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# EARLY PREDICTION OF CISPLATIN NEPHROTOXICITY IN HEAD AND NECK CANCER PATIENTS – AN EVALUATION WITH URINARY BIOMARKERS

U. V. Saleena [1]*, K. Nalini [2], K. Gopalakrishna [2], R. Prabhu[3], B. M. Vadhiraja [4], M. S. Athiyamaan [5], Asha Kamath [6] and M. S. Vidyasagar [5]

Department of Medical Laboratory Technology [1], School of Allied Health Sciences, Departments of Biochemistry [2], Nephrology [3], Radiotherapy and Oncology [5], Community medicine [6], Kasturba Medical College, Radiotherapy and Oncology [4], Manipal Hospital, Bangalore, Manipal University, Manipal, Karnataka - 576104, India

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**Correspondence to Author:**
**Dr. Saleena Ummer Velladath**

Associate Professor and Head Department of Medical laboratory Technology, School of Allied Health Sciences, Manipal University, Manipal – Karnataka, Pin - 576 104, India

**E-mail**: saleena.ummer@manipal.edu

**ABSTRACT: Background:** Nephrotoxic Acute Kidney Injury (AKI) is a common condition associated with considerable morbidity and mortality. Acute exposure to potentially nephrotoxic drugs requires early appraisal of the extent of renal injury to determine the need for specific interventions. Hence this study was designed to evaluate two urinary biomarkers for the early diagnosis of AKI due to cisplatin chemotherapy, including Neutrophil gelatinase-associated lipocalin (uNGAL) and Cystatin C (uCysC). **Methods:** Urinary biomarker levels in cisplatin treated cancer patients were estimated before and at 2hrs, 6hrs, 12hrs, 24hrs and 48hrs after cisplatin administration. Diagnostic performances of biomarkers were studied by ROC analysis with AUC and predictive values. **Results:** uNGAL was identified as the earlier biomarker of AKI induced by cisplatin as it detected kidney injury as early as 2hrs after the exposure of nephrotoxic drug with an AUC of 0.8, which is 46hrs before the elevation of serum creatinine. uCysC detected AKI 6hrs after cisplatin administration with AUC 0.73. **Conclusion:** Indication of AKI by biomarker elevations can provide an early warning signal which may have implications in therapy by either stopping the nephrotoxic drug or reducing its dose or even by substituting it with a less nephrotoxic one. The research in this direction should focus on evolving rapid procedures with an eventual point-of-care test for urinary biomarker determinations that will transform the scope of biomarkers significantly in the field of early renal injury.

**INTRODUCTION:** Nephrotoxic Acute Kidney Injury (AKI) is the third most common cause of hospital-acquired AKI associated with considerable morbidity and mortality.

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Progression of kidney diseases can be prevented if diagnosed during early stages, especially if the damage is due to nephrotoxic drugs or agents [1]. Hence detection of kidney injury in the early, reversible, and potentially treatable stages is of paramount clinical importance. The presently used marker of AKI, the serum creatinine detects AKI only after a substantial injury to the kidney. Hence it is not considered a good indicator to initiate therapy at the appropriate time [2].

The current situation has warranted the identification of novel AKI biomarkers that can

help detect kidney injury at an early stage [3]. Animal studies conducted in the past have identified interventions that prevent or treat AKI if initiated early in the course of disease, before the serum creatinine begins to rise. However the paucity of early biomarkers has hampered our ability to translate them to promising therapies for human AKI [4-7].

This study was undertaken to evaluate the predictive power of the emerging urinary biomarkers for AKI including Neutrophil gelatinase-associated lipocalin (uNGAL) [8-10] and Cystatin C (uCysC) [11-13] and compare their performance with that of the conventional marker serum creatinine.

The aforesaid biomarkers were evaluated in an AKI model of cisplatin induced kidney injury. Cisplatin is one among the most effective anticancer agents but having a potential side effect of nephrotoxicity. In cisplatin-induced kidney injury the S3 segment of the proximal tubule is the most susceptible. Proteins released from this site into urine due to up regulation or impaired dysfunction can predict kidney injury [14-16].

Recent studies show that Neutrophil gelatinase-associated lipocalin (NGAL) expression is up regulated in injured renal tubular epithelia and its urinary level is markedly increased in mice 3h after cisplatin administration. NGAL has also been identified as an early marker of AKI after cardiac surgery [8, 9, 17]. Urinary Cys-C levels were found to be elevated in tubular dysfunction after cardiac surgery and are predictive of requirement for renal replacement therapy [11-13].

There is a need for research in patient settings where timing and etiology of AKI are well defined so as to assure more reliable cut-off values for the biomarkers in question. This is an essential prerequisite before biomarkers get actually introduced in the routine clinical practice [18]. The present study was designed in a manner and setting where the time of insult and etiology of AKI could be clearly defined and temporal elevation of biomarkers monitored accurately which makes it distinct from similar work conducted in this area. Identifying renal tubular injury at an early stage has important implications for early intervention, clinical trials of therapeutic agents, and evaluation of potential nephrotoxicity of pharmaceuticals in humans[16].

## METHODOLOGY:

This project was approved by institutional ethics committee (UEC/30/2009) and conducted as a single centre prospective observational cohort study in patients with head and neck malignancies qualified for cisplatin chemotherapy. The primary objective was to evaluate the diagnostic efficiency and the temporal patterns of the urinary biomarkers, Neutrophil Gelatinase Associated Lipocalin (uNGAL) and Cystatin C (uCysC) for the early prediction of cisplatin induced AKI. This was done by studying the performance characteristics of urinary levels of these biomarkers at baseline (before cisplatin administration) and then 2hrs, 6hrs, 12hrs, 24hrs and 48hrs after the administration of cisplatin. All the patients above 18 years of age qualified for cisplatin based chemotherapy were included after obtaining informed consent.

The baseline samples were collected before starting the first cycle of the 3 weekly cisplatin administration after confirming the normal renal function by serum creatinine (< 1.4mg/dL) and/or estimated Glomerular Filtration Rate (eGFR) using Cockcroft Gault [19] formula (> 60ml/min.). Patients with any pre-existing renal insufficiency, peripheral vascular disease, urinary tract infections, anuric patients and patients on any other nephrotoxic drugs were excluded. The main outcome measure was identification of patients with clinically diagnosed AKI based on AKIN criteria [20].

The clinical as well as the biochemical data of all the included patients were collected and analysed. The percentage of AKI cases were calculated to find out the proportion of AKI in cisplatin treated cancer patients.

### Estimation of urinary biomarkers:

Venous blood samples were collected from all the patients after obtaining consent before the administration of cisplatin (baseline), and at 12 hours, 24 hours, 48 hours and 20days after the cisplatin infusion. Similarly, a random urine sample

was collected before the cisplatin administration and at 2 hrs, 6 hrs, 12 hrs, 24hrs and 48hrs after cisplatin administration.

The serum and urine creatinine was estimated using modified kinetic Jaffe's reaction [21]. uNGAL and uCysC was estimated by sandwich ELISA [Biovendor ELISA kit]. The temporal pattern and diagnostic performance of each biomarker at different time intervals were studied with respect to serum creatinine levels.

**Statistical analysis:**

The data was summarised as median and interquartile range for continuous variables and as frequency and percentages for categorical variables. A comparison between the AKI and non-AKI groups was made by analysing continuous variables using Mann-Whitney U test and categorical variables using Chi-square test. The performance characteristics of each biomarker at different time intervals was studied by constructing receiver operating characteristics curve (ROC) and calculating the area under curve (AUC). An AUC of >0.7 was considered as diagnostic by the markers in predicting AKI. A probability of 0.05 or less was considered as statistically significant. Analyses were performed with the statistical software SPSS, version 15.

**RESULTS:**

We assessed 238 patients for eligibility of which 11 were excluded as they failed to meet the eligibility criteria. After obtaining informed consent, 226 patients were included who qualified for concurrent chemoradiation with cisplatin.

**Proportion of AKI in cisplatin treated patients:**

Based on AKIN criteria, 56 cancer patients (24.7%) were diagnosed with AKI and constituted the study group and remaining 170 made the non-AKI group. When the AKI group was categorised based on the severity of kidney injury by AKIN criteria, 49 (87.5%) were in stage 1, 5(8.9%) were in stage 2 and 2 (3.6%) were in stage 3. After the sample collection 20days after cisplatin administration all the patients were followed up to one month. During this period 2 patients diagnosed with AKI advanced to failure stage.

**The demographic and clinical characteristics of the patients:**

All patients enrolled in this study were between 21 to 73yrs. Majority of the patients were in the >45 years age group with a median age of 50yrs. The great majority of the patients recruited were males, constituting 75% of the study population. A significant difference in proportion was observed with age >45yrs ($p$=0.009), female gender ( $p$=0.010), T4 -tumour status ($p$=0.015) and history of smoking ( $p$ = 0.05) between AKI and non-AKI groups.

**Performances of urinary biomarkers for predicting AKI:**

After cisplatin administration uNGAL exhibited an AUC of 0.80(**Fig. 1**) with 79% sensitivity and 74% specificity from 2hrs for the prediction of AKI. The AUC remained high in subsequent time intervals with highest value at 48hrs (AUC-0.93, sensitivity-91%, specificity-71% at cut-off value 24.6ng/mgCr) after cisplatin administration (**Table 1**). The uNGAL was normalised to urinary creatinine (ng/mg uCr) which gave the same pattern as with absolute uNGAL values in ng/ml, when compared with serum creatinine. uCysC showed a moderate AUC of 0.73(**Fig. 2**) at 6hrs interval after cisplatin administration (sensitivity = 69% and specificity = 74% at cut-off value 98ng/mgCr.). The AUC remained high in subsequent time intervals with highest value at 48hrs (AUC-0.84, sensitivity - 83%, specificity - 72%) after cisplatin administration (**Table 2**).

**TABLE 1: PERFORMANCE CHARACTERISTICS OF UNGAL AT DIFFERENT TIME INTERVALS**

| Time interval | Optm. Cut off value(ng/mg Cr) | Sensitivity | Specificity | PPV | NPV | AUC | 95% CI for AUC |
|---|---|---|---|---|---|---|---|
| 2 hrs | 22.5 | 79% | 74% | 70% | 79% | 0.80 | 0.73 – 0.89 |
| 6 hrs | 28.3 | 82% | 71% | 77% | 76% | 0.84 | 0.76 – 0.91 |
| 12 hrs | 34.5 | 87% | 69% | 85% | 68% | 0.88 | 0.77 – 0.92 |
| 24 hrs | 45.7 | 89% | 71% | 86% | 67% | 0.91 | 0.81 – 0.97 |
| 48 hrs | 52.8 | 91% | 71% | 92% | 66% | 0.93 | 0.86 – 0.99 |

**TABLE 2: PERFORMANCE CHARACTERISTICS OF uCysC AT DIFFERENT TIME INTERVALS**

| Time interval | Optm. Cut off value (ng/mg Cr.) | Sensitivity | Specificity | PPV | NPV | AUC | 95% CI of AUC |
|---|---|---|---|---|---|---|---|
| 2 hrs | 43.6 | 51% | 64% | 48% | 67% | 0.57 | 0.51 – 0.64 |
| 6 hrs | 76.8 | 69% | 74% | 65% | 66% | 0.73 | 0.68 – 0.81 |
| 12 hrs | 88.3 | 77% | 72% | 78% | 71% | 0.81 | 0.76 – 0.91 |
| 24 hrs | 99.5 | 86% | 70% | 83% | 69% | 0.85 | 0.78 – 0.93 |
| 48 hrs | 125.6 | 89% | 72% | 84% | 68% | 0.90 | 0.82 – 0.97 |

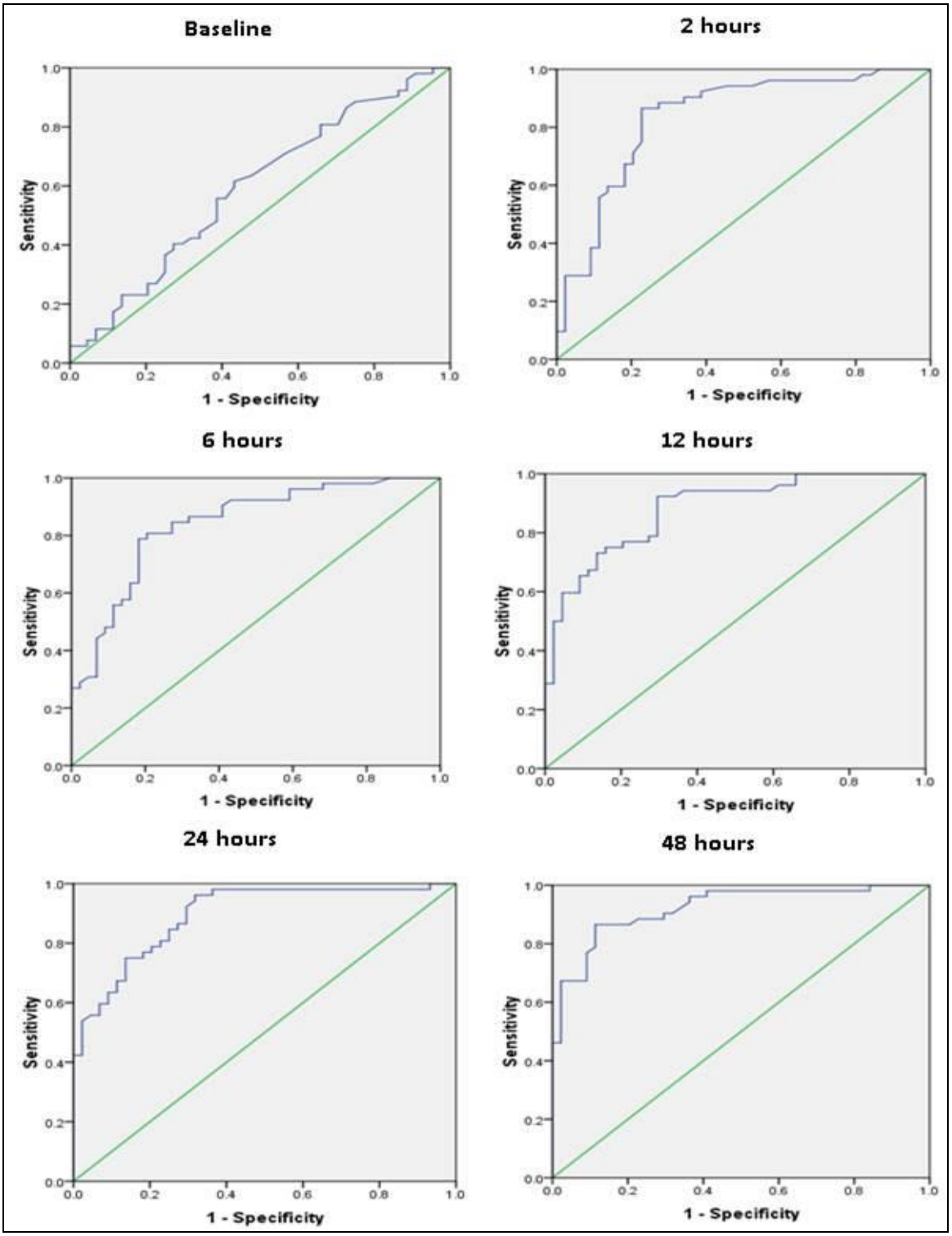


**FIG.1: ROC ANALYSIS OF URINARY NGAL AT DIFFERENT TIME INTERVALS**

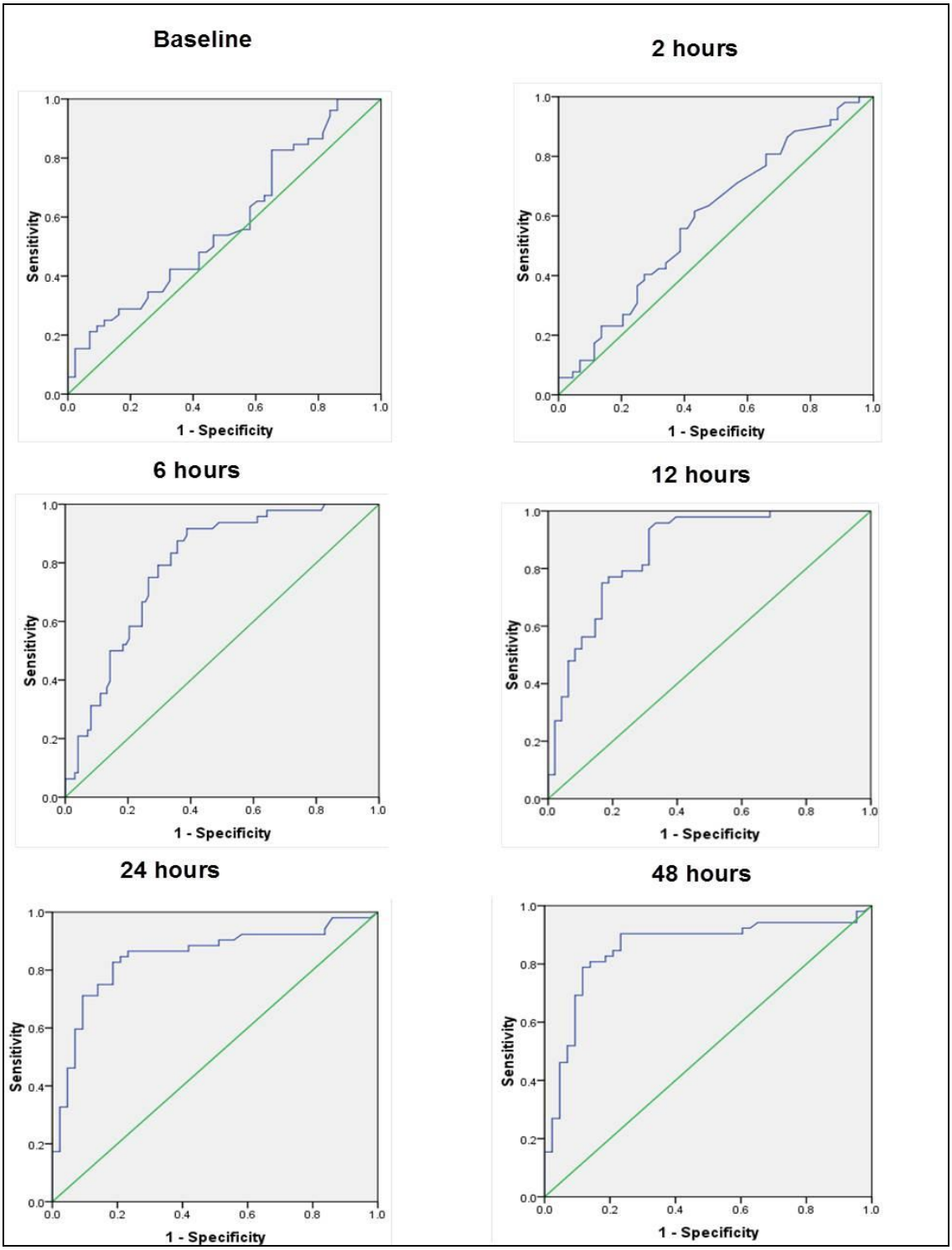


**FIG. 2: ROC ANALYSIS OF URINARY CYSC AT DIFFERENT TIME INTERVALS**

**Temporal pattern of urinary Biomarkers:**

The median uNGAL levels significantly increased at all the time intervals after the administration of cisplatin in AKI patients compared with non-AKI group from 2hrs till the peak value at 48hrs ($p < 0.001$) whereas the median serum creatinine levels in AKI patients showed a significant difference only after 48hrs after cisplatin administration ($p < 0.001$). The median serum creatinine value at 24hrs was high in AKI patients compared to Non-AKI group. But the difference was not statistically significant. A significant difference in the median uCysC values between AKI and Non-AKI patients was seen from 6hrs after cisplatin administration till 48hrs in an increasing pattern ( $p<0.001$). **(Fig. 3)**

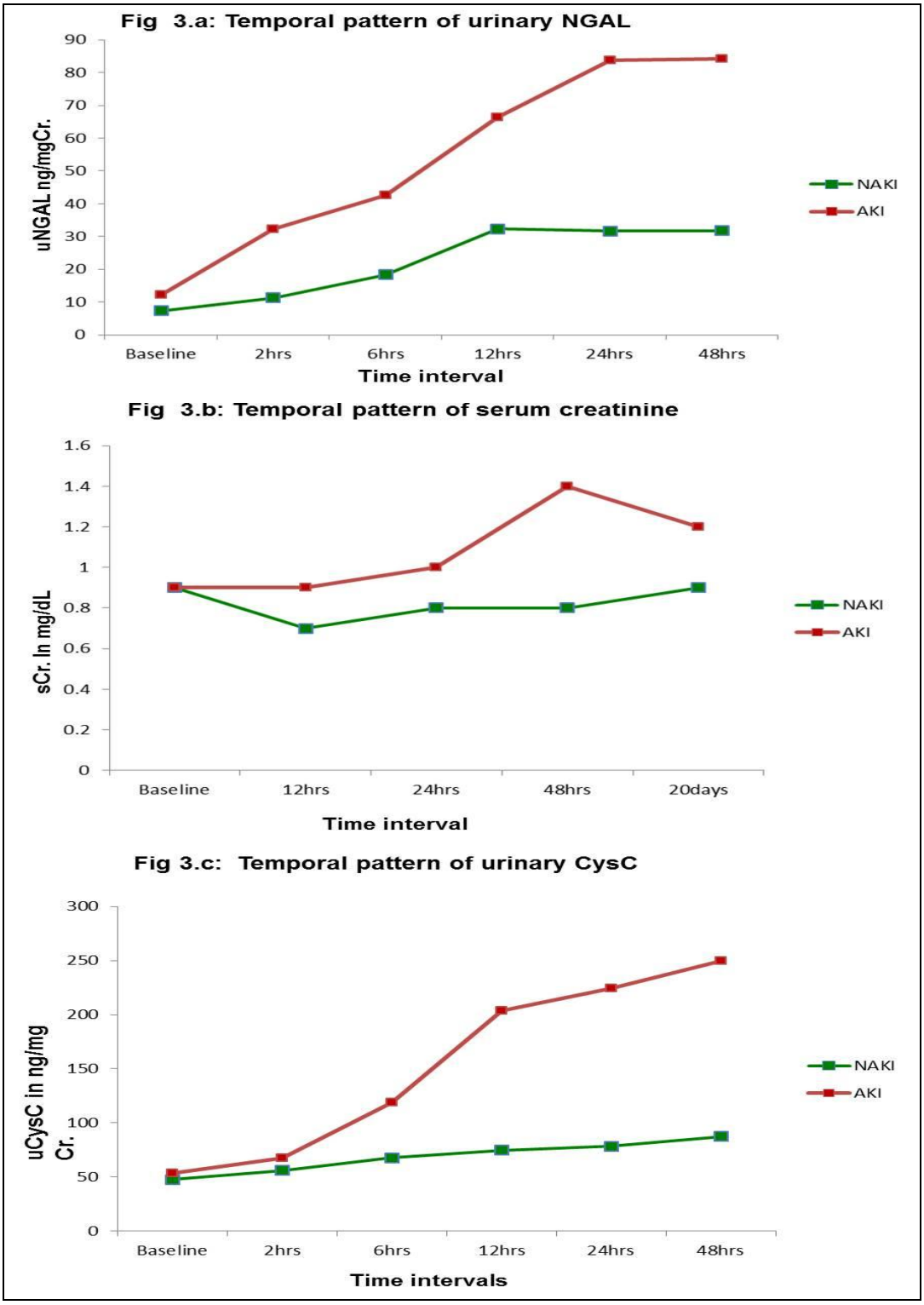


**FIG. 3: COMPARISON OF TEMPORAL PATTERNS**

**DISCUSSION:** Current criteria for diagnosing AKI depend heavily on serum creatinine changes. But the duration between changes in serum creatinine and GFR may not predict the time or severity of kidney injury accurately. Moreover the early phase of AKI may not be associated with a significant serum creatinine increase due to many reasons including the fact that change in serum creatinine is slowed down after kidney injury [22, 23]. Hence serum creatinine is not a good indicator of kidney injury and therefore recent studies have focused on the discovery and validation of early biomarkers of AKI.

This study was carried out in head and neck cancer patients qualified for cisplatin chemotherapy. The efficacy of cisplatin which is widely used in concurrent chemoradiation is dose dependent, but associated with the risk of nephrotoxicity. This model of AKI was selected because it provides a better clinical model to study the early biomarkers of kidney injury, as the normal renal function can be confirmed before the exposure of nephrotoxic drug and the time of insult defined clearly so that the time of biomarker elevation can be detected accurately.

The study period was during the first cycle of the 3 weekly cisplatin administrations. Here the patients were given with sufficient hydration before and after cisplatin administration. Of the total 226 patients, 56 of them were diagnosed with AKI, based on AKIN criteria [20], from baseline which constitute around 25% of the studied patients. A number of studies reveal that, around one-third of the patients receiving cisplatin-based chemotherapy get diagnosed with clinical AKI, even after adopting these preventive measures [14,15]. Our results are consistent with the findings of those studies. Among the 56 cases of AKI two patients advanced to failure stage and then death due to cardiac arrest.

**The time of insult and biomarker elevation:**

Our study attains significance in the field of early diagnosis of AKI for the following reasons. It was designed in a manner to evaluate biomarkers at an early phase of AKI, early enough for the preventive and therapeutic interventions to be effective which promises a better prognosis for the patient. Many studies in the past designed to estimate the diagnostic and prognostic characteristics of the emerging biomarkers in various clinical settings failed to point out precisely the time of insult. We started the evaluation of biomarkers before the administration of nephrotoxic cisplatin after the confirmation of normal renal function and monitored after the insult at different time intervals.

Hence the optimal interval between the nephrotoxic insult and the biomarker elevations could be defined clearly. Stephen and Alasdair have concluded their in-depth review on biomarkers of early nephrotoxicity by stressing the need for human studies to clarify the optimal interval between the nephrotoxic insult and biomarker detection [61]. Selection of this present patient population for this study is thus justified to ensure the time of insult as well as for the controlled monitoring of the biomarker elevations at fixed time intervals.

**Early detection of AKI:**

This is the first study to demonstrate a temporal pattern of uNGAL and uCysC elevations in AKI due to cisplatin chemotherapy. We found that uNGAL and uCysC were able to predict AKI at 2hrs and 6hrs respectively after nephrotoxic insult. Here the timing is exact from the time of insult. Our findings are in accordance with the observations of Mishra J et al [26] who have shown that the gene for NGAL is up-regulated significantly in the kidney after ischemic and nephrotoxic injury, and the protein is over-expressed in renal tubular cells. Our result is consistent with other clinical as well as experimental studies [27, 28]. Nephrotoxic agents mainly damage tubular cells and hence may interfere with the tubular reabsorption and metabolism of CysC. Our results showed a significant elevation of uCysC from 6hrs after cisplatin administration suggestive of tubular damage with good predictive values. These observations are in accordance with the reported studies where the urinary excretion of CysC in patients with renal tubular damage is increased by up to three orders of magnitude. Studies in other clinical settings like cardiac surgery, ICU and sepsis have demonstrated the good diagnostic value of uCysC [29, 30].

Although the efficiency of uNGAL, and uCysC to detect AKI has been reported in various clinical conditions, their ability to predict the time of insult at the very early stage of AKI in humans with nephrotoxicity induced by cisplatin has not been investigated so far. Our data show that kidney injury due to cisplatin chemotherapy as indicated by the elevated levels of uNGAL and uCysC is a better AKI model to study the ability of these biomarkers to predict the time of insult during the early stage of kidney damage in humans. The findings can point out the utility of these biomarkers in the detection and management of

nephrotoxic acute kidney injury in the early and reversible stages. One of the strength of this study is the prospective recruitment of a relatively homogeneous cohort of adult subjects in whom the only obvious aetiology for AKI was the nephrotoxic cisplatin. These patients comprise an ideal and important population for the study of AKI biomarkers because they do not exhibit common comorbid variables such as diabetes, hypertension and atherosclerosis that complicate similar studies in adults with other aetiologies.

All subjects started with normal kidney function, and the study design allowed for the precise temporal definition of altered urinary biomarker concentrations and a direct comparison with subsequent changes in serum creatinine. These biomarkers were measured in the urine because urinary diagnostics have several advantages, including the non-invasive nature of sample collection along with reduced number of interfering proteins. Though our results are encouraging and of clear statistical significance, it certainly needs to be validated in a larger randomized prospective trial, including adults with the usual confounding variables and comorbid conditions that normally build up with an increasing age.

There are several renal protection strategies in practice, which include hydration combined with mannitol or furosemide. But the disappointing results in cisplatin induced AKI may be due to multiple targets. In cisplatin therapy the balance between anticancer effects and renal protection is difficult to achieve. This may be the reason that renal protection strategies are ineffective, especially if the renal protective approach restricts the anticancer effects, which is unacceptable.

To conclude, the introduction of these early AKI biomarkers will offer new possibilities in the prevention of cisplatin-induced AKI. We hope new clinical trials using these early biomarkers will initiate the possibility of an effective approach towards a simultaneous anticancer and reno-protective strategy in cisplatin chemotherapy.

These findings have important implications in interventional studies that are reported to be beneficial in preclinical studies, but failed being introduced in clinical practice due to lack of early diagnostic markers of kidney injury. Indication of AKI by biomarker elevations can provide an early warning signal which may have implications in therapy by either stopping the nephrotoxic drug or reducing its dose or even by substituting it with a less nephrotoxic one.

Future translational work to validate the expression of these biomarkers in the urine of patients with mild and early forms of renal injury in different clinical settings from various centres is required. The research in this direction will have to focus on evolving rapid procedures with an eventual point-of-care test for urinary biomarker determinations that will transform the scope of biomarkers significantly in the diagnosis of early renal injury.

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