Urine survivin as a diagnostic biomarker for bladder cancer: a systematic review

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CRD summary
This review concluded that the clinical utility of urine survivin as a bladder tumour marker remained uncertain. Only studies that investigated diagnostic accuracy were included in the review. Limitations of the review and the methodological limitations and paucity of available evidence mean that the estimates of diagnostic accuracy could be overestimated. The uncertainty expressed in the authors’ conclusions seems appropriate.

Authors' objectives
To determine the clinical utility of urine survivin as a bladder tumour marker.

Searching
PubMed, The Cochrane Library and SCOPUS were searched for studies published in English from 1997 to March 2011; search terms were reported.

Study selection
Eligible studies evaluated the diagnostic accuracy of urine survivin to detect bladder cancer and used cystoscopy and/or histopathology as the reference standard. Studies had to provide sufficient data to produce 2x2 tables of test performance on a per patient basis. Case reports were excluded.

Across the studies, the most common methods were natural voiding for urine collection and real-time polymerase chain reaction (PCR) for survivin detection. The gold standard in all studies was cystoscopy. Most participants were recruited in Asian countries or USA. Where reported, mean age ranged from 48.5 to 73.5 years. From 69.6% to 95% of participants were men.

Titles and abstracts were selected by one reviewer. Full papers were selected by two independent reviewers; disagreements were resolved by consensus or referral to a third reviewer.

Assessment of study quality
Study quality was assessed by two independent reviewers using the 14-point QUADAS tool; disagreements were resolved by consensus or referral to a third reviewer.

Data extraction
Data were extracted in order to produce 2x2 tables of test performance. Sensitivity, specificity, positive and negative likelihood ratios (LR+/-) and diagnostic odds ratio (DOR) were calculated.

It seemed that data extraction was conducted by two independent reviewers and disagreements were resolved by consensus or referral to a third reviewer.

Methods of synthesis
Pooled estimates of sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios, with 95% confidence intervals (CI), were calculated using a random-effects model. Summary receiver operating characteristic curves (SROC) were calculated using the Moses-Littenberg model. Heterogeneity was assessed using the Χ² and I² statistics (I²>50% was considered substantial heterogeneity). The present of a threshold effect was investigated using Spearman's rank correlation. Subgroup analysis was used to investigate the impact of the type of urine survivin test used.

Results of the review
Fourteen studies (2,051 participants, range 20 to 378, 1,038 with bladder cancer and 1,013 controls) were included in the review. Only three studies reported being prospective, two reported consecutive recruitment of patients and four reported blinding of interpreters of test results.
For urine survivin, pooled sensitivity was 77.2% (95% CI 74.5 to 79.7), specificity was 91.8 (95% CI 89.9 to 93.4), LR+ was 8.34 (95% CI 4.82 to 14.43), LR- was 0.25 (95% CI 0.18 to 0.34) and diagnostic odds ratio was 49.67 (95% CI 22.9 to 107.7); heterogeneity was substantial for both analyses. There was no evidence of a threshold effect.

Accuracy estimates were higher for urine survivin tests compared to cytology for sensitivity (74.8% versus 43.3%) and diagnostic odds ratio (52.98 versus 41.43). Accuracy estimates were higher for cytology compared to urine survivin for specificity (98.3 versus 94.2), LR+ (25.77 versus 12.38) and LR- (0.60 versus 0.27).

Results from further subgroup analyses were reported.

Authors' conclusions
The clinical utility of urine survivin as a bladder tumour marker remained uncertain; there was some suggestion that urine survivin tests may be beneficial for the detection of bladder cancer but their value for predicting cancer recurrence and progression remained unclear. There was no clear evidence of a difference between cytology and urine survivin tests for the prediction of tumour recurrence and progression in the longer term.

CRD commentary
The review addressed a clear research question supported by reproducible inclusion criteria. However, the review set out to address the clinical utility of the test (impact of testing on patient management and clinical outcomes) but presented only data for diagnostic accuracy. Relevant sources were searched, but studies in languages other than English were excluded and unpublished studies were not sought so studies may have been missed. Most of the review process was conducted in duplicate, which reduced risks of error and bias; selection of titles and abstracts was conducted by one reviewer. Appropriate criteria were used to assess study quality but the assessment results were not reported in full. From the results that were reported, it seemed that the studies were potentially subject to substantial bias which could overestimate accuracy.

The authors stated in the discussion that they used the bivariate random-effects model to produce summary estimates of diagnostic accuracy. However, the software cited and pooling of sensitivity and specificity separately are not characteristic outputs for this type of analysis. Therefore it was not clear whether the methods used for pooling data were robust. Pooling of sensitivity and specificity separately from heterogeneous studies can overestimate accuracy.

Limitations of the review and the methodological limitations and paucity of available evidence mean that the estimates of diagnostic accuracy could be overestimated. The uncertainty expressed in the authors’ conclusions seems appropriate.

Implications of the review for practice and research
Practice: The authors stated that the review showed that urine survivin tests were not sufficiently superior to replace cystoscopy as the reference standard but could be used to replace or complement cytology for detecting and monitoring bladder cancer. They also stated that although urine survivin tests may not be ready to replace cystoscopy, there may be a role for modified protocols that increase the intervals between cystoscopies. The authors stated that a combination of cytology and urine survivin tests might be suitable for triage of patients with symptoms of bladder cancer but there were no data from the present meta-analysis with which to evaluate specific test combinations due to the very limited number of studies.

Research: The authors stated that prospective validation would be required to assess and confirm the clinical value of urine survivin.

Funding
None reported.

Bibliographic details

PubMedID
22353238
Record Status
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 the reliability of the review and the conclusions drawn.