



HAL
open science

Impact of multimorbidity on disease modifying antirheumatic drug therapy in early rheumatoid arthritis: Data from the ESPOIR cohort

Aurélie Beltai, Bernard Combe, Amandine Coffy, Cécile Gaujoux-Viala, Cédric Lukas, Alain Saraux, Maxime Dougados, Jean-Pierre Daurès, Charlotte Hua

► To cite this version:

Aurélie Beltai, Bernard Combe, Amandine Coffy, Cécile Gaujoux-Viala, Cédric Lukas, et al.. Impact of multimorbidity on disease modifying antirheumatic drug therapy in early rheumatoid arthritis: Data from the ESPOIR cohort. *Joint Bone Spine*, 2022, 89 (3), pp.105326. 10.1016/j.jbspin.2021.105326 . hal-03619424

HAL Id: hal-03619424

<https://hal.science/hal-03619424>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Impact of multimorbidity on disease modifying anti-rheumatic drug therapy in early rheumatoid arthritis: data from the Espoir cohort

Aurélie Beltai^a, Bernard Combe^a, Amandine Coffy^b, Cécile Gaujoux-Viala^{c,d}, Cédric Lukas^{a,d}, Alain Saraux^e, Maxime Dougados^f, Jean Pierre Daurès^b, Charlotte Hua^{c,d}

^a Department of Rheumatology, CHU Montpellier, University of Montpellier, 371 Av. du Doyen Gaston Giraud, 34090 Montpellier, France; ^b Biostatistiques, Nouvelles Technologies, 641 Av. du Doyen Gaston Giraud, 34090 Montpellier, France; ^c Department of Rheumatology, CHU Nîmes, Place du Professeur Robert Debré, 30000 Nîmes, France; ^d Institut Desbrest d'Epidémiologie et de Santé Publique UMR INSERM - University of Montpellier, 641 Av. du Doyen Gaston Giraud, 34090 Montpellier, France; ^e Department of Rheumatology, CHU de Brest, INSERM UMR 1227, University of Brest, 2 Avenue Foch, 29200 Brest, France; ^f Department of Rheumatology, CHU Cochin, University of Paris 5, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France

Corresponding Author: Dr Charlotte HUA, Service de Rhumatologie, CHU Nîmes, 1 Place du Professeur Robert Debré, 30000 Nîmes, France. Mail: charlotte.hua@chu-nimes.fr.

ABSTRACT

Objective. Multimorbidity is frequent in rheumatoid arthritis (RA) and could interfere with the therapeutic response. The aim of this study was to evaluate multimorbidity in the French cohort of early arthritis, the ESPOIR cohort, and its possible impact on the therapeutic response.

Methods. We included patients fulfilling 2010 ACR/EULAR criteria for RA. An adapted MultiMorbidity Index (aMMI) was developed. Each patient was assigned scores of binary aMMI (0= no comorbidity, 1= at least 1 comorbidity) and counted and weighted aMMI. The primary endpoint was achievement of Clinical Disease Activity Index (CDAI) low disease activity after initiation of a first disease-modifying anti-rheumatic drug (DMARD) according to the aMMI. We collected data from the visit preceding the first DMARD initiation and the visit after at least 3 months of treatment. The impact of aMMI on therapeutic maintenance at 1, 3, 5 and 10 years was evaluated.

Results. Analyses involved 472 patients: 302 (64%) had at least 1 comorbidity. Overall, 45.3% and 44.7% with binary aMMI= 0 or 1, respectively (non significant), achieved CDAI low disease activity. Similar results were found with counted and weighted aMMI. Therapeutic maintenance was significantly better with binary aMMI = 1 than binary aMMI = 0 (OR at 10 years= 14.0 [CI 95% 3.3-59.4]). Increased counted aMMI was associated with increased probability of still being on the first initiated DMARD at each time point.

Conclusion. In the ESPOIR cohort, therapeutic response to a first DMARD was not affected by multimorbidity but therapeutic maintenance was better in multimorbid patients.

KEYWORDS: Multimorbidity, Comorbidity, Rheumatoid arthritis, Therapeutic response, Therapeutic maintenance

1. INTRODUCTION

Management of comorbidities is now an integral part of the latest updates of guidelines on rheumatoid arthritis (RA) management (1). Indeed, even if nowadays it is increasingly less the case, mortality was higher in RA patients than in the general population. This excess mortality is linked to chronic inflammation, toxic effects of treatments but also, and more importantly, frequent comorbidities. RA patients have approximately 2 comorbid conditions associated with RA (2). This number is increasing with age as well as duration and activity of the disease. The most frequent comorbidities reported in RA patients are depression, asthma, chronic obstructive pulmonary disease, cardiovascular diseases and solid malignancies (3). The coexistence of these comorbidities can be grouped under the multimorbidity concept, a holistic concept, taking into account all potential interactions of co-existing morbidities and their effect on the patient's overall well-being (4).

Comorbidities affect the life expectancy of patients with RA and could also affect the therapeutic response to disease-modifying antirheumatic drugs (DMARDs), whether due to pathological interactions, polypharmacy or their effect on patient-reported outcomes used to evaluate RA outcome. Some studies have highlighted that RA patients with comorbidities have lower response rates to therapy than those without comorbidities (5–7). Most of those studies investigated established RA.

The aim of our study was to evaluate multimorbidity in an inception cohort of patients with early arthritis and the possible impact of multimorbidity on the short-term response to a first DMARD as well as long-term (up to 10 years) therapeutic maintenance of this first DMARD.

2. METHODS

2.1 Study population: ESPOIR is a longitudinal prospective cohort of adults (18-70 years old) with possible early RA. (ClinicalTrials.gov: NCT03666091). Patients were referred by

rheumatologists and general practitioners to one of the 14 regional centers in France. The objective and design of the cohort have been described elsewhere (8). The main inclusion criteria were at least 2 inflammatory joints for at least 6 weeks up to 6 months; clinical diagnosis of RA as certain or probable; never prescribed DMARDs or glucocorticoids (except if prescribed for < 2 weeks with a maximum of 20 mg/day prednisone or intra-articular injection < 4 weeks before inclusion). Patients were excluded if they had a clearly defined inflammatory rheumatic disease other than RA. Patients were routinely cared for and followed by their rheumatologists according to the standard of care and without predefined therapeutic strategies. All patients were referred to each regional center once every 6 months during the first 2 years and once every year thereafter. A total of 813 patients were enrolled between 2003 and 2005. The protocol of the ESPOIR cohort study was approved in July 2002 by the ethics committee of Montpellier, France (no. 020307). All patients gave their signed informed consent before inclusion.

Patients were included in the current study if during the first year of follow-up they fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA and had initiated a DMARD (as monotherapy or in combination) within the first 21 months of follow-up in the ESPOIR cohort. This time-range was chosen in order to take into account as many patients as possible. The non-inclusion of patients initiating a DMARD after the first 21 months of follow-up in the ESPOIR cohort was justified in order to homogenize the periods between the baseline visit and follow-up visit (maximum of 8 months between the 2 visits, see below). The “DMARD population” was defined as patients who retained this treatment until the follow-up visit.

2.2 Objectives: The primary objective was to evaluate the impact of multimorbidity on treatment response to a first DMARD by using the Clinical Disease Activity Index (CDAI). Secondary objectives were evaluations of the impact of multimorbidity on the following:

- 1) treatment response to a first DMARD by using the Disease Activity Score in 28 joints erythrocyte sedimentation rate (DAS28 ESR) and the Simplified Disease Activity Index (SDAI).
- 2) retention rate of the first DMARD.

2.3 Assessment of multimorbidity status: To assess multimorbidity and to match as much as possible with the comorbidities collected according to a pre-established form in the ESPOIR cohort, we adapted the MultiMorbidity Index (MMI). This MMI includes 40 morbid conditions and was developed by Radner et al. based on the impact of multimorbidity on health-related quality of life [table S1; See the supplementary material associated with this article online] (7). Our adapted MMI (aMMI) includes 17 comorbid conditions (Table 1). This aMMI was evaluated in 3 ways: binary aMMI (0, no comorbidity; 1, ≥ 1 comorbidity associated with RA); counted aMMI (range 0-17: sum of comorbidities associated with RA) and weighted aMMI (range 0-58; sum of weights assigned to each comorbidity). For the weighted aMMI, we used the weight values elaborated by Radner et al. for the MMI, according to the impact of each comorbidity on health-related quality of life.

2.4 Assessment of therapeutic response: Patients of the ESPOIR cohort could be started on a DMARD, either conventional synthetic DMARD (i.e., hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, gold salts) or biologic DMARDs, at any time during the follow-up (e.g., between the ESPOIR visits). To evaluate the therapeutic response changes occurring from pre- to post-initiation of DMARDs, we needed a definition of “baseline” (before initiation) and

“follow-up” (after initiation) visits. The baseline visit was defined as the last ESPOIR cohort visit before the initiation of the first DMARD or the visit that occurred within 7 days of DMARD initiation. The follow-up visit was defined as the first visit occurring after at least 3 months of the first DMARD initiation. Because of the schedule of ESPOIR visits, the maximum time between baseline and the follow-up visit was 8 months.

2.5 Statistical analysis

2.5.1 Impact of multimorbidity status on response to the first DMARD. We estimated the probability of reaching CDAI low disease activity (LDA) ($CDAI \leq 10$) at the follow-up visit, depending on the binary, counted and weighted aMMI. Patients who had stopped their first DMARD before the follow-up visit were excluded from this primary analysis. Patients who were still on the same DMARD at the follow-up visit but who had another DMARD prescribed during this period (i.e., treatment intensification) were not excluded but were considered non-responders (LDA not reached). Two sensitivity analyses were performed for this primary objective: 1) analysing proportions of CDAI LDA even in patients who had stopped their first DMARD before the follow-up visit and 2) not considering patients who were prescribed a treatment intensification as non-responders. Differences between the patients reaching or not LDA according to aMMIs were analysed by Kruskal-Wallis nonparametric test for continuous variables and chi-square test for categorical variables. Similar analyses were conducted to compare proportion of patients reaching or not LDA according to several variables chosen upon their clinical relevance: age, sex, weight, smoking status, number of drugs at baseline visit, positivity for rheumatoid factor and/or anti-citrullinated protein antibodies, disease activity at baseline visit (CDAI and tertiles of CDAI) and glucocorticoids intake. A multivariable model by logistic regression was used in case of significant differences on univariable analysis at the 20% threshold. The multivariable logistic regression model was designed using backward

deletion of variables with $p > 0.05$. Odds ratios and their 95% confidence intervals were estimated by the Wald test.

For secondary outcomes, rates of patients reaching DAS28 ESR LDA ($\text{DAS28 ESR} \leq 3.2$) or SDAI LDA ($\text{SDAI} \leq 11$) at the follow-up visit depending on binary, counted and weighted aMMIs were assessed similarly, as were rates of responders according to EULAR criteria and to CDAI and SDAI criteria (9,10).

2.5.2 Impact of multimorbidity on first DMARD retention rate. We used similar analyses as described previously to estimate the probability of maintaining the first DMARD at 1, 3, 5 and 10 years, depending on binary and counted aMMIs.

3. RESULTS

In total, 663 of the 813 patients included in the ESPOIR cohort fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism criteria in the first year; 574 had initiated a first DMARD within the first 21 months (“maintenance population”) and 472 had retained it until the follow-up visit (DMARD population) (Fig. 1). The first initiated DMARD was mainly methotrexate (70.0%), followed by hydroxychloroquine (12.1%), sulfasalazine (9.3%), leflunomide (5.1%), gold salts (1.9%), and biologic DMARDs (1.1%) (Table S2).

3.1 Baseline characteristics (Table 2): Mean age was 48.5 (SD 12.1) years and 76.3% of the patients were female. Overall, 64% of the patients had at least one comorbidity (binary aMMI = 1), 96.8% had < 4 comorbidities, and the mean weighted aMMI was 4.0 (SD 4.9). The most frequent comorbidity associated with RA was obesity (20.6%), followed by high blood pressure (18.6%), alcoholism (18.1%) and dyslipidemia (15.5%) (Table S3). The two groups of binary aMMI did not differ in baseline characteristics (age, sex, immunopositivity, CDAI, first

initiated DMARD) except for mean age, which was higher with a binary aMMI = 1 than aMMI = 0 (51.2 vs 43.8 years, $p < 0.001$) (Table S2). During follow-up in the ESPOIR cohort, proportion of patients initiating a biological DMARD did not differ between patients with binary aMMI= 0 (14.4%) and patients with binary aMMI= 1 (16.7%). For 93% of the patients, a first DMARD was initiated within the first 6 months of follow-up in the ESPOIR cohort. Consequently, according to our study design described in the Methods section, M0 visit of the ESPOIR cohort was the baseline visit for 93% of the patients while it was M6 visit for 3.6% of them. M6 and M12 visits of the ESPOIR cohort were the follow-up visits for respectively 87.1% and 8.3% of the patients. Mean duration between the baseline and follow-up visits was 6.2 (SD 1.9) months.

3.2 Primary endpoint. The proportion of patients achieving CDAI LDA at follow-up visit was similar between the two groups of binary aMMI: 45.3% and 44.7% with aMMI = 1 and aMMI = 0 (p-value non significant) (Table 3). There was no loss to follow-up for this primary analysis. Mean counted aMMI was 1.0 (SD 1.1) for patients achieving CDAI LDA at follow-up visit and 1.1 (1.1) for non-responders (p-value non significant) (Table 3). Moreover, the proportion of patients achieving or not the CDAI LDA at follow-up visit did not differ for each counted aMMI value (Fig. 2A). The mean weighted aMMI was 4.1 (SD 5.2) for patients achieving CDAI LDA at the follow-up visit and 4.0 (4.7) for non-responders (p-value non significant) (Table 3). Because of no significant result on univariable analyses, multivariable analyses were not performed.

Results were not affected in the sensitivity analyses by not considering patients who were prescribed a treatment intensification as non-responders or by retaining those patients who had stopped their first DMARD before the follow-up visit (data not shown). Performing analyses only on the 411 patients having M0 as baseline visit and M6 as follow-up visit did not impact

the results (data not shown). Results were also not affected by performing the analysis in patients with at least two or three comorbidities (table S4). For the most frequent comorbidities (i.e comorbidities with a frequency above 5% in our study population: obesity, high blood pressure, alcoholism, dyslipidemia and thyroid disorders), proportions of patients reaching or not CDAI LDA at follow-up visit were similar (table S5). Analysis of patients reaching not only CDAI LDA but also CDAI remission did not affect the results (data not shown).

3.3 Secondary endpoints (DAS28 ESR and SDAI). The proportion of patients achieving DAS28 ESR or SDAI LDA at the follow-up visit was similar between the two groups of binary aMMI (p-values non significant) (Table 3). The mean counted aMMIs were similar for patients achieving or not DAS28 ESR or SDAI LDA at the follow-up visit (p-values non significant) (Table 3). For each counted aMMI value, the proportion of patients achieving or not DAS28 ESR or SDAI LDA at the follow-up visit did not differ (Fig. 2B and 2C). Mean weighted aMMIs were similar for patients achieving or not DAS28 ESR or SDAI LDA at follow-up visit (p-values non significant) (Table 3).

3.4 Secondary endpoints (EULAR, CDAI and SDAI response criteria; (tables S6, S7 and S8). Overall, 43% of the patients had good EULAR response at the follow-up visit, and 30.4% and 26.6% had a moderate response or no response. The proportion of patients who were good, moderate or non-responders was similar between the 2 categories of binary aMMI. Means of counted and weighted aMMI values did not differ between the 3 types of EULAR response. In total, 20.2% of the patients achieved a major CDAI response at the follow-up visit and 16.6% and 18.6% had a moderate and minor response, respectively; 44.6% were non-responders. Proportions of patients with a CDAI major, moderate, minor or lack of response were similar between the 2 categories of binary aMMI. Means of counted and weighted aMMI values did

not differ between the 4 types of CDAI response. Finally, 18.1% of the patients achieved a major SDAI response at the follow-up visit and 17.4% and 22.3% had a moderate and minor response, respectively; 44.2% were non-responders. The proportion of patients with a SDAI major, moderate, minor or no response was similar between the 2 categories of binary aMMI. The mean weighted aMMI was significantly lower for patients with a minor SDAI response versus other types of response (2.9 [3.7] vs 4.3 [5.2]; $p < 0.05$), but otherwise means of counted and weighted aMMI values did not differ between the 4 types of SDAI response.

3.5 Secondary endpoints (first DMARD retention rate; Table 4). The retention rate of the first DMARD at 1, 3, 5 and 10 years was 52.3%, 49.7%, 20.2% and 7.0%, respectively. On univariable analysis, for each time point, significantly fewer patients maintained their first DMARD with binary aMMI = 0 than binary aMMI = 1. The retention rate of the first DMARD at 1, 3, 5 and 10 years was 2.1%, 1.7%, 1.6% and 0.3%, respectively for patients with binary aMMI = 0 while it was 52.0%, 47.9%, 18.6% and 6.6%, respectively for patients with binary aMMI = 1 (Table 4). Multivariable analyses including significant variables confirmed that the probability of still being on the first initiated DMARD at 1, 3, 5 and 10 years was higher with binary aMMI = 1 than binary aMMI = 0 (Table 4).

On univariable analyses, at each time point, counted aMMIs were higher for patients maintaining than not maintaining their first DMARD. This finding was confirmed by multivariable analysis: increased counted aMMI was associated with increased probability of still being on the DMARD at 1, 3, 5 and 10 years (Table 4).

4. DISCUSSION

Our study reveals that comorbidities do not affect the therapeutic response to a first DMARD in early RA. These results were consistent regardless of how we evaluated multimorbidity (binary, counted, weighted aMMI) or how we assessed therapeutic response (achievement of CDAI, DAS28 ESR or SDAI LDA, EULAR, CDAI or SDAI response criteria).

Data from the literature are heterogenous but are mostly discordant with our findings in early RA, showing a negative impact of multimorbidity on the therapeutic response in patients with established RA. Radner et al., who have developed the MMI, showed lower remission rates in multimorbid patients (7). In an Italian retrospective analysis, increased multimorbidity (evaluated by the Rheumatic Disease Comorbidity Index) lowered the likelihood of achieving good to moderate EULAR response at 1 year (11). However, in this study, when the Rheumatic Disease Comorbidity Index was used as a binary value, proportions of patients with good to moderate EULAR response or DAS28 ESR remission/LDA were similar between patients without comorbidities and those with at least one comorbidity (11). In a Japanese RA cohort, therapeutic response was negatively affected by multimorbidity (evaluated by the Charlson Comorbidity Index [CCI]), but results were statistically significant for only patients with at least 3 comorbidities associated with RA (12). In a study of 1548 RA patients from the CORRONA registry, the probability of reaching CDAI remission was decreased by 71% for patients with > 9 versus < 3 comorbidities ($p= 0.001$) (5). In another North American study, the probability of achieving CDAI LDA at 6 months after etanercept initiation was inversely correlated with the number of comorbidities (13). Besides the differences between the evaluated comorbidities in the various studies, due to use of several multimorbidity indexes, the apparent discrepancy between the literature and our study may also be the included population. Indeed, the studies cited above included patients with long-duration RA, who were older and with more

comorbidities, than in our study, which concerned early RA patients who largely (79.2%) had < 3 comorbidities.

By contrast, our study revealed that the retention rate of the first DMARD at 1, 3, 5 and 10 years was higher for patients with than without multimorbidity. The literature data on the impact of multimorbidity on therapeutic maintenance are somewhat discordant. In 2 Italian studies, the presence of comorbidities predicted better tumor necrosis factor (TNF) blocker maintenance at 3 and 4 years (14,15). However, Radner et al. found increased continuous MMI linked to a decrease in the proportion of patients still on the same DMARD at 1 year (7). For Biggioggero et al, multimorbidity was associated with a higher rate of TNF blocker discontinuation at 2 years (hazard ratio 1.2 [95% confidence interval 1.0-1.4]; $p < 0.05$) (11). A closer medical monitoring and a greater experience in medication intake, improving the therapeutic adherence of patients with comorbidities, could explain our results. Improvement of therapeutic adherence in multimorbid patients with chronic diseases was previously demonstrated (16,17). However, in this case, it could be expected that patients with better therapeutic adherence would have a better therapeutic response, which was not retrieved in our study. Another hypothesis that could have explained the better therapeutic maintenance in multimorbid patients would be that in these patients, DMARDs with lower risk of side effects were chosen, and because the treatment was less “invasive”, it could be pursued for a longer time. It might also be considered that, for an equal state of disease activity, therapeutic switches and intensifications are less frequent in multimorbid patients, either to avoid riskier treatments as previously discussed or because the rise in disease activity parameters is assigned to comorbidities and not only to RA. However, we were not able to confirm these assumptions in our study because the type of the first initiated DMARD did not differ between patients with and without multimorbidity and there was no difference in terms of biological DMARD initiation between patients with and without comorbidities.

Some strengths of our study include the prospective design and the high number of included patients. Our population is also homogenous, notably regarding disease duration. Finally, the observational design of the study gives real life results, which are important regarding patients with comorbidities who are frequently excluded from clinical trials.

Nevertheless, this observational design is also a limitation of our study because it can imply potential biases such as confounding by indication resulting from the lack of randomization. However, this lack of randomization could lead to prescription of less invasive and hence less effective treatments in multimorbid patients, which would have led to decreased therapeutic response in multimorbid patients, which was not the case in our study. Moreover, comparison of baseline characteristics across the categories of aMMI did not reveal significant differences except for age. Another limitation is related to the ESPOIR cohort protocol with systematic visits planned regardless of the first DMARD initiation date. As a result, therapeutic response could not be assessed at fixed intervals. However, delays between baseline and follow-up visits were not so disparate, with baseline and follow-up visits at month 0 and month 6 for 93% and 87.1% of patients, respectively. Finally, the last but not least limitation of our study was the multimorbidity evaluation. Indeed, numerous indices evaluating multimorbidity have been described, and we had not only to choose one of them but also to adapt it for applicability to the ESPOIR cohort. We chose the MMI because, unlike the well-known Charlson Comorbidity Index (CCI) or other multimorbidity indices, it was specifically elaborated for RA patients and initially aimed to evaluate impact of multimorbidity on quality of life, which appears more pertinent for therapeutic response than, for example, mortality used to develop the CCI. Moreover, the MMI had already been used by Radner et al. to evaluate the therapeutic response of RA patients. Unfortunately, we could not use the original version of the MMI because not all the comorbidities of the MMI were collected in the ESPOIR cohort. To keep this aMMI relevant, we selected comorbidities that were part of the EULAR list of comorbidities to

consider when treating inflammatory rheumatism (18). Nevertheless, one has to keep in mind that this aMMI has not been previously validated for multimorbidity evaluation in RA patients. Even if our study needs to be validated by further research, we found that therapeutic response in early RA does not appear to be negatively impacted by multimorbidity. The issue of DMARDs effectiveness should therefore not be an obstacle in treating patients with early RA and comorbidities.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The ESPOIR cohort is sponsored by the French Society for Rheumatology. An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years. Two additional grants from INSERM were obtained to support part of the biological database. Pfizer, Abbvie, Lilly and more recently Fresenius and Biogen also supported the ESPOIR cohort.

Conflicts of interest: AB, AC and JPD declare no conflict of interest with regard to this study. BC received honoraria from AbbVie; Bristol-Myers Squibb; Gilead; Janssen; Lilly; Merck; Novartis; Pfizer; Roche-Chugai; and Sanofi; and research grants from Novartis, Pfizer, and Roche. CGV reports serving as a consultant and on a speaker's bureau for AbbVie; Amgen; Bristol-Myers Squibb; Celgene; Eli Lilly; Galapagos; Gilead Sciences, Inc.; Janssen; Medac; Merck-Serono; Mylan; Nordic Pharma; Novartis; Pfizer; Roche; Sandoz; Sanofi; and UCB. CL has participated as speaker's bureau for Abbvie, Amgen, Janssen, Lilly, MSD, Novartis, Pfizer, Roche-Chugai and UCB was consultant for Abbvie, Amgen, Janssen, Lilly, MSD, Novartis, Pfizer, Roche-Chugai and UCB and has received research grants from Pfizer, Novartis and Roche-Chugai. AS received honoraria or research grants from AbbVie; Bristol-Myers Squibb; Lilly; Nordic; Novartis; Pfizer; Roche-Chugai; Sanofi and UCB. MD has participated at advisory boards and/or symposium organized by Pfizer, Abbvie, Lilly, UCB, Merck, BMS,

Roche, Biogen, Sanofi, Novartis, Sandoz and his department has received research grants from Pfizer, Abbvie, Lilly, UCB, Merck, BMS, Roche, Biogen, Sanofi, Novartis, Sandoz. CH has participated as speaker's bureau for Abbvie, Amgen, Lilly, Novartis, Pfizer, Roche-Chugai and BMS.

Acknowledgements: We are grateful to Nathalie Rincheval (Montpellier) for expert monitoring and data management and all the investigators who recruited and followed the patients (F. Berenbaum, Paris-Saint Antoine; MC. Boissier, Paris-Bobigny; A. Cantagrel, Toulouse; B. Combe, Montpellier; M. Dougados, Paris-Cochin; P. Fardellone and P. Boumier, Amiens; B. Fautrel, Paris-La Pitié; RM. Flipo, Lille; Ph. Goupille, Tours; F. Liote, Paris-Lariboisière; O. Vittecoq, Rouen; X. Mariette, Paris-Bicêtre; P. Dieude, Paris Bichat; A. Saraux, Brest; T. Schaeverbeke, Bordeaux; and J. Sibia, Strasbourg).

Author contributions: All authors had full access to the data and reviewed and approved the manuscript for publication. CH takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conceptualization and Methodology: Hua, Combe ; Investigation: Beltai, Hua; Writing -

Original Draft: Beltai, Hua, Combe; Formal analysis: Coffy, Daures; Writing- Reviewing and

Editing and Visualization: All authors

REFERENCES

1. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–699.
2. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis* 2014;73:62–68.
3. Dougados M, Soubrier M, Perrodeau E, Gossec L, Fayet F, Gilson M, et al. Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: results of a prospective, multicentre, randomised, controlled trial (COMEDRA). *Ann Rheum Dis* 2015;74:1725–1733.
4. Radner H, Yoshida K, Smolen JS, Solomon DH. Multimorbidity and rheumatic conditions-enhancing the concept of comorbidity. *Nat Rev Rheumatol* 2014;10:252–256.
5. Ranganath VK, Maranian P, Elashoff DA, Woodworth T, Khanna D, Hahn T, et al. Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. *Rheumatol Oxf Engl* 2013;52:1809–1817.
6. Ajeganova S, Andersson ML, Hafstrom I, Group BS. Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: a long-term followup from disease onset. *Arthritis Care Res* 2013;65:78–87.
7. Radner H, Yoshida K, Frits M, Iannaccone C, Shadick NA, Weinblatt M, et al. The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs. *Rheumatol Oxf Engl* 2015;54:2076–2084.
8. Combe B, Benessiano J, Berenbaum F, Cantagrel A, Daures JP, Dougados M, et al. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. *Jt Bone Spine Rev Rhum* 2007;74:440–5.
9. Gestel AM van, Prevoo ML, Hof MA van 't, Rijswijk MH van, Putte LB van de, Riel PL van. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996;39:34–40.
10. Aletaha D, Martinez-Avila J, Kvien TK, Smolen JS. Definition of treatment response in rheumatoid arthritis based on the simplified and the clinical disease activity index. *Ann Rheum Dis* 2012;71:1190–1196.
11. Biggioggero M, Mesina F, Favalli EG. The Use of Rheumatic Disease Comorbidity Index for Predicting Clinical Response and Retention Rate in a Cohort of Rheumatoid Arthritis Patients Receiving Tumor Necrosis Factor Alpha Inhibitors. *BioMed Res Int* 2019;2019:6107217.

12. Nakajima A, Inoue E, Shimizu Y, Kobayashi A, Shidara K, Sugimoto N, et al. Presence of comorbidity affects both treatment strategies and outcomes in disease activity, physical function, and quality of life in patients with rheumatoid arthritis. *Clin Rheumatol* 2015;34:441–449.
13. Martin WJ, Shim M, Paulus HE, Chaudhari S, Feng J, Elashoff D, et al. Older age at rheumatoid arthritis onset and comorbidities correlate with less Health Assessment Questionnaire-Disability Index and Clinical Disease Activity Index response to etanercept in the RADIUS 2 registry. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis* 2014;20:301–305.
14. Marchesoni A, Zaccara E, Gorla R, Bazzani C, Sarzi-Puttini P, Atzeni F, et al. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. *Ann N Y Acad Sci* 2009;1173:837–846.
15. Iannone F, Gremese E, Atzeni F, Biasi D, Botsios C, Cipriani P, et al. Longterm retention of tumor necrosis factor- α inhibitor therapy in a large italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. *J Rheumatol* 2012;39:1179–1184.
16. Glader E-L, Sjölander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. *Stroke* 2010;41:397–401.
17. Deshpande CG, Kogut S, Willey C. Real-World Health Care Costs Based on Medication Adherence and Risk of Stroke and Bleeding in Patients Treated with Novel Anticoagulant Therapy. *J Manag Care Spec Pharm* 2018;24:430–439.
18. Baillet A, Gossec L, Carmona L, Wit M de, Eijk-Hustings Y van, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis* 2016;75:965–973.

Table 1: List of 17 comorbidities and their assigned weights included in the adapted MultiMorbidity Index (aMMI).

Morbid condition	Assigned weight
Diabetes	0.5
Hypertension	0.5
Dyslipidemia	0.5
Atrial fibrillation	0.5
Stroke/transient ischemic attack	2
Chronic kidney disease	2
Obesity	4
Cancer	0.5
Chronic obstructive pulmonary disease	5
Hepatitis (viral)	10
Diverticulitis	0.5
Inflammatory bowel disease	3
Dyspepsia	10
Osteoporosis	1
Thyroid disorders	3
Alcohol problems	9
Depression	6

Table 2: Baseline characteristics of patients with rheumatoid arthritis and taking disease-modifying anti-rheumatic drugs: the “DMARD population” (n=472)

Age, mean (SD)	48.5 (12.1) years
Female	76.3%
Immunopositivity (RF and/or ACPA)	56.7%
Baseline CDAI score, mean (SD)	28.1 (13.8)
Baseline DAS28 ESR score, mean (SD)	5.3 (1.3)
Baseline SDAI score, mean (SD)	30.2 (14.7)
Current smoking	44.7%
Number of ongoing treatments, mean (SD)	3.2 (2.1)
Current GC therapy	44.9%
Binary aMMI = 0	36%
Counted aMMI= 1	35.2%
Counted aMMI= 2	18%
Counted aMMI= 3	7.6%
Counted aMMI > 3	3.2%
Weighted aMMI, mean (SD)	4.0 (4.9)

SD= standard deviation; RF= rheumatoid factor; ACPA= anti-citrullinated peptide antibodies; GC= glucocorticoids; aMMI= adapted MultiMorbidity Index; CDAI= Clinical Disease Activity Index; DAS28 ESR= Disease Activity Score in 28 joints; SDAI= Simplified Disease Activity Index;

Table 3: Impact of aMMIs on CDAI, DAS28 ESR and SDAI low disease activity (LDA) achievement at follow-up visit

	LDA achievement					
	CDAI		DAS28 ESR		SDAI	
	Yes	No	Yes	No	Yes	No
Binary aMMI, n						
(%)						
0	77 (45.3)	93 (54.7)	85 (50.0)	85 (50.0)	80 (47.1)	90 (52.9)
1	135 (44.7) ^{§,*}	167 (55.3)	131 (43.4) ^{§,*}	171 (56.6)	141 (46.7) ^{§,*}	161 (53.3)
Counted aMMI, mean (SD)	1.0 (1.1)	1.1 (1.1) &,*	1.0 (1.1)	1.1 (1.1) &,*	1.1 (1.1)	1.1 (1.1) &,*
Weighted aMMI, mean (SD)	4.1 (5.2)	4.0 (4.7) #,*	4.0 (5.2) #,*	4.1 (4.7)	4.0 (5.0)	4.0 (4.9) #,*

aMMI= adapted MultiMorbidity Index; CDAI= Clinical Disease Activity Index; SDAI= Simplified Disease Activity Index

§ Proportion of patients achieving LDA were compared between patients with binary aMMI= 0 and binary aMMI= 1. Analyses were performed on the “DMARD population” (n= 472). Univariable analyses were performed first. Because of no statistically significant results, no multivariable analysis was performed.

& Counted aMMI was compared between patients achieving or not LDA. Analyses were performed on the “DMARD population” (n= 472). Univariable analyses were performed first. Because of no statistically significant results, no multivariable analysis was performed.

Weighted aMMI was compared between patients achieving or not LDA. Analyses were performed on the “DMARD population” (n= 472). Univariable analyses were performed first. Because of no statistically significant results, no multivariable analysis was performed.

**p-value non significant (univariable analysis)*

Table 4: Probability of first DMARD maintenance at 1, 3, 5 and 10 years (multivariable analysis)

Time point	First initiated DMARD maintained or stopped	Binary aMMI [#]		Counted aMMI [§]
		0	1	
1 year (n= 530)	Maintenance (n= 300)	12	288	1.71 (0.93)
	OR [95% CI]*	> 999 [286.2->999]		221.3 [84.0-583.0]
	Withdrawal (n= 230)	205	25	0.12 (0.37)
3 years (n= 493)	Maintenance (n= 285)	10	275	1.66 (0.94)
	OR [95% CI]*	153.9 [73.0-324.5]		26.1 [15.1-45.3]
	Withdrawal (n= 208)	175	33	0.22 (0.64)
5 years (n= 459)	Maintenance (n= 116)	9	107	1.72 (1.05)
	OR [95% CI]*	10.9 [5.1-23.3]		2.2 [1.8-2.7]
	Withdrawal (n= 343)	163	180	0.82 (1.0)
10 years (n= 415)	Maintenance (n= 40)	2	38	1.58 (0.84)
	OR [95% CI]*	14.0 [3.3-59.1]		1.6 [1.2-2.0]
	Withdrawal (n= 375)	158	217	0.99 (1.12)

[#]data are number of patients

[§] data are mean (standard error)

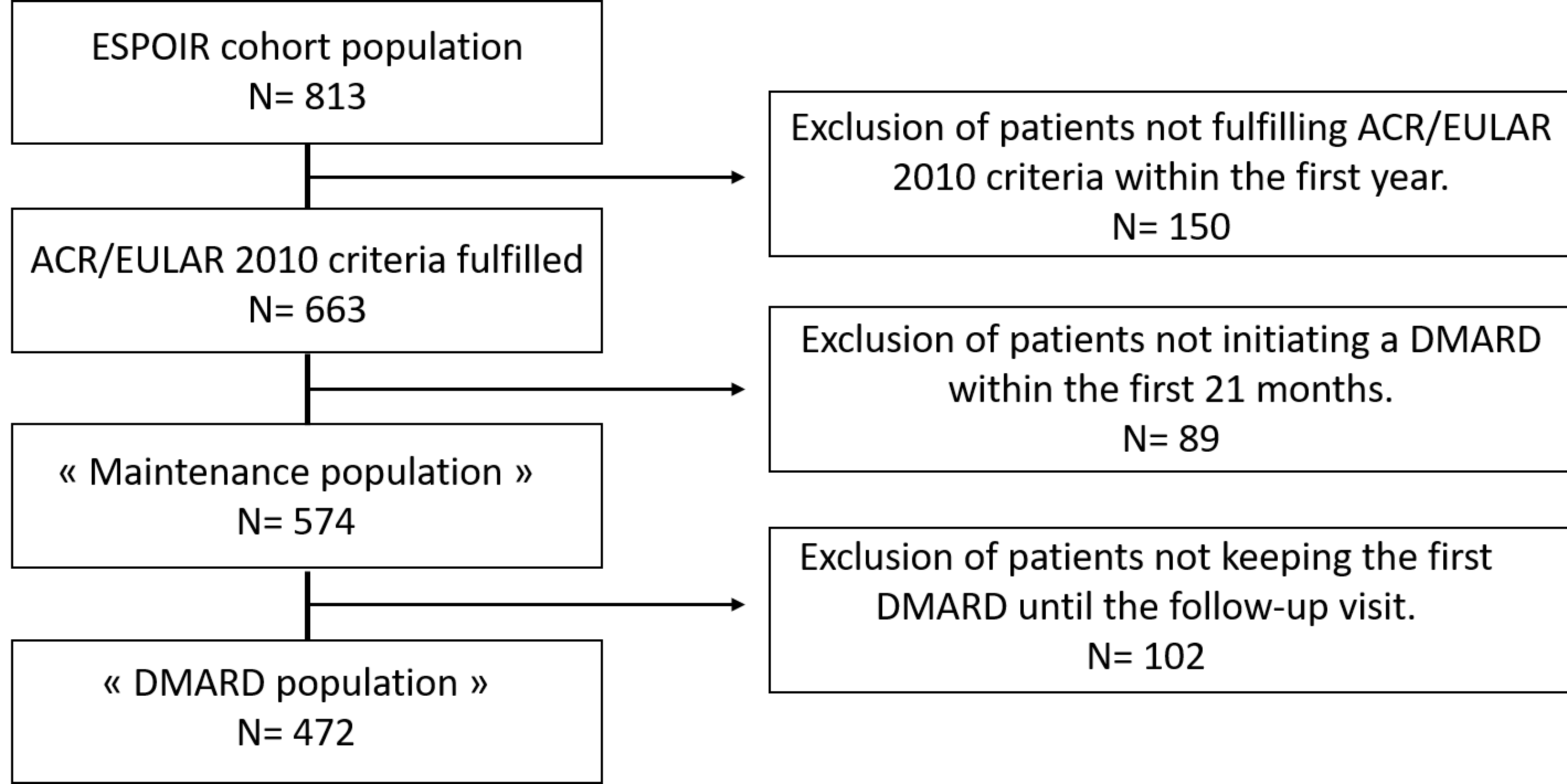
* data are odds ratios (ORs) and 95% confidence intervals (95% CI) of still being on the first initiated DMARD at 1, 3, 5 and 10 years between patients with binary aMMI = 1 and with binary aMMI = 0 and according to counted aMMI, per additional point.

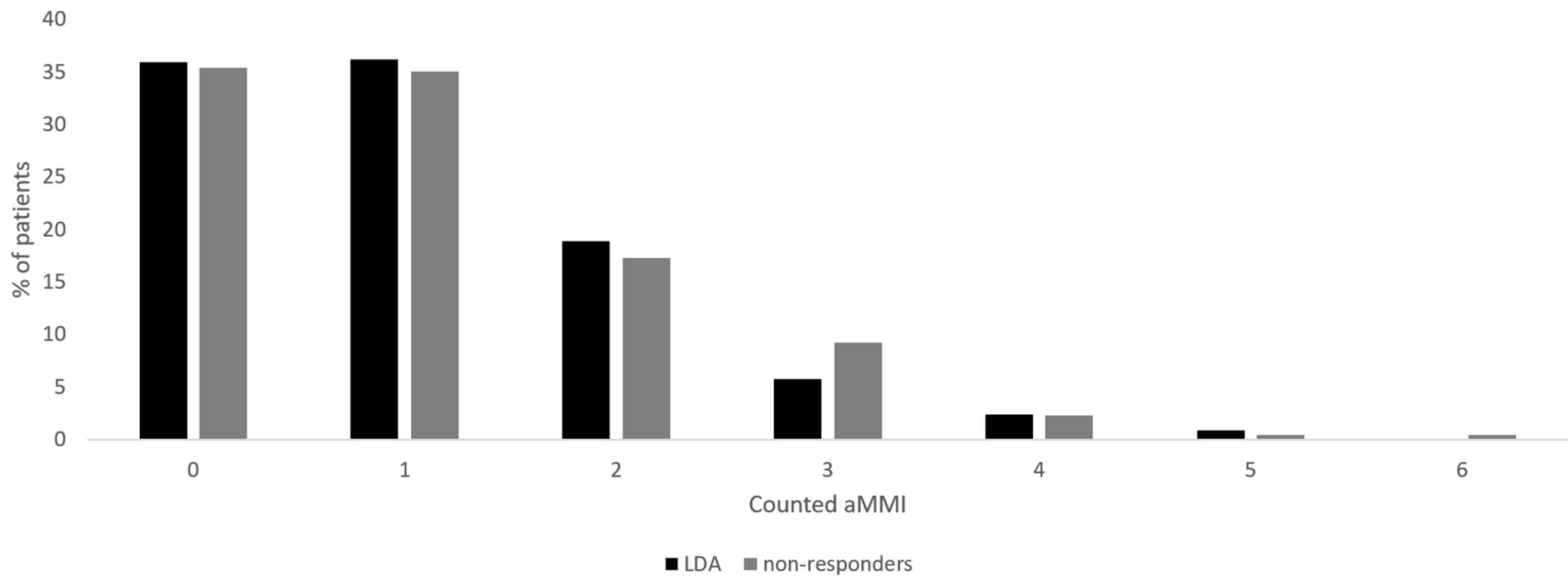
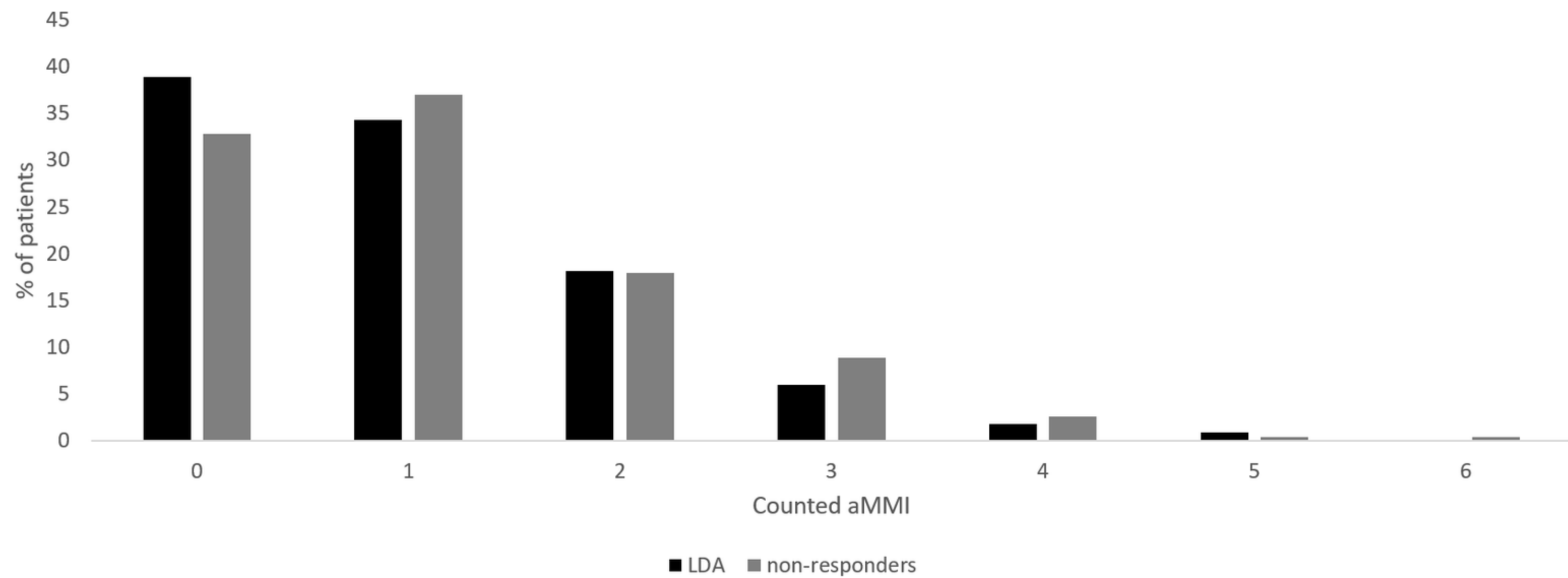
The variables included in multivariable analyses were sex, rheumatoid factor and/or anti-citrullinated peptide antibody positivity, age, CDAI at baseline visit, number of treatments at baseline visit.

FIGURES LEGENDS:

Figure 1: Study population

Figure 2: Percentage of patients achieving CDAI (A), DAS28 ESR (B) and SDAI (C) low disease activity (LDA) at the follow-up visit by level of counted MultiMorbidity Index (aMMI).



A**B****C**