



## ORIGINAL ARTICLE

SERUM CYSTATIN C AS A BIOMARKER OF ACUTE KIDNEY INJURY  
IN PRE-ECLAMPTIC PATIENTSSaqibah Rehman, Tariq Mahmood Ahmad\*, Asma Hayat\*, Ayesha Qamar\*,  
Syeda Basma Bukhari\*, Saima Bashir

Department of Pathology, Gomal Medical College, DI Khan, \*Army Medical College, Rawalpindi, Pakistan

**Background:** Pre-eclampsia is a common multisystem disorder of pregnancy especially kidney damage. Cystatin C is a reliable marker to be used for kidney function. Objective of this study was to evaluate diagnostic accuracy of cystatin C in comparison of serum creatinine for the early diagnosis of acute kidney injury in patients of pre-eclampsia. **Methods:** This case control study was conducted in Department of Chemical Pathology of a tertiary care hospital in Rawalpindi from Jun 2024 to Apr 2025. A sample size of 70 (35 patients, 35 controls) with 95% confidence interval was calculated with 1:1 case to control ratio using online WHO calculator. Simple consecutive sampling was used. Patients diagnosed with pre-eclampsia with >20 weeks of gestation were included according to the American Obstetric and Gynaecologists guidelines. Controls were healthy pregnant mothers of the same gestational duration. Five mL of blood was collected from each patient for estimation of random blood glucose, serum creatinine, uric acid, and cystatin C. Statistical analysis was performed using Pearson's correlation, *t*-test and ROC curve analysis. **Results:** Mean age of participants was 28.7±2.6 years. Mean gestational age was 29.1±2.8 weeks. Mean cystatin C value were higher among cases (0.830±0.28 mg/L) than controls (0.167±0.19 mg/L). Cystatin C had 88% sensitivity and 98% specificity. Serum creatinine and uric acid had much less sensitivity and specificity as compared to cystatin C. **Conclusion:** Serum cystatin C is an important biomarker that more accurately captures early renal impairment compared to conventional indicators.

**Keywords:** Cystatin C, serum creatinine, uric acid

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## INTRODUCTION

Pre-eclampsia is most common pregnancy related complication that is associated with maternal morbidity and mortality.<sup>1</sup> According to World Health Organization, 16.1% maternal deaths in developed countries are due to pre-eclampsia.<sup>2</sup> Worldwide, 76,000 maternal and 500,000 infant deaths each year are due to pre-eclampsia.<sup>3</sup>

Pre-eclampsia is a multisystem disorder characterized by blood pressure of 140/90 mmHg or more with proteinuria.<sup>4</sup> According to American College of Obstetricians and Gynaecologists guidelines (ACOG), pre-eclampsia is established when maternal blood pressure is >140/90 mmHg measured on two intervals at least 6 hours apart and proteinuria >300 mg within 24 hours, after 20 weeks of gestation.<sup>5</sup> Renal function derangement is an essential pathophysiological component of pre-eclampsia during pregnancy.<sup>6</sup> Renal function requires close monitoring to avoid serious renal complications.<sup>7</sup> Early diagnosis of renal function impairment and progression of pre-eclampsia during pregnancy is a great challenge for clinicians. It is worth stating that even in its current state of imperfection, cystatin C has still been found to provide a more accurate estimate of glomerular filtration rate (GFR) than creatinine in certain patient populations.<sup>8</sup>

Serum creatinine has been used as an important marker for GFR, but pregnancy related

vasodilatation of renal vessels leads to changes in glomerular filtration rate thus limiting the use of serum creatinine as GFR marker. Another predictive GFR marker of pre-eclampsia is uric acid.<sup>9</sup> It was considered as a good predictor in clinical observation due to increase in its concentration with severity of pre-eclampsia.<sup>10</sup> However, some studies have reported uric acid as poor hypertensive disorder estimator.<sup>11</sup>

Cystatin C is a new endogenous marker for assessment of GFR.<sup>11</sup> It is produced at constant rate in all nucleated cells and eliminated by glomerular filtration.<sup>8</sup> Proteases such as cysteine proteases (cathepsins) are responsible for the degradation of extracellular matrix associated with the trophoblastic invasion seen in normal placental development.<sup>12</sup> Cystatin C is a member of the cystatin super family of cysteine protease inhibitors and is proved to be better GFR marker in individuals with small to moderate reduction in GFR.<sup>13,14</sup> The maternal decidua is thought to control or limit the process of placentation by a coordinated expression of cystatin C.<sup>15</sup> The finding of increased placental expression and higher serum concentrations of cystatin C in women with clinically evident symptomatic pre-eclampsia suggests that cystatin C may be involved in the aetiology of pre-eclampsia.<sup>16</sup>

Traditional markers of renal function are unable to assess renal impairment at an early stage in pre-eclampsia, hence the utility for an emerging renal

function marker like cystatin C is suggested for early diagnosis and timely management. No local study has been carried out on the utility of this biomarker. This study was designed to evaluate diagnostic accuracy of serum cystatin C as an early marker of acute kidney injury in patients of pre-eclampsia.

## METHODOLOGY

This case control study was conducted in Department of Chemical Pathology of a tertiary care hospital. The total duration of the study was 10 months from Jun 2024 to Apr 2025. Study was approved by ethical review committee and consent was taken from each participant.

A sample size of 70 (95% confidence interval) was calculated with 1:1 case to control ratio using WHO Sample Size Calculator. Participants were divided in two groups; cases (pregnant women with pre-eclampsia) and controls (healthy pregnant women). Simple consecutive sampling technique was used for distribution of participants into both groups. Urine analysis and blood pressure measurements were performed at the time of confirmation of pregnancy to avoid confounders like pre-existing proteinuria and renal disease. The inclusion criterion was based on gestation age  $\geq 20$  weeks and absence of concomitant disease in both groups. Cases were defined as pregnant ladies with systolic blood pressure (SBP)  $\geq 140$  mmHg and diastolic blood pressure (DBP)  $\geq 90$  mmHg, and proteinuria on dipstick (Roche diagnostics) checked in spot urine sample after 20<sup>th</sup> week of gestation. Controls were defined as healthy pregnant mothers with SBP  $< 140$  mmHg and DBP  $< 90$  mmHg without proteinuria. Mothers with affected glomerular filtration rate due to pre-gestational hypertension, diabetes mellitus, thyroid illness and other renal diseases confirmed by previous documents or medications were excluded from study. A questionnaire was used for other parameters like parity, weight, height, BMI, systolic and diastolic BP, gravidity etc.

A total of 5 mL blood was withdrawn from each participant. Two mL blood was taken in sodium fluoride tube for glucose estimation and 3 mL in plain gel tube for renal function tests, uric acid, cystatin C and thyroid stimulating hormone estimation. The sample was centrifuged at 4,000 rpm and tests were performed. Serum cystatin C, serum creatinine and uric acid were measured with particle enhanced immunoturbidimetric method, Jaffe's and standard enzymatic PAP method respectively on Selectra E.

Data were analysed using SPSS-22. Descriptive statistics (percentages, mean, SD) were used to describe the data. Pearson's correlation was applied for the correlation between creatinine and cystatin C among the cases. Independent *t*-test was applied for comparison of cystatin C, creatinine and uric acid level in both groups. ROC analysis was used for diagnostic evaluation of cystatin C, creatinine and uric acid.

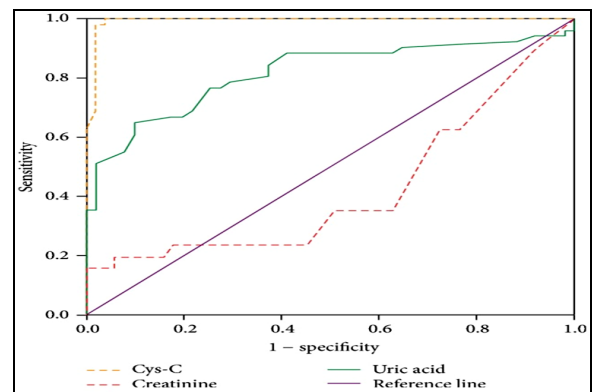
## RESULTS

Total 70 participants were included in study. There were 35 (50%) patients of pre-eclampsia while 35 (50%) were healthy pregnant women. The mean age of cases was  $26.7 \pm 2.6$  years and that of controls was  $25.4 \pm 2.3$  years. Mean BMI was  $24.6 \pm 1.90$  (Kg/m<sup>2</sup>) among cases, and  $22.4 \pm 1.44$  (Kg/m<sup>2</sup>) in controls. Mean gestational age among all participants was  $29.1 \pm 2.8$  weeks. Mean SBP was  $134 \pm 26.4$  mmHg and mean DBP was  $83.3 \pm 13.7$  mmHg was noted in controls while  $145 \pm 28.1$  mmHg SBP and  $97 \pm 15.7$  mmHg DBP was noted in cases.

The renal markers diagnostic evaluation using the receiver operating curve (ROC) showed that the sensitivity and specificity of cystatin C was 88% and 98%, while that of creatinine was 63% and 27.5%, and of uric acid was 79% and 71% respectively. Cystatin C had 98% positive predictive value (PPV), and 89% negative predictive value (NPV). Creatinine had 47% PPV, and 42.2% NPV, and uric acid had 66.7% PPV, 82% NPV. There was a positive correlation between cystatin C and creatinine among pre-eclamptic mothers ( $r=0.4323$ ). ROC analysis showed better diagnostic accuracy of cystatin C with area under curve (AUC) of 0.9 compared to creatinine (0.4) and uric acid (0.8).

**Table-1: Comparison of cystatin C, creatinine and uric acid between cases and controls (Mean $\pm$ SD)**

Biochemical parameters	Cases (n=35)	Controls (n=35)	<i>p</i>
Cystatin C (mg/L)	0.830 $\pm$ 0.28	0.167 $\pm$ 0.19	<0.001
Creatinine ( $\mu$ mol/L)	66.20 $\pm$ 7.4	63.91 $\pm$ 7.1	0.193
Uric acid ( $\mu$ mol/L)	431.4 $\pm$ 48.9	271.3 $\pm$ 41.5	<0.001



**Figure-1: ROC showing diagnostic accuracy of cystatin C compared with other renal markers**

## DISCUSSION

Altered renal function is an essential component of the pathophysiological process in pre-eclampsia. The kidneys play a significant part in the turnover of most low molecular weight substances such as creatinine, urate and cystatin C.<sup>17</sup> Bellos I *et al*<sup>18</sup> reported a meta-analysis which concluded that cystatin C seems to be a promising biomarker for the detection of pre-eclampsia during 3<sup>rd</sup> trimester of pregnancy with 85% sensitivity

and 84% specificity. Our study had 88% sensitivity but 98% specificity. Padema Y *et al*<sup>19</sup> concluded that maternal serum cystatin C, creatinine and uric acid were all significantly elevated at the end of pregnancy in pre-eclampsia compared to those of healthy pregnant women. Our study is in agreement to them. Wattanavaekin K *et al*<sup>20</sup> also suggested that cystatin C is a valid biomarker to predict AKI in pre-eclampsia.

Chew JS *et al*<sup>21</sup> reported that despite the superior diagnostic accuracy of cystatin C compared with serum creatinine for detection of early renal impairment and also prediction of long-term outcomes, there is still a paucity of evidence that it actually leverages important clinical decisions more effectively than the use of serum creatinine alone or eGFR.

## LIMITATIONS

The study was conducted with a small sample size at a single centre, hence the findings cannot be generalized.

## CONCLUSION

Serum cystatin C seems to be a more specific biomarker for detection of AKI in pre-eclampsia during 3<sup>rd</sup> trimester of pregnancy. Further work is recommended to assess its predictive accuracy in early pregnancy and instituting appropriate management strategies.

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## Address for Correspondence:

**Dr Saqibah Rehman**, Department of Pathology, Gomal Medical College, DI Khan, Pakistan. **Cell:** +92-336-9994060

**Email:** [drsaqibah2@yahoo.com](mailto:drsaqibah2@yahoo.com)

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Authors approved the draft and are accountable in ensuring that questions related to accuracy or integrity of the work are duly investigated and resolved.

**SR:** Data collection, analysis and manuscript Drafting

**TM:** Case diagnosis, final review

**AH:** Diagnosis, data analysis

**AQ:** Statistical analysis, revision

**SBB:** Revision, script editing

**SB:** Literature search, bibliography

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