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ORIGINAL ARTICLE

Does Proteinuria Measured by Dipstick Method Reflect Reality in Patients with Preeclampsia?

Preeklampsi Hastalarında Dipstick Yöntemiyle Ölçülen Proteinüri Gerçeği Yansıtıyor mu?

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ABSTRACT

Aim: The aim of our study is to compare the proteinuria levels measured by dipstick in complete urine analysis at admission with the proteinuria levels measured in 24-hour collected urine for patients hospitalized with a presumptive diagnosis of preeclampsia. By doing so, we intend to review the reliability of the widely used dipstick proteinuria in patients with preeclampsia.
Material and Methods: Urine specimens were obtained from 70 pregnant women visiting high-risk maternity centers at a third-level healthcare institution. Patients were divided into four groups based on their urine dipstick screening test results: negative, +1, +2, +3, and higher. Proteinuria was considered to be present if the urinary dipstick test showed +1 or higher, while protein levels measured in the 24-hour urine collection were considered to indicate proteinuria if they exceeded 300 mg. The degree of correlation between the urine dipstick test and both 24-hour urine samples and spot urine protein-to-creatinine ratio (Pr/Cr) was compared.
Results: The mean age of the 70 preeclampsia patients in the study group was 31.7±6.2, and the mean gestational age was 32.5±4.6. The dipstick test had a sensitivity of 81.4% and a specificity of 85.2%. The dipstick test results were grouped as 0, +1, +2, +3, and higher. Statistically significant differences were detected between the groups in terms of systolic blood pressure, diastolic blood pressure, the amount of protein in the 24-hour urine, and spot urine Pr/Cr ($p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). When examining the correlation between the urine dipstick test and both 24-hour urine samples and spot urine Pr/Cr, a moderate correlation was found ($r=0.65$, $p<0.001$, $r=0.55$, $p<0.001$, respectively).
Conclusion: In hypertensive pregnant individuals, urine dipstick tests demonstrated inadequate performance in ruling out preeclampsia. Consequently, according to our investigation, we posit that the dipstick urine test can be employed as a routine and reliable diagnostic tool for preeclampsia due to its rapid results and cost-effectiveness.

Keywords: Diagnostic test accuracy, dipstick, preeclampsia, proteinuria, sensitivity, specificity.

ÖZ

Amaç: Çalışmamızın amacı, preklampsi ön tanısıyla hastaneye yatırılan hastaların kabulde tam idrar analizi ile dipstick yöntemiyle ölçülen proteinüri seviyelerini, 24 saat toplanan idrarda ölçülen proteinüri seviyeleriyle karşılaştırmaktır. Bunu yaparak, preklampsili hastalarda yaygın olarak kullanılan dipstick proteinürisinin güvenilirliğini değerlendirmeyi amaçlamaktayız.
Materyal ve Metod: Üçüncü basamak sağlık kuruluşundaki yüksek riskli gebelik merkezlerini ziyaret eden 70 gebe kadından idrar örnekleri alındı. Hastalar, idrar dipstick tarama testi sonuçlarına göre dört gruba ayrıldı: negatif, +1, +2, +3 ve daha yüksek. İdrar dipstick testi +1 veya daha yüksek gösterdiğinde proteinüri var kabul edildi, 24 saatlik idrar toplama ile ölçülen protein seviyeleri ise 300 mg'ı aştığında proteinüriyi gösterdiği kabul edildi. İdrar dipstick testi ile hem 24 saatlik idrar örnekleri hem de anlık idrar protein/kreatinin oranı (Pr/Cr) arasındaki korelasyon derecesi karşılaştırıldı.
Bulgular: Çalışma grubundaki 70 preklampsi hastasının ortalama yaşı 31.7±6.2, ortalama gebelik yaşı ise 32.5±4.6 idi. Dipstick testinin %81.4 duyarlılık ve %85.2 özgüllük gösterdiği bulundu. Dipstick test sonuçları 0, +1, +2, +3 ve daha yüksek olarak gruplandırıldı. Sistolik kan basıncı, diyastolik kan basıncı, 24 saatlik idrarda protein miktarı ve anlık idrar Pr/Cr açısından gruplar arasında istatistiksel olarak anlamlı farklar tespit edildi (sırasıyla $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$). İdrar dipstick testi ile hem 24 saatlik idrar örnekleri hem de anlık idrar Pr/Cr arasındaki korelasyon incelendiğinde, orta derecede bir korelasyon saptandı (sırasıyla $r=0.65$, $p<0.001$, $r=0.55$, $p<0.001$).
Sonuç: Hipertansif gebelerde, idrar dipstick testlerinin preklampsiyi dışlama performansı yetersiz bulunmuştur. Sonuç olarak, araştırmamıza göre, hızlı sonuçları ve maliyet etkinliği nedeniyle idrar dipstick testinin preklampsi için rutin ve güvenilir bir tanı aracı olarak kullanılabileceğini öne sürmekteyiz.

Anahtar Kelimeler: Duyarlılık, dipstick, preeklampsi, proteinüri, tanı testi, özgüllük.

Introduction

Preeclampsia is a complex pregnancy-associated condition characterized by the emergence of hypertension and proteinuria following 20 weeks of gestation, impacting around 5-8% of pregnancies globally (1). This condition poses a significant risk to both maternal and fetal health with severe cases potentially leading to maternal organ dysfunction, preterm birth, intrauterine growth restriction and increased perinatal morbidity and mortality (2). Early detection and management of preeclampsia are crucial to reduce adverse pregnancy outcomes. Proteinuria, the presence of an abnormal level of protein in the urine, is a key diagnostic criterion for preeclampsia (Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis,

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and Management Recommendations for International Practice) (3). Various methods are available for measuring proteinuria, including the gold standard, 24-hour urine protein collection, as well as spot urine protein-to-creatinine ratio (Pr/Cr) and dipstick tests (4). The dipstick method is widely used in clinical practice due to its simplicity, rapid results, and cost-effectiveness (5).

However, the accuracy and reliability of the dipstick method in measuring proteinuria among patients with preeclampsia remain controversial. Some studies have reported high sensitivity and specificity for the dipstick test (6) while others have considered it less accurate compared to the gold standard (7). No dependable approach currently exists for proteinuria screening in pregnant individuals. Due to its affordability and user-friendliness, dipstick urinalysis for proteinuria screening is the prevalent method utilized for women with low or elevated risk of preeclampsia, and this technique is endorsed by international guidelines (8, 9).

In light of these conflicting findings, our study aims to evaluate the diagnostic accuracy of the dipstick method for proteinuria measurement in patients with preeclampsia and to determine its suitability as a reliable diagnostic tool in clinical settings.

Material and Methods

Study Design

This investigation encompassed all patients diagnosed with Preeclampsia (70 pregnant individuals) admitted to the Department of Obstetrics, Health Sciences University Kütahya, Turkiye, between May 2021 and January 2023. Study participants were within the 28 to 36 weeks of gestation range and had a singleton pregnancy affected by preeclampsia, but they did not have any co-existing medical conditions. Criteria for exclusion encompassed chronic secondary or essential hypertension, autoimmune diseases like autoimmune thyroiditis, diabetes mellitus, pre-existing kidney conditions, intrauterine fetal demise, multiple pregnancies, gestational diabetes, emergency cesarean section, presence of bacteria in urine, pregnancies resulting from assisted reproductive techniques and premature membrane rupture. The study received approval from the Ethics Committee at Kutahya Health Sciences University (no: 2020/08-08) and adhered to the principles of the Declaration of Helsinki. All participants submitted written informed consent for their involvement in the study.

Patients

Following clinical and laboratory assessments in accordance with the ISSHP classification, patients diagnosed with preeclampsia were categorized into four groups based on their urine dipstick test results: 0, +1, +2, and +3 or higher. The study flow diagram can be found in Figure 1, while the baseline characteristics of the study population are detailed in Table 1.

Preeclampsia (PE) was diagnosed in patients exhibiting increased blood pressure (based on 24-hour respiratory rate records) and the recent onset of proteinuria, specifically when resting blood pressure was ≥140/90 mmHg on two separate occasions at least 4 hours apart, and significant proteinuria was detected in urine samples. If proteinuria was not present, preeclampsia was identified in women with hypertension accompanied by thrombocytopenia (platelet count <150,000/μL), impaired liver function (doubling of typical liver aminotransferase blood levels), newly developed renal insufficiency (serum creatinine levels >1.02 mg/dL), pulmonary edema, recent cerebral or visual disruptions, or uteroplacental dysfunction, such as fetal growth restriction (FGR). FGR was ascertained by a fetal abdominal circumference/estimated fetal weight <10th percentile coupled with a pulsatility index in the umbilical artery >95th percentile, a pulsatility index in the uterine artery >95th percentile, an abdominal circumference/estimated fetal weight <3rd percentile, or a lack of end-diastolic flow in the umbilical artery (10).

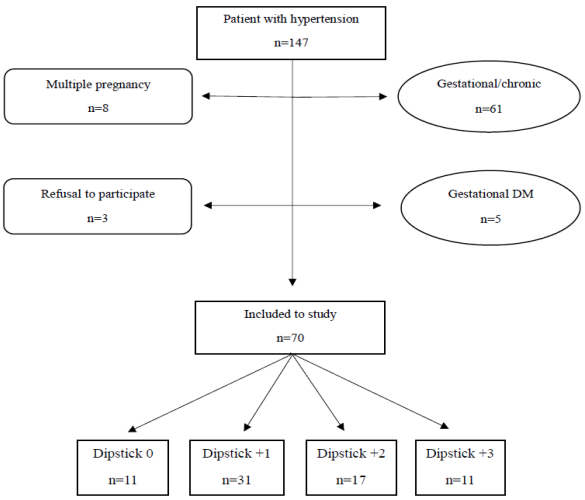

Figure 1. Study flow diagram. Patients were classified into four groups based on urine dipstick proteinuria assessment: Dipstcik non-proteinuria, +1, +2 and +3 proteinuria.

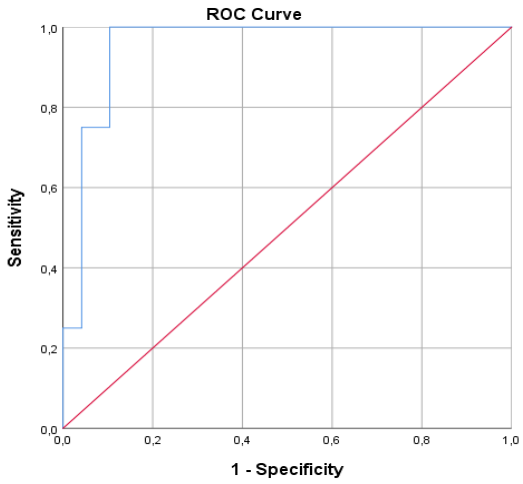

Figure 2. Correlation between the urine dipstick test and 24-hour urine protein

Table 1. Demographic and laboratory findings of the study group

	Study Group n=70
Age (year)	31.7±6.2
	32.0 [27.0; 37.0]
Parity	1.0±1.1
	1.0 [0.0; 2.0]
Gestational Age (week)	32.5±4.6
	34.0 [30.0; 36.0]
Systolic BP (mm/Hg)	146.6±15.8
	140.0 [140.0; 150.0]
Diastolic BP (mm/Hg)	89.6±10.6
	90.0 [80.0; 100.0]
Birth Weight (gr)	2670.8±660.1
	2800.0 [2320.0; 3100.0]
24h Urine Volume (mL)	2657.8±1088.2
	2550.0 [1835.0; 3475.0]
24h Urine Protein (mg)	670.0±760.2
	392.1 [178.5; 874.5]
Urine Dipstick	1.1±1.1
	1.0 [0.0; 2.0]
Urine Dansity	1030.6±119.5
	1016.0 [1008.0; 1022.0]
Urine Spot Cr (mg/dL)	77.4±38.5
	80.0 [50.0; 95.0]
Urine Spot Protein (mg)	40.3±66.5
	21.0 [8.0; 38.0]
Spot Urine Pr/Cr	0.5±0.6
	0.3 [0.2; 0.6]
Albumin (gr/dL)	3.0±0.4
	3.0 [2.8; 3.3]
Thrombocyte (10^3/µL)	218.4±63.3
	221.5 [166.0; 257.0]
AST (U/L)	76.2±278.4
	21.0 [16.0; 37.0]
ALT (U/L)	44.7±130.0
	13.0 [9.0; 19.0]
Direct Bil (mg/dL)	0.1±0.1
	0.1 [0.1; 0.1]
Ind Bil (mg/dL)	0.4±0.2
	0.3 [0.2; 0.5]

Values are presented as mean±SD, median [interquartile range], n; number, Abbreviations BP; Blood pressure, h; hours, Cr; Creatinin, Pr; Protein, AST; aspartate aminotransferase, ALT; alanine transaminase, Bil; Billirubi, Ind; Indirect.

Methods

Proteinuria evaluation involved the use of urine dipstick tests, spot urine Pr/Cr, and total protein measurements in 24-hour urine samples for each patient during their hospital stay. The urine dipstick test was conducted twice, with a positive result deemed significant. Following this, creatinine, AST, ALT, and complete blood count (CBC) were assessed. Serum and urine biochemical parameters were analyzed using the Architect analytical system (Abbott) while CBC was analyzed with the Sysmex analytical system (Sysmex). The urine dipstick test was carried out using the Iris urinalysis system (Beckman Coulter).

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was employed to assess normal distribution. For multiple comparisons of normally distributed data based on group, a one-way analysis was utilized, and the Tukey HSD test was applied for paired comparisons. The Kruskal Wallis test was used for multiple comparisons of non-normally distributed data according to group, and Bonferroni correction employed for paired comparisons. Quantitative data analysis results were reported as mean ± standard deviation and median [interquartile range] while categorical data were presented as frequency (percentage). A p-value below 0.05 was deemed statistically significant in all tests.

Results

During the period from May 2021 to January 2023, a total of 70 women were diagnosed with pre-eclampsia. Among them, 59 had proteinuric disease and 11 had non-proteinuric disease. Demographic and laboratory features of these 70 preeclamptic women are detailed in Table 1. The urine dipstick test was conducted on preeclamptic pregnant women to determine proteinuria levels. The results showed that 11 were non-proteinuric, 31 had +1 proteinuria, 17 had +2 proteinuria, and 11 had +3 proteinuria. The grouping of preeclamptic pregnant women based on urine dipstick results and their comparison with other proteinuria measurement methods are presented in Table 2.

Table 2. Comparison of Other Variables According to Urine Dipstick Protein Measurement

	Dipstick 0 n=11	Dipstick +1 n=31	Dipstick +2 n=17	Dipstick +3 n=11	p value
Systolic BP (mm/Hg)	142.6±10.9	144.5±6.9	144,1±9,4	163,6±28,0	0.001[a]
	140.0 [140.0; 150.0]	140.0 [140.0; 150.0]	140,0 [140,0; 150,0]	160,0 [140,0; 180,0]	
Diastolic BP (mm/Hg)	85.5±8.9	87,3±6,5	89,4±8,3	103,6±10,3	<0.001[b]
	80.0 [80.0; 90,0]	90,0 [80,0; 90,0]	90,0 [90,0; 90,0]	100,0 [100,0; 110,0]	
24h Urine Protein (mg)	262,3±189,6	683,3±667,0	900,4±612,6	2276,4±1252,2	<0.001[a]
	213,8 [133,7; 321,0]	439,5 [182,4; 874,0]	852,1 [456,0; 1015,0]	1831,3 [1572,8; 2980,0]	
Spot Urine Pr/Cr	0,2±0,3	0,6±0,6	0,5±0,5	1,4±0,7	<0.001[a]
	0,2 [0,1; 0,3]	0,4 [0,2; 0,8]	0,4 [0,2; 0,5]	1,1 [0,8; 2,2]	

Values are presented as mean±SD, median [interquartile range], Abbreviations; BP:Blood pressure, h:hours, Pr:protein, Cr:creatinin n; number. p-values were calculated with [a]One-way ANOVA or [b]Kruskal Wallis test. The significant pairwise group comparison results were as represented below; For systolic BP: 0 vs 3: p<0.0001, 1 vs 3: p=0.013, 2 vs 3: p=0.004, (Post Hoc test: Bonferroni), For Diastolic BP: 0 vs 3: p<0.001, 1 vs 3: p<0.001, 2 vs 3: p<0.001 (Post Hoc test: Tamhane's T2) For 24h Urine Protein: 0 vs 2: p=0.006, 0 vs 3: p<0.001, 1 vs 3: p<0.001, 2 vs 3: p<0.001 (Post Hoc test: Bonferroni), For Spot Urine Pr/Cr: 0 vs 3: p<0.001, 1 vs 3: p=0.009, 2 vs 3: p=0.001.

Proteinuria was evaluated using three different methods, namely urine dipstick test, spot urine Pr/Cr, and total protein in a 24-hour urine sample. In the preeclamptic group, 10% (7/70) of the patients had a falsely negative result on the urine dipstick test while 6% (4/70) had a false positive result. When compared to proteinuria in the 24-hour urine, the urine dipstick test had a sensitivity of 81% and a specificity of 85%. The correlation between the urine dipstick test values and 24h urine protein values is shown in Figure 2. There was a significant relationship between the urine dipstick test and the 24h urine protein, with a correlation rate of r=0.65, p<0.001. The area under the ROC curve (AUC) (Fig. 2) was 0.95. There was a significant relationship between the spot urine protein/creatinine and the 24h urine protein, with a correlation rate of r=0.77, p<0.001. When compared to proteinuria in the 24-hour urine, the spot urine Pr/Cr had a sensitivity of 88.4% and a specificity of 88.9%.

Preeclamptic patients were divided into 4 groups as urine dipstick test result 0,+1,+2,+3 and above. The groups were compared between themselves with the results of systolic BP, diastolic BP, 24h urine protein and spot urine Pr/Cr.

In the urine dipstick test groups, there is a statistically significant difference between the systolic blood pressure (BP) values (p=0.001). Upon conducting a subgroup analysis for systolic BP values, a statistically significant difference was observed between the dipstick test results of 0 and +3, +1 and +3, and +2 and +3 and above groups (p<0.001, 0.013, and 0.004, respectively). Furthermore, a statistically significant difference was found between diastolic BP values in the urine dipstick test groups (p<0.001). When performing a subgroup analysis for diastolic BP values, a statistically significant difference was noted between the dipstick test results of 0 and +3, +1 and +3, and +2 and +3 and above groups (p<0.001 for all three comparisons).

There is also statistically significant difference between the 24-hour urine protein values in the urine dipstick test groups (p<0.001). Upon examining the subgroup analysis for 24-hour urine protein values, there was statistically significant difference between the dipstick test results of 0 and +2, 0 and +3, +1 and +3, and +2 and +3 groups (p=0.006, <0.001, <0.001, and <0.001, respectively). Lastly, a statistically significant difference was observed between the spot urine Pr/Cr ratios in the urine dipstick test groups (p<0.001). When analyzing the subgroup analysis for spot urine Pr/Cr ratios, there was statistically significant difference between the dipstick test results of 0 and +3, +1 and +3, and +2 and +3 groups (p<0.001, 0.009, and 0.001, respectively).

Discussion

The primary objective of this study was to assess the reliability of the urine dipstick test in confirming significant proteinuria in pre-eclampsia as a diagnostic tool. Moreover, the study aimed to establish an optimal threshold for diagnosis confirmation. The results of this investigation indicate that the urine dipstick test can be an effective diagnostic tool for pre-eclampsia as it demonstrated a moderate correlation (r=0.65, p<0.001) with 24-hour urine protein and had an AUC of 0.95.

The dipstick analysis, which employs reagent strips for visual examination, offers a rapid, convenient and straightforward method. Nonetheless, urine samples are collected at different times throughout the day. This test presents challenges due to its relatively high rates of false positives and false negatives (6, 11, 12). As a result, it is typically succeeded by the gold standard test, the 24-hour urine collection, for verification. In the studied group, spot urine Pr/Cr ratio and urine dipstick test were both determined to be suitable for diagnosing preeclampsia. Their sensitivity and specificity levels were sufficiently high for accurately identifying preeclampsia patients. However, although the 24-hour urine test is deemed the gold standard for proteinuria assessment, the test is intricate, labor-intensive, and susceptible to pre-analytical errors (13). These factors may lead to patient noncompliance and discomfort. As demonstrated earlier, the spot urine Pr/Cr remains unaffected by fluctuations in urine concentration and the volume of urine excreted over a 24-hour period (14). Our research reveals that spot urine Pr/Cr is as useful as the 24-hour urine test for patients with preeclampsia. Moreover, a spot urine Pr/Cr threshold of 0.3 mg/dL aligns with proteinuria observed in the corresponding 24-hour urine sample.

In a meta-analysis comprising 19 studies by Teeuw et al., it has been demonstrated that, in pregnant women with suspicion of preeclampsia at or beyond the 20th gestational week, automated measurements of urine dipstick tests were more sensitive compared to manual assessments. They also discovered that the sensitivity of spot urine Pr/Cr measurements was similar to that of urine dipstick tests (15). In the January 2020 publication of the American College of Obstetricians and Gynecologists (ACOG) guideline titled "Gestational Hypertension and Preeclampsia," it has been shown that urine dipstick tests with +1 proteinuria yield false-positive results in 71% of cases, while +3 proteinuria leads to a 7% false-positive rate. The guideline suggests that adopting a threshold of +2 proteinuria for the diagnosis of proteinuria in preeclampsia, when compared to 24-hour urine collection results, would provide a more accurate assessment (16, 17). In our study, among 31 preeclamptic pregnant women with +1 proteinuria on urine dipstick tests, 4 were false-positive cases (13%). In a study examining the diagnostic performance of urine dipstick tests for the prediction of significant proteinuria in pregnancy, 2212 urine samples from 1033 women were analyzed. The false-positive rate for 1+ on the dipstick test was notably high at 78% (18). In our study involving 70 preeclamptic pregnant women, the false-positive rate for preeclamptic patients with a +1 urine dipstick test result, based on the 24-hour urine proteinuria findings, was found lower compared to the rates reported in the literature. Stefanska et al. found similar results to our study with 88 patients. In their investigation comparing two groups with preeclampsia and gestational hypertension, they discovered

that 9% (4/44) of the urine dipstick results were false positive in the preeclampsia group, consisting of 44 pregnant women (19). There are several factors that could contribute to the observed differences in false-positive rates between our study and the literature. First, variations in patient demographics, clinical characteristics and disease severity among the study populations may lead to different outcomes. Second, the possibility of random variation in the results, as sample size and statistical power can influence the observed rates. The lower false-positive rate observed in our study may be attributed to a smaller sample size or other factors unique to our study population.

Despite the high false-positive rates reported in the literature for the urine dipstick test, there is still a need for a rapid, economical, highly sensitive and specific test to detect the presence of proteinuria in pregnant women with suspected preeclampsia during the referral process (20). Although the 24-hour urine collection is the gold standard for diagnosing proteinuria, waiting for 24 hours in pregnant women with suspected preeclampsia can lead to delayed diagnosis. Therefore, in the past decade, the use of the spot urine Pr/Cr test has been increasingly adopted in clinics for rapid proteinuria diagnosis (21). In recent years, several studies have compared the efficacy of the spot urine Pr/Cr and the 24-hour urine test in diagnosing preeclampsia in pregnant women. In a meta-analysis by Geneen et al., which included 29 studies, a spot urine Pr/Cr threshold of 0.3 mg/dL demonstrated high diagnostic accuracy in identifying significant proteinuria when compared to the reference test of a 24-hour urine collection, with a sensitivity of 91% and specificity of 89% (22). In the same study, it was discovered that when using a PCR threshold above 60 mg/mmol, specificity remained consistently high (albeit with lower sensitivity), allowing for the identification of clinically significant proteinuria with a positive test result. Conversely, at a threshold below 30 mg/mmol, sensitivity was consistently high (despite lower specificity), enabling the exclusion of clinically significant proteinuria with a negative test result. The variability in results between 30 and 60 mg/mmol indicates a grey area, suggesting the potential necessity for repeated PCR testing within this range.

Limitation of our study is the small sample size consisting of a limited number of patients. Among the strengths of our research is the inclusion of only patients diagnosed with preeclampsia according to the ACOG criteria, and another strength is the separate evaluation and comparison of urine dipstick protein levels.

Conclusion

In conclusion; a key finding of our study is the significant correlation between the urine dipstick test, spot urine Pr/Cr and proteinuria in 24-hour urine samples. Although the latter serves as the gold standard for diagnosing proteinuria, it postpones the diagnosis by 24 hours, it is poorly tolerated by patients, and is unsuitable for emergency room settings. Timely decision-making can potentially alleviate patients' anxiety, decrease hospital stays, reduce associated costs, and facilitate the treatment of women with genuine pathological conditions.

Disclosure of interests

The authors declare that they have no conflict of interest.

Contribution to Authorship

CS and MMI conceived and designed the study; CS, performed the experiments, contributed reagents, materials and analysis tools, MMI analyzed the data, CS and MMI drafted the manuscript. CS participated in the writing of the final version of the manuscript.

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