Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Review

A critical evaluation of biochemical markers for the diagnosis of acute pancreatitis

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Article Info

Article history:

Received: April 30, 2024
Accepted: December 23, 2024
Published: January 31, 2025

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Abstract

Acute pancreatitis (AP) is a common but poorly understood gastrointestinal illness. One explanation for this lack of awareness is the absence of clear recommendations on the use of biochemical markers to identify this illness. This is because knowledge in this field is always expanding. Serum amylase and lipase are two extensively utilized biochemical indicators in the diagnosis of AP. The lack of agreement on the optimal use of these markers, notably amylase and lipase, has an impact on diagnostic outcomes. Through a critical study of the current literatures, this review intends to explore in depth the use of biochemical markers in the diagnosis of AP. A comprehensive review of the literature had a glance at biochemical indicators in the context of AP diagnosis, diving into topics including pancreatic anatomy, functions, pathology, mechanisms of AP, etiologies, symptoms, and also diagnostic approaches. This review revealed areas of agreement and disagreement about biochemical indicators in the diagnosis of AP, as well as potential future research directions.

Keywords: Acute pancreatitis, Biochemical markers, Serum amylase and lipase, Diagnosis, Pancreatic pathology.

1. Introduction

Acute pancreatitis (AP) is a life-threatening condition necessitating immediate medical attention. Swift diagnosis and medical intervention are paramount. Despite being one of the most prevalent gastrointestinal tract disorders [1], AP remains partially enigmatic [2], leading to considerable complexity in clinical diagnosis. Biochemical assessments are integral to the diagnostic procedure. A range of biochemical markers can be measured to assist in AP diagnosis, with serum amylase and lipase being the most prevalent, though there appear to be inconsistencies within clinical application without a universally accepted standard. This review provides a comprehensive examination of the utilization of biochemical markers for AP diagnosis, achieved through a meticulous evaluation of existing literature. This literature demonstrates substantial consensus concerning the structure and role of the pancreas. It has been characterized with respect to its general anatomical location, shape, intricate duct system, and its adjacency to neighboring organs. The pancreas assumes a critical function in digestion and regulation of blood sugar levels via its endocrine and exocrine activities. Adequate comprehension exists regarding pancreatic pathology and the spectrum of disorders linked to this organ.

1.1. Physiology of the pancreas

Situated in the posterior section of the upper abdomen, nestled behind the stomach and intestines while facing the spine, is the pancreas, a gland of considerable importance [3,4].This organ holds a pivotal role within the digestive framework, while simultaneously exerting influence on other systems within the human body. With a distinctive configuration, the pancreas spans approximately 6 inches from one extremity to the other, presenting a curvature on one end and a tapered point on the opposite end (Figure 1) [5]. For diagnostic purposes, it has been anatomically segmented into several components, encompassing the head, uncinate process, neck, body, and tail [5]. The head, characterized by its curved structure, aligns itself with the curvature of the duodenum. An integral component of the head is the uncinate process, which establishes a connection with the mesenteric artery and the superior mesenteric vein. Bridging the head to the body, the neck serves as the intermediary, while the body constitutes the central

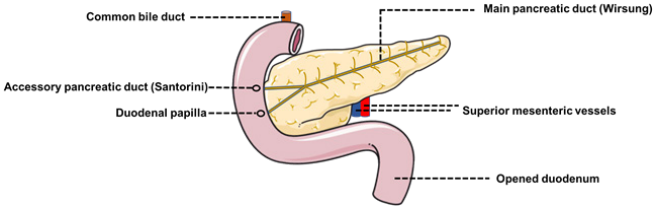

Fig. 1. The duct system of the pancreas. Figure adapted from [5].

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Doi: http://dx.doi.org/10.14715/cmb/2025.70.1.3

segment of the pancreas. Lastly, the tail, terminating in a pointed configuration, abuts the spleen [5]. The diagnosis of AP revolves around the observation of inflammatory processes affecting these distinct sections of the pancreas.

The pancreas was additionally detailed by [6] as being composed of the principal pancreatic duct, also known as the duct of Wirsung. This duct courses from the tail, traversing through the body, and concluding at the pancreas's head, where the common bile duct gains entry into the second portion of the duodenum by means of the sphincter of Oddi. The supplementary duct, recognized as Santorini, extends from the lower section of the head, anterior to the primary duct, and subsequently opens into the duodenum at a position above it. The evaluation of issues within this intricate ductal system contributes to the diagnostic assessment of AP.

The existing literature has mentioned significant interconnections between the pancreas and neighboring organs. The pancreas's close proximity to other organs is graphically depicted in Figure 2 below, with accessory ducts establishing connections. According to [6], on the anterior side of the pancreas, moving from right to left, one encounters the transverse colon, the lesser sac of the omentum, and the stomach. Positioned at the posterior aspect of the pancreas are the bile duct portal vein, splenic vein, vena cava, aorta, and superior mesenteric artery. Adjacent to the pancreas's left side resides the psoas muscles, kidney, and adrenal gland. The nearness of the pancreas to these neighboring organs introduces the possibility that inflammation within the pancreas can lead to not only pancreatic damage but also complications or adverse effects on these surrounding organs [5]. Additionally, disruptions in the functioning of neighboring organs can impact the normal operations of the pancreas. Conditions like AP can be linked to and exacerbated by issues in these neighboring structures [5]. Therefore, diagnosing AP necessitates a broader perspective that not only concentrates on the pancreas itself but also takes into account its intricate relationships with nearby organs.

2. Function of the pancreas

The pancreas functions as a gland responsible for generating enzymes essential for food digestion and the regulation of blood glucose levels. Despite its weight ranging from approximately 70g to 100g, it possesses the remarkable capability to discharge 200 to 800 ml of pancreatic fluids within a single day [7]. These fluids play a pivotal role in supporting both the exocrine and endocrine functions of the pancreas organ [7].

2.1. Exocrine and endocrine function

Many of the cells within the pancreas, specifically the acinar cells depicted in Figure 3 below, carry out an exocrine role by producing digestive enzymes [7]. The exocrine contents, as identified by [8] as well as [6], encompass substances such as amylase, lipase, trypsin, chymotrypsin, elastase, carboxypeptidase, phospholipase, and various other enzymes. Furthermore, bicarbonate serves the purpose of counteracting stomach acids and the enzymes responsible for breaking down proteins, carbohydrates, and fats [9,10]. The secretion of these enzymes is regulated by factors like cholecystokinin, pancreozymin, secretin, and other agents [11,12]. Deviations in the levels of these enzymes could potentially signify the presence of pancreatic disorders, including AP [13].

The remaining cells fulfill an endocrine role by producing hormones that regulate metabolism upon their release into the bloodstream. As described by [14], a relatively small portion of pancreatic cells, approximately one million in number, are organized into clusters known as islets of Langerhans, depicted in Figure 3. These clusters comprise four distinct cell types including alpha (α), beta (β), gamma (γ), and pancreatic polypeptide (PP) cells which are stimulated by autonomic and peptidergic nerves and responsible for generating hormones that manage metabolic functions [14]. The α cells within these clusters produce glucagon [15], the β cells generate insulin and C-peptide [16], the γ cells yield somatostatin [17], and the PP cells produce enzymes of the same name along with some quantities of gastrin [17]. According to [6], the endocrine operations of the pancreas are managed by the following hormones: insulin, glucagon, pancreatic polypeptide, and somatostatin. These hormone outputs play a crucial role in orchestrating metabolism across the entirety of the body [6]. The release of these substances is meticulously coordinated to collectively influence the metabolism of diverse organs and cells, spanning from adipose tissue to muscles [6]. Any disruption in this coordinated secretion could potentially lead to the development of pancreatic disorders, such as AP and other related health conditions [13].

3. Pathology of the pancreas

Several pancreatic disorders have been identified in the

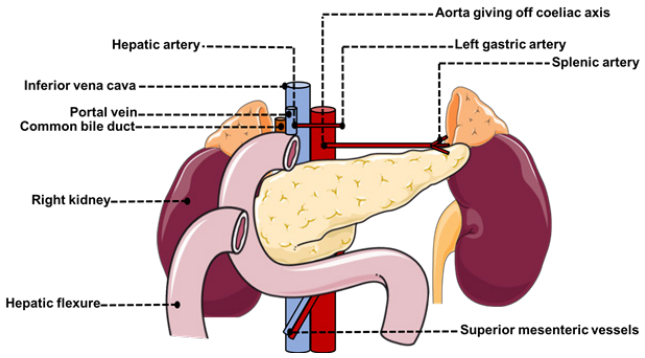

Fig. 2. Principal relations of the pancreas. Figure adapted from [5].

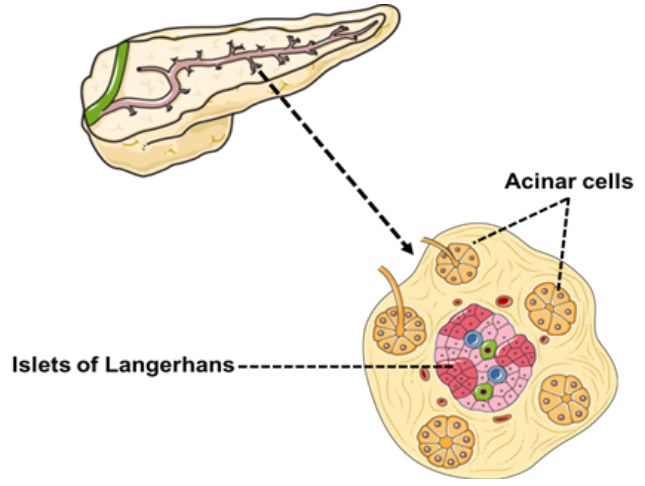

Fig. 3. The cells of pancreas. Acinar cells are responsible for releasing enzymes involved in digestion, while the islets of Langerhans play an important role in producing hormones. Figure adapted from [14].

literature. A slight discrepancy arises when categorizing these pancreatic diseases as either primary or secondary, especially in the context of pancreatic diabetes. Based on the discussions surrounding pancreatic disorders in the literature, primary pancreatic diseases seem to encompass conditions that originate directly within the pancreas or stem from abnormalities in its function. In contrast, secondary pancreatic diseases refer to conditions that develop as a consequence of, or complications arising from, primary pancreatic disorders. Notably, there is no significant contradiction in this regard. The classification relies on the perspective taken in assessing the pathological relationships among pancreatic diseases. However, a consensus exists that various pancreatic disorders are interconnected. The medical diagnosis of one disease often involves considering the contributory, coexisting, or complicating roles of other pancreatic disorders, as well as the exclusion of their effects. Biochemical markers play a valuable role in diagnosing pancreatic diseases, differentiating between them, and elucidating the causal chain of events associated with the interaction among diverse pancreatic disorders [2,18].

Pancreatic diabetes stands out as one of the identified pancreatic diseases in the literature. As highlighted by [6], diabetes ranks as the most prevalent pancreatic disorder, followed by pancreatitis. The onset of pancreatic diabetes is attributed to endocrine insufficiency. The decline in beta cell function and reduced secretion capacity of insulin by the pancreas serve as explanations for the emergence of pancreatic diabetes [6]. Alternative viewpoints presented by other researchers [19,20] position pancreatic diabetes more as a consequential or complicating state resulting from pancreatic disorders like pancreatitis, rather than an inherent primary disorder of the pancreas.

Pancreatic diabetes can manifest as a prolonged complication of pancreatitis. Approximately 40% to 60% of individuals with pancreatitis develop pancreatic diabetes as a complication [21]. Additionally, the presence of diabetes can elevate the susceptibility to severe acute pancreatitis [21]. While there may exist disparities in how diabetes is categorized as a primary pancreatic disease, its connection with other pancreatic disorders, particularly acute pancreatitis, remains pronounced [22]. This interrelation holds significance in the context of diagnosis, severity assessment, and the tracking of disease progression.

Chronic pancreatitis arises when alterations in the pancreas's structure are evident upon examination through a CT scan [6]. The presence of scarring and fibrosis within the pancreas, resulting from previous instances of AP, becomes apparent as observable indications of chronic pancreatitis. These structural changes within the pancreas are enduring and irreversible, potentially escalating the risk of pancreatic cancer [20,21]. Chronic pancreatitis might also be construed as a complication or a long-term consequence of AP [19]. Therefore, the consensus in these literatures might affirm that chronic pancreatitis represents a distinct pancreatic disorder, even though it maintains a close association with AP.

Pancreatic cancer displays a higher occurrence in men compared to women. On a global scale, the rate of pancreatic cancer is 5.5 cases per 100,000 for men and 4.0 cases per 100,000 for women [23]. Pancreatic cancer is regarded as one of the potential outcomes of acute pancreatitis, occasionally manifesting concurrently with the onset of pancreatic diabetes [20,21]. Usually, pancreatic cancer refers to adenocarcinoma, which originates within the pancreatic ducts or in the cells responsible for producing exocrine enzymes [19]. While other forms of cancer can emerge in the pancreas, they are exceedingly rare occurrences, therefore, the precise causative factors behind pancreatic cancer remain uncertain [24]. However, it is understood that gender is not a determinant, while genetics, smoking, obesity, and diabetes stand as risk factors [20]. Yet, the exact degree of influence these factors exert has not been definitively established [24]. While pancreatic cancer can arise as a possible complication of acute pancreatitis, it can be produced from other triggers [24].

Other pancreatic tumors are infrequent, occurring at a rate of 1 for every 500,000 individuals [6]. These tumors originate from the endocrine cells within the pancreas [19]. Instances of uncommon endocrine tumors include insulinoma, acinar carcinoma, lymphoma, and sarcoma [25]. Pancreatic tumors have the potential to induce acute pancreatitis AP by causing bile duct obstruction or disrupting normal pancreatic function [20]. Furthermore, these tumors may serve as contributing factors to the development of AP [19,20].

Pancreatic trauma is an infrequent and challenging-to-diagnose aberrant condition that impacts the pancreas [26]. It can be detected through occurrences of internal bleeding, edema, and infiltration of the soft tissue of the pancreas [19]. If left undiagnosed and untreated, this condition has the potential to give rise to complications, including AP and pancreatic cancer, particularly when the damage obstructs the flow of enzymes through the ducts and coincides with gallstones that block these ducts [27].

3.1. Acute pancreatitis

Acute pancreatitis is an inflammatory disorder affecting the pancreas and is widely recognized as a prevalent pancreatic disease [28–30]. Its clinical presentation can range from mild to severe. In many instances of mild cases, the condition is reversible [31]. It primarily arises due to inflammation triggered by gallstones and alcohol consumption [6,20]. As noted by [20], gallstones represent the most frequent obstructive cause of AP and are more prevalent in women than men, particularly affecting those between the ages of 50 and 60 years. Anatomical variations in pancreatic ducts are associated with an increased risk of obstruction [32]. Although 75% of individuals with gallbladder stones exhibit no symptoms, approximately 8% of patients with gallstones will eventually experience the onset of AP [33]. It has been elucidated that alcoholic AP is more prevalent in men than women [6]. In most, though not all populations, this stands as the second most common cause of pancreatitis following gallstones [6]. Among children, trauma serves as the most frequently identifiable cause of AP [34].

Altogether, pancreas disorders are interrelated. Understanding the associative link of these disorders may hold more significance in diagnosing AP than simply categorizing them as primary or secondary. Diseases of the pancreas are all linked to AP as either causative factors, complications, or coexisting conditions. Pancreatic trauma and tumors occurring alongside gallstones can act as causative factors. Pancreatic diabetes, pancreas cancer, and chronic pancreatitis can manifest as its complications. A noteworthy implication for diagnosis is the necessity of consider-

ing these interrelations when determining the presence and severity of AP in patients who display the causative factors and/or known complications. Abnormalities in biochemical markers further support the diagnosis of the association between diseases of the pancreas and AP [35].

3.1.1. Pathophysiology of acute pancreatitis

There is general agreement regarding the noticeable circumstances during the emergence and advancement of AP. Nonetheless, there exists a slight divergence in how these noticeable conditions are organized into distinct periods or stages. In earlier studies, there was inconsistency in the stages employed to delineate the underlying processes of AP. In contrast, later studies emphasized the use of an adequate number of phases to more precisely characterize the evolution of AP. Within these phases, the commencement of AP is contingent upon both primary and secondary causal factors, while its progression begins at a localized level and then extends systemically. This trend toward using sufficient phases can be attributed to the increasing comprehension of the underlying processes of AP. Alterations in biochemical indicators align with the onset and advancement of the disease [36].

In four phases, as outlined in an early study [37], the observable conditions of AP were delineated, with each major condition corresponding to a specific phase. The first phase encompasses cellular damage, which can occur due to auto-digestion in cases of biliary AP or involvement of alcohol. Moving to the second phase, there is inflammation of the cellular organ or localized inflammation. Progressing to the third phase, systematic inflammation becomes evident, affecting the lungs, liver, and kidneys. Finally, the fourth phase involves the infection of the necrotic pancreas.

Other studies categorized the observable conditions of AP into dual phases: the initial and subsequent advanced stages. In the initial phase, these discernible conditions encompassed inflammation and potential necrosis [38,39]. The initiation of inflammation and its subsequent transition into necrosis were contingent upon the underlying etiology of AP, as depicted in Figure 4 below. In cases of biliary AP, injury to the acinar cell due to auto-digestion leads to the inflammation of the gland [39]. Shifting to the later advanced phase, the observable conditions materialized as systemic complications, culminating in organ failure and infection of necrotic tissue (Figure 4) [38].

The study conducted by [37] categorised the initial two phases within the early stage, while the subsequent two phases were designated as the advanced stage. While this binary categorization into two phases simplified the classification process for characterizing the onset and progression of acute pancreatitis, it concurrently limited the precision of discerning the exact disease progression stage, especially when compared to use of four phases.

The first phase pertains to localized inflammation resulting from the obstruction of the pancreatic or bile ducts, direct cytotoxicity affecting pancreatic cells, exogenous toxins, infectious agents, alcohol consumption, traumatic events, or idiopathic origins. This local inflammation subsequently triggers the premature activation of pancreatic enzymes, such as trypsinogen and zymogen, either within the ductal system or the acinar cellular milieu. This enzymatic activation induces the secretion of enzymes that are primarily intended for the digestion of dietary proteins and fats; however, their action culminates in cellular degradation and self-digestion of pancreatic tissue (Figure 4). In its early stages, the inflammatory process remains confined, engendering focal pancreatic damage and edematous changes. As the severity of this event escalates, the inflammation assumes a generalized nature, precipitating necrosis in the pancreatic ducts and associated vascular structures, consequently resulting in haemorrhagic events. The presence of necrosis encompassing more than 30% of the pancreatic tissue amplifies both the morbidity and mortality rates [37].

The second stage involves an array of complications resulting from the activation of enzymes, the inflammatory response, and the ensuing necrotic processes. Among patients grappling with severe AP, fluid accumulations manifest in approximately 30% to 50% of cases. Over a temporal continuum, these fluid accumulations might be encapsulated by a fibrinous or granulation boundary, thus engendering a pseudocyst. Notably, pseudocysts do not manifest during the initial phase of AP; instead, they tend to evolve after a duration of 4 to 6 weeks. In select instances, a minority of cases may observe the infection of fluid collections, necrotic regions, or pseudocysts, typically after a span of several weeks. Furthermore, provocation of the neighboring bowel frequently occurs, inciting edematous changes within the bowel wall, instances of ileus, and the redistribution of fluids. The development of ascites is a frequent occurrence, and when coupled with bowel edema, it can give rise to substantial intravascular fluid depletion, ultimately leading to hypotensive states [37]. With the advent of multiorgan dysfunction syndrome (MODS), the concluding phase takes place. Consequently, the systemic immune response syndrome (SIRS), arising from the release of inflammatory mediators due to the initial localized inflammatory reaction, leads to the onset of multiple organ failure (Figure 4) [37].

In another investigation by [29], a cross-sectional delineation of the stages of acute pancreatitis (AP) was provided. This delineation, as illustrated in Figure 5, aligned with the 2012 reformation of the Atlanta classification, originally disseminated in 1992 [41]. The grading of AP severity encompasses mild, moderate, and severe, whereas the discernible manifestations have been classified into the domains of organ failure and localized and systemic complexities. Therefore, the incorporation of the moderate grade within the spectrum of severity enhances diagnostic accuracy substantially.

Regarding the diagnostic aspect of AP, the classifica-

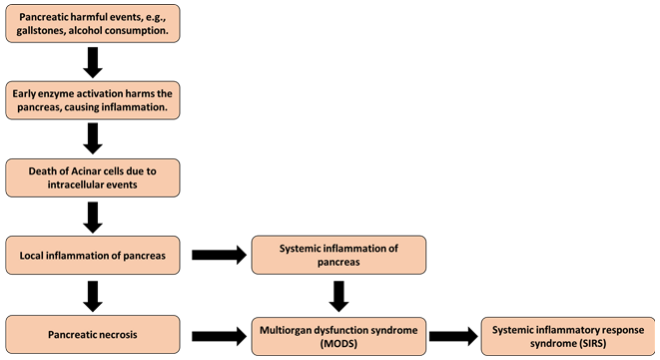

Fig. 4. Pathophysiology of acute pancreatitis. Figure adapted from [37,40].

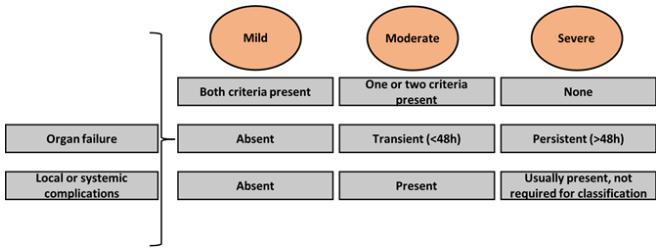

Fig. 5. Cross-sectional presentation of the pathophysiology of acute pancreatitis. Figure adapted from [29].

tion of observable manifestations throughout the course of AP into three distinct phases, as well as the cross-sectional classification, signifies advancements in comprehending the disease. Each of these observable conditions within their respective phases correlates with alterations in biochemical markers, a notable instance being the auto-activation observed in biliary AP. The utilization of biochemical markers proves crucial role in the diagnostic process of AP, serving to determine its initiation and severity. These diagnostic methodologies also lend support to the potential expansion of the cross-sectional classification to encompass four phases, along with more precisely defined observable conditions. This expansion could further heighten the precision of diagnostics.

4. Etiology of acute pancreatitis

The etiology of AP presents a notably intricate facet in comprehending this disease. Various causative factors for AP have been identified within existing literature. Approximately 80% of instances stem from either gallstone (45%) or alcohol consumption (35%) [6]. Nonetheless, even in cases of these prevalent causative agents, the precise role played by these aetiologies continues to be subject to considerable controversy or indistinctness. It is noteworthy to acknowledge that a substantial proportion, approximately 30% of AP occurrences are categorized as idiopathic, indicating unknown causative origins [42]. Nevertheless, a more refined understanding of AP resulting in heightened diagnostic accuracy has prompted the suggestion that the proportion of idiopathic cases should be within the range of 20% to 25%, or even 10% [43].

Gallstones have been widely documented as a prevalent etiological factor underlying episodes of AP. Approximately 40% to 45% of instances of AP are attributed to the presence of gallstones [6,43]. This specific manifestation of AP resulting from gallstones is referred to as biliary pancreatitis [6,43]. The precise mechanistic underpinnings of biliary pancreatitis have been elucidated to a certain extent. This involves either the exertion of pressure upon the pancreatic duct walls by a calculus lodged within the bile duct or the obstruction caused by a stone located within the shared conduit of the pancreatic duct and the common bile duct [44]. Smaller calculi exhibit a greater propensity to traverse the cystic duct with ease, albeit carrying an elevated susceptibility to provoking episodes of AP. Notably, stones measuring less than 5mm in diameter pose a heightened risk for precipitating AP in comparison to their larger counterparts [43]. The imposition of obstruction or pressure upon the pancreatic duct precipitates either the reflux of bile or an elevation in pancreatic secretory pressure. Either of these mechanisms culminates in the exudation of pancreatic enzymes, thereby initiating the onset of pancreatitis [29]. This etiology of pancreatitis allows potential for intervention and management. However, its misunderstanding augments the possibility of AP recurrence [29].

Alcohol represents the alternate prevalent cause of AP, in which about 35% of instances of AP arise from alcohol consumption [6]. The precise mechanisms by which alcohol precipitates the beginning of AP remain incompletely comprehended. Possible pathways encompass the deleterious impacts of the ethanol metabolite acetaldehyde, disturbances in lipid metabolism resultant from ethanol exposure, or the induction of sphincter of Oddi spasms [45]. Alcohol ingestion might also generate aldehydes and esters, which possess direct cytotoxicity toward pancreatic acinar cells. Alternatively, alcohol might heighten the sensitivity of acinar cells to the actions of cholecystokinin, potentially influencing subsequent zymogen synthesis and activation processes [20]. Both acute alcohol consumption and persistent alcohol exposure elicit a heightened monocyte response to inflammatory cues, potentially contributing to escalated inflammatory processes within the pancreas [45]. Individuals afflicted by alcoholic pancreatitis commonly exhibit a history of chronic alcohol utilization from 5 to 10 years prior to the manifestation of pancreatitis symptoms [43].

Certain pharmaceuticals and substances have also been linked to the onset of AP. Numerous drugs and toxic agents possess the capacity to provoke pancreatitis, encompassing didanosine, pentamidine, oral contraceptives, and specific varieties of scorpion venoms [46]. Instances of AP attributed to drug-related causation encompass an array of pharmaceutical agents, including furosemide, corticosteroids, thiazides, sulindac, azathioprine, diverse antibiotics, and pentamidine [43]. The majority of drug-induced pancreatitis cases tend to manifest as mild to moderate in severity; however, instances of severe and fatal outcomes are also documented [47]. Clinicians encounter challenges in comprehending the clinical symptoms and the underlying mechanisms of pancreatic injury in relation to individual drug effects [48].

The emergence of infection has also been entwined with the initiation of AP. As described by [42], the initiation of pancreatitis may lead to both viral and bacterial sources. Notably, mumps and Coxsackievirus B infection stand as the two dominant viral culprits behind pancreatitis. Furthermore, within the demographic of patients afflicted with human immunodeficiency virus (HIV) infection, the incidence of pancreatitis is elevated in comparison to the general population [49]. Within this cohort, heightened susceptibility to opportunistic infections, untoward effects of HIV infection pharmaceutical agents, and the manifestation of acquired immunodeficiency syndrome (AIDS)-related malignancies collectively contribute to an augmented susceptibility toward pancreatitis [49].

Both blunt and penetrating trauma to the abdominal region has the potential to disrupt the intricate cascade of pancreatic ducts and cells, consequently initiating a sequence of enzymatic events that culminate in the development of AP [27]. Despite this recognition, current investigations have yet to provide a comprehensive elucidation of the precise causal mechanisms underpinning the direct association between abdominal trauma and the onset of AP [26].

AP has additionally exhibited an association with med-

ical interventions, encompassing procedures involving the biliary, pancreatic, and gastric domains [43]. This association arises from instances where patients have manifested AP subsequent to undergoing these specific medical interventions. Notably, post-operative occurrences of pancreatitis have been widely acknowledged, carrying a mortality rate exceeding that observed in relation to other initiating factors [42]. However, the specific causal contribution of these medical treatments to the onset of AP remains unclear [50].

Endoscopic retrograde cholangiopancreatography (ERCP) stands out as the source of iatrogenic-induced AP. Post-ERCP pancreatitis entails the emergence of abdominal pain accompanied by heightened levels of amylase in the bloodstream, necessitating hospitalization following an ERCP procedure [43]. Incidences of pancreatitis can arise due to inadvertent ductal injury in a range 1% to 10% of ERCP interventions [42]. However, the precise mechanisms through which ERCP precipitates the occurrence of AP remain largely unresolved [51].

Hypertriglyceridemia is another recognized etiological agent. Pancreatitis can be caused by hypertriglyceridemia or increased triglyceride levels exceeding 500 mg/dL [52]. Levels surpassing 11 mmol/L have been reported in 4% of all patients with AP [43]. Hypertriglyceridemia accounts for up to 10% of all AP cases and even up to 50% of all acute pancreatitis cases in pregnant women [20]. Hydrolysis of triglycerides by pancreatic lipase and excessive formation of fatty acids with inflammatory changes, capillary injury, and hyperviscosity are suggested as explanations for the development of hypertriglyceridemia-induced pancreatitis (HTGP) [52]. The clinical features of HGTP are not different from patients with AP of other causes, but HTGP seems to be associated with higher severity and complication rates [52]. There is no clear evidence regarding which hypertriglyceridemia patients will develop AP and which will not [52].

Hypercalcemia may contribute to the onset of pancreatitis, potentially through the deposition of calcium crystals within the pancreatic ducts or via the activation of pancreatic enzymes mediated by elevated calcium levels [43]. However, the precise causal mechanism underlying hypercalcemia-induced acute pancreatitis remains unclear [53].

Altogether, all cases of acute pancreatitis with undefined causes have been classified as idiopathic AP. It has been documented that acute idiopathic pancreatitis constitutes approximately 10% to 35% of cases of AP within the general population [54]. Given the advancements in AP diagnosis, there exists a current debate regarding the incidence of idiopathic AP cases [54]. According to [43,55] on the incidence of idiopathic AP at 20% to 25% is now largely outdated and they suggested that the rate should be at the 10% level. The understanding of idiopathic AP can be enhanced by using a comprehensive investigative approach. The process of ruling out potential causes can be facilitated through the utilization of CT scans or endoscopic ultrasonography. It is imperative to take into consideration uncommon triggers of AP. In instances of recurrent idiopathic episodes, particularly when observed in the patient's family members, medical practitioners should seek genetic consultation. Therefore, by systematically eliminating possibilities, a more accurate determination of the underlying cause or causes of AP can be determined [43,55].

Causes linked to AP are relevant across the general population. Nevertheless, distinct etiologies have been identified in the literature for two specific demographic groups: children and women. AP in children has been associated with the same causes as in adults. So, the increase in the incidence of AP among pediatric patients has been correlated with the rising incidence of obesity, which stands as a notable and independent risk factor for acute biliary pancreatitis, which is a common cause of AP in children [56,57]. The most reliable approximations indicate a range of 3.6 to 13.2 cases of acute pancreatitis per 100,000 pediatric individuals annually, reflecting an incidence rate that aligns closely with that observed in adults [58,59].

Pregnant women have been documented to face a heightened susceptibility to developing AP compared to non-pregnant women, with an incidence rate ranging from 1 in 1,000 to 10,000 pregnant individuals [60]. Although the precise causal connection remains largely undefined, several potential explanations have been put forward. Notably, both gallstones and elevated triglyceride levels can serve as triggers for AP [61]. Hormonal shifts during pregnancy may lead to heightened triglyceride levels [61]. Moreover, these hormonal changes can elevate the risk of gallstone formation in pregnant women, a condition that can precipitate AP [62]. On the other side, ethnicity plays a role in determining incidence, with Hispanic women exhibiting the highest reported rates, and obesity serves as a coexisting factor [60].

Therefore, the identification of these causes among patients definitively diagnosed with AP has formed the basis for establishing causal link to this disease. Nevertheless, the causative mechanisms of the identified AP causes remain unclear. The presence of undefined etiologies for AP might lead to challenges for clinical diagnosis. Etiologies of AP are implicated with biochemical markers, which have been subjected to study and continue to be explored to elucidate the underlying causes of AP. Certain biochemical markers prove valuable in indicating the onset of AP. Moreover, specific biochemical markers serve the purpose of identifying an etiology, aiding in confirming the diagnosis while ruling out other potential causes. The discovery of the dynamic role that biochemical markers play in the diagnosis of AP enhances their significance as diagnostic tools, highlighting the distinct roles of various biochemical markers in diagnosing specific etiologies of AP.

5. Symptoms of acute pancreatitis

The common symptoms of AP have been established. Nevertheless, even these shared symptoms do not consistently present uniformly among AP patients. General symptoms act as pointers indicating the need for a more thorough examination of all symptoms to validate the emergence of AP and its specific etiology. Studies focused on AP, rooted in observations of specific triggers, identify the potential clinical representation of AP. Observing these particular symptoms, particularly in instances of the two most prevalent causes of AP, proves valuable not only for confirming the presence of AP but also for identifying the primary disease cause.

Abdominal pain constitutes a prevalent symptom of AP that necessitates additional examination to validate the presence of the condition. The emergence of consistent abdominal pain, particularly within the epigastric region,

should raise suspicions of acute pancreatitis in patients [29,63]. Continuous pain may also extend towards the sides and the back, making it challenging for the patient to precisely determine the exact origin of the pain [39,64]. Spreading pain could suggest the initiation of infection in cases of severe AP [65].

On the other side, nausea, vomiting, and restlessness are also symptomatic of AP [48]. In cases of severe AP, heightened pain levels are prone to lead to increased nausea and more frequent events of vomiting [44]. Restlessness is the behavioral response of patients to pain, often resulting in frequent changes of position or movement in an attempt to relieve the experienced pain level [64,66].

Jaundice has been identified as a specific symptom of biliary AP [67]. This symptom is connected to the accumulation of the metabolic enzyme bilirubin in the blood circulation due to the obstruction of pancreatic ducts by gallstones [44,48]. This manifestation is particularly associated with AP primarily triggered by gallstones [44,48,67]. Moreover, Weight loss and jaundice are symptoms that specifically point to autoimmune pancreatitis. In a study conducted by [68] focusing on cases of AP linked to autoimmune factors, 63% of patients displayed jaundice, and 35% exhibited abdominal pain. Among these symptoms, jaundice emerged as a more prevalent manifestation in cases of autoimmune AP in contrast to abdominal pain. Conversely, weight loss is a less common symptom associated with metabolic abnormalities and the engagement of other organs [69].

According to existing literature, broad symptoms provide robust indications of the initiation of AP. It is the particular symptoms that enable medical professionals to differentiate the etiology of AP and assess its severity. The application of biochemical markers aids in discerning the symptoms distinct to various causes of AP. The depth of comprehension regarding biochemical markers and advancements in their utilization, alongside symptoms identification, within clinical practice, are expected to enhance diagnostic capabilities in the coming years.

6. Diagnostic methods for acute pancreatitis

Diagnostic techniques for AP, as detailed in the provided Table 1, can be categorized into clinical history, physical examination, imaging modalities, and biochemical markers, as covered in this literature. Clinical history and physical examination are fundamental diagnostic approaches for illnesses. Imaging technology proves valuable in confirming diagnoses. The utilization of biochemical markers, particularly serum amylase and lipase, is distinctive to the diagnosis of AP. These diagnostic techniques are often employed in combination or sequentially for diagnosing AP. However, practical experience with these diagnostic methods has led to identifying advantages and disadvantages. These pros and cons could guide the optimal utilization of these diagnostic approaches, particularly in distinguishing between different etiologies of AP.

Clinical history pertains to the facets of the patient's life and well-being that are relevant to the diagnosed condition. This covers the family history of illnesses, preceding medical conditions, lifestyle, occupational type, and all additional factors that contribute to elucidating the medical issue under-diagnosis. In the case of AP, the patient's clinical history should cover past diagnoses and treatments of AP, alcohol consumption habits, medication usage, family history of AP, and medical interventions for other conditions related to AP [39]. Clinical history serves as a robustly indicative method in diagnosing AP, bringing together all medical and non-medical information collected from the patient and their records [70]. This process acts as an initial step in ruling out other potential diseases. Nevertheless, even when the probability of AP in the patient is considerable, clinical history may not always definitively distinguish the underlying cause of the experienced AP [39,70]. Thus, relying solely on clinical history is not sufficient enough as the sole diagnostic method for AP.

Physical examination involves a medical professional assessing the body to determine overall health or health conditions. Approaches for examining the body include observing the body and its movements, applying pressure, tapping, and listening with a stethoscope [75]. In the case of AP cases, physical examination involves observing visible disease symptoms [20]. Similar to clinical history, physical examination strongly suggests AP in a patient [70]. In cases where epigastric pain, abdominal tenderness, and abnormal vital signs are observed, AP becomes a primary consideration [64]. However, the accuracy of physical examination as an AP diagnostic method is only moderate when numerous abnormal physical symptoms point to various potential diseases [64]. While valuable as an initial diagnostic tool for AP, physical examination alone is insufficient for confirming the disease; other diagnostic methods are required.

Various imaging techniques have been employed for diagnosing AP. An abdominal CT scan can establish an initial diagnosis of AP, distinguish between different types of AP, assess the severity of AP, and monitor complications and severity scores [30,40]. However, utilizing this imaging technique during admission is not recommended due to the limited ability of CT scan images to detect minor abnormalities during the early stages of the mild phase of AP disease [64,71]. Additional imaging methods have gained traction in the diagnosis of AP. MRI is gaining popularity for AP diagnosis due to its ability to provide clearer identification of necrosis and fluid collections compared to CT scans [30,40,76]. Furthermore, MRI emerges as a valuable imaging modality in cases where pancreas divisum is under consideration as the presumed etiology [64]. Nevertheless, its limitations encompass its infeasibility for patients with concurrent attachment to numerous lines and surveillance apparatus, coupled with the protracted duration essential for executing an MRI scan [40]. However, these drawbacks are anticipated to impact merely a minor fraction of the patient cohort. The application of MRI for the purpose of diagnosing AP is expected to endure.

Apart from MRI, abdominal radiography can be used as an alternative technique for visualizing pancreatic anatomical features and adjacent organs; however, its utility is compromised in the presence of intestinal gas or when gallstones obstruct the distal bile duct [64].

On the other side, endoscopic ultrasound represents an invasive technique for capturing imagery within the gastrointestinal tract and proximate organs. It finds utility in instances of suspected AP with unclear origins, aiming to exclude certain etiological inferences including gallstones, neoplasms, and pancreas divisum [40]. Nonetheless, due to its invasive nature, it bears the potential of inducing hemorrhage and precipitating cardiopulmonary complications [48]. Electrocardiography (ECG) is additional technique

Table 1. Advantages and disadvantages of the methods of diagnosis for acute pancreatitis.

Diagnostic method	Description	Advantages	Disadvantages
Clinical history	Identification of prior AP, alcoholism, drug intake, family history of AP, other diseases associated with AP.	Highly suggestive [70].	Frequently non-specific [70].
Physical examination	Abdominal examination, vital signs, pain threshold, fever, jaundice, etc.	Highly suggestive [70].	Moderate accuracy when there is a lot of abnormal physical symptoms [64].
Computed tomography (CT)	Cross-sectional imaging of the abdomen area.	Determines differentiation and severity of the disease [40]; confirms AP diagnosis and facilitates follow-up on complications and severity scores [30].	Not advisable as a sole diagnostic method for assessing severity at admission [64,71].
Magnetic resonance imaging (MRI)	Imaging of organs and structures in the abdomen area.	Identifies necrosis and fluid collections better than CT scan [30,40]; especially useful in diagnosis of pancreas divisum [64].	Not practical for acutely ill patients connected to multiple lines and monitoring devices and duration of MRI studies is longer [40].
Abdominal radiography	Imaging of organs and structures in the abdomen area.	May show localised ileus in severe AP [30].	Limited prognostic utility, especially when overlying bowel gas is present or gallstones are in the distal bile duct [64].
Endoscopic ultrasound	Imaging of the digestive tract and proximate organs.	Useful in idiopathic AP to detect gallstones, tumours and pancreatic divisum [40].	May lead to complications such as bleeding and cardiopulmonary disorders [48].
Serum amylase	Measurement of amylase activity with activity greater than 3 times the upper reference limit (URL) indicating AP [70].	Useful diagnostic method in the early presentation of AP.	Lack of universally agreed URL; shorter period of elevation; hypertriglyceridemia and other factors may interfere with amylase assays.
Serum lipase	Measurement of lipase activity with activity greater than 3 times the URL indicating AP [64].	Useful diagnostic method during the early and latter presentation of AP; lipase assay is unaffected by triglycerides.	Lack of universally agreed URL.
Urinary trypsinogen-2	Testing of urine for trypsinogen-2 with level of 50 mg/L indicating AP.	Early diagnosis of post- ERCP pancreatitis with high sensitivity and specificity second to serum lipase [72].	Limited systematic assessment of diagnostic value for AP and ERCP-induced AP [73].
Other biochemical markers	Using specific laboratory tests for different AP aetiologies.	May confirm specific aetiologies of AP [64].	Largely unproven diagnostic merit for AP; secondary or supportive diagnostic method [74].

employed to confirm AP, particularly subsequent to an initial clinical examination showing aberrant vital parameters [77]. It assumes a subsidiary or adjunctive diagnostic role, given its limitation in providing visualization of the pancreatic and abdominal regions [30]. Imaging procedures serve the dual purpose of confirming AP and discerning its etiology and severity. However, the selection of the optimal imaging technique hinges upon the patients' condition and an accurate assessing of potential drawbacks.

Due to their confirmed diagnostic accuracy in clinical practice, serum amylase and lipase are the most extensively utilized biochemical indicators of AP [31]. When the measured activity of serum amylase and lipase exceeds three times the agreed upper reference limit (URL), it indicates AP [64]. Both are helpful diagnostic procedures, but they have drawbacks. A typical disadvantage is a lack of URL standards. Amylase URLs ranging from 114 U/L to 1000 U/L were reported [70] and lipase URLs ranging from 51 U/L to 540 U/L [64]. Changing the URL impacts the biochemical marker's diagnostic sensitivity and specificity, which will be discussed in depth in the next subsection. In the literature, a comparison of the disadvantages of serum amylase and lipase seems to favor the latter. Serum amylase is beneficial during the early stages of the illness, although the increase in activity fades quickly, and some circumstances interfere with amylase assays [78]. Serum lipase is beneficial throughout the early stages of the illness and throughout its course since it is unaffected by triglycerides, which decrease the time of elevation [64,70].

Only urinary trypsinogen-2 has been shown to be a meaningful biochemical indication of AP. It has a higher sensitivity and specificity than serum amylase in the early detection of post-ERCP pancreatitis [73]. However, further clinical testing is required to address the limited sys-

tematic evaluation of this marker's diagnostic significance for AP, especially post-ERCP AP.

Biochemical indicators, among other diagnostic approaches, should not be neglected in the early and late phases of AP presentation. Preliminary diagnostic approaches include clinical history and physical examination. Imaging is most effective when the illness has already advanced to the point where structural abnormalities are visible or when imaging technologies can capture the probable etiology of the disease. Despite universal agreement that serum lipase has superior sensitivity and specificity as a standalone biochemical marker than serum amylase, serum amylase and lipase remain the leading diagnostic techniques for AP. Trypsinogen-2 and other biochemical markers have limited diagnostic usefulness. A thorough look at biochemical indicators for the diagnosis of AP is required.

6.1. Biochemical markers for diagnosing acute pancreatitis

This review has covered biochemical markers as significant measures for diagnosing AP. Amylase and lipase are the most often used biochemical indicators for diagnosing AP [31]. Both of these biochemical indicators serve as diagnostic tools for determining the beginning of the illness. Other biochemical indicators, especially trypsinogen-2, have been proposed for use in AP diagnosis, however proof of diagnostic value is still insufficient [73]. On the other hand, alanine transaminase (ALT) enzyme is a diagnostic biochemical marker exclusively related to biliary AP, whereas C-reactive protein, interleukin-6, interleukin-8, phospholipase A, and procalcitonin are all indicators for the severity of AP by detecting necrosis [31]. It has been also identified that some of the emerging biochemical markers are used for AP diagnosis, which are pancreatic elastase-1, activation peptide of carboxypeptidase B, and circulating cell-free DNA [79]. Low sensitivity and a problematic reference range have been observed for serum elastase-1 levels [80]. In addition to its limitations in detecting total elastase, serum elastase-1 assays must be validated using large cohort studies [80]. Acinar cells have carboxypeptidase B activation peptide and its diagnostic accuracy is lower than that of traditional AP biochemical indicators [81]. Circulating cell-free DNA has been linked to the diagnosis of early stages of AP, however further studies are needed to prove its accuracy [82]. [83] reported on a research that found the trypsinogen-3 test to be useful in identifying AP, especially alcoholic AP, but that the results needed to be validated further.

Other biochemical indicators have a role in both the confirmation of AP diagnosis and the identification of etiology and severity. Serum amylase and lipase levels are particularly reliable in detecting the presence of AP in patients. Other biochemical indicators, on the other hand, appear to be more adapted to detecting the precise etiology of the disease and its consequences. As a result, before employing additional biochemical markers to support the diagnosis of etiology and severity of the disease, serum amylase and lipase must first be used to establish the presence of AP. Because these two biochemical indicators are the key biochemical markers for diagnosing AP, an in-depth look at this review on these two biochemical markers is necessary.

6.2. Serum amylase and lipase tests for diagnosing acute pancreatitis

Amylase and lipase are two biochemical indicators routinely utilized to identify patients with AP [63]. Amylase and lipase are pancreatic enzymes that are secreted into the digestive system [84]. Lipase is produced in the pancreas while the highest levels of amylase are produced in the pancreas and salivary glands [84,85]. Lipase is a biochemical marker specific to AP, although amylase can identify AP as well as other diseases [86].

The role of amylase and lipase as biochemical markers of AP has been explained in this review. Amylase and lipase are two enzymes that perform separate functions in digestion. Amylase assists in the digestion of starch and glycogen [87], whereas lipase aids in the digestion of fats and the maintenance of cell permeability, allowing for the smooth absorption of nutrients by the cell and the excretion of wastes [88,89]. Levels of these enzymes are elevated during the onset of pancreatitis [90]. Serum amylase is an effective diagnostic marker during the early stages of AP, but serum lipase is an effective diagnostic measure both during the early and late stages of AP [86]. Amylase activity increases rapidly within the first 12 hours of symptom onset and recovers to baseline within three to five days [91] while lipase levels are elevated for 8 to 14 days from the onset of the disease [78]. At the same time, several factors may also interfere with the elevation of amylase while elevation of lipase is unaffected by triglycerides unlike amylase [31]. Based on this comparison, lipase has been suggested as a better diagnostic measure for AP [86]. Nonetheless, both biochemical indicators are still utilized in the clinical diagnosis of AP and succession depending on the situation might favor one over the other [86].

Total serum amylase is the widely used laboratory test for acute pancreatitis. A total serum amylase test means that both salivary and pancreatic amylase are being measured. Several total serum amylase assays exist, including α-Glucosidase, maltose phosphorylase, α-Glucosidase combined with 4-nitrophenol-glycoside substrates, α-Glucosidase combined with blocked 4-nitrophenol-glycoside substrates, and 2-chloro-p-nitrophnol [92]. By measuring amylase released by the salivary glands and pancreas, the results have lower specificity in the diagnosis of AP [93]. Results of the total serum amylase test can indicate conditions other than AP, such as macroamylasemia, gastroenteritis, intestinal blockage, mumps and infection of the salivary glands [79,94]. Therefore, the use of the total serum amylase is not specific to AP by indicating other possible conditions.

Serum amylase can be separated into salivary (s-amylase) and pancreatic amylase (p-amylase) [95]. Separating s-amylase from p-amylase and using only p-amylase has been suggested as a way of increasing the specificity of serum amylase for the diagnosis of AP [96,97]. Amylase isoenzyme differentiation tests, amylase isoform, separation tests, electrophoresis and precipitation are laboratory methods for separating s-amylase and p-amylase may constitute an additional test to increase specificity but with added cost and waiting time [92]. Total serum amylase is preferred when cost and time are paramount issues in diagnosing patients who exhibit symptoms of AP. However, a p-amylase test result is expected to have higher diagnostic accuracy, but the extent of comparative accuracy still needs to be validated [98]. Amylase is also eliminated

through the urine tract. Urinary amylase tests have been developed. Amylase has been proven to have a longer time of rise in urine than in blood because amylase levels in urine might become high after blood levels have fallen [99]. Serum amylase levels rise within 6-48 hours of the beginning of AP, although not in proportion to the severity of the disease and return to normal within 5-7 [100]. Urine amylase rises in proportion to serum amylase and stays increased for several days after serum amylase levels have returned to normal [78,101,102].

A serum lipase test has higher specificity rating as a diagnostic biochemical marker for AP [86,103,104]. However, use of the serum lipase test has increased only recently. Turbidimetric and colorimetric lipase assays [105] and the OSR6130 and OSR6230 [106] are serum lipase tests with comparable precision. Use of colipase in serum lipase assays account for the development of and growing preference for lipase tests. Colipase is present in the blood of patients with AP in varying concentrations, which may not be able to fully activate pancreatic lipase [107]. By adding colipase, the serum lipase test is able to detect more accurately the elevation in lipase levels [108]. As a biochemical marker specific to the pancreas, serum lipase is a valuable diagnostic tool for AP.

According to AP diagnosis using amylase and lipase biomarkers, the interpretation of the results depends on the normal threshold used. No standard has emerged on this aspect, except for the lower threshold in children and higher threshold for adults. Normal amylase levels can range from 19 to 86 U/L while normal lipase levels can range from 7 to 59 U/L, depending on the age, gender, and other pre-existing conditions of the patient together with the standards adopted by the physician and healthcare facility [109]. In addition, abnormal levels of both amylase and lipase also vary. Following the assessment of 50 patients with a validated diagnosis of AP, amylase was raised to seven times its upper limit of normal range and lipase was raised up to 10 times its upper limit of normal range [93]. However, 42 only of the 50 individuals had both amylase and lipase enzymes elevated, whereas the remaining 8 had amylase normal but lipase elevated. Therefore, it is in the standards used for interpreting the results of amylase and lipase tests that variances in clinical practice emerge.

The lack of standards in the interpretation of the amylase and lipase tests has an impact on the diagnosis of AP. Lower standards allow more people to be included but result in more false positives, whereas higher thresholds reject more patients but result in more accurate diagnoses. It is possible that this is why both amylase and lipase are needed in the diagnosis of AP, even though lipase has been proposed as an adequate diagnostic test on its own. A further in-depth examination of these two biochemical indicators is still required.

6.3. Comparison of amylase and lipase tests for diagnosis of acute pancreatitis

Four parameters, as shown in Table 2, have been used to compare the diagnostic merit of amylase and lipase for the purpose to deciding the issue over the combined or single use of these diagnostic measures in the clinical diagnosis of AP.

The first parameter is sensitivity, which relates to the probability of obtaining a positive result when utilizing a biochemical marker as a diagnostic test for patients who clearly have AP [120]. It has also been characterized as the biochemical marker's capacity to accurately identify an individual as positive for AP [121]. Patients with AP are more likely to be positively identified by a biochemical test with a higher sensitivity rating. According to the findings of multiple studies, amylase sensitivity ranges from 61% to 95% [74,110–113] and lipase sensitivity ranges from 91% to 96% [74,110,113,114] depending on URL applied (Table 2). The URL is the amount of elevation of a biochemical marker measured in units of the biochemical marker per litre (U/L), suggesting the possibility of AP if achieved [91]. In the investigations that measured the sensitivity of amylase and lipase, using a higher URL resulted in a higher sensitivity rating for both biochemical indicators. However, regardless of the URL range employed, the sensitivity rating for lipase is consistently high, at or over 90% in all of the studies (Table 2). The sensitivity of amylase varies from 61% when using a low URL to 95% when using a high URL (Table 2). Therefore, lipase has a more consistent sensitivity rating, leading to the conclusion that it is the better biochemical marker based on comparing sensitivity ratings [78,122].

Specificity is the second parameter. This refers to the possibility that a negative test for AP utilizing biochemical markers will be confirmed [120]. Again, higher specificity rating for amylase and lipase reflects their ability to correctly diagnose a patient as negative for AP [122]. The rating is established in the studies by comparing the total number of patients initially classified as not having AP using either amylase or lipase tests to the number of

Table 2. Comparison of amylase and lipase for diagnosis of acute pancreatitis.

	Amylase	Lipase
Sensitivity	62% at 330U/L (3x110U/L) [110]; 63.6% at 423U/L (3x141 U/L) [74]; 89% at >250IU/L [111]; 91% at >300IU/L [112]; 95% at >360U/L [113]; 61% at 1000 IU/L [112].	91% at 180U/L (3x60U/L) [110]; 95.5% at 153U/L (3x51U/L) [74]; 94% at >350 U/L [114]; 96% at >540 U/L [113].
Specificity	88% at >250U/L [114]; 93% at 330U/L(3x110U/L) [110]; 95% at >360 U/L [113]; 99.4% at 423 (3x 141U/L) [74]; 99% at 1000 U/L [115].	96% at >350 U/L [114]; 99.2% at 153 (3x 51U/L) [74]; 92% at 180 U/L (3x60U/L) [110]; 96% at >540 U/L [113].
Positive predictive value	51% at 330U/L [116]; 78.8% at 970U/L [117]; 98% at 550U/L [118].	41% at 900U/L [116]; 79.7% at 1400 U/L [117]; 62% at 270U/L and 87% at 483U/L [119]; 30% at >540 U/L [113].
Negative predictive value	99% at 330U/L [116]; 82% at 550U/L [118]; 35.9% at 970U/L [117].	100% at 270U/L and 99% at 483U/L [119]; 99% at 900 U/L [116]; 37.9% at 1400U/L [117].

patients who really tested negative for this condition. Several studies that examined the specificity rating for amylase and lipase tests found that both biochemical indicators had good ratings, with amylase having a somewhat larger range. The specificity rating for amylase at low URL is 88% [114]. When utilizing a high URL, this rises to 99.4% [74]. Lipase has a high specificity grade of 92% to 99.2% regardless of whether the URL is lower or higher (Table 2) [74,110,113,114]. Although the specificity rating difference between amylase and lipase is minor, it has been utilized in conjunction with the more considerable difference in sensitivity rating to suggest that lipase is a more reliable diagnostic test for AP [78,122].

The third parameter is positive predictive value (PPV), which is calculated by the percentage of patients who had AP and obtained a positive test [120,121]. A high PPV reflects better predictive value. In the case of amylase, use of a higher URL results in higher PPV values; at 330U/L, the PPV is 51% [116] while at 970U/L, the PPV is 78.8% (Table 2) [117]. In the case of lipase, significant differences emerged in the PPV values obtained by studies using different URLs. Lipase recorded 62% PPV for URL of 270U/L [119] while 41% PPV was reported for URL of 900U/L [116], and 79.7% PPV was also reported for URL of 1400U/L (Table 2) [117]. Differences in reported PPV for various URLs can be linked to the patient population segment studied. Using a patient cohort that includes all patients hospitalized for abdominal pain may result in lower PPV ratings since there are more persons who were initially diagnosed with AP but were later discovered to have other diseases following additional testing [36]. Because of the possibility of more AP confirmations, using a patient cohort consisted of people who were originally diagnosed with AP is likely to result in a higher PPV rate [120]. With regard to positive predictive value, there is no absolute advantage of amylase over lipase and vice versa.

The fourth parameter is negative predictive value (NPV), which is calculated by calculating the percentage of patients who have a negative test result but do not have AP [120,121]. Based on the results of studies that determined NPV of amylase and lipase, there is also a wide variance in NPV ratings for both biochemical markers (Table 2). In the case of amylase, 99% NPV was reported at 330U/L [116], and 82% NPV was reported at 550U/L [118], and 35.9% NPV was reported for 970U/L [117]. There is no clear trend indicating the nature of the relationship of NPV rating with the level of URL used. A similar situation emerged for lipase, in which 100% and 99% NPV were reported at 270U/L and 483U/L respectively [119]. Moreover, 99% NPV was also reported at 900U/L [116], and 37.9% NPV was reported at 1400U/L [117]. The wide difference in NPV values in studies that used high URLs indicate the need for more study on the predictive accuracy of biochemical markers. Due to this limitation, there is no ground for considering amylase to be better than lipase or vice versa in terms of NPV.

Several conclusions were drawn from studies that established the sensitivity, specificity, PPV, and NPV of amylase and lipase. Because of the continuously high sensitivity rating of this biochemical test, there is considerable support for utilizing serum lipase, which increases the chance of accurately identifying individuals with AP. Its advantage also resides in the longer time of elevation, which allows it to be used as a diagnostic tool even when patients seek medical treatment several days after the onset of the initial symptoms. Studies also agreed that utilizing serum lipase increases the likelihood of accurately differentiating individuals who do not have AP, however, the difference in specificity ratings for amylase and lipase is minor when compared to the larger difference in sensitivity ratings for the two biochemical markers. There was no discernible difference between PPV and NPV ratings.

Furthermore, even without assessing sensitivity, specificity, PPV, or NPV ratings, several retrospective investigations compared the diagnostic accuracy of amylase and lipase for AP. According to one study [102], amylase tests can be normal in certain individuals with AP, but in rare situations, lipase tests can also be normal in patients with AP. Three cases of normal lipase tests that were later on reversed by additional tests were presented to indicate the need to proceed with additional or confirmatory tests even with normal amylase or lipase test results, but more so for normal amylase test results [102]. Another study [93] examined serum amylase and lipase diagnosis accuracy in 50 individuals with AP. All 50 patients had raised blood lipase levels, 42 had elevated serum amylase and lipase levels, and 8 had normal serum amylase levels. Therefore, it has been suggested that using a single serum lipase test for the diagnosis of pancreatitis, particularly in smaller hospitals with limited diagnostic equipment, to ensure a more accurate and cost-effective AP diagnosis [93].

All the studies considered in the comparison of amylase and lipase as diagnostic tests for AP did not focus on etiology. Thus, a number of studies focused on the diagnostic accuracy of amylase and lipase for three aetiologies of AP, as shown in Table 3.

In the case of biliary AP, lipase has a higher sensitivity rating than amylase at 97% and 80% respectively (Table 3) [110]. A 17% gap in sensitivity rating represents a significant number of patients who were initially diagnosed with

Table 3. Comparison of amylase and lipase for diagnosing specific etiologies of acute pancreatitis.

Etiology	Amylase	Lipase
Biliary AP	80% sensitivity [110].	97% sensitivity [110]; detected 12% more cases of biliary AP [123].
Alcoholic AP	52% sensitivity [110]; 55% sensitivity [120].	91% sensitivity [110]; 100% sensitivity [120]; detected 23% more cases of alcoholic AP [123].
Post-operative AP	No clinical diagnostic significance to AP following pancreatic surgery [124]; clinical diagnostic significance to AP following choledochal cyst excision with amylase elevation dependent on post-operative AP [125].	Could be a predictor of AP after choledochal cyst excision with lipase elevation occurring with or without post-operative AP [125].

biliary AP but were later on found not to have AP or have AP of another origin [110]. Another comparative study [123] also found that use of amylase and lipase as diagnostic tests for biliary AP resulted to lipase test detecting 12% more confirmed cases of biliary AP when compared to the amylase test. Based on the results of these studies, lipase test appears to be a better diagnostic measure for biliary AP.

In the diagnosis of alcoholic AP (Table 3), amylase test has been reported to have 52% [110] to 55% [120] sensitivity while lipase test has been shown to have 91% [110] to 100% sensitivity [120]. Case comparison has also shown that lipase test was able to detect 23% more cases of confirmed alcoholic AP when compared to the amylase test [123]. Some cases of alcoholic AP have been associated with low amylase levels during testing. Therefore, lipase test has been considered a strong biochemical marker and superior to amylase test for determining alcoholic AP [123].

With regard to the diagnosis of post-operative AP, an earlier study showed that the amylase test is not a significant diagnostic test for determining AP following pancreatic surgery [124]. This is because diagnosis depends on other or a combination of biochemical markers. Another study found the amylase test to be a significant diagnostic test for pancreatic surgery, while lipase test may be of use for AP following choledochal cyst excision [125]. Amylase test in this specific condition appears to be superior to lipase test. However, more studies that consider a greater number of cases of post-operative AP are needed to support the comparative accuracy of the amylase and lipase tests for this specific AP etiology.

6.4. Combining amylase and lipase tests

Some studies investigated the use of both amylase and lipase in the diagnosis of AP. The purpose of combining amylase and lipase in the diagnosis of AP was to investigate whether utilizing both offers substantial advantages over using only one biochemical marker, particularly lipase.

It has been reported that combining amylase at 330U/L and lipase at 900U/L resulted in 50% sensitivity and 99% specificity rating [116]. The combined sensitivity is equivalent to the amylase sensitivity rating but significantly inferior to the lipase sensitivity rating. When amylase and lipase are used as single diagnostic tests, the combined specificity rating is similar [116]. In terms of sensitivity, it is preferable to utilize lipase as the only diagnostic test because it has a substantially greater sensitivity rating than the combination test [86,116,126]. In terms of specificity, there is no discernible benefit to combining the amylase and lipase tests for the diagnosis of AP as compared to applying simply a lipase test [86,116,126].

In another study, a combined amylase and lipase test with 93% sensitivity was reported, representing two percent improvement in the sensitivity rating for lipase and 31 percent improvement in the sensitivity rating for amylase as sole diagnostic tests [110]. When it comes to sensitivity requirements, adopting a combination test is just marginally better than using lipase as the only test [110].

Altogether, despite there being a variance in the reported combined sensitivity rating, the reported results indicate that using lipase as a sole diagnostic measure is better than using a combined test. When cost is an issue, using only lipase may be more practical than combining amylase and lipase tests at more cost. As reported in the study performed in the UK, the cost of amylase test was £1.94 while the cost of lipase test was £2.50 [116]. Therefore, a combined test would cost £4.44 for a result that is not more accurate than a lipase test.

Moreover, some studies described the use of the lipase/amylase ratio for differentiation of AP etiologies. The ratio of lipase/amylase >3 and >4 can differentiate alcoholic and non-alcoholic AP [127,128]. It has been shown in a study of a patient population in South India that reported the differentiation of alcoholic AP from non-alcoholic AP at > 4 ratio with 84% sensitivity and 59% specificity [127]. These ratings concur with another study that reported the lipase/amylase ratio to have relatively low sensitivity rating in predicting alcoholic AP [117]. The lipase/amylase ratio has also been considered in the prediction of biliary AP. It has been found that the lipase/amylase ratio can be used to distinguish mild acute biliary pancreatitis from non-pancreatitis, however, the study also explained that the critical value of the lipase/amylase appears to be dependent on the diet and cultural characteristics of the patient population [129]. Therefore, using the lipase/amylase ratio, which involves testing for both amylase and lipase still needs further studies.

6.5. Guidelines on the use of amylase and lipase for the diagnosis of acute pancreatitis

The usage of amylase and/or lipase for the diagnosis of AP can be established by examining the guidelines given by professional organizations in various countries. Table 4 summarizes some of the more extensively used and established standards released by professional organizations in France, Great Britain and Ireland, Italy, Japan, and the United States. Professional organization recommendations on the use of amylase and lipase reflect current acceptable practice.

The French National Society of Gastroenterology issued a document in 2001 containing its recommendations on the diagnosis of acute pancreatitis. In a conference, agreement was achieved on the preference for lipase testing over amylase testing, using the ≥ 3 x URL threshold, due to the higher sensitivity of lipase [79]. Amylase testing was considered an acceptable diagnostic method for AP, but in general cases and when cost and time are paramount issues, lipase test is deemed sufficient. The limitation of the amylase and lipase tests in determining the etiology and severity of AP has been recognised. Use of the biochemical marker trypsinogen-2 has been raised as a confirmatory test [78].

Similarly, the Japanese Society of Emergency Abdominal Medicine arrived at the same recommendation. Lipase is the superior diagnostic test for AP because of its consistently high sensitivity rating across studies. Lipase test was included in the routine diagnosis for AP. Pancreatic amylase test was deemed acceptable only in situations when lipase test is difficult to do for one reason or another [130]. In contrast, the Japanese organisation did not set a diagnostic threshold for lipase, citing the limited evidence establishing a defined threshold. Factors relevant to each case of suspected AP is used to interpret the diagnostic implications of a lipase test result. Imaging tools have been identified as the confirmatory test following the lipase test. Diagnostic imaging can rule out other pancreatic diseases

Table 4. Guidelines on amylase and lipase testing for the diagnosis of acute pancreatitis.

Organisation	Biochemical marker recommendation	Diagnostic threshold recommendation	Additional related recommendation
French National Society of Gastroenterology	Lipase preferred over amylase	≥ 3 x URL	Trypsinogen-2 as confirmatory test.
Japanese Society of Emergency Abdominal Medicine	Lipase preferred except when lipase measurement is difficult then pancreatic amylase is measured.	Not set	Diagnostic imaging to confirm etiology.
British Society of Gastroenterology; Association of Surgeons of Great Britain & Ireland; Pancreatic Society of Great Britain & Ireland; Association of Upper GI Surgeons of Great Britain and Ireland	Lipase preferred over amylase, but amylase has acceptable diagnostic accuracy.	Cautious interpretation depending on the period since onset of AP	Other biochemical markers to confirm.
American College of Gastroenterology	Serum lipase preferred; unnecessary to use both amylase and lipase [46].	≥ 2 to ≥ 4 x URL	Amylase and lipase not advisable in determination of severity.
American Gastroenterological Association	Lipase recommended but serum amylase and/or lipase test upon admission is acceptable.	≥ 3 x URL	Clinical symptoms and imaging to confirm.
American Family of Physicians	Serum lipase more sensitive but initial laboratory tests include amylase and lipase are required.	Not set	Trypsinogen-2, C-reactive protein (CRP), procalcitonin, phospholipase A2, interleukin-6 and interleukin-8 for confirmation.
Working Group of the Italian Association for the Study of the Pancreas	Lipase preferred.	Not set	Systematic review of tests.

as well as confirm the existence of AP [130].

Several British organisations were also in agreement over the preference for lipase test in the diagnosis of AP. The high sensitivity of lipase test when compared to amylase test has also been cited in support of this recommendation. Even so, amylase test is still considered to have acceptable accuracy. Unlike the Japanese organisation, which explicitly agreed on the sole use of lipase test subject to particular exceptions, British organisations accept amylase and/or lipase test for the diagnosis of AP. Unlike the French organisation but like the Japanese organisation, the British organisations also did not set a diagnostic threshold. The lack of standards on the threshold led to the recommendation of caution in the interpretation of the amylase and lipase test results by considering the period since the initial presentation of AP and the symptomatic manifestations. Use of other biochemical markers facilitate the confirmation of the disease and determination of severity [79].

Slight differences have been observed in the recommendations of American organisations. The American College of Gastroenterology explicitly prefer lipase test over amylase test because of the relatively higher sensitivity and consistently high specificity ratings of the former biochemical marker. It also recommended that it is not necessary to order both lipase and amylase tests in the routine diagnosis of potential AP cases. Like the French organisation, the threshold for lipase test has been set at ≥ 2 to ≥4URL. Other biochemical markers and tests have to be made in order to determine severity, especially in the confirmed cases of AP [46]. Both the American Gastroenterological Association and the American Family of Physicians express a more permissive approach to amylase and lipase testing. Both organisations recommend the use of serum lipase but deem acceptable the physician orders for both amylase and lipase tests in the diagnosis of AP [31,46]. The American Gastroenterological Association has set the threshold at ≥ 3 x URL [46] while the American Family of Physicians has not set any threshold [31]. Moreover, in considering the additional related recommendations of the three American organisations, confirmation of AP, identification of etiology and determination of severity can be achieved through clinical symptoms, imaging, and testing for other biochemical markers.

The Italian organisation, Italian Association for the Study of the Pancreas, concurred with the French organisation, Japanese organisation, and the American College of Gastroenterology over the preference for lipase testing [131]. It has not set a threshold for lipase testing due to lack of agreement over the appropriate normal and abnormal limits. Diagnosis for AP involves a systematic process that includes the consideration of clinical symptoms, lipase testing, imaging and/or testing for other biochemical markers. Interpretation of the lipase test result would consider the wider context of each case.

At the least, there is widespread agreement over the higher sensitivity of lipase test over amylase test, but the acceptable sensitivity rating of amylase test is also recog-

nised. At the most, there is growing trend towards the routine sole use of lipase test for the diagnosis of AP. Amylase test is used only when lipase test is not doable or when doing this test is necessary. In practice, physicians in Great Britain and United States still order both amylase and lipase tests because guidelines were permissive towards this practice and lacked force in suggesting the shift towards the lipase test. Use of the lipase test only is likely to be more common in France, Japan, and Italy where the organisation of clinicians has concurred over the preference for lipase test. Amylase test is ordered only in exceptional circumstances. Systematic diagnosis is a recommended practice in all of the countries. Biochemical tests form part of a thorough step-by-step process of diagnosing and managing AP.

7. Discussion and conclusion

Diagnosis of acute pancreatitis is an evolving aspect of the academic and clinical study of this disease. In this review, developments in the range of diagnostic methods for AP and the understanding of the benefits and downsides of using one or a combination of these methods have been covered. There are some variances in the reported accuracy rating of these diagnostic methods, which can be attributed to the relative advantages and disadvantages. Most diagnostic methods work best in certain situations but work less effectively in other situations. As such, there is common understanding of the need to adopt a multiple-method approach to the effective diagnosis of AP and select a mix of methods that best fit the situation. At the same time, some extent of standardisation is also necessary to provide guidelines, based on best practices, to facilitate effective and appropriate implementation in the clinical setting.

Biochemical markers are crucial to the diagnosis of AP. These cannot be excluded from the mix of methods used to diagnose AP and AP etiology as well as the classification or scoring methods used to determine severity. Amylase and lipase are the commonly used biochemical markers for diagnosing AP. Other biochemical markers have been explored to determine their diagnostic relevance.

Amylase, particularly total serum amylase, is more commonly used in clinical practice. However, this has lower specificity because amylase can also be released by the salivary gland. High amylase levels can indicate AP or other conditions. Several laboratory methods have been introduced to differentiate amylase produced by the pancreas from amylase in the salivary glands. Determining only the amylase produced by the pancreas increases the specificity of AP of the test results. Diagnosis of AP becomes more accurate. While these methods have been relatively established, the amylase pancreas tests take more time and cost more. Urinary amylase is a more recent method for diagnosing AP. Amylase levels in urine takes a longer time to drop when compared to amylase in the blood. The test involves the collection of three urine samples at intervals within 24 hours. Like total serum amylase, results of urinary amylase assays can be affected by other conditions. It cannot be used as the only biochemical test for diagnosing AP. Limitations of amylase assays have been frequently cited in this review. Focus is shifting towards the wide use of serum lipase assays.

Use of serum lipase is increasing. Since lipase is only produced by the pancreas, serum lipase assays have been shown to have higher specificity when compared to serum amylase. Lipase is retained in the blood longer when compared to amylase in the blood and in urine. Lipase assays apply as diagnostic methods for AP in patients seeking medical attention when the symptoms are still starting or already severe. Symptoms and pain tolerance differ in individual patients. Serum amylase may not be appropriate for patients admitted several hours or days after the onset of the symptoms. Lipase tests are completed in 12 hours, which is half the time it takes to complete urinary amylase. In the emergency care setting, when time is a factor, total serum amylase is still ordered to have results in less time. Exploration of alternative biochemical markers focused on simple biochemical tests.

Many of the recently published studies recognized the greater accuracy of lipase in the diagnosis of AP. Several of these studies recommended the use of serum lipase as the only test for diagnosing AP. This recommendation was based on comparative sensitivity and specificity ratings, case statistics, diagnosis of specific aetiologies, and guidelines of different professional organisations in the health sector in various countries. A persisting issue in the use of biochemical markers in the diagnosis of AP, for both amylase and lipase, is the varied URL and threshold limits employed for interpreting the results of biochemical tests. Different specificity and sensitivity ratings are achieved depending on the URL and threshold limits used. No standards exist on the URL and threshold for biochemical markers using patient and medical parameters. This could explain the difficulty in establishing lipase as the preferred test.

In practice, many physicians still order total serum amylase or both serum amylase and lipase tests in diagnosis of AP. Varied recommendations by professional organisations on the biochemical test to use for diagnosing AP explain the lack of standardisation across different countries. In the US and UK, professional organisations are less unified over the comparative benefits, including the cost advantage, of using lipase test in routine diagnosis. As such, American and British organisations recognise the higher accuracy of serum lipase over serum amylase but consider the use of either or both tests as acceptable. Ordering both serum amylase and lipase has been shown not to have any additional benefits, in terms of accuracy and cost, to using serum lipase alone. This point could be a factor for consideration during reviews on guidelines by organisations in these countries. Organisations in France, Japan and Italy have explicitly recommended the sole use of serum lipase in diagnosis of AP by establishing standard URL and threshold values. Accuracy, expediency and cost-effectiveness have been cited as justification for this preference. Further empirical studies, especially on the URL and threshold, success in the clinical setting and cost-effectiveness, are needed to support a compelling case for the adoption of serum lipase test as preferred diagnostic method in different countries.

Biochemical markers are useful in determining AP etiology. In diagnosing cause, lipase has been reported to be more predictive of biliary, alcoholic and post-operative AP than amylase. Biliary and alcoholic AP are the most common diagnoses in the clinical setting. Preference for lipase assays will be able to determine the presence of the disease and its causes in most cases. There are other biochemical markers suggested in determining AP etiology. ALT is a test specific to biliary AP. Trypsinogen-3 has

been suggested in the diagnosis of alcoholic AP. However, there is no standard practice on the use of ALT in clinical diagnosis and trypsinogen-3 needs to be validated in the actual health setting. Less common aetiologies can be diagnosed using other biochemical markers in combination with medical history, physical examination and imaging. History of a specific AP etiology in the family, pregnancy and trauma in the abdominal areas are indicative of AP and its specific cause. In uncommon cases and in idiopathic AP, diagnosis of etiology requires a contextual approach and even a process of elimination. Yet, standards on the combined use of biochemical markers and other tests have not emerged. On one hand, this could be due to the need to have a flexible diagnostic process to accommodate individual differences in the presentation of symptoms. On the other hand, some standards could make it easier to indicate which biochemical test to use in particular clinical situations, but subject to validation in cohort and large-sample studies.

Several biochemical markers, apart from amylase and lipase, have been studied to determine their effectiveness for diagnosing AP severity. Two interrelated strands of investigation into biochemical markers for diagnosing AP severity exist. One strand focuses on single variable predictors for determining severity. Amylase and lipase work best in the diagnosis of the onset of AP and the most common etiologies, but other biochemical markers are more useful in determination of severity. Some biochemical markers work best during the early stage of the disease, such as interleukin-6, interleukin-8 and trypsinogen activation peptide. Other biochemical markers can be used throughout the progression of the disease, such as phospholipase A2 and procalcitonin. Some biochemical markers are specific to certain symptoms of severe AP, such as C-reactive protein and procalcitonin for necrosis and copeptin plasma and b-type natriuretic factor for cardiovascular-related severity presentations. Apart from trypsinogen-2, validity of other biochemical markers has not been widely established. As a result, guidelines on the use of specific biochemical markers have not emerged. The other strand considers biochemical markers as part of classification or scoring systems. By integrating the different methods for diagnosing AP, the results can determine the presence of AP, etiology and severity. Several classification systems have emerged; Atlanta classification, Ranson's criteria, APACHE II, and Glasgow score are the earlier scoring systems. While these scoring systems are widely used, limitations and areas for improvement have been identified. Critical is a category that has been recommended for inclusion in the Atlanta classification. APACHE II is comprehensive, but it has been criticised for including parameters that may not be relevant to AP. BALI, BISAP, HAPS, Panc 3, JSS, and SNNAP are newer scoring systems developed to address these criticisms. These were intended to simplify the diagnosis of severity. Further studies are needed to validate these scoring systems and establish the clinical contexts where these scoring systems best apply.

Biochemical markers are also closely linked to AP management and treatment. Despite the lack of standards on the use of biochemical markers for diagnosing AP and its etiology and severity, standards exist on the appropriate intervention and timing of treatment. However, there are aspects of the management of AP that remain under debate, such as the use of antibiotics and ERCP. Differences in opinion emerge from the variances in reported clinical observations of effective treatment. Continuing studies on these controversial aspects should result to some degree of consensus in the coming years. A deeper understanding of biochemical markers can facilitate not only the better diagnosis of AP but also the improved treatment of the disease.

This review has shown widespread agreement over much of the aspects of biochemical markers for the diagnosis of AP. Yet, there are key areas of debate that have to be resolved. The results pointed to areas for future research. One is on the further investigation into the accuracy and validity of biochemical markers in the diagnosis of AP, especially the comparative predictive accuracy of amylase and lipase in the clinical setting. Specific biochemical markers can be studied more closely to establish diagnostic validity, particularly for specific etiologies. Another is the deeper investigation into the reasons for the limited adoption of lipase testing in the clinical setting, even if it has been shown to be more accurate than amylase. Last is on the ways of developing standards on biochemical markers for AP diagnosis. Developments on achieving consensus over the URL and threshold limits for the interpretation of the results of tests for biochemical markers and other related standards of practice have important implications on the effective diagnosis of AP.

Conflict of interests
The author has no conflicts with any step of the review preparation.

Consent for publications
The author read and approved the final manuscript for publication.

Ethics approval and consent to participate
No humans or animals were used in the present review.

Informed consent
The author declares that no patients were used in this review.

Author's contributions
The author confirms sole responsibility for the conception, design, literature review, drafting, and finalization of the manuscript. All aspects of the work were performed independently by the author.

Funding
None

Acknowledgements
The author would like to thank Najran University for providing necessary tools to conduct this review.

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