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Original Article

Original Article

Horizontal duodenal papilla is associated with a special spectrum of pancreaticobiliary diseases: a retrospective magnetic resonance cholangiopancreatography-based study

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Abstract

Background: Horizontal duodenal papilla (HDP) is not an uncommon ectopic major papilla. The impact of HDP on the occurrence of pancreaticobiliary diseases remains unclear. Here, we explored the associations in patients who underwent magnetic resonance cholangiopancreatography (MRCP).

Methods: Consecutive patients who underwent MRCP at Xijing Hospital (Xi'an, China) between January 2020 and December 2021 were eligible. Patients were divided into HDP and regular papilla (RP) according to the position of the major papilla. The primary outcome was the proportion of congenital pancreaticobiliary diseases.

Results: A total of 2,194 patients were included, of whom 72 (3.3%) had HDP. Compared with the RP group ($n = 2,122$), the HDP group had a higher proportion of congenital pancreaticobiliary diseases, especially choledochal cyst (CC) or anomalous pancreaticobiliary junction (APBJ) (6.9% vs 1.4%, $P = 0.001$). More gallbladder cancer (6.9% vs 1.2%, $P < 0.001$) and pancreatic cysts (27.8% vs 16.3%, $P = 0.01$) were also identified in the HDP group. Morphologically, the HDP group had a longer extrahepatic bile duct (8.4 [7.6–9.3] cm vs 7.2 [6.5–8.1] cm, $P < 0.001$), and larger angles between the common bile duct-duodenum and pancreatic duct-duodenum. Multivariate analysis showed that the presence of HDP was an independent risk factor for gallbladder cancer.

Conclusions: This study confirmed that HDP was not rare in patients underwent MRCP. A higher prevalence of congenital pancreaticobiliary malformations (especially CC or APBJ), gallbladder cancer and pancreatic cysts was observed in patients with HDP, as well as distinctive morphologic features.

Keywords: horizontal duodenal papilla; MRCP; congenital pancreaticobiliary diseases; gallbladder cancer; pancreatic cyst

Introduction

Major duodenal papilla (MDP) is normally located in the descending duodenum [1]. Its opening is controlled by the sphincter of Oddi, which regulates the flow of bile and pancreatic juice into the duodenum [2]. The variations of MDP are not rare in the general population, such as the variations in the location, size, shape, and even number [3]. An ectopic MDP is a condition in which the opening of the bile and pancreatic ducts is located in an abnormal place, including duodenal bulb, horizontal duodenum, and even pylorus [4–7]. The ectopic papilla in duodenal bulb has been most frequently reported, most of which may be secondary to the misplacement of the normal papilla associated with fibrotic scarring during the recovery of duodenal ulcer [4, 8]. In contrast, ectopic papillae found in other locations are likely to be predominantly congenital in nature.

The variations of MDP can pose a high risk for certain biliary and pancreatic disorders, which can also result in difficulties when performing endoscopic retrograde cholangiopancreatography (ERCP) [9, 10]. In pediatric patients, it has been reported that certain congenital biliary diseases, such as choledochal

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cyst (CC) and anomalous pancreaticobiliary junction (APBJ), are associated with a higher proportion of ectopic distal location of the papilla [11, 12]. However, these studies were limited by small sample size and patient selection. It remains unknown whether the spectrum of pancreaticobiliary diseases differs in adult patients with horizontal duodenal papilla (HDP), which located in the third portion of the duodenum. We hypothesize that adult patients with HDP may also have a higher proportion of congenital diseases, such as congenital CC, APBJ, pancreas divisum, and annular pancreas.

Magnetic resonance cholangiopancreatography (MRCP) is currently the best non-invasive modality for evaluating the location of major papilla. It offers the opportunity to assess the proportions of ectopic papilla and investigate the spectrum of pancreaticobiliary diseases in patients with regular or HDP. The aim of study was to investigate the proportions and morphological characteristics of HDP, as well as its association with pancreaticobiliary diseases in patients who underwent MRCP.

Methods

Patients

This retrospective study enrolled consecutive patients who underwent MRCP for suspected pancreaticobiliary diseases at Xijing Hospital (Xi'an, China) between January 2020 and December 2021. Patients with suspected masses or stones in the pancreatic head, ampullary carcinoma, or pancreatitis with local complications (e.g. pseudocyst and walled-off necrosis), and other conditions compromising the identification of the location of major papilla were excluded. Those with prior gastrointestinal (GI) reconstruction surgery or duodenal stricture were also excluded. Furthermore, patients were not included if the imaging of MRCP was not clear enough to determine the location of major papilla.

The study was approved by the ethics committee of Xijing Hospital. (KY20232374).

Data collection

Demographic characteristics (age and sex), imaging findings related to pancreaticobiliary diseases, symptoms, and laboratory test data (if available) were collected retrospectively for each patient.

All MRCP examinations were performed on 1.5 T or 3.0 T scanners (Optima MR360, GE Company, USA) and phased-array abdominal coil. Only the initial MRCP was used for analysis when the patient underwent multiple examinations. Image analysis, annotation, and measurements were conducted by a single trained investigator (T.Z.) on the MRCP coronal sequence using the OsiriX software (Pixmeo SARL, Switzerland). The training was overseen by J.Z., who has more than 20 years of professional experience in abdominal cross-sectional imaging. X.W., with over 5 years of professional experience in diagnostic imaging, validated a subset of the reads. The investigators were blinded to any other individual data. When the interpretation of imaging results was uncertain, a decision was made after discussion by an expert imaging group.

All abnormalities or pathological signs of the common bile duct (CBD), pancreatic duct (PD), gallbladder and pancreatic parenchyma were recorded, including stones, strictures, irregularities, cysts, and masses. The diagnosis of biliary and pancreatic diseases was classified into five types: bile duct diseases, gallbladder diseases, pancreatic diseases, suspected sphincter of Oddi dysfunction (SOD), and congenital abnormalities. If the diagnosis based on MRCP was unclear, the final diagnosis was determined through expert discussion, which involved reviewing electronic medical records and conducting follow-up phone calls.

To determine the location of papilla, we first identified the major papilla and the descending-horizontal junction (DHJ) of the duodenum. The major papilla is indicated by the confluence point of the terminal common bile duct into the duodenum. HDP was considered if the major papilla was located distal to the DHJ, while the position of the papilla was considered regular if it was in the descending duodenum and above the DHJ (Figure 1). Patients were divided into the HDP group and the regular papilla (RP) group. Other possible variants of the position of the major papilla, such as those in the pylorus, bulb, bulb-descending junction (BDJ), and stomach, were also recorded if they existed.

Outcome

The primary outcome was the proportion of congenital diseases of the biliary or pancreatic duct, including CC, APBJ (with a common channel of the pancreaticobiliary duct $\geq$ 15 mm), complete pancreas divisum and annular pancreas. The secondary outcomes included the proportions of other diseases, such as CBD stones, biliary stricture, pancreatitis, pancreatic cysts, suspected SOD, gallbladder stones and carcinoma, and morphological measurements of biliary and pancreatic ducts. The latter contained: (i) length of the extrahepatic bile duct: the total length of the common bile duct from the bifurcation of the hepatic hilum to the distal end; (ii) CBD angle: the most prominent angle observed in the common bile duct; (iii) CBD-duodenum angle: the angle between distal CBD and adjacent duodenum; (vi) CBD-PD angle: the angle between distal CBD and PD; (v) PD-duodenum angle: the angle between distal PD and adjacent duodenum. These measurements were performed three times by the trained investigator (T.Z.) with an interval of 1–2 weeks, and the mean values were considered final measurement results.

Statistical analysis

We hypothesized that the proportions of the congenital abnormalities in pancreaticobiliary diseases in the HDP and RP groups were 8% and 2%, respectively. Based on the previous reported that HDP can be detected in 8% of patients who underwent MRCP [13], a total of 2,045 patients were required to achieve 80% power at a two-side alpha level of 0.05.

Continuous variables are presented as mean and standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if non-normally distributed. The nonparametric Wilcoxon–Mann–Whitney test or Student's *t*-test were used for comparison between groups. Categorical variables are presented as frequency or percentage, and comparisons were made using either the chi-squared test or Fisher's exact test. Univariate logistic regression analysis was conducted to identify potential risk factors for gallbladder cancer. Variables with a P value < 0.1 from the univariate analysis were included in a multivariate logistic analysis using the forward stepwise method to assess the risk factors associated with gallbladder cancer. The results of the regression analysis were reported as odds ratio (OR) value with corresponding 95% confidence intervals (CI). All statistical analyses were performed using SPSS 25.0 software (IBM, Armonk, NY, USA). All tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Patients

A total of 3,003 MRCP examinations were performed from January 2020 to December 2021. After excluding patients

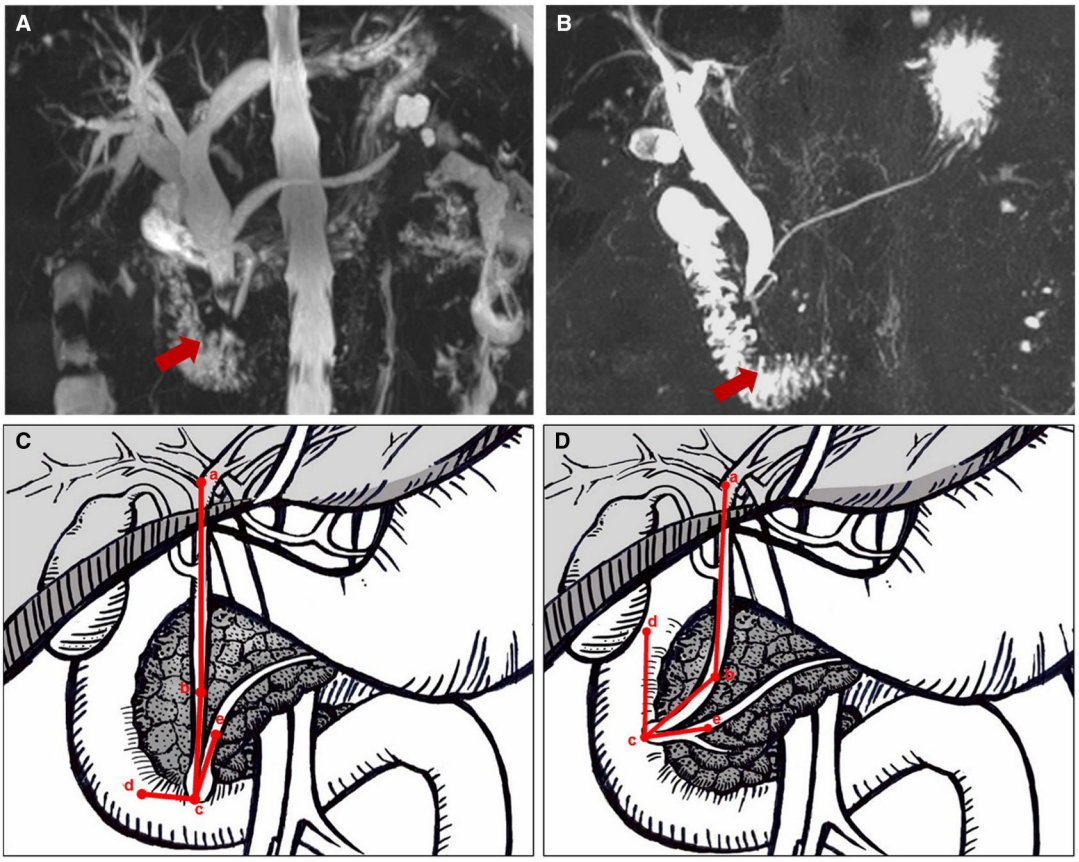

Figure 1. Identification of major papilla and measurement of morphological features of pancreaticobiliary ducts in patients with HDP or regular papilla. Major papilla was identified as the confluence point where the terminal of bile duct flowed into the duodenum. (A) MRCP image of a HDP patient, the major papilla was located distal to DHJ (red arrow); (B) MRCP image of a RP patient, the major papilla was in the descending duodenum and above the DHJ (red arrow). Measurement of pancreaticobiliary duct in HDP (C) or RP patient (D) were presented by schematic illustration: length of extrahepatic bile duct was calculated by the sum length of Line ab and Line bc; CBD angle was measured between Line ab and Line bc; CBD-duodenal angle was measured between Line bc and Line cd; CBD-PD angle was measured between Line bc and Line ce; PD-duodenum angle was measured between Line cd and Line ce. CBD = common bile duct, DHJ = descending- horizontal junction, HDP = horizontal duodenal papilla, MRCP = magnetic resonance cholangiopancreatography, PD = pancreatic duct, RP = regular papilla.

($n = 809$) who met the exclusion criteria, including suspected masses or stones in the pancreatic head ($n = 93$), ampullary carcinoma ($n = 41$), pancreatitis with local complications ($n = 114$), prior GI reconstruction surgery ($n = 105$), duodenal stricture ($n = 54$), inadequate image quality to determine the position of the major papilla ($n = 207$), or repeated examinations ($n = 195$), 2,194 patients were finally included in the study (Figure 2). The median age of the included patients was 55-(43–65) year old and 50.0% were male (1,097/2,194).

A total of 72 patients with HDP were identified, accounting for 3.3% (72/2,194) of the study population. The remaining patients (96.7%) had RP located in the descending duodenum. No ectopic papilla was found in the duodenal bulb, BDJ, gastric antrum or pylorus in this study. Symptoms and laboratory findings were available for analysis in 1,340 patients. The most common symptom was abdominal pain (68.3%), followed by jaundice (30.7%) and fever (23.6%).

As shown in Table 1, there were no statistically significant differences in baseline characteristics between the HDP and RP groups.

Spectrum of pancreaticobiliary diseases in patients underwent MRCP

In the overall study cohort ($n = 2,194$), 33.3% of patients had normal findings on MRCP. The main diagnosis based on MRCP included bile duct diseases (33.6%), gallbladder diseases (24.3%), pancreatic diseases (25.3%), and congenital abnormalities (4.3%). Of the 1,340 patients for whom clinical and laboratory data were available, 6.0% were considered to have suspected SOD.

Compared to the RP group, patients in the HDP group had a higher proportion of congenital diseases of the pancreaticobiliary duct (11.1% vs 4.1%, $P = 0.01$). Specifically, the proportion of CC or APBJ was more common in the HDP group than in the RP group (6.9% vs 1.4%, $P = 0.001$). The proportions of complete pancreas divisum and circular pancreas were similar between the two groups. Interestingly, we also found the HDP group had a higher proportion of gallbladder cancer (6.9% vs 1.2%, $P < 0.001$) and pancreatic cysts (27.8% vs 16.3%, $P = 0.01$). There were no significant differences in other pancreaticobiliary diseases between the two groups (Table 2).

Anatomic measurement of pancreatic and biliary system

The anatomical characteristics of the pancreaticobiliary duct were measured based on MRCP images. As shown in Table 3 and Figure 1, compared to the RP group, patients in the HDP group had a longer extrahepatic bile duct (8.4 [IQR 7.6–9.3] cm vs 7.2 [IQR 6.5–8.1] cm, $P < 0.001$). Patients in the HDP also had a larger CBD-duodenum angle (88.3 [IQR 76.1–95.7]° vs 40.8 [IQR 30.7–53.2]°, $P < 0.001$), a smaller CBD-PD angle (22.2 [IQR 14.0–36.1]° vs

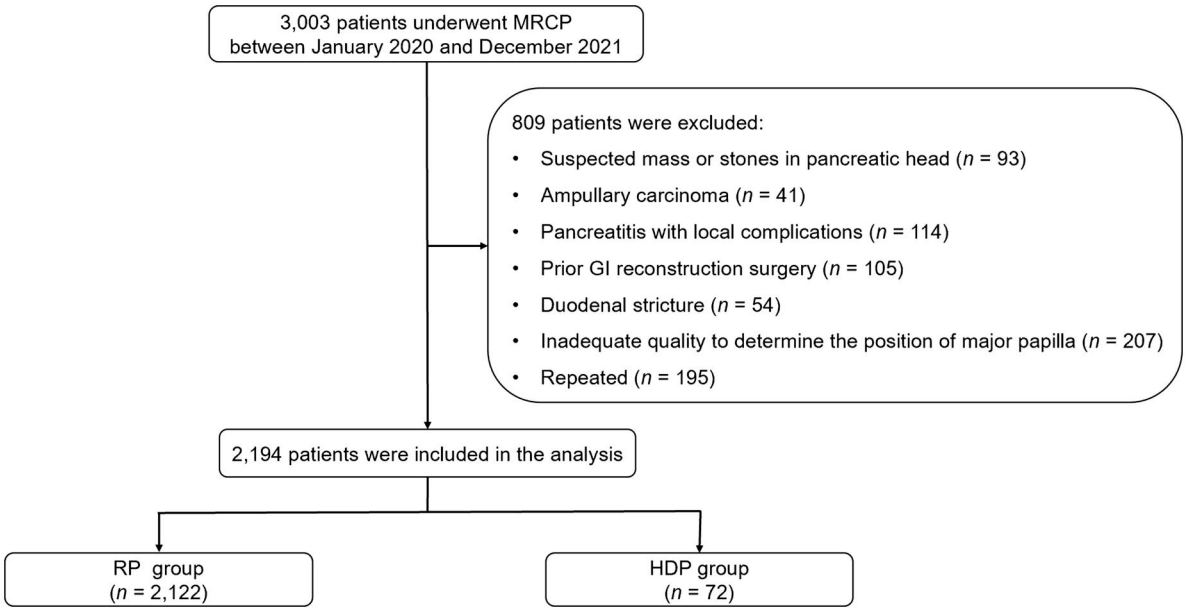

Figure 2. Flowchart of this study.

Table 1. Baseline characteristics of the study population

Characteristic	Overall (n = 2,194)	HDP group (n = 72)	RP group (n = 2,122)	P value
Age (years), median (IQR)	55 (43–65)	60 (42–69)	55 (43–65)	0.12
Male, n (%)	1,097 (50.0)	31 (43.1)	1,066 (50.2)	0.23
Prior cholecystectomy, n (%)	670 (30.5)	24 (33.3)	646 (30.4)	0.60
Symptoms[a], n (%)				–
Abdominal pain	915 (68.3)	26 (70.3)	889 (68.2)	
Jaundice	411 (30.7)	13 (35.1)	398 (30.5)	
Fever	316 (23.6)	10 (27.0)	306 (23.5)	
Others	109 (8.1)	4 (10.8)	105 (8.1)	
Laboratory test[a]				
WBC ($\times 10^9$/L), median (IQR)	6.5 (5.0–9.0)	7.3 (5.7–10.2)	6.5 (5.0–9.0)	–
HGB (g/L), median (IQR)	132.0 (117.0–145.0)	134.0 (120.0–147.0)	132.0 (116.0–145.0)	–
ALT (IU/L), median (IQR)	43.0 (21.0–107.5)	38.0 (16.5–106.5)	43.0 (21.0–108.0)	–
TBIL (μmol/L), median (IQR)	25.0 (15.1–72.2)	24.8 (13.3–58.0)	25.0 (15.2–72.2)	–
ALP (IU/L), median (IQR)	118.0 (76.0–224.5)	97.0 (68.0–185.0)	118.0 (77.0–228.0)	–
GGT (IU/L), median (IQR)	113.0 (29.0–334.3)	70.0 (25.0–331.0)	114.0 (29.0–335.0)	–

[a] The information of symptoms and laboratory test was only available for 1,340 patients, including 37 with HDP and 1,303 with regular papilla.
ALP = alkaline phosphatase; ALT = alanine transaminase; GGT = γ-glutamyl transferase; HDP = horizontal duodenal papilla; HGB = hemoglobin; IQR = interquartile range; RP = regular papilla, TBIL = total bilirubin; WBC = white blood cell.

39.4 [IQR 28.5–51.3]°, $P < 0.001$), and a greater PD-duodenum angle (108.3 [IQR 96.0–123.3]° vs 78.1 [IQR 63.3–95.9]°, $P < 0.001$). These differences in anatomy may be helpful in discriminating between HDP and RP. There was no significant difference in the CBD angle between the two groups.

Risk factors for patients with gallbladder cancer

A total of 31 patients with gallbladder cancer were identified in this study. Among them, 77.4% were at advanced stages (III-IV) (Supplementary Table 1). Logistic regression analysis was performed to identify risk factors associated with gallbladder cancer. Univariate analysis revealed that age > 70 years, gallbladder stones, CC or APBJ and HDP were associated with the occurrence of gallbladder cancer (Table 4). Although gallbladder cancer was more common in women (61.3% vs 49.8%), there was no statistical difference between the two groups. In the multivariate logistic analysis, age > 70 years (OR 5.22, 95% CI 2.50–10.93, $P < 0.001$), gallbladder stones (OR 2.58, 95% CI 1.24–5.35, $P = 0.01$), CC or APBJ (OR 5.12, 95% CI 1.09–24.10, $P = 0.04$) and HDP (OR 4.97, 95% CI 1.77–13.96, $P = 0.002$) were identified as independent risk factors for gallbladder cancer (Table 4).

Discussion

Ectopic papilla is common in patients undergoing ERCP or MRCP. It may cause difficulties for ERCP and be related to the development of pancreaticobiliary diseases [14, 15]. While several studies have investigated the role of ectopic papilla in patients with pancreaticobiliary diseases, they were often limited by small sample size and focused on ectopic papilla located in bulb instead of other positions [16, 17]. The current retrospective study, involving 2,194 patients who underwent MRCP, showed the follow findings: (1) The proportion of HDP was 3.3% while no other ectopic papilla was identified; (2) Patients with HDP had higher rates of CC or APBJ, gallbladder cancer, and pancreatic cysts; (3) HDP was accompanied by longer extrahepatic bile duct and

Table 2. Differences in the spectrum of pancreaticobiliary diseases in patients with HDP or regular papilla who underwent MRCP

Diagnosis, *n* (%)	Overall (*n* = 2,194)	HDP group (*n* = 72)	RP group (*n* = 2,122)	*P* value	OR (95% CI)
Normal MRCP	731 (33.3)	19 (26.4))	712 (33.6)	0.21	0.71 (0.42–1.21)
Bile duct diseases					
CBD stones	464 (21.1)	18 (25.0)	446 (21.0)	0.42	1.25 (0.73–2.16)
Biliary stricture	291 (13.3)	12 (16.7)	279 (13.1)	0.39	1.32 (0.70–2.49)
Gallbladder diseases					
Gallbladder stones	516 (23.5)	15 (20.8)	501 (23.6)	0.59	0.85 (0.48–1.52)
Gallbladder cancer	31 (1.4)	5 (6.9)	26 (1.2)	<0.001	6.02 (2.24–16.15)
Pancreatic diseases					
Acute pancreatitis	123 (5.6)	3 (4.2)	120 (5.7)	0.78	0.73 (0.23–2.34)
Chronic pancreatitis	68 (3.1)	4 (5.6)	64 (3.0)	0.38	1.89 (0.67–5.34)
Pancreatic cysts[a]	366 (16.7)	20 (27.8)	346 (16.3)	0.01	1.97 (1.16–3.35)
Other[b]	27 (1.2)	1 (1.4)	26 (1.2)	0.60	1.14 (0.15–8.49)
Suspected SOD[c]	80 (6.0)	1 (2.7)	79 (6.1)	0.62	0.43 (0.06–3.18)
Congenital abnormality	95 (4.3)	8 (11.1)	87 (4.1)	0.01	2.92 (1.36–6.29)
CC or APBJ	34 (1.5)	5 (6.9)	29 (1.4)	0.001	5.39 (2.02–14.25)
Complete pancreas divisum	62 (2.8)	3 (4.2)	59 (2.8)	0.74	1.52 (0.47–4.97)
Circular pancreas	1 (0.0)	0 (0.0)	1 (0.0)	1.00	–

[a] Pancreatic pseudocysts were not included.
[b] Masses in pancreatic body or tail and suspected autoimmune pancreatitis.
[c] 1,340 patients with available clinical and laboratory information were analyzed for the diagnosis, including 37 with HDP and 1,303 with regular papilla.
APBJ = anomalous pancreaticobiliary junction, CBD = common bile duct, CC = choledochal cyst, CI = confidence interval; HDP = horizontal duodenal papilla, MRCP = magnetic resonance cholangiopancreatography, OR = odds ratio, RP = regular papilla, SOD = sphincter of Oddi dysfunction.

Table 3. Morphological features of the pancreaticobiliary duct system in patients with HDP and regular papilla who underwent MRCP

Variable	HDP group (*n* = 72)	RP group (*n* = 2,122)	*P* value
Extrahepatic bile duct length, median (IQR), (cm)	8.4 (7.6–9.3)	7.2 (6.5–8.1)	<0.001
CBD angle, median (IQR), °	136.7 (126.6–148.2)	134.7 (123.6–143.1)	0.09
CBD-duodenum angle, median (IQR), °	88.3 (76.1–95.7)	40.8 (30.7–53.2)	<0.001
CBD-PD angle, median (IQR), °	22.2 (14.0–36.1)	39.4 (28.5–51.3)	<0.001
PD-duodenum angle, median (IQR), °	108.3 (96.0–123.3)	78.1 (63.3–95.9)	<0.001

CBD = common bile duct, HDP = horizontal duodenal papilla, IQR = interquartile range, PD = pancreatic duct, RP = regular papilla.

Table 4. Logistic regression analysis of risk factors for gallbladder cancer

Variable, *n* (%)	GB cancer group (*n* = 31)	Non-GB cancer group (*n* = 2,163)	Univariate		Multivariate	
			OR (95% CI)	P	OR (95% CI)	P
Age > 70 years						
No	17 (54.8)	1,881 (87.0)	Ref		Ref	
Yes	14 (45.2)	282 (13.0)	5.49 (2.68–11.27)	<0.001	5.22 (2.50–10.93)	<0.001
GB stones						
No	17 (54.8)	1,661 (76.8)	Ref		Ref	
Yes	14 (45.2)	502 (23.2)	2.73 (1.33–5.57)	0.004	2.58 (1.24–5.35)	0.01
CC or APBJ						
No	29 (93.5)	2,131 (98.5)	Ref		Ref	
Yes	2 (6.5)	32 (1.5)	4.59 (1.05–20.07)	0.08	5.12 (1.09–24.10)	0.04
HDP						
No	26 (83.9)	2,096 (96.9)	Ref		Ref	
Yes	5 (16.1)	67 (3.1)	6.02 (2.24–16.15)	<0.001	4.97 (1.77–13.96)	0.002

APBJ = anomalous pancreaticobiliary junction, CC = choledochal cyst, GB = gallbladder; HDP = horizontal duodenal papilla.

distinct CBD-duodenum and PD-duodenum angles. To the best of our knowledge, this study is the first and largest to demonstrate the association of HDP with a unique spectrum of pancreaticobiliary diseases. Based on these findings, further investigation into the impact of HDP on the diagnosis and treatment of certain pancreaticobiliary diseases is warranted.

HDP was first reported by Lurje *et al.* (1937), who discovered 16 cases (8.3%) where the CBD terminated at the horizontal duodenum among 194 autopsy cases [13]. Lindner *et al.* reviewed 1,000 cases of cholangiography from five hospitals and discovered 58 cases (5.8%) where the major papilla was located in the horizontal portion of the duodenum [18]. While Sezgin *et al.* found that HDP accounted for only 0.3% of 1,040 consecutive patients who underwent ERCP [17]. By evaluating MRCP imaging in consecutive patients, the current study found a prevalence of HDP to be 3.3%. The varying rates of HDP in different studies can be attributed to differences in patient populations. For patients who underwent operative cholangiography, the higher proportion of HDP may be related to highly selective indications for hepatobiliary and pancreatic surgery. For patients undergoing ERCP procedure, the positions of the major papilla and DHJ may not be routinely recorded, resulting in an underestimation of the proportion of HDP. MRCP, as a non-invasive imaging technique, is widely used to depict the natural state of the CBD, PD, and duodenum simultaneously [19]. It is not affected by surgical or endoscopic manipulations. Thus, MRCP (especially secretin MRCP) can be an ideal tool to estimate the real prevalence of HDP in the general population [20, 21]. The present study showed that among every 30 patients who underwent MRCP in a tertiary hospital, one patient with HDP could be identified, further demonstrating that HDP is common in patients with suspected hepatobiliary and pancreatic diseases.

The exact causes of HDP remain unclear. Although HDP could be secondary to abnormal traction of the duodenum, the present study did not find any secondary HDP after excluding patients with duodenal strictures and obvious periampullary diseases. Therefore, most of HDP is supposed to be a congenital anatomic variant resulting from unknown errors in embryogenesis, like other congenital variations of the extrahepatic biliary tract [17].

The presence of HDP was accompanied by the abnormal development of pancreaticobiliary ducts. The current study revealed a higher proportion of congenital CC or APBJ in adult patients with HDP, which was consistent with previous studies on children. Li *et al.* found that 67.8% (82/121) of children with CC who underwent ERCP had a distal opening of the major papilla to the descending duodenum [22]. Additionally, two studies reported that some patients with HDP were complicated by APBJ [23, 24]. At present, the mechanism underlying the association between HDP and congenital abnormalities of the pancreaticobiliary duct remains unclear. A postulation is that an ectopic distally budded liver diverticulum during embryogenesis might have resulted in the co-occurrence of HDP and CC/APBJ, with the latter could be ascribed to a subsequently elongated common bile duct and a longer distance between the ventral and dorsal pancreatic buds [12, 22]. Our study indicated that the position of the major papilla should be clearly illustrated when diagnosing CC or APBJ through regular imaging.

In the current study, HDP was first found to be an independent risk factor for gallbladder cancer in addition to old age (>70), gallbladder stones and CC/APBJ. The latter three are well-known risk factors for gallbladder cancer [25–27]. However, the reason for the increased risk of gallbladder cancer in patients with HDP is unclear. Possible explanations may relate to its anatomic characteristics. First, the longer extrahepatic bile duct and sharper CBD-PD angle in HDP may be associated with disturbed hydrodynamics of bile and pancreatic juice, such as bile stasis and biliopancreatic reflux, which were related to the carcinogenesis of biliary epithelium [28, 29]. Additionally, the absence or poor development of the sphincter of Oddi has been observed in ectopic papilla [30]. Combined with its horizontal location, there may be an increased risk of duodenal-biliary reflux, and chronic inflammation of biliary system induced by refluxing intestinal bacteria and contents may ultimately trigger the cancerous process [31]. It is also worth investigating whether a similar genetic background or common epigenetic changes predispose to the development of both HDP and gallbladder cancer.

Among the 2,194 consecutive patients who underwent MRCP, only 31 cases of GB cancer were identified. It reflects that the incidence of GB cancers is low in the real world. In the present study, logistic regression analysis was performed to identify the risk factors associated with GB cancers. Ideally, a rule of thumb with events per variable (EPV) of 10 or even more should be followed in sample size calculation when using a logistic regression model [32]. The EPV was about 8 in the current study, which can lead to biased and imprecise estimates, unreliable confidence intervals, and model convergence problems. Although the multiple analysis showed that HDP was an independent risk factor for GB cancer (OR 4.97, 95%CI 1.77–13.96, $P = 0.002$), the results derived from the small sample size were not robust enough and should be interpreted with caution. Further studies involving more cases of GB cancer are warranted to determine the reliability of our findings.

Since the presence of HDP significantly increases the risk of GB cancer, prophylactic cholecystectomy could be a good choice for some HDP patients, especially those with concomitant APBJ [27] or acute or chronic cholangitis. Extrahepatic bile duct resection is also recommended for those with congenital biliary dilatation [27]. Even asymptomatic HDP patients without any other abnormalities require close monitoring and long-term follow-up.

An ectopic papilla located in the duodenal bulb was the most commonly reported type of ectopic papilla in previous studies [8, 33]. However, in this study, no ectopic papilla with an orifice located in the bulb was observed. Several reasons for this are postulated. First, our study excluded patients with duodenal stenosis. As previously reported, the ectopic opening of the major papilla in the duodenal bulb often occurs as a result of secondary changes associated with duodenal narrowing and scar repair [34]. Second, some MRCP images might not be clear enough to identify the location of the major papilla, leading to an underestimation of the rate of ectopic papilla in the bulb. However, the typical appearance of an ectopic papilla located in the bulb has distinctive features, which were indeed not identified in the MRCP images of this study. Third, it is also possible that the primary ectopic papilla in the bulb is very uncommon, and the limited sample size in this study might not be sufficient to detect a positive one.

There are some limitations of this study. First, this is a single-center retrospective study, which inevitably introduces selective bias. Second, the diagnosis of pancreaticobiliary diseases in this study was mainly based on MRCP images, making it difficult to distinguish between benign and malignant biliary stenosis. Similarly, the exact diagnosis of pancreatic cysts was not possible with MRCP alone. Finally, the study included patients with suspected pancreaticobiliary diseases and may not be representative of the general population. Therefore, the incidence of HDP in the general population remains to be determined.

In summary, this study confirmed that HDP was not rare in adults. It also demonstrated for the first time that the presence of HDP was accompanied by higher rates of certain special

pancreaticobiliary diseases, including CC or APBJ, gallbladder cancer and pancreatic cysts. HDP was also characterized by a distinctive morphological feature of pancreaticobiliary duct system. These findings deepen our understanding of HDP and may have valuable implications for the management of pancreaticobiliary diseases in this specific condition.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

T.Z. and X.W. drafted and edited the manuscript. X.S. and J.L. analyzed and interpreted the data. Y.P. revised the manuscript. All authors acquired the data, read and approved the final manuscript.

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Conflicts of Interest

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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