Journal of Gastrointestinal Surgery (2019) 23:1148–1156
https://doi.org/10.1007/s11605-018-3971-y

ORIGINAL ARTICLE

Retrospective Study of Cystic Echinococcosis in a Recent Cohort of a Referral Center for Liver Surgery

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Received: 18 July 2018 / Accepted: 9 September 2018 / Published online: 21 September 2018

Abstract

Background Cystic echinococcosis (CE) is a zoonosis endemic in Spain caused by the larval stage of the cestode *Echinococcus granulosus* and is one of the 18 neglected tropical diseases recognized by the WHO. The aim of this study was to describe the epidemiological and clinical data of CE in a surgical referral hospital.

Methods A retrospective descriptive study of all adults' patients diagnosed with CE and followed at Vall d'Hebron University Hospital in Barcelona, Spain, between 2000 and 2015.

Results We found 151 cases, 78 (51.7%) women, and median age at diagnosis was 68 (range, 15–92) years. Diagnosis was a radiological finding in 97 (64.2%) and the most frequent location was the liver [135 (89.4%) patients]. Nearly 80% of the cysts were calcified and serology was positive in 48 (51.6%). The WHO-IWGE classification was only available in 70 of the 104 (67.3%) cases of liver cysts that had an ultrasound. First therapeutic plan was "watch and wait" followed by surgery. International recommendations were not always followed, particularly in CE4 and CE5 stages, and 20% needed a change of treatment because of progression or recurrence. Patients treated surgically were younger, more symptomatic, and had larger and less calcified cysts in multiple sites. Serology was not useful for CE diagnosis and neither serology nor calcification of the cyst helped to predict viability.

Conclusions The formation of multidisciplinary teams in reference hospitals could help to improve CE diagnosis, its management, and follow-up, since international recommendations are not usually followed.

Keywords Hydatidosis · Hydatid cyst · Cystic echinococcosis · *Echinococcus granulosus*

Introduction

Cystic echinococcosis (CE) is a zoonosis caused by the larval stage of the cestode *Echinococcus granulosus*,[1] and it is one of the 18 neglected tropical diseases recognized by the World Health Organization (WHO).[2,3] The highest prevalence rate is found in areas that raise sheep, and CE is still endemic in many regions of the world. It is usually asymptomatic unless complications occur.[4]

The spectrum of CE has changed in recent years due to the aging of the population, immigration, and immunosuppression. Diagnosis is based on epidemiological factors and radiological features, and immunodiagnostic tests can help support the diagnosis, but they are not confirmatory. Confirmation is obtained by histology. There are four different therapeutic options: percutaneous therapy, surgery, chemotherapy, and observation without intervention (watch and wait), but to date, there is still a need for consensus on the most appropriate treatments depending on cyst stages.[4]

CE is endemic in Spain and although its notification is mandatory, its impact is undervalued since officially reported

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data underestimate the real burden of the disease due to underdiagnosis.[5–7] After the implementation of control programs (slaughterhouse hygiene, public education, periodic treatment of dogs with praziquantel), a continuous decrease of CE has been reported.[8] In Spain, the number of cases decreased until 2011 and increased in 2012, remaining stable since then. One hundred fifty cases were reported in 2014 with an incidence of 0.3 cases per 100,000 inhabitants, the highest reported incidence being 1.6–2.1 cases per inhabitants in some regions.[9]

The aim of this study was to describe epidemiological and clinical data of cases of CE in a tertiary hospital in Barcelona, Spain, between 2000 and 2015.

Methods

A retrospective descriptive study was performed at Vall d'Hebron University Hospital, a 1000-bed tertiary referral hospital in Barcelona (Spain), between 2000 and 2015. Inclusion criteria were as follows: (1) patients ≥ 18 years old, (2) diagnosed with CE according to radiological findings and/or compatible histopathological features, and (3) followed in our center with available information regarding treatment and follow-up. We did not include patients younger than 18 years old; they were treated and followed by a different team and we did not have access to all medical records.

Clinical data were obtained by medical records review and recorded in a relational database created specifically for the study. All data were anonymized through a data coding system. For each patient, we collected socio-demographic and clinical data, presence of eosinophilia defined by a total number of eosinophils > 500/mm^3 or absolute percentage > 7%, lesion location, number and size, image procedures performed for the diagnosis, WHO-Informal Working Group on Echinococcosis (WHO-IWGE) classification when staging was available on the imaging report,[10] the original therapeutic plan, the need for a change of treatment because of progression or recurrence, signs of viability in pathologic samples, median follow-up, death, and whether it was associated or not with CE.

Serologic tests included different techniques depending on the period when they were performed: indirect hemagglutination inhibition assay (IHA) from 01/01/2000 to 31/7/2008, enzyme-linked immunosorbent assay (ELISA) from 01/08/2008 to 30/06/2015, and chemiluminescence immunoassay (CLIA) from 01/07/2015 to 31/12/2015. If the result of the test was doubtful, we considered it negative.

Chemotherapy consisted of albendazole (400 mg every 12 h if weight was > 60 kg or 15 mg/kg/day divided into two doses if weight was < 60 kg) for at least 3 to 6 months depending on tolerance. Regarding the surgical procedure, the surgical field was always prepared with gauze soaked in povidone-iodine before manipulating the cysts to avoid contamination of the field or the release of the content of the cyst to the peritoneal cavity. Subsequently and before introducing intracystic liquids, it was necessary to aspirate the content of the cyst. Otherwise, the injection of decontaminating solutions could open by hyper pressure the possible connections of the cystic content with the blood circulation or with the bile duct, being able to cause an anaphylactic shock or the passage of hydatids to the main bile duct. We usually used laparoscopic trocars to keep the cysts connected to a vacuum cleaner and to instill decontaminating substances at the same time (povidone-iodine). We recommended that the decontamination and aspiration maneuvers lasted a minimum of 30 min to consider its lethal effect and until its contents had been completely emptied. The intention was always to perform a radical cystectomy. This could be achieved by hepatic resection in which the cyst was included or by a pericystectomy where the entire cyst was resected and scarcely hepatic parenchyma. Radical cystectomy was the best option; otherwise, if pieces of capsule remained, the probability of residual abscesses, biliary fistulas, or recurrence of the cyst were high. However, it was not always possible to perform a radical treatment and remove the entire cyst for the following reasons: adherence to the vena cava with a wide margin of contact, either longitudinal or circumferential and/or adherence to the hepatic hilum with margin of contact to the portal or biliary confluent and/or large size of the cyst with involvement of two suprahepatic veins, and a conservative surgery had to be performed. All patients undergoing surgery received 400 mg of albendazole every 12 h 4 days before surgery and 26 days after. Cysts were classified as viable or not according to the presence of germinal layer, protoscolices, or daughter cysts.

Category variables were expressed as absolute frequencies and percentages, whereas continuous parameters were expressed as medians and ranges. Differences in proportions between groups were assessed by the χ^2 test or by Fisher's exact test for categorical variables and by the Mann-Whitney U test for continuous variables. Statistical analyses were performed using SPSS software version 21; two-tailed p value < 0.05 was statistically significant.

The STROBE statement guidelines were used to improve the quality of the study.[11] The study was conducted according to the Declaration of Helsinki, and it was approved by the Ethics Committee for Clinical Investigation and Research Projects of Vall d'Hebron University Hospital [PR (AG) 25/2016]. Informed consent was not required.

Results

We selected 368 possible cases of hydatid disease from the hospital diagnostic records, the Hepatic Surgery registry, and Microbiology registry. One hundred fifty-one patients fulfilled the inclusion criteria (Fig. 1). Seventy-eight (51.7%) patients

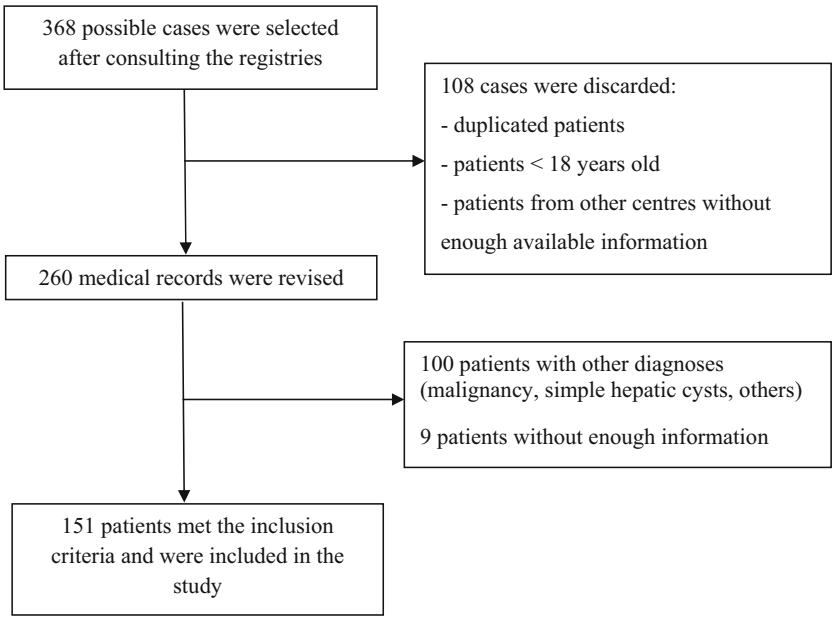

Fig. 1 Flow diagram of patients

were women and the median age at diagnosis was 68 (15–92) years. One-hundred twenty-nine (85.4%) patients were autochthonous (autonomous communities of origin are represented in Fig. 2) and 22 (14.6%) patients were immigrants (7 patients came from Morocco, 6 from Romania, 3 from Peru, 1 from Argentina, 1 from Bolivia, 1 from the Dominican Republic, 1 from Georgia, 1 from Italy, and 1 from Western Sahara). Thirty (19.9%) patients had an immunosuppressant condition: 5

Fig. 2 Geographical distribution regarding autonomous communities of origin of Spanish patients with CE. Values are expressed as the number of patients (%)

patients had HIV infection, and 25 had an oncohematological disease.

Symptoms led to the diagnosis in 54 (35.8%) cases and it was an incidental radiological finding in the remaining 97 (64.2%) patients. Most common symptoms were as follows: pain in 44 (29.1%) patients, fever in 6 (4%), jaundice in 4 (2.6%), and respiratory symptoms in 4 (2.6%). Less frequent symptoms were a tumor in 2 (1.3%), urological symptoms in 2 (1.3%), 1 patient had a constitutional syndrome without evidence of malignancy or other medical explanation, and 1 presented saddle anesthesia because of soft tissue and bone involvement. Only 2 (1.3%) patients had eosinophilia, and 2 (1.3%) had a hypersensitivity reaction: 1 had an urticaria and the other had an episode of anaphylaxis secondary to hydatid cyst rupture during surgery.

The liver was the most frequent location [135 (89.4%) patients], followed by multiple locations in 5 (3.3%) patients. Five (3.3%) patients had bone and/or soft tissue involvement, 2 (1.3%) patients had spleen lesions, 2 (1.3%) had renal involvement, 1 (0.7%) had lung lesions, and 1 (0.7%) had heart involvement. The median number of lesions was 1 (1–10) and median size was 65 (13–300) mm.

Serology test was only available for 93 (61.6%) patients, and it was positive for 48 (51.6%) patients. Different imaging tests were performed depending on the location or suspicion of complication. In 125 (83.3%) patients, a computed tomography scan was performed, in 112 (74.7%) an ultrasound, and in 29 (19.3%) a magnetic resonance. Radiological signs of calcification were observed in 120 (79.5%) cases. The WHO-IWGE classification was available in 70 of the 104 (67.3%) cases of liver cysts that had an ultrasound (Table 1).[10]

The original therapeutic approach was "watch and wait" in 76 (50.3%) patients, surgery in 67 (44.4%), and chemotherapy in 8 (5.3%). All 5 patients with hepatic and extra-hepatic involvement were treated surgically. The PAIR (puncture-aspiration-injection-re-aspiration) technique was not performed in our hospital. Thirty-one (20.5%) patients needed a change of treatment plan because of progression or recurrence. Table 1 shows the therapeutic approach and recurrences depending on the WHO-IWGE classification, and Fig. 3 shows the first therapeutic approach and treatment of those who progressed or recurred. When we compared clinical data between the patients treated surgically and the other patients (Table 2), we found that surgical patients were younger ($p < 0.01$), there were less immunosuppressed patients in this group ($p < 0.01$), more patients were symptomatic ($p < 0.01$), the liver was less frequently affected ($p < 0.01$), multiple site location was more frequent ($p = 0.01$), hydatid cysts were larger ($p < 0.01$), cysts were less calcified ($p < 0.01$), and there were fewer deaths ($p < 0.01$). We did not find significant differences in the frequency of recurrence between patients treated conservatively (21.4%) and those treated surgically (19.4%), $p = 0.76$.

Of the initial 53 liver cysts that underwent surgery, a radical surgery was performed in 34 (64.2%) (a pericystectomy in 22, and a liver resection in 12), a conservative surgery in 14 (26.4%), and the extent of the intervention was unknown in 5 (9.4%). Of the 25 liver cysts that underwent surgery after a first recurrence, a radical surgery was performed in 16 (64%) (a pericystectomy in 10, and a liver resection in 6), a conservative surgery in 4 (16%), and the extent of the intervention was unknown in 5 (20%). From the total of 78 patients who underwent liver surgery (53 as initial approach and 25 as second treatment), 27 (34.6%) presented surgical complications: there were 16 infections, 5 hemorrhages, 4 biliary complications, and 2 had other complications (Budd-Chiari-like syndrome secondary to suprahepatic vein stenosis, and pleural effusion).

Table 1 Therapeutic approach and outcome in 70 patients with liver cyst and available WHO-IWGE classification

WHO-IWGE classification	$N = 70$	Therapeutic approach	Outcome
CE1	2 (2.9%)	2 ➔ watch and wait	1 (50%) relapse
CE2	0	–	–
CE3a	1 (1.4%)	1 ➔ surgery (viable cyst)	0 relapses
CE3b without calcification	8 (11.4%)	3 ➔ watch and wait 3 ➔ surgery (2 viable and 1 non-viable cyst) 2 ➔ chemotherapy	1 (33.3%) relapse 0 relapses 1 (50%) relapse
CE3b with calcification	5 (7.1%)	4 ➔ watch and wait 1 ➔ surgery (viability unknown)	1 (25%) relapse 0 relapses
CE4	13 (18.6%)	6 ➔ surgery (4 viable, 1 non-viable, and 1 unknown) 5 ➔ watch and wait 2 ➔ chemotherapy	1 (16.7) relapse 1 (20%) relapse 0 relapses
CE5	41 (58.6%)	32 ➔ watch and wait 7 ➔ surgery (3 viable, 2 non-viable, 2 unknown) 2 ➔ chemotherapy	2 (6.7%) relapses 2 (28.6%) relapses 1 (50%) relapse

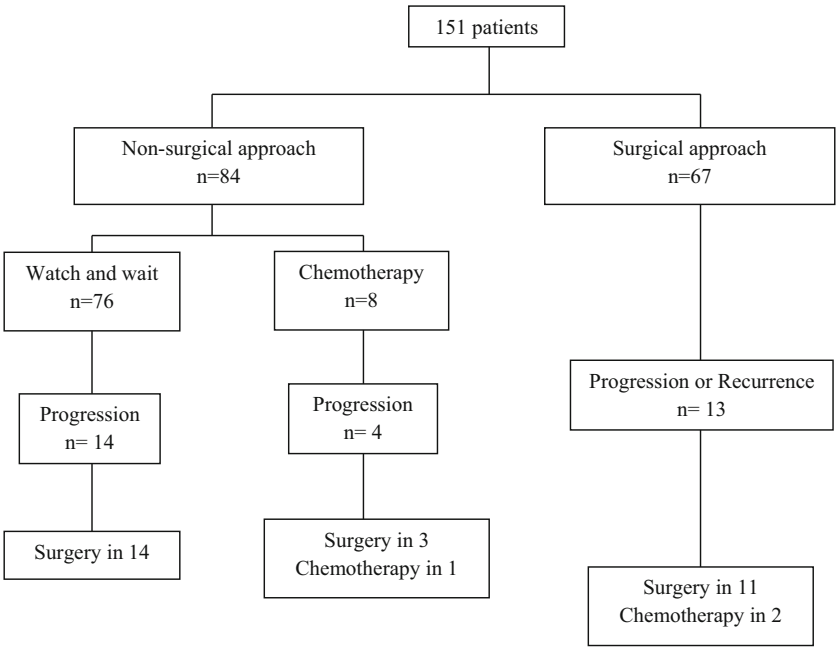

Fig. 3 Therapeutic approach

The incidence of biliary fistula in liver cyst without surgery was 5.9% and after surgery 3.8%.

From the 94 surgeries including all locations, we had histological information of 62 pathology samples. Thirty-six (58.1%) samples had signs of viability and 26 samples (41.9%) had no signs. In 43 patients, both information about cystic calcification and viability were available. The proportion of viable cysts was higher in cysts without calcification compared with those with calcification [72.7% (8 out of 11) vs. 56.2% (18 out of 32), $p = 0.48$]. Regarding serology results and

Table 2 Comparison of epidemiological and clinical features between the patients undergoing a surgical treatment and those undergoing non-surgical treatment

	Surgical approach (*n*/%) (*N* = 67)	Non-surgical approach (*n*/%) (*N* = 84)	*p* value
Women	33 (49.3)	45 (53.6)	0.60
Age at diagnosis (years), median (range)	52 (15–80)	69 (22–92)	< 0.001
Immunosuppression	5 (7.5)	25 (29.8)	< 0.001
Cyst location			
Liver	53 (79.1)	82 (97.6)	< 0.001
Multiples sites	5 (7.5)	0	0.02
Bone and/or soft tissue	4 (6)	1 (1.2)	0.17
Spleen	2 (3)	0	0.20
Kidney	2 (3)	0	0.20
Lung	1 (1.5)	0	0.44
Heart	0	1 (1.2)	1
Presence of symptoms	42 (62.7)	12 (14.3)	< 0.001
Positive serology	33 (49.3)	15 (17.9)	0.19
Number of lesions, median (range)	1 (1–10)	1 (1–5)	0.65
Size (mm), median (range)	80 (40–300)	50 (13–150)	< 0.001
Cyst calcification	46 (68.7)	74 (88.1)	0.01
Change of therapeutic plan	13 (19.4)	18 (21.4)	0.76
Follow-up (months), median (range)	58 (5–590)	58.5 (1–285)	0.97
Deaths	7 (10.5)	21 (25)	0.02

viability in pathology samples, information from 39 patients was available. The proportion of viable cysts was slightly higher in patients with positive serology compared with those with negative serology [63.6% (14 out of 22) vs. 58.8% (10 out of 17), $p = 0.76$].

Median follow-up was 58 (1–590) months, and during this period, there were 28 (18.5%) cases of deaths, none of them related to CE.

Finally, we compared demographic characteristics and clinical data between two groups depending on immunosuppression (Table 3). We found that immunocompromised patients were older ($p = 0.01$), diagnosis was more frequently a radiological finding ($p < 0.01$), there were fewer lesions ($p = 0.05$), hydatid cysts were smaller ($p = 0.03$), initial approach was more often non-surgical ($p < 0.01$), time of follow-up was shorter ($p = 0.04$), and there were more deaths ($p = 0.01$).

Discussion

We found that our population with CE was predominantly autochthonous and there was a non-depreciable group of immunocompromised patients. The diagnosis was mainly due to a radiological finding and the most frequent location was the liver. Serology was positive only in half of the patients. The most frequent original therapeutic plan was "watch and wait" followed closely by surgery, and therapeutic algorithm suggested by WHO was not always followed, particularly in CE4 and CE5 stages. Less than a quarter needed a change of treatment plans because of progression or recurrence.

Our cases with CE were predominantly autochthonous which reinforces the fact that in recent years, the incidence of this disease remained stable, despite being a notifiable disease and the prevention measures established in each community.

Nearly 20% of the patients in our series were immunocompromised, mostly secondary to an oncohematological disease. The diagnosis was due to a radiological finding and lesions were smaller in these patients, probably due to incidental diagnoses occurred during extension studies carried out periodically in this population. We could not find any differences in serology results depending on the state of immunosuppression, but we do not discard that serology may be less useful in these groups of patients due to higher a number of false negatives. Given that oncohematological patients had a worst prognosis and they were susceptible to drug toxicity because of concomitant chemotherapy, "watch and wait" was the preferred therapeutic plan. Follow-up was shorter and they suffered more deaths related to their oncohematological disease, so we were not able to compare the evolution of the hydatid cyst between the two groups, which could have been influenced by the immunological state. No studies have assessed the characteristics of CE in this population and further studies are needed to know if this disease behaves more aggressively with faster growth in this population.

As in previous studies, most patients had a single cystic lesion and the most frequent location was the liver.[12–14] Serological tests were positive in 51.6%, which suggests that the sensitivity is lower than in previous studies, which established a sensitivity using IHA, ELISA, or latex agglutination, with hydatid cyst fluid antigens, between 85 and 98% for liver cysts, 50–60% for lung cysts, and 90–100% for multiple organ cysts.[10,15,16] Moreover, since specificity of all tests is limited by cross-reactions due to other cestode infections, other helminth diseases, malignancies, and liver cirrhosis,[15–17] serology may be useful only to support the diagnosis of CE, but not to reject it, due to its limitations in sensitivity and

Table 3 Comparison of epidemiological and clinical features between immunocompromised (IC) and non-immunocompromised (non-IC) patients with CE

	Non-IC (*n*/%) (*N* = 121)	IC (*n*/%) (*N* = 30)	*p* value
Women	60 (49.6)	18 (60)	0.31
Age at diagnosis (years), median (range)	62 (15–92)	69 (27–88)	0.01
Spanish origin	103 (85.1)	27 (90)	0.77
A radiologic finding	70 (57.9)	27 (90)	0.001
Positive serology	41 (33.9)	7 (23.3)	0.16
Number of lesions, median (range)	1 (1–10)	1 (1–5)	0.05
Size (mm), median (range)	70 (18–300)	45 (13–150)	0.03
Cyst calcification	95 (78.5)	25 (83.3)	0.53
Initial surgical approach	62 (51.2)	5 (16.7)	< 0.001
Change of therapeutic plan	28 (23.1)	3 (10)	0.13
Signs of viability	26 (61.9)	1 (33.3)	0.56
Follow-up (months), median (range)	73 (1–590)	36 (1–285)	0.04
Deaths	18 (14.9)	10 (33.3)	0.01

specificity.[18–20] When we studied if there was any relationship between positive serology and viability in pathology samples, we did not find any significant difference. We also did not find any significant difference between clinical features.

As for imaging procedures, computed tomography was the most used technique and ultrasound the second one. Interestingly, a positron emission tomography was performed in 6 patients for other reasons, but in none of them, hydatid cysts showed increased metabolism. However, none of the 6 patients underwent surgery to confirm that there were no signs of viability in pathology samples. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography has been proposed as a non-invasive tool for the three-dimensional detection of metabolic activity in hepatic alveolar echinococcosis lesions,[21] but its utility in CE is still unknown.

Unfortunately, the WHO-Informal Working Group on Echinococcosis (WHO-IWGE) classification[10] was only available in 67.3% of ultrasound radiological reports of the liver cysts. This could be explained because some patients came from other hospitals to undergo surgery and a CT scan was the only image performed, or because at the beginning there was not a multidisciplinary team of radiologists, surgeons, and infectious diseases specialists that discussed and followed every case. This suggests that the therapeutic algorithm of international recommendations might have been difficult to apply in some cases or might not have been used at all to decide treatment, as previously reported.[22,23] In fact, international recommendations were not followed in some patients with liver cysts in stages CE4 and CE5, which received chemotherapy in 13.4% and 4.9% of cases, respectively, or surgical treatment in 46.2% and 17.1%, respectively. This was probably because our hospital is a referral center for liver surgery and because sometimes WHO's recommendations were not appropriate for individual cases with large calcified symptomatic cysts or that had a high risk for complications since they were close to important structures.

We lack high-quality comparative clinical trials of the four treatment options to resolve important questions such as efficacy, effectiveness, rate of adverse events, relapse rates, and cost. Data are mostly derived from case series and small clinical trials, and treatment guidelines remain at the level of expert opinion. Moreover, clinical decision-making is even more difficult in extra-hepatic and extra-pulmonary locations.[24,25] In our cohort, an initial non-surgical approach was the most frequent treatment. Theoretically, surgery is indicated mainly in cases of large hydatid cysts with daughter vesicles or complicated cysts.[13] Although patients treated surgically had larger symptomatic cysts, only 58.1% pathology samples showed signs of viability, suggesting that perhaps the surgical option may have been wrongly chosen in some occasions, with the comorbidities and the economic expense that it may entail.[26] More clear criteria for the watch and wait option might avoid unnecessary surgical interventions and save health services money.[24] It should be noted that because we do not perform PAIR, surgical approach may have been overused. The reported success rate of percutaneous treatment in non-complicated cysts is similar to that of surgery with the advantage of a shorter duration of hospital stay and lower incidence of biliary fistula and residual cavity relapse, which reinforces the need to train our radiologists in this procedure.[27,28]

Twenty percent of patients needed a change of therapeutic plan because of progression or recurrence, as in previous reports where recurrence rates range from 2 to 25%.[29] Surprisingly, the rate of progression or recurrence was similar in patients treated conservatively or surgically. The postoperative complication rate was like the previous studies.[30]

Although it is established that usually inactive cysts only require radiological monitoring, it is known that the presence of calcification is not a reliable indicator of non-viability. It is more frequent in CE4 and CE5, but it may be observed at all stages.[4,31,32] Interestingly, we did not find any significant relationship between the presence of calcification and the absence of signs of viability in pathology samples, although our sample size was small. The reported mortality rate from CE is low (about 2–4%).[10] In our study, there were 18.5% of deaths, none of them related to CE, which may reflect an aging population and a high number of patients with oncologic diseases.

Considering the low sensitivity of the serology, the absence of cyst stage information in near half of radiological reports, and that in 42% of the surgical samples there were no signs of viability, we want to emphasize the importance of creating multidisciplinary teams formed by radiologists, surgeons, and infectious diseases specialists to optimize the therapeutic management of these patients. Referral centers should be designed in different autonomous communities in Spain to allow a better diagnosis, treatment, and follow-up. We believe that this would improve the notification of new cases and this could help to optimize prevention measures to try to reduce the incidence of CE in our population.

The main limitation of this study was the retrospective nature and single-center design. In consequence, some cases may have been lost due to wrong codification and many different specialists may have been involved in the management of these patients across time. In addition, serologic tests included different techniques depending on the period when they were performed, which did not allow us to analyze serologic evolution. Moreover, as previously mentioned, in many cases, we did not have the WHO-IWGE ultrasound classification of echinococcal cysts to evaluate therapeutic plans. However, the strengths of the study include the large number of cases and the follow-up, which allowed us to evaluate recurrences. Nowadays, there are a few

studies that describe epidemiological and clinical data of CE in a European country.

Conclusion

Patients with CE in our study were predominantly autochthonous, in most of them the diagnosis was due to a radiological finding, and there was a non-depreciable group of immunocompromised patients. Serology was not useful for CE diagnosis and neither serology nor calcification of the cyst helped to predict viability. The most frequent initial therapeutic approach was non-surgically, although international recommendations regarding treatment were not always followed. Patients treated surgically were younger, immunocompetent, more symptomatic, and had larger and less calcified cysts that affected multiple sites. Only 58.1% of pathology samples showed signs of viability, suggesting surgical option may be overused in some cases. Although further larger and prospective studies are needed, we suggest that management of CE should not be based on the presence of calcification, since the viability of the cyst is not related to this finding. Continuous education and training of the relevant health professionals are needed because CE is still endemic in our country. The formation of multidisciplinary teams in reference hospitals to evaluate patients with CE could help improve the diagnosis, management, follow-up of these patients, and the number of notifications.

Author Contributions All authors have made substantial contributions to the manuscript, have participated in the acquisition, analysis, and interpretation of data, and have participated in the drafting and revision of the work.

Compliance with Ethical Standards

The study was conducted according to the Declaration of Helsinki, and it was approved by the Ethics Committee for Clinical Investigation and Research Projects of Vall d'Hebron University Hospital [PR (AG) 25/2016]. Informed consent was not required.

Conflict of Interest The authors declare that they have no competing interests.

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