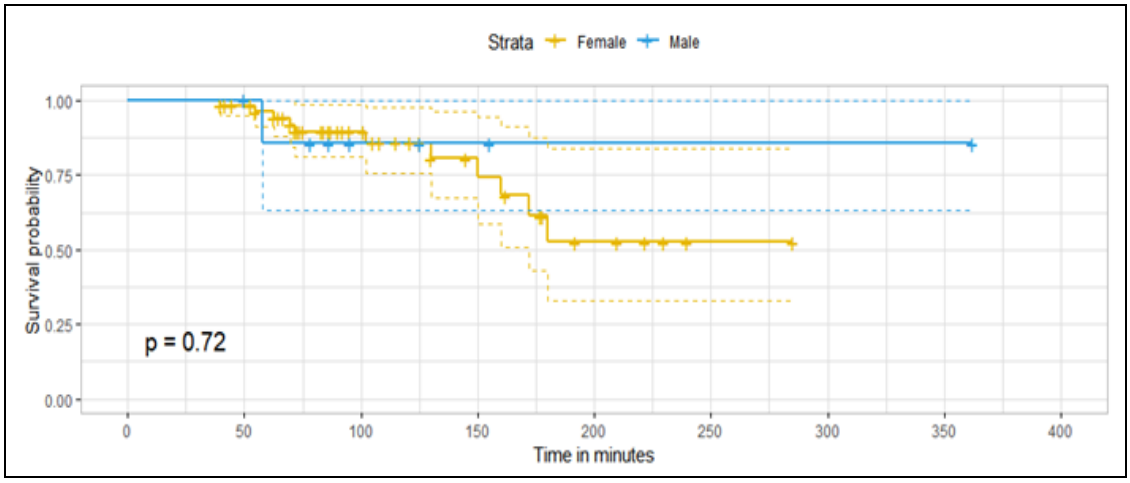

Figure 9: Kaplan-Meier survival analysis for Cystatin C TRIBE defined AKI by sex.

4. Assessment of Renal Tubular Cell Damage as A Measure of The Pre- to Post-Op Increases in Urinary β-N-Acetyl-β-D-glucosaminidase Activity:

Urinary NAG activity among studied subjects was not significantly different between the pre and post-op periods (8.21 (7.79-8.64) vs 8.48 (7.69-9.05), p=0.131) (Fig. 10).

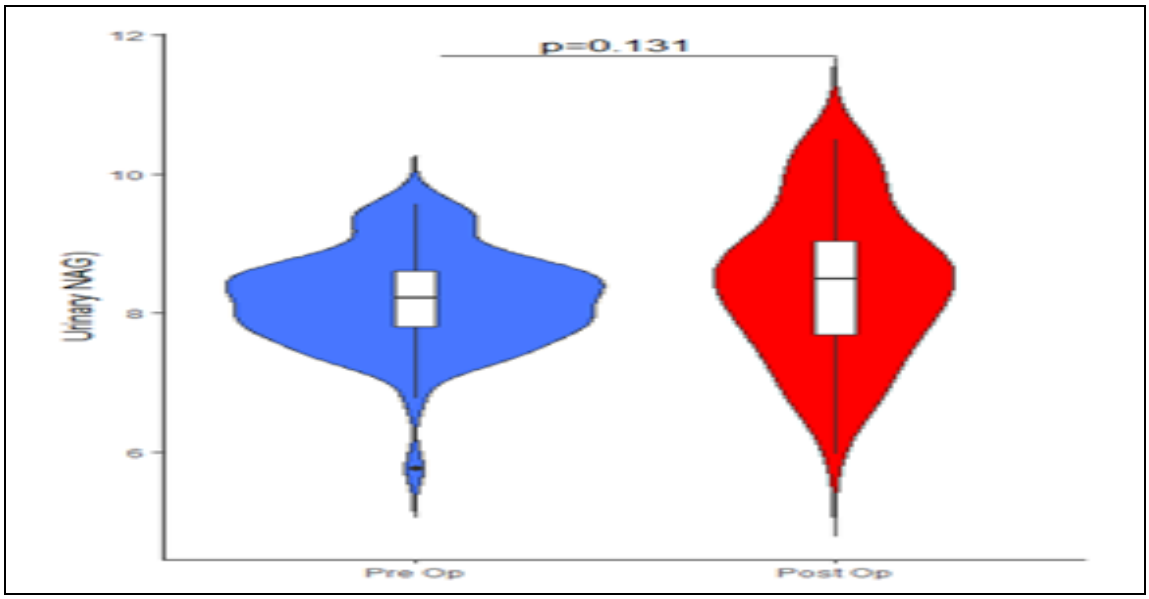

Fig. 10: Assessment of renal tubular cell injury by β-N-Acetyl-β-D-glucosaminidase.

DISCUSSION

A quasi- longitudinal experimental study was conducted among 69 Ghanaian ASA-PS I and II adult patients with no pre-existing renal compromise. They received GA with isoflurane for planned general surgery at KATH in accordance with anaesthesia protocol. All patients had a pre-op renal function of SCr ≤ 115µmol/l, urea ≤ 5.7mmol/l, and a

Cockcroft-Gault, eGFR adjusted for body surface area (CGBSA), of 116.04±30.66 ml/min/1.73m^2. Incident AKI was adjudged by the KDIGO and TRIBE criteria, with elevated SCr and SCysC levels of ≥ 26.5 μmol/l and ≥ 25%, respectively, from baseline 48 hours post-surgery.

The study found 9.4% and 18.8% post-op AKI incidence for KDIGO creatinine and TRIBE cystatin C criteria. The reported 9.4% incidence falls within the 21% incidence proportion for hospital-acquired AKI, which is reported among low- and middle-income countries using a correspondent KDIGO diagnostic criterion (Hoste *et al*., 2018).

A single-centre 2016 prospective study at Korle Bu Teaching Hospital (KBTH) reported a postoperative AKI incidence of 4.5% among general surgical patients (Wemakor 2016). The disparities in incidence observed in this study relative to the KBTH may be attributed to the surgical case mix with the potential to necessitate other techniques of anaesthesia such as spinal anaesthesia or a combined epidural and GA, which are reported to reduce the incidence of post-op AKI than a solely administered GA (Goren and Matot 2015).

Admittedly, 9.4% incidence in our study is lower than the KDIGO creatinine determined the incidence of 13.2% noted among general surgical patients of African ancestry in a seven-year historical cohort (Grams *et al*., 2016). The discordant incidence reporting was due to the mixed type of surgical case, different baseline preoperative characteristics, and study design adopted in each study.

Some studies have assessed the relationship between haemodynamics and AKI progression (Badin *et al*., 2011 & Dunser *et al*., 2009). Maintaining mean arterial pressure (MAP) above 60 to 65 mmHg is suggested to maintain adequate renal blood flow and perfusion (Prowle *et al*., 2012 & Joannidis *et al*., 2010**)**. Poukkanen *et al.*, in their study of 423 patients, had 153 (36.2%) progression of AKI. Patients with AKI progression had significantly lower MAP, 74.4 mmHg, than those without progression, 78.6 mmHg (Poukkanen *et al.*,2013). Our study MAP in the preoperative, intra-op, and post-op periods were 98.74 mmHg, 81.34 mmHg, and 93.72, respectively. Our post-op AKI incidences were 9.4% and 18.8% for KDIGO creatinine and TRIBE cystatin C criteria. The incidences of post-op AKI detected in our study were lower than those of Poukkanen *et al.* This may be attributed to high MAP in our study due to different anaesthesia protocols, types of patients, and cases. In our study population, MAP was > 79 mmHg in the perioperative period, with proper fluid replacement and maintaining haemoglobin; therefore, adequate renal blood flow and perfusion were maintained.

SCr is not a real-time marker, and early renal injury may evade detection until about 50% of renal function is lost before a sufficient increase in SCr becomes detectable (Meersch *et al.*,2017). This lag is noted to occur about 42 hours from the time of injury to detection (Awdishu and Mehta 2017). Martensson *et al*. showed that the inflammatory response produced by sepsis did not influence the plasma levels of SCysC (Martensson *et al.*,2012). Furthermore, Doi et al. showed that sepsis reduced the production of SCr, which blunted the increase in SCr after sepsis (Doi *et al.*,2009). It indicates that SCysC might have benefits over SCr as a marker of AKI. The higher incidence of SCysC ascertained post-op AKI than SCr in this study might be attributed to the distinct physiologic profile such as its abbreviated half-life, complete degradation following glomerular filtration, direct correspondence with stable or variable GFR.

Furthermore, its concentration depends on race, age, gender, volume status, or muscle bulk (Murty *et al.*,2013 & Odutayo *et al.*,2012). These properties potentially characterise SCysC as a

prospective biomarker of GFR with superior and early AKI diagnostic capabilities in clinical settings. For any prevention strategies to be effective, patients with a high risk of AKI need to be diagnosed and treated as early as possible to prevent further deterioration in renal function.

Conclusion:

A post-op AKI incidence of 9.4% and 18.8% were reported for serum creatinine, and serum cystatin C detected AKI. The superior diagnostic utility of serum cystatin C relative to serum creatinine as a sensitive AKI biomarker was accentuated. There was no evidence of the direct effects of isoflurane GA to induce nephrotoxicity as quantified by urinary β-N-Acetyl- β-D- glucosaminidase on the renal tubular cells. This possibly implicates its indirect impact on intraoperative haemodynamics in AKI development. Novel biomarkers are proposed as a faster and more accurate way for early identification of AKI, predict the outcome, and prove beneficial in early intervention to prevent further deterioration in renal function.

Study Limitations:

As a single-centre study, the generalisation of study findings will be finite. Also, a urethral catheter (UC) induced strictures, and other complications were the reason for entirely avoiding or momentarily retaining UC among surgical patients. Limited peri-op urine output measurements left AKI detected late. The blood loss was assessed from the drain output and swabs used. For appropriate blood loss assessment, quantitative measurement should have been done. The blood loss and fluid administration should have been compared and replaced. Additional monitoring devices like arterial lines and central venous pressure monitors would have enforced a robust intraoperative haemodynamic monitoring. A prolonged follow-up period is needed to assess the long-term outcomes of AKI and evaluate the possible role of novel biomarkers in predicting long-term outcomes.

Abbreviations:

ADQI: acute dialysis quality initiative
AKI: Acute kidney injury
ARF: Acute renal failure
ASA: American Society of Anaesthesiologists
BMI: Body mass index
BP: Blood pressure
BSA: Body surface area
BUN: Blood urea nitrogen
CG: Cockcroft- Gault
CKD-EPI: Chronic Kidney Disease Epidemiology
GRF-Glomerular filtration rate
HR: Heart rate
IVC: Inferior vena cava
KATH: Komfo Anokye Teaching Hospital
KDIGO: Kidney disease improving global outcomes
MAC: Minimum alveolar concentration
MAP: Mean arterial pressure
mmHg: Millimeter mercury
P-AKI: Perioperative acute kidney injury
SA-AKI: Surgery-associated AKI
SCr: Serum creatinine
SCysC: Serum cystatin C
SOP: Standard operating protocol
SUA: Serum uric acid
TRIBE : Translational Research in Biomarker Endpoint
uNAG: Urinary N-acetyl- β-D-glucosaminidase

Data Availability: All the data are available within the manuscript. In addition, the datasets used and analysed during the current study are available from the corresponding author based on reasonable request.

Ethical Approval: Ethical clearance and approval were obtained from the Committee on Human Research Publications and Ethics Kwame Nkrumah University of Science and Technology (no: CHRPE/AP/056/19 dated February 19, 2019). Permission to conduct the study was obtained from each speciality

department and RD Komfo Anokye Teaching Hospital, Kumasi.

Consent: The study was explained to the patients, and written informed consent was obtained from them. Patients were informed that the care would not be compromised in any way, and their confidentiality was assured. Name and other identifying information were not used in the study.

Disclosure: The authors declare that this paper is their original work and has never been published. However, all directly quoted material has been appropriately referenced.

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Conflicts of Interest: The authors declare that they have no conflicts of interest.

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