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Research Article

Factors associated with the Lack of Response to Conservative Management in Patients with Acute Cholecystitis over 72 Hours of Evolution

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Abstract

Introduction: Acute lithiasic cholecystitis is one of the most common gallbladder pathologies. Conservative treatment can hardly be considered as a definitive treatment. The objective of this study is to determine the factors associated with the lack of response of such management in patients with acute cholecystitis with more than 72 hours of disease evolution.

Material and methods: An observational, analytical and retrospective case-control study was carried out at the Cayetano Heredia National Hospital. The cases were patients who needed emergency surgery after the start of conservative treatment; and the controls those who had a good response to this treatment. The factors associated with the failure of conservative management were analyzed; and then, through a logistic regression analysis, identify the best predictive model for this poor response was identified.

Results: A total of 136 patients were included, being the cases 44. The factors that had a greater degree of association with the lack of response to conservative

management were advanced age (OR=2.34 CI=1.05-5.28), thickened gallbladder wall (OR=7.38 CI=3.22-16.96), gallbladder distention (OR=6.38 CI=2.56-15.92), persistent fever (OR=3.55 CI=1.57-8.04), leukocytosis at admission (OR=2.20, CI=1.04-4.64) and at 48 hours (OR=2.73 CI=1.26-5.94), tachycardia at admission (OR=3.11 CI=1.29-7.48) and obesity (OR=2.45 CI=1.08-5.60). A predictive model was developed, which predicts 96.78% failure to conservative management.

Conclusions: There are several factors associated with the failure in the conservative management of acute cholecystitis with more than 72 hours of disease evolution. Considering these factors might allow early identification of patients who have a high probability of failure to such treatment.

Keywords: Acute cholecystitis; Conservative management; Patients at risk; Failure

1. Introduction

Among vesicular pathologies, within these, acute lithiasic cholecystitis (ALC); it is one of the most frequent in Peru and worldwide. The diversity of patients, the associated comorbidities and the different forms of presentation make it difficult to standardize both medical and surgical therapeutic procedures, which can lead to failure [1].

Currently, according to the 2018 Tokyo guide, there are various therapeutic approaches for this pathology: emergency laparoscopic cholecystectomy in patients with ALC grade I (disease time of less than 72 hours of illness), percutaneous cholecystostomy in patients with ALC grade III (disease time of less than 72 hours of illness), and conservative management with antibiotics plus delayed cholecystectomy after 6-8 weeks in patients with ALC grade II (disease time of more than 72 hours) [2].

Although, several studies indicate that an early cholecystectomy is highly beneficial due to its cost-effectiveness; in various contexts, such as in developing countries, emergency laparoscopic cholecystectomy is not used routinely. This is due to the particular conditions of space and time in state health institutions, in which the evolution time of illness last usually beyond 72 hours. On the other hand, some patients seek medical consultation after 72 hours of the onset of symptoms presenting of acute plastron cholecystitis, for which therapeutic options are considered, such as conservative management and delayed cholecystectomy (after 6-8 weeks) [3].

Conservative treatment can hardly be considered as a definitive treatment for ALC. And it is used to prevent patients with illness time greater than 72 hours from undergoing emergency surgery, that might expose a patient to a higher frequency of intraoperative and postoperative complications [4].

In some studies, it has been shown that there is a lack of response to conservative management in approximately 15-20% of ALC cases. In a systematic review, conservative treatment during initial admission is 87% successful in patients with ALC. Among the factors most associated with non-response to conservative treatment, the following have been reported: advanced age, comorbidities such as diabetes mellitus, tachycardia at the time of admission and gallbladder distention measured by ultrasound. Other factors, such as an elevated white blood cell count, are also associated with the development of complications

[1, 5, 6, 7].

In Peru, conservative management for ALC grade II is used frequently. There is little information on the factors related to the failure of this treatment. The main purpose of this study is to identify the associated factors that make this group of patients with ALC fail to respond adequately to conservative management. The determination of these factors will make it possible to identify the patients who will require early surgery and to not delay the surgical intervention time.

2. Material and Methods

An observational, analytical and retrospective case-control study was carried out. The study population was made up of patients who attended the emergency service of the Cayetano Heredia National Hospital between the years 2012-2017 with a diagnosis of ALC, a disease evolution time of more than 72 hours, and who received conservative management. This treatment is characterized by intravenous hydration, oral restriction, intravenous antibiotic therapy against gram negatives and anaerobes, plus analgesics.

The inclusion criteria were patients who had received conservative management for ALC, diagnosed based on clinical and radiological criteria, and 18 years old of age or older. The exclusion criteria were patients with incomplete data in the medical records, with a diagnosis of acute allithiasic cholecystitis, and with a definitive diagnosis of acute cholangitis or acute biliary pancreatitis. A case was defined as the patient who presented absence of clinical improvement and needed emergency surgery, after the start of conservative management. A control was defined as the patient who presented a good response to conservative management and did not require emergency surgery, being discharged and scheduled for elective surgery 6-8 weeks later.

For the sample estimation the following condition were taken into account, a safety level of 95%, power of 90%, percentage of exposed controls of 40%, percentage of exposed cases of 70% and number of controls per case from 2 to 1. A sample size consisting of a total of 136 patients, 44 cases and 92 controls, was determined using the Epi program Info. The study variables considered were advanced age, gender, diabetes mellitus, immunosuppression, thickened gallbladder wall, gallbladder distention, persistent fever, tachycardia on admission, leukocytosis on admission, leukocytosis at 48 hours, body mass index (BMI) and obesity.

For the analysis plan, initially, a descriptive analysis of the demographic and clinical characteristics of the patients included in the study was carried out. For the descriptive analysis of the data, tables of frequency distribution, measures of central tendency and measures of dispersion were used. To determine the degree of association, the categorical variables were evaluated with the chi-squared test or with Fisher's exact test, for a significance level of 0.5. Continuous variables were evaluated using the Student's T-test comparison test. The degree of association of the independent variables was evaluated with the odds ratio (OR). The statistical test was significant if $p < 0.05$. A multivariate analysis was performed, for which the logistic regression test was used to evaluate the associated factors controlled for confounding factors. Finally, a goodness-of-fit test was used to obtain the best predictive model. The analyzes were carried out using the statistical program STATA.

This study was submitted for the review and approval to Ethics Committees of both Cayetano Heredia Peruvian University and Cayetano Heredia National Hospital.

3. Results

The present study consisted of 136 patients, who came with the diagnosis of ALC with a disease evolution time of more than 72 hours to the emergency room at the Cayetano Heredia National Hospital and who received initial conservative management. A total of 55 (40.44%) patients were male. The mean age was 49.94 years ± 16.48. The average BMI was 27.31 ± 3.65. One hundred and thirteen (83.09%) patients received as an antibiotic regimen ceftriaxone 2g every 24 hours and metronidazole 500mg every 8 hours. Seventeen (12.5%) received ciprofloxacin 200mg every 12 hours and metronidazole 500mg every 8 hours, and six patients received another antibiotic therapy regimen.

Of the total number of patients, 9 (6.62%) presented the diagnosis of diabetes mellitus, 10 (7.35%) immunosuppression, 63 (46.32%) thickened gallbladder wall, 27 (19.85%) gallbladder distention, 33 (24.26%) persistent fever, 26 (19.12%) tachycardia at the time of admission. Leukocytosis on admission was present in 72 (52.94%) of the patients and 39 (28.68%) presented it at 48 hours. The mean length of hospital stay was 4.28 days ± 1.53 for the controls and 10.43 days ± 4.6 for the cases. Within the group of cases, the average time in which the surgery was performed was 6.34 days ± 2.35.

Forty-four patients were included as cases and ninety-two as controls. Among the variables studied, it was found that gender, diabetes mellitus and immunosuppression were not shown as factors associated with poor response to conservative management (Table 1). Both the average age and the BMI were similar in both groups studied (Table 2). Among the factors that showed a greater association with a poor response in conservative management are thickened gallbladder wall (OR = 7.386, CI = 3.22–16.96, p <0.001) and gallbladder distention (OR = 6.385, CI = 2.56–15.92, p <0.001) (Table 2). Other associated factors are advanced age (OR = 2.349, CI = 1.05-5.28, p = 0.034), persistent fever (OR = 3.554, CI = 1.57-8.04, p = 0.002), tachycardia on admission (OR = 3.111, CI = 1.29–7.48, p = 0.009), leukocytosis at admission (OR = 2.203, CI = 1.04-4.64, p = 0.036), leukocytosis at 48 hours (OR = 2.736, CI = 1.26-5.94, p = 0.01), and obesity (OR = 2.457, CI = 1.08-5.6, p = 0.03) (Table 1).

		Controls		Cases		OR	CI (95%)	P value*
		n=92	%	n=44	%			
Age	**<60**	74	72.5	28	27.45	2.3492	1.05-5.28	0.034
	≥60	18	52.97	16	46.06			
Gender	Female	58	71.6	23	28.4	1.5575	0.75 – 3.22	0.23
	Male	34	61.82	21	38.18			
Diabetes	No	86	67.72	41	32.28	1.0487	0.25 – 4.40	0.948
	Yes	6	66.67	3	33.33			
Immunosuppression	No	85	67.46	41	32.54	0.8885	0.22 – 3.61	0.869
	Yes	7	70	3	30			
Thickened gallbladder wall	< 5 mm	63	86.3	10	13.7	7.3862	3.22 – 16.96	0
	≥ 5 mm	29	46.03	34	53.97			
Gallbladder distention	< 50 mm	83	76.15	26	23.85	6.3846	2.56 – 15.92	0
	≥ 50 mm	9	33.33	18	66.67			
Persistent fever	< 48 hours	77	74.76	26	25.24	3.5538	1.57 – 8.04	0.002
	≥ 48 hours	15	45.45	18	54.55			
Tachycardia at admission	< 100 x min	80	72.73	30	27.27	3.1111	1.29- 7.48	0.009
	≥ 100 x min	12	46.15	14	53.85			
Leukocytosis at admission	< 12000	49	76.56	15	23.44	2.2031	1.04 – 4.64	0.036
	≥ 12000	43	59.72	29	40.28			
Leukocytosis at 48 hours	< 12000	72	74.23	25	25.77	2.736	1.26 – 5.94	0.01
	≥ 12000	20	51.28	19	48.72			
Obesity	< 30	76	72.38	29	27.62	2.4568	1.08 – 5.60	0.03
	≥ 30	16	51.61	15	48.39			

*Chi-squared test

** OR: odds ratio, CI: confidence interval

Table 1: Bivariate analysis of associated factors (categorical variables).

	Controls n = 92	Cases n = 44	OR	CI (95%)	P value*
	X ± SD	X ± SD			
Age (years)	47.69 ± 15.29	51.86 ± 18.60	1.0155	0.99 – 1.04	0.16
Thickened gallbladder wall (mm)	4.45 ± 1.75	6.20 ± 2.89	1.4927	1.20 – 1.85	0
Gallbladder distention (mm)	40.47 ± 7.77	44.34 ± 8.57	1.0637	1.01 – 1.11	0.009
Tachycardia at admission (beats/min)	83.30 ± 11.54	92.34 ± 13.26	1.0605	1.03 – 1.09	0.0001
Leukocytosis at admission (leukocytes/mm^3)	12 279.35 ± 5 132.93	15 259.77 ± 6 644.55	1	1.0000 – 1.0001	0.005
Leukocytosis at 48 hours (leukocytes/mm^3)	9 129.89 ± 4 086.40	11 888.66 ± 5 963.74	1.0001	1.0000 – 1.0001	0.01
BMI (kg/cm^2)	26.89 ± 3.33	28.18 ± 4.15	1.1025	0.99 – 1.22	0.053

*T-student

** SD: standard deviation, OR: odds ratio, CI: confidence interval

Table 2: Analysis of continuous variables.

When performing the logistic regression analysis using a goodness of fit test, the result was that the model that best predicts a poor response to the conservative model included the following categorical variables: thickened gallbladder wall (OR = 6.668, CI = 2.67-16.66), gallbladder distention (OR = 4.291, CI = 1.56-11.82), persistent fever (OR = 4.094, CI = 1.55-10.79), with a prediction of 96.78%; and with which a proposed score was established for each of the variables (Table 3). The predictive formula with these mentioned variables is: -2.5136 + 1.8972 (thickened gallbladder wall) + 1.4565 (gallbladder distention) + 1.4095 (persistent fever).

	OR	CI (95%)	P value	Proposed score
Thickened gallbladder wall	6.6676	2.67 – 16.66	0	6 points
Gallbladder distention	4.2911	1.55 – 11.82	0.005	4 points
Fever	4.0943	1.55 – 10.79	0.004	4 points

* Goodness of fit test: 0.9678

Table 3: Logistic regression analysis.

4. Discussion

Acute lithiasic cholecystitis is a very common disease in Peru. Early laparoscopic cholecystectomy is the treatment of choice; however, many of the patients come to the health care settings with a time of illness that exceeds 72 hours of evolution, then a conservative management is often considered in this context. The lack of accessibility to health services, the over-demand of emergency centers and the delay in diagnosis could be the reasons why patients with ALC come with a time of illness greater than 72 hours [6, 8].

Of the group of patients who receive conservative management, it is known that approximately 20% do not respond adequately, having to be intervened by laparoscopic cholecystectomy or emergency cholecystostomy. The latter procedure is used mostly in high-risk patients and as an alternative to surgical treatment in those patients who did not respond to conservative management [6, 9, 10].

Some demographic characteristics of patients with ALC were similar to those reported by previous studies. ALC is known to be predominating in the female gender. In our study most patients were women. The average ages of all patients were 49.94 years. Comparing the averages of both age (p = 0.169) and BMI (p = 0.053), no significant difference was observed between the group of patients who had a good response, compared to those who did not. However, when analyzing these variables as categorical variables, an association was observed between age (OR = 2.34, CI = 1.05-5.28) and BMI> 30 (OR = 2.45, CI = 1.08-5.60); and the poor response to conservative management.

Barak identifies diabetes mellitus, advanced age, tachycardia on admission, and gallbladder distention as factors associated with failure facing conservative management. In the present research work, there is also an association of non-response to conservative management with the last three factors already mentioned. However, regarding the diabetes mellitus factor, this association cannot be confirmed, this could be due to a small number of patients with a definitive diagnosis of said pathology.

Persistent fever, leukocytosis on admission and control at 48 hours, and being male have been proposed in various studies as possible factors associated with poor prognosis in patients with ALC. In our study, similarly, both fever (OR = 3.55, CI = 1.57-8.04) and leukocytosis at admission (OR = 2.20, CI = 1.04-4.64) and at 48 hours (OR = 2.74, CI = 1.26- 5.24) showed a significant relationship with the presence of failure in conservative treatment. However, there was no association between the failure of conservative treatment for ALC with the gender variable.

One of the most useful complementary imaging examinations for gallbladder pathologies is abdominal ultrasound. Barak found that among 25 patients who required emergency intervention, 20 presented gallbladder distention (p = 0.001) and 19 presented thickened gallbladder wall (p = 0.56). In the current study, where 44 patients required emergency surgical intervention, 18 presented gallbladder distention (OR = 6.38, CI = 2.56-15.92, p <0.001) and 34 presented thickened gallbladder wall (> 5mm) (OR = 7.39, CI = 3.22-16.96, p <0.001), both factors had a highly significant relationship with the presence of failure to conservative management.

The final prediction model obtained included three

variables (96.78% prediction). A proposed score was established for each of the variables. The identification of predictive variables can allow early identification of patients who have a high probability of failure to conservative treatment. This might help clinicians and surgeons to act at the right time, carrying out timely and early interventions, without the need to delay the waiting time. Additionally, an early intervention can make possible to avoid possible complications and reduce the hospital stay in this group of patients. In the study, the average time in which surgery was performed was 6.34 days and an average length of hospital stay of 10.43 days. These periods of time could have been reduced significantly if the factors associated with failure of conservative management could have been identified early.

In this study we propose a preliminary predictive score, which needs to be validated in subsequent research studies and different clinical contexts. In this way, this tool can be used for a proper management of patients with acute cholecystitis who receive conservative management in the clinical practice for both medical and surgical groups.

5. Conclusion

The factors associated with the failure in the conservative management of acute cholecystitis with more than 72 hours of disease evolution were advanced age, thickened gallbladder wall, gallbladder distention, persistent fever, leukocytosis on admission and 48 hours later, tachycardia and obesity. These factors might allow surgeons an early identification of patients who have a high probability of failure to conservative treatment; and then to plan timely interventions, without the need to delay time and consequently support the reduction of complications and length of hospital stay.

6. Funding Information

No funding was received for this article.

7. Conflicts of Interest

The authors have no conflicts of interest to declare.

8. Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

9. Data Sharing

Data sharing requests will be considered by the management group on written request to the corresponding author.

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