Original Article

Establishing the diagnostic accuracy of point-of-care ratiometric urine protein:creatinine test with 24-h total protein measurement for preeclampsia

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Abstract:

INTRODUCTION: Preeclampsia, a multisystemic, multifactorial disorder, is the second leading cause of maternal deaths in the Philippines. It is diagnosed by the presence of hypertension and proteinuria or significant end-organ damage in a parturient carrying at least 20 weeks age of gestation. Proteinuria, in preeclampsia, is diagnosed by having 300 mg protein in a 24-h urine sample, a 0.3 mg/mg urine protein:creatinine ratio, or 2+ protein on a urine dipstick. All currently available diagnostic tests have their advantages and disadvantages. A novel diagnostic test, the spot ratiometric urine protein:creatinine dipstick test kit, was developed to meet the limitations of the currently available methods. Early diagnosis of preeclampsia will help in the prompt management to decrease maternal and neonatal complications.

OBJECTIVES: The objective of this study was to compare the diagnostic accuracy of the spot ratiometric urine protein:creatinine dipstick test (SUPCR) in comparison to 24-h urine protein (24HUP) in the diagnosis of preeclampsia.

MATERIALS AND METHODS: A non-experimental cross-sectional study comparing spot ratiometric urine protein:creatinine dipstick test (SUPCR) to 24HUP and urine dipstick among parturients with elevated blood pressure in a tertiary hospital to diagnose preeclampsia.

RESULTS: A total of 190 parturients were included. SUPCR showed a sensitivity of 88.36%, a specificity of 93.18%, and a likelihood ratio (LR) of 12.96. Urine dipstick (2+) showed a sensitivity of 26.03%, a specificity of 95.45%, and an LR of 5.73.

CONCLUSIONS: SUPCR can be an alternative to 24HUP in detecting preeclampsia among pregnant patients due to its high sensitivity, specificity, and LR values. This novel diagnostic can be used in low-resource settings due to its fast results, low cost, and ease of use.

Keywords:
24-h urine protein, preeclampsia, proteinuria, spot protein/creatinine ratio, urine dipstick

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Introduction

Hypertensive disorders of pregnancy (HDP) occur in 7.7% of reproductive-age women worldwide and cause 36.7% and 18% of maternal deaths in the Philippines and worldwide, respectively. Preeclampsia, a multisystemic, multifactorial disorder under HDP, is the leading and second-leading cause of maternal deaths worldwide and in the Philippines, respectively.[1] It accounts for 3.49% of total births and 50% of HDP. In a tertiary hospital in Manila, preeclampsia occurred in 2% of all the total deliveries in the year 2020.

Gestational hypertension is diagnosed with a systolic blood pressure of 140 and above or a diastolic blood pressure of 90 and above in a 20-week pregnant patient.

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Preeclampsia includes hypertension with proteinuria or significant end-organ damage in a parturient carrying at least 20 weeks age of gestation. Prompt diagnosis and institution of appropriate management are needed to prevent severe clinical complications of the disease. Proteinuria, though not 100% necessary to diagnose preeclampsia, should be screened in the first prenatal visit and upon diagnosis of hypertension[2] to rule out nonhypertensive kidney-related disorders and diagnose preeclampsia.

There are currently three accepted methods to diagnose proteinuria for preeclampsia, namely urine dipstick, urine protein:creatinine ratio, and 24-h urine protein (24HUP), each having its own advantages and limitations.[3] Proteinuria is diagnosed by having 300 mg of protein in a 24-h urine sample,[4] a 0.3 mg/mg urine protein:creatinine ratio, and 2+ on a urine dipstick.[5] 24HUP is considered the gold standard technique but is time-consuming, tedious, inconvenient, prone to errors, and may delay management.[1] It may only be available in secondary or tertiary-level settings.[4] Protein levels vary throughout the day. This may be affected by the amount of water taken and excreted, diet, physical activity, and even position and recumbency.[1] To answer this variability, laboratory-analyzed urine protein-to-creatinine ratios are not widely available; however, a timely, rapid, valid, accurate quantitative method was developed.[6] Finally, the least accurate but most used method in low-resource settings is the urine dipstick due to its wide availability, ease of use, and low cost.[4] Urine dipstick previously used a 1+ protein to diagnose proteinuria for preeclampsia, but the recent guidelines of ACOG in 2022 have increased the threshold to 2+. The result of a urine dipstick is also affected by the hydration status, similar to 24HUP.

A novel diagnostic test was developed to meet the limitations of the currently available methods. A spot ratiometric urine protein:creatinine dipstick test (SUPCR) to detect proteinuria for preeclampsia is similar to the already known urine dipstick test, with the addition of detection of creatinine. This low-cost urine dipstick test that detects both protein and creatinine was made in the year 2015 to improve the accuracy of detecting proteinuria by adjusting for urine dilution and in an attempt to normalize the protein measurement with creatinine measurement to account for the level of hydration of the patient. Results from this kit are available after 60 s from contact with the urine sample, allowing prompt diagnosis. The test has two detection pads, with color-changing chemical formulations to detect protein and creatinine levels. Once the color changes, this is compared with the easy-to-use reference color chart on the product label. A matrix table comparing the protein and creatinine levels is used to determine the specific protein–creatinine ratio to detect preeclampsia [Figure 1].[7]

This test will try to detect preeclampsia in comparison to the gold standard (24HUP), as well as urine dipstick, since this kit can also determine protein levels qualitatively. SUPCR has been studied by Zwisler *et al.*[8] and Gerth-Guyette *et al.*[7] in comparison with the reference clinical laboratory analyzer, with 82% and 50.7% sensitivity and 70% and 69.2% specificity, respectively.

Significance of the study

Preeclampsia is the second leading cause of maternal mortality in the Philippines and can be addressed by prompt diagnosis to prevent its severe clinical complications. A point-of-care diagnostic test is necessary to help in the early screening and detection of proteinuria for the diagnosis of preeclampsia, especially in low- to middle-income countries. The three current diagnostic tests available all have their own limitations, and this novel test aims to overcome these.

Due to the novelty of this test kit, there have been no published studies comparing its diagnostic accuracy with the usual methods of proteinuria detection in the Philippines and even worldwide. The only published studies available compared it to a reference clinical analyzer in detecting protein and creatinine levels and not with 24HUP, the gold standard.[7,8] This study aimed to answer whether this simple colorimetric urine protein-to-creatinine test can help diagnose preeclampsia by determining the diagnostic accuracy of the SUPCR with 24HUP.

Objectives
General objective
To determine the diagnostic accuracy of the SUPCR in comparison to 24HUP in the diagnosis of proteinuria for preeclampsia.

Specific objectives
1. To determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios (LRs) of SUPCR for proteinuria for preeclampsia
2. To determine the sensitivity, specificity, PPV, NPV, and LRs of urine dipstick 2+ and 1+ for proteinuria for preeclampsia.

Materials and Methods

Study design, area, and participants
A nonexperimental cross-sectional study was employed to establish the accuracy of SUPCR and urine dipstick (protein 2+) in comparison to 24HUP. The protocol was submitted to the institution's research ethics review board for approval. It was held in a Tertiary

Figure 1: Protein and creatinine reference values and matrix table to diagnose preeclampsia using spot urine protein-to-creatinine ratio

Hospital's Delivery Room, Pay and Service Division, a Level III accredited hospital for residency training by the Philippines Obstetrical and Gynecological Society. The source of study participants was chosen for accessibility and convenience to the researcher for data collection. The participants of the study were pregnant women who had their prenatal consults at this hospital. All participants were provided with written informed consent for their participation in the study.

Inclusion and exclusion criteria
All service outpatient and pay and service admitted pregnant women carrying a singleton gestation noted to have elevated blood pressure (systolic of 140mmHg or diastolic of 90mmHg) without other comorbidities and without prior evidence of proteinuria or end-organ damage, from January 2021 to April 2023, were included in the study. Those gravid women with chronic hypertension, immunologic diseases, preexisting renal disease, diabetes mellitus, symptomatic or asymptomatic bacteriuria, and multiple gestations were excluded from the study. As well as those who did not consent were also excluded.

Sample size computation and sampling technique

$$n = \frac{z^2 (p)(q)}{d^2}$$

where

n = sample size

z = z-deviate (1.96 for 95% confidence level)

p = prevalence of preeclampsia (Morris *et al.*[9] and institution's 2020 statistics)

$q = 1-p$

d = maximum tolerable error (2%)

$$n = \frac{(1.96)^2 (0.02)(0.98)}{(0.02)^2} = 188$$

A minimum of 188 pregnant women diagnosed with gestational hypertension by their attending physicians from both the pay and service divisions were required

to participate in the study. The researchers utilized convenience sampling and extended the intended sampling duration in an attempt to meet the sample size.

Method of data collection
All participants were tested for proteinuria using three different diagnostic tests, namely SUPCR, 24HUP, and urine dipstick. The time they were collected was recorded. A few patients were tested more than once; like those diagnosed with gestational hypertension, they were initially tested for proteinuria and, when negative, may be tested again at a later time in their pregnancy.

Only one urine sample was used for SUPCR and urine dipstick. The patient's urine, not the first voided specimen of the day, was collected once before the start of the 24HUP collection, and an aliquot was obtained for SUPCR. The test kit was dipped into the urine specimen; a color change was observed and compared to the reference protein and creatinine levels. After this, the researcher will compare the kit to the matrix table on the container to determine the presence of preeclampsia [Figure 1]. Only the primary investigator reads the SUPCR color chart to remove inter-observer bias.

The rest of the specimen was sent to the hospital's laboratory for a urine dipstick. After which, 24HUP collection was started and the sample was brought to the laboratory for quantitative protein determination.

Specimens for 24HUP were placed in the Beckman Coulter UniCel DxC 800, which made use of the biuret or Piotrowski's colorimetric method with cupric ions in an alkaline medium for protein quantification. These machines, according to the laboratory, undergo regular calibration, which included the time frame of the study.

For the urine dipstick, the hospital's laboratory made use of a test strip to measure the specific gravity, pH, protein, and sugar. This was done through an automatic laboratory analyzer. A positive urine dipstick result is when the protein value shows at least two ++ values.

All measurements except the spot SUPCR were done through the help of laboratory technicians who were blinded to the clinical conditions of the patients in the central laboratory of the hospital.

Potential biases and methods of control
No randomization was done, as all tests were applied to all subjects. The primary investigator read the result of the SUPCR and recorded it, even before the results of the 24HUP and urine dipstick, to lessen the risk of observer bias, even though the clinical information was available to the reader of the index test. The results of SUPCR, as well as the clinical data of participants, were not available to laboratory technicians reading the urine dipstick and 24HUP results.

Data processing and analysis
Statistical analysis was done using the RStudio statistical package.

The sensitivity, specificity, PPV, NPV, and LRs of SUPCR and urine dipstick for prediction of significant proteinuria were computed using the results of the 24HUP as the gold standard. This was done using two-by-two tables [Table 1].

Results

There were a total of 190 study participants, and all were included in the analysis. The study population showed a mean age value of 31 years old, with the majority married, carrying a term gestation at 38–39 weeks, with no prior history of gestational hypertension, preeclampsia, or eclampsia in her previous pregnancy/ies. Patients in the gestational hypertension group were mostly in the 1–4 parity group, whereas the preeclampsia group was nulliparous [Table 2].

Table 1 shows the different true positives, true negatives, false positives, and false negatives for SUPCR and urine dipstick compared to the gold standard (24HUP).

Table 3 shows the specificity (88.36%), sensitivity (93.18%), PPV (97.73%), NPV (29.31%), LR+ (12.96), and LR− (0.12)

Table 1: 2×2 table for spot urine protein-to-creatinine ratio with 24-h urine protein and urine dipstick with 24-h urine protein

Diagnostic Test Result	24HUP		Diagnostic Test Total
	Positive	Negative	
SUPCR			
Positive	129	3	132
Negative	17	41	58
Reference Standard Total	146	44	190
Urine dipstick (2+)			
Positive	38	2	40
Negative	108	42	150
Reference Standard Total	146	44	190
Urine dipstick (1+)			
Positive	59	6	65
Negative	87	38	125
Reference Standard Total	146	44	190

24HUP: 24-h urine protein, SUPCR: Spot urine protein-to-creatinine ratio

Table 2: Characteristics of pregnant patients (*n*=190)

Mean/modal characteristics of pregnant patients	Gestational hypertension - Diagnosed negative by the gold standard, the 24-h protein	Preeclampsia - Diagnosed positive by the gold standard, the 24-h protein
Total patients (190)	45	145
Maternal age (years)	30.75556	31.6069
Marital status		
Single	10	62
Married	35	81
Separated	-	2
Mean gestational age	38 2/7	38
Previous gestational hypertension		
No	38	126
Yes	7	19
Previous preeclampsia		
No	44	131
Yes	1	14
Previous eclampsia		
No	45	142
Yes	-	3
Parity		
0	18	79
1–4	21	52
>4	6	15

Table 3: Performance of spot urine protein-to-creatinine ratio and urine dipstick (2+and 1+) compared to 24-h urine protein as a reference

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
SUPCR	88.36	93.18	97.73	29.31	12.96	0.12
Urine dipstick (2+)	26.03	95.45	95.00	72.00	5.73	0.77
Urine dipstick (1+)	40.41	86.36	90.77	69.60	2.96	0.69

PPV: Positive predictive value, NPV: Negative predictive value, LR: Likelihood ratio, SUPCR: Spot urine protein-to-creatinine ratio

of SUPCR. Urine dipstick (2+), on the other hand, had a specificity (26.03%), sensitivity (95.45), PPV (95%), NPV (72%), LR+ (5.73), and LR− (0.77).

Discussion

There have been several studies on the comparison of the different methods to diagnose proteinuria for preeclampsia, mostly between 24HUP and urine protein and creatinine ratio. SUPCR is a novel point-of-care test, similar to a urine dipstick, that can be made widely available in remote areas to promptly diagnose proteinuria for preeclampsia. This study tested SUPCR in comparison to the gold standard, 24HUP, and the results showed high sensitivity (88.36%) and specificity (93.18%) for SUPCR.

Zwisler *et al.*[8] studied this test by comparing it with the reference clinical laboratory analyzer but not with 24HUP. The test had 85% sensitivity and 71% specificity for the kit in determining protein and creatinine levels, not for determining proteinuria for preeclampsia. Gerth-Guyette *et al.*,[7] on the other hand, used this test in Ghana as a point-of-care test, obtaining a 50.7% sensitivity and 69.2% specificity against a laboratory test

analyzer. The sensitivity values cannot be compared due to the different types of studies. However, with the high sensitivity and specificity from the results of this study, this test can help rule in preeclampsia. Its false-negative rate is 11.64%, meaning only 12% of cases are misdiagnosed with not having preeclampsia. The false-positive rate is 6.82%, having only 7% of cases misdiagnosed to be preeclamptic when they are not. Since the aim is to make use of SUPCR as a point-of-care test to diagnose preeclampsia and give timely management, this kit is a potential alternative to the current diagnostic methods.

SUPCR showed a high PPV (97.73%), meaning the patient who tests positive for proteinuria using SUPCR has a high probability of having preeclampsia, whereas the low NPV (29.31%) of the test means that it lacks the strength to determine those who are truly nonpreeclamptic. Due to the high sensitivity, specificity, and PPV, SUPCR is a potential tool to timely determine patients who are preeclamptic even at primary care settings.

There have been a lot of studies comparing urine dipstick with 24HUP; these mostly diagnosed proteinuria with

a +1 value. In this study, the cutoff value of protein +2 was used as suggested by ACOG (2022).[5] Urine dipstick (2+) showed a low sensitivity (26.03%) but high specificity (95.45%), even higher than SUPCR. The time interval between the SUPCR test and the urine dipstick and 24HUP tests was not measured; hence, conclusions on time affecting urine dipstick test results could not be made. Rest assured, the urine samples were immediately brought to the laboratory within the required time frame of the laboratory after the SUPCR test, which is 30 min to 1 h.

A meta-analysis done by Teeuw et al.[10] showed sensitivity and specificity values of 68% and 85% for a +1 threshold, respectively. Although initially not part of the study, diagnostic accuracy using a 1+ threshold for urine dipstick was also calculated. This showed a sensitivity of 40.41% and a specificity of 86.36%, which were comparable to the results of Teeuw et al. They concluded urine dipstick to perform poorly at excluding preeclampsia, which this study concurs.

Comparing urine dipstick 2+ and 1+ in relation to the diagnosis of preeclampsia, the results of a lower sensitivity and higher specificity for the urine dipstick 2+ are expected due to the more stringent criteria of needing a 2+ protein in urine dipstick to diagnose preeclampsia.

Comparing urine dipstick (2+) with SUPCR, the former was more specific, while the latter was more sensitive. The two dipstick tests are very similar to each other, making use of dipsticks to detect protein levels. The SUPCR only detects two things, protein and creatinine, while a urine dipstick detects a lot more than just protein levels. The advantage of SUPCR over dipstick is the use of creatinine levels to account for the hydration status of the patient, which is not present in urine dipstick.

This novel test may help remote areas in diagnosing proteinuria by replacing urine dipstick as a screening test. The SUPCR test is priced at 240 per strip, in comparison to the urine dipstick, which is 40–100 per strip. Although at a higher price, SUPCR may be a possible point-of-care screening tool for preeclampsia, especially in remote areas without 24HUP since it has a high sensitivity, specificity, and PPV, in relation to the gold standard.

Conclusions

SUPCR showed high sensitivity, specificity, PPV, and LR+ values and may be used as a potential new screening tool for proteinuria for preeclampsia, especially in low-resource areas where the gold standard is not easily accessible.

This novel test may also replace dipstick as a relatively low-cost, easy-to-use, point-of-care test to diagnose proteinuria for preeclampsia due to its higher LR, especially with the edge of adding creatinine levels to account for the hydration status of the patient.

Limitation
The study had 190 participants. This is sufficient, as it is still more than the minimum sample size required by the tests employed. A limitation of the study is not comparing the test kit with the urine protein-to-creatinine test done in the laboratory.

Recommendation
It is recommended to conduct a better version of the research with the following changes. Random sampling is advised to minimize sampling bias. Since the chosen population size is relatively small, the study should be spread out for double the study length, around four years, to allow for randomization.[7] Since the current sample is limited to qualified patients admitted at a tertiary hospital in Manila, the population is gestational hypertensive and preeclamptic patients at this hospital. Conclusions from this study may not be appropriate to generalize and describe the larger population of all gestational hypertensive and preeclamptic women in the country; hence, a multicenter study is recommended.

Authorship contributions
Zabrina T. Cua-Lam, M.D. - Involved in the conceptualization, methodology, formal analysis, data curation, writing of the original draft, review and editing, visualization, funding acquisition.

Catherine Joie Carelle R. Ong, M.D. - Involved in conceptualization, resources, review and editing of the draft.

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Conflicts of interest
There are no conflicts of interest.

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