The Patient Global Assessment in RA Precludes the Majority of Patients Otherwise in Remission to Reach This Status in Clinical Practice. Should We Continue to Ignore This?

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Word count: 493

Conflicts of Interest: The authors declare no conflicts of interest regarding this manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Dear Editor,

In this journal, Aletaha et al. recently reported,(1) using first year's data from three clinical trials, that about one third of patients who achieved SDAI or CDAI remission failed to attain Boolean Remission. Patient global assessment (PGA) was the main factor accounting for this difference. The authors concluded that "*the differences between these measures are not meaningful and confirm the ACR-EULAR recommendations to use them as alternatives for the definition of remission*".(1) We would question these conclusions: these definitions disagree in the classification of the remission status (yes/no) of 14 to 29% of all patients included, in line with previous reports.(2)Another conclusion: "*DAS28 remission ... does not constitute clinical remission*" is also questionable given that the radiographic outcomes did not differ significantly between remission categories, in this paper. Adopting the most stringent definition of remission is not without risk as it implies an inherent risk of overtreatment(3) if patients not in remission are submitted to increased immunosuppressive therapy, as recommended.(4) This is especially obvious in PGA-near-remission, i.e. patients missing remission solely because of PGA >1/10, which is a commonly observed status in clinical practice.

We performed a systematic literature review in PubMed (till 15/nov/2019; further details in Appendix) aimed at synthesizing the prevalence of ACR/EULAR Boolean-based remission(5) and the prevalence of PGA-near-remission cross-sectionally, in clinical practice cohort studies. Two reviewers independently assessed study inclusion and extracted the data (Appendix). Random effects meta-analyses of proportions with double arcsine transformation were performed (also by disease duration subgroups) using MEDCALC®. A final set of 8 studies concerning 12 cohorts was analysed (n= 23,297 patients). The pooled prevalence of Boolean remission was 12% (95%CI= 10-15%, $p<0.005$) while the prevalence of PGA-near-remission was 19% (95%CI=

15-23%, p<0.005) (Figure 1A and 1B). The proportion of patient in PGA-near-remission versus "full" remission is higher in patients with ≥2y versus <2y disease duration (p<0.001; 1E and 1F). In summary, over 61% of all RA patients otherwise in remission fail to satisfy the Boolean definition of remission solely due to a high PGA.

These data highlight that the definitions of remission adopted by the ACR/EULAR recommendations, which have been developed for group level analysis in RCTs, may have unpredicted serious adverse effects in clinical practice. The use of PGA in the definition of treatment target exposes a substantial proportion of patients to the risk of overtreatment with immunosuppressive agents, while being deprived of the adjunctive therapy they probably need. The use of the SDAI/CDAI as alternatives to the Boolean definition may reduce but will not solve this problem. We support that the integration of the global patient's perspective in a single target used to guide immunosuppressive treatment, through a general question(6) which bears little or no relationship with disease activity(7) must be reconsidered. We propose that the patients perspective merits being considered, as a separate treatment target, in addition to disease activity, measured by instruments that are discriminative enough to guide the choice of appropriate adjuvant therapies, as required: a dual target strategy.(8)

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Figure 1 - Meta-analyses of prevalence of ACR/EULAR Boolean-based and PGA-Near-remission in clinical cohorts and by disease duration

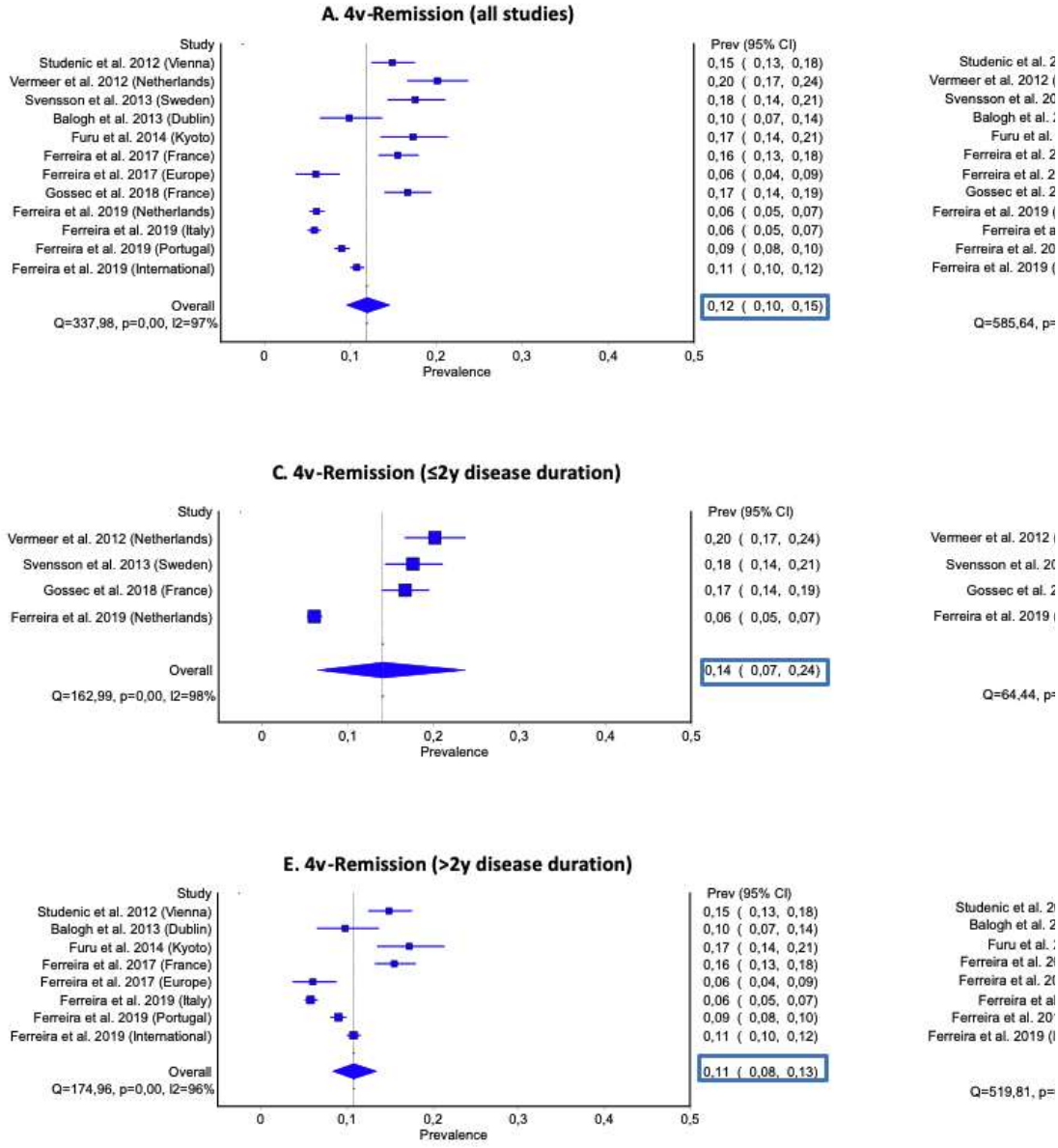

Figure Footnote: The figures on the left side represent the proportion of patients in ACR/EULAR Boolean-Based remission (=4v-Remission) while the right- side figures represent the proportion of patients that failed that stratus solely because of PGA. Figures A & B represent all pat, while Figures C & D only patients with early arthritis (≤ 2 years) and Figures E & F only patients with established disease (>2 years).

Legend: 4V-Remission = Swollen 28-Joint counts (SJC28), Tender 28-Joint Counts (TJC28), C-Reactive Protein (CRP, in mg/dl), and Patient Global Assessment (PGA, 0-10), all ≤1; PGA-Near-remission= SJC28, TJC28, CRP (mg/dl), all ≤1 and PGA >1/10.

Appendix – Methods of the Sistematic Literature Review and Meta-Analyses

Databases (period)	**Search Strategy**	**Exclusion criteria**	**Results**	**D**
PubMed (1/jan/2011 to 15/oct/2019)	(("Rheumatoid arthritis") AND (Boolean OR "Boolean definition" OR "ACR/EULAR Boolean" OR "ACR/EULAR remission" OR "Near-remission" OR "Near-misses")) AND (PtGlobal OR "Patient global" OR PGA OR PtGA OR "patient global assessment" OR "Patient's global assessment")	• if any of the four Boolean criteria were not considered (e.g. CRP not assessed) • if only patients with low disease activity or remission were selected. • if the same sample was presented in more than one study we selected only the biggest sample • if different time assessments were provided (to assess remission state), we selected the 1y follow-up (as the most common in the studies).	41 studies were retrieved, of which: • 31 excluded because not allowing to determine the frequency PGA-near-remission in clinical practice cohorts. Among the 10 remaining studies:* • 1 study was excluded because did not assess CRP; • 1 study was excluded because was repeated • 2 cohorts were excluded because were repeated • 1 cohort (India) was excluded due to highly heterogeneous data (5 patients out 8,936 in remission). Resulting in: 8 Studies (12 cohorts)**	•

** Excluded studies:*

Masri K. et al. J Rheumatol; 2012;39:1139-45[CRP not assessed]

Ferreira R., et al. Arthritis Care Res. 2018;70(3):369-78 [sample included in Ferreira et. al. 2019]

** Excluded sub-samples:*

RAID sub-sample from Gossec et al. 2018 [the same as in Ferreira et al. 2017 – France]

CoimbRA sub-sample from Ferreira et al. 2017 [sample included in Ferreira et. al. 2019]

India sub-sample from Ferreira et al. 2019 [due to high heterogeneity]

* *Included studies:*

Studenic P. et al Ann Rheum Dis. 2012;71:1702-5;

Vermeer M. et al. Rheumatology (Oxford) 2012;51:1076-80;

Svensson B. et al. BMJ open. 2013;3:e003554;

Balogh E, et al. Arthritis Res Ther 2013;15:R221;

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Ferreira R. et al. Rheumatology (Oxford) 2017;56(9):1573-8;

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