Subphenotypes of ANCA-associated vasculitis identified by latent class analysis

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ABSTRACT

Objective. *ANCA-associated vasculitides (AAV) are a heterogeneous group of rare diseases with unknown aetiology and the clinical spectrum ranging from life-threatening systemic disease, through single organ involvement to minor isolated skin changes. Thus, there is an unmet need for phenotype identification, especially among patients with granulomatosis with polyangiitis (GPA). Patients with microscopic polyangiitis (MPA) seem to be clinically much more uniform. Recently, three subcategories of AAV have been proposed and described as non-severe AAV, severe PR3-AAV, and severe MPO-AAV.*

Methods. *In line with these attempts, we decided to use an unbiased approach offered by latent class analysis (LCA) to subcategorise GPA and MPA in a large cohort of Polish AAV patients included in a multicentre POLVAS registry.*

Results. *LCA of our AAV group identified a four-class model of AAV, including previously proposed three subphenotypes and revealing a fourth (previously not described) clinically relevant subphenotype. This new subphenotype includes only GPA patients, usually diagnosed at a younger age as compared to other groups, and characterised by multiorgan involvement, high relapse rate, relatively high risk of death, but no end-stage kidney disease.*

Conclusion. *Based on multiple clinical and serological variables, LCA methodology identified 4-class model of AAV. This newly described fourth class of AAV may be of clinical relevance and may require prompt diagnosis and aggressive treatment due to the multiorgan involvement, high risk of relapse and marked mortality among these relatively young GPA subjects.*

Introduction

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) and microscopic polyangiitis (MPA) belong to the group of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), systemic diseases involving small to medium-size vessels. Nomenclature of these entities was proposed in 2012 (1). GPA is mostly associated with the presence of proteinase 3 (anti-PR3) antibodies, while anti-myeloperoxidase (anti-MPO) antibodies dominate in MPA patients. Already in the original description of the vasculitis nomenclature it was suggested, however, to add ANCA specificity to the clinical description of the disease (1). As both entities are associated with severe organ damage and mortality, we are witnessing an ongoing search for precise AAV prognostic factors. In general, GPA is associated with higher rate of relapse and more heterogeneous clinical manifestation, while MPA is characterised by more uniform clinical presentation and higher mortality (2, 3). AAV classification based on clinical symptoms and laboratory results has been recently challenged by the results of genome-wide association studies showing that association of some gene variants with anti-PR3 and anti-MPO-ANCA was stronger than with clinical phenotypes of AAV (4, 5). This led to the concept of ANCA-specificity as a critical prognostic determinant in AAV patients in relation to their organ damage, relapse

rate and mortality (6). However, both forms of AAV may have heterogeneous, sometimes atypical symptomatology (7) and overlapping ANCA-specificity, as exemplified by a notable group of clinically typical GPA patients showing the presence of anti-MPO antibodies (8). As a consequence Mahr *et al*. combined both clinical symptomatology and ANCA specificity to better define prognosis clustering AAV patients into three main AAV subsets with important differences in their relapse rate and mortality (3). Recently, three subcategories of AAV have been proposed and named as: non-severe AAV, severe PR3-AAV and severe MPO-AAV (9). In line with these attempts to subcategorise AAV we decided to use latent class analysis (LCA) on a large multicentre cohort of AAV patients to identify potential new subphenotypes or confirm already proposed ones.

LCA is appreciated by its virtue of an unbiased approach through parametrisation while describing optimal number and characteristics of classes in the studied group (10).

Materials and methods

Subjects studied

We conducted a multicentre retrospective study of all adult patients diagnosed with GPA and MPA in the frame of POLVAS consortium (11-14). Out of 625 records included into POLVAS registry (11), 523 records of patients with AAV (417 diagnosed with GPA and 106 with MPA) were subjected to LCA analysis. Only patients who fulfilled requirements for the nomenclature of GPA and MPA according to CHCC 2012 (1) were included in the study. Analyses here described have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; the locally appointed Ethics Committee of each partner has approved the research protocol and informed consent has been obtained from the subjects (or their legally authorised representative). The study protocol was approved by Bioethical Commission of Jagiellonian University, decision no 122.6120.25.2016.

ANCA serotypes

In the earliest patients included in the Registry (1990-2000), ANCA positivity was detected only by an indirect immunofluorescence (IIF) method and identified as cANCA or pANCA positivity. Later, ANCA positivity was detected by ELISA (anti-PR3 or anti-MPO antibodies) and, if necessary, by IIF (11).

Treatment

Treatment of AAV patients was left to the discretion of the physicians from the participating centres. Remission induction treatment in the majority of patients (93.5%) consisted of pulsed, intravenous glucocorticosteroids and in 84.5% of patients pulsed cyclophosphamide (10-15 mg/kg/d with adjustment when necessary for renal function and age) every 4 weeks. Rituximab was used in only 8.75% of patients. Maintenance treatment in the majority of patients (84.3%) included azathioprine or methotrexate or mycophenolate mofetil (14).

Latent class analysis

Latent class analysis (LCA) approach was used as a model based clustering method of objects described by various parameters - dichotomous (*e.g*. gender) and polytomous (*e.g*. number of relapses) variables supported by quantitative covariates (*e.g*. age at diagnosis). The following parameters were included in the LCA for the whole AAV group: dichotomous (gender; ANCA status - cANCA, pANCA; organ involvement - skin, eye, ENT, respiratory, heart, GI, renal, urinary, CNS, peripheral nerves) and polytomous (number of relapses during the disease course) variables supported by quantitative covariates (age at diagnosis, CRP at diagnosis, maximal serum creatinine concentration ever). LCA was conducted on data from the retrospective registry, meaning it contains all the data from the whole course of the disease, confirmed at the last follow up.

The latent class model seeks to stratify the cross-classification table of observed (or "manifest") variables by un unobserved ("latent") unordered categorical variable that eliminates all confounding between the manifest variable. The main assumption of the LCA model is "conditional" or "local" independence, *i.e*. conditional upon values of latent variable responses to all of the manifest variable are assumed to be statistically independent. Covariates are included in our model through their effects on the prior probabilities of latent class membership. Our model allows individuals to vary depending upon their observed covariates.

The R package poLCA (10) was used for estimating parameters of LCA models and for identification of the optimal model according to AIC (Akaike information criterion) in a stepwise manner by the analysis of models with the number of classes starting from 1 to 6. AIC is founded on information theory and deals with the trade-off between the goodness-of-fit of the model and the complexity of the model (15). When the best model was determined, each subject was then allocated.

LCA analysis was performed with the inclusion and exclusion of ANCA specificity to compare its possible influence and importance on subphenotype identification.

Other statistical analysis

Categorical data were summarised as percentages; significant differences or associations were analysed using the χ^2 test or Fisher exact tests. Continuous variables are presented as mean and/or median and interquartile range [IQR], depending on normality of data distribution demonstrated by Kolmogorov-Smirnov test. Associations of quantitative data were analysed with Student *t*-test and with the non-parametric Mann-Whitney U-test or the Kruskal-Wallis test. For analysis of risks related to mortality and chronic renal replacement therapy (CRRT), logistic regression model was applied. Statistical analysis was performed using Statistica 13 software (Statistica, Tulsa, OK, USA).

Results

Results of LCA on our AAV group returned two possible models of AAV subphenotypes, *i.e*. three- and four-class model. The parameters describing the optimal number of identified classes have lowest value (indicating

the optimal number of clusters) in 3 class model (BIC and χ^2) and in 4 class model (LL, AIC and G^2) in two variants, with an inclusion and an exclusion of ANCA as a variable (Supplementary Table S1).

In the 3-class model 87% of the cases were allocated to the identified classes while in a the 4-class model 72% of cases were allocated, both with a probability higher than 90%. In the variant of analysis which excludes ANCA specificity probability of proper class allocation was only 66% and 48%, respectively.

The main characteristics of the respective classes in both models are summarised in Supplementary Tables S2, S3, S4 and S5.

Three-class model including ANCA specificity

Class 1

One hundred and seventy-eight patients were allocated to class 1, with only two (1%) patients diagnosed with MPA and the remaining 176 (99%) with GPA. ANCA serotype of this group showed cANCA/anti-PR3 positivity in 132 (74%) cases. Male to female ratio in this class was 1:2 (64:114), with the median age at diagnosis of 50.6 years. The mean number of organs involved was 2.7 with the most commonly affected: ENT 157 (85%), respiratory system 117 (66%), eye 63 (35%), and kidney 15 (9%). This class has been characterised by a significantly lower maximal creatinine concentration (median 1.0 mg/dL) compared to class 2 and 3 ($p<0.00001$, for both). Median CRP at the time of diagnosis was 28 mg/L (Suppl. Table S2).

Class 2

To the second class 243 patients were allocated, with 13 (5%) subjects diagnosed with MPA and 230 (95%) with GPA. Their ANCA pattern was in 95% cANCA/anti-PR3 positive. Male to female ratio in this class was 3:2 (151:92), with a median age at diagnosis of 53.3 years. In this group there was a significantly higher mean number of organs affected (3.55) as compared to class 1 and 3 ($p<0.00001$, for both). The most common organs affected were: kidney 238 (98%) and respiratory system 194 (80%), ENT 155 (63%) and skin 96 (40%). Maximal creatinine concentration median was 2.5 mg/dL (median). CRP at the time of diagnosis was 48.5 mg/L (median).

Class 3

By LCA 102 patients were allocated to class 3, 91 (90%) of whom were diagnosed with MPA and 11 (10%) with GPA. Prevalent serotype was pANCA/anti-MPO (101 subjects). Male to female ratio in this class was 1:1 (49/53), with significantly higher median age at diagnosis (63.6 years) as compared to class 1 and 2 ($p<0.00001$ for both). The mean number of organs involved was 2.64 and the most common organs affected were: kidneys 100 (99%), respiratory system 64 (63%). This class was characterised by the highest maximal creatinine concentration (median 3.8 mg/dL). Median CRP at the time of diagnosis was 33 mg/L.

Four-class model including ANCA specificity

In the four-class model classes 1-3 corresponded roughly by the phenotype to the classes 1-3 from the 3-class model, but a new class 4 was formed by 97 patients extracted both, from classes 1 and 2 of the three-class model (Suppl. Table S3).

Class 4

Ninety-seven patients were allocated to this class (48 patients from class 1 and 49 from class 2 of the three-class model), all of whom were diagnosed with GPA and carrying mainly cANCA/anti-PR3 serotype. Male to female ratio in this class was 1:1 (49/48), with the lowest median age at diagnosis among all classes – 43.1 years ($p<0.02$, $p<0.0001$, $p<0.0001$ *vs.* class 1, 2 and 3, respectively). Patients diagnosed before the age of 18 years (n=15) were evenly distributed between these classes. Class 4 was characterised by the highest mean number of organs involved (4.45) compared to all other three classes ($p<0.0001$, $p<0.002$, $p<0.00001$ *vs.* class 1, 2 and 3 respectively). The most common organs affected were: ENT 96 (99%), respiratory system 94 (97%), kidney 53 (55%) skin 47 (48%) and eye 43 (44.3 %). Maximal creatinine concentration was 1.16 mg/dL (median). Interestingly, CRP concentration at time of diagnosis was here the highest among all classes (median of 79 mg/L). This new class could be named renal non-severe PR3 AAV (Table II). Isolation of this class from the cohort of AAV patients changed the characteristics of classes 1 and 2 from the three-class model. In the class 1 peripheral nerve involvement is now lower ($p<0.05$), together with lower serum CRP concentration at diagnosis ($p>0.005$), and lower number of organs involved (median 2.7 *vs.* 2.3; $p<0.05$). Class two has now significantly lower eye involvement ($p<0.05$), lower CNS involvement, as well as lower total number of organs involved (median 3.55 *vs.* 3.2; $p<0.01$). In contrast, maximal serum creatinine concentration is now higher in this class (3.3 *vs.* 2.5 mg/dL; $p<0.01$).

Classes differed in terms of the cumulative cyclophosphamide dose (Suppl. Table S3). In patients with severe kidney damage (low GFR) total dose of CTX was reduced. In the MPO patients (class 3) there was an additional age related CTX dose reduction. The highest cumulative CTX dose was a hallmark of the class 4 – young GPA patients with a high relapse rate.

Three-class model excluding ANCA specificity

In this model only 66% of cases were allocated to one of the classes with the probability of proper allocation exceeding 90% (Suppl. Table S4).

Class 1

One hundred and seventy-five patients were allocated to this class, with 81 (46 %) diagnosed with MPA and 94 (54%) with GPA. Male to female ratio was 1.5:1 (101:74), with a median age at diagnosis of 59.7 years. There were no subjects diagnosed before the age of 18 years in this group. The mean number of organs involved was 2.26. The most common organs affected were: kidney 168 (96%), respiratory system 115 (66%) and ENT 39 (22%). This class was characterised by the highest maximal creatinine concentration median

3.85 mg/dL. Median CRP concentration at time of diagnosis was 32 mg/L.

Class 2
One hundred sixty nine patients were allocated to this class with 21 (12%) diagnosed with MPA and 148 (88%) with GPA. Male to female ratio in this class was 1.5:1 (100:69), with a median age at diagnosis of 51.0 years. The mean number of organs involved was 4.3 and the most common organs affected were: kidney – 169 patients (100%), respiratory system – 141 (83.4%), ENT – 136 (80.5%), and skin – 88 (52.5%). Maximal creatinine concentration (median) was 2.0 mg/dL. Median CRP concentration at the time of diagnosis was 62 mg/L.

Class 3
One hundred and seventy-nine patients were allocated to this class, with 4 (2%) diagnosed with MPA and 175 (98%) with GPA. Male to female ratio in this class was 1:2 (63:116), with a median age at diagnosis of 51.0 years. The mean number of organs involved was 2.8 and the most common organs affected were: ENT – 158 (88%), respiratory system – 119 (66%) and eye involvement in 66 (37%). This class was characterised by the lowest maximal creatinine concentration (median 1.0 mg/dl). Median CRP at time of diagnosis was 30.0 mg/l.

Four-class model excluding ANCA specificity
When ANCA specificity as a variable was excluded from the analysis, LCA suggested also the possible existence of 4 classes of AAV phenotype. This fourth LCA class, described below, resembled somehow the 4th class phenotype identified by LCA with the inclusion of ANCA specificity. However, probability of the proper inclusion of subjects to this four class model was very low. Only 48% of cases were allocated properly with the probability exceeding 90%.
Basically, in this model classes 1–3 corresponded to the classes 1–3 in the 3-class model while the new 4th class was formed by 137 patients extracted from classes 2 and 3 of the three-class LCA model (Suppl. Table S5).

Class 4
To this class 137 patients were allocated. Six subjects (4.4%) were diagnosed with MPA and 131 (95.6%) with GPA. Their ANCA serotype was mainly cANCA/anti-PR3 109 whereas 13 were pANCA/anti-MPO. Male to female ratio in this class was 1:1 (66/71), with the lowest median age at diagnosis among all classes (46.2 years). The mean number of organs involved was 3.67 with the most common organs affected: ENT – 129 patients (94.2%), respiratory system – 126 (92%), kidney – 56 (40.9%) and eye involvement – 51 (37.2%). Kidney involvement in this group did not require temporary or permanent renal replacement therapy. Maximal creatinine concentration (median) was 1.0 mg/dL. Median CRP concentration at time of diagnosis was 49 mg/L.
Our 4-class model in the variant with exclusion of ANCA specificity identified the presence of three classes already described by Mahr *et al*. (3) (class 1, 2 and 3) (Suppl. Table S5), but confirmed also the existence of our new renal non-severe AAV (Suppl. Table S6).

Outcome characteristics
We next analysed the outcome of AAV depending on the LCA class. Mortality, and the requirement for renal replacement therapy were used as the outcome measures. (Table I). Logistic regression analyses were performed with the inclusion of ANCA specificity as the variant excluding ANCA as a variable resulted in the low percentage of patients allocated with high probability to a proper phenotypic class. In both, three- and the four-class model, model, class 1 (non-severe AAV) was used as a reference group.
In the three-class model patients in class 2 (severe PR3-AAV) have significantly higher risk of death and CRRT, whereas class 3 (severe MPO-AAV) differed significantly only in the risk for CRRT (Tab. I). In the 4-class LCA model logistic regression returned better statistical significance for the risk of both, death and CRRT as compared to the 3-class model (Table I).
Interestingly, the highest relapse rate together with the low rate of severe renal damage was seen in the newly identified 4-class patients with a trend towards increased risk of death (OR 2.37, but with C.I. of 0.83 to 68) even if the median age of this group was significantly lower compared to class 1. The low rate of chronic renal damage in this group contrasted with the highest number of other organs (CNS included) involved (Suppl. Table S3).

Discussion
It is clear now that the categorisation of AAV consisting of only two individual subsets (GPA and MPA) using clinical nomenclature or ANCA status do not allow for proper identification of all major phenotypes of ANCA-positive small-vessel vasculitides. More importantly, single clinical or serological descriptors are not sufficient to predict clinical course and outcome of AAV in an individual patient. In 2013 Mahr *et al*., based on their cluster analysis of 673 AAV patients, identified main AAV subsets, differing by mortality and relapse rates (3). Recently, based on these subphenotypes and vast clinical experience Jayne, Mahr and Specks (9) proposed subcategorisation of AAV into three clinically relevant subphenotypes. Their subclassification incorporates clinical, histopathological, serological and prognostic aspects. However, while awaiting discovery of precise causes of AAV, we still need an unbiased confirmation of those subphenotypes and their possible therapeutic relevance.
Cluster analysis used by Mahr *et al*. in their original paper could use only dichotomous variables and, moreover, gives no detailed information about the optimal number of clusters, leaving it to the discretion and criticism of the researchers. In contrast, LCA methodology offer an unbiased approach (10) and uses all types of variables (see Methods). LCA has been already successfully applied to describe phenotypes of another immune-mediated heterogeneous, multiorgan condition, namely IgG4-related disease (16). Using this methodology, we were able to identify two models of AAV sub-classification in our multicentre cohort of AAV patients. The 3-class model corroborates with the AAV sub-classification re-

Table I. Risk for death and CRRT depending on the LCA class (3- and 4-class model). Logistic regression analysis.

	Death			CRRT		
	OR	Cl 95%	p	OR	Cl 95%	*p*
3 Class Model						
Class 1 Non severe AAV	Reference class (OR=1)			Reference class (OR=1)		
Class 2 Severe PR3 AAV	2.02	1.01-4.06	0.047	16.3	5.0-53.0	<0.0001
Class 3 Severe MPO AAV	1.84	0.79-4.27	0.15	31.8	9.5-106.9	<0.0001
4 Class Model						
Class 1 Non severe AAV	Reference class (OR=1)			Reference class (OR=1)		
Class 2 Severe PR3 AAV	3.34	1.34-8.33	0.01	24.7	5.9-103.3	<0.0001
Class 3 Severe MPO AAV	2.75	0.99-7.6	0.051	34.9	8.1-149.5	<0.0001
Class 4 Renal non-severe PR3 AAV	2.37	0.83-6.8	0.1	NA	NA	0.99

cently proposed by Jayne, Mahr, and Specks (9), with their three subgroups of AAV, identified as: non-severe AAV with high relapse rate, low mortality and low rate of serious organ involvement; severe PR3-AAV with intermediate relapse rate and serious organ involvement; and severe MPO-AAV with low relapse rate but high mortality and high risk of serious organ involvement, especially kidney.

Our 4-class model identified a new PR3+ AAV subphenotype extracted mainly from the cohort of PR3-AAV patients (Table II, Fig. 1). Subjects in this subgroup were younger at the time of diagnosis than patients from the other subgroups (median age lower by 8.7, 12.4 y and 20.4 years compared to classes 1, 2 and 3, respectively). With the highest number of organs involved and highest relapse rate, their risk of death was not significantly different from the patients in other classes suggesting potential clinical relevance of this group identification – especially if one considers significantly lower age at AAV diagnosis in this group. Even if symptoms of kidney involvement was present in more than half of these patients, none of them required permanent haemodialysis treatment. Interestingly enough, this subgroup of AAV included significantly more patients with heart and GI involvement, originally identified as having unfavourable outcome by Mahr *et al*. (3). Identification of this new subphenotype from among the patients in class 1 and 2 of the 3-class model changed also some characteristics of those subphenotypes (Suppl. Tables S7 and S8).

LCA analysis objectively assigned over 90% MPA to one class confirming rather homogeneous nature of this form of AAV. In contrast, LCA confirmed heterogeneity of GPA. This new, fourth class with its relatively young age at diagnosis, high relapse rate and multiorgan involvement, clearly differed from classes 1 and 2. Logistic regression analysis speaks also in favour of the 4-class model showing better stratification of outcome than in 3-class model. Once a patient is assigned to the proper LCA class (Fig. 1) the disease outcome depends on that class instead of multiple variables, frequently overlapping which need to be analysed when only MPA or GPA diagnosis is considered for outcome analysis (11).

Retrospective identification of the 4-class model might also become clinically relevant. These patients might probably need prompt, more aggressive treatment to prevent relapses, and decrease mortality. However, to implement such aggressive approach it would be necessary in the future to identify specific and sensitive markers (clinical and/or serologic) which would allow to ascribe AAV patient to this new subphenotype early, preferably at the time of diagnosis. Future prospective clinical trials would be needed to confirm real clinical significance of such four-class AAV subcategorisation, especially in terms of the most effective treatment.

Our as well as others (3, 9) efforts to subcategorise AAV patients clearly indicate that such subcategorisation is mostly required for PR3+ AAV patients.

Table II. AAV subcategorisation. Summary of clinical characteristics and ANCA specificity.

	Class 1	Class 2	Class 3	Class 4
No. of patients	130	194	102	97
AAV type	Mainly GPA	Mainly GPA	mainly MPA	Only GPA
Age at diagnosis	Middle age	Middle age	Old	Young
Male/female ratio	1:2	2:1	1:1	1:1
Main organ involvement	ENT, respiratory, eye	Renal, respiratory, ENT	Renal, respiratory, skin	Multiorgan involvement
Relapse rate	intermediate	intermediate	low	high
Modified class description (based on ref. [9])	Non severe AAV	Severe PR3 AAV	Severe MPO AAV	**Renal non-severe PR3 AAV**

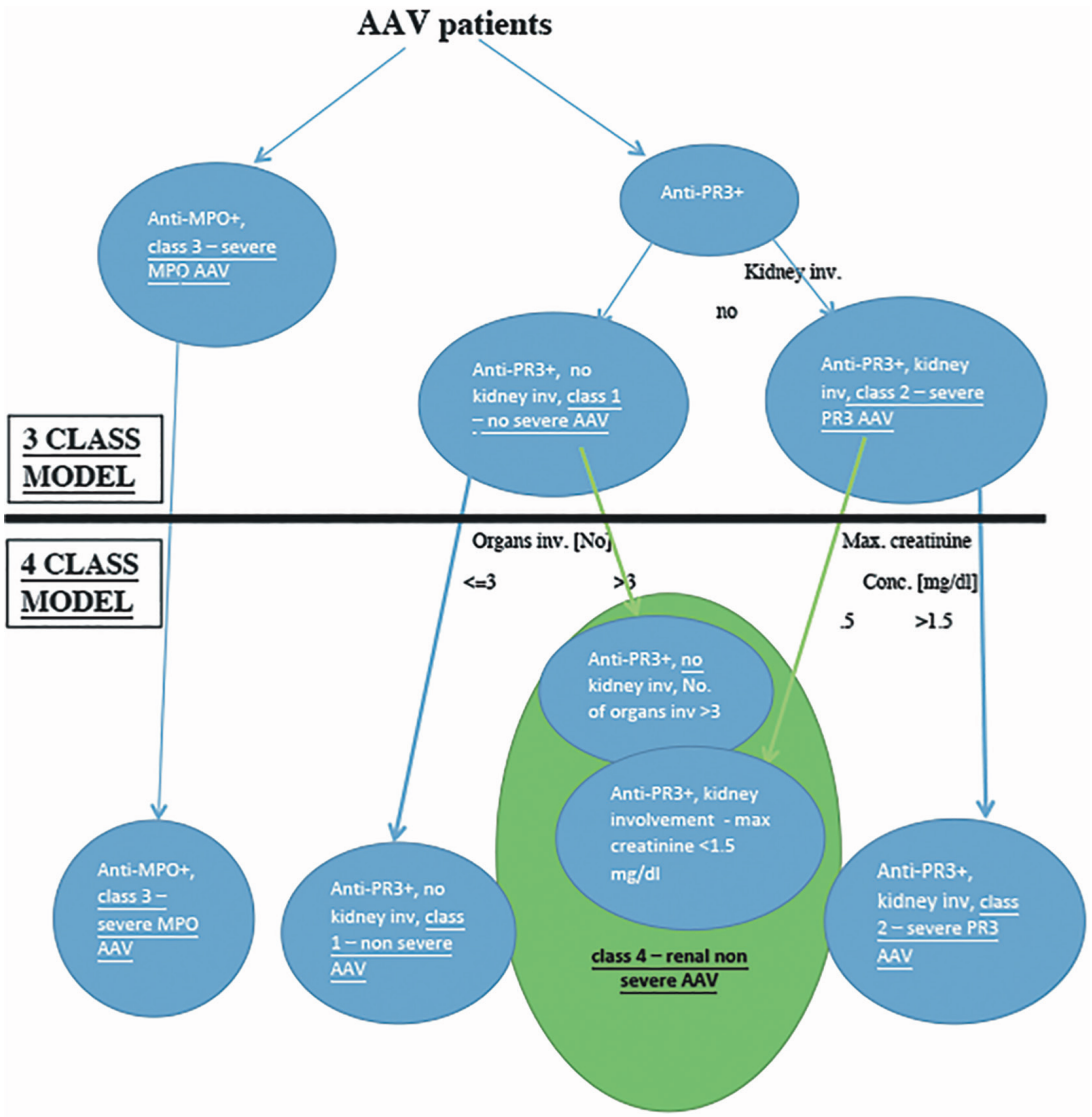

Fig. 1. Graphical presentation of the key features differentiating LCA classes (3- and 4-class model, for comparison).

It has been already suggested that varying proportions of vasculitic and granulomatous involvement in PR3-positive patients may be responsible for this phenomenon (9). Driving pathogenesis behind these two phenomena in an individual patient still needs to be elucidated. Purely vasculitic pathogenic component in MPO-positive patients may, on the other hand, be responsible for more uniform symptomatology of this phenotypic group.

There is an ongoing debate about the significance of AAV clinical presentation versus their ANCA specificity for the optimal identification of AAV patients. It was fueled by discoveries about genetic susceptibility of ANCA specificity which also influenced clinical course of the disease and the response to treatment (4, 6). Recently, a contrasting view was presented by Deshayes *et al*. (17). The authors suggested that clinical presentation of AAV is crucial and sufficient for identification of AAV entity with negligible significance of the ANCA serotype. For this reason, we performed two variants of LCA, with and without ANCA as a variable. Such analysis revealed much better allocation of AAV cases when ANCA was included into this specific analysis. Exclusion of ANCA specificity as a variable only allowed for less than 70% of patients to be included in the proper LCA subcategory. This could be considered a direct proof that ANCA specificity should indeed be included in any clinically relevant analysis of AAV subcategories.

Our analysis indicates that it would be unlikely at present to predict AAV disease course and its outcome based only on patient's initial clinical presentation and laboratory results. It is better exemplified by eventual requirement for chronic renal replacement therapy which becomes apparent in most cases only after months/years after establishing diagnosis of AAV and sometimes after several courses of treatment. CRRT was revealed as one of the most important risk factors for mortality in AAV (2, 11, 18, 19). Thus, it seems that continuous retrospective observation was indispensable to precisely describe the disease and identify its subphenotypes. On the other hand, it would be necessary to perform well planned, prospective studies to validate our observations and find the most effective ways of treatment for various AAV subcategories.

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