Severity of disease and frequency of predisposing factors in patients with rheumatoid arthritis in southern Albania

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Abstract

Aim: We aimed to assess the severity of disease in patients with rheumatoid arthritis (RA) and to investigate the association of various risk factors for rheumatic diseases with the RA severity.
Methods: This is an observational study that included 194 patients with RA living in the southern Albania during the years 1995-2011. The data collection was achieved in two phases: the retrospective phase (years 1995-2009) and the prospective phase (years 2010-2011). The main study endpoint was RA disability.
Results: During 1995-2011, 194 patients with RA were identified. Eighty-nine patients were in RA stages III or IV and more than 1/3 of patients (n=69) had disabilities: three in stage II, 57 in stage III and nine in stage IV. Variables that showed a significant association with disability were age at the onset of disease, duration of disease, stages, male gender, occupation, smoking and alcohol consumption. Age at the onset of disease, disease duration, disability, alcohol and familial history showed a significant association with the RA stages. In the multivariate analysis, male gender, delay in diagnosis, occupation, age and RA stages were independently associated with disability, whereas alcohol consumption, age and age at the onset of disease were independently associated with the advanced RA stages.
Conclusion: This study shows that nearly half of the patients with RA in the southern Albania are in the RA stages III and IV and 35.6% of them have disabilities. A series of predisposing factors for rheumatic diseases were independently associated with the RA severity.

Keywords: disability, disease stages, rheumatoid arthritis, risk factors.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by joint swelling, joint tenderness and destruction of synovial joints, leading to severe disability and premature mortality (1). RA affects all aspects of quality of life in both sexes and across all age groups (2). The influence of RA in patients can be assessed according to the International Classification Functioning Disability and Health (ICF) criteria (3). RA affects approximately 1% of the population and although its prevalence increases with age, the peak age at the onset of the disease is still well within the working age (4,5). Consequently, work disability is a common outcome of RA. Nearly one third of RA patients leave the workforce within 2-3 years after the disease onset (6). Almost 20% to 70% of people affected by RA become disabled for work after 7-10 years (7). Factors directly associated with RA, such as rheumatoid factor, disease duration, functional/ structural disorders, environmental (type of work) or personal factors (i.e. age, sex, educational level, and more) are possible predictive factors for work disability. The effect of these factors on RA severity in the region of Gjirokaster, as well as in our country, has not been studied. The objective of this study was two-fold: first to assess the severity of disease in patients with RA, and second, to investigate the association of various risk factors for rheumatic diseases with the RA severity in these patients.

Methods

Type of study

This is an observational study that analysed the clinical and demographic characteristics of patients with RA, focusing on the effect of various factors on the course and severity of the disease. The collection of data was achieved in two phases: the retrospective phase which included patients with RA between the years 1995 until 2009 and the prospective phase, which included prospective collection of the data (RA cases) during the years 2010 and 2011. The endpoints of this study were disability and stages of the disease.

Inclusion criteria

The study included patients with RA diagnosed before the year 1995 or during the 1995-2011 years, living in southern Albania (the region of Gjirokaster). This region includes three districts (Gjirokaster, Permet and Tepelene). It has an area of 2884 km^2 and a population of 102549 inhabitants and 57.7% of the population live in rural area (National Institute of Statistics, 2010).

Patients were diagnosed in the Rheumatology Service, Regional Hospital of Gjirokaster and all cases were confirmed in the Rheumatology Service, University Hospital Centre in Tirana (n=145) or in centres for rheumatologic diseases abroad (n=49). The diagnosis of RA was based on the American College of Rheumatology 1987 criteria (8); in the last two years, the diagnosis was based on the classifying criteria of the American College of Rheumatology and European League Against Rheumatism 2010 (ACR/EULAR) (9). The data were obtained from the documentation of the polyclinic of Gjirokaster, hospital of Gjirokaster, regional medical committee for work disability (KEMP), health centres and family practitioners, as well as the University Hospital Centre in Tirana.

Data collection and definitions

For all the identified patients, the following data were collected: general information (name, gender, birthday); demographic data (place of birth, residence defined as urban or rural area); data on the history of the disease (year of onset, year of diagnosis and the institution that made the diagnosis); data on the risk factors (relatives with the disease, smoking, alcohol consumption, education, profession) and data on the duration of the disease, delay in diagnosis, stage(s) of the disease and disability. The professions were grouped into two groups: physical work (worker, miner, farmer, technician, etc.) and non-physical

work (pupil, student, teacher, economist, etc.). According to the level of education, patients were divided in three groups: low education (8 years), high school education (8-12 years), and higher education (>12 years). Family history, smoking and alcohol consumption were studied only qualitatively due to limited numbers of patients.

The severity of disease was assessed using the functional stage(s) and disability for work of the patient. The RA stages were assessed using the classification of global functional status of the American College of Rheumatology 1991 criteria (10). According to this classification, patients were classified into four functional stages, based in their ability of self-care and non-professional activity. Thus, patients who are able to perform the usual everyday activities (self-care, professional, non-professional activities) are classified as belonging to the stage I. Those who perform usual self-care and professional activities, but are limited in non-professional activities belong to the stage II. Patients who perform usual self-care activities but are limited in professional and non-professional activities are classified as belonging to the stage III, and patients who have limited abilities to perform usual self-care, professional and non-professional activities are classified as belonging to the stage IV.

Disability is defined based on the medical criteria for the ability to work of 1991 and 2010 (11). According to these criteria, preserved mobility, but with pain is not considered as disability (stage I); reduced mobility but without biological activity of the disease is considered as group IV of disability. These patients have the ability to work part time (stage II, IIIa). Limited mobility plus biological activity of the disease is considered as group II of disability. Disability for work includes stages IIIb, IV.

Statistical analysis

Continuous variables are presented as means ± standard deviations in case they had a normal distribution, or as medians with 25th and 75th percentiles in case they had a skewed distribution. The normality of the distribution of the continuous data was assessed with the Kolmogorov-Smirnov test. The comparison of the data with normal distribution was done with the t-test (for two independent groups). Data with skewed distribution were analysed using the Mann-Whitney U test. Categorical variables (proportions) are presented as absolute numbers and percentages and are compared with the chi-square test or Fisher's exact test, when appropriate. The association between risk factors and clinical variables with the disability or stages of the disease was analysed using the multiple logistic regression model. All analyses were performed using the SPSS statistical package (version 15). A two-sided p-value of ≤ 0.05 was considered as statistically significant.

Results

The study included 194 patients with RA living in the region of Gjirokaster between the years 1995 and 2011. Most of the patients were females (n=154) and the female-to-male ratio was 4:1. Patients were in four RA stages: stage I (9.8%), stage II (44.3%), stage III (41.2%) and stage IV (4.6% of the patients). More than one third of the patients (n=69; 35.6%) had disabilities: three patients in stage II, 57 patients in stage III and nine patients in stage IV. Parameters were evaluated according to the disability and stages of the disease.

Data according to disability

The data according to disability are shown in Table 1. As seen in Table 1, patients were found to be in all four stages of the disease. The majority of the patients are in stage III (82.6%) and all patients in stage IV were disabled. As a matter of fact, stage IV patients (n=9) comprise 13% of all cases with disability. Mean age of individuals with disability was 55.8±10.6, which appears to differ little from the age of patients without disability (56.8±12.7 years; Table 1).

Table 1. Demographic data according to disability

Variables	Disability (n=69)	No disability (n=125)	P
Age in 2011 (years)	55.8±10.6	56.8±12.7	0.629
Age at the RA onset (years)	40.2±9.7	46.3±12.5	0.001
Duration of RA (years)	15.4±10.8	10.6±8.6	0.001
Disability years (years)*	6.0 [2.5; 16]	0.0 [0.0;0.0]	<0.001
Delay in diagnosis (years)	1.6±1.4	1.9±2.2	0.200
Gender			0.032
Females	49 (71.0%)	105 (84.0%)	
Males	20 (29.0%)	20 (16.0%)	
Residence			0.868
Village	24 (35.0%)	42 (33.6%)	
City	45 (65.0%)	83 (66.4%)	
Education			0.568
Low	40 (58.0%)	74 (59.2%)	
High-school	25 (36.2%)	39 (31.2%)	
High education	4 (5.8%)	12 (9.6%)	
Occupation			0.005
Physicalwork	60 (87.0%)	86 (69.0%)	
Non-physical work	9 (13.0%)	39 (31.0%)	
Smoking	18 (26.0%)	15 (13.6%)	0.012
Alcohol	8 (11.6%)	2 (1.6%)	0.003
Familial history	16 (23.2%)	16 (12.8%)	0.062
Stage			<0.001
I	0 (0.0%)	19 (15.2%)	
II	3 (4.4%)	83 (66.4%)	
III	57 (82.6%)	23 (18.4%)	
IV	9 (13.0%)	0 (0.0%)	

Data are means± standard deviations, medians [25th and 75th percentiles], or numbers of the patients (%).

* Disability years have non-Gaussian distribution therefore are presented as median with 25th and 75th percentiles and are compared with the Mann-Whitney test.

People with disability have a younger age at the RA onset compared to non-invalids (40.2±9.7 versus 46.3±12.5 years; P=0.001). Duration of the disease was longer in people with disability compared to those without disability (15.4±10.8 years versus 10.6±8.6 years; P=0.001). Moreover, individuals with disabilities had more years with disease than those without disabilities (9.6±9.1 years versus 1.3±3.6; P<0.001).

According to the gender, 20 males (50.0%) and 49 females (32.0%) had disabilities (odds ratio [OR]=2.14, 95% confidence interval [CI] 1.06-4.30; P=0.032), showing that males with RA had more than two times higher odds to become disabled compared to females.

Individuals with disabilities practiced professions that are considered as physical work more often than those without disabilities (87% versus 69%; OR=3.02 [1.36-6.70]; P=0.005). Thus, the odds for an association with disability were three times higher for professions qualified as physical work compared to professions qualified as non-physical works.

Smoking was also associated with disability. Thus, 18 out of 69 invalids smoked compared to 15 of 125 non-invalids (OR=2.58, [1.20-5.50]; P=0.012). From these data patients with RA who smoked were at a 2.6 times higher odds to be associated with disability than patients with RA that did not smoke.

Alcohol consumption was more frequent among invalids than among non-invalids (11.6% versus 1.6%; OR=8.06, [1.52-56.84]; P=0.0026). Based on these data, invalids had more than 8 times higher odds to consume alcohol than non-invalids. With regard to the familial history, 23.2% of invalids and 12.8% of non-invalids had relatives diagnosed with muscle-skeletal diseases, showing a strong trend for an association between familial history for muscle-skeletal disease and disability (P=0.062). On the other hand, education and residence (living in a city or in a village) appeared to differ little among invalids and non-invalids (Table 1).

Thus, based on the univariate analysis, parameters associated with disability were: age at the onset of the disease, disease duration, stages of the disease, male gender, occupation (physical work), smoking and alcohol consumption. The association between familial history and disability remained at the threshold of statistical significance.

Data according to RA stages

Patients' data according to the RA functional stage are shown in Table 2. There was no difference according to gender between different stages. In the first two stages only 2.8 % of the patients were invalids, whereas in the stages III+IV invalids comprised 78% of the patients (P<0.001). There were no significant differences regarding the actual age (P=0.325). Patients in stages III and IV had a younger age at the onset of disease than patients in early RA stages (P=0.018). Patients in the stages III and IV of RA had a longer duration of the disease compared to the patients of the other two stages (15.3±10.6 years versus 9.8±8.2 years; P<0.001). Patients in stage I+II had a mean 0.2±2.1 disability

Table 2. Demographic data according to RA stages

Variable	Stage I+II (n =105)	Stage III+IV (n = 89)	P
Age in 2011 (years)	55.7±12.7	57.5±11.1	0.325
Age at the RA onset (years)	46.0±12.4	41.9±11.0	0.018
Duration of RA (years)	9.8±8.2	15.3±10.6	<0.001
Disability years (years)*	0.0 [0.0; 0.0]	6.0 [2.0;11]	<0.001
Delay in diagnosis (years)	1.8±1.9	1.8±2.0	0.996
Gender (%)			0.345
Female	86 (81.9 %)	68 (76.4%)	
Male	19 (18.1%)	21 (23.6%)	
Residence			0.408
Village	33 (31.4%)	33 (37.0%)	
City	72 (68.6%)	56 (63.0%)	
Education			0.883
Low	60 (57.2%)	54 (60.1%)	
High school	36 (34.2%)	28 (32.0%)	
Higher education	9 (8.6%)	7 (7.9%)	
Occupation			0.5
Physicalwork	77 (87.0%)	69 (77.5%)	
Non-physicalwork	28 (13.0%)	20 (22.5%)	
Smoking	15 (14.3%)	18 (20.0%)	0.338
Alcohool	2 (1.9 %)	8 (9.0%)	0.046
Familial history	12 (11.4%)	20 (22.5%)	0.039
Disability	3 (2.8%)	66 (74.0%)	<0.001

Data are means± standard deviations, medians [25th and 75th percentiles], or numbers of the patients (%).

*Disability years have a non-Gaussian distribution therefore are presented as median with 25th and 75th percentiles and are compared with the Mann-Whitney test. The mean± standard deviation for this parameter was: 0.2±2.1 years (stage I+II) and 9.0±8.5 years (stages III+IV).

years compared to 9±8.5 years in patients of stages III and IV (P<0.001). Delay in diagnosis showed no significant difference according to RA stage (Table 2).

There were no significant differences among patients in various RA stages regarding the residence place, occupation or education. A statistically significant difference was observed with regard to familial history and alcohol consumption. Thus, a positive familial history was observed in 20 patients in the stages III+IV and in 12 patients in the stages I+II (OR=2.25 [1.03-4.90]; P=0.039). Thus, patients who had relatives diagnosed with muscle-skeletal diseases had a 2.3 times higher odds to develop advanced stages of RA compared to patients with no familial history for musculoskeletal diseases. The alcohol consumption had a positive association with the stages of disease (OR=5.09 [1.05-24.60]; P=0.046), showing that patients in the advanced stages of RA had a 5-time higher odds to consume alcohol compared to patients in the early stages of the disease.

Thus, based on the results of univariate analysis, age at the onset of the disease, disease duration, disability, alcohol and familial history showed a significant association with the RA stages.

The results of the multivariate analysis

The association of various factors (variables) with the two study end points (disability and RA stages) was assessed using the multiple logistic regression model. The Wald backward variable selection method was used. For the association with disability, the following variables were entered into the model: age, gender, residence, education, age at the onset of the disease, duration of the disease, delay in diagnosis, occupation, familial history, smoke, alcohol consumption and RA stages. The model identified gender (males), delay in the diagnosis, occupation (physical work), age and stages of the disease as independent correlates of disability. The beta coefficients and the probability of association are shown Table 3.

Table 3. Independent correlates of disability

Independent variables	Beta coefficients	P-value
Gender (males)	1.656	0.033
Delay in diagnosis	0.277	0.034
Occupation *(physical vs. non-physical work)*	1.490	0.015
Age 2011	0.064	0.01
Stages (4 stages)	5.461	<0.001

For the association with RA stages, variables entered into the model were: age, gender, education, residence, age at the onset of the disease, disease duration, delay in the diagnosis, occupation, familial history, smoking, and alcohol consumption. The dependent parameter (stage) was divided in two categories: category 1 (stage I + II) and category 2 (stage III+IV). This regrouping was done to compensate for the small numbers of the patients in individual RA stages. The model identified the following variables as independent correlates of RA stage: alcohol, age and age at the onset of the disease. The beta coefficients and the probability of association are shown in Table 4.

Table 4. Independent "predictors" of the RA stages

Independent variables	Beta coefficients	P value
Alcohol consumption	1.751	0.032
Age in 2011	0.560	0.002
Age at the RA onset	-0.062	0.001

Discussion

Disability is a common outcome of patients with RA. It has been reported that during the course of the disease up to 50% of the patients become invalids (after 20.9 years), mainly during the late course of the disease (12). Meanwhile, 30% of the patients with RA become disabled after five years of living with the disease (13). In our study, 69 patients (35.9%) showed various degrees of disability and their number increased up to 45.8% in advanced stages of the disease. The number of patients in the III and IV stage was higher than the number of invalids, because these patients had a late onset or a slower progression of the disease, which may have allowed them to reach the age of retirement. The influence of RA on the quality of life of the individual was assessed by estimating the years lived with disability (14). In our study, invalids had an average of 9.6±9.1 years of disability. Likewise, patients in stage III and IV had an average of 9.0±8.5 years of disability.

Younger age at the onset of the disease is a bad prognostic factor for some autoimmune diseases. However, for some other diseases including RA, data are contradictory (15). Our study showed that younger age at the onset of RA was associated with a higher frequency of disability. Although explanatory mechanisms for this association are not clear, we suppose that factors like more severe forms of RA in younger age, the longer duration of the disease or non-effective therapies at the time of RA diagnosis might offer some support for the observed findings.

A number of environmental and genetic factors influence the course of RA, and they may predict an unfavourable course of the disease. Thus, occupation (physical work) has an increased risk for disability (16). In our study we found a risk three times higher for an association between physical work and disability. A significant and independent association between occupation and disability was found in the univariate and multivariate analyses, which showed a strong influence of this factor. On the other hand, our study revealed that the association of physical work with the stages of the disease lost its significant association after adjustment in the multivariable analysis. Although, the factors that might have influenced the loss of this association are not clear, we suppose that these data can be explained by the presence, in the advanced RA stages, of a number of patients who have reached the retirement age.

Although RA is encountered more often in females than in males (in our study a 4:1 female/male ratio was found), males were at a two-time higher risk of disability than females. This independent and significant association of the male sex with disability was found also in the multivariate analysis. These data are supported by prior studies that have reported no consistent findings regarding disability in women (5).

RA is partially inheritable (17). The role of heredity in the bone destruction is evidenced in 45-58% of the patients (18). In our study, the genetic factors were associated with the propensity to develop advanced stages of the disease. However, these data were not supported by the results of the multivariate analysis, which did not substantiate a significant and independent association between familial history and the RA stages.

With regard to association between smoking and disability we found that invalids were at a 2.6-time higher risk of being smokers than non-invalids. These data are consistent with the data of prior studies, which found that smoking is an important risk factor that doubles the risk for RA (2). Alcohol is seen as a possible risk factor with a role in arthritis (19), but alcohol consumption has not been considered a great issue in patients with rheumatic disease (20). Our study found that alcohol consumption was increased in invalids and in patients of the III and IV stage. Although, the reasons behind this association remain unknown in the setting of present study, the alcohol use for analgesic purposes may not be ruled out. Nevertheless the causality in the relationship between alcohol consumption and disability remains unproven.

In conclusion, this study conducted in the region

of Gjirokaster during the time period between years 1995 and 2011 showed that more than a third of patients with RA had various degrees of disability and nearly half of them were in the advanced stages of the disease. Disability and advanced stages of RA were influenced by a number of demographic and environmental factors. Gender, delay in diagnosis, profession (physical work), age and stages of disease were independently associated with disability from RA whereas, age of the patients, age at the onset of disease and alcohol consumption were independently associated with advanced RA stages.

Conflicts of interest: None declared.

References

1. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108-11.
2. Uhlig T, Loge JH, Kristiansen IS, Kvien TK. Quantification of reduced health-related quality of life in patients with rheumatoid arthritis compared to the general population. J Rheumatol 2007;34:1241-7.
3. World Health Organization. International Classification of Functioning, Disability and Health (ICF). Geneva, 2011. www.who.int/ classifications/ icf. Accessed March 7, 2013.
4. Shanahan EM, Ahern M. Inflammatory arthritis and work disability: what is the role of occupational medicine? Occup Med 2008;58:2-4.
5. De Croon EM, Sluiter JK, Nijssen TF, Dijkmans BA, Lankhorst GJ, Frings-Dresen MH. Predictive factors of work disability in rheumatoid arthritis: a systematic literature review. Ann Rheum Dis 2004;63:1362-7.
6. Lenssinck ML, Burdorf A, Boonen A, Gignac MA, Hazes JM, Luime JJ. Consequences of inflammatory arthritis for workplace productivity loss and sick leave: a systematic review. Ann Rheum Dis 2013;72:493-505.
7. Burton W, Morrison A, Maclean R, Ruderman E. Systematic review of studies of productivity loss due to rheumatoid arthritis. Occup Med 2006;56:18-27.
8. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
9. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.
10. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992;35:498-502.
11. Kriteret orientuese për përcaktimin e aftësisë në punë të invalidëve (Ministria e Financave, Drejtoria e Sigurimeve Shoqërore Shtetërore, Tinanë 1991), 2010.
12. Wolfe F, Hawley DJ. The longterm outcomes of rheumatoid arthritis: Workdisability: a prospective 18 year study of 823 patients. J Rheumatol 1998;25:2108-17.
13. Young A, Dixey J, Kulinskaya E, Cox N, Davies P, Devlin J, et al. Which patients stop working because of rheumatoid arthritis? Results of five years' follow up in 732 patients from the Early RA Study (ERAS). Ann Rheum Dis 2002;61:335-40.
14. Woolf AD, Erwin J, March L. The need to address the burden of musculoskeletal conditions. Best Pract Res Clin Rheumatol 2012;26:183-224.
15. Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases? Autoimmune Dis 2012;2012:251730. doi: 10.1155/ 2012/ 251730.
16. Sokka T. Work disability in early rheumatoid arthritis. Clin Exp Rheumatol 2003;21(5 Suppl 31):S71-4.
17. Stahl EA, Raychaudhuri S. Rheumatoid arthritis. Evidence for a genetic component to disease severity in RA. Nat Rev Rheumatol 2012;8:312-3.
18. Knevel R, de Rooy DP, Zhernakova A, Gröndal G, Krabben A, Steinsson K, et al. Association of variants in IL2RA with progression of joint destruction in Rheumatoid Arthritis. Arthritis Rheum 2013; doi: 10.1002/ art.37938.
19. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet 2010;376:1094-108.
20. Çay HF, Illeez, Ö, Kocabas H, Sezer I, Kaptanoglu E, Kacar C. Alcohol consumption among inflammatory rheumatic patients: A survey from Turkey. Turk J Rheumatol 2012;27:179-84.