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Research article

Maternal serum uric acid, creatinine and blood urea levels in the prediction of pre-eclampsia among pregnant women attending ANC and delivery services at Bahir Dar city public hospitals, northwest Ethiopia: A case-control study

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ABSTRACT

Background: Pre-eclampsia (PE) is a metabolic disorder that adversely affects the lives of mother and their infants. Even though, several studies have been conducted on PE, no effective diagnostic and therapeutic agents were developed so far. Hence, this study was designed to evaluate serum uric acid, blood urea and creatinine levels in the prediction of PE.

Methods: A hospital-based case-control study was conducted among pregnant women. A simple random sampling technique was applied to select study participants. The socio-demographic and clinical data were collected using an interview-administered questionnaire. Serum samples were used to determine the maternal uric acid, urea and creatinine levels via an automated chemistry analyzer. Independent sample t-test, Pearson correlation test and receiver operating characteristic (ROC) curve analysis were performed to check the association and diagnostic accuracy of variables to PE.

Results: The mean ages (in years) of the case and control groups were 27.98 ± 5.64 and 27.33 ± 4.45, respectively. The mean serum uric acid and blood urea levels were significantly higher in pre-eclamptic women than in normotensive pregnant women (6.27 ± 0.20 vs 4.43 ± 0.15, and 8.50 ± 3.99 vs 5.67 ± 2.19), respectively but the serum creatinine level is non-significantly increased in cases as compared to controls (0.70 ± 0.05 vs 0.50 ± 0.01). The areas under the ROC curve of serum uric acid, creatinine and blood urea levels were 0.785, 0.735 and 0.764 (sensitivity: 69%, 60.7%, 67.9%; specificity: 73.8%, 75%, 71.4%) with the cutoff points of ≥5.25 mg/dL, ≥0.565 mg/dL and ≥6.5 mg/dL, respectively.

Conclusion: In this study, we observed a significantly higher concentration of serum uric acid and blood urea values in pre-eclampsia as compared with normotensive pregnant women. Therefore, this suggested that serum uric acid; blood urea and creatinine values can be associated with PE. Moreover, serum uric acid, blood urea and creatinine levels could be carefully utilized as a diagnostic marker for PE, but their inclusion in routine diagnostic test to PE requires large-scale multi-center prospective studies that corroborate our findings.

1. Introduction

Pre-eclampsia (PE) is defined as a new-onset of hypertension (≥140/90 mmHg) occurring after the 20th week of gestation accompanied by one or more new-onset proteinuria, maternal organ dysfunction, or uteroplacental dysfunction [1]. The etiology of PE is not yet fully explained, but poor placentation is an important agent for PE. The role of the placenta in PE development is strongly supported by the rapid resolution

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of symptoms after delivery [2]. To date, two-stage models are proposed to designate the pathogenesis of PE, in which reduced placental perfusion (stage 1) leads to the maternal syndrome (stage 2) is likely to provide a simplified accurate description of the origin of severe early-onset PE, but it is less relevant for later-onset mild PE [3, 4, 5]. Abnormal placentation leads to placental ischemia resulting in excess production of free radicals and lipid peroxides and also immune maladaptation triggers endothelial dysfunction and maternal syndrome [6, 7, 8].

Liver and renal function tests are relevant to assess the degree of organ impairment in preeclamptic women [9]. Uric acid is the metabolic end product of purine nitrogen base which is used for the diagnosis and the prediction of disease severity and complications of the disease [10, 11, 12]. Moreover, measurement of maternal serum uric acid level will serve as the assessment of adverse maternal and fetal outcomes of hypertensive disorders of pregnancy [13]. Some reports showed that elevated maternal serum uric acid concentration could be used for the prediction of adverse fetal outcomes such as; preterm labor, low birth weight, neonatal death [14, 15, 16] and intrauterine fetal death (IUFD) [17]. Higher serum uric acid concentration in preeclamptic women occurs primarily due to a reduction in glomerular filtration rate that leads to endothelial dysfunction or it may be due to an increase in xanthine oxidase activity which could be served as the biomarkers of PE [18].

Creatinine is the metabolic end product of creatine. Creatine is made from the amino acid methionine, glycine and arginine. Creatine is involved in adenosine triphosphate (ATP) homeostasis when the tissue energy requirement is greater than the rate of ATP synthesis [19]. During normal pregnancy, serum creatinine concentration have been decreased due to an increased fluid volume, but in case of PE maternal serum creatinine concentration might be increased as a consequence of damage of endothelial cells as a result of decreased vascular endothelial growth factors (VEGF) [20]. Change in the renal function is an important pathophysiological process in PE and therefore close renal function monitoring is relevant to prevent permanent renal damage [21]. Hence, this study was designed to evaluate the diagnostic importance of maternal serum uric acid, creatinine and BUN levels in the prediction of PE among pregnant women attending antenatal care (ANC) and delivery services at Bahir Dar city public hospitals, northwest Ethiopia.

2. Methods and materials

2.1. Study design and setting

Hospital based unmatched case-control study was conducted at Bahir Dar city public hospitals. Bahir Dar is the capital city of Amhara Regional State and is located at a distance of 565 km northwest of Addis Ababa, Ethiopia. Bahir Dar city is located between the great Lake Tana and the longest river Abay (Blue Nile). In the city, there are three governmental hospitals which provide antenatal care (ANC) and delivery service for pregnant mothers. The study was conducted in Felege Hiwot Referral Hospital and Addis Alem primary Hospital. All pregnant women attending ANC and delivery services were our source populations. Those selected pregnant mothers that fulfill the inclusion criteria were our study populations.

2.2. Sample size and sampling procedure

Epi-Info version 7 software was used to calculate the sample size using the double population proportion formula by considering 85% power of the study, 95% confidence level, the proportion of controls with exposure 37.37%, the proportion of cases with exposure 61.1%, the ratio of cases to controls was 1:1. Primigravida is the common risk factor for pre-eclampsia used in the current study to calculate the sample size with an odds ratio of 2.68 [22]. Based on this assumption, the final sample size required for this study was 168 (84 cases and 84 controls). The selection of study participants was performed using a simple random sampling technique until the required sample size was reached. Cases and controls were proportionally allocated, for every case a control was selected.

2.3. Inclusion and exclusion criteria

The cases were women with blood pressure ≥140/90 mmHg on two occasions at least 4 h apart after 20 weeks of gestation in the woman with previously normal blood pressure plus proteinuria. In the absence of proteinuria, preeclampsia can be diagnosed by new-onset hypertension along with the presence of a severe feature of the disease: blood pressure ≥160/110 mmHg or more on two occasions at least 4 h apart, thrombocytopenia (platelet count $<100\times 10^9$/L), renal insufficiency (serum creatinine concentrations >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease), elevated liver enzymes (increased twice the upper limit normal), pulmonary edema, new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, or visual symptom [23]. The controls were normotensive pregnant women who were attending antenatal care and delivery service from the two hospitals with the gestational age of ≥20 weeks. Women with known chronic hypertension, gestational hypertension, diabetes mellitus, renal disease and those women who could not give consent during data collection were excluded from the study. The diagnosis involves history taking, physical examination and laboratory tests.

2.4. Definition of terms

- **Hypertension:** Systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg that is measured at least two times within 4 h interval.
- **Proteinuria:** Urinary protein excretion ≥300 mg/24-h urine sample or ≥1 + on qualitative dipstick examination or a total protein to: creatinine ratio ≥0.3 mg/dL and more.
- **Pre-eclampsia:** Hypertension diagnosed at ≥20 weeks of gestation plus proteinuria [24].
- **Hyperuricemia:** is defined as the serum uric acid level >7 mg/dL or elevated urinary uric acid concentrations which increases the risk for hypertension, chronic kidney disease and cardiovascular disease [25].

2.5. Data collection

Socio-demographic and clinical data were collected using pretested interviewer-administered questionnaire by midwifes. The blood sample was collected by laboratory technologists aseptically from pre-eclamptic and normotensive pregnant women. About 5 ml of blood was taken from the vein of pre-eclamptic and normotensive pregnant women and we allowed forming a clot in the serum separator test tube. After waiting about 30 minutes the serum was separated by centrifugation at a speed of 4000 rpm for about 5 minutes. Then, the serum was stored in deep freezer (−80 °c) until the laboratory analysis was performed.

2.6. Laboratory analysis

Maternal serum concentrations of uric acid, creatinine and blood urea nitrogen (BUN) were determined by closed system Dimension EXL 200 Integrated chemistry analyzer at Tibebe Ghion Specialized Hospital. We used the products of Siemens Healthineers reagents for the determination of uric acid, creatinine and BUN. Uric acid was determined by uricase method with the analytical sensitivity of 0.1 mg/dL and 0.1–20.0 mg/dL measurement ranges while creatinine was determined by modified Jaffe technique with an analytical sensitivity of 0.15 mg/dL and 0.15–20.00 mg/dL measurement ranges. BUN was determined by enzymatic techniques with the analytical sensitivity of 1 mg/dL and 1–150 mg/dL measurement ranges. The tests were performed in batches according to the manufacturers' instruction. Before performing the laboratory analysis the machine was calibrated and validated with standards. In addition

internal quality control was performed to maintain the quality of generated data.

2.7. Data analysis

The data were entered and analyzed by SPSS version 20 statistical software. Normality was checked by Shapiro-wilk test with the p-value of <0.05. Therefore, we performed sensitivity tests (parametric and nonparametric tests) to evaluate non-normally distributed continuous variables but there is no difference on the test results. In addition, we used large sample size hence we preferred using parametric tests for the analysis of continuous variables. Continuous variables were analyzed by independent sample t-test and presented in table in mean ± SD. Pearson correlation tests were executed between serum uric acid, creatinine and blood urea concentrations with blood pressure. The diagnostic accuracy of serum uric acid, creatinine and BUN values were evaluated by ROC curve analysis. Variables significant in univariate model were entered into logistic regression model analysis to control confounders. Variables with p-value <0.05 were considered as statistically significant.

2.8. Ethical approval

This study was reviewed and approved by the Ethical Review Committee of Bahir Dar University, Science College (Ref.no: PGRCSVD/143/2012) and Amhara Public Health Institute (APHI (Ref.no/3/851/2012)). The study was conducted in accordance with the ethical principles for medical research involving human subjects. Prior to the data collection hospital managers were communicated through the official letter written by APHI. Data collection was started, after we obtained an informed written consent from each study participant.

3. Results

3.1. Socio-demographic and clinical characteristics of study participants

A total of 168 study participants were included in this study (84 cases and 84 controls). The mean age (± standard deviation) of the cases and controls were 27.98 ± 5.642 and 27.33 ± 4.446, respectively. In this study, there is no significant difference in the mean values of BMI among the cases and controls which was 24.73 ± 3.931 and 23.61 ± 3.584, respectively. In the current study, there is a statistical significant difference in the mean values of gestational age (GA), expected fetal weight (EFW), systolic blood pressure (SBP) and diastolic blood pressure (DBP) between the cases and controls (Table 1).

3.2. ROC curve and boxplot of serum uric acid, creatinine and BUN in PE

The mean serum uric acid, creatinine and BUN levels were significantly higher in pre-eclamptic women than in normotensive pregnant women. ROC showed maternal serum uric acid, creatinine and BUN concentration could be utilized for the diagnosis of PE. The areas of uric acid under the ROC curve were 0.785 with the sensitivity and specificity of 69% and 73.8%, respectively with the cut-values of serum uric acid level ≥5.25 mg/dL. The areas of creatinine under the ROC curve were 0.735 (sensitivity: 60.7%; specificity: 75%) with the cut-off point of ≥0.565 mg/dL. The areas of BUN under the ROC curve were 0.764 (sensitivity: 67.9%; specificity: 71.4%) with the cut-values of ≥6.5 mg/dL Figure [1(A, B, C, D, E, F)].

3.3. Correlations of uric acid, creatinine and blood urea with blood pressure

Maternal serum uric acid, creatinine and blood urea nitrogen levels showed positive significant correlation with systolic and diastolic blood pressure Figure [2(A, B, C, D, E, F)].

Table 1. Demographic and clinical characteristics of the study participants at Bahir Dar city public hospitals, northwest Ethiopia, 2022.

S. No	Parameters	N	Cases (N = 84) (Mean ± SD)	Control (N = 84) (Mean ± SD)	p-value
1	Mean age in years	168	27.98 ± 5.642	27.33 ± 4.446	0.413
2	BMI (kg/m^2)	168	24.73 ± 3.931	23.61 ± 3.584	0.056
3	GA in weeks	168	35.50 ± 4.207	37.98 ± 3.828	<0.001*
4	EFW in grams	168	2317.43 ± 747.356	2927.73 ± 602.05	<0.001*
5	SBP in mmHg	168	155.30 ± 10.856	110.75 ± 8.49	<0.001*
6	DBP in mmHg	168	99.38 ± 7.701	71.25 ± 7.53	<0.001*
7	Uric acid mg/dL	168	6.27 ± 1.85	4.43 ± 1.38	<0.001*
8	Creatinine mg/dL	168	0.70 ± 0.47	0.50 ± 0.11	<0.001*
9	BUN mg/dL	168	8.50 ± 3.99	5.67 ± 2.19	<0.001*
10	UA: Cr ratio	168	9.83 ± 2.43	9.08 ± 2.99	0.078
11	Urea: Cr ratio	168	14.23 ± 7.57	11.76 ± 4.61	0.012*
12	Urea: UA ratio	168	1.47 ± 0.77	1.42 ± 0.84	0.702

BMI-body mass index, BUN- blood urea nitrogen, Cr-creatinine blood urea nitrogen, EFW- expected fetal weight, DBP- diastolic blood pressure, GA-gestational age, kg/m^2-killo gram per meter square, mg/dL-millimeter per deciliter, mmHg-millimeter mercury, N- sample size, SBP- systolic blood pressure, SD -standard deviation, UA-uric acid * Statistically significant at p < 0.05.

3.4. Multivariable logistic regression analysis

Six independent variables were analyzed by multivariable logistic regression model to know their association with PE. Variables significant in univariate analysis at a p-value ≤ 0.056 were entered into the multivariable logistic regression model. In the multivariable logistic regression model, three variables were significantly associated with PE at 95% CI. The analysis revealed that maternal serum uric acid and BUN concentration were 1.55 and 1.42 times higher in preeclamptic women as compared to normotensive pregnant women, respectively. A maternal serum creatinine value was 12.94 times higher in PE as compared with normal controls but the association is non-significant. Expected fetal weight (EFW) was determined by ultrasound and which is significantly reduced in cases than controls (Table 2).

4. Discussion

PE is the most common public health problem that affects high number of pregnant women in developing and developed countries; and results in poor maternal and fetal outcomes. Currently, several biomolecules have been proposed as the biomarkers for the diagnosis of pre-eclampsia, although their usefulness and versatility are controversial. Developing cost effective and efficient diagnostic tool is important for the early detection of the disease, albeit the challenge is tremendous due to simplicity and cost issues.

In this study, the maternal serum uric acid level was significantly higher in preeclamptic women than in normal pregnant women (6.27 ± 0.20 versus 4.43 ± 0.15), which is in congruous with the studies conducted in some countries [9, 12, 21, 26, 27, 28]. Higher uric acid concentration is one of the most common clinical findings in pre-eclamptic women. Hyperuricemia in pre-eclampsia occurs due to impaired glomerular filtration rate as a result of endothelial dysfunction [15]. Hyperuricemia decreases the synthesis of endothelial nitric oxide synthase (eNOS) which is responsible for the production of nitric oxide (NO) [29] and increased the expression of cyclooxygenase 2 (COX-2) and thromboxane resulting in renal disease progression [30]. The vasoconstrictive effect of uric acid in the placentae of pre-eclamptic women compromises placental perfusion leading to intrauterine fetal restriction [31].

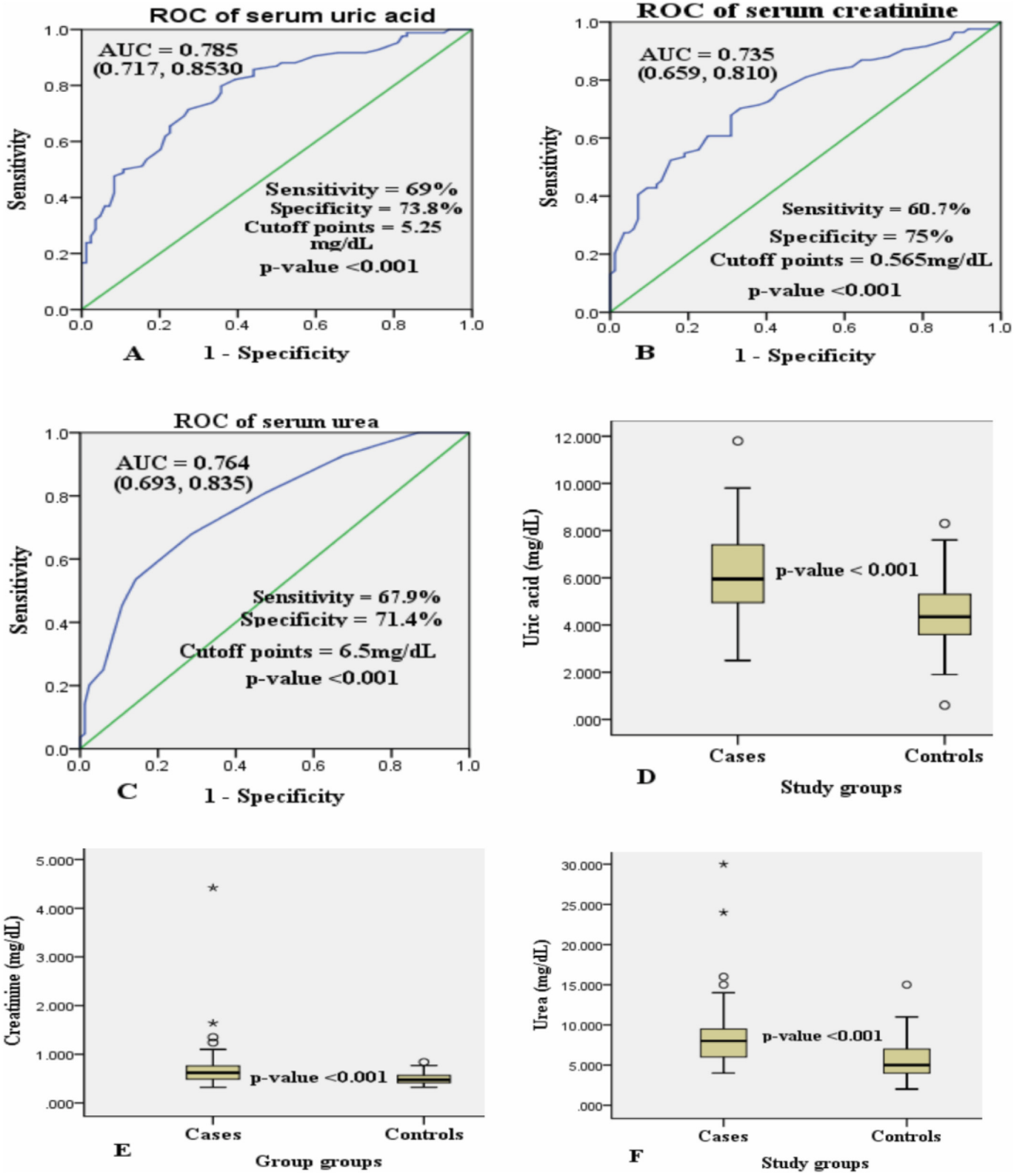

Figure 1. ROC and Boxplot of serum uric acid, creatinine and BUN levels among the cases and controls. Figure A, B & C showed ROC of uric acid, creatinine and BUN whereas D, E & F showed the boxplot of uric acid, creatinine and BUN levels among the cases and controls.

Uric acid is mainly synthesized in the liver, intestines and vascular endothelium. In vascular endothelium, uric acid production is increased due to enhanced enzymatic activities of xanthine oxidase or xanthine dehydrogenase [32]. Uric acid acts as a powerful free radical scavenger in humans. Although, uric acid acts as an antioxidant, high serum uric acid level is associated with an increase in oxidative stress, cardiovascular disease, type 2 immune response and pre-eclampsia [25]. Elevated uric acid concentration reduces the production of NO which alters the endothelium of the blood vessel of preeclamptic women. On the other hand, decreasing the uric acid level by allopurinol treatment improves

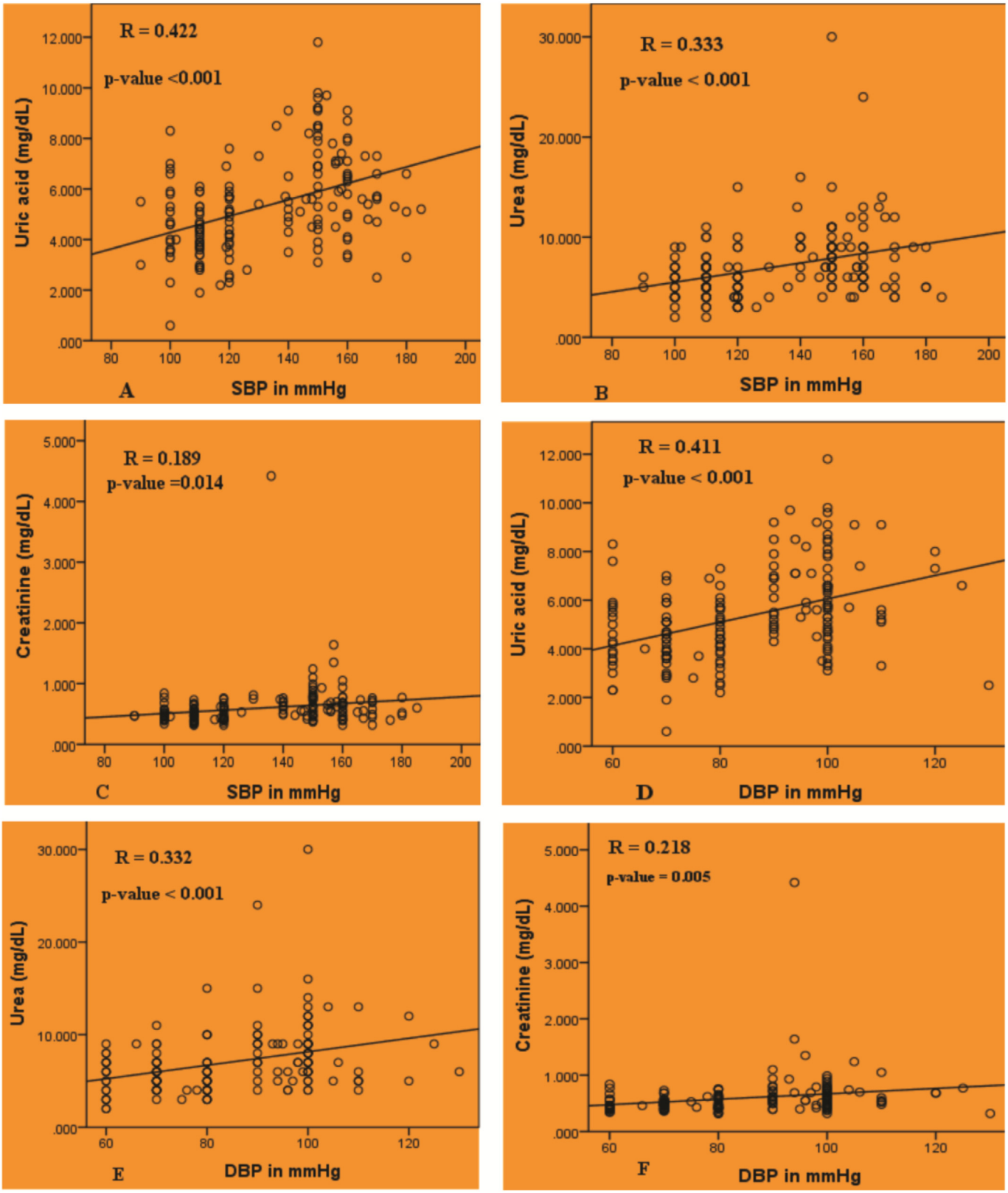

Figure 2. Pearson correlation of serum uric acid, creatinine and blood urea levels with systolic and diastolic blood pressure.

the endothelial-dependent vasodilatations that are seen in diabetic and congestive heart failure patients [33, 34, 35]. In the prospective and retrospective study conducted in China using uric acid as the biomarker for the early detection of pre-eclampsia is somewhat controversial. In the first and second trimesters of pregnancy, the serum uric acid level was not significantly different but the serum uric acid level was significantly raised in the third trimester of pregnancy in pre-eclamptic women as compared to normotensive pregnant women [36], although, other reports showed that the serum uric acid level is elevated as early as 10 weeks of gestation before the onset of the disease [31].

Table 2. Multivariable logistic regression analysis of factors for the prediction of pre-eclampsia among pregnant women attending ANC and delivery services at Bahir Dar city public hospitals, northwest Ethiopia, 2022.

Variable	B	Std. Error	Wald	df	p-value	Exp(B)	95% Confidence Interval for Exp (B)	
							Lower Bound	Upper Bound
Uric acid mg/dL	0.439	0.171	6.617	1	0.010*	1.551	1.110	2.166
Urea mg/dL	0.353	0.094	14.038	1	0.000*	1.424	1.183	1.712
Creatinine mg/dL	2.561	1.546	2.743	1	0.098	12.943	0.625	267.976
GA in weeks	−0.007	0.080	0.008	1	0.930	0.993	0.850	1.161
BMI in kg/m2	0.097	0.058	2.840	1	0.092	1.102	0.984	1.234
EFW in grams	−0.001	0.001	6.195	1	0.013*	0.999	0.998	1.000

BMI-body mass index, EFW- expected fetal weight, GA-gestational age, mg/dL-millimeter per deciliter, kg/m^2-killo gram per meter square* statistically significant at $p < 0.05$.

Urea is commonly known as blood urea nitrogen (BUN) which is the metabolic end product of nitrogen-containing compounds like;- proteins and nitrogen bases produced in the liver through the urea cycle and filtered by the kidneys [37]. BUN is served as the diagnostic biomarker for renal disease, liver disease and PE [38, 39]. We found that serum blood urea level was significantly increased in pre-eclamptic pregnant women (8.50 ± 3.99) as compared with normal controls (5.67 ± 2.19). Similar findings were reported from other studies [40, 41]. The increased serum blood urea level may be due to renal impairment as a complication of PE.

In this study, the maternal serum creatinine level was non-significantly increased in preeclamptic women as compared to normal pregnant women (0.70 ± 0.05 versus 0.50 ± 0.01). Supporting evidences were reported from other studies [21, 27, 41]. Creatinine is the metabolic end product of creatine which is produced in our body at a constant rate and freely filtered and excreted from the body by the kidneys. Serum creatinine serves as the biomarker for the estimation of kidney and muscle function. Elevated serum levels of creatinine are associated with impaired kidney function due to the inability of the kidney to clear creatinine [42]. Due to the physiological changes in pregnancy, serum creatinine level decreases as the result of an increase in the fluid volumes [43]. Serum creatinine level rapidly decreased in the first trimester, reached a plateau in the second, and slowly increased in the third trimester of pregnancy towards the prepregnancy level [44].

To date, several diagnostic biomarkers for PE have been known. However, most of them are not utilized in clinical practice as some of them require advanced laboratory settings [45, 46, 47]. Hence, identifying simple and cost-effective diagnostic biomarkers is applicable to developing countries like Ethiopia. Maternal serum uric acid, creatinine and blood urea levels are simple biomolecules that could be used for the early prediction of PE. In this study, we found that maternal serum uric acid, creatinine and blood urea levels were significantly elevated in pre-eclamptic women. Therefore, uric acid, creatinine and blood urea could be utilized as the potential diagnostic biomarkers for PE together with other laboratory parameters, such as medical history and physical examination.

Our report has limitations. First, the current study is only limited on these diagnostic markers (serum uric acid, blood urea nitrogen and creatinine) as well as on women at the third trimester. Therefore, since variations are inevitable across trimesters with several diagnostic markers, working on additional parameters across the trimesters are required. Second, our study is an institutional-based case-control study that is merely a prediction of associations. We believe a multi-center prospective cohort study in the country or elsewhere shouldn't be lay away task.

5. Conclusions

Our study showed that significantly raised levels of maternal serum uric acid, creatinine and blood urea in pre-eclamptic women as compared to normal pregnant women. Serum levels of uric acid, creatinine and blood urea showed significant positive correlations with systolic and diastolic blood pressure. The ROC curve analysis showed serum uric acid concentration had better diagnostic accuracy for PE as compared to serum blood urea and creatinine values. This suggests that serum uric acid, blood urea and creatinine levels could be carefully utilized in the prediction of PE. Moreover, to check their diagnostic accuracy and to include into routine tests large-scale multi-center prospective cohort study will be required.

Declarations

Author contribution statement

Endalamaw Tesfa: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Abaineh Munshea, Endalkachew Nibret and Solomon Tebeje Gizaw: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Daniel Mekonnen: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Mulusew Alemneh Sinishaw: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

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