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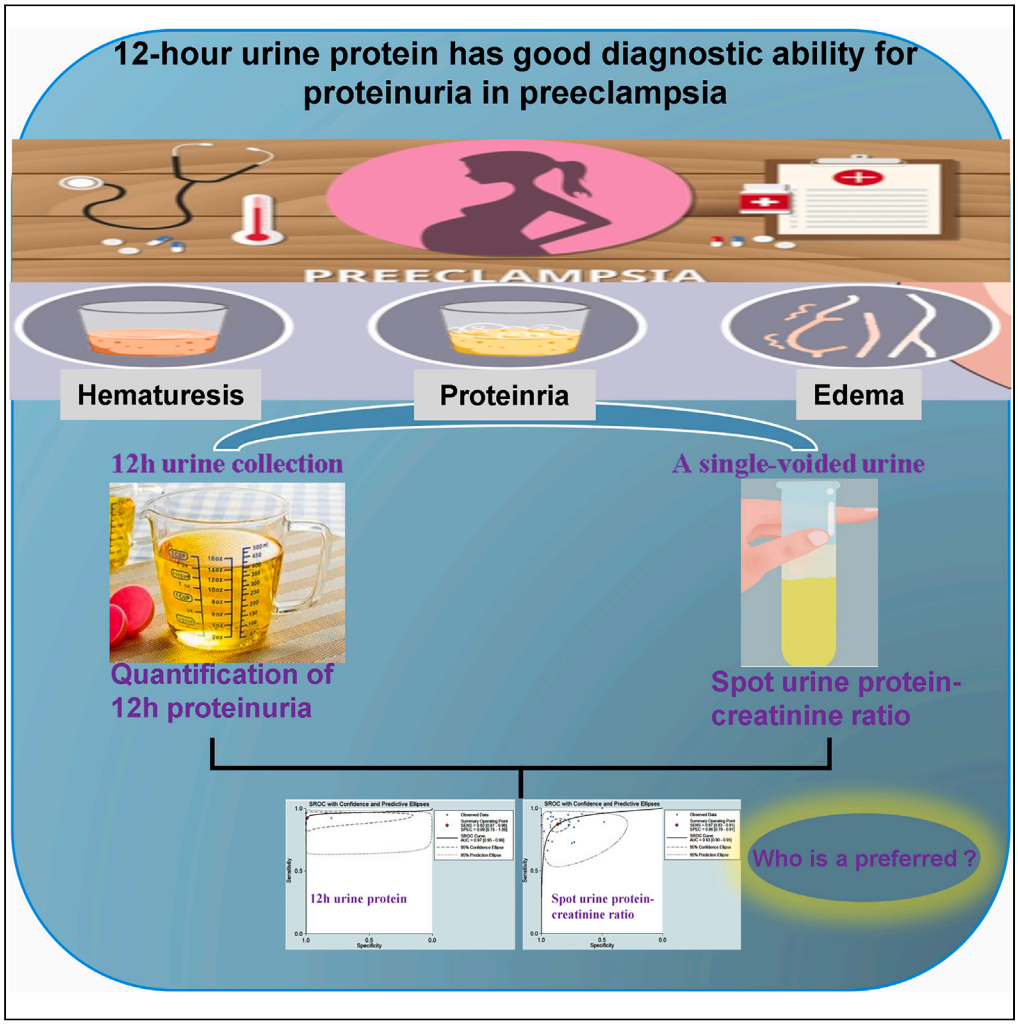

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Highlights

The 12-h proteinuria shows good clinical value for diagnosis of preeclampsia

12 h urine collection is reasonable for detection of proteinuria in preeclampsia

Spot urinary PCR shows promising diagnostic value for certain preeclampsia patients

Tian et al., iScience 27, 109026
February 16, 2024
https://doi.org/10.1016/j.isci.2024.109026

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A meta-analysis on diagnostic accuracy of spot urinary protein to creatinine ratio versus 12-h proteinuria in preeclampsia

Ming Tian,[1] Ming Chen,[1,4,*] Luyan Huang,[2,4,*] and Qingquan Liu[3,4,5,*]

SUMMARY

To systematically review the diagnostic accuracy of spot urinary protein to creatinine ratio (PCR) and 12-h proteinuria in preeclampsia and to estimate which is a preferred alternative method for 24-h proteinuria, we carried out this meta-analysis. 25 primary studies were included based on searching strategy. For spot urinary PCR, our results showed pooled sensitivity of 87% (95% confidence interval [CI] 83%–91%) and specificity of 86% (95% CI 79%–91%), with an area under curve (AUC) of 0.93 (0.90–0.95). For 12-h proteinuria, pooled sensitivity and specificity were 92% (95% CI 87%–96%) and 99% (95% CI 75%–100%), respectively, with an AUC of 0.97 (0.95–0.98). Fagan plot and likelihood ratio scattergram showed that 12-h proteinuria yielded a better discriminatory performance on diagnosis of proteinuria (≥0.3 g/24 h). These results indicated that 12-h proteinuria estimation shows better clinical value than spot urine PCR for diagnosis of preeclampsia. However, due to the severity of condition and the fact that preeclampsia patients cannot wait for 12 h, spot urine PCR can be used as one of the diagnostic indicators.

INTRODUCTION

Preeclampsia is a common cause of adverse maternal and perinatal complications which occurs in up to 2%–8% of all pregnancies.[1,2] It is determined by the occurrence of hypertension accompanied with significant proteinuria (≥0.3 g/24 h) developing after 20th week of gestation in a previously normotensive, non-proteinuric patient.[3,4] Even though proteinuria previously as a main point of diagnosis for preeclampsia was discarded by the American College of Obstetricians and Gynecologists Task Force if there are other suggestive findings of end organ involvement (thrombocytopenia, elevated liver transaminases, renal insufficiency, pulmonary edema, or new-onset neurologic symptoms),[5] accurate detection of proteinuria still remains necessary in the absence of these severe features.

Traditional test for quantifying proteinuria is the 24-h urine collection, when significant proteinuria is defined as proteinuria of 0.3 g/day or more. However, urine collection over 24 h is cumbersome, inconvenient, and time-consuming which may delay the best treatment opportunity. Moreover, this "gold standard" for total protein estimation is also not without errors, the most obvious being variable and incomplete collection. Due to the high mortality of patients with preeclampsia, a rapid and reliable diagnosis is mandatory. These include urinary dipsticks, urine collections over a shorter period, and the urinary spot protein to creatinine ratio (PCR). Although dipsticks appears as a quick and inexpensive method for detecting proteinuria, inaccuracy exists with both high false-positive[6] and false-negative rates.[7] Meanwhile, more and more studies and guidelines have suggested to use a shorter-timed urine collection or spot PCR for diagnosis of preeclampsia in pregnancy.[8,9]

Urinary spot PCR compares the urine protein excretion to urine creatinine excretion, accordingly normalizing protein excretion to the glomerular filtration rate. Therefore, spot PCR avoids the varying results of spot protein excretion. In addition, urinary spot PCR had been proposed as an alternative of 24-h urine collection by The Australasian Society for the Study of Hypertension in Pregnancy and the International Society for the Study of Hypertension in Pregnancy.[10] A 12-h urine collection shortens the diagnostic span, thereby possibly becoming another alternative test.

Several studies have shown that urinary spot PCR[11,12] or 12-h urine collection[13,14] correlated well with 24-h urine collection. We performed this systematic review and meta-analysis to evaluate the diagnostic utility of urinary spot PCR and 12-h urine collection and to estimate which is a preferred alternative method for 24-h urine collection.

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https://doi.org/10.1016/j.isci.2024.109026

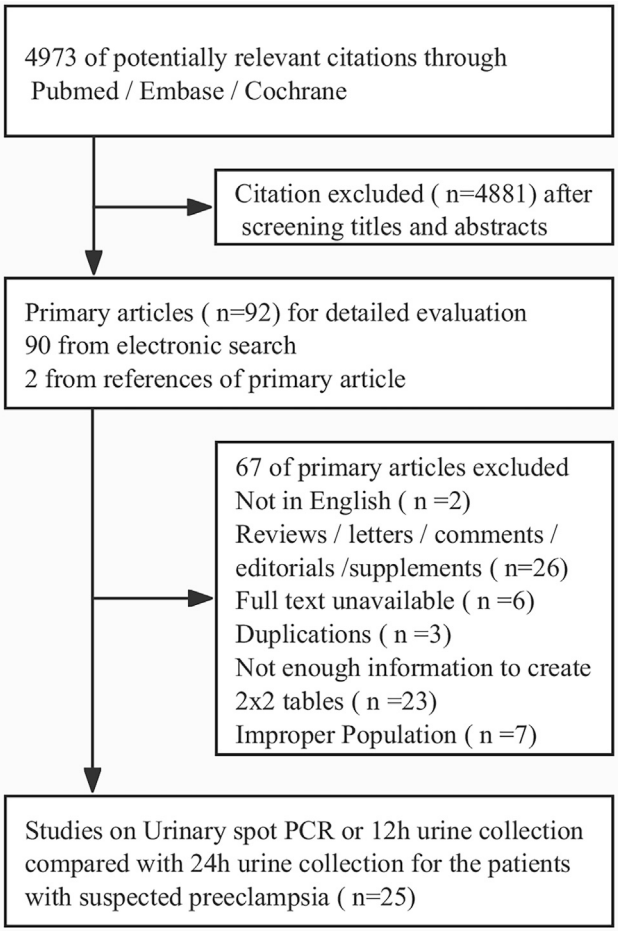

Figure 1. Flow of studies through systematic review

RESULTS

Search results

A total of 4,973 potentially relevant literatures based on our searching strategy were selected out from PubMed and EMBASE database. After screening the title and abstract, 4,881 studies uncorrelated with the comparison of spot urine PCR or 12-h urine collection with 24-h urine collection were excluded and 92 studies were then evaluated in detail. Then 67 selected articles were excluded because of not being in English (n = 2), unmatched article types (n = 26), full text unavailable (n = 6), duplications (n = 3), inadequate information to create 2 × 2 tables (n = 23), and improper populations (n = 7). Figure 1 summarized this selection process. Finally, 25 primary studies[13,15–38] meeting our inclusion criteria were included into meta-analysis with 3,904 participants.

Description of the included studies

The characteristics of the included 25 studies and included participants were detailed in Table 1. Most of these are prospective studies, and one is reported as retrospective study. Among these articles, twelve excluded patients with confirmed urinary tract infections, ten studies excluded patients with previously existing chronic hypertension, twelve excluded chronic renal disease, and five studies excluded patients with diabetes. The exclusion of patients with inadequate urine collection was reported in eleven literatures. Spot urine collection before 24-h urine collection was demonstrated in thirteen studies. Bar chart showing quality assessment using quality assessment of diagnostic accuracy studies criteria was shown in Figure 2. Notably, only 23.1% of included articles fulfilled the item of blinding for reference test results and 26.9% fulfilled the item of blinding for index test results, which reflect unclear and undetailed reports. All the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) scores of these studies were above 7, indicating these 25 studies were suitable to be included.

Diagnostic accuracy of spot urine PCR for prediction of significant proteinuria

The pooled sensitivity was 87% (95% confidence interval [CI] 83%–91%) and pooled specificity was 86% (95% CI 79%–91%) when urinary spot PCR was compared with 24-h urine collection. High significant heterogeneity was observed both in sensitivity ($Q = 121.55$; $p<0.01$; $I^2 = 83.55\%$)

Table 1. Study and population characteristics of pregnant women with preeclampsia

Study (Year)	Country	Number (n)	Number of proteinuria[a]	Method of protein test	Method of creatinine test	Timing of collecting spot urine	Blind	Inpatient or outpatient	Bed rest or modified bed rest	Cut point for 12 h urine(mg)	QUADAS Score
Rinehart (1999)	America	29	25(86%)	Unkown	–	–	Unkown	Inpatient	No	150	10
Adelberg (2001)	America	65	45(69%)	PRM	–	–	Unkown	Mixed	Yes	165	9
Schubert (2006)	America	15	9(60%)	PRM	–	–	Unkown	Inpatient	Yes	150	8
Rabiee (2007)	Iran	57	8(14%)	PRM	–	–	Unkown	Mixed	Yes	100	12
Moslemizadeh (2008)	Iran	36	26(72%)	PRM	–	–	No	Inpatient	No	148	11
Tun (2012)	America	86	28(33%)	PRM	–	–	Yes	Inpatient	Yes	165	12
Rani (2014)	India	125	106(85%)	NS	–	–	Unkown	Inpatient	NS	150	12

Study (Year)	Country	Number (n)	Number of proteinuria[a]	Method of protein test	Method of creatinine test	Timing of collecting spot urine	Blind	Inpatient or outpatient	Bed rest or modified bed rest	Cut point for PCR	QUADAS score
Saudan (1997)	Australia	100	61(61%)	BCT	Jaffe	Before	No	Mixed	Yes	0.27 mg/mg	7
Ramos (1997)	Brazil	47	17(36%)	SAT	Jaffe	Before	No	Inpatient	Yes	0.5 mg/mg	11
Robert (1997)	Canada	71	29(41%)	PRM	AIC	During	Unkown	Inpatient	Yes	Unkown	9
Rodriguez (2001)	America	138	69(50%)	PRM	Jaffe	Before	No	Unkown	Unkown	0.19 mg/mg	9
Durnwald (2003)	America	220	168(76%)	Biuret	Jaffe	Before	Unkown	Mixed	No	0.39 mg/mg	8
Ragip (2004)	Turkey	185	39(21%)	TCA	Jaffe	Before	Unkown	Inpatient	Unkown	0.19 mg/mg	11
Yamasmit (2004)	America	42	29(69%)	PRM	Jaffe	Before	No	Inpatient	Unkown	0.25 mg/mg	12
Schubert (2006)	America	15	9(60%)	PRM	Jaffe	Before	Unkown	Inpatient	Yes	0.15 mg/mg	8
Taherian (2006)	Iran	100	73(73%)	TCA	Jaffe	Before	Unkown	Unkown	Yes	0.18 mg/mg	11
Leanos (2007)	Mexico	927	282(30%)	Bradford	Jaffe	Before or after	Unkown	Inpatient	Yes	0.3 mg/mg	11
Wheeler (2007)	America	126	68(54%)	Biuret	Jaffe	Before	Unkown	Inpatient	Unkown	0.21 mg/mg	11
Dwyer (2008)	America	116	56(48%)	PRM	Jaffe	Before or After	Yes	Outpatient	Unkown	0.28 mg/mg	13
Aggarwal (2008)	India	120	104(87%)	Biuret	Jaffe	After	Unkown	Inpatient	Yes	1.14 mg/mg	10
Tun (2012)	America	86	28(33%)	PRM	Unkown	Before	Yes	Inpatient	Yes	0.15 mg/mg	12

(*Continued on next page*)

Table 1. *Continued*

Study (Year)	Country	Number (n)	Number of proteinuria[a]	Method of protein test	Method of creatinine test	Timing of collecting spot urine	Blind	Inpatient or outpatient	Bed rest or modified bed rest	Cut point for PCR	QUADAS score
Cade (2012)	Australia	121	103(85%)	PRM	Jaffe	Before	Unkown	Outpatient	Unkown	0.27 mg/mg	9
Kumari (2013)	India	400	310(78%)	CBB-G250	Jaffe	During	Unkown	Inpatient	Unkown	0.3 mg/mg	9
Mohseni[10am] (2013)	Iran	67	48(72%)	PRM	Jaffe	At 10 a.m.	Unkown	Outpatient	No	0.47 mg/mg	9
Mohseni[4pm] (2013)	Iran	67	48(72%)	PRM	Jaffe	At 4 p.m.	Unkown	Outpatient	No	0.595 mg/mg	9
Lamontagne (2014)	Canada	91	43(47%)	PRM	Jaffe	Before	Yes	Mixed	No	0.27 mg/mg	12
Bhide (2015)	England	117	76(65%)	PRM	Jaffe	Unkown	Unkown	Unkown	Unkown	0.27 mg/mg	9
Demirci (2015)	Turkey	264	211(80%)	Biuret	Jaffe	Before	Unkown	Inpatient	Yes	0.45 mg/mg	9
Valdés (2016)	Chile	72	49(68%)	Unkown	Unkown	Unkown	Unkown	Inpatient	Unkown	0.36 mg/mg	7

[a]0.3 g/day or more; PRM, pyrogallol red-molybdate method; BCT, benzethonium chloride turbidometric method; SAT, sulfosalycilic acid turbidometric method; AIC, ammonia iminohydrolase colorimetric; PCR, protein to creatinine ratio; QUADAS, quality assessment of diagnostic accuracy studies.

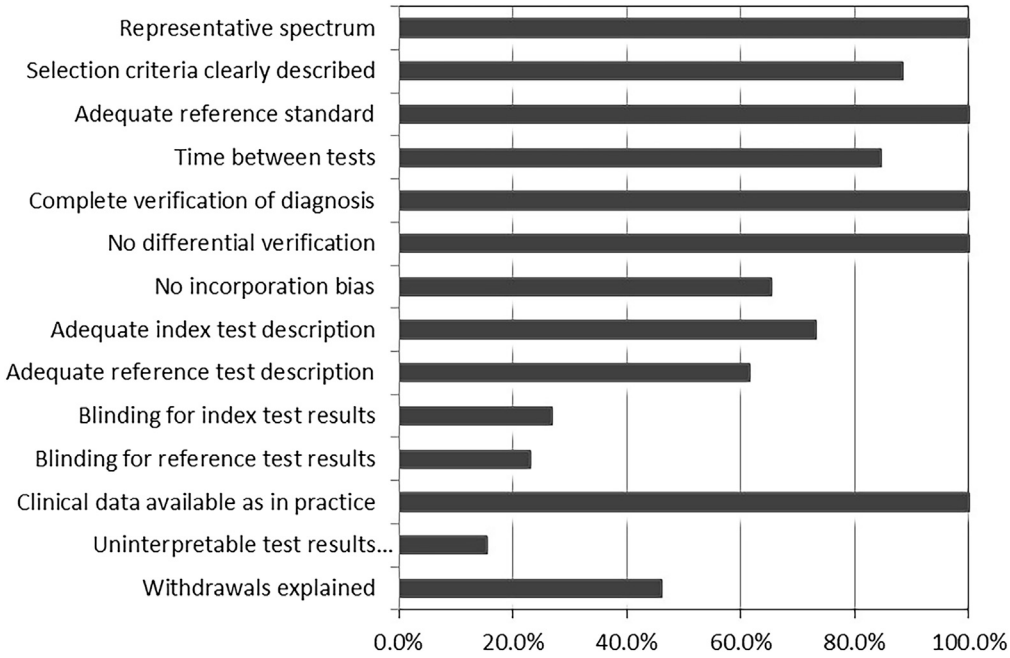

Figure 2. Bar chart showing quality assessment using quality assessment of diagnostic accuracy studies criteria

(Figure 3A) and specificity (Q = 133.49; p<0.01; I^2 = 85.02%) (Figure 3B). Symmetric receiver operator characteristic curve (SROC) was shown in Figure 4A with area under curve (AUC) of 0.93 (0.90–0.95). The Fagan plot showed that, when patients with suspected preeclampsia were tested by spot urine PCR, positive likelihood ratio (PLR) increased by 37% with a decrease of 37% on negative likelihood ratio (NLR) (Figure 5A). As shown in Figure 6A, tests with PLRs greater than 10 or NLRs less than 0.1 are considered clinically useful. Summary PLR and NLR for index test was located in the fourth quadrant of likelihood ratio scattergram, indicating spot urine PCR had a limited clinical significance for testing proteinuria.

Diagnostic accuracy of 12-h urine collection for prediction of significant proteinuria

For 12-h urine collection compared with 24-h urine collection, the pooled sensitivity and specificity were 92% (95% CI 87%–96%) and 99% (95% CI 75%–100%), respectively. There also existed moderate significant heterogeneity in sensitivity (Q = 11.61; p<0.01; I^2 = 48.33%) (Figure 3C) and high significant heterogeneity in specificity (Q = 24.27; p<0.01; I^2 = 75.28%) (Figure 3D). SROC was shown in Figure 4B, and the AUC was 0.97 (0.95–0.98). The Fagan plot for 12-h urine collection was displayed in Figure 5B, which reported an increase of 49% on PLR and a decrease of 43% on NLR. Summary PLR and NLR for index test was settled in the first quadrant of likelihood ratio scattergram, revealing that the application of 12-h urine collection to verify proteinuria is a feasible method in clinical practice (Figure 6B).

Exploring source of heterogeneity

To explore possible sources of heterogeneity, meta-regression and subgroup analysis were conducted according to items of inpatient, rest, and testing method. Because of inadequate numbers of articles which compared 12-h urine collection with 24-h urine collection, we just performed meta-regression and subgroup analysis in studies which compared spot urine PCR with 24-h urine collection. For all the analyzed items, test method (p<0.01) may be a main source of heterogeneity for sensitivity. We did not observe any other significant sources of heterogeneity (p>0.01). Subgroup analysis according to these confounding factors was shown in Table 2. We observed significant heterogeneity in sensitivity and specificity in almost all subgroups, except testing method of using Biuret method and cutoff point of 0.15–0.19, in which heterogeneity of studies was not statistically significant for sensitivity.

Publication bias

The linear regression test of funnel plot asymmetry demonstrated that there was no significant publication bias for pot urine PCR (p>0.1) or 12-h urine collection (p>0.1) compared with 24-h urine collection (Figures 7A and 7B).

DISCUSSION

Qualification of proteinuria is crucial to diagnose preeclampsia for pregnant women with newly presented hypertension. Shortcomings of 24-h urine collection as golden standard to qualify proteinuria are well recognized. Over the past years, people were committed to find

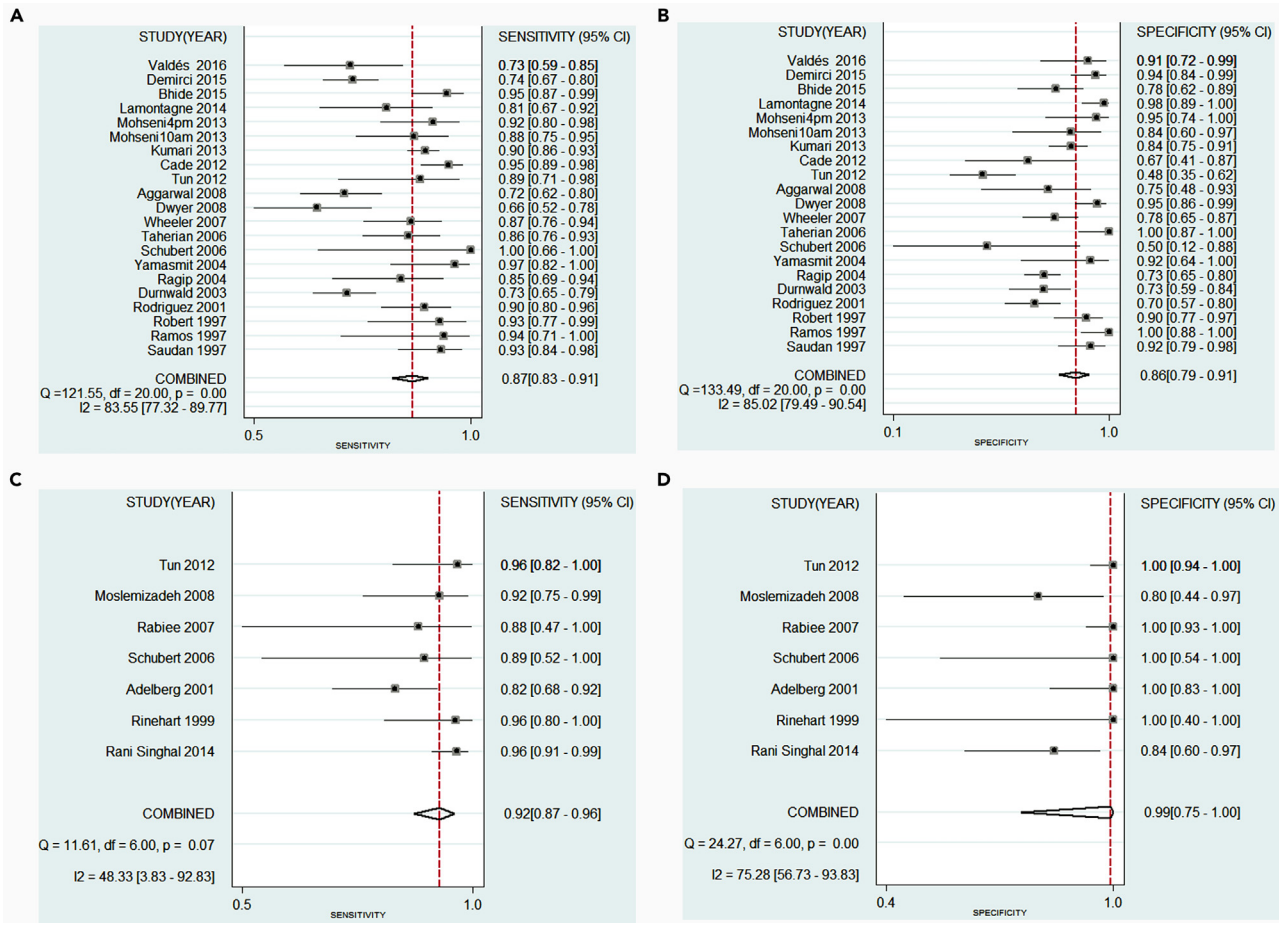

Figure 3. Diagnostic accuracy of spot urine PCR and 12-hour urine collection for prediction of significant proteinuria in preeclampsia

Diagnostic accuracy of spot urine protein:creatinine ratio (A and B) and 12-h urine collection (C and D) for prediction of proteinuria in pregnant women with suspected preeclampsia.

an alternative test method of 24-h urine collection for pregnant women. Recently, several systematic reviews and meta-analyses[9,10,39,40] reported that urinary spot PCR and 12-h urine collection showed reliable diagnostic accuracy for proteinuria in hypertensive pregnant women. Anne-Marie et al. demonstrates spot PCR as a reasonable "rule-out" test for proteinuria of 0.3 g/day or more and recommended best cutoff points of 0.27 mg/mg[10]. Moreover, Stout and colleagues reported that 12-h urine protein was highly predictive of significant proteinuria and optimal cutoff point based on the receiver operating characteristic curve was 150 mg[9]. We perform this meta-analysis to compare the diagnostic accuracy of these two testing methods.

The major findings of our study suggest that, as an alternative testing method of 24-h urine collection, 12-h urine collection may be a better choice on the aspect of sensitivity and specificity for detecting proteinuria than urinary spot PCR. The AUCs of these two tests were 0.93 (95% CI 0.90–0.95) and 0.97(95% CI 0.95–0.98), respectively. Particularly, the 95% CIs of these two AUC are not overlapping, revealing there exists significant statistical differences between 12-h urine collection and urinary spot PCR for predicting significant proteinuria. In addition, the application of 12-h urine collection elevated the value of PLR and NLR more than the application of urinary spot PCR. Moreover, likelihood ratio scattergram indicated confirmed clinical significance of 12-h urine collection and only ambiguous clinical application value for urinary spot PCR. From the aforementioned findings, considering only statistical aspects, 12-h urine collection possessed better diagnostic accuracy than urinary spot PCR.

However, the best management depends on accurate and timely diagnosis. 12-h urine collection shares some limitations same as 24-h urine collection. The urine needs to be refrigerated, and the collection is time-consuming and tiring for patients and hospital staff. Sometimes it could not be accomplished, for example, when delivery occurs. At this time, 12-h and 24-h urine collection may result in an undetermined proteinuria status and an unsubstantiated diagnosis of preeclampsia. Quick tests are still necessary and pivotal when some emergency occurs. Urinary spot PCR as a quick testing method has been demonstrated to have relatively high sensitivity and specificity based on a large body of evidence.[12,41] Our study also demonstrated high value of pooled sensitivity of 87% and pooled specificity of 86% indicating that, in some circumstances of urgency, urinary spot PCR could be a reliable testing method for predicting significant proteinuria.

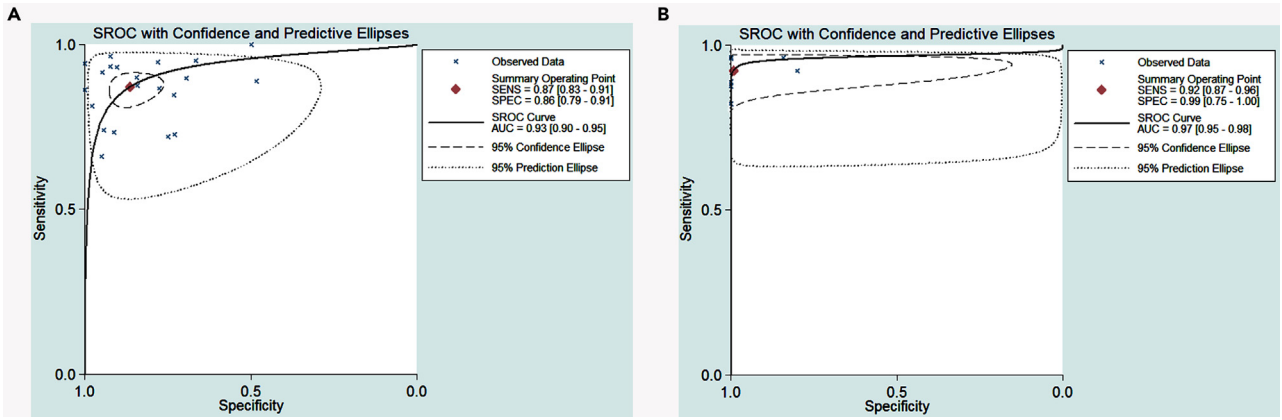

Figure 4. Summary receiver operating characteristics curve for constrained estimates of sensitivity and specificity

(A) Spot urine protein:creatinine ratio for prediction of proteinuria in pregnant women with preeclampsia.

(B) 12-h urine collection for prediction of proteinuria in pregnant women with preeclampsia.

In conclusion, as an alternative of 24-h urine collection, 12-h urine collection shows better clinical value of application than urinary spot PCR. Under certain circumstances which require rapid prediction of significant proteinuria, urinary spot PCR is also a reliable diagnostic approach. Future research may be directed to search for the best cutoff points of 12-h urine collection and urinary spot PCR.

Limitations of the study

Firstly, even though strong efforts had been made to obtain additional information by contacting corresponding authors, we only included articles with sufficient information to create 2 × 2 tables. Secondly, we excluded articles published in a language other than English. Thirdly, as

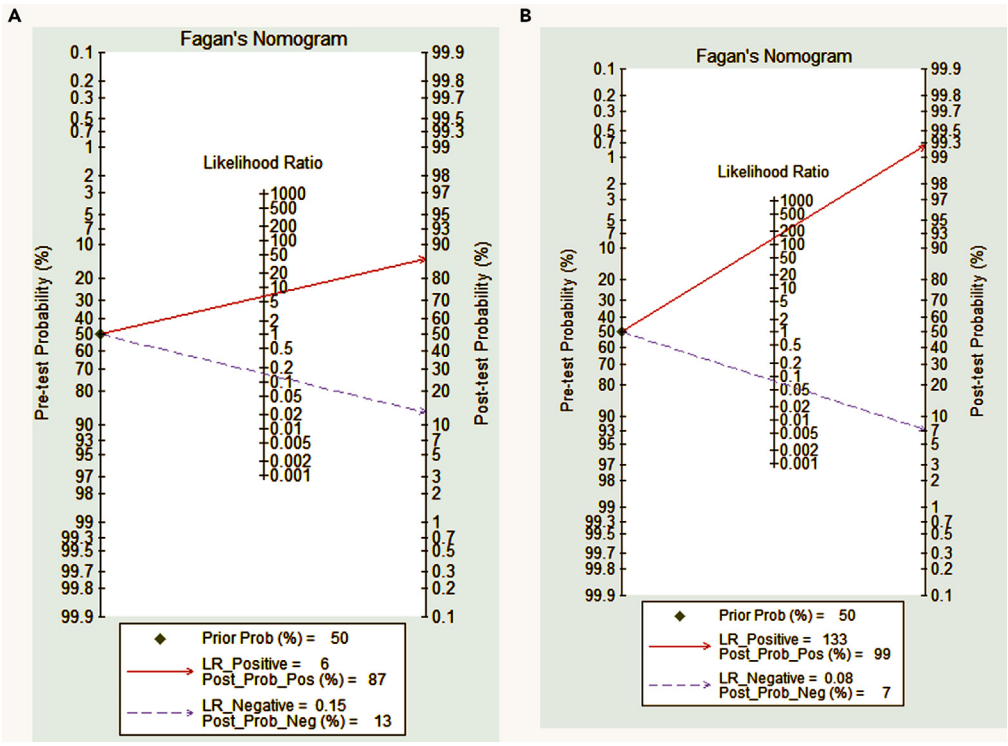

Figure 5. The Fagan plot showing the positive likelihood ratio and negative likelihood ratio

(A) Spot urine protein:creatinine ratio for prediction of proteinuria in pregnant women with preeclampsia.

(B) 12-h urine collection for prediction of proteinuria in pregnant women with preeclampsia.

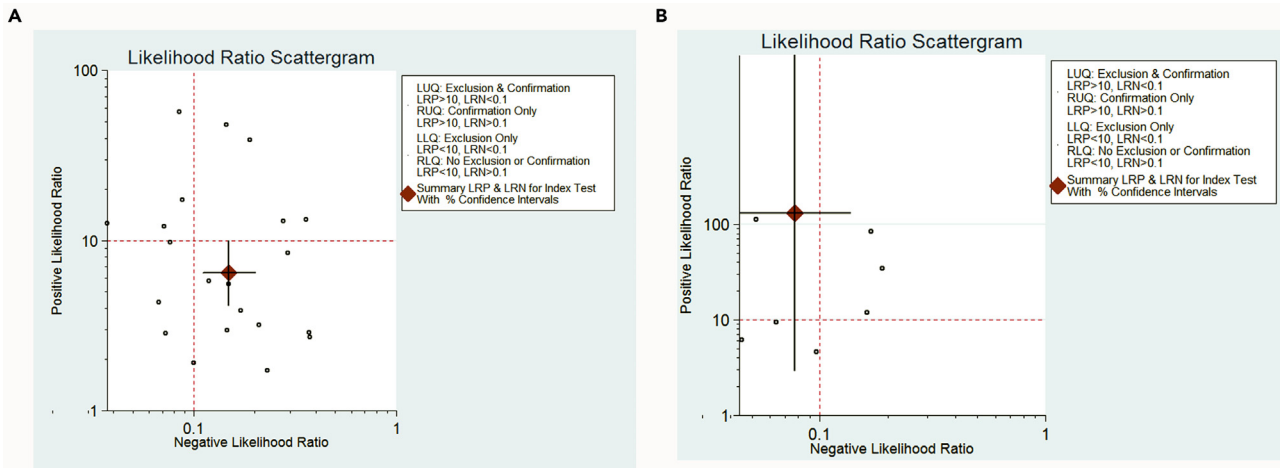

Figure 6. The likelihood ratio scattergram showing the positive likelihood ratio and negative likelihood ratio

(A) Spot urine protein:creatinine ratio for prediction of proteinuria in pregnant women with preeclampsia.

(B) 12-h urine collection for prediction of proteinuria in pregnant women with preeclampsia.

shown in Figure 2, included articles rarely declare a double-blind design, and several studies did not detail the inclusion and exclusion of pregnant women. Besides, description of index test and reference test was inadequate in a few literatures. Finally, significant heterogeneity existed. Through stratified and meta-regression analysis, we found testing method of urine protein and different cutoff point caused heterogeneity. Moreover, considerable variations among the including population may be another main source of heterogeneity.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability

Table 2. Subgroup analysis to explore the source of heterogeneity

Subgroup	SEN (95% CI)	I^2 (SEN, p value)	SPE (95%CI)	I^2 (SEN, p value)
Patient				
Inpatient	0.86(0.80–0.91)	80.73 p<0.01	0.84(0.73–0.91)	86.57 p<0.01
Outpatient	0.88(0.74–0.95)	89.37 p<0.01	0.87(0.73–0.95)	79.68 p<0.01
Others	0.88(0.80–0.93)	87.99 p<0.01	0.89(0.73–0.96)	84.75 p<0.01
Rest				
Yes	0.87(0.78–0.93)	83.57 p<0.01	0.90(0.72–0.97)	92.76 p<0.01
No	0.83(0.74–0.90)	86.25 p<0.01	0.91(0.77–0.97)	83.37 p<0.01
Unknown	0.89(0.82–0.93)	82.71 p<0.01	0.81(0.73–0.87)	66.97 p<0.01
Testing method				
PRM	0.91(0.85–0.94)	77.77 p<0.01	0.83(0.71–0.91)	87.83 p<0.01
Biuret	0.75(0.71–0.78)	50.57 p = 0.11	0.82(0.70–0.90)	66.88 p<0.01
Cutoff point				
0.15–0.19	0.89(0.83–0.92)	0.00 p = 0.72	0.74(0.47–0.90)	84.99 p<0.01
0.21–0.27	0.90(0.82–0.94)	85.80 p<0.01	0.88(0.77–0.94)	77.15 p<0.01
>0.3	0.83(0.75–0.89)	86.98 p<0.01	0.89(0.80–0.94)	66.53 p<0.01

SEN, sensitivity; SPE, specificity; CI, confidence interval.

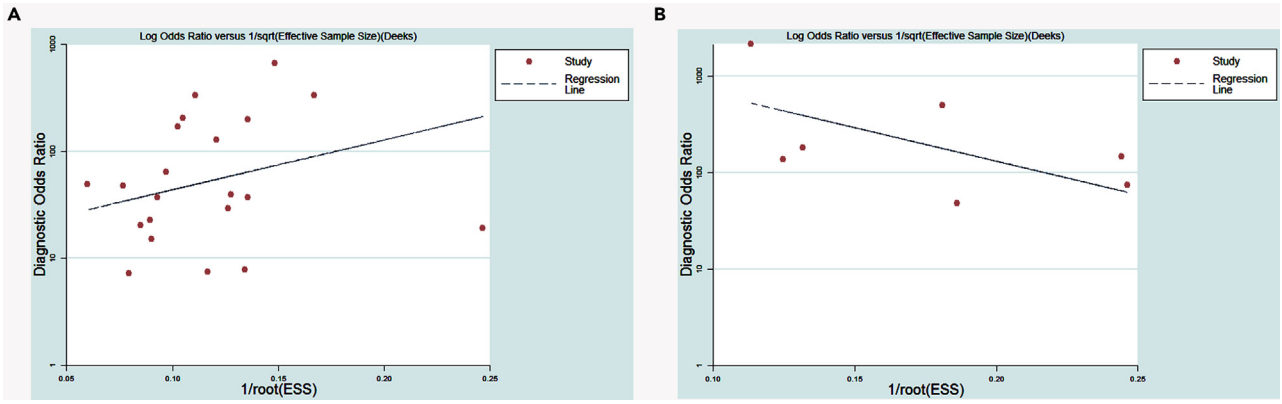

Figure 7. The linear regression test of funnel plot asymmetry for publication bias

(A) Funnel plot asymmetry for spot urine protein:creatinine ratio compared with 24-h urine collection.

(B) Funnel plot asymmetry for 12-h urine collection compared with 24-h urine collection.

ACKNOWLEDGMENTS

We thank Huiquan Liu for his helpful advice on our article. This study did not receive any specific grants from funding agencies in the public, commercial, or non-profit sectors. We would also like to thank the anonymous reviewers for their helpful comments.

AUTHOR CONTRIBUTIONS

All authors designed the project and the first hypothesis. M.C. and M.T. performed the systematic search, reviewed the literature, and extracted data; M.T. and L.H. analyzed data and wrote the first draft of the paper; Q.L. supervised and revised the manuscript. All of the authors reviewed and approved the final article proof for submission.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: July 29, 2023
Revised: December 14, 2023
Accepted: January 22, 2024
Published: January 24, 2024

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
PubMed	https://pubmed.ncbi.nlm.nih.gov/	N/A
EMBASE	https://www.embase.com/	N/A
Software and algorithms		
Stata software Version 12.0	Downloaded STATA software	https://www.stata.com/products/
Endnote	Clarivate Analytics LLC	https://endnote.com/downloads
Review Manager 5.4	The Cochrane Collaboration	https://revman.cochrane.org/info

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Qingquan Liu (qqliutj@163.com).

Materials availability

This study is a meta-analysis and did not use or generate any reagents.

Data and code availability

The data used in this meta-analysis came from published studies, and no new data or codes were used. All data are described in the ''key resources table'' section. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Our study does not use experimental models typical in the life sciences.

METHOD DETAILS

Search strategy

To identify all published studies concerning the correlation of urinary spot PCR or 12-hour urine collection with 24-hour urine collection in pregnancy, we conducted an electronic, comprehensive search on PubMed and EMBASE database (updated to March 1, 2023) using the key words "protein to creatinine ratio" or "24 hours urine collection" or "12 hours urine collection" and "Pregnancy-Induced Hypertension" or "Pre-eclampsia". The Search was limited to "human and English". Sources from the reference lists of both primary articles and national and international guidelines for pregnancy hypertension were included.

Eligibility criteria

The included papers should meet criteria listed below: (1) study evaluate the performance of spot PCR or 12-hour urine collection compared to 24-hour urine collection in pregnant women with hypertension; (2) 24-hour urine collection is used as reference standard test for assessing proteinuria (3) the study included more than 15 patients; (4) data consists of 2×2 table can be extracted from the article (5) articles should be written in English.

Data extraction

All retrieved articles were imported into EndNote 20 . Two reviewers (M Tian and M Chen) independently extracted data from eligible articles and resolved conflicts through discussions with L.Y. Huang and Q.Q Liu. The selected information was recorded in a table composed of Study, Year, Country, Total number of samples, Number of samples with proteinuria, Inpatient, Bed rest, Timing of spot urine, Test method of protein, Test method of creatinine, Blind, Cutoff point. Two reviewers had reached a consensus on each terms.

QUANTIFICATION AND STATISTICAL ANALYSIS

Quality assessment

The quality of the screened literature was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) 2 tool.[42] This assessment tool includes four main components: patient selection, index test, reference standard, and process and progress. Two reviewers (M Tian and M Chen) in our group used the tool of QUADAS to assess the quality of included studies.

Data Synthesis and analysis

The results of each study containing true positive, false positive, false negtive and true negtive were collected in order to calculate pooled sensitivity, specificity and their 95% confidence intervals (95%CI). We perfomed this meta-analysis using DerSimonian-Lair random effects models irrespective of existing statistical heterogeneity. Then symmetric receiver operator characteristic curves (SROC) were profiled according to pooled data and area under SROC (AUC) were calculated to evaluate the diagnostic accuracy. Fagan plot and likelihood ratio scattergram were used to predict the clinical application of these two tests.

Higgin's I^2 statistic and Cochrane's Q test were applied to assess the degree of statistical heterogeneity between studies. We considered I^2 estimates of 25, 50 and 75 % as low, moderate and high heterogeneity, respectively.[43] Meta regression and subgroup analysis were then applied to find possible factors influencing heterogeneity.[44] We examined funnel plot for DORs (Deek's funnel plot) to explore the possibility of publication bias.[45] Statistical meta-analyses were performed using the command of Midas module in Stata software (Version 12.0), and all P-values were calculated as two-sided.

ADDITIONAL RESOURCES

The study was registered in INPLASY, the DOI number is https://doi.org/10.37766/inplasy2023.12.0031.