

Original Article

## Tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 as a predictor of acute kidney injury in obstetric patients

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### Abstract

**Background:** This study seeks to evaluate the role of the combination of cell cycle arrest urine biomarkers, Tissue inhibitor of metalloproteinase-2 (TIMP2) and insulin-like growth factor binding protein 7 (IGFBP7) for early prediction of AKI in critically ill obstetric patients.

**Methodology:** This prospective observational study was conducted at Obstetrics Intensive Care Unit. Blood and urine samples were taken from critically sick obstetric patients on the day of admission, and the second urine sample was taken after 48 hours. Following admission, the APACHE 2 score was determined. According to the manufacturer's instructions, an ELISA kit was used to perform the final estimation of [TIMP2]\*[IGFBP7]. AKI was diagnosed and staged as per KDIGO 2012 guidelines.

**Results:** At the time of admission, AKI was not present in any of the 131 critically ill obstetric patients who met the study's inclusion requirements. Only 127 out of the 131 patients were analysed, four patients were excluded, 3 patients died within 48 hours, and 1 patient left against medical advice. Pregnancy-related hypertensive disorders accounted for the majority of AKI as risk factors (57.1%), followed by haemorrhage (48.1%), which included abruption in 19.5%, placenta previa/accreta/percreta (10.4%), and PPH (14.3%). Patients who developed AKI had a substantially higher mean [TIMP2]\*[IGFBP7] on the day of admission ( $3.47 \pm 3.66$  (ng/ml)<sup>2</sup>/1000) than those who did not ( $0.22 \pm 0.12$  (ng/ml)<sup>2</sup>/1000). ROC curve analysis was used to determine the diagnostic accuracy of [TIMP2]\*[IGFBP7] levels on Day 1. [TIMP2]\*[IGFBP7] exhibited a sensitivity of 94.8% and specificity of 94% for predicting AKI at a cutoff value of  $\geq 0.41$  (ng/ml)<sup>2</sup>/1000, with a 95% confidence interval and an AUC of 0.990.

**Conclusion:** Patient risk of developing AKI was accurately predicted by the urine biomarker [TIMP-2]\*[IGFBP7]. It also has good prognostic value.

**Keywords:** Acute Kidney Injury; Pregnancy-Related Acute Kidney Damage; PRAKI; Intensive Care Unit; Tissue Inhibitor of Metalloproteinase-2; TIMP2; Insulin-Like Growth Factor Binding Protein 7; IGFBP7.

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## Introduction

One potentially fatal pregnancy complication is pregnancy-related acute kidney damage (PRAKI), which can occur during the antenatal, intrapartum, or postpartum period and usually occurs due to obstetrical complications.

Obstetric patients account less than 2% of intensive care unit admissions in developed nations, but 10% in developing nations.<sup>[1]</sup> With an incidence of 4%–26% in developing nations versus 1.0%–2.8% in developed nations, PRAKI is more prevalent in the former.<sup>[2,3]</sup> PRAKI accounts for up to 20% of all AKI cases in India, occurring in 1 in 50 pregnancies.<sup>[4]</sup>

Pregnancy-related AKI development exhibits a bimodal distribution. It is observed between 7<sup>th</sup>–16<sup>th</sup> weeks of pregnancy as well as between 34<sup>th</sup>–36<sup>th</sup> weeks of gestation.<sup>[5,6,7]</sup> In first trimester, septic shock and hyperemesis gravidarum are associated with AKI.<sup>[8]</sup> In late third trimester, the major risk factors are hypertensive disorder of pregnancy, haemorrhage, sepsis, thrombotic microangiopathy, haemolytic uremic syndrome, disseminated intravascular coagulation (DIC).<sup>[9,10,11,12]</sup> As per one systematic review a serum creatinine of >77 µmol/l (0.87 mg/dl) was considered above the normal range for pregnancy or abnormal value.<sup>[13]</sup>

AKI is described by KDIGO 2012,<sup>[14]</sup> as either rise in creatinine or fall in urine production. The creatinine (glomerular filtration rate marker) is not sensitive since it does not increase until a major decline in GFR or significant parenchymal injury has already taken place.<sup>[15]</sup> Therefore, there is need of a biomarker that aids in the early and accurate diagnosis of AKI. Insulin Like Growth Factor Binding Protein 7 [IGFBP7] and Tissue Inhibitor of Metalloproteinase-2 [TIMP-2] are two newly discovered urine biomarkers of tubular damage.<sup>[16]</sup> In the early phases of tubular cell injury caused due to a variety of stress factors, including inflammation, ischaemia, oxidative stress, medications, and toxins, TIMP-2 and IGFBP7 are both produced under cellular stress.<sup>[17]</sup> As a protective mechanism, kidney tubular cells inhibit cyclin-dependent protein kinase complexes under stress, causing G1 cell-cycle arrest in the early stages of stress.<sup>[18]</sup> However, maladaptive repair and ultimately fibrosis may result from prolonged cell cycle arrest in renal tubular cells during an acute insult.

Based on the background information provided above, the purpose of this study was to assess the role of urine [TIMP2]\*[IGFBP7] for prediction of acute kidney injury in critically ill obstetric patients.

## Method:

From December 2022 to March 2024, the Department of Obstetrics & Gynaecology, in collaboration with the Department of Pathology, King George's Medical University, Lucknow, U.P., India conducted this prospective observational study in the Obstetric ICU. After informed consent and ethical clearance approved (Reference code *XIV-PGTSC-IIA/P83*) from institutional ethics committee. A total of 447 critically ill obstetric patients were admitted in ICU over 1 year, out of these 243 patients were of AKI. On admission, 131 patients who were enrolled for the study as per inclusion criteria were not having AKI. Only 127 out of the 131 patients were analysed since, according to the exclusion criteria, 3 patients deceased within 48 hours, and 1 patient left against medical advice.

Obstetric patients who were critically ill based on their APACHE II score and who needed to be admitted and managed in the intensive care unit. Gynaecological patients admitted in ICU, non-critically ill obstetric patients, patients with pre-existing renal impairment or history of renal dysfunction or requirement of renal replacement therapy prior to the hospitalization, post renal transplant patients, patients in which nephrotoxic drugs or contrast material was used, who were admitted to the ICU for a low risk condition such as airway monitoring and patients not willing to participate in the study were excluded from the study.

After admission to ICU, APACHE 2 score was calculated for all patients, patients who had score more than 15 were taken as critically ill patient. Blood and urine samples were taken twice following a detailed history and physical examination. First sample during the enrollment and second 48 hours later. For haematological analysis, 2 ml of blood was extracted in an aseptic setting. In accordance with manufacturer instructions, a 2 ml urine sample was centrifuged for 10 minutes at 3000 rpm, and the supernatant was collected in an Eppendorf tube and kept at -80 °C for the final evaluation of the [TIMP2] \* [IGFBP7] level using the ELISA technique.

Combination of urinary TIMP2 and IGFBP7 was expressed as product of concentration of both biomarkers, measured as ng/ml<sup>2</sup> and then divided by 1000 represented as [TIMP2]\*[IGFBP7].<sup>[19,20]</sup> AKI was diagnosed and staged according to KDIGO guidelines.<sup>[14]</sup>

**Statistical Analysis-**

Data was analyzed using SPSS 25.0 (IBM Inc.) software. Qualitative/categorical data has been depicted as numbers and percentages and has been compared using chi-square test. Continuous data has been depicted as mean ± SD. Comparison of continuous data has been done using independent samples ‘t’-test when comparison was made between two groups and ANOVA (Analysis of variance) was used when comparison was being made among more than two groups. ‘p’ value less than 0.05 was considered as significant. Receiver-operator characteristic curve analysis was performed to derive a cut-off value of a continuous variable for a categorical outcome. Selection of optimum cut-off value was done using maximum Youden’s index as the criteria. Efficacy of this cut-off value for prediction was shown as sensitivity and specificity.

**Results:**

A total of 447 critically ill obstetrics patients admitted in ICU, out of which 243 patients had AKI, thus the incidence of AKI was 54.4 %. Of the 243 patients, 66.7% had established AKI at the time of admission, and the rest 33.3% developed AKI during hospitalization.

Mean age of patients who developed AKI was 27.83±5.47 years and who did not develop, 28.88±5.47 years. 60.6% of patients developed AKI and 39.4% of patients did not develop AKI.

In both groups, majority of patients (91.3%) were antenatal .In the AKI group, postpartum patients 1.3%, abortion 2.6% and ectopic 2.6%. In AKI group, the mean APACHE 2 score and mean ICU care days were 21.87±4.74 and 4.12±1.85 respectively, which were significantly higher in AKI as compared to non-AKI. [Table 1]

**Table 1- Demographic profile of patients**

	AKI group	Non-AKI group	p value
Mean Age (years)	27.83±5.47	28.88±5.47	0.293
<b>Residence</b>			
Rural	72.7 %	74 %	0.874
Urban	27.3 %	26 %	
<b>Booking status</b>			
Booked	27.3 %	24 %	0.681
Unbooked	72.7 %	76 %	
<b>Referral</b>	92.2 %		
	7.8 %		

Referred		80 %	0.043
Not referred		20 %	
<b>Education status</b>			
Illiterate	59.7 %	50 %	0.280
Literate	40.3 %	50 %	
<b>Socioeconomic status</b>			
Lower			
Lower middle	36.4 %	32 %	0.212
	31.2 %	48 %	
<b>Distribution of cases</b>			
Abortion	2.6 %	0.0 %	0.139
ANC	93.5 %	86 %	
Ectopic	2.6 %	8 %	
Postpartum	1.3 %	6 %	
APACHE 2 score	21.87±4.74	18.52±3.89	<0.001
ICU care days	4.12±1.85	3.36±1.14	0.011
Ventilator care days	2.04±1.40	1.61±0.85	0.054
Inotropic support days	0.62±1.02	0.26±0.56	0.025

The most common risk factor for AKI in pregnancy was hypertensive disorder of pregnancy (57.1%), followed by haemorrhage (48.1%) includes abruption (19.5 %), placenta previa/accreta/percreta (10.4 %), PPH (14.3%). [Table 2]

**Table 2: Comparison of risk factors in AKI Vs. Non-AKI group (n=127)**

SN	Risk factor	AKI (n=77)		Non-AKI (n=50)		Chi. Sq. Test	
		No.	%	No.	%	$\chi^2$	'p'
1.	Gastroenteritis	1	1.3 %	0	0.0%	0.655	0.419
2.	Heartdisease	9	11.7%	4	8 %	0.449	0.503
3.	HTN disorder of pregnancy (Sev PE/HELLP/ APE)	44	57.1 %	18	36 %	5.424	0.020
	Sev preeclampsia /HELLP	16	20.8%	6	12 %	1.631	0.202
	APE	27	35.1%	10	20 %	3.332	0.068
4.	PPE	2	2.6%	4	8 %	1.966	0.161
5.	Hemorrhage	37	48.1%	24	48%	0.000	0.995
	Antepartum haemorrhage	23	29.9%	20	40 %	2.054	0.152
	Abruption	15	19.5%	5	10 %	2.054	0.152
	Placenta previa, accreta and percreta	8	10.4%	15	30 %	7.8	0.005
	PPH	11	14.3%	2	4 %	3.490	0.062
	Rupture ectopic	2	2.6%	4	8 %	1.966	0.161
	Ruptured Uterus	6	7.8%	3	6 %	2.243	0.326
6.	Sepsis	3	3.9%	1	2 %	2.861	0.091
	PuerperalSepsis	1	1.3%	1	2 %	0.818	0.366
	Septicabortion	2	2.6%	0	0.0%	1.995	0.158
7	Uterineinversion	1	1.3%	0	0%	0.655	0.419
8.	Jaundice/AFLP	7	9.1%	0	0 %	4.811	0.028
9.	Malaria/Hepatitis	1	1.3%	0	0 %	0.655	0.419
10.	Obstructed Labour	3	3.9%	1	2 %	0.357	0.550

11.	Severe anemia	23	29.9%	19	38 %	0.905	0.341
12.	Moderate anemia	25	32.5%	20	40 %	0.752	0.386
13.	Shock	23	29.9%	19	38 %	0.905	0.341
14.	Fever	13	16.9%	17	34 %	4.923	0.027
15.	Pulmonary Edema	27	35.1%	7	14 %	6.862	0.009

Liver enzymes (SGOT/SGPT), serum LDH and serum potassium levels were significantly higher in AKI group as compared to non-AKI group. [Table 3]

**Table 3: Comparison of Biochemical Laboratory parameters in AKI and non-AKI patients (n=127)**

SN		AKI (n=77)		Non- AKI (n=50)		Student's T-Test	
		Mean	SD	Mean	SD	't'	'p'
1	Hb(gm/dl)	8.45	2.31	8.65	2.21	-0.480	0.632
2	TLC (cells/mm <sup>3</sup> )	23255	9519	18472	9050	2.821	0.006
3	Platelet count (Lac cells/mm <sup>3</sup> )	1.33	0.68	1.49	0.65	-1.285	0.201
4	Hematocrit (%)	28.31	7.74	28.16	5.97	0.115	0.909
5	S. Urea (mg/dl)	65.42	35.23	29.18	16.97	6.775	<0.001
6	S. LDH (U/L)	1119	888	767	452	2.264	0.026
7	TSB (mg/dl)	1.70	2.15	0.72	0.31	3.218	0.002
8	DSB (mg/dl)	1.03	1.38	0.43	0.23	3.078	0.003
9	SGPT (IU/L)	262.34	1002.16	99.37	85.26	1.146	0.254
10	SGOT (IU/L)	247.41	409.67	112.78	95.49	2.281	0.024
11	S. ALP (IU/L)	490.80	284.90	419.05	324.46	1.312	0.192
12	Sodium (mmol/l)	134.13	4.68	134.56	5.75	-0.455	0.650
13	Potassium (mmol/l)	4.77	0.17	4.08	0.88	6.785	<0.001
14	Calcium (mg/dl)	4.05	1.22	4.20	0.84	-0.755	0.452
15.	pH	7.29	0.13	7.33	0.11	-1.924	0.057

59.7% developed stage 1 AKI, 22.1% stage 2 AKI and 18.2 % stage 3 AKI. 92.2% of the AKI patients were non-oliguric. Complete renal recovery was achieved in 80.5% of AKI patients, partial recovery in 13% and chronic kidney disease was found in 3.9% and required dialysis. 2.6% of patients were deceased. [Table 4]

**Table 4- Distribution of AKI cases by AKI staging (n=77)**

	Frequency (%)
<b>AKI stages</b>	
Stage 1	59.7 %
Stage 2	22.1 %
Stage 3	18.2 %
Oliguric AKI	7.8 %
Non oliguric AKI	92.2 %
<b>Renal outcome</b>	
Complete Recovery	80.5 %
Partial Recovery	13 %
CKD	3.9 %
Expired	2.6 %

The mean level of [TIMP2]\*[IGFBP7] on day of admission was  $3.47 \pm 3.66$  (ng/ml)<sup>2</sup>/1000 in patients who developed AKI on follow up (approximately 15 folds high) as compared to those who did not develop AKI ( $0.22 \pm 0.12$  ng/ml)<sup>2</sup>/1000) later on. [Table 5]

In patients who developed AKI, on day 3, mean levels of [TIMP2]\*[IGFBP7] was  $10.49 \pm 10.06$  (ng/ml)<sup>2</sup>/1000 (approximately 3 fold rise) as compared to day 1 value ( $3.47 \pm 3.66$  (ng/ml)<sup>2</sup>/1000) and approximately 43 fold increased in levels as compared to who did not develop AKI ( $0.24 \pm 0.14$  (ng/ml)<sup>2</sup>/1000) on follow up. [Table 5]

**Table 5- Comparison of mean serum creatinine and urine marker [TIMP2]\*[IGFBP7] levels in AKI and Non-AKI on Day 1 and day 3 (n=127)**

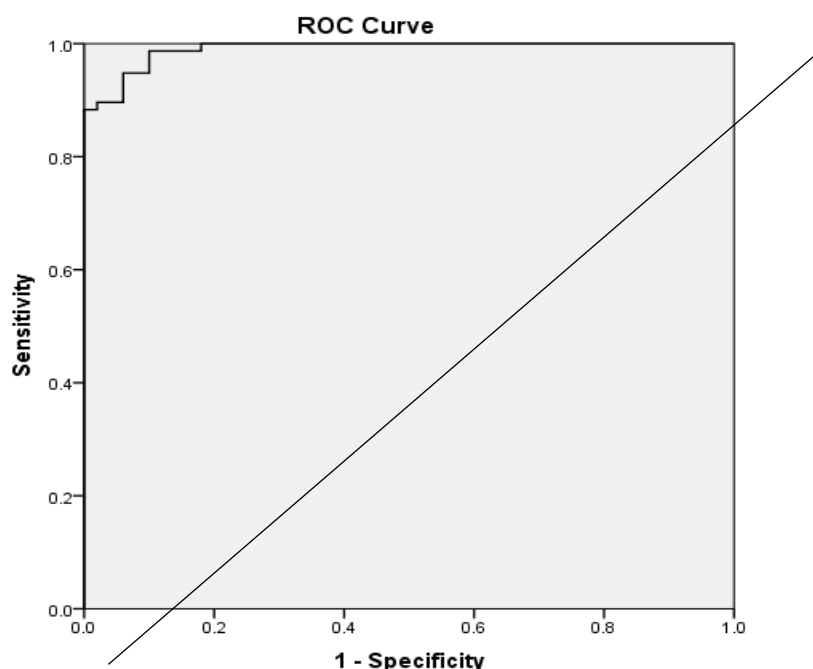
	Parameters	AKI Group (n=77) Mean±SD	Non-AKI Group (n=50) Mean±SD	P value
<b>Day 1</b>	Serum creatinine (mg/dl)	0.78±0.06	0.69±0.10	<0.001
	[TIMP2]*[IGFBP7] (ng/ml) <sup>2</sup> /1000	3.47±3.66	0.22±0.12	<0.001
<b>Day 3</b>	Serum creatinine (mg/dl)	1.97±0.87	0.74±0.09	<0.001
	[TIMP2]*[IGFBP7] (ng/ml) <sup>2</sup> /1000	10.49±10.06	0.24±0.14	<0.001

The mean value of [TIMP2]\*[IGFBP7] was increased with the disease severity, highest in stage 3 AKI and lowest in stage 1 (AKI stage 3 > stage 2 > stage 1). [Table 6]

**Table 6- Correlation of [TIMP2]\* [IGFBP7] with AKI stages on Day 1 and Day 3 (n=77)**

	Parameters	AKI Stage 1 (n=46) Mean±SD	AKI Stage 2 (n=17) Mean±SD	AKI Stage 3 (n=14) Mean±SD	P value
Day 1	[TIMP2]*[IGFBP7] (ng/ml) <sup>2</sup> /1000	1.01±0.37	4.31±0.77	10.52±1.04	<0.001
Day 3	[TIMP2]*[IGFBP7] (ng/ml) <sup>2</sup> /1000	3.86±1.19	13.05±2.19	29.18±6.39	<0.001

ROC curve analysis was performed to evaluate diagnostic accuracy of [TIMP2]\*[IGFBP7] to discriminate the AKI patients from non-AKI patients (Day 1). At cut off value of  $\geq 0.41$  (ng/ml)<sup>2</sup>/1000, it had 94.8% sensitivity and 94% specificity for prediction of AKI at confidence interval of 95% and AUC (0.990). [Figure 1]



**Figure 1: Receiver operating characteristic curve analysis for prediction of AKI.**

At cut off value of  $\geq 0.41$  ng/ml<sup>2</sup>/1000, [TIMP2]\*[IGFBP7] had sensitivity of 94.8 % and specificity of 94 % for prediction of AKI at confidence interval of 95% and AUC (0.990).

**Discussion**

In current study, incidence of AKI in critically ill obstetric patients was 54.4%, whereas another study reported 61%.<sup>[19]</sup> The mean age of study population with PRAKI was 27.83±5.47 years, another study reported age between 25 and 27 years.<sup>[10,19,21]</sup>

In the present study, majority of the patients were from rural areas (72.7%). Other studies reported 30% and 51.3% of cases were from urban areas while 70% and 48.7% from rural areas.<sup>[10,11]</sup> In current study among AKI group, only 27.3% received antenatal care while in another study, 13.3% of patients received antenatal care and 33.4% had approached for institutional delivery.<sup>[10]</sup> In our study majority of patients

were illiterate and belonged to lower socioeconomic status. Socioeconomic factors including poverty, lack of proper healthcare facilities, inadequate antenatal visit and lack of awareness of this condition and delayed referral practices, all contribute to the rise in numbers of PRAKI cases in developing countries.

In present study, 93.5 % AKI women were antenatal, out of these, 89.6% patients in third trimester of pregnancy and 1.3% were of postpartum. Another author reported that 82 % of patients who developed AKI were postpartum and only 15.3 % of patients developed AKI during pregnancy.<sup>[11]</sup> Reports from another study reported that 88.09 % of AKI patients were antenatal while 11.9 % were postnatal and 76.19 % were in third trimester of pregnancy.<sup>[22]</sup>

In our study, all patients were critically ill but APACHE 2 score and need for ionotropic support was high in AKI group, requirement of mean ICU care was  $4.12 \pm 1.85$  days, while other studies reported, duration of ICU stay was 5 days and 2 days.<sup>[19,23]</sup>

In current study, hypertensive disorder of pregnancy (HDP) was the most common risk factor associated with AKI in critically ill obstetric women (57.1%). Other studies reported the association of HDP with AKI in, 45%, 44.5%, and 54.5%.<sup>[19,21,24]</sup> of cases respectively. Haemorrhage was second common risk factor found in 48.1%, jaundice/AFLP in 9.1% and sepsis in 3.9%. This contrasts with the outcome of another study that reported maternal haemorrhage in 28% and sepsis in 33 %.<sup>[19]</sup> The variance of patterns when compared to this study is observed from another study in India that reported, antepartum haemorrhage in 9.52 %, abruption in 2.38 %, PPH in 4.76 %, sepsis in 4.76 % and AFLP in 2.38 %.<sup>[22]</sup>

In present study 59.7% developed stage 1 AKI, 22.10 % developed stage 2 AKI and 18.2 % developed stage 3 AKI. Two studies reported 46.2 % and 50 % AKI stage 1, 30.8 % and 10 % AKI stage 2 and 23.1 % and 40 % AKI stage 3 in critically ill obstetric patients.<sup>[9,19]</sup> This study was conducted in a tertiary facility with a higher volume of referred patients. This may be the reason for this high incidence of PRAKI.

In our study, 7.8% of patients in the AKI group had oliguria, while the remaining 92.2% of patients did not. This differs from the pattern of, 43.2 % who were non- oliguric, 33.3% who developed oliguria and 23.5 % who developed anuria in a study by Yadav et al in India.<sup>[25]</sup> The reported rates of 23.5% and 31.% anuric and oliguric patients respectively<sup>[26]</sup> and 66% of oliguric patients<sup>[27]</sup> from other studies of PRAKI patients in ICU also shows the variability in findings from various studies due to different inclusion criteria and use of criteria like RIFLE criteria when compared to this study. Despite these variations in the rates of AKI patterns, the studies show that PRAKI is a significant problem and accounts for significant ICU morbidity and mortality.

In this current study, we found that 80.5% of patients recovered completely, 13% recovered partially, 3.9% patients progressed to CKD, and 2.6% patients died. According to one study, 76.19% of patients showed full recovery of renal function, 9.52% had partial recovery, and 7.14% had no recovery or progression to CKD.<sup>[22]</sup> Though the specific proportion of AKI outcomes differ from the findings from this study the trend and pattern of AKI outcomes are similar with that reported in this study.

In this study, baseline [TIMP2]\*[IGFBP7] value was approximately 15 folds higher in patients who developed AKI in comparison to those who did not, on the day of ICU admission. The elevated level of this biomarker which was because of sub clinical kidney injury is like the report of other studies<sup>[20,28]</sup>, indicating that these biomarkers are more sensitive as compared to serum creatinine in detection of AKI. Sakyi et al<sup>[20]</sup> in similarity with this study reported that baseline value of [TIMP2]\*[IGFBP7] was higher in patients who developed AKI than those who did not. Ferrari et al<sup>[28]</sup> also documented similar findings with the baseline value of this biomarker higher in the AKI group 5.02 vs non AKI, 0.4 (ng/ml)<sup>2</sup>/ 1000.

This elevation of [TIMP2]\*[IGFBP7] is probably due to the stress response as proximal tubular cells undergo cellular arrest as a protective measure. Elevated TIMP2 and IGFBP7 are implicated during early stage of cellular stress in G1 cell-cycle arrest via blocking the effect of cyclin- dependent protein kinase complexes and causing failure of reabsorption of TIMP2 and IGFBP7, therefore resulting in an increase in urinary excretion of TIMP2 and IGFBP7 much earlier than the rise of serum creatinine levels.<sup>[29]</sup>

The index study showed that on day 3 of ICU admission, the value of [TIMP2]\*[IGFBP7] significantly increased (approximately 3 folds) in the AKI group. While in another study done on cardiac surgery patients where an increase from the baseline value of 0.70 (ng/ml)<sup>2</sup>/1000 was observed after 6 hours with a value of 1.49( ng/ml)<sup>2</sup>/1000 (2 fold increase).<sup>[30]</sup> Similar elevations from the baseline has also been reported from a study done on patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) reporting an increase in [TIMP-2]\*[IGFBP7] from a mean of 0.49±0.24 at baseline to 1.51±0.57, four hours after surgery (3 fold increase).<sup>[31]</sup>

In our study, the level of [TIMP2]\*[IGFBP7] increased with the increasing severity of AKI. [AKI Stage 1 (1.01 ng/ml<sup>2</sup>/1000) to stage 3 AKI (10.52 ng/ml<sup>2</sup>/1000)]. Similarly, another study reported an increasing trend in patients who developed AKI, from stage 1(0.5) to stage 3(1.69) (ng/ml)<sup>2</sup>/1000. This value was higher in patients who developed severe AKI.<sup>[28]</sup> Sayki et al also documented a similar trend and reported that the mean levels of [TIMP2]\*[IGFBP7] increased with increasing severity of AKI (AKI stage 1, 1.6 ng/ml<sup>2</sup>/1000 and in AKI Stage 3 it was 12.1 ng/ml<sup>2</sup>/1000.<sup>[20]</sup> Hence, with increasing severity of AKI, there was a significant increment in the biomarker [TIMP2]\*[IGFBP7] values. Hence, [TIMP2]\*[IGFBP7] can be used as prognostic marker for the diagnosis, follow up and prognostication of patients with AKI as the values increase with AKI stage and severity.

At cut off value of  $\geq 0.41$ (ng/ml)<sup>2</sup>/1000, [TIMP2]\*[IGFBP7] had a sensitivity of 94.8 % and specificity of 94 % for prediction of AKI at confidence interval of 95% and AUC (0.990). [TIMP2]\*[IGFBP7] has good sensitivity and specificity, thus it is a good biomarker for early prediction of AKI. Other studies.<sup>[20,28]</sup> also revealed that [TIMP-2]\*[IGFBP7] had 95.8% sensitivity and 77.2% specificity at a cut off value of 0.30 (ng/ml)<sup>2</sup>/1000, with an AUC of 0.94. <sup>[20]</sup> Ferrari et al <sup>[28]</sup> reported 92% sensitivity and 66% specificity at an area under the curve of 0.81, with a cutoff value of 0.3(ng/ml)<sup>2</sup>/1000. <sup>[20,28]</sup>

The cell cycle arrest biomarker showed a significant increase in value before serum creatinine level rise and decreased urine volume. The [TIMP2]\*[IGFBP7] combination biomarker showed good predictive and prognostic value, aiding in earlier AKI prediction and better management, thus enhancing the prevention of AKI.

This was the first single-center study on the North Indian population found encouraging results, but larger studies are needed before clinical application of these biomarkers.

### Conclusion:

This study found that critically ill patients who developed AKI had significantly increased levels of [TIMP2]\*[IGFBP7] when compared to those who did not develop AKI. This study sheds light on the significant burden of PRAKI and various etiological factors and prognostic and predictive value of [TIMP2]\*[IGFBP7]. [TIMP2]\*[IGFBP7] has a good diagnostic value for early prediction of AKI (sensitivity 94.8% and specificity 94%). Significant rise in biomarkers with disease progression (stage 3 > stage 2 > stage 1) indicates also its good prognostic value. It is advocated that the use of [TIMP2]\*[IGFBP7] for the early prediction of Aki before development of disease is useful in the formulation of management guidelines and will also help in the avoidance of nephrotoxic drugs in those identified at risk for AKI using the [TIMP2]\*[IGFBP7].

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