

Utility of Gamma Glutamyl Transpeptidase as an early predictive factor for choledocholithiasis

Luis Raúl Cajamarca Bermeo M.D.
 Carol Estefanía Márquez Maldonado M.D.
 Walter Eduardo Castro García M.D.
 Milton Paul Yunga Guaman M.D.
 Andrea Monserrat Velez Lara M.D.
 Henry Samuel Santander Muñoz M.D.
 Kerlly Katherine Pizarro Lindao M.D.
 Christian Adrián Macías Arguello M.D.
 Anabel Gabriela Cajamarca Bermeo M.D.
 Jorge Darwin Plaza Ronquillo M.D.

Cuenca, Ecuador

ABSTRACT:

Gamma glutamyl transpeptidase (GGT), is a hepatic enzyme whose elevation is observed in 93% of biliary obstructive pathology, mainly in choledocholithiasis, hence its importance for the early detection of this pathology. Therefore, the objective is to determine the diagnostic value of GGT as an early predictive factor of choledocholithiasis in patients treated at the Vicente Corral Moscoso Hospital during the year 2018.

KEYWORDS: Complications, diagnosis, etiology, choledocholitis, prevalence, incidence, enzymes.

Original Article

General Surgery

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Introduction

Choledocholithiasis is defined as the presence of stones at the level of the main bile duct [1]. Most of the stones are of vesicular origin, and when they pass and are located in the common bile duct, they grow due to the addition of cholesterol that causes dilatation of the bile duct [2].

This pathology occurs mainly in the West, more frequent in women; only a portion, approximately 20%, presents symptoms, and complications occur between 2 and 3%, with the most frequent complications being acute cholecystitis, acute pancreatitis, biliary obstruction and cholangitis [3].

There are several diagnostic options to assess the bile duct, including cholangiography (IOC), endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography (MRC) [4]. In addition, the protocol for suspected choledocholithiasis includes physical examination, blood biochemistry with their respective enzymes or cholestasis parameters, and ultrasound [5].

A positive correlation has been shown between the presence of choledocholithiasis and laboratory criteria such as elevated hepatobiliary enzymes, mainly GGT, alkaline phosphatase (AP), total bilirubin (BT); and sonographic criteria such as dilatation of the bile duct, presence of stones and acute cholecystitis [1].

GGT is produced by mitochondria at the level of hepatocytes, it is excreted by the biliary tract,

mainly by the intrahepatic bile duct, this enzyme is increased to a greater or lesser degree in all liver diseases and its activity can be induced by various medications, such as anticonvulsants and oral contraceptives and non-hepatic diseases including chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and acute myocardial infarction (AMI) [6].

Methods

A study of diagnostic tests was carried out to determine the usefulness of the GGT in the diagnosis of choledocholithiasis at the Vicente Corral Moscoso Hospital during the year 2018. Sociodemographic variables were included to characterize the population. The programs used for the different statistical analyzes were SPSS v 20.0, Excel 2013 and EPIDAT 4.2.

Results

The mean age in the studied sample was 58.3 years. It was found that most of the patients studied correspond to older and married adults. There was a male to female ratio of 1:1.5; In addition, the majority of patients come from rural areas and have a primary education level (Table 1).

Regarding the clinical manifestations, we can observe that abdominal pain is the main symptom that occurred in more than two thirds of the population

Age groups (WHO*)	n°(290)	%
Young adult	56	19,3
Average adult	38	13,1
Adulto mayor	67	23,1
	129	44,5
Sex		
Men	116	40
Women	174	60
Marital status		
Single	14	4,83
Married	145	50,00
Widower	15	5,17
Divorced	73	25,17
Free Union	43	14,83
Origin		
Urban	87	30
Rural	203	70
Occupation		
Mid-level technicians and professionals	7	2,41
Office workers	8	2,76
Service worker and trader	82	28,28
Agricultural and fishing worker	7	2,41
Plant and machine operators	7	2,41
Unskilled workers	24	8,28
Inactive	155	53,45
Instruction		
None	32	11,03
Primary	130	44,83
Secondary	102	35,17
Third level	26	8,97

Table 1. Sociodemographic characteristics. *WHO. World Health Organization.

studied. About half of the patients with choledocholithiasis presented nausea. Other signs such as jaundice, fever, choloria and acholia were present but less frequently. (Table 2)

GGT elevation occurred in the vast majority of patients and about a tenth of the study population had normal GGT (Table 3).

By linking high levels of GGT and choledocholithiasis, it was found that patients with

Abdominal pain	N°(290)	%
Present	252	86,89
Absent	38	13,11
Jaundice		
Present	45	15,52
Absent	245	84,48
Fever		
Present	40	13,79
Absent	250	86,21
Coluria		
Present	44	15,17
Absent	246	84,83
Acolia		
Present	28	9,66
Absent	262	90,34
Nausea		
Present	139	47,93
Absent	151	52,07

Table 2. Clinical characteristics.

high values of said enzyme were 2.47 times more likely to have choledocholithiasis compared to those with normal GGT values, with a statistically significant p-value. significant 0.011 (Table 4). Regarding the main clinical manifestations and their relationship with choledocholithiasis, it can be seen that patients who presented abdominal pain have a probability of 2.81 times more of presenting choledocholithiasis than those patients who did not have such a symptom OR 2.81 (95% CI : 1.39–5.66 p-value 0.004). Likewise, patients who presented jaundice were 3.56 times more likely to have choledocholithiasis than those who did not have jaundice OR 3.56 (95% CI: 1.05–11.9 p value 0.018). Although it is true that fever could occur in patients with choledocholithiasis, this relationship in the present study was not statistically significant (OR 1.02; 95% CI: 0.44 – 2.35. P value 0.572). With regard to coluria and acholia, there was also no clear probability of manifesting in patients with choledocholithiasis (OR 0.56; 95% CI: 0.26–1.22. p value 0.095) and (OR 2.84; CI 95%: 0.64-12.51 (p value 0.114) respectively, (Table 5).

GGT	n°(290)	%
Elevated	257	88,62
Normal	33	11,38

Table 3. GGT Levels

GGT Level	choledocholithiasis		No choledocholithiasis		OR N %	IC 95%
	N	%	value p			
High	203	70,0	44	15,2	2,47 1,21-	5,01 0,011
Normal	28	9,6	15	5,2		

Table 4. Association between levels of GGT and choledocholithiasis

When performing a validation analysis of GGT elevation as an early predictor of choledocholithiasis, we can see that it has a good ability to detect true patients (sensitivity) 88.38%; however, the ability to detect true healthy individuals (specificity) is very low at 10.20%. The probability that a patient suffers from choledocholithiasis with an elevated GGT (PPV) is high 82.88%; likewise, the probability that a patient with a low GGT is really healthy (NPV) is very low 15.15%. Using the Youden Index, we can see that the performance of the GGT test is low to predict choledocholithiasis - 0.11. Taking the PVR values ≥ 10 as a cut-off point, we observed that the elevation of the GGT was 0.98, which means that it is a poor test to detect patients with the disease, this is corroborated by its confidence intervals < 10 (95% CI 0.89 – 1.09). Taking NVR values < 0.1 as a cut-off point, we observed that GGT was 1.14, which means that it is a poor test for detecting patients without the disease; this is corroborated by their confidence intervals > 0.1 (95% CI 0.46-2.80) (**Table 6**).

The discriminating power to predict choledocholithiasis with an elevated GGT is low, with an AUC of 0.56. (**Graphic 1**).

The discriminating power to predict choledocholithiasis with an elevated GGT is low, with an AUC of 0.56. When obtaining the p value, we observed that there is no statistically significant difference between elevated GGT and choledocholithiasis, so it is considered that the GGT enzyme alone is not a good predictor of choledocholithiasis (**Table 7**).

Discussion

Choledocholithiasis is a common health problem in our environment with an incidence of 8 to 15%, which must be identified early through various diagnostic methods [7,8].

An important limitation in this study was that the association between choledocholithiasis was only made with GGT and not with other important liver markers that were made in other studies.

Clinical manifestations	choledocholithiasis		No choledocholithiasis		OR LI	IC 95%		
	N	%	value pn	%		LS	LS	
Abdominal pain								
Yes	204	70,3	43	14,8	2,81	1,39	5,66	0,004
No	27	9,3	16	5,5				
Jaundice								
Yes	37	14,5	3	1,1	3,56	1,05	11,9	0,018
No	194	68,6	56	19,3				
Fever								
Yes	32	11,1	8	2,7	1,02	0,44	2,35	0,572
No	199	68,6	51	17,6				
Coluria								
Yes	29	10,0	12	4,2	0,56	0,26	1,22	0,095
No	202	69,7	47	16,2				
Acolia								
Yes	21	7,2	2	0,7	2,84	0,64	12,51	0,114
No	210	72,4	57	19,6				

Table 5. Association between the main clinical manifestations and choledocholithiasis.

Gamma Glutamyl Transpeptidase (GGT)	Value	IC (95%)	
Sensitivity (%)	88,38	84,71	92,63
Specificity (%)	10,20	0,71	19,70
Positive predictive value (%)	82,88	78,08	87,68
Negative predictive value (%)	15,15	1,40	28,90
Youden index	- 0,01	- 0,11	0,08
Positive likelihood ratio	0,98	0,89	1,09
Negative likelihood ratio	1,14	0,46	2,80

According to Velázquez D. et al. the mean age of presentation of choledocholithiasis was 56 ± 15.88 (SD). Tawfik K. et al. in 2019 found that older age is related to more cases of choledocholithiasis ($p < 0.001$) [5,11].

Choledocholithiasis occurs more in women with a 1:1.5 ratio, probably due to hormonal factors Velázquez D. et al. in 2010, a male/female ratio of 1/1.3 was observed, very similar to our study. [5,12].

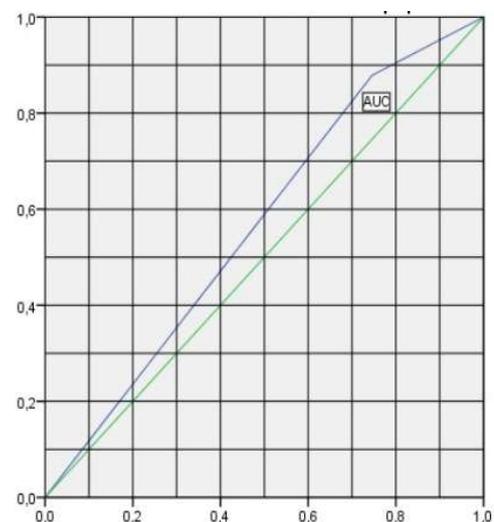
By associating the elevation of GGT and choledocholithiasis, it was found in the present investigation that patients who present elevated values of this enzyme have 2.47 times more probability of presenting choledocholithiasis than those who have normal GGT values OR 2, 47 (95% CI: 1.21–5.01 p value 0.011). Tozatti J. et al. observed such an association ($p = 0.042$). Pérez H. in 2017, found that the biochemical markers with the greatest relationship with the diagnosis of choledocholithiasis are BT, GGT, BD, FA, TGO and TGP, with a significance for all of $p < 0.05$. Regarding GGT as a diagnostic marker for choledocholithiasis, it presented a statistically significant relationship ($p < 0.05$) [7,10].

Regarding the main clinical manifestations, we found that patients who presented abdominal pain have a probability of 2.81 times more of presenting choledocholithiasis than those patients who did not have such symptom OR 2.81 (95% CI: 1.39–5, 66 p-value 0.004). Likewise, patients who presented jaundice were 3.56 times more likely to have choledocholithiasis than those who did not have jaundice OR 3.56 (95% CI: 1.05–11.9 p value 0.018). could occur in patients with choledocholithiasis, this relationship in the present study is not statistically significant according to the p value OR: 1.02 (95% CI 0.44 - 2.35 p value 0.572).

Tozatti J. et al, in 2015, identified jaundice and fever as the signs and symptoms with the highest statistical significance ($p = 0.010$) (7). Velázquez D, et al. in 2014 reported that the classic triad as pain, fever and jaundice occur in 89%, 82% and 74% respectively [5,7].

Regarding the elevation of GGT as a predictive marker of choledocholithiasis, we found that it has a high sensitivity of 88.38%, but a low specificity of 10.2%, a high PPV 82.8% and a low NPV 15, fifteen%.

Tozatti J. et al, maintain that GGT as an early predictor of choledocholithiasis has a sensitivity of 93%, specificity 63%. It concludes that although it is very sensitive, it does not constitute by itself a marker for the diagnosis of choledocholithiasis. Gomez. et al, in Quito-Ecuador in 2012, found that GGT is a good marker for the diagnosis of choledocholithiasis, it has



Graphic1. Area under the ROC curve of GGT to predict Choledocholithiasis. X axis: specificity. Y axis: Sensitivity.

SCORE	AUC	IC (95%)	p value
GGT	0,567	0,481 – 0,652	0,470

Table 7. Statistical analysis of the GGT test as a predictor of choledocholithiasis.

a sensitivity and NPV of 98 and 95%, respectively, and that if it is within normal parameters, we can say that the patient does not have choledocholithiasis with a very high probability [7,9].

Hinojosa PG et al, in Peru 2018, showed that the GGT has a high sensitivity of 92.8%, but a very low specificity of 8.6%, PPV 62.6% and NPV 42.1%. These figures are similar to the present investigation and corroborate that GGT alone is not a useful tool for predicting choledocholithiasis [13].

GGT alone was found to be of little use in detecting and ruling out choledocholithiasis PPV: 0.98; NPV, 1.14. Hinojosa et al. in 2018 they find that the GGT presents a PPV of 1.02 and a NPV of 0.78. Similar data to the present study [13].

The discriminant power to predict choledocholithiasis with an elevated GGT is low, AUC 0.56. When obtaining the p value, we observe that there is no statistically significant difference between elevated GGT and choledocholithiasis $p=0.470$, so it is considered that this enzyme by itself is not a good predictor of choledocholithiasis. Mei Y. et al, in 2019 showed that the value under the curve for GGT, FA and GGT+ FA was 0.88, 0.647 and 0.923 respectively, concluding that the elevation of serum GGT has an important value in the diagnosis of choledocholithiasis and that the combination of serum GGT and FA has better diagnostic performance, data that do not agree with our results because the analysis was only done with GGT and not with other enzymes as other studies do. [6]

Conclusion

Patients with elevated GGT are 2.47 times more likely to have choledocholithiasis than those with normal GGT values. According to our study, GGT has high sensitivity but low specificity. Although it is true that there is an association between elevated GGT and choledocholithiasis, its discriminative power for the diagnosis of this pathology is very low.

Conflicts of Interests

The authors declare no conflict of interest.

Acknowledgements

We thank the "Vicente Corral Moscoso" Hospital for allowing the study to be carried out

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Luis Raúl Cajamarca
General Surgery Department
Hospital Vicente Corral Moscoso
Cuenca, Ecuador
dr.raulcajamarca@hotmail.com