Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children: a meta-analysis
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CRD summary
This review found that cystatin C is more accurate than serum creatinine for the diagnosis of renal impairment but the results are not conclusive, and that cystatin C is able to accurately rule in renal impairment in patients in whom this is suspected. Limitations in the analysis and failure to investigate variability between the studies mean that these conclusions should be interpreted with caution.

Authors' objectives
To compare the accuracy of cystatin C (CysC) with serum creatinine (SCr) for the diagnosis of renal dysfunction in adults and children.

Searching
MEDLINE and EMBASE were searched from 1984 to February 2006; some details of the search terms were reported. The reference lists of retrieved articles were screened for additional relevant studies. The manufacturer of the CysC assay kit was contacted to locate unpublished studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Diagnostic cohort/cross-sectional and case-control studies were eligible for inclusion.

Specific interventions included in the review
Studies that assessed both CysC and SCr were eligible for inclusion. Studies that used the MDRD equation (which uses SCr) or a CysC-based equation were also eligible for inclusion. Assays eligible for inclusion for CysC were particle-enhanced immunoturbidimetry and particle-enhanced immunonephelometry. Assays eligible for inclusion for SCr were the standard and modified Jaffe assay and the enzymatic assay. Thresholds to define an abnormal test result ranged from 0.82 to 1.64 mg/L for CysC, and from 70.7 to 130.74 micromol/L for SCr.

Reference standard test against which the new test was compared
Studies that used the following acceptable reference standards to measure glomerular filtration rate as an indication of renal function were eligible for inclusion: exogenous inulin, Cr-EDTA, Tc-DTPA, iohexo or I-Iothalamate. Studies had to define abnormal renal function between 60 and 90 mL/minute to be included. The median threshold to define abnormal renal function was 80 mL/minute per 1.73 m2 (range: 60 to 90).

Participants included in the review
Studies of patients of all ages and in all settings were eligible for inclusion. The ages of included patients ranged from 0.2 to 93 years. The participants in the included studies were patients with various renal conditions (mixed age and paediatric), miscellaneous disorders (paediatric), diabetes, liver cirrhosis, mild impairment renal function, post renal transplant, liver diseases; non-cirrhotic patients; intensive care unit patients; geriatric (hospitalised) patients; people without diabetes; and healthy controls.

Outcomes assessed in the review
Studies that reported sufficient data to construct a 2x2 table were eligible for inclusion. The primary outcome measures were sensitivity and specificity. Likelihood ratios (LRs) and diagnostic odds ratios were also reported.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened studies for inclusion and any disagreements were resolved through consensus. Authors were contacted for missing information.

Assessment of study quality
Two reviewers independently assessed the quality of the included studies using a modification of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria.

**Data extraction**
The data were extracted as 2x2 tables of test performance, together with details of the threshold used to define a positive test result. The data were either extracted directly from the paper, derived from the data reported, or obtained by contacting the corresponding author. The sensitivity and specificity were calculated for each set of 2x2 data. Positive and negative LRs were calculated for studies that used inulin as the reference standard at a threshold of 60 to 79 mL/minute per 1.73 m2 and a threshold of between 0.9 and 1.4 mg/L for CysC. The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**
How were the studies combined?
Pooled sensitivity, specificity, and positive and negative LRs were estimated using both fixed-effect and random-effects models. A summary receiver operating characteristic (SROC) curve analysis, based on the Moses-Littenberg models, was conducted. For studies that used multiple thresholds, the threshold that maximised sensitivity and specificity was selected. All pooled estimates reported in this abstract were based on random-effects models.

How were differences between studies investigated?
The chi-squared test was used to assess heterogeneity (p<0.10 was the level of statistical significance). Heterogeneity was also assessed visually using forest plots and SROC plots.

**Results of the review**
Twenty-three studies reporting data for 27 population groups were included (n=2,007).

In 24 of the 27 population groups, the spectrum of patients was representative of patients who will receive the test in practice. Twenty-three of the 27 groups reported that all patients participated in the evaluation of the accuracy of the tests. Twenty-five of the 27 groups described the analytical methods. Twenty-one of the 27 groups described the study population. In all studies the reference standard was likely to correctly classify the target condition and patients received the same reference standard test.

CysC.

The sensitivity ranged from approximately 58% (read from graph) to 100% and the specificity from approximately 72% (read from graph) to 100%. The pooled sensitivity and specificity were 81% (95% confidence interval, CI: 76, 85) and 88% (95% CI: 84, 91), respectively. Forest plots suggested substantial heterogeneity; the results of the statistical assessment of heterogeneity were not reported.

SCr.

The sensitivity ranged from approximately 28% to 92% (read from graph) and the specificity from approximately 44% (read from graph) to 100%. The pooled sensitivity and specificity were 69% (95% CI: 61, 76) and 88% (95% CI: 83, 92), respectively. Forest plots suggested substantial heterogeneity; the results of the statistical assessment of heterogeneity were not reported.

The SROC analysis showed that the SROC curve for CysC is further towards the upper left hand corner than that for SCr, suggesting greater accuracy of the CysC test. The plot showed substantial heterogeneity for both tests.

**Authors’ conclusions**
The results suggest that CysC is more accurate than SCr for the diagnosis of renal impairment, but these results are not conclusive. CysC is able to accurately rule in renal impairment in patients in whom this is suspected.

**CRD commentary**
The review addressed a focused question that was supported by clearly defined inclusion criteria. However, some of the inclusion criteria, for example those relating to threshold to define abnormal renal function, appear to have been applied post hoc rather than defined a priori. The literature search was limited to two electronic databases but steps were taken to minimise language and publication bias. The quality of the included studies was assessed using appropriate criteria and the results of this assessment were presented. Appropriate steps were taken to minimise bias in the selection and quality assessment of the studies, but it is unclear whether such steps were applied in the data extraction.

Details of the studies were tabulated clearly. The methods of analysis were acceptable but a more sophisticated analysis, based on more robust models and which compared the accuracy of the two tests within studies rather than basing such comparisons on summary measures, would have been preferable. The main analysis on which the authors’ conclusions were based related to a subset of 3 of the 27 groups that were selected based on the similarity of the thresholds for the index test and reference standard. An analysis that had investigated reasons for the observed heterogeneity, for example patient population or study quality, rather than limiting the analysis in this way is likely to have been more representative of the included studies. The results of this analysis, and hence the authors’ conclusions, should therefore be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies are needed to assess the accuracy of the MDRD equation and other CysC-based equations in identifying patients with renal impairment.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on
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