PIERS Proteinuria: Relationship With Adverse Maternal and Perinatal Outcome

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Abstract

Objective: To examine the ability of three different proteinuria assessment methods (urinary dipstick, spot urine protein:creatinine ratio [Pr/Cr], and 24-hour urine collection) to predict adverse pregnancy outcomes.

Methods: We performed a prospective multicentre cohort study, PIERS (Preeclampsia Integrated Estimate of RiSk), in seven academic tertiary maternity centres practising expectant management of preeclampsia remote from term in Canada, New Zealand, and Australia. Eligible women were those admitted with preeclampsia who had at least one antenatal proteinuria assessment by urinary dipstick, spot urine Pr/Cr ratio, and/or 24-hour urine collection. Proteinuria assessment was done either visually at the bedside (by dipstick) or by hospital clinical laboratories for spot urine Pr/Cr and 24-hour urine collection. We calculated receiver operating characteristic area under the curve (95% CI) for each proteinuria method and each of the combined adverse maternal outcomes (within 48 hours) or adverse perinatal outcomes (at any time). Models with AUC ≥ 0.70 were considered of interest. Analyses were run for all women who had each type of proteinuria assessment and for a cohort of women ("ALL measures") who had all three proteinuria assessments.

Results: More women were proteinuric by urinary dipstick (≥ 2+, 61.4%) than by spot urine Pr/Cr (≥ 30g/mol, 50.4%) or 24-hour urine collection (≥ 0.3g/d, 34.7%). Each proteinuria measure evaluated had some discriminative power, and dipstick proteinuria (categorical) performed as well as other methods. No single method was predictive of adverse perinatal outcome.

Conclusion: The measured amount of proteinuria should not be used in isolation for decision-making in women with preeclampsia. Dipstick proteinuria performs as well as other methods of assessing proteinuria for prediction of adverse events.

Key Words: Proteinuria, preeclampsia, receiver operating characteristic curve, diagnostic accuracy

Competing Interests: None declared.

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Résumé

Objectif : Examiner la capacité de trois méthodes d'évaluation différentes de la protéinurie (test d'urine par bandelette réactive, rapport protéine:créatinine [Pr/Cr] d'échantillon d'urine ponctuel et collecte d'urine sur 24 heures) de prédire les issues de grossesse indésirables.

Méthodes : Nous avons mené une étude de cohorte multicentrique prospective (PIERS ou *Preeclampsia Integrated Estimate of RiSk*) dans sept centres de maternité tertiaires universitaires pratiquant la prise en charge non interventionniste de la prééclampsie ne se manifestant pas à terme au Canada, en Nouvelle-Zélande et en Australie. Les femmes admissibles étaient celles qui étaient hospitalisées en raison d'une prééclampsie et qui avaient subi au moins une évaluation prénatale de la protéinurie au moyen d'un test d'urine par bandelette réactive, du rapport Pr/Cr d'échantillon d'urine ponctuel et/ou de la collecte d'urine sur 24 heures. L'évaluation de la protéinurie a été effectuée de façon visuelle au chevet

de la patiente (au moyen d'une bandelette réactive) ou par l'intermédiaire des laboratoires cliniques hospitaliers pour ce qui est du rapport Pr/Cr d'échantillon d'urine ponctuel et de la collecte d'urine sur 24 heures. Nous avons calculé la surface sous la courbe d'efficacité du récepteur (IC à 95 %) pour chacune des méthodes d'évaluation de la protéinurie et chacune des issues maternelles indésirables combinées (dans un délai de 48 heures) ou chacune des issues périnatales indésirables (à quelque moment que ce soit). Les modèles dont la surface sous la courbe étaient ≥ 0,70 ont été considérés dignes d'intérêt. Les analyses ont été menées pour toutes les femmes qui ont subi chacun des types d'évaluation de la protéinurie et pour une cohorte de femmes (« TOUTES les mesures ») ayant subi les trois types d'évaluation de la protéinurie.

Résultats : Plus de femmes se sont avérées être protéinuriques au moyen d'un test d'urine par bandelette réactive (≥ 2+, 61,4 %) qu'au moyen du rapport Pr/Cr d'échantillon d'urine ponctuel (≥ 30 g/mol, 50,4 %) ou de la collecte d'urine sur 24 heures (≥ 0,3 g/d, 34,7 %). Chacune des mesures de la protéinurie évaluée comptait un certain pouvoir discriminateur; de plus, l'évaluation de la protéinurie au moyen d'un test d'urine par bandelette réactive (catégorique) a obtenu un rendement équivalant à celui des autres méthodes. Aucune méthode unique n'a permis de prédire les issues périnatales indésirables.

Conclusion : La quantité mesurée de protéinurie ne devrait pas être utilisée de façon isolée aux fins de la prise de décision chez les femmes qui présentent une prééclampsie. L'évaluation de la protéinurie au moyen d'un test d'urine par bandelette réactive offre un rendement équivalant à celui des autres méthodes pour ce qui est de la prédiction des événements indésirables.

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INTRODUCTION

Maternal and perinatal complications cluster with the diagnosis of preeclampsia, usually defined as gestational hypertension with proteinuria, and place the assessment of urinary protein excretion as a core element of antenatal care. As the amount of protein excretion in women with preeclampsia may reflect maternal and perinatal risk, various definitions of heavy proteinuria have been incorporated into definitions of severe preeclampsia and suggested as a specific indication for delivery.[1,2]

Options for quantifying proteinuria include dipstick testing, spot urinary protein to creatinine ratio, and various timed urine collections for estimation of protein excretion, the most common being the 24-hour collection. There are insufficient data to define an abnormal albumin to creatinine ratio in pregnancy[3,4] and there is no information about its prognostic significance related to adverse pregnancy outcomes.

While accepted as the gold standard for assessing proteinuria, the 24-hour urine collection is often affected by inaccurate collecting.[5] Also, it is unclear whether there is a level of protein excretion that usefully defines patients as being at increased risk of adverse outcomes.[6] From a number of small, heterogeneous studies, heavy proteinuria (5 g/d, 10 g/d, or an increase by 2 g/d) may be somewhat useful or useful as test for predicting eclampsia, stillbirth, perinatal death, SGA infants, or NICU admission.[7–15]

Within a cohort of women admitted to hospital with preeclampsia, we examined whether the amount of antenatal proteinuria assessed by urinary dipstick, spot urinary Pr/Cr, or 24-hour urine collection is predictive of adverse maternal or perinatal outcomes.

METHODS

PIERS is a multicentre study of women with preeclampsia admitted to academic tertiary obstetric care centres in which there is a general policy of expectant management of preeclampsia remote from term in Canada (British Columbia's Women's Hospital/University of British Columbia, Vancouver, BC; Kingston General Hospital/Queen's University, Kingston, ON; The Ottawa Hospital [General Campus]/University of Ottawa, Ottawa, ON; and Centre Hospitalier universitaire de Sherbrooke/Université de Sherbrooke, QC), the United Kingdom (St. James Hospital/University of Leeds, Leeds, Yorkshire), New Zealand (Christchurch Women's Hospital/University of Otago, Christchurch), and Australia (King Edward Memorial Hospital for Women/University of Western Australia, Subiaco, Western Australia).

PIERS was conducted as a continuous quality improvement project in three sites using predetermined guidelines for the initial assessment and ongoing surveillance of women admitted to hospital with suspected or confirmed preeclampsia.[16–18] In four sites, women were required to give informed consent. Women were included in the study if they were admitted to hospital with preeclampsia, or developed preeclampsia following admission, and had one or more measures of proteinuria before delivery. Women were excluded if they were admitted to hospital in spontaneous labour or had achieved any component of the maternal outcome prior to fulfilling either the eligibility criteria or the collection of the potential predictors we chose to evaluate.

ABBREVIATIONS

AUC	area under the curve
BP	blood pressure
HELLP	hemolysis, elevated liver enzymes, low platelet count
PIERS	Preeclampsia Integrated Estimate of RiSk
Pr/Cr	protein:creatinine ratio
ROC	receiver operating characteristic

Preeclampsia was defined as (1) blood pressure ≥ 140/90 mmHg (at least one component twice, ≥ 4 hours apart, after 20 weeks' gestation) and either proteinuria (≥ 2+ by dipstick, ≥0.3 g/d by 24-hour urine collection, or ≥ 30 mg/mmol by spot urine Pr/Cr) or hyperuricemia (greater than local upper limit of normal for non-pregnant individuals), (2) HELLP syndrome even in the absence of hypertension or proteinuria,[19] or (3) superimposed preeclampsia, defined as pre-existing hypertension with new proteinuria, new hyperuricemia, and/or accelerated hypertension (diagnosed by the clinician and defined as either rapidly increasing requirements for antihypertensives, a systolic BP > 170 mmHg, or a diastolic BP > 120 mmHg). This inclusive definition was chosen to reflect both the variable and multisystem nature of preeclampsia at presentation and the spectrum of women seen in clinical practice.[20,21]

The components of the combined adverse maternal outcome were developed by Delphi consensus (members of consensus listed in the Appendix),[22,23] as follows:

1. maternal mortality, or one or more of hepatic dysfunction, hematoma, or rupture
2. eclampsia, Glasgow coma score < 13
3. stroke
4. reversible ischemic neurological deficit
5. transient ischemic attack
6. posterior reversible encephalopathy
7. cortical blindness or retinal detachment
8. need for positive inotrope support
9. infusion of a third parenteral antihypertensive
10. myocardial ischemia/infarction (symptoms, ECG changes [ST segment changes, Q waves], biochemical markers [troponin, CK-MB]), coronary artery intervention, or pathological findings
11. acute renal insufficiency (serum creatinine >150 μM/L [women without pre-existing renal disease] or > 200 μM/L [with pre-existing renal disease]), dialysis, pulmonary edema, requirement ≥ 50% FiO_2 for ≥ 1 hour
12. intubation (other than for Caesarean section)
13. transfusion of any blood product.

The adverse perinatal outcome was defined as perinatal or infant mortality, admission to NICU for greater than 48 hours, or both.

Outcomes were assessed first at 48 hours after eligibility, as that is the time frame for corticosteroid administration remote from term and decisions about the place of delivery, in utero transfer from level one and two units, and labour induction. Epochs of seven days and "any time" were also evaluated. The worst value (e.g., highest dipstick proteinuria) prior to outcome occurrence or completion of the relevant epoch was used in the analysis.

Assessment of proteinuria was among the possible maternal and fetal predictors of adverse outcomes.[24,25] Methods considered were urinary dipstick testing (from negative to 4+), spot urine Pr/Cr (mg/mmol), and 24-hour urinary protein (g/d). Dipstick proteinuria was assessed using bedside visual interpretation, and results of testing analyzed as both a continuous and categorical variable to determine which analytical approach would be more informative. For laboratory measurement of proteinuria, pyrogallol red (n = 6 centres) or benzathonium chloride (n = 1 centre) were used in routine hospital laboratories as part of clinical care. All results were freely available to clinicians. Proteinuria results were assessed as continuous variables without designation of an arbitrary cut-off.

Proteinuria measurements were collected antenatally and within 48 hours of eligibility, and the most abnormal values in any 24-hour period were recorded. If absent, the last observation carried forward method was used such that any observation performed within 14 days before admission was used. This approach underestimates the effect of a variable in modelling.[26] Also, clinicians do not re-evaluate what they believe has not changed. Missing values and misclassification were addressed by abstractor training, development and validation of the PIERS Access database, feasibility and development studies using that database, and random re-abstraction of charts. Misclassification errors were minimized by database surveillance and reabstraction, which occurred randomly in 5% of cases and for all cases of adverse maternal or perinatal outcomes, suspected or confirmed. The study was pragmatic and therefore consistent with clinical care. Test reproducibility was not examined. We relied on local laboratory quality control procedures for ensuring test reproducibility.

Customized case report forms and a Microsoft Access database were created for data entry and utilized by all participating sites. Data were collected from patient medical records.

Univariable logistic regression was used to evaluate the relationship between each measure of proteinuria (i.e., dipstick, spot Pr/Cr, and 24-hour) and each of the following: the adverse maternal outcome (over the first 48 hours, 7 days, and at any time) and the adverse perinatal outcome (at any time). The analyses were performed for women who had one of the three measures of proteinuria and for women who had all three measures of proteinuria. Beta-coefficients were exponentiated to obtain odds ratios, which reflected the change in the odds of the outcome

Table 1. Baseline characteristics of women with antenatal preeclampsia in PIERS cohort

	Full cohort N = 2002	Women with ALL measures of proteinuria N = 434	Dipstick proteinuria cohort N = 1949	Spot urine Pr/Cr cohort N = 1411	24-hour urinary protein cohort N = 676	*P**
			Median (IQR)			
Maternal age, years	31 (27–36)	33 (28–36)	31 (27–36)	31 (27–36)	32 (27–36)	0.154
GA at eligibility–weeks	36.0 (32.9–38.3)	34.2 (31.1–36.4)	36.0 (32.9–38.3)	36.0 (33.0–38.1)	33.9 (30.6–36.3)	< 0.001
			n (%)			
GA < 34 weeks at eligibility	633 (31.6)	203 (46.8)	615 (31.6)	438 (31.0)	341 (50.4)	< 0.001
Multiple pregnancy	192 (9.6)	54 (12.4)	183 (9.4)	130 (9.2)	79 (11.7)	0.079
Parity ≥ 1	573 (28.6)	140 (32.2)	558 (28.6)	416 (29.4)	204 (30.2)	0.485
Description of preeclampsia						0.047
Hypertension and proteinuria	1330 (66.4)	295 (67.9)	1297 (66.5)	946 (67.0)	456 (67.5)	
Hypertension and hyperuricemia	317 (15.8)	33 (7.6)	310 (15.9)	215 (15.2)	64 (9.5)	
HELLP without hypertension or proteinuria	52 (2.6)	13 (3.0)	51 (2.6)	39 (2.8)	19 (2.8)	
Superimposed preeclampsia	303 (15.1)	93 (21.4)	291 (14.9)	211 (15.0)	137 (20.3)	
Peak blood pressure† (mmHg)			Median (IQR)			
Mean arterial pressure	120 (114–130)	120 (113–128)	121 (114–129)	120 (113–128)	121 (115–130)	0.004
Systolic BP	160 (150–176)	160 (150–174)	160 (150–176)	160 (150–175)	162 (150–178)	0.007
Diastolic BP	102 (97.25–110)	100.5 (96–110)	102 (98–110)	100 (96–110)	102 (99–110)	0.008
			n (%)			
On anti-hypertensive treatment	1369 (68.4)	337 (77.6)	1327 (68.1)	977 (69.2)	527 (78)	< 0.001
Smoking (any) during pregnancy	246 (12.3)	52 (12.0)	236 (12.1)	180 (12.8)	82 (12.1)	0.887

GA: gestational age; IQR (interquartile range).

* Continuous variables were compared by ANOVA or Kruskal-Wallis, and categorical variables by chi-square.

† Not mutually exclusive.

occurring for every unit change in the independent variable (i.e., proteinuria assessment in this study). For each analysis, area under the curve of the receiver operating characteristic was computed in which, over a range of possible cut-points that could define a positive test, the relation between the true-positive and false-positive ratios was shown. An AUC ROC of > 0.7 is considered the minimum to indicate an adequately discriminative test; 1.0 indicates perfect discrimination and 0.5 is non-discriminative (i.e., no better than flipping a coin). For an adequately discriminative test, sensitivity, specificity, false-positive probability, and false-negative probability were calculated based on different cut-points. Statistical analyses were performed using the statistical software R (R Foundation for Statistical Computing, Vienna, Austria).

A sensitivity analysis was performed excluding women diagnosed on the basis of hyperuricemic hypertension rather than proteinuric hypertension.

Research ethics board approval for the study was obtained at all participating sites.

RESULTS

Between September 1, 2003, and January 31, 2010, data from 2023 women were entered into the PIERS database from seven international sites. Antenatal assessment of proteinuria by one or more methods was documented for 2002 women, of whom 434 women had proteinuria assessment by urinary dipstick, spot urine Pr/Cr, and 24-hour urine collection (i.e., the ALL measures cohort). The amount of proteinuria (median and interquartile range) did not vary between centres for each method of proteinuria assessment (data not shown).

Demographic characteristics for the ALL measures cohort (n = 434) and the cohorts for each of the three methods of proteinuria assessment are shown in Table 1. For completeness, data on the full PIERS cohort with any antenatal assessment of proteinuria (n = 2002) are included in Table 1. Women in the ALL measures cohort and 24-hour urinary protein cohort were enrolled earlier in pregnancy. Compared with the other groups, women in the 24-hour

Table 2. Antenatal measures of proteinuria

	Full cohort N = 2002 n (%)	Women with ALL measures of proteinuria* N = 434 n (%)	Dipstick proteinuria cohort N = 1949 n (%)	Spot urine Pr/Cr cohort N = 1141 n (%)	24-hr urinary protein cohort N = 676 n (%)	*P*†
Dipstick proteinuria (+)						0.018
Negative/trace	485 (24.2)	109 (25.1)	485 (24.9)	358 (31.4)	146 (21.6)	
1+	298 (14.9)	65 (15.0)	298 (15.3)	217 (19.0)	92 (13.6)	
2+	421 (21.0)	89 (20.5)	421 (21.6)	288 (25.2)	134 (19.8)	
3 or 4+	745 (37.2)	171 (39.4)	745 (38.2)	499 (43.7)	285 (42.2)	
Spot Pr/Cr (mg/mmol)						0.465
spot Pr/Cr ≥ 30 mg/mmol	1101 (55.0)	332 (76.5)	1064 (54.6)	1101 (96.5)	341 (50.4)	
spot Pr/Cr ≥ 40 mg/mmol	943 (47.1)	281 (64.7)	915 (46.9)	943 (82.6)	287 (42.5)	
spot Pr/Cr ≥ 50 mg/mmol	851 (42.5)	260 (60.0)	826 (42.4)	851 (74.6)	266 (39.3)	
24-hr urinary protein excretion (g/d)						0.472
women with 24-hr urinary protein ≥ 0.3 g/d	535 (26.7)	333 (76.7)	523 (26.8)	340 (29.8)	535 (79.1)	
women with serum albumin < 20 g/L	15 (2.8)	5 (1.5)	14 (2.7)	5 (1.5)	15 (2.8)	
women with 24-hr urinary protein ≥ 0.5 g/d	417 (20.8)	256 (59.0)	407 (20.9)	261 (22.9)	417 (61.7)	
women with serum albumin < 20 g/L	15 (3.6)	5 (2.0)	14 (3.4)	5 (1.9)	15 (3.6)	
women with 24-hr urinary protein ≥ 3 g/d	148 (7.4)	84 (19.4)	144 (7.4)	86 (7.5)	148 (21.9)	
women with serum albumin < 20 g/L	11 (7.4)	3 (3.6)	10 (6.9)	3 (3.5)	11 (7.4)	

* These women had all three measures of proteinuria assessment.

† Continuous variables were compared by ANOVA or Kruskal-Wallis, and categorical variables by chi-square.

urinary protein cohort more often had superimposed preeclampsia and higher BP, although the absolute increase was small. Women in the dipstick cohort more frequently had preeclampsia based on the definition requiring hypertension and hyperuricemia. Otherwise, the groups were similar, including use of antihypertensive therapy and smoking.

Data on the results of proteinuria testing are shown in Table 2. The degree of proteinuria as assessed by Pr/Cr or 24-hour urinalysis did not differ between groups. The degree of proteinuria as assessed by dipstick proteinuria did differ between groups, although the difference was not felt to be clinically significant (e.g., between 37% and 43% of women in each group had dipstick proteinuria of 3 or 4+). Twenty-two percent of women had nephrotic-range proteinuria (i.e., ≥ 3 g/d) and < 6% had a serum albumin < 20 g/L. All measures were done in the context of clinical care without reported adverse effects of the tests themselves.

The incidence of the combined adverse maternal outcome within 48 hours of eligibility (Table 3) did not differ between the cohorts, but the occurrence of combined adverse perinatal outcome was significantly different between the cohorts (Table 4). The combined perinatal outcome occurred least frequently in the dipstick cohort (4%) and most frequently in the 24-hour urinary protein cohort (10.2%). Women in the ALL measures and 24-hour urinary protein cohorts delivered earlier, had greater prolongation of pregnancy (days from admission to delivery), and lower birth weights than the dipstick proteinuria or spot urine Pr/Cr cohorts.

In univariable analysis, all measures of proteinuria had a weak discriminative ability to distinguish between women with and without an adverse maternal outcome within 48 hours after eligibility (Table 5). Dipstick proteinuria, when considered as a categorical (rather than continuous) variable, yielded higher point estimates for AUC and odds ratios in women with 3+ or 4+ dipstick results than in women with negative or trace results. For the 24-hour urine collection, the AUC was 0.551 for all women who had the test and 0.578 for those who had all measures of proteinuria including a 24-hour urine collection. However, for all tests in the test-specific cohort and the ALL measures cohort, the 95% confidence intervals for AUC were wide and compatible with a weakly discriminative test.

For prediction of the combined adverse maternal outcome within seven days of eligibility, all point estimates for AUC were < 0.70, but for all of dipstick, spot urine Pr/Cr, and 24-hour urinary protein, the upper 95% CI crossed 0.70 (data not shown).

Table 3. Maternal outcomes characteristics, including the PIERS combined adverse maternal outcome within 48 hours of eligibility

	Full cohort N = 2002	ALL measures of proteinuria N = 434	Dipstick proteinuria cohort N = 1949	Spot urine Pr/Cr cohort N = 1411	24-hour urinary protein cohort N = 676	*P*
Days eligible until delivery, median (IQR)	2 (1–6)	5 (2–11)	2 (1–5.75)	2 (1–7)	4 (2–10)	0.829
Induction, n (%)	1179 (58.9)	272 (62.7)	1142 (58.9)	836 (59.2)	420 (62.1)	0.322
Ceasarean section, n (%)	1157 (57.8)	222 (51.2)	1132 (57.9)	794 (56.3)	360 (53.2)	0.023
One or more of PIERS maternal adverse outcomes* within 48 hours:	106 (5.3%)	39 (9.0%)	101 (5.2%)	82 (5.8%)	50 (7.4%)	0.010
Maternal death	0	0	0	0	0	
Maternal morbidities:						
Central nervous system						
Eclampsia (≥1)	6	1	6	5	1	
Glasgow coma score <13	1	0	1	1	0	
Stroke or reversible neurological deficit	0	0	0	0	0	
Cortical blindness or retinal detachment	0	0	0	0	0	
Posterior reversible encephalopathy	0	0	0	0	0	
Bell's palsy	0	0	0	0	0	
Cardiorespiratory						
Positive inotropic support	0	0	0	0	0	
Infusion of a 3rd parenteral antihypertensive	0	0	0	0	0	
Myocardial ischemia/infarction	1	0	1	1	0	
Pulmonary edema	23	10	22	19	14	
Requirement of ≥ 50% FiO_2 for >1 hr	12	4	12	10	6	
Oxygen saturation < 90%	13	6	12	12	7	
Intubation	1	0	1	0	0	
Hematological						
Platelet count < 50 × 10^9/L without transfusion	22	7	21	19	9	
Transfusion of any blood product	31	10	31	21	14	
Hepatic						
Dysfunction	9	4	9	7	4	
Hematoma/rupture	0	0	0	0	0	
Renal						
Renal failure	7	4	7	6	5	
Dialysis	1	1	1	1	1	
Other						
Placental abruption	15	7	13	11	7	

FiO_2: fractional inspired oxygen tension

* These are not mutually exclusive, as some women suffered more than one outcome.

For prediction of the combined adverse maternal outcome at any time after eligibility, all point estimates for AUC were < 0.70, with most of the upper 95% confidence intervals reaching 0.70 (data not shown).

For prediction of the combined adverse perinatal outcome, all point estimates for AUC were < 0.70 (Table 6). When dipstick proteinuria was assessed as a categorical variable, there were increased odds of outcome in women with 3+ or 4+ proteinuria compared with women with a negative or trace dipstick result (OR 2.25; 95% CI 1.74 to 2.92).

None of the models for a method of proteinuria assessment was sufficiently robust to proceed with determinations of cut-offs that optimized sensitivity and specificity.

Excluding women with non-proteinuric hyperuricemic hypertension tended to make all AUC values fall, particularly

Table 4. Perinatal demographics and outcomes including the PIERS combined adverse PERINATAL outcome

	Full cohort N = 2002	ALL measures of proteinuria N = 434	Dipstick proteinuria cohort N = 1949	Spot urine Pr/Cr cohort N = 1411	24-hr urinary protein cohort N = 676	*P**
GA at delivery, wk, median (IQR)	36.9 (34.1–38.6)	35.6 (32.6–37.5)	36.9 (34.1–38.6)	36.9 (34.4–38.6)	35.3 (31.7–37.3)	< 0.001
Birthweight, g, median (IQR)	2600 (1785–3254)	2160 (1480–2940)	2603 (1785–3254)	2610 (1838–3245)	2100 (1338–2868)	< 0.001
Birth weight < 3rd centile for age, n babies (%)	164 (8.2)	48 (11.1)	161 (8.3)	120 (8.5)	68 (10.1)	0.108
Apgar score < 7 at 5 minutes, n babies (%)	136 (6.8)	29 (6.7)	133 (6.8)	84 (6.0)	62 (9.2)	0.112
Fetal acidaemia, n (%)	49 (2.4)	7 (1.6)	48 (2.5)	35 (2.5)	16 (2.4)	0.870
One or more of combined perinatal mortality, infant mortality, or morbidity†, n	581 (29.0)	150 (34.6)	568 (29.1)	370 (32.4)	287 (42.5)	< 0.001
Stillbirth	20	4	19	6	12	
Neonatal or infant death	26	13	26	17	20	
NICU admission > 48 hours	536	133	523	347	255	

* Chi-square

† These are not mutually exclusive, as some women suffered more than one outcome.

the 24-hour urine value, in predicting adverse maternal outcomes. For dipstick proteinuria, the ALL measures AUC became 0.521 (95% CI 0.461 to 0.581) for maternal outcomes and 0.623 (95% CI 0.560 to 0.686) for perinatal outcomes. For Pr/Cr, the respective AUC values became 0.533 (95% CI 0.469 to 0.596) and 0.564 (95% CI 0.478 to 0.649), and for 24-hour urine collection, 0.452 (95% CI 0.369 to 0.535) and 0.625 (95% CI 0.553 to 0.698).

DISCUSSION

In this cohort of women admitted to hospital with preeclampsia, we found that the degree of proteinuria (as assessed by either dipstick testing, spot urine Pr/Cr, or 24-hour urine collection) was not strongly associated with the incidence of either the combined adverse maternal or adverse perinatal outcomes. Dipstick proteinuria assessment performed as well as other measures for prediction of adverse outcomes, particularly in the ALL measures cohort that consisted of women who had all three types of proteinuria assessment.

The strengths of this study include having a cohort of women with well-defined preeclampsia, investigated in a standardized fashion with defined laboratory methods and standardized, composite outcomes, rather than individual, unusual events. Women in the ALL measures cohort underwent all three measures of proteinuria assessment, and so results from this group were controlled for investigational and management decisions except for the proteinuria assessment. Also, proteinuria results were examined as a continuous variable, rather than dichotomized according to arbitrary or historical thresholds.

Weaknesses of the study include the multicentre design and having a sample size that resulted in wide 95% confidence intervals for the AUC, particularly for the ALL measures cohort. The PIERS project provided guidelines for the assessment of women with preeclampsia. Nevertheless, more of the 2023 women underwent dipstick proteinuria assessment (96.3%) than spot Pr/Cr (69.7%) or 24-hour urine collection (33.4%). This may reflect the reluctance of clinicians to pursue further testing beyond the triage urinary dipstick, perhaps in the face of certainty about the need for delivery at term, when most preeclampsia arises.[27] Women who underwent 24-hour urine collection did present earlier in gestation and more frequently at < 34 weeks, a gestational age at which expectant management may be considered, and was, in fact, the standard of care in PIERS centres. Lindheimer and Kanter have previously reviewed the origins, measurement uncertainty, and interpretation of proteinuria in pregnancy.[6] Our findings are consistent with a recent quantitative overview of relevant observational studies in which the level of proteinuria was not found to

Table 5. Univariate analysis of the relationship between the proteinuria assessment method performed within 48 hours of admission and adverse maternal outcome within 48 hours of eligibility

Variable	Population studied	N	OR (95% CI)	*P*	AUC (95% CI)
Dipstick proteinuria (+)	As a categorical variable*				
	All women with test performed	1949			0.545 (0.488 to 0.601)
	1+		0.93 (0.30 to 2.89)	0.895	
	2+		0.80 (0.28 to 2.35)	0.689	
	3 or 4+		1.39 (0.60 to 3.19)	0.439	
	ALL measures cohort	434			0.559 (0.465 to 0.653)
	1+		0.68 (0.34 to 1.37)	0.281	
	2+		0.69 (0.37 to 1.27)	0.230	
	3 or 4+		1.02 (0.63 to 1.67)	0.925	
	As a continuous variable				
	All women with test performed	1949	1.04 (0.89 to 1.21)	0.644	0.512 (0.454 to 0.570)
	ALL measures cohort	434	1.11 (0.86 to 1.43)	0.419	0.539 (0.443 to 0.634)
Spot Pr/Cr (mg/mol)	All women with test performed	1411	1.00 (0.99 to 1.01)	0.731	0.484 (0.422 to 0.546)
	ALL measures cohort	434	1.00 (0.99 to 1.01)	0.770	0.575 (0.487 to 0.662)
24-hr urinary protein (g/d)	All women with test performed	676	1.00 (0.98 to 1.02)	0.987	0.551 (0.470 to 0.631)
	ALL measures cohort	434	1.07 (0.99 to 1.16)	0.109	0.578 (0.491 to 0.665)

* Compared with negative/trace

Table 6. Univariate analysis of the relationship between the proteinuria assessment method performed within 48 hours of admission and perinatal outcome

Variable	Population studied	N	OR (95% CI)	*P*	AUC ROC (95% CI)
Dipstick proteinuria (+)	As a categorical variable*				
	All women with test performed	1949			0.605 (0.577 to 0.623)
	1+		0.86 (0.60 to 1.23)	0.413	
	2+		1.22 (0.90 to 1.66)	0.203	
	3 or 4+		2.25 (1.74 to 2.92)	< 0.001	
	ALL measures cohort	434			0.598 (0.542 to 0.654)
	1+		0.72 (0.36 to 1.44)	0.355	
	2+		0.81 (0.44 to 1.51)	0.516	
	3 or 4+		1.77 (1.07 to 2.93)	0.028	
	As a continuous variable				
	All women with test performed	1949	1.36 (1.26 to 1.47)	< 0.001	0.612 (0.583 to 0.640)
	ALL measures cohort	434	1.23 (1.06 to 1.45)	0.006	0.576 (0.518 to 0.634)
Spot Pr/Cr (mg/mmol)	Full cohort with test performed	1411	1.00 (1.00 to 1.00)	0.001	0.570 (0.534 to 0.605)
	ALL measures cohort	434	1.00 (1.00 to 1.00)	0.140	0.538 (0.479 to 0.597)
24-hr urinary protein (g/d)	Full cohort with test performed	676	1.00 (0.99 to 1.01)	0.845	0.643 (0.601 to 0.686)
	ALL measures cohort	434	1.09 (1.02 to 1.16)	0.013	0.602 (0.544 to 0.659)

* Compared with negative/trace.

be clinically useful for prediction of adverse maternal or perinatal outcomes.[28] However, as the limits of the 95% confidence intervals of the likelihood ratios could not rule out some predictive capacity (for perinatal outcomes), the authors of the quantitative overview identified the need for future studies. We have been able to address the criticism of heterogeneity in terms of women enrolled, proteinuria testing methods, preeclampsia definition, and outcomes (chosen and defined) in previous publications.[25] In particular, in this publication we have shown that despite differences in the definition of preeclampsia (more often hypertension and hyperuricemia for the dipstick cohort) or gestational age at presentation (lower for the ALL measures and 24-hour urinary protein cohorts), we were unable to demonstrate important differences in test performance for any of the three measures of proteinuria. We were unable to address the issue of statistical power adequately.

Use of a dipstick to assess proteinuria appeared to perform as well as other assessment methods, despite being neither sensitive nor specific for abnormal 24-hour protein excretion. A first possible explanation for this may be that detecting an abnormal amount of urinary protein excretion ($\geq$ 0.3 g/d) with reference to the 95% confidence intervals for normal pregnancy, as we did, is not necessarily appropriate in identifying women (or babies) at increased risk of problems. A second possible explanation is that because dipstick proteinuria is a measurement of both protein excretion *and* urine concentration,[29] dipstick proteinuria may also reflect plasma volume reduction or subclinical renal dysfunction. A third possible explanation is that dipstick proteinuria testing is inexpensive and widely available.

In this study, the level of proteinuria failed to predict adverse pregnancy outcomes. Proteinuria reflects only one aspect of the complex syndrome of preeclampsia,[6] and according to our findings, as well as those of Thangarantinam et al.,[28] proteinuria is clearly insufficient as a stand-alone predictor of adverse outcomes. Although it is possible that some of the predictive power of proteinuria may have been attenuated by delivery because of higher levels of proteinuria,[1] a central role of proteinuria (either in the definition of severe preeclampsia or as a delivery indication) should be revisited. In their recent review of the role of proteinuria assessment in pregnancy, Lindheimer and Kanter "recommend that current cut-off for abnormal proteinuria be used to diagnose preeclampsia, but the level of proteinuria should not guide management. Other variables, such as status of blood pressure control, evidence of increasing organ damage in the liver and hematological systems, evidence of falling glomerular filtration rate, and signs of neurological involvement, are more reliable indicators of severity of preeclampsia."[6] In view of the findings of the multivariable PIERS modelling study,[25] we concur with that view.

We found that no method of proteinuria assessment was strongly associated with adverse maternal or perinatal outcomes. However, some discriminatory power could not be ruled out. Dipstick proteinuria performed as well as other methods. These findings should encourage reconsideration of the central role of proteinuria in the classification of the hypertensive disorders of pregnancy. Suggestions that dipstick proteinuria not be used in pregnancy at all should also be reconsidered.[6] All variables defining preeclampsia and its severity should be based on an assessment of the risk of adverse maternal and perinatal outcomes.[25]

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APPENDIX

Members of the PIERS Delphi Consensus

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