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Review

Use of Protein:Creatinine Ratio Measurements on Random Urine Samples for Prediction of Significant Proteinuria: A Systematic Review

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Background: **Proteinuria is recognized as an independent risk factor for cardiovascular and renal disease and as a predictor of end organ damage. The reference test, a 24-h urine protein estimation, is known to be unreliable. A random urine protein:creatinine ratio has been shown to correlate with a 24-h estimation, but it is not clear whether it can be used to reliably predict the presence of significant proteinuria.**

Methods: **We performed a systematic review of the literature on measurement of the protein:creatinine ratio on a random urine compared with the respective 24-h protein excretion. Likelihood ratios were used to determine the ability of a random urine protein:creatinine ratio to predict the presence or absence of proteinuria.**

Results: **Data were extracted from 16 studies investigating proteinuria in several settings; patient groups studied were primarily those with preeclampsia or renal disease. Sensitivities and specificities for the tests ranged between 69% and 96% and 41% and 97%, respectively, whereas the positive and negative predictive values ranged between 46% and 95% and 45% and 98%, respectively. The positive likelihood ratios ranged between 1.8 and 16.5, and the negative likelihood ratios between 0.06 and 0.35. The cumulative negative likelihood ratio for 10 studies on proteinuria in preeclampsia was 0.14 (95% confidence interval, 0.09–0.24).**

Conclusion: **The protein:creatinine ratio on a random urine specimen provides evidence to "rule out" the presence of significant proteinuria as defined by a 24-h urine excretion measurement.**

Proteinuria is recognized as an independent risk factor for cardiovascular and renal disease and as a predictor of end organ damage *(1)*. In particular, detection of an increase in protein excretion is known to have both diagnostic and prognostic value in the initial detection and confirmation of renal disease *(2)*, and the quantification of proteinuria can be of considerable value in assessing the effectiveness of therapy and the progression of the disease *(3–5)*. Although some investigators advocate the use of albumin as an alternative to the total protein measurement *(6–8)* and others have suggested that the profile of proteins excreted has differential diagnostic and prognostic value *(9)*, the National Kidney Foundation has recommended that an increase in protein excretion be used as a screening tool in patients at risk of developing renal disease *(10)*. An increase in protein or albumin excretion has been used in the early detection of several specific conditions, e.g., preeclampsia, diabetic nephropathy, and nephrotoxicity attributable to drugs. In all of these clinical scenarios, it is acknowledged that the definitive measurement of protein or albumin excretion is based on a timed urine collection over 24 h.

It is also recognized, however, that there are problems associated with the collection of a 24-h urine, with several reports identifying poor compliance. This further adds to the cost of what can already be an expensive procedure *(11–13)*. The use of a 24-h collection is necessitated by the variation in protein excretion throughout the day, which negates the use of concentration measurements in random urine collections *(14, 15)*.

Because the excretion of creatinine and protein is reasonably constant throughout the day when the glomerular filtration rate is stable *(16)*, some have proposed the use of a ratio measurement of protein to creatinine in urine samples collected over shorter time periods, or even random (or "spot") urine samples. Others have proposed

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the use of urine specific gravity or osmolality in the denominator of the ratio *(17)*. Newman et al. *(18)* recently showed that variations in protein and albumin excretion in urine samples collected throughout the day are much less when their concentrations are expressed as a ratio to creatinine or specific gravity.

Several authors have studied the relationship between the protein (or albumin):creatinine ratio and 24-h excretion *(16, 19–41)*. In some of these studies, the predictive value for detecting significant proteinuria was calculated. However, although the correlation statistics indicated a close relationship between the ratio measurements and 24-h protein excretion, the data did not indicate the confidence with which a random or spot urine ratio measurement might be used to "rule in" or, alternatively, "rule out" significant proteinuria.

We therefore conducted a systematic review of the literature to evaluate the utility of the protein:creatinine ratio in a random urine to rule in or rule out proteinuria. We also extended the search to include data on the ratio to osmolality. The measurement of 24-h protein excretion was used as the reference (gold standard) method.

Materials and Methodology

We performed an electronic search of the Medline and EMBASE databases, using the MeSH terms "urine protein creatinine ratio", "proteinuria", "sensitivity", and "specificity". Only full papers and letters were included in the search. After identifying potentially relevant papers, using the inclusion criteria described below, we also searched the reference lists of the papers included for additional relevant papers.

All titles and abstracts generated by the search were reviewed and relevant full papers obtained. Each of the papers was read by 2 authors (C.P.P. and R.G.N.). Inclusion of papers in the data extraction stage was based on the following criteria: (*a*) the main objective of the paper was to assess use of a ratio measure for detection of proteinuria; (*b*) the patient population was defined, including age and pathology; (*c*) the number of patients and any exclusion criteria were identified; (*d*) the timing of collection of random urines was identified; (*e*) analytical methods were defined; (*f*) cutoff values were defined for the ratio and reference method; (*g*) 24-h urine protein reference data were available for each urine sample; and (*h*) data were available to enable calculation of sensitivities, specificities, and positive and negative likelihood ratios.

The 2 × 2 contingency tables derived from the data presented in the papers were used to calculate sensitivities, specificities, and positive and negative predictive values. In some cases these values were not provided in the original publications and had to be calculated from the raw data. Positive and negative likelihood ratios were determined by the "score" method as recommended by Altman et al. *(42)*.

STATISTICAL ANALYSIS

Data from the studies examined were summarized by graphical analysis and metaanalysis. Forest plots of test sensitivities and specificities were constructed to allow graphical comparisons among studies. Heterogeneity among the studies for these measures was assessed by χ^2 testing according to the Cochran method *(43, 44)*. Summary measures for sensitivity, specificity, positive likelihood ratio [LR(+)],[3] negative likelihood ratio [LR(−)], and diagnostic odds ratio (DOR) across the 10 preeclampsia studies were calculated by random-effects ANOVA. Cumulative metaanalysis of LR(−) and LR(+) was used to characterize the progressive narrowing of confidence intervals for their summary measures as information was added from successive studies. Such information is useful in assessing the need for further studies. The SAS procedure GENMOD was used to carry out these calculations, incorporating the restricted maximum likelihood estimation method. Likelihood ratios were computed for each study and used in constructing a summary ROC curve by the method of Moses et al. *(45)*. The statistical significance of the slope estimate, β, in the Moses analysis was used to assess whether factors beyond variation in the test threshold contributed to heterogeneity among the studies.

Results

OVERVIEW OF SEARCH

The initial electronic search covering the period 1984–2004 yielded a total of 276 titles. After a review of titles and abstracts for relevance, 46 papers were selected and full copies obtained; hand searching generated 2 additional papers. A total of 16 papers were subsequently found to meet the inclusion criteria; these papers were carried through to the data extraction stage. A summary of the selection of studies to include in the review is illustrated in Fig. 1. It was apparent that several of the papers did not include the raw data on true- and false-positive and -negative rates, and these rates had to be calculated or extrapolated from the information given in the publication.

The basic descriptions of the patient cohorts are documented in Table 1. A total of 10 studies included pregnant women, either in the general population or as those specifically considered to be at risk of preeclampsia, and 4 included patients attending renal clinics, including 2 cohorts of patients who had received kidney transplants. One study focused specifically on proteinuria in the elderly and another on patients attending a rheumatology clinic.

Although the usual definition of significant proteinuria is a protein excretion >300 mg/24 h, not all of the studies used this threshold. The relationship between the sensi-

[3] Nonstandard abbreviations: LR(+) and LR(−), positive and negative likelihood ratios, respectively; DOR, diagnostic odds ratio; 95% CI, 95% confidence interval.

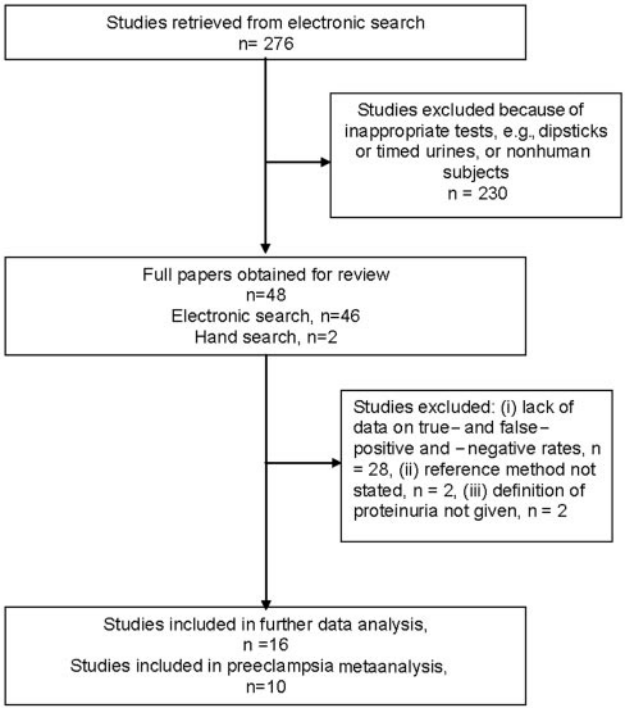

Fig. 1. Details of the selection process for papers identified from the initial electronic search and journal hand-searching routines.

tivities, specificities, and the cutoff values chosen by the researchers is plotted in Fig. 2; it should be noted that all concentrations have been expressed in SI units to make comparison across studies possible.

CORRELATION STATISTICS

A majority of the studies calculated correlation coefficients between the protein ratio and 24-h urinary protein excretion, in some cases with no further analysis. These data are summarized in Table 2 and indicate that the *r* value was >0.9 in most cases. The data include additional studies that did not furnish sufficient information for the full analysis outlined above.

POOLED ESTIMATES OF SENSITIVITY AND SPECIFICITY

Forest plots of the sensitivities and specificities from the 16 studies are shown in Fig. 3. Because of dissimilarities in the underlying patient populations across the studies, summary estimates of sensitivity, specificity, DOR, LR(+), and LR(−) were computed only for the 10 studies performed in preeclamptic women. The pooled estimate of mean sensitivity for the protein:creatinine ratio from the 10 preeclampsia studies was 0.90 [95% confidence interval (95% CI), 0.86–0.93]. Similarly, the pooled estimate of mean specificity was 0.78 (0.68–0.88). There was apparent heterogeneity among the specificities of the studies ($P < 0.0001$), but no statistically significant heterogeneity was detected among the sensitivities ($P = 0.15$). The summary estimate of the DOR was 32 (95% CI, 14–75). There was significant heterogeneity in the DORs among the studies ($P = 2 \times 10^{-5}$), deriving primarily from the much lower DORs (6.1 and 5.2) observed in the studies of Young et al. *(20)* and Durnwald and Mercer *(26)*, respectively.

A summary ROC plot including all of the studies is shown in Fig. 4. It should be noted that these data are based on the cutoff values chosen by the investigators, some of which were determined by ROC curve analysis. In view of the nonsignificant β-coefficient in a Moses-type summary ROC analysis (β coefficient = −0.50; $P = 0.09$), no significant heterogeneity was seen in odds ratios across the 16 studies that was not accounted for by variation in test threshold among studies. Although the summary ROC plot indicated that ratio measures have high value in predicting proteinuria, it did not enable the quality of these tests in either the rule-in or rule-out modes to be easily judged. We therefore focused further analysis on likelihood ratios.

Forest plots of the LR(+) and LR(−) for the 16 studies are shown in Fig. 5. As with the specificities, there was significant heterogeneity in the LR(+) and LR(−) across the 10 preeclampsia studies ($P < 0.0001$ and $P = 0.015$, respectively). Heterogeneity in the LR(−) stemmed primarily from the unusually high value (0.34) noted in the study of Durnwald and Mercer *(26)*. Summary estimates of the LR(+) and the LR(−) across the 10 preeclampsia studies were 4.2 (95% CI, 2.6–6.9) and 0.14 (0.09–0.24), respectively.

To determine the reliability of the data and whether there is a need for more data to be produced, we performed a cumulative metaanalysis of the likelihood ratios in the 10 preeclampsia studies after placing the studies in chronologic order. The cumulative data for the LR(−) in these studies are shown in Fig. 6. The first data point in the cumulative values (i.e., first study) is therefore that from the study of Quadri et al. *(19)*, whereas the last data point in the cumulative values (bottommost value) represents the summary estimate (with 95% CI) of the LR(−) from all 10 studies. The upper limit of the 95% CI for the cumulative LR(−) is 0.24, suggesting that based on current evidence, the ratio of protein to creatinine in a random urine sample can provide some evidence to rule out the presence of proteinuria as judged by measurement of protein in a 24-h urine sample.

Discussion

An increase in urinary protein excretion is a widely accepted tool in the detection, diagnosis, and management of people considered to be at risk of developing renal disease and has been advocated as part of a regular check-up in such individuals *(10)*. The origins of this recommendation lie in the fact that it is widely believed that there will be a change in the amount of protein excreted before any demonstrable change in glomerular filtration, for example, as reflected in the creatinine clearance *(1)*. Despite these recommendations, there remains considerable variation in the use of methods for

Table 1. Details of patient cohort, study design, and cutoff values.

Authors, year (Ref.)	Patient group	Study design	No. of patients	Reference method cutoff, mg/day	Ratio cutoff value, mg/mmol
Quadri et al., 1994 *(19)*	Pregnant; high-risk obstetrics clinic	Prospective cross-sectional	75	300	33.9[a]
Young et al., 1996 *(20)*	Pregnant; suspected hypertension	Consecutive recruitment	45	300	17.0
Robert et al., 1997 *(21)*	Pregnant; gestational age 22–41 weeks; hypertension	Consecutive recruitment	71	300	19.3
Saudan et al., 1997 *(22)*	Pregnant; hypertension	Consecutive recruitment	100	300	30.0
Ramos et al., 1999 *(23)*	Pregnant; gestational age ≥20 weeks; hypertension	Prospective cross-sectional	47	300	56.5
Evans et al., 2000 *(24)*	Pregnant; investigation for renal disease	Prospective longitudinal	51	300	33.9
Rodriguez-Thompson et al., 2001 *(25)*	Pregnant; 84% in third trimester	Observational	138	300	21.5
Durnwald and Mercer, 2003 *(26)*	Pregnant; gestational age >24 weeks; suspected preeclampsia	Prospective recruitment	220	300	33.9
Al et al., 2004 *(27)*	Pregnant; new-onset mild hypertension	Retrospective consecutive review	185	300	21.5
Yamasmit et al., 2004 *(28)*	Pregnant; gestational age 26–42 weeks; hypertension	Prospective recruitment	42	300	21.5
Ginsberg et al., 1983 *(16)*	Adult ambulatory renal clinic	Recruitment not clear	46	200	22.8
Dyson et al., 1992 *(32)*	Adult renal transplant clinic	Prospective cross-sectional	148	500	40.0
Chitalia et al., 2001 *(34)*	Renal clinic; some proteinuria	Prospective cross-sectional	170	250	29.4
Torng et al., 2001 *(35)*	Adult renal transplant clinic	Consecutive recruitment	289	500	40.0
Ralston et al., 1988 *(36)*	Adult rheumatology clinic	Consecutive recruitment	102	300	40.0
Mitchell et al., 1993 *(37)*	Elderly attending outpatient clinic	Recruitment not clear	52	150	17.1

[a] All values were converted to SI units.

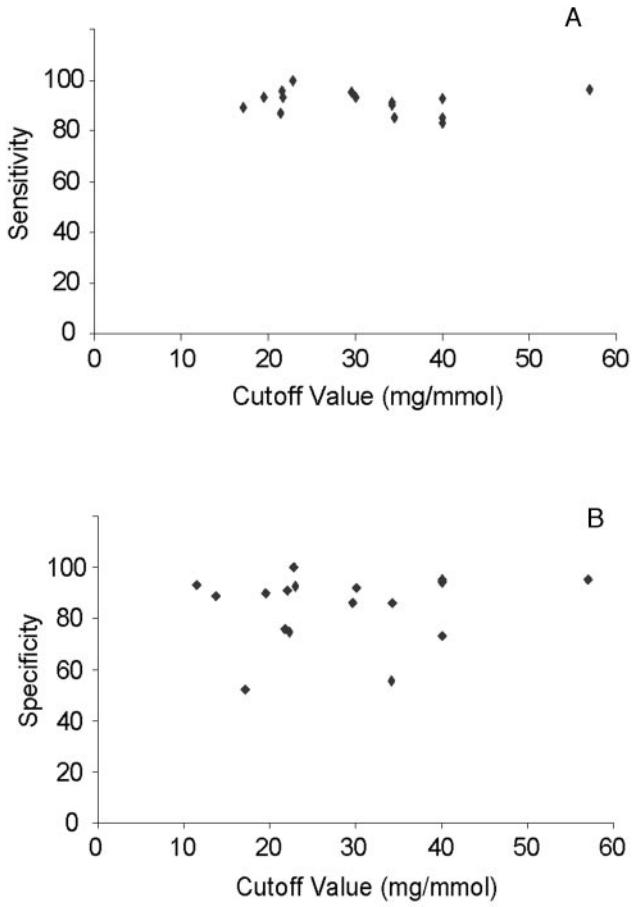

Fig. 2. Plots of the sensitivities (*A*) and specificities (*B*) reported in each of the studies compared with the cutoff values used for the protein:creatinine ratio measurement in each of the patient cohorts studied.

assessing the amount of protein excretion as well as doubts about many of the techniques used. However, it is acknowledged that estimation of urinary protein excretion over a 24-h period is the reference, or gold standard, method. This approach, however, is considered by many to be impractical in some circumstances, particularly in the outpatient setting, because of the difficulties associated with obtaining a complete collection. In a study of elderly patients, Mitchell et al. *(37)* had to discard >20% of the samples returned because they were considered to be incomplete; Chitalia et al. *(34)* in their study had to discard 10% of the samples received for similar reasons.

The need for a 24-h collection is a result of the high degree of variation in the urinary protein concentration during the course of the day. This precludes the use of a shorter collection period or the use of a random urine sample for protein concentration measurements, the latter of which would be the most practicable. Several authors have investigated the variation in protein excretion during the day and found that values can vary from 100% to 500%. This variation is thought to be attributable to several factors, including (*a*) variation in water intake and excretion, (*b*) rate of diuresis, (*c*) exercise, (*d*) recumbency, and (*e*) diet. The variation may be further exacerbated by pathologic changes in blood pressure and renal architecture.

An alternative approach that has been proposed, and used in some clinical situations for many years, is that of expressing the protein excretion in a random urine collection as a ratio to the creatinine concentration. It is assumed that both the protein and creatinine excretion rates are fairly constant during the day, as long as the glomerular filtration rate remains constant, and that the major reason for changes in the protein concentration in individual samples during the day is variation in the amount of water excreted. To support this proposal, several investigators have demonstrated a smaller variation in the protein:creatinine ratio compared with the protein concentration alone in urine samples collected throughout the day. Thus, Newman et al. *(17)* found that the mean intraindividual variation in the protein:creatinine ratio was 38.6%, whereas that of the protein excretion was 96.5%. Koopman et al. *(14)* had made a similar observation.

Several investigators studied the relationship between the protein:creatinine ratio and 24-h protein excretion. Ginsberg et al. *(16)* reported a correlation coefficient of 0.972; these authors also studied the variation of this relationship during the course of 24 h by studying the ratio and absolute amount of protein excreted in urine samples from 46 patients collected over timed periods throughout the day. They found that the relationship varied by as much as 30% but that during normal daylight activity—when most random samples are likely to be collected—the variation was minimal. The greatest differences were seen during the times when the patients were most likely to be recumbent. These authors concluded on the basis of these data that the protein:creatinine ratio of a spot urine could be used as a reliable indicator of the 24-h protein excretion. Several investigators have made similar observations and drawn similar conclusions *(30)*, whereas others have stated a preference for the first sample collected after the first morning void *(14, 32)*. However, some authors have pointed out that regression analysis and the reporting of a correlation coefficient indicate the degree of linear association between the two variables but do not enable a reliable decision to be made to replace one with the other *(34)*. Thus, the high degree of association between the protein:creatinine ratio and the 24-h protein excretion does not necessarily give reliable information on whether use of the ratio in a random sample will enable clinicians to reduce their dependence on the 24-h urine collection.

The reliability of a test result to enable a clinician to make a decision and take appropriate action depends on the context in which the test is used, the additional and complementary information available, and on the additional tests that might be required. Thus, a screening test

Table 2. Summary statistics from correlation for ratio of protein to creatinine (or osmolality) on a spot urine with 24-h protein excretion.

Authors, year (Ref.)	Ratio studied	No. of patients studied	*r*	*P*
Quadri et al., 1994 *(19)*	Protein:creatinine	75	0.92	<0.0001
Young et al., 1996 *(20)*	Protein:creatinine	45	0.80	<0.001
Robert et al., 1997 *(21)*	Protein:creatinine	71	0.94	<0.001
Saudan et al., 1997 *(22)*	Protein:creatinine	100	0.93	<0.001
Ramos et al., 1999 *(23)*	Protein:creatinine	47	0.94	Not stated
Evans et al., 2000 *(24)*	Protein:creatinine	51	0.95	<0.0001
Rodriguez-Thompson et al., 2001 *(25)*	Protein:creatinine	138	0.80	<0.001
Durnwald and Mercer, 2003 *(26)*	Protein:creatinine	220	0.64	<0.0001
Al et al., 2004 *(27)*	Protein:creatinine	185	0.56	<0.01
Yamasmit et al., 2004 *(28)*	Protein:creatinine	42	0.95	<0.001
Combs et al., 1991 *(29)*	Protein:creatinine	329	0.98	<0.0001
Ginsberg et al., 1983 *(16)*	Protein:creatinine	46	0.97	Not stated
Schwab et al., 1987 *(30)*	Protein:creatinine	101	0.96	Not stated
Abitbol et al., 1990 *(31)*	Protein:creatinine	64	0.95	<0.001
Dyson et al., 1992 *(32)*	Protein:creatinine	148	0.77	<0.001
Steinhauslin et al., 1995 *(33)*	Protein:creatinine	318	0.93	<0.001
Chitalia et al., 2001 *(34)*	Protein:creatinine	170	0.97	Not stated
Torng et al., 2001 *(35)*	Protein:creatinine	289	0.79	<0.0001
Ralston et al., 1988 *(36)*	Protein:creatinine	102	0.92	<0.001
Mitchell et al., 1993 *(37)*	Protein:creatinine	52	0.98	<0.0001
Wilson et al., 1993 *(40)*	Protein:osmolality	270	0.91	Not stated
Kim et al., 2001 *(41)*	Protein:osmolality	53	0.88	<0.001

(the first-line test) should ideally generate no false-negative results and only few false-positive results. A diagnostic test (in this context the term is used to denote a test on which a decision to intervene will be made) should exhibit a minimal number of false-positive and false-negative test results. An initial, or screening, test can be used in two ways: to rule in or rule out the presence of a condition (in this case, the presence of proteinuria). Focusing on the concept of a rule-out test, it must be reliable in its confirmation of the absence of proteinuria because no further action will be taken. An increased (or positive) test result would then lead to the collection of a 24-h specimen to make a definitive diagnosis of proteinuria; thus, the test can tolerate some false-positive results because these will be detected as "normal" when the reference method is used. Few authors have made reference to the use of the protein:creatinine ratio for the purposes of ruling out proteinuria; however, Dyson et al. *(32)* drew attention to this usage and to the fact that it can reduce the dependence on a test procedure (i.e., 24-h urinary protein) that is both unreliable and costly.

This systematic review of the literature has illustrated many of the problems associated with the explicit understanding of the way in which a test is used. Many of these problems have been noted in reviews on the quality of data presented in papers on the diagnostic accuracy of tests *(46, 47)*. Deeks *(44)* and others have identified the statistical techniques that should be used in the systematic review of the diagnostic performance of a test. Deeks makes the point that although several statistical tech-

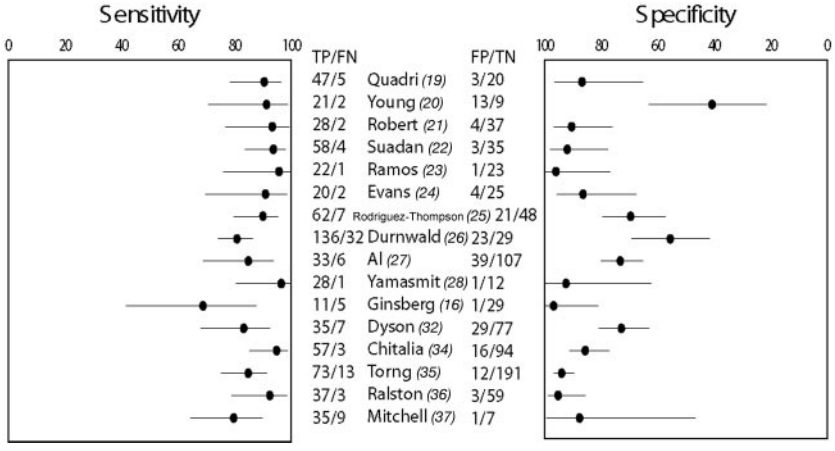

Fig. 3. Forest plots of the sensitivities and specificities (with 95% CIs) observed in each of the 16 studies.

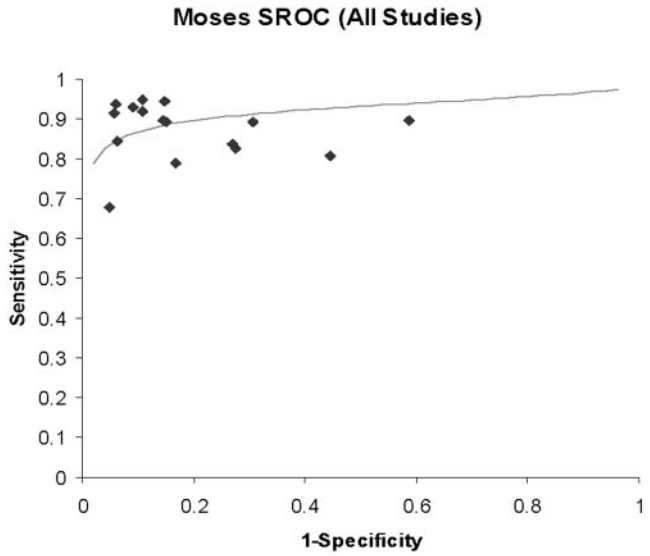

Fig. 4. Summary ROC plot of all 16 studies in which the random urine protein ratios were compared with the 24-h excretion of protein or creatinine.

The fitted summary ROC curve was derived by the method of Moses et al. *(46)*.

niques are available, the way that the data are presented means that they are not always readily interpretable by the practicing clinician. However, the most important factor is to have a clear definition of the way in which the test is to be used.

This review has assessed all of the relevant literature on the use of the protein:creatinine ratio to determine its reliability as a means of ruling out proteinuria. It is implicit in this goal that those patients in whom a positive result was found would then be followed up for full quantification of protein excretion. The sensitivities and specificities found in the studies, as represented in the summary ROC curve (Fig. 4), indicate a fairly high concordance among the studies, even when recognizing that there are multiple primary and secondary pathologies represented. In addition, it must be acknowledged that some of the studies used different cutoff values. It is generally thought that an excretion rate in excess of 300 mg/day constitutes a significant increase in protein excretion; normal excretion is thought to be 150–200 mg/day. The fact that investigators have chosen to use different 24-h values as well as different ratio values may assuage concerns about the high variability in protein excretion. On the other hand, it may indicate that different cutoffs should be used in different clinical settings, e.g., a higher value in patients with preexisting renal dysfunction. The slightly higher values found for sensitivity compared with specificity would suggest that the ratio test might be more valuable as a rule-out test. Similarly, the higher clustering of negative predictive values compared with positive predictive values would support this tentative conclusion. It should be noted, however, that the prevalence of proteinuria in the populations studied is relatively high, reflecting the fact that the investigators have studied those patients in whom there was a high pre-test probability of proteinuria. The conclusion drawn from this review, therefore, cannot necessarily be extrapolated to clinical situations in which there is a significantly lower prevalence of proteinuria.

Likelihood ratios provide the clearest data on the way in which the test can be used reliably. A likelihood ratio >10 is considered to be indicative of convincing evidence of the diagnostic performance of a test in rule-in mode, whereas a likelihood ratio <0.1 is indicative of convincing evidence of the diagnostic performance of a test in rule-out mode *(44, 48, 49)*. Ratios >5 or <0.2 are indicative of strong evidence. The data in Figs. 5 and 6 indicate that there is some evidence suggesting that the ratio of protein to creatinine, in a random urine, will identify those patients in whom an increase in 24-h protein excretion is unlikely to be present. Furthermore, the data in Fig. 6 indicate that when all of the data from the studies of pregnant women thought to be at risk of developing preeclampsia are accumulated in a stepwise fashion, the likelihood ratio does not change substantially and that there thus is no need for additional data. It must be noted that all of these studies were carried out at fixed thresholds for the ratio of protein to creatinine in urine. It is possible that by adjusting the threshold used for the ratio

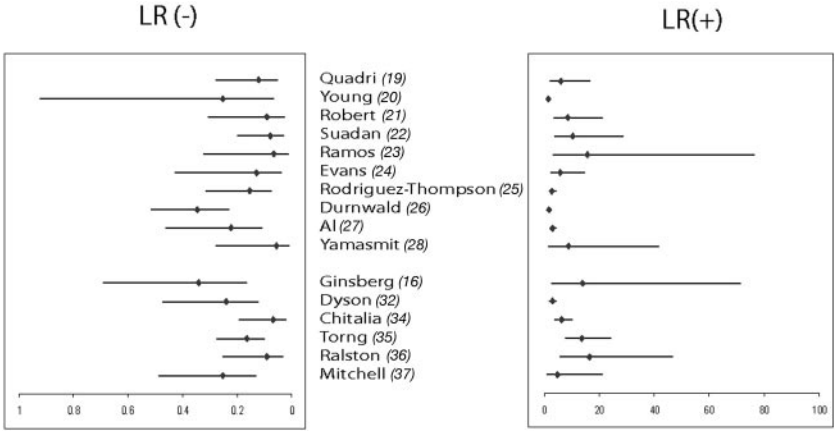

Fig. 5. Forest plots of the LR(+) and LR(−), with 95% CIs, for the 16 studies.

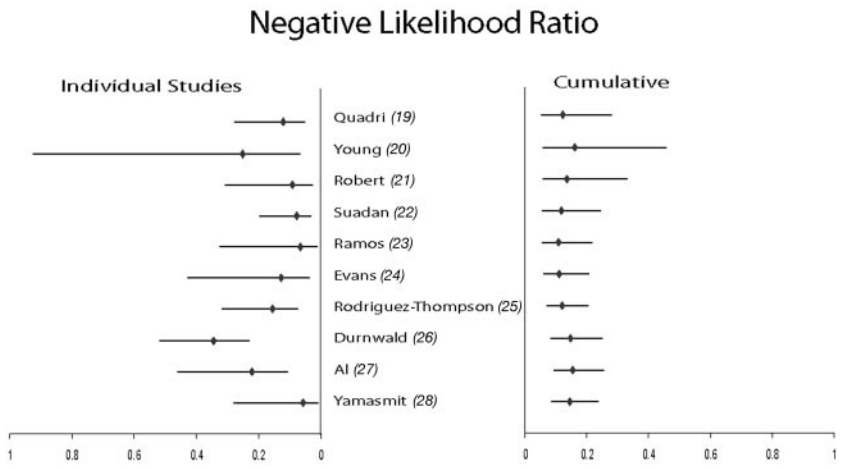

Fig. 6. Forest plots of the LR(−) for the 10 studies involving preeclamptic patients.

Results (with 95% CIs) for the individual studies are plotted to the *left*, and cumulative summary estimates (with 95% CIs) in chronologic order of study are plotted to the *right*. Note that the 95% CIs of the cumulative summary estimates decrease with the added information from each study.

to lower values, the sensitivity of the test for proteinuria might be further increased, and the LR(−), correspondingly, reduced to even lower values. Such lower values would improve the utility of the ratio as a rule-out test.

It is well known that there is considerable variation in the measurement of total protein in urine, most probably a consequence of differences in the analytical specificities of the methods as well as variation in the calibration of the methods. This may have contributed to the variation in the diagnostic performance among the studies. It has been suggested that the measurement of albumin might offer a means of reducing methodologic variation while also having the potential for increased clinical diagnostic sensitivity *(6–8)*.

This review has shown concordance among studies despite variations in the patient cohorts studied. It should be noted that there was significant heterogeneity in the approaches taken to validate the ratio tests. In the case of the studies in pregnant women, gestational age could have had a major impact on the findings, but it was not always possible to ascertain gestational age in the patients studied. Despite these limitations, there was a reasonably high concordance between the two variables in all of the studies. It is interesting to note that the cutoff values used to define proteinuria, both in the 24-h excretion as well as in the ratio, were quite variable. This may reflect the need for different cutoff values to be used in different clinical settings, reflecting the threshold for compromised renal function in different disease states.

We therefore conclude that there are sufficient data in the literature to demonstrate a strong correlation between the protein:creatinine ratio in a random urine sample and 24-h protein excretion. Most importantly, we have shown that the protein:creatinine ratio for a random urine sample (particularly with adjustment of the test threshold to a lower value) might be used to rule out the presence of significant proteinuria as defined by a quantitative measure of the 24-h protein excretion. Use of the ratio negates the uncertainty associated with the use of dilute or concentrated urine. Used in this way, the random urine measurement might thus reduce the number of unnecessary 24-h urine collections and their associated unreliability. When results above the cutoff value for the protein:creatinine ratio are obtained, a full 24-h collection and quantification are indicated. Similar, but fewer, data exist for use of the albumin:creatinine ratio. Further prospective studies will be required in specific patient populations to validate these conclusions.

The findings of this review may be helpful in achieving the goals associated with screening for proteinuria in at-risk populations *(10)*. Craig et al. *(50)*, in a systematic review involving metaanalysis and cost-effective methodologies of the literature on mass screening for proteinuria, suggested that screening middle-aged and older men for proteinuria (in their case, Australians) and treating some with angiotensin-converting enzyme inhibitors might be a viable primary prevention strategy for preventing end stage renal disease. The authors suggested that the use of a protein:creatinine ratio measurement might be more reliable than the protein concentration measurement when a random urine sample is used. Boulware et al. *(51)*, in a cost-effectiveness analysis, suggested that screening for proteinuria would be useful only in high-risk populations, e.g., older people and persons with hypertension.

References

1. Barnas U, Schmidt A, Haas M, Kaider A, Tillawi S, Wamser P, et al. Parameters associated with chronic renal transplant failure. Nephrol Dial Transplant 1997;12(Suppl 2):82–5.
2. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. Kidney Int 1998; 53:1209–16.
3. Redon J. Renal protection by antihypertensive drugs: insights form microalbuminuria studies. J Hypertens 1998;16:2091–100.
4. Bianchi S, Bigazzi R, Campese VM. Microalbuminuria in essential hypertension: significance, pathophysiology, and therapeutic implications. Am J Kidney Dis 1999;34:973–95.
5. The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? Ann Intern Med 2001;134:370–9.

6. Ballantyne FC, Gibbon J, O'Reilly D. Urine albumin should replace total protein for the assessment of glomerular proteinuria. Ann Clin Biochem 1993;30:101–3.
7. Beetham R, Cattell WR. Proteinuria: pathophysiology, significance and recommendations in clinical practice. Ann Clin Biochem 1993;30:425–34.
8. Newman DJ, Thakkar H, Medcalf EA, Gray MR, Price CP. Use of urine albumin measurement as a replacement for total protein. Clin Nephrol 1995;43:104–9.
9. Hofmann W, Guder WG. A diagnostic programme for quantitative analysis of proteinuria. J Clin Chem Clin Biochem 1989;27:589–600.
10. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(2 Suppl 1): S1–266.
11. Shaw AB, Risdon P, Lewis-Jackson JD. Protein creatinine index and Albustix in assessment of proteinuria. BMJ 1983;287:929–32.
12. Ruggenenti P, Gaspari F, Perna A, Remuzzi G. Cross-sectional longitudinal study of spot morning urine protein:creatinine ratio, 24-hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. BMJ 1998;316:504–9.
13. Boler L, Zbella EA, Gleicher N. Quantitation of proteinuria in pregnancy by the use of single voided urine samples. Obstet Gynecol 1987;70:99–100.
14. Koopman MG, Krediet RT, Koomen GCM, Strackee J, Arisz L. Circadian rhythm of proteinuria: consequences of the use of protein:creatinine ratios. Nephrol Dial Transplant 1989;4:9–14.
15. Kassirer JP, Harrington JT. Laboratory evaluation of renal function. In: Schrier RW, Gottschalk CW, eds. Diseases of the kidney, 4th ed., Vol. 1. Boston: Little Brown, 1988:393–426.
16. Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. New Engl J Med 1983;309:1543–6.
17. Moore RR, Hirate-Dulas CA, Kasiske BL. Use of urine specific gravity to improve screening for albuminuria. Kidney Int 1997;52: 240–3.
18. Newman DJ, Pugia MJ, Lott JA, Wallace JF, Hiar AM. Urinary protein and albumin excretion corrected by creatinine and specific gravity. Clin Chim Acta 2000;294:139–55.
19. Quadri KHM, Bernardini J, Greenberg A, Laifer S, Syed A, Holley JL. Assessment of renal function during pregnancy using random urine protein to creatinine ratio and Cockcroft-Gault formula. Am J Kidney Dis 1994;24:416–20.
20. Young RA, Buchanan RJ, Kinch RA. Use of the protein/creatinine ratio of a single voided urine specimen in the evaluation of suspected pregnancy-induced hypertension. J Fam Pract 1996; 42:385–9.
21. Robert M, Sepandj F, Liston RM, Dooley KC. Random protein-creatinine ratio for the quantitation of proteinuria in pregnancy. Obstet Gynecol 1997;90:893–5.
22. Saudan PJ, Brown MA, Farrell T, Shaw L. Improved methods of assessing proteinuria in hypertensive pregnancy. Br J Obstet Gynaecol 1997;104:1159–64.
23. Ramos JGL, Martins-Costa SH, Mathias MM, Guerin YLS, Barros EG. Urinary protein/creatinine ratio in hypertensive pregnant women. Hypertens Pregnancy 1999;18:209–18.
24. Evans W, Lensmeyer JP, Kirby RS, Malnory ME, Broekhuizen FF. Two-hour urine collection for evaluating renal function correlates with 24-hour urine collection in pregnant patients. J Matern Fetal Med 2000;9:233–7.
25. Rodriguez-Thompson D, Lieberman ES. Use of a random urinary protein-to-creatinine ratio for the diagnosis of significant proteinuria during pregnancy. Am J Obstet Gynecol 2001;185:808–11.
26. Durnwald C, Mercer B. A prospective comparison of total protein/creatinine ratio versus 24-hour urine protein in women with suspected preeclampsia. Am J Obstet Gynecol 2003;189:848–52.
27. Al RA, Baykal C, Karacay O, Geyik PO, Altun S, Dolen I. Random urine protein-creatinine ratio to predict proteinuria in new-onset mild hypertension in late pregnancy. Obstet Gynecol 2004;104: 367–71.
28. Yamasmit W, Chaithongwongwatthana S, Charoenvidhya D, Uerpairojkit B, Tolosa J. Random urinary protein-to-creatinine ratio for prediction of significant proteinuria in women with preeclampsia. J Matern Fetal Neonatal Med 2004;16:275–9.
29. Combs CA, Wheeler BC, Kitzmiller JL. Urinary protein/creatinine ratio before and during pregnancy in women with diabetes mellitus. Am J Obstet Gynecol 1991;165:920–3.
30. Schwab SJ, Christensen L, Dougherty K, Klahr S. Quantitation of proteinuria by use of protein to creatinine ratios in single urine samples. Arch Intern Med 1987;147:943–4.
31. Abitbol C, Zilleruelo G, Freundlich M, Strauss J. Quantitation of proteinuria with urinary protein/creatinine ratios and random testing with dipsticks in nephrotic children. J Pediatr 1990;116: 243–7.
32. Dyson EH, Will EJ, Davison AM, O'Malley AH, Shepherd HT, Jones RG. Use of the urinary protein creatinine index to assess proteinuria in renal transplant patients. Nephrol Dial Transplant 1992;7: 450–2.
33. Steinhauslin F, Wauters JP. Quantitation of proteinuria in kidney transplant patients: accuracy of the urine protein/creatinine ratio. Clin Nephrol 1995;43:110–5.
34. Chitalia VC, Kothari J, Wells EJ, Livesey JH, Robson RA, Searle M, et al. Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine protein-creatinine ratio. Clin Nephrol 2001; 55:436–47.
35. Torng S, Rigatto C, Rush DN, Nickerson P, Jeffery JR. The urine protein to creatinine ratio (P/) as a predictor of 24-hour urine protein excretion in renal transplant patients. Transplant 2001; 72:1453–6.
36. Ralston SH, Caine N, Richards I, O'Reilly D, Sturrock RD, Capell HA. Screening for proteinuria in a rheumatology clinic: comparison of dipstick testing, 24 hour urine quantitative protein, and protein/creatinine ratio in random urine samples. Ann Rheum Dis 1998;47:759–63.
37. Mitchell SCM, Sheldon TA, Shaw AB. Quantification of proteinuria: a re-evaluation of the protein/creatinine ratio for elderly subjects. Age Ageing 1993;22:443–9.
38. Claudi T, Cooper JG. Comparison of urinary albumin excretion rate in overnight urine and albumin creatinine ratio in spot urine in diabetic patients in general practice. Scand J Prim Health Care 2001;19:247–8.
39. Ng WY, Lui KF, Thai AC. Evaluation of a rapid screening test for microalbuminuria with a spot measurement of urine albumin-creatinine ratio. Ann Acad Med 2000;29:62–5.
40. Wilson DM, Anderson RL. Protein-osmolality ratio for the quantitative assessment of proteinuria from a random urinalysis sample. Am J Clin Pathol 1993;100:419–24.
41. Kim HS, Cheon HW, Choe JH, Yoo KH, Hong YS, Lee JW, et al. Quantification of proteinuria in children using the urinary protein-osmolality ratio. Pediatr Nephrol 2001;16:73–6.
42. Altman DG. Diagnostic tests. In: Altman DG, Machin D, Bryant TN, Gardiner MJ, eds. Statistics with confidence, 2nd ed. London: BMJ Books, 2000:105–19.
43. Normand ST. Tutorial in biostatistics. Meta-analysis: formulating, evaluating, combining, and reporting. Statist Med 1999;18:321–59.
44. Deeks JJ. Systematic reviews of evaluations of diagnostic and

screening tests. In: Egger M, Davey Smith G, Altman DG, eds. Systematic reviews in health care: meta-analysis in context. Systematic reviews, 2nd ed. London: BMJ Books, 2001:248–82.

45. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Statist Med 1993;12:1293–316.
46. Reid MC, Lachs MS, Feinstein AR. Use of methodological standards in diagnostic test research. Getting better but still not good. JAMA 1995;274:645–51.
47. Bruns DE, Huth EJ, Magid E, Young DS. Toward a checklist for reporting studies of diagnostic accuracy of medical tests. Clin Chem 2000;46:893–5.
48. Jacschke R, Guyatt GH, Sackett DL, for the Evidence-Based Medicine Working Group. Users' guide to the medical literature. VI. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? JAMA 1994;271:703–7.
49. Sackett DL, Strauss SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine. How to practice and teach EBM. Edinburgh: Churchill Livingstone, 2000:1–261.
50. Craig JC, Barratt A, Cumming R, Irwig L, Salkeld G. Feasibility study of the early detection and treatment of renal disease by mass screening. Intern Med J 2002;32:6–14.
51. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA 2003;290:3101–14.