Diagnostic value of Epstein-Barr virus capsid antigen-IgA in nasopharyngeal carcinoma: a meta-analysis

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CRD summary
This review concluded that the presence of Epstein-Barr virus capsid antigen-immunoglobulin A in peripheral blood was a valuable predictor for nasopharyngeal carcinoma. Weaknesses in the search strategy, reporting of the methodological quality of included studies and meta-analytic methods mean that this conclusion should be viewed with caution.

Authors' objectives
To assess the accuracy of Epstein-Barr virus capsid antigen-immunoglobulin A for the diagnosis nasopharyngeal carcinoma.

Searching
The Chinese Biomedical Literature Database (CBMdisc), the database of National Knowledge Infrastructure (CNKI) and the full paper database of Chinese Science and Technology of Chongqing (VIP) were searched from 1979 to 2008. Search terms were reported; these included methodological terms for test accuracy studies. Bibliographies of retrieved articles were screened for additional studies.

Study selection
Studies that assessed the diagnostic accuracy of the virus capsid antigen-immunoglobulin A test in patients with suspected nasopharyngeal carcinoma, using a diagnostic threshold of antibody titre of 1:5 or more for a positive test, were eligible for inclusion. Studies were required to use the reference standard of histological analysis of standard paraffin-embedded sections to determine the presence or absence of nasopharyngeal carcinoma, and to report sufficient data to populate 2x2 contingency tables (numbers of true positive, false negative, false positive, and true negative test results).

Conference abstracts and studies of less than ten specimens were excluded.

Included studies used enzyme-linked immunosorbent assay (most studies) or indirect immunofluorescence assay. The most frequently used antibody titre thresholds in included studies were 1:10 and 1:5. All included studies were Chinese articles.

Studies were independently assessed for inclusion by two reviewers and disagreements were resolved by discussion.

Assessment of study quality
The methodological quality of included studies was assessed using 25-item STARD (Standards for Reporting Diagnostic Accuracy) checklist and the 14-item QUADAS (Quality Assessment for Studies of Diagnostic Accuracy) tool. Overall quality scores (maximum 25 for STARD and maximum 14 for QUADAS) were calculated.

Quality assessment was undertaken independently by two reviewers and disagreements were resolved by consensus.

Data extraction
Data to populate 2x2 contingency tables were independently extracted by two reviewers and disagreements were resolved by consensus. Sensitivity and specificity values, with 95% confidence intervals (CIs), were calculated for each data set.

Methods of synthesis
Pooled estimates of sensitivity, specificity, positive and negative likelihood ratios (LRs), and diagnostic odds ratio
(DOR), with 95% confidence intervals, were calculated using a random-effects model.

Summary receiver operating characteristic (SROC) curves were constructed using the Moses and Littenberg model. To assess the effects of methodological quality on estimates of test accuracy, quality scores (STARD and QUADAS) were included as covariates in univariate regression analyses.

Cochrane Q test and $I^2$ tests were used to assess between-study heterogeneity.

Publication bias was examined visually by inspecting funnel plots and statistically using the Egger regression model.

**Results of the review**

Twenty studies (n=12,334 patients) were included in the review, 4,671 patients with nasopharyngeal carcinoma and 7,663 patients without nasopharyngeal carcinoma. STARD score ranged from 7 to 18 and QUADAS scores ranged from 8 to 11.

The pooled sensitivity of Epstein-Barr virus capsid antigen-immunoglobulin A tests was 0.91 (95% CI 0.90 to 0.92) and the pooled specificity was 0.92 (95% CI 0.92 to 0.93). The pooled positive likelihood ratio was 31.65 (95% CI 10.99 to 91.15) and the pooled negative likelihood ratio was 0.10 (95% CI 0.07 to 0.13). The pooled estimate of diagnostic odds ratio was 414.59 (95% CI 174.96 to 982.42). There was significant between study heterogeneity for all estimates ($p<0.001$).

Regression analyses (for STARD score or QUADAS score) showed no significant effect on the diagnostic odds ratio.

Funnel plots and the Egger test indicated potential for publication bias.

**Authors' conclusions**

The sensitivity and the specificity of serum virus capsid antigen-immunoglobulin A were very high, suggesting that the presence of virus capsid antigen-immunoglobulin A in peripheral blood was a valuable predictor for nasopharyngeal carcinoma.

**CRD commentary**

The research objective for the study was clearly stated and appropriate inclusion criteria were defined. Searches were restricted to Chinese literature databases and the search strategy included methodological terms for test accuracy studies; this approach has been shown to reduce the sensitivity of searches and is not recommended by the Cochrane collaboration. Consequently, it was likely that relevant studies have been missed. Measures to reduce error and bias were reported throughout the review process.

The methodological quality of included studies was assessed, but reporting was limited to an overall quality score. Overall scores were also used to assess the effect of study quality on estimates of test accuracy. This approach is not recommended in the guidance documents for QUADAS, because it potentially obscures the effects of individual quality items. Summary estimates of test performance were reported, but were of limited value, given the presence of significant unexplained heterogeneity in all cases.

Given the methodological limitations outlined, the authors' conclusions should be viewed with caution.

**Implications of the review for practice and research**

The authors made no specific recommendations for practice or research.

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