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ORIGINAL ARTICLE

# Epidemiological of cat scratch disease among inpatients in the Spanish health system (1997–2015)

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## Abstract

Cat scratch disease, whose causative agent is *Bartonella henselae*, is an anthropozoonosis with a worldwide distribution that causes significant public health problems. Although it is an endemic disease in Spain, the available data are very limited. The aim of our study was to describe cat scratch disease inpatients in the National Health System (NHS) of Spain. This was a retrospective descriptive study using the minimum basic data set (CMBD in Spanish) in patients admitted to hospitals of the NHS between 1997 and 2015 with a diagnosis of cat scratch disease (ICD-9: 078.3). We found 781 hospitalized patients diagnosed with cat scratch disease. The mean age (± SD) was 30.7 ± 25.3 years old. The male/female ratio was 1.1:1. The incidence rate over the study period was 0.93 (95% CI, 0.86–0.99) cases per million person-years. The incidence rate in men was 0.98 cases per million person-years and that in women was 0.88 cases per million person-years. The cases were more frequent from September to January. A total of 652 (83.5%) cases were urgent hospital admissions. The average hospital stay was 8.4 ± 8.9 days. The overall lethality rate of the cohort was 1.3%. We have demonstrated that CSD causes a substantial burden of disease in Spain, affecting both adult and pediatric patients with a stable incidence rate. Our data suggest that CSD is benign and self-limited, with low mortality, and its incidence is possibly underestimated. Finally, there is a need for a common national strategy for data collection, monitoring, and reporting, which would facilitate a more accurate picture and the design of more strategic control measures. Hospital discharge records (HDRs) could be a good database for the epidemiological analysis of the hospital management of CSD.

**Keywords** Cat scratch disease · *Bartonella henselae* · Spain · Burden · Epidemiology

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## Introduction

Cat scratch disease (CSD) is caused by aerobic, intracellular gram-negative bacilli; these infectious agents have relatively fastidious growth characteristics and are in the genus *Bartonella* [1–3]. The main species responsible for CSD is *Bartonella henselae*, although some cases produced by *B. clarridgeiae* have also been described [4].

Cats, especially younger and stray cats, constitute the fundamental reservoir of both *Bartonella* species [5]. *Ctenocephalides felis* is the arthropod vector responsible for the horizontal transmission of *B. henselae* between cats [1, 2, 4, 5]. Transmission to humans occurs primarily through inoculation (perhaps from infected flea feces) of a cat scratch or bite wound and less commonly through contact with mucosa (e.g., conjunctiva). In a study conducted in Korea, cat ownership was significantly associated with *B. henselae* seropositivity. A total of 9.8% of individuals who had cats showed seropositivity, compared with 2.0% of those without contact with cats [6]. In a Spanish study [7], 31.6% of healthy seropositive individuals reported exposure to cats.

*B. henselae* has a special tropism for endothelial cells as well as for CD-34 hematopoietic precursors [1–3, 5]. The host response to *B. henselae* infection differs depending on the immune state [3]. In immunocompetent individuals, a granulomatous and suppurative response develops, whereas in immune-compromised individuals, a vascular proliferation response is elicited [1–3].

*B. henselae* infection and CSD occur worldwide. Considering the data provided in the literature, the prevalence of infection, verified through serological studies, indicates the prevalence of infection is much higher than clinically detected. It seems to be that serology is influenced by seasonality [8]. Thus, seroprevalence studies demonstrate the presence of *B. henselae* infection in many countries in Europe [7, 9–17] (including Spain [7, 14–17]), Asia [18, 19], and America [20, 21]. The seroprevalence rate is highly variable, ranging from 0.7 to 57.0% depending on the country [7, 9–21], study group (general population, veterinarians [17], or forest workers [13]), subjects (healthy [7, 9–12, 14, 15, 20, 21], HIV-infected individuals [14, 16], and febrile patients [18]), and, above all, the serologic titer cut-off point used to define positive cases (1:64 [7, 11, 14, 16, 17],, 1:128 [15, 21], or 1:256 [9, 10, 12, 19, 20], respectively). The true incidence of CSD is difficult to determine, since it is not a reportable disease in many countries. Most of the data on the incidence of CSD come from the USA, with the annual incidence estimated at 9.3/100,000 inhabitants for outpatients and at 0.8/100,000 persons for inpatients [22]. In addition, differences between geographical areas [22, 23] and even within the same state [24] have been verified.

Most patients with CSD present a benign, self-limiting clinical picture characterized by isolated lymphadenopathy with fever and no other signs or symptoms [3]. However, between 4.0 and 9.6% of patients present more serious manifestations that require hospital admission [25–28], and several factors of the host (i.e., age, sex, immune status) and the causative agent (inoculum size, strain specificity, and source of infection) have been related to this clinical variability [28]. Atypical manifestations of CSD like retinitis/neuroretinitis, conjunctivitis, neuritis, encephalitis, hepatosplenic disease, osteomyelitis, erythema nodosum, and endocarditis range between 1.5 and 20% [29]. In the literature, there are few studies about the characteristics of inpatients with CSD [25–27, 30]. Therefore, the aim of this study was to evaluate the clinical and epidemiological impact of CSD in inpatients in Spain.

## Materials and methods

We conducted a retrospective descriptive analysis of hospitalized patients with cat scratch disease, ICD-9-CM diagnosis code 078.3, from January 1, 1997, to December 31, 2015, in Spanish public hospitals. This study analyzes the data provided by hospital discharge records (HDRs). HDRs catalog all hospital discharges produced in the network of general hospitals in the National Health System (NHS). The data contained in HDRs are those established in the hospitalization minimum data set (CMBD in Spanish). CMBD is the main database for the associated morbidity and the care process of patients treated in hospitals. It provides usual demographic data (age, sex, and place of residence; *urban areas*: agglomerations with more than 5000 inhabitants; *rural areas*: agglomerations with less than 5000 inhabitants), clinical variables (diagnoses and procedures), and variables related to the episode of hospitalization, such as circumstance of admission (urgent: an urgent admission is one that does not meet the requirements of the programmed admission and has been regularly attended in the emergency area; or programmed: an admission is programmed when it has been concerted with a previous date, independently of the patient comes from a waiting list or not), patient discharge (discharge to their home, transfer to another hospital, or death), and average length of stay. Diagnoses and procedures collected were coded using the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM). The primary diagnosis is defined as the condition, after study, which occasioned the admission to the hospital, according to the ICD-9-CM code refers to the condition that, at the end of the hospitalization process, is considered the cause of the patient's admission to the hospital for the patient's admission to the hospital. Secondary diagnosis codes (up to 13) are diagnoses that coexist with the primary diagnosis at the time of admission or develop during admission.

A case was defined as any patient with the ICD-9-CM code for cat scratch disease (078.3) listed as either a primary or secondary diagnosis in their HDR. Patient records with missing data were excluded from this study.

## Statistical analysis

The incidence rates were calculated by dividing the number of new cases of cat scratch disease (numerator) per year by the population at risk (denominator) in a period of time (person-years) multiplied by 1,000,000 and expressed as "cases per million person-years." As it is not possible to accurately measure disease-free periods, the total person-time at risk can be estimated satisfactorily when the size of the population is stable by multiplying the average population size studied by the duration of the observation period. Thus, the population at risk was obtained from annual data published by the National Institute of Statistics (INE, http://www.ine.es/). The 95% confidence interval (95% CI) for the incidence rate was calculated for a better clinical application of the results. Incidence rates were computed by age, sex, autonomous community, and year to assess temporal and geographical patterns. Mean rates by autonomous community for the whole study period were plotted on maps. The lethality rate was calculated by dividing the number of primary diagnosis deaths (numerator) by the number of individuals with a primary diagnosis of a specific disease (denominator) (× 100). The results were expressed as absolute value ($n$), proportion ($n/N$), and percentage (%) for categorical variables and as the mean, standard deviation (SD), median, interquartile range (IQR) (Q1–Q3), and range (minimum value, maximum value) for continuous variables. A $\chi^2$ test was used to compare the association between categorical variables, such as clinical and demographic variables, and the measured outcome was expressed as the odds ratio (OR) together with the 95% CI for the OR. Continuous variables were compared with Student's $t$ test or the Mann-Whitney test for two groups, depending on whether the data had a normal or non-normal distribution. The ANOVA allowed us to analyze the influence of independent nominal variables on a continuous dependent variable. Additionally, we applied the corresponding regression models for multivariate analysis. We considered a statistically significant difference from chance at a $p$ value < 0.05. Data analysis was performed using SPSS 25 (Statistical Package for the Social Sciences).

### Ethics statement

This study is based on medical data of patients collected in the CMBD. These data are the responsibility of the Ministry of Social Services of Health and Equality (Ministerio de Servicios Sociales, Sanidad e Igualdad, MSSSI) that compiles and organizes them. All patient data provided by the CMBD are anonymized and deidentified by the MSSSI before they are provided to the applicants. According to this confidentiality commitment signed with the MSSSI, researchers cannot provide the data to other researchers, so other researchers must request the data directly from the MSSSI. The protocol and ethics statement of this study were approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Because the data were obtained from an epidemiological database, written consent was not obtained. All data analyzed were anonymized.

## Results

### Incidence and geographic distribution

A total of 781 cases with the ICD-9-CM code for cat scratch disease were registered in Spain during the 19-year study period. The incidence rate over the study period was 0.93 (95% CI, 0.86–0.99) cases per million person-years. The incidence rate in men was 0.98 (95% CI, 0.89–1.08) cases per million person-years, and in women, it was 0.88 (95% CI, 0.79–0.97) cases per million person-years. Chronologically, we observed an irregular distribution of cases during the study period. The annual incidence rate was highest in 1997, 1.25 (95% CI, 0.90–1.60) cases per million person-years (49 cases). Annual incidence rates were lowest in 2006 and 2011, both 0.74 (95% CI, 0.50–0.99) cases per million person-years (33 and 35 cases, respectively). In the last 2 years of the period, annual incidence rates increased, 1.18 (95% CI, 0.87–1.49) cases per million person-years (55 cases) in 2014 and 1.20 (95% CI, 0.89–1.51) cases per million person-years (56 cases) in 2015 (Fig. 1).

The distribution of CSD cases by month of diagnosis in which it was diagnosed is shown in Fig. 2. The cases were more frequent from September to January (autumn and winter seasons).

We analyzed the incidence rates in different regions of Spain (see map, Fig. 3). Incidence was highest in the north—Asturias had 3.28 (95% CI, 2.49–4.06) cases per million person-years and Cantabria had 2.99 (95% CI, 1.95–4.02) cases per million person-years—and lowest in the central region; Madrid autonomous community 0.24 (95% CI, 0.15–0.33) had cases per million person-years. A total of 551 (70.6%) cases originated from urban environments, 188 (24.1%) cases originated from rural environments, and the origins of 42 (5.4%) cases were unknown. No statistically significant differences related to the urban vs. rural origin of the cases were observed ($p > 0.05$).

### Distribution by age and sex

Table 1 shows the main epidemiological and clinical data of the patients studied. The proportions of men (51.9%) and

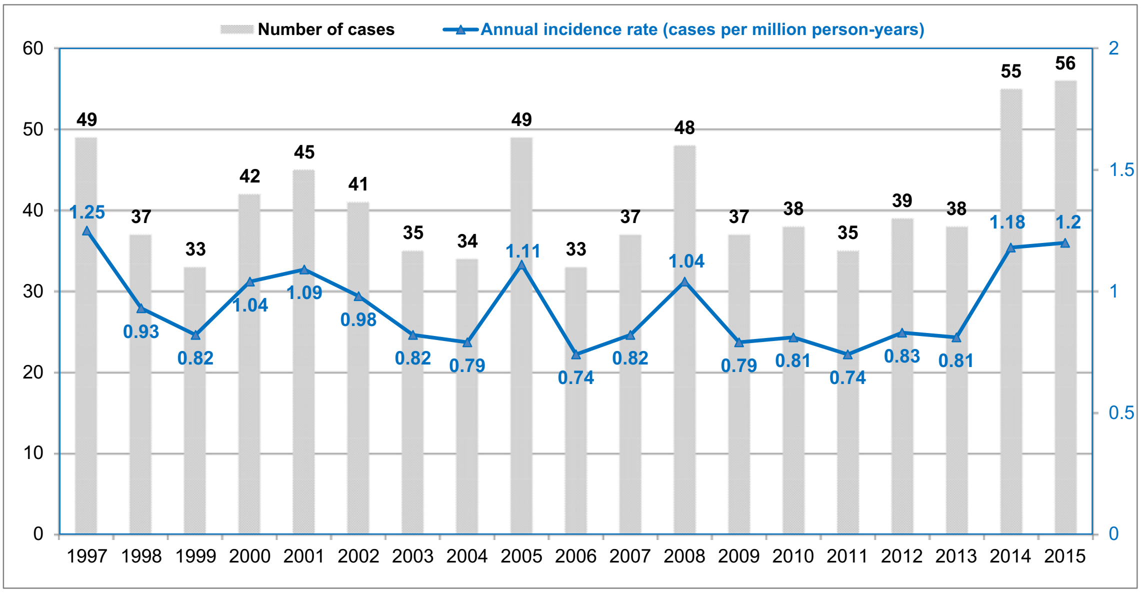


**Fig. 1** Temporal distribution of cat scratch disease inpatients in Spain, 1997–2015: cases and annual incidence rate (*cases per* million *person-years*)

women (48.1%) were similar. The mean (SD) age was 30.7 years (25.3), 333 cases (42.6%) were in children (0–14 years), 338 (43.3%) in adults (> 14–64 years), and 110 (14.1%) in elderly patients.

Figure 4 shows the distribution age (5-year groups) of CSD (number of cases and incidence rates). The highest overall average incidence rates by 5-year age groups were among children 0–14 years of age (ages 0–4, 2.16 cases per million person-years; ages 5–9, 3.00 cases per million person-years; and ages 10–14, 2.97 cases per million person-years). As of 15 years of age, overall average incidence rates by 5-year age groups were less than 1 case per million person-years. In boys, the highest average incidence rate was for 10–14 years of age (3.54 cases per million person-years), and in girls, the highest average incidence rate was for 5–9 years of age (2.65 cases per million person-years).

There were significant differences between the seasonal distribution of cases and the demographic variables. The number of cases was higher in women in spring (50.4%) and summer (57.1%), while the number of cases was higher in men in autumn (51.9%) and winter (55.5%) ($p$ = 0.046). Half of the cases (50.9%) that occurred in the autumn season

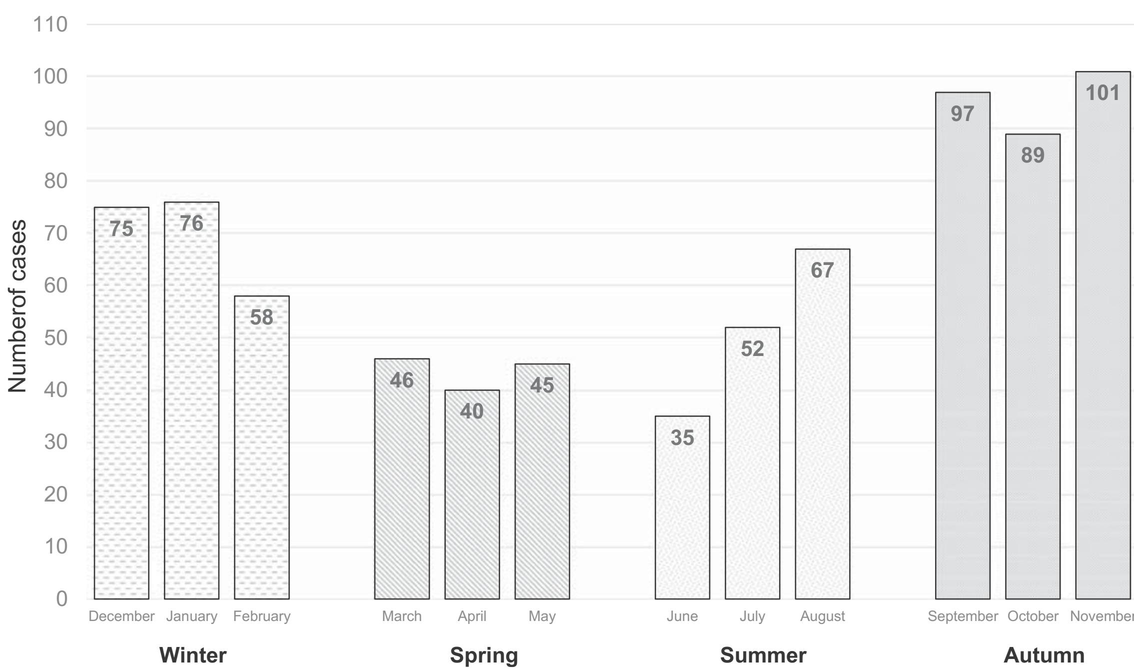


**Fig. 2** Distribution of cat scratch disease cases in the months of the year ($p < 0.001$)

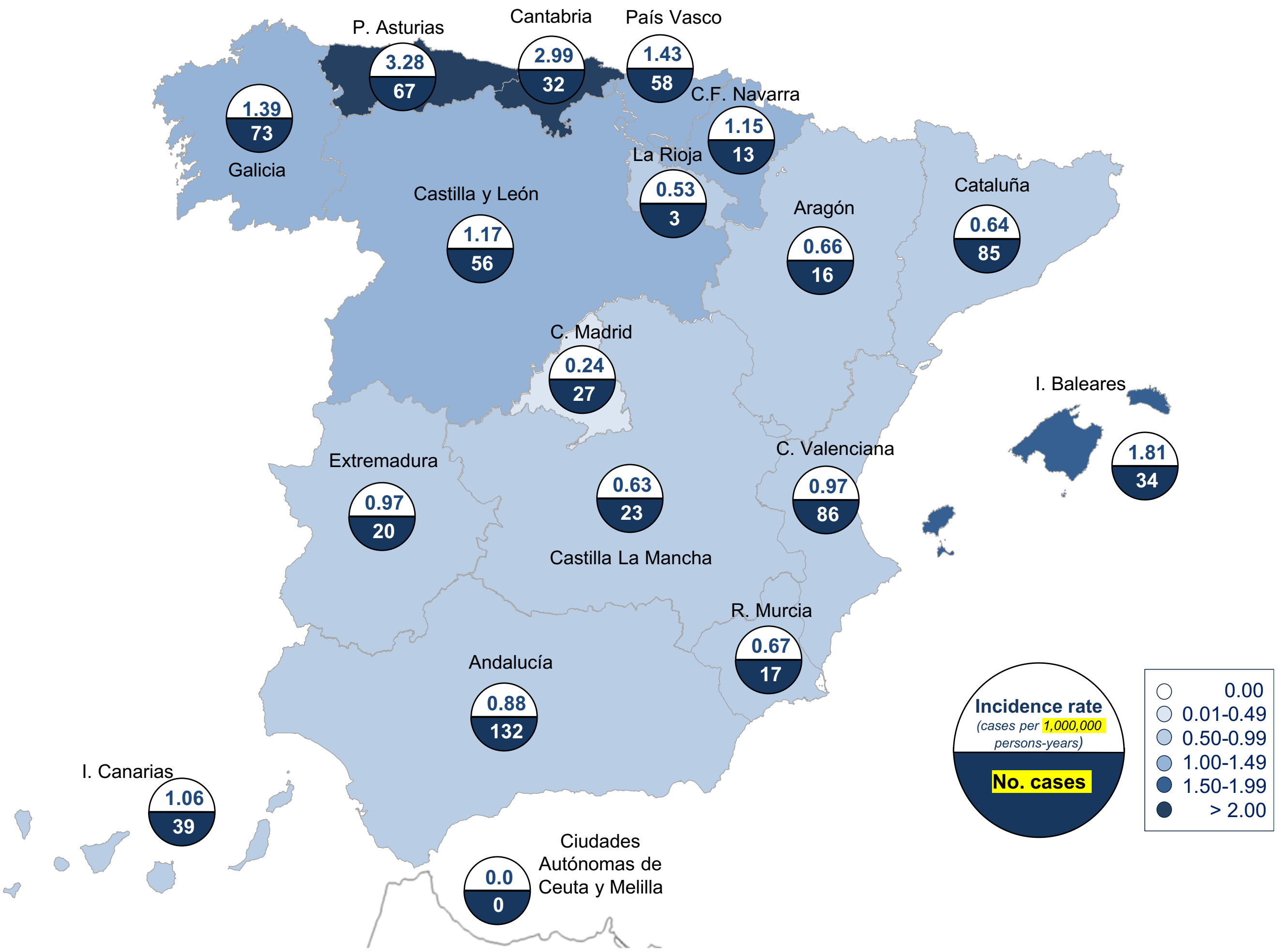


**Fig. 3** Cat scratch disease incidence by region, Spain (1997–2015)

were in the pediatric population (0–14 years old). In the summer months, the percentage of cases increased significantly, up to 24%, in the population over 65 ($p < 0.001$).

## Clinical features

A total of 652 (83.5%) cases were urgent hospital admissions. Most patients (758, 97.1%) were sent home after hospital discharge. The average (SD) hospital stay was 8.4 days (± 8.9) (median (IQR), 6 (3–10)) (see Table 1). Hospitalizations with cat scratch disease as the primary diagnosis were 568 (72.7%), with 213 (27.3%) cases as the secondary diagnosis. In Table 2, epidemiological, clinical, and mortality differences between patients with primary and secondary diagnosis codes were compared. Forty (5.1%) patients had neoplasms: eight digestive cancer, six hematological neoplasm, four lung neoplasm, three breast cancer, two leiomyoma sarcoma, and others. Only two had HIV. The mean age of patients with a primary diagnosis code was lower than those with a secondary diagnosis code (mean ± SD, 28.6 ± 24.1 *vs.* 36.3 ± 27.7, $p < 0.001$). Additionally, average hospital stays increased by 3 days among patients with secondary diagnosis codes (mean ± SD, 7.8 ± 6.4 vs. 10.1 ± 13.3, $p = 0.001$). In relation to the service responsible for patient hospital care, 1 out of 5 cases (228, 28.2%) was referred and treated in the Internal Medicine Service and 164 (21.0) cases in the Pediatric Service.

## Cohort mortality

The overall lethality rate of the cohort was 1.3% (10 deaths), 6 women and 4 men. The lethality rate of a primary diagnosis of cat scratch disease was 0.53 per 100 (3 primary diagnosis deaths/568 primary diagnoses); 2 deaths were in 1997 (lethality rate, 4.76 per 100) and 1 death was in 2012 (lethality rate, 3.13 per 100). Mortality among people > 65 years was 3.6% (4/110), and among the population aged 15–64, it was 1.8% (6/338), that is, 3.6% vs. 1.8% (OR = 2.08 95% CI (1.1–7.5)). The mortality distribution was 3 in Cantabria autonomous community, 2 in Andalusia, and 1 in Aragon, Castile and Leon, Castile La Mancha, Madrid, and Catalonia, with no significant differences ($p = 0.125$). All deaths with a primary

**Table 1** Main data patients included in the study

| Variables | $N$ = 781 cases $n$ (%) |
|---|---|
| Gender | |
| Male | 405 (51.9) |
| Female | 376 (48.1) |
| Age (years) | |
| Mean ± SD | 30.7 ± 25.3 |
| Range (minimum value, maximum value) | (0, 91) |
| Age 0–14 years | 333 (42.6) |
| Age 15–64 years | 338 (43.3) |
| Age ≥ 65 years | 110 (14.1) |
| Type of diagnosis (ICD-9-CM code 078.3) | |
| Primary diagnosis | 568 (72.7) |
| Secondary diagnosis | 213 (27.3) |
| Comorbidity | |
| Neoplasms | 40 (5.1) |
| Enlarged lymph nodes | 140 (17.9) |
| HIV | 2 (0.3) |
| Type of hospital admission | |
| Urgent | 652 (83.5) |
| Programmed | 129 (16.5) |
| Type of discharge | |
| Home | 758 (97.1) |
| Transfer to another hospital | 4 (0.5) |
| Transfer to social-health center | 2 (0.3) |
| Voluntary discharge | 5 (0.6) |
| Others/unknown | 2 (0.3) |
| Overall mortality | 10/781 (1.3) |
| Cat scratch disease primary diagnosis mortality | 3/568 (0.53) |
| Secondary diagnosis mortality | 7/213 (3.28) |
| Hospital stay (days) | |
| Mean ± SD | 8.4 ± 8.9 |
| Median (IQR) | 6 (3–10) |
| Range (minimum value, maximum value) | (0, 91) |

diagnosis of CSD (3 patients) were in the Cantabria autonomous community (lethality rate, 12.50 per 100).

## Discussion

A total of 781 hospitalized patients with cat scratch disease were registered with HDR in Spain between January 1997 and December 2015. The incidence rate for our cohort of patients during the study period was 0.93 cases per million person-years, and it remained stable with a small increase in the last two years of the study. Our cohort showed a similar incidence rate with respect to that of Nelson et al. [27] and presented a higher number of cases in autumn, unlike other studies [27], which showed an increase in cases in January. One of the most interesting points of our series is that all patients who were hospitalized had symptomatic disease since most epidemiological studies in Europe and Spain are based on screening studies of different asymptomatic groups [7, 9–12, 14, 15, 20, 21]. This makes it difficult to compare our study with others, except for the work of Nelson et al. [27] carried out in inpatients. Our figures were much higher than those of the latter study. This report also analyzed possible risk factors associated with *Bartonella* infection.

Previously published studies indicate that *B. henselae* infections are more common in children than in adults [31]. Nevertheless, other works do not show this tendency to pediatric involvement [12]. Indeed, one of the highlights of our study is that approximately 60% of patients are adults, perhaps because we only analyzed inpatients. However, the impact of disease on the pediatric group is definite, as we show in Fig. 4. Our data differ from those of other authors on the way it does not show significant differences with respect to sex, as observed in the study of Pons et al. in Spain and Aydin et al. in Turkey [7, 32]. Some studies show that the *B. henselae* seroprevalence was 8.3% in urban areas, 11.9% in semi-rural areas, and 0% in rural areas [7]. However, our analysis shows no differences regarding the origin of disease for rural vs. urban patients. We hypothesize that these seroprevalence studies are not comparable with our work due to methodological design.

Given the methodological limitations of this study, we would like to highlight the difficulty of considering cases such as those with a secondary diagnosis.

CSD is the main and most frequent clinical presentation of *B. henselae* infection and typically presents as subacute regional lymphadenopathy after a scratch or bite from a cat [33]. Although the literature describes that in immunocompetent patients, CSD occurs mostly in children and adolescents and rarely in older persons [34], in our study, most of the patients were adults without immunosuppression. However, *B. henselae* infection can be particularly severe for immunocompromised patients, such as those with AIDS, in whom vascular proliferative lesions (bacillary angiomatosis and bacillary peliosis) may develop [35]. When assessing risk factors, in our data, it should be noted the low incidence of HIV with CSD symptoms; there were only two HIV cases and 40 cases of patients with tumors identified in contrast to the available literature [14, 16].

The prognosis for complete recovery in immunocompetent patients with CSD is excellent. Significant morbidity occurs in 5–10% of cases, usually due to central or peripheral nervous system involvement or to multisystemic disseminated disease. One episode of cat scratch disease confers lifelong immunity to all patients [36].

Very few studies analyze the overall mortality attributed to CSD, which is generally considered a benign disease. The fatal cases were patients with endocarditis and cerebral

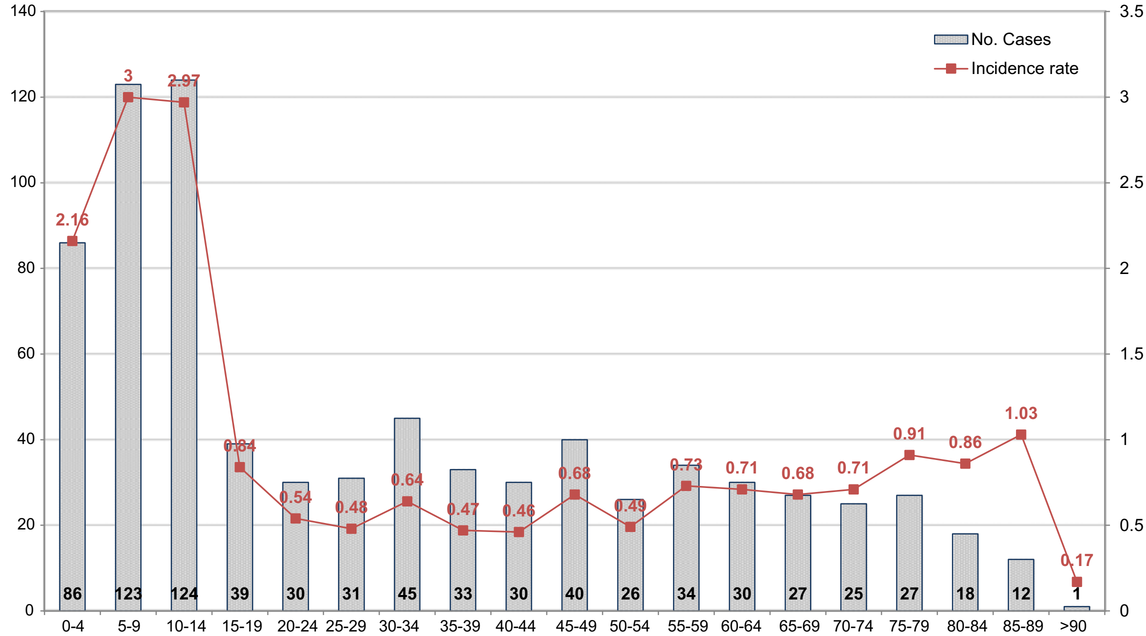


**Fig. 4** Distribution age (5-year groups) of cat scratch disease (No. of cases and incidence rates—*cases per* million *person-years*), Spain, 1997–2015

involvement, usually with delays in diagnosis [27, 28]. The lethality rate in our study was approximately 1.3%. Our data show that older patients have a higher mortality. The delay in diagnoses in this group could be one of the essential factors for a worse prognosis. Therefore, carrying out a timely diagnosis and an early start of treatment are essential to improve the prognosis and may result in fewer hospitalizations and serious complications.

Because the CMBD provides information from a network of hospitals that covers more than 99% of the population living in Spain (http://www.msssi.gob.es/), this study provides fairly accurate estimates. However, there were several factors that were limitations in our study: (*i*) the use of sources such as the CMBD for purposes other than research and clinical care; (*ii*) the use of the ICD-9, which has certain classification limitations with respect to the ICD-10, which is more modern and has fewer qualifying errors; (*iii*) encoding error may exist and cannot be amended as the data included in the CMBD are irreversible; (*iv*) not being able to access the medical history did not allow us to confirm the diagnosis, identify the possible associated factors involved, and find information about the tests used for CSD diagnosis (which

**Table 2** Primary diagnosis vs. secondary diagnosis

| Variables | Primary diagnosis, $N_1 = 568$ $n$ (%) | Secondary diagnosis, $N_2 = 213$ $n$ (%) | $p$ value* |
|---|---|---|---|
| Age (years), mean ± SD; n (%) | 28.6 ± 24.1 | 36.3 ± 27.7 | < 0.001* |
| Age 0–14 years | 254 (44.7) | 79 (37.1) | 0.004* |
| Age 15–64 years | 248 (43.7) | 90 (42.3) | |
| Age ≥ 65 years | 66 (11.6) | 44 (20.7) | |
| Gender, *n* (%) | | | |
| Male | 306 (53.9) | 99 (46.5) | 0.065 |
| Female | 262 (46.1) | 114 (53.5) | |
| Type of hospital admission, *n* (%) | | | |
| Urgent | 477 (84.0) | 175 (82.2) | 0.542 |
| Programmed | 91 (16.0) | 38 (17.8) | |
| Type of discharge, *n* (%) | | | |
| Home | 558 (98.8) | 200 (97.1) | 0.110 |
| Others | 7 (1.2) | 6 (2.9) | |
| Mortality, *n* (%) | 3 (0.5) | 7 (3.3) | 0.002* |
| Hospital stay (days); mean ± SD | 7.8 ± 6.4 | 10.1 ± 13.3 | 0.001* |

*Statistical significance level of 5% ($p < 0.05$)

lowers the quality of the data in this matter), the diagnostic techniques used in our patients and the clinic where they received care. For example, the 078.3 code could have been inappropriately used for care of a cat scratch wound but not actual CSD. Additionally, in some cases, the 078.3 code may have been recorded as a rule-out diagnosis when CSD was not actually confirmed. To our knowledge, there are no data on the sensitivity and specificity of the 078.3 code for CSD. (*vi*) In considering only patients in public hospitals and not including nonhospital cases or private centers, for example, those who are ill who are not admitted or who did not receive medical care, in addition to those treated in private hospitals, would be excluded; thus, hospital records underestimate the real burden of CSD in Spain. This study only reflects the patients who died while hospitalized, which could underestimate the mortality; and finally, (*vii*) the estimated cost is not evaluated in this study. In any case, our findings reported here have potential implications for public policy. We not only aimed to relieve the lack of official epidemiological data but we also expect to have contributed to generating hypotheses that will be worthy of further investigation. Our data showed that the systematic search of HDR may be an adequate method for studying those diseases with scarce epidemiological data.

We have demonstrated that CSD causes a substantial burden of disease in Spain, affecting both adult and pediatric patients with a stable incidence rate. Our data suggest that CSD is benign and self-limited, with low mortality, and that its incidence may be underestimated. Finally, there is a need for a common national strategy for data collection, monitoring, and reporting, which would facilitate a more accurate picture and the design of more strategic control measures. HDRs could be a good epidemiological database for the study of hospital management of CSD.

**Author Contributions** Study design: MBG, BRA, and JLPA
Data collection: VVT, MAS, ALB, and ARA
Data analysis: MAS and HMRA
Writing: MBG, JLPA, JPLL, and BRA

## Compliance with ethical standards

This study is based on medical data of patients collected in the CMBD. These data are the responsibility of the Ministry of Social Services of Health and Equality (Ministerio de Servicios Sociales, Sanidad e Igualdad, MSSSI) that compiles and organizes them. All patient data provided by the CMBD are anonymized and deidentified by the MSSSI before they are provided to the applicants. According to this confidentiality commitment signed with the MSSSI, researchers cannot provide the data to other researchers, so other researchers must request the data directly from the MSSSI.

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** The study protocol was approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Because it is an epidemiological study, written consent was not obtained. All data analyzed were anonymized.

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