



Early prediction of acute kidney injury with cell cycle arrest biomarkers using plethysmography directed fluid management in major abdominal surgery

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ABSTRACT

Background: Acute kidney injury (AKI) is a known complication after major abdominal surgery. Use of the usual functional AKI biomarkers for detection shows delayed results, and so, the use of cell cycle arrest biomarker was proposed.

Purpose: The aim of the present study was to assess the arrest biomarker as an early tool for AKI prediction in major abdominal surgery.

Methods: After receiving approval from the Ethics Committee and taking informed written consent, a prospective randomized study was conducted. Forty adult patients were scheduled for major abdominal surgery. Patients were randomly categorized using closed-envelope technique into two equal groups (25 patients each): the control group (20 patients) with intraoperative standard fluid therapy and the goal-directed fluid therapy (GDT) (20 patients) using plethysmography. Urinary cycle arrest biomarkers were measured at 4 and 12 h after ICU admission.

Results: The mean value of the arrest biomarkers showed a significant increase in the control group only at 4 h period ($p = 0.017$). Moreover, there was a statistically significant increase in the number of positive patients in the control group at 4 h period only ($p = 0.044$). Urine arrest biomarkers were higher in AKI patients than in the non-AKI ones at 4 h ($p = 0.003$) and 12 h ($p = 0.004$). The arrest biomarker AUROC values at 4 and 12 h were 0.887 and 0.875, respectively.

Conclusion: From these results, we concluded that cell cycle arrest biomarkers can predict AKI after major abdominal surgery. In addition, AKI incidence showed no difference between the control group and the GDT group.

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1. Introduction

Acute kidney injury (AKI) is a known complication after surgery and is linked to a significant rise in mortality, risk of long-term dialysis, and chronic kidney disease together with health-care costs [1].

During surgery, the standard of care for prevention and treatment of AKI is intravenous fluid therapy to increase urine output and decrease ischemic insults to the kidney. Additionally, hypovolemia reversal and organ perfusion maintenance aid as well [2].

However, excessive intravenous fluid administration in major abdominal surgery can result in fluid overload, especially in the presence of coexisting comorbidities, causing complications including renal function affection [2].

Traditionally, AKI is defined by two functional biomarkers (serum creatinine (sCr) and urine output). However, their limitations are delayed changes following AKI together with low sensitivity and specificity. Several new biomarkers were used for early AKI detection and were found to be more sensitive than sCr [3].

Recently, newly approved cell cycle arrest biomarkers are viewed to represent “renal stress”, rather than established renal damage [4].

2. Patient and methods

After obtaining the approval from the Ethical Committee in the Faculty of Medicine, Alexandria University, and taking patient’s written informed consent, a single-blinded prospective controlled randomized study was conducted. Forty adult patients of both sex (after sample size calculation), physical status American Society of Anesthesiologists (ASA) I and II who were planned for elective major abdominal surgery (was defined as any surgery with intraperitoneal approach done under general anaesthesia and the predictable postoperative hospitalization and length of stay at least 2 days) with combined general epidural anaesthesia, were admitted to Alexandria Main University Hospital. Patients were randomly grouped using closed-envelope technique to two groups (20

patients each as calculated by the Department of Biostatistics in the High Institute of Public Health, Alexandria University). They were a control group with intraoperative standard fluid therapy and goal-directed fluid therapy (GDT) using plethysmography. all the following patients were excluded: patients below 18 years and above 65 years, patients with chronic kidney disease, patients with perioperative use of nephrotoxic drugs, post-renal transplant patients, diabetic, cardiac, hepatic, vascular patient-sand pregnant females . Moreover, any patient with plethysmography reading with a corresponding core temperature not within the range of $36^{\circ} \pm 1^{\circ}\text{C}$ at any time during the surgery was excluded (Figure 1).

The primary outcome was to assess the capability of AKI early prediction using urinary cell cycle arrest biomarkers in patients undergoing major abdominal surgery. The return of normal peristalsis and the duration of hospital stay were assessed as secondary outcomes.

General anaesthesia induction was done by intravenous fentanyl (2 $\mu\text{g}/\text{kg}$) and propofol titration (1–2 mg/kg). Endotracheal intubation was facilitated with rocuronium (0.6 mg/kg). Anaesthesia maintenance was

done with isoflurane (1 Mac) using anaesthetic gas analyzer. Neuromuscular monitoring by nerve stimulator was used for further rocuronium administrations. A dosage of 0.1–0.2 mg/kg rocuronium was repeated on the second response appearance of train-of-four (TOF) stimulation.

In both groups, fluid management was given as demonstrated in the flowchart in Figure 2. Haemodynamic parameters were continuously monitored [heart rate (HR), invasive measurement of mean arterial blood pressure (MABP), oxygen saturation ($\text{SpO}_2\%$), and end-tidal carbon dioxide]. All the parameters were recorded before the induction, except for end-tidal carbon dioxide, which was recorded after intubation. Afterwards, they all were recorded every 30 min until the end of the surgery.

Intraoperative laboratory haemoglobin level was recorded after induction and repeated every hour till the end of the surgery. In addition to this, the total amount of blood loss, packed red blood cells (PRBCs) and fresh-frozen plasma (FFP) given were tabulated. the crystalloid and colloid volumes ,the number of patients who received noradrenaline and its duration along with the urine output (UOP) were plotted.

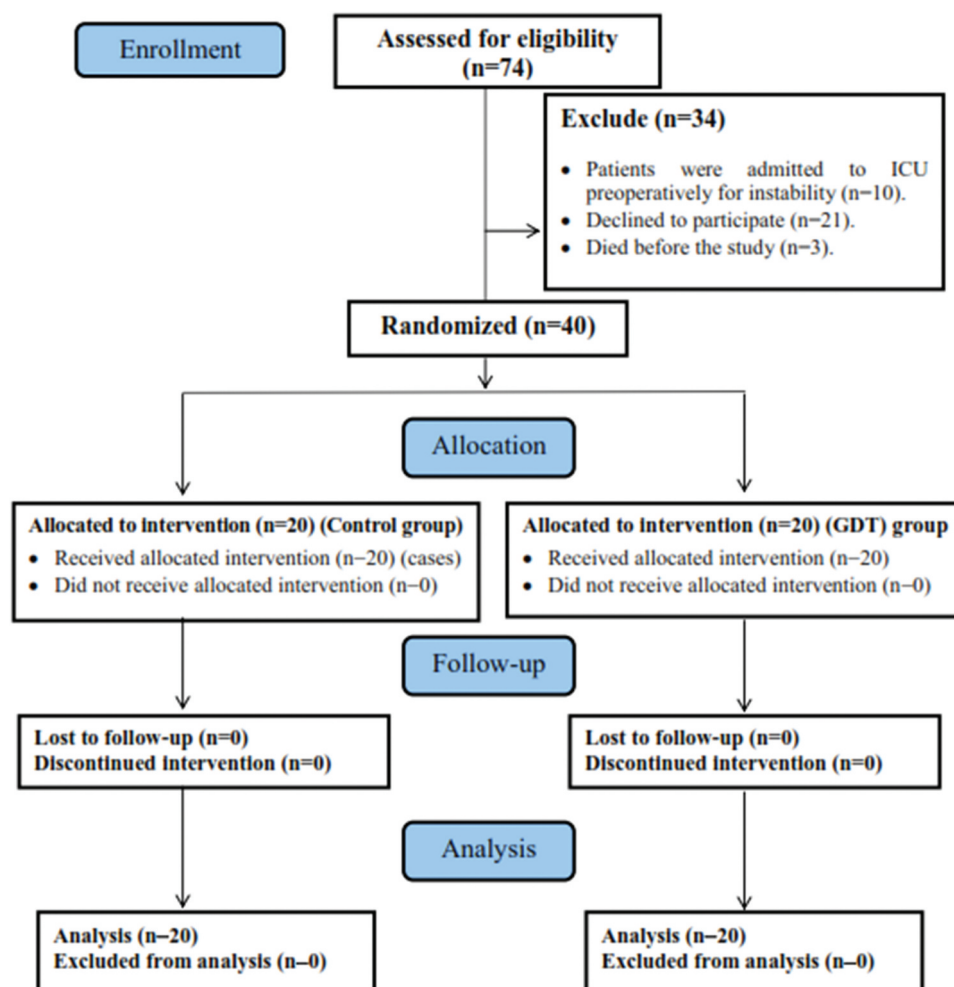


Figure 1. Study design. GDT: goal-directed fluid therapy.

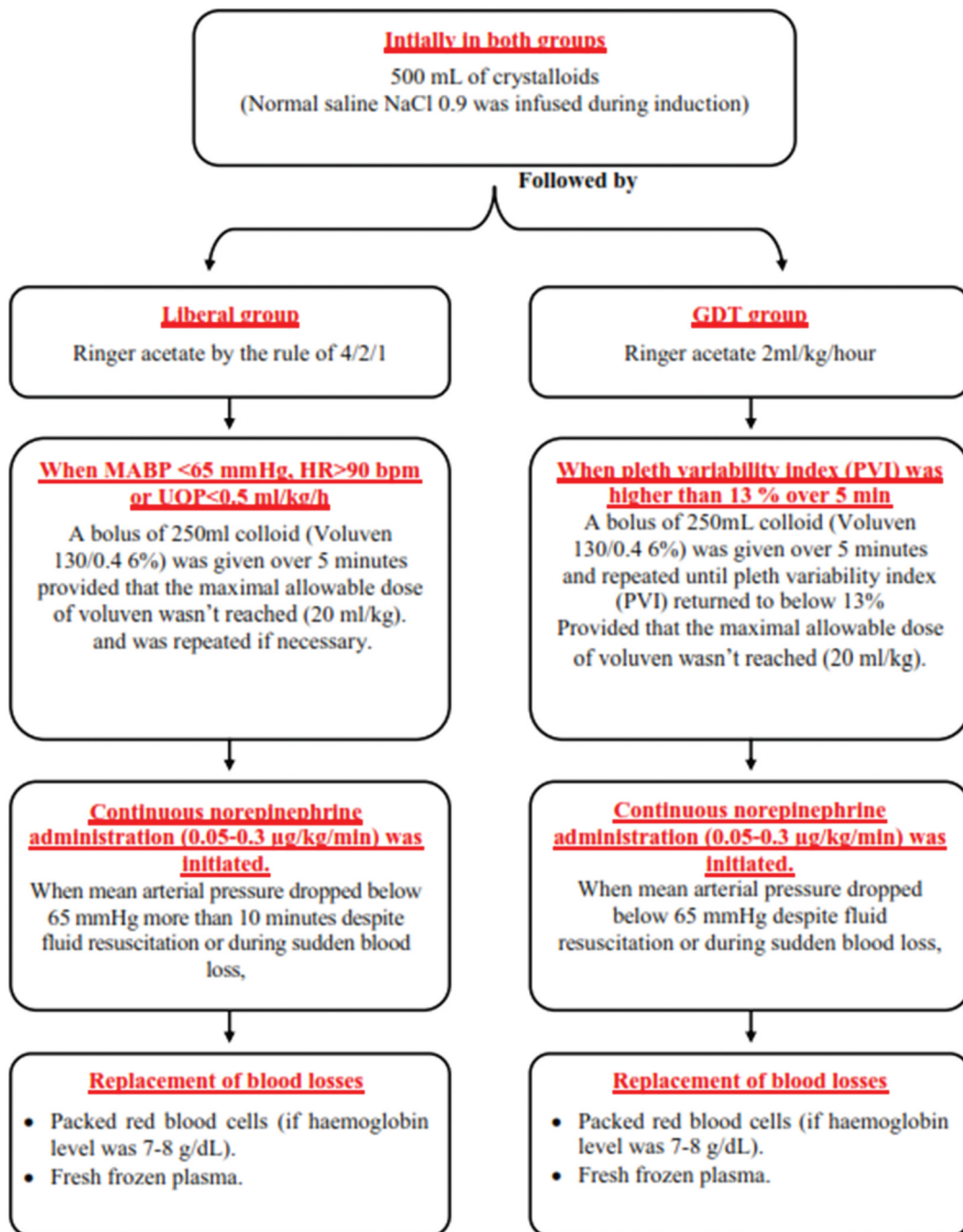


Figure 2. Fluid flowchart of the intraoperative period in both groups.

Postoperative staging of AKI according to KDIGO (i.e., rise in sCr by >0.3 mg/dl from baseline within the first 48 h postoperatively) on ICU admission (baseline) was recorded every 6 h for 2 days.

Postoperative kidney perfusion indices were tabulated. This included postoperative UOP, sCr, creatinine clearance, and blood urea nitrogen (all were measured every 6 h for 2 days after the end of the surgery). Urinary G1 cell cycle arrest biomarkers [(tissue inhibitors of metalloproteinases TIMP-2) \times (insulin growth factor-binding protein IGFBP7)] were measured by an ELISA technique in 100 ml urine sample collected at 4 and 12 h after ICU admission. The cutoff point for prediction was more than 0.3 (ng/ml)².

3. Results

Data were processed and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp.). Qualitative data were expressed in number and percent. Quantitative data were in the form of ranges (minimum and maximum) and mean together with standard deviation and median. The normality of distribution was done using Kolmogorov–Smirnov test. Significance was set at the 5% level. The used tests were as follows: (1) Chi-square test was used for categorical variables comparing between different groups; (2) Fisher's exact or Monte Carlo correction was used for correcting the chi-square; (3) Student t-test was used for normally distributed quantitative

variables ; (4) Mann–Whitney test was used for abnormally distributed quantitative variables ; (5) ANOVA was used for repeated normally distributed measures ; (6) *Post hoc* test (Bonferroni adjusted) was used for pairwise comparisons; (7) Friedman test was used for abnormally distributed quantitative variables ; (8) *Post hoc* test (Dunn's) and Spearman coefficient and lastly (9) receiver operating characteristic curve (ROC).

No significant difference was found between the two studied groups in age, gender, body mass index, the type of operation, and duration of the surgery.

Haemodynamic parameters such as HR, MABP, SpO₂ %, and end-tidal carbon dioxide were of no significant difference.

While comparing the intragroup data of each group, there was a statistically significant difference within the control group readings of HR in between 90 and 450 min. However, the HR significance within the GDT group showed a statistically significant difference only between 180 and 300 min.

Additionally, there was a statistically significant difference within the control group readings of MABP in the control group between 120 and 420 min, while it was significant within the GDT group only between 150 and 330 min.

There was no statistically significant difference between the number of hypotensive episodes in each patient, haemoglobin level, intraoperative blood loss along with total amount of PRBCs, and FFP given between both groups until the end of the surgery.

A statistically significant increase was found in the amount of crystalloid and colloid volume received in the control group compared to GDT group till the end of the study ($p < 0.001$ and 0.009 , respectively)

No statistically significant difference was found in the number of patients who received noradrenaline between both groups. However, a statistically significant increase was detected in the duration of noradrenaline received in the control group compared to GDT group till the end of the study ($p = 0.003$).

Moreover, no statistically significant difference was found in the intraoperative and postoperative 48 h UOP. To add, the control group readings showed a statistically significant decrease from baseline readings at the sixth intraoperative period and at the 18th hour of the postoperative period ($p = 0.019$ and 0.028 , respectively). However, the GDT group showed no statistically significant difference from baseline at any time through the intra- and postoperative 48 h.

There was no statistically significant difference in the blood urea nitrogen levels, creatinine, and creatinine clearance in the postoperative 48 h data in both studied groups.

Only five patients in the control group developed AKI (KDIGO I), while only one patient developed AKI in the GDT group, which revealed no statistically significant difference.

The mean value of the arrest biomarkers showed a statistically significant increase in the mean value of the cell cycle arrest biomarkers in the control group only at 4 h period ($p = 0.017$) (Table 1) (Figure 3). In addition, a statistically significant increase was in the number of patients with positive results in the control group at 4 h period ($p = 0.044$) (Table 2) (Figure 4).

From the 40 patients in the present study, 8 patients only had positive cell cycle arrest biomarkers (7 in the control group and 1 in the GDT group) at 4 h and 6 patients were positive at 12 h (5 in the control group and 1 in the GDT group). Out of which, only six patients developed AKI (five in the control group and one in the GDT group).

Urine TIMP-2*IGFBP-7 was more elevated in AKI patients than in the non-AKI patients at 4 h ($p = 0.003$) and 12 h ($p = 0.004$). The AUROC value of urinary TIMP-2*IGFBP7 at 4 and 12 h was 0.887 with a 95% confidence interval of 0.709–1.065 and 0.875 with a 95% confidence interval of 0.668–1.082, respectively (Table 3; Figure 5).

Applying the previously proposed cut-off level of 0.3 to the results, it returned in sensitivity/specificity of 83.33/91.18, respectively, at 4 h and 83.33/97.06, respectively, at 12 h Negative predictive values (NPV) were 96.88 at 4 h and 97.06 at 12 h.

Table 1. Comparison between the two studied groups according to postoperative urinary G1 cell cycle arrest biomarkers (ng/ml)².

Postoperative urinary G1 cell cycle arrest biomarkers (ng/ml) ²	Control (n = 20)	*GDT (= 20)	U	
4 h				
Median (Min.–Max.)	0.238 (0.115–0.760)	0.175 (0.100–0.770)	112.50*	0.017*
Mean ± SD	0.360 ± 0.236	0.207 ± 0.141		
12 h				
Median (Min.–Max.)	0.255 (0.120–0.730)	0.235 (0.060–0.750)	139.0	0.102
Mean ± SD	0.348 ± 0.217	0.238 ± 0.134		

U: Mann–Whitney test.

p: *p* value comparing between the two studied groups.

*Statistically significant at $p \leq 0.05$.

GDT: Goal-directed therapy.

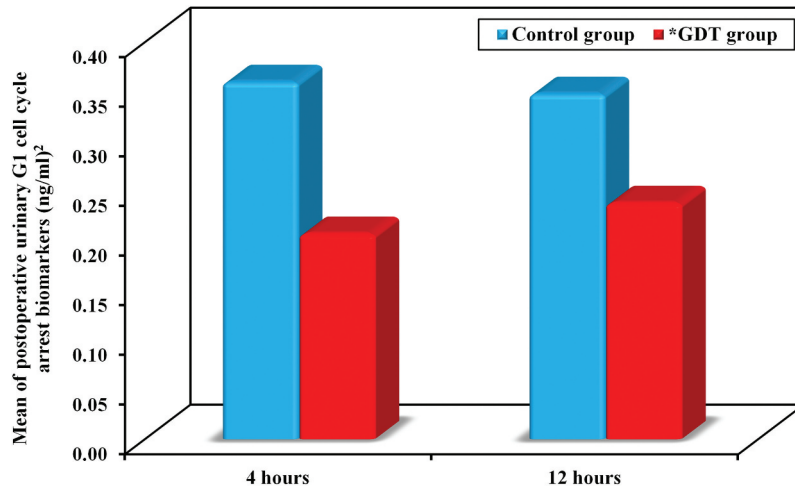


Figure 3. Comparison between the two studied groups according to postoperative urinary G1 cell cycle arrest biomarkers values (ng/ml)².

Table 2. Comparison between the two studied groups according to the number of patients with positive postoperative urinary G1 cell cycle arrest biomarkers.

Number of patients with positive postoperative urinary G1 cell cycle arrest biomarkers	Control group (n = 20)		*GDT group (n = 20)		χ²	FE p
	No.	%	No.	%		
4 hours	7	35.0	1	5.0	5.625*	0.044*
12 hours	5	25.0	1	5.0	3.137	0.182

χ²: Chi square test; FE: Fisher exact test.
 p: p value comparing between the two studied groups.
 *Statistically significant at p ≤ 0.05.
 †GDT: goal-directed therapy.

The present study attempted to draw some correlations between the cell cycle biomarker values and intraoperative haemodynamics, fluids, blood products received, and urine output in the patients of both the control and the GDT groups.

A statistically significant positive correlation was drawn between the positive marker values and hypotensive episodes, the estimated total amount of blood losses, the amount of crystalloid, and colloid volumes along with the duration of noradrenaline infusion in the control group, while there was no correlation between the previous parameters and the GDT group. In addition, both groups showed no statistically significant correlation in between the positive marker values and the total amount of PRBCs and FFP given.

To add, there was a statistically significant negative correlation between the positive marker values and the intraoperative and postoperative urine output in the control group at intraoperative 2nd, 3rd, 4th, 5th, 6th, 7th, and 8th hour, while there was no correlation between the intraoperative and postoperative urine output in the GDT group.

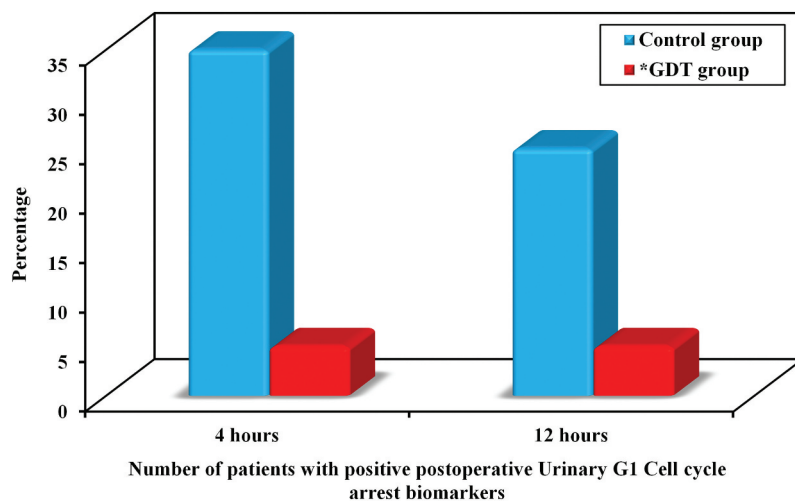


Figure 4. Comparison between the two studied groups according to number of patients with positive postoperative urinary G1 cell cycle arrest biomarkers.

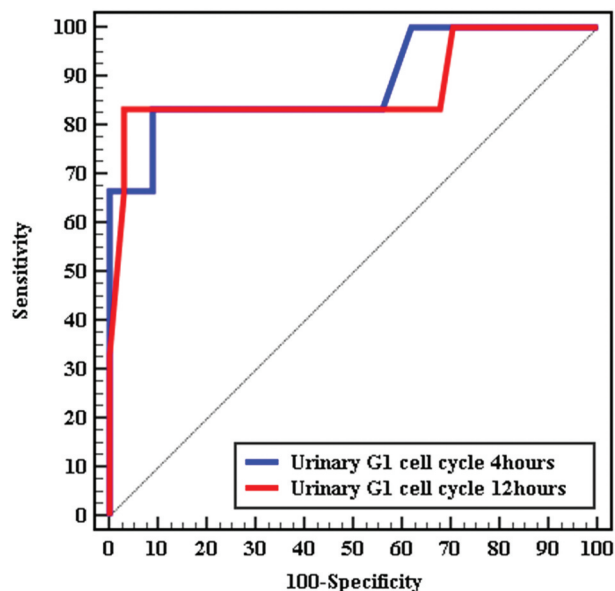
Table 3. Validity (AUC, sensitivity, and specificity) for postoperative urinary G1 cell cycle arrest biomarkers at 4 and 12 h to prognose patients with KDIGO ($n = 6$) from non-KDIGO ($n = 34$).

Urinary G1 cell cycle arrest biomarkers	AUC	p	95% CI	Cutoff	Sensitivity	Specificity	PPV	NPV
4 h	0.887	0.003*	0.709–1.065	>0.3	83.33	91.18	62.50	96.88
12 h	0.875	0.004*	0.668–1.082	>0.3	83.33	97.06	83.33	97.06

AUC: area under a curve; p value: probability value; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.

*Statistically significant at $p \leq 0.05$.

#Cutoff was chosen according to Youden index.

**Figure 5.** ROC curve for postoperative urinary G1 cell cycle arrest biomarkers at 4 and 12 h to predict patients with KDIGO ($n = 6$) from non-KDIGO ($n = 34$).

There was a statistically significant increase in the patients' number returning to normal peristalsis in the GDT group at 0–6 h along with a significant increase in the number of hospital stay days in the control group.

4. Discussion

Regarding the early AKI prediction of the arrest biomarkers, they predicted AKI in the postoperative period in major abdominal surgery using either usual or GDT fluid management.

In agreement with this, Jia et al. [5] conducted a meta-analysis on the urinary cell cycle arrest biomarkers for the early AKI prediction. They included nine studies assessing post-surgical patients. They agreed that the biomarkers are effective as AKI early predictors.

Moreover, Okuda et al. [6] designed a study to assess different biomarkers including the arrest biomarkers after emergency laparotomy. They found that arrest biomarkers are among the markers of AKI early prediction.

In addition, Gunnerson et al. [7] planned a subgroup analysis of the critically ill surgical patients in the previously reported studies of the arrest biomarker validation [8,9] including non-cardiac patients. They confirmed that a single reading of the arrest biomarkers can early predict AKI.

Again, Klein et al. [10] carried out a meta-analysis where 41 studies were included to evaluate 13 different biomarkers. The arrest biomarkers showed earlier AKI identification, and they had the highest predictive power.

On the contrary, Gocze et al. [11] studied urinary TIMP-2*IGFBP-7 in major non-cardiac surgeries. They performed a subgroup study only assessing hepatic surgeries and documented higher levels of urinary TIMP-2*IGFBP-7, which was not linked to AKI development. The authors explained that by early postoperative fluid deficit replacement which may have influenced the cell cycle arrest biomarkers and AKI development.

Schiefer et al. [12] conducted an observational study where the biomarkers were assessed in orthotopic liver transplantation (OLT). A rise in the urinary TIMP-2*IGFBP-7 was observed in OLT; however, there was no AKI predictive role. They suggested that this may be due to assessing the marker after 24 h, which may have missed a positive result during the first postoperative day. In addition, the authors included patients with comorbid conditions that may have changed the predictive power of the marker.

Waskowski et al. [13] performed an observational study in 93 patients with an abdominal aortic repair. They detected inadequate markers' sensitivity/specificity for postoperative AKI. It may be because of its assessment after the first postoperative day with the fact that the study was only an observational one.

Regarding the correlations drawn in the present study, a statistically significant *positive correlation* was found between the positive marker values and *hypotensive episodes in the control group*, while there was no correlation between the hypotensive episodes in the GDT group. The correlation may be attributed to the longer significant changes in the HR and MABP when compared to the baseline reading within the control group.

Agreeing with the present study, Kobayashi et al. [14] analyzed in a single-center retrospective cohort study the intraoperative modifiable factors to prevent AKI in elective non-cardiac surgery. They detected a positive correlation with intraoperative hypotension and postoperative AKI.

In the current study, a statistically significant *positive correlation* was found between the positive marker values and *estimated total amount of blood losses in the*

control group, while there was no correlation between the total amount of blood losses in the GDT group. This may be because blood loss would compromise the haemodynamic stability and oxygen delivery to renal tissues.

In agreement with this, Mizunoya et al. [15] used multivariate analysis to assess 135 patients who developed AKI following hepatectomy. They detected a positive correlation between the intraoperative blood loss and postoperative AKI.

Nishimoto et al. [16] studied the link between intraoperative fluid balance and the postoperative AKI in non-cardiac surgery and agreed to the same results.

A non-statistically significant correlation was detected between the positive marker values and total amount of PRBCs and FFP received in the control group and the GDT group. This could be due to the low transfusion threshold (only below 7–8 g/dl) adopted in both groups.

Yu et al. [17] disagreed with the present study. They assessed 850 patients in a single-center retrospective cohort to identify the factors associated with AKI in liver resection. Their results may be different because it included elderly patients with multiple comorbid condition with different transfusion thresholds.

A statistically significant positive correlation was detected between the positive marker values and the amount of crystalloid and colloid volumes in the control group, while there was no correlation between them.

Nishimoto et al. [16] reported a positive correlation between increased intraoperative fluids and postoperative AKI.

On the contrary, Kadam et al. [18] studied the incidence of AKI during the perioperative period in colorectal surgery. They detected no correlation between AKI and intraoperative fluid management, but their study included different fluid protocols for fluid management together with both open and laparoscopic approaches.

Moreover, Carrier et al. [19] conducted an observational cohort assessing different factors causing AKI after liver transplantation. They observed no effect of fluid balance on AKI. This could be attributed to the fact that their study was an observational one with different fluid management protocols included.

A statistically significant positive correlation was detected between the positive marker values and the duration of noradrenaline infusion in the control group, while there was no correlation in the GDT group. Vasopressors may help at first, but prolonged infusions may cause lactic acidosis and impaired oxygen delivery to the tissues, which may explain the positive correlation.

In agreement with this, Cordova-Sanchez et al. [20] conducted a retrospective study on 264 patients who developed AKI after oncological surgery. They reported a positive correlation between the duration of noradrenaline and the occurrence of AKI. Additionally, Giglio et al. [21] detected comparable results.

A statistically significant negative correlation was detected between the positive marker values and the intraoperative urine output in the control group at intraoperative 2nd hour up to the 8th hour, while there was no correlation between the intraoperative and postoperative urine output in the GDT group.

Kadam et al. [18] and Giglio et al. [21] agreed to have a negative correlation between urine output and postoperative AKI.

Regarding the secondary outcomes, Lee et al. [22] and Cavaleri et al. [23] agreed to have comparable results concerning the return to normal peristalsis. Furthermore, McEvoy et al. [24] agreed for the significant increase in the duration of hospital stay in the control group as in the present study.

On the contrary, Gottin et al. [25] showed insignificant results regarding the return to normal peristalsis. This may be because they addressed only pancreatic surgery unlike the present study.

Rollins et al. [26] reached an insignificant result in both the return of normal peristalsis and length of hospital stay, but they included studies that poorly documented the fluid regime used.

Regarding complications, there was only one case with biliary leak in the control group. Yet, no statistically significant difference was detected between the two groups.

The present study had some limitations, first, being a single-center study that might have limited the inclusion of more representable data. Second, the use of ELISA for the detection of the arrest biomarkers might have caused some delay in the observation and assessment of the target patients. Third, the use of the KDIGO creatinine definition of AKI only might have underestimated the load of the postoperative AKI as patients were followed only for the postoperative 48 h.

5. Conclusion

The present study concluded that cell cycle arrest biomarkers can predict AKI after major abdominal surgery. In addition, AKI incidence showed no difference between the control group and the GDT group. However, more fluid administration did expose more patients to the risk of AKI even if it was a transient injury. Lastly, GDT protocol showed earlier return of normal peristalsis and shortened hospital stay after major abdominal surgery.

Disclosure statement

No potential conflict of interest was reported by the authors.

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