

Comparison of proteinuria diagnostic methods in pregnant patients

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Abstract

Objective: This study aimed to compare spot urine protein-to-creatinine ratio and 24-hour urine methods in pregnant patients and to evaluate the accuracy of spot urine protein-to-creatinine ratio against the reference standard 24-hour urine method.

Methods: This retrospective study included 399 pregnant patients diagnosed with proteinuria, gestational hypertension, or preeclampsia. Urinary protein concentrations were measured by spot dipstick urine analysis, spot urinary protein-to-creatinine, and 24-hour total proteinuria via 24-hour urine collection. The 24-hour total proteinuria measurement was accepted as the reference standard for diagnosis of proteinuria, and significant proteinuria was defined ≥ 300 mg of protein in the 24-hour urine collection.

Results: According to the receiver operating characteristics analysis of the spot urinary protein-to-creatinine ratio measurements, the cut-off value of the protein-to-creatinine ratio method was ≥ 0.443 mg protein/mg creatinine, the area under the curve was 0.887, the sensitivity was 77.14%, the specificity was 87.76%, and the accuracy was 84.96%. According to the receiver operating characteristics analysis of the 24-hour total proteinuria measurements, these values were >0.405 mg/day, 0.874, 82.86%, 84.64%, and 84.17%, respectively. No difference was observed between these two proteinuria methods regarding the receiver operating characteristics analysis ($p=0.475$). There was a strong and significant correlation between the spot urine protein-to-creatinine ratio and the 24-hour total proteinuria ($r=0.842$, $p<0.001$).

Conclusion: Our findings revealed that there was a strong and significant correlation between the spot urine protein-to-creatinine ratio and the 24-hour total proteinuria, and it may be used as an alternative to the 24-hour total proteinuria. In addition, the spot urine protein-to-creatinine ratio is noteworthy, especially in an emergency situation in pregnant women for whom the time is limited to make a rapid clinical decision.

Keywords: Proteinuria, diagnosis, pregnancy, urine protein-to-creatinine ratio.

Introduction

Proteinuria is a general term used to define proteins such as albumin and globulin in the urine with an amount greater than 150 mg per day, and it is utilized for the diagnosis, prognosis, and therapy of various clinical conditions including transient (e.g., fever, urinary tract infection, and pregnancy) and permanent (e.g., renal disease, diabetes mellitus, and cardiovascular disease) cases.^[1,2] The diagnosis of proteinuria in pregnancy plays a major role in maternity care since it is one of the main symptoms of preeclampsia which is a pregnan-

cy-specific disorder with the possibility of maternal and perinatal morbidity and mortality.^[3,4] The 24-hour urine collection has been well established and accepted as the reference standard for measuring urinary protein excretion.^[5-7] However, it has serious drawbacks such as being an inconvenient and costly method, delayed diagnosis, and incomplete collection possibility causing inexact results.^[6-8] Thus, researchers are studying on the development of simpler, quicker, and also reliable alternative methods for detecting proteinuria.^[6,9] One of these methods, the spot protein-to-creatinine (P/C) ratio has

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been recommended in the US National Kidney Foundation Guidelines.^[10] The use of the spot P/C ratio method has been reported in several studies and some have reported successful findings regarding the correlation with the 24-hour urine collection method,^[7,10-12] whereas others claimed inadequate prediction of proteinuria.^[6,8,13] Another widely used and basic method for urine screening is the dipstick method; however, it is not suggested for diagnosis in critical clinical cases, as it can provide imprecise or negative false data.^[6,14] Since, still, there is not a standardized method for detection of proteinuria, the awareness of clinicians for different laboratory techniques is crucial for the most convenient medical treatment.^[9]

This study aimed to compare the protein quantities determined via spot urine P/C ratio and 24-hour urine methods in pregnant women and to evaluate the accuracy of spot urine P/C ratio against the reference standard 24-hour urine method.

Methods

This retrospective study was conducted in Health Science University, Hamidiye Medical School, Başakşehir City Hospital, İstanbul, Türkiye, at the Department of Obstetrics & Gynecology and Division of Perinatology between May 2020 and February 2022 and included all pregnant women who were diagnosed with proteinuria, gestational hypertension, or preeclampsia. According to these criteria, 422 patients met the inclusion criteria and of these, 23 were excluded during the study due to the lack of 24-hour urine collection and/or P/C measurement. The patients were not recruited in the study more than once. The patients having systemic diseases likely to cause proteinuria and those having proteinuria before the pregnancy were excluded. In addition, the urine samples with >10 leucocytes or erythrocytes were excluded. Urinary protein concentrations were measured by spot dipstick urine analysis, spot urinary P/C, and 24-hour total proteinuria via 24-hour urine collection. Dipstick urine analysis was performed at admission and spot urine P/C measurement was carried out soon after 24-hour urine collection. In the spot dipstick urine analysis, values were displayed as negative (-), trace amount, +1, +2, and, +3. The cases with negative or trace amounts of proteinuria were accepted as negative proteinuria and the others were accepted as positive protein-

uria. The clean-catch method was used to collect the urine samples of the patients except for the severe cases where urethral catheter was utilized.

Protein and creatinine levels of spot urinary and 24-hour total proteinuria samples were measured using the turbidimetry technique with an autoanalyzer (Cobas 8000, c720 module, Roche, Basel, Switzerland). The laboratory technicians were blinded to the clinical conditions of the patients, and the magnitude ≥ 300 mg of proteinuria in the 24-hour urine collection was set as significant and positive for proteinuria. The 24-hour total proteinuria measurement was accepted as the reference standard for diagnosis of proteinuria in this study. The study was approved by the Ethics Committee of Health Science University, Hamidiye Medical School, Başakşehir City Hospital (date: 26.01.2022; approval number: 32). The study was carried out in accordance with the World Medical Association Declaration of Helsinki. Patient confidentiality was protected according to the universally accepted guidelines and rules.

Statistical analysis

Data analysis was performed using the MedCalc® (version 20.104, MedCalc Software Ltd., Ostend, Belgium) package software. A p-value of <0.05 was set as statistically significant. The descriptive statistical data were expressed as mean and minimum–maximum (range) for numerical variables. The discriminant cut-off values and threshold values, sensitivity and specificity of spot urine P/C ratio and 24-hour total proteinuria were calculated by receiver operating characteristic (ROC) curves. The evaluated prediction parameters were as follows: sensitivity, specificity, and AUC at varying discrimination thresholds. The least-square method using a single-slope linear model and Spearman's correlation test were used to analyze the relationship between P/C ratio and 24-hour total proteinuria. The comparison of the ROC analysis curves obtained with P/C ratio and 24-hour total proteinuria methods were evaluated using ROC curve analysis.

Results

The mean maternal age of the patients was 28.2 ± 4.8 years, the mean weight was 64.5 ± 9.4 kg, the mean height was 157.5 ± 8.4 cm, the mean gravity was 1.6 ± 0.9 , the mean parity was 0.5 ± 0.8 , and the mean gestational

age was 27.7 ± 3.8 weeks. The median spot urine P/C ratio was calculated 0.235 (0.2140–0.2706) g/day and the median 24-hour total proteinuria was found 0.282 (0.2500–0.3101) g/day.

According to the spot dipstick urine analysis of the patients, the rate was 45.61% for negative, 28.07% for trace amount, 9.78% for 1+, 6.76% for 2+, and 9.78% for 3+ values on dipstick test.

The ROC analysis of the P/C ratio proteinuria measurements are shown in **Fig. 1**. Accordingly, the cut-off value of the P/C ratio method was calculated ≥ 0.443 mg protein/mg creatinine, the area under the curve (AUC) was found 0.887, sensitivity was 77.14%, specificity was 87.76%, and accuracy was 84.96%. The ROC analysis of the 24-hour total proteinuria measurements is shown in **Fig. 2**. Accordingly, the cut-off value of the 24-hour total proteinuria method was calculated >0.405 mg/day, the AUC was found 0.874, sensitivity was 82.86%, specificity was 84.64%, and accuracy was 84.17%. There is no significant difference between these two proteinuria methods regarding ROC analysis

($p=0.475$). For various cut-off values of proteinuria in the 24-hour total proteinuria method, the corresponding cut-off, AUC, sensitivity and specificity values of the P/C ratio proteinuria method are summarized in **Table 1**.

The correlation analysis between the spot urine P/C ratio and the 24-hour total proteinuria and the formula are shown in **Fig. 3**. There was a strong and significant correlation between the spot urine P/C ratio and the 24-hour total proteinuria ($r=0.842$, $p<0.001$).

Discussion

The findings of the present study revealed that there was a strong and significant correlation between the spot urine P/C ratio and the 24-hour total proteinuria test results in parallel with previous studies^[7,11,12,15,16] with the range of the sensitivity between 81% and 90%, and specificity between 70% and 93%. In our study, similar values were obtained with the above-mentioned literatures with a sensitivity of 77.14% and

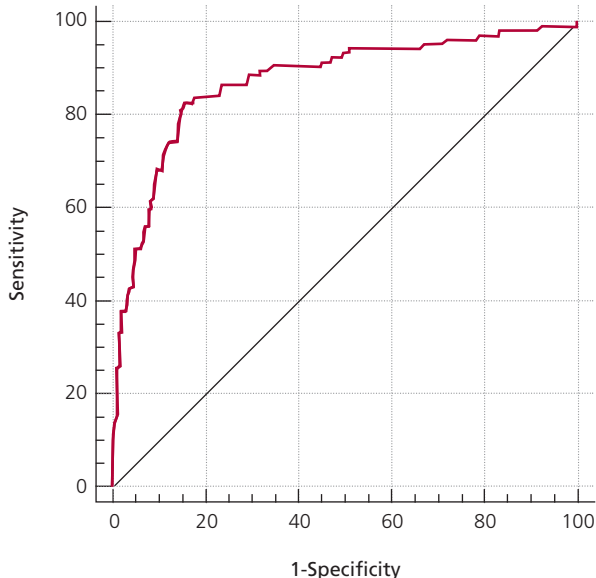


Fig. 1. The receiver operating characteristics (ROC) curve analysis of the protein-to-creatinine ratio (P/C) proteinuria measurements; cut-off value of the P/C ratio method was calculated ≥ 0.443 mg protein/mg creatinine [the area under the curve =0.887 (95% CI: 0.852–0.916; $p<0.001$); sensitivity was 77.14%, specificity was 87.76%, the negative predictive value was 91.48%, the positive predictive value was 69.23%, and accuracy was 84.96%.

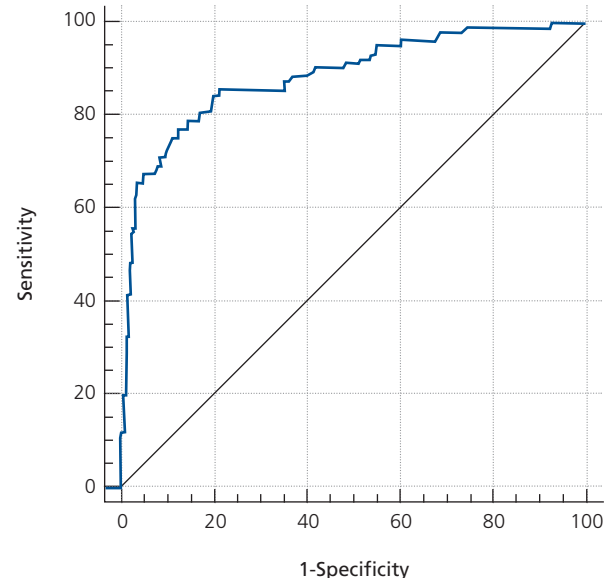


Fig. 2. The receiver operating characteristics (ROC) curve analysis of the 24-hour total proteinuria measurements; cut-off value of the protein-to-creatinine ratio method was calculated >0.405 mg/day mg protein/mg creatinine [the area under the curve =0.874 (95% CI: 0.838–0.905; $p<0.001$); sensitivity was 82.86%, specificity was 84.64%, the negative predictive value was 93.23%, the positive predictive value was 65.9%, and accuracy was 84.17%.

a specificity of 87.76% between the spot urine P/C ratio and 24-hour total proteinuria tests. For various cut-off values of proteinuria in the 24-hour total proteinuria method (Table 1), the corresponding cut-off, AUC, sensitivity, and specificity values of the P/C ratio proteinuria could be determined for the prediction of significant proteinuria which revealed increased sensitivity of spot urine P/C test with an increased protein threshold.

A significant and relatively high correlation was found between protein/creatinine ratio and total proteinuria in 24-hour urine ($r=0.722$; $p<0.001$). This correlation value was found to be similar to the results of some studies such as $r=0.80$ by Rodriguez-Thompson and Lieberman, $r=0.82$ by Kayatas et al., $r=0.94$ by Robert et al., and $r=0.81$ by Hossain et al.^[7,13,15,16] In our study, the area under the ROC curve was 0.887 (95% CI: 0.852–0.916) for P/C and 0.874 (95% CI: 0.838–0.905) for 24 hours. Both values are interpreted as good. The P/C value was similar to the results of some studies such as 0.91 by Rodriguez-Thompson and Lieberman, 0.91 by Kucukgoz et al., 0.74 (95% CI: 0.66–0.809) by Kayatas et al., and 0.90 (95% CI: 0.834–0.965) by Hossain et al., and they showed that this method can be applied successfully among different sample and patient groups.^[7,12,13,16]

Although the 24-hour urine test has been a reference standard for proteinuria management, a long urine collection period is a major issue, and also there are several patient-dependent variables such as diet and water intake affecting the results. Prolonged collection of urine may result in delayed diagnosis and treatment especially an emergency situation in pregnant women where time is limited to make a rapid clinical decision.

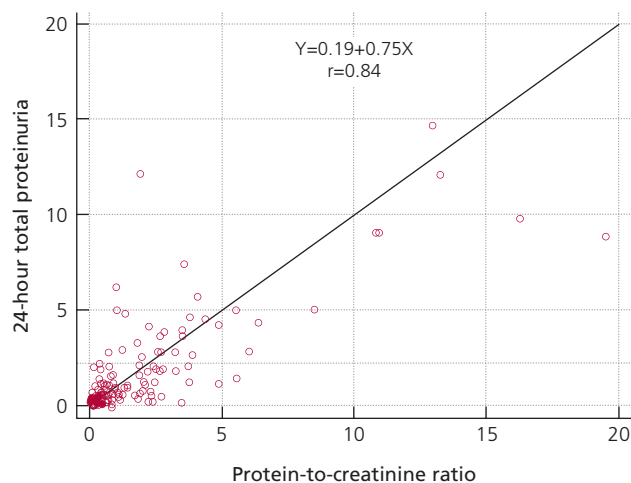


Fig. 3. The correlation analysis between the spot urine protein-to-creatinine ratio and the 24-hour total proteinuria.

Possibly prolonged hospital stays and inaccurate results due to incomplete collection are other drawbacks. Thus, a quicker, simpler, and low-cost urinary dipstick analysis is the most commonly used first-step tool for the diagnosis and management of preeclampsia.^[3,9,12] The spot protein-to-creatinine ratio is important for the clinicians with decision-making, such as determining a diagnosis or recommending a treatment for a patient.

The accuracy, sensitivity, specificity, and methodologic quality of dipstick urinalysis in pregnancy for predicting proteinuria are inadequate and can cause misdiagnosis.^[5,8,17] In a previous study, it was reported that 10% of the urine dipstick test results were falsely negative and 51% were falsely positive which may be due to the different reagents used and analytical phas-

Table 1. Discriminant spot urine protein-to-creatinine ratios for various proteinuria thresholds.

24-h urine total protein threshold mg/dL	AUC (95% CI)	Discriminant values of spot urine P/C ratio mg/mg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	p-value
≥300	0.887 (0.852–0.916)	>0.443	77.14 (67.9–84.8)	87.76 (83.5–91.3)	<0.0001
≥500	0.949 (0.915–0.977)	>0.425	77.13 (66.7–84.8)	87.07 (82.7–90.7)	<0.0001
≥1000	0.949 (0.912–0.981)	>0.515	71.43 (61.8–79.8)	90.48 (86.5–93.6)	<0.0001
≥2000	0.95 (0.924–0.969)	>0.675	67.62 (57.8–76.4)	94.56 (91.3–96.9)	<0.0001

AUC: area under the curve; P/C: protein-to-creatinine ratio.

es of the technique.^[14] Our results, in line with the literature, support the idea that the spot urine P/C test could replace the 24-hour urine collection as being not only a simpler and faster method like dipstick analysis, but also an accurate and reliable diagnostic tool for significant proteinuria in pregnancy.^[7,10,11] Furthermore, some study results have shown that the spot urine P/C test has even higher accuracy compared to the reference standard 24-hour urine collection.^[18] Contrary to these reports, there are some studies claiming that spot urine P/C test cannot be utilized as an alternative to 24-hour total protein analysis due to problems such as interlaboratory bias and lack of P/C test-specific universally accepted cutoff values.^[6,8,13] It should be noted that we do not claim that the spot urine P/C test should replace the standard 24-hour test. The present study demonstrates that spot urine P/C is an alternative, at least in pregnant women for whom prompt clinical judgment is required.

Since the sampling and scaling strategies for proteinuria have not been universally standardized yet, clinicians must be aware of different types of urinary proteins, laboratory tools, and urine handling techniques.^[9] Even though the alternative methods have not been agreed upon to completely replace 24-hour urine collection analysis, in a previous study spot urine P/C test or albumin-to-creatinine test provide an insight into the selection of prediction and evaluation methods for significant proteinuria in high-risk group patients.^[19]

The present study has several limitations which include being a single-center retrospective study and a lack of the comparison of these two methods regarding the severity of the proteinuria in patients with different diagnoses.

Conclusion

The findings of the present study revealed that there was a strong and significant correlation between the spot urine P/C ratio and the 24-hour total proteinuria test results suggesting spot urine P/C ratio as an alternative to the 24-hour total proteinuria test. The spot urine P/C ratio, as a quicker, simpler, and low-cost urinary dipstick analysis, is important for the clinicians with decision-making, such as determining a diagnosis, recommending a treatment or follow-up when managing these pregnant women, especially as outpatients.

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