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Association of periampullary diverticulum types with post-ERCP hyperamylasemia: a retrospective observational study

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Abstract

Background This study aimed to assess the prevalence of periampullary diverticulum (PAD) among endoscopic retrograde cholangiopancreatography (ERCP) patients in Southwestern Turkey and investigate the association between the new PAD classification, post-ERCP hyperamylasemia, and post-ERCP pancreatitis (PEP).

Materials and methods We retrospectively reviewed 1,317 ERCP procedures performed between January 1, 2022, and December 31, 2023, at Antalya Training and Research Hospital. The PAD type was determined according to the He-xian Shi classification. Hyperamylasemia was defined as an increase of three times the normal level of amylase at 4 to 6 h, and PEP was defined as hyperamylasemia along with abdominal pain lasting more than 24 h.

Results A total of 594 naive patients who underwent ERCP were analyzed. PAD was present in 137 patients (23.1%), and the success rate of choledochal cannulation in the first ERCP procedure was 94.3%. There was no difference in the choledochal cannulation rate between patients with and without PAD (95.6%-93.4%, $p = 0.59$). Asymptomatic hyperamylasemia was observed in 19.3% of the patients. Post-ERCP hyperamylasemia rates were similar between patients with and without PAD (17.5% and 21.2% respectively, $p = 0.31$). PEP was observed in 8.0% of the patients. Presence of PAD was not a risk factor for post-ERCP pancreatitis (7.3% compared to 8.8%, $p = 0.82$). When we checked the results according to the type of PAD, the prevalence of post-ERCP hyperamylasemia was significantly lower in patients with type 2b PAD than in those with type 1 and type 2a patients.

Conclusion PAD is a common finding in ERCP patients, with a prevalence of 23.1% in our cohort. The rate of choledochal cannulation, post ERCP hyperamylasemia and PEP did not differ between the patients with and without PAD. However, the type of PAD is important; post-ERCP hyperamylasemia is significantly lower in patients with type 2b than in type 1 and type 2a PAD patients. Different subtypes of PAD may have different associations on ERCP outcomes. Further investigations with refined and standardized PAD classification systems are needed.

Keywords Periampullary diverticulum types, Endoscopic retrograde cholangiopancreatography, Hyperamylasemia

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential procedure for the management of pancreaticobiliary disorders. However, post-ERCP complications, including hyperamylasemia and post-ERCP pancreatitis (PEP), remain significant concerns [1]. Hyperamylasemia, characterized by elevated serum amylase levels, is a frequently observed biochemical abnormality following ERCP and is often considered a marker of pancreatic irritation. While not all cases of hyperamylasemia progress to PEP, its occurrence may reflect procedural stress on the pancreas and serve as an early indicator of potential PEP [2–4].

The diagnosis of PAD in endoscopic retrograde cholangiopancreatography (ERCP) varies, with reports ranging from 4.6 to 19.8% in Turkey, and up to 46.1% globally [5–7]. The presence of PAD has been claimed to be associated with increased difficulty of cannulation and post-ERCP complications, though the results are conflicting [6, 8–18]. Previous studies that utilized traditional PAD classification systems (Lobo and Boix) [8, 19] may have obscured the relationship between different PAD subtypes and ERCP outcomes [20]. More recently, Shi and colleagues proposed a new classification that distinguishes PAD located at the inner and outer margins of the ampulla [21]. The comparative analysis of the Lobo, Boix, and Shi classification systems is presented in Table 1.

In our daily clinical practice, we have observed that the presence of PAD is a common finding, and the success of ERCP in patients with PAD depends not only on the presence of diverticula but also on the type of PAD and location of the papilla. In this study we aimed to find the prevalence of PAD in ERCP patients from Southwestern Turkey and to investigate the influence of various PAD subtypes, as defined by the He-Xian Shi classification, on the occurrence of hyperamylasemia and pancreatitis following ERCP. It remains unclear whether different PAD subtypes confer different risks for post-ERCP complications; our study applies a novel classification (He-Xian Shi) to investigate this.

Materials and methods

Study design and patient selection

The study was conducted at Antalya Training and Research Hospital. 1317 ERCP procedures performed between January 1, 2022, and December 31, 2023 were inspected retrospectively. Patient medical reports were cautiously collected. We collected data only from ERCP-naive patients. In our medical reports, PAD was described and classified according to the Lobo or Boix classifications [8, 19]. From the papilla pictures of the records and procedure reports, the type of the PAD was re-defined according to He-xian Shi classification [21]. Double confirmation of diverticulum types with both procedure photos and reports, in addition to the experienced endoscopists performing the procedures, provided a concise and healthy assessment of diverticulum types. According to this classification, periampullary diverticula are classified as follows: “papilla located entirely within the diverticulum (Type I), papilla located at the inner margin (Type IIa) or outer margin (Type IIb) of the diverticulum, and papilla located outside the diverticulum (Type III)” (Fig. 1). Patients were grouped based on the presence or absence of PAD and further classified into subtypes of PAD following the He-xian Shi classification.

The exclusion criteria were patients below age of 18, elevated amylase or lipase levels before ERCP and surgeries that altered gastrointestinal anatomy. All patients underwent endoscopic sphincterotomy (either small or normal). Other therapeutic ERCP procedures, including balloon sweeping, and basket extraction, and when necessary, plastic or metal stent insertion, were included. Out of 1,317 ERCP cases reviewed, 688 were repeat procedures, 19 had elevated enzymes, 13 had altered anatomy and 3 patients were below age of 18; thus 594 unique ERCP-naïve patients with normal pre-procedure enzymes were included.

ERCP procedure

In our unit, ERCP for an ERCP-naive patient typically requires a one-night hospitalization before the procedure. All ERCP procedures were performed by four endoscopist with an experience of 800–2000 procedures. Standard preparatory protocols included administering 100 mg rectal indomethacin immediately before the procedure and providing hydration at a rate of 2–3 ml/kg/h with Ringer’s lactate for 4 h prior to ERCP. Anesthesiology preparation was completed beforehand, and all procedures were performed under sedation with an anesthesiologist’s supervision. Prophylactic pancreatic stenting was very low, with only two patients receiving a pancreatic stent. Post-ERCP evaluation involved measuring amylase and lipase levels 4–6 h after the procedure, and patients without enzyme elevation or pain were

Table 1 Comparison of PAD classification systems

Location of Papilla	Completely Inside	Inner Margin	Outer Margin	Outside
Lobo	Intradiverticular	Juxtapapillary	Juxtapapillary	Juxtapapillary
Boix	Type 1	Type 2	Type 2	Type 3
He-xian Shi	Type 1	Type 2a	Type 2b	Type 3

PAD: Periampullary diverticulum

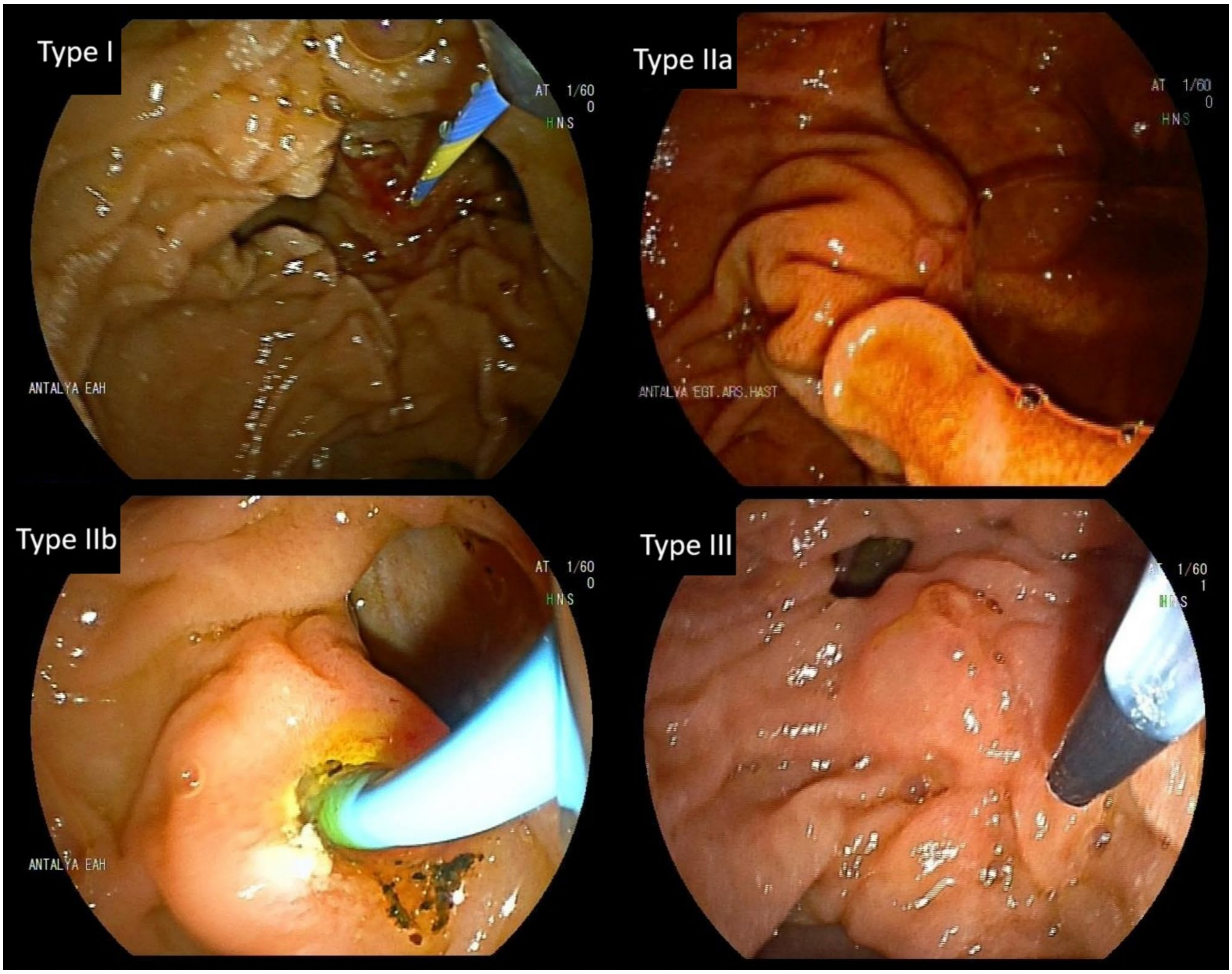

Fig. 1 Periampullary diverticulum types according to He-xian Shi classification

considered for discharge the following day. Hyperamylasemia was defined as at least 3 times elevation from upper limit of normal level at 4-6th hour. Post-ERCP pancreatitis was defined as hyperamylasemia at 24 h plus abdominal pain concomitant with pancreatitis for more than 24 h. Post-ERCP pancreatitis-diagnosed patients fulfilled the criteria according to the 2020 ESGE guidelines, and treatment was administered as necessary [1].

Statistical analysis

Data were collected in an Excel format. Statistical analyses were conducted using SPSS version 27 for Windows. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as medians with ranges. The Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to assess the normality of data distributions. The significance of age difference between PAD and non-PAD patients was evaluated using the Mann-Whitney U test. To minimize the confounding effects of age and sex on other variables, we performed propensity score matching with a 1:1 ratio and continued the analysis with the matched group. Appropriate statistical tests, including the Chi-Square goodness-of-fit test, Fisher's Exact test, Mann-Whitney U test, and Kruskal-Wallis tests, were utilized for group comparisons. In cases where post-hoc analysis was necessary, Bonferroni correction was applied. Effect size is calculated by Cramers V. To quantify the risk associated with each PAD type, a binary logistic regression was performed. A two-tailed p-value less than 0.05 was considered statistically significant.

Results

A total of 594 ERCP-naïve patients were analyzed. Male to female ratio was 1. The Kolmogorov-Smirnov and Shapiro-Wilk tests showed that age was not normally distributed ($p < 0.001$). The median age of the population was 66 years old (range 18–97). Of 594 patients, 137 (23.1%) had PAD. Patients with PAD were older than the non-PAD patients median age was 76 (34–96) versus 62 (18–97)

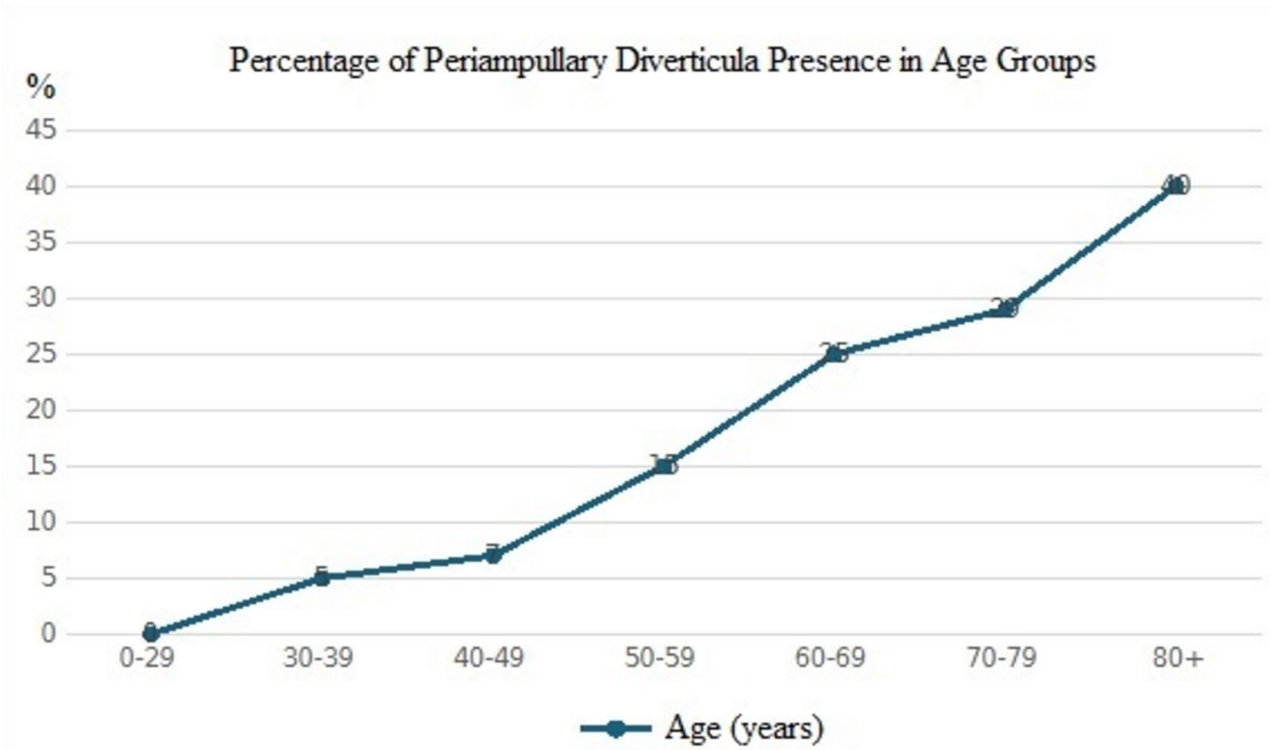

Fig. 2 Percentage of periampullary diverticula presence in age groups

Table 2 Baseline characteristics of the study population (after 1:1 propensity score matching)

	PAD $n = 137$	non-PAD $n = 137$	*p* Value
Age years (median and range)	76 (34–96)	76 (34–96)	matched
Female sex, n (%)	70 (51.1%)	73 (53.4)	matched
CBD stone, n (%)	125 (91.2%)	87 (63.5%)	< 0.001 *
Successful cannulation, n (%)	131 (95.6%)	128 (93.4%)	0.59
Biliary stent placement, n (%)	57 (41.6%)	50 (36.5%)	0.46
Elevation of amylase, n (%)	24 (17.5%)	29 (21.2%)	0.31
Post-ERCP pancreatitis, n (%)	10 (7.3%)	12 (8.8%)	0.82

PAD: Periampullary diverticulum, CBD: Common bile duct, ERCP: Endoscopic retrograde cholangiopancreatography

years old, ($p < 0.000$). Increase in PAD percentage according to age category is shown in Fig. 2.

After propensity score matching to minimize effects of sex and age, we compared the patients with and without PAD. Common bile duct stone was more common in patients with PAD (91.2% (125/137) vs. 63.5% (87/137), $p < 0.001$). There were no differences in cannulation rate of the common bile duct, biliary stent placement, elevation of amylase, and PEP rate between patients with and without PAD. Results are presented in Table 2.

The Fisher Exact Test analysis of the subtypes of PAD showed that there were no differences in sex distribution and age of the different subtypes of PAD. The cannulation ratios, biliary stent placement ratios, and PEP ratios were similar among the subtypes of PAD. However, there was a statistically significant difference in post-ERCP hyperamylasemia rates among the four PAD subtypes ($p = 0.04$). Elevation of amylase was observed in 3.7% of patients with PAD Type IIb, compared to 27.3%, 27.8% and 15.5% in patients with PAD Type I, IIa and III respectively. Results are presented in Table 3.

To further explore the differences of post-ERCP hyperamylasemia rates among subtypes of PAD, pairwise Fisher's Exact Tests were performed. However, after applying a Bonferroni correction for multiple comparisons (adjusted $\alpha = 0.0083$), none of the pairwise comparisons reached statistical significance. The largest observed differences were between PAD Type I and Type IIb, and between Type IIa and Type IIb, but these did not remain significant after adjustment. This suggests that while there is an overall difference in complication rates across groups, individual group differences do not reach statistical significance when adjusted for multiple testing.

Effect size analysis using Cramér's V revealed a moderate association between PAD type and hyperamylasemia ($V = 0.350$), indicating a potentially clinically relevant relationship despite the lack of statistically significant pairwise differences. To quantify the risk associated with each PAD type, a binary logistic regression was performed with PAD Type IIb as the reference group. The analysis revealed significantly increased odds of post-ERCP hyperamylasemia in patients with: PAD Type I: $OR = 11.250$, 95% CI [1.244–101.759], $p = 0.031$, PAD

Table 3 Frequencies of and analysis between different PAD types

	Type 1	Type 2a	Type 2b	Type 3	p Value
	n = 22 (16.1%)	**n = 19 (13.9%)**	**n = 31 (22.6%)**	**n = 65 (47.4%)**	
Age (years, mean ± SD)	76.77 ± 10.18	73.32 ± 14.45	70.55 ± 16.07	73.66 ± 11.36	0.38
Female sex (%)	68.2%	47.4%	41.9%	50.8%	0.29
Successful cannulation (%)	95.6%	94.4%	100%	94.8%	0.98
Biliary stent placement (%)	40.9%	44.4%	44.4%	37.9%	0.94
Elevation of amylase (%)	27.3%	27.8%	3.7%*	15.5%	0.04
PEP (%)	13.6%	10.5%	3.2%	6.2%	0.42

PAD: Periampullary diverticulum, SD: Standard deviation, PEP: Post-ERCP pancreatitis

Table 4 Association between PAD type and post-ERCP hyperamylasemia

PAD Type	Odds Ratio (OR)	95% Confidence Interval	p-value
Type 1	11.250	1.244–101.759	0.031
Type 2a	10.714	1.142–100.521	0.038
Type 2b	Reference	–	–
Type 3	5.455	0.666–44.686	0.114

PAD: periampullary diverticulum. ERCP: Endoscopic retrograde cholangiopancreatography. Binary logistic regression

Type IIa: OR = 10.714, 95% CI [1.142–100.521], $p = 0.038$, PAD Type III also showed elevated odds compared to Type IIb (OR = 5.455, 95% CI [0.666–44.686]), but this result did not reach statistical significance ($p = 0.114$). Results are presented in Table 4.

Discussion

With this study, we aimed to find the prevalence of PAD in our ERCP patients and to investigate the influence of various PAD subtypes on ERCP outcomes.

We found a high prevalence of periampullary diverticula at 23.1%, the highest reported rate from Turkey, potentially due to an older patient population and our status as a referral center in our region [5, 6, 22–25]. Globally, the prevalence ranges from 4.6 to 46.1%, encompassing our findings [5, 7, 9, 10, 16, 26, 27]. Consistent with prior research, patients with periampullary diverticula were older, suggesting advanced age as a risk factor. However, we did not observe significant sex differences, aligning with mixed results in the literature. We found a significantly higher prevalence of common bile duct stones in patients with periampullary diverticula, corroborating the established association between the two conditions [14, 16, 21, 28–31]. An important finding in our study was the low pancreatic stenting rate. Despite the low pancreatic stenting rate, PEP prevalence was ~8%. Nonetheless, prophylactic pancreatic stenting will surely be protective against PEP development and we would like to acknowledge this topic which we will implement to our daily practice aswell.

In terms of procedural outcomes, we found no difference in cannulation success rates between PAD and non-PAD patients. PAD patients tended to have more bile duct stones, which we adjusted for in interpretation. The biliary stenting rate, post-ERCP hyperamylasemia and PEP ratios were also similar in PAD and non-PAD patients. The findings of our study align with literature [11, 14, 16, 17, 26, 27, 29, 32].

Besides determining the prevalence and influence of PAD in our ERCP population, the other scope of the study was to find if the subtypes of PAD had any association with post ERCP outcomes. Traditionally, the PAD classifications defined by Lobo and Boix have been used in many studies [1–9, 13, 15–18, 24–27]. The Lobo classification divides diverticula into two types. Intradiverticular papilla and Juxtapapillary diverticulum, humps the papilla in the margin and outside of diverticula in the same category. The Boix classification, one of the most widely used, divides these diverticula into three types, highlighting the difference of papilla in the margin. It can predict difficulties with cannulation especially in type I diverticula but does not differentiate cannulation difficulty differences in type II diverticula. However, as clearly reported in meta-analysis the existence of multiple classification systems causes variability in studies which can lead to challenges in comparing study outcomes, assessing clinical significance, and determining the impact of PAD on ERCP procedure [10–11]. The need of refinement of PAD classification systems to decrease variability in results across studies and for better clinical interpretation is underscored [20, 33]. The Li-Tanaka classification, a more comprehensive classification, divides diverticula into four types, and in subtypes of type II and IV considers being the papilla in the inner or outer margin diverticula which has an impact on biliary cannulation [20]. More recently, Shi et al. proposed a new and easy system to predict cannulation challenges [21]. Comparing the classification systems of PAD is beyond the scope of this study, however a more detailed differentiation of type 2 PAD is reported to be important [20, 21]. For finding nuances between different PAD types on ERCP outcomes we analyzed our results according to He-xian Shi classification. We analyzed post-ERCP hyperamylasemia and PEP as they were the most common ERCP complications [3, 4]. Our results support a potential association between PAD subtype and post-procedural enzyme elevation.

Some cases of hyperamylasemia progress to PEP [1]. The pathogenesis of these complications may involve complex interrelations between many factors related to the patient and the procedure. Among the procedure related risk factors experience of the endoscopist, mechanical trauma and prolonged manipulation during ERCP are well-known risk factors for these complications. Presence of PAD is a patient related factor and as an overall it is not a risk factor for complications of post ERCP hyperamylasemia and PEP. However, there are differences in PAD subtypes. Logistic regression analysis revealed significantly increased odds of hyperamylasemia in patients with PAD Types 1 and 2a compared to Type 2b, suggesting that PAD type 2b may carry a lower risk. Type IIb PADs, having a lower risk profile, might not necessitate extra precaution beyond standard prophylaxis, whereas type I and IIa PADs might warrant particular care or preventive measures during ERCP (though our data did not show higher pancreatitis rates, only enzyme elevation). These findings, although based on a relatively small sample size, align with previous observations that the anatomical relationship between the papilla and diverticulum may influence post-ERCP complications [20, 21, 24].

In two different classification systems both He-Xian Shi and Yue P reported that cannulation is easier in type 2b PAD [20, 21]. We hypothesized that in type 2b PAD the good position of the papilla entrance, better axial alignment of the CBD, and sphincter dysfunction resulted in reduced papillary manipulation during cannulation, leading to less hyperamylasemia. We believe that the lower frequency of hyperamylasemia in type 2b PAD may be due to easier cannulation with minimal papillary manipulation, thereby reducing mechanical and chemical insult to the pancreas. Additionally, the presence of PAD may alter the biliary direction and angulation of the sphincterotome is not necessary, which may facilitate cannulation. Also, the presence of PAD may lead to partial or complete loss of sphincter function, resulting in a patulous sphincter potentially facilitating easier cannulation compared with non-PAD, as reported by Panteris et al. [34].

There are limitations in our study. The single-center retrospective nature of our study in a relatively small sample size for each PAD type are the main limitations of our study. Additionally, we lacked objective data on cannulation difficulty, such as the number of cannulation attempts, cannulation time or different accessories and techniques used for cannulation. Bleeding and perforation are other important post-ERCP complications. They were very rare in our cohort. This may be due to our clinical approach, tendency for small sphincterotomy and deciding biliary stenting easily in difficult cases. Also, we do not have any comprehensive data about cholangitis complication and some procedure-related data such as procedure time. Infrequent use of prophylactic pancreatic stents can also be considered a limitation of the study. Our low use of pancreatic stents may have contributed to the overall hyperamylasemia and PEP rate. Consequently, comparison of patients with or without prophylactic pancreatic stenting was not possible, which would have been a valuable addition of data to the study.

Conclusion

PAD is a common finding in ERCP patients, with a prevalence of 23.1% in our cohort from Southwestern Turkey. Patients with PAD tended to be older than those without. Common bile duct stones were the most frequent indication for ERCP and were significantly more common in patients with PAD.

The cannulation success rates and post ERCP consequences did not differ between PAD and non-PAD patients. However different subtypes of PAD may have different outcomes. Our results demonstrated that hyperamylasemia is less frequent in ype IIb PAD than in type 1 and type 2a patients. The type of PAD seems more important than merely the presence of PAD. Larger, prospective studies are needed to confirm these findings and further elucidate the anatomical and clinical mechanisms behind this association.

Abbreviations

CBD	Common Bile Duct
ERCP	Endoscopic retrograde cholangiopancreatography
PAD	Periampullary diverticulum
PEP	Post-ERCP pancreatitis

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Author contributions

Conceptualization: SA, SO, AHC; Methodology: SA, SO, OCB, AHC; Formal analysis and investigation: SA, GEA, SO, OCB, GK, MDI, BK, HD, FAH AHC; Writing - original draft preparation: SA, GEA, SO, OCB, FAH AHC; Writing - review and editing: SA, GEA, SO, OCB, FAH AHC; Funding acquisition: None; Supervision: SA, SO, OCB, FAH, AHC. All authors consent for this version of the paper to be published.

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Data availability

Study data is available upon reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective cohort study received approval from the Antalya Training and Education Hospital Ethics Committee (approval number 4/24-2024-074). Since this is a retrospective study, the need for consent to participate was waived by the ethics committee. The study was conducted in concordance with the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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