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 ranged 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.

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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
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 $2 \times 2$ 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 data 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 $\chi^2$ 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 7 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, $\beta$, in the Moses analysis was used to assess whether factors beyond variation in the test threshold contributed to heterogeneity among the studies.

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

<sup>a</sup> All values were converted to SI units.
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, of which were determined by ROC curve analysis. In view of the nonsignificant $\beta$-coefficient in a Moses-type summary ROC analysis ($\beta$ 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 values) 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 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

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

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

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

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**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 SROC curve was derived by the method of Moses et al. (46).

**Fig. 5.** Forest plots of the LR(+) and LR(−), with 95% CIs, for the 16 studies.
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, 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 (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-
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 patholo-
gies 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 ex-
cretion; normal excretion is thought to be 150–200 mg/
day. The fact that investigators have chosen to use differ-
ent 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 dysfunc-
tion. 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 com-
pared 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 extrap-
olated to clinical situations in which there is a signifi-
cantly 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 thresh-
olds for the ratio of protein to creatinine in urine. It is
possible that by adjusting the threshold used for the ratio
to lower values, the sensitivity of the test for proteinuria
might be further increased, and the LR(−), correspond-
ingly, 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 sen-
sitivity (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 sam-
ple (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 mea-
sure 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 unneces-
sary 24-h urine collections and their associated unreliabil-
ity. 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 prospec-
tive studies will be required in specific patient popula-
tions 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 method-
ologies 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. Boullware 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


