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The Accuracy of Random Urine Albumin–to–Creatinine Ratio Diagnosing Pre-Eclampsia Compared with Random Microalbuminuria

Alamtaj Samsami[1], Zahra Soltani[2], Fatemeh Pouraminaee[3], Hadi Raeisi Shahraki[4], Marjan Zare[5], Mojgan Akbarzadeh-Jahromi[3,5*]

1. Department of Obstetrics & Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
2. School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
3. Department of Pathology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
4. Department of Epidemiology and Biostatistics, School of Health, Shahrekord University of Medical Sciences, Shahrekord, Iran
5. Maternal-fetal Medicine Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

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Abstract

Pre-eclampsia (PEC) is a multisystem complication diagnosed by hypertension and proteinuria or multi-organ problem without signs of proteinuria, which occurs after 20 weeks of gestation. 24-hour Urine Protein to Creatinine Ratio (24-hour UPCR) is a valid test diagnosing PEC; however, collecting urine for 24 hours has several difficulties in practice. Measuring random urine albumin to creatinine ratio (random UACR) in a random urine sample may be an appropriate alternative. It aimed to investigate the diagnostic accuracy of random UACR diagnosing PEC compared with Random microalbuminuria. In a cohort study, suspected pregnant women referring to Hazrat Zeynab hospital during June and September 2017 were followed for PEC development. 24-hour urine samples were taken from the subjects to measure the 24-hour Urine Protein; in addition, random urine samples were taken to measure the random UACR for each. Receiver operator characteristic curve was applied and area under roc curve (AUC), sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) with 95% Confidence Interval ;(95% C.I) were estimated using SPSS v.22 at significance level<0.05. From 69 subjects, 33% (23/67) developed PEC and the remaining 67% (46/67) were non-PEC control group. Random UACR greater than 40 mg/g could diagnose PEC with AUC, sensitivity, specificity, PPV, and NPV equal 0.81(0.69-0.93), 0.70 (0.47-0.87), 0.70, and 0.85, respectively. Random microalbuminuria greater than 53.5 mg/lit could diagnose PEC with AUC, sensitivity, specificity, PPV, and NPV equal 0.78(0.66-0.91), 0.70 (0.47-0.87), 0.85(0.71-0.94), 0.70, and 0.85, respectively. Random UACR is accurate enough diagnosing PEC. It is highly recommended to use random UACR as a quicker and cheaper test diagnosing PEC especially in emergencies.

Keywords: Proteinuria; Pre-eclampsia; Pregnancy; Diagnostic accuracy; Urinalysis

Introduction

Pre-eclampsia (PEC) is one of the important pregnancy-related complications affecting 2-8% of pregnancies in developed countries with an increasing trend in developing countries (1, 2). It causes perinatal complications for mother and fetus (3). PEC is a multisystem complication diagnosed by hypertension and proteinuria or multi-organ problem without signs of proteinuria, which occurs after 20 weeks of gestation (4, 5). Women with autoimmune disease, chronic hypertension, diabetic mellitus, past history of PEC, and obesity have a higher risk of PEC than normal population (6, 7). Several laboratory methods have been suggested for the diagnosis of proteinuria. Dipstick method in a random urine sample is the easiest method for semi-quantitative estimation of proteinuria. The diagnosis is based on two occasions (at least 4 hours apart) dipstick result of >+1 (indicating presence of >30mg/dl protein), which can diagnose proteinuria with a sensitivity of 59% and specificity of 67% (8). However, the mother's hydration status, exercise, infection, orthostatic proteinuria, and the presence of contaminations can affect dipstick results (8). Actually, urine dipsticks can't exclude PEC from hypertension (9). Microalbuminuria, as the other way, refers to the excretion of albumin in the urine, which is usually 30-300 mg/g creatinine(10), in which immunoturbidimetric, radioimmunoassay, and high-performance liquid chromatography methods can confirm the diagnosis (11).

The gold standard method for diagnosis of proteinuria is generally based on >300 mg/24-hour proteinuria in a 24-hour urine test

***Corresponding author:** Mojgan Akbarzadeh-Jahromi, Department of Pathology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, Email: akbarzadeh@sums.ac.ir

However, this diagnostic test has several limitations, including difficulty for the patient to collect 24-hour urine, going to labor before collecting all samples that may lead to underdiagnoses of PEC, no cut–off point for severe PEC, and the fact that urinary protein level might be affected by several factors, such as steroids and renal pathology (12, 13). Accuracy of The 24-hour urine protein to creatinine ratio (24-hour UPCR) was investigated (13). 24-hour UPCR in a random urine sample has been correlated with 24-hour urinary protein, suggested to be able to successfully rule out cases without PEC(14, 15); nevertheless, there is much discrepancy among studies about the diagnostic accuracy rates and the most appropriate cut–off values (16, 17). In a recent meta-analysis, it has been reported that at a threshold above 60 mg/mmol, 24-hour UPCR showed high specificity and positive tests could be considered as significant proteinuria; under threshold of 30 mg/mmol, 24-hour UPCR showed high sensitivity and negative tests could rule out significant proteinuria; between 30 and 60, the test needed to repeat. studies on 24-hour UACR showed that a threshold of 2 mg/mmol has high sensitivity (98%); this cut-off point can be used as a highly accurate method for ruling out significant proteinuria (18, 19). determining a less time-consuming test, random urine albumin to creatinine ratio (random UACR) could be an appropriate alternative for 24-hour urine test (20, 21). Thus, it aimed to investigate the accuracy of random UACR and random albuminuria diagnosing PEC compared with Random microalbuminuria.

Materials and methods

Study design and setting

In a cohort study, suspected PEC patients referred to the prenatal care center of Hazrat Zeynab hospital affiliated with the Shiraz University of Medical Sciences during June and September 2017 were followed for PEC development. PEC was defined based on the International Society for the Study of Hypertension in Pregnancy (ISSHP) as systolic blood pressure at ≥140 mm Hg and/or diastolic blood pressure at ≥90 mm Hg on at least two measurements 4 hours apart and is accompanied by one or more of the following new-onset occasions at or after 20 weeks of gestation (22):

1. Proteinuria (i.e. ≥0.3 mg/dL, proteinuria ≥ 300 mg/24 hour; or ≥ 2+dipstick);
2. Evidence of other maternal organ dysfunction, including: acute kidney injury (creatinine ≥90 µmol/L; 1 mg/dL); liver involvement (elevated transaminases, e.g. alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain; neurological complications (e.g. eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata); or hematological complications (thrombocytopenia–platelet count <150 000/µL, disseminated intravascular coagulation, hemolysis); or
3. Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth).

The remaining subjects referring to the same center at the same time matching on the diet, activity level, multiple gestation, history of blood pressure, history hypertension, and history of kidney disease before pregnancy were taken as non-PEC control group.

Inclusion/exclusion criteria: Pregnancy age above 20 weeks with at least one systolic blood pressure above 140 after 20 weeks of gestation. Due to the high diagnostic importance of proteinuria compared to other PEC criteria, proteinuria indicating an impaired kidney, liver dysfunction, fatty liver patients, and platelet drop were set as exclusion criteria. In addition, incorrect collection of 24-hour urine samples and time interval more than 36 hours from the time of sample collection were considered as exclusion criteria.

Variable definition and measurement: age (years), gestational age by ultrasound measured at the time of urine sampling (weeks), weight (kg), aspartate aminotransferase; AST: (IU/L), alanine transaminase; ALT: (IU/L), gravidity, systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) measured by the same physician in the sitting position after 15 minutes rest, random albuminuria (mg/L), random creatinine (mg/L), random urine albumin to creatinine ratio (random UACR), 24–hour proteinuria (mg/dL), 24–hour creatinine (mg/L), 24-hour urine protein to creatinine ratio (24-hour UPCR). The Pars test microalbumin and creatinine measurement kit was installed on the urinalysis machine of Zainabieh Hospital. Urine samples of the patients were collected and the amount of microalbumin in random urine was checked by the immunotrub method.

Ethical statement:

All study steps were performed in accordance with the declaration of Helsinki 1964; an informed consent form was obtained from all participants in the study.

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences with ethic number of IR.sums.med.rec. 1396.s206.

Sample size consideration:

Using the information from Aggarwal and colleagues study (23), considering type I error =0.01, type II error=0.05, estimated AUR curve= 0.79, attrition rate of 10%, and using the following formula:

$$n \geq \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 var(\widehat{AUR})}{d^2}$$

where,

$z_{1-\alpha/2}$= 2.57, $z_{1-\beta}$ = 1.64, $var(AUR)$ is estimated variance for AUR,

and d is required absolute precision on either side of area under ROC curve

The minimum sample size was estimated 69 patients for the study (MedCalc version 20.015 software tool). The convenient sampling method was done until saturation of the sample size.

Laboratory examination

Random urine sample of the patients obtained from the 24-hour urine samples was sent to laboratory within 36

hours. The 24-hour urine sample of patients was sent to the laboratory for measurement of urinary protein and creatinine, measured by corresponding commercial kits (*Pars Azmoon, Tehran, Iran*) according to manufacturer's instructions. Pre-eclampsia was confirmed by proteinuria ≥300 mg/day in 24-hour urine test. Patients' albuminuria was measured by a non-linear immunoturbidimetry method with BT 3000 auto-analyzer and Pars Azmoon microalbumin kit in random urine sample with a diagnostic accuracy of 3.

Creatinine level of random urine samples was measured by commercial kit (*Pars Azmoon kit, Tehran, Iran*) with BT3000 autoanalyzer. Pregnant women with incorrect collection of 24-hour urine sample, interval >36 hours between the random urine sample and 24–hour urine sample, known cases of glomerulonephritis and chronic hypertension were excluded from the study.

Statistical analysis

Qualitative and quantitative variables were described by frequency (relative frequency) and mean±standard deviation (SD) or median (IQR), respectively. One-sample Kolmogorov–Smirnov normality test, independent sample t-test, non-parametric Mann–Whitney U test, Chi-square test, and Pearson's or Spearman's correlation coefficient tests were applied to analyze the data. Receiver operating characteristic (ROC) analysis with Uden index=sensitivity+specificity-1 (to determine cut-offs), were used. In addition, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. IBM SPSS Statistics version 21.0 (IBM Corp. 2012. Armonk, NY: IBM Corp.) And MedCalc version 20.015 software tools were used at significance level <0.05 for all tests. Matching on confounding variables as well as considering eligibility criteria, the confounding effect was tried to go minimized.

Results

69 out of 106 random urine samples were selected and analyzed; the subject selection chart has been depicted in Figure 1.

Out of the 69 participants, pre-eclampsia was confirmed in 23 women (33.3%). The demographic, clinical, and laboratory features have been compared between pre-eclampsia and control groups in Table 1.

Mean age of the patients was 30.0±6.6 years and mean GA was 32.4±3.9 weeks. The results of comparison of mean age, weight, gravidity, GA, liver enzymes, and systolic and diastolic blood pressure values between patients with and without pre-eclampsia are shown in table 1. As indicated, women with pre-eclampsia had a significantly lower mean age than women without pre-eclampsia (26.0 vs. 32.0 years, P<0.001), but there was no significant difference between the two groups in term of mean weight, gravidity, GA, serum levels of AST, ALT, and systolic and diastolic blood pressure (P>0.05) (Table 1). The results of Mann Whitney test revealed that women with pre-eclampsia had a

significantly higher median urinary albuminuria in random urine test (163.0 versus 33.5, P<0.001) and 24-h proteinuria (1.60 versus 0.10, P<0.001) (Table 1).

Spearman's correlation coefficient confirmed positive correlations between R-UACR and random micro albuminuria (r=0.72, P<0.001) and 24-h proteinuria (r=0.47, P<0.001); (Table 2).

Using ROC curve analysis and based on Youden index, optimal cut-off point for pre-eclampsia diagnosis using R-UACR was calculated as 40.0 with AUC equal to 81%, sensitivity of 69.57%, and specificity of 84.78%, (Table 3). Moreover, ROC analysis revealed 53.5 as the optimal cut-off point for diagnosis of pre-eclampsia using random albuminuria with AUC, sensitivity, and specificity of 78%, 70%, and 85%, respectively (Table 3 and figure 2).

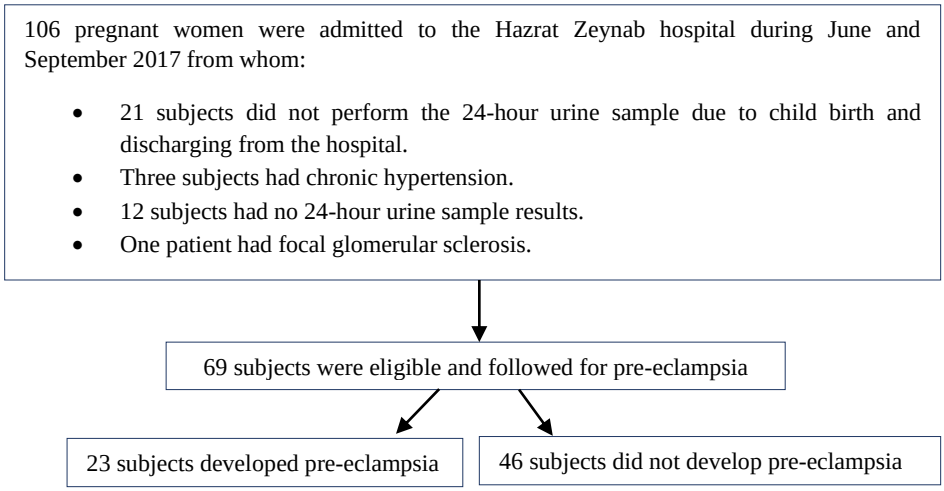

Figure 1. Subject selection flowchart

Table 1. The comparison of demographic, clinical, and laboratory features between pre-eclampsia and control groups

Variable	Pre-eclampsia group (n=23)	Control group (n=46)	P–value
Age (years), mean± SD	26.0±5.0	32.0±6.4	<0.001*
Gestational age (weeks), mean± SD	31.7±3.8	32.7±4.0	0.29*
Weight (kg), mean± SD	75.7±12.2	80.3±13.3	0.17*
AST (U/L), mean± SD	23.2±13.7	23.1±20.9	0.98*
ALT (U/L), mean± SD	20.9±16.4	26.9±16.7	0.64*
Gravidity, mean± SD	2.3±1.3	2.9±1.7	0.15*
Systolic blood pressure (mm Hg), mean± SD	136.7±15.9	132.3±16.6	0.29*
Diastolic blood pressure (mm Hg), mean± SD	85.4±10.8	87.6±10.0	0.41*
Random urine albuminuria (mg/L), median (IQR)	163.0 (311.7)	33.5 (27.0)	<0.001†
Random urine creatinine (mg/L), median (IQR)	1.19 (0.59)	1.32 (1.39)	0.11†
Random urine albumin to creatinine ratio, median (IQR)	116.4 (372.4)	26.3 (19.7)	<0.001†
24–hour proteinuria (mg/dL), median (IQR)	1.60 (4.43)	0.10 (0.09)	<0.001†
24–hour creatinine (mg/L), median (IQR)	1.25 (0.53)	1.00 (0.61)	0.04†
24–hour proteinuria to creatinine ratio, median (IQR)	1.27(7.89)	1.12(-.18)	<0.001

SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine transaminase, IQR: Interquartile range, *independent sample t-test, † :Mann–Whitney U test

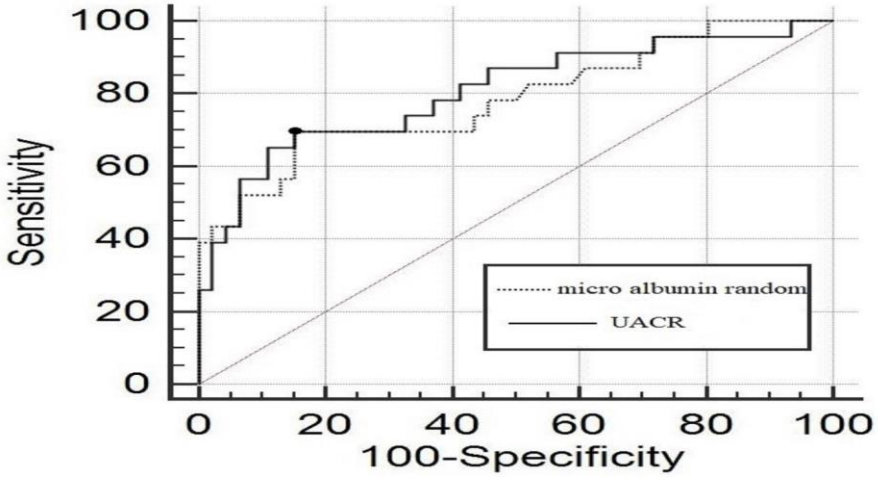

Figure 2. ROC curves Random Urine Albumin–to–Creatinine Ratio Diagnosing Pre-eclampsia (solid line) and with Random microalbuminuria (dotted line)

Table 2. The correlation between the results of random and 24-hour urinary test

Characteristic	Random albuminuria	24–h proteinuria	Random Urine Albumin–to–Creatinine Ratio
Random microalbuminuria	1.00	0.50 (P<0.001)	0.72 (P<0.001)
24-h proteinuria		1.00	0.47 (P<0.001)
Urine Albumin-to-Creatinine Ratio			1.00

Table 3. The diagnostic accuracy of random urine albumin-to-creatinine ratio and random albuminuria

Characteristic	AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cut-off point
Random Urine Albumin-to-Creatinine Ratio	0.81 (0.69-0.93)	0.70 (0.47-0.87)	0.85 (0.71-0.94)	0.70	0.85	40.0
Random microalbuminuria	0.78 (0.66-0.91)	0.70 (0.47-0.87)	0.85 (0.71-0.94)	0.70	0.85	53.5

*AUC: Area under curve

Discussion

The results of the present study showed that 33.3% of women suspected of having pre-eclampsia based on clinical symptoms had a final diagnosis of pre-eclampsia based on 24-hour proteinuria >300 mg/day, in women with a mean GA of 32.4 weeks. Then, we tested whether R-UACR was significantly correlated with 24-h proteinuria and the results confirmed our hypothesis, although the effect size was not considerable (r=0.47). According to the evidence, the random urine sample is the easiest and most appropriate method, when there is insufficient time for 24-hour urine test (24). However using UPCR for evaluating urinary protein in a random urine sample is still controversial (17), as many factors such as patients' regimen, and renal pathology (12), as well as processing and storage conditions (25) may affect the urinary protein levels, although it is correlated with 24-hour urinary protein and can successfully rule out pre-eclampsia (14, 26).

R-UACR can be an appropriate alternative for 24-hour proteinuria (27-29). In the study by *Wikström* and colleagues, random UACR was poorly correlated with 24-hour urine albumin (r=0.42), which improved after adjustment for maternal age and nifedipine medication (r=0.60) (21). However, as they indicated, R-UACR could be affected by several factors, such as variability during the day, different regimens, creatinine clearance, and proteinuria levels (21). In the study by AI and colleagues, the Spearman's correlation between UACR and 24-h proteinuria was about 0.8 with a small variation during the day by pooled analysis (30). *Sachan* and colleagues also reported a strong correlation between UACR levels and 24-h urinary proteins (27). In the study of *Kaul* and colleagues, there was a positive linear correlation between ACR and 24-hour urinary protein (r= 0.836). In this study spot urinary micro ACR cut-off of 20.4 is considered as positive for proteinuria and correlates well with 24-hour urine protein with sensitivity of 88.5% and specificity of 75%. These results confirm that of the present study on the association of UACR and 24-hour proteinuria.

In the next step, we used ROC curve analysis for calculating the optimal cut–off and diagnostic accuracy. Based on *Youden* index, optimal cut-off point of R-UACR for diagnosis of pre-eclampsia was calculated as 40.0 mg/g with AUC equal to 81%, sensitivity of 69.57%, and specificity of 84.78%. In the study by *Gangaram* and colleagues, the sensitivity, specificity, PPV, and NPV of urinary albumin/creatinine ≥300 mg/g on spot midstream urine, compared with 24-h proteinuria was 63%, 81%, 82%, and 62%, as evaluated by *Clinitek*® 50 dipstick (31). The sensitivity and specificity reported by these authors are close to that in the present study, although the PPV and NPV values of R-UACR were different in the present study (70%, and 85%, respectively), which could be due to the difference in laboratory methods. *Gangaram* and colleagues suggested neither visual nor albumin/creatinine dipsticks as appropriate alternatives for 24-hour proteinuria, which could be due to the variation in the albumin fraction of the total urinary protein of pre-eclampsia (31). AI and colleagues determined the appropriate cut–off values for random and 8-hour urine sample and their diagnostic accuracy according to ROC analysis and reported the sensitivity, specificity, PPV, and NPV of random UACR at 94%, 68%, 48%, and 97%, respectively, for cut-off value of 0.6, when the sample is collected at 8 am; 82%, 94%, 82%, and 94%, respectively, for cut-off value of 1.4, when the sample is collected at 4 pm; and 82%, 96%, 87%, and 94%, respectively, for cut-off value of 1.6, when the sample is collected at 0 am (30). Although they have reported variation in diagnostic accuracy across the day, compared with the results of the present study, the sensitivity in their study was higher than ours, while the specificity in their study at 4 pm and 0 am was higher than that of the present study (94% and 82% vs. 70%), and at 8 am was lower than that in the present study (68% vs. 85%) (30).

Considering R-UACR as a screening test to rule out albumin excretion ≥2gr, they reported the appropriate cut-off value at 0.37 with 58% false positive rate and 35% PPV at 8 am, at 0.39 with 47% false positive rate and 42% PPV at 4 pm, and at 0.36 with 47% false positive rate and 41% PPV at 0 am (30). The optimal cut-off point of this study at three different times of the day is close to that in the present study (optimal cut-off point of 40.0 mg/g), although we considered the optimal cut-off point for pre-eclampsia diagnosis, while they have calculated the diagnostic accuracy as a screening test to rule out albumin excretion ≥2gr, which could be the main reason for different diagnostic accuracy rates. *Gangaram* and colleagues have additionally collected an 8-hour urine sample of 00–08 am and reported NPV and sensitivity of 100% for R- UACR within the range of 0.36 (30); nevertheless, we have only considered one random urine sample.

Another important finding in the present study was the association of random albuminuria with 24-h proteinuria (r=0.50) and R-UACR (r=0.72); and the results of ROC analysis revealed 53.5 as the optimal cut-off point for diagnosis of pre-eclampsia using random albuminuria with AUC, sensitivity, and specificity of 78%, 70%, and 85%, respectively. In another study, *Justesen* and colleagues compared the diagnostic accuracy of urinary microalbumin/creatinine of 3.5 mg/mmol (30 µg/mg) with 24-hour albumin excretion in 119 women with gestational diabetes and reported specificity and PPV of 100%, NPV of 99%, and sensitivity of 83%, however, all women with an albumin excretion >300mg/24 hours had R-UACR of >25mg/mmol and all women with an albumin excretion <30mg/24hours had UACR of <2.5mg/mmol (32). The diagnostic accuracy reported by *Justesen* and colleagues is higher than the sensitivity and specificity of the present study (70%, and 85%, respectively); however, they also concluded that R- UACR could not be an appropriate alternative for 24-h albuminuria.

One of the limitations of each study including the present study that compared random urine with 24-hour urine is that the random urine sample is taken at different times of the day which could affect the diagnostic accuracy of UACR. In addition, the severity of pre-eclampsia and its possible effect on the study outcome was not investigated.

Conclusion

In conclusion, the results of the present study showed positive correlation of R-UACR with Random microalbuminuria. These results show that the results of R-UACR are reliable. In the next step, we analyzed the diagnostic accuracy of R-UACR and the results showed the optimal sensitivity, specificity, PPV, and NPV at cut-off value of 40.0 mg/g (AUC: 81%, sensitivity and specificity of 69.57% and 84.78%, respectively). These results indicate that in emergencies, R-UACR can rule out significant proteinuria, if the test result is lower than 40.0 (NPV=85%). This issue can help physicians to decide on admitting the patient or choose outpatient treatment.

Considering several factors that could affect R-UACR, investigating the effect of age, severity of pre-eclampsia, renal function, and time of the sample collection, and adjusting the diagnostic accuracy for these confounders could show better results for the diagnostic accuracy of R-UACR.

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Conflict of Interest

The authors declare no conflict of interest.

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