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ORIGINAL ARTICLE

Comorbidity burden and clinical characteristics of patients with difficult-to-control rheumatoid arthritis

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Abstract

Introduction Difficult-to-treat rheumatoid arthritis (RA) is a significant clinical problem despite no clear definition. We aimed to provide clinical characteristics and associated comorbidities of RA patients in relation to disease control.

Methods RA characteristics and physician-recorded comorbidities were analyzed in a sample of 1937 RA patients. Patients treated for RA for 5.2 y (IQR, 2.1–11.3) were classified as difficult-to-control when presenting with DAS28-ESR > 3.2 despite previous use of at least 2 csDMARDs. A comparison of demographic and RA-related characteristics between difficult-to-treat and low disease activity patients (DAS28-ESR ≤ 3.2) was performed. Comorbidity burden was assessed by calculating Rheumatic Diseases Comorbidity Index (RDCI). Logistic regression model was constructed for difficult-to-control disease.

Results Hypertension (46.9% (95%CI, 44.7–49.2)), coronary artery disease (CAD) (18.5% (95%CI, 16.8–20.3)), and diabetes (14.4% (95%CI, 12.9–16.0)) were the most prevalent conditions in RA patients. When compared with the adequate control group, difficult-to-control patients were increasingly burdened with hypertension (52.7% (95%CI, 47.5–57.8) vs. 42.0% (95%CI, 36.6–47.6); $p = 0.006$), cardiovascular diseases (24.2% (95%CI, 20.1–28.9) vs. 11.1% (95%CI, 8.0–15.1); $p < 0.001$), respiratory system diseases (7.0% (95%CI, 4.8–10.2) vs. 3.3% (95%CI, 1.8–5.9); $p = 0.03$) and gastroduodenal ulcers (2.3% (95%CI, 1.2–4.4) vs. 0.3% (95%CI, 0.1–1.8); $p = 0.04$). Patients with higher RDCI had lower chance to obtain low disease activity (OR 0.69 (95%CI, 0.61–0.79); $p < 0.001$). In multivariate analysis, RDCI was independently associated with difficult-to-control disease (OR 1.46 (95%CI, 1.21–1.76); $p < 0.001$).

Conclusions RA patients suffer from a variety of comorbidities. Cardiovascular and respiratory system diseases occur twice as often in difficult-to-control patients. RDCI may provide a valuable tool in evaluating a risk for difficult-to-control RA.

Key Points

- *Hypertension, coronary artery disease and diabetes are the most prevalent comorbidities in rheumatoid arthritis.*
- *Cardiovascular and respiratory tract diseases as well as gastroduodenal ulcers are more common among difficult-to-control patients, when compared with subjects with adequately controlled RA.*
- *Rheumatic Diseases Comorbidity Index is an independent predictor for difficult-to-control RA.*

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Keywords Cardiovascular disease · Comorbidities · DAS28 · Epidemiology · Rheumatoid arthritis RDCI

Introduction

The concept of "difficult-to-treat" rheumatoid arthritis (RA) has recently gained recognition from the rheumatologist community, underscoring the necessity to achieve a universally accepted definition. Most common concepts include 28-joint disease activity score (DAS28) > 3.2 or active RA signs, and failure of at least 2 conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and 2 biologic DMARDs (bDMARDs) [1]. It should be emphasized that eligibility for bDMARDs is not equal to treatment availability, with strict reimbursement criteria and inequitable access across Europe [2]. Countries with strictly defined bDMARD inclusion criteria, divergent from expert recommendations, or limited financial resources may have an underrepresented population of these bDMARD refractory patients. As evidenced by epidemiological studies reporting bDMARD therapy in only 2.9% of Polish RA patients [3], the recruitment of multiple bDMARD refractory patients would be exceedingly difficult and would not represent the actual population of "difficult-to-treat" RA encountered by Polish rheumatologists. This concept is not limited to Poland and likely applies to other "low bDMARD access" European countries. We approached the former definition by designating "difficult-to-control" RA, understood as inadequate control of disease activity achieved in daily practice under means available to the rheumatologist that is failure of at least two csDMARDs.

When asked to define additional characteristics of "difficult RA," rheumatologists most frequently described conditions, which were termed under "interfering comorbidities" [1]. The findings of early RA studies have indicated that patients' age and comorbidity at diagnosis [4], age at RA onset [5], treatment, and disease activity [6] are contributors to developing comorbidity burden in RA. Large patient populations are necessary to assess the validity of the earlier findings. Furthermore, a clinically relevant population of "difficult-to-control" RA should be investigated. In this context, we sought to evaluate coexisting diseases in the setting of demographics, RA characteristics and treatment decisions. Furthermore, we investigated features characterizing difficult-to-control RA patients.

Methods

Patient recruitment

The records of the Polish Chamber of Physicians and Dentists were screened and analyzed to identify RA-treating centers in Poland, from which one hundred rheumatologists with ≥ 5 year experience were selected to representatively model the national RA treatment structure. Each rheumatologist recruited 20 sequential patients, at or over the age of 18, with a diagnosis RA. Data collection was performed from December 2014 to February 2015 from 1937 patients. Clinical characteristic of the analyzed patients is presented in Table S1. The present study is a part of a national project aiming to characterize the burden, and determine the character of RA in Poland, in a follow-up to the previously published epidemiological results, where methodology is described in greater detail [3]. Comorbidity data and analyses were not included in the previous publication and are unique to this study. We defined patients as difficult-to-control as those who present with DAS28-ESR > 3.2 and failure of at least 2 csDMARDs (n = 355). They were compared to patients with low disease activity defined as DAS28-ESR ≤ 3.2 (n = 307). A flowchart presenting the numbers of patients included into the study according to the analyzed groups is provided on Fig. 1.

Each participant has given an informed, written consent prior to inclusion in the study. The study was approved by the Bioethics Committee of the Regional Chamber of Physicians in Krakow, Poland (Decision No. L.dz.OIL/KBL/OIL/9/214) and conducted in accordance with the Helsinki Declaration.

Data collection

The participating rheumatologists completed a detailed questionnaire about each participant. The questionnaire comprised both closed and open-ended questions, reflecting: (a) demographic characteristics, (b) the diagnostic process, (c) indicators of RA activity, (d) medicines used to treat RA currently and in the past, (e) diagnosed diseases. The data were obtained during a face-to-face interview and completed through reviewing medical records. Due to the data being completed by rheumatologists rather than fulfilled by patients, we did not use Sangha index. Rheumatic disease comorbidity index (RDCI) [7] was calculated since the data collected was not detailed to complete Charlson or modified RDCI indices.

Statistical analysis

The prevalence rates are shown with 95% confidence intervals calculated using the Wilson method. The Shapiro-Wilk test was used to test whether the quantitative data have normal distribution. In vast majority of cases, data did not meet this assumption, thus the Mann-Whitney U test was used to compare quantitative parameters. The data are expressed as median with 25th–75th percentile. Qualitative data were analyzed using chi-squared test

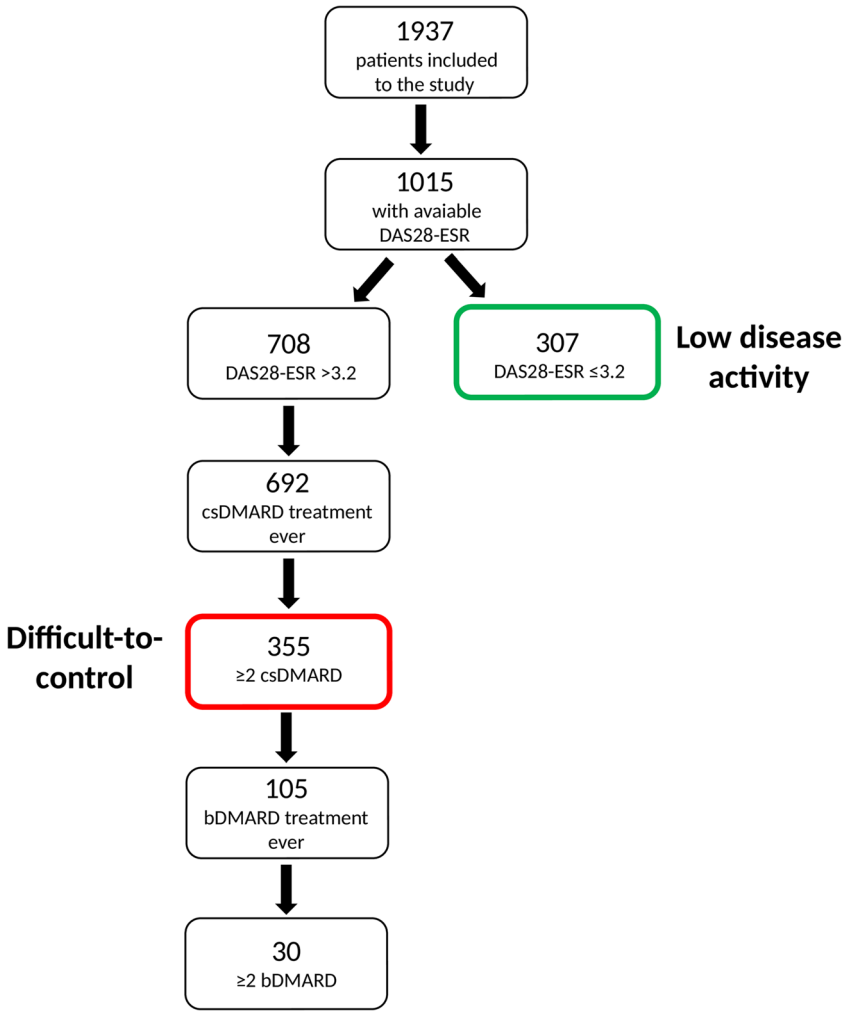

Fig. 1 The numbers of patients included into the study according to disease control and treatment applied. Red box indicates difficult-to-control patients defined as DAS28-ESR > 3.2 and previous use of at least 2 csDMARDs. Green box indicates patients with low disease activity defined as DAS28-ESR ≤ 3.2. csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs; DAS28-ESR, 28-joint Disease Activity Score using erythrocyte sedimentation rate

or the Fisher exact test as appropriate. Logistic regression was performed using difficult-to-control group compared to low disease activity group as dependent variable. In multivariate logistic regression, independent variables were those describing demographic characteristic (quantitative: age, weight, RDCI; and qualitative: sex, economic activity) and RA course (quantitative: RA duration since diagnosis; and qualitative: treatment with bDMARDs, NSAIDs and steroids). Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. P values < 0.05 were considered statistically significant.

Results

Prevalence of comorbidities

The prevalence of comorbidities in RA patients is presented in Table 1. The most commonly observed comorbidity was hypertension, and it was reported in 46.9% (95% CI, 44.7–49.2) of patients. It was followed by cardiovascular diseases with coronary artery disease observed in 14.8% (95% CI, 13.3–16.5) of cases. The prevalence of diabetes was 14.4% (95% CI, 12.9–16.0). Other comorbidities in order of decreasing prevalence were: osteoporosis, osteoarthritis, respiratory system diseases, thyroid gland diseases, gastro-intestinal diseases, psoriasis, cancers and chronic kidney disease, and depression. We observed a surprisingly low prevalence of COPD 0.72% (95%CI, 0.43–1.21) and depression 0.57% (95%CI, 0.32–1.01). Hypertension, CV diseases and MI history were more prevalent in men. Conversely, osteoporosis and thyroid gland diseases were predominate in women. Most patients presented with one or no co-existing disease (33 and 34% respectively) besides RA. Twenty percent had two, and 10 % presented with three comorbidities. Less than 3% of patients suffered from 4 or more diseases. Detailed numbers and coexistence of comorbidities are presented in Supplementary Material Excel Sheet.

Table 1 Prevalence of comorbidities in patients with rheumatoid arthritis, among women and men

	Women and men $n = 1937$			Women $n = 1523$			Men $n = 414$			Men vs women
	Prevalence (%)	95% CI	*N*	Prevalence (%)	95% CI	*N*	Prevalence (%)	95% CI	*N*	*p* value
Hypertension	46.93	44.71–49.15	909	45.31	42.82–47.81	690	52.90	48.09–57.66	219	**0.006**
Cardiovascular diseases (w/o HT)	18.48	16.82–20.27	358	16.87	15.08–18.84	257	24.40	20.51–28.76	101	**< 0.001**
CAD	14.82	13.30–16.47	287	14.05	12.40–15.89	214	17.63	14.26–21.60	73	0.07
Past myocardial infarction	4.90	4.03–5.96	95	3.55	2.73–4.60	54	9.90	7.38–13.16	41	**< 0.001**
Past stroke	0.98	0.63–1.53	19	0.85	0.50–1.45	13	1.45	0.67–3.13	6	0.27
Diabetes mellitus	14.40	12.91–16.04	279	13.85	12.21–15.68	211	16.43	13.17–20.30	68	0.19
Osteoporosis	8.05	6.92–9.35	156	8.86	7.54–10.40	135	5.07	3.34–7.63	21	**0.01**
Past osteoporotic fracture	5.32	4.40–6.41	103	5.71	4.65–6.99	87	3.86	2.39–6.19	16	0.14
Osteoarthritis	6.92	5.87–8.14	134	6.83	5.67–8.21	104	7.25	5.12–10.16	30	0.77
Respiratory system diseases	6.50	5.49–7.69	126	6.83	5.67–8.21	104	5.31	3.54–7.91	22	0.27
Interstitial lung disease	4.34	3.52–5.34	84	4.79	3.83–5.98	73	2.66	1.49–4.69	11	0.06
Asthma	1.08	0.71–1.65	21	1.25	0.80–1.94	19	0.48	0.13–1.74	2	0.28
COPD	0.72	0.43–1.21	14	0.59	0.31–1.12	9	1.21	0.52–2.80	5	0.19
Thyroid gland diseases	4.96	4.08–6.01	96	5.91	4.83–7.21	90	1.45	0.67–3.13	6	**< 0.001**
Hypothyroidism	3.15	2.46–4.02	61	3.74	2.90–4.82	57	0.97	0.38–2.46	4	**0.002**
Hyperthyroidism	0.52	0.28–0.95	10	0.59	0.31–1.12	9	0.24	0.04–1.36	1	0.70
Gastro-intestinal diseases	4.23	3.42–5.22	82	4.01	3.13–5.11	61	5.07	3.34–7.63	21	0.34
Gastroduodenal ulcers	1.19	0.79–1.78	23	0.92	0.55–1.54	14	2.17	1.15–4.08	9	0.07
Inflammatory bowel disease	0.26	0.11–0.60	5	0.26	0.10–0.67	4	0.24	0.04–1.36	1	1
Psoriasis	2.58	1.96–3.39	50	2.43	1.77–3.33	37	3.14	1.84–5.30	13	0.42
Cancers	2.01	1.48–2.74	39	1.97	1.38–2.80	30	2.17	1.15–4.08	9	0.79
Chronic kidney disease	1.55	1.09–2.20	30	1.31	0.85–2.02	20	2.42	1.32–4.39	10	0.11
Depression	0.57	0.32–1.01	11	0.59	0.31–1.12	9	0.48	0.13–1.74	2	1

Numbers in bold indicate statistical significance

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HT, hypertension; CI, the Wilson confidence interval. Chi-squared test or Fisher exact test were used as appropriate

Prevalence of comorbidities in relation to disease control

We compared prevalence of RA comorbidities in difficult-to-control RA with patients with low disease activity (Table 2). Difficult-to-control subjects had doubled prevalence of cardiovascular and respiratory system diseases (24.2% (20.1–28.9) vs. 11.1% (8.0–15.1); $p < 0.001$ and 7.0% (4.8–10.2) vs. 3.3% (1.8–5.9); $p = 0.03$, respectively) in comparison with those with DAS28-ESR below 3.2. Substantial differences were also observed in prevalence of hypertension (52.7% (47.5–57.8) vs. 42.0% (36.6–47.6); $p = 0.006$) and gastrointestinal ulcers (2.3% (1.2–4.4) vs. 0.3% (0.1–1.8); $p = 0.04$).

Characteristics of difficult-to-control RA patients

We observed no differences in demographic characteristics of RA patients such as age, sex, weight, disease duration, or age at RA diagnosis (Table 3). Difficult-to-control patients had slightly reduced economic activity and presented higher DAS28-ESR initially at RA diagnosis. According to treatment applied, difficult-to-control group was characterized by increased present use of steroids and NSAIDs, what is understood in active disease. No differences were found in frequencies of bDMARDs treatment, presently neither in the past. We observed evident relationship between RDCI and disease control. Patients with higher RDCI had less chance to achieve optimal disease control (OR 0.69 (95% CI, 0.61–0.79); $p < 0.001$ for simple unadjusted logistic regression); (Fig. 2)Interestingly, after adjusting for the possible confounders, multivariate logistic regression analysis revealed that each extra point in RDCI was associated with 46% increase in odds for difficult-to-treat RA ($p < 0.001$), (Table 4).

Table 2 Prevalence of concomitant diseases in rheumatoid arthritis patients with difficult-to-control disease defined as DAS28-ESR over 3.2 despite previous use of at least 2 csDMARDs in comparison with low disease activity patients

	Difficult-to-control RA	DAS28-ESR ≤ 3.2	*p* value
Number of patients	355	307	
Hypertension	52.7 (47.5–57.8)	42.0 (36.6–47.6)	**0.006**
Cardiovascular diseases (w/o HT)	24.2 (20.1–28.9)	11.1 (8.0–15.1)	**< 0.001**
CAD	19.4 (15.7–23.9)	9.8 (6.9–13.6)	**< 0.001**
Past myocardial infarction	6.5 (4.4–9.5)	3.9 (2.3–6.7)	0.14
Past stroke	1.4 (0.6–3.3)	1.0 (0.3–2.8)	0.73
Diabetes mellitus	14.7 (11.4–18.7)	12.1 (8.9–16.2)	0.33
Osteoporosis	7.9 (5.5–11.2)	6.8 (4.5–10.2)	0.61
Past osteoporotic fracture	4.2 (2.6–6.9)	2.6 (1.3–5.1)	0.26
Osteoarthritis	8.2 (5.8–11.5)	6.8 (4.5–10.2)	0.52
Respiratory system diseases	7.0 (4.8–10.2)	3.3 (1.8–5.9)	**0.03**
Interstitial lung disease	3.7 (2.2–6.2)	2.9 (1.6–5.5)	0.60
Asthma	1.1 (0.4–2.9)	0.3 (0.001–1.8)	0.38
COPD	1.4 (0.6–3.3)	0	0.07
Thyroid gland diseases	7.6 (5.3–10.8)	4.2 (2.5–7.1)	0.07
Hypothyroidism	4.8 (3.0–7.5)	2.9 (1.6–5.5)	0.22
Hyperthyroidism	0.6 (0.2–2.0)	0	0.50
Gastro-intestinal diseases	5.9 (3.9–8.9)	3.3 (1.8–5.9)	0.11
Gastroduodenal ulcers	2.3 (1.2–4.4)	0.3 (0.1–1.8)	**0.04**
Inflammatory bowel disease	0.3 (0.1–1.6)	0	1
Psoriasis	1.1 (0.4–2.9)	2.3 (1.1–4.6)	0.36
Cancers	2.8 (1.5–5.1)	1.0 (0.3–2.8)	0.10
Chronic kidney disease	0.9 (0.3–2.5)	1.3 (0.5–3.3)	0.71
Depression	0.9 (0.3–2.5)	0	0.25

Numbers in bold indicate statistical significance

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HT, hypertension; RA, rheumatoid arthritis. Values are presented as percentages with 95% Wilson confidence interval. Chi-squared test or the Fisher exact test were used as appropriate

Discussion

Following the multinational Comorbidities in Rheumatoid Arthritis (COMORA) study [8], and increasing attention attributed to "difficult-to-treat" RA [1], we report the prevalence of comorbidities and evaluate characteristics of difficult-to-control disease in Poland. Previous estimates of comorbidity burden in COMORA did not include Polish data, while existing studies are small and single-center reports [9]. To our knowledge, we provide the first national, multicenter data describing comorbidity burden and difficult-to-control disease in a large population of RA patients recruited in routine care. Patients were categorized into the latter if they had a DAS28 > 3.2 and previous use of at least 2 csDMARDs. These patients had similar demographic characteristics, RA duration and age at diagnosis, with present cs- and bDMARD use similar between both groups.

Taylor et al. recently published multinational, cross-sectional data showing 27% of 1147 RA patients have inadequate control of RA (defined DAS28 > 3.2) [10]. On average, 46% of that study population had prior bDMARD use. Similar findings of disease control (26.6%) were observed in Norway, which ranks among the highest in bDMARD access [11]. Listing et al. reported German registry data on RA patients with failure of ≥ 2 DMARDs, and observed that although bDMARDs improve clinical outcomes substantially, the overall success remains low [12]. These studies confirm that there remains a proportion of patients with incomplete control of RA, despite access to biological therapies. When considering only disease scores, 70% of patients had inadequate control in our study. Addition of the criterium of prior use of at least 2 csDMARDs resulted in 54% fulfilling our definition of difficult-to-control. This suggests a considerable disparity in achieving treatment outcomes across Europe. Our data may be considered inconsistent with a substantially high subset of patients with access to bDMARDs in both difficult and adequately controlled groups. This is drawn from the observation that rheumatologists recruited in our study were employed in multiple sites, with an overrepresentation of biological centers when analyzed, which was later weighed to account for this limitation in the epidemiological part of the study [3].

We observed that RDCI is the only predictor of difficult-to-control patients in multivariate logistic regression. RDCI is a

Table 3 Characteristics of rheumatoid arthritis patients with difficult-to-control disease defined as DAS28-ESR over 3.2 despite previous use of at least 2 csDMARDs in comparison with low disease activity patients

		Difficult-to-control RA	DAS28-ESR ≤ 3.2	*p* value
Number of patients		355	307	
Sex male (%)		23.9	18.5	0.09
Economic activity (%)		45.3	53.5	**0.04**
Weight (kg)		70 (61–80)	69 (60–78)	0.22
Age (y)		57 (50–64)	57 (44–64)	0.11
Age at RA diagnosis (y)		47 (39–56)	47 (33–56)	0.33
RA duration since diagnosis (months)		85 (35–168)	73.6 (33.0–135.4)	0.14
DAS28-ESR at RA diagnosis		6.0 (5.5–6.5)	5.8 (5.1–6.4)	**0.01**
Tender joint count (0–28)		11 (8–15)	10 (6–13)	**0.003**
Swollen joint count (0–28)		7 (4–10)	7 (4–10)	0.78
ESR (mm/h)		42 (27–54)	40 (26–53)	0.14
VAS general health (0–100)		64 (40–80)	60 (34–73)	0.10
DAS28-ESR at last visit		4.5 (3.9–5.5)	2.5 (2.2–2.9)	**< 0.001**
Tender joint count (0–28)		6 (3–10)	1 (0–2)	**< 0.001**
Swollen joint count (0–28)		4 (2–7)	0 (0–1)	**< 0.001**
ESR (mm/h)		21 (15–33)	11 (7–15)	**< 0.001**
VAS general health (0–100)		40 (25–60)	12 (10–24)	**< 0.001**
Steroids treatment ever (%)		88.5	86.6	0.48
Steroids daily dose >5 mg prednisone (%)		43.7	37.1	0.09
NSAIDs treatment ever (%)		94.7	96.7	0.19
NSAIDs treatment over 3 months (%)		48.2	40.7	0.05
Methotrexate treatment ever (%)		87.6	84.7	0.28
csDMARD treatment ever (%)		100	98.1	**0.01**
Number of csDMARDs used ever (%)	0–1	0	48.5	**< 0.001**
	2–3	85.6	45.9	
	4–7	14.4	5.5	
bDMARD treatment ever (%)		29.6	25.1	0.20
Number of bDMARDs used ever (%)	0	70.4	74.9	0.33
	1	21.1	16.9	
	2–4	8.5	8.1	
Steroids treatment at present (%)		61.7	41.0	**< 0.001**
NSAIDs treatment at present (%)		69.0	58.6	**0.005**
csDMARD treatment at present (%)		96.9	94.1	0.08
Methotrexate treatment at present (%)		74.1	78.8	0.15
bDMARD treatment at present (%)		23.1	20.2	0.37
RDCI (range, 0–7)	0	33.0	52.1	**< 0.001**
	1–2	53.0	39.1	
	> 2	14.1	8.8	

Numbers in bold indicate statistical significance

RA, rheumatoid arthritis; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs; DAS28-ESR, 28-joint disease activity score using erythrocyte sedimentation rate. Qualitative data were compared using Chi-squared test or the Fisher exact test as appropriate. The Mann-Whitney *U* test was used to compare quantitative data. Values are expressed as median (25th–75th percentile)

validated tool developed specifically for rheumatic diseases, which predicts mortality and physical function [7]. It has been favored in previous nonsystematic reviews [13], and utilized to predict clinical response and bDMARD retention rates [14]. Studies demonstrated that higher comorbidity burden is associated with increased disease activity, even when patients are initiated DMARDs at diagnosis [15]. We provide real world data suggesting an increasing difficulty in RA management

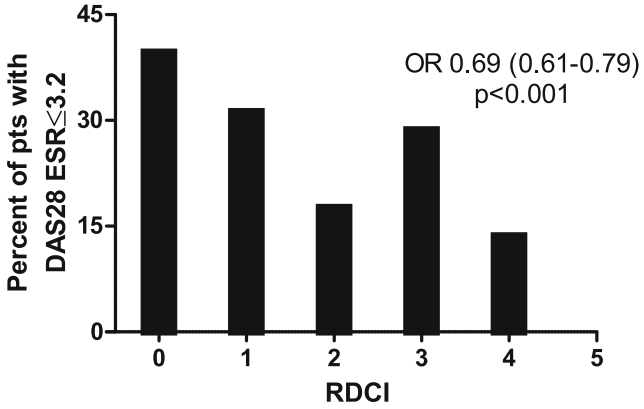

Fig. 2 Relationship between percentage of patients with well-controlled disease and Rheumatic Disease Comorbidity Index (RDCI). Pts, patients; DAS28-ESR, 28-joint Disease Activity Score using erythrocyte sedimentation rate; OR, odds ratio. Unadjusted logistic regression was performed

with the added burden of comorbidities. This should translate into evidence-based recommendations for the most frequently co-occurring conditions, as previously published for cardiovascular diseases (CVD) [16].

Previously, the COMORA study evaluated the prevalence of co-existing diseases in RA patients worldwide [8]; however, Poland was not included. The present study was conducted on a much bigger cohort of patients than each single country in COMORA (1937 vs. 30–411). Keeping in mind a wide intercountry variability reported by the former, our results do not deviate from the range of other countries and usually place around the mean values. Known intersex differences were also observed as higher prevalence of CVD in men, and higher prevalence of osteoporosis and thyroid gland diseases in women. We provide data that coronary artery disease and hypertension are significantly more prevalent among patients with difficult-to-treat RA. Among RA comorbidities, CV conditions are influenced by disease activity to the greatest extent [17]. DAS28 indices have been associated with coronary artery calcifications, independently from traditional CV and genetic risk scores [18], highlighting RA itself as a risk factor. Time-averaged disease activity was previously implicated as the main contributor to CV risk [19]. Our findings lend further support to the link between CV conditions and RA disease control. We observed that patients with difficult-to-control RA are more often treated with ongoing glucocorticoids (GCs) schemes and NSAIDs, which may reflect failing attempts to control disease activity.

Table 4 Multivariate logistic regression analysis estimating predictors of difficult-to-control rheumatoid arthritis defined as DAS28-ESR over 3.2 despite the use of at least 2 csDMARDs

	Difficult-to-control RA ($n = 355$)		
	OR	95% CI	p value
RDCI	**1.46**	1.21–1.76	**< 0.001**
Steroids treatment ever	1.12	0.68–1.85	0.67
RA duration since diagnosis (mo)	1.001	0.999–1.003	0.29
Age (y)	1.00	0.98–1.02	0.98
Sex (male)	1.40	0.90–2.18	0.13
Weight (kg)	0.996	0.98–1.01	0.64
Economic activity	0.93	0.62–1.40	0.72
NSAIDs treatment ever	0.66	0.28–1.55	0.34
bDMARDs treatment ever	1.19	0.81–1.73	0.38

Numbers in bold indicate statistical significance. n=355 difficult-to-control RA and 307 low disease activity RA

NSAIDs, nonsteroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs; RDCI, Rheumatic Disease Comorbidity Index; RA, rheumatoid arthritis; DAS28-ESR, 28-joint disease activity score using erythrocyte sedimentation rate; OR, odds ratio; CI, confidence interval

There are strengths and weaknesses that should be addressed. Firstly, the adopted definition of difficult-to-treat RA may not reliably account for disease flares, which may skew disease activity measures. A major oversight of this study was the limited scope of data gathered, particularly regarding cumulative GC dose, hypovitaminosis D, smoking status, and height for body mass index calculation. Therefore, we cannot account for confounding factors and assess the impact of difficult-to-control RA on each comorbidity. However, we provide prevalence data in a large, real-world sample of RA patients, including the difficult-to-control population. This study was based on physician-reported data from routine RA care, in which particular assessments (e.g., DAS28) were missing from records, were not performed, or not completed in queries. Figure 1 describes the inclusion of patient records due to available data and definition criteria. It should be outlined that physician investigations may be limited to an extent by time and financial constraints of public healthcare. Importantly, we have to consider whether several conditions may have been underreported or remain undiagnosed. In COMORA, depression was the most frequently observed comorbidity with an inter-country variability between 2 to 33%. The authors suggested, that at least in part, varying definitions may account for these differences. However, this does not explain our observed prevalence of 0.6% and necessitates further, rigorous study over this potential area of unmet need. Similarly, COPD prevalence of 0.72% is surprising, especially that no cases were observed in low disease activity group. There were however countries with extremely low prevalence of COPD in COMORA study such as 0% in Taiwan and 1% in Japan, Korea, and Morocco. Fibromyalgia and inflammatory flares may constitute another important factor, which is rarely accounted for in studies. Previous works have also suggested that disease

activity measures can be skewed by co-existing fibromyalgia and osteoarthritis [20]. Although our investigation did not comprise the former, osteoarthritis was reported and did not differ significantly across RA control groups. Our study cannot overcome potential underreporting; however, it serves as the first Polish benchmark, which will allow further studies to re-examine these findings and evaluate interventions. We also have to consider that conventional diagnostic instruments utilized in practice may not be sufficiently sensitive, as in the case of radiographs and high resolution computed tomography [21]. Rheumatologists may also be concerned about the adversity of medication profiles, such as methotrexate [22]. Our key message is that comorbidities should be increasing acknowledged in RA, particularly in the difficult-to-control populations.

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Compliance with ethical standards

Disclosures None.

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