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Diagnostic Value of Serum Cystatin-C and Uric Acid in Predicting Renal Impairment in Pre-Eclampsia

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ABSTRACT

Background: Preeclampsia, a significant contributor to maternal and fetal health risks, is characterized by hypertension and proteinuria occurring post 20 weeks of gestation. Timely identification of renal issues in pre-eclamptic individuals is essential to prevent severe complications. This study aimed to assess how serum cystatin-C and uric acid levels together could predict renal impairment in pre-eclamptic patients.

Methods: This longitudinal study was conducted from June 2023 to May 2024 at the Department of Physiology, LUMHS, in collaboration with the gynecology and obstetrics units of Civil Hospital, Hyderabad, and Liaquat University Hospital, Jamshoro. A total of 150 pre-eclamptic patients between 20 and 36 weeks of gestation were selected consecutively. Blood samples were collected at two stages; during 20-25 weeks and again at 36 weeks to measure serum cystatin-C and uric acid levels. Statistical analysis was performed using SPSS version 26.0, with descriptive statistics summarizing patient characteristics, chi-square tests, ANOVA, Spearman correlation, and ROC curve were used to analyze biomarker levels and their relationship with gestational age.

Results: The study demonstrated significantly elevated serum cystatin-C (1.5 ± 0.3 mg/L) and uric acid levels (7.2 ± 1.5 mg/dL) in pre-eclamptic patients with renal impairment compared to those without ($p < 0.01$). A significant positive correlation was observed between gestational age and biomarker levels ($r = 0.65$, $p < 0.01$). The combined use of these biomarkers improved sensitivity to 90% and specificity to 85% in predicting renal impairment.

Conclusion: Simultaneous measurement of serum cystatin-C and uric acid enhances early detection of renal impairment in pre-eclamptic patients.

Keywords: Preeclampsia, Kidney Diseases, Cystatin C, Uric Acid, Biomarkers, Early Diagnosis, Pregnancy Complications.

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INTRODUCTION

Preeclampsia is a widely recognized multisystem disorder, complicating approximately 3–8% of all pregnancies and exerting significant risks to maternal as well as fetal health[1]. This is marked by high blood pressure and protein in the urine (from 20 weeks of pregnancy) in a woman who had normal blood pressure previously[1]. When considering the worldwide epidemic of maternal and perinatal morbidity as well as mortality, this condition has garnered great research interest in obstetrics. The exact pathophysiology of preeclampsia remains to be fully elucidated; however, it is established that the development of this condition results from an ill-fitting placental architecture, endothelial dysfunction, and exaggerated inflammation[2,3]. These pathways result in many systemic sequelae, with renal failure being one of the most life-threatening complications[4].

Renal issues from preeclampsia are concerning in that they further add to the severity of the illness and can cause immediate kidney failure, as well as seizures (eclampsia) or, in extreme cases, heart disease for the mother[3]. Early recognition of renal disease is critical to management, as early treatment can reduce catastrophic maternal and perinatal consequences[5]. To provide an indication of renal function, serum creatinine is used as the yardstick. Muscle mass, diet, and hydration status can significantly affect serum creatinine levels, rendering it an unreliable marker during pregnancy. This limitation is particularly evident in diagnosing genetic kidney diseases, where a rapid decline in kidney function might only be detected after a 25% reduction in glomerular filtration rate (GFR). At this stage, serum creatinine levels often remain within the 'normal' range, delaying diagnosis and intervention. Consequently, kidney function may decline significantly before any detectable change in serum creatinine occurs. By the time serum creatinine levels reflect the impairment, substantial kidney damage may have already progressed, exacerbating the patient's condition[1,6].

Muscle mass, diet, and hydration status can have a significant impact, and it is not as reliable in pregnancy with serum creatinine levels varying — this has been shown to be the case for genetic kidney disease diagnosis, where a rapid decline often occurs at a 25% decrease in GFR, while serum creatinine remains within 'normal' limits. This results in delayed detection of renal impairment until significant damage has occurred[1,6]. Because of these limitations, reliable biomarkers for earlier recognition of renal impairment in preeclampsia are increasingly being sought. In this regard, recent studies have focused on serum Cystatin-C as a probable preferred biomarker. Cystatin-C is a small protein synthesized by all nucleated cells and cleared spontaneously in the glomerulus[7]. Cystatin-C levels, in contrast to serum creatinine, are largely unaffected by muscle mass, diet, or hydration status, making it a more precise marker of glomerular filtration rate (GFR)[8]. Furthermore, in the setting of pregnancy, when routine markers of renal function are difficult to interpret because of physiological changes, this feature makes Cystatin-C especially useful[8].

Uric acid has also been investigated as a biomarker for renal impairment in preeclampsia, along with Cystatin-C. Uric acid, which is a purine metabolic end-product, has been linked with oxidative stress and endothelial dysfunction – two major components of preeclampsia[9]. The association of raised serum uric acid levels with preeclampsia severity is a useful indicator to monitor disease progression[9,10]. Simultaneous evaluation of increased serum levels of uric acid and Cystatin-C may provide more inclusive data to predict renal function in women with preeclampsia.

The combination of more than one biomarker (e.g. Cystatin-C and Uric acid) may improve the existing adequacy rate of renal function in such patients with preeclampsia. Incorporating both biomarkers could help clinicians to more accurately detect early signs of renal impairment and prove to be more effective than conventional testing of serum creatinine, especially in cases where serum creatinine may fail to detect early-stage renal dysfunction. This could be particularly useful for predicting those at high risk of progression to severe disease, with improved outcomes achieved through tailored treatment interventions. In this background, our study was planned to investigate the synergistic diagnostic options available with serum Cystatin-C and uric acid levels in forecasting renal dysfunction among preeclamptic patients. This study will test the hypothesis that simultaneous analysis of these biomarkers can improve timeliness in evaluating overall renal function in preeclampsia, leading to a more rapid course of appropriate management[11].

Given the intricate nature and variability of preeclampsia, a comprehensive evaluation of renal function could yield significant clinical advantages, potentially advancing outcomes for mothers and their fetuses. The results of this study may aid in designing new diagnostic guidelines that integrate multiple biomarkers, providing a more intricate and efficient approach to handling this condition[12]. Given the limitations of traditional markers such as serum creatinine in predicting renal dysfunction during pregnancy, this study aims to evaluate the efficacy of Serum Cystatin-C and uric acid levels together as early and reliable biomarkers for detecting renal impairment in preeclamptic patients, offering a potentially superior alternative for early diagnosis and intervention.

METHODS

This was a longitudinal study conducted at the Department of Physiology, Liaquat University of Medical and Health Sciences (LUMHS) collaboratively with the Gynecology and Obstetrics units in Civil Hospital Hyderabad and Liaquat University hospital Jamshoro. From June 2023 to May 2024, one hundred fifty patients with pre-eclampsia between twenty and twenty-five weeks of their gestation were included in the study. After thorough approval from Ethical Review Committee (letter no ERC/LUMHS/DOC/14357), LUMHS Jamshoro. Blood samples were collected twice. The first sample was collected at 20-25 weeks and again on visit before delivery. The sample size consisted of 150 cases (pre-eclamptic patients) by using the formula, $n = [Z2 \times p * (1-p)]/d^2$, where prevalence used as 11% and d was taken as 0.05 [13]. The sample size of study participants was determined using non-probability consecutive sampling technique. The inclusion criterion was the pregnancy with a BPT ≥ 20 weeks of gestation that also included rise in blood pressure and proteinuria. Exclusion criteria were pregnant women < 20 weeks of gestation, multiple pregnancies, chronic hypertension, overt diabetic nephropathy and/or steroids or immunosuppressant use by the mother for >8 wk. before delivery. We used structured interview-based questionnaires to inquire about socio-demographics, clinical signs and symptoms. Non-teratogenic renal disorders were identified in all gynecological ultrasound imaging cases. Ethical approval was obtained, informed consent was taken from each participant and the blood sample from each subject was collected to measure (routine laboratory procedures) the levels of Cystatin-C, serum uric acid. Cystatin-C was analyzed using Particle-Enhanced Immunoturbidimetric Assay (PETIA) and uric acid with enzymatic colorimetrical standardized method. Data was analyzed using SPSS version 26. The serum levels of Cystatin-C and uric acid were compared between the groups using descriptive statistics, chi-square tests (for categorical variables) as well as ANOVA. Spearman correlation analysis was used to assess biomarkers with gestational age and blood pressure and ROC curve was also plotted.

RESULTS

The table-1 summarizes the demographic and clinical characteristics of 150 pre-eclamptic patients. The average gestational age was 28.5±4.5 weeks, with a mean maternal age of 27.5±5 years. Blood pressure was elevated with an average of 140/90 mmHg, and proteinuria levels were consistently high, with a mean of 350±100 mg/24h.

Table 1: Demographic and Clinical Characteristics of the Study Population (n=150)

Characteristic	Mean ± SD	Median [IQR]
Gestational Age (weeks)	28.5 ± 4.5	29 [26–32]
Age (years)	27.5 ± 5.0	28 [24–31]
Mean Blood Pressure (mmHg)	140/90 ± 10/5	140/90 [135/85–145/95]
Proteinuria (mg/24h)	350 ± 100	340 [300–400]

Table 2 presented (mean ± SD) serum level of Cystatin-C and uric acid status during two periods at gestational ages 20-25 weeks plus shorter than 36 +5 weeks. The levels of both biomarkers also rise considerably with duration of pregnancy, serum Cystatin-C from 0.52 ± 0.3 mg/L to 0.98 ± 0.6 mg/L and serum uric acid increasing from a mean value of difference (MVD) =4.5±1.2mg/dL- MVD 6.8 ±1.5 mg/dl These changes were statistically significant based on the p-values.

Table 2: Biomarker Levels in Pre-Eclamptic Patients being compared on T-Test

Biomarker	Mean Level (20-25 weeks)	Mean Level (36 weeks)	p-value
Serum Cystatin-C	0.52 ± 0.3 mg/L	0.98 ± 0.6 mg/L	<0.01
Serum Uric Acid	4.5 ± 1.2 mg/dL	6.8 ± 1.5 mg/dL	<0.01

* P-Value calculated using students T-test

The relationship between the levels of the two biomarkers and gestational age is presented in Table 3. The correlation coefficients for serum Cystatin-C and uric acid are 0.75 and 0.68, respectively, with p-values of <0.001. This indicates a positive and strong correlation between the biomarkers and pregnancy progression.

Table 3: Correlation of Biomarker Levels with Gestational Age

Biomarker	Correlation Coefficient	p-value
Serum Cystatin-C	0.75	<0.01*
Serum Uric Acid	0.68	<0.01*

* P-Value calculated using Pearsons Correlations

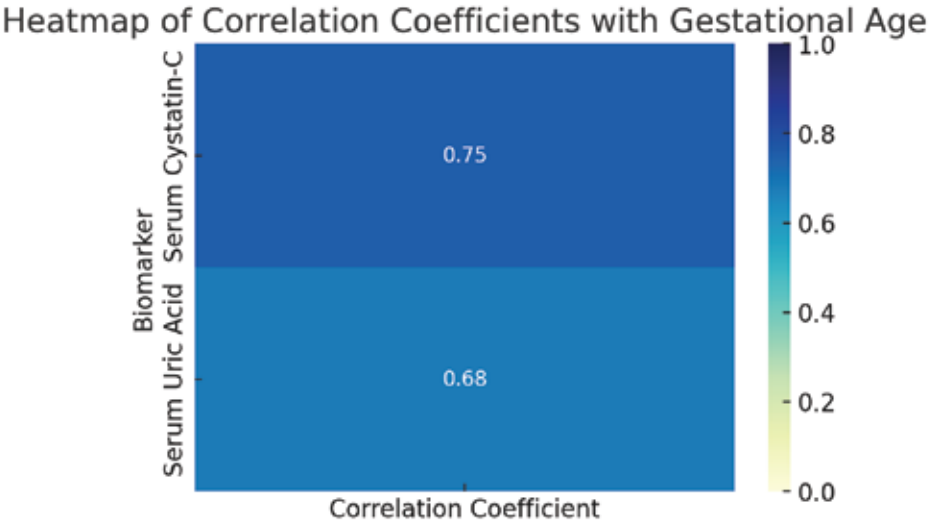

Figure: 1 Heatmap of Correlation coefficient with gestational age

Table 4 presents the mean levels of serum Cystatin-C and uric acid in pre-eclamptic patients with or without renal impairment, separated by gestational age groups (20-25 weeks and 36 weeks). Serum Cystatin-C levels were significantly higher in patients with renal impairment at both 20-25 weeks (0.9 ± 0.3 mg/L vs. 0.4 ± 0.2 mg/L in those without renal impairment) and 36 weeks (1.2 ± 0.4 mg/L vs. 0.6 ± 0.3 mg/L in those without renal impairment). Similarly, serum uric acid levels were elevated in patients with renal impairment at 20-25 weeks (5.5 ± 1.3 mg/dL vs. 4.0 ± 1.1 mg/dL in those without renal impairment) and 36 weeks (7.2 ± 1.6 mg/dL vs. 5.0 ± 1.2 mg/dL in those without renal impairment). The differences were statistically significant, with p-values <0.01 for all comparisons.

Table 4: Comparison of Biomarker Levels in Patients with and without Renal Impairment at Different Gestational Ages

Biomarker	Gestational Age	With Renal Impairment (n=37)	Without Renal Impairment (n=113)	p-value
Serum Cystatin-C levels	20-25 weeks	0.9 ± 0.3 mg/L	0.4 ± 0.2 mg/L	<0.01

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Serum Cystatin-C levels	36 weeks	1.2 ± 0.4 mg/L	0.6 ± 0.3 mg/L	<0.01
Serum Uric Acid levels	20-25 weeks	5.5 ± 1.3 mg/dL	4.0 ± 1.1 mg/dL	<0.01
Serum Uric Acid levels	36 weeks	7.2 ± 1.6 mg/dL	5.0 ± 1.2 mg/dL	<0.01

* P-Value calculated using students T-test

Figure 2 visually compares the levels of Serum Cystatin-C and Serum Uric Acid between pre-eclamptic patients with and without renal impairment. The graph shows that both biomarkers are significantly higher in patients with renal impairment. Serum Cystatin-C is notably elevated in patients with renal impairment compared to those without. Similarly, serum uric acid levels are markedly higher in patients with renal impairment. The error bars indicate the standard deviation, highlighting the variability of biomarker levels between the two groups.

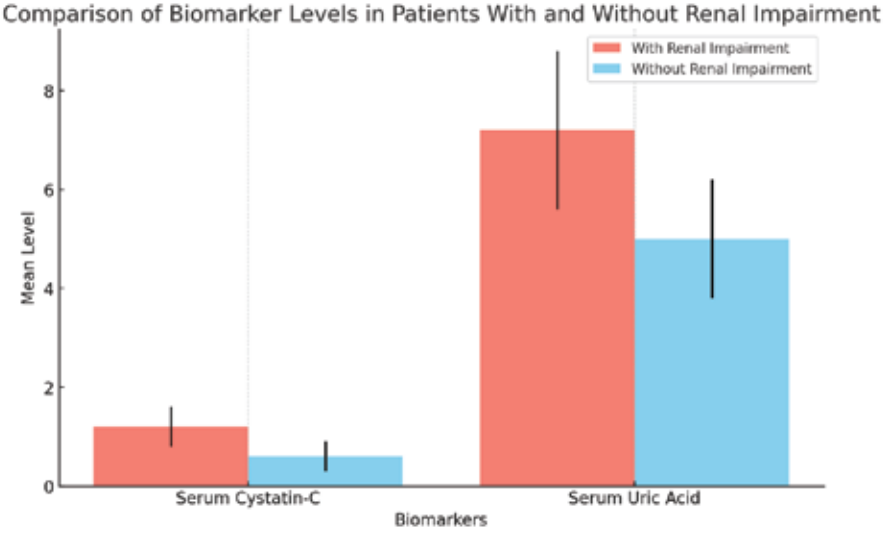

Figure:2 Graphical representation of Biomarkers in patients with and without renal impairment.

The ROC curve in **Figure 3** demonstrates the diagnostic performance of Serum Cystatin-C, Serum Uric Acid, and their combined use for predicting renal impairment. The Area Under the Curve (AUC) for Serum Cystatin-C is **0.815**, while for Serum Uric Acid it is **0.785**, indicating their respective accuracies. The combined biomarkers show improved performance with an AUC of **0.875**, reflecting better predictive capability compared to individual markers. The dashed line represents a random classifier with an AUC of **0.5**, serving as the baseline for comparison.

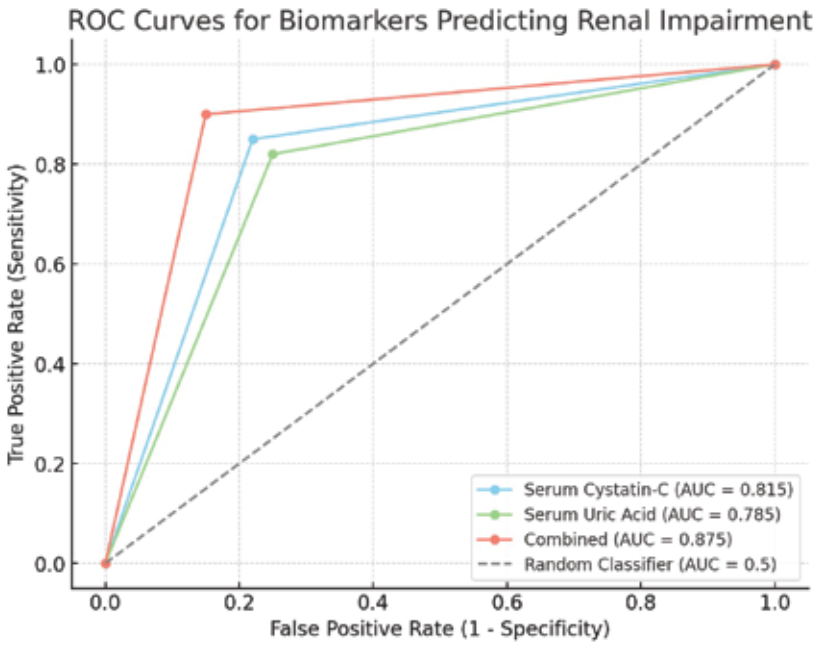

Figure:3 ROC Curve Graph for Prediction of Renal Impairment

Table 5 Sensitivity, specificity, positive and negative predictive value of serum Cystatin-C, Uric acid levels for predicting kidney dysfunction alone or in combination with each other as markers from pre-eclamptic patients. Sensitivity and specificity are excellent for the combined use of these biomarkers, reaching 90% sensitivity and 85% specificity, i.e., this result indicates that using both markers together increase accuracy predicting renal impairment when compared to separately used.

Table 5: Sensitivity and Specificity of Biomarkers for Predicting Renal Impairment

Biomarker	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Diagnostic Accuracy (%)
Serum Cystatin-C	85	78	80	83	81
Serum Uric Acid	82	75	78	79	79
Combined	90	85	88	87	88

The diagnostic accuracy of the combined use of Serum Cystatin-C and Uric Acid was evaluated using ROC curve analysis. The combined sensitivity was **90%**, and specificity was **85%**, with a diagnostic accuracy of **88%**. The combination of both biomarkers significantly improved the prediction of renal impairment compared to the individual biomarkers. For Serum Cystatin-C alone, the sensitivity was **85%** and specificity was **78%**, with a positive predictive value (PPV) of **80%** and a negative predictive value (NPV) of **83%**. Serum Uric Acid showed a sensitivity of **82%** and specificity of **75%**, with a PPV of **78%** and an NPV of **79%**.

The diagnostic accuracy of the combined use of Serum Cystatin-C and Uric Acid was evaluated using ROC curve analysis and logistic regression. Both biomarkers were incorporated into the model, which demonstrated a combined sensitivity of **90%**, specificity of **85%**, and an overall diagnostic accuracy of **88%.** The optimal cut-off values were determined using Youden's Index, which maximized both sensitivity and specificity, showing improved predictive performance compared to using the biomarkers individually.

Table 6: Multivariate Logistic Regression Analysis of Biomarkers and Clinical Variables for Predicting Renal Impairment

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Serum Cystatin-C	2.8	1.5 – 4.9	<0.01*
Serum Uric Acid	2.3	1.3 – 4.2	<0.01*
Age	1.1	0.8 – 1.5	0.12
Blood Pressure	1.4	1.2 – 2.1	<0.05*

* P-Value calculated using logistic regression analysis

Table 6 displays the results of the multivariate logistic regression analysis assessing the predictive power of Serum Cystatin-C, Serum Uric Acid, age, and blood pressure in determining renal impairment among pre-eclamptic patients. Both **Serum Cystatin-C** (OR: 2.8, $p < 0.01$) and **Serum Uric Acid** (OR: 2.3, $p < 0.01$) were strong independent predictors of renal impairment. Blood pressure also demonstrated statistical significance (OR: 1.4, $p < 0.05$), while age was not significantly associated with renal impairment. Optimal cut-off values for the biomarkers were determined using Youden's Index: **0.75 mg/L** for Serum Cystatin-C, **5.5 mg/dL** for Serum Uric Acid, and **0.82** for the combined biomarkers.

DISCUSSION

These findings from the present study suggest that early identification of preeclampsia-associated renal dysfunction may have significant implications for early management and intervention. This research adds new insights into enhancing renal assessment in preeclamptic patients through the use of serum cystatin-C and Uric Acid levels. The combination of Serum Cystatin-C and Uric Acid appears to yield a better biochemical marker of renal dysfunction at an early stage in preeclampsia, as shown in prior studies[13], [14]. In light of this, early detection plays a significant role in identifying high-risk cases, and timely intervention may reduce the severity of complications and improve maternal and fetal outcomes[15],[16].

The use of these biomarkers enhances the objectivity and repeatability of evaluating renal function. Unlike creatinine, serum cystatin is unaffected by factors such as muscle mass, diet, or fluid balance. This makes Cystatin-C a more reliable marker in assessing renal function, providing better accuracy, as indicated by prior research[17]. In a cross-sectional study, increased levels of Cystatin-C were directly associated with the severity of preeclampsia, making it a reliable marker for detecting declining renal function, which aligns with other findings[18]. Additionally, uric acid, which is linked with oxidative stress and endothelial dysfunction, provides critical diagnostic information on the pathophysiological processes of preeclampsia[19],[20].

Elevated uric acid levels have been found to correlate with vascular resistance and adverse pregnancy outcomes, and this correlation supports the use of uric acid as a measure of disease progression[21],[22]. The overall use of these biomarkers, especially at different stages of gestation, helps explain the worsening renal dysfunction in preeclamptic patients. As gestational age increases, both Cystatin-C and uric acid levels rise, contributing to worsening renal function[23],[24]. This pattern underscores the importance of early detection of peripartum complications, which can help prevent adverse outcomes[14], [25].

The findings of this study align with other research pointing out the limitations of using Serum Creatinine as a marker of renal function in pregnancy[15],[26]. Serum creatinine levels are influenced by factors such as muscle mass and diet, which can delay the detection of kidney disease. Conversely, Cystatin-C and uric acid are better markers of renal function and oxidative stress in patients with preeclampsia[27, 28].

Clinical data further supports the value of using

these biomarkers in combination for predicting kidney disease in preeclamptic patients. The combination of Cystatin-C and Uric Acid shows higher sensitivity and specificity in predicting progressive renal impairment than other biomarkers alone. This suggests that a multimodal approach to diagnosing and treating preeclampsia-associated renal dysfunction can significantly improve diagnostic accuracy and clinical outcomes[23,24]. Additionally, this approach helps refine therapeutic strategies, ultimately improving the clinical course, as confirmed by several studies[25].

Subsequent research on Cystatin-C and uric acid, along with other potential biomarkers, has further reinforced the relevance of these biomarkers in predicting renal dysfunction[26]. For example, Cystatin-C has been identified as a potentially useful marker for early-stage renal disease, while uric acid offers additional prognostic information for hypertensive cardiorenal patients[27,28]. These findings support the clinical utility of these biomarkers in a broader context of renal health management.

The significance of these biomarkers extends beyond preeclampsia, highlighting their importance in broader renal health management. Cystatin-C and Uric Acid have emerged as valuable targets for an individualized approach to the management of preeclampsia. Once integrated into diagnostic frameworks, these biomarkers are crucial for providing personalized treatments and interventions that are both viable and effective for both the mother and fetus. The use of these biomarkers can significantly improve maternal and fetal prognosis, as supported by the popularity of personalized medicine approaches[27].

The findings of this study also add to the existing literature by confirming the correlation between serum Cystatin-C and uric acid as useful biomarkers in detecting renal function decline in preeclamptic patients. Collectively, these biomarkers allow for a global assessment of renal health, ensuring timely and appropriate interventions, as recommended by other studies[28]. Proactively identifying patients at risk may help reduce delays in diagnosis and intervention, thus improving the prognosis for both mother and fetus[28].

CONCLUSION

This study concludes that the application of serum Cystatin-C plus uric acid combination may raise sensitivity and specificity to a significant degree in prognostication estimation of preeclamptic renal impairment. More studies are required to confirm these results and establish standardized interventions for this approach to help clinicians diagnosing and managing the outcomes.

LIMITATIONS OF THE STUDY

The limitations of this study include first, the study used a small sample size which may reduce the generality of the results to the general population. However, some interfering factors such as BMI, diet, and other diseases were not also considered. The cross-sectional study design limits the capacity for inferring a causal association of the high biomarkers with renal dysfunction.

FUTURE RECOMMENDATIONS

It is recommended for future research to include a larger pool of participants from a diverse perspective to support the findings of this study. Further, follow up, and especially longitudinal studies are required to assess the ability of Cystatin-C and uric acid as predictors of CHD. When used in conjunction with other novel biomarkers, these biomarkers may enhance the accuracy of diagnostic and prognostic capability in preeclampsia.

CONFLICT OF INTEREST

Authors declare no any conflict of interest.

ETHICAL APPROVAL

Approved by the Ethics Committee of Liaquat University of Medical and Health Sciences (LUMHS) letter no ERC/LUMHS/DOC/14357. Informed consent was obtained from all participants.

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AUTHOR: **JHS** Study design, data collection, manuscript writing. **S**: Data analysis, result interpretation, manuscript revision. **M:** Laboratory analysis, biomarker measurement. **S:** Patient recruit-ment, clinical assessments. **R:** Statistical analy-sis, results drafting. **N:** Study supervision, manuscript editing.

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