

ORIGINAL ARTICLE

Diagnosis and treatment in chronic pancreatitis: an international survey and case vignette study

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Abstract

Background: The aim of the study was to evaluate the current opinion and clinical decision-making process of international pancreatologists, and to systematically identify key study questions regarding the diagnosis and treatment of chronic pancreatitis (CP) for future research.

Methods: An online survey, including questions regarding the diagnosis and treatment of CP and several controversial clinical case vignettes, was sent by e-mail to members of various international pancreatic associations: IHPBA, APA, EPC, ESGE and DPSG.

Results: A total of 288 pancreatologists, 56% surgeons and 44% gastroenterologists, from at least 47 countries, participated in the survey. About half (48%) of the specialists used a classification tool for the diagnosis of CP, including the Mayo Clinic (28%), Mannheim (25%), or Büchler (25%) tools. Overall, CT was the preferred imaging modality for evaluation of an enlarged pancreatic head (59%), pseudocyst (55%), calcifications (75%), and peripancreatic fat infiltration (68%). MRI was preferred for assessment of main pancreatic duct (MPD) abnormalities (60%). Total pancreatectomy with auto-islet transplantation was the preferred treatment in patients with parenchymal calcifications without MPD abnormalities and in patients with refractory pain despite maximal medical, endoscopic, and surgical treatment. In patients with an enlarged pancreatic head, 58% preferred initial surgery (PPPD) versus 42% initial endoscopy. In patients with a dilated MPD and intraductal stones 56% preferred initial endoscopic ± ESWL treatment and 29% preferred initial surgical treatment.

Conclusion: Worldwide, clinical decision-making in CP is largely based on local expertise, beliefs and disbeliefs. Further development of evidence-based guidelines based on well designed (randomized) studies is strongly encouraged.

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Background

Chronic pancreatitis (CP) is a disabling disease with a severe impact on the quality of life and social functioning of patients.^{1,2} It is associated with severe abdominal pain and the potential development of diabetes mellitus (DM) and malabsorption. During the course of the disease various complications may arise including common bile duct or duodenal stenosis, pseudocysts, fistulas formation and thrombosis or aneurysms of the large abdominal veins.

The complexity and diversity of clinical and morphological presentation of CP and lack of high quality randomized controlled trials and evidence based guidelines, results in a clinical decision making that for most part is based on local expertise, beliefs and disbeliefs. There is little insight into what drives the decision making of surgeons and gastroenterologist in the various aspects of the diagnostic workup and treatment of CP. The aim of this multidisciplinary international study therefore was to gain more insight into the current opinion and

clinical decision making of international pancreatologists and to systematically identify key study questions regarding the diagnosis and treatment of CP for future research.

Methods

Study design

We developed an online survey and several clinical case vignettes pertaining the clinical decision-making in the diagnosis and treatment of CP. Members of several major international associations of pancreatology and HPB-surgery, including the International Hepato-Pancreato-Biliary Association (IHPBA), American Pancreatic Association (APA), European Pancreatic Club (EPC), European Society of Gastrointestinal Endoscopy (ESGE), and the Dutch Pancreatitis Study Group (DPSG), were invited to participate via email. The online survey was sent by the associations and since the membership lists are confidential and known to be partially overlapping, the exact number of invitees could not be retrieved. Non-responders received up to two reminders. Incomplete responses were excluded. We used Google Forms Survey® to assess the opinions of the expert pancreatologists because it is easy accessible and anonymous (even to the study coordinators). The survey was tested for clarity and content among the members of the writing committee before sending to the different international associations.

The survey (see [Appendix](#)) consisted of several short questions regarding the country of origin, the specialty, type of hospital the specialist worked at, and the working experience as a registered specialist. The survey proceeded with questions and statements regarding several controversial clinical cases of CP (which included CT, MRI and ERCP images), with the focus on the treatment of CP. The specialists were asked about their preferred choice of treatment for each individual case in multiple-choice questions. Finally, at the end of the cases we proposed one or more statements regarding the case. Clinical history was similar for all cases; i.e. all patients were 50-year old men, with no significant co-morbidity, with CP due to alcohol and normal pancreatic endocrine and exocrine function. All patients had stopped drinking alcohol and smoking. The entire survey can also be found at: https://docs.google.com/forms/d/18bP2UJW04MFd58ETuwU4lGmICk-nZ8WS0WbYdQ8AQmQ/viewform?usp=send_form.

Data-analysis

The data was analyzed using IBM SPSS Statistics version 20. Data are presented as number and percentages, mean [$\pm$ standard deviation (SD)] or median [interquartile range (IQR)], where appropriate. We used the chi squared test and ANOVA for the analysis of discrete data. A p value of <0.05 was considered statistically significant. For correction for multiple testing the Bonferroni correction was used. In subgroup analysis we compared answers between specialty (i.e., surgery vs gastroenterology) and between continents. Because the response rate of

South-America, Africa and Oceania were relatively low compared with the other continents, these continents were combined into one group.

Results

Expert profile

A total of 288 pancreatologists, 160 (56%) surgeons and 128 (44%) gastroenterologists, participated in the survey. The majority (54%) was registered as a specialist for more than 10 years and 77% works at an academic center in Europe (59%), North-America (16%), or Asia (15%). Of the gastroenterologists, 40% had performed more than 75 therapeutic ERCP's (i.e. cannulation and stenting of the main pancreatic duct (MPD)). The majority of the surgeons (61%) had performed more than 25 operations for CP, and 13% more than 100 operations for CP (not including pseudocyst drainage). Responses were received from at least 47 countries (the responders who choose to send their contact information). Details are provided in [Table 1](#).

Diagnostics in CP

Classification tools

About half of the specialists (48%) used a classification tool for the diagnosis of CP, of which the Mannheim (25%), B  chler (25%), and Mayo Clinic tools (28%) are used most. The specialists in Europe used a classification tool significantly more often compared with specialists from other continents ($p = 0.02$). The Mannheim was used more often in Europe ($p = 0.01$), while the Mayo Clinic tool was used more often in North-America ($p = 0.001$). The B  chler tool was more often used by surgeons, whereas gastroenterologists more often used the Rosemont criteria (21% vs 2%, $p < 0.001$) ([Table 2](#)).

Imaging

Overall, for both the gastroenterologists and surgeons, CT was the preferred imaging modality for evaluation of an enlarged pancreatic head (59%), pancreatic pseudocyst (55%), pancreatic calcifications (75%), and peripancreatic fat infiltration (68%) and MRI/MRCP for assessment of MPD abnormalities (60%). In case of an enlarged pancreatic head, pseudocysts and calcifications, gastroenterologists preferred EUS as often as CT ([Table 3](#)).

Treatment

Extracorporeal shock wave lithotripsy

About half (59%) of the gastroenterologists used extracorporeal shock wave lithotripsy (ESWL) in the treatment of CP, of whom 29% indicated ESWL to be available in their center, while the remaining 30% refer their patients. Interestingly, 41% of the gastroenterologists indicated not to use ESWL in the treatment of CP, even when available in their hospital (13%) or when they could refer their patients to a center with ESWL (28%).

Table 1 Expert profile

			Gastroenterology 128 (44%)	Surgery 160 (56%)
Specialty	- Gastroenterologist performing endoscopy		112 (88%)	
	- Gastroenterologist not performing endoscopy		16 (12%)	
Registration as specialist	<5 years		21 (16%)	36 (23%)
	5–10 years		37 (29%)	38 (24%)
	>10 years		70 (55%)	86 (53%)
CP experience ^a	Gastroenterology ^b	Surgery ^c		
	<25 ERCP's	<25 operations	63 (49%)	62 (39%)
	25–75 ERCP's	25–100 operations	14 (11%)	65 (40%)
	>75 ERCP's	>100 operations	51 (40%)	33 (21%)
Type of hospital	Academic		94 (73%)	130 (81%)
	Non-academic teaching		30 (23%)	21 (13%)
	Non-teaching		4 (3%)	9 (6%)
Continent	Europe		84 (66%)	85 (53%)
	North-America		21 (16%)	26 (16%)
	Asia		15 (12%)	29 (18%)
	Other		8 (6%)	20 (13%)

^a Number of therapeutic ERCP's or operations for chronic pancreatitis (CP).

^b Only treatment of the PD – cannulation and stenting.

^c Not including pseudocyst drainage.

Surgical procedures

The most performed surgical procedures for CP were the longitudinal pancreatico-jejunostomy (PJ) (41%), the pylorus-preserving pancreaticoduodenectomy (PPPD) (39%) and the Frey procedure (39%). Followed by the Beger (17%), Berne (11%), Izbicki (7%) procedures, and total pancreatectomy with auto-islet cell transplantation (TP-IAT) (7%). The Berne procedure was more often used in Europe compared with other continents ($p = 0.008$), while TP-IAT was more often performed in North-America ($p < 0.001$) (Table 4).

Case-vignettes (Table 5)

Dilated main pancreatic duct

In patients with a dilated MPD due to an intraductal stone in the pancreatic head and recent onset of symptoms (<2 months)

requiring the use of weak opioids (e.g., Tramal), 29% of the specialists favored a surgical treatment (PJ or Frey), 11% would prescribe stronger opioids, and 56% opted for endoscopic therapy (of which 47% in combination with ESWL). In patients with casting stones over the entire MPD, 59% prefer surgery (Frey) versus 41% endoscopic therapy (with or without ESWL). Regarding the timing of surgery, 58% of the specialists regard early surgical intervention (as soon as opioid analgesics are required) superior compared with the current step-up approach of medical treatment, if needed followed by endoscopic interventions and surgery.

Groove pancreatitis

The majority (68%) of the pancreatologists consider groove pancreatitis as a separate disease entity within the clinical

Table 2 Diagnosis – Classification tools for the diagnosis of CP

	Total (n = 288)	Europe (n = 169)	Asia (n = 44)	North-America (n = 47)	Other (n = 28)	p-value	Surgery (n = 160)	GE (n = 128)
None	150 (52%)	77 (46%)	28 (64%)	25 (53%)	20 (71%)	0.02	83 (52%)	67 (52%)
Mayo Clinic	38 (13%)	20 (12%)	0 (0%)	13 (28%)	5 (18%)	0.001	18 (11%)	20 (16%)
Buchler	35 (12%)	26 (15%)	4 (9%)	3 (6%)	2 (7%)	0.24	33 (21%)	2 (2%)
Mannheim	35 (12%)	29 (17%)	4 (9%)	1 (2%)	1 (4%)	0.01	18 (11%)	17 (13%)
Rosemont	7 (2%)	6 (4%)	1 (2%)	0 (0%)	0 (0%)	0.43	0 (0%)	7 (6%)
Cambridge	5 (2%)	3 (2%)	0 (0%)	2 (4%)	0 (0%)	0.39	1 (1%)	4 (3%)
Other ^a	18 (6%)	8 (5%)	7 (16%)	3 (6%)	0 (0%)	0.002	7 (4%)	11 (9%)

^a Classification tools: Japanese, Cremer, Inspire, Dive, Verona, German S3 guidelines.

Table 3 Diagnosis – Imaging modalities evaluation of specific morphological abnormalities with CP

	CT		MRI/MRCP		EUS		US		ERCP	
	Surg	GE	Surg	GE	Surg	GE	Surg	GE	Surg	GE
Enlarged pancreatic head	120 (75%) ^c	51 (40%) ^c	15 (9%)	13 (10%)	20 (13%) ^c	55 (43%) ^c	4 (3%)	8 (6%)	1 (1%)	1 (1%)
Main duct abnormalities ^a	30 (19%)	8 (6%)	103 (64%)	71 (56%)	16 (10%)	29 (23%)	2 (1%)	4 (3%)	9 (6%)	16 (13%)
Pancreatic pseudocysts	106 (66%) ^c	53 (41%) ^c	22 (14%)	26 (20%)	16 (10%) ^c	42 (33%) ^c	16 (10%)	7 (6%)	0 (0%)	0 (0%)
Pancreatic calcifications ^b	134 (84%) ^c	81 (63%) ^c	10 (6%)	7 (7%)	9 (6%) ^c	25 (20%) ^c	6 (4%)	12 (9%)	1 (1%)	1 (1%)
Peripancreatic fat infiltration	109 (68%)	87 (68%)	41 (26%)	22 (17%)	4 (3%)	11 (9%)	6 (4%)	7 (6%)	0 (0%)	1 (1%)

GE, gastroenterology.

^a Dilatation, strictures, stones.

^b Parenchymal/ductal.

^c $p < 0.001$ (p -values less than 0.002 were deemed significant, after the Bonferroni correction for multiple testing).

Table 4 Treatment – Type of procedures performed for CP (multiple answers were possible)

	Total (n = 288)	Europe (n = 169)	Asia (n = 44)	North-America (n = 47)	Other (n = 28)	p-value
PJ	118 (41%)	62 (37%)	21 (48%)	21 (45%)	14 (50%)	0.34
PPPD	113 (39%)	61 (36%)	21 (48%)	21 (45%)	10 (36%)	0.43
Frey	111 (39%)	64 (38%)	22 (50%)	15 (32%)	10 (36%)	0.33
Beger	48 (17%)	31 (18%)	7 (16%)	7 (15%)	3 (11%)	0.76
Berne	31 (11%)	27 (16%)	2 (5%)	1 (2%)	1 (4%)	0.008
TP-IAT	21 (7%)	10 (6%)	1 (2%)	10 (21%)	0 (0%)	<0.001
Izbicki	19 (7%)	14 (8%)	2 (5%)	2 (4%)	1 (4%)	0.59
PD	6 (2%)	2 (1%)	1 (2%)	2 (4%)	1 (4%)	0.56
DP	5 (2%)	3 (2%)	2 (5%)	0 (0%)	0 (0%)	0.34
TP	5 (2%)	2 (1%)	1 (2%)	2 (4%)	0 (0%)	0.45
Other	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.70

spectrum of CP, especially in Europe (72%) and Asia (71%), and less in North-America (49%) ($p = 0.003$). Two-third (67%) of the specialists preferred a PPPD as first-line treatment in patients with groove pancreatitis. In case of groove pancreatitis with dilated MPD, 40% would perform the PPPD compared with 22% endoscopic treatment.

Enlarged pancreatic head with dilated main pancreatic duct and intraductal stones

In patients with an enlarged pancreatic head with dilated MPD and intraductal stones, 58% of the pancreatologists preferred a surgical treatment (44% PPPD, 26% Frey and 15% Beger). Forty-two percent would perform endoscopic therapy (of which 42% in combination with ESWL). Surgery was the preferred treatment especially in Asia compared to North-America (81% vs 55%, $p = 0.007$).

Solitary pancreatic tail lesion

Distal pancreatectomy (57%) or endoscopic therapy with or without ESWL (39%) were the preferred treatments in patients with focal CP of the tail (i.e. a solitary intraductal stone with upstream dilatation of the MPD in the pancreatic tail with normal MPD in the pancreatic head and corpus). Although 62%

of the specialists reported that endoscopic therapy ($\pm$ ESWL) was feasible in these patients, the majority (71%) still preferred a surgical pancreatic tail resection as first-line treatment.

Parenchymal calcifications and refractory pain despite maximal therapy

TP-IAT and EUS-guided celiac plexus block was the preferred treatment in patients with CP and severe pain with calcifications of the entire pancreatic parenchyma without MPD abnormalities and in patients with CP and refractory pain despite maximal medical, endoscopic, and surgical treatment. About half (58%) of the pancreatologists considered TP-IAT as treatment option in CP, especially in North-America (79%) compared with Europe (52%) or Asia (59%) ($p = 0.001$).

Discussion

This survey showed that the current opinion and clinical decision-making process of international pancreatologists differ vastly in various aspects in the diagnosis and treatment of CP. This lack of consensus was visible in different clinical cases, such as in patients with a dilated MPD and intraductal stones, about half of the responders choose endoscopic treatment in

Table 5 Case-vignettes: choice of treatment

	Parenchymal calcifications	Groove pancreatitis	MPD dilatation	Refractory pain despite maximal medical, endoscopic and surgical treatment	MPD cast stones	Enlarged pancreatic head	Solitary tail lesion
Endoscopic/ESWL	35 (12%)	68 (24%)	161 (56%)	–	119 (41%)	121 (42%)	111 (39%)
Endoscopic treatment	10 (3%)	63 (22%)	84 (29%)	–	44 (15%)	70 (24%)	35 (12%)
ESWL + Endoscopic	18 (6%)	5 (2%)	75 (26%)	–	68 (24%)	51 (18%)	58 (20%)
ESWL	7 (2%)	0 (0%)	2 (1%)	–	7 (2%)	0 (0%)	18 (6%)
Surgical treatment	137 (48%)	179 (62%)	83 (29%)	140 (49%)	169 (59%)	167 (58%)	171 (60%)
PJ	12 (4%)	9 (3%)	31 (11%)	1 (1%)	27 (9%)	6 (2%)	4 (1%)
Frey procedure	11 (4%)	23 (8%)	31 (11%)	1 (1%)	79 (27%)	44 (15%)	–
Beger procedure	4 (1%)	11 (4%)	4 (1%)	1 (1%)	17 (6%)	25 (9%)	–
PPPD	10 (3%)	114 (40%)	8 (3%)	67 (23%)	20 (7%)	74 (26%)	–
Distal pancreatectomy	10 (3%)	1 (1%)	2 (1%)	3 (1%)	3 (1%)	2 (1%)	164 (57%)
TP-IAT	79 (27%)	5 (2%)	3 (1%)	61 (21%)	–	1 (1%)	–
Other	11 (4%)	16 (6%)	–	2 (1%)	16 (6%)	15 (5%)	3 (1%)
Splanchnic therapy	75 (26%)	18 (6%)	3 (1%)	119 (41%)	–	–	6 (2%)
EUS celiac plexus block	59 (20%)	14 (5%)	3 (1%)	84 (29%)	–	–	5 (2%)
Percutaneous RFA	4 (1%)	0 (0%)	–	14 (5%)	–	–	1 (1%)
Th. splanchnicectomy	12 (4%)	4 (1%)	–	21 (7%)	–	–	0 (0%)
Other medical treatment	41 (14%)	23 (8%)	41 (14%)	29 (10%)	–	–	–
Stronger opioids	23 (8%)	15 (5%)	32 (11%)	–	–	–	–
Anticonvulsant adjuvants	11 (4%)	3 (1%)	7 (2%)	12 (4%)	–	–	–
Antidepressant adjuvants	5 (2%)	4 (1%)	2 (1%)	15 (5%)	–	–	–

combination with ESWL, 30% preferred initial surgical treatment, and 20% would prefer stronger opioid therapy. Or in patients with an enlarged pancreatic head, were about half of the pancreatologists would perform initial surgery (PPPD) and the other half would prefer initial endoscopic treatment. This survey also showed, that about half of the specialists use a classification tool for the diagnosis of CP. Overall, CT is the preferred imaging modality for evaluation of an enlarged pancreatic head, pseudocyst, calcifications, and peripancreatic fat infiltration. MRI was preferred for assessment of MPD abnormalities. About half of the gastroenterologists use ESWL in the treatment of CP. TP-IAT was the preferred treatment in patients with parenchymal calcifications without MPD abnormalities and in patients with refractory pain despite maximal endoscopic and surgical treatment.

There is still much controversy and debate about diagnosing CP. An important finding of this study was that about half of the specialists do not use a classification tool for the diagnosis of CP. However, a well-established tool would probably lead to a better management in the diagnosis and treatment of patients with (suspected) CP, and a lower burden of additional examinations.³ The use of standardized tools for CP diagnosis and staging would also lead to more uniform and homogeneous patient populations in clinical research studies which aids in the extrapolation of study results into clinical practice.^{4,5} Drawback of the current

classification tools is that they have marked differences in the criteria used, none of the tools are validated, and most of the tools are too comprehensive for clinical practice, which limits their clinical utility.^{6,7}

The diagnosis of CP is usually made by using imaging techniques. In our study, CT, MRI and EUS were the preferred diagnostic imaging modalities to assess morphological abnormalities of the pancreas, compared with abdominal US or ERCP. This is in line with recommendations from recent guidelines.^{3,8–10} ERCP and EUS have the highest diagnostic sensitivity (82%) of all imaging modalities in the detection of CP, followed by CT and MRI (75–78%) and US (67%). Specificity ranges from 91 to 98%.^{11–17} However, ERCP is an invasive technique, with risk of complications, such as post-ERCP pancreatitis. To date diagnostic ERCP is largely replaced by EUS and cross-sectional imaging modalities like CT and MRI/MRCP.^{8,18}

Another remarkable finding is that about half of the respondents do not use ESWL in the treatment of CP despite the fact that several studies have shown that ESWL in combination with endoscopic therapy achieves complete or partial pain relief in 50–90% of the patients with a follow-up between 6 and 77 months.^{19–25} Moreover, the clinical guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends ESWL as first-line treatment of obstructive painful CP, with pancreatic (head) stones ≥ 5 mm obstructing the MPD, followed

by endoscopic extraction of stone fragments.²⁶ Relative contraindication for ESWL is when there are extensive calculi over the entire length of the MPD of the pancreas, or in patients with isolated calculi in the pancreatic tail, in which surgery is suggested as the first line treatment. The reason seems to be an increased chance of collateral damage to the spleen and because it is more challenging and clinical success is less certain.^{26,27} Notably, about half of the responders still choose for an endoscopic therapy in combination with ESWL in the survey in these cases. Clearly, there is no consensus regarding these specific cases.

The same could be concluded for patients with CP with dilated MPD due to an intraductal stone in the pancreatic head, “early” in the treatment phase (since 2 months developed pain symptoms with since 2 weeks Tramal). The responses were almost equally divided between endoscopic treatment alone or in combination with ESWL, surgical treatment and medical treatment (opioid analgetics). The timing of surgery remains an important dilemma, as conclusive evidence is lacking. Different studies suggest early surgical intervention is associated with improved pain control, and is currently under investigation.^{4,28,29}

Interestingly, about half of the specialists considered TP-IAT to have a place in the treatment of CP, especially in North-America. Particularly the cases in which patients present with total parenchymal pancreatic calcifications without MPD abnormalities, or in patients with refractory pain as a last resort for patients who have failed to respond to previous endoscopic and surgical treatment. The primary indication for TP-IAT is to treat intractable pain in patients with CP in whom medical, endoscopic, or prior surgical therapy have failed.^{30,31} It has been suggested that prolonged disease and prior surgical procedures (i.e. PJ or distal pancreatectomy) compromise islet mass (up to 50% reduction in islet yield).^{32,33} TP-IAT is performed in few centers worldwide, especially in the USA and UK.^{34,35} The clinical outcome regarding pain relief and insulin independence varies much. Complete pain relief has been reported up to 81% of patients after a median follow-up of 8 months, but there are also studies that showed that 2 years after TP-IAT 23% of patients had a similar pain score as before the procedure and 40% of patients were still using opioid analgesics.^{30,36} Postoperative insulin independence was reported in two different meta-analysis. Wu *et al.* reported rates at 1 and 2 years follow-up off 28.4% and 19.7%, respectively.^{37,38}

Also a clinical dilemma is the treatment of patients with CP and an enlarged pancreatic head. About half of the responder would opt for a PPPD, while the other half would perform an endoscopic treatment first. A reason for this finding could be the lack of evidence for the superior treatment, so the experience and beliefs and disbeliefs of the pancreatologist predominates. Maybe differences in morphology in CP exist between continents could be an explanation.³⁹ These differences could perhaps be explained in reference patterns between centers or in the timing and type of surgery.

A strength of this survey is the participation of members of several major international associations of pancreatology and HPB-surgery. This study also has limitations. First, because the survey was sent by the associations, which has confidential membership lists, the total number of invitees could not be retrieved. However, a large group of 288 pancreatologists from at least 47 countries replied. Second, although CP is a heterogeneous disease, for study purposes case descriptions are kept concise and highlight those clinical items that are currently considered most relevant to focus on the clinical dilemma. It was not meant to be the full range of clinical presentation of CP. We focused on the most controversial clinical cases of CP. As we know the clinical presentation (i.e. pain), pancreatic function of patients with CP often does not match the degree of morphological abnormalities seen on imaging.^{40–47} Furthermore, one can debate the extent to which case vignettes reflect actual clinical practice or only physician competence.^{48–51}

In conclusion, this survey showed that the current opinion and clinical decision-making process of international pancreatologists differ vastly in various aspects in the diagnosis and treatment of CP. Future (preferably randomized) studies should address these aspects. Large, well-designed studies should focus on these clinical dilemma's, focusing on the optimal use of imaging and optimal treatment using ESWL, endoscopy and surgical therapy, concerning the different morphological and clinical presentations of patients with CP.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.hpb.2017.07.006>.