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Position statement on the definition, incidence, diagnosis and outcome of acute on chronic pancreatitis

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ABSTRACT

Background: Acute on chronic pancreatitis (ACP) is a relatively common condition, but there are significant gaps in our knowledge on the definition, incidence, diagnosis, treatment and prognosis.
Methods: A systematic review that followed PICO (Population; Intervention; Comparator; Outcome) recommendation for quantitative questions and PICo (Population, Phenomenon of Interest, Context) for qualitative research was done to answer 10 of the most relevant questions about ACP. Quality of evidence was judged by the GRADE criteria (Grades of Recommendation, Assessment, Development and Evaluation). The manuscript was sent for review to 12 international experts from various disciplines and continents using a Delphi process.
Results: The quality of evidence, for most statements, was low to very low, which means that the recommendations in general are only conditional. Despite that, it was possible to reach strong levels of agreement by the expert panel for all 10 questions. A new consensus definition of ACP was reached. Although common, the real incidence of ACP is not known, with alcohol as a major risk factor. Although pain dominates, other non-specific symptoms and signs can be present. Serum levels of pancreatic enzymes may be less than 3 times the upper limit of normal and cross-sectional imaging is considered more accurate for the diagnosis in many cases. It appears that it is less severe and with a lower mortality risk than acute pancreatitis.

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Conclusions: Although the evidence base is poor, this position statement provides a foundation from which to advance management of ACP.

1. Introduction

Chronic pancreatitis (CP) is a fibroinflammatory disease [1] that can be complicated by episodes of acute pancreatic inflammation (acute on chronic pancreatitis (ACP)). The rates of presentation to emergency department of both acute pancreatitis (AP) and ACP are increasing [2,3]. Although similar in clinical presentation, the relationship between ACP and AP is poorly understood and there is some evidence to suggests that the underlying pathophysiology and clinical course are different [4,5]. For example, serum pancreatic enzyme levels are often lower in ACP compared with AP patients and they also appear to have a reduced inflammatory and cytokine response and a lower risk of complications including organ failure. The long-term metabolic sequelae also appear to be different because ACP patients are at greater risk of developing exocrine and endocrine insufficiency than AP patients, which is likely to be related to the co-existent CP. Despite these differences and the lack of supportive evidence, current guidelines recommend a similar approach to the diagnosis and treatment of AP and ACP [6–9]. It is important to note that these guidelines were developed for AP and not for ACP. The definition of ACP is not consistent and the implications for concomitant CP not addressed. There are several different terms used for an acute inflammation of the pancreas in patients with CP, but these terms refer also to an acute exacerbation of pain in patients with chronic pain syndrome associated with CP [10]. The lack of uniform definition and the entity being defined, makes it challenging to evaluate and integrate the available evidence and to provide consistent recommendations for the management of ACP.

The aim of this study was to develop consensus amongst experts on the definition, incidence, diagnostic criteria and outcomes for ACP, based on a systematic review of the available literature. It is anticipated that this will facilitate better interpretation of research findings, improve communication among peers and allow for a better evaluation of the efficacy of future diagnostic strategies and therapeutic interventions.

2. Methods

A working group (WG) was established, consisting of a multidisciplinary team of gastroenterologists (AMD, SSO), surgeons (TBM, JBP, JAW, SAWB) and a radiologist (JBF) and chaired by TBM. In a Delphi process, a minimum of 12 respondents is generally considered necessary for consensus to be achieved, with larger sample sizes providing diminishing returns which can compromise the validity of the process [11–13]. Hence, an expert panel (EP) of 12 invited international specialists (MB, IED, PG, PH, JML, EM, SP, VR, AS, VS, MS, DY) in pancreatitis was appointed from representative specialities and 9 countries. The study was endorsed by the European Pancreatic Club.

The WG formulated 10 clinically relevant questions after repeated discussions. These covered all aspects of this entity, i.e., name, definition, incidence, risk factors (alcohol, tobacco, smoking, duct obstruction, etc.), diagnose and prognosis, attempting to create a common ground facilitating future research and allow therapeutic guidelines. The questions were based on the PICO (Population, Intervention, Comparison, Outcome) recommendations for quantitative questions and PICo (Population, Phenomenon of Interest, Context) approach for qualitative questions [14]. A search strategy was developed with an expert librarian, agreed to by the WG and included the following terms: “acute on chronic pancreatitis”, “acute attack of chronic pancreatitis”, “exacerbation of chronic pancreatitis”, “acute flare of chronic pancreatitis”, “acute inflammation on chronic pancreatitis” or “acute bouts of chronic pancreatitis”. A systematic literature review was conducted using three bibliographic databases (MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials) to identify relevant papers for inclusion, based on pre-determined inclusion criteria. The inclusion criteria were: (1) randomized studies, observational cohort studies and systematic reviews focusing on CP patients with an acute pancreatic inflammation or the description of the diagnosis corresponding to the search terms (above), (2) studies published in English language, (3) studies available in full text, and (4) studies published after 1993, being the date of the original Atlanta classification for AP [15].

The WG then drafted a response to the questions, developed a consensus and made recommendations based on both the literature review and their expertise. The majority of the WG members met face to face to develop the different sections of the position statement, utilizing online meetings when working with JAW and SAWB. The WG used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [16] for evaluating the quality of the available evidence [16–19]. Although expert opinion is not a category of quality of evidence in the GRADE system [16], in the absence of any evidence, ‘expert opinion’ was sometimes used, representing very low quality of evidence. Because recommendations on diagnostic tests and strategies present unique challenges, the strength of evidence was modified, according to GRADE Working Group's suggestions [20]. After determining the GRADE of evidence, the WG drafted the initial manuscript. This was sent to the EP for scoring and commenting according to a modified Delphi process [21]. The EP voted on their level of agreement with the recommendations on a nine-point Likert scale from 1 (“strongly disagree”) to 9 (“strongly agree”). The strength of agreement was classified as “strong” if 80% of votes were 7 or above on the Likert scale, “conditional” if 65%–79% of votes were 7 or above, and “weak” if less than 65% of votes were 7 or above. In the first round, the strength of agreement was “strong” in 7 of the 10 questions and “conditional” in the other 3 questions. The WG revised the questions with conditional agreement and sent them back to the EP in the second round of the Delphi process. Any questions arising from this process were resolved online between EP members and TBM and AMD. After the Delphi process, the WG met to consider any remaining issues and finalised a commentary to each statement to explain the underlying evidence, highlight gaps in knowledge and provide support for the statement. The document was then finalised and circulated to all authors for final approval.

3. Results

Overall results of the systematic literature review highlight the sparsity of specific literature about this topic and, therefore, the evidence level was usually low, reflecting a paucity of randomized

trials and high-quality observational studies (Fig. 1). Each of the 10 clinically relevant questions are presented here, along with consensus answer, the judged quality of evidence, recommendation, level of agreement and a commentary on the issue addressed.

Question 1: What is the best term to describe an acute pancreatic inflammation in CP?

Answer: "Acute on chronic pancreatitis" is the best term to describe an acute pancreatic inflammation in patient with CP.
Quality assessment: Low
Recommendation: Conditional
Agreement: Strong

Commentary: In the literature, several terms are used to describe an acute pancreatic inflammation in a patient with CP. The two most frequently used terms are "acute on chronic pancreatitis" and "(acute) exacerbations of chronic pancreatitis" [10]. The terms "exacerbation of chronic pancreatitis" and "acute exacerbation of chronic pancreatitis" are ambiguous as it is not clear whether this is referring to increased clinical symptoms (e.g., pain aggravation in setting of a chronic pain syndrome), altered biochemistry (e.g., elevated serum pancreatic enzyme levels), new radiological features (e.g., peri- and pancreatic oedema, acute fluid collection and/or inflammatory mass) or a combination of these. The same issues apply to the term "acute on chronic pancreatitis" which also suggests AP superimposed on CP. This is not strictly accurate since a second disease process (AP) is unlikely, but the condition rather represents an acute worsening in the already present inflammation associated with CP. It is worth noting that the phrase "acute on chronic" is often used in other disease settings, including liver failure ("acute-on-chronic liver failure") and kidney disease ("acute-on-chronic kidney disease"), and is meant to imply an acute worsening of a chronic disease [22–26]. Because "acute on chronic pancreatitis" is used most often in the literature [10] and is probably better understood, there was consensus by the EP that this is the preferred term. When new causes for an acute pancreatic inflammation occurs in a patient with CP as e.g., after endoscopic retrograde cholangiopancreatography (ERCP), this should normally be labelled post-ERCP AP rather than ACP.

Question 2: What is the optimal definition of ACP?

Answer: ACP is defined as "an acute worsening of the inflammatory process associated with CP, resulting in a deterioration of the patient's clinical condition, typically resulting in increased pancreatic pain" (Fig. 2).
Quality assessment: Low
Recommendation: Conditional
Agreement: Strong

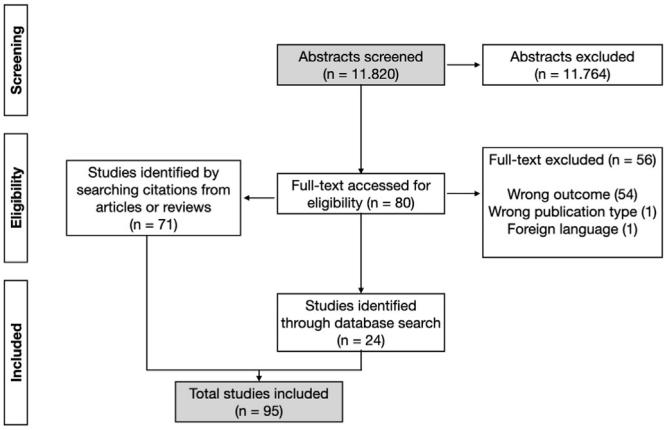

Fig. 1. Flowchart of the literature review.

Commentary: There are several definitions of ACP in the literature [10]. A good definition should be easily understood and include the fundamental features that characterize ACP, or more specifically distinguish ACP from AP and CP. These features are the presence of co-existent CP, the acute onset, the increased inflammation and a deterioration in the patient's clinical condition. This definition is an adaption of the definition from Olesen et al. [27] that was the most comprehensive and meaningful definition found in the previous literature review [10]. CP is characterized by an ongoing fibroinflammatory process and, as such, inflammation is already present in many patients [1]. Therefore, ACP is most often considered an increase in the underlying pancreatic inflammation and not a *de novo* inflammation. The recommendation to use the phrase "patient's clinical condition" (rather than specifically refer to increased abdominal or pancreatic pain) is because patients can present with a range of variable symptoms and/or signs, including jaundice and duodenal obstruction [28–31]. ACP is distinguished from recurrent acute pancreatitis by the diagnosis of CP prior to ACP. The authors do, however, appreciate this can be difficult in the clinical setting.

Question 3: What is the incidence of ACP?

Answer: The incidence of ACP is difficult to accurately determine because of the lack of a consistent definition in the literature.
Quality assessment: Very low
Recommendation: Conditional
Agreement: Strong

Commentary: There are no reliable data to determine the incidence of ACP. This stems from the lack of a universally accepted definition of ACP. The literature indicates an increase in the diagnosis of ACP during emergency department visits [2] and the incidence of ACP appears to be increasing relative to AP [33]. This might reflect a true increase in the incidence of ACP or alternatively an increased awareness of ACP, and improved diagnostic accuracy due to the more widespread use of cross-sectional imaging modalities. About 12–14% of the admissions for acute pancreatic inflammation are in patients with CP [2,33,34]. A small cohort study

Acute on chronic pancreatitis	**Definition**	An acute worsening of the inflammatory process associated with CP, resulting in a deterioration of the patient's clinical condition, typically resulting in increased pancreatic pain	
		Known CP	Previously unknown CP
	Diagnostic criteria	Typical pancreatic pain + Amylase / lipase > 3x upper limit of normal or Typical pancreatic pain or deterioration in clinical condition + Cross-sectional imaging showing acute pancreatic inflammation	Cross-sectional imaging with: Criteria of CP + Acute pancreatic inflammation
Painfull exacerbation	**Definition**	Acute worsening of the chronic pain syndrome associated with CP, without overt inflammation	
	Diagnostic criteria	Onset or worsening of abdominal pain that require admission in emergency department, without fulfilling ACP criteria	

Fig. 2. Summary of definition and diagnostic criteria of acute on chronic pancreatitis and painful exacerbation of chronic pancreatitis. CP: chronic pancreatitis. ACP: acute on chronic pancreatitis.

of patients with alcohol related CP found an average of 2 (and a maximum of 5) episodes of ACP over a two-year period [35]. In contrast, in a retrospective study with the duration of 20 years, of 1415 patients with CP only 3.5% were diagnosed with ACP [36]. Given that there was no definition or diagnostic criteria for ACP in these two studies, it is difficult to draw any meaningful incidence estimate from these conflicting results.

Question 4: What are the risk factors for ACP?
Answer: Alcohol intake is a risk factor for ACP episodes, whereas the contribution of smoking and main pancreatic duct obstruction is not known.
Quality assessment: Very low
Recommendation: Conditional
Agreement: Strong

Commentary: The lack of an agreed definition of ACP makes it difficult to determine whether any data on risk factors are in reference to acute pancreatic inflammation or to an increase in pain or both. Alcohol is known to be associated with inflammatory complications of CP [27] and some authors conclude that alcohol consumption is an independent risk factor for episodes of ACP [37,38]. Alcohol abstinence appears to protect against ACP [39]. There is some evidence to suggest that alcohol preferentially induces ACP rather than AP [40,41]. This evidence suggests that abstinence from alcohol will decrease the number of ACP episodes. Also, smoking may increase the number of "acute exacerbations" (a term used by the Hungarian Pancreatitis Study Group to describe what is assumed to be an ACP, but due to lack of consensus on description this is not clear) [37]. Olesen et al. showed that smoking was associated with development of fibrosis-related complications, but not to ACP [27]. Turner et al. showed that patients often increased their intake of alcohol and coffee prior to an ACP episode [42]. Another possible risk factor for ACP is main pancreatic duct obstruction [43–45] but, again, it is difficult to distinguish between an ACP episode and an aggravation of the underlying chronic pain syndrome without an overt inflammatory response. Well-designed studies, including a clear distinction between episodes of ACP and aggravation of the chronic pain syndrome associated with CP, are needed to evaluate these putative risk factors. While evidence is lacking regarding other risk factors, abstinence and control of all known risk factors for CP in general should be recommended as it may reduce the frequency of ACP episodes and decrease risk of disease progression towards end-stage CP.

Question 5: What are the symptoms and signs of ACP?
Answer: Although pain is the dominant symptom of ACP, non-specific symptoms or signs such as vomiting or jaundice may be seen. Despite being rare, a diagnosis of ACP in the appropriate clinical setting should not be discarded based on the absence of pain.
Quality assessment: Low
Recommendation: Conditional
Agreement: Strong

Commentary: The typical symptoms and signs in patients with ACP overlap with those of AP [46]. The dominant symptom is typically pancreatic type abdominal pain (acute onset, epigastric and often radiating to the mid-back). However, patients with ACP may, in rare cases, present without pain and exhibit atypical or unspecific symptoms and/or signs. Hence, patients may present with vomiting, especially those with groove pancreatitis [47], or with transient jaundice during ACP episodes [48]. This may be due to pancreatic head swelling accompanying the inflammatory process, unlike persistent jaundice of chronic pancreatitis due to fibrosis [49]. There are also case reports of episodes of ACP without abdominal pain, where the patients presented subcutaneous nodules of panniculitis [28,31] or abnormal electrocardiographic findings [29].

Question 6: Are serum markers useful for diagnosing ACP?
Answer: Serum lipase should be preferred as serum marker to aid the diagnose ACP but, in case of unavailability, serum amylase can also be used. Serum levels of both lipase and amylase less than 3 times the upper limit of normal does not exclude ACP. Additional biomarkers might aid in more accurate diagnosis of ACP but require further validation.
Quality assessment: Low
Recommendation: Conditional
Agreement: Strong

Commentary: The diagnosis of AP is based on the Revised Atlanta Classification [7] where two of three criteria are required. These are typical pancreatic pain, an increase in the level of serum amylase or lipase to over three times the upper limit of normal and/or radiological evidence of AP. There is some agreement that smaller increases in serum pancreatic enzymes could be accepted for the diagnosis of ACP [50–55] which is consistent with a decreased acinar cell mass, secondary to the fibroinflammatory process and pancreatic atrophy associated with CP [56]. In a study of ACP patients, serum amylase and lipase levels were increased to at least three times the upper limit of normal in only 20% and 60% of episodes and were within normal range in 36% and 24%, respectively [5]. Despite these findings, the panel consider that there is insufficient evidence to support a lower diagnostic threshold from that used in AP (Fig. 2). While both amylase and lipase levels can be within normal range in ACP, it appears that lipase is a more sensitive diagnostic marker of ACP [53]. This is supported by the finding that CP tissue shows a greater decline in amylase activity compared with lipase activity (91% vs 26%) [51]. This is also supported by studies suggesting that a lipase/amylase ratio > 2–3 is indicative of ACP [57,58] and points to lipase being more accurate for diagnosing ACP.

Other biomarkers might contribute to the diagnosis of ACP, but they all require further validation. Urine trypsinogen was found to be useful for identifying pancreatitis in patients with pancreatic insufficiency in the presence of normal amylase or lipase levels [59]. The value of this biomarker in ACP is not well established. Other serum markers include carbohydrate antigen 19-9 (CA 19-9) which can be elevated in "acute exacerbations" of CP [60], but can also be elevated in cancer and cholangitis. Because CA 19-9 is not specific for ACP and 10% of the population cannot express this biomarker, it is unlikely to be useful as a diagnostic marker for ACP. It has been found that the acute phase protein ceruloplasmin can be significantly increased in ACP [61], probably reflecting the acute inflammatory process in the pancreas. It has also been noted that there is a close correlation between marked eosinophilia and ACP, but the diagnostic value has yet to be determined [62]. Other inflammatory markers such as C reactive protein and pro-inflammatory cytokines have not been shown to increase the accuracy of diagnosing ACP.

Question 7: Is cross-sectional imaging useful to diagnose ACP in a patient with CP and worsening of pain?
Answer: Cross-sectional imaging should be used to support the diagnosis of ACP and rule out complications or other conditions in CP patients.
Quality assessment: Low
Recommendation: Conditional
Agreement: Strong

Commentary: Worsening pain in a patient with CP can be due to ACP, but might also be due to a complication of CP (e.g., development of a pseudocyst, ductal obstruction from a stone or stricture, inflammatory mass or malignancy), other diseases causing abdominal pain unrelated to CP or due to an increase in pain associated with a chronic pain syndrome. Cross-sectional imaging is indicated when there is a strong clinical suspicion of ACP and pancreatic enzymes are <3 times upper limit of normal or when complications of CP are suspected. This approach differs from the recommendation in AP [7], where cross-sectional imaging is not usually recommended in the early phase of uncomplicated AP. In patients with CP and suspicion of ACP, the most appropriate imaging modality is contrast enhanced computed tomography (CT) scan [63]. Magnetic resonance imaging can also be used to diagnose/rule out ACP and address ductal/cystic and potential necrotic inflammatory changes in more details. Ultrasonography is used in some centres to diagnose ACP, but this is highly operator-dependent and often of limited valued due to bowel gas shadows obscuring some or all of the pancreas [64]. Endoscopic ultrasonography can overcome this limitation but is invasive and can be unpleasant for patients, especially in the acute phase, and requires considerable expertise which hinders a wider application. To improve the accuracy of diagnosing ACP it is important to compare any images with previous studies to establish that the findings observed represent acute inflammatory changes in a patient with pre-existing CP morphology. If cross-sectional imaging does not suggest ACP, signs of complications of CP or other abdominal pathology, a worsening of the chronic pain syndrome (without overt inflammation) should be assumed and the term "painful exacerbation of CP" should be used rather than ACP (Fig. 3).

Question 8: Is cross-sectional imaging more accurate than serum levels of pancreatic enzymes for diagnosing ACP?

Answer: Cross-sectional imaging is more accurate than serum levels of pancreatic enzymes for the diagnosis of ACP.
Quality assessment: Very Low
Recommendation: Conditional
Agreement: Strong

Commentary: It is well recognized that pancreatic enzymes can be elevated for many reasons other than ACP [65] and ACP may not result in the same degree of elevation of pancreatic enzymes as in AP (see question 6). Cross-sectional imaging in patients with ACP is able to detect acute inflammatory pancreatic changes, including increased pancreatic and peri-pancreatic oedema, inflammation in surrounding tissue ('dirty fat'), inflammatory masses, acute fluid collections, acute splanchnic thrombosis (including splenic, portal and/or superior mesenteric veins) and can be used to assess the severity of ACP [63] (Fig. 4). Importantly, when radiological criteria of CP are present, cross-sectional imaging enable the distinction between ACP from AP.

Notwithstanding the need for imaging to diagnose ACP in the absence of elevated pancreatic enzymes, any request for a contrast-enhanced CT scan should take into consideration the clinical picture of the patient and recent observations, to balance the correct diagnosis against the risk of excessive radiation exposure. Since some patients experience frequent exacerbations of symptoms for which they are referred to the hospital, cross-sectional imaging should only be pursued when a definitive diagnosis and severity assessment of ACP will alter the treatment approach. Hence, we suggest avoiding repetitive CT scans, in recently admitted patients, when symptoms are similar to recent admissions and appropriate imaging has confirmed an ACP and excluded other complications.

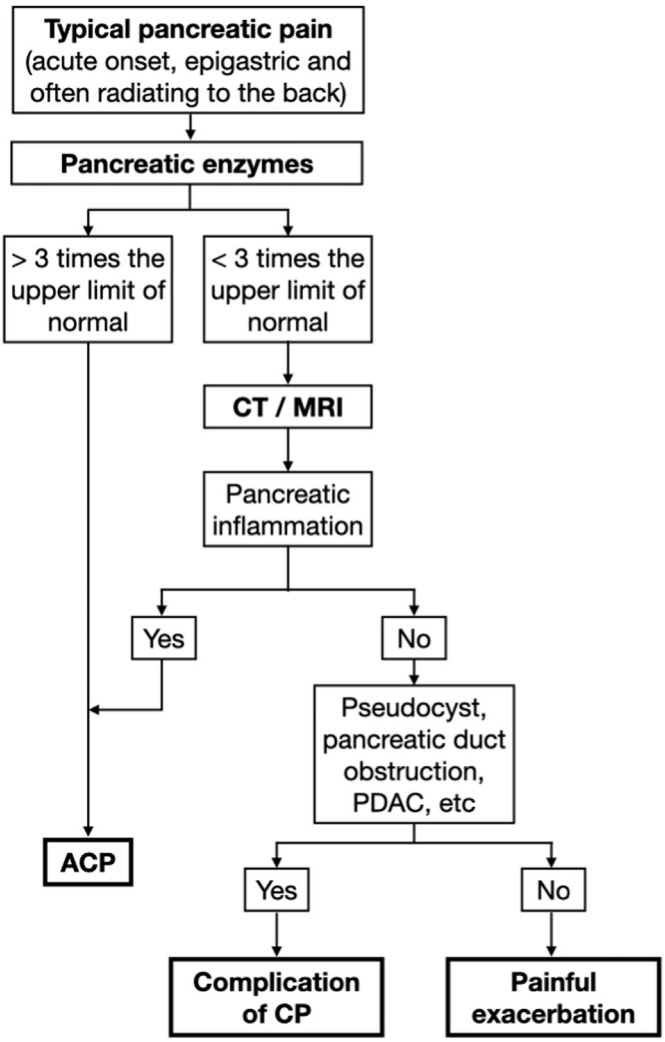

Fig. 3. Flowchart suggesting the diagnostic approach to chronic pancreatitis patient presenting with abdominal pain and suspicion of acute on chronic pancreatitis. CT: Computed Tomography; MRI: Magnetic resonance imaging; ACP: acute on chronic pancreatitis; CP: chronic pancreatitis; PDAC: Pancreatic ductal adenocarcinoma.

Question 9: Is the severity of ACP comparable to AP in patients without CP?

Answer: ACP tends to be less severe compared with AP.
Quality assessment: Very Low
Recommendation: Conditional
Agreement: Strong

Commentary: According to the Revised Atlanta classification [7], severity is based on presence of organ failure (transient or persistent), local complications (peripancreatic acute fluid collections, acute necrotic collections, pseudocyst and walled off necrosis) or systemic complications (exacerbations of underlying comorbidities). These factors have not been systematically studied in patients with ACP and, as a result, there are no specific guidelines or severity classification that can be applied to patients with ACP. By default, there is a tendency to use the categories of severity for AP even though these were not designed or validated for this purpose.

There is a common understanding that patients with ACP have a more favourable outcome compared to patients with AP [66–71]. It is assumed that pancreatic fibrosis has a role in limiting acinar cell necrosis [72,73]. Factors associated with increased severity in ACP

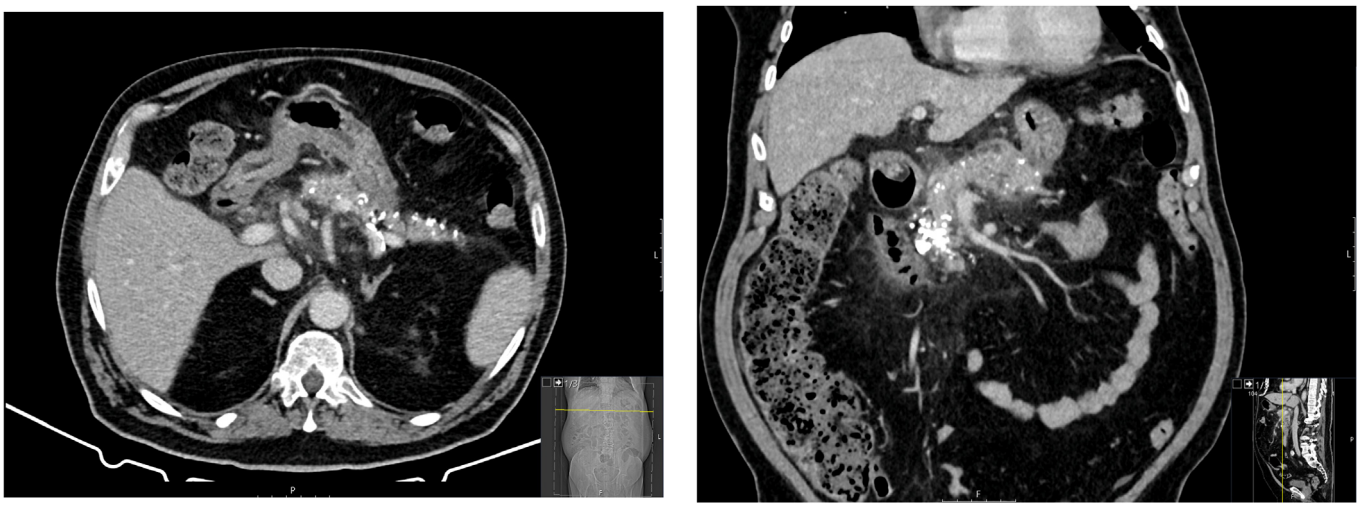

Fig. 4. Contrast-enhanced abdominal computed tomography with axial and coronal views of a patient with known chronic pancreatitis (moderate gland atrophy and parenchymal calcifications) and co-existing acute inflammation with interstitial oedematous pancreatitis of the surrounding peripancreatic fat.

are age, comorbidity and weight loss [33]. According to Akshintala et al., patients with ACP have lower rates of multisystem organ failure, need for intensive care unit, and mortality [33]. However, in a study from Weitz et al. comparing ACP with AP, renal failure and the need for intensive care unit were more frequent in patients with ACP, even though there was a lower rate of severe episodes in that cohort [68]. There are a number of pancreas related complications that are common in ACP. For example, in a study from Kim and Kim [34], the incidence of pancreatic pseudocysts in ACP was 41.8%, compared with 14.6% in AP. The higher incidence of pseudocysts in ACP is probably due to the fact that they often are chronic pseudocysts that usually persists for very long periods in CP. There is also a consensus among experts, that necrotic parenchyma is rarely seen on a background of well-established CP and, since the imaging changes seen in ACP are typically mild with only minimal necrosis, the use of the Revised Atlanta Classification [7] is often not appropriate. Furthermore, ACP is not expected to be seen in end-stage CP where the inflammation disappears and only the fibrotic process remains. Further research is required to evaluate the rate of organ failure, systemic and local complications in ACP.

Question 10: What is the prognosis of ACP?
Answer: Overall, episodes of ACP are associated with a lower mortality than episodes of AP without CP.
Quality assessment: Low
Recommendation: Conditional
Agreement: Strong

Commentary: In the study from Akshintala et al., after adjusting for all risk factors for mortality, patients with ACP were 53% less likely to die (in-hospital mortality) when compared to patients with AP without underlying CP [33]. Furthermore, in a large Danish cohort of CP patients, ACP had no influence on overall survival [74]. Patients with CP usually die from extra-pancreatic causes (Ochi, 1999, cited in Sakagami, 2004) [75–77] and ACP is rarely a cause of death.

4. Conclusions

This systematic literature review revealed a paucity of evidence relating specifically to ACP (Fig. 1) and it highlights a number of knowledge gaps that require further research. ACP is a common and important condition, but has lacked a universally accepted definition which in turn has impeded studies to determine its incidence, clinical course and prognosis. There is a need to formally evaluate the proposed diagnostic criteria and to develop a severity scoring system that is specific to ACP. Meanwhile, this position statement, based on low level evidence and expert opinions, serves as a foundation for future work to improve the accuracy of diagnosis, the quality of care of patients and stimulate future research to address the knowledge gaps about ACP.

Conflicts of interest and source of funding

The authors declare that they have no competing interests.

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