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Review Article

Unveiling the Deregulated Pathophysiology for Precision Diagnostics and Personalized Clinical Management of Acute on Chronic Pancreatitis: A Narrative Review

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Abstract

Acute on chronic pancreatitis (ACP) is a transitional condition between acute and chronic pancreatitis, which often gets missed due to overlapping clinical features with other pancreatitis states. The low sensitivity of standard tests like serum amylase and lipase, leading to underreported epidemiological data. This review examines the current knowledge on ACP's pathophysiology, risk factors, and molecular diagnostic markers differentiating it as a separate entity. ACP clinically presents as ductal obstruction, premature enzyme activation, acinar cell injury, oxidative stress, or / and inflammation. Over the time, it can lead to complications like formation of pseudocyst(s) and type 3 pancreatogenic diabetes mellitus (T3cDM) which could be life threatening, if not treated properly. Sometimes, ACP might also progress to CP, thereby affecting the patients' quality of life. Literature survey from 2007 to 2025, identifies sphincter of Oddi dysfunction, chronic alcohol consumption, smoking, and medications like hydrochlorothiazide and ACE inhibitors, as accountable factors. Limited studies available highlight a handful of molecular markers, like oxidative stress indicators and inflammatory cytokines as predictors of ACP events, having a potential for improving diagnostic accuracy, but more laboratory studies are needed to validate their utility for addressing the critical gaps. In context to the above scenario, a holistic approach needs to be adopted to deal with ACP inclusive of novel molecular markers for precision diagnosis of ACP events and risk prediction, followed by personalized therapeutic interventions to target inflammation, and other co-morbidities to improve outcomes in ACP patients.

Keywords: Inflammation; oxidative stress; biomarkers; cytokines; pancreatitis

Abbreviations:

ACP: Acute on chronic pancreatitis
AP: Acute Pancreatitis
CP: Chronic Pancreatitis
SO: Sphincter of Oddi
MDA: Malondialdehyde
4-HNE: 4-hydroxynonenal
IL-6: Interleukin-6
IL-17: Interleukin-17
IFN-γ: Interferon- gamma

Introduction:

Acute pancreatitis (AP) and chronic pancreatitis (CP) are known as two distinct forms of pancreatic disorders caused by inflammation occurring in the pancreas [1,2]. Clinically, an intermediate state occurs between AP and CP that is Acute on Chronic Pancreatitis (ACP), a state generally associated with recurrent (≥2) episode of AP. ACP is known to mimic symptoms of AP, such as epigastric pain, nausea and vomiting but differs in the severity of the attack and clinically in the development of increased intra-pancreatic fat in the pancreas [3]. Globally, the exact incidence of ACP is not known but Shah et al. [4] estimated an annual incidence of ACP in the US is 8–10 per 100,000 persons, and its estimated prevalence is 110–140 per 100,000 persons per

year. In a developing country like India, official data regarding the incidence of pancreatitis is still not available. In support, Krishnan et al. [5] conducted a multicenter study in India and observed that no specific data has been reported on incidence of ACP. However, the incidence is on the rise as information on sporadic cases is available at the gastroenterology departments of various healthcare centres they studied. Most likely, since there are no specific guidelines available in revised Atlanta classification (2012) for diagnosing ACP [6]; therefore, the incidence of ACP is not separately recorded in the literature and hence this entity is often overlooked. The conventional biomarkers, serum amylase and lipase, are used for pathological diagnosis of pancreatitis but they are not reliable diagnostic markers for differentiation of pancreatitis states. It has been observed that during episodes of ACP, the diagnostic performance of serum amylase and lipase deviates, that it decreases from the standard upper limit which is expected to be 3 times higher [7]. It has been also reported in a study conducted by Li and co-workers (2023) that in only 20% of cases of ACP, the levels of serum amylase and lipase were three times higher than the upper limit of the normal range [8]. Thus, failing in the accurate diagnosis of the state of ACP is responsible for missing incidence of such patients in epidemiological record. Hence, this review aims to define and highlight the clinical state of ACP and its deregulated pathophysiology. Additionally, it presents an overview of the factors that contribute to the development of this state and its related co-morbidities during the progression of ACP leading to diverse clinical outcomes, along with molecular markers that can aid in non-invasive early diagnosis of ACP.

Identifying Key Factors as Triggers

The appropriate clinical intervention received by the patients with AP often result in the resolution of their diseased state. However, when AP does not resolve, there are specific triggers, such as sphincter oddi (SO) dysfunction, alcohol, smoking, and certain medications, that lead to recurrent episodes of ACP. There are case reports and small cohort studies to show the association of risk factors with the recurrent episodes of ACP. A case study conducted by Shayesteh and group [9], involved a 42-year old female suffering from acute pancreatitis with a SO dysfunction who experienced multiple episodes of ACP after she underwent sphincterectomy. In another case study conducted by Raut and his colleagues [10], the detrimental effects of chronic alcoholism on the pancreas was highlighted that lead to episodes of ACP. This study was on a 28-year-old patient with a 12-year history of chronic alcoholism and recurrent episodes of ACP, between 2022-23. The recurrent ACP episodes led to the development of chronic calcified pancreatitis and a pseudocyst. Way back in 2009, Yadav and his colleagues [11] assessed 460 ACP patients with a habit of smoking a pack of cigarette per day and found that these patients had an increased risk for the recurrence of ACP were increased to 13.6%. In a retrospective study conducted by Sun et al. [12], considered 81 ACP patients, they found that smoking 10 cigarettes daily was associated with a 32.2% increased risk of recurrent ACP episodes. A recent case report by Linkous and his colleagues [13] reported a case of a 58-year-old African female patient admitted with a previous history of pancreatitis. The healthcare providers discontinued the drug hydrochlorothiazide (HCTZ) being used by her for urinary complications. However, after 16 months, the patient had another episode of ACP, due to HCTZ, which she kept consuming without medical consultation.

The studies mentioned above demonstrate the role of triggers in initiating a recurrent episode of ACP. However, comprehensive understanding of the underlying pathophysiology is critical for the accurate diagnosis of patients with ACP.

Deregulated pathophysiology of ACP

The trigger(s) associated with ACP lead to obstruction in the pancreatic duct and hypertension in the intraductal region of the pancreas. The SO dysfunction is mainly due to narrowing of the sphincter or an abnormal spasm (dyskinesia) [14]. The inflammation generated during an episode of ACP, is primarily due to the release of pancreatic juices that flow into the duodenum and induce bile reflux. This further, ushers to oxidative stress and inflammation which increases the release of inflammatory cytokines and leads to three different types of SO dysfunction [15]. Type 1 dysfunction patients suffer from severe abdominal pain. Due to the dilation of the common bile and/or main (central) pancreatic duct, prolonged drainage of higher levels of serum pancreatic enzymes takes place. Type II dysfunction occurs in patients having symptoms like upper abdominal pain, which radiates to the back along with elevated liver enzymes. Patients with type III dysfunction present only abdominal pain with no rise in serum pancreatic enzymes [16], and therefore, an episode of ACP might be overlooked when it recurs.

The Nardi test is considered as gold standard examination to assess dysfunction of the SO. This test involves administering morphine and neostigmine simultaneously. Morphine causes contractions in the bile ducts, while neostigmine tightens the Sphincter of Oddi. If a patient's symptoms are related to SO dysfunction, the increased pressure from the bile being pushed into the contracted sphincter will replicate the symptoms [17]. But this test is generally not undertaken because post examination it raises the risk of an episode of ACP in 27% of the patients [18].

The above discussed triggers of ACP also lead to abnormal calcium signaling which results in elevated levels of intracellular calcium in the acinar cells along with oxidative stress. Consequently, the higher calcium levels trigger a premature activation and conversion of trypsinogen into trypsin within the pancreatic acini and not in the pancreatic duct lumen as in a canonical pathway. This abnormal activation of trypsin within the acinar cells leads to acinar injury or damage along with inflammation during ACP episode [19]. The role of trypsin in ACP pathophysiology is significant, as it is a key enzyme involved in protein digestion, and its premature activation can lead to tissue damage and inflammation [20]. Furthermore, the inflammation exacerbates complications such as pancreatic fluid accumulation during the second episode of ACP and the formation of a pseudocyst in the third episode of ACP [21]. Moreover, when the pancreatic tissue (acinar cells) gets damaged, enzymes drain out from the damaged acinar cells and get collected in the surrounding tissue, leading to peri-pancreatic fluid collection. When the accumulated fluid is not drained through surgical intervention, it results in a pancreatic pseudocyst (Fig1). The unresolved pseudocysts can rupture into the peritoneum (abdominal cavity) and cause pancreatic ascites or haemorrhagic shock, which may result mortality in 40% of ACP patients [22].

Molecular markers for diagnosis of ACP

The conventional biomarkers, serum amylase and lipase, are not considered sensitive enough for monitoring complications or organ damage occurring during ACP. Also, the invasive Nardi test is troublesome during the examination of SO dysfunction and may result in recurrence of ACP. Therefore, to address the pathophysiology involving oxidative stress and inflammation the biomarkers for monitoring these phases can be of use during an episode of ACP. In literature, few studies have been conducted on the markers associated with oxidative stress and inflammation which could aid in governing the plausible event of ACP to occur. In a study conducted

by Bhopana et al. [23], ACP patients and controls were assessed for their oxidative stress and antioxidant levels. It was reported that during recurrence of an episode of ACP the reduced levels of malondialdehyde (MDA) and 4-hydroxynoneal (HNE) in serum samples of ACP patients corresponded to their increased oxidative stress and decreased antioxidant levels.

The release of cytokines marks as a sign for an inflammation occurring during ACP. Pendharkar et al., [24] examined ACP patients with and without hyperglycemia for their inflammatory cytokines and incretin levels. His group found that IL-6 levels were increased in serum whereas GIP (glucose-dependent insulinotropic polypeptide), an incretin marker was decreased in ACP patients with hyperglycemia. Park and his colleagues [25] conducted a study in which the circulating cytokine levels of IFN-gamma, IL-13, IL-1 beta IL-27 and IL-31 showed higher levels in ACP patients when compared with the controls. Similarly, Lee et al. [26] also assessed IL-17 levels in the serum of ACP patients, which were higher in ACP patients than in the controls. A comprehensive overview of the study cohort, methodology adopted and salient findings are provided in (Table 1).

S. No.	Assessment of Markers	Cohort	Study region	Method	Findings	References
	Oxidative stress markers					
1.	The markers, 4-hydroxynonenol (4-HNE), malondialdehyde (MDA) were assessed along with antioxidant levels using Ferric reducing ability of plasma (FRAP) assay, glutathione peroxidase, Vitamin C levels were evaluated	50 ACP patients 50 controls	**India**	**Enzyme linked immunosorbent assay**	Higher plasma levels of 4-HNE and MDA; lower antioxidant levels suggested that oxidative stress plays a key role in causing recurrent episodes of ACP in patients.	**[23]**
Inflammatory markers						
2.	Evaluation of following markers was done: Pro-inflammatory markers-IL-6, TNF and MCP-1 and gut hormones – cholecystokinin, gastric inhibitory peptide, ghrelin, glicentin, glucagon like peptide-1 (GLP-1), oxyntomodulin, peptide YY, secretin and vasoactive intestinal peptide	ACP with hyperglycemia-19 patients ACP without hyperglycemia-64 patients	**New Zealand**	**Enzyme linked immunosorbent assay**	Increased IL-6 levels and decreased GIP levels in ACP patients with hyperglycemia.	**[24]**
3.	62 analytes inclusive of cytokines/ chemokines and adhesion molecules	ACP- 20 patients, CP patients-20 Controls-41individuals	**USA**	**Multiplex immunoassay**	IFNγ, IL-13, IL-1b, IL-27, IL-31, and FASL were expressed in ACP patients. The biomarker levels were higher than CP and controls.	**[25]**
4.	92 analytes inclusive of cytokines and chemokines	ACP- 56 patients Controls - 56	**USA**	**Multiplex immunoassay**	IL-7 levels in serum of ACP patients were higher when compared with controls	**[26]**

Abbreviations: ACP: Acute on chronic pancreatitis, AP: Acute Pancreatitis,CP: Chronic Pancreatitis, SO:Sphincter of Oddi, MDA:Malondialdehyde, 4-HNE: 4-hydroxynonenal ,IL-6:Interleukin-6,IL-17: Interleukin-17,IFN-γ:Interferon- gamma

Table 1: Studies on biomarkers available in the literature for assessment and diagnosis of an ACP event.

These studies on ACP reveal the key biomarkers that can be developed clinically for a non-invasive diagnosis. Elevated oxidative stress markers (4-HNE, MDA) and reduced antioxidant levels in Indian cohorts indicate that oxidative stress drives recurrent ACP episodes [23]. The increased IL-6 levels and decreased GIP in ACP with hyperglycemia suggest inflammatory and metabolic dysregulation [24]. Multiplex immunoassays in US studies show elevated IFNγ, IL-13, IL-1b, IL-27, IL-31, FASL, and IL-7 in ACP than CP [25,26], highlighting distinct cytokine/chemokine profiles as identifiers. Hence, these biomarkers could enhance non-invasive ACP diagnosis and monitoring.

Varied Physiological and Clinical Outcomes of ACP

Recurrent episodes of ACP lead to loss of endocrine and exocrine function of the pancreas and may result in the development of type 3c diabetes (T3cDM), pancreatic pseudocysts or progression to CP.

Loss of endocrine function

Patients with ACP may gradually develop loss of the endocrine function due to the insults caused during an episode of ACP, resulting in damage to the endocrine cells and may lead to pancreatic cancer also. Specifically, it is the loss of β-cells in the pancreas that regulate the production and release of insulin and glucose, facilitating glucose metabolism in the body. This β-cell

loss initiates an inflammatory response and releases IL-6 [27], which impairs the phosphorylation of insulin receptors and insulin receptor substrate. This results in pancreatogenic or type 3c diabetes (T3cDM), characterized by insulin resistance and its deficiency. In a study conducted by Das et al. [28] it has been reported that there was a 40% prevalence of T3cDM after ACP. Another study conducted by Shen et al. [29] concluded that the overall risk of T3cDM increases two-fold after the second episode of ACP. During T3cDM, there is a loss of secretion of the glucoregulatory hormones produced by the islets (insulin, glucagon, and pancreatic polypeptide). It also contributes to abnormal secretion of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which are adversely affected by the loss of exocrine function as well, because exocrine cells also get damaged during ACP episode [30] (Fig.2). This can result in fluctuations of glycemic levels in patients that can be fatal, if not addressed immediately [31].

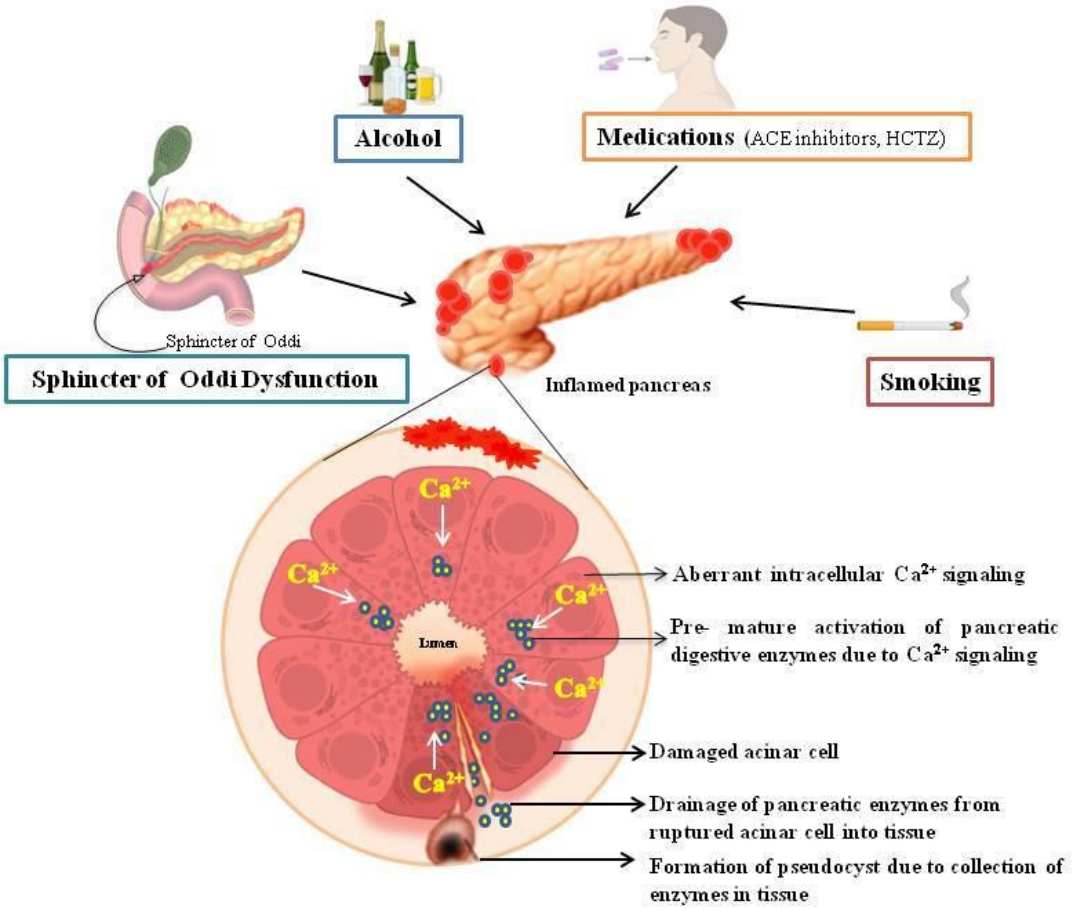

Figure 1: Triggers causing injury and inflammation in the pancreas, leading to aberrant calcium signaling during an episode of acute on chronic pancreatitis (ACP).

Loss of exocrine function

Exocrine insufficiency in ACP occurs when there is damage to exocrine cells due to inadequate secretion of pancreatic enzymes to maintain normal digestion. Progressive exocrine dysfunction results in the generation of inflammation that disrupts the digestion of fats due to lipase deficiency. This results in impaired absorption of the fat-soluble vitamins A, D, E, and K [32]. Vitamin D deficiency additionally leads to a loss of bone density, ultimately resulting in osteoporosis (Fig 2). The sequel to loss of fat digestion is an impaired incretin-mediated insulin release due to altered GLP-1 secretion from the proximal and distal small bowel in ACP patients [33]. The loss of endocrine and exocrine functions, further add to burden of disease in ACP. The other clinical scenario of exocrine dysfunction is the formation of fluid filled pseudocyst. The repeated episodes of ACP lead to collection of digestive enzymes into a sac walled off by fibrous tissue. A spontaneous resolution of pseudocyst can occur in patients who are given conservative management, such as low-fat diet and treatment through analgesics and antiemetics. But the unresolved pseudocyst can lead to the complications like rupture of the pseudocyst and flow of its fluid into the peritoneal cavity causing increased intra-abdominal pressure, abdominal pain leading to a new organ failure or even death [34].

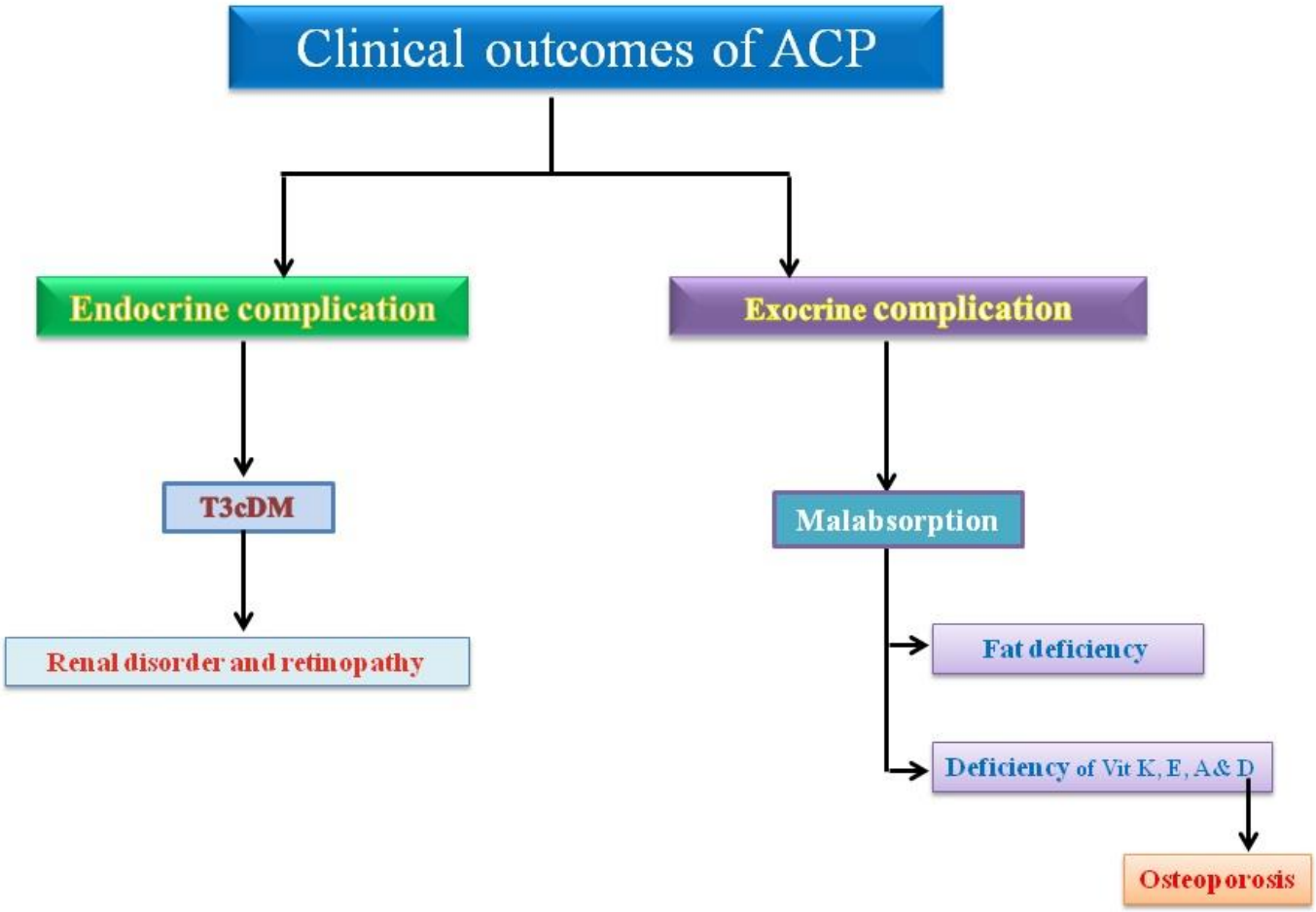

Figure 2: Flowchart showing complications arising after repeated episodes of ACP.

Personalized intervention for management of ACP

Diagnosis of ACP based on molecular markers is precise and can enable targeted therapeutic interventions to halt the inflammatory flares and prevent progression to CP [35]. The management includes surgical and/or endoscopic interventions for patients with unresolved pancreatic fluid pseudocysts using lumen opposing metal stent to prevent rupture of the fluid to mitigate systemic inflammation and to maintain gut barrier function [22]. Pancreatic enzyme replacement therapy (PERT) is used to address emerging exocrine insufficiency during T3cDM and improve glycemic control [36, 37]. Biomarker-guided immunomodulation using drugs such as tocilizumab for lowering high IL-6 levels or Anakinra for targeting elevated IL-1β and

NLRP3 inflammasome activation, can dampen cytokine storms and pyroptosis to avert fibrosis escalation. Emerging anti-fibrotic agents like pirfenidone or TLY012, alongside lifestyle modifications such as alcohol and smoking cessation, can further retard progression by controlling oxidative stress and irreversible pancreatic damage due to ACP [38].

Conclusion

To summarize, ACP, an often-missed clinical entity, is characterized by repeated episodes of pancreatic inflammation and injury, with significant implications for increased morbidity and poor quality of life. The risk of developing ACP is influenced by factors like SO dysfunction, smoking, alcohol consumption and certain medications and therefore, understanding the underlying patho-physiology is essential since recurrent episodes can cause pancreatic tissue damage. Conventional biochemical tests fail to diagnose the onset of an episode of ACP or predict its complications. Our analysis of gaps in research suggests that a diagnostic panel of molecular markers should be established for early intervention. Since limited studies are available on molecular markers, more multi-centric validations are also advocated for instituting their clinical utility. The holistic approach for clinically addressing ACP should include identification of etiology & pathophysiology of the patient using molecular precision diagnosis and risk prediction of possible complications followed by personalized intervention for better management of ACP.

Statement & Declarations

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