KIDNEY INJURY MOLECULE-1 AND HUMAN NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN AS NOVEL URINARY BIOMARKER FOR EARLY DETECTION OF PLATINUM-BASED DRUGS INDUCED NEPHROTOXICITY: CLINICAL STUDY

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ABSTRACT

Background The most severe side effect of platinum-based anticancer drugs is nephrotoxicity, which is the main barrier to the use of large dosage protocols to maximize the curative advantages. A common biomarker to detect drug-induced acute nephrotoxic injury is serum creatinine level. **Objectives** This research necessitates the search for new biomarkers in those patients. **Methodology** Fifty-nine patients getting platinum-based drugs participated in a cross-sectional study. According to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines 2012, acute renal damage was detected by routinely testing serum creatinine levels. On the first day of therapy and for three days after the drugs` cycle, serum creatinine and urine biomarkers (kidney injury molecule- 1 and human neutrophil gelatinase-associated lipocalin) were assessed. **Results** Thirty-nine patients (66.1% of patients) experienced nephrotoxicity. The previous urine biomarkers showed a significant increase in samples collected. Compared to their baseline levels, all indicators considerably increased on the third day ($P < 0.001$). The optimum previous kidney injury molecule- 1 and human neutrophil gelatinase-associated lipocalin biomarkers` cutoffs for diagnosing platinum-based drugs-induced nephrotoxicity are ≥1.345 with an area under the curve of 0.87, 92.3% sensitivity, and 80 % specificity, & ≥418.95 with an area under the curve of 0.772, 87.2% sensitivity, and 80 % specificity respectively. Compared to serum creatinine, urinary biomarkers are more accurate than serum creatinine for predicting nephrotoxicity caused by platinum-based drugs. **Conclusion** The most precise biomarker for platinum-based drug patients' early nephrotoxicity prediction is kidney injury molecule -1.

Keywords: Cisplatin, Nephrotoxicity, Oxaplatin, Platinum-based drugs, Urinary biomarkers.

INTRODUCTION

The kidney is a crucial organ that is targeted by the toxicities of several chemotherapeutics. Around 8–60% of hospital-acquired acute kidney injuries are caused by chemicals **(Dasta et al., 2005).** According to studies, the incidence of acute renal injury increased dramatically between 1980 and 2005, going from 18 cases per 100,000 people in 1980 to 365 cases in 2005 **(Bentensky et al., 2012).** Diagnosis and management of drug-induced acute nephrotoxic damage (ANI) mostly depends on serum creatinine which depends on

creatinine's pharmacokinetics and volume of distribution leading to inaccurate interpretation **(Hsu, 2009).** Moreover, unnoticeable increases in serum creatinine were recorded in high rates of mortality. Thus, serum creatinine has limited utility as a diagnostic tool in instances of ANI **(Xue, 2009).**

To identify the stage of renal impairment before renal filtration capacity disruption happens, many biomarkers were examined and researched. These more recent biomarkers, as opposed to conventional renal function indicators, are necessary for accurate screening of renal functions. N-acetyl-glucosaminidase (NAG), Cystatin-C (Cys-C), 2-microglobulin (2M), Kidney Injury Molecule-1 (KIM-1), and Human Neutrophil Gelatinase-Associated Lipocalin (NGAL) are promising renal biomarkers **(Vaidya et al., 2008).** KIM-1 and NGAL have been shown to have a strong predictive effect in previous studies **(Abdelsalam et al., 2018).** Their effectiveness as biomarkers for acute renal injury were supported by other clinical investigations **(Jani et al., 2006; Hau et al., 2010).**

In treating various cancers, platinum-based anticancer drugs (PBD) such as carboplatin, oxaliplatin, and cisplatin are frequently utilized. Acute nephrotoxic injury was observed in around 25–34% of patients who received a single dose of cisplatin **(Ali et al., 2013);** nephrotoxicity incidence and severity increased in the following cycles **(Kuriakose and Kurup, 2008).** The most difficult problem facing patients with ANI is the necessity to lower the dosage of cisplatin which limits the drug's clinical utility or leads to modifying the chemotherapy regimen **(Kawai et al., 2009).** Moreover, only a few cases of ANI who received oxaliplatin chemotherapy were reported **(Barabas et al., 2008).** The least nephrotoxic PBD is carboplatin, however, its myeloablative dosages of 800 mg/m^2 are nephrotoxic **(Misra et al., 2010).** Furthermore, acute interstitial nephritis occurred in individuals who received carboplatin (**Azadeh et al., 2014)** with 4-5% of individuals taking carboplatin were reported to have grade 1 or 2 nephrotoxicity **(Isnard-Bagnis et al., 2008).**

As far as we are aware, only a few studies have searched the usefulness of novel renal biomarkers for detecting drug-induced acute nephrotoxic damage. Therefore, this investigation aims to evaluate urine KIM-1 and NAGL levels as biomarkers for early diagnosis of ANI in patients receiving PBD in a prospective trial at Zagazig University hospitals in Egypt.

MATERIALS AND METHODS

Ethical approval:

A letter of approval was obtained from the Zagazig University Faculty of Medicine's Ethics Committee for Research (ZU-IRB # 10431/12-2-2023). Before collecting the sample, a written informed consent describing the study's purpose and the participant's right to withdraw at any time without affecting the health services offered. Patient anonymity is protected through the gathering of anonymous data, and the data will only be utilized for research. This study was conducted in conformity with the Declaration of Helsinki, which is the World Medical Association's code of ethics for human subjects studies.

Study population

The patients included in this cross-section study were admitted to the Clinical Oncology and Nuclear Medicine department at Zagazig University Hospital in Egypt and who had undergone the curative PBD regimen (Table 2) between March 2023 and May 2023.

Inclusions and exclusion criteria:

1-In our study, patients who were either male or female and had normal kidney function assessments (serum creatinine less than 1.1 mg/dl, which indicated that the patient's glomerular filtration rates exceeded 90 ml/min according to The Modification of Diet in Renal Disease MDRD equation declared by **Andrew et al. (2006)** were included.

2-The patients who started therapy with renal dysfunction, active infection, heart failure, diabetes mellitus, thyroid, or suprarenal diseases were excluded, as were those who received palliative platinum-based medication therapy.

3-Those with a history of renal disease, taking nephrotoxic medications, or who had contrast-enhanced imaging within the preceding four weeks were not included in this study.

4-Those who had brain metastases, anemia, dehydration, or increased liver enzyme levels were also disqualified. Only 59 patients were

included in this study due to these exclusion criteria.

All patients received the recommended amount of water according to the hydration regimen **(Aubrie et al., 2020).** Every patient enrolled was well hydrated. Sodium chloride 0.9% in 1000 mL, 20 mmol KCL in 500 mL, and 10 mmol MgSO4 in 500 mL were given before PBD. After PBD, 1000 mL of sodium chloride 0.9% with 20 mmol KCL and 10 mmol MgSO4 is administered IV in the same manner during PBD administration **(Ming-Jium and Shin-yu 2020).** Observation during chemotherapy, keep an eye on patients' urine output at frequent intervals. Pre-discharge: Make sure the patient can maintain a healthy oral fluid intake, encourage the patient to drink a lot of fluids and instruct the patient to call the hospital in case of persistent vomiting.

Study design

Questionnaire includes:

Age, gender, cancer type, PBD agent received, and sociodemographic information are all covered in the questionnaire.

Serum creatinine level:

Prior to beginning PBD medication, and for the next three days of the treatment cycle, five ml of venous blood samples were taken. Blood samples were centrifuged at 5000 g for 10 minutes to separate the serum after being allowed to clot for 15 minutes. The modified rate Jaffe method was used to measure the levels of creatinine. For human sample use, its DetectX® kits were marketed in Germany **(Heinegard and Tiderstrom, 1973).**

Urinary KIM-1 and NAGL levels:

At the same time as blood samples were taken, 10 ml of urine was collected in cups without the addition of preservatives. Supernatants were collected and kept at - 20 °C after centrifuging urine samples at 1000 g for 5 min. According to the manufacturer's instructions, urine KIM and NAGL levels were assessed using an ELISA kit from Sunred Biological Technologies, China. According to **Heinegard and Tiderstrom, (1973),** inter-assay and intra-assay variability for biomarkers were assessed in the following table:

Table (1): Inter-assays and inter-assay variability of the studied urinary biomarkers ELISA assays.

Urinary biomarker	Inter-assay variability	Intra-assay variability
KIM-1	High (10 ng/ml) = 9.1%	5.64%
	Low (0.1 ng/ml) =10.56%	
NGAL	High (1000 ng/ml) =9.1%	6..81%
	Low (10 ng/ml) =4.5%	

KIM: Kidney injury molecule- 1. NGAL: Human neutrophil gelatinase-associated lipocalin

Drugs regimen given according to cancer type:

Gastrointestinal cancer: patients were given paclitaxel 175mg/m^2 + carboplatin (AUC5) 5 fu 1000 mg/m^2 D1- D4 + cisplatin 75 mg/m^2 5 fu + oxaliplatin (FOLFOX or Xelox).

Respiratory cancer: patients were given (Cisplatin 75 mg/m^2 + paclitaxel 135 mg/m^2 Or Carboplatin AUC 5 + paclitaxel 225 mg/m^2 in a case of non-small cell lung cancer) and Cisplatin 75 mg/m^2 + vespid 100 mg/m^2 D1- D3 in a case of small lung cancer).

Reproductive cancer: patients were given (Bleomycin 30 units IV D1, D8, D15 + Etoposide 100 mg/m^2 d1- D5 + Cisplatin 20 mg/m^2 D1- D5 in a case of testicular cancer) and (taxol 175 mg/m^2 + carboplatin AUC 5 in a case of ovarian cancer).

Neuroendocrine cancer : patients were given (cisplatin 45 mg/m^2 CIV D2-D3 + vespid 130 mg/m^2 CIV D1- D3).

Osteosarcoma: patients were given (Adriamycin 25mg/m^2 D1-D3 + cisplatin 100 mg/m^2 CIV D1).

Urological cancer: cisplatin was given to all the patients.

Patients' groups: Patients with (ANI +) or without (ANI -).

Statistical analysis

The data were verified. Using PRISM 5, all statistical operations were carried out (GraphPad Software Inc., San Diego, CA). The statistical analysis of variations in the concentrations of the investigated biomarkers during the study was performed using repeated measures of two-way ANOVA. To compare baseline values with distinct data groups, Dunnett's multiple comparisons test was applied. To calculate the specificity and sensitivity of the markers. Two unpaired groups of data were compared using an independent t-test, whereas nominal data were compared using a Chi-square test. Where p-values were less than 0.05, statistical results were deemed statistically significant.

RESULTS

This study included 59 patients with an age range from 25 to 88 years and a mean age of 51.81 years. Males and females represented 59.3 % and 40.7 % respectively of all patients included in our study. About 51 % had GI malignancy and 54.2 % received Cisplatin. The mean baseline creatine was 0.74 mg/dl which increased to 1.31 mg/dl after therapy and 66.1 % developed acute nephrotoxic injury. The mean baseline KIM-1 was 1.003, which increased over time to reach 1.35 on day 1, 1.79 on day 2, and 2 on day 3. The mean baseline NGAL was 410.73, which increased over time to reach 421.46 on day 1, 530 on day 2, and 549.73 on day 3 (Table 2). Thirty-nine patients (66.1 %) developed acute nephrotoxic injury (Fig. 1).

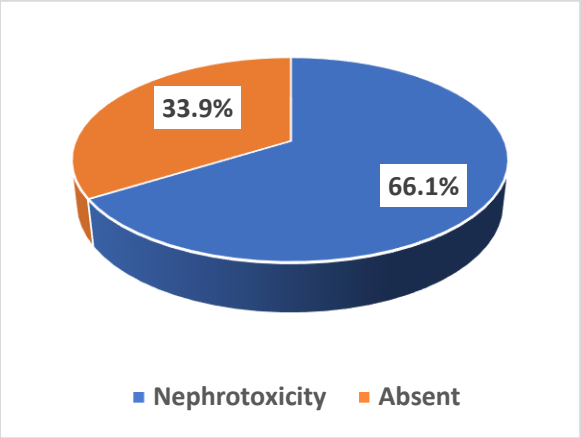

Figure (1): Pie chart showing the distribution of patients according to nephrotoxicity.

There was a statistically non-significant relation between acute nephrotoxic injury and either age, gender, organ affected, type of cancer, or drug used. There was a statistically non-significant relation between acute nephrotoxic and baseline creatinine, KIM-1, and NGAL (Table 3).

There was a statistically significant relation between acute nephrotoxic injury and creatinine after therapy and both KIM-1 and NGAL serial measurement after therapy (higher level significantly associated with nephrotoxicity) (Fig 2,3), (Table 4).

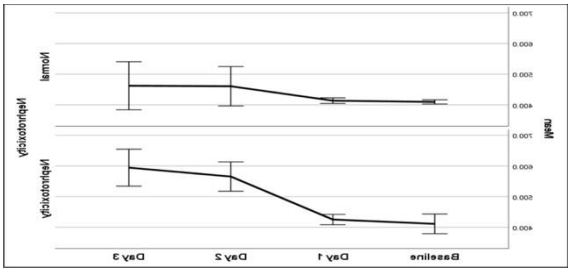

Figure (2): Multiple line graph showing the comparison between groups regarding NGAL before and after therapy.

Table (2): Baseline data of the study patients.

	N=59	%
Gender		
Male	35	59.3%
Female	24	40.7%
Age (year) [mean ± SD]	51.81 ± 15.5	25 – 88
Organ affected		
GIT	30	50.8%
Respiratory	8	13.6%
Reproductive	4	6.8%
Neuroendocrine	4	6.8%
Osteosarcoma	3	5.1%
Urological	10	16.9%
Drugs		
Cisplatin	32	54.2%
Oxaliplatin	17	28.8%
Carboplatin	10	16.9%
Cis/carb	0	0%
	Mean ± SD	**Range**
Creatinine baseline	0.74 ± 0.12	0.5 – 1
Creatinine after treatment	1.31 ± 0.46	0.6 – 2.2
KIM baseline	1.003 ± 0.12	0.11 – 1.12
KIM day 1	1.35 ± 0.1	1.1 – 1.51
KIM day 2	1.79 ± 0.55	1 – 2.51
KIM day 3	2.0 ± 0.53	1.24 – 3.41
NGAL baseline	410.73 ± 26.33	218 – 422
NGAL day 1	421.46 ± 15.71	329.7 – 439
NGAL day 2	530.0 ± 73.15	420.1 – 592
NGAL day 3	549.73 ± 91.42	412 – 621.7

Table (3): Relation between incidence of acute nephrotoxic injury and baseline parameters of the studied patients.

	ANI (-) N=20 (%)	**ANI(+) N=39 (%)**	**χ^2**	**P**
Age (year) [mean ± SD]	50.2 ± 17.0	52.64 ± 14.98	t=(-0.566)	0.574
Sex:				
Male	10 (50%)	25 (64.1%)	1.09	0.297
Female	10 (50%)	14 (35.9%)		
Organ affected				
GIT	11 (55%)	19 (48.7%)	0.209	0.648
Respiratory	2 (10%)	6(15.4%)	Fisher	0.704
Reproductive	0 (0%)	4 (10.3%)	Fisher	0.289
Neuroendocrine	2 (10%)	2 (5.1%)	Fisher	0.598
Osteosarcoma	0 (0%)	3 (7.7%)	Fisher	0.544
Urological	5 (25%)	5 (12.8%)	1.393	0.238
Drugs				
Cisplatin	13 (65%)	19 (48.7%)	1.412	0.235
Oxaliplatin	6 (30%)	11 (28.2%)	0.021	0.885
Carboplatin	1 (5%)	9 (23.1%)	Fisher	0.141

χ^2Chi square test t independent sample t-test. ANI: Acute nephrotoxic injury. Patients with (ANI +) or without (ANI -).

Table (4): Relation between the incidence of acute nephrotoxic injury and laboratory parameters of the studied patients.

	ANI (-)	**ANI (+)**	**T**	**P**
Creatinine before	0.76 ± 0.09	0.74 ± 0.09	0.506	0.615#
Creatinine after	1.02 ± 0.11	1.25 ± 0.24	-4.993	<0.001**
KIM				
Baseline	0.96 ± 0.2	1.03 ± 0.04	-1.962	0.055#
Day 1	1.27 ± 0.11	1.39 ± 0.07	-4.67	<0.001**
Day 2	1.27 ± 0.47	2.06 ± 0.36	-7.285	<0.001**
Day 3	1.51 ± 0.43	2.26 ± 0.37	-6.934	<0.001**
NGAL				
Baseline	409.7 ± 6.94	411.26 ± 32.15	-0.213	0.832#
Day 1	413.78 ± 9.06	425.4 ± 16.99	-2.851	0.006*
Day 2	460.75 ± 64.21	565.51 ± 47.83	-6.438	<0.001**
Day 3	462.37 ± 78.34	594.53 ± 60.09	-7.201	<0.001**

t independent sample t-test. **p ≤0.001 is statistically highly significant. ANI: acute nephrotoxic injury. Patients with (ANI +) or without (ANI -). **KIM:** Kidney injury molecule-1. **NGAL:** Human neutrophil gelatinase-associated lipocalin. **Day 0, day 1, day 2, and day 3** means the day of PBD intake, one, two, and three days after starting PBD intake. **SD** = Standard Deviation. ** means p < .001 and # non-significant.

Table (5): Performance of serum creatinine after therapy in prediction of acute nephrotoxic injury.

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P
≥1.075	0.804	71.8%	65%	80%	54.2%	69.5%	0.001**

AUC: area under curve. PPV: positive predictive value. NPV: negative predictive value. ** p ≤0.001 is statistically highly significant.

Table (6): Performance of KIM before and after therapy in the prediction of acute nephrotoxic injury during the period of study.

KIM	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P
Baseline	≥1.003	0.742	74.4%	65%	80.6%	56.5%	71.2%	0.003*
Day 1	≥1.345	0.87	92.3%	80%	90%	84.2%	88.1%	<0.001**
Day 2	≥1.67	0.829	89.7%	80%	89.7%	80%	86.4%	<0.001**
Day 3	≥1.77	0.856	89.7%	80%	89.7%	80%	86.4%	<0.001**
				NGAL				
Baseline	≥412.5	0.772	76.9%	55%	76.9%	55%	69.5%	0.001**
Day 1	≥418.95	0.792	87.2%	80%	89.5%	76.2%	84.7%	<0.001**
Day 2	≥499.75	0.819	89.7%	80%	89.7%	80%	86.4%	<0.001**
Day 3	≥520	0.847	89.7%	80%	89.7%	80%	86.4%	<0.001**

AUC: area under curve. PPV: positive predictive value. NPV: negative predictive value. **p≤0.001 is statistically highly significant. **KIM:** Kidney injury molecule-1. **NGAL:** Human neutrophil gelatinase-associated lipocalin. **Day 0, day 1, day 2, and day 3** means the day of PBD intake, one, two, and three days after starting PBD intake.

Table (7): Correlation between baseline creatinine and KIM, NGAL before and after therapy.

	R	P
KIM Baseline	0.026	0.845
KIM Day 1	-0.129	0.332
KIM Day 2	-0.131	0.323
KIM Day 3	-0.076	0.567
NGAL Baseline	0.194	0.141
NGAL Day 1	-0.181	0.17
NGAL Day 2	-0.11	0.409
NGAL Day 3	-0.134	0.312

r: Pearson correlation coefficient. **KIM:** Kidney injury molecule-1. **NGAL:** Human neutrophil gelatinase-associated lipocalin. **Day 0, day 1, day 2, and day 3** means the day of PBD intake, one, two, and three days after starting PBD intake.

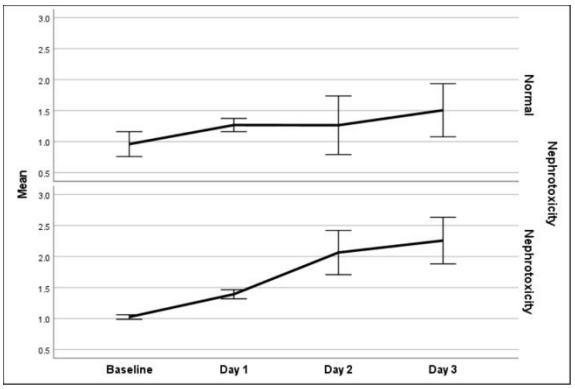

Figure (3): Multiple line graph showing a comparison between groups regarding KIM before and after therapy.

The best cutoff value of creatinine after therapy in the prediction of acute nephrotoxic injury is ≥ 1.075 mg/dl with the area under curve 0.804, sensitivity of 71.8 %, specificity of 65 %, positive predictive value of 80 %, negative predictive value of 54.2 % and overall accuracy 69.5 % ($p<0.001$) (Table 5).

At the cutoff value of baseline, KIM can predict acute nephrotoxic injury is ≥ 1.003 with area under curve 0.742, sensitivity 74.4 %, specificity 65 %, positive predictive value 80.6 %, negative predictive value 56.5 % and overall accuracy 71.2 % ($p=0.003$). A cutoff value of KIM day 1 after therapy can predict acute nephrotoxic injury is ≥ 1.345 with the area under curve 0.87, sensitivity 92.3 %, specificity 80 %, positive predictive value 90%, negative predictive value 84.2 %, and overall accuracy 88.1 %. At cutoff value of KIM day 2 after therapy can predict nephrotoxicity is ≥ 1.67 with area under curve 0.829, sensitivity 89.7 %, specificity 80 %, positive predictive value 89.7%, negative predictive value 80 %, and overall accuracy 86.4 %. The cutoff value of KIM day 3 after therapy can predict acute nephrotoxic injury is ≥ 1.77 with the area under curve 0.856, sensitivity 89.7 %, specificity 80 %, positive predictive value 89.7%, negative predictive value 80%, and overall accuracy 86.4 %. At the cutoff value of baseline, NGAL can predict acute nephrotoxic injury is ≥ 412.5 with the area under curve 0.772, sensitivity 76.9%, specificity 55 %, positive predictive value 76.9 %, negative predictive value 55 % and overall accuracy 69.5 % ($p=0.001$). At a cutoff value of NGAL day 1 after therapy can predict acute nephrotoxic injury is ≥ 418.95 with the area under curve 0.792, sensitivity 87.2 %, specificity 80 %, positive predictive value 89.5 %, negative predictive value 76.2 % and overall accuracy 84.7 %. At a cutoff value of NGAL day 2 after therapy can predict acute nephrotoxic injury is ≥ 499.75 with the area under curve 0.819, sensitivity 89.7 %, specificity 80%, positive predictive value 89.7 %, negative predictive value 80 % and overall accuracy 86.4 %. At a cutoff value of NGAL day, 3 after therapy can predict acute nephrotoxic injury is ≥520 with the area under curve 0.856, sensitivity 89.7%, specificity 80%, positive predictive value 89.7%, negative predictive value 80% and overall accuracy 86.4 % (Fig 4,5) (Table 6).

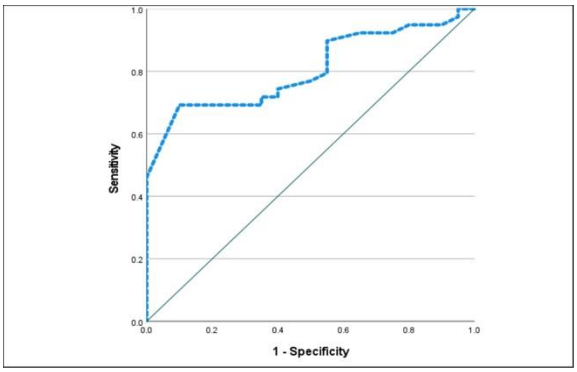

Figure (4): ROC curve showing the Performance of serum creatinine after therapy in prediction of nephrotoxicity.

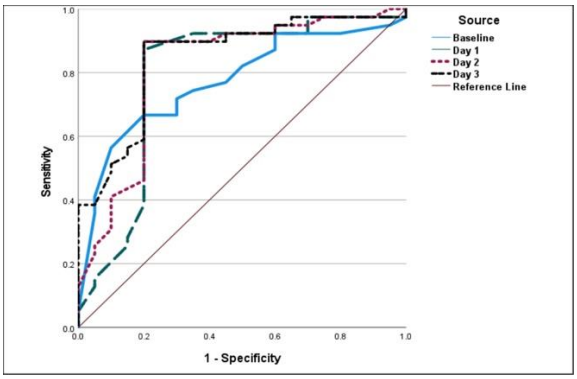

Figure (5): ROC curve showing performance of KIM in performance of NGAL before and after therapy in prediction of nephrotoxicity.

There was a statistically non-significant correlation between baseline creatinine and either KIM or NGAL before or after therapy (Table 7).

DISCUSSION

Platinum-based anticancer drugs are excellent chemotherapeutic treatments used in many tumors, but they create a substantial risk of ANI. In the current investigation, two well-known urine biomarkers (KIM-1, and NGAL) of renal tissue damage were compared to the commonly used serum creatinine for the early prediction of PBD-induced ANI. 66.1 % of the 59 individuals who received PBD in the current trial went on to develop ANI. 54.2 %, 28.8 %, and 16.9 % of them received cisplatin, oxaliplatin, and carboplatin respectively.

According to recent research, 34 % of chemotherapy patients using cisplatin experienced ANI. These trials' higher cisplatin dosages (60 mg/m2) with a larger number of study's population and longer duration may be to blame for the discrepancy. The incidence of ANI among patients who got oxaliplatin was shown to be 30.8 %, which is significantly higher than anticipated. This increased occurrence may be caused by the patient's overall health, the dose that was administered by the protocol, and their adherence to the hydration guidelines. Carboplatin and oxaplatin were given to some of our patients as substitute chemotherapeutic medications in their therapy program since they had a lower nephrotoxic effect **(Chaturvedi et al., 2009; Faig et al., 2017).**

While the basal levels of these biomarkers differ among the healthy population, repeated measurement statistics were utilized in the current investigation to compare the basal value of the urinary biomarkers with the subsequent value in the same individual.

According to KDIGO 2012 criteria, ANI was identified on the third day after PBD therapy using serum creatinine **(Andrajati et al., 2015).** According to the latest results, samples taken a day before an ANI diagnosis indicated a significant rise in all of the investigated markers ($P<0.001$ for both KIM-1 and NGAL). Also, KIM-1 data revealed a significant increase two days ahead of an increase in serum creatinine.

It's interesting to note that patients without renal PBD drawbacks did not have an increase in the measured markers, which was specific to renal injury.

These modifications are in line with several earlier research. The rise in NGAL at day 2 post-treatment was a strong predictor of eventual ANI, according to **Gaspari et al. (2010). Lin et al.**

(2013) assessed the reliability of both NGAL and KIM-1 to screen cisplatin-ANI. Lin and his collaborators observed that in patients who suffered ANI, NGAL significantly increased 12 hours after cisplatin administration. **Lin et al's** findings may differ from our study's results because they used a smaller sample size of patients (33 individuals, with only 10 cases of ANI), a different definition of ANI (according to RIFLE criteria), and different methods and time points for measuring urine's biomarkers.

Moreover, **Tekce et al. (2015)** examined 22 patients in Turkey and discovered that KIM-1 was markedly elevated in 8 cases of ANI. In instances diagnosed on the third day following therapy, urinary KIM-1 levels dramatically rose.

24 hours later, which is consistent with the most recent evidence. There is a discrepancy between our findings and **Lin et al's** study, regarding the changes in the biomarkers in cases of PBD-induced ANI throughout the study. Lin et al. showed an early increase in the biomarkers from the basal line within 6 h in cases developed ANI, then the levels declined (but still above the basal levels), before increasing again for another peak within 48 h. The various hydration protocols and the timing of the sample collection about fluid consumption may be to blame for the discrepancy in the data, as hydration can muddle urinary biomarkers. Also, throughout the trial, increasingly frequent samples were taken every hour.

CONCLUSION

Our results have significant therapeutic implications since they demonstrate the value of these biomarkers for early detection of PBD-induced ANI and demonstrate that an increase in blood creatinine is a late event in the progression of ANI.

RECOMMENDATIONS

For the early detection of ANI cases, the information from the current investigation is essential. It has certain limitations, though, such as the recommendation of future more extensive multicenter studies for more reliable data that will examine the data in other patient groups with various malignancies and varied PBD and grades of ANI. Frequent cooperation with the Clinical Oncology Department and availability of these kits for more determination of these markers. So These biomarkers will become a novel trend for early detection of ANI with traditional laboratory tests such as serum creatinine and creatinine clearance. These will help clinical oncologists modify the dose regimen of PBD or even change the chemotherapy protocols regarding the increase in these markers. Such investigations can identify finer cut-off points with greater sensitivity and specificity for various markers, particularly KIM-1, which performed better as an early biomarker.

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AVAILABILITY OF DATA AND MATERIALS

All data are included in our research.

AUTHORS' CONTRIBUTIONS

Dalia M. Amin: Study design and supervision of data collection and results interpretation. Data collection with revision of inclusion and exclusion criteria, submission, and scientific writing. Shaimaa Hamed and Samah El-Nagdy: Data collection and statistical analysis and scientific writing. Mona Salah and Ibtesam Ragab: Clinical diagnosis, assessment, and clinical follow-up of the cases enrolled in the study. Rasha Omar: Clinical management of the participants with follow-up of the hydration protocol. Rehab Atef: Laboratory work for creatinine and urinary biomarkers. All the authors read and approved the final form of the manuscript.

COMPETING INTEREST

The authors declare that they have no competing interests.

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الملخص العربي

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مقدمة: يُعد التأثير الجانبي الأكثر خطورة للأدوية المضادة للسرطان ذات الأساس البلاتيني هو السمية الكلوية، التي تشكل عائقًا رئيسيًا أمام استخدام الجرعات العالية لتحقيق أقصى فعالية علاجية. يعد مستوى الكرياتينين في الدم من الاختبارات الأكثر شيوعًا، ولكنها تعتبر مؤشرات مؤقتة فقط للسمية الكلوية الحادة الناجمة عن هذه الأدوية.
الأهداف: يهدف هذا البحث إلى استكشاف مؤشرات حيوية جديدة ودقيقة للتنبؤ بالسمية الكلوية لدى المرضى الذين يتلقون الأدوية المضادة للسرطان ذات الأساس البلاتيني.
الاشخاص والطرق: شارك في هذه الدراسة المقطعية تسعة وخمسون مريضا يتلقون العلاج باستخدام الآدوية المضادة للسرطان ذات الآساس البلاتيني. وفقًا لإرشادات أمراض الكلى العالمية كديجو لعام ٢٠١٢، تم تحديد السمية الكلوية الحادة من خلال التحليل الروتيني لمستويات الكرياتينين في الدم. تم تقييم الكرياتينين، بالإضافة الي ومؤشرات الحيوية للبول جزيء إصابة الكلى -١ والليبوكالين المرتبط بالجيلاتيناز البشري في اليوم الأول من العلاج وثلاث أيام بعد العلاج.
النتائج: أظهرت النتائج أن تسعة وثلاثون مريضا (٦٦.١٪ من المرضى) عانوا من السمية الكلوية الحادة. كما أظهرت جزيء إصابة الكلى -١ والليبوكالين المرتبط بالجيلاتيناز البشري زيادة ملحوظة في العينات التي تم جمعها، حيث ارتفعت هذه المؤشرات بشكل كبير في اليوم الثالث مقارنة بالمستويات الطبيعية (P <٠.٠٠١). وقد تم تحديد الحد الأمثل لـــ جزيء إصابة الكلى -١ والليبوكالين المرتبط بالجيلاتيناز البشري، لتشخيص السمية الكلوية الناجمة عن الأدوية المضادة للسرطان ذات الأساس البلاتيني عند مستوي هو ≤١.٣٤٥ و≤ ٤١٨.٩٥علي التوالي، مع مساحة تحت المنحنى تبلغ ٠.٨٧ و٠.٧٧٢ ، وحساسية ٣.٩٢%و ٢.٨٧%، ونوعية ٨٠%، و خصوصية ٨٠% لكل منهما علي التوالي. مقارنة بالكرياتينين في الدم، تبين أن كلاً من جزيء إصابة الكلى -١ والليبوكالين المرتبط بالجيلاتيناز البشري أكثر دقة في التنبؤ بالسمية الكلوية الحادة الناجمة عن الأدوية البلاتينية. الاستنتاج: تُعد مؤشرات جزيء إصابة الكلى -١ والليبوكالين المرتبط بالجيلاتيناز البشري من العلامات الحيوية الأكثر دقة للتنبؤ المبكر بالسمية الكلوية الحادة لدى المرضى الذين يتلقون الأدوية المضادة للسرطان ذات الأساس البلاتيني.