Diagnostic value of the mean corpuscular volume in the detection of vitamin B12 deficiency

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Authors' objectives
To review the diagnostic value of mean corpuscular volume (MCV) for vitamin B12 (hereafter referred to as just B12) in both anaemic and non-anaemic patients. The MCV had to be measured using an electronic counting-based method.

Searching
MEDLINE was searched from 1988 onwards using two separate search strategies: the search strategy suggested by the NHS Centre for Reviews and Dissemination to find reviews and meta-analyses (see Other Publications of Interest), and a search using the MeSH terms 'macrocytosis' and 'B12 deficiency'. In addition, the reference lists of all retrieved studies were searched for additional articles. Only studies published in the English language were included.

Study selection
Study designs of evaluations included in the review
Diagnostic accuracy studies including descriptive studies of retrospective and prospective designs.

Specific interventions included in the review
For inclusion in the review, the studies were required to have evaluated the MCV, a measure of macrocytosis, for its ability to predict B12 deficiency.

Reference standard test against which the new test was compared
The studies were required to have measured B12 levels and/or made a clinical diagnosis of B12 deficiency. The authors of the review accepted the reference standards used in the included studies. A wide range of definitions had been used, but in all studies this was a combination of a serum B12 concentration below a cut-off value with at least one of the following: abnormal Schilling test part I (and part II); high serum methyl malonic acid and/or homocysteine concentration; antibodies to intrinsic factor; response to therapy with B12; reticulocytosis; decrease of MCV; achlorhydria; antibodies to parietal cells; high serum gastrin concentration; megaloblastic marrow; megaloblastic anaemia.

Participants included in the review
The included studies were of patients being screened for B12 deficiency, those being treated for B12 deficiency, and those with pernicious anaemia. Both anaemic and non-anaemic patients were included.

Outcomes assessed in the review
For inclusion in the review, the studies were required to have provided data on the sensitivity and/or specificity of MCV in relation to B12 deficiency, in a format that enabled measures of diagnostic performance to be estimated. The outcomes presented in the review included the sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of the MCV test.

How were decisions on the relevance of primary studies made?
One reviewer screened all the studies located by the search while a second author checked the results. Any disagreements were resolved by discussion.

Assessment of study quality
The studies were assessed for validity according to the following criteria: prospective study design; no pooling of B12 and folate deficient patients; measurement of B12 with an immunological assay without interference, owing to non-specific binding of less active B12 analogues; reporting of the cut-off limits of MCV and B12; no selection bias; reporting of the clinical definition of B12 deficiency used in the study, where macrocytosis not used as a criteria for that diagnosis. One reviewer assessed the validity of the included studies while a second author checked the results. Any disagreements were resolved by discussion.
Data extraction
One reviewer extracted the data from the included studies while a second author checked the results. Any disagreements were resolved by discussion. Data were extracted on the following: the study's first author; year of publication; study design (including whether the study was retrospective or prospective); MCV cut-off point; B12 cut-off point; type of B12 assay; whether the quality criteria were met; and whether the report was published as an abstract only.

Methods of synthesis
How were the studies combined?
The studies were grouped according to whether the patients were pre-selected for a high MCV or not. Of those which included patients with any MCV level, the studies were grouped according to the reason the patients were given the test, i.e. screening, part of their treatment or patients with pernicious anaemia. The sensitivities of the MCV test from individual studies were pooled by dividing the sum of the numbers of true positives, by the sum of the total number of patients confirmed to have the deficiency (i.e. by using original patient numbers and not the point estimates of each study).

How were differences between studies investigated?
The homogeneity of the sensitivity levels was tested using a chi-squared test. A multivariate logistic regression model was used to identify the variables that were associated with differences in the sensitivity of MCV for B12 deficiency.

Results of the review
A total of 37 studies were included in the review. No information was reported on the number of patients included in these studies.

In the population that was randomly screened for low serum B12, the sensitivity of the MCV for B12 deficiency was 17%; the sensitivity was 30% for B12 deficiency in patients with anaemia. When the measurement of serum B12 was ordered to exclude B12 deficiency as part of the patient's treatment, the sensitivity was 30% for low serum B12 concentrations, 58% for B12 deficiency, and 75% for people with serum B12 deficiency and anaemia.

The three factors that proved to be independently significant in the multivariate analysis were the study design, the B12 cut-off point and the MCV cut-off point.

Only five studies presented sufficient data to calculate the PPV and NPV. The NPV ranged from 73.3% (with a corresponding PPV of 55.0%) to 98.9% (with a corresponding PPV of 18.5%). The PPV ranged from 0% (with corresponding NPVs of 96.6 and 94.3%) to 55.0% (with a corresponding NPV of 73.3%).

Authors' conclusions
A high MCV can be used to make the diagnosis of B12 deficiency more probable, while a normal or low MCV can be used to make the diagnosis of B12 deficiency less probable.

CRD commentary
The review answered a well-defined question that clearly specified the participants that might be included in the incorporated studies, the intervention to be studied and the outcomes of interest. The literature search appears to have been appropriate, but restricting the search to English language publications indexed in MEDLINE could mean that significant numbers of studies may have been missed. This particularly applies to research conducted outside of North America.

In addition, the search strategies devised by the NHS Centre for Reviews and Dissemination (see Other Publications of Interest) mention topic-specific terms, but the authors did not report such terms added to the search strategy specific to this review.

The authors assessed the validity of the included studies and compared those studies which met all the criteria with all others. Unfortunately, it is difficult to reconcile which studies and which patients were incorporated in this comparison. Also, only five studies proved sufficient data to calculate a 2x2 contingency table. As this level of data reporting is
required to calculate pertinent diagnostic indices, it might have been useful to have incorporated a criterion into the validity assessment which pertained to the completeness of the reported data.

The study details given were appropriate, but it is important to note that important data were omitted and important analyses were not reported. In particular, a table detailing the sensitivity of the intervention was provided whereas the specificity of the intervention was not reported. Even in those studies where a 2x2 table was reported to have been constructed, the specificity was not included in the review. As the sensitivity details are meaningless in the absence of specificity data, this omission seriously weakens the study. Nevertheless, the conclusions drawn, and the clinical recommendations, appear to follow from what information is presented.

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

*Practice:* The authors state that the diagnostic value of MCV in assessing B12 deficiency is too low to justify its use as the only parameter to assess this deficiency.

*Research:* The authors did not state any implications for further research.

**Bibliographic details**


**PubMedID**

10757449

**Other publications of related interest**

NHS Centre for Reviews and Dissemination. Search strategies to identify reviews and meta-analyses in MEDLINE and CINAHL. Available from: [http://www.crd.york.ac.uk/crdweb/searchstrategies.asp](http://www.crd.york.ac.uk/crdweb/searchstrategies.asp) [accessed July 2014].

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