Diagnostic Accuracy of Urine Microalbumin and Serum Uric Acid: A Case-control Study of Patients with Preeclampsia in the Komfo Anokye Teaching Hospital, Kumasi, Ghana

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Abstract

Background: There is increasing prevalence of preeclampsia coupled with the need to identify and institutionalize more sensitive diagnostic tools for preeclampsia. This study evaluated the diagnostic accuracy of urine microalbumin and serum uric acid as early markers of preeclampsia among Ghanaian women attending antenatal care at the Komfo Anokye Teaching Hospital (KATH). **Methods:** A case-control study was conducted among pregnant women at the Obstetrics and Gynaecology (O&G) department of the KATH, Kumasi-Ghana from October 2011 to May 2012. One hundred and twenty-three (123) participants were recruited for this study after written informed consent was obtained. Socio-demographic characteristics, medical history and previous obstetric history was obtained through medical records of the eligible participants. Blood pressure and anthropometrics were measured according to standard procedure; urine samples were collected for estimation of spot urine protein and microalbuminuria; and venous blood sample was taken for biochemical analysis and platelet count. **Results:** A significant positive linear correlation was observed between spot urine protein and urine microalbumin (r=0.324, p=0.006). A negative linear correlation was observed between uric acid and spot urine micro albumin (r=0.033, p=0.786). A urinary micro albumin value of 75.45 mg/g was identified as the best threshold to detect a spot urine protein of > +2 with a sensitivity of 92.7% and a specificity of 80.0%, PPV of 81.03% and NPV of 33.3%. Area under the curve = 0.835; asymptomatic p-value of 0.0001 at 95% CI (0.678-0.991). In contrast, serum uric acid level of 263.5 mg/g was identified as the best cut-off point to detect a spot urine protein of > +2 with sensitivity and specificity of 89.1% and 33.3% respectively (PPV of 77.2% and NPV) of 20.8%. Area under the curve = 0.552; asymptotic p-value of 0.538 at 95% CI (0.364-0.740). **Conclusion:** Urine levels of microalbumin, as a measure of proteinuria are elevated in preeclamptics and can be used in place of spot macro protein estimation to diagnose preeclampsia especially in the early stages.

Keywords: Preeclampsia; Microalbuminuria; Uric acid; Proteinuria

Abbreviations: KATH: Komfo Anokye Teaching Hospital; O&G: Obstetrics And Gynaecology; NPV: Negative Predictive Value; PPV: Positive Predictive Value; BMI: Body Mass Index; SMS: School Of Medical Sciences; KNUST: Kwame Nkrumah University Of Science And Technology; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ROC: Receiver Operator Characteristic; AST: Aspartate Transaminase; Alanine Transaminase; ALK PHOS: Alkaline Phosphatase; WHR: Waist To Hip Ratio; ALB: Albumin

Introduction

Preeclampsia is defined as a multisystem ailment of unknown etiology depicted by the development of elevated blood pressure to the level of 140/90 mmHg or more with proteinuria induced by pregnancy after 20 weeks of pregnancy in a previously normotensive and non-proteinuria pregnant woman. [1,2] In preeclampsia, there is elevated levels of serum uric acid due

to reduced glomerular filtration rate, increased reabsorption and decreased secretion of serum uric acid, [3-5] proteinuria, high blood pressure and edema. Therefore, measurement of uric acid has been considered as a part of a panel of tests in women with preeclampsia to observe the severity of the disease to help with the management of the patients. [6,7]

According to Komfo Anokye Teaching Hospital (KATH) Annual Reports (2009 and 2013), Pre-eclampsia/eclampsia topped the first ten (10) causes of the admissions in the Directorate of Obstetrics and Gynaecology. In addition, preeclampsia/eclampsia was the major cause of maternal mortality spanning the period 2009 to 2013 (Biostatistics unit, O & G, KATH, 2013). There are many options for diagnosis of proteinuria, including urinary dipstick testing, urinary protein: creatinine ratio, and various timed urine collections (most commonly, 24-hour urine). Most studies have focused on methods that best match the quantification of urinary protein by 24-hour urine collection, considered to be the gold standard. However, a 24-hour urine collection is time-consuming, inconvenient, and often not completed. [8] Also, the urinary protein: creatinine ratio has been accepted for diagnosis by the International and Australasian pregnancy hypertension societies.

Urinary dipstick testing is inexpensive, easy, and widely used. Its usefulness is uncertain for screening either women with hypertension or those who are at increased risk of preeclampsia. Hence, more information on the determination of proteinuria using other measures of proteinuria like microalbuminuria is needed before clinical use of the urinary microalbumin can be recommended. The increasing prevalence of hypertensive disorders of pregnancy, coupled with the need to identify and institutionalize more sensitive diagnostic tools has necessitated this study. In the light of the afore-mentioned, this study sought to determine the diagnostic accuracy of urine microalbumin and serum uric acid in patients with preeclampsia at the Komfo Anokye Teaching Hospital (KATH), Kumasi. The findings of this study will help to identify more sensitive markers that will help in early diagnosis of preeclampsia.

Materials and Methods

Study design/area

This non-randomized case-control study was conducted at the Obstetrics and Gynaecology (O&G) department of the Komfo Anokye Teaching Hospital (KATH) the major specialist and referral centre for the northern parts of the country from October 2011 to May 2012.

Ethical considerations

The participation of the respondents who are all indigenes of Ghana was voluntary and written informed consent was obtained from each of them. The study was approved by the Committees on Human Research Publication and Ethics, SMS/KNUST and the Research Directorate of KATH.

Inclusion and exclusion criteria

Pregnant women with gestational age 20 weeks or more were considered eligible to participate in this study. For controls, we enrolled women in good health, normotensive and without dipstick proteinuria. Participants with elevated blood pressure (≥140/90 mmHg) with dipstick proteinuria (≥"+") were enrolled as cases. Pregnant women with chronic hypertension, on antihypertensive therapy, eclampsia, diabetes, autoimmune disease and renal disease were excluded.

Study population

One hundred and twenty-three (123) participants (≥ 20 weeks gestation) who met the eligibility criteria were recruited for this study. This comprised 53 age-matched, normotensive pregnant women, and 70 pregnant women with preeclampsia, receiving antenatal care at the O and G department of KATH. Participants with elevated blood pressure (≥ 140/90 mmHg) on two occasions, at least four hours apart, with visible dipstick proteinuria (≥ "+"), were considered to have PE.

Anthropometric measurements

Height (to the nearest 0.1 cm) and weight (to the nearest 0.1kg) were measured a wall-mounted ruler a bathroom scale (Zhongshan Camry Electronic Co. Ltd, Guangdong, China) respectively. Body mass index (BMI) was calculated using the formula; weight (kg)/height (m^2).

Waist circumference (in centimetres) was measured with a Gulick II spring-loaded measuring tape (Gay Mill, WI). Hip circumference (in centimetres) was also measured in and the waist to hip ratio (WHR) was calculated by dividing the waist circumference (cm) by the hip circumference (cm).

Blood pressure measurement

Trained personnel took duplicate measurements of blood pressure with a mercury sphygmomanometer and stethoscope in accordance with the recommendation of the American Heart Association [9].

Urine macroprotein and microalbumin determination

Dipstick, semi-qualitative method was used to determine urine protein as per manufacturer's instructions (CYBOW™ DFI Co Ltd, Gimhae-City, and Republic of Korea). The presence of urine protein in concentrations ≥ "+", using the semi-quantitative colour scale on the urine reagent dipstick was considered as proteinuria in participants with pre-eclampsia [ref]. Urine microalbumin was estimated based on the pyrogallol red molybdate complex method (ref).

Blood sample collection and biochemical analysis

After an overnight fast (8-12 hours), 6 ml of venous blood sample was taken from each participant into serum separator tubes, allowed to clot and then centrifuged at 500 g for 15 min. The serum was stored at - 80°C until assayed.

The remaining 2 ml were dispensed into tubes containing 2.5 μg K2EDTA. Platelet concentration (PLT) was determined by an automated blood analyzer CELL-DYN 1700®, version 1.08, (Abbott Diagnostics, Abbott Park, Illinois, USA) while serum

Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALK PHOS), albumin (ALB), serum creatinine (Scr) and uric acid were estimated on the ATAC 8000 Random Access Chemistry System (Elan Diagnostics, Smithfield, RI, USA).

Statistical analysis

Continuous variables were expressed as their mean ± SEM, while categorical variables were expressed as proportion. Comparisons of the women with PE against the control group were performed using unpaired t tests, Chi-square (χ2) tests, or Fisher exact tests where appropriate. GraphPad Prism version 5.00 for windows was used for these statistical analyses (GraphPad software, San Diego California USA, www.graphpad.com).

Also, association between spot urine protein and microalbumin and between uric acid and spot urine protein was by Pearson Correlation Coefficient. Sensitivity and specificity of microalbuminuria and uric acid as diagnostic markers was performed using receiver operating characteristics (ROC) curve. P < 0.05 was interpreted as statistically significant for all comparison.

Results

Of the 123 study participants studied, 53 (40%) were classified as controls and 70 (60%) as cases presenting with preeclampsia.

Table 1 shows the demographic, clinical and biochemical characteristics of the study participants. The preeclamptics had higher blood pressure (SBP and DBP) compared to the controls (p < 0.001). Also, biochemical parameters [(uric acid and hepatic enzymes (ALT and AST)] were significantly elevated in cases than the controls. The mean urine microalbumin concentration was higher in the preeclamptics than the controls (p=0.005) while the mean platelet count and serum albumin levels were similar in the cases and the controls (p=0.307).

Table 2 shows the demographic, clinical and biochemical characteristics of study participants stratified by urine microalbumin concentration. The preeclamptics with microalbuminuria >30-300 mg/g had insignificantly elevated DBP (p=0.817), uric acid (p=0.588) Creatinine (p=0.331) and transaminases (p=0.760; p=0.832). However, platelets count (p=0.683) and serum albumin (p=0.611), SBP (p=0.856) were reduced in the preeclamptics with urine microalbumin levels <30 mg/g though the differences were not significant.

Table 3 represents the demographic, clinical and biochemical characteristics of studied participants stratified by serum uric acid concentrations. Preeclamptics with uric acid levels <360 umol/L had significantly elevated serum albumin levels compared to those with uric acid levels >360 umol/L but blood pressure [SBP (p=0.542) and DBP (p=0.512)] were reduced in preeclamptics with uric acid <360 umol/L. Conversely, serum creatinine (p=0.780), transaminases [AST (p=0.538) and ALT (p=0.051)], platelets (p=0.116) and urine microalbumin (p= 0.073) levels were elevated in the preeclamptics with >360 umol/L though not significant.

Table 1: Demographic, clinical and biochemical data of studied participants.			
Parameters	Pre-eclampsia N=70	Controls N=53	P-value
Age (yrs)	30.51 ± 0.75	30.52 ± 0.65	0.996
BMI (kg/m²)	25.09 ± 0.48	25.98 ± 0.68	0.276
SBP (mmHg)	161.60 ± 2.22	107.20 ± 1.36	0.001
DBP (mmHg)	101.90 ± 2.83	66.63 ± 1.33	0.001
UA (umol/L)	360.70 ± 18.28	165.80 ± 7.38	0.001
ALB (g/l)	32.50 ± 0.58	34.24 ± 0.69	0.058
CRT (umol/L)	73.07 ± 4.94	82.70 ± 2.88	0.128
AST (IU)	42.10 ± 5.42	22.39 ± 1.03	0.003
ALT (IU)	51.65 ± 12.74	9.316 ± 0.56	0.005
PLT (10⁶)	242.20 ± 9.90	264.90 ± 22.04	0.307
MA (mg/g)	154.70 ± 14.75	85.60 ± 8.60	0.001

BMI=Body Mass Index, SBP=Systolic Blood Pressure, DBP= Diastolic Blood Pressure, ALB=Albumin, CRT=Creatinine, UA=Uric Acid AST=Aspartate Aminotransferase, ALT=Alanine Aminotransferase, PLT= Platelets, MA=Microalbumin

Table 2: Demographic, clinical and biochemical data of studied participants stratified by concentration of urine microalbumin.			
Parameters	MA <30 (mg/g)	MA 30-300 (mg/g)	P-value
Age (yrs)	31.50 ± 2.36	31.18 ± 0.82	0.919
BMI (kg/m²)	25.68 ± 1.53	25.06 ± 0.45	0.458
SBP (mmHg)	162.5 ± 7.50	160.7 ± 2.55	0.856
DBP (mmHg)	105.0 ± 2.89	106.0 ± 3.00	0.817
UA (umol/L)	317.5 ± 72.46	357.8 ± 18.94	0.588
ALB (g/l)	33.85 ± 1.99	32.49 ± 0.69	0.611
CRT (µmol/l)	55.20 ± 5.31	77.18 ± 5.88	0.331
AST (U/L)	36.35 ± 11.60	44.06 ± 6.57	0.76
ALT (U/L)	68.00 ± 1.155	55.41 ± 15.56	0.832
PLT (10⁶/L)	251.50 ± 28.60	236.4 ± 9.50	0.683

MA=Microalbumin

Table 3: Demographic, clinical and biochemical data of studied participants stratified by serum uric acid concentration.

Parameters	UA< 360 umol/l	UA > 360 umol/l	P-value
Age (yrs)	30.50 ± 0.94	30.55 ± 1.30	0.978
BMI (kg/m²)	25.08 ± 0.61	25.11 ± 0.73	0.981
SBP (mmHg)	162.50 ± 2.64	159.50 ± 4.18	0.541
DBP (mmHg)	103.20 ± 3.40	99.18 ± 5.14	0.512
ALB (g/l)	33.33 ± 0.79	30.69 ± 0.56	0.036
CRT (umol/l)	72.13 ± 6.41	75.13 ± 7.35	0.780
AST (U/L)	39.81 ± 4.14	47.08 ± 14.89	0.538
ALT (U/L)	34.88 ± 8.15	88.24 ± 35.79	0.051
PLT (10⁶/l)	231.70 ± 10.70	265.20 ± 20.68	0.116
MA (mg/g)	136.80 ± 14.68	193.60 ± 33.42	0.074
UA=Uric Acid			

Table 4: Demographic, clinical and biochemical data of studied participants stratified by spot urine albumin concentration.

Parameters	Spot urine Albumin < 2+ dipstick	Spot urine Albumin ≥2+ dipstick	P-value
Age (yrs)	34.20 ± 1.45	29.51 ± 0.84	0.012
BMI (kg/m²)	24.36 ± 0.90	25.29 ± 0.56	0.431
SBP (mmHg)	158.70 ± 5.42	162.40 ± 2.46	0.500
DBP (mmHg)	100.10 ± 7.19	102.40 ± 3.05	0.741
UA (umol/l)	355.30 ± 48.79	362.10 ± 19.36	0.880
ALB (g/l)	32.29 ± 1.06	32.56 ± 0.69	0.852
CRT (umol/l)	59.97 ± 11.76	76.64 ± 5.37	0.168
AST (IU)	33.31 ± 5.63	44.50 ± 6.71	0.401
ALT (IU)	29.30 ± 6.37	57.75 ± 16.06	0.363
PLT (10⁶/l)	238.00 ± 21.20	243.30 ± 11.28	0.826
MA (mg/g)	91.31 ± 32.73	172.00 ± 15.88	0.024

Table 5: Demographic, clinical and biochemical data of studied participants stratified by gestational age (second trimester T2).

Parameters	Control T2	Case T2	p-value
Age (yrs)	31.21 ± 0.90	30.63 ± 1.28	0.722
BMI (kg/m²)	24.24 ± 0.91	23.54 ± 0.58	0.651
SBP (mmHg)	105.50 ± 2.28	168.80 ± 5.15	< 0.001
DBP (mmHg)	65.71 ± 2.13	107.50 ± 5.26	< 0.001
UA (umol/L)	163.60 ± 9.37	323.80 ± 26.83	< 0.001
ALB (g/l)	35.25 ± 0.93	33.13 ± 2.34	0.317
CRT (umol/l)	82.85 ± 4.60	69.19 ± 6.01	0.105
AST (IU)	23.31 ± 1.64	24.10 ± 2.75	0.799
ALT (IU)	9.92 ± 0.92	14.76 ± 1.09	0.006
PLT (106/L)	247.20 ± 34.06	235.60 ± 24.05	0.835
MA (mg/g)	68.73 ± 13.74	167.60 ± 44.10	<0.001
CRT (umol/l)	82.85 ± 4.60	69.19 ± 6.01	0.105
AST (IU)	23.31 ± 1.64	24.10 ± 2.75	0.799
ALT (IU)	9.92 ± 0.92	14.76 ± 1.09	0.006
PLT (10⁶/L)	247.20 ± 34.06	235.60 ± 24.05	0.835
MA (mg/g)	68.73 ± 13.74	167.60 ± 44.10	<0.001
T2= second trimester			

Table 4 shows the demographic, clinical and biochemical characteristics of preeclamptic participants stratified by spot urine albumin concentration. The preeclamptic participants with spot urine albumin concentration ≥2+ were younger (p=0.010) and had higher urine microalbumin levels (p=0.024) than those with spot urine albumin <2+. Transaminases (ALT, AST), creatinine, albumin, blood pressure (DBP and SBP), uric acid and platelets were elevated in the preeclamptic with spot urine albumin ≥2+ though not significant (p>0.05).

Tables 5 and 6 show the demographic, clinical and biochemical characteristics of preeclamptics stratified by gestational age (in trimester). The preeclamptics in their second and third trimester had significantly elevated blood pressure (SBP and DBP), uric acid, hepatic transaminases compared to the controls. However, though platelet count, albumin, microalbumin and creatinine were elevated in the controls compared to the preeclamptics the difference was not statistically significant.

Figure 1 shows the relationship between spot urine protein and urine microalbumin. A significant positive linear correlation was observed between spot urine protein and urine microalbumin (r=0.324, p=0.006).

Figure 2 shows the relationship between uric acid and spot urine

protein. A negative linear correlation was observed between uric acid and spot urine microalbumin (r=0.033, p=0.786).

Figure 3 shows the Receiver operating characteristic curve analyses in women with preeclampsia. Urinary micro albumin value of 75.45 mg/g was identified as the best threshold to detect a spot urine protein of > +2 with a sensitivity of 92.7% and a specificity of 80.0%, PPV of 81.03% and NPV of 33.3%. Area under the curve = 0.835; asymptotic p-value of 0.000 at 95% CI (0.678-0.991). In contrast, serum uric acid level of 263.5 mg/g was identified as the best cut-off point to detect a spot urine protein of > +2 with sensitivity and specificity of 89.1% and 33.3% respectively PPV of 77.2% and NPV of 20.8%). Area under the curve = 0.552; asymptotic p-value of 0.538 at 95% CI (0.364-0.740).

Discussion

This study evaluated the accuracy of urine microalbumin and serum uric acid as diagnostic parameters among preeclamptics at the Komfo Anokye Teaching Hospital (KATH). In this study, the mean BMI of the preeclamptics were lower compared to the controls though the difference was not significant (p=0.276). This observation is consistent with the findings of Fatema et al., [10] and Anderson et al. [11] Also, the mean serum uric acid levels in this study were significantly higher (p=0.001) in participants with preeclampsia than in normal pregnant women and was consistent with previous reports by Koike T, et al. and Many A, et al. [12,13] The hyperuricaemia recorded in preeclamptics in this study could be a protective response, capable of opposing harmful effects of free radical activity as described by Many A, et al. [13]

| Table 6: Demographic, clinical and biochemical data of studied participants stratified by gestational age (third trimester).			
Parameters	**Controls** T3	**Cases** T3	**P-value**
Age (yrs)	28.46 ± 0.83	30.50 ± 0.84	0.164
SBP (mmHg)	108.30 ± 1.96	160.60 ± 2.41	< 0.001
DBP (mmHg)	67.71 ± 2.17	106.50 ± 1.79	< 0.001
UA (umol/L)	174.10 ± 12.33	365.40 ± 20.31	< 0.001
ALB (g/l)	34.01 ± 1.02	32.42 ± 0.60	0.175
CRT (umol/l)	83.11 ± 2.69	73.57 ± 5.53	0.306
AST (IU)	20.47 ± 1.12	44.42 ± 6.05	0.019
ALT (IU)	9.52 ± 0.79	56.41 ± 14.30	0.049
PLT (10^6/L)	295.70 ± 39.42	243.00 ± 10.80	0.08
MA (mg/g)	82.19 ± 11.08	172 ± 9.50	< 0.001

T3=Third Trimester
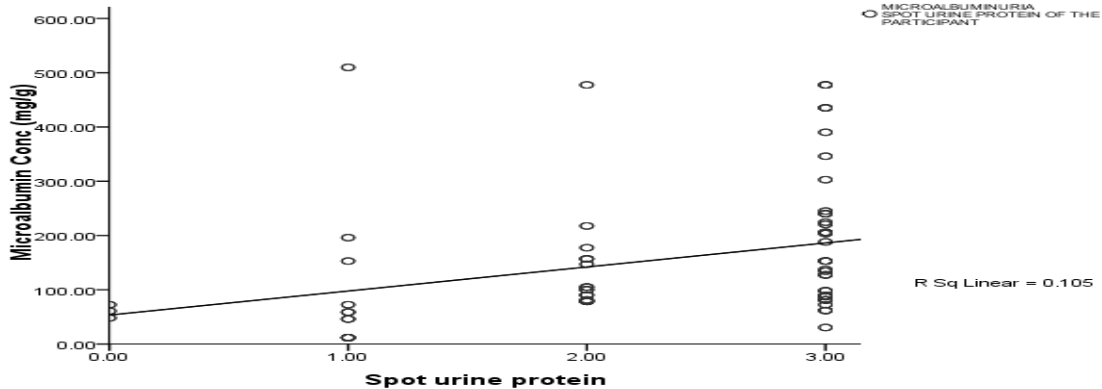
Figure 1: Correlation between spot urine protein and urine microalbumin concentration of pre-eclamptic patients.
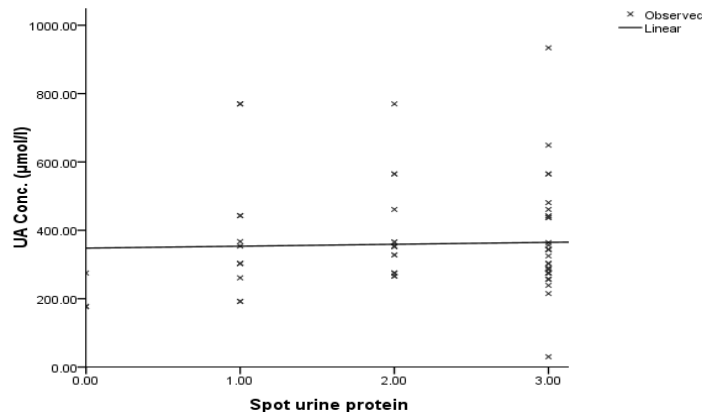
Figure 2: Correlation between spot urine albumin and uric acid levels of pre-eclamptic patients.
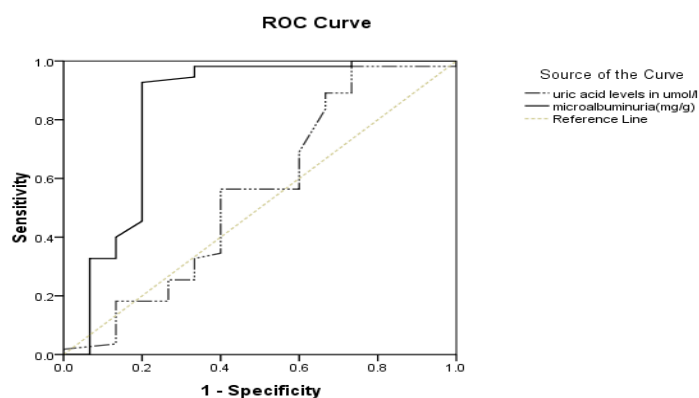
Figure 3: Receiver operating characteristic curve analyses in women with pre-eclampsia.

Again, the preeclamptic patients excreted higher amount of urinary protein (p= 0.003) compared to healthy controls. In the present study microalbuminuria concentration for preeclamptics was markedly elevated, consistent with previous researches conducted by Poon LC et al and Rodriguez MH et al. [14,15] Moreover the current study recorded a high urinary protein with decreased serum albumin concentration among preeclamptic women compared to the healthy pregnant women though the difference was not statistically significant (p=0.0585). This finding is in accordance with reports of several studies[16,17] which concluded that preeclamptic patients have lower serum albumin concentration than normotensive controls. Furthermore, the findings of this study showed that the mean SBP and DBP were low among preeclamptics with uric acid levels >360 μmol/l compared with the group who had <360 μmol/l. According to Table 4, microalbuminuria concentration was significantly higher among preeclamptics in the ≥2+ spot urine albumin group than in <2+ spot urine albumin group. Also, the ≥2+ spot urine albumin group was significantly (p=0.0102) older compared to the other group. This explains age as a risk factor for preeclamptics who diagnostically present ≥2+ urine protein. In addition, there were no significant correlation between spot urine protein and uric acid levels (Figure 2) although the data in this study suggest a statistically significant difference between the mean uric acid value of the preeclamptics and healthy pregnant control groups (Table 2), its diagnostic ability for preeclampsia is questionable. Our study could not identify an obvious cut off point on the receiver operator curve (ROC) for uric acid level that was sufficiently sensitive and specific to distinguish preeclampsia. The best sensitivity (89.1%) and specificity (66.7%) was related to cut off point of 263.50 μmol/l. These figures are close to the values of some other studies, and the findings are consistent with those studies that did not find a clinical utility for serum uric acid in the prediction of preeclampsia [18,19] and in contrast to a study conducted by Roberts et al. [20] This might be because most of the studies that have reported a strong correlation between elevated serum uric acid and the severity of preeclampsia, have examined pregnant women with the most severe form of the disease. [21] This shows that a single estimate of uric acid is of little or no value in the prediction of preeclampsia. This is further confirmed by the insignificant (p=0.538) results shown by our ROC analysis (Figure 3).

Finally, a significant positive correlation (r=0.324, p=0.006) was established between spot urine protein (macroalbumin) and microalbuminuria. This finding partly agrees with the observations made in other studies where 24 hour urine was used in the detection of macroalbuminuria. [22,23] The use of microalbumin in the diagnosis will aid early detection of proteinuria a key diagnostic determinant of preeclampsia. The study is limited in the sense that it could not generalize the prevalence and incidence to the whole Ghanaian population in Kumasi, since it was a hospital-based study.

Conclusion

According to the ROC curve analysis, sensitivity (92.7%) and specificity (80.0%) of microalbuminuria were best identified at a threshold point of 75.45 mg/g with PPV of 81.03% and NPV of 33.3%. In comparison with uric acid accuracy, urinary microalbumin can be used as an alternative diagnostic marker to spot urine protein for predicting early onset of preeclampsia.

Acknowledgements

Conflict of Interest

All authors disclose that there was no conflict of interest.

Availability of Data and Materials

Data will not be shared in order to protect the anonymity of the participants

Author Contributions

ME did the literature searches, and the bench work under the guidance and supervision of KB-A and CAT. ME and RKDE did the first draft of the manuscript. RKDE and EOA did the statistical analysis. KB-A and RKDE designed the experiments and did the final draft of the manuscript. CAT recruited and did the monitoring of the patients. All the authors read and approved the final manuscript.

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