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Original Article

Quantification of proteinuria in mild preeclampsia with random albumin creatinine ratio

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Abstract

Objective: To investigate the whether spot urine albumin/creatinine ratio (ACR) compared to the 24h urinary protein (gold standard) to detect significant proteinuria in patients with preeclampsia. Study design: 80 pregnant patients diagnosed to have hypertension in late pregnancy were instructed to collect urine during a 24-hour period. Albumin creatinine ratio was evaluated in a random urinary specimen and morning samples for quantization of proteinuria. Out of these, 78 patients fulfilled the inclusion criteria. The predictive value of the random urinary ACR for the diagnosis of significant proteinuria was estimated by using various cutoff values of urinary ACR in comparison to 24-h urine collection as the gold standard.
Results: 70 (89%) patients had preeclampsia. The mean morning systolic blood pressure on the day of the urine collections was 150 mmHg and mean diastolic blood pressure 114 mmHg. The mean total protein was 1961.46+1683.02 mg/24h, and the urinary ACR in random samples was 781.31+1041 mg/g creatinine, while in the morning sample urinary ACR was 886.43+1180.9 mg/g creatinine. There was a statistically significant positive correlation between in 24-hours urine proteins and ACR in both daytime and morning urine samples. The best cutoff point for ACR in random sample was 262.5 mg /g creatinine as with a sensitivity of 85.5% and a specificity of 81.8%, the positive predictive value was 96.7% and negative predictive value was 47.4%. While the best cutoff point for ACR in morning sample was 240 mg /g creatinine with a sensitivity of 94.2% and a specificity of 63.6%, the positive predictive value was 94.2% and negative predictive value was 63.6%.
Conclusion: Albumin/creatinine ratio is not an ideal diagnostic test to replace 24-hour urine collection for the diagnosis of preeclampsia. However, it can be used as a screening test with sensitivity 94% when the cut point of albumin/creatinine ratio of the morning urine sample is set below 240 mg/g creatinine.

Key words: Albuminuria; hypertension; pregnancy; kidney disease.

Running title: Urine albumin creatinine ratio in mild preeclampsia.

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Introduction

Preeclampsia group includes mild preeclampsia, severe preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) [1]. Mild preeclampsia is systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥90 mmHg with proteinuria, severe preeclampsia is proteinuria with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110mmHg or the presence of cerebral or visual disturbances [2]. Reported incidence of preeclampsia ranges from 2% to 7%. Multiple risk factors for the development of preeclampsia include diabetes, obesity, primiparity, extremes of age, chronic kidney disease, preexisting hypertension, personal history of preeclampsia, molar pregnancy, multifetal gestation [3].
Proteinuria can be measured by quantification of either urine total protein or albumin. The two methods give similar results in preeclampsia, an increase in total protein or albumin excretion is considered to be a sign of aggravation of preeclampsia, reflecting severe nephropathy. The present gold standard for quantification of excreted total protein or albumin is 24-hour urine collection [4]. When preeclampsia develops, urinary total protein or albumin excretion is monitored in frequent 24-hour samples. Twenty four hour collection is

however, time consuming and not always reliable because collections are cumbersome for patients and, therefore, prone to under and over collection, compromising accuracy. The 24-hour urine collection is needed due to the high degree of variation in the urinary protein concentration during the course of the day [5].
There has been considerable discussion regarding the best way to measure daily urinary excretion of protein in preeclampsia and as collection of 24-h urine samples is still a burde, alternatively, random spot urine P/C have been used for some time as an accurate representation of the 24-h urine collection [6].
An alternative method for detecting possible aggravation of pre-eclampsia is to use the random urinary total protein/creatinine ratio or albumin/creatinine ratio. In the presence of a stable glomerular filtration rate, urinary creatinine is excreted at a fairly constant rate which makes it useful as an internal reference [7]. The usefulness of this method for assessing proteinuria in a non pregnant population is substantiated in the literature [8]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) has accepted spot urine protein/creatinine ratio as a method for identification of significant proteinuria (300 mg/24 hours) [9]. Several previous studies have also shown a strong linear correlation between random urinary PCR or ACR and 24-hour urine protein measurement in both healthy and hypertensive pregnant women [10-12]. Other studies have yielded conflicting results, with poor correlation between the amount of protein in a 24-hour collection and PCR or ACR [13,14]. The correlation has also been found to be lower when the protein excretion is more than 1–2 g per 24-hour period [15].
The aim of this study is to evaluate the correlation between albuminuria measured as ACR and amount of protein in 24-hour urine samples in women with preeclampsia with significant albuminuria.

Material and methods

It is a prospective observational cross sectional study; all women were admitted to the Department of Obstetrics and Gynaecology, Ain Shams Maternity University Hospital, Cairo, Egypt between January 2008 and October 2008. The study protocol was reviewed and approved by the clinical research ethics committees and patients' written consents were obtained.

Study population:

80 pregnant patients more than 20 weeks gestational age enrolled in the study, they had new onset hypertension defined as $\geq$140/90 in two different measurements obtained at intervals of more than 6 hours, repeated positive urinary test strip for proteinuria of +1 or +2 corresponding to an albumin concentration of 300mg/l or more. Patients with the following criteria were excluded: Women with a concurrent diagnosis of upper urinary tract infection, chronic hypertension (hypertension before pregnancy and persistent elevation of blood pressure before the 20th week of gestation), diabetes mellitus and pre-existing renal disease.

Sample collection and laboratory analysis:

A planned 24-hour urine collection for albumin measurement was eligible for inclusion in the study. The 24-hour collections were commenced during daytime by spontaneous voiding, all patients were at rest throughout the sampling period, time 24 was defined as including the first morning void at the end of the 24-h collection, completeness of the 24-h urine protein samples was assessed by comparing the total creatinine in the sample with the predicted creatinine {22-(age/9)* kg in women and 28-(age/6)* kg in men}. Collections were considered accurate if measured/expected ratios were between 0.8 and 1.2. Then the 24-hour samples were sent for analysis of albumin and albumin/creatinine ratio (ACR). Blood samples were taken during the period of collection for serum creatinine and albumin levels. A single voided urine specimen (5ml) was obtained randomly during the 24-hour urine collection period. All random samples were collected during daytime and none was first voided sample, because these first voided samples were collected and analyzed separately. The single voided samples were stored at +4 °C immediately and within 24 hours they were moved to storage at –18C°. The analyses were performed when all samples had been collected (storage time, 1–10 months).

Assessment of albumin in urine:

Methods: Is by the use of colorimetric method (pyrogallol red-molibdate complex).
Principle: In acidic medium albumin in the specimen reacts with pyrogallol red in the presence of molibdate ions to form a purple color complex. This color complex absorbs maximally at 600nm and the optical density is directly proportional to concentration of the test sample.

Assessment of creatinine in urine:

Method: Kinetic method.
Principle: Creatinine in alkaline solution reacts with plcrate to form a colored complex. The rate of complex formation was measured photometrically at 492nm.
Statistical analysis: The SPSS 15.0 (SPSS, Chicago, IL) statistical package was used for statistical analysis. All data were tabulated and comparisons of the different data were calculated. The relationship between the urine albumin: Creatinine ratio and the 24-h protein excretion was assessed with the Pearson correlation coefficient. An ROC curve was constructed to calculate sensitivity, specificity, and predictive values of the random urine albumin: Creatinine ratio at various cutoffs for prediction of significant proteinuria were estimated using the results from the 24-h urine collection as the gold standard. ROC curve is a graphical plot of the sensitivity vs (1_specificity) for a binary classifier system. It evaluates the prediction with sensitivity, specificity and area under ROC at varying discrimination thresholds.

Results

80 pregnant women, with an initial diagnosis of mild pre-eclampsia (blood pressure more than or equal to 140/90 mmHg plus presence of proteinuria 1+ or 2+, detected by dipsticks were enrolled, two were excluded because of incorrect sampling of urine for ACR measurement.

Among the 78 subjects included in the study we found out 7 cases were not pre-eclamptic, in spite of the fact that they were albumin + on dipstick at the start of the study, The strengths of the present review include our focus on mild pre-eclampsia and pregnant women admitted to hospital who reflect those seen in clinical practice for evaluation of proteinuria. These women had a wide range of proteinuria therefore the percentage of pre-eclamptic subjects in our sample was 91%.

The mean maternal age was 25.23 years (range, 18-37 years), mean gestational age was 29.75 years (range, 24-36 years), median of parity was 1(2), mean BMI was 24.8 kg/m2 (range, 22–28 Kg/m2). Serum creatinine values varied between 0.7-1.5 mg/dl, with a mean of 1.08mg/dl. Serum albumin values varied between 2 and 3.6 g/dl, with a mean of 2.77 g/dl, which is lower than the average for pregnant women. The morning systolic blood pressure on the day of the urine collections varied from 140 to 158 mmHg (mean, 150 mmHg) and the diastolic blood pressure varied from 90 to 105 mmHg (mean, 114 mmHg). The total volume of urine produced during the 24-hour collection varied between 600 and 3000 ml (mean, 1580 ml). The mean total protein was 1961.46±1683.02 mg/24h, and the urinary albumin/ creatinine ratio in random samples was 781.31+1041 mg/g creatinine, while in the morning sample urinary albumin/creatinine ratio was 886.43+1180.9 mg/g creatinine.

In order to evaluate the association between 24-hours total protein in urine and albumin/creatinine ration in both random and morning urine samples, scatter plot diagrams were plotted and correlation coefficients were calculated between those variables, there was a statistically significant positive correlation between total proteins in 24-hours urine and urine albumin/creatinine ratio in random sample and urine albumin/creatinine ratio in morning sample (table1 and figure 1,2).

Table 1. Pearson correlation coefficient between urine albumin/creatinine ratio (ACR) in random and morning samples and total protein in 24-hours urine.

	Total protein in 24-hours urine	
	R^2 value	P value
Urine ACR in random sample	0.191	<0.05
Urine ACR in morning sample	0.276	<0.05

ACR: Albumin/Creatinine ratio, p value < 0.05 is significant

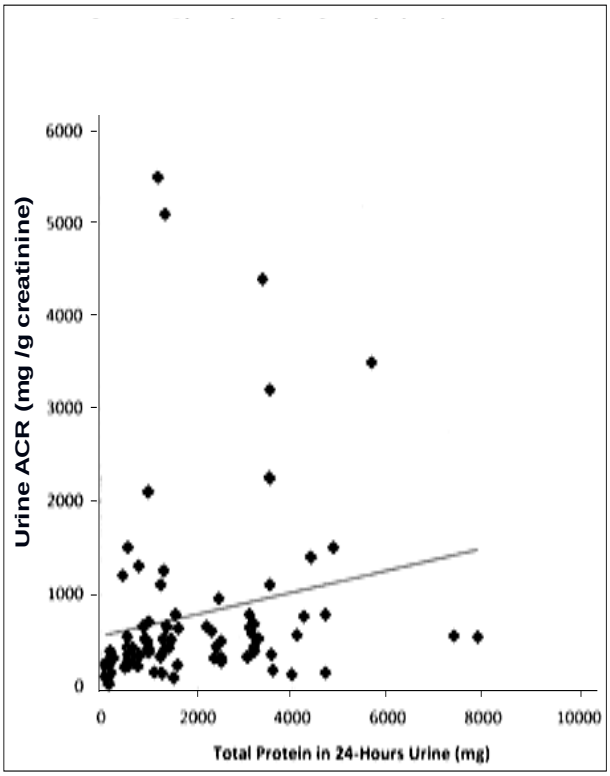

Fig. 1. Scatter plot showing correlation between total protein in 24-hours urine and random urinary albumin/creatinine ratio in all patients.

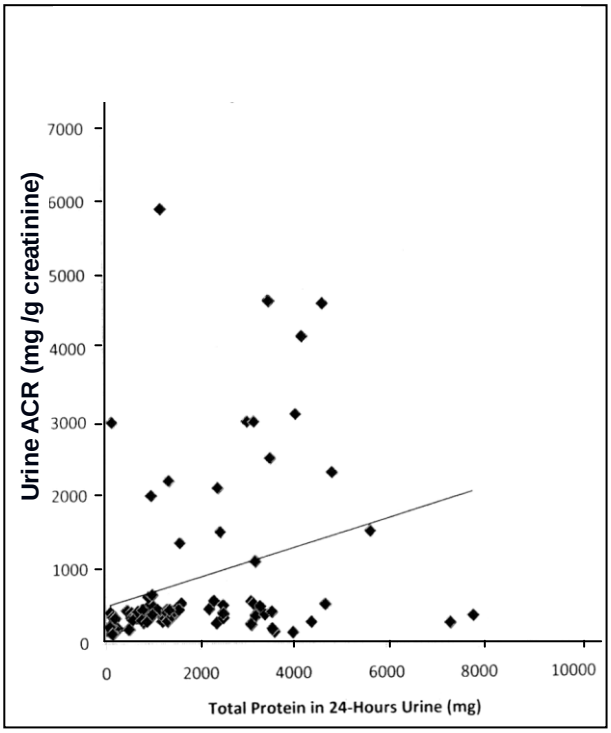

Fig. 2. Scatter plot showing correlation between total protein in 24-hours urine and morning urinary albumin/creatinine ratio in all patients.

Test result variables and ROC curve showed the best cutoff point for albumin/creatinine ratio in random sample was 262.5 mg /g creatinine with a sensitivity of 85.5% and a specificity of 81.8% figure 3.

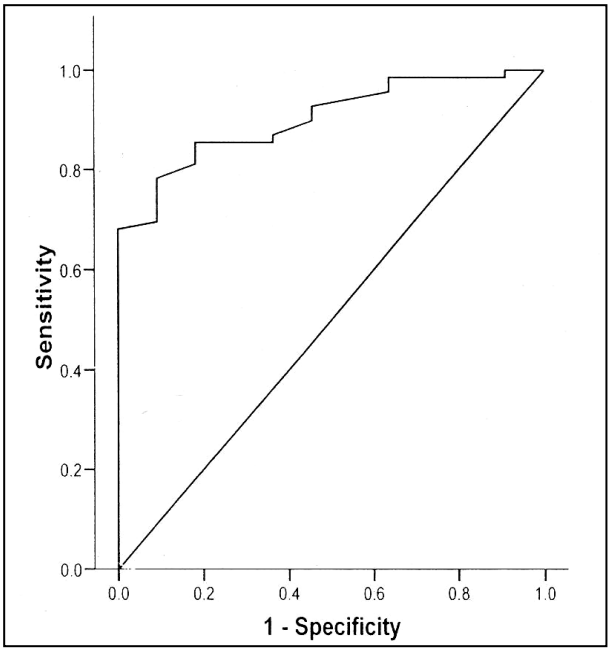

Fig. 3. ROC curve for albumin/creatinine ratio (ACR) in random urine sample**.**

AUC	*Standard error*	*Asymptomatic significance*	*Asymptomatic 95% CI*	
			Lower bound	*Upper bound*
0.902	0.031	<0.001	0.829	0.975

Test result variables and ROC curve showed the best cutoff point for albumin/creatinine ratio in morning sample was 240 mg/g creatinine with a sensitivity of 94.2% and a specificity of 63.6% figure 4.

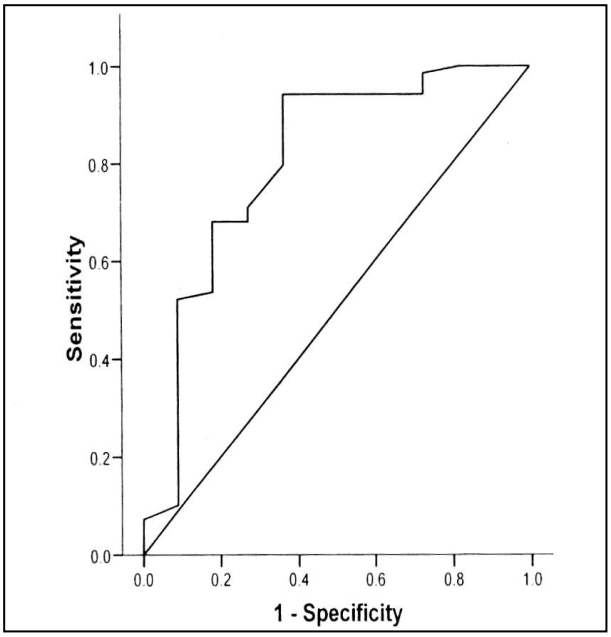

Fig. 4. ROC curve for albumin/creatinine ratio (ACR) in morning urine sample

AUC	*Standard error*	*Asymptomatic significance*	*Asymptomatic 95% CI*	
			Lower bound	Upper bound
0.801	0.084	<0.05	0.636	0.966

The best cutoff point for albumin/creatinine ratio (ACR) in random sample was 262.5 mg/g creatinine as shown in table 2 with a sensitivity of 85.5% and a specificity of 81.8%, the positive predictive value was 96.7% and negative predictive value was 47.4% (table 4).

Table 2. Sensitivity and 1- specificity (test result variables) for random albumin/creatinine ratio for detection of best cut off value.

Positive if greater than or equal to	*Sensitivity*	*1-specificity*	*Positive if greater than or equal to*	*Sensitivity*	*1-specificity*
24	1	1	515	0.52173913	0
60	1	0.909090909	530	0.47826074	0
97.5	1	0.909090909	545	0.449275362	0
102.5	0.985507246	0.727272727	555	0.434782609	0
117.5	0.985507246	0.636363636	565	0.420289855	0
137.5	0.971014493	0.636363636	585	0.405797101	0
147.5	0.956521739	0.636363636	615	0.391304348	0
152.5	0.942028986	0.545454545	635	0.376811594	0
165	0.927536262	0.454545455	645	0.362318841	0
192.5	0.913043478	0.454545455	665	0.31884058	0
215	0.898550725	0.454545455	690	0.304347826	0
225	0.869565217	0.363636364	730	0.289855072	0
235	0.855072464	0.363636364	770	0.275362319	0
247.5	0.855072464	0.272727273	865	0.231884058	0
262.5	0.855072464	0.181818182	1025	0.217391304	0
290	0.811594203	0.181818182	1150	0.188405797	0
315	0.782608696	0.090909091	1225	0.173913043	0
330	0.753623188	0.090909091	1275	0.15942029	0
345	0.724637681	0.090909091	1350	0.144927536	0
360	0.710144928	0.090909091	1450	0.130434783	0

375	0.695652174	0.090909091	1800	0.101449275	0
385	0.68115942	0	2175	0.086956522	0
400	0.666666667	0	2725	0.072463768	0
415	0.652173913	0	3350	0.057971014	0
422.5	0.623188406	0	3950	0.043478261	0
427.5	0.608695652	0	4750	0.028985507	0
460	0.579710145	0	5300	0.014492754	0
495	0.550724638	0	5501	0	0

While the best cutoff point for albumin/creatinine ratio in morning sample was 240 mg /g creatinine as shown in table 3 with a sensitivity of 94.2% and a specificity of 63.6%, the positive predictive value was 94.2% and negative predictive value was 63.6% (table 4).

Table 3. sensitivity and 1-sensitiviy (test result variables) for morning albumin/creatinine ratio for detection of best cut off value.

Positive if greater than or equal to	*Sensitivity*	*1-specificity*	*Positive if greater than or equal to*	*Sensitivity*	*1-specificity*
119	1	1	425	0.51739	0.090909
125	1	0.909091	435	0.492754	0.090909
135	1	0.818182	445	0.478261	0.090909
145	0.985507	0.727273	455	0.405797	0.090909
170	0.971014	0.727273	467.5	0.391304	0.090909
195	0.942029	0.727273	472.5	0.376812	0.090909
210	0.942029	0.545455	500	0.362319	0.090909
225	0.942029	0.454545	512	0.347826	0.090909
240	0.942029	0.363636	522	0.333333	0.090909
255	0.927536	0.363636	535	0.304348	0.090909
265	0.913043	0.363636	550	0.289855	0.090909
275	0.898551	0.363636	565	0.275362	0.090909
285	0.884058	0.363636	595	0.26087	0.090909
292.5	0.869565	0.363636	637.5	0.246377	0.090909
297.5	0.855072	0.363636	877.5	0.231884	0.090909
310	0.826087	0.363636	1227.5	0.217391	0.090909
330	0.797101	0.363636	1427.5	0.202899	0.090909
345	0.710145	0.272727	1750	0.173913	0.090909
352.5	0.681159	0.272727	2050	0.15942	0.090909
357.5	0.681159	0.181818	2150	0.144928	0.090909
362.5	0.666667	0.181818	2250	0.130435	0.090909
367.5	0.652174	0.181818	2400	0.115942	0.090909
375	0.637651	0.181818	2750	0.101449	0.090909
385	0.623188	0.181818	3050	0.072464	0
395	0.594203	0.181818	3627.5	0.057971	0
405	0.57971	0.181818	4377.5	0.043478	0
412.5	0550725	0.181818	4620	0.028986	0
417	0.536232	0.181818	5270	0.014493	0

Table 4. Diagnostic test characteristics of random albumin/creatinine ratio and morning albumin/creatinine ratio for diagnosing significant proteinuria in all included women.

	Sensitivity	*Specificity*	*Positive predictive value*	*Negative predictive value*
Random ACR cutoff point of 262.5mg per mg/dl	85.5%	81.8%	96.7%	47.4%
Morning ACR cutoff point of 240 mg per mg/dl	94.2%	63.6%	94.2%	63.6%

Discussion

Measurement of proteinuria is one of the most routinely undertaken laboratory procedures. It is mandatory in evaluating women with hypertensive disorders of pregnancy, and is necessary to establish the diagnosis of pre-eclampsia, as well as its severity. Urinary protein excretion during a 24-h period, however, is considered to be cumbersome and subject to error due to inadequate collection.

In the present study, we ensured the completeness of 24-h urine collection by excluding those samples in which the predicted and measured creatinine excretion did not agree (i.e., under or over collected samples). On the basis of an adequate 24-h urine collection to measure protein, we considered that the possibility of misclassification of a urine sample from a pregnant woman as positive or negative for significant proteinuria should be negligible.

This study aimed at assessment of urine albumin/creatinine ratio in detection of mild pre-eclampsia. As the use of quick test ACR could save time and possibly also be less expensive than conventional 24 hour albumin measurement. In the present study, all patients were admitted to the hospital and were at rest throughout the sampling period.

The power to identify correctly a difference of a certain size could be increased by increasing the sample size. Small samples often lead to type II errors (i.e. there is not sufficient power to detect differences of clinical importance); therefore, we increased the number of patients participating in our study to 80 patients.

Two cases were excluded from this study due to faulty collection of samples. The percentage of pre-eclamptic subjects in our study was 91% which is considered to be a high percent in comparison to other studies [13,14,16]; Ramos et al., had 46% pre-eclamptic patients in their study [16], Durnwald and Mercer had 76 % [14] and Al et al., had 21% [13].

Most of the studies collected the urine sample for random albumin/creatinine ratio measurement during the daytime and avoided the first void, a potential source of error [17]. Otherwise, random samples could be collected before the 24-hour sample [18], after the 24-hour sample [19] or either [20]. In the present study we measured both morning samples and another random sample taken any time during the day time (in the same day of 24 hour urine collection).

The variability of the albumin/creatinine ratio might be explained by the established variation in protein excretion with posture, with an increase in excretion in the erect position [17]. It is therefore also important to know the ambulatory status of the women. Our study was performed on women admitted to Ain Shams university maternity hospital and already diagnosed with pre-eclampsia. They all had moderate bed rest. Our results are only valid, for women with a similar regimen.

Previous studies have shown a strong correlation between random albumin/creatinine ratio and 24hour urine total protein level in women who underwent evaluation for pre-eclampsia. One study conducted in Mexico upon 927 pregnant women with new onset hypertension (87% of women), chronic hypertension with suspected pre-eclampsia (6%), or normal blood pressure (7%) where albumin/creatinine ratio was measured in a single random daytime urine sample (not first morning void). Researchers found out that protein excretion was more than 300 mg/24 hour in 30% of women and more than 2 g/24-hour in 8.8%. The correlation coefficient between the 24-hour urine protein measurements and the random urine albumin/creatinine ratio was 0.98. The area under the receiver operating characteristics curve was 0.998 for both criteria. The optimal albumin/creatinine ratio cut-point was 0.3 to detect significant proteinuria and 1.45 to detect severe proteinuria [21].

Alfredo et al., measured albumin/creatinine ratio in random urine samples and protein contents of 24 hour urine samples in a cross-sectional study of 927 hospitalized pregnant women at >20 weeks of gestational age. They found out that protein excretion was >300 mg/24 hour in 282 patients (30.4%). The urine albumin/creatinine ratio and the 24 hour protein excretion were significantly correlated. The cutoff value of albumin/creatinine ratio as an indicator of protein excretion more than 300 mg/24 hour was >300mg/g. The sensitivity and specificity were 98.2% and 98.8%, respectively. Positive and negative predictive values were 97.2% and 99.2%, respectively [22]. The results of the present study have shown similar results as we measured a significant positive correlation between random albumin/creatinine ratio and 24 hours urine total protein level in pre-eclamptic patients ($r=0.191$, $p<0.05$) in addition we found that albumin/creatinine ratio in morning samples also positively correlated with the 24 hour urine total protein level ($r=0.276$, $p<0.05$). For the random ACR the area under the receiver operating characteristics curve (ROC curve) was 0.902, meanwhile for morning ACR the area under ROC curve was 0.801.

A study conducted by Edimarlei et al., showed that urine ACR is strongly correlated with the 24- hour proteinuria at all four periods of the day as well as the first sample obtained on arrival. These findings were corroborated by the ROC curve in which the values of four day periods and that of the first sample were equal to or greater than 0.930. They concluded that in hypertensive pregnant women, the single voided urine sample albumin/creatinine ratio irrespective of sampling time is strongly correlated with the 24-hour proteinuria, as is the sample obtained on arrival [12]. This agrees with the results of our study as we measured random sample albumin/creatinine ratio and morning sample albumin/creatinine ratio and both were found to have significant positive correlation with 24 hours total proteinuria ($r = 0.191$, $p<0.05$) and ($r=0.276$, $p<0.05$) respectively.

Although a number of cutoff points for random abumin/creatinine ratio have been described previously, there is no universally accepted cutoff value for this test. Young et al., found no single value to distinguish ideally significant proteinuria after ROC analysis but found that a value of < 0.15 (150 mg/g) efficiently ruled out significant pregnancy-induced hypertension [20]. Rodriguez-Thompson and Lieberman performed ROC analysis and found a high area under the curve (0.91), but they were unable to identify a clear cutoff point for delineating significant proteinuria, they elected to use a cutoff point of 190 mg/g [18].

To determine a potentially more appropriate cutoff, the

present ROC analysis was performed and found no clear shoulder to the curve. To optimize sensitivity and specificity, we found 262.5 mg /g creatinine to be the "optimal" cutoff value for the random albumin/creatinine ratio in the detection of significant proteinuria, but this and the other cutoffs that were studied yielded a poor negative predictive value which suggested the lack of usefulness of this test for the exclusion of significant proteinuria when pre-eclampsia is suspected. Alternatively, the positive predictive value of a random albumin/creatinine ratio above any cutoff between 200 and 500 mg/g was high and did not vary greatly (86%-96%).

With the cutoff point that was used, we found that random albumin/creatinine ratio of < 262.5 mg /g creatinine accurately diagnoses significant proteinuria on 24-hour urine collection in most women. However, an abumin/creatinine ratio of < 262.5 mg/g failed to identify significant proteinuria in 7 of the cases.

A previous study suggested that most false-negative and false-positive results were within 50 mg of the 300-mg cutoff point for 24-hour urine protein levels and that no patients with proteinuria over 380 mg were missed [18]. However, we found a wide variation in the 24hour urine result for women with false-negative or false positive albumin/creatinine ratio.

Furthermore, our study confirms that maternal age, body size, gestational age, and parity are not confounding factors with regard to the urinary protein: creatinine ratio, a finding previously reported by Neithardt et al. [23].

Albumin/creatinine ratio is not an ideal diagnostic test to replace 24-hour urine collection for the diagnosis of preeclampsia. However, it can be used as a screening test for detection of significant proteinuria with high sensitivity 94%.

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