Value of Random Urinary Albumin-Creatinine Ratio in Detection of Proteinuria in Preeclampsia

Mohamed Elsayed Younes Elsayed Khalaf, Rahma Aly Mohamed Ahmed, Mahmoud Mahmoud Mohamed Abdelalim, Tamer Shawkey Gouda Ahmed*, Ezz El din Salama Abdel Atti El Sayed
Department of Obstetrics & Gynecology, Al Galaa Teaching Hospital, Cairo, Egypt
*Corresponding author: Tamer Shawkey Gouda Ahmed, **Mobile:** (+20) 01002066869, **E-Mail:** tamershw2y@gmail.com

ABSTRACT

Background: Outside of pregnancies, the protein-to and albumin-to creatinine ratios have been extensively investigated and applied. In most cases, these tests (rather than a 24-hour urine collection) are currently what the National Kidney Foundation advises for diagnosing proteinuria. The aim of the present study is to compare the diagnostic accuracy of the random urine albumin-creatinine ratio (ACR) to that of the gold standard, the 24-hour urinary protein, in patients with preeclampsia.

Patients and methods: At Said Galal Hospital, we enrolled 100 women who had been diagnosed with hypertension problems during pregnancy and were admitted for further diagnostic testing. Albumin 24 hour collection and albumin creatinine ratio (ACR) were measured for all participants.

Results: Albumin in a 24-hour urine collection was positively correlated with albumin-to-creatinine ratio in a random urine sample (r = 0.935, P <0.001). ACR of 303 mg/g creatinine was found to be the "ideal" cutoff value for the identification of substantial proteinuria with a sensitivity of 96% and a specificity of 92%. Albumin creatinine ratio cutoff value for predicting severe proteinuria in cases of preeclampsia was 2 gm/24hr. We found that cutoff value of >1238 mg/g creatinine had a sensitivity of 100% and a specificity of 86%.

Conclusion: Since ACR in random urine corresponds well with 24-hour urine protein, using it as a substitute was deemed appropriate. Thus, it can be used as a clinical screening test, benefiting from the fact that the ACR rarely changes significantly throughout the day, more easy and rapid method, not affected by urine concentration.

Keywords: Albumin-Creatinine Ratio, Proteinuria, Preeclampsia, Diagnostic Test.

INTRODUCTION

Common names for preeclampsia include defective placental angiogenesis, as well as pregnant hypertension with proteinuria [1].

Gestational hypertension, preeclampsia, eclampsia, a combination of preeclampsia and chronic hypertension, and chronic hypertension are the four types of hypertensive disorders that can occur during pregnancy [2].

In non-pregnant people, 150 mg/day is commonly regarded as the cutoff after which urine protein excretion is deemed excessive; nevertheless, both lower and higher levels have been recommended. These thresholds typically double during pregnancy, with 300 mg/day being the most common value [3].

Collection of urine over the course of 24 hours is considered the gold standard for measuring proteinuria, although it has significant drawbacks. Patient inconvenience, inaccuracy from under collection, and a wait of at least 24 hours for results are all issues with this method [4].

Spot urine protein-to-creatinine ratios (PCRs) or urine albumin-to-creatinine ratios (ACRs) are now the preferred procedures for evaluating proteinuria and albuminuria because they account for fluctuations in protein concentration caused by measuring creatinine at the same time [5].

There has been extensive research and clinical application of the spot protein: creatinine ratio and the spot albumin: creatinine ratio outside of pregnancy. Without mentioning pregnancy by name, the National Kidney Foundation now recommends these tests (instead of 24-hour urine collection) to identify proteinuria in most instances. Both NICE and SOMANZ endorse the spot protein-creatinine ratio test as a reliable way of detecting proteinuria in the general population [6].

Contradictory findings have been found while analyzing the efficacy of the spot PCR for use during pregnancy. High correlations between PCR and 24-hour collections have been used to justify its use by some researchers, while others have warned against using it too quickly because to the rapid decline in renal function that occurs in preeclampsia [7].

It has been recognized by a number of worldwide groups, such as the International Society for the Study of Hypertension in Pregnancy and the Society of Obstetric Medicine of Australia and New Zealand., and the Canadian obstetricians and gynecologists have agreed that the spot urine ACR is a reliable approach for diagnosing high proteinuria (> 0.3 g/24 h) in pregnant women [8].

The aim of the present study is to compare the diagnostic accuracy of the random urine ACR to that of the gold standard, the 24-hour urinary protein, in patients with preeclampsia.

PATIENTS AND METHODS
Patients:
At Said Galal Hospital, we enrolled 100 women who had been diagnosed with hypertension problems during pregnancy. All participants were admitted for further diagnostic testing.

Inclusion criteria: Age: 20-36 years, parity: any parity, and all pregnant women had resting blood pressure ≥ 140/90 mmHg after 20 weeks' gestation.

Exclusion criteria: Women who have been diagnosed with both a yeast infection and a UTI, preexisting renal disease, chronic hypertension with prior proteinuria (preexisting hypertension or sustained BP increase before 20 weeks of pregnancy), diabetes mellitus, and liver disease (by history and investigations).

Methods:
For all patients included in this study, the following was done:

1. Thorough history taking was taken from all patients. They were asked about last menstrual period, previous pregnancies and their outcomes, any symptoms suggesting of severe preeclampsia such as persistent headache, blurred vision, epigastric pain, etc… Also, they were asked about any symptoms to exclude any liver or kidney disease.

2. Full examination:

i. General examination: Blood pressure: Diastolic blood pressure of at least 90 mmHg and/or systolic blood pressure of at least 140 mmHg are the thresholds above which hypertension is diagnosed. It was measured by the auscultatory method by a stethoscope placed over anticubital artery. At least two readings, at least 6 hours apart, were taken to establish these readings. Having a blood pressure reading that is 30 mmHg higher than the patient's baseline or 15 mmHg higher than the patient's baseline, respectively, is no longer required as it has not been shown to be a useful prognostic indication. Finally, lower limbs were examined for edema and deep tendon reflexes.

ii. Abdominal examination: For epigastric and right hypochondrium tenderness.

Sample collection:
Urine samples were to be collected from all patients and placed in standardized containers. Total collecting period was 24 hours. Also, a random urine sample was taken during collection time (not first voiding sample) for calculation of random urinary albumin-creatinine ratio.

Daytime urination sparked the start of the 24-hour collection period. After a period of 24 hours, the samples were sent off for protein analysis. During the time of collection, blood was drawn for a complete blood count, liver function testing, and kidney function tests.

During the 24-hour urine collection period, a single void urine specimen (5 ml; not the initial sample) was taken at random. The single void samples were processed the following day after being stored at 4°C.

Albumin and creatinine levels in the urine were quantified. Urine albumin level (mg/dl) was measured by immuno-turbidity method. Urine creatinine was measured by fixed kinetic time method. Then the random urinary protein-creatinine ratio was calculated by the following equation.

ACR or the ratio of serum albumin to creatinine: it is the amount of albumin in the urine divided by the amount of creatinine in the urine, typically given as mg of albumin excreted per mg of creatinine.

$$ACR\ (mg/g) = \frac{\text{Microalbumin concentration (mg/dl)}}{\text{Creatinine concentration (mg/dl)}} x1000$$

ACR (1 mg/g = 1 μg/mg = 0.113 mg/mmol)

Ethical consent:
An approval of the study was obtained from Said Galal Hospital Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:
The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). In order to convey the findings, tables and graphs were employed. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi2$) or Chi-square for Linear Trend was done to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean, median, standard deviation, and confidence intervals. Independent samples t-test was used to compare between two independent groups of normally distributed variables. P-value ≤0.05 was considered significant.

RESULTS
Table 1 summarizes the demographic data of the participant women.

Table (1): Demographic data of included women.

Variable	Mean ± SD (range)
Age (years)	24.79 ± 4.72 (20 – 36)
Gestational age (weeks)	33.3 ± 4.2 (21.4-40)
BMI (kg/m²)	24.8 ± 1.1 (22-28.5)
Parity	2 (1 – 4) (0 – 5)

Table 2 shows that systolic blood pressure mean at the study beginning was 147.5 mmHg, diastolic blood pressure mean was 92.5 mmHg, and arterial blood pressure mean was 100.8 mmHg.

(2): Descriptive statistics of blood pressure in included women.

Variable	Mean ± SD (range)
Systolic arterial blood pressure (mmHg)	152.35±9.25 (140-170)
Diastolic arterial blood pressure (mmHg)	96.90±6.31 (90-110)
Mean arterial blood pressure (mmHg)	115.39±6.13 (106.7-130)

Table (3) shows that the mean albumin 24 hour collection was) 913.65 mg/24 hours and mean albumin creatinine was 1008.87 mg/g. Of the included 100 women, 42 (42%) women had a non-proteinuric pre-eclampsia, 37 (37%) women had mild proteinuria, and 21 (21%) women had severe proteinuria.

Table (3): Descriptive statistics of albumin 24 hour urine collection (mg/24 hours) and ACR in random urine sample.

Variable	Mean	SD
Albumin 24 hour collection (mg/24 hours)	913.65	217.47
Albumin creatinine (mg/g)	1008.87	244.4

Table 4 shows comparisons of blood pressure of the studied groups, with no significant differences between them.

Table (4): Comparisons between blood pressure of the studied groups.

Variable	Non proteinuric hypertension		Mild proteinuria		Severe proteinuria		One Way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F-test	P-value
Systolic	149.88	8.52	153.51	9.42	155.24	9.55	2.921	0.059
Diastolic	95.36	5.23	97.57	6.52	98.81	7.40	2.499	0.087
Mean	113.53	5.37	116.22	6.03	117.62	6.93	3.865	0.024

Table 5 shows that albumin in the 24-hour urine collection was correlated positively with ACR in the random urine sample ($r = 0.935$, $P < 0.001$), as shown in figure (1).

Table (5): Correlation between albumin 24 hour urine collection (mg/24 hours) and ACR in random urine sample.

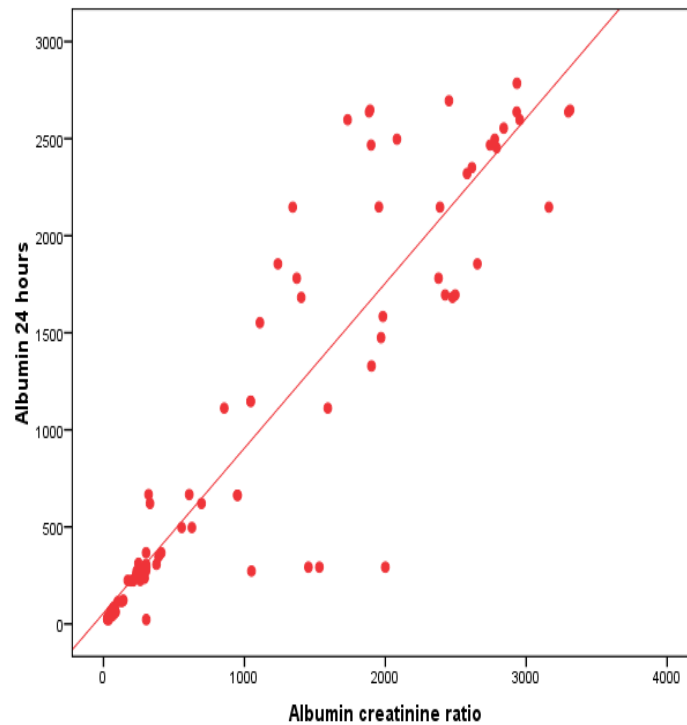| Variables	Albumin creatinine ratio	
	R	P-value
Albumin at 24 hours	0.935	< 0.001**

Figure (1): Correlation between albumin 24 hour urine collection and ACR in random urine sample.

A safe clinical application of the albumin/creatinine ratio as a prediction of substantial proteinuria requires that its cutoff value have optimal sensitivity and specificity. We determined that ACR of 303 mg/g creatinine was the "ideal" threshold value for the diagnosis of severe proteinuria, with a sensitivity of 96% and a specificity of 92% (Table 6).

Table (6): Prediction threshold for proteinuria based on albumin to creatinine ratio

Cut off point	AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value
>303 *	96.2	96.00	92.00	92.3	95.8

This threshold value (>1238 mg/g creatinine) was found to have a sensitivity of 100% and a specificity of 100%, when predicting substantial proteinuria in cases of severe preeclampsia (2 gm/24hr) was 86% (**Table 7 and Figure 2**).

Table (7): Proteinuria severity in severe preeclampsia predicted by albumin to creatinine ratio

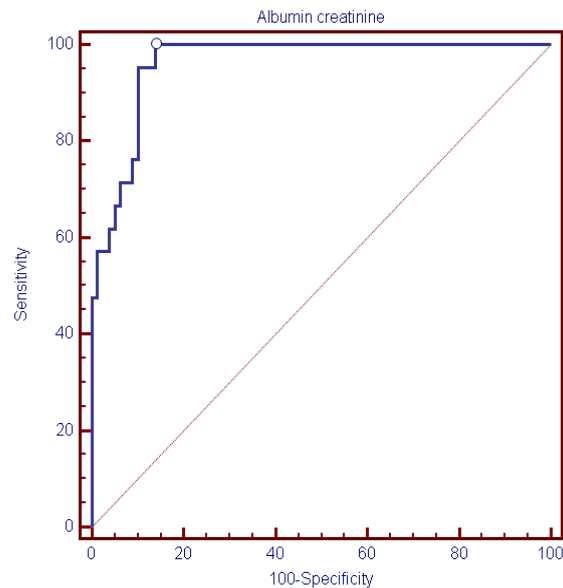| Cut off point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
>1238.67	100.00	86.08	65.6	100.0

Figure (2): ROC curve of severe proteinuria and ACR random sample.

DISCUSSION

Urinary total protein/albumin excretion is routinely checked in 24-hour samples when preeclampsia is suspected. Because there is significant fluctuation in urine protein concentration during the day, a 24-hour sample is required [9].

During pregnancy, there are significant alterations to the urine collecting system. Ureters, renal pelvices, and calyces enlarge, and the smooth muscle of the ureters becomes hypertrophied, while the connective tissue of the ureters also grows at an accelerated rate. This dilatation, which is typically more pronounced on the right side, can occur as early as the first trimester and is seen in over 90% of gravidas at term. Although the reasons why a pregnant woman's urinary tract might change are up for debate, the implications of these changes are not. The most crucial of these concerns the timing of urine collections for diagnostic purposes [3].

The primary objective of this diagnostic investigation was to compare the diagnostic accuracy of the random urine albumin-creatinine ratio to the gold standard 24-hour urinary protein in a sample of 100 pregnant women with preeclampsia at El-Galaa Maternity Hospital.

In the present study, urine albumin concentration (mg/dl) was measured by immuno-turbidity method.

Women were considered to have hypertensive disorders of pregnancy if they met the criteria of having a systolic arterial blood pressure of at least 140 mm Hg and a diastolic arterial blood pressure of at least 90 mm Hg, with or without proteinuria (detected by dipsticks).

Women mean age was 24.79 years, and the median parity was two. The recruitment mean gestational age was 33.3 weeks, and BMI mean value was 24.8.

Mean albumin 24 hour collection was 913.65 mg/24 hours and mean albumin creatinine was 1008.87 mg/g.

Of the included 100 women, 42 (42%) women had a non-proteinuric pre-eclampsia, 37 (37%) women had mild proteinuria and 21 (21%) women had severe proteinuria.

In our study, albumin in the 24-hour urine collection was correlated positively with ACR in the random urine sample (r = 0.935, p <0.001).

In our study, we determined that ACR of 303 mg/g creatinine was the "cut off" threshold value for the diagnosis of severe proteinuria, with a sensitivity of 95.8% and a specificity of 92%.

Our results were in great agreement with those of **Risberg et al.** [10] who in 19 hypertensive pregnant women discovered positive relationships (r=0.8-1.0) between ACR and 24-h albumin excretion.

Also, **Nisell et al.** [11] examined the use of this ratio in identifying patients with substantial albuminuria who may have preeclampsia. According to their findings, ACRs on spot urine can be used instead of the time-consuming 24-hour urine collection in most circumstances.

We also agreed with efforts of **Nisell et al.** [11] who discovered that a ratio of 27 mg albumin/mmol creatinine (238 mg/g creatinine) has 95% sensitivity and 100% specificity. This test had a perfect positive predictive value of 100% and an 86% negative predictive value.

Values of ACR at this gestational age were supposed to be much lower than our cutoff point as our study involves patients beyond 20 weeks (i.e. mid second trimester and third trimester) with normally higher excretion rates in these trimestres

in relation to late first trimester and early second trimester (12-20 weeks) in **Baweja** *et al.* [12] study.

Their higher cutoff point seems to be due to the used method of albumin measurement which is high-performance liquid chromatography (HPLC). Due to HPLC's ability to quantify both immunoreactive and immunounreactive intact albumin, it has been shown in studies to detect much higher levels of albumin in the urine than traditional tests.

In accordance with our results, **Haung** *et al.* [8] who evaluated the correlation between albuminuria as measured by ACR and the amount of albumin in a 24-hour urine collection in women with preeclampsia and found strong correlation between ACR and 24 hour protein which was in close intimate to our results (r = 0.938; P <0.001).

On the other hand, they disagreed with us regarding their lower cutoff values 22.8 mg/mmol (201 mg/g creatinine), this discordance seems to be owing to their study design as they divided patients into two groups, mild preeclampsia ($\geq$ 0.3 g protein in 24 hour) and severe preeclampsia ($\geq$ 2 g protein in 24 hour) so they stated another higher ACR values consistent with severe preeclampsia 155.6 mg/mmol (1376 mg/g creatinine). They also reported two results groups of sensitivity and specificity for mild and severe cases.

Against our study, **Wikstrom** *et al.* [9] who analysed the effect of potential confounders on the correlation between albuminuria as measured by ACR and amount of albumin in 24-hour urine samples in women with pre-eclampsia with significant albuminuria, and who determined the variability of ACR in single urine samples over the course of a 24-hour period.

Since the correlation between PCR or ACR of a single void sample and the 24-hour urine protein measurement is only poor (although correlation is evident P 0.01), they did not recommend using either method for quantifying proteinuria in women with obvious preeclampsia (Pearson correlation coefficient of 0.65). Therefore, they recommended 24-hour urine collection.

Despite the widespread advice to assess ACR, its use in clinical and research contexts is limited by the lack of agreed-upon standards for sample collection, ACR measurement, and reporting. However, due to inconsistencies in test reliability and prevalence between studies, the current body of evidence is insufficient to guide clinical application of the albumin to creatinine ratio. Furthermore, there is not enough data to reliably predict a negative pregnancy result.

In conclusion, since ACR in random urine corresponds well with 24-hour urine protein, using it as a substitute was deemed appropriate. So, it can be used as a clinical screening test, benefiting from the fact that the ACR rarely changes significantly throughout the day, more easy and rapid method not affected by urine concentration. A cut-off value of 303 mg/g creatinine can be used safely with high degree of sensitivity and powerful screening capability.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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