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Letter to the Editor

LETTER TO THE EDITOR

The impact of reclassification by the 2022 ACR/EULAR classification criteria on risk factors for relapse in patients with ANCA-associated vasculitis

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To the Editor,

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare, life-threatening disease with inflammation of the small vessels. Within AAV, three phenotypes can be specified based on clinical features: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1, 2]. The distinguishment between GPA, MPA, and EGPA is a clinical, physician-based diagnosis. The AAV subtypes can be further specified by their type of ANCAs, i.e. proteinase 3 (PR3) or myeloperoxidase (MPO) [2]. The majority of GPA patients are PR3+ (84–85%), MPA patients MPO+ (75–97%), and EGPA patients ANCA-negative (70%) [2]. As such, EGPA is often studied as a separate entity with a different treatment strategy, while GPA and MPA have similar treatment strategies and are often studied together [2]. However, there is a clinically relevant distinction with respect to disease relapse rates between MPA and GPA. It is well-established that risk factors for relapse are the GPA subtype, presence of PR3-ANCAs, ear, nose, or throat (ENT) involvement and pulmonary involvement [1–3]. It is, therefore, that most studies conduct sub-analysis for GPA and MPA when studying relapse rates, which is often the primary endpoint in clinical trials [4]. For the same reason, it is very relevant to capture the AAV subtype in routine clinical practice to personalize (the withdrawal of) immunosuppressive treatment regimens [2].

In order to improve subtyping of AAV patients, the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) presented the new classification criteria for all three AAV subtypes in 2022 [5–7]. These criteria were composed based only on patients with a moderate to high certainty of their subtype diagnosis by the treating physician, confirmed by another vasculitis expert or the DCVAS steering committee [5–7]. Sensitivities of 85–93% were reported but lowered with approximately 10% when classification was compared directly to physician-based diagnosis [5–7]. The primary purpose of these classification criteria is to ensure homogeneous populations for clinical trials. However, it is unknown to what extent the novel 2022 ACR/EULAR criteria lead to reclassifications of AAV patients and potential influence on the GPA/MPA study population in future AAV trials. Therefore, in the present study we investigated to what extent reclassification by the novel classification criteria will lead to adjunction of AAV diagnosis and whether this impacts relapse rates for GPA and MPA.

As described in the supplementary methods (see online supplementary material), the records of 337 previously identified AAV patients with a confirmed clinical diagnosis of AAV

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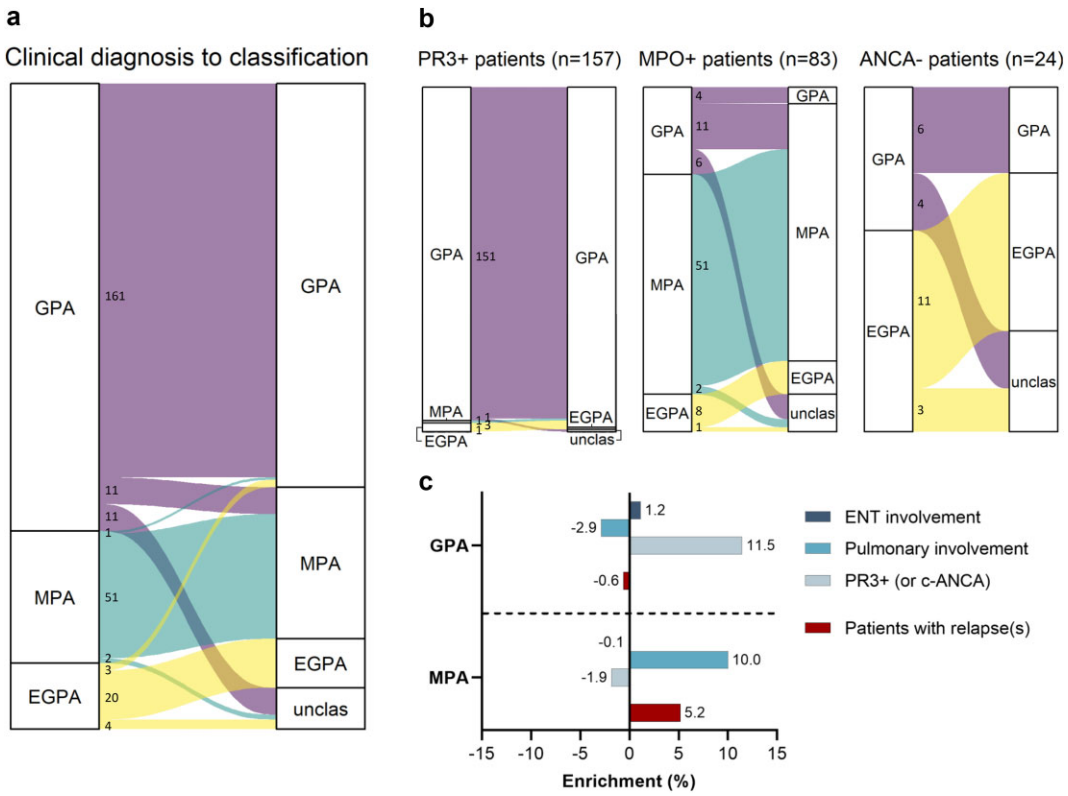

Figure 1: Impact of reclassification. Reclassification of clinical diagnosis (1a), reclassification specified to serology (1b) and impact of reclassification on enrichment of risk factors for relapse (blue bars) and enrichment of patients with relapse(s) (red bars) in GPA and MPA patients (1c). ANCA, antineutrophil cytoplasmic antibody; c-, cytoplasmatic; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose and throat; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

Table 1: Characteristics of included patients

	GPA ($n = 183$)	MPA ($n = 54$)	EGPA ($n = 27$)
Females (%)	71 (39)	20 (37)	7 (26)
Age, median [IQR]	68 [54–78]	70 [59–75]	62 [47–69]
Disease years, median [IQR]	7 [4–16]	7 [3–10]	5 [3–8]
Serology (%)			
PR3+ (or c-ANCA)	152 (83)	1 (2)	4 (15)
MPO+ (or p-ANCA)	21 (11)	53 (98)	9 (33)
ANCA negative	10 (5)	0 (0)	14 (52)

ANCA, antineutrophil cytoplasmic antibody; c-, cytoplasmatic; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IQR, inter-quartile range; MPA, microscopic polyangiitis; MPO, myeloperoxidase; p-, perinuclear, PR3, proteinase 3.

underwent manual review to collect disease characteristics. Thirty-four patients were excluded because AAV diagnosis was not specified, and 38 patients were excluded because of insufficient data. Of 264 included patients, 183 had a clinical diagnosis of GPA, 54 of MPA and 27 of EGPA. Patient and disease characteristics are shown in Table 1.

When applying the three different 2022 ACR/EULAR classification criteria to all patients, 88% (232/264) of patients would be classified according to their clinical diagnosis, as shown in Fig. 1A. We determined sensitivities of 88% for GPA, 94% for MPA, and 74% for EGPA. Reclassification occurred in 12% (22/183) of GPA patients: 6% (11/183) reclassified as MPA and 6% (11/183) did not meet any classification criteria and remained unclassified. One GPA patient was classified as both GPA and MPA. Reclassification occurred in 6% (3/54) of MPA patients: 2% (1/54) reclassified as GPA and 4% (2/54) remained unclassified. A total of 26% (7/27) of EGPA patients were reclassified: 11% (3/27) reclassified as GPA and 15% (4/27) remained unclassified.

Focusing on serology (Fig. 1B), we observed that PR3+ patients ($n = 157$) are slightly more often considered GPA (97% to 99%) after reclassification and less often MPA (1% to 0%) or EGPA (3% to 1%) and 1% unclassified. MPO+ patients ($n = 83$) are notably more often considered MPA (64% to 75%) after reclassification and less often GPA (25% to 7%) or EGPA (11 to 10%). In total, 12% of MPO+ patients were unclassified. ANCA-negative patients ($n = 24$) were less often considered EGPA (58% to 46%) or GPA (42% to 25%), but often remained unclassified (29%). This results in 94% of GPA patients being PR3+ and 100% of MPA patients being MPO+ after reclassification.

Three typical risk factors (ENT involvement, pulmonary involvement, and PR3-positivity) for relapse in GPA and MPA patients are embedded in the classification criteria (Table S1, see online supplementary material) [2]. When comparing enrichment of these risk factors before and after reclassification, we observed an 11% enrichment of PR3-positivity in GPA patients (83% to 94%) and a 10% enrichment of pulmonary involvement in MPA patients (22 to 32%), as shown in Fig. 1C. Subsequently, we observed a 5% increase of MPA patients with relapse(s) (22 to 27%) and a 1% decrease in GPA patients with relapse(s) (26 to 25%).

Here, we present the first European study comparing classification using the new EULAR/ACR classification criteria to physician-based clinical diagnosis to establish the impact on future AAV studies. Our reported sensitivities for GPA (88%) and MPA (94%) were comparable to sensitivities reported in the validation study [6, 7]. Since GPA and MPA are often studied together and only 5% of GPA and MPA patients were unclassified and no patients were reclassified as EGPA, the impact on inclusion rate in future studies can therefore be anticipated to be small. Of note, comparable results were reported in Korean and Japanese cohorts [8–10]. On the contrary, for EGPA the sensitivity was 75%, which was lower than reported during the validation of the criteria (85%), but the same as the sensitivity reported based on clinical diagnosis (75%) [5]. It is important to realize this could reduce inclusions rates for future studies in EGPA, which is already the least prevalent AAV subtype. Moreover, 11% of EGPA patients were reclassified as GPA patients, which could impact immunosuppressive treatment strategy [2].

We noted a large impact of serology on reclassification of GPA and MPA patients. Reclassification from GPA to MPA occurred only in MPO+ GPA patients ($n = 11$, 6%) and the only PR3+ MPA patient was reclassified as GPA. The reclassification rate from GPA to MPA was even higher in a Korean cohort (25%) and a Japanese cohort (41%), in accordance with higher MPO+ rates in Asian countries [8–10]. Most notably, in all three cohorts, only MPO+ GPA patients were reclassified as MPA and all patients classified as MPA were MPO+ [8–10]. Since 95% (215/227) of clinical GPA or MPA patients of our cohort were classified according to their corresponding serology, it can be postulated that the new 2022 classification criteria are a step closer towards a serology-based classification. Focusing on risk factors for relapse, we noticed an increase of pulmonary involvement in MPA patients, likely due to reclassification of MPO+ GPA patients with pulmonary involvement to MPA. Subsequently, although frequency of relapse was low, we observed a relevant increase in actual MPA patients with a relapse. Clearly, our study, together with other reports, demonstrated a clinically relevant impact on MPA phenotypes and relapse rate, which may limit the comparability between conducted trials and future trials employing the new classification criteria. Formal confirmation of our data could be performed in historically conducted randomized trials.

In conclusion, the new 2022 ACR/EULAR classification criteria potentially have a negative impact on patient selection for EGPA studies, but not for GPA/MPA studies. Also, reclassification shifts the distribution of typical risk factors for relapse in the AAV subtypes, impacting relapse rates in MPA.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

Y.K.O.T., P.B., and T.R. contributed to the conception of the work. J.R.L. and S.H. contributed to the acquisition of the data. J.R.L., S.H., D.W., and Y.K.O.T. contributed to the analysis and interpretation of the data. J.R.L. and Y.K.O.T. drafted the manuscript. All authors revised the manuscript, gave final approval over the work and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

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