ramr
Revista Americana de Medicina Respiratoria

RAMR 2016;3:214-220
ISSN 1852 - 236X

Factors associated with the presentation of respiratory diseases in patients with rheumatoid arthritis in a Colombian institution between 2012 and 2015

Correspondence:
Yeison Santamaria-Alza
e-mail: yeison-1807@hotmail.es

Received: 01.04.2016
Accepted: 07.04.2016

Authors: Santamaria-Alza Yeison, Sánchez Robayo Kelly Johana

Industrial University of Santander. Medicine Directed towards Tobacco Intervention (MEDITA) Research Team

Abstract

Introduction: Rheumatoid arthritis affects 1% of the world population, and up to 73% of patients present respiratory disorders. In Colombia, there are no studies evaluating the relationship between the presence of pulmonary disorders and rheumatoid arthritis.

Objective: To determine the factors associated with respiratory diseases in patients with rheumatoid arthritis.

Methods: Case-control study (1:2) in 125 patients with rheumatoid arthritis. Descriptive, bivariate and multivariate analysis.

Results: The mean age was 60.19 for cases and 53.15 years old for controls. 66.67% of cases and 86.75% of controls were female. The respiratory rate (RR), Disease Activity Score (DAS 28), smoking, exposure to biomass, dyspnea, weight loss and severe disease activity were higher in cases. The use of nonsteroidal antiinflammatory drugs (NSAIDs) and leflunomide predominated in controls. The bivariate analysis showed statistical significance with positive correlation between respiratory disorders and age, sex, smoking, exposure to biomass, dyspnea, weight loss, RR, DAS 28 and severe disease activity. There was a statistically significant negative correlation with leflunomide and NSAIDs. The multivariate analysis showed statistical significance in patients older than 65 years old, exposure to biomass, cough, dyspnea, severe activity and use of NSAIDs.

Discussion: The results obtained are similar to those found in other studies. In addition, the presence of exposure to biomass appears as a variable strongly associated with the presentation of pulmonary disorders in patients with rheumatoid arthritis in our midst.

Key words: Rheumatoid arthritis, infection, pulmonary diseases

Introduction

Rheumatoid arthritis is a disease with high prevalence in the general population, representing 1% in Spain[1]. In 1998, Anaya J. M. et al calculated a prevalence of rheumatoid arthritis of 0.4% in Colombia; however, this study only includes African Colombian patients; thus, such information does not represent the whole country[2]. The manifestations of this disease could have a strong impact on the quality of life of patients due to functional disability, affecting multiple systems and causing chronic degenerative processes with biological treatments that can increase the immunosuppression process and generate high health-care system[3] costs.

One of the most frequent complications occurs at the respiratory system level, where different diseases may affect the present structures, causing morphological and functional disorders and making the system more susceptible to infectious processes. Such infections, together with the underlying immunosuppression, may lead to sepsis and death[3, 4].

Some of the main pulmonary complications already described are the interstitial pulmonary disease[5-7], the pleural disease (with findings of pleural

thickening in up to more than 73% of rheumatoid arthritis [RA] patients on whom an autopsy had been performed[8]), the airway disease, rheumatoid nodules, and toxicity with pulmonary damage caused by certain drugs such as methotrexate, cyclophosphamide and D-penicillamine[9, 10].

At local level, there isn´t any study describing the current situation of pulmonary complications in patients suffering from this disease or their impact on the affected patients; thus, a case-control study has been conducted. The main objective of the study was to determine which variables are associated with the presentation of respiratory diseases in patients with rheumatoid arthritis. In addition, the study searched for the prevalence of such variables and described the general characteristics of the affected population.

Method

Study Design

Analytical, observational, case-control study of patients with diagnosis of rheumatoid arthritis who receive medical care at the Santander University Hospital in the city of Bucaramanga, Colombia. Trained personnel gathered information from institutional clinical records. The Medical Ethics Committee of the *Instituto Neumológico del Oriente* approved the protocol. The study was considered not to entail any risk, since data gathering had been based on clinical records, in accordance with the 0084 Resolution of October 4th, 1993.

Patients

The study included subjects diagnosed with rheumatoid arthritis by the rheumatology service, who received in-patient hospital care at the data collection institution between 2012 and 2015. Patients who presented mixed connective tissue diseases, those younger than 18 years old and the ones with incomplete clinical records were excluded. Patients who presented respiratory disorders such as pleural effusion, pleuritis, adult respiratory distress syndrome, alveolar hemorrhage, interstitial pneumonitis, diaphragmatic dysfunction, lung thromboembolism, pulmonary hypertension, upper airway disease, lower airway disease, pneumothorax or lung infections were considered as cases. Both acute and chronic diseases were included, since the purpose of the study was to evaluate the full lung disease spectrum in patients with rheumatoid arthritis. Subjects with rheumatoid arthritis who, having received medical care at the same institution, did not show the already mentioned disorders at the chest X-ray were selected as controls. Data were collected from magnetic clinical records of the Santander University Hospital. Diagnostic imaging reports of the radiology department of the same institution were also included.

Measurements

The measured variables included identification data, personal history, respiratory system exposure, used medication, symptoms, signs, laboratory tests and disease activity (DAS28). Lab tests requested at hospital admission and the signs and symptoms registered at first assessment were also included.

Sample Size Calculation

We calculated the sample size in accordance with the association reported by Wang J. X. and Du C. G., who found an odds ratio (OR) of 3.72 of presenting interstitial lung disorders in subjects with positive rheumatoid factor[4]. 95% confidence level, 80% power and 2 controls per case ratio were determined. 42 cases and 83 controls were calculated through the Kelsey method, for 125 subjects in total.

Statistical Analysis

We performed the descriptive analysis of qualitative variables by means of relative and absolute frequencies. Quantitative variables were evaluated by means of the Shapiro-Wilk test in order to define the normality of distribution and, depending on the results, were expressed in mean and standard deviation or median and interquartile ranges. We made a group comparison through Mann-Whitney or Fisher tests; we determined the association between each independent variable and the result calculating the OR, 95% confidence intervals (95% CI) and p values. The selected variables were those with the greatest association, defined by $p < 0.20$, and we performed a logistic regression analysis in order to adjust the raw OR to reduce confusion. Regarding lost data, variables with more than 20% data loss were excluded from the analysis.

Results

Descriptive Analysis

125 subjects with rheumatoid arthritis were included. 42 of the 125 subjects presented respiratory disorders, with presence of infection and pulmonary hypertension as the most frequent. Table 1 summarizes the frequency of pulmonary disorders. Mean age was greater in cases. Regarding the vital signs, we found that the mean heart and respiratory rates were much higher in cases, whereas the median for oxygen saturation was similar in cases and controls. Additional tests to measure disease activity were altered in cases and controls, with higher erythrocyte sedimentation rate (ESR) and DAS 28 levels in cases. We observed a similar behavior in the duration of rheumatoid arthritis, the smoking index, heart rate, temperature, leukocytes and reactive C-protein (RCP).

On the other hand, hemoglobin levels were lower in cases, with similar trends in the hematocrit and platelet variables.

Regarding qualitative variables, we found that both in cases and controls, the female gender predominated. Most frequent co-morbidities in the group of cases were arterial hypertension (50%), heart failure (30.95%), previous lung infections (30.95%), gastroesophageal reflux (16.67%) and hypothyroidism (16.67%). In the group of controls, the most frequent medical records included arterial hypertension (30.13%), gastroesophageal reflux (15.66%) and hypothyroidism (16.67%).

With regard to toxicology, wood smoke exposure, smoking, alcoholism and inhaled drug use were greater in cases.

The most commonly used drugs both in cases and controls were corticosteroids, with predominance in the group of controls. Other frequently used drugs in cases and controls were methotrexate, chloroquine, nonsteroidal antiinflammatory drugs (NSAIDs) and leflunomide.

The most commonly found symptoms were dyspnea, cough, and fever in cases, and malaise, dyspnea, and cough in controls. The physical examination showed abnormal respiratory sounds, predominant in cases.

The classification of the disease activity evaluated by DAS 28 showed greater remission and mild and moderate disease activity in controls. The disease activity was mostly classified as severe in cases.

Table 2 summarizes the descriptive analysis of the evaluated quantitative and qualitative variables.

We excluded the variables rheumatoid factor, anti-citrulline antibodies, retraction, temperature, and blood pressure from the analysis due to a data loss of more than 20%.

Bivariate Analysis

28 independent variables with $p < 0.05$ were found. With regard to age older than 65 years old, we found an OR of 2.64, with statistical significance given by $p = 0.01$, together with male gender showing an OR of 3.27 with $p = 0.0096$.

History of heart failure, previous lung infections, arterial hypertension, chronic renal failure, smoking, alcohol use and wood smoke exposure is associated with the presentation of pulmonary disorders, with an OR of 11.95 ($p = 0.0000$), 36.75

TABLE 1. Frequency of Found Pulmonary Disorders.

Pulmonary complication	n	Percentage
Lung infection	23	54.76
Pulmonary hypertension	21	50
Interstitial pneumonitis	14	33.33
Pleural effusion	13	30.95
Lower airway disease	8	19.05
Pleuritis	7	16.77
Adult respiratory distress syndrome	5	11.9
Lung thromboembolism	2	4.76
Upper airway disease	2	4.76
Alveolar hemorrhage	1	2.38
Diaphragmatic dysfunction	1	2.38
Pneumothorax	1	2.38

TABLE 2. Descriptive Analysis. Quantitative and qualitative variables.

Variable	CASES (N= 42) n, (%)	CONTROLS (N=83) n, (%)	P value
Identification			
Gender (n=125)			0.0083
Female	28 (66.67 %)	72 (86.75 %)	
Male	14 (33.33 %)	11 (13.25 %)	
Age (n=125) (mean, SD [standard deviation])	60.19 (17.15)	53.15 (14.12)	0.0231
Disease duration in months (n=125) (median, IQR [interquartile range])	6.5 (10)	5 (7)	0.3047
History			
Heart failure (n=125)	13 (30.95 %)	3 (3.61%)	< 0.0001
Previous lung infections (n=125)	13 (30.95 %)	1 (1.20 %)	< 0.0001
Smoking (n=125)	14 (33.33 %)	8 (9.64%)	0.0011
Smoking index (n=22) (median, IQR)	20 (18)	2.5 (4.25)	0.0268
Wood smoke index (n=125)	15 (35.71%)	8 (9.64%)	0.0004
Treatment			
Corticosteroid (n=125)	31 (73.81%)	71 (85.57%)	0.1113
Methotrexate (n=125)	28 (66.67%)	58 (69.88 %)	0.7153
NSAIDs (n=125)	14 (33.33 %)	48 (57.83%)	0.0100
Leflunomide (n=125)	11 (26.16 %)	38 (45.78 %)	0.0348
Symptoms and Signs			
Dyspnea (n=125)	31 (73.81 %)	9 (10.84 %)	< 0.0001
Fever (n=125)	17 (40.48%)	3 (3.61 %)	< 0.0001
Nonpurulent sputum (n=125)	7 (16.67%)	3 (3.61 %)	0.0114
Hemoptisis (n=125)	4 (9.52 %)	1 (1.20 %)	0.0256
Cough (n=125)	26 (61.90 %)	9 (10.84 %)	< 0.0001
Heart rate (n=120) (median, IQR)	85 (23)	78 (12)	0.0007
Respiratory rate (n=118) (median, IQR)	20 (5)	18 (3)	< 0.0001
Oxygen saturation (n=110) (median, IQR)	95 (3)	96 (4)	0.0806
Abnormal respiratory sounds (n=125)	28 (66.67 %)	2 (2.41 %)	< 0.0001
Lab tests			
Hemoglobin (n=115) (mean, SD)	10.15 (2.43)	11.54 (1.82)	0.0080
Hematocrit (n=115) (mean, SD)	31.36 (6.98)	36.95 (5.33)	0.0021
C-reactive protein (n=118) (median, IQR)	58.4 (78.8)	12 (90)	0.0131
Erythrocyte sedimentation rate (n=125) (median, IQR)	58 (78)	28 (24)	< 0.0001
Disease Activity			
DAS 28 (n=125) (mean, SD)	5.28 (1.36)	4.16 (1.28)	< 0.0001
Remitting disease (n=125)	1 (2.38%)	11 (13.25%)	0.0522
Low disease activity (n=125)	2 (4.76)	5 (6.02%)	0.7728
Mild disease activity (n=125)	17 (40.48%)	49 (59.04%)	0.0505
Severe disease activity (n=125)	22 (52.38%)	18 (21.69%)	0.0005

(p = 0.0000), 2.32 (p = 0.0003), 11.08 (p = 0.0099), 4.68 (p = 0.0014), 5.33 (p = 0.0140) and 5.20 (p = 0.0005), respectively.

Regarding the use of drugs, treatment with NSAIDs and leflunomide is found to be associated with a less frequent presentation of respiratory disorders, with an OR of 0.36, an interval of 0.016 to 0.79 and p = 0.0091, and an OR of 0.42 with an interval of 0.18 - 0.94 with p = 0.0313, respectively.

Symptoms with a statistically significant relationship were dyspnea, with an OR of 32.17 (p = 0.0000); fever, with an OR of 18.13 (p = 0.0000), nonpurulent sputum, with an OR of 5.33 (p = 0.0140); weight loss, with an OR of 11.04 (p = 0.0005); hemoptisis, with an OR of 8.63 (p = 0.0294); cough, with an OR of 13.36 (p = 0.0000) and malaise, with an OR of 11.73 (p = 0.0009).

Vital signs associated with the presence of respiratory disorders in patients with arthritis were heart rate of more than 90 beats per minute and respiratory rate of more than 17 breaths per minute, with an OR of 7.26 (p = 0.0001) and 4.80 (p = 0.0015), respectively. Oxygen saturation of more than 94% was found as a protective factor given by an OR of 0.16 with 95% CI of 0.03 to 0.84 and p = 0.0159.

Clinical findings with a strong statistical relationship were abnormal respiratory sounds, with an OR of 80.99 (p = 0.0000), rhonchus, with an OR of 13.66 (p = 0.0032) and reduction of respiratory sounds, with an OR of 49.02 (p = 0.0000).

A statistically significant relationship was also found in the ESR higher than 22 with an OR of 4.46 (p = 0.0039), hemoglobin higher than 10 with an OR of 0.22 (p = 0.0028), hematocrit higher than 35 with an OR of 0.20 (p = 0.0031) and severe disease activity (DAS 28 higher than 5.1) with an OR of 4.63 (p = 0.0001). Table 3 summarizes the information of bivariate and multivariate analyses.

Multivariate Analysis

For the multivariate analysis, we selected variables with a p value of less than 0.2 in the bivariate analysis. We performed a multivariate logistic regression, in which we discarded variables until we got statistically significant variables.

In this analysis, we found 6 statistically significant variables, associated with the presentation of respiratory disorders in patients with rheumatoid arthritis. The variables were age older than 65 years old (p = 0.05), wood smoke exposure (p = 0.02), use of NSAIDs (p = 0.038), presence of cough (p = 0.001), presence of dyspnea (p = 0.001) and severe disease activity measured by the DAS 28 scale (p = 0.001).

Table 3 summarizes the variables of the multivariate analysis with adjusted ORs.

Discussion

Rheumatoid arthritis and its systemic complications, mostly pulmonary disorders, represent one of the main causes of disability in our environment, and are the second cause of productive life year loss in Colombia[11].

The purpose of this study was to determine the variables associated with the presentation of these diseases and contribute to early identification in patients at risk, thus taking timely preventive and therapeutic actions to reduce their impact. One of its main objectives was to start a line of study of pulmonary disorders in patients with collagen diseases, since there isn´t any relevant study at local level.

One of the main risk factors found in relation to the presentation of pulmonary disorders in patients with RA was age older than 65 years old, with a 3.98 times increased probability compared to subjects of less than 65 years old. Similar studies, such as the one conducted by Yin Y. et al[12], showed a higher risk of presenting pulmonary disorders with an OR of 1.06 when evaluating the age of the subjects.

Pre-existing pulmonary diseases also show a strong risk association. In a Japanese research[13], an OR of 8.17 was found, whereas our study reported an almost three times higher risk of presenting lung infections with pre-existing RA, with an OR of 36.75. The difference in the magnitude of the measurement could relate to the difference in sample size and the low prevalence of pre-existing lung infections in the control subjects of our study.

With regard to toxicology, as for example, smoking, different studies reported similar risk association findings. The already mentioned study conducted by Sawada T et al[13] showed an OR of 3.97, and another research carried out by Mori S et al[14] determined an OR of 2.78. In our study, smoking was associated with a 4.68 times higher possibility of presenting the event in question, compared to subjects who never smoke. In Colombia, exposure to biomass smoke is an important etiology that contributes to the development of multiple pulmonary diseases; but there is no information about it in the revised studies. However, in our study we did find a statistically significant association with the presence of pulmonary disorders, both in the bivariate and in the multivariate analysis, thus indicating the strong association of the exposure with the result. Previous findings can relate to the physiopathological and respiratory mechanisms already described in the literature of smoking and wood smoke, which cause similar disorders

TABLE 3. Bivariate and Multivariate Analysis

Variable	Raw OR	95% CI	Adjusted OR	95% CI
More than 65 years old	2.64	1.16-5.96	3.98	1.09-14.50
Wood smoke exposure	5.20	1.98-13.66	2.4	1.34-5.70
Use of NSAIDs	0.36	0.16-0.79	0.24	0.07-0.81
Cough	13.36	5.26-33.89	9.31	2.54-34.07
Dyspnea	23.17	8.73-61.47	7.39	2.27-24.05
Severe activity (DAS 28 higher than 5.1)	4.63	2.09-10.26	7.97	2.34-27.14

in patients with rheumatoid arthritis who have a baseline-modified immune reaction, increasingly compromising the respiratory system due to inflammation and remodeling of the pulmonary structure.

The already mentioned study[14] also reported a 5.18 times higher risk factor in patients who presented altered respiratory sounds. In our study, we found a stronger risk association with these variables given by the presentation of rhonchus with an OR of 13.66 and reduced respiratory sounds with an OR of 49.02. Although there is a similar association, the magnitude is different probably because there are few controls in our study with altered respiratory sounds.

With regard to the drugs used to treat rheumatoid arthritis, the work of Alarcon GS, et al[15] determined that the use of disease-modifying drugs increases the risk of presenting pulmonary lesions. This information agrees with the study conducted by Sawada et al[13], which concludes that the use of leflunomide is associated with a greater probability of presenting interstitial pulmonary disease. However, in our study we found statistical significance, with risk reduction, in the use of leflunomide and NSAIDs. The other drugs did not present a statistical association. The discrepancy with leflunomide could relate to the presence of a small sample size, the study design or intrinsic differences in the study populations. Association with the NSAIDs could relate to the fact that patients who control the symptoms with these drugs show less inflammatory activity, thus showing fewer systemic alterations.

Additional tests are important in patients with arthritis and help predict the presence of pulmonary disorders in previous studies. Alarcon, G. S.[15] et al found an association with hypoalbuminemia; Yin Y. et al[11] and Wang J. X. et al[5] found a statistically significant relationship with the presence of anti-citrulline antibodies and rheumatoid factor levels. In our study, we found statistical significance with hemoglobin, hematocrit and ESR. The hemoglobin and hematocrit findings could be similar to the findings of Alarcon GS et al, since they do not physiologically explain the presence of pulmonary disorders but do indicate the presence of a systemic disease.

With respect to the ESR, we believe it is a very valuable finding, since it is one of the additional tests used to determine disease activity. With this finding, we are able to suggest that the greater the inflammatory activity, the stronger the probability to find pulmonary disorders in these patients. Lack of association with the rheumatoid factor and anti-citrulline antibodies in our study has to do mainly with the loss of data of those variables. DAS 28 and classification as severe activity show the systemic compromise of rheumatoid arthritis, since with our study we are able to state that subjects who show a higher score in the DAS 28 scale and, thus, a higher classification of the disease, have an increased risk of presenting pulmonary disorders.

The main strength of this study is the fact that it is the first of its kind in the region, thus, it generates important information related to pulmonary disorders in patients with rheumatoid arthritis in the northeastern region of Colombia. For that reason, also, we can generate hypotheses and future studies.

One disadvantage of the study is that, being a case-control study, there may be selection bias, and since it is a restrospective study, it could have information bias. For that reason, an external evaluator has validated the data. In addition, the confusion generated in the study has been mitigated after adjusting the OR in the multivariate analysis. The classification bias was reduced by reading the chest X-rays made by field specialists.

The multivariate analysis related to the increased risk of presenting pulmonary disorders in patients with rheumatoid arthritis was statistically significant for the age older than 65 years old, wood smoke exposure, presence of cough, dyspnea and severe disease activity measured by DAS 28 and presented a lower risk of developing these complications with the use of NSAIDs. Taking into account the fact that the variables wood smoke exposure and use of NSAIDs as risk factor and protective factor, respectively, have not been described in the literature, it is imperative to conduct future studies with epidemiological designs to mitigate the bias that have arisen and corroborate the hypotheses presented in this original text.

Conflicts of Interest: The authors declare there is no conflict of interest related to the topic of this publication.

References

1. Gomez C, Bonilla H, Pulmonary Manifestations of Collagen Diseases, Archivos de bronconeumología 2013; 49: 249-60.
2. Anaya JM, Correa P, Mantilla RD. Prevalence and Sever-

ity of Rheumatoid Arthritis in African Colombians from Quibdó. Acta médica Colombiana 1998; 23(6): 322-33.
3. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009; 11(3): 229.
4. Assayag D, Ryerson C. Determining Respiratory Impairment in ConnectiveTissue Disease–Associated Interstitial Lung Disease. Rheum Dis Clin N Am, 2015: 1-11.
5. Wang JX, Du CG. A Retrospective Study of Clinical Characteristics of Interstitial Lung Disease Associated with Rheumatoid Arthritis in Chinese Patients. Med Sci Monit. 2015; 21: 708–715.
6. Antin-Ozerk D. Evans J, Rubinowitz A. Pulmonary manifestations of rheumatoid arthritis. Clin Chest Med 31 (2010) 451-478.
7. Fischer A, Bois R. Intertitial lung disease in connective tissue disorders. Lancet 2012; 380: 689-98.
8. Baggenstoss AH, Rosenberg EF. Visceral lesions associated with chronic infectious (rheumatoid) arthritis. Arch Pathol 1943; 35: 503.
9. Clements PJ, Furst DE, Wong WK, et al. High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. Arthritis Rheum 1999; 42(6): 1194-203.
10. Malik SW, Myers JL, DeRemee RA, et al. Lung toxicity associated with cyclophosphamide use. Two distinct patterns. Am J Respir Crit Care Med 1996; 154(6 Pt 1): 1851-6.
11. Clinical Practice Guideline for the early detection, diagnosis and treatment of rheumatoid arthritis. Ministry of Health and Social Protection – Colciencias, 2014: 26- 28.
12. Yin Y, Liang D, Zhao L, Li Y, Liu W, et al. (2014) Anti-Cyclic Citrullinated Peptide Antibody Is Associated with Interstitial Lung Disease in Patients with Rheumatoid Arthritis. PLoS ONE 9(4): e92449. doi:10.1371/journal.pone.0092449
13. Sawada T, Inokuma S, Sato T, Otsuka T, Saeki Y, et al. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. Rheumatology 2009; 48: 1069-1072.
14. Mori S, Koga Y, Sugimoto M. Small airway obstruction in patients with rheumatoid arthritis. Modern Rheumatology. 2011; 21(2): 164-173.
15. Alarcon GS, Kremer JM, Macaluso M, Weinblatt ME, Cannon GW, et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. Ann Intern Med. 1997 Sep 1; 127(5): 356-64.