

## Glutathione S- Transferase as a Marker of Acute Kidney Injury in Pediatric Intensive Care, Zagazig University Children Hospital

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### ABSTRACT

**Background:** Glutathione S-transferases (GST) are major phase II detoxification enzymes having central roles in the cellular detoxication of a diverse group of exogenous and endogenous harmful compounds.

**Objective:** The aim of the work was to investigate the role of GST in development of acute kidney injury in PICU, Zagazig University Children Hospital.

**Patients and Methods:** A prospective cohort study was conducted on 50 pediatric patients admitted to PICU who were divided into two groups according to incidence of Acute Kidney Injury (AKI). Patients were subjected to clinical, laboratory, and plasma & urinary GST evaluation.

**Results:** AKI developed in 24% of patients. There was no significant relation between presence of AKI and patient age, gender, weight, height, or clinical outcome. There were significant relations between plasma and urine GST and presence of AKI. There is statistically non-significant relation between Pediatric Risk, Injury, Failure, Loss, End-Stage renal disease (pRIFLE) staging and plasma and urine GST. There were statistically significant negative correlations between each of plasma and urine GST on one side and both heart rate and estimated creatinine clearance on the other side. Plasma GST can predict presence of AKI at cutoff  $\geq 30.5$ , with AUC 0.964, sensitivity 100%, specificity 84.%, PPV 66.7%, NPV 100% , accuracy 88%. Urinary GST in prediction of AKI was  $\geq 12.5$ , with AUC 0.95, sensitivity 91.7%, specificity 84.2%, with accuracy 86%.

**Conclusion:** It could be concluded that AKI had significant incidence in PICU admission. High levels of plasma and urine GST Pi after admission in PICU are associated with an increased development of AKI and GST Pi is a valuable tool for early diagnosis of AKI.

**Keywords:** Kidney injury, Glutathione Transferase.

### INTRODUCTION

Acute kidney injury (AKI) is defined as the abrupt loss of kidney function that results in a decline in glomerular filtration rate (GFR), retention of urea and other nitrogenous waste products, and dysregulation of extracellular volume and electrolytes. The term AKI has largely replaced acute renal failure (ARF), as more clearly defines renal dysfunction as a continuum rather than a discrete finding of failed kidney function <sup>(1)</sup>.

If renal function of the patient returns to baseline within 48h, this is called rapid reversal AKI while persistent AKI is beyond 48 hrs. If renal dysfunction that persists for 7 days is categorized as Acute Kidney Disease (AKD) and the term Chronic Kidney Disease (CKD) is used for patients with kidney disease persistent after 90 days period <sup>(2)</sup>.

The role of creatinine as a marker of renal function is not enough, by the fact that its half-life increases from 4 h to 24–72 h if the glomerular filtration rate (GFR) decreases. Rise of serum concentration may take 24–36 h after a definite renal insult. True decrease in GFR may not be adequately reflected by serum creatinine in cases with sepsis, liver disease, and/or muscle wasting <sup>(3-4)</sup>.

Some of new biomarkers e.g. (Cystatin C, Glutathione S-Transferase, Alkaline phosphatase and Angiopoiten 1 and 2) may also provide information

about the underlying etiology and indicate different stages of the pathophysiological processes involved in AKI from acute stage to recovery <sup>(5)</sup>.

The GST protein family, which is divided into 3 major subclasses alpha ,bi, gamma are ubiquitous enzymes which have a role in the detoxification of free radicals .The GST proteins family have been purified from a wide variety of human tissues (e.g. kidneys , testes ovaries , small intestine, liver and adrenal glands). In renal tubules contain alpha and pi forms in high amounts thus GST is a good marker for diagnosis of AKI <sup>(6)</sup>.

This study was aimed to find and investigate the role of GST in development and outcome of acute kidney injury in PICU of Zagazig University Children Hospital.

### PATIENT AND METHODS

This prospective, cohort study included a total of 50 critically ill infants and children, attending at PICU, Faculty of Medicine, Zagazig University Children Hospital. This study was conducted between September 2018 to end of February 2019.

**Approval for doing the research was obtained from Pediatrics and Medical Biochemistry Departments, Zagazig University, after receiving Institutional Review Board (IRB) approval. The**



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study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Written informed consent of all the subject parents was obtained.

#### **Inclusion criteria**

- Patient's age from 1 month up to 16 years.
- Patient with admission more than 24 hours
- Both males and females were included.

#### **Exclusion criteria**

- Patient with chronic kidney injury and those admitted for less than 24 hours.

The included subjects were divided into two groups; **Non-AKI Group (control)** consisted of 38 Infants and children who lack the diagnostic criteria of acute kidney injury and **AKI Group (cases)** consisted of 12 Infants and children who developed acute kidney injury (AKI).

#### **AKI was diagnosed according to:**

##### **A- pRIFLE criteria <sup>(7)</sup>:**

- RISK (eCC decreased by 25%, UOP less than 0.5 ml/kg/h. for 8 hours).
- Injury (eCC decreased by 50%, UOP less than 0.5 ml/kg/hour for 16 hours).
- Failure (eCC decreased by 75% or eCC less than 35 ml/min/1.73 m<sup>2</sup>, UOP less than 0.3 ml/kg/h. for 24 hours) or anuric for 12 h.
- Loss (persistent failure more than 4 weeks).
- End stage renal disease (persistent failure more than 3 months).

##### **B- KDIGO stages <sup>(8)</sup>:**

**Stage 1:** One of the following:

- Serum creatinine increased 1.5-1.9 times baseline.
- Serum creatinine increase >0.3mg/dl (26.5µmol/l).
- Urinary output <0.5ml/kg/h during a 6-hour block.

**Stage 2:** One of the following:

- Serum creatinine increase 2.0-2.9 times baseline.
- Urinary output <0.5ml/kg/h during two 6 hours blocks.

**Stage 3:** One of the following:

- Serum creatinine increase 3 times baseline.
- Serum creatinine increases to > 4.0 mg/dl (353µmol/l).
- Initiation of renal replacement therapy.
- Urinary output < 0.3ml/kg/h during more than 24 hours.
- Anuria for more than 12 hours.

#### **Study Assessments and Data Collection**

For each eligible patient, the following data was reported:

- **Full history taken:** personal history, history of present illness, past history, perinatal history, developmental, dietetic, vaccination and family history.
- **Complete clinical examination:** general and local with stress on: Vital signs, Hydration of the patients and capillary refill.
- **Investigations:**

Venous blood was withdrawn to perform serum and urine Glutathione S-Transferase, complete blood picture, Complete urine analysis, Calculation of urine output, serum electrolytes, serum urea and creatinine, abdominal ultrasound (if needed).

Estimated creatinine clearance (eCC) was calculated according to the Schwartz formula.

$$eGFR \text{ (ml/min/1.73m}^2\text{)} = k \times \text{length (cm) / Serum creatinine (mg/dl).}$$

Where (**k**) is 0.33 for low-birth weight infants <1 yr. old, 0.45 for term infants <1 yr old whose weight is appropriate for gestational age, 0.55 for children and adolescent girls, and 0.70 for adolescent boys <sup>(9)</sup>.

**Serum and urine Glutathione S-Transferase determination were done by using a double-antibody sandwich enzyme-linked immune-sorbent assay (ELISA).**

#### **Statistical analysis**

Data were analyzed by Statistical Package of Social Science (SPSS), software version 24.0. Continuous data were presented as the Mean ± SD if normally distributed or Median (Range) if not normally distributed. Normality was checked by Shapiro test. Categorical data were presented by the count and percentage. *Chi-squared test:* is used to discover if there is a relationship between two categorical variables. *Independent-samples t-test:* is used to determine if a difference exists between the means of two independent groups on a continuous dependent variable. *Mann-Whitney u test* (nonparametric alternative to independent-samples t-test). *Fisher's Exact Test:* for (2X2) (RXC) table. It is an alternative to chi-squared test when the expected cell count is less than five. *Pearson's and Spearman correlation coefficients* were used to estimate the strength of linear relationship between two continuous variables; at least one of the two variables must follow a normal and not normal distribution respectively. *P-value* <0.05 indicates significant difference and *P-value* ≥0.05 indicates non-significant difference

## RESULTS

AKI developed in 24% of patients (table 1). The current study showed that there was statistically non-significant relation between presence of AKI and patient age, gender, weight or height (**Table 1**). Also, there was statistically non-significant relation between presence of AKI and fate of patients (table 2)

On assessing relation between GST in urine and plasma and presence of AKI, statistically highly significant relations were detected (table 3). There was statistically non-significant relation between pRIFLE staging and GST (plasma and urine) (Table 4).

There were statistically significant negative correlations between each of plasma and urine GST

on one side and both heart rate and estimated creatinine clearance on the other side (Table 5). There was statistically non-significant correlation between either plasma, urine GST and age, height, weight, other vital signs or other laboratory parameters (Table 5).

Plasma GST could predict presence of AKI at cutoff  $\geq 30.5$ , with AUC 0.964, sensitivity 100%, specificity 84%, PPV 66.7%, NPV 100%, positive likelihood ratio 6.6 and negative likelihood ratio 0 with accuracy 88% (Figure 1)

The best cutoff of urinary GST in prediction of AKI was  $\geq 12.5$ , with AUC 0.95, sensitivity 91.7%, specificity 84.2%, PPV 64.7%, NPV 97% , positive likelihood ratio 5.8 and negative likelihood ratio 0.1 with accuracy 86% (Figure 2).

**Table (1): Comparison between patients with and without AKI regarding demographic characteristics:**

	Non-AKI No=38		AKI No=12		Test of sig.	P
<b>Age (month)</b> <b>Median (Range)</b>	7 (1.03-144)		9 (1.6-156)		Z (-1.493)	0.135
<b>Height (cm)</b> <b>Median</b>	63		71		Z (-0.671)	0.502
<b>Weight (kg)</b> <b>Median</b>	6		8		Z (-0.273)	0.785
	<b>N=38</b>	<b>%</b>	<b>N=12</b>	<b>%</b>	$\chi^2$	<b>P</b>
<b>Gender:</b>						
Male	19	50	2	16.7	Fisher	0.051
Female	19	50	10	83.3		

(Z):Mann-Whitney test; ( $\chi^2$ ):Chi -square test. ;  $p > 0.05$  is statistically non-significant.

**Table (2): Comparison between patients with and without AKI regarding outcome:**

Outcome	Non-AKI No=38		AKI No=12		$\chi^2$	p
	N	%	N	%		
<b>Died</b>	8	21.1	4	33.3	Fisher	0.448
<b>Survived</b>	30	78.9	8	66.7		

$\chi^2$ : Chi square test,  $p < 0.05$  is statistically significant.

**Table (3): Comparison between patients with and without AKI regarding plasma and urine GST:**

	Non-AKI No=38	AKI No=12	Test of Sig.	P
<b>Plasma GST (<math>\mu\text{g/L}</math>)</b> <b>(Mean <math>\pm</math> SD)</b>	19.26 $\pm$ 4.46	39 $\pm$ 3.54	Z (-4.815)	<0.001
<b>Urine GST (mg/L)</b> <b>(Mean <math>\pm</math> SD)</b>	10.68 $\pm$ 2.08	16.58 $\pm$ 2.97	t(-7.697)	<0.001

(Z):Mann-Whitney test ; (t): independent sample t test.;  $p \leq 0.001$  is statistically significant

**Table (4): Comparison between plasma and urine GST regarding pRIFLE in the studied patients:**

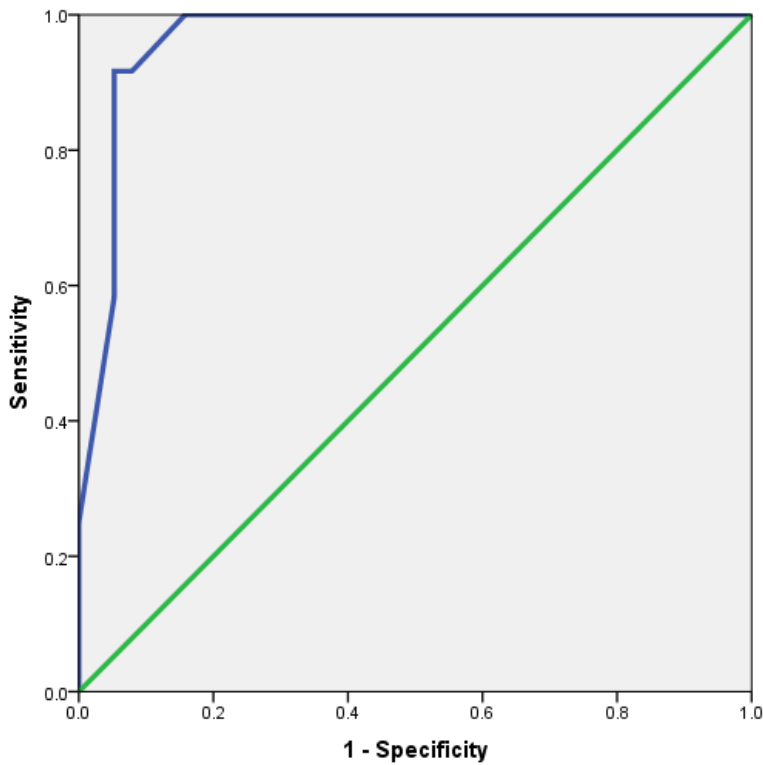
	<b>R</b>	<b>I</b>	<b>F</b>	<b>t</b>	<b>P</b>
	Mean ± SD	Mean ± SD	Mean ± SD		
<b>Plasma GST (µg/L)</b>	37±5.19	39 ± 2.738	39.25 ± 4.349	0.209	0.839
<b>Urine GST (mg/L)</b>	17.66±4.04	16.8± 2.949	16 ± 1.414	2.017	0.071

p>0.05 is statistically significant, (t): independent sample t test, (T):T test ; (R):Risk; (I):Injury; (F):Failure.

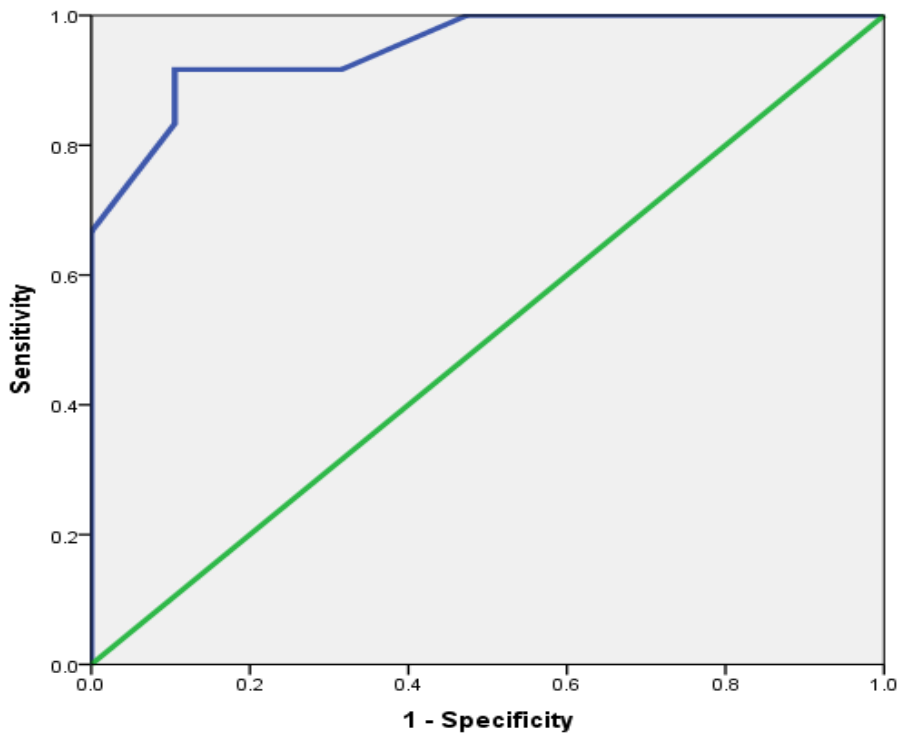
**Table (5): Correlation between plasma GST and vital signs in the studied patients:**

	<b>Plasma GST</b>		<b>Urine GST</b>	
	<b>r</b>	<b>p</b>	<b>r</b>	<b>p</b>
<b>Age (month)</b>	0.233	0.103	0.234	0.103
<b>Temperature (C°)</b>	-0.193	0.179	-0.076	0.639
<b>Respiratory rate /min</b>	-0.07	0.639	0.001	0.996
<b>Heart rate /min</b>	-0.337	0.017*	-0.303	0.032*
<b>Systolic blood pressure (mmHg)</b>	0.004	0.977	0.079	0.585
<b>Diastolic blood pressure (mmHg)</b>	0.092	0.524	0.266	0.062
<b>TLC</b>	-0.132	0.361	0.071	0.622
<b>Platelet count</b>	-0.168	0.243	-0.08	0.580
<b>Hemoglobin (g/dl)</b>	-0.105	0.466	-0.110	0.449
<b>eCC (ml/min)</b>	-0.345	0.014*	-0.318	0.024*
<b>Urea</b>	0.425	0.002	0.252	0.078
<b>Sodium (mmol/L)</b>	-0.218	0.127	-0.036	0.806
<b>Potassium (mmol/L )</b>	-0.174	0.228	0.045	0.757
<b>Calcium (mg/dL )</b>	-0.214	0.136	-0.158	0.272
<b>Duration of stay in PICU</b>	0.161	0.236	0.2	0.165
<b>Duration of stay on MV</b>	-0.255	0.306	-0.260	0.298

r Correlation coefficient



**Figure (1): ROC curve showing performance of plasma GST in detection of acute kidney injury among the studied patients.**



**Figure (2): ROC curve showing performance of urinary GST in detection of acute kidney injury among the studied patients.**

## DISCUSSION

Acute kidney injury (AKI) is common in critically ill children admitted to intensive care. The etiology of AKI is multifactorial and the incidence varies between 1 and 41%, probably due to the different definitions used in clinical studies <sup>(10)</sup>. The term AKI has largely replaced acute renal failure, as it more clearly defines renal dysfunction as a continuum rather than a discrete finding of failed kidney function. Pediatric AKI presents with a wide range of clinical manifestations from a minimal elevation in serum creatinine to anuric renal failure, and it occurs in a variety of clinical settings <sup>(11)</sup>.

Glutathione S-transferase comprises a multigene family of detoxification enzymes present in many organs with expression in specific tissues. These enzymes are significant in catalyzing the conjugation of many electrophilic substances to glutathione. Based on immunological, biochemical, and structural properties, soluble GS is separated in four basic classes: alpha, mu, pi, and theta. GST Pi has a significant role in protecting cells from cytotoxic and carcinogenic agents and is expressed in different concentrations in normal tissues and in a different concentration in different types of cells <sup>(12)</sup>.

Glutathione S-transferase pi can be detected in urine after renal tubular damage, and as a free radical scavenger, it can help decrease the extent of tubular damage. The GST Pi isoform is present in proximal tubules and Bowman's capsule until the 35th week of gestation. After this time, the

isoenzyme is downregulated in proximal tubules and Bowman's capsule, and expression is restricted to distal tubular cells and collecting tubules. <sup>(13)</sup>.

In the current study, frequency of AKI was (24%), representing (12) cases, out of (50) cases admitted to the PICU Zagazig University Children Hospital.

As regard to the incidence of AKI in different studies, it ranged from 30.6% to 35.8% <sup>(14-15)</sup>. **Plotz et al.** <sup>(16)</sup> and **Akcan et al.** <sup>(7)</sup> reported incidence of AKI respectively (58%) and (82%). This variation can be explained by specific epidemiological characteristics according to the area of study. The high incidence of AKI on admission suggests that future studies that seek to assess risk factors for development of this complication should include data obtained prior to PICU admission and appears to indicate an unmet need for strict monitoring of renal function in the emergency department.

The present study demonstrated that, there was no significant difference between the (AKI) and (Non AKI) groups regarding the age, height, weight and gender in agreement with a previous study <sup>(15)</sup>.

A previous study by **Mehta et al.** <sup>(17)</sup>, did not agree with ours regarding age who found that younger age was independent risk factor for AKI in their study. **Cabral et al.** <sup>(18)</sup> reported a significant relation between AKI and age, height and weight.

For outcome between (AKI) and (Non-AKI) Groups, there was statistically non-significant

difference between both groups. In our present study (Non-AKI) group was twice times bigger in mortality than that of (AKI) group, this is may be due to small number of AKI cases. It is not in agreement with Friere *et al.* <sup>(15)</sup>, who reported that the mortality in AKI cases was ten times bigger than that in non-AKI cases. **Plotz *et al.*** <sup>(16)</sup> identified a five times bigger mortality in AKI cases than that in Non-AKI cases. **Akcan *et al.*** <sup>(7)</sup> found no statistically significant difference for both groups' mortality. **Hoste *et al.*** <sup>(19)</sup> identified three times bigger mortality rates in the exposed group. **Ostermann and Chang** <sup>(14)</sup> identified that AKI patients had a four times bigger mortality versus non-AKI patients. This can be explained by that AKI is associated with a number of life-threatening complications, which increase the mortality rate in these cases.

In the present study the (AKI) group was subdivided into three subgroups representing the classes of AKI (severity) regarding pRIFLE: Class (R) Risk, Class (I) injury and Class (F) failure. Frequency of (R) class is 25%, frequency of (I) class is 41.7%, frequency of (F) class is 33.3%, the AKI level incidence was variable at different studies as Friere *et al.*, <sup>(15)</sup> reported that the maximal RIFLE score found during the patients stay was 39.1% for class (R), 37.2% for class (I) and 21.8% for class (F) while **Akcan *et al.*** <sup>(7)</sup> found 48.8%, 26% and 25.2%, respectively. **Plotz *et al.*** <sup>(16)</sup> reported incidences of 52%, 37% and 11%, respectively.

In a study by **Mehta *et al.*** <sup>(20)</sup>, maximum cases of AKI had Stage 1(65.8%), followed by Stage 2(17.8%) and Stage 3(16.4%). Similar pattern of AKI level (R, I, F) was reported by **Akcan *et al.*** <sup>(7)</sup>, i.e., 48.8%, 26%, 25.2%, and **Plötz *et al.*** <sup>(16)</sup>, i.e., 52%, 37%, 11%, respectively.

This variability of incidences can be explained can be attributed to different populations studied, and the different ICU characteristics.

Our study showed that, plasma and urine GST Pi was highly sensitive biomarker for early detection of AKI in pediatric cases of PICU (100% and 91.7% respectively). This was in agreement with **Coca *et al.*** <sup>(21)</sup>, regarding (urine GST Pi) who reported that, urine glutathione-S-transferase-pi performed best for facilitating early diagnosis of AKI.

**Sundberg *et al.*** <sup>(22)</sup>, showed that, two GSTs (alpha and Pi) are released in urine during renal injury, which makes them a very early indicator of tubular injury. This is in agreement with our study because of GST Pi in urine and plasma is highly sensitive biomarker for early detection of AKI in pediatric intensive care unit.

Numerous studies have evaluated urinary GST as a biomarker of AKI in adults and children

and have emphasized alpha GST and GST Pi as having a potential role in the diagnostic evaluation of AKI <sup>(23-24)</sup>. This was in agreement with our study because of GST pi was highly sensitive indicator in early detection of AKI in PICU. This can be supported by the finding that there is significant negative correlation between plasma, urinary GST and estimated creatinine clearance.

The strength of the current study is being prospective study that started with patients admitted to PICU and were followed up for development of AKI and also can identify actual role of GST in AKI.

The study had some limitations. The number of the participants was not large and being applied in one center. So, large scale multicenteric studied should be applied to verify role of GST in pathogenesis of AKI. Special attention should be applied to decrease incidence of AKI in PICU.

## CONCLUSION

It could be concluded that AKI had significant incidence in PICU admission. The conclusion of our study is that high levels of plasma and urine GST Pi after admission in PICU are associated with an increased development of AKI in critically ill children in PICU. Our data demonstrated that GST Pi is a valuable tool (because of its high sensitivity and specificity) for early diagnosis of AKI and prediction of prognosis after admission in PICU which keep morbidity and mortality are less.

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