Association of types of periampullary diverticulum and types of extrahepatic bile duct stones: a cross-sectional study

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Abstract

Background/Aims: Periampullary diverticula are associated with an increased incidence of choledocholithiasis. There are different types of diverticula based on its location relative to the major papilla, and there are different types of bile duct stones. This study aims to determine the relationship between the types of diverticula and the types of duct stones.

Methods: This is a cross-sectional study of 380 patients with choledocholithiasis and who underwent ERCP from February 2015 to October 2020. Official reports and videos were reviewed. Outcome measures include types of periampullary diverticula using the Li-Tanaka Classification and types of bile duct stones. T-test and Chi-square Goodness of Fit test were used for data analysis.

Results: There were 275 patients with no diverticula and 105 patients with diverticula. Type III (papilla ≥1 cm outside the diverticulum margin) was most common (42.85%). There was significantly different age between the groups (p<0.001) with Type IVa (2 diverticula with papilla <1 cm outside the margins of at least one) having the highest mean age of 67.45±15.9 years. There was also a significant difference in failed cannulation (p<0.01) with Type IVa having 27%. Though there was no significant difference in duct diameters, duct stone numbers, and duct stone sizes, Types I (intradiverticular papilla not adjacent to the margin) and IIa had larger duct diameters (1.7±0.71 cm and 1.54±0.55 cm respectively), more multiple duct stones (50% and 75%, respectively), and larger duct stone sizes (1.3±0.85 cm and 1.56±0.75 cm, respectively). There was a significant difference in the types of stones with Type IVa having 71% brown stones, p=0.018).

Conclusion: Type of periampullary diverticulum may influence the type of stone in the extrahepatic bile duct, with Type IVa having the highest proportion of brown stones. Type IVa was also associated with failed cannulation and older age.

Keywords: periampullary diverticulum, choledocholithiasis, bile duct stones

Introduction

Periampullary Diverticula (PAD) are extraluminal outpouchings of the duodenal mucosa, submucosa and muscularis mucosa extending through the intestinal serosa with the Ampulla of Vater located inside, adjacent or outside the diverticula.[1]
The prevalence of PAD has been reported as 0.16% to 27% depending on the diagnostic method, with its prevalence at ERCP ranging from 5% to 27%.2 There are several classifications based on the characteristics of the diverticulum and the location of the major papilla.

Gallstone disease is a common disorder with a prevalence of 10-20% in Western countries and with rising numbers in Asian countries.3 Gallstones are mostly found in the gallbladder, but may be found in the cystic duct, extrahepatic duct and intrahepatic ducts, the latter two better termed as bile duct stones. Stones originating in the gallbladder may be composed predominantly of yellow cholesterol and black pigment stones. Stones originating in the bile ducts are mostly brown pigment stones. Brown pigment stones are made predominantly of calcium bilirubinate, contain more cholesterol than black stones, and are associated with biliary stasis and bacterial infection. Black stones are made primarily of bilirubin polymers, are associated with cirrhosis and hemolytic disorders.[4]

Several studies have recognized the association of PAD with choledocholithiasis.5 But few studies have shown the clinical influence of the type of PAD. While literature has suggested the association of PAD with choledocholithiasis and its association with pigment stones, the relationship of the different types of PAD and types of stones have not yet been explored; for example, types of stones also have different harness (i.e. brown stones are easily fragmented while black stones are hard and brittle when crushed).6 Knowing of such relationship may help predict the type of bile duct stones and help decide whether to proceed with mechanical lithotripsy or cholangioscopy or plastic stenting when faced with a large bile duct stone during ERCP.

Methods

A. Type of Study, Time Period, Setting, Target Population and Sample Size

This is a cross-sectional, single-center study of 380 patients with findings of choledocholithiasis in imaging studies and who underwent Endoscopic Retrograde Cholangiopancreaticogram (ERCP) in a tertiary hospital from February 1, 2015 to October 31, 2020, as this was the period with videos still accessible. Excluded were patients with a) incomplete data, b) difficult to visualize periampullary area due to anatomical reasons or previous gastrointestinal surgeries, c) known or diagnosed liver, gallbladder, bile duct, and pancreatic tumors, d) biliary stricture, and e) choledochoenteric fistula and bile duct injury.
The sample size calculation requires a minimum of 208 patients for this study based on 59.6% and 35% prevalence of common bile duct stones among patients with and without PAD, respectively, 5% level of significance and 95% power.[7,8]

B. Operational Definitions

• Periampullary diverticulum refers endoscopically to a depressed lesion or outpouching of >5mm with intact mucosa within a radius of 2.5 cm from the papilla.[9]

• Types of PAD were classified using the Li-Tanaka Classification. The authors used this classification as it was more detailed with regards to the number of diverticula and anatomical relationship to the major papilla.[10] (Figure 1)

- Type I refers to PAD with the papilla located inside the diverticulum and not adjacent to the margin.

- Type IIa refers to PAD with the papilla located inside the margin of the diverticulum.

- Type IIb refers to PAD with the papilla located <1 cm outside the margin of the diverticulum.

- Type III refers to PAD with papilla located ≥1 cm outside the margin of the diverticulum.

- Type IVa refers to PAD with 2 diverticula and with papilla located <1 cm outside the margins of at least one diverticulum.

- Type IVb refers to PAD with 2 diverticula and with papilla located ≥1 cm outside the margins of all the diverticula.

• Successful Cannulation refers to deep instrumentation of the CBD with full visualization of the biliary tree.

C. Description of Outcome Measures

• Bile Duct (BD) stones were described by number and size and classified by the color as black pigment stones, brown pigment stones, yellow cholesterol stones according to the National Institutes of Health-International Workshop.

D. Description of the Study Procedure, Data Collection and Ethical Consideration

Patient confidentiality were ensured by encoding patient data on data collection forms with an assigned patient number. The videos and screenshots of the papilla and stones were reviewed by two investigators (SJBP, JCAO). Disagreements on PAD and stone classifications were resolved on review of the study adviser (MCU). The study was approved by the Institutional Review Board of the hospital (MDH IRB 2021-006_R). A waiver of informed consent was requested from the Institutional Review Board, since the study had minimal risk to privacy with the retrieval of information from past records. Information documented was considered non-sensitive, and anonymity was maintained, in accordance to the National Ethical Guidelines of Health and Health-Related Research 2017. Patients involved were not given direct or financial benefits. No pharmaceutical company sponsored this research.

E. Data Analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables and mean and SD for normally distributed continuous variables. One-way ANOVA and Fisher's exact test were used to determine the difference of mean and frequency, respectively, within with and without PAD as well as its different types. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant factors of 2 or more number of CBD stones, color of CBD stones and CBD size. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis

Results

A total of 1,214 patients underwent ERCP from February 1, 2015 to October 31, 2020 (Figure 3). Eight-hundred-thirty-four patients were excluded due to unavailability of the procedure's video, incomplete data, findings of mass, stricture, choledochoenteric fistula, altered intestinal anatomy due to surgery and absence of CBD stone during ERCP. Hence, 380 patients were included in this study, with 105 patients with PAD and 275 patients without PAD. Out of 105 patients with PAD, 74 patients had a virgin papilla with CBD stones successfully extracted. The non-PAD group with CBD stones total to 275 patients, with 165 patients with virgin papilla and extracted CBD stones.

Table 1 shows the demographic characteristics of the 380 patients included in the study. Of the six types of PAD, Type III was the most common (43%, 45 of 105). In the Chi-square test for independence analysis done for age, sex and ERCP indications, the results show that it was only in terms of age where there was a significant correlation with the presence of PAD with Type IVa (67.45±15.9) and Type IIa (67.14±8.19) having the oldest age (p-value < 0.01). History of cholecystectomy was noted more in Type IIa (29% with p-value <0.01).

Table 2 shows the rate of CBD cannulation among patients with virgin papilla between the non-PAD and PAD groups. Type IVa had the highest failure rate (27%, p=0.015).

The main analysis on CBD stones and PAD was done with the population of patients with stones successfully retrieved and properly visualized in the videos. In this sub-group of patients, we also excluded those with failed cannulation and who had previous ERCP and sphincterotomy since sphincterotomy has been found to be a risk for stone formation (Table 3).11 The Chi-square test for independence for mean size of CBD, and number and mean size of CBD stones showed no significant difference among groups, but it showed a significant difference in the color of CBD stones, specifically brown stones. Type IIa tend to have the highest proportion of black stones (75%, p=0.264), while Type I tend to have the highest proportion of yellow stones (50%, p=0.151), while Type IVa tend to have the highest proportion of brown stones (71%, p=0.018). Descriptively, Types I and IIa tend to have larger mean CBD diameters (Type I = 1.7±0.71, Type IIa = 1.54±0.55; p =0.549), 2 or more CBD stones (Type I = 50%, Type IIa = 75%; p =0.667) and larger CBD stone diameter (Type I = 1.3±0.85, Type IIa = 1.56±0.75; p =0.954).

Discussion

In our cross-sectional study, 28% of patients with choledocholithiasis had PAD (105 of 380), with the most common type being Type III with papilla ≥ 1 cm from the diverticulum. Jakubczyk et al noted that papilla located within 3 cm outside the margins of one diverticulum was the most common type of PAD (43.9%, 29 of 66).[12] Mohammed Alizadeh et al reported that the most common type of PAD was that of papilla outside but within 2 cm to 3 cm of the diverticulum with frequency of 44.5%, followed by PAD with papilla adjacent to the diverticulum (43%) and then PAD with papilla within the diverticulum (12.5%).[13] These are in contrast to a study by Zoepf reporting on the incidence of the types of PAD in patients, stating that 54% of patients with juxtapapillary duodenal diverticula had papilla inside the diverticulum, 37.7% had papilla outside the diverticulum and 7.4% had papilla between two diverticula.[14] There was no obvious difference among the types of studies that could account for this contrast. All these are ERCP studies involving patients of roughly the same age and sex. Jakubczyk et al was done in Poland, Mohammed Alizadeh et al was done in Iran, while Zoepf was done in Germany.

In our study, there was a significant difference in the mean age of the different groups (p=0.001), with the highest mean age of 67.45±15.9 years in patients with Type IVa PAD, followed closely by Type IIa PAD (67.14±8.19 years). Those without PAD have the lowest mean age at 49.43±18.64 years. Likewise, in several studies, the mean age of patients with duodenal diverticula ranged 9 to 11 years higher than the group without PAD.[14,15]

Vaira et al also reported that PAD was seen more frequently in older patients, similar to what was seen in our study, suggesting that PAD may occur later in life with its incidence increasing in age.[16]

In our study, there was significant difference in the rate of failed cannulation (p=0.015) with Type IVa PAD having the highest rate of failed cannulation at 27%. However, the finding of our study is different from other studies Previous studies have reported that failure of deep cannulation of the major papilla ranges from 6.6% to 14.4% in patients with PAD (compared to those without PAD).[17,18] Several studies noted that there was a higher rate of cannulation failure in PAD with intradiverticular papilla compared to other PAD types. Zoepf et al noted that cannulation failure was highest with papilla inside the diverticulum (62.5%) compared to those with the papilla outside (25%) and those with the papilla on the bridge between two diverticula (12.5%); while Panteris et al noted that cannulation was less successful in those with papilla inside or at the middle of the bottom edge of the diverticulum or between two adjacent diverticula (84%) compared to those with papilla at the rim or within 2 cm from the edge of the diverticulum (96.8%).[14,18] In a cohort by Yue, the highest difficult cannulation rate was noted in the Li-Tanaka PAD Type I (23.1%, P=0.01).[10] One factor to consider is the small population of patients with intradiverticular papilla in our study, compared to other PAD types.

Overall, the mean CBD diameters among groups were not statistically significant, but the PAD types with papilla inside and within the margin of the diverticulum (Types I and IIa) had larger mean CBD size compared to the non-PAD group and the rest of the other PAD types. Similarly, PAD with intradiverticular papilla was noted to have wider CBD diameter in a study by Kim CW et al, but also of no statistical significance (non-PAD = 11.3±4.5 mm, PAD with intradiverticular papilla 14.3±4.7 mm; papilla in the margin of the diverticulum = 12.3±5.3 mm, papilla outside the diverticulum = 11.5±3.7 mm; p=0.081).1 In contrast, Yue et al noted that CBD diameters were not significant among the types of PAD using the Li-Tanaka classification but Type IV had the largest CBD diameter (Type I = 14±4 mm, Type II = 14±5 mm, Type III = 14±6 mm, Type IV = 15±5 mm, p=0.56); and, in a cohort by Katsinelos et al, CBD diameter size was significantly higher in patients with papilla located at the rim or margin of the diverticulum (papilla within the rim of the diverticulum = 12.29±2.24 mm; papilla within 2 cm outside the diverticulum = 11.95±1.26 mm; PAD with intradiverticular papilla or papilla between 2 adjacent diverticula = 10.01±1.53 mm; p=0.001), while Hu et al reported that PAD with intradiverticular papilla have a smaller CBD diameter compared to other types where papilla was located outside or at the margin of the diverticula (10.2±3.5 vs 13.5±3.4 mm; p-value 0.005).[10,19,20] Notably, in these studies, the CBD size was proportional to the size of the CBD stone. These studies were also done via ERCP involving patients roughly the same age and sex, with Kim et al done in South Korea, Yue et al and Hu et al done in China, and Katsinelos et al done in Greece.

The presence of PAD is an important risk factor for choledocholithiasis as several studies suggest that PAD is a risk factor for the accumulation of sediments in the bile duct. The most common mechanism frequently mentioned was the effect of the pressure exerted by the diverticula into the distal part of the common bile duct thus interfering with biliary drainage.[21] A study by Tham and Kelly reports that localization of the major ampulla in the vicinity of the diverticulum significantly increases the incidence of stones in the common bile duct.[22] Chen et al reported the presence of bile duct stones in 63.26% of patients with PAD and 35.60% in those without PAD (p<0.001), and PAD per se was still an important factor to CBD stone formation even after adjusting for age and sex [OR 3.124 (95% CI: 2.691-3.627), p<0.001], proving that proximity of the major papilla to the duodenal diverticulum as a risk factor for choledocholithiasis.[23] In a study by Bruno et al, they found no association with the type of diverticulum with choledocholithiasis (p=0.58).21 However, Ozogul et al noted that papilla within 3 cm of a diverticulum was associated with choledocholithiasis (p=0.016) and was also associated with gallbladder stones (p=0.014).[24]

In our study, the mean diameter of largest CBD stone was not significant among the groups, but both PAD with intradiverticular papilla (Type I) and within the margin of the diverticulum (Type IIa) also showed a trend toward a larger stone size. Kim KH et al reported that PAD with intradiverticular papilla have significantly larger stone size (intradiverticular papilla = 17.8±6.7 mm; papilla in the margin of the diverticulum = 15.9±5.5 mm; papilla outside the diverticulum = 16.1±6.2 mm; p=0.514).[25] Kim CW et al showed that PAD with intradiverticular papilla significantly had bigger stone size (intradiverticular papilla = 12.5±6.2 mm) compared to non-PAD group and other types (non-PAD = 8.2±5.7 mm, papilla in the margin of the diverticulum = 9.9±5.9 mm, papilla outside the margin of the diverticulum = 9.7±4.4 mm; p=0.022).[1] Yue et al study a modified versions of the Li-Tanaka classification noted that Types I and IV PAD had the larger CBD stone size (Type I = 13±5, Type II = 12±6, Type III = 12±6, Type IV = 13±8, p=0.58).[10] Based on our study and the aforementioned studies, it would seem that the size of the CBD stone and duct correspond to each other, and not to the type of PAD.

In our study, the number of bile duct stones is not statistically significant among the different groups but PAD with intradiverticular papilla (Type I) and within the margin of the diverticulum (Type IIa) tend to have 2 or more stones. This is almost similar to a study by Hu et al showing that PAD with intradiverticular papilla was noted to have 3 stones or more within the CBD (50%, p-value 0.001).[20]

To our knowledge, this is the first study exploring the association of the different types of PAD and the color of CBD stones, as previous studies compared color of CBD stones between the PAD group and the non-PAD group and not among the types of PAD. Our study found a significant difference in the proportion of brown stones among the non-PAD and different PAD types (p=0.018) with PAD Type IVa having the highest proportion of brown stones (71%). Studies have shown that calcium bicarbonate stones are more common than cholesterol stones in CBD patients with PAD.[26,27] Sandstad et al found that PAD was associated with brown pigment stones (22 of 42 patients with brown pigment stones had PAD, p<0.01).[28] Likewise, Kim et al reported that brown stones were more common in PAD, but there was no significant difference with those without PAD (p=0.144).[25] Brown pigment stones may result from stasis or infection with bacteria. A correlation between bacteria and calcium bilirubinate pigment stones have also been studied, suggesting that bacteria play a significant part in the pathogenesis of bile duct stones.[29] Furthermore, duodenal diverticula was noted to have increased levels of ß-glucuronidase producing bacteria and subsequent deconjugation of bilirubinate glucuronides which results in pigment precipitation and stone formation.30 Functional stasis within the CBD may also predispose to infection, which may influence brown stone formation. It has been reported that patients with PAD have decreased SOD muscular tone and contractions leading to bile reflux into the CBD. This was observed to be due to the sustained mechanical compression of the lower CBD by a distended PAD. Such decrease in SOD pressure may allow reflux of ß-glucuronidase producing bacteria, hence, this would also contribute to the development of lithiasis, particularly of brown pigment stones.[15] The two diverticula near the papilla in PAD Type IVa may act synergistically to decrease the SOD pressure, thus, increasing the risk for brown stone formation. The reason that PAD Type IVb does not have more brown stones may be because the diverticula are too far away from the papilla (≥1 cm from the diverticula). Being able to predict that extrahepatic biliary stones are usually brown stones in patients with Type IVa PAD, we can surmise that these stones are amenable to lithotripsy since they are usually soft and easily fragmented.

Though not significant, our study also found PAD Types I and IIa to have the highest proportion of black stones (50% and 75% respectively), and PAD Type I the highest proportion of yellow stones (50%). But, in a study by Kim KH et al, the non-PAD group had more black stones than the PAD group (19% vs 9.9%, p=0.144), although this study did not compare the different types of PAD.[25] However, our study is limited with the few patients having PAD Types I and II.

There are some limitations in this study such as it is a retrospective study with a small sample size, with some PAD Types having been observed in less than 20 patients. Aside from that, the color of biliary stones were based on gross morphology alone as observed in the videos. There were no cytologic or spectrometric studies done on the stones to accurately characterize them. Mixed-type stones could also not be differentiated in this study based on observation alone and were more likely classified under stones with brown color. History of patients that may also identify risk for formation of types of stones such as cirrhosis or hemolytic disorders were not mentioned in the endoscopy reports. Other risk factors for gallstone disease such as obesity, pregnancy, use or oral contraceptives and the like were also not taken account due to lack of documentation in this retrospective cross-sectional study. We were also not able to retrieve all patient charts due to manpower limitations in the Records Section due to COVID-19 restrictions during the conduct of this study.

Studies with a more rigorous design such as a prospective study comparing the different types of PAD with types of stones preferably by spectrometry is recommended to establish a definite causality. In addition, a prospective cohort may also see into the correlation of the different types of PAD with ERCP complications.

In conclusion, the type of periampullary diverticulum may influence the type of stone in the extrahepatic bile duct, with Type IVa having the highest proportion of brown stones. Type IVa was also associated with failed cannulation and older age.

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TABLE

TABLE 1. Demographic and clinical profile of patients in the study.

	Total (n=380)	No PAD (n=72)	Types of PAD						P-value
			I (n=2)	IIa (n=7)	IIb (n=31)	III (n=45)	IVa (n=11)	IVb (n=9)	
	Frequency (%); Mean + SD								
Age	51.82 ± 18.63	49.43 ± 18.64	64.5 ± 2.12	67.14 ± 8.19	54.23 ± 18.59	55.71 ± 16.79	67.45 ± 15.9	63.56 ± 17.11	**<0.001**
Sex									
Male	170 (45)	121 (44%)	0	6 (86)	13 (42)	21 (47)	4 (36)	5 (56)	0.297
Female	210 (55)	154 (56%)	2 (100)	1 (14)	18 (58)	24 (53)	7 (64)	4 (44)	
Indications for ERCP									
Ascending Cholangitis	36 (9.5)	25 (9.1)	1 (50)	0	2 (6.5)	4 (8.9)	4 (36.4)	0	0.285
Obstructive Jaundice	136 (35.8)	102 (37.1)	0	0	12 (38.7)	15 (33.3)	5 (45.5)	2 (22.2)	
CBD stone in imaging	200 (52.6)	141 (51.3)	1 (50)	7 (100)	16 (51.6)	26 (57.8)	2 (18.2)	7 (77.8)	
Gallstone Pancreatitis	6 (1)	5 (1.8)	0	0	1 (3.2)	0	0	0	
Only dilated CBD in imaging	2 (0.5)	2 (0.7)	0	0	0	0	0	0	
Clinical Profile									
With GB stones	67 (18)	50 (18)	1 (50)	2 (29)	3 (10)	8 (18)	2 (18)	1 (11)	**<0.001**
Post- Cholecystectomy	65 (17)	48 (17)	0	2 (29)	7 (23)	6 (13)	1 (9)	1 (11)	**<0.001**
With ERCP and sphincterotomy	52 (14)	41 (15)	2 (100)	1 (14)	18 (58)	24 (53)	7 (64)	4 (44)	**<0.001**

Abbreviations: CBD, common bile duct; ERCP, endoscopic retrograde pancreaticography; GB, gallbladder; PAD, periampullary diverticulum or diverticula.

TABLE 2. Comparison of cannulation rate in patients with virgin papilla and without periampullary diverticulum and with virgin papilla and with periampullary diverticulum.

Cannulation Rate	**Total (n=328)**	**No PAD (n=234)**	**Types of PAD**						**P-value**
			I (n=2)	**IIa (n=4)**	**IIb (n=27)**	**III (n=41)**	**IVa (n=11)**	**IVb (n=9)**	
	Frequency (%)								
Successful	313 (95.43)	223 (95)	2 (100)	4 (100)	26 (96)	41 (100)	8 (73)	9 (100%)	**0.015**
Failed	15 (4.57)	11 (5)	0	0	1 (4)	0	3 (27)	0	

Abbreviation: PAD, periampullary diverticulum or diverticula.

TABLE 3. Comparison of CBD size and stones in patients with virgin papilla and without PAD and the different types of PAD.

Cannulation Rate	Total (n=239)	No PAD (n=165)	Types of PAD I (n=2)	IIa (n=4)	IIb (n=20)	III (n=32)	IVa (n=7)	IVb (n=9)	P-value
	Frequency (%); Mean ± SD								
CBD Size	1.35±0.64	1.34±0.64	1.7±0.71	1.54±0.55	1.36±0.76	1.38±0.54	1.26±0.87	1.41±0.49	0.549
Number of CBD Stones									
1	145 (61)	103 (62)	1 (50)	1 (25)	14 (70)	17 (53)	4 (57)	5 (56)	0.677
2/more	94 (39)	62 (38)	1 (50)	3 (75)	6 (30)	15 (47)	3 (43)	4 (44)	
Size of Largest CBD Stone	1.15±0.79	1.14±0.84	1.3±0.85	1.56±0.75	1.22±0.66	1.09±0.52	1.24±0.85	0.8±0.34	0.954
Color of CBD Stone									
Black	90 (38%)	59 (36%)	1 (50%)	3 (75%)	8 (40%)	12 (38%)	1 (14%)	6 (67%)	0.264
Yellow	105 (44%)	80 (48%)	1 (50%)	0	7 (35%)	14 (44%)	1 (14%)	2 (22%)	0.151
Brown	44 (18%)	26 (16%)	0	1 (25%)	5 (25%)	6 (19%)	5 (71%)	1 (11%)	**0.018**

Abbreviations: CBD, common bile duct; cm, centimeters; ERCP, endoscopic retrograde pancreaticography; GB, gallbladder; PAD, periampullary diverticulum or diverticula.

FIGURES

FIGURE 1. Images of periampullary diverticulum/diverticula as noted in the videos, based on the Li-Tanaka Classification.

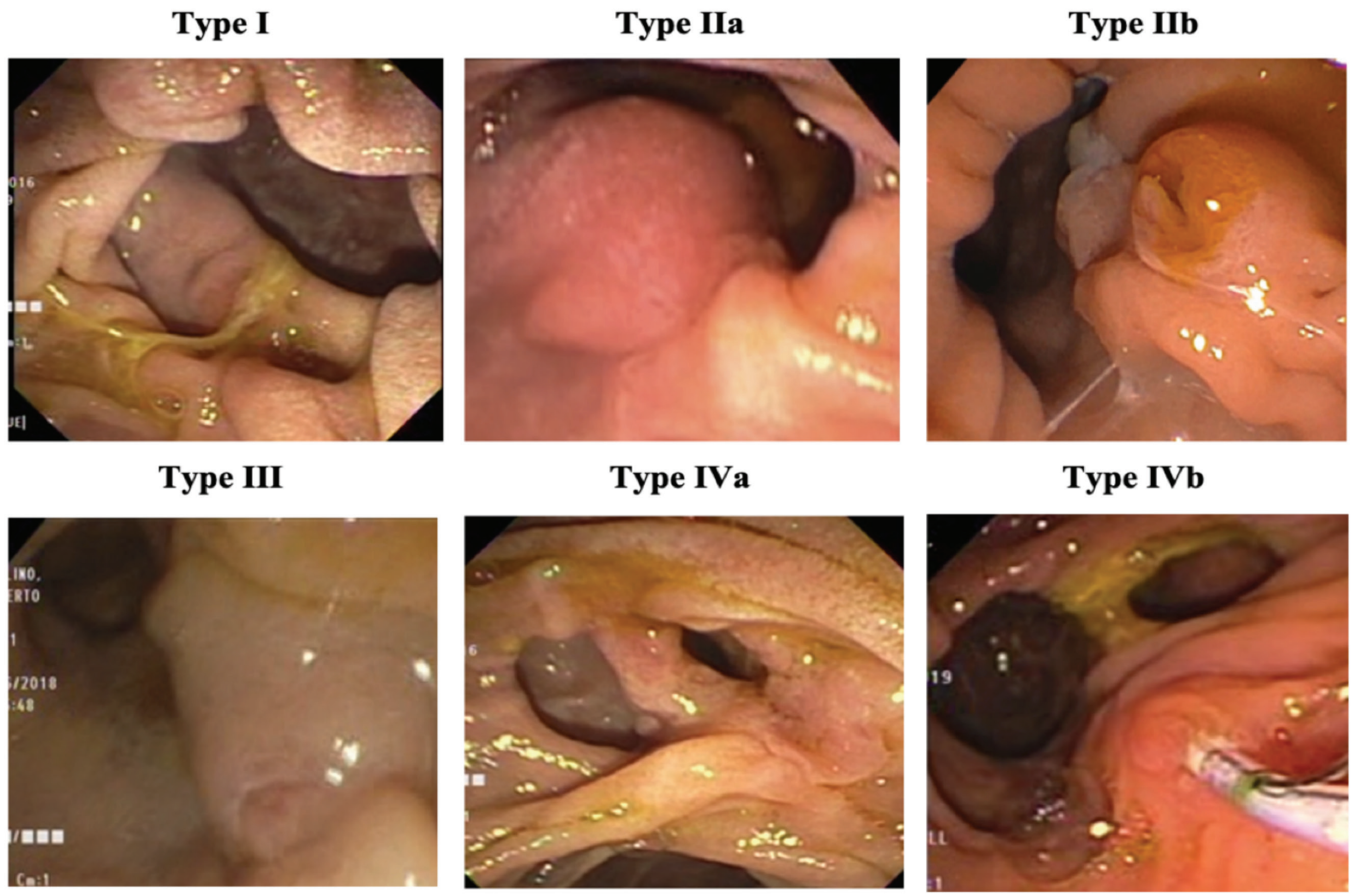

FIGURE 2. Classification of stones based on the gross color of stones as seen in the videos.

FIGURE 3. Flow of the study.