Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review

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CRD summary
The review covered the broad topic of biomarkers in the work-up of acute kidney injury. Searches were restricted to English language and few data were identified. Performance characteristics of biomarkers varied widely and diagnostic thresholds were unreported. Given the limitations of the data, the conclusion that biomarkers had great potential seemed optimistic. The suggestions for further research were reasonable.

Authors' objectives
To assess the accuracy and reliability of serum and urinary biomarkers for the diagnosis and/or risk stratification of patients with established or early acute kidney injury (AKI).

Searching
Two reviewers independently searched MEDLINE and EMBASE (January 2000 to March 2007). Search terms were reported. Additional studies were sought through manual searching of the bibliographies of included studies and review articles, Science Citation Index and by searching the top 50 citations for each paper through the related articles function of PubMed. The search was restricted to English language articles.

Study selection
Diagnostic cohort or case-control studies or randomised controlled trials assessing the diagnostic performance of serum or urinary biomarkers in 20 or more patients with AKI or acute renal failure were eligible for inclusion if they were scored as good or fair quality (see below). Biomarkers assessed were: cystatin C; carbamylated haemoglobin; neutrophil gelatinase-associated lipocalin (NGAL); interleukin-18 (IL-18); interleukin-6 (IL-6); interleukin-8 (IL-8); interleukin-10 (IL-10); glutathione-S-transferase (GST); N-acetyl-β-D-glucosaminidase (NAG); α-1 microglobulin (α-1M); kidney injury molecule-1 (KIM-1); matrix metalloproteinase-9 (MMP-9); sodium hydrogen exchanger 1 (NHE3); prohormone of atrial natriuretic peptide (proANP(1-98); neutrophil CD11b; glutamyl transpeptidase (GT); alkaline phosphatase (AP); lactate dehydrogenase (LDH); retinol-binding protein; β-2 microglobulin; and γ-glutamyltransferase (GGT). Diagnostic thresholds were not reported.

Two reviewers independently assessed studies for inclusion and disagreements were resolved by consensus.

Assessment of study quality
A 10-point quality assessment check list drawn from the 25-item STARD criteria for the reporting of test accuracy studies was used to generate an overall quality score. The checklist assessed the generalisability of the study population, adequacy of sampling (consecutive or convenience), prospective or retrospective study, reporting of reference standard and index test(s), blinding of readers of the index test and reference standard, reporting of withdrawals and time interval between tests.

Studies were classified as good quality if the score was 9 or more, fair quality if the score was 7-8 and poor quality if the score was 6 or less. Two reviewers independently assessed study quality and disagreements were resolved by consensus.

Data extraction
Where reported, data were extracted on sensitivity, specificity and area under the receiver operating characteristic (ROC) curve (AUC). Sensitivity and specificity values were used to estimate the positive likelihood ratios (LR).

Data were extracted using standard forms. No further details of the data extraction process were reported.
Methods of synthesis

Formal meta-analysis was not undertaken due to significant heterogeneity in the diagnostic threshold (for index test and reference standard) in studies of similar biomarkers.

Studies were combined in a narrative synthesis. The results of individual studies were tabulated, grouped by target condition (diagnosis of established AKI, diagnosis of early AKI, prediction of severity of AKI). Studies were further stratified by biomarker medium (serum or urine) and type.

Results of the review

A total of 31 studies were included in the review, of which 25 were classified as good quality. The total number of participants was unclear (numbers were reported by data set, rather than by study).

Diagnosis of established AKI (14 studies):

Six studies assessed serum cystatin C. Three studies (n = 181) reported sensitivity and specificity. Sensitivity ranged from 0.87 to 0.97 and specificity ranged from 0.85 to 1.0. Sensitivity and specificity data were reported for other markers in single studies only (full details reported in Table 2 in the paper).

Early diagnosis of AKI (14 studies):

Three studies assessed serum cystatin C. Two studies (n = 114) reported sensitivity (0.5 and 0.82) and specificity (0.5 and 0.95). Four studies assessed urine NGAL and all (n = 355) reported sensitivity and specificity. Sensitivity ranged from 0.73 to 1.0 and specificity ranged from 0.72 to 0.98. Four studies assessed urine IL-18 and three (n = 346) reported sensitivity and specificity. Sensitivity ranged from 0.25 to 0.5 and specificity ranged from 0.81 to 0.94. Sensitivity and specificity data were reported for other markers in single studies only (full details reported in Table 3 in the paper).

Prediction of severe AKI, defined as duration >48 hours, renal replacement therapy (RRT) or death (nine studies):

The sensitivity and specificity values of six biomarkers were reported by single studies. Sensitivity values ranged from 0.53 for urine IL-8 in the prediction of illness duration >48 hrs to 0.92 for urine cystatin C in the prediction of RRT. Specificity values ranged from 0.54 for urine NGAL in the prediction of RRT to 0.93 for serum cystatin C in the prediction of RRT (full results reported in Table 4 in the paper).

Data were also reported for the relationship between timing of sample collection and performance characteristics of the biomarker.

Authors' conclusions

The published data suggested that serum and urinary biomarkers had great potential to improve the management of AKI, but further research was needed.

CRD commentary

The general research area to be covered by the systematic review was stated, but no clear objective was provided. Inclusion criteria were broad. A number of sources were searched to identify relevant studies, but the limitation to English language may have resulted in the omission of relevant data and risk of language bias. The review process incorporated some measures to minimise error and bias in the selection of studies and assessment of methodological quality. The methodological quality of included studies was assessed using relevant criteria. However, the aggregation of quality assessment results to give overall scores minimises the informative value of these data. Few studies reported data on the sensitivity and specificity of biomarkers and data for individual biomarkers were often derived from single studies. No diagnostic thresholds were reported and no details of the reference standards used in included studies were given. The range of reported sensitivities and specificities was wide and values in individual studies were frequently below 0.8. In view of the limitations described, the authors' conclusion regarding the potential of biomarkers seemed optimistic, although the suggestions for further research were reasonable.
Implications of the review for practice and research

Practice: It was anticipated that a combination of multiple biomarkers would be needed to accurately identify patients with established AKI and to risk-stratify for the need for dialysis, or for death.

Research: Larger validation studies were needed and the generalisability of biomarkers to different types of AKI, as well as their incremental prognostic value over other clinical variables, should be assessed.

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