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Comorbidities of rheumatoid arthritis: A cross-sectional retrospective study

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ABSTRACT

Objective. Understanding comorbidities of rheumatoid arthritis (RA) and their burden definitely redefines the holistic approach of RA in daily practice. This study aimed to explore a range of comorbidities in patients with RA and to analyze their involvement in the choice of individualized treatment in real-life to achieve better disease outcomes.

Material and method. A retrospective cross-sectional observational study in a cohort of 201 consecutive adult RA (diagnosed by either ACR 1987 or EULAR/ACR 2010 criteria) examining the association between comorbidities and different drug prescriptions for RA.

Results. Comorbidities were recognized in 90% of patients; top five associated disorders were hypertension (n=106; 52.72%), osteoporosis (n=73; 36.32%), dyslipidemia (n=58; 28.86%), interstitial lung disease (n=43; 21.39%), chronic kidney disease (n=35; 17.41%). Antimalarials were the most commonly prescribed drugs (n=84; 41.79%) followed by methotrexate (n=76; 36.81%) and biologics (n=63; 31.34%) with a comparable distribution between TNF inhibitors (n=27; 13.43%) and anti-IL-6 drugs (n=28; 13.93); only 13 cases (6.47%) received tsDMARDs. 16% patients with concomitant hypertension, 11% with diabetes, 15% with osteoporosis and 15.52% with dyslipidemia received intermittent low doses of glucocorticoids. Reported in 24 cases (11.94%), hepatitis B and C significantly affect the use of medication, including bDMARDs (only 4 cases on etanercept given together with antivirals), while RA with interstitial lung disease received biologics in one third of cases.

Conclusion. Exploring RA journey from the perspective of comorbidities in real-life underpins management challenges related to associated conditions as comorbidities of RA patients may impact treatment regimens of RA and/or the prescribed drugs may worsen associated disorders.

Keywords: rheumatoid arthritis, comorbidities, cardiovascular disease, infections, biological therapy

INTRODUCTION

Among the most common rheumatological diseases, rheumatoid arthritis (RA) is an autoimmune condition characterized by chronic systemic inflammation, persistent synovitis as well as structural joint damage. It is a complex multifactorial syndrome with significant clinical (articular and systemic manifestations), evolutive (very early, early, definite and established RA), pathobiological (seropositive versus seronegative RA subtypes) and therapeutic (synthetic conventional, targeted and biological anti-rheumatic drugs) heterogeneity [1-5]. Recent advances in understanding the complex pathobiological RA pathways have resulted in better diagnostic criteria, improved serological testing (anti-cyclic citrullinated peptide antibodies), newer drugs, and better guidelines and recommendations to manage patients with RA. Current strategies include early aggressive treatment with one or more conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) and/or biologic and targeted DMARDs, in addition to symptomatic therapy with NSAIDs, low-dose prednisone bridging, physical therapy, occupational therapy, rest and patient education [6,7].

Comorbidities in RA patients remain a challenging topic as recent data underpin the role of increasing knowledge about a variety of disorders associated with RA and their place in the RA management.

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Overall, comorbidities may precede or may accompany a disorder, or may be caused by the therapeutic armamentarium used to control a specific disease. Concomitant disorders are frequently seen in patients with RA as long-term systemic inflammation and immune dysregulation underlying the disease may promote comorbidity and/or medications used to treat the disease may also be associated with various comorbidities and related-complications [3, 8].

Several real-world studies have already emphasized a higher prevalence of comorbidities in patients with RA than in those without RA and general population, advancing the burden of comorbidities in such patient population. Comorbidities in RA are often associated with poor health outcomes and increased mortality [2,3,6], while multimorbidities may affect disease activity as well as treatment efficacy [8]. Besides, there is a direct association between the number of co-occurring disorders in patients with RA and the lower likelihood of reaching treatment targets as patients with more comorbidities strive to comply with treat-to-target strategies and achieve anticipated target [2,3,6].

Several comorbidities of RA require particular attention due to their particularly devastating effects [9]. For many of them, such as hypertension, cardiovascular disease, chronic pulmonary disease, and upper gastrointestinal disease, arthritis and its treatment may also represent a risk factor [10].

Therefore, it is important to understand that exploring RA's journey from the perspective of comorbidities accounts for the better application of evidence-based data on comorbidities and their consequencse on more holistically and personalized care in these patients.

This study aimed to explore a range of comorbidities in patients with rheumatoid arthritis and to analyze their involvement in the choice of individualized treatment in real-life to achieve better disease outcomes

MATERIALS AND METHODS

We conducted a cross-sectional observational study of 201 consecutive adult RA patients (diagnosed by either the ACR 1987 criteria or EULAR/ACR 2010 criteria) who attended at least once an academic outpatient department in North-East Romania (Rheumatology 2 Clinic, Clinical Rehabilitation Hospital in Iasi) between January and June 2021.

We performed a systematic retrospective analysis of patient's files focusing on (i) demographic characteristics; (ii) RA-related variables such as disease duration, serology for rheumatoid factor (RF) and anti-cyclic citrullinated antibodies (ACPA), tender and swollen joints count on 28-evaluable joints, inflammatory parameters (erythrocyte sedimentation rate ESR and C reactive protein, CRP level) and disease activity score based on CRP (DAS28-CRP); as well as (iii) comorbidities according to a standardized protocol. We were interested in collecting data about key associated medical conditions diagnosed by a physician including cardiovascular disease and cardiovascular risk factors (hypertension, dyslipidemia, diabetes, stroke, myocardial infarction or angina, pericarditis), malignancies, respiratory conditions (interstitial lung disease, asthma, chronic pulmonary obstructive disorder), chronic kidney disease, infections (hepatitis B and C, tuberculosis), metabolic conditions (thyroid disease, osteoporosis) and depression.

We also recorded data about disease-modifying anti-rheumatic drugs (DMARDs) regimens (synthetic, targeted and biologic DMARDs) prescribed by rheumatologists to control disease.

The frequency of different comorbidities and the association between comorbidity and DMARRDs prescriptions was statistically analyzed using the Microsoft Excel; p-values were two-sided and $p< 0.05$ was considered statistically significant.

RESULTS

Demographics and RA-related parameters

The demographic profile of patients with RA is shown in Table 1.

TABLE 1. Characteristics of RA patients

Variable	Frequency n (%)
Age, years	60.69
Gender men: women	1:3.2
Women	154 (76.62%)
Seropositive RA	147 (73.13%)
Rheumatoid factor	138 (68.66%)
ACPA*	63 (31.34%)
Duration of disease, years	
0-5	47 (23.38%)
6-10	60 (29.85%)
11-15	41 (20.4%)
16-20	22 (10.95%)
>20	31 (15.42%)

**Abbreviation: ACPA, anti-cyclic citrullinated peptide antibodies*

As expected, the frequency of RA was higher in women (76.62% vs. 23.35%); 47 patients (23.38%) had a disease duration under 5 years, 60 cases (29.85%) of 6 to 10 years, 41 cases (20.4%) between 10 and 15 years, 22 patients (10.95%) between 16 and 20 years, while 31 patients (15.42%) were diagnosed with RA for more than 20 years.

147 patients (73.13%) were seropositive: rheumatoid factor was detected in 138 RA (68.66%), while anti-cyclic citrullinated peptide antibodies known as disease biomarkers in 63 (31.34%) cases. Studied patients had all spectrum of disease activity (low, moderate and high disease activity); the average DAS28-CRP was 4.5, classifying RA as moderate disease activity despite medications.

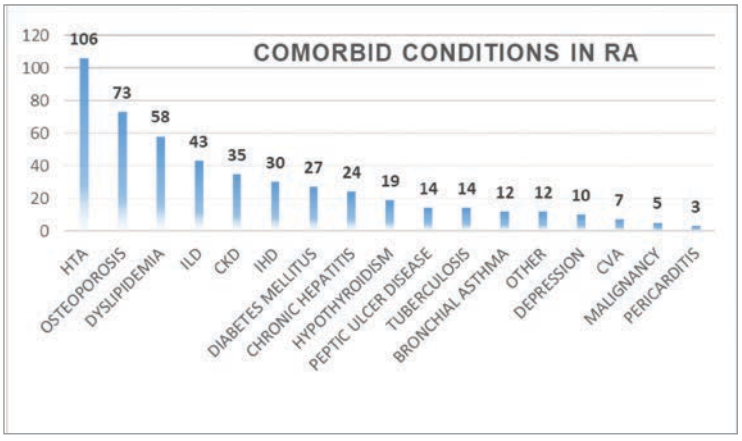

FIGURE 1. Prevalence of comorbidities in our RA cohort
Abbreviations: HTA, arterial hypertension; ILD, interstitial lung disease; CKD, chronic kidney disease; CVA, stroke

Comorbidities in RA

Up to 90% (180 cases) presented with at least one comorbid condition.

Top five comorbidities were hypertension which was diagnosed in n=106 cases (52.72%), osteoporosis in n=73 cases (36.32%), dyslipidemia in n=58 (28.86%), interstitial lung disease (ILD) in n=43 (21.39%) and chronic kidney disease (CKD) in n=35 patients (17.41%). We also reported ischemic heart disease (IHD) in n=30 RA patients (14.93%), diabetes mellitus (DM) in n=27 (13.43%), chronic hepatitis in n=24 (11.94%), hypothyroidism in n=19 (9.45%), peptic ulcer in n=14 (6.97%), latent tuberculosis (ILTB) in n=14 (6.97%), asthma in n=12 (6.97%), depression in n=10 RA (4.98%), stroke in n=7 (3.48%), malignancy in n=5 (2.49%), and pericarditis in n= 3 (1.48%) cases.

Comorbidities in RA patients are shown in Table 2 and Figure 1.

TABLE 2. Comorbidities in studied RA patients

Comorbidity	Number of patients (%)
Arterial hypertension	106 (52.72%)
Osteoporosis	73 (36.32%)
Dyslipidemia	58 (28.86%)
Interstitial lung disease	43 (21.39%)
Chronic kidney disease	35 (17.41%)
IHD*	30 (14.93%)
DM*	27 (13.43%
Chronic Hepatitis	24 (11.94%)
Hypothyroidism	19 (9.45%)
Peptic Ulcer Disease	14(6.97%)
Latent tuberculosis	14 (6.97%)
Bronchial asthma	12 (6.97%)
Depression	10 (4.98%)
Stroke	7 (3.48%)
Malignancy	5 (2.49%
Pericarditis	3 (1.48%

**Abbreviation: IHD, Ischaemic Heart Disease; DM, Diabetes mellitus*

Overall, in bi- and multivariate analysis, the presence of comorbidities was associated with a longer disease history ($p<0.05$) and positive serology for RF and/or ACPA ($p<0.05$).

RA-drug prescription

Usually, the presence of comorbidities guides the choice of medication in RA patients. In our cohort, 171 patients (85.08%) received at least one conventional synthetic drug (csDMARDs) as follows: the most commonly used was hydroxychloroquine given in n=84 RA (41.79%) and methotrexate (76; 36.81%). 55 patients (27.26%) were taken leflunomide and 14 (6.97%) sulfasalazine. About one-third (n=63; 31.34%) were under biologic agents with a balanced distribution between TNF inhibitors (n=27 patients) and anti-IL-16 drugs (n=28 patients). Only n=13 RA patients (6.47%) were taking tsDMARDs (3.48% baricitinib and 2.99% tofacitinib). Although extensively recommended in RA, glucocorticoids were not commonly given in our cohort (n=34; 16.92%); only 6 patients were under chronic administration of small doses (<7.5 mg daily) oral prednisone.

The pattern of drug prescription in RA with comorbid conditions is shown in Table 3.

42.2% patients with hypothyroidism received biological therapy and those with RA and concomitant interstitial lung disease were suitable for bDMARDs in one-third of cases. Hepatitis B was demonstrated in n=13 cases (6.47%) and hepatitis C in n=11 patients (5.47%); both types of hepatitis significantly affect the use of medication, including bDMARDs; we reported 4 cases with RA and B hepatitis treated with etanercept and concomitant antivirals.

DISCUSSION

We examined the comorbidities of patients diagnosed with RA using a local cohort of 201 consecutive patients followed-up in our rheumatology de-

TABLE 3. Pattern of DMARDs prescription in RA with comorbidities

Comorbid disease	Number of patients	Prescription of drug in patients with specific comorbid conditions Medication, n (%)						
		Methotrexate	Hydroxychloroquine	Leflunomide	Sulfasalazine	bDMARDs	tsDMARDs	GCS
Hypertension	106	39 (36.79)	48(45.28)	31(29.25)	8(7.55)	35(33.02)	6(5.66)	17(16.04)
Osteoporosis	73	22 (30.14)	34(46.58)	19(26.03)	5(6.85)	29(39.73)	3(4.11)	11(15.07)
Dyslipidemia	58	15 (25.86)	22(37.93)	17(29.31)	2(3.45)	13(22.41)	3(5.17)	9(15.52)
ILD*	43	14 (34.88)	10(23.26)	11(25.58)	4(9.3)	16(37.21)	4(9.3)	7(16.28)
CKD*	35	9 (25.71)	13(37.14)	9(25.71)	3(8.57)	13(37.14)	1(2.86)	7(20)
IHD*	30	12 (40)	8(26.67)	4(13.33)	5(16.67)	8(26.67)	2(6.67)	2(6.67)
Diabetes mellitus	27	11 (40.74)	11(40.74)	5(18.52)	2(7.41)	5(18.52)	4(14.81)	3(11.11)
Chronic hepatitis	24	10(41.67)	11(45.83)	6(25)	1(4.17)	8(33.33)	0	4(16.67)
Hypothyroidism	19	6(31.58)	7(36.84)	5(26.32)	1(5.26)	8(42.11)	1(5.26)	2(10.53)
Peptic ulcer disease	14	4(28.57	7(50)	5(35.71)	1(7.14)	3(21.43)	1(7.14)	4(28.57)

**Abbreviation:ILD, Interstitial Lung Disease; CKD, Chronic Kidney Disease; IHD, Ischaemic Heart Disease*

partment and we explored how do concomitant disorders affect the choice of RA treatment. The most frequently (top five) associated conditions in our study included hypertension (52.72%), osteoporosis (36.32%), dyslipidemia (28.86%), interstitial lung disease (21.39%) and chronic kidney disease (17.41%), data that partly correspond with earlier national or international cross-sectional studies, including COMORA.

According to Center for Disease Control and Prevention (CDC), the term *comorbidity*, *co-existing* or *co-occurring* condition is generally used to define the presence of one or more chronic diseases in addition to a primary disease, while *multimorbidity* is designed to describe multiple disorders simultaneously occurring in the same individual [1-6].

Coexisting diseases can be classified according to the classification scheme of comorbidities, the so-called *"three Cs"*, from *Causality, Complications and Coincidence*: *causality* comorbidities are the result of the disease and, apparently, pathophysiologically linked based on inflammatory process (leading to cardiovascular disease), physical effects or mental health issues related to coping with the disease, while *complications* result from medication used to treat the disease aiming to amend pain and inflammation while delaying structural damage, but that can result in severe complications and, even, organ disease [1-6].

Associations between RA and other diseases have been assumed and continue to be refined as our RA knowledge about pathogenesis and genetic basis is still evolving [9]. Up to 67% of RA patients have one or more comorbid conditions contributing to poor health outcomes, excess of disability, morbidity and, even, mortality. Key comorbidities are cardiovascular gastrointestinal, respiratory and renal disorders, but also infections, osteoporosis, mood disorders and cancers may occur [16]. Significant data is provided by the COMORA study, an international population-based COMOrbidities in RA evaluating the prevalence of comorbidities in a large cohort of multinational, multi-country patients (3,920 RA, 17 countries); the most common comorbidities were depression (15%), asthma (7%), cardiovascular events (6%), solid-organ malignancies (5%) and chronic obstructive pulmonary disease (4%) [3], while an increased risk for mortality in RA was increased by simultaneous cardiovascular disease, infections and cancers [3].

We reported a very high prevalence of comorbidities in our RA cohort, irrespective of the RA clinical settings (early-onset or established disease, seropositive or seronegative-disease, csDMARDs-resistant or failure to bDMARDs RA); up to 90% of patients presented with more than one comorbid condition, particularly cardiovascular disease (arterial hypertension), metabolic (diabetes, dyslipidemia, osteoporosis), respiratory conditions, infections (viral B and C hepatitis, bacterial infections - TB), gastroduodenal disease (peptic ulcer), psychiatric diseases (depression), and cancers. The prevalence of RA comorbidities and multimorbidity was higher in our study as compared to literature [3,11]; several factors driving these discrepancies are potentially related to a particular lower income and/or lower educational experience that have affected referral to the healthcare providers; another valid explanation would be the presence of a specific genetic background allowing co-existing chronic disorders. However, we

do not have a non-RA control group to explore the prevalence of various types of comorbidities in general population.

Only two predictors were associated with the presence of comorbidities in our cohort: longer disease evolution and positive RF serology and/or ACPA, in accordance with data described in other studies [1-6]; it seems that there was no significant influence of age, gender, disease activity, systemic inflammation, structural damage, duration and type of anti-rheumatic medication on comorbidity background in our cohort.

A closer look to different categories of comorbidities highlighted several characteristics related to the studied RA population.

Cardiovascular disease (CVD) is a major comorbidity affecting patients with RA and a leading cause of morbidity and mortality in this population [3]; *cardiovascular risk* is related to both traditional (high incidence smoking, hypertension, hyperlipidemia and diabetes) and RA-specific factors such as chronic persistent (local and systemic) inflammation driving early atherosclerosis, but also medication (mainly steroid use) [14]. The CARRE study (CARdiovascular research and RhEumatoid arthritis) showed that patients with RA had a high risk of CV events, almost double compared to the general population [3]; furthermore, even patients with early disease had a 33% higher CVD risk than matched controls without RA [3]. In the current study, patients with RA had an increased prevalence of cardiovascular disease and risk factors (hypertension 52.72%, ischemic heart disease 14.93%, hyperlipidemia 28.86%). The presence of CV disease may impact RA management and outcomes; thus, Choi et al. showed that methotrexate reduced overall mortality by 60% and cardiovascular mortality by 70% in their study of 18 years of follow-up in 1,240 RA patients [13]. In our study, methotrexate was prescribed in more than one third of patients (36.79%) with RA and hypertension, but also in up to 40% of those with concomitant with ischaemic heart disease, being the most common prescribed drug in our RA patients with CV comorbidities. On the other hand, the presence of CV disease significantly limited the use of glucocorticoids [15]; only 16 % with HTA received low doses of GC.

Osteoporosis can be found in 30–50% of patients with RA, depending on age and sex, with prevalence and fracture risk both increasing with disease duration and seropositivity [21]. RA disease activity has been shown to negatively affect bone mineral density (BMD): disease remission is associated with preservation of BMD, whereas even low to moderately active disease is associated with higher structural damage and lower hip BMD [12]. Although csDMARDS and biologics have not been credibly related with bone loss and increased fracture risk, over and above the risk related to RA itself [17,18], both oral and parenteral glucocorticoids have been clearly shown to rapidly increase fracture risk in these patients. The relationship seems constant as there is no safe lower dose of corticosteroids below which fracture risk is not increased [19]. Furthermore, the risk of osteoporosis is multiplied by 2 in RA due to disease itself and prolonged use of glucocorticoids. Interesting, in our cohort, osteoporosis was reported in about one third of patients (73 cases; 36.32%) being classified as the second comorbidity in a top 10 co-occurring disorders in RA; only 15% patients with osteoporosis received glucocorticoids.

Interstitial lung disease. The most common extra-articular manifestation of RA remains lung involvement, which can develop in up to 60% cases during the disease course [21]; the treatment of RA-ILD complication can be significantly challenging [21]. In addition, most of DMARDs used in RA are potentially at risk to develop or enhance ILD. In our cohort, ILD was found in only one out of five cases (21.39%); 34.88% of patients with ILD in our cohort received MTX. Similar to MTX, controversy exists for both TNF inhibitors and rituximab in the treatment of ILD, with some studies showing improvement and others demonstrating development or progression of ILD [21]. Up to one third of patients with ILD in our study were suitable for treatment with bDMARDs.

Thyroid abnormalities in RA patients should be taken in account by clinicians due to potential overlap between the symptoms of RA and thyroid diseases. Thyroid dysfunction and/or autoimmune thyroid disease were detected in one third patients with RA, which can be due to the natural feature of autoimmune disease and their tendency to overlap [24]. It seems that anti-TNF-a treatment may improve thyroid function in hypothyroid patients with RA since proinflammatory cytokines may play a pathogenic role in thyroid dysfunction [24]. In our cohort, 9.45% patients associated hypothyroidism; biologic therapy was prescribed in about half of patients with RA and hypothyroidism in our study.

Although kidney issues during RA may be related to secondary renal amyloidosis, glomerulonephritis and nephrotoxic effects of antirheumatic medication, *renal dysfunction* in RA is commonly related to age and hypertension [26]. In our study, more than half of those patients with RA and comorbid chronic kidney disease have also hypertension. Indeed, specific RA-medication may further accentuate renal impairment and in advance stages synthetic DMARDs and specific targeted synthetic drugs (e.g. baricitinib) require dose adaptation or even discontinuation; however, different biologic agents are known to improve RA-related renal amyloidosis

and most of them are not contraindicated in advanced CKD and, even, in dialyzed RA patients [26].

The prevalence of depression is significantly higher in RA patients as compared to general population; a number of factors are associated with increased risk of depression including RA-specific factors such as patients reported outcomes including level of pain, fatigue, disability, but also disease activity [3]. In addition, inconsistent associations have been found between pro-inflammatory cytokines such as TNF and depression in RA [27]. In our study, 4.98% patients were diagnosed with concomitant depression.

Among comorbidities as a result of medication, *glucocorticoid-induced diabetes* was described in 11% of our patients who received concomitant low doses of GC. Moreover, several studies have emphasized the influence of various biologic agents, particularly old TNF inhibitors (infliximab, adalimumab and etanercept) as well as tocilizumab on insulin sensitivity in patients with RA [20]. In our study 18.52% patients with diabetes were under biological agents.

Infections are a leading cause of morbidity and mortality in RA; the increased risk for infections has been attributed to the impact of inflammatory process and immune dysregulation underlying RA, immunocompromising comorbid conditions, as well as the use of treatment regimens with GCs and DMARDs (immunosuppressive, biologics, targeted synthetic) therapy [3]. Besides, reactivation of latent infections under biologics may account also for increased infectious risk of RA patients; for example, reactivation of a latent tuberculosis infection (LTBI) is a major concern of TNF inhibitors, and screening for latent and active TB is recommended before initiating treatment and, if negative, on an annually basis thereafter, during the treatment [22].

Up to 7% of patients in our study were diagnosed with ILTB before initiation of biologic therapy and 3 patients had a reactivation of tuberculosis under TNF inhibitors (one for of etanercept, certolizumab and adalimumab).

Immunosuppressive drugs were shown to induce viral reactivation in B and C-hepatis positive patients, and in most instances, flares are asymptomatic [23]. In our cohort, 11.94% patients had chronic hepatitis (5.47% Hepatitis B and 6.47% Hepatitis C) and among them, 4 patients were treated with etanercept. In patients with positive anti-HBs antibodies and positive anti-Hb core antibodies, no further action is required and such patients with RA and naturally immunized B hepatitis may benefit from biologic agents if active rheumatic disease; however, patients with latent infection (hepatitis B core antibody positive and negative hepatitis B surface antigen antibodies) require close monitoring and concomitant antiviral therapy started one month before biologics and continued up to 6 or 12 months after bDMARDs discontinuation.

Despite evidence supporting the increased susceptibility of patients with RA, infections are still underestimated (prevented, screened, managed) [3].

*NSAID ulcers a*ssociated with RA are not as common as they were before the advent of DMARDs and the changing paradigm in treating RA. NSAIDs are clearly recommended as "adjuvant", "transition" therapy, to enhance the control of pain either early in the disease evolution, or related to flares; their administration should be shortened, discontinued, or switched to on-demand use as rapidly as the cs-/ b-/ ts- antirheumatic drugs result in controlling patient reported outcomes including joint pain [25]. In our study, only 6.97% patients had NSAIDs-induced ulcer.

Our study has several strengths, but also limitations. Although quite a lot of studies addressing the burden of comorbidities in RA have already been published, the majority included mainly western populations; as per our knowledge, this is the first analysis of comorbidities in a real-life cohort of adult-RA patients in north-east Romanian population. Like many other studies, our data also lack a comparator group without RA. Moreover, the causality comorbidities could not be explored due to the cross-sectional design of our study, meaning that our patients were examined at only on time-point and not during a period of time.

CONCLUSION

Overall, we assume that comorbidities among RA patients are a part of the holistic management of RA, prompt the debate around personalized therapy and may impact the disease trajectory during synthetic, biological and targeted treatment. Furthermore, the clinical interest in understanding disease-related, disease-complication, treatment-related comorbidities of RA is, undoubtedly, amplified by findings from real-life practice.

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