Epidemiology and comorbidities of patients with rheumatoid arthritis in Spain during the period 2002-2017

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune rheumatic disease that is associated with multiple comorbidities and has a significant economic impact on the Spanish health system. The objective of this study was to estimate the hospital burden of rheumatoid arthritis, its variants and their associated comorbidities. Methods: Observational descriptive study that reviewed hospital records from the CMBD. We included all hospitalizations of patients in Spain whose main diagnosis or comorbidity in the ICD-9-CM was rheumatoid arthritis during the period of 2002-2017. Results: A total of 315,190 hospitalizations with the RA code were recorded; 67.3% were in women. The mean age of the patients was 68.5 ± 13.9 years. The median length of hospital stay was 7 days (IQR 3-11 days). In 29,809 of the admissions, RA was coded as the main diagnosis (9.4%). When RA was not coded as the main diagnosis, the most frequent main diagnoses were diseases of the circulatory system (18.9%) and diseases of the respiratory system (17.4%). The hospitalization rate during the period of 2002-2017 was 43.8 (95% CI: 43.7-44.0) per 100,000 inhabitants. The total cost for the healthcare system was 1.476 million euros, with a median of 3,542 euros per hospitalization (IQR 2,646-5,222 euros). Conclusions: In Spain, the highest hospitalization rates for RA were registered within the continental climate region. The hospitalization rate of patients with RA increased during the study period, despite the decrease in the hospitalization rate when RA was the main diagnosis.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease that preferentially affects the joints symmetrically; however, it can also damage internal organs and thus should be considered a systemic disease. This chronic inflammation causes decreased mobility and joint function. Systemic involvement and comorbidities can reduce life expectancy (1).

RA is associated with multiple comorbidities and psychosocial problems, which include cardiovascular diseases, interstitial lung disease, osteoporosis, infections, fatigue and depression (2,3) and an increased risk of early mortality (4,5), amongst others. RA is also associated with an increased incidence of lymphomas, leukaemia and lung cancer (6). Many of the comorbidities associated with RA cause a significant increase in mortality, disability and costs, which is why they are a priority addressed by the new strategies of the World Health Organization (WHO) (7).

The worldwide prevalence of RA is estimated to be 0.24%, whereas the prevalence of this disease is 0.66% in Northern Europe (8) and 0.44% in Western Europe (9). In Spain, the prevalence of RA is 0.5% (0.8% in women and 0.2% in men), with approximately 200,000 cases and a 4:1 ratio between women and men, according to the EPISER study (National Survey on the Prevalence of Rheumatic Diseases in Spain) (10). The incidence of RA in our country is 8.3 cases/100,000 inhabitants, which increases with age in both sexes (11). According to the National Health Survey (ENSE 2011/2012), in the section “Chronic Problems of the Adult Population”, under the label of “Arthrosis, Arthritis and Rheumatism”, RA
was classified as the primary disease in women (affecting 25.1% of women) and as the third most common disease in men (affecting 11.1% of men) (12).

RA has a significant economic impact, both in direct costs (due to the use of biological medicine treatments) and indirect costs (increase in sick leave (13)). In Spain, 74% of the total RA costs correspond to direct costs, and 26% correspond to indirect costs (14). The aim of our study was to estimate the burden of hospitalization associated with RA during the period of 2002–2017 in Spain, stratified by year, sex, age and autonomous community. We also aimed to determine the main variants of RA that result in hospitalization and the various comorbidities when RA was not the main diagnosis upon admission.

Methods

Study design. An observational descriptive study was performed using data from the Minimum Basic Data Set (CMBD) of the Ministry of Health, Social Services and Equality of Spain. The CMBD is a compulsory registry for both public and private hospitals that provides statistical knowledge of hospital morbidity. This information helps in the planning and evaluation of health systems (15) and includes an estimated 98% of hospital admissions, covering 99.5% of the Spanish population (16).

Sampling and variables. Our registry included 315,190 hospital admissions from a period of 16 years (from January 1, 2002 to December 31, 2017). A total of 69 variables were collected; from these, this study analysed sex, age, year, average stay, cost of hospitalization, autonomous community of admission, primary diagnosis and secondary diagnoses (up to thirteen diagnoses). The main diagnostic variable was considered the reason for hospitalization, and the rest of the diagnostic variables were assessed as comorbidities. RA and its variants were coded in one or more of fourteen diagnostic variables based on the Ninth Edition of the International Classification of Diseases (ICD–9-CM). According to this classification, RA and all its variants were registered with the code 714 followed by one or two figures.

The patients were grouped into the following age ranges: under 20 years old, 20–30 years old, 30–40 years old, 40–50 years old, 50–60 years old, 60–70 years old, 70–80 years old, 80–90 years old and over 90 years old. To calculate the hospitalization rates (by year, age and autonomous community), the number of hospitalizations of RA patients was used as the numerator and the official population figure of the National Institute of Statistics (17) was used as the denominator, calculated per 100,000 inhabitants.

Statistical analysis. The qualitative variables were described with their frequency distribution and were compared using Pearson's Chi-square test or Fisher's exact test if their application criteria were not met. The quantitative variables were described with the mean and standard deviation (SD) or the median and interquartile range (IQR) if they did not follow normal laws and were compared using Student's t-test when the data followed a normal distribution or with the Mann-Whitney U test otherwise. Quantitative variables with more than two categories were compared using analysis of variance (ANOVA), and when the application conditions were not met, the non-parametric Kruskal-Wallis test was used. The statistical analysis was performed using the statistical program SPSS 22.0 (SPSS Inc., Chicago, IL). Statistically
Significant differences were those with $p < 0.05$; all estimates were described with their 95% confidence intervals. Patient information was anonymized before performing the analysis.

**Results**

A total of 315,190 hospitalizations were recorded for RA patients, both in primary and secondary diagnosis, during the period of 2002–2017. Of these admissions, 211,967 were women (67.3%), and 103,199 were men (32.7%). The mean age of the patients was $68.5 \pm 13.9$ years, corresponding to $68.2 \pm 14.5$ years in women and $69.1 \pm 12.6$ years in men ($p > 0.05$). The median length of hospital stay over the entire study period was 7 days (IQR 3–11 days); the length of stay was significantly higher in 2002 (8 days, IQR 4–13 days) compared to 2017 (6 days, IQR 3–10 days) ($p < 0.05$). In 2002, the cost of hospitalization for RA patients was 38 million euros, with a median hospitalization cost per admission of 2,314 euros (IQR 2,032–3,417 euros), whereas the total cost was 142 million euros in 2017, with a median hospitalization cost per admission of 4,396 euros (IQR 3,384–5,945 euros) ($p < 0.05$). The overall cost of hospitalizations for patients with RA in the Spanish Health System was 1.476 million euros during the period of 2002–2017, with a median hospitalization cost per admission of 3,542 euros (IQR 2,646–5,222 euros).

**Hospitalization rates by sex, age, year and diagnosis.** The hospitalization rate in Spain for RA during the period of 2002–2017 was 43.8 (95% CI: 43.7–44.0) hospitalizations per 100,000 population-years. By sex, the rate of hospitalization was 58.1 (95% CI: 58.0–58.3) per 100,000 population-years in women and 29.1 (95% CI: 29.0–29.3) in men ($p < 0.05$). When stratified by age, the lowest hospitalization rate corresponded to those under 20 years old: 0.53 (95% CI: 0.49–0.56) per 100,000 population-years, and the highest corresponded to those between 80–90 years old: 219.0 per 100,000 population-years (95% CI: 217.5–220.6) (Table 1). When comparing the annual rate of hospitalization without differentiating whether RA was coded as the main diagnosis or a comorbidity, there was an annual increase in this rate from 31.6 per 100,000 inhabitants in 2002 to 56.3 per 100,000 inhabitants in 2017 ($p < 0.05$) (Figure 1).

The overall hospitalization rates during the study period were 4.1 (95% CI: 4.0–4.2) per 100,000 inhabitants when RA was coded as the main diagnosis and 39.7 (95% CI: 39.6–39.8) when it was a comorbidity at admission. The highest annual hospitalization rate for RA as the main diagnosis was 8.1 (95% CI: 7.9–8.2) per 100,000 inhabitants in 2003, whereas the lowest was 1.9 (95% CI: 1.8–2.0) in 2017; overall, there was a declining trend since 2003. Conversely, the data displayed an increasing trend of annual hospitalization rates when RA was a comorbidity; the lowest rate was in 2002: 24.5 (95% CI: 24.1–24.9) per 100,000 inhabitants, whereas the highest was in 2017: 54.5 (95% CI: 54.0–54.9) per 100,000 inhabitants (Table 2).

**Rheumatoid arthritis as the main diagnosis or comorbidity on admission.** When RA was the main diagnosis, a total of 29,809 hospitalizations were recorded during the study period, with a hospitalization rate of 4.1 (95% CI: 3.9–4.3) per 100,000 population-years. The mean age of the patients admitted was $60.4 \pm 14.7$ years, and 71.6% of the patients were women. The average hospital stay was $7.1 \pm 8.3$ days,
and the average cost per hospitalization was 3,503 ± 2,224 euros. RA (code 714.0) was classified as the main diagnosis in 9.2% of cases, followed by rheumatic lung and non-specific inflammatory polyarthritis in 0.1% and 0.03% of cases, respectively. The rest of the variants of RA were classified as the main diagnosis in less than 0.03% of cases (Table 3). Amongst the 285,381 hospitalizations of patients with RA as a comorbidity, the most frequent causes of admission were diseases of the circulatory system \( (n = 54,123, 18.9\%) \), diseases of the respiratory system \( (n = 49,876, 17.4\%) \) and diseases of the osteomyoarticular system and connective tissue \( (n = 32,003, 11.2\%) \) (Table 4).

**Regional rates of hospitalization for rheumatoid arthritis in Spain.** In Spain, the highest rates of hospitalization for RA per 100,000 population-years by autonomous communities (as the main diagnosis or comorbidity) were found in Castilla y León (69.9), Cantabria (69.9), Asturias (62.1) and Extremadura (55.8). By contrast, the lowest rates were found in Melilla (16.7), Ceuta (17.1), Canary Islands (27.9) and Balearic Islands (30.1) (Figure 2).

**Discussion**

In our study, the rate of hospitalization for RA in women was much higher than that for men; furthermore, the rate of hospitalization increased with age, reflecting a trend that is consistent with the literature (10,11). The cost of hospitalization was similar to a recent study published using the same database (CMBD) and the same time period, specifically for Parkinson’s disease (18); both of these studies reflect the high cost for chronic autoimmune diseases.

The finding in our study of a decrease in the annual hospitalization rate when RA is coded as the main diagnosis (and therefore considered the cause of hospitalization) could be a result of the recent widespread use of new therapies with drug modifiers such as disease and biological agents (19). The increase in the hospitalization rate when RA was coded as a comorbidity could be explained by the increase in the pluripathology and chronicity in patients affected by this disease for years (20). This increase occurred despite the recent treatment trend of tighter control of the activity of the disease with the introduction of “treat to target” strategies and biological therapies.

The main causes of hospitalization in patients with RA were diseases of the circulatory, respiratory, osteomyoarticular and connective tissue systems, which constituted almost 50% of all admission pathologies. This corroborates what has been published in several studies demonstrating that cardiovascular diseases are one of the main comorbidities that accompany RA (8,21–23). In our study, only 2.61% of RA patient admissions were due to infections; however, in the literature, the recurrence of infections that accompany patients with this disease has been noted, particularly opportunistic infections such as herpes zoster or tuberculosis (23,24).

Several studies have shown that RA is associated with an increase in the incidence of leukaemia, non-Hodgkin lymphomas and lung cancer (9,23); however, this finding was not confirmed in our series in which malignant neoplasms were only the sixth cause of hospitalization. Patients with RA also report a significant worsening of their quality of life when they have two or more associated comorbidities (25).
These comorbidities that accompany RA, which have also been observed in other studies, can be explained by the mechanism of inflammation inherent in the disease itself and by the side effects of different therapies used to treat this pathology (23).

In Spain, the highest hospitalization rates for RA were registered in the autonomous communities of the centre and north-west of the peninsula, within the continental climate region, which is characterized by cold winters. Conversely, the lowest rates were found in Melilla, Ceuta and both archipelagos (Canary and Balearic Islands) and in the regions located in the Mediterranean climatic zone (with the exception of Navarra); these areas have a climate characterized by mild temperatures in the winter and hot summers. Therefore, our data support another study conducted in Spain that showed a greater tendency of patients affected by RA to visit the emergency room when the ambient temperature was lower than average (26). The literature also indicates that there is a difference in the incidence of RA and its exacerbations between populations within the same country, likely because of variations in climate, environmental exposure, genetic factors and behavioural factors, amongst others (27,28).

The limitation of this study derives from the use of a secondary information source. Improve the analysis of big data or big data will be a long-term commitment for institutions and health authorities, not without risk or complexity, because they do not yet know all the possibilities that technologies and techniques can offer around the management and large-scale data analysis (29). The quality of the CMBD depends on the clinical history and its codification, which leads to variability between hospital centres. However, since 2001, quality control measures have been developed to assess the internal validity of the database and improve it (30). A strength of our work is filling knowledge gaps in the field of rheumatological diseases. A thorough bibliographic search revealed that there are few references found in Spanish studies that use the CMBD as a database and more specifically in the field of rheumatological diseases. Therefore, we consider this study to be novel and of great interest.

In conclusion, the epidemiology reported in our work follows the line of other international studies on RA and its variants. The rate of hospitalization of patients with RA increased during the period of 2002–2017 despite the decrease in the rate of RA as the main diagnosis and the use of biological therapies and more aggressive strategies to control the disease. The cost of treating these patients continues to be very high, mainly because of the increase in hospitalizations due to other concomitant diseases and the comorbidities of elderly patients. Therefore, this work is open to future lines of research through the exploitation of the CMBD and other databases that allow us to collect more information on RA to evaluate, manage and plan the processes related to this pathology in our environment.

**List Of Abbreviations**

CMBD: Minimum Basic Data Set

CI: confidence intervals

RA: Rheumatoid arthritis
Declarations

Ethics approval and consent to participate

No ethical approval was needed for this study because it was based on secondary analysis of the data obtained from the CMBD (Minimum Basic Data Set) of the Ministry of Health, Social Services and Equality of Spain. The data were completely anonymous and this study uses data with no identifiable information on the survey participants.

Consent for publication

Not applicable

Availability of data and materials

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they do not have competing interests.

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This study was carried out without any funding.

Authors’ contributions

JADML designed the study, carried out the study, performed the statistical analysis and drafted the manuscript. MGC participated in the study design and revised it critically for important intellectual content. RGP participated in the study design and drafted the manuscript. AGM participated in the study design and drafted the manuscript. RME participated in the study design and revised it critically for important intellectual content and drafted the manuscript. All authors read and approved the final version.

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Author’s information

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2002–2017.

Tables

Table 1. Hospitalization rates for rheumatoid arthritis in Spain (2002-2017) by age. Hospitalization rate per 100,000 inhabitants

| Age       | Rate | 95% CI     |
|-----------|------|------------|
| <20 years | 0.53 | 0.49-0.56  |
| 20-30 years | 2.93 | 2.83-3.04  |
| 30-40 years | 7.93 | 7.78-8.08  |
| 40-50 years | 17.98| 17.76-18.21|
| 50-60 years | 45.95| 45.62-46.28|
| 60-70 years | 101.24| 100.50-102.04|
| 70-80 years | 183.29| 182.31-184.36|
| 80-90 years | 219.08| 217.59-220.62|
| >90 years  | 136.58| 133.73-139.65|
| Total     | 43.88| 43.77-44.00|

Table 2. Annual hospitalization rates in Spain (2002-2017) for rheumatoid arthritis as the main diagnosis or comorbidity. Annual hospitalization rates per 100,000 inhabitants*
### Table 3. ICD-9-CM codes of rheumatoid arthritis and its variants when rheumatoid arthritis was coded as the main diagnosis*

| Type of rheumatoid arthritis                              | Code   | Principal diagnostic N | %   |
|-----------------------------------------------------------|--------|-------------------------|-----|
| Rheumatoid arthritis                                      | 714.0  | 29,059                  | 9.22%|
| Polyarticular arthritis                                   | 714.1  | 37                      | 0.01%|
| With visceral or systemic implication                     | 714.2  | 40                      | 0.01%|
| Active polyarticular juvenile RA                          | 714.30 | 78                      | 0.02%|
| Juvenile onset polyarticular RA                           | 714.31 | 19                      | 0.01%|
| Pauciarticular juvenile RA                                | 714.32 | 11                      | 0.003%|
| Osteoarticular juvenile RA                                | 714.33 | 12                      | 0.004%|
| Osteoarticular RA                                          | 714.34 | 19                      | 0.01%|
| Rheumatic arthritis chronic RA                            | 714.4  | 412                     | 0.13%|
| Rheumatic polyarticular arthropathy                       | 714.81 | 83                      | 0.03%|
| Rheumatic polyarticular arthropathy non-specific polyarthropathy | 714.9  | 29,809                  | 9.46%|
| Other RA                                                  | 285,381| 90.54%                  |     |
| Other pathologies                                          | 315,190| 100%                    |     |

* RA = rheumatoid arthritis.

### Table 4. Causes of hospitalization when rheumatoid arthritis was not coded as the main diagnosis

| Year | RA as main diagnosis | Rate | 95% CI       | RA as comorbidity | Rate | 95% CI       |
|------|----------------------|------|--------------|-------------------|------|--------------|
| 2002 |                      | 7.11 | 6.97-7.25    | 24.50             | 24.08-24.92 |
| 2003 |                      | 8.10 | 7.98-8.22    | 26.67             | 26.25-27.10 |
| 2004 |                      | 7.42 | 7.28-7.55    | 27.79             | 27.36-28.22 |
| 2005 |                      | 7.10 | 6.97-7.24    | 31.57             | 31.13-32.02 |
| 2006 |                      | 5.70 | 5.55-5.85    | 32.37             | 31.93-32.82 |
| 2007 |                      | 4.28 | 4.14-4.43    | 33.90             | 33.46-34.34 |
| 2008 |                      | 4.23 | 4.08-4.37    | 35.00             | 34.56-35.44 |
| 2009 |                      | 3.82 | 3.69-3.96    | 37.99             | 37.54-38.44 |
| 2010 |                      | 3.38 | 3.25-3.52    | 39.99             | 39.55-40.44 |
| 2011 |                      | 3.34 | 3.20-3.47    | 43.08             | 42.63-43.53 |
| 2012 |                      | 2.78 | 2.64-2.90    | 43.71             | 43.26-44.15 |
| 2013 |                      | 2.56 | 2.44-2.68    | 45.66             | 45.21-46.11 |
| 2014 |                      | 2.18 | 2.06-2.30    | 48.21             | 47.76-48.66 |
| 2015 |                      | 2.09 | 1.98-2.21    | 50.12             | 49.67-50.57 |
| 2016 |                      | 2.03 | 1.91-2.15    | 53.74             | 53.29-54.19 |
| 2017 |                      | 1.93 | 1.82-2.05    | 54.45             | 54.00-54.91 |
| Total|                      | 4.15 | 4.11-4.19    | 39.73             | 39.62-39.84 |

* RA = rheumatoid arthritis.
| ICD-9-MC codes                                                                 | N    | %   |
|------------------------------------------------------------------------------|------|-----|
| 1. Infectious and parasitic diseases (001-139)                               | 7,447| 2.61%|
| 2. Neoplasms (140-239)                                                        | 20,514| 7.19%|
| 3. Endocrine, metabolic, and nutritional diseases                             | 5,500| 1.93%|
| 4. Diseases of the blood and haematopoietic organs (280-289)                 | 5,434| 1.90%|
| 5. Mental, behavioural and neurodevelopmental disorders (290-319)            | 2,429| 0.85%|
| 6. Diseases of the nervous system and the sense organs (320-389)             | 6,726| 2.36%|
| 7. Diseases of the circulatory system (390-459)                               | 54,123| 18.97%|
| 8. Diseases of the respiratory system (460-519)                               | 49,876| 17.48%|
| 9. Diseases of the digestive system (520-579)                                | 31,864| 11.17%|
| 10. Diseases of the genitourinary system (580-629)                            | 15,675| 5.49%|
| 11. Complications of pregnancy, childbirth and puerperium (630-679)           | 3,466| 1.21%|
| 12. Diseases of the skin and subcutaneous tissue (680-709)                    | 4,915| 1.72%|
| 13. Diseases of the osteomyoarticular system                                  | 32,003| 11.21%|
| and connective tissue (710-739)                                              |      |     |
| 14. Congenital anomalies (740-759)                                            | 383  | 0.13%|
| 15. Signs, symptoms and ill-defined states (780-799)                         | 12,385| 4.34%|
| 16. Injuries and poisoning (800-999)                                          | 27,579| 9.66%|
| 17. Factors that influence the state of health and contact                    | 4,922| 1.72%|
| with health services (V01-V89)                                                |      |     |
| 18. Lost to follow-up (ZZZ.ZP)                                                | 140  | 0.05%|
| Total                                                                        | 285,381| 100%|

**Figures**
Figure 1

Figure 1. Annual hospitalization rates for rheumatoid arthritis in Spain (2002-2017)
Figure 2

Figure 2. Hospitalization rates for patients with rheumatoid arthritis, by autonomous community, during the period of 2002-2017.