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## **A paradigm of diagnostic criteria for polyarteritis nodosa: analysis of a series of 949 vasculitides**

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Abbreviations: ACR, ANCA, CSS, ELISA, ENT, EUVAS, FVSG, HBeAg, IIF, MI, MPA, MST, PAN, RA, SLE, WG

## SUMMARY

**Objective:** To establish a set of clinical and paraclinical criteria potentially useful as a diagnostic screening tool for polyarteritis nodosa (PAN).

**Methods:** The abilities of individual descriptive items to predict PAN diagnosis were evaluated by screening available data for 949 patients entered in the French Vasculitis Study Group's (FVSG) database, including 262 with PAN and 687 control vasculitides. Selected items were tested in a logistic-regression model to establish a minimal set of non-redundant PAN predictive criteria. The discriminative accuracy of these items and of 1990 ACR criteria were assessed by reapplying them to the initial patient sample and a subgroup restricted to PAN and microscopic polyangiitis (MPA) patients. A computer-simulation procedure was conducted on artificially generated patient data to evaluate the usefulness of these criteria to predict PAN diagnosis.

**Results:** The analysis retained 3 positive-predictive (HBV-antigen and/or DNA in serum, arteriographic anomalies, mono- or polyneuropathy) and 5 negative-predictive parameters (indirect immunofluorescence ANCA detection, asthma, ENT signs, glomerulopathy, and cryoglobulinemia), yielding 70.6% sensitivity for all control vasculitides and 89.7% for MPA controls, with 92.3% specificity for all controls and 83.1% for MPA. The discriminant abilities of this set of items outperformed the 1990 ACR criteria in all analytical situations, showing better robustness to variations in the prevalence of individual vasculitides.

**Conclusion:** The use of positive and negative discriminant criteria could constitute a sound basis for developing a PAN diagnostic tool for clinicians. Further prospective analyses and validations in different populations are needed to confirm these items as satisfactory diagnostic criteria.

## INTRODUCTION

Systemic vasculitides are a heterogeneous group of diseases that have blood-vessel inflammation as a common trait. In 1990, relying on many previous efforts, the American College of Rheumatology (ACR) proposed a set of classification criteria, selected by a panel of experts based on an analysis of multicenter patient data (1). Seven distinct entities were thus characterized, including polyarteritis nodosa (PAN) (2). Although the primary purpose of the 1990 ACR criteria was to standardize classification of vasculitis patients to facilitate communication among researchers (3), their good discriminative accuracy indicated by the initial assessments, with sensitivities between 71–94% and specificities between 87–92% for different types of vasculitides, suggested a potential usefulness for diagnostic prediction (4). However, subsequent evaluations of the set of 1990 ACR criteria used for diagnostic screening under routine clinical conditions yielded inconstant and unsatisfactory results, with positive-predictive values ranging from 17% to 75% for different types of vasculitides and high percentages of false positive diagnoses (4). Further assessments, extended to other classification systems, like the Chapel Hill Nomenclature (5, 6) were equally disappointing, highlighting the necessity to develop separate criteria for classification and diagnostic purposes (7).

We conducted a prospective analysis of the French Vasculitis Study Group (FVSG) patient database, intended to evaluate the feasibility of establishing a minimal set of predictive clinical and paraclinical features, which could serve as a screening tool for PAN diagnosis in situations in which the clinical picture is suggestive of systemic vasculitis. Because the 1990 ACR criteria do not distinguish between PAN and microscopic polyangiitis (MPA), formally defined by the Chapel Hill

Nomenclature in 1992 (8), a secondary objective of our analysis was to achieve better discrimination between PAN and MPA.

## **METHODS**

The analytical design comprised two distinct stages. The first stage was to select a minimum set of low redundant positive and/or negative PAN predictive items, among those exhibiting the highest individual accuracy in distinguishing PAN from other systemic vasculitides. The selection of this set relied on clinical judgment supported by a combination of uni- and multivariate statistical analysis of clinical and paraclinical items used to describe patient characteristics in the FVSG database. During the second stage, the PAN-predictive abilities of the selected set of criteria were evaluated through an unsupervised computer-simulation procedure, designed to reproduce the case-based aspect of the clinical diagnostic reasoning. Both analytical stages were compared to the 1990 ACR classification criteria considered to be the most reliable reference to date.

### **Analysis of capabilities of available clinical and paraclinical items to predict PAN**

The FVSG patient database contains a large set of clinical and paraclinical items, designed to describe systemic vasculitides characteristics with a good level of detail. Our analysis relied on patient information extracted from the FVSG database, after filtering for missing items and secondary vasculitides associated to other systemic diseases, like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). This procedure selected 949 patients with primary systemic vasculitides for which definitive diagnostic evidence was available; in all cases diagnoses were based on compatible clinical manifestations, biochemical parameters including antineutrophil cytoplasm antibody (ANCA) testing, histology, and, when available, angiograms. The histological confirmation of the clinical diagnosis relied on the same elements as those used by the 1990 ACR

analysis (1, 2), and was a mandatory selection criterion, used only as diagnostic reference to ensure a reliable assessment of the available clinical and paraclinical items.

The selected patient sample had the following distribution of vasculitis types: 262 (27.6%) with PAN, among whom 108 had hepatitis B virus (HBV)-related PAN (41.2% of all PAN), 256 (27%) with Wegener's granulomatosis (WG), 207 (21.8%) with MPA, 150 (15.8%) with Churg–Strauss syndrome (CSS), 18 (1.9%) with cryoglobulin-associated vasculitis and 56 (5.9%) with other primary systemic vasculitides.

Analysis of these data, in the search for a minimal set of low-redundant PAN predictive items, was conducted in two steps. During a first step, the entire list of over 100 clinical and paraclinical items used to describe patient characteristics in FVSG database, including all the 1990 ACR criteria, was subjected to univariate analysis to assess the individual discriminative value of each available feature. Among these items, the presence of HBV surface antigen, one of the 1990 ACR criteria, was replaced by markers reflecting active HBV replication, such as the detection of HBV e-antigen (HBeAg) and/or DNA  $>10^5$  copies/mL in serum (9). An indirect immunofluorescence assay (IIF) was used to test for ANCA according to European Vasculitis Study (EUVAS) group recommendations (10). Because ANCA specificity (anti-myeloperoxidase or proteinase 3) was not systematically determined, it was ignored.

The univariate analysis assessed the strength of individual associations between PAN diagnosis and available clinical or paraclinical features by relying on a normalized, pairwise, mutual information (MI) measure, which is a well-established entropic approach for quantifying mutual dependence (e.g. positive or negative) between variables (11). A short presentation of the MI measure is provided online as supplementary data, together with other formal aspects

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pertaining to the analytical strategy of the study (12). The univariate analysis enabled quantification of the usefulness of the information provided by each clinical and paraclinical item to diagnose PAN, and allowed to rank available items by the decreasing order of their PAN-predictive value.

To establish a minimal set of low-redundant PAN-predictive criteria we conducted an exploratory multivariate analysis that relied on available parameters to build a logistic-regression model through a forward inclusion approach based on the  $R^2$  criterion. The inclusion procedure was directed by clinical judgment and the PAN-predictive value of individual items, as determined by the univariate analysis, and was reiterated until the logistic-regression model could no longer be significantly improved by further inclusion of additional items. This analysis was conducted in two distinct situations, one in which all non-PAN vasculitides were considered as controls, and the second in which controls were restricted to MPA in order to favor the selection of discriminant items capable to distinguish between PAN and MPA not differentiated by the 1990 ACR analysis. Also, taking into consideration the current trend of reduction of the incidence of HBV infection, induced by systematic vaccination programs, and its diminishing association with PAN, the discriminant performances of these criteria were separately evaluated on a subgroup of vasculitides including only HBV-negative PAN.

The resulting FVSG set of criteria, selected by the multivariate analysis, was further used to derive a set of relevant positive and negative association rules, based on an implementation (13) of a decision-tree inference algorithm (14), designed to optimize the ratio between diagnostic prediction accuracy and its cost (e.g. the number of required items). This analysis was undertaken to devise a tool for future clinical use of this criteria by exposing the most relevant association rules between selected items. Finally, the PAN-predictive accuracy of the FVSG set of

criteria and the 1990 ACR classification criteria were comparatively assessed, in terms of sensitivity and specificity, by receiver operating characteristics (ROC) curve analysis (15), in each of the above-mentioned analytical situations.

### **Computer simulation of PAN-predictive abilities of FVSG and 1990 ACR criteria**

During the second analytical stage, computer simulations were run to evaluate the PAN-predictive abilities of the two sets of criteria under various conditions simulated through artificially generated vasculitis patient data. The computer-simulation procedure was designed to reproduce the case-based reasoning aspect of medical diagnostic reasoning, which attempts to ascribe unambiguous labels (e.g. corresponding to distinct pathological entities) to clusters of cases with similar clinical and paraclinical features. The aim of this simulation was to test the dependence of the PAN-predictive performances of these sets on the prevalence of individual vasculitides in the analyzed patient samples. The Boolean aspect of the presence or absence of clinical and paraclinical features in vasculitis patients suggested the possibility of relying on a model of aggregated dependent Bernoulli trials to represent the real joint distributions of the clinical and paraclinical parameters specific to each vasculitis. To ensure a good reproducibility of the computer-simulation results we considered two distinct approaches to quantify and express marginal distributions and dependencies between individual parameters.

The first approach relied on the Bahadur–Lazarsfeld theoretical framework, which computes a complete representation of the joint distribution of a set of  $n$  correlated Bernoulli trials (e.g. corresponding to  $n$  clinical or paraclinical items) through an expansion of a binomial law (16). A short formal presentation of the Bahadur–Lazarsfeld framework is provided online as supplementary data (12). Despite its good theoretical accuracy, a major drawback of the

Bahadur–Lazarsfeld expansion is its requirement of a high number of dependency parameters (e.g. correlation parameters expressing dependencies between Bernoulli trials from the 2<sup>nd</sup> to the  $n^{\text{th}}$  order), which challenges the computational tractability of the model, even for a moderate number of trials. These considerations suggested the usefulness of a recently proposed theoretical solution, which relies on the maximum entropy principle to optimize the inference of missing parameters of a truncated Bahadur–Lazarsfeld expansion (e.g. which considers as input parameters only marginal probabilities and second-order correlations) (17), thereby allowing to achieve a highly precise reproduction of the clinical and paraclinical characteristics of real vasculitis patients in artificially generated data. The required marginal probabilities and the second-order correlations between clinical and paraclinical items were computed from the patient sample extracted from the FVSG database.

The second approach used to generate artificial patient data relied on a maximum-spanning tree (MST) dependence-modeling technique, which approximates dependencies between individual parameters by arbitrarily limiting them to those expected to have the most impact on the results (18, 19). The principle of the MST dependence-modeling technique resides in estimating the joint distribution of item presence by relying on an MST representation of their strongest interdependencies. Further details are provided online as supplementary data (12). The marginal probabilities of clinical and paraclinical items and the pairwise MI coefficients, required by the MST approach, were computed from the FVSG patient sample.

The generation of artificial vasculitis patient data aimed to reflect two types of situations. The first was a reference situation, in which patient data were artificially generated by using either the maximum entropy correction of a truncated Bahadur–Lazarsfeld extension or the MST method to simulate intricate interdependencies between various clinical and paraclinical

parameters seen in the FVSG patient database. In this situation the relative frequencies of the four main types of vasculitides represented within artificially generated patient samples were chosen to reflect the prevalence reported in the French population: 34.03% PAN, 27.83% MPA, 26.27% WG, and 11.86% CSS (20). In the second situation, the relative frequencies of PAN cases were modified to test the effect of variations in vasculitis-prevalence on predictive performances of the two sets of criteria. To this purpose the relative frequency of PAN patients was arbitrarily reduced to 10% of all generated cases, while increasing relative frequencies of the other three vasculitides to 30% for each.

The artificial patient data, thus generated, was further used in a computer simulation to evaluate the usefulness of the two sets of criteria when used to screen potential vasculitis patients for positive PAN diagnosis. To achieve this goal, we relied on a combination of an unsupervised hierarchical clustering approach, used to group artificially generated cases based on the similarities of their clinical and paraclinical profiles, and a supervised labeling procedure, which assigns to each resulting cluster of similar cases the true label of the cases that form the majority of its content.

The clustering approach starts by grouping the two most similar cases together to form a first cluster, and then reiterates the agglomerative procedure until all cases are collected in a single cluster, thereby generating a new partition of cases into clusters at each iterative step. The choice of the optimal partition of clusters (e.g. reflecting the actual distribution of distinct pathological entities in the analyzed patient data) is a fundamental issue in unsupervised learning. A popular solution to this problem is to simplify it by finding the partition that provides the best trade-off between the homogeneity of the clusters and their isolation on the partition (21). Although there is no best approach to fit all situations, the computation of the Silhouette

index, a well-understood partition quality indicator, was shown to be a simple yet robust strategy for predicting optimal clustering partitions (12, 22). After identifying the optimal partition and labeling its clusters, the predictive abilities of the two sets of criteria were evaluated by computing estimations of sensitivity, specificity, and of positive- and negative-predictive values from the contingency table reflecting the attribution of cases to each vasculitis type. The differences between the estimated performances of the ACR and FVSG sets, computed from 30 independent iterations of the simulation procedure, were assessed for statistical significance with a chi-square test comparing distributions of discrete variables, and a paired Student's t-test to evaluate mean values from continuous distributions. All statistical analyses and simulations were conducted by using SPSS version 13.0 (SPSS Inc., Chicago IL), and the R software environment for statistical computing (23).

## RESULTS

The logistic-regression analysis, performed while considering all non-PAN vasculitides as controls, retained a set of 8 minimally redundant PAN-predictive items (table 1), including 3 positive and 5 negatively associated parameters (table 2A). When restricted to the subgroup of HBV-negative PAN, this analysis confirmed the PAN-predictive abilities of one positive and 5 negatively associated parameters (table 2B). Combining these items yielded sensitivities of 70.6% for all forms of PAN and 76.6% for HBV-negative PAN, with specificities of 92.3% and 88.9% respectively. When controls were restricted to MPA alone, the non-redundant PAN-predictive abilities were confirmed only for 4 of the previously identified items, 2 were positively associated with PAN diagnosis, and 2 were more frequent in MPA (table 2A). One positive and 2 negatively associated parameters (table 2B), showed significant non-redundant PAN-predictive abilities

when considering only the subgroup of HBV-negative PAN. The combined sensitivity of these items was 89.7% for all forms of PAN and 83.1% for HBV-negative PAN cases, with specificities of 83.1%, and 83.6% respectively.

The logistic-regression analysis confirmed the abilities of 7 items from the 1990 ACR classification criteria to identify PAN (table 3A). However, the positive association with PAN diagnosis, indicated by the 1990 ACR analysis, could not be confirmed for one item (renal insufficiency), which occurred more frequently in non-PAN vasculitides. These 7 criteria yielded a combined sensitivity of 48.9%, with 95.6% specificity when all other vasculitides served as controls. When considering only the subgroup of HBV-negative PAN cases and all other non-PAN vasculitides as controls, the non-redundant PAN-predictive abilities of the 1990 ACR criteria were confirmed only for 4 positive and one negatively associated parameters (table 3B), resulting in a major decrease of sensitivity to 8.4%, with 98% specificity in this situation. When controls were restricted to MPA, the discriminant abilities of non-redundant PAN items were confirmed only for 3 of them (table 3A), 2 of which were positively associated with PAN diagnosis, while one (renal insufficiency) occurred more frequently in MPA. In the latter settings the 3 discriminant items yielded 50.8% sensitivity for all forms of PAN, with 96.1% specificity. One positive and one negatively associated parameters (table 3B), showed significant non-redundant PAN predictive abilities when considering only the subgroup of HBV-negative PAN, yielding 12.3% sensitivity, with 99% specificity in this situation.

The two sets of association rules established from selected FVSG set of criteria are presented in table 4. When all other vasculitides served as controls 4 positive and 5 negative association rules could be established, based on 7 of the 8 previously selected features (excepted asthma), giving this model a combined sensitivity of 70.2%, with 88.2% specificity. When the

controls were restricted to MPA, 3 positive and 2 negative association rules were established, including all the 4 features identified by the logistic-regression analysis (table 4).

ROC curve analyses performed considering all other vasculitides as controls (fig 1A) yielded areas under the curves of 0.916 [0.898–0.934] for the FVSG selected items and 0.711 [0.671–0.750] for the 1990 ACR criteria, confirming significantly better discriminant accuracy of the FVSG item set ( $p$ -value  $<0.05$ ). The asymptotic significance for these curves was acceptable for both sets of criteria ( $p$ -value  $<0.001$ ). When controls were restricted to MPA (fig 1B), ROC curve analyses yielded areas under the curves of 0.906 [0.878–0.934] for the selected FVSG criteria, and 0.588 [0.537–0.639] for the 1990 ACR criteria, thereby confirming significantly better predictive accuracy of the FVSG set of items in this situation too ( $p$ -value  $<0.05$ ). Again, the asymptotic significance of ROC curves was acceptable for both sets of criteria ( $p$ -value  $<0.001$ ).

Computer-simulation results are summarized in figure 2. No significant differences were observed between the datasets obtained with the two distinct approaches used to generate artificial patient data, thus indicating the good robustness and reproducibility of our simulation procedures (data not shown). Application of the two sets of criteria to artificially generated data suggested a significant relationship between the sparseness and the quality (i.e. in terms of intra-cluster homogeneity) of the resulting cluster partitions, and the positive-predictive value of the sets of criteria used to generate these partitions. Indeed, case partitions obtained with selected FVSG items displayed significantly lower sparseness and higher intra-cluster homogeneity than those generated with the 1990 ACR criteria (fig 2A and 2B), particularly when used to distinguish between PAN and MPA ( $p$ -value  $<0.05$ ). Most notably, the FVSG set of items yielded higher PAN predictive performances, in terms of positive-predictive value and sensitivity (fig 2C and 2E), than the 1990 ACR criteria ( $p$ -value  $<0.05$ ). This better performance was conserved even when the

prevalence of PAN cases in generated patient populations was artificially lowered. The gain in PAN predictive ability achieved with the FVSG criteria was not accompanied by any significant decrease of the specificity or the negative-predictive value (fig 2D and 2F), as compared to the 1990 ACR criteria.

## **DISCUSSION**

Validated diagnostic criteria for systemic diseases could be a useful tool for clinicians who cannot obtain a histological diagnosis or want to avoid taking biopsies due to the risk of side effects. Despite inconstant performances reported in the literature (4, 7) many clinicians still inappropriately use the 1990 ACR classification criteria for diagnostic purposes. As some analysts suggested, a potential explanation for the inconstant results obtained with those criteria for diagnostic predictions, could be the dependence of their discriminant abilities on the prevalence of individual vasculitides within the analyzed populations (24, 25). Moreover, similar reports related to other vasculitis classification systems, like the Chapel Hill Nomenclature (8), showed similar unsatisfactory performances when used for diagnostic purposes (5, 6) and highlighted the need to develop separate criteria for classification and diagnosis of the various systemic vasculitides (7, 26).

Herein, we reported our analysis of patients data accumulated in the FVSG database that targeted two main objectives. The first was to establish a minimal set of non-redundant criteria positively or negatively predictive of PAN and potentially useful not only for classification but also for diagnostic purposes. The discriminant accuracy of the selected FVSG item set (table 1) was evaluated comparatively with that of 1990 ACR criteria on a sample of patients with histologically proven systemic vasculitides selected from the FVSG database. The second objective aimed to evaluate the PAN-predictive abilities of each of these sets of criteria during a computer-

simulation procedure relying on an unsupervised hierarchical classification algorithm applied to artificially generated patient data.

The results of our analysis showed that, when applied to the FVSG database, 1990 ACR criteria did not confirmed their initially reported PAN discriminant abilities (2). By contrast, the selected FVSG item set, established by our analysis, significantly outperformed the 1990 ACR criteria, regardless of the analytical situation considered (tables 2 and 3 and fig. 1). The difference between the discriminant performances provided by the two sets of criteria was even more significant when the analysis was restricted to the subgroup of HBV-negative PAN, which could not be distinguished from non-PAN vasculitides by using the 1990 ACR criteria, as shows the extremely low sensitivity yielded by these criteria in this particular situation.

Furthermore, although 7 of the 9 original items of the 1990 ACR criteria (excepted histology) were found to have significantly non-redundant usefulness to distinguish PAN from other systemic vasculitides in the FVSG database, a significant positive association with PAN diagnosis could not be confirmed for three of them (table 3). Moreover, the renal insufficiency, which yielded significant discriminant ability to distinguish PAN in our analysis, had a lower frequency in PAN patients than in other systemic vasculitides or in MPA (table 3). These findings are in agreement with previous reports (4) that indicated low PAN positive-predictive value of the 1990 ACR criteria.

As previously suggested, in addition to some epidemiological differences between patient samples, another potential explanation for this phenomenon could be the non-distinction between PAN and MPA inherent in the 1990 ACR analysis. Indeed, a strong argument supporting this hypothesis are the poorly discriminant performances of the 1990 ACR criteria in our analyses

when used to distinguish between histologically confirmed PAN and MPA (table 3), which was already shown to be a major drawback of these criteria (25, 27, 28).

Finally, a third possible explanation of the differences in discriminant abilities observed between the 1990 ACR criteria and the selected FVSG item set could reside in the methodological differences between the two analyses. While the 1990 ACR analysis focused on the selection of positive discriminant criteria for classification purposes, our analysis sought to maximize the combined predictive relevance of the selected items by considering both positively and negatively parameters associated with PAN. Indeed, this strategic difference could potentially explain why significant negative discriminant items, as for example the immunofluorescence ANCA positivity, could have been missed by the 1990 ACR analysis. The importance of ANCA positivity in vasculitis diagnosis was first recognized by the Chapel Hill Nomenclature (8). In our analysis the ANCA positivity yielded the strongest discriminant ability, covering 22% of the variance in the logistic-regression model used to distinguish PAN from other vasculitides, and 50% of the logistic-regression model variance when used to distinguish PAN from MPA (table 2). It is well-acknowledged that the IIF ANCA detection provides a lower specificity than the ELISA antigen-specific techniques (10), and therefore it should be expected that the combination of these two detection methods may further improve the discriminant performances of the FVSG item set.

In the end, the assessment of the relevance of the two sets of criteria to diagnose PAN was complemented by a computer-simulation procedure that relied on both sets of items to perform an unsupervised classification task on artificially generated patient data. Although the numbers of case clusters, contained by the optimal partitions, were not the same as the real number of vasculitis entities (e.g. four in our case) represented in the artificial patient samples, in either of the considered analytical conditions, the FVSG item set yielded 2–5 times fewer clusters

(e.g. closer to the real number of vasculitis entities) than those obtained with the 1990 ACR criteria. This lower sparseness of the partitions obtained with the FVSG items was associated with significantly better intra-cluster homogeneity of the resulting case clusters than that provided by the 1990 ACR criteria, thereby confirming the superior PAN-predictive abilities of the FVSG item set.

Pertinently, the FVSG item set exhibited also significantly stronger robustness when the prevalence of vasculitides was artificially varied in generated patient samples, thus suggesting better adaptability of this set to various epidemiological conditions. Also the low sensitivities and positive predictive values obtained with the 1990 ACR criteria during the computer-simulation procedure are in accordance with the high percentages of false-positive PAN diagnoses previously reported with this criteria set (4), indicating good reliability of computer-simulation analyses.

To conclude, the results of the analyses described herein suggest that the combined use of positive and negative criteria could significantly improve discriminant performances, while providing a more appropriate support for analytical medical reasoning as it examines, with equal importance, both positive and negative rationale for considering a diagnosis. Indeed, as the results of our computer-simulation suggest, the combination of positive and negative discriminant criteria may prove beneficial for the establishment of a diagnostic screening tool for vasculitis patients. Further prospective validation of this set of criteria in a multicenter international study, including different populations and epidemiological settings, is needed before confirming that these items provide a satisfactory diagnostic tool.

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## TABLES AND FIGURES

**Table 1.** The FVSG minimal set of low redundant PAN predictive criteria derived from the analysis of the FVSG patient database.

\* Significant positive (+) or negative (–) association with PAN diagnosis in the FVSG patient database.

**Table 2.** Discriminant performances of a minimal set of low redundant FVSG predictive criteria, to distinguish PAN from other systemic vasculitides or MPA in the FVSG patient database: (A) considering all PAN cases, and (B) considering only HBV-negative PAN cases.

\* Stepwise estimation of odds ratio.

\*\* Incremental  $R^2$  computed at each step of the logistic regression model.

\*\*\* ENT signs, e.g. maxillary sinusitis or otitis media.

**Table 3.** Discriminant performances of significant and non-redundant items of 1990 ACR criteria set, to distinguish PAN from other systemic vasculitides or MPA in the FVSG patient database: (A) considering all PAN cases, and (B) considering only HBV-negative PAN cases.

\* Stepwise estimation of odds ratio.

\*\* Incremental  $R^2$  computed at each step of the logistic regression model.

\*\*\* Items showing no significant usefulness to distinguish PAN.

**Table 4.** Two sets of positive and negative association rules illustrating the potential use of the FVSG set of discriminant items to distinguish PAN from other systemic vasculitides or from MPA in clinical conditions.

\* 1 indicates the presence of the respective items while 0 indicates their absence

\*\* Rule's precision evaluated on FVSG data.

\*\*\* Number of cases in which the rule was applicable.

**Figure 1.** ROC curve analyses comparing PAN discriminant performances of the FVSG set of items versus 1990 ACR classification criteria to identify PAN in two situations: (A) considering all systemic vasculitides as controls; and (B) restricting controls at MPA cases.

**Figure 2.** Results of computer simulations evaluating the potential usefulness of FVSG discriminant set of items compared to 1990 ACR criteria to diagnose PAN. Artificial patient data were generated by relying on the Bahadur–Lazarsfeld extension, either respecting the reported French prevalence (FVSG  or ACR ) of the four main types of vasculitides (PAN, WG, CSS, MPA), or after arbitrarily modifying them to low PAN (FVSG  or ACR ). The box plots report the median (horizontal line within the box), the first and the third quartiles (the upper and lower limits of the box), and the range (T bars), computed from 30 consecutive iterations of the simulation procedure (see text for detailed explanations).

**Table 1.** The FVSG minimal set of low redundant PAN predictive criteria derived from the analysis of the FVSG patient database.

Criterion	PAN Association*	Definition
1. HBV infection	(+)	Markers reflecting active HBV replication such as the presence of HBeAg in serum and/or the detection of HBV DNA >10 <sup>5</sup> copies/mL
2. ANCA positivity	(-)	ANCA presence in serum tested by indirect immunofluorescence
3. Asthma	(-)	Personal antecedents of asthma
4. ENT signs	(-)	Maxillary sinusitis or otitis media signs
5. Cryoglobulin positivity	(-)	Cryoglobulin detection in serum
6. Glomerulopathy	(-)	Glomerulopathy signs such as proteinuria and/or hematuria with or without renal insufficiency, not due to urinary tract infections, urolithiasis, hematologic or other non-glomerular causes
7. Arteriographic anomalies	(+)	Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other non-inflammatory causes
8. Mono-/polyneuropathy	(+)	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy

**Table 2.** Discriminant performances of a minimal set of low redundant FVSG predictive criteria, to distinguish PAN from other systemic vasculitides or MPA in the FVSG patient database: (A) considering all PAN cases, and (B) considering only HBV-negative PAN cases.

<b>A) FVSG discriminant items</b>	<b>Odds ratio [95% CI]<sup>*</sup></b>	<b>R<sup>2</sup>**</b>
<b>PAN/Other vasculitides</b>		
1 (+) HBV infection (active replication)	16.41 [7.34–36.68]	0.323
2 (-) ANCA positivity	0.04 [0.02–0.08]	0.539
3 (-) Asthma	0.10 [0.04–0.21]	0.598
4 (-) ENT signs <sup>***</sup>	0.09 [0.03–0.25]	0.629
5 (-) Cryoglobulin positivity	0.13 [0.04–0.40]	0.644
6 (-) Glomerulopathy	0.36 [0.22–0.58]	0.656
7 (+) Arteriographic anomalies	3.48 [1.68–7.22]	0.668
8 (+) Mono-/polyneuropathy	1.87 [1.19–2.94]	0.674
<b>PAN/MPA</b>		
1 (-) ANCA positivity	0.03 [0.01–0.08]	0.508
2 (+) HBV infection (active replication)	18.40 [6.10–55.51]	0.607
3 (-) Glomerulopathy	0.19 [0.10–0.33]	0.648
4 (+) Arteriographic anomalies	6.13 [2.13–17.65]	0.669

<b>B) FVSG discriminant items</b>		<b>Odds ratio [95% CI]<sup>*</sup></b>	<b>R<sup>2</sup>**</b>
<b>HBV-negative PAN/Other vasculitides</b>			
1 (-)	ANCA positivity	0.02 [0.01–0.07]	0.336
2 (-)	Asthma	0.10 [0.04–0.23]	0.427
3 (-)	ENT signs <sup>***</sup>	0.10 [0.03–0.29]	0.468
4 (-)	Glomerulopathy	0.37 [0.23–0.61]	0.485
5 (-)	Cryoglobulin positivity	0.19 [0.06–0.56]	0.503
6 (+)	Arteriographic anomalies	3.18 [1.49–6.77]	0.515
<b>HBV-negative PAN/MPA</b>			
1 (-)	ANCA positivity	0.02 [0.01–0.07]	0.495
2 (-)	Glomerulopathy	0.18 [0.10–0.33]	0.556
3 (+)	Arteriographic anomalies	5.61 [1.86–16.89]	0.581

**Table 3.** Discriminant performances of significant and non-redundant items of 1990 ACR criteria set, to distinguish PAN from other systemic vasculitides or MPA in the FVSG patient database: (A) considering all PAN cases, and (B) considering only HBV-negative PAN cases.

<b>A) 1990 ACR criteria</b>		<b>Odds ratio [95% CI]*</b>	<b>R<sup>2</sup>**</b>
<b>PAN/Other vasculitides</b>			
1 (+)	HBV infection	25.53 [13.67–47.67]	0.323
2 (+)	Arteriographic anomalies	4.40 [2.43–7.95]	0.356
3 (-)	Renal insufficiency	0.31 [0.18–0.56]	0.377
4 (+)	Livedo reticularis	2.11 [1.24–3.58]	0.387
5 (+)	Mono-/polyneuropathy	1.69 [1.16–2.46]	0.397
6 (+)	Testicular pain or tenderness	3.12 [1.19–8.20]	0.402
7 (+)	Diastolic BP >90 mmHg	1.66 [1.06–2.61]	0.408
8 <sup>***</sup>	Weight loss ≥4 kg	0.75 [0.52–1.08]	-
9 <sup>***</sup>	Myalgias	1.40 [0.98–2.00]	-
<b>PAN/MPA</b>			
1 (+)	HBV infection	21.21 [8.17–55.09]	0.293
2 (-)	Renal insufficiency	0.13 [0.07–0.25]	0.380
3 (+)	Arteriographic anomalies	7.45 [2.94–18.86]	0.427

<b>B) 1990 ACR criteria</b>		<b>Odds ratio [95% CI]<sup>*</sup></b>	<b>R<sup>2</sup><sup>**</sup></b>
<b>HBV-negative PAN/Other vasculitides</b>			
1 (+)	Arteriographic anomalies	4.42 [2.38–8.21]	0.043
2 (-)	Renal insufficiency	0.27 [0.15–0.51]	0.080
3 (+)	Livedo reticularis	2.07 [1.21–3.55]	0.095
4 (+)	Myalgias	1.55 [1.07–2.25]	0.108
5 (+)	Diastolic BP >90 mmHg	1.69 [1.06–2.71]	0.116
6 <sup>***</sup>	Testicular pain or tenderness	2.69 [0.98–7.41]	-
7 <sup>***</sup>	Weight loss ≥4 kg	0.72 [0.50–1.05]	-
8 <sup>***</sup>	Mono-/polyneuropathy	1.45 [0.99–2.15]	-
<b>HBV-negative PAN/MPA</b>			
1 (-)	Renal insufficiency	0.13 [0.07–0.26]	0.147
2 (+)	Arteriographic anomalies	6.99 [2.68–18.20]	0.209

**Table 4.** Two sets of positive and negative association rules illustrating the potential use of the FVSG set of discriminant items to distinguish PAN from other systemic vasculitides or from MPA in clinical conditions.

Rules *	Confidence **	Cases ***
<b>PAN/Other vasculitides: positive PAN association</b>		
1. <i>If HBV = 1 and arteriographic anomalies = 1 then PAN = 1</i>	100%	31
2. <i>If HBV = 1 and ANCA = 0 and neuropathy = 1 then PAN = 1</i>	97%	96
3. <i>If HBV = 1 and cryoglobulin = 0 and glomerulopathy = 0 and ENT signs = 0 then PAN = 1</i>	96%	80
4. <i>If ANCA = 0 and arteriographic anomalies = 1 and ENT signs = 0 then PAN = 1</i>	79%	66
<b>PAN/Other vasculitides: negative PAN association</b>		
1. <i>If HBV = 0 and ANCA = 1 then PAN = 0</i>	99%	401
2. <i>If ANCA = 1 and glomerulopathy = 1 and arteriographic anomalies = 0 then PAN = 0</i>	99%	270
3. <i>If ENT signs = 1 then PAN = 0</i>	98%	253
4. <i>If neuropathy = 0 and arteriographic anomalies = 0 then PAN = 0</i>	86%	377
5. <i>If HBV = 0 and arteriographic anomalies = 0 then PAN = 0</i>	83%	779

**PAN/MPA: positive PAN association**

1.	<i>If HBV = 1 and ANCA = 0 then PAN = 1</i>	96%	108
2.	<i>If ANCA = 0 and arteriographic anomalies = 1 then PAN = 1</i>	93%	57
3.	<i>If ANCA = 0 and glomerulopathy = 0 then PAN = 1</i>	86%	221

**PAN/MPA: negative PAN association**

1.	<i>If ANCA = 1 then PAN = 0</i>	94%	138
2.	<i>If HBV = 0 and glomerulopathy = 1 and arteriographic anomalies = 0 then PAN = 0</i>	85%	161

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Figure 1

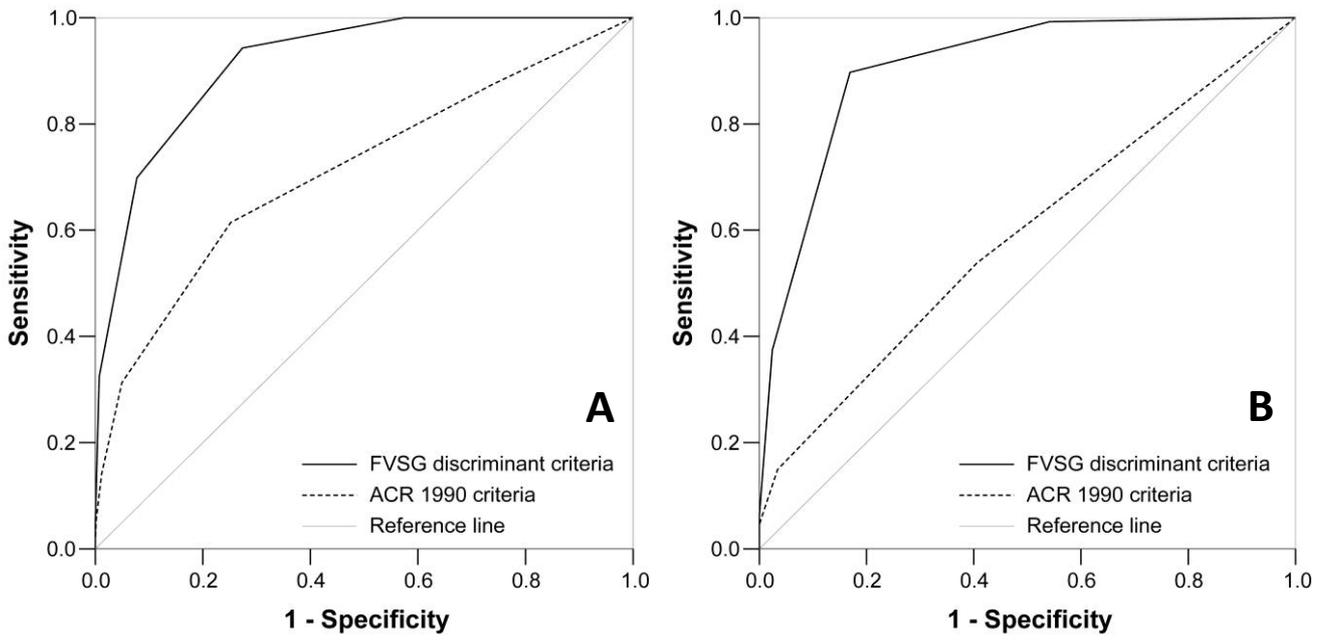


Figure 2

