ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH PRE-SURGICAL COMPLICATIONS IN PATIENTS WITH CYSTIC ECHINOCOCCOSIS FROM ENDEMIC AREAS OF PERU

Juana Pacífico[1,a,b], Rufino Cabrera[2,c], Sara Salgado-Díaz[3,d,e], Wilfredo Mormontoy[4,f], Luis Suárez-Ognio[2,d,g]

[1] Departamento de Estadística, Demografía, Humanidades y Ciencias Sociales, Facultad de Ciencias y Filosofía, Universidad Peruana Cayetano Heredia, Lima, Perú.

[2] Escuela de Medicina, Facultad de Ciencias de la Salud, Universidad Peruana de Ciencias Aplicadas, Lima, Perú.

[3] Servicio de Cardiología, Hospital Militar Central "Luis Arias Schereiber", Lima, Perú.

[4] Departamento de Estadística, Demografía, Humanidades y Ciencias Sociales, Facultad de Ciencias y Filosofía, Universidad Peruana Cayetano Heredia, Lima, Perú.

[a] Pharmaceutical Chemist; [b] Master in Epidemiology; [c] Biologist; [d] Physician; [e] Specialist in Cardiology; [f] Master in Public Health; [g] Specialist in Field Epidemiology.

This study is part of the thesis of Pacífico J. Factores de riesgo para desarrollar complicaciones preoperatorias en pacientes con equinococosis quística en un área endémica de los Andes centrales del Perú [Thesis for specialization in Statistics for Research]. Lima: Facultad de Ciencias y Filosofía, Universidad Peruana Cayetano Heredia; 2020.

ABSTRACT

Objective: To identify risk factors to pre-surgical complications in patients with cystic echinococcosis (CE) in endemic areas of Peru. **Materials and methods**: Study of cases (n=43) and controls (n=127) not paired was designed, with a case-control ratio of 1:3 based on a secondary source. A case was defined as a patient with CE who presented pre-surgical complications related or not with the disease and the control without pre-surgical complication. The response variable was preoperative complication and the exposure variables were age, gender, degree of instruction, occupation, number, size (diameter in centimeters) and location of the cyst. To identify the risk factors, a bivariate logistic regression analysis was performed to obtain the crude odds ratios (cOR) and then the variables with significant association were adjusted by a multivariate logistic regression analysis using the Stata® version 14 software, obtaining the adjusted odds ratios (aOR). **Results**: Fifty eight point eight percent (24/43) of the cases were women and the median age was 35 years and 59.1% (75/127) of the controls correspond to the female gender and the median age was 27 years. The multivariate logistic regression analysis found that being over 56 years old has an aOR 2.91 (95% confidence interval [CI]: 1.007-8.433) and having ≥3 cysts has an aOR 4.26 (95% CI: 1.62-11.22) for present pre-surgical complications in patients with CE. **Conclusion**: It was identified that being over 56 years old and having ≥3 cysts are risk factors for presenting pre-surgical complications in CE.

Keywords: Echinococcosis; Risk Factors; Case-Control Studies; Neglected Diseases; Peru (source: MeSH NLM).

Cite as: Pacífico J, Cabrera R, Salgado-Díaz S, Mormontoy W, Suárez-Ognio L. Factores asociados a complicaciones prequirúrgicas en pacientes con equinococosis quística de áreas endémicas del Perú. Rev Peru Med Exp Salud Publica. 2021;38(1):33-40. doi: https://doi.org/10.17843/rpmesp.2021.381.5295.

Correspondence: Juana Pacífico; Jr. Puno N.o 1002, Lima, Perú; juana.pacifico@unmsm.edu.pe

Received: 25/02/2020
Approved:23/09/2020
Online: 04/01/2021

INTRODUCTION

Cystic echinococcosis (CE), also known as hydatidosis, is a parasitic zoonosis caused by the larvae (metacestode) of *Echinococcus granulosus*, a parasitic helminth found in its adult form in the intestine of dogs and other canids [(1)]. CE is usually asymptomatic; the clinical picture is variable and depends on factors related to both the host and the parasite [(2)].

CE affects more than one million people per year [(2)] and causes 1,009,662 disability-adjusted life years (DALYs) due to the human burden [(3)]. In Peru, the estimated annual cost of human CE is USD 2,420,348 (95% CI: 1,118,384 – 4,812,722) [(4)]. In five countries in the Americas, between 2009 and 2014, Peru had 70.3% (20,785) of the total number of cases with an annual cumulative incidence rate (ACIR) between 10 to 12.5 per 100,000 population [(5)].

On the other hand, CE has been recognized by the World Health Organization (WHO) as one of the 17 neglected tropical diseases [6] and recommended enabling echinococcosis control strategies, through pilot projects, in countries where it has been considered a public health problem [7]. Currently, control tools are already available for large-scale use [7].

Percutaneous treatment, conventional surgery, the use of antiparasitic drugs and follow-up or observation are the international standard [8]; however, a considerable proportion of patients develop complications that require protocolized attention [3]. Complications may be due to rupture inside or outside of the compromised organ, superinfection of cysts, anaphylaxis reactions to parasite antigens, among others [8]. They can be detected in the pre-surgical and post-surgical stages, the most common being the cystobiliary fistula in the hepatic location, which significantly increases the post-surgical hospital stay [9].

In a series of CE in Peru, 4% presented preoperative complications and 10.8% postoperative complications. Malnutrition, acute abdomen and empyema were the most frequent postoperative complications [10]. It is known that morbidity in hepatic hydatidosis can reach up to 80% and lethality up to 10%, which is associated to complications of the disease and surgical procedures [11].

Age, hepatic location, size, number of cysts, rupture and biliary fistula have been identified as risk factors or predictors of postoperative complications or morbidities [12-19]. Predictors of mortality [12], risk factors for complications during surgery [20] and factors associated with peritoneal perforation [21,22] have also been investigated, but there have been no studies aimed at identifying risk factors for developing preoperative complications. Identification of these factors is very important to reduce hospitalization costs and the risk of death. Surgical techniques have been associated with the risk of death [11-12] and up to 20% of complications have been reported in patients who have undergone surgery [22]; therefore, we consider it to be necessary to study the factors associated with pre-surgical complications.

The aim of this study was to identify factors associated with preoperative complications in patients with CE from endemic areas of the central Andes of Peru.

KEY MESSAGES

Motivation for the study: Most people with cystic echinococcosis (CE) or hydatidosis, caused by larvae of the dog tapeworm Echinococcus granulosus, do not develop symptoms; however, a proportion of them become complicated before and/or after surgery.

Main findings: In this study, being older than 56 years and having ≥3 cysts were found to be associated with pre-surgical complications in patients with CE.

Implications: The results are of interest for decision making before submitting a patient to surgery.

MATERIALS AND METHODS

Study design

This article was written following the STROBE recommendations for observational studies [23]. A case-control, unpaired study was designed with a case-control ratio of 1:3 according to a secondary source. A "case" was defined as a patient with CE who had pre-surgical complications related or not to the disease in the original study (empyema, respiratory failure, pneumonia, hemoptysis, atelectasis, pneumothorax, acute abdomen, chronic calculous cholecystitis, cardiac compromise, malnutrition, anaphylactic shock, portal hypertension, sepsis, type II diabetes, epilepsy, obesity and gestation) [10]. A "control" was defined as a patient with CE without any pre-surgical complications. Exposure variables were retrospectively compared between cases and controls to identify those associated with pre-surgical complications.

Study population

This was a secondary source study and used the database of a series of CE cases from the central Andes of Peru [10]. The distribution of those cases by location was as follows: 85.6% were from the department of Junín, 8.4% from Huancavelica, 3.4% from Pasco, 1.3% from Lima, and 0.5% from Huánuco [10].

We included all cases and controls from the original study that had complete information on potential risk factors for developing presurgical complications.

Variables

Pre-surgical complication was considered as the dichotomous response variable (yes, no), and was collected according to the definition described above [10]. The exposure variables were age, gender, education and occupation and the clinical variables were: number of cysts, cyst size (diame-

https://doi.org/10.17843/rpmesp.2021.381.5295

ter) and cyst location (liver and other [lung, abdomen and others]).

Sample size

The sample size for the unpaired case-control design was calculated using the Epi.Info software version 7.1.5.2 of the Centers for Disease Control and Prevention of the United States of America. The sample size was calculated taking into account the following parameters: 95% confidence level, statistical power of 80% and three controls for each case, the latter being used to increase statistical efficiency [24]. Likewise, having two or more hydatid cysts was used as an exposure variable, whose original values were rounded, 54% among cases (with pre-surgical complications), 30% among controls and an expected odds ratio (OR) of 2.74 [14]. This source was used because no previous study on risk factors for developing pre-surgical complication was found. The calculated sample size was 43 cases and 127 controls.

Sample selection

Controls (n = 127) were selected by simple random sampling performed with the Stata version 14 software (StataCorp LLC), all selected controls were checked to see that they had complete information and those that did not were randomly replaced until the sample was complete (Figure 1). Forty-three of 44 cases from the original study database were included [10].

Statistical analysis

From the data of the original study, we created a database in Microsoft Excel with the selected cases and controls, and then imported the information into Stata version 14 (StataCorp LLC) for analysis.

The exploratory analysis of the categorical variables was carried out using relative and absolute frequencies. To obtain the p-value, we evaluated the assumptions of using Chi-square or Fisher's exact test. The employment variable was measured as a polytomous variable and the degree of education as an ordinal variable, which was recategorized from eight to four categories. For continuous variables, normality was assessed using the Shapiro Wilk test and homogeneity of variances using the Levene's test. For variables with a non-normal distribution, we used the non-parametric Mann-Whitney U. rank sum test (Wilcoxon or Wilcoxon-Mann-Whitney test) to determine the p value; in addition, since it was a non-normal distribution, the interquartile range (IQR) and the median were obtained.

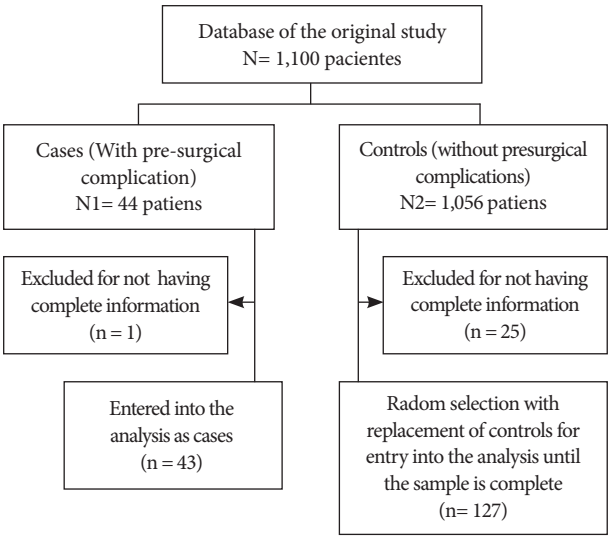

Figura 1. Flow chart for the selection of study participants.

Continuous variables such as the age of the patients, the number and size (diameter) of the cyst were each categorized into a dichotomous variable. Regarding age, in China was reported that the mean age of deaths due to CE was 56 years [25] and we consider that China and Peru are countries with very high prevalence in the world [1] that could have similar epidemiological characteristics. Likewise, we set as a cut-off point, 3 or more for the number of cysts according to a previous study [13] and 14 cm for the diameter of the cyst.

Then, a multivariate analysis was performed to identify the variables or factors that could be associated with pre-surgical complications independently or controlling the effect of the other variables. For this purpose, we applied the multivariate logistic regression model and the variables that entered the model were those with a $p < 0.2$. Finally, the adjusted ORs (ORa) were calculated with a 95% confidence interval.

Biases were controlled by random selection of controls, inclusion criteria for cases and controls, in addition to multivariate regression analysis of potential risk factors. In the multivariate analysis, cyst size was considered as a potential confounder.

Ethical Aspects

This study was approved by the Institutional Research Ethics Committee of the Universidad Peruana Cayetano Heredia and was authorized by the National Center for Epidemiology, Prevention and Disease Control (CDC) of the Ministerio de Salud for the use of the database.

RESULTS

A total of 170 participants were included in the study, of which 43 were cases and 127 were controls. Of the cases, 55.8% (24) were female and the median age was 35 years, while 59.1% (75) of the controls were female and the median age was 27 years. Other characteristics of the cases and controls are presented in Table 1.

Table 2 shows the results of the bivariate logistic regression analysis. An association was found between being older than 56 years, educational level and having ≥3 cysts with the risk of developing pre-surgical complications in patients with CE, considering a $p < 0.05$.

The results of the multivariate logistic regression analysis

Table 1. Characteristics of cases (with pre-surgical complications) and controls (without complications) from cystic echinococcosis endemic areas.

Variable	Cases (with complications) (n = 43)		Controls (without complications) (n = 127)		p Value
	n	%	n	%	
Gender					
Female	24	55.8	75	59.1	0.710*
Male	19	44.2	52	40.9	
Age (years)					
Median (IQR)¶	35 (41)		27 (27)		0.457**
Older than 56 years	8	18.6	10	7.9	0.050***
Younger or equal to 56 years	35	81.4	117	92.1	
Level of education					
Superior	4	9.3	17	13.4	0.419*
Secondary school	12	27.9	49	38.6	
Preschool and elementary school	25	58.1	57	44.8	
Without education level	2	4.7	4	3.2	
Employment					
Farmer	1	2.3	7	5.5	0.625*
Housewife	8	18.6	30	23.6	
Student	20	46.5	62	48.8	
Other	14	32.6	28	22.0	
Time of illness (years)					
Median (IQR)¶	0.16 (0.70)		0.25 (0.60)		0.912**
Number of cysts					
Median (IQR)¶	1 (2)		1 (1)		0.044**
≥3 cysts	11	25.6	10	7.9	0.002*
1-2 cysts	32	74.4	117	92.1	
Cyst size (diameter)					
Median (IQR)¶	10 (4)		10 (3)		0.988**
Bigger than 14 cm	10	23.3	17	13.4	0.126*
Smaller or equal to 14 cm	33	76.7	110	86.6	
Cyst location					
More than one location	6	14.0	23	18.1	0.531*
One location	37	86.0	104	81.9	
Affected organ					
Liver	30	69.8	81	63.8	0.476*
Other organ	13	30.2	46	36.2	

¶ Non-normally distributed variable. * Chi-square test. ** Wilcoxon rank sum. *** Fisher's exact test.
IQR: interquartile range.

https://doi.org/10.17843/rpmesp.2021.381.5295

Table 2. Bivariate and multivariate logistic regression analysis to assess the risk of presenting pre-surgical complications in patients with cystic echinococcosis.

Variable	Crude Model		Adjusted Model ¶	
	OR (95% CI)	p Value	ORa (95% CI)	p Value
Gender				
Female	1.14 (0.56-2.29)	0.710	--	
Male	Reference			
Age (years)				
Older than 56 years	2.67 (0.98-7.29)	0.050	3.05 (1.07-8.64)	0.035
Younger or equal to 56 years	Reference		Reference	
Level of education				
Superior	Reference			
Secondary school	1.04 (0.29-3.66)	0.950	--	
Preschool and elementary school	1.86 (0.56-6.10)	0.304	--	
Without education level	2.12 (0.28-15.96)	0.464	--	
Employment				
Farmer	Reference			
Housewife	1.86 (0.19-17.45)	0.584	--	
Student	2.25 (0.26-19.48)	0.459	--	
Other	3.5 (0.39-31.31)	0.262	--	
Number of cysts				
≥3	4.02 (1.56-10.31)	0.002	3.97 (1.50-10.46)	0.005
1-2	Reference		Reference	
Cyst size (diameter)				
Bigger than 14 cm	1.96 (0.81-4.69)	0.126	1.05 (0.97-1.13)	0.186
Smaller or equal to 14 cm	Reference		Reference	
Cyst location				
More than one location	0.73 (0.27-1.94)	0.531	--	
One localization	Reference			
Affected organ				
Liver	1.31 (0.62-2.75)	0.476	---	
Other organ	Reference			

¶ Adjusted for the variables shown in the column.
OR: odds ratio.

are shown in the same table. According to the methodology described, variables with a p value < 0.200 were included in the model. We found that being older than 56 years and ≥3 cysts are risk factors for presenting pre-surgical complications in patients with CE.

DISCUSSION

In this unpaired case-control study, where eight variables were evaluated as potential risk factors for developing pre-surgical complications in patients with CE from endemic areas of the central Andes of Peru, using multivariate logistic regression analysis, we identified that being older than 56 years and having three or more hydatid cysts were risk factors for pre-surgical complications.

This is the first study to identify risk factors for pre-surgical complications in patients with CE, based on one of the largest published historical case series of CE from the central highlands of Peru [10]. Most studies in other endemic countries have identified risk factors or predictors for developing post-surgical complications or morbidities [12,14-19], predictors of mortality [12], risk factors during surgery [20] and factors associated with peritoneal perforation [21-22]. It is crucial to

identify pre-surgical complications, because it would allow timely hospitalization, avoiding severe complications that could worsen the prognosis [21] or would allow safer and more appropriate interventions to reduce the risk of death. In addition, surgical techniques have been identified as a factor associated with the risk of dying [11-12]. Surgical intervention during the identification of risk factors for developing post-surgical complications in hydatidosis could be a bias.

In this study, we identified that patients with CE older than 56 years have 3.05 times the chance of having pre-surgical complications compared to those aged 56 years or younger. In a historical series of deaths produced by echinococcosis in China, reported between 2008 and 2016, the median age was 56 years [25]. For that reason, we took age categorized into two strata as the cutoff point for the analysis and also because of similar epidemiological characteristics [1]. In a case-control study in Chile, where the authors did not calculate the sample size, they found that cases (with post-surgical morbidity) with an average age of 59 ± 18.8 years had a 1.07 times higher risk of presenting morbidity compared to controls with an average age of 41 ± 16.3 years [14]. In another retrospective longitudinal study, although age was not associated with complications or mortality, the mean age of 491 patients with CE was 59.5 ± 20.4 [22].

In this study, the median age of the cases was 35 with a IQR of 41 years, higher than the median and IQR of the controls (27 years). In a study on predictors of morbidity and mortality in patients with hepatic CE, who underwent surgery, it was found that being older than 40 years had a risk (OR) of 2.84 times more compared to those who were less than 40 years old, and the risk increased with age [12].

Being older than 56 years as a risk factor for pre-surgical complications has plausibility, because it could be associated with permanent exposure to risk, i.e., to *E. granulosus* eggs, given that the central Andes are hyperendemic areas with very high incidence rates [5]. On the other hand, it has been suggested that in older people, the development of complications could be associated with comorbidities [15], and may also be related to the growth of cysts.

In the bivariate analysis of categorized age, we found an association in strata ≥40 years and <40 years and between ≥60 years and <60 years, but no increase in the magnitude of the association was observed. In Spain, the mean age in a retrospective cohort of patients with complications was 59 years ± 20.3 years [26] and was a risk factor, evidencing that the cutoff point taken in this analysis has an epidemiological basis.

In this study, we also identified that patients with three or more cysts have 3.97 times more chance of presenting pre-surgical complications compared to those with one to two cysts. A greater number of cysts would increase the risk of post-surgical complications of CE, but mainly, of death [12]. Patients who have three or more cysts have between 2.55 to 3.1 times more risk than those who have between one and two cysts to develop post-surgical morbidity or complication [13,16]. In a case series in Turkish patients, it was found that having several cysts and of the bilobular type significantly increased the risk of intrabiliary rupture [20]. The fact that having three or more cysts in CE patients is a risk factor for pre-surgical complications may be due to multiple exposures of individuals in endemic areas. In a cross-sectional study of participants from three districts of the Junin region, the mean age and length of residence showed a significant statistical association for being seropositive for *E. granulosus* larvae [27]. Peru does not yet have a national CE control program and interventions have been highly focused.

In our study, gender, education level, occupation, size and location of the cyst were not identified as risk factors for presenting pre-surgical complications; however, in a previous study, patients with hepatic CE with central hepatic location of the main lesion of uncomplicated cysts have 3.94 times more risk compared to those with lateral location for presenting post-surgical morbidity [14]. In a systematic review, it was identified that patients with hepatic hydatidosis with cysts located in the "hepatic dome" have 2.84 times more risk than other hepatic locations for developing post-surgical morbidity [13].

On the other hand, in a prospective cohort study that investigated whether cysto-biliary communication is a risk factor for post-surgical morbidity, the authors found that patients with 15.4 ± 6.8 cm in diameter had a relative risk (RR) of 1.49 times more compared to those with cysts with smaller diameters; however, the risk was higher (3.41) when comparing the group without cysto-biliary communication (CBC) and with two or more episodes of CBC [14]. In a historical series, the authors found that patients with cysts >10 cm in diameter had a 2.8 (OR) chance of morbidity or death compared to those patients with ≤10 cm [12].

In another study in Turkey, when comparing patients with and without peritoneal perforation, the authors found significant differences in patients with cysts >10 cm in diameter versus those with smaller cyst diameters [20]. In a case-control study, cyst size was found to be associated with

 https://doi.org/10.17843/rpmesp.2021.381.5295

anaphylactic shock during surgery with an OR of 3.028 (95% CI: 1.259-7.283) [19]. The failure to identify cysts >14 cm in diameter as a risk factor for developing pre-surgical complications could be due to the age characteristics of the cases, i.e., it could be associated with cyst size; however, further studies are required, given that currently imaging techniques have a higher resolution capacity to detect small cysts or to have better precision with respect to cyst diameter.

This study contributes to the identification of risk factors for complications or pre-surgical morbidity, which would allow timely hospitalization of patients [21], appropriate management and access to diagnostic imaging. It has been proposed that surgery in clinical practice is frequently associated with complications in older adults or those with comorbidity [26]. Likewise, post-surgical complications are one of the most common causes associated with mortality [22]; therefore, cystectomy is not considered a definitive cure [28]. Conventional surgical techniques have a high risk of developing morbidity and mortality in patients with hepatic cystic echinococcosis [12], thus, complications such as anaphylaxis, cyst infection, biliary fistula and intra-abdominal abscess are frequent in surgical patients [28-29].

Therefore, studying the factors associated with pre-surgical complications may be more important and useful than studying post-surgical complications to reduce the risk of complications, death, hospital stay and the economic impact on families.

This study has limitations such as the age of the data, the use of a secondary source, the limited characterization of pre-surgical complications in the original study [10], the inclusion of cases with complications not necessarily related to the disease, the small sample size of the cases, and the biases associated with the design.

In conclusion, this case-control study identified that being older than 56 years and having three or more cysts in patients with CE are risk factors associated with the development of pre-surgical complications in patients from the central highlands of Peru.

Author contributions: JP and RC participated in the conception and design of the article, selection of cases and controls, data analysis and interpretation. SSD participated in data collection in the original study. WM was involved in advising on the statistical analysis, review of drafts, and approval of the submission version. JP, RC, SSD and LSO participated in drafting the article, critical review and approval of the submission version.

Funding: The original study from which the database was obtained was funded by the National Center for Epidemiology, Disease Control and Prevention (CDC), Ministerio de Salud.

Conflicts of interest: The authors have no conflicts of interest to declare.

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 https://doi.org/10.17843/rpmesp.2021.381.5295