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Research Article

Uric Acid as a Predictor of the Severity of Preeclampsia: A Cross-Sectional Study in Sidi Bel Abbes, Algeria

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ABSTRACT

Background: Preeclampsia is a pregnancy complication characterized by elevated blood pressure and organ failure, endangering the health of both the fetus and the mother. The research aimed to examine the predictive value of uric acid levels on outcomes in preeclamptic pregnant women.

Subjects and Methods: The study consisted of 151 preeclamptic pregnant women, categorized into two groups: 99 with severe preeclampsia (SPG) and 52 with moderate preeclampsia (MPG). The researchers compared uric acid levels between groups and looked at LDH, ASAT, and ALAT biomarkers. The study employed Receiver Operating Characteristic (ROC) curve analysis to evaluate the predictive capacity of uric acid levels regarding outcomes.

Results: The study revealed that women with severe preeclampsia exhibited markedly elevated uric acid levels ($p = 0.003$). The cohort with severe preeclampsia encountered more pronounced feto-maternal complications at a statistically significant level ($p \leq 0.001$). The ROC curve analysis indicated that uric acid levels exhibited a moderate capacity to predict the severity and complications of preeclampsia, with diagnostic accuracy rates of 0.691 ($p \leq 0.001$) and 0.635 ($p=0.007$), respectively. The predictive value of uric acid was demonstrated to be inferior to that of the other biomarkers in the study.

Conclusions: While elevated uric acid levels are associated with preeclampsia severity, they may not be as strong a predictor of adverse outcomes as other biomarkers such as ASAT, ALAT, and LDH.

Introduction

Preeclampsia (PE) is a multifactorial disease and one of the most frequent complications in obstetrics, affecting10 million pregnancies annually and contributing to approximately 76,000maternal and 500,000 fetal and neonatal deaths worldwide [1]. The American College of Obstetrics and Gynecology (ACOG) defines PE as a hypertensive disease that arises after 20 weeks of gestation characterized by systolic blood pressure (SBP)≥140mmHgand/or diastolic blood pressure (DBP) ≥90mmHg, and/or proteinuria≥0.3g/24 h [2].

Preeclampsia is a condition involving maternal endothelial dysfunction, primarily affecting the placenta [3] and leading to a various organ complication, including acute renal failure, placental abruption, stroke, eclampsia, HELLP syndrome, and hemolytic uremic syndrome. The symptoms and severity of PE can vary significantly among affected women. The fetus is often impacted, with potential outcomes including intrauterine growth restriction, preterm birth and fetal death [4].

Multiple biological tests help doctors determine preeclampsia severity through measurements of transaminases (ASAT, ALAT) and albumin and lactate dehydrogenase (LDH) and platelet count and uric acid levels. The medical community uses uric acid testing to evaluate the severity of hypertensive pregnancies. The biomarker shows potential for predicting preeclampsia complications because it indicates oxidative stress and tissue damage and renal dysfunction [5]. The body produces higher uric acid levels during preeclampsia because of renal vasoconstriction and fetal DNA release into blood circulation which leads to liver uric acid production [6]. Research indicates that elevated uric acid levels contribute to the development of hypertension and kidney disease [7].

The condition of preeclampsia (PE) leads to high uric acid levels in patients and healthcare providers use this marker to evaluate the severity of maternal and fetal complications [9]. The elevated levels of uric acid in the blood occur because of poor kidney function which leads to vascular problems and inflammation that are central to preeclampsia. The presence of elevated uric acid serves as a risk indicator which helps doctors predict when preeclampsia will develop [10]. The scientific community remains divided about this theory because different research studies have produced contradictory results [11,12]. The assessment of uric acid as a prognostic factor in preeclamptic pregnancies requires evaluation against LDH and ASAT and ALAT biomarkers because of worldwide inconsistent research results. The evaluation of uric acid against other biomarkers will determine its ability to predict PE severity and its effects on maternal and fetal health and its diagnostic capabilities.

Subjects and Methods

This analytical cross-sectional study was performed at the Maternity Ward of Sidi Bel Abbes, Algeria, from March 2021 to January 2022, encompassing 202 pregnant women diagnosed with preeclampsia. 151 participants were included, with 99 show severe preeclampsia (SPG) and 52 with moderate preeclampsia (MPG).

A verified diagnosis of preeclampsia post-20 weeks of gestation to be included, this is according to the American College of Obstetricians and Gynecologists (ACOG) standards: hypertension (≥140/90 mmHg on two distinct measurements) and proteinuria (≥300 mg/24h), in addition to signed informed consent for participation.

Exclusion criteria encompassed a history of chronic kidney disease, preexisting diabetes, chronic hypertension not associated with pregnancy (unless categorized as superimposed preeclampsia), autoimmune or inflammatory diseases, the use of medications influencing uric acid metabolism, instances of intrauterine death, and absence of consent to participate. The final sample was divided into two groups based on how bad the preeclampsia was, according to the American College of Obstetricians and Gynecologists (ACOG) guidelines.

According to the American College of Obstetricians and Gynecologists (ACOG) guidelines, a person is diagnosed with Moderate Preeclampsia Group (MPG) if they meet at least three of the following five criteria: Systolic Blood Pressure (SBP) ≥140 mmHg and/or Diastolic Blood Pressure (DBP) ≥90 mmHg, proteinuria ≥300 mg/24h, and no severe features present.

Severe Preeclampsia Group (SPG) is diagnosed if the individual meets one or more of the following criteria: SBP ≥160 mmHg and/or DBP ≥110 mmHg (measured twice, 6 hours apart); creatinine >1.4 mg/dL; HELLP syndrome; placental abruption; intrauterine growth restriction (IUGR); eclampsia; thrombocytopenia (platelet count <100,000/μL); pulmonary edema; or cortical blindness.

The study protocol is adapted to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent (approved by our Institutional Ethics Committee) was obtained from each patient in the study.

Data collection was carried out through face-to-face interviews and patient file consultation together anthropometric, sociodemographic and clinical information. Blood pressure measurements were performed using a sphygmomanometer on two occasions, with at least 4 hours between measurements.

Intrauterine Growth Restriction (IUGR) was defined as a fetal weight below the10th percentile for gestational age (13).

Body Mass Index (BMI) was calculated as the ratio of weight (kg) to height square (m)2 derived on maternal height and pregnancy weight report. Patients will be classified based on their BMI into one of the following categories according to the WHO global classification: 18.5 to 24.9 kg/m2 is considered as normal weight; 25.0 to 29.9kg/m2 considered as overweight; 30.0-34.9 obesity class I; 35.0-39.9 obesity class II; above 40 obesity class III (14).

Regarding maternal complications, the most common in our population were HELLP syndrome, eclampsia, and placental abruption. Fetal complications included intrauterine growth restriction (IUGR).

Uric acid levels were categorized into two groups: cases with normal uremia (34 -65mg/L) cases with hyperuricemia (≥65mg/L).

Biochemical tests were carried out at the maternity laboratory, where venous blood samples were collected to measure the serum concentration of various biochemical parameters, including blood sugar, urea, creatinine, total protein, LDH, ASAT, ALAT, and uric acid. The analyses were performed using the ERBAXL-300 analyzer in accordance with the manufacturer's protocol (ERBA kit). Uric acid levels were measured using the enzymatic colorimetric method (ERBAR agent), with reference values ranging from34to65mg/L.

The statistical analysis was conducted by the SPSS, version 20. We used the Student's t-test and the chi-Square Test to compare the two groups. Continuous variables were shown as mean ± standard deviation, and categorical variables were shown as counts (percentages). A p-value of ≤0.05 was considered statistically significant.

A Receiver Operating Characteristic (ROC) curve analysis was performed to assess the prognostic efficacy of uric acid relative to ASAT, ALAT, and LDH. This analysis assessed classical indicators,

including the area under the curve (AUC), sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV).Additionally, specific cutoffs values were determined for the study sample. The screening test is considered non-informative if the AUC is less than 0.5. A test is deemed to have good performance if the AUC falls between 0.7 and 0.8, very good performance if the AUC isbetween0.8 and0.9, andexcellentperformanceiftheAUCexceeds0.9.

Results

Of the study population, 52 participants (39.9%) were categorized into the Moderate Preeclampsia Group (MPG), while 99 participants (60.1%) were classified in the Severe Preeclampsia Group (SPG). The mean age of the MPG was 33.15 □ 6.62 years and for SPG, itwas32.38□6.85years (Table1).

Table 1: Baseline of characteristics of study population

Parameters	MPG n (%)	SPG n(%)	P value
Age(years)	33.15± 6.62	32.38± 6.89	0.410
BMI Kg/m2			
Normal	06(4.1%)	20(13.5%)	
Overweight	22(14.9%)	29(19.6%)	0 .178
Obesity 1	16(10.8%)	28(18.9%)	
Obesity 2	11(7.4%)	09(6.1%)	
Obesity 3	04(2.7%)	03(2.0)	
Origin			
Urban	25(16.9%)	36(40.4%)	0.474
Rural	34(23%)	53(35.8%)	
Occupation			
Housewife	43(29.1%)	77(52.5%)	0.050*
Worker	16(10.8%)	11(7.4%)	
GA weeks			
20-30weeks	05(8.9%)1	15(17%)	0.366
31-34weeks	8(32.1%)	28(31.8%)	
35-38weeks	33(58.9%)	45(51.1%)	
complication			
Presence	04(5.9%)	06(8.7%)	0.025*
Absence	55(69.6%)	44(63.8%)	
Eclampsia			
Presence	00(0.0%)	21(22.8%)	≤ 10-3***
Absence	59(100%)	71(77.2%)	
Placental abruption			
Presence	00(0.0%)	21(22.8%)	≤ 10-3***
Absence	59(100%)	71(77.2%)	
HELLP Syndrome			
Presence	00(0.0%)	27(29.3%)	≤ 10-3***
Absence	59(100%)	63(68.5%)	
IUGR		42(45.7%)	
Yes	04(6.8%)	47(51.1%)	≤ 10-3***
No	55(93.2%)		

(*) p value for student test; p≤0.05 was considered as statistically significant, p***≤10-3. Moderate preeclampsia group (MPG), Severe preeclampsia group (SPG), BMI=Body Mass Index, Gestational age (GA), HELLP=Hemolysis Elevated Liver Enzymes Low Platelets, Intrauterine Growth Restriction (IUGR).

The chi-square test revealed no statistically significant differences ($p > 0.05$) between the two groups regarding most characteristics, with the exception of occupation. Housewives exhibited a significantly higher prevalence of severe preeclampsia compared to employed women (52.5%vs7.4%). The incidence of adverse feto-maternal outcomes was also significantly higher in the SPG compared to the MPG ($p \leq 0.001$) (Table1).

Comparing the means of variables between the two groups, significant differences ($p \leq 0.05$) were observed in SBP, DBP, ASAT, ALAT, urea, and creatinine levels. However, no significant differences were found regarding blood glucose, uric acid, albumin, or total protein levels (Table2).

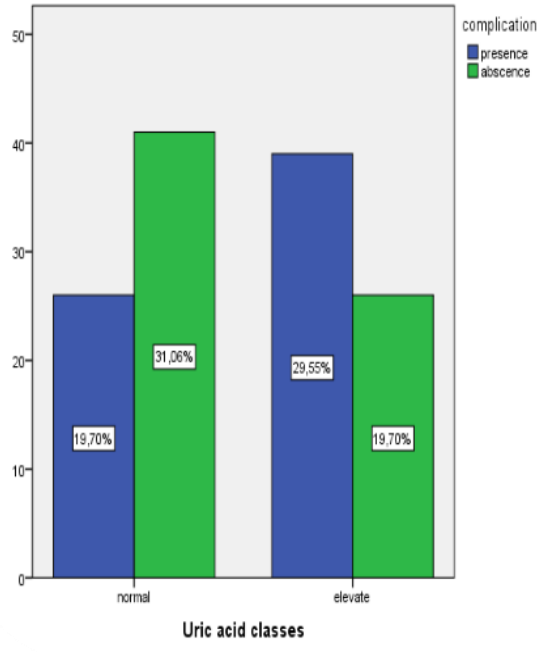
Table 2: Clinical and biochemical characteristics of study population

Parameters	MPG (M ±SD)	SPG (M±SD)	p-value
SBP (mmHg)	14.50 ±0.50	17.05 ± 2.13	0.010*
DBP (mmHg)	9.40 ± 0.93	10.19 ± 1.21	0.032 *
Glycemia(g/L)	0.90 ±0.22	1.15±0.05	0.064
ASAT (IU/L)	21.24±8.88	62.20 ±90.85	≤10-3***
ALAT(IU/L)	14.38 ± 7.84	44.58 ±56.04	≤10-3***
Urea (g/ L)	0.23 ±0.07	0.35 ± 0.23	≤10-3***
Creatinine (mg/ L)	8.55 ± 2.50	11.45 ± 6.84	0.026 *
Uric acid (mg/L)	59.50 ±17.97	74.36 ± 22.44	0.263
Albumin (g/L)	32.93 ±3.42	31.23 ±3.86	0.719
Protein (g/L)	61.16 ± 6.38	59.68 ±7.91	0.646
LDH (UI/L)	364.64 ±130.17	652.50 ± 396.67	0.032

Data are presented as mean ± standard deviation, (*) p value for student t test; p≤ 0.05 was considered as statistically significant. SBP=systolic blood pressure, DBP=diastolic blood pressure, AST=aspartate transaminase, ALT= alanine transaminase, LDH=lactate dehydrogenase. *p <0.05; *** p≤ 0.001.

Figure 1 illustrates the association between serum uric acid and severity of preeclampsia. Elevated uric acid levels were more prevalent in the SPG, with 38.64% of cases, compared to10.61% in the MPG. Hyperuricemia was also correlated with adverse maternal and fetal outcomes, as 29.55% of hyperuricemic preeclamptic patients experienced complications, compared to 19.70% of those with normal uric acid levels.

The ROC curve for uric acid indicated moderate discriminatory power for predicting the severity of preeclampsia, with an AUC of 0.691 ($p \leq 0.001$) for severity (Figure 2.A). For predicting severity, the optimal cut-off value was 65.50 µmol/L, yielding moderate sensitivity (Se: 62.5%) and specificity (Sp: 60.0%), with a positive predictive value (PPV: 45.58%) and negative predictive value (NPV: 18.46%).



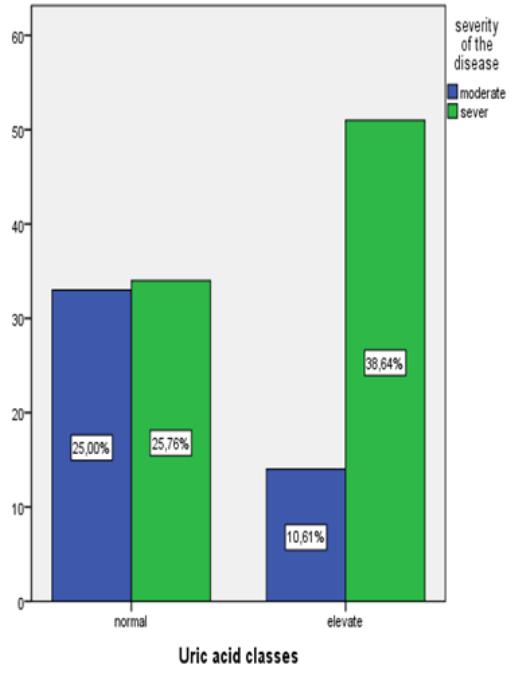
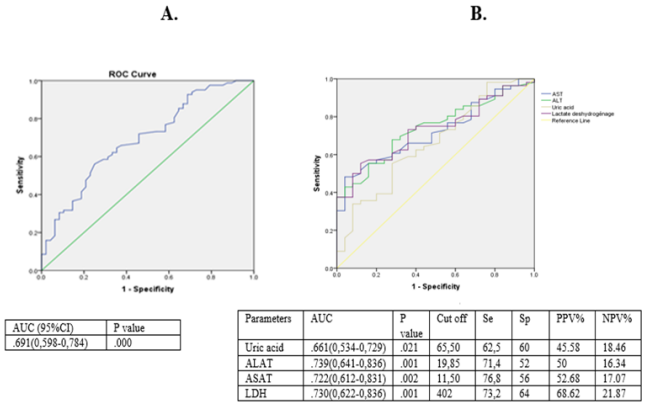


Figure 1: Association of uric acid classes with severity and feto-maternal outcomes in preeclampsia.

When comparing the predictive performance of uric acid to other biomarkers, uric acid remained a relatively poor predictor of severity (AUC: 0.662 vs 0.722, 0.739, and 0.730 for ASAT, ALAT, and LDH, respectively) (Figure 2.B) and of feto-maternal outcomes (AUC: 0.659).



AUC (95%CI)	P value
.691(0,598-0,784)	.000

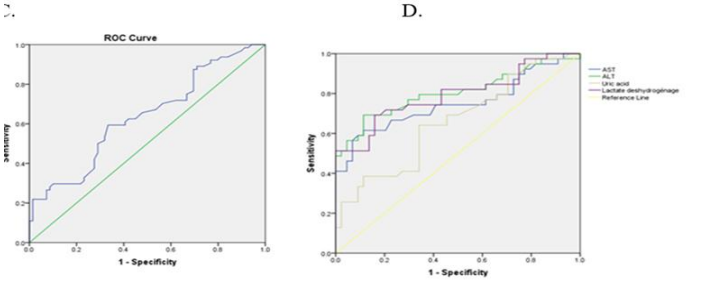
Parameters	AUC	P value	Cut off	Se	Sp	PPV%	NPV%
Uric acid	.661(0,534-0,729)	.021	65,50	62,5	60	45.58	18.46
ALAT	.739(0,641-0,836)	.001	19,85	71,4	52	50	16.34
ASAT	.722(0,612-0,831)	.002	11,50	76,8	56	52.68	17.07
LDH	.730(0,622-0,836)	.001	402	73,2	64	68.62	21.87

Figure 2: Receiver operating curves (ROC) for predicting severity of preeclampsia.

A. Using maternal serum uric acid level alone; **B**. Maternal serum: uric acid, LDH, ASAT and ALAT levels. Lactate dehydrogenase (LDH); Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Area under the ROC curve (AUC), Confidence Interval (CI), Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV).

The ROC curve for uric acid indicated moderate discriminatory power for predicting both the severity and complications of preeclampsia, with an AUC of 0.635 (p = 0.007) for complications (Figure 3.C). For predicting complications, the optimal cut-off point was 66.50 µmol/L, with Se: 66.7%, Sp: 54.5%, PPV: 68.65%, and NPV: 75.38%.

In contrast, the ROC curves for ASAT, ALAT, and LDH demonstrated stronger discriminatory power in detecting preeclampsia complications. ALAT had the highest predictive accuracy, with an optimal cut-off value of 12.85 U/L, yielding Se: 79.5%, Sp: 65.9%, PPV: 60.0%, NPV: 88.09%, and AUC: 0.804. ASAT had an AUC of 0.751 with a cut-off of 20.75 U/L, yielding Se: 74.4%, Sp: 58.1%, PPV: 63.41%, and NPV: 78.44%. LDH showed an AUC of 0.793 with a cut-off of 406 U/L, yielding Se: 79.5%, Sp: 56.8%, PPV: 56%, and NPV: 78.78% (Figure 3.D).



AUC (95%CI)	Pvalue
.635(0,541-0,729)	.007

Parameters	AUC	P value	Cut off	Se	Sp	PPV%	NPV%
Uric acid	.659(0,539-0,784)	.013	66.50	66.7	54.5	68.65	75.38
ALAT	.804(0,541-0,776)	.000	12.85	79.5	65.9	68	88.09
ASAT	.751(0,640-0,862)	.000	20.75	74.4	58.1	63.41	78.84
LDH	.793(0,693-0,893)	.000	406	79.5	56.8	56	78.78

Figure 3: Receiver operating curve (ROC)for predicting complications of preeclampsia.

B. Using maternal serum uric acid level alone. Maternal serum: uric acid, LDH, ASAT and ALAT levels. According to the outcomes of preeclampsia: hemolysis elevated liver enzyme low platelets (HELLP syndrome), placental abruption, eclampsia, Intrauterine growth restriction (IUGR); Lactate dehydrogenase (LDH); Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), AUC=area under the ROC curve, Confidence Interval (CI), Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV).

Discussion

Preeclampsia, also known as pregnancy toxemia, is a multifactorial condition resulting from a defect in trophoblast remodeling, caused by the vasodilation of the placental blood vessels, which ultimately causes is chemisorb placental infarction. This can result in severe forms of the disease and various feto-maternal complications [15].

Given the severity of preeclampsia and its associated complications, several biomarkers have been proposed to predict risk and mitigate damage, though their clinical utility remains controversial. Among these, angiogenic markers such as s-Eng or the s-Flt-1/PlGF ratio are considered the most promising [16]. Uric acid has also been proposed as a potential biomarker due to its association with pre-eclampsia; however, its clinical relevance remains debated [11-17].

Our results indicate that hyperuricemia is correlated with preeclampsia and is present in both moderate and severe forms of the disease, with significantly higher levels observed in patients with severe preeclampsia($p=0.003$). Several studies support the role of uric acid in the severity of preeclampsia [18]. The mean (±SD) serum uric acid was significantly elevated in severe preeclampsia and eclampsia patients, as found by Akter et al. [19]. Williams et al. also mentioned in their study that elevated uric acid levels are present in pregnant women with HELLP syndrome, unlike those without HELLP syndrome [20]. The causes of hyperuricemia in preeclampsia are multifactorial, with the most common cause being renal dysfunction, particularly glomerular endotheliosis, which is frequently observed in severe cases of PE [17–21]. This renal impairment reduces uric acid clearance, resulting in elevated serum levels. Consistent with this, our study also found significantly higher levels of urea and creatinine in SPG compared with those in MPG ($p = 0.001$; $p = 0.046$, respectively). Thus, our findings suggest that renal dysfunction in severe cases may contribute to hyperuricemia, a relationship also demonstrated by Dan Lui et al. Though further studies are needed to confirm this [22].

A previous systematic review, which reported a wide range of sensitivities and specificities of uric acid, led the authors to conclude that serum uric acid cannot be employed to predict which women will develop preeclampsia [23]. Hence, the prognostic value of uric acid remains a topic of debate. While some researchers affirm its predictive value (17–24), others argue against its utility [25], Zhao et al. (2021) [17], Ugwuanyi et al. (2021) [26], Thangaratinam et al. (2006) [27], and Dekker &Sibai (1998) [28] concluded that uric acid is a weak predictor of severity and feto-maternal complications, which aligns with our findings. Our ROC curve analysis revealed that uric acid has low prognostic performance for predicting preeclampsia severity, with an AUC of 0.691, a very low NPV value of 18.46%, and a PPV of 45.58%. The research shows uric acid provides average ability to forecast feto-maternal complications through its AUC value of 0.635 and its NPV of 75.38% and PPV of 68.65% while achieving sensitivity of 66.7% and specificity of 54.5%. The research results from Loannis Bellos support our findings because his meta-analysis showed uric acid provides average risk assessment for adverse perinatal results with sensitivity between 67.3% and 82.7% and specificity between 47.7% and 70.7% [8].

The research shows uric acid provides lower disease severity prediction than transaminases and LDH because its AUC value reaches 0.661 while its NPV remains below 21% for all three parameters. The study shows uric acid provides average complication prediction (NPV of 75.38%) but transaminases (ASAT and ALAT) and LDH show better predictive ability with NPVs of 78.84%, 88.09% and 78.78% respectively. The research by Maryam Kasraeian et al. shows LDH provides superior prognostic value than uric acid and other biomarkers for preeclampsia severity assessment [29]. The research findings demonstrate that uric acid makes poor predictions about preeclampsia severity and complications when compared to ASAT and ALAT and LDH. The research shows that severe preeclampsia clinical symptoms become more pronounced when patients have elevated uric acid levels [30]. The research conducted by Loannis Bellos [8] confirms our results because he proved uric acid functions as a predictive factor for severe preeclampsia cases that result in feto-maternal complications. The research conducted by Ana Corominas et al. demonstrates that PE severity directly correlates with rising uric acid levels [1] and Chen et al. discovered that uric acid levels increase after patients develop clinical symptoms [24]. The research conducted by Khairun Nahar et al. demonstrates that women with preeclampsia who have elevated serum uric acid levels develop more severe preeclampsia [30].

The measurement of uric acid does not produce reliable results for predicting preeclampsia severity or its related maternal and fetal complications. The biomarker functions as a disease progression indicator because it works together with LDH and ALAT and ASAT measurements. The monitoring of uric acid levels throughout pre-complication periods will help scientists understand how elevated uric acid levels create complications in preeclampsia patients. The evaluation of uric acid levels before complications occur and during their development will reveal when uric acid concentrations rise and how these changes impact complication severity. Scientists need to study how reducing hyperuricemia levels in severe and complicated cases helps them understand the relationship between elevated uric acid and disease severity and complication development.

The limitations of this study include differences in demographic characteristics, eating habits, and gestational age among the people who took part. Because uric acid levels change during pregnancy, it is important to adjust the concentration of uric acid based on gestational age in order to see how well they predict outcomes. Future studies should focus on various hospital populations and evaluate uric acid levels across multiple laboratories to mitigate the variability inherent in assay

Conclusion

While elevated uric acid levels are associated with preeclampsia severity, they may not be as strong a predictor of adverse outcomes as other biomarkers such as ASAT, ALAT, and LDH.

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This research did not receive any specific fund.

Conflict of Interest

Authors declare no conflict of interest.

Data availability

Data are available upon reasonable request

Author Contributions

FB contributed to the conception, design, data acquisition, analysis, and interpretation of the study. FK contributed to the conception, design, drafting of the manuscript, and revision. BKM was responsible for proofreading. DB contributed to the revision of the manuscript. IB contributed to the analysis. All authors read and approved the final version of the manuscript.

All authors meet the ICMJE criteria for authorship and agree to be accountable for all aspects of the work.

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