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Salivary Uric Acid Levels in Pregnant Women with Preeclampsia and Its Relationship with Disease Severity and Complications

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Abstract

Background

Hypertensive disorders in pregnancy, particularly preeclampsia, represent a major cause of maternal and perinatal morbidity and mortality worldwide. We aimed to determine salivary uric acid levels and their association with the severity and complications of preeclampsia.

Methods

This descriptive-analytical study included 100 pregnant women with preeclampsia who referred to Amir Al Momenin Hospital in Zabol, Iran, during 2020–2021. Patients were classified into non-severe (n = 84) and severe (n = 16) preeclampsia groups based on clinical and laboratory findings. Salivary uric acid levels were measured, and demographic, anthropometric, and maternal-perinatal complication data were collected from medical records.

Results

The mean salivary uric acid level in the study population was 5.30 ± 1.18 mg/dL (range: 3.40–8.50 mg/dL). Patients with severe preeclampsia had significantly higher salivary uric acid levels (7.18 ± 0.90 mg/dL) compared to those with non-severe preeclampsia (4.94 ± 0.84 mg/dL) ($P < 0.001$). Salivary uric acid levels were significantly associated with liver dysfunction ($P = 0.005$), placental abruption ($P = 0.034$), and neonatal NICU admission ($P = 0.033$). ROC curve analysis demonstrated that salivary uric acid with a cutoff value of 6.35 mg/dL predicted severe preeclampsia with 87.5% sensitivity and 97.6% specificity (AUC = 0.965).

Conclusion

Salivary uric acid was significantly associated with preeclampsia severity and several adverse outcomes. Larger prospective studies with multivariable analysis are required to confirm these findings.

Introduction

Hypertensive disorders in pregnancy, particularly preeclampsia, are the leading cause of maternal and perinatal morbidity and mortality in both developing and developed countries (1). These disorders affect 5–10% of pregnancies and, together with hemorrhage and infection, form a major contributor to maternal mortality (2). Preeclampsia syndrome, either alone or superimposed on chronic hypertension, ranks among the most life-threatening conditions (3).

Oxidative stress is believed to play a crucial role in the pathological consequences of preeclampsia and poor placental perfusion. Hyperuricemia, a marker of oxidative stress, has been associated with preeclampsia severity and fetal outcomes (4). Hyperuricemia is a common finding in preeclamptic pregnancies, with elevated uric acid often preceding the onset of hypertension and proteinuria (5). Serum urate has also been considered a predictor of preeclampsia (6).

Several potential sources of uric acid elevation exist in preeclampsia, including abnormal renal function, increased tissue breakdown, acidosis, and increased activity of xanthine oxidase/dehydrogenase enzyme. Outside of pregnancy, elevated serum uric acid is associated with a wide range of conditions including hypertension, increased cardiovascular mortality, obesity, and metabolic syndrome (7–9).

Blood urate represents the product of endogenous urate production (intracellular urate), dietary intake, renal excretion, and gastrointestinal elimination. In the intestine, urate undergoes bacterial degradation (intestinal uricolysis) (10). Approximately 5% of blood uric acid is bound to plasma proteins; however, blood uric acid is completely filtered by the glomerulus, with 90% subsequently reabsorbed in the early proximal tubules. Following this, 50% of blood urate is secreted into nephrons through the second part of the proximal tubule, with final reabsorption and secretion occurring in the terminal portions of the proximal tubules (11).

Numerous studies have reported positive correlations between serum uric acid (UA) levels and adverse maternal and fetal outcomes (12–14). The salivary antioxidant system includes enzymes and molecules such as peroxidase systems. Uric acid, as one of the main salivary antioxidants, neutralizes risk factors and provides a protective environment between damaging agents and the oral mucosal lining, playing an important role in the anticancer function of saliva (15).

Despite extensive research on serum uric acid in preeclampsia, limited data exist regarding salivary uric acid levels in this condition. Previous studies have primarily focused on comparing preeclamptic women with healthy pregnant controls, without adequately examining the relationship between salivary uric acid and disease severity across the preeclampsia spectrum. Furthermore, the association between salivary uric acid and specific preeclampsia-related complications — particularly placental abruption, liver dysfunction, and neonatal outcomes — remains poorly characterized. Additionally, no previous study has established a validated cutoff value for salivary uric acid to differentiate non-severe from severe preeclampsia. Therefore, this study was conducted to address these gaps.

Materials and Methods

Study Design and Population

This descriptive-analytical study was conducted on 100 pregnant women with preeclampsia who referred to Amir Al Momenin Hospital in Zabol, Iran, during 2020–2021. The objective of this study was to determine salivary uric acid levels in pregnant women with preeclampsia and their relationship with disease severity and complications. This study was approved by the Ethics Committee of Zabol

University of Medical Sciences, Zabol, Iran (IR.ZBMU.REC.1400.071), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment in the study.

Inclusion and Exclusion Criteria

Inclusion criteria were: consent to participate in the study, diagnosis of preeclampsia according to established criteria confirmed by a specialist, no history of chronic diseases such as hypertension and diabetes, absence of any oral diseases including lichen planus, and age between 20 and 45 years. The only exclusion criterion was unwillingness to continue participation in the study.

Sampling Method and Data Collection

Convenience sampling was employed, including all eligible patients with preeclampsia who presented to the hospital during the study period.

After approval of the proposal by the Research and Technology Deputy of Zabol University of Medical Sciences and obtaining informed consent, all eligible pregnant women with preeclampsia were evaluated. Demographic and anthropometric information, including age, weight, family history, and various pregnancy complications related to preeclampsia, were collected and recorded in each patient's data form.

Salivary Uric Acid Measurement

All patients underwent salivary uric acid measurement. After 10 minutes of mouth rinsing, 5 mL of saliva was collected in a wide-mouth vial and kept refrigerated at 4°C until processing within 4 hours in the pathology laboratory. Saliva samples were centrifuged for 5 minutes at 3000 rpm, and the supernatant was aspirated (16). Salivary uric acid was measured using the Accurex uric acid kit with a photometer based on the following enzymatic reactions:

Uric acid + H_2O ⟶ Uricase Allantoin + H_2O_2

H_2O_2 + Phenolic chromogens ⟶ Peroxidase Red colored compound (17)

Disease Classification

Patients were divided into two groups based on specialist diagnosis: non-severe preeclampsia and severe preeclampsia (18).

Statistical Analysis

Descriptive statistics including tables, charts, frequencies, and percentages were used to describe the data. Independent samples t-test and Chi-squared test were employed for group comparisons. ROC curve analysis was performed to determine the predictive value of salivary uric acid for severe preeclampsia. Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA), and P-values < 0.05 were considered statistically significant (19). Due to the limited sample size, particularly in the severe preeclampsia subgroup, multivariable analysis was not performed.

Assuming a mean difference of 2.0 mg/dL in salivary uric acid between severe and non-severe preeclampsia with a common standard deviation of 1.0 mg/dL, a minimum sample size of 14 patients per group was required to achieve 80% power at $\alpha = 0.05$ (two-tailed). We enrolled 100 patients to account for possible exclusions and to explore complication subtypes.

Results

Patient Characteristics

A total of 100 pregnant women with preeclampsia participated in this study. The number of patients with non-severe and severe preeclampsia was 84 (84%) and 16 (16%), respectively **(Table 1)**. The calculated effect size (Cohen's d) for this difference was 2.58, indicating a very large effect. The mean parity in the study population was 3.74 ± 1.73, ranging from 1 to 6 births.

Pregnancy Complications

Table 2 shows the association between preeclampsia severity and neonatal complications. Severe preeclampsia was significantly associated with preterm delivery and liver dysfunction. Among women with preterm delivery, 66.7% had severe preeclampsia, compared with 14.4% among those without preterm delivery (p = 0.015). Similarly, severe preeclampsia was more frequent among women with liver dysfunction (50.0%) than among those without liver dysfunction (12.2%) (p = 0.002). However, no significant associations were observed between preeclampsia severity and thrombocytopenia (p = 0.232), ICU admission (p = 0.978), or 5-minute Apgar score < 7 (p = 0.850).

Salivary Uric Acid Levels

The mean salivary uric acid level in the studied women with preeclampsia was 5.30 ± 1.18 mg/dL, ranging from 3.40 to 8.50 mg/dL. The mean salivary uric acid level in women with non-severe and severe preeclampsia was 4.94 ± 0.84 mg/dL and 7.18 ± 0.90 mg/dL, respectively **(Table 3)**. Patients with severe preeclampsia had significantly higher salivary uric acid levels compared to those with non-severe preeclampsia (P<0.001) **(Table 4)**.

Association of Salivary Uric Acid with Complications

Table 5 shows the association between salivary uric acid levels and maternal and neonatal complications. The analysis revealed that women who experienced preterm delivery had significantly

higher mean salivary uric acid levels compared to those who delivered at term (6.20 ± 1.15 mg/dL vs. 4.86 ± 0.92 mg/dL, P<0.001). Similarly, patients with liver dysfunction exhibited markedly elevated salivary uric acid levels relative to those with normal liver function (6.75 ± 1.40 mg/dL vs. 5.14 ± 1.04 mg/dL, P=0.005). Although women with thrombocytopenia showed higher salivary uric acid levels than those without, this difference did not reach statistical significance (5.58 ± 0.27 mg/dL vs. 5.28 ± 1.21 mg/dL, P=0.093).

Notably, patients complicated by placental abruption had significantly higher salivary uric acid concentrations compared to those without this condition (7.13 ± 0.70 mg/dL vs. 5.24 ± 1.14 mg/dL, P=0.007). In contrast, no significant difference in salivary uric acid levels was observed between women requiring ICU admission and those managed in regular wards (5.15 ± 1.27 mg/dL vs. 5.33 ± 1.16 mg/dL, P=0.577). Regarding neonatal outcomes, mothers of infants with a 5-minute Apgar score below 7 had lower salivary uric acid levels than those with higher Apgar scores, although this difference was not statistically significant (4.88 ± 1.09 mg/dL vs. 5.37 ± 1.18 mg/dL, P=0.145). Importantly, women whose neonates required NICU admission demonstrated significantly higher salivary uric acid levels compared to those whose infants did not require such care (5.84 ± 1.33 mg/dL vs. 5.15 ± 1.09 mg/dL, P=0.033).

ROC Curve Analysis

The diagnostic accuracy of salivary uric acid in predicting severe preeclampsia was evaluated using receiver operating characteristic (ROC) curve analysis **(Figure 1)**. The area under the curve (AUC) was 0.965 (95% confidence interval: 0.93–0.99), indicating excellent discriminatory power of salivary uric acid for distinguishing between severe and non-severe preeclampsia. Using the Youden index to determine the optimal cutoff value, a salivary uric acid concentration of 6.35 mg/dL predicted severe preeclampsia with a sensitivity of 87.5% and a specificity of 97.6%. These findings demonstrate that salivary uric acid measurement has high diagnostic accuracy and may represent a potential non-invasive biomarker for identifying severe cases of preeclampsia.

Discussion

Our findings demonstrated that salivary uric acid levels increase significantly with preeclampsia severity and are associated with adverse maternal and perinatal outcomes. These findings align with the growing body of evidence supporting the utility of salivary uric acid as a non-invasive biomarker in preeclampsia.

Salivary Uric Acid and Preeclampsia Severity

Our finding that patients with severe preeclampsia had significantly higher salivary uric acid levels (7.18 ± 0.90 mg/dL) compared to those with non-severe preeclampsia (4.94 ± 0.84 mg/dL) is consistent with previous research. Hyperuricemia is a common finding in preeclamptic pregnancies, often preceding the development of hypertension and proteinuria (20). The mechanisms underlying hyperuricemia in preeclampsia are multifactorial, including oxidative stress, renal dysfunction secondary to placental ischemia and reduced glomerular filtration rate, increased tissue breakdown, acidosis, and increased uric

acid production due to placental involvement from increased xanthine oxidase/dehydrogenase activity (4, 8, 21).

Studies have shown that both salivary and serum uric acid levels increase significantly in preeclampsia compared to normal pregnancy, with significant correlations between salivary and serum levels, suggesting that salivary uric acid can serve as a effective surrogate for serum uric acid monitoring (22). Our findings are consistent with multiple studies demonstrating that uric acid is associated with adverse maternal and perinatal outcomes and predicts disease severity (12, 23, 24).

Salivary Uric Acid and Preterm Delivery

In the present study a significant association between salivary uric acid levels and preterm delivery was observed. Patients with preterm delivery had significantly higher salivary uric acid levels (6.20 ± 1.15 mg/dL) compared to those without preterm delivery (4.86 ± 0.92 mg/dL) ($P < 0.001$). Similar findings have been reported by Ryu et al. (25), who reported that preeclamptic women with preterm delivery had significantly higher serum uric acid levels (6.2 ± 1.7 mg/dL) compared to those with term deliveries (5.1 ± 1.3 mg/dL). Similarly, a large meta-analysis by Bellos et al. (12) encompassing 196 studies and 39,540 women demonstrated that elevated uric acid levels were significantly associated with adverse perinatal outcomes, including preterm birth. More recently, Wehlie et al. (24) reported that hyperuricemia in preeclamptic women was associated with a two-fold increased risk of adverse outcomes, including low birth weight and NICU admission.

While the association between hyperuricemia and adverse perinatal outcomes is well-established, the optimal cutoff values for predicting specific outcomes vary across studies. For instance, Ryu et al.(25) identified a serum uric acid threshold of 6.35 mg/dL for predicting low birth weight, whereas our study identified a salivary uric acid cutoff of 6.35 mg/dL for predicting severe preeclampsia. These variations may be attributed to differences in study populations, sample types (serum vs. saliva), and outcome definitions. Further prospective studies with standardized methodologies are needed to validate these thresholds and establish salivary uric acid as a potential clinical tool for predicting preterm delivery and other adverse outcomes in preeclamptic women.

Salivary Uric Acid and Liver Dysfunction

Patients with liver dysfunction had significantly higher salivary uric acid levels compared to those with normal liver function ($P = 0.005$). Comparable results were demonstrated in a study by Hassen et al. (26), who reported significantly higher serum uric acid and liver enzyme (AST, ALT) levels in preeclamptic women compared to normotensive pregnant women, suggesting that serum uric acid and liver function tests should be considered as biomarkers of organ damage in preeclampsia. Sarmah et al. (27) similarly demonstrated significantly higher mean AST and ALT levels in preeclamptic women compared to controls. Ekun et al. (28) also found significantly elevated transaminases in preeclamptic patients. This elevation in liver enzymes may result from placental ischemia following a systemic inflammatory response, leading to endothelial dysfunction, vasoconstriction, and subsequent hepatic and renal impairment.

Salivary Uric Acid and Thrombocytopenia

Although patients with thrombocytopenia showed higher salivary uric acid levels than those without, this difference did not reach statistical significance (P = 0.093). Bellos et al. (12) found that higher maternal serum uric acid levels were significantly associated with severe preeclampsia, eclampsia, hemolysis, elevated liver enzymes, and thrombocytopenia (HELLP syndrome), with sensitivity and specificity ranging from 67.3–82.7% and 47.7–70.7%, respectively, for predicting adverse perinatal outcomes.

Salivary Uric Acid and Placental Abruption

Patients with placental abruption had significantly higher salivary uric acid levels (7.13 ± 0.70 mg/dL) compared to those without this complication (5.24 ± 1.14 mg/dL) (P = 0.007). This finding highlights the potential of salivary uric acid as a marker for severe placental complications in preeclampsia.

Placental abruption represents one of the most severe obstetrical complications associated with preeclampsia, resulting from acute placental ischemia and hemorrhage (29, 30). The association between elevated uric acid and placental abruption observed in our study aligns with previous research demonstrating that hyperuricemia correlates with adverse placental outcomes. Asgharnia et al. reported that higher uric acid levels in preeclamptic women were associated with increased maternal complications, including placental abruption (29). Similarly, Madaan et al. emphasized that preeclampsia frequently results in placental abruption, and their study demonstrated that elevated salivary uric acid levels could predict maternal complications with good diagnostic accuracy (31).

Elevated uric acid may contribute to placental abruption through the role of uric acid in promoting oxidative stress and endothelial dysfunction. Elevated uric acid levels reflect underlying placental ischemia and the subsequent release of inflammatory mediators, which can weaken the decidual-placental interface and predispose to abruption (8). These findings suggest that salivary uric acid may help identify patients at higher risk for severe placental complications, enabling closer surveillance and timely intervention.

Salivary Uric Acid and Neonatal Outcomes

Our study demonstrated that women whose neonates required NICU admission had significantly higher salivary uric acid levels compared to those whose neonates did not require NICU admission (P = 0.033). Madaan et al. (31) similarly found that NICU admission rates were significantly higher in severe preeclampsia compared to non-severe preeclampsia and control groups, concluding that salivary uric acid is significantly associated with maternal complications and NICU admission in preeclamptic patients. Comparable results were reported by Sachan et al. (32), where 25.9% of neonates from mothers with severe preeclampsia required NICU admission compared to only 6.5% in the control group. Wolde et al. (33) also found that 15.3% of neonates from mothers with severe preeclampsia required NICU admission compared to 0.9% from mothers with mild preeclampsia.

Study Limitations and Strengths

This study has several limitations that should be acknowledged. First, the single-center design and small sample size (particularly only 16 patients with severe preeclampsia) limit the generalizability of our findings and preclude multivariable analysis to control for potential confounders such as maternal age, body mass index, gestational age at sampling, and parity. Second, the cross-sectional design means that salivary samples were collected after the diagnosis of preeclampsia; therefore, causality cannot be inferred, and the predictive value of salivary uric acid before disease onset remains unknown. Third, serum uric acid was not measured concurrently, preventing direct comparison between salivary and serum levels to determine whether saliva truly reflects systemic concentrations. Fourth, the absence of a normotensive control group means we cannot determine whether salivary uric acid is elevated in any preeclampsia versus a normal pregnancy. Finally, our findings may not be generalizable to other populations with different ethnic, dietary, or healthcare system characteristics.

Despite these limitations, the study provides preliminary evidence supporting the association between salivary uric acid levels and preeclampsia severity.

Conclusion

The results of this study demonstrate that salivary uric acid levels increase significantly with preeclampsia severity and are associated with adverse maternal and perinatal outcomes including preterm delivery, liver dysfunction, placental abruption, and neonatal NICU admission. With excellent predictive accuracy for severe preeclampsia (AUC = 0.965) and high sensitivity (87.5%) and specificity (97.6%) at a cutoff value of 6.35 mg/dL, salivary uric acid measurement represents a promising non-invasive, effective biomarker for predicting preeclampsia severity and associated complications.

Recommendations

Further large-scale, multicenter prospective studies are required to validate the present findings and to establish standardized reference values for salivary uric acid in preeclampsia. Future research should include appropriate control groups and longitudinal follow-up to determine the temporal relationship between salivary uric acid levels and disease progression, as well as to clarify its potential role in early risk stratification. Simultaneous assessment of serum and salivary uric acid concentrations and the application of multivariable analytical models would help to define the independent clinical value of this non-invasive biomarker. Such investigations may provide stronger evidence for the integration of salivary uric acid measurement into routine assessment and monitoring of patients with preeclampsia, particularly in settings where minimally invasive and cost-effective approaches are desirable.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Zabol University of Medical Sciences, Zabol, Iran (Approval code: IR.ZBMU.REC.1400.071). The study was conducted in accordance with the Declaration

of Helsinki. Written informed consent was obtained from all participants prior to enrollment in the study.

Consent for publication

Not applicable.

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Author Contribution

S.H. contributed to data collection, laboratory procedures, and manuscript drafting. Z.S. conceived and designed the study, supervised the research process, analyzed and interpreted the data, and critically revised the manuscript. K.R.K. contributed to study design, data interpretation, and manuscript revision. H.J. supervised the pathological and laboratory assessments and contributed to interpretation of the findings. All authors read and approved the final manuscript.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Distribution of preeclampsia severity in the study population (n = 100)

Severity	Frequency (N)	Percentage (%)
Non-severe	84	84%
Severe	16	16%

Data are presented as number (%). Abbreviations: N, number of patients.

Table 2. Maternal and neonatal complications among women with preeclampsia (n = 100)

Data are presented as numbers (%). Abbreviations: N, number of patients; ICU, intensive care unit; NICU, neonatal intensive care unit.

Table 2: Association between preeclampsia and neonatal complications

Complication	category	Preeclampsia		p-value*
		Non sever, n (%)	Sever, n (%)	
Preterm delivery	yes	1(33.3)	2(66.7)	0.015
	no	83(85.6)	14(14.4)	
Liver dysfunction	yes	5(50)	5(50)	0.002
	no	79(87.8)	11(12.2)	
Thrombocytopenia	yes	4(66.7)	2(33.3)	0.232
	no	80(85.1)	14(14.9)	
ICU admission	yes	16(84.2)	3(15.8)	0.978
	no	68(84.0)	13(16.0)	
5-minute Apgar score <7	yes	12(85.7)	2(14.3)	0.850
	no	72(83.7)	14(16.3)	

The p-value for the chi-square test. The p-value less than 0.05 is significant.

Table 3. Salivary uric acid levels according to preeclampsia severity

Preeclampsia Severity	n	Mean ± SD (mg/dL)	Range
Non-severe	84	4.94 ± 0.84	3.40–5.70
Severe	16	7.18 ± 0.90	5.30–8.50

Data are presented as mean ± standard deviation and range. Abbreviations: N, number of patients; SD, standard deviation; mg/dL, milligrams per deciliter.

Table 4. Comparison of salivary uric acid levels between preeclampsia severity groups

Variable	Mean ± SD mg/dL	P Value
Non-severe preeclampsia (n = 84)	4.94 ± 0.84	**<0.001***
Severe preeclampsia (n = 16)	7.18 ± 0.90	

Data are presented as mean ± standard deviation. Abbreviations: N, number of patients; SD, standard deviation; mg/dL, milligrams per deciliter. Independent samples t-test was used for comparison. Statistical significance was set at P < 0.05.*

Table 5. Association between salivary uric acid levels and maternal and neonatal complications

Complication	Category	Salivary Uric Acid (Mean ± SD mg/dL)	P Value
Preterm delivery	Yes (n=33)	6.20 ± 1.15	**<0.001***
	No (n=67)	4.86 ± 0.92	
Liver dysfunction	Yes (n=10)	6.75 ± 1.40	**0.005***
	No (n=90)	5.14 ± 1.04	
Thrombocytopenia	Yes (n=6)	5.58 ± 0.27	0.093
	No (n=94)	5.28 ± 1.21	
Placental abruption	Yes (n=3)	7.13 ± 0.70	**0.007***
	No (n=97)	5.24 ± 1.14	
ICU admission	Yes (n=19)	5.15 ± 1.27	0.577
	No (n=81)	5.33 ± 1.16	
5-min Apgar <7	Yes (n=14)	4.88 ± 1.09	0.145
	No (n=86)	5.37 ± 1.18	
NICU admission	Yes (n=22)	5.84 ± 1.33	**0.033***
	No (n=78)	5.15 ± 1.09	

Data are presented as mean ± standard deviation. Abbreviations: N, number of patients; SD, standard deviation; mg/dL, milligrams per deciliter; ICU, intensive care unit; NICU, neonatal intensive care unit. An independent samples t-test was used for comparison between groups. Statistical significance was set at P < 0.05.*

Figures

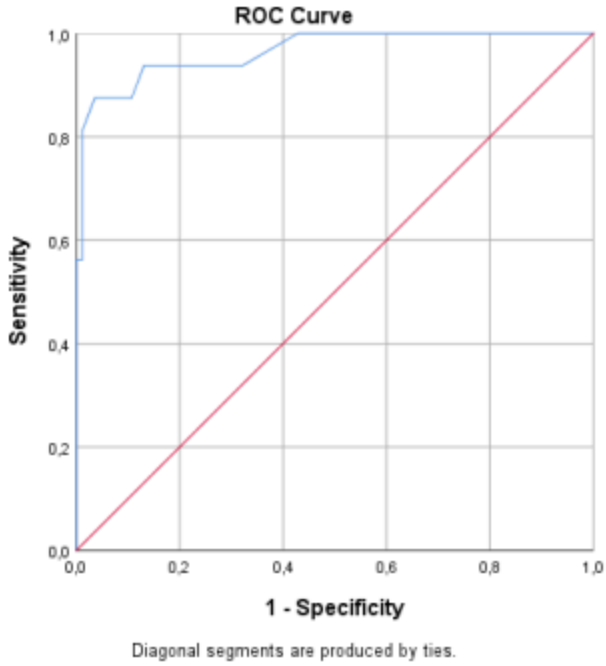


Figure 1

ROC curve for salivary uric acid in predicting severe preeclampsia

The ROC curve plots sensitivity (true positive rate) against 1-specificity (false positive rate) at various cutoff values of salivary uric acid. The diagonal dashed line represents the line of no discrimination (AUC = 0.5).