

Diagnostic Validity of Biliopancreatic Endosonography in the Diagnosis of Acute Cholangitis Secondary to Biliary Obstruction

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Abstract

Diagnosis of obstructive cholangiopathy with biliopancreatic endosonography (BUS) has been extensively studied, and its role in the diagnosis of choledocholithiasis, biliopancreatic junction tumors and extrinsic biliary compression syndromes is widely recognized. Endosonographic diagnosis of cholangitis, a more frequent complication of biliary obstruction which is responsible for much of its morbidity and mortality, has not been sufficiently studied.

Our study's objective is to define the diagnostic validity of endosonography for patients with acute cholangitis in order to limit morbidity and mortality due to diagnostic delay.

This is a descriptive study that analyzes clinical histories of patients who underwent biliopancreatic endosonography because of obstructive jaundice of any etiology and who later underwent endoscopic retrograde cholangiopancreatography (ERCP) to manage biliary obstruction. We compared endosonographic findings compatible with acute cholangitis: thickening of the bile duct of 1.5 mm or more, periportal halo sign of at least 1.5 cm in length, mixed echogenicity of bile duct content, and purulent drainage during ERCP.

Patients with cholangitis most frequently presented thickened gallbladders (92.6% of cases) periportal halo signs (59.3% of cases) and mixed echogenicity of bile duct content (66.7% of cases). We also found an ascending association of frequencies with the degree of severity of cholangitis.

Studies with greater statistical power are needed for validation of our results and for future inclusion of EUS in the diagnostic algorithm for clinical practice guidelines in cases of acute cholangitis.

Keywords

Endoscopic endosonography, cholangitis, diagnostic imaging of cholangitis, obstructive cholangiopathy, biliary obstruction, biliary infection.

INTRODUCTION

Acute cholangitis, the most frequent complication of biliary obstructions, has a mortality rate of up to 10% in patients whose bile ducts are not drained early. (1) Clinical presentation at an early stage only occurs in 26.4% of cases, so international guidelines recommend complex criteria combining clinical findings and diagnostic imaging. Still, sensitivity does not reach 90% and specificity is less than 80%. (2)

The cornerstone for treatment of acute cholangitis is early decompression and biliary drainage. The presence of purulent material in drained liquid is a pathognomonic sign of acute cholangitis. ERCP is the best method for biliary drainage: it has a 98% success and has lower complication rates than surgery. (3, 4) Recent evidence suggests that biliary drainage in the first 24 hours in patients with severe cholangitis and within a maximum of 48 hours for patients with mild to moderate cholangitis is ideal for reducing morbidity and mortality. (1)

BUS can explore almost 100% of the bile duct and has been shown to have the same sensitivity as ERCP for detection of choledocholithiasis. (8, 9, 10, 11, 12) Similarly, it has shown its value for detection of pancreatic cancer with a sensitivity of 93% to 100%, for tumors of the bile duct with a sensitivity of 80%, (12, 13) and for benign biliary strictures. (14, 16, 17)

Nevertheless, there has been only one study done whose primary interest has been in the diagnostic role of radial endosonography for acute cholangitis. This study found that thickening of the wall beyond 1.5 mm, changes in echogenicity in the area around the bile duct of more than 15 mm in length, and the luminal echogenic content with or without acoustic shadow were the most relevant endosonographic findings. These are highly predictive of choledocholithiasis and allow early biliary drainage by ERCP within the first 12 hours of diagnosis. (15)

Our study sought associations between these endosonographic indicators and acute cholangitis evidenced in biliary drainage by ERCP. We also looked for possible associations of these findings with degrees of severity of cholangitis and their prognostic implications.

MATERIALS AND METHODS

We developed a descriptive, retrospective, observational and analytical study whose objective was to determine the positive predictive value of endosonography for diagnosis of acute cholangitis determined by ERCP. Similarly, we sought to characterize endosonographic findings according to etiology, severity of cholangitis, and patients' age and sex. Patients included were treated at the Union de Cirujanos SAS, Clínica de La Presentación in Manizales, Colombia between April and October 2016.

The project was presented to the postgraduate and bioethics committee of the University of Caldas where it was approved and where it was confirmed that it corresponded to the ethical standards of the Declaration of Helsinki as modified in 2005. Following approval, we proceeded to collect data through an instrument that had also been approved by the committee.

Data were extracted from the clinical histories of patients who had undergone pancreatobiliary endosonography due to biliary obstructions and who had subsequently undergone ERCP to treat the condition. Clinical histories with insufficient data regarding endosonographic indications of cholangitis and/or drainage were excluded.

The data were processed with IBM's SPSS Statistics version 23. Categorization of variables was designed to respond to the study objectives. Demographic variables used were sex and age. Age was dichotomized into groups over and under 75 years old following the suggestion of

the Tokyo guidelines regarding increased risk above this age. We used the most frequent causes of cholangitis in our environment, so iatrogenic causes were not taken into account due to their infrequency. None had occurred at the time of the study. The Tokyo classification of 2013 was followed for variables of the severity.

Endosonographic findings chosen to be independent variables were those described most frequently in the literature. The analysis used 2 x 2 tables and the Chi squared and Fisher's exact tests to determine association given the small sample size in this study.

RESULTS

Thirty patients who met the inclusion criteria were evaluated. Due to the limited sample size, demographic variables were heterogeneous. In particular, there were more women (70%) than men (30%).

The causes of biliary obstruction were diverse. Choledocholithiasis was responsible for 63.3% of the obstructions, malignant lesions of the biliopancreatic junction caused 16.7%, benign stenoses caused 13.3%, and there were two cases of extrinsic compression of the bile duct (6.7%), one of which occurred in a woman, and the other in a man. Categorization of the causes of biliary obstruction by sex revealed similar patterns: choledocholithiasis accounted for 55.6% of the biliary obstructions in men and 66.7% of those in women, and malignant stenoses accounted for 11.1% in men and 19% in women. Five of these malignancies in women (80%) caused jaundice, were women which does not match the historical occurrence of neoplasms at the biliopancreatic junction which tend to occur more frequently among men. This can be explained by the limited sample size.

Benign stenoses caused 22.2% the biliary obstructions in men, but only 9.5% of those in women. Although only one case of extrinsic compression occurred in each sex, it accounted for 11% of cases among men and only 4.8% of those among women (Table 1). When the causes were analyzed with age dichotomized at 75 years old, the age of risk according to the Tokyo guidelines of 2013, we found that 56.7% of the cases occurred among patients under 75 years of age but with not statistically significant differences with a p of 0.64.

Similarly, choledocholithiasis was the main cause of biliary obstructions in both groups: 70.6% of those under 75 years of age and 53.8% of those over 75. Interestingly, 17.6% of those under 75 had malignant stenoses which is a higher percentage than that found in the older group of only 15.4%. The evaluation of malignant stenosis and extrinsic compression is problematic because in the first case there were no patients younger than 75 years, and in the second case there were no patients older than 75 years (Table 2).

Table 1. Etiological frequencies of biliary obstruction according to sex

	Patient's sex according to clinical history	
	Male	Female
Lithiasis	26.3%	73.7%
Malignant stenosis	20.0%	80.0%
Benign stenosis	50.0%	50.0%
Extrinsic Compression	50.0%	50.0%

Causes of biliary obstruction in the Gastroenterology Service of the Union of SAS Surgeons classified by sex.

Table 2. Etiological frequencies of biliary obstruction according to age dichotomized by risk (cross tabulation).

Cause of bile duct obstruction as per final diagnosis		Dichotomized Age			Total
		Under 75 years	Over 75 years		
		n	n	n	
Lithiasis	n	12	7	19	
	%	70.6%	53.8%	63.3%	
Malignant stenosis	n	3	2	5	
	%	17.6%	15.4%	16.7%	
Benign stenosis	n	0	4	4	
	%	0.0%	30.8%	13.3%	
Extrinsic compression	n	2	0	2	
	%	11.8%	0.0%	6.7%	
Total	n	17	13	30	
	%	100.0%	100.0%	100.0%	

Causes of biliary obstruction in the gastroenterology service of the Union of Surgeons SAS, discriminated by age of patients dichotomized by ages over and under 75 years in which the risk of severity increases according to the Tokyo guidelines of 2013.

Endosonographic findings associated with acute cholangitis were analyzed for all patients and were characterized according to the sex of the patient and the age groups of interest in order to define whether there were any associations of endosonographic findings with these characteristics. No associations of demographic variables with endosonographic indications were found. Similarly, it was possible to determine that frequencies differentiated for each endosonographic finding did not vary in constant or statistically significant ways with respect to age or sex of the patients. This establishes that they are independent variables in the endosonographic diagnosis of the acute cholangitis.

Separate analysis of each endosonographic finding showed that when the walls of the bile duct were 1.5 mm or thicker, 89.3% of all patients were shown to have acute cholangitis by ERCP. Only 7.4% did not present biliary thickening evidenced in endosonography. Only three patients' (10%) had final ERCP diagnoses of anything other than

acute cholangitis, but none of those patients had thickening of the bile duct walls (Tables 3 and 4).

Table 3. Frequency of bile ducts thicker than 1.5 mm in patients with acute cholangitis as evidenced in ERCP (cross tabulation).

Bile ducts thicker than 1.5 mm as evidenced by EUS			Final diagnosis of cholangitis by ERCP		Total
			Yes	No	
			n	n	
Yes	n	25	3	28	
	%	89.3%	10.7%	100.0%	
No	n	2	0	2	
	%	100.0%	0.0%	100.0%	
Total	n	27	3	30	
	%	90.0%	10.0%	100.0%	

Coincidence of endosonographic finding of thickening of the biliary wall with ERCP finding of purulent drainage which evidences a frequency of possibility of 89.3% of the cases.

Table 4. Frequency of diagnosis of acute cholangitis in patients with thickened bile ducts diagnosed by endosonography (cross tabulation)

Final ERCP diagnosis of cholangitis			Bile duct walls thicker than 1.5 mm as determined by EUS		Total
			Yes	No	
			n	n	
Yes	n	25	0	27	
	%	92.6%	7.4%	90%	
No	n	3	0	3	
	%	100.0%	0.0%	10%	
Total	n	28	3	30	
	%	93.3%	6.7%	100.0%	

Purulent drainage was found during ERCP in 92.6% of patients. Three patients (10% of the sample) presented false positive endosonographic findings.

Although these findings suggest that endosonography tends to find thickened bile duct walls in the vast majority of cases of cholangitis confirmed in ERCP, with a predictive value of 90% calculated for this finding, the application of statistical tests fails to find association with a p of 0.626. The presence of a periportal halo larger than 1.5 cm was less common and was found in 59.3% of the patients diagnosed with cholangitis by ERCP. The majority of these patients had endosonographic findings of periportal halo (88.9%) and had final diagnoses of acute cholangitis (Tables 5 and 6).

Bile duct contents seen in endosonography and the final diagnosis of cholangitis were evidenced in 63% of the cases. However, 94.7% of the patients whose endosonographic findings were positive had acute cholangitis. We again encountered the problems of the small total number of cases and the small number of patients without final

diagnoses of cholangitis which prevented us from adequate calculation of the predictive value of these findings. Eleven patients did not present intraductal content in endosonography, but 81.8% had acute cholangitis. This shows a tendency toward low sensitivity that would require a larger sample for statistically significant demonstration.

Table 5. Frequency of periportal halos larger than 1.5 cm in patients with acute cholangitis as evidenced in ERCP (cross tabulation).

		Final diagnosis of cholangitis by ERCP		
		Yes	No	Total
1.5 cm hypoechoic periportal halo found by EUS	Yes	n 16	2	18
		% 59.3%	66.7%	60.0%
	No	n 11	1	12
		% 40.7%	33.3%	40.0%
Total		n 27	3	30
		% 100.0%	100.0%	100.0%

Periportal halos were found in 59.3% of patients with purulent drainage of the bile duct found by ERCP. Two thirds of the patients who were negative for cholangitis in ERCP also presented this finding, but the small number of patients who were negative for cholangitis in ERCP is worth mentioning.

Table 6. Frequency of diagnosis of acute cholangitis in patients with periportal halo in endosonography (crossed tabulation).

		1.5 cm hypoechoic periportal halo in EUS		
		Yes	No	Total
Final diagnosis of cholangitis by ERCP	Yes	n 16	11	27
		% 88.9%	91.7%	90.0%
	No	n 2	1	3
		% 11.1%	8.3%	10.0%
Total		n 18	12	30
		% 100%	100.0%	100.0%

Purulent drainage was found during ERCP in 88.9% of patients who had endosonographic periportal halos. Purulent drainage was also found in a high proportion of patients who were negative for this endosonographic finding. No statistical significance was found.

Endosonographic evaluation of severity according to the Tokyo criteria showed that thickening of the bile duct was present in all patients with severe cholangitis: in 93.8% of patients with moderate cholangitis and in 90.9% of patients with mild cholangitis with a non-significant p of 0.851 (Tables 7 and 8). The periportal halo was present in 100% of patients with grade III cholangitis, in 50% of patients with grade II cholangitis and in 36.6% of patients with grade I cholangitis, with a non-significant p value of 0.256. (Table 9).

Table 7. Severity of acute cholangitis in endosonographic thickening of the bile duct (cross tabulation).

		Bile duct wall thicker than 1.5 mm found by EUS		
		Yes	No	Total
Severity of cholangitis according to patient's clinical diagnosis	Grade III: organ failure	n 3	0	3
		% 10.7%	0.0%	10.0%
	Grade II: systemic inflammatory response	n 15	1	16
		% 53.6%	50.0%	53.3%
	Grade I: no inflammatory response or organ failure	n 10	1	11
		% 35.7%	50.0%	36.7%
Total		n 28	2	30
		% 100.0%	100.0%	100.0%

There was evidence of thickening of the bile duct in patients with severe cholangitis, which corresponds to 10.7% of the sample. The majority of patients had moderately severe cholangitis with a high frequency of endosonographic evidence of thickening of the bile duct.

Table 8. Frequency of endosonographic findings of thickened bile ducts in relation to clinical severity according to the Tokyo guidelines of 2013 (cross-tabulation).

		Severity of cholangitis			Total
		Grade III	Grade II	Grade I	
Bile duct wall thicker than 1.5 mm in EUS	Yes	n 3	15	10	28
		% 100.0%	93.8%	90.9%	93.3%
	No	n 0	1	1	2
		% 0.0%	6.3%	9.1%	6.7%
Total		n 3	16	11	30
		% 100%	100%	100.0%	100.0%

Biliary thickening was found in 100% of the patients with severe cholangitis, 93.8% of those with moderate cholangitis and 90.9% of those with mild cholangitis which suggests greater coincidence of this finding with greater degrees of cholangitis and possible prognostic utility that requires additional study to demonstrate statistical significance.

Bile duct content showed the same behavior in severe cholangitis and was found in only 68% of the patients with grade II cholangitis and in only 45% of the patients with mild cholangitis. The search for associations of frequencies of causes showed no significance or tendency towards greater positivity of findings with respect to the etiology.

DISCUSSION

Establishing more precise diagnoses of acute cholangitis may reduce the time between diagnosis and treatment of this

Table 9. Frequency of endosonographic periportal halos in bile ducts according to clinical severity in accordance with the Tokyo guidelines of 2013 (cross-tabulation).

		Severity of cholangitis according to patient's clinical picture			
		Grade III	Grade II	Grade I	Total
EUS finding of 1.5 cm hypoechoic periportal halo	Yes	n 3	8	7	18
		% 100.0%	50.0%	63.6%	60.0%
	No	n 0	8	4	12
		% 0%	50.0%	36.4%	40.0%
Total		n 3	16	11	30
		% 100.0%	100.0%	100.0%	100.0%

Endosonographic findings of periportal halo were present in all patients with severe cholangitis, in 50% of those with moderate cholangitis and in 63.6% of those with severe cholangitis.

disease whose mortality rate is high and increases prohibitively as treatment is delayed. (5) Boender et al. have found a 67% mortality rate when treatment is delayed but a 1% mortality rate when biliary drainage occurs within 72 hours. (6, 7) This study has examined the validity of linear biliopancreatic endosonography for diagnosis of acute cholangitis.

We found that concentric thickening of the bile duct greater than 1.5 mm was present in 89.3% of the cases of acute cholangitis and that this had a positive predictive value of 90%. Similarly, cholangitis was confirmed in 88.9% of the cases with EUS periportal halos, and it was confirmed in 94.7% of the cases who had EUS findings of intraductal content.

These results, although promising, did not show statistical validity in association calculations which may be due to the small sample size. Also, the study had no control group of patients who had been diagnosed with cholestasis but had no clinical diagnosis of cholangitis. This could have allowed an accurate calculation of predictive values and could have allowed us to obtain a representative sample. This was the case in the study by Emrah et al. In that study, the authors described similar endosonographic characteristics and compared the group of patients with a control group of patients who did not present the condition. In the control group 68% of the patients had thickened duct walls, 46% had EUS periportal halos, and 64% had mixed echoes for duct content. These data correspond to measures of association with p less than 0.05 for the presence of thickening of the bile duct, but without measurable association for the other two parameters (15).

Both studies show that the diagnostic capacity of endosonography tends to make an early diagnosis of cholangitis. In both studies, thickening of bile duct wall is the most

important finding, but it is not possible to determine greater precision than that of current diagnostic criteria. This could be due to methodological biases within both studies and the small numbers of patients studied.

CONCLUSIONS

Acute cholangitis is a pathology with a high prevalence and important morbidity and mortality rates despite treatment with antibiotics. Endosonographic methods have not been sufficiently evaluated for diagnosis of cholangitis. At this point, their performance remains unknown, despite the high resolution of biliopancreatic structures with EUS and its excellent diagnostic performance for a large number of structural pathologies.

This study failed to obtain association results that would allow extrapolation of data to the general population, but it has been possible to obtain trend data from the high frequency of endosonographic findings that suggest acute cholangitis when this is confirmed by purulent drainage in ERCP. Among the endosonographic findings, the most valuable for this study is thickened bile duct walls which were found in most patients with acute cholangitis.

Other findings are periportal halos and hypoechoic bile duct content which were found with more variable frequencies but always tending towards diagnostic confirmation. Nevertheless, there is less clarity for these findings.

Equally relevant are our findings of higher frequencies of each endosonographic change in relation to severity, since, in all cases there were greater frequencies as severity increased. This is of paramount importance since it implies that EUS may have a role not only for diagnosis but also for prognosis of acute cholangitis. This could lead to earlier treatment which would probably reduce morbidity and mortality rates in the future.

For now, additional studies are needed in order to obtain greater statistical power and arrive at conclusions that can be applied in clinical guidelines. We recommend that future studies obtain larger sample sizes for adequate calculation and that they also use healthy controls to achieve the desired statistical power.

Similarly, we think it is advisable for all clinical endosonographic studies of biliary obstruction to measure the bile duct wall and to check for the presence of periportal halo and mixed intraductal content so that these factors can be taken into account in diagnosis. The result of these findings is to accelerate the implementation of adequate measures for drainage of the bile duct and the reduction of morbidity and mortality associated with cholangitis. Despite the absence of strong evidence, the trend and potential benefit exceed the risk of accelerating measures that patients require for management of their underlying disease.

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REFERENCES

1. TG13: Updated Tokyo Guidelines for acute cholangitis and acute cholecystitis. *J Hepatobiliary Pancreat Sci.* 2013;20:24-34.
2. Kochar R, Banerjee S. Infections of the biliary tract. *Gastrointest Endoscopy Clin N Am.* 2013;23:199-218. Doi: <https://doi.org/10.1016/j.giec.2012.12.008>
3. Kinney TP. Management of ascending cholangitis. *Gastrointest Endosc Clin N Am.* 2007;17(2):289-306. Doi: <https://doi.org/10.1016/j.giec.2007.03.006>
4. Cohen S, Bacon BR, Berlin JA, et al. National Institutes of Health State of the Science Conference Statement: ERCP for diagnosis and therapy, January 14-16, 2002. *Gastrointest Endosc.* 2002;56(6):803-9. Doi: [https://doi.org/10.1016/S0016-5107\(02\)70351-9](https://doi.org/10.1016/S0016-5107(02)70351-9) / <https://doi.org/10.1067/mge.2002.129875>
5. Welch JP, Donaldson GA. The urgency of diagnosis and surgical treatment of acute suppurative cholangitis. *Am J Surg.* 1976;131(5):527-32. Doi: [https://doi.org/10.1016/0002-9610\(76\)90003-9](https://doi.org/10.1016/0002-9610(76)90003-9)
6. O'Connor MJ, Schwartz ML, McQuarrie DG, et al. Acute bacterial cholangitis: an analysis of clinical manifestation. *Arch Surg.* 1982;117(4):437-41. Doi: <https://doi.org/10.1001/archsurg.1982.01380280031007>
7. Boender J, Nix GA, de Ridder MA, et al. Endoscopic sphincterotomy and biliary drainage in patients with cholangitis due to common bile duct stones. *Am J Gastroenterol.* 1995;90(2):233-8.
8. Chak A, Cooper GS, Lloyd LE, et al. Effectiveness of ERCP in cholangitis: a community-based study. *Gastrointest Endosc.* 2000;52(4):484-9. Doi: <https://doi.org/10.1067/mge.2000.108410>
9. Verma D, Kapadia A, Eisen GM, et al. EUS vs MRCP for detection of choledocholithiasis. *Gastrointest Endosc.* 2006;64:248-54. Doi: <https://doi.org/10.1016/j.gie.2005.12.038>
10. DiMagno EP, Buxton JL, Regan PT, et al. Ultrasonic endoscope. *Lancet.* 1980;1:629-31. Doi: [https://doi.org/10.1016/S0140-6736\(80\)91122-8](https://doi.org/10.1016/S0140-6736(80)91122-8)
11. Mohamed AM, Wael AA. Endoscopic ultrasound in gastroenterology: from diagnosis to therapeutic implications. *World J Gastroenterol.* 2014;20(24):7801-7. Doi: <https://doi.org/10.3748/wjg.v20.i24.7801>
12. Harinck F, Bruno MJ. Endosonography in the management of biliopancreatic disorders. *Best Practice & Research Clinical Gastroenterology.* 2009;23:703-10. Doi: <https://doi.org/10.1016/j.bpg.2009.06.008>
13. Legmann P, Vignaux O, Dousset B, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. *Am J Roentgenol.* 1998;170:1315-22. Doi: <https://doi.org/10.2214/ajr.170.5.9574609>
14. DeWitt J, Misra VL, Leblanc JK, et al. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. *Gastrointest Endosc.* 2006;64(3):325-33. Doi: <https://doi.org/10.1016/j.gie.2005.11.064>
15. Alper E, Unsal B, Buyraç Z, et al. Role of radial endosonography in the diagnosis of acute cholangitis. *Digestive Diseases and Sciences.* 2011;56(7):2191-6. Doi: <https://doi.org/10.1007/s10620-010-1552-3>
16. Şurlin V, Săftoiu A, Dumitrescu D. Imaging tests for accurate diagnosis of acute biliary pancreatitis. *World J Gastroenterol.* 2014;20(44):16544-9. Doi: <https://doi.org/10.3748/wjg.v20.i44.16544>
17. International workshop on the clinical impact of endoscopic ultrasound in Gastroenterology. Working Party Report. *Endoscopy.* 2000;32:549-84.