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Original article

Risk factors for gallbladder polyp malignancy in two public hospitals of Peru

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Abstract

Introduction: In most patients, gallbladder polyps, both benign and malignant, are usually an incidental finding. However, imaging studies cannot accurately establish their degree of malignancy. **Objective:** To determine the risk factors for gallbladder polyp malignancy in two Peruvian public hospitals. **Methodology:** Retrospective cohort study conducted on secondary data from patients who underwent cholecystectomy between 2004 and 2012 in Lima and another in Callao, Peru. The malignancy of the polyp was established according to the histopathological type of adenocarcinoma. Relative risks and their 95% confidence intervals (95%CI) were obtained. Moreover, ROC curves were used to determine sensitivity and specificity according to the size of the polyp. **Results:** Of 368 biopsies, 26 (7%) were adenocarcinomas. The median size of the polyps was 4mm (range: 1-65mm). 176 patients (51%) had multiple polyps, and 85 (23%) had associated gallstones. Multivariate analysis showed that the risk of malignancy increased by 26% (95%CI:14-40%, p-value:<0.001) per millimeter of polyp size and by 182% (95%CI:46-445%, p-value=0.002) based on vesicular wall size, adjusted for patient age, lithiasis and vesicular size. For a size of 6mm, sensitivity was 81%, and specificity was 85%. **Conclusion:** The size of the polyp and the thickness of the vesicular wall are associated with the malignancy of vesicular polyps.

Keywords

Gallbladder neoplasms, polyps, adenocarcinoma, risk factors.

INTRODUCTION

Gallbladder cancer is the fifth most common gastrointestinal cancer worldwide (1). It has a poor prognosis once detected, with an average survival time of 6 months (2, 3). Its incidence varies, ranging from the lowest rates in developed countries to the highest in some South American ethnic groups (4). In Peru, it is one of the most frequent neoplasms in elderly women (5).

The presence of gallbladder polyps is one of the main risk factors associated with the development of this type of cancer since they occur in 4% to 7% of healthy individuals (6). Of the gallbladder polyps that will be classified as malignant, 85 % are adenocarcinomas (7, 8) and are usually diagnosed incidentally through abdominal ultrasound (9). Other factors associated with gallbladder malignancy include being over 60 years old and polyp size larger than 10 mm (10-12), the occurrence of symptoms (11, 13),

vesicular lithiasis (10, 14), and the number of polyps (11, 14), among others (15).

In Peru, several studies have been conducted to identify the characteristics of this type of cancer, such as the work carried out in a population being treated in a private healthcare center in a suburban area of the country (16), yet analyses determining the association between different variables and this disease have not been conducted. Therefore, the aim of this study is to determine the risk factors for gallbladder polyp malignancy in two public hospitals from Peru.

MATERIALS AND METHODS

Study design and population

An observational retrospective cohort study was carried out using secondary data analysis. Databases were obtained from the archives of the Hospital Nacional Arzobispo Loayza (HNAL) and the Hospital Nacional Daniel Alcides Carrión (HNDAC) during the 2004-2012 period. These are public hospitals and most patients come from socioeconomic groups C, D and E.

Reports of gallbladder biopsies performed in patients who underwent cholecystectomy and in which a gallbladder polyps anatomic pathology diagnosis was later confirmed were included. Patients without complete primary data were excluded. Non-probabilistic quota sampling was used.

Procedures and variables

Permission was requested at both hospitals for using the data. After creating a database in Excel for Windows 2013, data were cleared and those that met the selection criteria were chosen. This research was approved by a local committee endorsed by the National Health Institute of Peru.

The dependent variable was the diagnosis of polyp malignancy according to the anatomopathological characteristics of gallbladder polyps. Adenoma, hyperplastic, cholesterol, and inflammatory polyps were considered benign, while adenocarcinoma polyps were classified as malignant.

Independent variables included the patient's age and sex (for statistical analysis, the female sex was considered the variable of interest); anatomopathological characteristics: polyp size (measured in millimeters; in cases of multiple polyps, only the largest polyp size measurement was considered and number of polyps (multiple polyps were defined as the presence of 2 or more polyps); and gallbladder characteristics: size of the gallbladder diameter (measured in centimeters according to the length of the gallbladder) and thickness of the gallbladder wall (measured in millimeters according to the wall thickness at the polyp site).

Statistical analysis

Stata 11.1 for Windows was used for data analysis. Frequencies and percentages were used to describe categorical variables and means and standard deviations for quantitative variables. The chi-square (χ^2) and Student's t statistical tests were used to calculate p-values for variations in categorical and quantitative variables, respectively. For the bivariate and multivariate analyses, crude (cRR) and adjusted (aRR) relative risks were calculated with their corresponding 95 % confidence intervals (95 % CI). The receiver operating characteristic (ROC) curve was used exploratorily to determine sensitivity and specificity based on the cut-off points of gallbladder polyp size. P-values < 0.05 were considered statistically significant.

RESULTS

Of the 368 biopsies performed on cholecystectomized patients diagnosed with gallbladder polyps, 264 (71.,7 %) were treated at HNAL and 104 (28.3 %) at HNDAC; 288 (78.3 %) were female and the mean age was 45.5 years (±15.5 years, range: 12-86 years). The median size of polyps was 4mm (range: 1-65mm). 176 patients (50.7%) had multiple polyps and 85 (23.1%) had associated cholelithiasis. There were 26 (7.1 %) malignant adenocarcinoma polyps, and the remaining polyps were benign: 237 (64.6 %) cholesterol, 53 (14.4 %) hyperplastic, 48 (13.1 %) adenoma, and 3 (0.8 %) inflammatory polyps.

Depending on the malignancy, differences were found regarding patient's age (p = 0.001), polyp size (p < 0.001), associated cholelithiasis (p < 0.001), size of the gallbladder (p = 0.001), and gallbladder wall thickness (p < 0.001) (**Table 1**).

When the analysis was based on the type of gallbladder polyp, statistically significant differences were observed in the median values of the following variables: age (p = 0.006), polyp size (p < 0.001), gallbladder wall thickness (p < 0.001), and gallbladder size (p < 0.001), (**Figure 1**).

P-values obtained using the ANOVA statistical test to determine the difference in each variable average value:

- 1A: Depending on the patient's age (years of age);
- 1B: Depending on polyp size (mm);
- 1C: Depending on gallbladder size (cm);
- 1D: Depending on gallbladder wall thickness (mm).

In the bivariate analysis, polyp size (p < 0.001), gallbladder wall thickness (p < 0.001), cholelithiasis (p < 0.001),

Table 1. Variables according to the type of polyp found in patients who underwent cholecystectomy at two hospitals from Peru.

Variable	Polyp type		*p-value*
	Malignant* n (%)	Benign n (%)	
Sex			
- Female	63 (85.1)	225 (76.8)	0.119***
- Male	11 (14.9)	68 (23.2)	
Age (years)**	51.6 ± 17.7	43.8 ± 14.5	0.001****
Polyp size (mm)**	10.7 ± 11.0	4.0 ± 3.0	< 0.001****
Number of polyps			
- Multiple	25 (36.8)	151 (53.9)	0.011***
- Single	43 (63.2)	129 (46.1)	
Associated lithiasis			
- Yes	35 (47.3)	50 (17.1)	< 0.001***
- No	39 (52.7)	243 (82.9)	
Gallbladder size (cm)**	7.9 ± 1.9	7.0 ± 1.7	< 0.001****
Gallbladder wall thickness (mm)**	3.5 ± 2.3	2.4 ± 0.8	< 0.001****

*Malignant polyp: adenocarcinoma + adenoma. **Median and range. ***Obtained using $\chi 2$ test. ****Obtained using Student's t-test.

patient age (p = 0.003), and gallbladder size (p = 0.004) were associated with gallbladder polyp malignancy. The multivariate analysis showed that the risk of malignancy increased by 26 % per millimeter of polyp size (95 % CI: 14 %-40 %, p-value < 0.001) and by 182 % per millimeter of gallbladder wall size (95 % CI: 46 %-445 %, p-value = 0.002), adjusted for patient age, lithiasis and gallbladder size (**Table 2**).

Figure 2 shows the ROC curves for polyp size (A = 0.78), gallbladder wall thickness (B = 0.67), gallbladder size (C = 0.66), and all variables in the multivariate model (D = 0.86).

The cut-off points for the continuous variable polyp size were determined using the ROC curve; the best cut-off point would be a size of 6 mm, with a sensitivity of 80.8 % and a specificity of 84.9 % (**Table 3**).

DISCUSSION

In our study, 7% of gallbladder polyps were malignant. This is important since the diagnosis of gallbladder polyps was incidental in most patients, usually following a routine abdominal ultrasound or after undergoing cholecystectomy

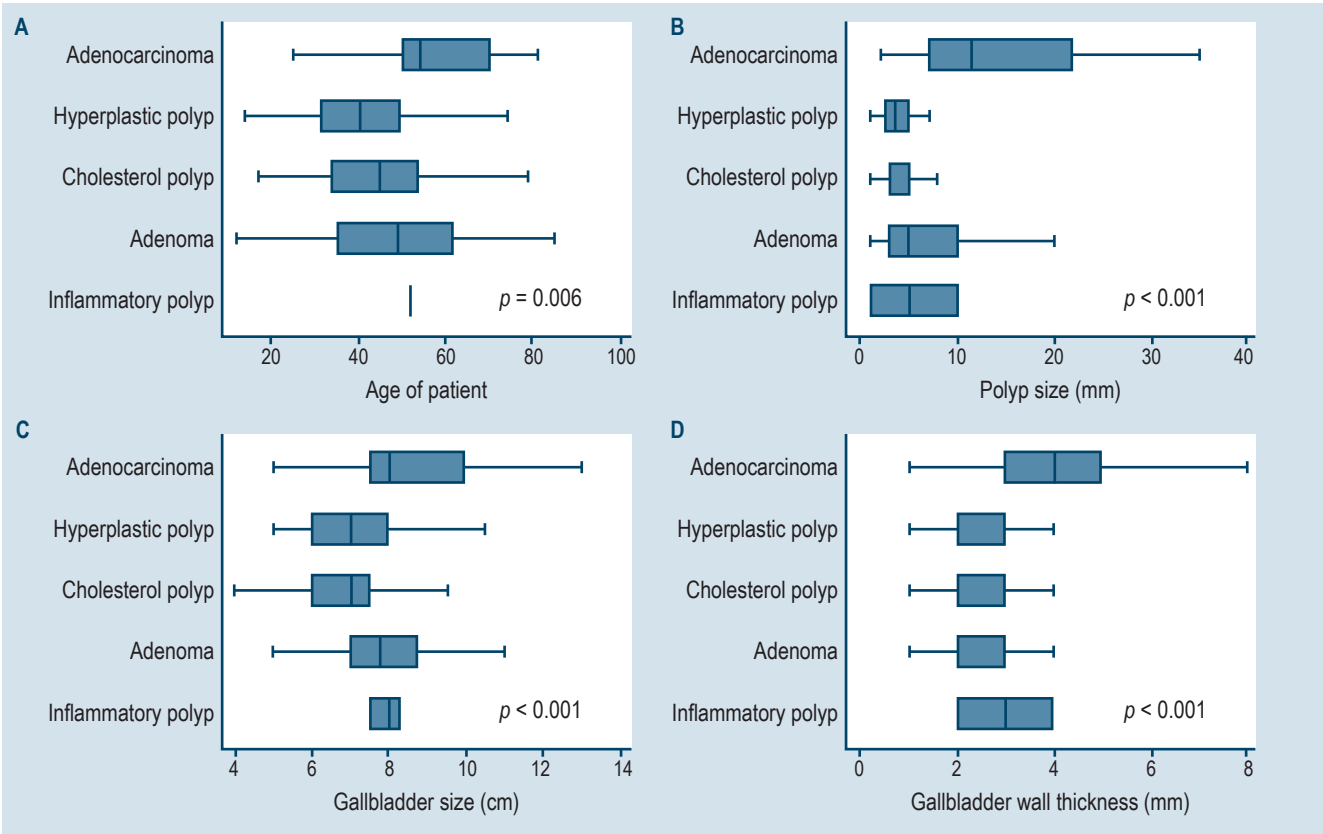

Figure 1. Differences in median values according to the type of gallbladder polyp in cholecystectomized patients treated at two hospitals in Lima and Callao.

Table 2. Risk factors for malignancy of gallbladder polyps in cholecystectomized patients treated at two hospitals in Lima and Callao.

Variable	Bivariate analysis		Multivariate analysis	
	p-value	cRR (95% CI)	*p-value*	aRR (95% CI)
Polyp size* (mm)	< 0.001	1.27 (1.18-1.37)	< 0.001	1.23 (1.12-1.34)
Wall thickness* (mm)	< 0.001	1.98 (1.51-2.59)	0.009	1.74 (1.15-2.62)
Multiple polyps	0.012	0.50 (0.29-0.86)	0.022	0.37 (0.16-0.87)
Gallbladder size* (cm)	0.001	1.31 (1.12-1.53)	0.032	1.36 (1.03-1.81)
Vesicular lithiasis	< 0.001	4.36 (2.52-7.55)	0.435	1.42 (0.59-3.41)
Age *(years)	0.001	1.03 (1.01-1.06)	0.316	1.01 (0.99-1.04)
Female sex	0.122	1.73 (0.86-3.47)	0.577	1.36 (0.46-4.05)

*Mean and standard deviation/p-value. 95 %CI: 95 % confidence interval; aRR: adjusted relative risk; cRR: crude relative risk.

Table 3. Sensitivity and specificity according to the size of malignant polyps

Polyp size (mm)	Sensitivity	Specificity	PPV	NPV	ROC Area
≥ 3	0 %	100 %	0 %	80.1 %	57.4 %
≥ 4	0 %	100 %	0 %	80.1 %	66.8 %
≥ 5	0 %	100 %	0 %	80.1 %	72.6 %
≥ 6	56.3 %	89.1 %	56.3 %	89.1 %	72.7 %
≥ 7	53.5 %	91.2 %	60.3 %	88.7 %	72.4 %
≥ 8	50.7 %	93.0 %	64.3 %	88.3 %	71.8 %
≥ 9	45.1 %	94.7 %	68.1 %	87.4 %	69.9 %
≥ 10	45.1 %	95.4 %	71.1 %	87.5 %	70.3 %

NPV: negative predictive value; PPV: positive predictive value.

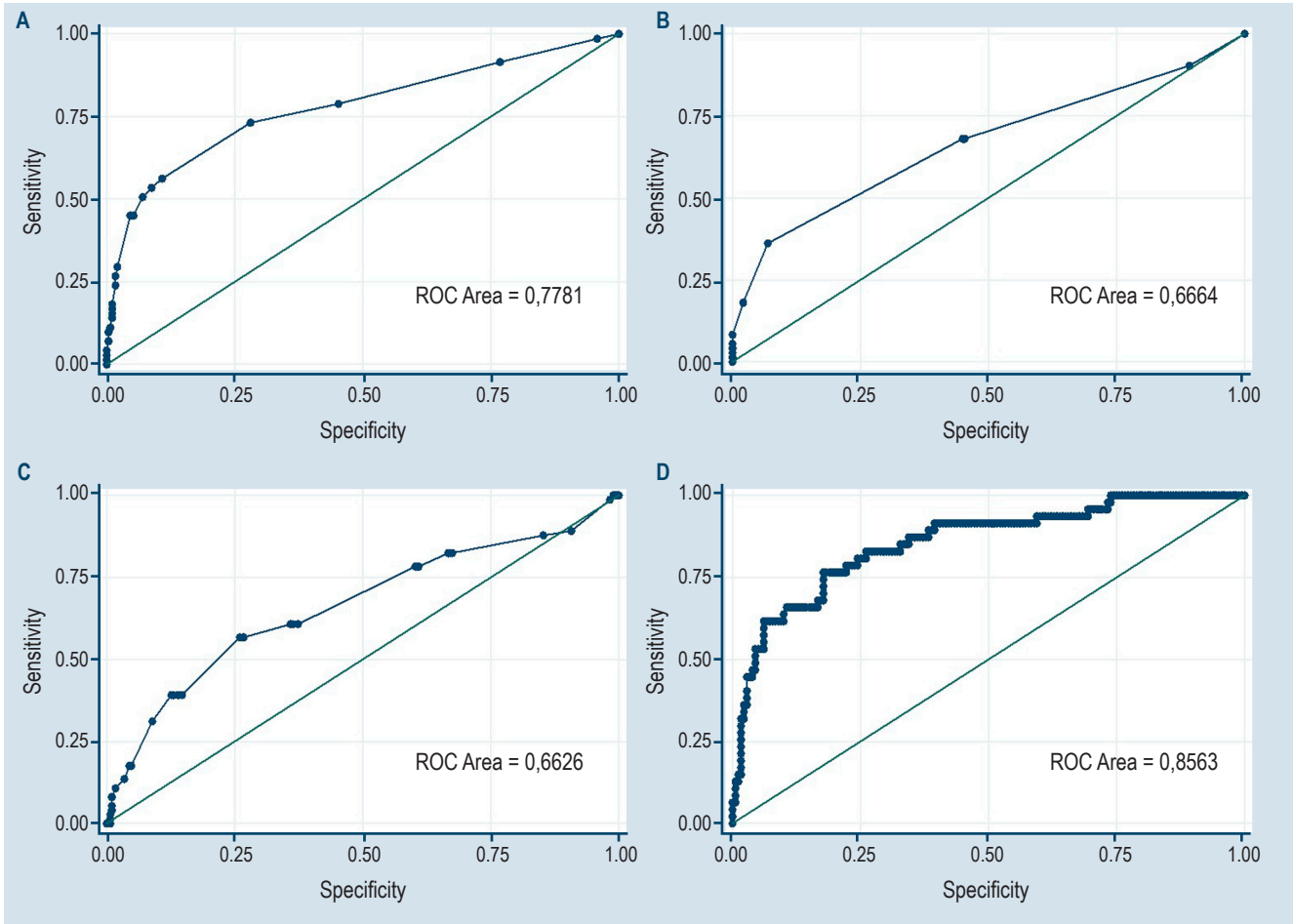

Figura 2. ROC curves for polyp size (A = 0.78), gallbladder wall thickness (B = 0.67), gallbladder size (C = 0.66) and all variables in the multivariate model (D = 0.86).

for treating biliary lithiasis or biliary colic (17). However, due to the development of new diagnostic imaging devices, the detection of gallbladder polyps is becoming more common (11). Although most gallbladder polyps are benign, differentiating them from malignant masses is important because gallbladder carcinoma usually has a late onset and a poor prognosis. Consequently, they must be detected early to change their prognosis (18).

Polyp size was associated with malignancy, which is consistent with most findings reported in similar studies (11, 19); also, there was almost a 13 mm difference between size averages depending on the malignancy. Various studies show that a polyp size ≥ 10 mm is a predictor of malignancy (20), while others describe that, a polyp size greater than 10-15 mm was observed in 45 % to 67 % of malignant polyp cases the cases (10, 21-23). In some studies, temporal follow-up has been reported in patients with polyps smaller than 10 mm, concluding that no adenocarcinomas or progression to malignancy were identified during the follow-up period (24). However, in our study several reports of malignancy in polyps smaller than 5 mm were found. Therefore, the cut-off points for each measurement were determined using the ROC curve and it was observed that the best measure was found in polyps ≥ 6 mm, with acceptable sensitivity and specificity values. This is consistent with the study of Zielinski et al. con ducted in a US population (25), which suggests surgical resection of gallbladder polyps ≥ 6 mm based on preoperative ultrasound testing. Furthermore, evidence of malignancy in polyps > 6 mm is easily detected during biopsies or examinations performed by qualified gastroenterologists, but not so much in imaging studies (26).

Gallbladder wall thickness was another factor associated with malignancy. This is consistent with the findings of Kim et al. (27), who concluded that wall thickness > 10 mm is a predictive factor for neoplastic thickening of the gallbladder wall. Similarly, Aldouri et al. (28) noted that severe thickening of the gallbladder wall is associated with an increased risk of developing gallbladder cancer. In turn, Sun et al. (29) included patients with a locally thickened, irregular gallbladder wall in their surgical indications for gallbladder polyps. Considering the above, further research into the thickness of the gallbladder wall is suggested to assess its relevance regarding the presence of malignant polyps.

No significant differences were found between sexes as a risk factor for malignancy in our study; however, female predominance was observed in the group of malignant polyps, which is in consistent with the findings of Manrique et al. (30) in their study of gallbladder cancer conducted in a population from Arequipa, Peru. This may be explained by the different reports on this variable since some show male predominance (31-34) and others the opposite (11, 14, 35). Although some studies have reported an association between age and gallbladder polyp malignancy (10, 11, 28), in our study age was not associated, nor was the prevalence of vesicular lithiasis, which is not always associated with malignancy (11).

One of the limitations of the study was the operator-dependent bias, as samples were analyzed by multiple physicians before being entered into the database. Nonetheless, since pathologists are highly qualified and the pathology report to be evaluated does not raise significant diagnostic doubt, we consider that this situation did not have a major impact on the results obtained.

Based on the data analyzed here, it is concluded that polyp size and gallbladder wall thickness were associated with the malignancy of gallbladder polyps.

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