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A practical approach to using spot urine protein/creatinine ratios for assessing proteinuria in pregnancy

Catherine A Marnoch MB ChB FRACP*, **Lucia Larson** MD*, **Sherry Weitzen** MS PhD†, **Maureen G Phipps** MD MPH†, **C James Sung** MD FCAP‡ and **Raymond O Powrie** MD FRCP(C)*

*Department of Medicine; †Division of Research, Department of Obstetrics and Gynecology and Community Health; ‡Department of Pathology, Women and Infants Hospital of Rhode Island, Warren Alpert Medical School of Brown University, Providence RI, USA

Summary

Objective: The aim of this study is to assess the diagnostic accuracy of the spot urine protein/creatinine ratio compared with the 24-hour urine protein in pregnancy.

Study Design: In this prospective cohort study of inpatient pregnant women, the protein/creatinine ratio and dipstick protein were assessed from a single urine sample collected at the start of the 24-hour urine. Both tests were compared with the 24-hour urine protein for correlation and test characteristics.

Results: In the 196 specimens analysed, we found a strong correlation between the spot urine protein/creatinine ratio and 24-hour urine protein ($r^2 = 0.78$, $P < 0.01$). A protein/creatinine ratio <0.1 ruled out significant proteinuria (≥ 300 mg/day) with sensitivity and negative predictive value 100%. A protein/creatinine ratio ≥ 0.4 detected significant proteinuria (specificity and positive predictive value of 100%). A protein/creatinine ratio ≥ 4.6 had a specificity and positive predictive value of 100% for detecting severe proteinuria (≥ 5000 mg/day). Urine dipsticks correlated poorly with the 24-hour urine protein ($r^2 = 0.40$, $P = 0.826$). Nineteen percent of dipsticks reading nil or trace were false-negative results.

Conclusion: The spot urine protein/creatinine ratio correlated well with the 24-hour urine protein and performed better than the urine dipsticks. Significant proteinuria in pregnancy was excluded if the protein/creatinine ratio was <0.1 and identified when it was ≥ 0.4.

Keywords: pregnancy, proteinuria, protein/creatinine ratio, sensitivity, specificity

INTRODUCTION

Accurate quantification of proteinuria is important for the diagnosis of pre-eclampsia. The current gold standard, the 24-hour urine protein, is less than ideal because it is cumbersome to collect and its processing is labour-intensive. As a result, clinical decision-making is often delayed. Urine protein dipsticks are inaccurate[1] and, although they may be improved with automated analysis,[2] should not be relied upon solely.

Urine protein/creatinine ratios have been investigated in pregnancy since 1987[3] when Boler *et al.* showed an excellent correlation with 24-hour urine protein ($r = 0.99$). Since then other investigators have confirmed these results in women suspected of having pre-eclampsia[2,4–10] and in other pregnant populations.[3,11,12] However, when screening test characteristics have been published, a variety of values of the protein/creatinine ratio consistent with significant proteinuria are reported, ranging from 0.15 to 0.5.[2,5,7,8,12,13] Moreover, the usefulness of the protein/creatinine ratio in pregnancy has been challenged by two recently published studies with larger numbers which did not find a good correlation with the 24-hour urine protein ($r^2 = 0.56$,[13] $r^2 = 0.41$[14]) or a single value with adequate sensitivity and specificity to clearly identify abnormal proteinuria.[13]

In the context of this conflicting literature, we undertook this study to further assess the ability of the spot urine protein/ creatinine ratio to diagnose significant proteinuria in pregnant patients undergoing 24-hour urine protein evaluation. We also set out to determine the protein/creatinine ratio value that would be equivalent to ≥ 300 mg protein/day and ≥ 5000 mg protein/day.

Correspondence to: Dr Catherine Marnoch
Email: catherine.marnoch@waitematadhb.govt.nz

MATERIALS AND METHODS

We performed a prospective cohort study of pregnant women admitted to the ante partum wards of Women and Infants Hospital of Rhode Island between February 2003 and March 2004. All the participants completed a 24-hour urine collection for the assessment of significant proteinuria in pregnancy, as requested by their admitting obstetrician. Consecutively, we collected a 5 mL spot urine sample from women at the start of the 24-hour urine collection. No first voided morning samples were used for this specimen. While most women were admitted for the investigation of hypertension in pregnancy, we also included women throughout gestation and with a history of chronic hypertension, renal disease and diabetes. We excluded samples

if the 24-hour urine testing was not completed and therefore not processed by the laboratory, and if the woman had pre-existing proteinuria (≥2+ on dipstick or ≥300 mg/day on 24-hour urine prior to 20 weeks of gestation). Two investigators reviewed the medical records for demographic and laboratory data at the time of urine collection. The Women and Infants Hospital of Rhode Island Institutional Review Board approved the study as a residual tissue collection on 25 November 2002.

Spot urine samples were tested for protein/creatinine ratio and dipstick analysis by our hospital's laboratory staff. For the dipstick, Multistix 10 SG Reagent Strips for Urinalysis (Bayer HealthCare LLC, Elkhart, IN, USA) were used and read on a Clinitek 500 Urine Chemistry Analyzer (Bayer Diagnostics, Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). Results were graded as nil, trace, 30 mg/dL (+), 100 mg/dL (++), 300 mg/dL (+++) or >300 mg/dL >+++). Urine protein was measured using a timed endpoint method reacting with pyrogallol red and molydate, and urine creatinine using a modified rate Jaffe method. A Synchron CX5 CE Chemistry Analyzer (Beckman Coulter, Inc., Fullerton, CA, USA) was used. The coefficient of variation, in our laboratory, for urine protein is 4–6% and for urine creatinine is 3–4.5%. We calculated the protein/creatinine ratio by dividing the protein (mg/dL) by creatinine (mg/dL) in both the spot urine and 24-hour urine specimens. The 24-hour urine protein was recorded in mg/day. At the time of the spot urine analysis laboratory staff were blinded to the results of the 24-hour urine.

Statistical analysis was performed using SPPS for Windows (SPPS Inc., Chicago, IL, USA) statistical programme. In the process of estimating our sample size, we calculated that 200 urine specimens were required to estimate a value for the protein/creatinine ratio equivalent to significant proteinuria (≥300 mg/day), with a sensitivity of 0.92, specificity of 0.85 and a margin of error of 5%. Reporting of demographic data was descriptive. A linear regression model was used to estimate the correlation between 24-hour urine protein excretion and spot urine protein/creatinine ratio; and 24-hour urine protein and spot urine dipsticks. Using the 24-hour urine protein results as the gold standard, we calculated the test characteristics of the protein/creatinine ratio to predict significant proteinuria (≥300 mg/day) as a range of values. We used the level of ≥5000 mg/day to indicate severe proteinuria[15] and calculated the test characteristics at this level also. Receiver-operating characteristic (ROC) curves (plotting sensitivity versus 1−specificity) were constructed and the area under the curves were calculated. For the urine dipsticks, we considered a result of the nil or trace to be negative and ≥30 mg/dL (+) positive with true-negative being <300 mg/day on the 24-hour urine collection and true-positive as ≥300 mg/day. Ninety-five percent confidence intervals (CI) were used and a *P*-value <0.05 was considered significant.

RESULTS

Two hundred and thirty-two spot urine samples were collected, but 24 were excluded because the 24-hour urine samples were not processed. The demographic characteristics of the remaining 208 samples obtained from 190 women are shown in Table 1. Of these, 12 subjects had significant proteinuria at <20 weeks of gestation and were excluded from the final analysis. Causes of proteinuria in these 12 samples were diabetic nephropathy (6 with type 1 diabetes; 2 with type 2 diabetes) and primary renal disease (4). Seven of the 12 excluded also had chronic hypertension due to diabetes or renal disease.

Table 1 **Characteristics of participants**

Characteristics	All (*n* = 190)	24-hour urine protein ≥300 mg/day (*n* = 75)	24-hour urine protein ≥5000 mg/day (*n* = 15)
Age (years)	28.8 ± 6.9	28.6 ± 6.5	29.5 ± 8.3
Ethnicity			
White	119 (64)	47 (64)	10 (67)
African-American	26 (14)	9 (12)	0
Hispanic	30 (16)	13 (18)	4 (27)
Asian	8 (4)	4 (5)	1 (6)
Other	3 (2)	1 (1)	0
Gestation at test (weeks)	29.8 ± 9.2	32.8 ± 5.6	32.2 ± 4.1
Gestation >20 weeks	181 (87)	80 (96)	16 (100)
Nulliparous	95 (50)	42 (56)	6 (40)
Gravidity	2 (1–12)	2 (1–8)	2 (1–12)
Parity	0 (0–6)	0 (0–3)	0 (0–6)
Multiple gestation	18 (9)	8 (11)	0 (0)
Significant proteinuria <20 weeks gestation	12 (6)	11 (13)	5 (31)
SCr >1.0 mg/dl (88 μmol/L) <20 weeks	4 (2)	2 (2)	0 (0)
UA >5.0 mg/dl (297 μmol/L) at study date	82 (40)	53 (64)	13 (81)
SCr >0.7 mg/dl (62 μmol/L) at study date	86 (46)	46 (55)	13 (81)
SCr >1.0 mg/dl (88 μmol/L) at study date	11 (5)	6 (7)	4 (25)

SCr, serum creatinine; UA, uric acid
We collected 208 samples from 190 women. Data are expressed as *n* (%), mean ± SD or median (range)
Significant proteinuria defined as ≥300 mg/day in the 24-hour urine protein

This left 196 pairs of spot urine and 24-hour urine samples in the final analysis. Spot urine dipstick results were available from 188 samples. Seventy-one women in the final study population had chronic medical conditions: type 1 diabetes ($n = 12$; 6%), type 2 diabetes ($n = 19$; 10%), primary renal disease ($n = 3$; 2%) and chronic hypertension ($n = 37$; 19%). Of those with chronic hypertension, 10 were secondary to renal disease or diabetes and 27 had essential hypertension or other secondary causes. Reasons for initiating the 24-hour urine test were either investigating the diagnosis of pre-eclampsia ($n = 167$; 85%) or the computation of baseline proteinuria in women with chronic medical conditions ($n = 29$; 15–27% with diabetes, two with chronic hypertension).

The degree of proteinuria from the 24-hour urine specimens collected ranged from 11 to 20,000 mg/day. Significant proteinuria (≥300 mg/day) was found in 72 of the 196 samples (37%). Eleven samples had ≥5000 mg protein/day. The spot urine protein/creatinine ratio results ranged from 0.04 (4.5 mg/mmol) to 13.96 (1579 mg/mmol).

Figure 1 demonstrates the relationship between the protein/creatinine ratio and the 24-hour urine protein level. A strong correlation was seen ($r^2 = 0.78$, $P < 0.01$). The area under our ROC curve was 0.94 (95% CI 0.91–0.97).

Urine dipsticks correlated poorly with the 24-hour urine protein. The square of the sample correlation coefficient was 0.40 ($P = 0.826$) and the area under the ROC curve was 0.84 (95% CI 0.78–0.91). One hundred and forty-four urine dipstick results were nil or trace. Of these, 116 (81%) were true-negative results and 28 (19%) were false-negative results when compared with the 24-hour urine protein. Forty-four dipstick results were

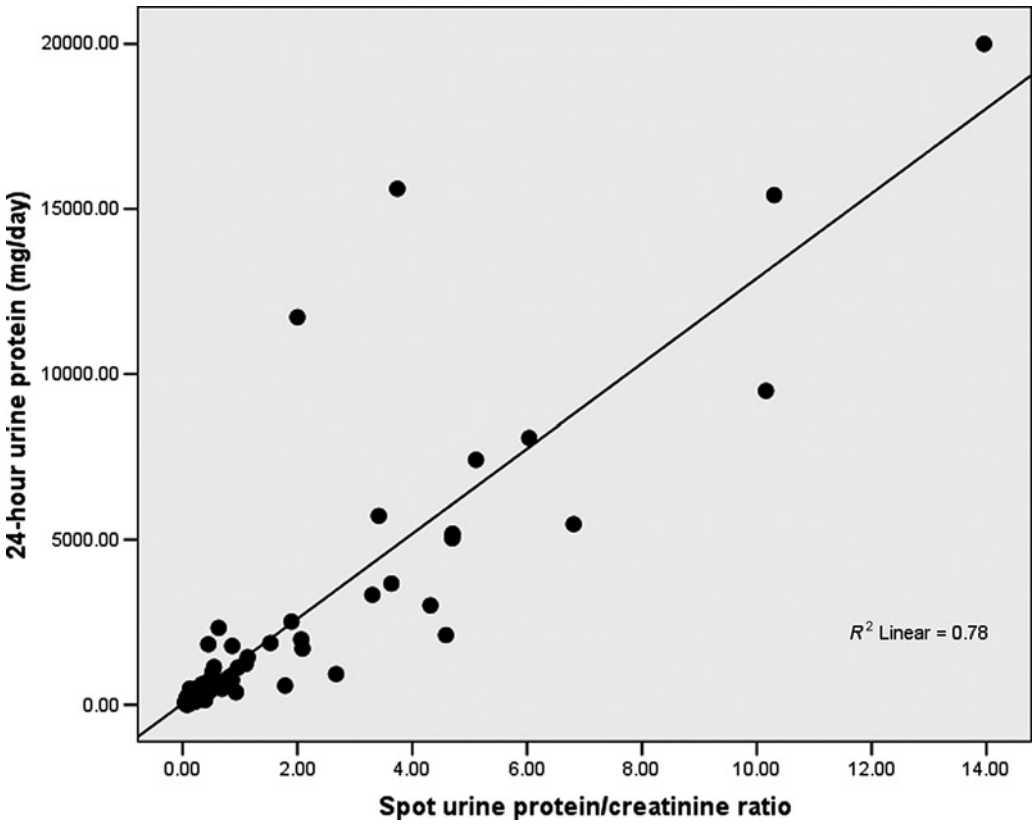

Figure 1 **Correlation between 24-hour urine protein vs. spot urine protein/creatinine ratio for significant proteinuria (≥300mg/day)**

≥30 mg/dL (+) and 41 (93%) had correctly identified protein ≥300 mg/day on the 24-hour urine protein.

Using ≥300 mg protein/day in the 24-hour urine as the gold standard for significant proteinuria, Table 2 demonstrates the sensitivity, specificity, positive- and negative-predictive values of the protein/creatinine ratio at a range of different cut-offs. A value of <0.1 (11 mg/mmol) for the protein/creatinine ratio had a sensitivity and negative-predictive value of 100% and a value of ≥0.4 (45 mg/mmol) had a specificity and positive-predictive value of 100%. Thirty-five (18%) protein/creatinine ratio results were <0.1 and 46 (23%) were ≥0.4.

The single best value to identify significant proteinuria was a protein/creatinine ratio of ≥0.2 (22.6 mg/mmol) with a sensitivity of 85% and specificity of 85%.

When assessing the diagnosis of severe proteinuria, defined as protein ≥5000 mg/day in a 24-hour urine collection ($n = 11$), the protein/creatinine ratio did not correlate well. The square of the sample correlation coefficient was 0.32 ($P = 0.07$). Nevertheless, the area under the ROC curve was 0.99 (95%CI 0.99–1.00) and the best cut-off for the protein/creatinine ratio to predict severe proteinuria was a level ≥3.0 (339 mg/mmol) with a sensitivity of 91% (95% CI 0.62–0.98) and a specificity of 98% (95% CI 0.95–0.99). A value of <2.0 (226 mg/mmol) had a sensitivity and negative-predictive value of 100%, and a value of ≥ 4.6 (519 mg/mmol) had a specificity and positive-predictive value of 100% for severe proteinuria.

We performed a subgroup analysis, including only samples from women who had the tests performed to investigate pre-eclampsia ($n = 167$). The square of the sample correlation coefficient to diagnose significant pre-eclampsia was 0.74 ($P < 0.001$), and area under the ROC curve was 0.94 (95% CI 0.90–0.97). The test characteristics with a range of cut-offs for this subgroup are shown in Table 3. Results were similar to those obtained for the entire study population. A protein/creatinine

Table 2 **Performance of spot urine protein/creatinine ratio for detection of significant proteinuria (≥300 mg/day) with various cut offs**

Cut off	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV	NPV	LR+	LR−	False-positive tests (*n*/196)	False-negative tests (*n*/196)
0.1	100 (95–100)	28 (21–37)	45	100	1.39	0	89	0
0.2	85 (75–91)	85 (77–90)	76	91	5.53	0.18	19	11
0.3	69 (58–79)	99 (96–100)	98	85	86.11	0.31	1	22
0.4	64 (52–74)	100 (97–100)	100	83	–	0.36	0	26
0.5	51 (40–63)	100 (97–100)	100	78	–	0.49	0	35
0.6	44 (34–56)	100 (97–100)	100	76	–	0.56	0	40

CI, confidence interval; PPV, positive-predictive value; NPV, negative-predictive value; LR+, likelihood ratio for a positive test; LR−, likelihood ratio for a negative test

Table 3 **Performance of spot urine protein/creatinine ratio for the detection of significant proteinuria (≥300 mg/day) with various cut offs when the test was performed in women to diagnose or exclude pre-eclampsia (*n* = 167)**

Cut off	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV	NPV	LR+	LR−	False-positive tests (*n*/167)	False-negative tests (*n*/167)
0.1	100 (95–100)	20 (13–29)	49	100	1.25	0	76	0
0.2	85 (75–91)	83 (74–89)	79	88	5.03	0.18	16	11
0.3	69 (58–79)	100 (93–100)	100	81	–	0.31	0	22
0.4	64 (52–74)	100 (96–100)	100	79	–	0.36	0	26
0.5	51 (40–63)	100 (96–100)	100	73	–	0.49	0	35
0.6	44 (34–56)	100 (96–100)	100	70	–	0.56	0	40

CI, confidence interval; PPV, positive-predictive value; NPV, negative-predictive value; LR+, likelihood ratio for a positive test; LR−, likelihood ratio for a negative test

ratio of <0.1 (11 mg/mmol) had a sensitivity and negative-predictive value of 100% and the protein/creatinine ratio value with specificity and positive-predictive value of 100% was ≥0.3 (34 mg/mmol).

DISCUSSION

Our study found a strong correlation of the spot urine protein/creatinine ratio compared with the 24-hour urine protein testing when assessing significant proteinuria (≥300 mg/day). As has been well established previously,[1,2,16] urine dipstick testing performed poorly when compared with the 24-hour urine protein with a clinically unacceptable number of false-negative results.

These findings, in favour of the spot urine protein/creatinine ratio, add to the debate on the usefulness of this test for the diagnosis of significant proteinuria in pregnancy, particularly its role in clinical practice. Some authors have recommended adopting this test into routine practice.[17,18] However, acceptance of this is not universal. Even with our good correlation, we were unable to find a single value of the protein/creatinine ratio that adequately 'ruled in' or 'ruled out' significant proteinuria. We do not think that the sensitivity (85%) and specificity (85%) obtained at the 0.2 cut-off value provides the clinician with enough assurance to replace a 24-hour urine protein with the protein/creatinine ratio in all the pregnant patients. However, we have identified two useful values: a lower cut-off (<0.1) at which the significant proteinuria is excluded and an upper cut-off (≥0.4) at which the significant proteinuria is diagnosed with certainty.

We therefore think it is the time to reconsider the role of the protein/creatinine ratio and view it as a useful test, but not the one that will entirely replace the 24-hour urine proteins in pregnancy. If no single value can be found to reliably correlate with ≥300 mg protein/24-hour, the test can still be used to improve the efficiency of care in this population. In pregnant patients for whom a 24-hour urine is being considered, the protein/creatinine ratio could be performed as an initial test. Based on our study, if the result is <0.1 or ≥0.4, significant proteinuria is excluded or confirmed and the number of 24-hour urine tests required is reduced by 41% (81/196 samples). If the result is within these values, a 24-hour urine protein may still be considered. However, we acknowledge that if a clinician wishes to determine the creatinine clearance or a more specific urinary protein value, a 24-hour urine may still be required even when the protein/creatinine ratio is ≥0.4. In our study if the gold standard test is performed whenever the spot urine protein/creatinine ratio is ≥0.1, the reduction of 24-hour urine tests required is 18% (35/196 samples).

We did not find a good correlation when assessing severe proteinuria defined as ≥5000 mg/day in the 24-hour urine. However, there were only 11 samples in this group. These numbers are too small to make any meaningful assessment about the correlation of the protein/creatinine ratio with the 24-hour urine for assessing severe proteinuria. Even so, in our study if the protein/creatinine ratio was ≥4.6, a clinician can be confident that the woman does have severe proteinuria as the positive-predictive value at this level was 100%.

Table 4 shows our results and the published results of four other investigators who also found protein/creatinine ratio values corresponding to a sensitivity, specificity, positive-predictive value and negative-predictive value of 100%, when compared with the gold standard of ≥300 mg protein in a 24-hour urine collection. All the authors chose to identify one single cut-off value for a positive test for the protein/creatinine ratio, with some sacrifice of sensitivity and specificity. Our approach of using a range of values could be followed using their results, with the lower value being the protein/creatinine ratio with sensitivity and negative-predictive

Table 4 **Other studies which found the cut offs for protein/creatinine ratio with sensitivity, specificity and predictive values of 100%, when compared with the 24-hour urine protein ≥300 mg/day**

Study	Number of subjects	Cut off with Sens/NPV 100%*	Cut off with Spec/PPV 100%*	Chosen cut off*	Test characteristics at chosen cut off sens/spec/PPV/NPV
Young *et al.*[7]	45	0.05	0.3	0.15	91/41
Saudan *et al.*[2]	100	0.18†	0.40†	0.27†	93/92/95/90
Ramos *et al.*[9]	47	0.3	0.8	0.5	94/80/72/96
Rodreguez-Thompson *et al.*[10]	138	0.14	Not reported	0.19	90/70/75/87
Marnoch *et al.*	196	0.1	0.4	0.2	85/85/79/91

Data for sensitivity, specificity and predictive values are expressed in percentages. NPV, negative predictive value; PPV, positive predictive value; Sens, Sensitivity; Spec, Specificity

*Units are mg dL^{-1}/mg dL^{-1}

†Original data by Saudan *et al.* is expressed as 20 mg/mmol, 45 mg/mmol, 30 mg/mmol, respectively (conversion factor to mg dL^{-1}/mg dL^{-1} = mg/mmol × 0.00884)

value of 100% and the upper value the protein/creatinine ratio with specificity and positive-predictive value of 100%. There is variation between the studies in the range of values identified, which may reflect different methods of analysing urine protein. We suggest that at the stage of introducing the protein/creatinine ratio into clinical practice, each centre should establish its own correlation of the spot urine protein/creatinine ratio with the 24-hour urine protein and determine the appropriate values for a positive, negative and indeterminate test.

Critics may say that we are proposing another screening test which is already the role of the urine protein dipstick. However, we found that the protein/creatinine ratio performed better than dipstick testing when compared with the 24-hour urine protein. In addition to the increased accuracy of the protein/creatinine ratio, the test still has a rapid turnaround time, is easily performed on 5 mL of fresh urine with minimal inconvenience to the patient and has very little potential for the errors in collecting or storing that plague 24-hour urine collections.

A limitation of our study could be the inclusion of women who may have had non-pre-eclampsia-related proteinuria, as our sample includes women with chronic medical conditions. We included these subjects as conditions such as chronic hypertension, renal disease, and diabetes are risk factors for pre-eclampsia, and we wanted our results to be generalizable to the patients we see in clinical practice. To limit confounding, we excluded from our analysis all the samples from women who had significant proteinuria prior to 20 weeks of gestation. In addition, a subgroup analysis including only women who had the test performed to diagnose or exclude pre-eclampsia, did not significantly change our correlation or predictive values at various cut offs. In fact in this subgroup we obtained tighter cut points of 0.1 (11 mg/mol) – 0.3 (34 mg/mol) to exclude and diagnose significant proteinuria.

Our study was performed on an inpatient population and there may be concerns that the results cannot be extrapolated to the ambulatory setting. We think this is unlikely as our prevalence of significant proteinuria is similar to other studies.[2,8,19] Other investigators also found a good correlation between the two tests measured in outpatient clinics or day stay units[2,3,5] and Valerio *et al.*[19] found that the first sample on arrival at their clinic correlated strongly with the 24-hour urine protein (Spearman $\rho = 0.8$).

In conclusion, the protein/creatinine ratio correlates well with the 24-hour urine protein in this study with a large number of pregnant patients. We identified the values which 'rule in' and 'rule out' significant proteinuria. Adoption of this test into more widespread usage could expedite decision-making in pre-eclampsia, avoid hospitalization of some women and perhaps improve patient satisfaction and compliance with testing.

DECLARATIONS

Competing interests

None of the authors of this paper have any known conflicts of interest.

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Contributorship

CAM, Principal Investigator for the study, developed the study concept and design, supervised the collection of samples, laboratory analysis and data entry, analysed and interpreted the data, drafted and revised all versions of the article, including the final version and supervised the study.

L.L.: Developed the study design, interpreted the data, revised the article for important intellectual content and approved the final version to be published.

S.W.: Developed the study design, analysed and interpreted the data, performed all statistical analysis and statistical data interpretation, revised the article for important intellectual content and approved the final version to be published.

M.G.P.: Developed the study design, interpreted the data, revised the article for important intellectual content and approved the final version to be published.

C.J.S.: Supervised laboratory aspects of the study, including study design, analysis of samples, interpretation of laboratory data, revised the article for important intellectual content and approved the final version to be published.

R.O.P.: Developed the study concept and design, analysed and interpreted the data, revised the article for important intellectual content, approved the final version to be published, and supervised the study.

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