Chronic Asymptomatic Pancreatic Hyperenzymemia (CAPH): Meta-analysis of pancreatic findings at second-level imaging

Giuseppe Vanella [a], Paolo Giorgio Arcidiacono [b], Gabriele Capurso [b, *]

[a] *Digestive Diseases Unit, Sant'Andrea Hospital, Sapienza University of Rome, Italy*
[b] *Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational and Clinical Research Centre, IRCCS San Raffaele Scientific Institute, Milan, Italy*

ARTICLE INFO

ABSTRACT

Background/Objectives: Data estimating the prevalence of significant findings during the investigation of patients with Chronic Asymptomatic Pancreatic Hyperenzymemia (CAPH) are scanty and heterogeneous, and the diagnostic approach is therefore uncertain. The aim of this study was to meta-analyze pancreatic abnormalities detected at second-level imaging in patients with CAPH.
Methods: Pubmed database was searched until September 2018 for articles evaluating CAPH patients through MRI-Cholangio-Pancreatography with/without secretin (MRCP or s-MRCP) or Endoscopic Ultrasound (EUS). The methodology was developed from PRISMA checklist. Pooled prevalences of pancreatic findings were calculated, with subgroup analyses according to imaging modality. Quality of the studies, publication bias and heterogeneity were analyzed.
Results: In 8 articles describing 521 patients with CAPH, pooled prevalence of normal imaging was 56.6% [95%CI (CI) 41.9—70.2; $I^2 = 88.6\%$]. Prevalences of neoplasia, chronic pancreatitis, pancreatic cysts and benign abnormalities were 2.2% [CI1.2—4.1; $I^2 = 0\%$], 16.2% [CI10.2—24.8; $I^2 = 71.5\%$], 12.8% [CI8.2—19.3; $I^2 = 64.7\%$] and 17.2% [CI11.9—24.2; $I^2 = 71.5\%$] respectively. In sub-analyses, EUS and s-CPRM were less frequently normal and diagnosed more "early" chronic pancreatitis, while neoplastic lesions were still rare.
Conclusions: In CAPH patients, second-level pancreatic imaging is normal in 56% of the cases, neoplastic lesions are rare and the rate of pancreatic cysts is similar to that seen as incidental findings. More than one third of patients are diagnosed with abnormalities whose prognostic significance is uncertain. Despite the superior sensitivity of EUS or s-CPRM, the less costly/invasive and more available contrast-enhanced MRCP does not seem to miss relevant findings in this setting.

Introduction

Chronic asymptomatic pancreatic hyperenzymemia (CAPH) is a relatively common occasional finding during laboratory evaluation for non-specific abdominal symptoms or routine checkups [1], often leading to evaluation in pancreatic disorders outpatients clinics.

CAPH may be associated with different clinical circumstances, ranging from a meaningless biochemical abnormality to the rarer eventuality of a neoplastic lesion [2,3].

In this scenario, the common diagnostic work-up include an imaging evaluation of both the pancreatic parenchyma and ductal system to exclude significant lesions. However, there are no guidelines on this condition, nor an evidence-based indication on the best imaging modality to fulfil this aim.

There are few studies on this topic, often limited to relatively small cohorts, employing different diagnostic tests, and reporting heterogeneous data, thus making difficult to accurately estimate the prevalence of pancreatic abnormalities in CAPH patients.

Aim of the study

Our aim was to perform a meta-analysis estimating the pooled rates of pancreatic findings among patients with CAPH undergoing second-level abdominal imaging for this indication.

* Corresponding author. PancreatoBiliary Endoscopy and EUS Division, Pancreas Translational & Clinical Research Center, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milan, Italy.
E-mail address: capurso.gabriele@hsr.it (G. Capurso).

Methods

Search strategy

Pubmed database was searched from inception to September the 16th 2018 for the following search terms: (pancreatic OR pancreas) AND (hyperenzymemia OR hyperamylasemia OR hyperlipasemia).

The aim was to retrieve any paper dealing with asymptomatic pancreatic hyperenzymemia. All the retrieved titles were screened in order to exclude articles not related to the study aim (Screening process). The remaining studies were further screened by abstract and full text analysis in order to identify those fulfilling all inclusion and exclusion criteria (Eligibility process). Only studies containing homogeneous cohorts of patients undergoing second-level imaging for CAPH were included in the quantitative synthesis through meta-analysis. References of included studies were also screened to find potential additional studies. The screening process was independently performed by G.V. and G.C., with disagreement resolved by consensus or by discussion with the third author (P.G.A).

The methodology was developed from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [4] checklist.

Definitions

Pancreatic hyperenzymemia (PH) was defined as any elevation of seric amylase and/or lipase above the normal upper reference limit (URL) as reported in each study. PH was defined asymptomatic (APH) in the absence of symptoms attributable to pancreatic disease. An APH was defined chronic (CAPH), when the elevation was confirmed in at least two occasions spaced over time.

Diagnostic modalities deemed appropriate for inclusion were Magnetic Resonance with Cholangiopancreatography (MRCP), secretin-stimulated MRCP (s-MRCP) and Endoscopic Ultrasound (EUS), hereinafter collectively called "second-level imagings". Indeed, when abdominal ultrasound or computed tomography have been used in the setting of CAPH, a low sensitivity in detecting relevant abnormalities has been demonstrated [5–7].

For morphological diagnosis of chronic pancreatitis (CP), studies using EUS generally relied on the Rosemont criteria [8], while non-EUS studies usually employed the Cambridge criteria [9]. During data extraction, CP was considered as early/mild when morphological abnormalities were categorized as "equivocal"/"mild" (instead of "moderate"/"severe") according to Cambridge classification and as "suggestive of" (instead of "consistent with") according to the Rosemont classification.

A s-CPRM diagnosis of sphincter of Oddi dysfunction (SOD) was suspected using criteria previously reported [10].

Inclusion criteria

All studies describing patients with CAPH undergoing a second-level pancreatic imaging were includible in this meta-analysis if a clear description of imaging findings for the whole cohort was provided.

Exclusion criteria

No article in languages other-than English was included, but analysis of English-written abstracts has not suggested a loss of relevant information. Case reports or case series containing <10 patients were excluded.

Studies were excluded when patients did not have PH, were symptomatic, underwent imaging modalities other than those investigated, or when imaging findings were not clearly reported for the cohort analyzed. Reasons for exclusion were recorded for each study.

In the case of cohorts' overlap, the most recent and/or the largest cohort was included.

Data extraction for quantitative synthesis

Data extraction was independently performed by G.V. and G.C. and disagreement resolved by consensus or by discussion with the third author (P.G.A). For the complete list of recorded variables, see Supplementary statement 1.

When one study separately reported the findings of more than one imaging of interest, these were separately considered in sensitivity analyses according to imaging modality, whereas only the technique detecting more pancreatic abnormalities was considered in the overall analysis.

During extraction, imaging findings were assigned to one of these categories:

- Neoplastic lesions. These included pancreatic ductal adenocarcinomas (PDACs), neuroendocrine tumors (pNETs) and main-duct intraductal papillary mucinous neoplasia (MD-IPMNs). Notwithstanding their different malignant potential, these entities were all considered worthy of evaluation for pancreatic surgery.
- Abnormalities worthy of follow-up. These included pancreatic cystic lesions (PCLs) and chronic pancreatitis (CP). Although most PCLs were small and undefined, therefore harboring an undefinable malignant potential, they were included in this category in a prudent approach. Moreover, while the prognostic relevance of minimal alterations suggestive of CP (see above for our definition of early/mild CP) is not established, they were included in this category in a prudent approach.
- Benign abnormalities. These included all abnormalities without likely prognostic implications, such as anatomical variants of pancreatic ductal system (e.g. pancreas divisum (PD), duodenal diverticula, ampullary inflammatory stenoses, suspected SODs).

When a patient was found with>2 abnormalities, it was categorized according to the most relevant from a prognostic point-of-view (i.e. CP, in a patient with CP + PD; PDAC in a patient with PDAC + CP).

Quality assessment

Quality of included studies was independently assessed by G.V. and G.C. using the Methodological Index for Non-Randomized Studies (MINORS) [11]. Disagreements were resolved by consensus or by discussion with the third author (P.G.A). Study quality was considered poor (score≤5), fair (6–10) or good (≥11), as previously reported [12–14].

Statistical analysis

Events were expressed as proportions. 95% confidence intervals (CI) were calculated using exact methods and assuming a Poisson distribution. A meta-analysis of includible studies was executed using Comprehensive Meta-Analysis (Biostat, Englewood, NJ,USA). A random effects model was chosen to consider heterogeneity between studies. Heterogeneity was evaluated by the I^2 statistics. Publication bias (PB) was assessed using the Begg and Mazumdar test [15]. A p value < 0.05 was considered statistically significant.

Sensitivity analyses

To explore heterogeneity among cohorts, *a priori* sensitivity analyses were developed according to study quality and imaging modality. Since all but one studies were conducted in Italy, no sub-analysis according to geographical area was planned.

Results

Study identification and selection

A total of 749 records were screened (Fig. 1) of which 448 were unrelated to study topic. Of 296 articles further assessed for eligibility, 70 were excluded after analysis of the full text. 226 articles were related to APH but 218 were not includible in the quantitative synthesis. 8 articles [16–23] (Table 1) described CAPH patients further studied with second-level imaging and were therefore included in the meta-analysis. No cohort overlap was found. References analysis of included articles did not retrieve additional studies.

Qualitative analysis of included studies

The included studies described 521 patients with CAPH. All studies were conducted in Italy, except for a multicentric study [23] conducted in Belgium and in the United States. All studies except two [16,23] were prospective.

All cohorts excluded patients with previous history of pancreatic diseases. In half of the cohorts [16,17,19,22], patients were explicitly screened for extrapancreatic causes of hyperenzymemia (e.g. kidney failure, alcohol abuse, macroenzymemia, viral hepatitis, celiac disease) and excluded if such tests were positive, but also in the others studies the hyperenzymemia was clearly deemed of pancreatic origin without stating the diagnostic work-up already executed.

In half of the cohorts [16,17,21,22], patients were previously screened with first-level imaging (US or CT-scan) and included when these were negative. Moreover, in one study using EUS [16] all patients had undergone a first-level imaging and 56% also underwent MRCP; notwithstanding, EUS found additional abnormalities in 15.6% of patients, thus suggesting a higher sensitivity.
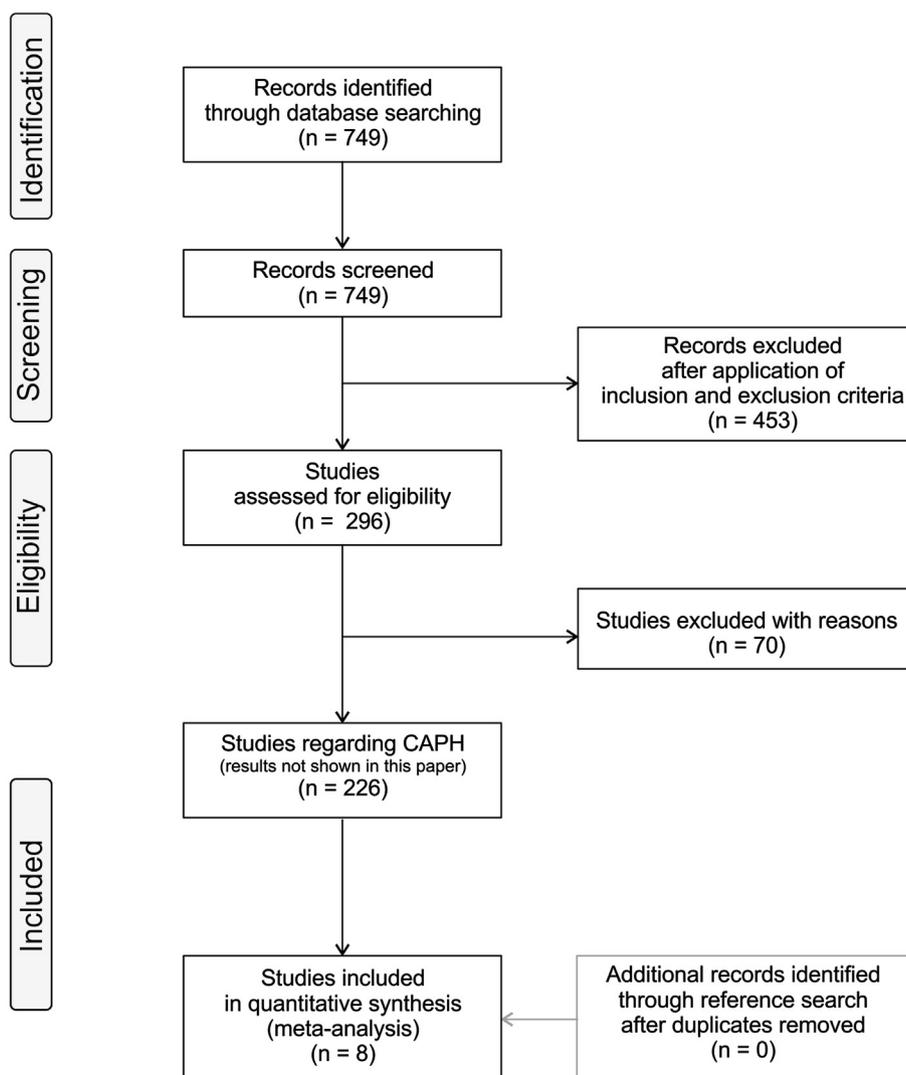

Fig. 1. Flow diagram showing the inclusion process of articles for meta-analysis.

Table 1
Characteristics of included studies and distribution of pancreatic abnormalities detected by each study.

First Author & Year	Pts (N)	Region	Control group	Exclusion of extrapancreatic reasons for CAPH	Previous negative first-level imaging	Type	Normal	Benign abnormalities			Abnormalities worth of follow-up				Neoplastic lesions			
								Total	PD	sSOD	Cysts	IPMNs	CP	Early CP	Total	PDAC	pNET	MD-IPMN
Mortelé 2004	54	Belgium/US	Yes	N.A.	N.A.	MRCP	**22 (40,7%)**	**12 (22,2%)**	7 (13%)	1 (1,9%)	**10 (18,5%)**		**10 (18.5%)**		**0**			
Gullo 2009	63	Italy	No	N.A.	Yes	MRCP	**57 (90.5%)**	**3 (4.7%)**	2 (3.2%)		**2 (3.2%)**		**1 (1.6%)**	1 (1.59%)	**0**			
Testoni 2009	25	Italy	Yes	Yes	Yes	MRCP	**20 (80%)**	**2 (8%)**	2 (8%)		**1 (4%)**		**2 (8%)**		**0**			
						S-MRCP	**11 (44%)**	**5 (20%)**	2 (8%)	3 (12%)	**1 (4%)**		**8 (32%)**		**0**			
Donati 2010	80	Italy	No	N.A.	N.A.	MRCP	**40 (50%)**	**14 (17,5%)**	10 (12,5%)		**24 (30%)**		**2 (2.5%)**	2 (2.5%)	**0**			
						S-MRCP	**25 (31.3%)**	**21 (26,3%)**	17 (21.3%)		**22 (27.5%)**		**12 (15%)**	12 (15%)	**0**			
Amodio 2012	160	Italy	No	Yes	N.A.	S-MRCP	**80 (50%)**	**21 (13,1%)**	13 (8,1%)	16 (10%)	**22 (13,8%)**	18 (11.3%)	**32 (20%)**	32 (20%)	**5 (3.1%)**	1 (0.6%)	4 (2.5%)	
Valente 2013	26	Italy	No	N.A.	N.A.	S-MRCP	**16 (61.5%)**	**7 (26,9%)**	5 (19.2%)		**2 (7.7%)**	2 (7.7%)	**1 (3.9%)**		**0**			
Di Leo 2016	68	Italy	Yes	Yes	Yes	EUS	**27 (39.7%)**	**9 (13.2%)**	9 (13.2%)		**9 (13.2%)**	9 (13.2%)	**21 (30,9%)**	18 (26.5%)	**2 (2.9%)**		1 (1.5%)	1 (1.47%)
						S-MRCP	**33 (48.5%)**	**15 (22,1%)**	11 (16.2%)	4 (5.9%)	**6 (8.8%)**	5 (7.4%)	**14 (20.6%)**		**0**			
Antonini 2017	45	Italy	No	Yes	Yes[a]	EUS	**38 (84.4%)**	**2 (4,4%)**			**4 (8,9%)**	3 (6.6%)	**1 (2.2%)**	1 (2.2%)	**0**			

[a] In this study, 56% of the patients with CAPH had already undergone MRCP and did not undergo EUS if MRCP detected pancreatic abnormalities. However, no cases of pancreatic cancer were present in the whole cohort of patients referred for CAPH.

3 studies [17,22,23] described a control group of patient without PH undergoing the same imaging.

Amodio [19] reported abnormalities detected with both MRCP and s-MRCP, but clinical interpretation was provided only for s-MRCP, whose findings were considered for meta-analysis. Pancreatic abnormalities were more frequent after secretin stimulation than in basal MRCP (50% vs 27.5%; p < 0.0001).

3 studies evaluated the same patients with two imaging modalities [17,20,22].

In the study by Testoni [22], pancreatic abnormalities were more prevalent in the study group than in a cohort of patients with recurrent abdominal pain without PH (44% vs 3.6%, p < 0.001). After secretin stimulation detection of pancreatic abnormalities significantly increased with respect to basal MRCP, due to the higher detection of signs of CP and SOD. Exocrine pancreatic function was normal in all subjects, thus questioning the clinical relevance of detected abnormalities in these asymptomatic patients without risk factors.

In the study by Donati [20], s-MRCP showed more abnormalities than MRCP (68.7% vs 50%), mainly PD and mild CP. After secretin stimulation primary diagnosis changed in 27.5% of patients. A mild reduction in pancreatic outflow at s-MRCP (an indirect measure of functional reserve) was observed in only 3 of 12 patients with signs of CP.

In the study by Di Leo [17], EUS detected more pancreatic abnormalities among CAPH patients than in patients with submucosal tumors (60.3% vs 13.2%; p < 0.001), the main difference being the rate of CP (32.4% vs 4.4%; p < 0.001). Moreover, EUS detected pancreatic abnormalities in 60.3% of patients whereas s-MRCP in 51.5%, with this latter being more frequently normal. However the majority (82%) of patients had endosonographic criteria "suggestive of" rather than "consistent with" CP. EUS and s-MRCP were discordant in 25% of patients, with EUS showing more CPs and PCLs and less ductal alterations and SODs; the most relevant difference was the finding of one pNET and one MD-IPMN by EUS only and confirmed by surgery.

In the study by Mortele [23], normal examinations, PD and small PCLs were more prevalent in the study group than in the control group, while no difference was found in CP. A single PDAC was diagnosed in the control group.

In the study by Gullo [21], only a minority of patients investigated with MRCP was diagnosed with minor pancreatic abnormalities.

Fecal elastase-1 levels were evaluated in two studies and indicated an exocrine insufficiency in 5.1% [19] and 4.4% [17] of patients, while the prevalence of CP in the same studies was 20% [19] and 30.9% [17] respectively.

Meta-analysis

Pooled prevalence of pancreatic findings in patients with CAPH

When data of included studies were meta-analyzed (Fig. 2), the prevalence of completely normal imaging was 56.6% [95%CI 41.9–70.2], with considerable heterogeneity ($I^2 = 88.6\%$) and significant PB (Begg and Mazumdar Kendall's $\tau = 0.7$ and p = 0.02) suggesting that studies with a higher prevalence of normal findings were less likely to be published (Supplementary Figure 1 for Funnel plot).

The pooled prevalence of benign abnormalities requiring no specific follow-up was 17.2% [95%CI 11.9–24.2; $I^2 = 71.5\%$], with no PB ($\tau = -0.39$; p = 0.17).

Among abnormalities deserving follow-up, the pooled prevalence of PCLs and of CP was respectively 12.8% [95%CI 8.2–19.3] and 16.2% [95%CI. 10.2–24.8], with intermediate heterogeneity ($I^2 = 64.7\%$ and 71.5% respectively) and no PB ($\tau = -0.5$; p = 0.06

and $\tau = -0.39$; p = 0.17).

The pooled prevalence of neoplastic lesions was 2.2% [95%CI 1.2–4.1], with no heterogeneity and no PB ($I^2 = 0\%$; $\tau = 0.07$; p = 0.9).

Pooled prevalence of pancreatic findings according to imaging modality

Pooling together only cohorts where the same imaging was used (222 patients for CPRM, 359 for s-CPRM, 113 for EUS), pooled prevalence of negative imaging was 68% [95%CI 42.1–86.3], 46.1% [95%CI 36.9–55.4] and 64.8% [95%CI 18.9–93.6] respectively for CPRM, s-CPRM and EUS ($I^2 = 90.9$, 61.8 and 94.8% respectively).

PCLs were detected at comparable rates with the different modalities. Signs of CP were more frequently detected in cohorts studied by EUS and (even further) by s-CPRM than by CPRM. Benign abnormalities were more prevalent in cohorts investigated through s-CPRM. Neoplastic lesions were rare in all the cohorts (Fig. 3).

Study quality

Quality was "fair" in 3 studies [18,21,23] and "good" in the remaining ones [16,17,19,20,22] (Supplementary Table 1). When pooled prevalence of normal imaging was sub-analyzed according to quality, "good"-quality studies demonstrated a normal imaging less frequently than "fair"-quality studies (49,9% [95%CI 34,7–65.1] and 68.1% [95%CI 32.1–90.6] respectively). However, heterogeneities of these sub-analyses remained high ($I^2 = 86.3$ and 92.4% respectively) and, therefore, no other imaging finding was sub-analyzed and study quality was not considered to have a role in explaining the heterogeneity.

Discussion

In this meta-analysis evaluating the incidence of pancreatic findings in CAPH patients undergoing second-level pancreatic imaging, no abnormalities were found in more than half of subjects, while the detection of pancreatic neoplasia was rare. One fifth of patients were diagnosed with meaningless abnormalities, while less than one third was found with abnormalities somehow deserving follow-up, namely small PCLs and minimal signs of CP.

While there is substantial agreement that pancreatic enzymes should be sampled only for excluding an acute pancreatic inflammation in patients with typical symptoms and/or specific risk factors (e.g. ERCP, pancreatotoxic drugs), amylase and lipase are not infrequently included in routine checkups of healthy people or in routine laboratory panels of hospitalized patients. This attitude has generated the relatively new problem of PH, and has "created" new "patients", asking for the meaning of this abnormality.

A number of extrapancreatic and pancreatic abnormalities may explain CAPH. First of all, an elevation of amylase and lipase levels is not always caused by pancreatic disorders, and the diagnostic work-up should be different for patients with isolated elevated amylasemia (beginning with isoenzymes determination) and those with hyperlipasemia or elevation of both enzymes [24,25]. An hyperenzymemia can, indeed, be related to salivary hyperamylasemia or to abnormalities in the metabolism of normally released enzymes (e.g. renal or hepatic insufficiency; macroenzymemia, where enzymes [more frequently amylase] bind with other molecules or self-polymerize and are therefore filtered with difficulty form renal glomeruli; reabsorption through an abnormally permeable intestinal mucosa, such us in Inflammatory Bowel Diseases or intestinal perforation) or even to paraneoplastic production [2]. When all these circumstances have been excluded, and a pancreatic origin of the elevation is presumed, sometimes PH is still not associated with any disease, and a diagnosis of Benign PH or Gullo's syndrome can be established [26]. However, the
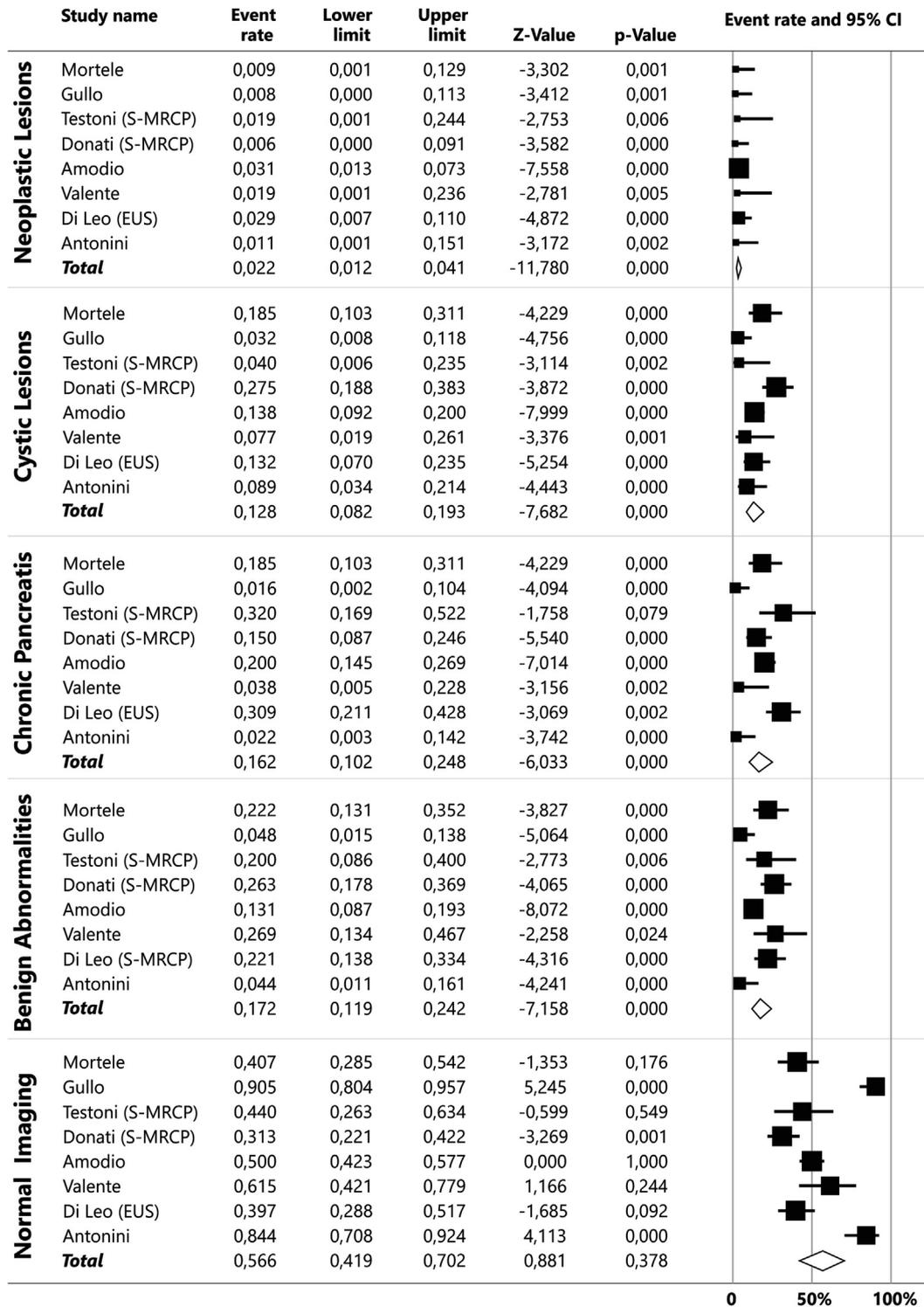
Fig. 2. Forest plot showing the pooled prevalence of neoplastic lesions (2.2% [95%CI (CI) 1.2—4.1; $I^2 = 0\%$;]), cystic lesions (16.2% [CI 10.2—24.8; $I^2 = 71.5\%$]), chronic pancreatitis (12.8% [CI 8.2—19.3 $I^2 = 64.7\%$]), benign abnormalities (17.2% [CI 11.9—24.2; $I^2 = 71.5\%$]) and normal imaging (56.6% [CI 41.9—70.2, $I^2 = 88.6\%$) among patients with CAPH evaluated with second-level imaging.

possibility to detect neoplastic and pre-neoplastic lesions during the workup of a PH makes a "wait and see" approach unsafe.

No guideline or nomogram help clinicians in building a tailored diagnostic work-up, which considers also patient's personal and family history, medications and comorbidities, behaviors and risk factors. Furthermore, no firm evidence exist on the best imaging

modality to investigate CAPH patients. Transabdominal ultrasound (US), frequently the first imaging prescribed [2,27], has a low negative predictive value for pancreatic abnormalities and this argues against its utilization as the only imaging test [5—7]. Of note, most patients included in this meta-analysis had already undergone negative US and CT-scan.
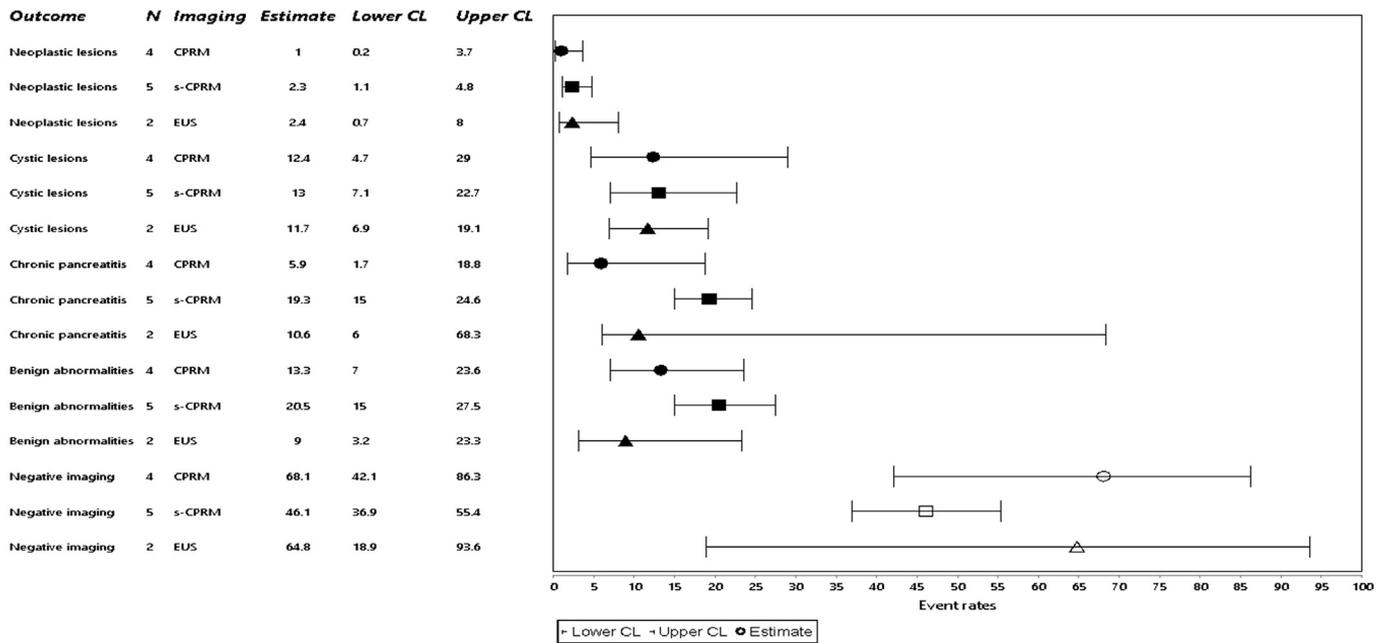
Outcome	N	Imaging	Estimate	Lower CL	Upper CL
Neoplastic lesions	4	CPRM	1	0.2	3.7
Neoplastic lesions	5	s-CPRM	2.3	1.1	4.8
Neoplastic lesions	2	EUS	2.4	0.7	8
Cystic lesions	4	CPRM	12.4	4.7	29
Cystic lesions	5	s-CPRM	13	7.1	22.7
Cystic lesions	2	EUS	11.7	6.9	19.1
Chronic pancreatitis	4	CPRM	5.9	1.7	18.8
Chronic pancreatitis	5	s-CPRM	19.3	15	24.6
Chronic pancreatitis	2	EUS	10.6	6	68.3
Benign abnormalities	4	CPRM	13.3	7	23.6
Benign abnormalities	5	s-CPRM	20.5	15	27.5
Benign abnormalities	2	EUS	9	3.2	23.3
Negative imaging	4	CPRM	68.1	42.1	86.3
Negative imaging	5	s-CPRM	46.1	36.9	55.4
Negative imaging	2	EUS	64.8	18.9	93.6

Fig. 3. Sub-analyses according to imaging modalities. Estimate rates and Forest Plot showing the results of sensitivity analyses evaluating the pooled prevalence of pancreatic findings stratified by imaging modality (CPRM = 4 studies with 222 patients; s-CPRM = 5 studies with 359 patients; EUS = 2 studies with 113 patients).

Among 521 patients, only 7 malignancies (1 PDAC, 5 pNETs and 1 MD-IPMN) were diagnosed, 5 of which were detected in one single cohort [19], suggesting a possible bias due to referral to a tertiary centre. In this study employing s-MRCP, all lesions were already visible at basal MRCP; the other 2 lesions (1 NET and 1 MD-IPMN) were detected in another study [17] by EUS only.

Our sensitivity analyses according to imaging modality suggest that, in CAPH patients, MRCP and EUS have comparable rates of negative results, higher than that of s-MRCP. However in 1 [16] of the 2 studies using EUS, most of patients were already studied with US, CT and MRCP (and excluded if abnormalities were detected), so the prevalence of abnormalities in this cohort could be misleadingly low. Conversely, as EUS detected further abnormalities in a share of patients with negative MRCP, this might suggest its higher sensitivity.

EUS and s-MRCP seem to be the most sensitive modalities, and complementarity of these two techniques in the initial evaluation of patients with CAPH has been proposed [17]. However, as EUS and s-MRCP are expensive, not widely available and strongly depending on the expertise of the centre, one of the two examinations might be appropriate depending on local scenario.

In our analyses, the higher sensitivity of EUS and s-MRCP is mainly related to the detection of subclinical abnormalities (e.g. early CP), which can eventually be explained also by aging alone. The clinical significance of these findings for asymptomatic individuals without risk factors, and whether they deserve follow-up is unclear [28,29].

Moreover, as suggested by day-to-day fluctuations in pancreatic enzymes in hyperenzymemic patients both with and without ductal abnormalities [21], the link between morphological abnormalities and enzymatic elevations might just be coincidental [7].

Our study has several limitations, intrinsic to its design. First, analyzed cohorts were not homogeneous in terms of inclusion and exclusion criteria, particularly concerning the work-up executed before second-level imaging, potentially influencing the prevalence of pancreatic abnormalities. Even if an extensive search was carried-out, including also references of included studies, PB may

influence the result; however using the Begg and Mazumdar test a PB was likely only in the analysis of pooled rate of normal imaging, with studies with a higher prevalence of normal findings being less likely to be published. Moreover, since all but one of the retrieved studies were conducted in Italy, these results might not be generalizable for different populations, although the study enrolling in Belgium/US showed similar results. Heterogeneity was high, but sensitivity analyses were conducted in order to try to explain it.

Notwithstanding all these limitations, this is the only study that quantitatively synthetize pancreatic abnormalities diagnosed among patients with CAPH investigated with second-level imaging. The present results might help assessing the risk of relevant pancreatic diseases in these subjects. Even if most subjects will not have any abnormality detected, a small fraction might be diagnosed with neoplastic lesions or findings deserving follow-up. In the workup of these patients, MRCP seems to be the best compromise [29] between clinical utility, accuracy, costs, safety and availability. The role of EUS in this setting must be further explored, but is promising [16] in light of its spreading, its high sensibility and the increasing experience in interpreting its findings. Studies investigating the long-term prognostic relevance of minimal abnormalities detected in CAPH patients are needed to establish the best approach.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.01.022.

References

[1] Galassi E, Birtolo C, Migliori M, Bastagli L, Gabusi V, Stanghellini V, et al. A 5-year experience of benign pancreatic hyperenzymemia. Pancreas 2014;43: 874—8. https://doi.org/10.1097/MPA.0000000000000138.

[2] Frulloni L, Patrizi F, Bernardoni L, Cavallini G. Pancreatic hyperenzymemia: clinical significance and diagnostic approach. JOP 2005;6:536—51.

[3] Pezzilli R, Morselli-Labate AM, Casadei R, Campana D, Rega D, Santini D, et al. Chronic asymptomatic pancreatic hyperenzymemia is a benign condition in only half of the cases: a prospective study. Scand J Gastroenterol 2009;44: 888—93. https://doi.org/10.1080/00365520902839683.

[4] Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP, Oxman A, et al. Preferred reporting items for systematic Reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6, e1000097. https://doi.org/10.1371/journal.pmed.1000097.

[5] Pezzilli R, Morselli-Labate AM, Calculli L, Casadei R. Long-standing pancreatic hyperenzymemia: is it a nonpathological condition? Case Rep Gastroenterol 2009;3:111—5. https://doi.org/10.1159/000213479.

[6] Gullo L. Benign pancreatic hyperenzymemia. Dig Liver Dis 2007;39:698—702. https://doi.org/10.1016/j.dld.2007.03.005.

[7] Mariani A. Chronic asymptomatic pancreatic hyperenzymemia: is it a benign anomaly or a disease? JOP 2010;11:95—8.

[8] Catalano MF, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc 2009;69:1251—61. https://doi.org/10.1016/j.gie.2008.07.043.

[9] Sarner M, Cotton PB. Classification of pancreatitis. Gut 1984;25:756—9.

[10] Mariani A, Curioni S, Zanello A, Passaretti S, Masci E, Rossi M, et al. Secretin MRCP and endoscopic pancreatic manometry in the evaluation of sphincter of Oddi function: a comparative pilot study in patients with idiopathic recurrent pancreatitis. Gastrointest Endosc 2003;58:847—52.

[11] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712—6.

[12] Elkhadem A, Mickan S, Richards D. Adverse events of surgical extrusion in treatment for crown-root and cervical root fractures: a systematic review of case series/reports. Dent Traumatol 2014;30:1—14. https://doi.org/10.1111/edt.12051.

[13] Ata-Ali J, Diago-Vilalta J-V, Melo M, Bagán L, Soldini M-C, Di-Nardo C, et al. What is the frequency of anatomical variations and pathological findings in maxillary sinuses among patients subjected to maxillofacial cone beam computed tomography? A systematic review n.d. doi:10.4317/medoral.21456.

[14] Vanella G, Crippa S, Archibugi L, Arcidiacono PG, Delle Fave G, Falconi M, et al. Meta-analysis of mortality in patients with high-risk intraductal papillary mucinous neoplasms under observation. Br J Surg 2018;105:328—38. https://doi.org/10.1002/bjs.10768.

[15] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088—101.

[16] Antonini F, Belfiori V, Pagano N, Buscarini E, De Minicis S, Lo Cascio M, et al. Endoscopic ultrasonography may select subjects having asymptomatic chronic pancreatic hyperenzymemia who require a stricter follow-up. Pancreas 2017;46:524—7. https://doi.org/10.1097/MPA.0000000000000796.

[17] Di Leo M, Petrone MC, Zuppardo RA, Cavestro GM, Arcidiacono PG, Testoni PA, et al. Pancreatic morpho-functional imaging as a diagnostic approach for chronic asymptomatic pancreatic hyperenzymemia. Dig Liver Dis 2016;48: 1330—5. https://doi.org/10.1016/j.dld.2016.08.109.

[18] Valente R, Antonelli M, Piciucchi M, Federici GF, Signoretti M, Iannicelli E, et al. Celiac Disease and CFTR mutations in patients with chronic asymptomatic pancreatic hyperenzymemia. Am J Gastroenterol 2013;108:618. https://doi.org/10.1038/ajg.2013.13.

[19] Amodio A, Manfredi R, Katsotourchi AM, Gabbrielli A, Benini L, Mucelli RP, et al. Prospective evaluation of subjects with chronic asymptomatic pancreatic hyperenzymemia. Am J Gastroenterol 2012;107:1089—95. https://doi.org/10.1038/ajg.2012.125.

[20] Donati F, Boraschi P, Gigoni R, Salemi S, Faggioni L, Bertucci C, et al. Secretin-stimulated MR cholangio-pancreatography in the evaluation of asymptomatic patients with non-specific pancreatic hyperenzymemia. Eur J Radiol 2010;75: e38—44. https://doi.org/10.1016/j.ejrad.2009.11.008.

[21] Gullo L, Lucrezio L, Calculli L, Salizzoni E, Coe M, Migliori M, et al. Magnetic resonance cholangiopancreatography in asymptomatic pancreatic hyperenzymemia. Pancreas 2009;38:396—400. https://doi.org/10.1097/MPA.0b013e31819d73b3.

[22] Testoni PA, Mariani A, Curioni S, Giussani A, Masci E. Pancreatic ductal abnormalities documented by secretin-enhanced MRCP in asymptomatic subjects with chronic pancreatic hyperenzymemia. Am J Gastroenterol 2009;104: 1780—6. https://doi.org/10.1038/ajg.2009.158.

[23] Mortelé KJ, Wiesner W, Zou KH, Ros PR, Silverman SG. Asymptomatic nonspecific serum hyperamylasemia and hyperlipasemia: spectrum of MRCP findings and clinical implications. Abdom Imag 2004;29:109—14. https://doi.org/10.1007/s00261-003-0072-4.

[24] Kameya S, Hayakawa T, Kameya A, Watanabe T. Clinical value of routine isoamylase analysis of hyperamylasemia. Am J Gastroenterol 1986;81: 358—64.

[25] Koehler DF, Eckfeldt JH, Levitt MD. Diagnostic value of routine isoamylase assay of hyperamylasemic serum. Gastroenterology 1982;82:887—90. https://doi.org/10.1016/S0016-5085(82)80251-5.

[26] Gullo L. Chronic nonpathological hyperamylasemia of pancreatic origin. Gastroenterology 1996;110:1905—8. https://doi.org/10.1053/gast.1996.v110.pm8964417.

[27] Birtolo C, Migliori M, Drewes AM, Tomassetti P, Imbrogno A, Fusaroli P, et al. Benign pancreatic hyperenzymemia. Pancreas 2017;46:5—7. https://doi.org/10.1097/MPA.0000000000000723.

[28] Lankisch PG. Pancreatic ductal abnormalities documented by secretin-enhanced MRCP in asymptomatic subjects with chronic pancreatic hyperenzymemia. Am J Gastroenterol 2010;105:703—5. https://doi.org/10.1038/ajg.2009.666.

[29] Frulloni L, Amodio A. Endoscopic ultrasonography in chronic asymptomatic pancreatic hyperenzymemia: the more we see, the less we know. Dig Liver Dis 2017;49:232—3. https://doi.org/10.1016/j.dld.2016.11.009.