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Novel Biomarkers for Prediction of Acute Kidney Injury After Open Heart Surgery: A Comparative Study

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Abstract
Background:
Acute kidney injury (AKI) patients have most elevated death indices, elongated hospital admissions, and a quicker progression of chronic kidney disease (CKD). In reaction to ischemia-reperfusion AKI, urine indicators are markedly elevated in the renal proximal tubules.
Aim: To evaluate new biomarkers that can predict acute renal injury following open heart surgery.
Patients and Methods: The 63 patients who underwent cardiovascular surgery for the current study were splited into double collections: the AKI group, which included 21 patients who experienced acute kidney injury following surgery, and the No AKI group, which included 42 patients who did not experience acute kidney injury following surgery. All patients have undergone thorough clinical examinations and history-taking procedures. Additionally, before and postoperative measurements of serum creatinine levels, sodium, potassium, blood urea, and urine output were made. At the ICU at 0, 3, 6, 12 and 24 hours following surgery, urinary hemojuvelin (HJV) and neutrophil gelatinase-associated lipocalin (uNGAL) levels were assessed.
Results: There was no statistically significant difference between postoperative hemojuvelin at 0 hr and hemojuvelin at 3,6,12, or 24 hours postoperatively, there were a statistical significance elevation in hemojuvelin at 3,6,12, and 24 hrs postoperatively in the AKI group compared to postoperative hemojuvelin at 0 hr. Additionally, there was a statistical significance rise in hemojuvelin at 3,6,12, and 24 hours after surgery in the AKI group compared to postoperative hemojuvelin at 0 hours, in contrast to the non-AKI group whereas there was no statistical significance differentiation between postoperative hemojuvelin at 0 hours and postoperative hemojuvelin at 3,6,12, and 24 hours after surgical operation. The ROC curve demonstrated that hemojuvelin and NGAL are effective predictors of acute kidney injury
Conclusion: According to our findings, combining urine biomarkers HJV and uNGAL can increase the clinical prediction power of AKI.

Keywords: Acute Kidney Injury, Open Heart Surgery, Urinary hemojuvelin.

1. Introduction

Acute kidney injury (AKI) patients had a higher death rate, a longer hospital admission, and a quicker development of chronic kidney disease (CKD) [1].
Despite improvements in contemporary medical care, AKI is accompanying with significant morbidity and death [2].
In clinical practise, it's critical to identify potentially substantial AKI as early as possible because doing so could help prompt quick care [3].
Despite having certain limits as an indicative predictor of AKI, serum creatinine has typically been used as a substitute for renal function. Lack of steady-state conditions and the deficiency of stable-state circumstances in vitally diseased persons and the variable nature of serum creatinine's determinants (rate of formation, apparent volume of distribution, and rate of elimination) in the ICU environment are some of serum creatinine's limitations [4].
New bio-markers can identify kidney tubular damage before testing serum creatinine when AKI is present [5].
These markers' indices in the urine, either alone or combined, may provide essential data about the development of AKI due to their link with renal tubular damage or function [6].
However, A collection of biomarkers may be applied to identify the development of advanced AKI or patient mortality following renal dysfunction. (e.g., Kidney Disease Improving Global Outcomes (KDIGO) stage 1) with temporary changes in serum creatin-immediate evaluation after potential kidney affection (e.g., cardiovascular surgery) [7]. To predict patient outcomes, other AKI intensity indices have also been created [8].
We also contrasted how the clinical Liano's score models contributed ***(Varricatt et al., 2009)***. The Cleveland Clinics of acute renal failure scale, Successive Organ Failure Assessment (SOFA) score, and urinary biomarkers were used to discover and test the most precise expectation example for progressed AKI and compound consequences in patients following open heart operation [2].
Our goal was to evaluate novel indicators that could predict acute renal impairment following open heart surgery.

2. Patients and methods

A prospective cohort study carried out at ICU Department, national Heart Institute and Faculty of medicine, Benha University during the period from January 2022 to July 2022. This study approved by ethical committee from the ethics unit at faculty of medicine Benha University, Cairo. A written consent had been taken from all cases before participation in this research.

The current study included 63 patients inwhich made cardiovascular procedure, involving coronary bypass and valvular procedures, all were separated into double collections:

- The first called (AKI group): contained 21 diseased candidates whom developed acute kidney injury after surgery.
- The second called (No AKI group): contained 42 patients who didn't develop acute kidney injury after surgery.

2.1. Exclusion criteria:

- Patients whom aged lesser than 18 years or elder than 70 years.
- Patients who received dialysis or kidney alternative cure.
- Patients with history of nephrectomy or used nephrotoxic drugs before or during the study
- Diseased persons with starting point serum creatinine above 1 mg/dl.

All patients had been submitted to suitable history, suitable general and local exams, with recorded serum creatinine levels, sodium, potassium, blood urea and urine output, preoperative and at every day postoperative. Urinary hemojuvelin and NGAL were measured at ICU at 0, 3, 6, 12 and 24 hours after surgery.

2.2. Sample Collection:

Within an hour, the urine collected samples were centrifuged, and the sediments were eliminated. Before to use, the urine samples were kept at 20 °C in single, sterile polypropylene tubes. Each sample was cooled to room temperature and being centrifuged at 800 g for 5 minutes and collecting the supernatant for ELISA testing.

2.3. Biomarker Measurements:

The urinary HJV and NGAL levels were measured using a human HJV ELISA Kits and a human neutrophil gelatinase-associated lipocalin ELISA kits respectively.. The minor limit of recognition for HJV and NGAL was 0.156 and 0.2 ng/mL, respectively. Assays were completed as described by the manufacturer's protocol.

2.4. Statistical analysis:

With the aid of the IBM SPSS software package version 20.0, data were loaded into the computer and evaluated (Armonk, NY: IBM Corp). Collected variables were shown as percentages and numbers. The range (minimum and maximum), mean, standard deviation, and median were used to express distributed data. The Student t-test and Chi-square test were employed. P value < 0.05 was regarded as significant.

3. Results

A total of 63 patients involved in this study who divided in patients with AKI (21 patients) and without AKI (42 patients), the age of participants was from 19 to 70 years, with Mean ± SD. 45.33 ± 16 years in the AKI group, and ranged from 20 to 70 years, with Mean ± SD. 46.81 ± 16.04 years in the no AKI group. There were 11(52.4%) females in AKI group and 25(59.5%) females in the no AKI group. There was no significant difference between the two groups as regards gender, age, and BMI (Table 1).

As regard comparing among the two groups as regards creatinine showed that there was non statistical significant difference between the two groups as regards preoperative creatinine and day one while there were statistical significance elevations in AKI group as regards creatinine at days two, and three postoperatively. There was statistically significant increase in creatinine at days two, and three postoperatively in the AKI group than preoperative creatinine, in contrast to non-AKI group where there was no statistically significant difference between preoperative creatinine and creatinine at days one, two, and three postoperatively (Table 2).

As regard comparing among the two groups as regards urea showed that there was non statistically significance variation between the two groups as regards preoperative urea and day one postoperatively while there were statistical significance elevations in AKI group as regards urea at days two, and three postoperatively. there were statistical significance elevations in serum urea values at days two, and three postoperatively in the AKI group than preoperative urea, in contrast to non-AKI group whereas there was no statistically significance variation between preoperative urea and urea at days one, two, and three postoperatively (Table 2).

The comparison between the two groups as regards urine output showed that there was no statistically significant difference between the two groups as regards preoperative urine output there were statistical significance reduction in AKI group as regards urine output at days one, two, and three postoperatively. There was statistically significant decrease in urine output at days one, two, and three postoperatively in the AKI group than preoperative urine output, in contrast to non AKI group where there was no statistically significant difference between preoperative urine output and urine output at days one, two, and three postoperatively (Table 2).

The comparing values between the double groups as regards hemojuvelin showed that there was statistically significant increase in AKI group as regards postoperative hemojuvelin at 0,3,6,12, 24 hrs postoperatively. There was statistically

significant increase in hemojuvelin at 3,6,12,24 hrs postoperatively in the AKI group than postoperative hemojuvelin at 0 hr, in contrast to non-AKI group where there was no statistically significant difference between postoperative hemojuvelin at 0 hr and hemojuvelin at 3,6,12,24 hrs postoperatively (Table 3).

The comparison between the two groups as regards NGAL showed that there was statistically significant increase in AKI group as regards postoperative NGAL at 0,3,6,12, 24 hrs postoperatively. There was statistically significant increase in NGAL at 3,6,12,24 hrs postoperatively in the AKI group than postoperative NGAL at 0 hr, in contrast to non-AKI group where there was no statistically significant difference between postoperative NGAL at 0 hr and NGAL at 3,6,12,24 hrs postoperatively (Table 4).

There was statistically significant association between AKI Severity and NGAL and hemojuvelin post operative, where their level increase as the severity increase (Table 5).

ROC curve showed that hemojuvelin and NGAL are good predictors of acute kidney injury postoperatively (Figure 1&2).

Table (1) Comparison between groups as regards demographic Data

	AKI group (n = 21)		**No AKI group (n = 42)**		**Test of sig.**	**P-value**
	No.	**%**	**No.**	**%**		
Gender					$\chi 2$ = 0.292	0.589
Male	10	47.6%	17	40.5%		
Female	11	52.4%	25	59.5%		
Age (years)					t = -0.345	0.732
(Min. – Max.)	(19 –70)		(20–70)			
Mean ± SD.	45.33 ± 16		46.81 ± 16.04			
BMI					t = -1.326	0.190
(Min. – Max.)	(21 –28)		(21–31)			
Mean ± SD.	24.17 ± 1.94		25.02 ± 2.58			

($\chi 2$): Chi-square Test **t:** Student T-Test

p: p value for comparing between the studied groups

Table (2) Comparison between AKI group and no AKI group as regards creatinine

	AKI group (n = 21)			**No AKI group (n = 42)**			**P-value**
	Mean ± SD			**Mean ± SD**			
Creatinine (Cr)							
Pre Cr	0.85	±	0.08	0.859	±	0.06	0.765
Cr Day 1	0.88	±	0.07	0.855	±	0.04	0.327
Cr Day 2	1.13	±	0.37	0.857	±	0.06	<0.001
Cr Day 3	1.33	±	0.48	0.856	±	0.06	<0.001
P pre and Day 1	0.203			0.733			
P pre and Day 2	<0.001			0.083			
P pre and Day 3	<0.001			0.785			
Urea							
Pre urea	49.33	±	16.635	49.12	±	17.104	0.799
Urea Day 1	57.51	±	29.003	49.31	±	17.173	0.527
Urea Day 2	60.16	±	31.136	49.37	±	16.649	<0.001
Urea Day 3	62.90	±	33.168	49.78	±	16.945	<0.001
P pre and Day 1	0.512			0.155			
P pre and Day 2	<0.001			0.159			
P pre and Day 3	<0.001			0.090			
Urine output							
Pre urine output	3043.14	±	677.303	3153.97	±	564.110	0.715

Urine output Day 1	1390.00	±	346.987	3181.97	±	562.667	<0.001
Urine output Day 2	1190.52	±	278.220	3159.26	±	563.924	<0.001
Urine output Day 3	1023.81	±	182.770	3156.56	±	520.640	<0.001
P pre and Day 1	<0.001			0.788			
P pre and Day 2	<0.001			0.856			
P pre and Day 3	<0.001			0.153			

Table (3) Comparison between AKI group and no AKI group as regards hemojuvelin

	AKI group (n = 21)			**No AKI group (n = 42)**			**P-value**
	Mean ± SD			**Mean ± SD**			
T0-hemojuvelin	757.95	±	186.96	521.88	±	181.98	<0.001
T3-hemojuvelin	946.33	±	241.27	522.48	±	181.91	<0.001
T6-hemojuvelin	1050.76	±	268.32	522.83	±	181.81	<0.001
T12-hemojuvelin	1169.81	±	310.24	523.45	±	182.07	<0.001
T24-hemojuvelin	1283.33	±	332.90	522.98	±	181.97	<0.001
P T0 and T3	<0.001			0.253			
P T0 and T6	<0.001			0.083			
P T0 and T12	<0.001			0.190			
P T0 and T24	<0.001			0.079			

p: p value for comparing between the studied groups

Table (4) Comparison between AKI group and no AKI group as regards NGAL

	AKI group (n = 21)			**No AKI group (n = 42)**			**P-value**
	Mean ± SD			Mean ± SD			
T0- NGAL	284.71	±	42.02	205.95	±	49.93	<0.001
T3- NGAL	310.67	±	46.74	210.02	±	51.22	<0.001
T6- NGAL	315.81	±	52.59	215.12	±	53.00	<0.001
T12- NGAL	342.48	±	63.08	216.88	±	56.27	<0.001
T24- NGAL	376.52	±	74.45	224.26	±	65.48	<0.001
P T0 and T3	<0.001			0.529			
P T0 and T6	<0.001			0.122			
P T0 and T12	<0.001			0.450			
P T0 and T24	<0.001			0.721			

p: p value for comparing between the studied group

Table (5) Association between AKI Severity and NGAL and hemojuvelin post operative

	AKI Severity									**P-value**
	Grade I (no=15) Mean ±SD			**Grade II (no=3) Mean ±SD**			**Grade III (no=3) Mean ±SD**			
T0-NGAL	265.67	±	31.63	314.33	±	10.02	350.33	±	7.51	<0.001
T3-NGAL	291.67	±	40.70	344.00	±	10.15	372.33	±	8.50	0.04
T6-NGAL	293.20	±	42.57	350.67	±	10.21	394.00	±	6.00	<0.001
T12-NGAL	315.53	±	52.72	392.33	±	18.50	427.33	±	4.51	0.002
T24-NGAL	345.20	±	62.69	433.00	±	26.06	476.67	±	7.51	0.002

T0-hemojuvelin	720.00	±	148.90	875.33	±	212.65	1030.33	±	129.64	<0.001
T3-hemojuvelin	837.20	±	167.67	1064.67	±	28.57	1373.67	±	15.50	<0.001
T6-hemojuvelin	925.93	±	185.23	1219.33	±	39.88	1506.33	±	85.94	<0.001
T12-hemojuvelin	1024.0	±	207.09	1350.67	±	50.64	1718.00	±	20.07	<0.001
T24-hemojuvelin	1128.1	±	224.49	1470.00	±	2.65	1872.67	±	39.51	<0.001

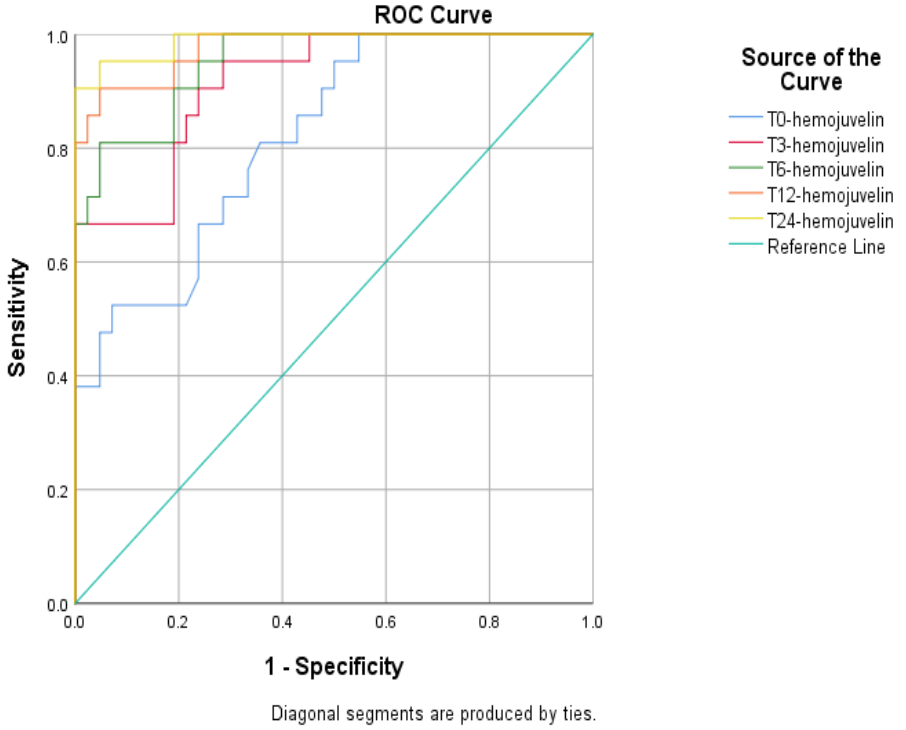

Fig. (1) ROC curve for hemojuvelin cutoff regard AKI

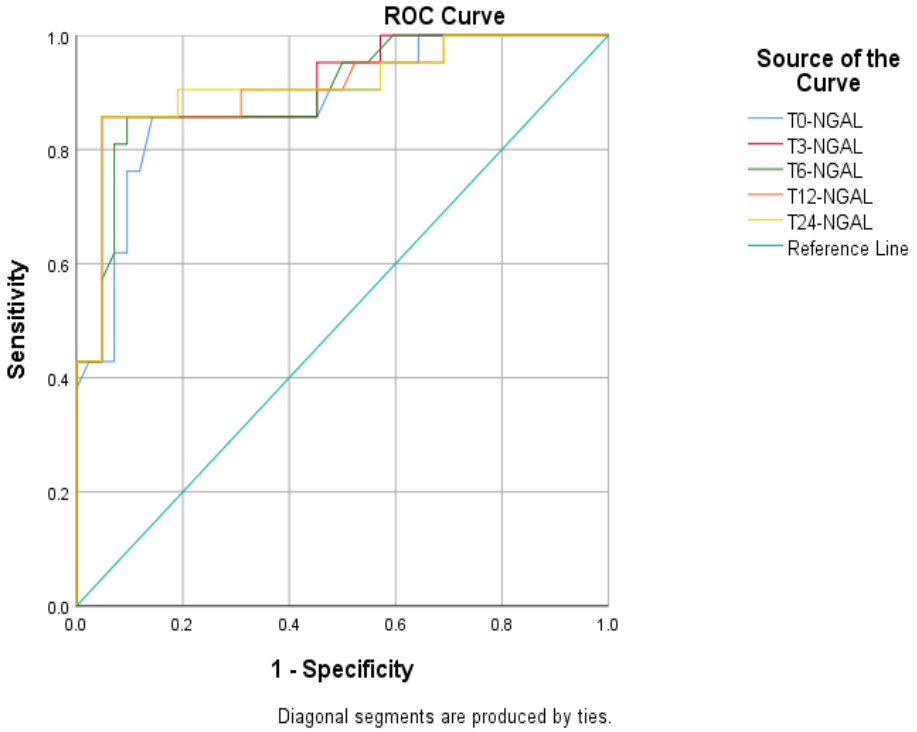

Fig. (2) ROC curve for NGAL cutoff regard AKI

4. Discussion

Acute kidney injury (AKI) patients had a higher death rate, a prolonged hospital admission, and a quicker progress of chronic renal disease (CKD). Despite improvements in contemporary medical care, AKI is accompanied with rised morbidity and death [10].

Urine haemojuvelin (uHJV), urinary kidney injury molecule-1 (uKIM-1), and urinary -glutathione S-transferase (u-GST), as well as one marker of distal tubule injury, are all considerably elevated in kidney proximal tubules in responding to ischemic-reperfusion AKI [2].

Other studies To authenticate the expectation of AKI following successive bio-marker readings after open heart surgical procedure, the well-established and investigated inflammatory bio-markers seen in both proximal and distal kidney tubular destruction was used. Furthermore, Several AKI severity scores had also been created for predicting diseased persons outcomes [11].

Our goal was to evaluate novel indicators that could predict acute renal impairment following open heart surgery.

According to our findings, there was a statistically significant rise in postoperative hemojuvelin at 0, 3, 6, and 12 hours postoperatively in the AKI group. In contrast to the non-AKI group, where there was no statistically significant difference between postoperative hemojuvelin at 0 hr and hemojuvelin at 3,6,12, or 24 hrs postoperatively, there were statistical significance rise in hemojuvelin at 3,6,12, and 24 hrs postoperatively in the AKI group compared to postoperative hemojuvelin at 0 hr. Hemojuvelin is a reliable indicator of acute kidney impairment following surgery, according to our study.

In the AKI candidates and non-AKI candidates, [12] showed the corresponding HJV values with or without normalization to urine creatinine at different postoperative time points. In the AKI group, postoperative rise of HJV was seen, according to GEE analysis (across time, p=0.032).

In a study by [2], they demonstrated how the novel HJV biomarker can forecast AKI following cardiac surgery. This finding supported our earlier observation that individuals with cardiac surgery and AKI due to rhabdomyolysis had elevated urine HJV levels. Even though HJV is strongly expressed in the liver, there was no discernible difference in post-surgery liver function between the groups with no AKI/ stage 1 AKI and stage 2/3 AKI. This finding suggested that kidney injury was the primary cause of the increased HJV levels found in patients with advanced AKI. Our animal model suggests that filtration after kidney tubular impairment, rather than the liver, should be the initial source of the rise of urine HJV in acute tubular necrosis.

We discovered that postoperative NGAL at 0, 3, 6, 12 and 24 hours postoperatively in the AKI group showed a statistically significant increase according to urinary NGAL. In contrast to the non-AKI group, where there was no statistically significant difference between postoperative NGAL at 0 hr and NGAL at 3,6,12,24 hrs postoperatively, there was a statistically significant increase in NGAL at 3,6,12,24 hrs postoperatively in the AKI group compared to postoperative NGAL at 0 hr. Our research demonstrated that NGAL is a reliable indicator of acute renal damage following surgery.

According to [13], preoperative baseline serum NGAL levels in the AKI group were higher (104.22 23.2 g/L) than in the non-AKI group (82.22 30.5 g/L) (p 0.01) and remained the same during all time fractions. The AKI group then showed an increase in the pre-operative time compared to the non-AKI group (p 0.01) (213.52 53.6 g/L vs. 156.25 45.9 g/L). In the postoperative periods, a stepwise rise began at 2 hours and continued until it peaked at 24 hours of CPB (154.14 63.5 g/L in the AKI group and 69.96 28.5 g/L in the non-AKI group, p 0.05). To demonstrate the degree of divergence between eras, the Kruskal-Wallis test impressively indicated a strong significance in the AKI group and the non-AKI group.

According to the results of the current investigation, there is a statistically significant relationship between post-operative NGAL and hemojuvelin levels and the degree of AKI severity.

In keeping with our findings, [12] demonstrated that the AUCs for HJV and NGAL were 0.768 and 0.682, respectively, at three hours following surgery. Adjusting for urine creatinine improved the diagnostic precision of NGAL and HJV (AUC of 0.784 and 0.694, respectively). After adjusting for urine creatinine, their data showed that the HJV had greater diagnostic accuracy than NGAL for both patients with and without advanced AKI (by AUC comparison, p=0.037).

Friedrich et al. [14] shown, in contrast to our findings, that there is no significant link between highest uNGAL values (at Tp2) and advanced

postoperative AKIN values for prediction. Additionally, there is no discernible link between the length of CPB and the values of uNGAL (at Tp1 and Tp2).

Our study also provides a number of advantages. It began by including a uniform patient population (after cardiovascular surgery). Second, our study examined urine specimens collected at the ICU at 0, 3, 6, 12 and 24 h after the conclusion of the procedure. This permitted the investigation about the dynamic alterations in their urine concentrations and produced more thorough and reliable results than previous researches. These biomarkers included signs of proximal and distal tubular damage. Urinary biomarkers can help diagnose AKI more precisely and can also be used to enroll more homogeneous patient populations in research trials.

5. Conclusion

Our findings suggest that urine biomarkers, particularly the combination of HJV and uNGAL, can enhance the clinical prognostic power of AKI. Clinical AKI score and biomarker-based risk prediction could improve critical care and help predict postoperative patient outcomes.

References

[1] Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail?. Kidney international, 87(1):46-61.2015.

[2] Wang JJ, Chi NH, Huang TM, Connolly R, Chen LW, Chueh SC, Kan WC, Lai CC, Wu VC, Fang JT, Chu TS. Urinary biomarkers predict advanced acute kidney injury after cardiovascular surgery. Critical care, 22(1):1-3.2018.

[3] Zarbock, A., Kellum, J. A., Schmidt, C., Van Aken, H., Wempe, C., Pavenstädt, H., Meersch, M. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. Jama, 315(20), 2190-2199.٢٠١٦.

[4] Dennen, P., Douglas, I. S., & Anderson, R. Acute kidney injury in the intensive care unit: an update and primer for the intensivist. Critical care medicine, 38(1), 261-275.2010.

[5] Young, G. H., Huang, T. M., Wu, C. H., Lai, C. F., Hou, C. C., Peng, K. Y., et al. Hemojuvelin modulates iron stress during acute kidney injury: improved by furin inhibitor. Antioxidants & redox signaling, 20(8), 1181-1194.٢٠١٤.

[6] Siew, E. D., Ware, L. B., & Ikizler, T. A. Biological markers of acute kidney injury. J Am Soc Nephrol, 22(5), 810-820. 2011.

[7] Arthur, J. M., Hill, E. G., Alge, J. L., Lewis, E. C., Neely, B. A., Janech, M. G., SAKInet Investigators. Evaluation of 32 urine biomarkers to predict the progression of acute kidney injury after cardiac surgery. Kidney international, 85(2), 431-438.٢٠١٤.

[8] Ohnuma, T., Uchino, S., Toki, N., Takeda, K., Namba, Y., Katayama, S., ... & Nagata, I. External validation for acute kidney injury severity scores: a multicenter retrospective study in 14 Japanese ICUs. American Journal of Nephrology, 42(1), 57-64.٢٠١٥.

[9] Varricatt, V. P., Rau, N. R., Attur, R. P., & Baig, W. W. Validation of Liano score in acute renal failure: a prospective study in Indian patients. Clinical and experimental nephrology, 13(1), 33-37.٢٠٠٩.

[10] Negi, S., Koreeda, D., Kobayashi, S., Yano, T., Tatsuta, K., Mima, T., et al. Acute kidney injury: Epidemiology, outcomes, complications, and therapeutic strategies. In Seminars in dialysis, 31) 5): 519-527.2018.

[11] Ma, J., Deng, Y., Lao, H., Ouyang, X., Liang, S., Wang, Y., et al. A nomogram incorporating functional and tubular damage biomarkers to predict the risk of acute kidney injury for septic patients. BMC nephrology, 22(1), 1-13.2021.

[12] Ko, Sheng-Wen & Chi, Nai-Hsin & Wu, Che-Hsiung & Huang, Tao-Min & Chueh, Shih-Chieh & Wang, Chih-Hsien & Lin, et al. Hemojuvelin Predicts Acute Kidney Injury and Poor Outcomes Following Cardiac Surgery. Scientific Reports. 8. 10.1038/s41598-018-20212-8.2018.

[13] Mosa, O. F. Prognostic significance of serum NGAL and troponin I against acute kidney injury in Egyptian ICU patients after open heart surgery: a pilot study. Kidney Diseases, 4(4), 246-254.2018.

[14] Friedrich, M. G., Bougioukas, I., Kolle, J., Bireta, C., Jebran, F. A., Placzek, M., & Tirilomis, T. NGAL expression during cardiopulmonary bypass does not predict severity of postoperative acute kidney injury. BMC nephrology, 18(1), 1-7.2017.