# Diagnostic Performance of Antineutrophil Cytoplasmic Antibody Tests for Idiopathic Vasculitides: Metaanalysis with a Focus on Antimyeloperoxidase Antibodies

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***ABSTRACT.*** ***Objective.*** The diagnostic value of tests for antimyeloperoxidase antibodies (anti-MPO) for systemic vasculitis is less established than that for cytoplasmic antineutrophil cytoplasmic antibody (cANCA)/antiproteinase 3 antibodies (anti-PR3). Controversy exists regarding the optimal utilization of indirect immunofluorescence (IIF) ANCA testing versus antigen-specific ANCA testing. To summarize the pertinent data, we conducted a metaanalysis examining the diagnostic value of ANCA testing systems that include assays for anti-MPO.

***Methods.*** We performed a structured Medline search and reference list review. Target articles in the search strategy were those reporting the diagnostic value of immunoassays for anti-MPO for the spectrum of systemic necrotizing vasculitides that includes Wegener's granulomatosis, microscopic polyangiitis, the Churg-Strauss syndrome, and isolated pauci-immune necrotizing or crescentic glomerulonephritis, regardless of other types of ANCA tests. Inclusion criteria required specification of a consecutive or random patient selection method and the use of acceptable criteria for the diagnosis of vasculitis exclusive of ANCA test results. Weighted pooled summary estimates of sensitivity and specificity were calculated for anti-MPO alone, anti-MPO + perinuclear ANCA (pANCA), and anti-MPO/pANCA + anti-PR3/cANCA.

***Results.*** Of 457 articles reviewed, only 7 met the selection criteria. Summary estimates of sensitivity and specificity (against disease controls only) of assays for anti-MPO for the diagnosis of systemic necrotizing vasculitides were 37.1% (confidence interval 26.6% to 47.6%) and 96.3% (CI 94.1% to 98.5%), respectively. When the pANCA pattern by IIF was combined with anti-MPO testing, the specificity improved to 99.4%, with a lower sensitivity, 31.5%. The combined ANCA testing system (anti-PR3/cANCA + anti-MPO/pANCA) increased the sensitivity to 85.5% with a specificity of 98.6%.

***Conclusion.*** These results suggest that while anti-MPO is relatively specific for the diagnosis of systemic vasculitis, the combination system of immunoassays for anti-MPO and IIF for pANCA is highly specific and both tests should be used together given the high diagnostic precision required for these conditions. Because patients with ANCA associated vasculitis have either anti-MPO with pANCA or anti-PR3 with cANCA, and rarely both, a combined ANCA testing system including anti-PR3/cANCA and anti-MPO/pANCA is recommended to optimize the diagnostic performance of ANCA testing. (J Rheumatol 2001;28:1584–90)

*Key Indexing Terms:*
ANTINEUTROPHIL CYTOPLASMIC ANTIBODY           ANTIPROTEINASE 3
ANTIMYELOPEROXIDASE           WEGENER'S GRANULOMATOSIS
MICROSCOPIC POLYANGIITIS           CHURG-STRAUSS SYNDROME
IDIOPATHIC NECROTIZING CRESCENTIC GLOMERULONEPHRITIS

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*Submitted September 7, 2000; revision accepted January 26, 2001.*

Antineutrophil cytoplasmic antibodies (ANCA) have been associated with the spectrum of vasculitis that includes Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), the Churg-Strauss syndrome (CSS), and isolated pauci-immune necrotizing and crescentic glomerulonephritis (iNCGN)[1-3]. The syndromes within this spectrum of vasculitis are characterized by: (1) overlapping clinical and histological features with frequent involvement of major organs, (2) the need for aggressive immunosuppressive treatment, and (3) serious morbidity and a sizable mortality. The management of these vasculitides often requires critical and timely decision making to prevent serious disease consequences and hazards from mistreat-

ment. Thus, accurate understanding of tests for ANCA, a noninvasive disease marker, for the diagnosis of these vasculitides cannot be overemphasized.

Different assays have been used to test for ANCA, including indirect immunofluorescence (IIF) and immunoassays that use either crude or highly purified preparations of specific antigens. Although several different ANCA antigens have been described, only antiproteinase 3 antibodies (anti-PR3) and antimyeloperoxidase antibodies (anti-MPO) have been shown to be of value in the diagnosis of vasculitis[4]. When used to stain ethanol fixed, cytocentrifuged normal human neutrophils by IIF, anti-PR3 produce a cytoplasmic pattern of staining called cANCA and anti-MPO produce a perinuclear or nuclear pattern called pANCA. Controversy exists regarding the optimal utilization of these IIF ANCA tests and antigen-specific ANCA assays.

The diagnostic value of tests for anti-MPO for systemic vasculitides is less established than that for cANCA/anti-PR3[5]. A previous metaanalysis evaluated the value of cANCA for the diagnosis of WG[6]. The authors did not include tests for anti-MPO, which account for a substantial portion of cases in many ANCA studies[7-13], nor did they look at the value of ANCA testing for MPA, CSS, and iNCGN.

To summarize the pertinent data, we conducted a metaanalysis on the performance of anti-MPO for the diagnosis of the spectrum of vasculitis that includes WG, MPA, CSS, and iNCGN. We also analyzed the diagnostic performance of the combination of IIF ANCA testing for pANCA with antigen-specific ANCA testing for anti-MPO. Lastly, we evaluated the performance of simultaneous testing for both anti-PR3/cANCA and anti-MPO/pANCA.

## MATERIALS AND METHODS

*Search strategy.* Because the primary objective of this metaanalysis was to summarize the diagnostic value of assays for the detection of anti-MPO for the diagnosis of WG, MPA, CSS, and iNCGN, target articles in the search strategy were those reporting the diagnostic value of anti-MPO regardless of other types of ANCA tests. To find pertinent articles, we performed a Medline search for English-language studies in humans published between 1966 and October 1998. Search strategies included: a comprehensive text-word and keyword search for "anti-myeloperoxidase," "antimyeloperoxidase", "antibodies and myeloperoxidase," or "antibody and myeloperoxidase" together with a comprehensive text-word and keyword search including "pulmonary-renal syndrome," "Wegener/Wegener's granulomatosis," "vasculitis or vasculitides," "glomerulonephritis or nephritis," "polyarteritis/polyangiitis," "microscopic polyangiitis," "Churg Strauss syndrome," "crescentic or necrotizing glomerulonephritis", or "Goodpasture syndrome." Using these search strategies, 449 articles were identified. An additional manual search of the reference lists of included articles and review articles revealed 8 more studies. Thus a total of 457 candidate articles were identified for the selection process.

*Article selection.* The main goal of article selection was to identify original articles that studied the diagnostic value of tests for anti-MPO in an appropriately selected group of well defined vasculitis patients, in comparison to controls. We adopted a stepwise article selection process similar to that of an ANCA metaanalysis by Rao, *et al*[6]. To be included in the final analysis,

all articles had to pass 4 stages of selection process (Figure 1). First, the abstracts of all the articles identified through the search method were independently examined by 2 authors (HKC and JLN). Articles were excluded at this stage if they were case reports or letters to the editor, or if they were irrelevant to the topic. If an article did not have an abstract, or if it was not clear that an article was a case report or a letter, or if either reviewer included it, it was retained for further review. Of 457 articles chosen from the search strategy, 135 were retained for stage 2 of the selection process. All 135 articles were photocopied and reviewed. Exclusion criteria at this stage were case reports (n = 1), reviews (n = 20), editorials (n = 2), letters to the editor (n = 1), and articles irrelevant to our topic (n = 38). Seventy-three of 135 articles remained for the next selection steps.

Stage 3 of the selection process involved detailed reviews of the Methods section of the 73 remaining articles. We excluded the articles that did not specify a reasonably unbiased patient selection method (consecutive or random) or the use of acceptable criteria as defined below for the diagnosis of WG, MPA, CSS, or iNCGN exclusive of ANCA test results (n = 35). To examine both specificity and sensitivity, we excluded case-series without controls (n = 26).

In stage 4, 2 authors independently reviewed each of the remaining 12 articles[7-18]. Among these 12 articles, one was excluded because it did not allow construction of a 2 by 2 contingency table[14]. Four additional articles were excluded because there were indications for duplicate counting of cases among articles by the same authors. We retained only the one article from any author that provided the most information about the combined ANCA testing systems in addition to anti-MPO alone. Disagreements between reviewers were resolved by consensus.

*Contingency table construction.* For the 7 articles chosen for analysis, we constructed 2 by 2 contingency tables for patients with and without the spectrum of vasculitis described above compared with patients with and without positive anti-MPO test results[7-13]. Subjects with anti-glomerular basement membrane disease were excluded from contingency tables because of the known association with ANCA[19].

We also examined the sensitivity and specificity of combined testing by IIF tests for pANCA together with antigen-specific immunoassays for anti-MPO in the diagnosis of WG, MPA, CSS, or iNCGN. With this system, to be considered ANCA-positive, the sera had to be positive for both anti-MPO and pANCA. Among the 7 articles, 6 allowed construction of a 2 by 2 contingency table to evaluate this combined testing system[7-10,12,13].

Lastly, we assessed the utility of a combined ANCA testing system for the same spectrum of the vasculitis employing both pANCA/anti-MPO and cANCA/anti-PR3. Among the 7 articles, 5 articles provided the additional information on cANCA/anti-PR3 necessary to construct 2 by 2 contingency tables to evaluate this all-inclusive combined testing system[7-9,12,13].

*Definitions of systemic vasculitic syndromes: WG, MPA, CSS, and iNCGN.* Acceptable case definitions of WG, MPA, and CSS in the metaanalysis were those matching the definitions of the Chapel Hill consensus conference[20]. iNCGN was defined as pauci-immune NCGN without features of systemic diseases. Additionally, the criteria for the diagnosis of WG defined by Fauci, *et al* were considered acceptable[21].

*Definition of a positive anti-MPO test, a positive combined test with anti-MPO and pANCA, and a positive combined ANCA with anti-MPO (with pANCA) or anti-PR3 (cANCA).* As with many serologic test reports, assays for anti-MPO, anti-PR3, cANCA, and pANCA have been reported in different ways: positive or negative or as a titer or unit of activity. Because of the lack of a uniform definition of positivity across studies, we accepted the determinations of positivity reported by the individual studies.

*Statistical analysis. Weighted pooled analysis.* Summary estimates of sensitivity and specificity were calculated by pooling results weighted by the number of subjects in each study[22]. Before determining the summary estimates, we evaluated a chi-square test of homogeneity for all selected studies. A fixed-effects model was applied when there was no heterogeneity and a random-effects model was used when there was heterogeneity[22,23]. We calculated 95% confidence intervals for all estimates, including the summary estimates.

*Summary receiver operating characteristics (SROC) analysis*. SROC analysis assumes that at least part of the variability in test performance reported in the source studies is explained by the use of different cutoff values or positivity criteria and adjusts for these differences[24]. SROC analysis also allows evaluation for important clinical covariates. To estimate the SROC curve, we used the model: $D = a + b * S$, where $D$ = logit sensitivity – logit (1 – specificity), $S$ = logit sensitivity + logit (1 – specifity), $a$ = intercept term, and $b$ = regression coefficient for $S$[24]. For each ANCA testing system, SROC curves were generated separately. The magnitude and p value of $b$ were evaluated by weighted least squares regression analysis with weights proportional to the inverse variance of $D$ to assess the influence of different cutoff values. Additionally, we assessed the influence of available variables including publication years (1990–1991 vs the later years), study design (case-control vs cohort), patient recruitment method (retrospective vs prospective), and methods of case definition (Table 1). We used a 2 sided significance level of $p < 0.05$.

## RESULTS

*Overview of the studies*. An overview of studies that were finally included in the metaanalysis is summarized in Table 1. The 7 studies[7-13] reported anti-MPO test results by antigen-specific assay in a total of 4261 study subjects (range 123–1282). There were 564 patients (13.2%) with the spectrum of vasculitis defined by our inclusion criteria (range 28–262). There were 3132 controls including 1052 normal controls. The total number of positive anti-MPO test results was 304 (range 10–144). Four studies recruited study subjects retrospectively[7-9,12], two prospectively[10,11], and one both prospectively and retrospectively[13].

Six of the 7 studies provided sufficient data to analyze a testing system combining anti-MPO and pANCA assays[7-10,12,13]. The total number of subjects with positive anti-MPO by antigen-specific assay and pANCA by IIF was 162 (range 10–74). Five of the 7 studies provided sufficient data to analyze a testing system combining tests for cANCA/anti-PR3 and pANCA/anti-MPO[7-9,12,13]. The total number of subjects with positive tests for cANCA/anti-PR3 or pANCA/anti-MPO was 358 (range 32–177).

*Weighted pooled results*. Weighted pooled estimates of the sensitivity and specificity of anti-MPO antigen-specific assays are shown in Table 2. From the 7 studies[7-13], the anti-MPO assays had a summary sensitivity estimate of 37.1% (confidence interval 26.6%–47.6%) and a summary specificity estimate of 96.9% (CI 95.2%–98.7%) with all controls. The summary specificity estimate of assays for anti-MPO using disease controls alone was 96.3% (CI 94.1%–98.5%). Specificity estimates of the 7 studies showed tighter 95% CI compared to sensitivity estimates (Table 2). There was statistically significant heterogeneity in both sensitivities and specificities both with all controls ($p < 0.001$) and with disease control only ($p < 0.001$) across the 7 articles.

*Table 1*. Overview of studies included in the metaanalysis. Cases met the case definition of Wegener's granulomatosis, microscopid polyangiitis, Churg-Strauss syndrome, or isolated pauci-immune necrotizing and crescentic glomerulonephritis.

| Reference | Patient Recruitment | Study Design | Method of Case Definition | Total Study Subjects, n | Vasculitis Cases | Positive ANCA[†] | | | Disease Controls[§] | All Controls[§††] |
| | | | | | | Anti-MPO | p-ANCA & anti-MPO | p-ANCA & anti-MPO or c-ANCA & anti-PR3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cohen[7] | Retro | Case-control | Biopsy | 156 | 32 | 12 | 12 | 32 | 75 | 124 |
| Niles[8] | Retro | Case-control | Biopsy | 1040 | 42 | 26 | 26 | 43 | 267 | 980 |
| Bygren[9] | Retro | Cohort | Biopsy* | 455 | 64 | 34 | 21 | 61 | 364 | 364 |
| Velosa[10] | Prosp | Cohort | Biopsy | 123 | 28 | 28 | 12 | NA | 75 | 87 |
| Sinico[11] | Prosp | Cohort | Biopsy | 920 | 92 | 27 | NA | NA | 412 | 412 |
| Bosch[12] | Retro | Case-control | Biopsy | 285 | 44 | 10 | 10 | 38 | 186 | 241 |
| Hagen[13] | Prosp & retro | Cohort | Chapel Hill & biopsy | 1282 | 262 | 114 | 74 | 177 | 184 | 924 |

*Renal biopsy with clinical features of ANCA associated vasculitis. [†]Positive ANCA among vasculitis cases. [††]Total controls include healthy, disease, and not well defined controls. [§]Control groups that were counted in the analysis.

*Taable 2*. Weighted pooled results.

| ANCA Testing System | No. of Studies | Sensitivity, % (95% CI) | Specificity, % (95% CI) | |
| | | | Disease Controls | All Controls |
|---|---|---|---|---|
| Anti-MPO | 7 | 37.1 (26.6, 47.6) | 96.3 (94.1, 98.5) | 96.9 (95.2, 98.7) |
| Anti-MPO plus p-ANCA | 6 | 31.1 (21.0, 42.1) | 99.4 (99.0, 99.9)* | 99.3 (98.8, 99.8) |
| Anti-MPO plus p-ANCA or anti-PR3 plus c-ANCA | 5 | 84.7 (70.7, 98.7) | 98.6 (97.9, 99.3)* | 99.2 (99.0, 99.6)* |

*A fixed-effect model for calculating summary estimates was used because chi-square testing suggested that there is no heterogeneity across studies. Other summary estimates were calculated with a random-effects model due to the suggested presence of heterogeneity across the studies.
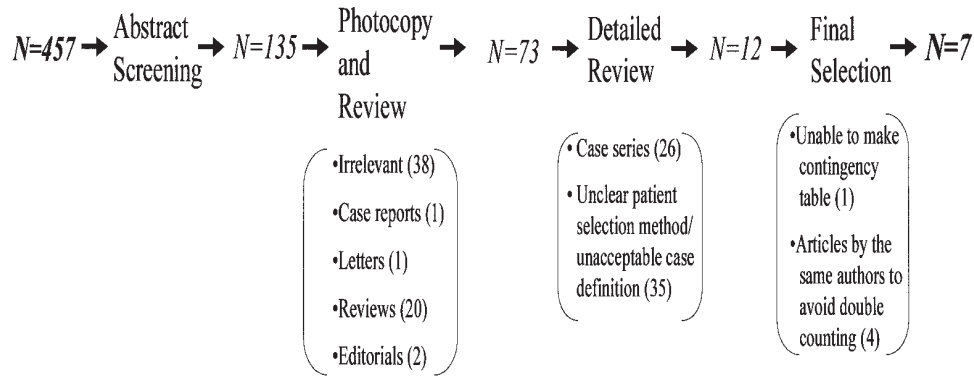
*Figure 1.* Summary of the article selection process. Numbers in parentheses denote articles excluded.

Testing for the combination of pANCA and anti-MPO from the 6 studies[7-10,12,13], the summary sensitivity estimate was 31.1% (CI 21.0%–42.1%) and the summary specificity estimate was 99.3% (CI 98.8%–99.8%) with all controls (Table 2). There was statistically significant heterogeneity in both these estimates across the 6 articles (p < 0.001 for sensitivity and p < 0.05 for specificity against all controls). However, when the estimation of summary specificity was limited to only disease controls across the 6 studies, there was no significant heterogeneity (p = 0.08) and the summary specificity estimate of assays for pANCA and anti-MPO with disease controls alone was 99.4% (CI 99.0%–99.9%) employing the fixed-effect model.

When testing for both pANCA/anti-MPO and cANCA/anti-PR3, the 5 studies gave a summary sensitivity estimate of 84.7% (CI 70.7%–98.7%), a summary specificity estimate of 99.2% (CI 99.0%–99.6%) with all controls, and a summary specificity estimate of 98.6% (CI 97.9%–99.3%) with disease controls alone (Table 2). There was statistically significant heterogeneity in sensitivity estimates across the 5 articles (p < 0.001), whereas there was no significant heterogeneity in specificities (p = 0.108 for specificity with all controls, p = 0.607 for specificity with disease control only).

*SROC analysis.* SROC curves in each ANCA testing system are presented with data points weighted by number of study subjects in Figure 2. In all 3 of the ANCA testing systems that we evaluated, beta coefficients evaluating the significance of the influence of different cutpoints across the studies were close to zero and not statistically significant (b = –0.23, –0.69, and –0.95 and p value = 0.4, 0.4, and 0.2 in anti-MPO alone, anti-MPO + pANCA, and all combined system with disease controls, respectively). In univariate SROC analysis for anti-MPO, publication years and study design were significant predictors. The discriminatory power of the test in the studies with the earliest years (1990–1991) was better than that of later studies (ß-coefficient, 2.67, 95% CI 0.85–4.48, p = 0.004). Performance increased with case-control design compared to cohort design (1.86, 95% CI 0.52–3.20, p = 0.007). Methods of case definitions and recruitment methods were not significant predictors (0.97, 95% CI –0.82 to 2.76, p = 0.29 and 0.84, 95% CI –0.63 to 2.33, p = 0.26, respectively).

**DISCUSSION**
We present a metaanalysis of available literature on the diagnostic values of tests for anti-MPO and combined ANCA testing systems. Our metaanalysis indicates that
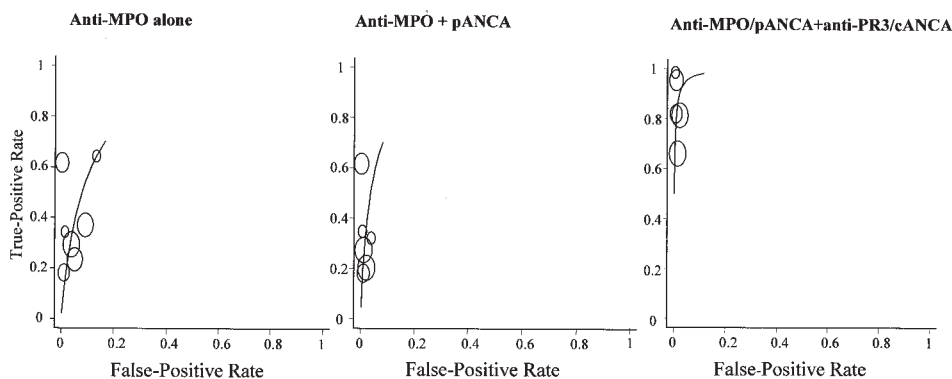


*Figure 2.* Summary receiver operating characteristic (SROC) curves for the 3 ANCA testing systems. Open circles denote data points with their sizes weighted by number of subjects.

antigen-specific assays for anti-MPO are relatively specific (96.3%, against disease controls) but not sensitive (37.5%) for the diagnosis of systemic vasculitis when used alone. (In contrast, the specificity of pANCA alone for disease controls was only 82%.) When pANCA pattern by IIF is combined with anti-MPO testing, the specificity improves to 99.4% with a lower sensitivity (to 31.5%). Finally, the combined ANCA testing system (anti-PR3/cANCA + anti-MPO/pANCA) increases the sensitivity to 85.5%, with specificity remaining high at 98.6%. These results strongly suggest that the combined ANCA testing system employing both antigen-specific testing and IIF for anti-PR3/cANCA + anti-MPO/pANCA should be used to optimize the testing characteristics of ANCA for the diagnosis of systemic vasculitis.

This high specificity of the combined ANCA testing system estimated in our analysis has been described in multiple other reports that did not include information to be able to appropriately assess the sensitivity of the assays, and hence did not meet our selection criteria (e.g., reports measuring specificity only or reports without specification of an unbiased patient selection method)[4,25]. Additionally, our results are in clear agreement with, and provide strong support for, a recent international consensus statement on ANCA testing[26].

Our results should be used with consideration of the clinical setting and presentation of individual patients suspected of vasculitis. The presence of characteristic features or combinations of features determines the probability of vasculitis at that point before pursuing an ANCA test (pretest probability of vasculitis). In Figure 3, we list 5 major clinical presentations of ANCA associated vasculitis. With each clinical setting, the probability of vasculitis is estimated from the literature[8,27-29]. For example, for a patient presenting with rapidly progressive glomerulonephritis, the diagnostic probability of vasculitis is 53% before any further evaluation is pursued, including ANCA tests. This pretest probability is too low to commit the patient to a course of longterm immunosuppression. Through ANCA testing, the diagnostic certainty of vasculitis can be improved employing Bayes' theorem[30]. If tests for anti-MPO/pANCA or anti-PR3/cANCA are positive, the probability of vasculitis rises to 99%, as shown in Figure 3 (positive predictive value). However, if the ANCA test is negative, the probability is reduced to 15%. These revised probabilities are often called post-test probabilities, corresponding to the y axis values in Figure 3. In an example with a moderate pretest probability, a patient with sinus involvement and glomerulonephritis would have a pretest probability for vasculitis estimated to be 30%. The post-test probability in this case increases to 96% with a positive ANCA test, and falls to 6% with a negative ANCA test. Finally, when a patient presents with sinus involvement alone, corresponding to a pretest probability of 1%, the diagnostic probability of vasculitis remains less than 40% despite a positive ANCA test result. This exercise illustrates that in addition to the diagnostic performance of the ANCA assays summarized in our analysis, the presence of specific
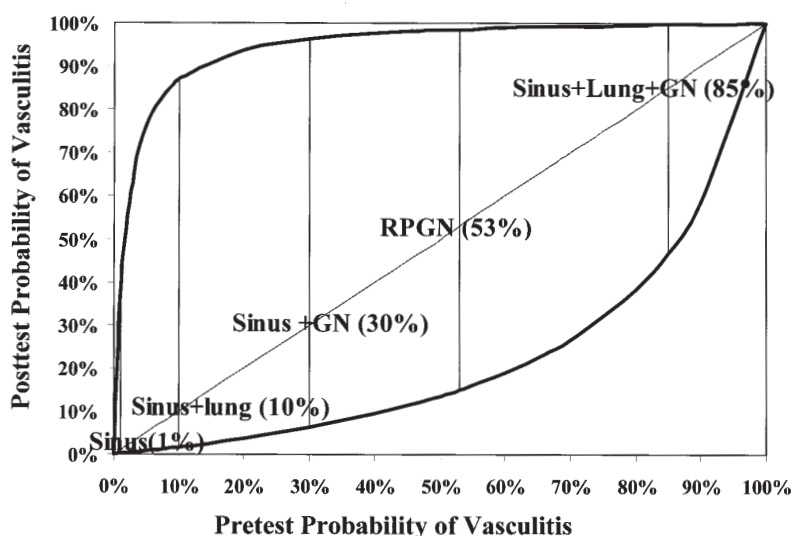


*Figure 3*. Diagnostic probability revision using a combined IIF and ELISA ANCA testing system (anti-MPO/pANCA and anti-PR3/cANCA), using the sensitivity and specificity estimates of the current metaanalysis. Five common clinical presentations of ANCA associated vasculitis are shown with the probability of vasculitis (pretest probability) estimated from the literature (in parentheses), corresponding to *x* axis values. Upper and lower curves show revised probabilities of vasculitis after ANCA test results are known (post-test probability), when ANCA test is positive and negative, respectively.

clinical features plays a major role in determining the diagnostic probability of vasculitis.

As with other tests, the sensitivity and specificity of ANCA have a reciprocal relationship, as seen in the SROC graphs shown in Figure 2. In a given clinical presentation, the positive predictive value can be raised to a certain degree with a sacrifice in negative predictive value by choosing a cutoff value with a higher specificity and lower sensitivity. Therefore, one could argue that in order to improve its positive predictive value, we could choose a stricter cutoff value in settings with lower pretest probabilities such as sinus involvement alone. However, the ultimate goal in managing the given clinical setting is to achieve the best outcome, not just making the correct diagnosis. Therefore, determination of optimal cutoff values of the ANCA test depends on the net benefits of the treatment in patients with vasculitis and net hazards of the mistreatment in patients with diseases other than vasculitis[30,31]. For example, patients with sinus involvement alone (with a pretest probability at 1%) might be treated with a less aggressive regimen, which is associated with less net hazards when misused. This counteracts the suggestion to choose a stricter cutoff value in this low pretest probability setting just to achieve a better positive predictive value for the diagnosis of vasculitis.

Other important factors besides the diagnostic performance of ANCA tests need to be considered before deciding to administer toxic immunosuppressive therapy. These include (1) the diagnostic probability of improvement and potential side effects with additional tests such as biopsy, (2) the consequences and costs of mistreating nonvasculitic disorders with immunosuppressive agents, and (3) the consequences and costs of delaying or missing the diagnosis. We have incorporated these factors and the summary ANCA sensitivity and specificity of this metaanalysis in a companion decision analysis[32]. This analysis looked at the need for a renal biopsy in the clinical setting of rapidly progressive glomerulonephritis, when the pretest probability of vasculitis is high, ranging from 40% to 66%[8,27,28]. The results suggest that the initiation of immunosuppression based on an ANCA test alone without renal biopsy can be justified in this clinical setting, which has a high pretest probability of vasculitis. Other clinical settings with different pretest probabilities require further analyses with relevant data.

The sensitivity and specificity of a diagnostic test estimated in a given study setting can be best applied to comparable clinical settings. Five of the 7 studies chosen for analysis had disease verification by renal biopsy. This means that all patients in the 5 studies had enough renal findings to justify a renal biopsy. Although there was no obvious difference in sensitivity and specificity of anti-MPO between studies with and without renal biopsy verification, it remains possible that the sensitivity and specificity of cases with and without renal findings are different given the limited number of studies available for comparison. Therefore, one could argue that our results are most applicable to those patients presenting with renal findings suggestive of vasculitis.

In contrast to the absence of heterogeneity in the specificity estimates among the combined ANCA systems (anti-MPO/pANCA with or without anti-PR3/cANCA), there was significant heterogeneity among the sensitivity estimates of all 3 ANCA testing systems and specificity estimates of anti-MPO alone. Our SROC univariate analyses suggested the studies of case-control design or the earliest studies found significantly better performance of anti-MPO test than those of cohort design or later studies, which is often the case in many clinical (observational) studies of other subjects. Other potential causes for the observed heterogeneity include ANCA assay variation between the different centers, including the use of different cutoff values, difference in the proportions of the 4 vasculitides considered in our analyses, disease activity or severity among the study subjects, and the possible use of immunosuppressive therapy at the time of ANCA.

The limitations of this metaanalysis fall into 2 categories: those attributable to the data available for analysis and those attributable to the techniques generally used to perform the metaanalysis. We were not able to meaningfully test for potential causes of the heterogeneities across the studies because the majority of the possible variables were not reported, and our attempt to assess available covariates through SROC analyses suffered a limited power due to small number of selected articles. Publication bias is another potential source for bias in this metaanalysis as in many other metaanalyses.

Our metaanalysis of published data suggests that although immunoassays for anti-MPO are relatively specific for the diagnosis of systemic vasculitis, the combination system of immunoassays for anti-MPO and IIF for pANCA is highly specific and both tests should be used together given the high diagnostic precision required for these conditions. Further, because patients with ANCA associated vasculitis have either anti-MPO with pANCA or anti-PR3 with cANCA, and rarely both, a combined ANCA testing system including anti-PR3/cANCA and anti-MPO/pANCA is recommended to optimize the diagnostic performance of ANCA testing.

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