DOI: 10.17816/KMJ2021-528

Diagnostic value of research methods in diagnostics of chronic pancreatitis

G.R. Aliyeva

Scientific Center of Surgery named after M.A. Topchubashov,
Baku, Azerbaijan

Abstract

Chronic pancreatitis remains an unsolved problem for clinicians. One of the biggest dilemmas is to establish a clear diagnosis. Diagnosis can be particularly elusive in patients with early chronic pancreatitis. Many studies have been undertaken to improve diagnostics in chronic pancreatitis, but this has been significantly limited by the lack of a "gold standard". The evaluation of patients with suspected chronic pancreatitis should follow a progressively non-invasive to more invasive approach. Computed tomography is the best primary imaging modality to obtain as it has good sensitivity for severe chronic pancreatitis and may exclude the need for other diagnostic tests. When ambiguous results are obtained, a magnetic resonance cholangiopancreatography may require for a more detailed evaluation of both the pancreatic parenchyma and ducts. If the diagnosis remains in doubt, endoscopic ultrasound with or without pancreas function testing becomes the preferred method. Endoscopic retrograde cholangiopancreatography remains a last line diagnostic test and generally should be used only for diagnostic purposes. Future researches in the field of diagnosis of early-stage chronic pancreatitis should purpose optimizing current diagnostic tools. A definitive diagnosis of chronic pancreatitis may not be made simply by clinical history, imaging or function testing alone, but rather by the data gathered by a combination of these diagnostic tools.

Keywords: chronic pancreatitis, magnetic resonance cholangiopancreatography, endoscopic ultrasound, endoscopic retrograde cholangiopancreatogram, computed tomography.

For citation: Aliyeva G.R. Diagnostic value of research methods in diagnostics of chronic pancreatitis. *Kazan Medical Journal*. 2021; 102 (4): 528–536. DOI: 10.17816/KMJ2021-528.

Introduction. Chronic pancreatitis (CP) is a chronic disease that is usually characterized by repeated attacks of acute pancreatitis, chronic abdominal pain, and ultimately, signs of pancreatic damage. Extensive fibrosis and inflammation in the gland lead to both exocrine and endocrine insufficiency.

The pathogenEUIs of the disease remains controversial; several theories have been proposed to explain it [1–3]. The most widely accepted theory of necrosis-fibrosis states that chronic fibrotic changes occur after a series of repeated acute injuries to the periductal areas [4]. Although no theory has been conclusively proven, it is likely that the pathogenEUIs of the disease is a complex interaction of several etiological factors [5].

CP remains an unsolved concern for doctors [6]. Despite extensive availability of several tests and imaging methods, establishing a diagnosis can be a burdensome task, as it is impossible to limit ourselves to the results of any one imaging method or analysis for an accurate diagnosis of CP.

Diagnosis can be especially difficult in patients with early CP (also known as CP with minimal changes). In this condition, patients usually present with clinical symptoms suggestive of CP, but they do not have obvious radiological abnormalities [7]. Other objective parameters that aid in diagnosis, such as indirect pancreatic function tests, can often remain normal for many years after symptoms appear.

In contrast to the above, subgroups of patients with signs of pancreatic fibrosis without clinical symptoms indicating CP have been described in the literature [8–10]. According to these sources, the degree of fibrosis does not directly correlate with the degree of exocrine and endocrine dysfunction [8–10].

To improve the diagnosis of CP, many studies have been conduct, but all of them are significantly limited owing to the lack of a "gold standard." Endoscopic retrograde cholangiopancreatography (ERCP), previously considered as a potential "gold

For correspondence: gunayaliyeva80@gmail.com Received 05.03.2021; accepted 19.04.2021.

standard" for the diagnosis of CP, assesses only the anatomy of the duct. In addition, sometimes with this method, secondary changes in the duct associated with phenotype, obesity, or age are attributed to CP [11–13].

Currently, histological verification of the diagnosis of CP is becoming the final stage in the diagnosis. However, as the diseased pancreatic tissue is obtained invasively for histological examination, safe and regular way to use this method is not available. In addition, even when studying autopsy tissue for the diagnosis of CP, there are serious age-related changes that can be mistaken for changes associated with CP [5].

The final diagnosis of CP can be made not only on the basis of medical history, imaging, or functional testing, but rather on the basis of data collected using the totality of all diagnostic methods [1, 5].

Clinical manifestation of the disease and risk factors. Clinical manifestations of CP include chronic abdominal pain, steatorrhea, diabetes mellitus, and unexplained weight loss. The initial assessment of patients with signs and symptoms related to CP should include careful history taking and screening for key risk factors, especially alcohol and smoking, as these increase the likelihood of illness.

In the United States, alcohol abuse remains the most common etiological factor of CP. Yadav et al. [14] found that the prevalence of alcohol consumption among men and women in the CP group was 38.4% and 11.0%, respectively. In the control group, these values were 10.0% and 3.6%, respectively. People who drink alcohol extensively have a higher incidence of CP than those who do not drink or drink alcohol in insignificant amounts [odds ratio = 3.10; 95% confidence interval (CI): 1.87–5.14] [14]. This study also concluded that cigarette smoking is an independent risk factor for CP, as well as for recurrent acute pancreatitis [14]. Smoking ≥1 pack per day increases the chances of developing CP by 3.3 times [14].

To assess the risk factors for the development of CP, two main classification systems were formulated: TIGAR-O (Etemad, Whitcomb, 2001) and MANNHEIM (Schneider, 2007) [15–17]. These help in choosing the timing of testing for CP.

Modern diagnostic methods are classified into two categories: imaging (computed tomography [CT], magnetic resonance imaging, endoscopic ultrasound [EUI], and ERCP) and pancreatic function tests (direct and indirect tests). Each of these methods plays a special role in establishing the diagnosis, and it is important that clinicians with CP follow the stated approach to avoid unnecessary tests and misdiagnosis [18].

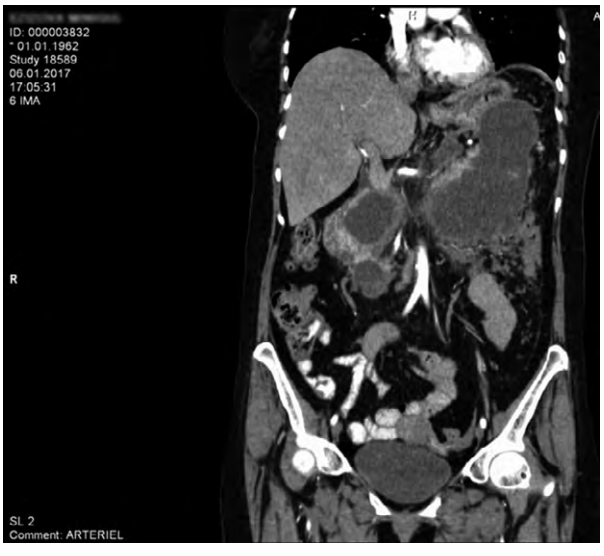

Fig. 1. Visualization of a pancreatic pseudocyst on a computed tomographic image [9].

Table 1. The frequency of detecting signs of chronic pancreatitis with computed tomography [13]

Signs	Frequency, %
Dilation of the pancreatic duct	68
Pancreatic atrophy	54
Pancreatic calcification	50
Accumulation of fluid	30
Focal enlargement of the pancreas	30
Dilation of the biliary tract	29
Changes in peri-pancreatic adipose tissue	16
Normal pancreas	7

Visualization methods in CP. *CT* is considered the best method for primary imaging when examining CP [19]. The advantages of CT are as follows: widely available, provides a detailed overview of changes in the morphology of the pancreas that occur in CP, and is especially useful for detecting changes observed in complications of the disease. CT quickly assesses the pathology of adjacent organs, clarifying various manifestations that mimic CP. Another advantage is the detection of various complications of acute pancreatitis and CP, such as pseudocysts (Fig. 1), obstruction of the bile ducts or duodenum, venous thrombosis, pseudoaneurysms, and pancreatic-pleural fistulas [9].

In CP, three classic signs are visualized on a computed tomogram: expansion of the pancreatic duct (68%), pancreatic atrophy (54%), and its calcification (50%) [13, 19] (Table 1).

As indicated in Table 1 [13], CP also manifests with normal morphology of the pancreas, according to CT data, which makes the diagnosis of this

Table 2. Pancreatic imaging criteria in chronic pancreatitis according to M-ANNHEIM [25]

Cambridge gradation	CT, USI, MRI/MRCP	EUI
Normal	Quality study showing all glands without abnormalities (0 points)	—
Doubtful	One abnormal feature (1 point)	Four or less abnormal signs (no distinction between questionable and mild) (1 point). Five or more abnormal signs (no distinction between moderate and severe) (3 points)
Insignificant changes	Two or more pathological signs, including, intact main pancreatic duct	
Moderate changes	Two or more pathological signs, including minor pathology of the main pancreatic duct (increase from 2 to 4 mm or increased echogenicity of the duct wall) (3 points)	
Significant changes	The same as above, with one or more characteristic pronounced changes (4 points)	—

Note: CT - computed tomography; USI - ultrasound investigation; MRI - magnetic resonance imaging; MRCP - magnetic resonance cholangiopancreatography; EUI - endoscopic ultrasound investigation.

condition difficult. Despite the fact that pancreatic atrophy is visualized in a significant proportion of patients with CP, it cannot serve as a specific sign, since atrophy is also characteristic of normal aging [13, 19]. In addition, with CP, enlargement of the pancreas can also be visualized. While CT visualizes changes in the pancreatic parenchyma in late stages of CP, it fails to visualize the classic changes observed in the pancreatic ducts, which makes the diagnosis of early CP unreliable [13, 19].

Magnetic resonance cholangiopancreatography (MRCP). Despite significant attempts in improving CT resolution over the past three decades (such as the development of multidetector and multiphase contrast imaging), there are significant limitations in the diagnosis of CP, especially in assessing the anatomy of the pancreatic duct, as well as in diagnosing early CP [20, 21]. MRCP and MRCP, enhanced with secretin, are sensitive and specific to parenchymal and ductal changes in the characteristics of pancreas in this pathology. A specific advantage of MRCP in CP is better visualization of the parenchyma and pancreatic ducts [22].

Parenchymal changes that are visualized via magnetic resonance imaging include pancreatic atrophy, decreased T1 signal, irregular head or body contour, heterogeneous parenchyma, and delayed increase in gadolinium accumulation in the pancreas after administration [23].

Ductal changes include intraductal filling defects, often indicative of stones; enlargement of the main pancreatic duct; lateral branch enlargement; irregular duct contour; and decreased compliance following secretin administration [23, 24].

Currently, there are no standardized criteria for diagnosing CP using MRCP, but there are systems for assessing the image of the pancreas, which describe the changes observed in normal conditions and in severe CP (Table 2) [25].

The Cambridge classification can be modified to categorize the results of MRCP [26]. According to this classification (Table 2), CP severity is directly proportional to the scores, i.e., the higher the score, the more pronounced changes in disease characteristics [26]. With the increase in the use of secretin-enhanced MRCP, it is necessary to create a formal classification system that would assess changes in both the parenchyma and ducts, increasing the focus in the early diagnosis of CP [26].

Secretin-enhanced MRCP is a non-invasive approach to assess exocrine pancreatic function. Secretin is a peptide that stimulates pancreatic duct cells to secrete bicarbonate-rich fluid into the small intestine. Similar to direct tests for assessing pancreatic function, using this method, secretin is administered intravenously, and then, changes in the intensity of the T2 signal occurring in the pancreatic duct are recorded [22, 27].

Secretin-enhanced MRCP allows for better visualization of the pancreatic ducts as well as lateral branches compared with traditional MRCP. Better visualization of the main pancreatic duct and pathologically altered lateral branches compared to MRCP without contrast enhances the sensitivity of CP diagnostics from 77% to 89% [20–22].

Before the advent of secretin-enhanced MRCP, conventional ERCP was considered the “gold standard” for diagnosis, as it is capable of detecting subtle changes in the pancreatic ducts and lateral branches upon retrograde administration of contrast, leading to excessive stretching of the pancreatic ducts [28]. Although this overstretching does not occur with physiological filling of the pancreatic ducts, adequate visualization of the main duct, lateral branches, and accessory ducts is possible with secretin-enhanced MRCP [29].

In healthy people, administration of secretin results in the expansion of the pancreatic duct on

average by two-thirds of its diameter [28]. This decreases with the aggravation of disease severity, which is probably associated with increased fibrosis in the gland [28]. Another indicator of pancreatic function that can be detected with secretin-enhanced MRCP is pancreatic duct blood flow velocity.

EUI is another method that is increasingly used in treating the complications of CP, such as urolithiasis of the Wirsung duct and pancreatic pseudocysts. As highlighted above, the diagnosis of CP is usually clear in people with severe illness, since they have classic symptoms, risk factors, and, as a rule, pathological features visualized by CT or MRCP. For early CP, the diagnosis is rarely unambiguous, which complicates the differential diagnosis. It is in early CP that EUI has the greatest potential to aid in diagnosis, since this method is rarely used for diagnostic purposes in late stages of CP [30, 31].

As with MRCP, EUI evaluates both parenchymal and ductal changes in the pancreas for diagnosing CP [12, 32]. The international working group has proposed nine criteria for EUI (4 parenchymal and 5 ductal) for diagnosing CP (Table 3).

The presence of more than five signs provides the final diagnosis of CP, and 2 or less excludes it [33]. Patients with 2–5 criteria have an uncertain diagnosis and should be additionally and carefully examined using functional testing of the pancreas [33, 34]. These nine criteria were associated with distinct histological changes noted in the samples collected at EUI [34]. Changes observed in EUI may be nonspecific and present in healthy people [35]. This conclusion was made based on the data obtained in several studies [34, 35], including data on the EUI results of 120 patients without pancreatic pathology. Reportedly, as age-related changes appear, the development of at least one parenchymal and one ductal anomaly is likely according to EUI data. This has been reported in 23%, 25%, and 39% of patients aged <40, 40–60, and >60 years, respectively [34–36].

Despite the fact that these criteria are useful in studying CP, there are several doubts about the interpretation of results, as these results can also be observed with physiological aging, smoking, or obesity [36].

Given the lack of standardization in the interpretation of EUI data in the context of CP, the Rosemont criteria were developed [25]. These criteria represented the unanimous opinion of 32 endoscopists and aimed at creating a more standard approach to interpreting the results of EUI in CP [25].

The main criteria were divided into groups A and B. The main criteria for group A included hyperechoic foci with shading and stones of the main duct of the pancreas. The main criteria for group B included swarm lobularity.

Table 3. International Working Group criteria for the diagnosis of chronic pancreatitis and histological correlations [25]

Criteria of endoscopic ultrasound investigation	Histological correlation
Parenchyma-specific features	
Hyperechoic foci	Focal fibrosis
Hyperechoic boundaries	Widespread fibrosis
– Lobular contour	Interlobular fibrosis
– Cysts	Cyst/pseudocyst
Duct-specific features	
– Dilation of the major duct	Head > 3 mm, body > 2 mm, tail > 1 mm
– Uneven flow	Focal dilation/narrowing
Hyperechoic fields	Periductal fibrosis
– Visible lateral branches	Lateral branch extension
– Calculi	Calcified calculi

Secondary criteria included [25, 37] the following:
– Dilated ducts (>3.5 mm)
– Presence of pancreatic cysts
– Irregular shape of the pancreatic duct
– Dilated lateral branches (>1 mm)
– Hyperechoic duct wall
– Cords, not shaded hyperechoic foci and lobed shape with non-adjacent lobules

In the diagnosis of CP, the Rosemont criteria have a great advantage in comparison with the standard criteria and functional testing of the pancreas [25].

Compared with the histological examination of the biopsied samples obtained invasively, when making the final diagnosis, the sensitivity of the EUI in the diagnosis of CP exceeded 80% and the specificity reached 100% [25]. Thus, EUI can be useful for diagnosing early CP owing to its high sensitivity in detecting pancreatic pathology [25, 36, 38]. The Rosemont criteria are the most widely used diagnostic criteria for CP but have suboptimal accuracy, especially for early CP. Given the large number of possible explanations for pancreatic EUI abnormalities, this method should not be used in isolation to clinically diagnosis CP. More research is needed to optimize this imaging modality, including assessment with new imaging techniques such as EUI, elastography, and assessment of duct diameter compliance with secretin administration during pancreatic stimulation [25].

Currently, *ERCP* is rarely used to diagnose CP. It provides a detailed pancreatogram that can show

characteristic changes associated with chronic fibrosis and atrophy [38]. However, after the advent of CT, MRCP, and EUI, the use of this method has been usually limited to therapeutic purposes (i.e., stenting, cannulation, and lithotomy of the pancreatic duct), rather than diagnostic purposes [39].

Specific findings observed on a retrograde pancreatogram include the caliber and contour of the main pancreatic duct, clear definition of its lateral branches, intraductal filling defects, strictures, and cavity formation. The normal caliber and contour of the main pancreatic duct are often described as smooth and progressively tapering from head to tail [11]. The normal final size of the main pancreatic duct is difficult to determine as it depends on age, race, and sex. For this reason, there exists considerable disagreement regarding the interpretation of pancreatogram results [13, 39].

Although ERCP is sensitive to changes in the pancreatic duct, the use of this method for diagnosing CP has several disadvantages. First, like EUI, it depends on the operator and is subject to variability depending on the observer. The differences observed in ERCPs are not only in the quality of the pancreatogram but also in the interpretation of images [39, 40]. Secondly, pancreatograms do not allow the assessment of classic changes in the pancreatic parenchyma observed in CP. Finally, ERCP is the most invasive diagnostic method that carries a postoperative risk, primarily pancreatitis.

For these reasons, the American Society for Gastrointestinal Endoscopy has recommended the use of ERCP for the diagnosis of CP only if other imaging methods are exhausted [40].

According to the data of a randomized clinical trial on patients with CP, the sensitivity of ESI, magnetic resonance imaging, and CT did not differ significantly [24]: 81% (95% CI: 70–89), 78% (95% CI: 69–85), and 75% (95 % CI: 66–83), respectively [41]. Specificity for ESI (90%; 95% CI: 82–95), ERCP (94%; 95% CI: 87–98), CT (91%; 95% CI: 81–96), magnetic resonance imaging (96%; 95% CI: 90–98), and transabdominal ultrasound (98%; 95% CI: 89–100) were also comparable [41].

Pancreatic function tests are usually classified as indirect (non-invasive) or direct (invasive) [40]. Non-invasive methods include assessments of the exocrine function of the pancreas without direct hormonal stimulation of the gland. An example of indirect methods is the determination of trypsinogen in blood serum as well as elastase in feces and fecal fat. Direct methods include hormonal stimulation of the pancreas with secretin or cholecystokinin.

The advantages of indirect functional tests include their cost-effectiveness, non-invasive nature and easy to use, and utility in an outpatient basis. One such tests is the collection of fecal fat in 72 h. Fecal fat collection is usually not performed in the diagnostic algorithm of CP; instead, its usefulness lies in assessing the degree of exocrine dysfunction in patients with confirmed CP and the effectiveness of treatment when prescribing pancreatic enzymes [42].

When performed correctly, this is an excellent test for quantifying steatorrhea. However, owing to the great need for patient collaboration for stool collection and coordination with the laboratory, many clinicians avoid this test, especially in the diagnostic assessment of CP.

The most commonly used indirect marker is fecal pancreatic elastase-1. Indirect tests are useful as an adjunct to imaging tests to determine the presence of disease. Alone, their results are not applicable in the interpretation of CP diagnosis [42].

Direct functional tests allow the evaluation of both acinar and ductal cells of the pancreas by aspiration of duodenal contents after stimulation with cholecystokinin or secretin [40, 42]. Pancreatic enzymes are determined in the duodenal contents after stimulation with cholecystokinin, and the concentration of bicarbonate is estimated after stimulation with secretin [40]. The main feature of secretin-related direct tests is the exclusion of CP in patients with signs and symptoms of CP, such as chronic abdominal pain.

Direct functional tests and EUI have advantages in the diagnosis of early CP. Functional tests of the pancreas can detect exocrine dysfunction and classic visual changes characteristic to CP; in addition, EUI allows the detection of early ductal and parenchymal changes indicative of CP. Stevens et al. [43] compared the results of EUI with direct tests for diagnosing CP with minimal changes. They showed 72% agreement between EUI and direct testing at an early stage of CP. The authors also concluded that direct tests (in particular with secretin) versus EUI in the early stages of the disease would not be accurate [43]. Finally, it has been suggested that the use of both EUI and direct tests in combination may further improve the specificity of diagnosing the disease, and pancreatic functional tests may add clarity to the diagnosis in patients with questionable EUI results [43].

Differential diagnostics of CP. A difficult clinical dilemma arises in the presence of focal anomalies in the pancreas, as differentiation is primarily conducted between pancreatic ductal adenocarcinoma, focal CP, and autoimmune pancreatitis [44].

Although CP can potentially develop in any part of the pancreas, it more often occurs in the head. The term “grooved pancreatitis” describes an anatomical variant of CP, which is characterized

by damage to the pancreatic head, duodenum, and pancreatoduodenal sulcus [32]. In focal CP, the parenchyma remains, which can also be confused with ductal adenocarcinoma of the pancreas [44]. Many patients with grooved pancreatitis have elevated serum glycoprotein CA 19-9 owing to biliary obstruction or acute inflammation, which further complicates diagnosis. In these cases, suspicions of pancreatic ductal adenocarcinoma should be made, and patients, owing to the impossibility of excluding malignant neoplasms, should undergo pancreatic resection [45, 46].

Nevertheless, the presence of ductal changes can be a distinguishing feature that makes it possible to differentiate focal CP from pancreatic ductal adenocarcinoma. Not narrowed, open main duct of the pancreas, passing in the area of focal changes is a sign characteristic of ductal adenocarcinoma, and the presence of duct penetration indicates CP [45]. In addition, the presence of calcifications in the pancreatic parenchyma and the tortuous main duct are characteristic of CP [1, 36]. Patients with focal autoimmune CP have high levels of serum immunoglobulin G4 and a characteristic extrapancreatic disease, and the tumor is excluded based on the results of fine needle biopsy and a positive response to steroid therapy.

Conclusion. In patients with a suspicious clinical picture and factors that increase the risk, examination for suspected CP should be conducted in a step-by-step manner: from a non-invasive to a more invasive method. After a thorough history and physical examination, basic laboratory tests such as blood lipase and amylase, metabolic parameters, and indirect pancreatic function tests (fecal elastase-1 and serum trypsin) should be performed.

CT remains the best primary imaging technique. It has good sensitivity for severe CP and will help eliminate the need for other diagnostic tests. If in doubt, MRCP should be performed for a more detailed assessment of the pancreatic parenchyma and ducts. If the diagnosis remains uncertain, EUI should be performed with or without pancreatic function testing. ERCP remains the final link in diagnostic tests, and owing to its invasiveness and increased risk of complications, this method should be rarely used for diagnostic purposes.

Further advances in diagnosing CP and its complications should be aimed at optimizing the existing diagnostic methods for a more accurate diagnosis of early CP, as it is in these patients that delayed CP progression may be of great importance. The best way to diagnose these patients is to test pancreatic function in the presence of uncertain EUI results. Studies of pancreatic juice biomarkers may complement the diagnosis.

Funding. The study had no external funding.

Conflict of interest. The author declares no conflict of interest.

REFERENCES

1. Löhr J.M., Dominguez-Munoz E., Rosendahl J. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United Eur. Gastroenterol. J.* 2017; 5 (2): 153–199. DOI: 10.1177/2050640616684695.

2. Wassef W., DeWitt J., McGreevy K., Wilcox M., Whitcomb D., Yadav D., Amann S., Mishra G., Alkaade S., Romagnuolo J., Stevens T., Vargo J., Gardner T., Singh V., Park W., Hartigan C., Barton B., Bova C. Pancreatitis quality of life instrument: A psychometric evaluation. *Am. J. Gastroenterol*. 2016; 111 (8): 1177–1186. DOI: 10.1038/ajg.2016.225.

3. Conwell D.L., Banks P., Greenberger N.J. Acute and chronic pancreatitis. In: *Harrison's principal of internal medicine*. Braunwald, eds. 19th ed. New York: Mc Graw Hill. 2015; 2090–2101.

4. Whitcomb D.C., Frulloni L., Garg P., Greer J.B., Schneider A., Yadav D., Shimosegawa T. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology*. 2016; 16 (2): 218–224. DOI: 10.1016/j.pan.2016.02.001.

5. Majumder S., Chari S.T. Chronic pancreatitis. *Lancet*. 2016; 387 (10 031): 1957–1966. DOI: 10.1016/S0140-6736(16)00097-0.

6. Ito T., Ishiguro H., Ohara H., Kamisawa T., Sakagami J., Sata N. Evidence-based clinical practice guidelines for chronic pancreatitis 2015. *J. Gastroenterol*. 2016; 51: 85–92. DOI: 10.1007/s00535-015-1149-x.

7. Ahmed Ali U., Issa Y., Hagenaars J.C., Bakker O.J., Goor van H., Nieuwenhuijs V.B., Bollen T.L., Ramshorst van B., Witteman B.J., Brink M.A., Schaapherder A.F., Dejong K., Spanier M.B.W., Heisterkamp J., Harst van der E., Eijck van C.H., Besselink M.G., Gooszen H.G., Santvoort van H.C., Boermeester M.A. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin. Gastroenterol. Hepatol*. 2016; 14 (5): 738–746. DOI: 10.1016/j.cgh.2015.12.040.

8. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J. Gastroenterol*. 2013; 19 (42): 7258–7266. DOI: 10.3748/wjg.v19.i42.7258.

9. Муслимов Г.Ф., Алиева Г.Р., Бехбудов В.В. Лапароскопическая цистогастростомия при гигантской псевдокисте поджелудочной железы: клинический случай. *Вестн. экстренной мед.* 2018; 11 (1): 66–71. [Muslumov G.F., Aliyeva G.R., Behbudov V.V. Laparoscopic cystogastrostomy in a giant pancreatic pseudocysts: a clinical case. *Vestnik ekstrennoy meditsiny.* 2018; 11 (1): 66–71. (In Russ.)]

10. Varadarajulu S., Eltoum I., Tamhane A., Eloubeidi M.A. Histopathologic correlates of noncalcific chronic pancreatitis by EUS: a prospective tissue characterization study. *Gastrointest. Endoscopy*. 2007; 66: 501–509. DOI: 10.1016/j.gie.2006.12.043.

11. Kolodziejczyk E., Jurkiewicz E., Pertkiewicz J., Wejnarska K., Dadalski M., Kierkus J. MRCP versus ERCP in the evaluation of chronic pancreatitis in children: Which is the better choice? *Pancreas*. 2016; 45 (8): 1115–1119. DOI: 10.1097/MPA.0000000000000644.

12. Rajan E., Clain J.E., Levy M.J., Norton I.D., Wang K.K., Wiersema M.J., Vazquez-Sequeiros E., Nelson B.J., Jondal M.L., Kendall R.K., Harmsen W.S., Zinsmeister A.R. Age-related changes in the pancreas identified

by EUS: a prospective evaluation. *Gastrointest. Endoscopy*. 2005; 61: 401–406. DOI: 10.1016/S0016-5107(04)02758-0.

13. Conwell D.L., Lee L.S., Yadav D., Longnecker D.S., Miller F.H., Mortele K.J., Levy M.J., Kwon R., Lieb J.G., Stevens T., Toskes P.P., Gardner T.B., Gelrud A., Wu B.U., Forsmark C.E., Vege S.S. American Pancreatic Association Practice guidelines in chronic pancreatitis: Evidence-based report on diagnostic guidelines. *Pancreas*. 2014; 43: 1143–1162. DOI: 10.1097/MPA.0000000000000237.

14. Yadav D., Hawes R.H., Brand R.E., Anderson M.A., Money M.E., Banks P.A., Bishop M.D., Baillie J., Sherman S., DiSario J., Burton F.R., Gardner T.B., Amann S.T., Gelrud A., Lawrence C., Elinoff B., Greer J.B., O'Connell M., Barmada M.M., Slivka A., Whitcomb D.C.; North American Pancreatic Study Group. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch. Intern. Med*. 2009; 169: 1035–1045. DOI: 10.1001/archinternmed.2009.125.

15. Forsmark C.E. Management of chronic pancreatitis. *Gastroenterology*. 2013; 144: 1282–1291. DOI: 10.1053/j.gastro.2013.02.008.

16. Muniraj T., Aslanian H.R., Farrell J., Jamidar P.A. Chronic pancreatitis, a comprehensive review and update. Part I: epidemiology, etiology, risk factors, genetics, pathophysiology, and clinical features. *Dis. Mon*. 2014; 60: 530–550. DOI: 10.1016/j.disamonth.2014.11.002.

17. Machicado J.D., Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: Similarities and differences. *Dig. Dis. Sci*. 2017; 62 (7): 1683–1691. DOI: 10.1007/s10620-017-4510-5.

18. Reddy N.G., Nangia S., DiMagno M.J. The chronic pancreatitis international classification of diseases, ninth revision, clinical modification code 577.1 Is inaccurate compared with criterion-standard clinical diagnostic scoring systems. *Pancreas*. 2016; 45: 1276–1281. DOI: 10.1097/MPA.0000000000000631.

19. Sinha A., Singh V.K., Cruise M., Afghani E., Matsukuma K., Ali S. Abdominal CT predictors of fibrosis in patients with chronic pancreatitis undergoing surgery. *Eur. Radiol*. 2015; 25: 1339–1346. DOI: 10.1007/s00330-014-3526-x.

20. Kamat R., Gupta P., Rana S. Imaging in chronic pancreatitis: State of the art review. *Indian J. Radiol. Imaging*. 2019; 29 (2): 201–210. DOI: 10.4103/ijri.IJRI_484_18.

21. Issa Y., Kempeneers M.A., van Santvoort H.C., Bollen T.L., Bipat S., Boermeester M.A. Diagnostic performance of imaging modalities in chronic pancreatitis: a systematic review and meta-analysis. *Eur. Radiol*. 2017; 27 (9): 3820–3844. DOI: 10.1007/s00330-016-4720-9.

22. Siddiqi A.J., Miller F. Chronic pancreatitis: ultrasound, computed tomography, and magnetic resonance imaging features. *Semin. Ultrasound, CT, and MR*. 2007; 28: 384–394. DOI: 10.1053/j.sult.2007.06.003.

23. Bülow R., Simon P., Thiel R., Thamm P., Messner P., Lerch M.M., Mayerle J., Völzke H., Hosten N., Kühn J.P. Anatomic variants of the pancreatic duct and their clinical relevance: an MR-guided study in the general population. *Eur. Radiol*. 2014; 24 (12): 3142–3149. DOI: 10.1007/s00330-014-3359-7.

24. Raman S.P., Salaria S.N., Hruban R.H., Fishman E.K. Groove pancreatitis: Spectrum of imaging findings and radiology-pathology correlation. *Am. J. Roentgenol*. 2013; 201: 29–39. DOI: 10.2214/AJR.12.9956.

25. Catalano M.F., Sahai A., Levy M., Romagnuolo J., Wiersema M., Brugge W., Freeman M., Yamao K., Canto M., Hernandez L.V. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointestinal. Endoscopy*. 2009; 69: 1251–1261. DOI: 10.1016/j.gie.2008.07.043.

26. Madzak A., Engjom T., Wathle G.K., Olesen S.S., Tjora E., Njolstad P., Laerum B.N., Drewes A., Dimcevski G., Frokjaer J., Haldorsen I. Secretin-stimulated MRI assessment of exocrine pancreatic function in patients with cystic fibrosis and healthy controls. *Abdom. Radiol. (NY)*. 2017; 42 (3): 890–899. DOI: 10.1007/s00261-016-0972-8.

27. Gillams A.R., Lees W.R. Quantitative secretin MRCP (MRCPQ): results in 215 patients with known or suspected pancreatic pathology. *Eur. Radiol*. 2007; 17: 2984–2990. DOI: 10.1007/s00330-007-0708-9.

28. Sanyal R., Stevens T., Novak E., Veniero J.C. Secretin-enhanced MRCP: review of technique and application with proposal for quantification of exocrine function. *Am. J. Roentgenol*. 2012; 198: 124–132. DOI: 10.2214/AJR.10.5713.

29. Hart P.A., Conwell D.L. Diagnosis of exocrine pancreatic insufficiency. *Curr. Trea. Options Gastroenterol*. 2015; 13: 347–353. DOI: 10.1007/s11938-015-0057-8.

30. Dimcevski G., Erchinger F.G., Havre R., Gilja O.H. Ultrasonography in diagnosing chronic pancreatitis: New aspects. *World J. Gastroenterol*. 2013; 19: 7247–7257. DOI: 10.3748/wjg.v19.i42.7247.

31. Shibukawa G., Irisawa A. Diagnostic efficacy of a brand-new endoscopic ultrasound processor for early-stage chronic pancreatitis. *Dig. Endosc*. 2015; 27 (1): 75. DOI: 10.1111/den.12430.

32. Fujii-Lau L.L., Levy M.J. Endoscopic ultrasound-guided pancreatic duct drainage. *J. Hepatobiliary Pancreat. Sci*. 2015; 22 (1): 51–57. DOI: 10.1002/jhbp.187.

33. Iglesias-García J., Lariño-Noia J., Lindkvist B., Domínguez-Muñoz J.E. Endoscopic ultrasound in the diagnosis of chronic pancreatitis. *Rev. Esp. Enfermedades Dig*. 2015; 107: 221–228. PMID: 25824921.

34. Guo J., Sun S. Endoscopic ultrasound for the diagnosis of chronic pancreatitis. *Pancreapedia Exocrine Pancreas Knowl Base*. 2015. https://www.pancreapedia.org/sites/default/files/DOI%20V1.%20CP-EUS%20Guo%20and%20Sun%207-15-15.pdf (access date: 26.02.2021).

35. Janssen J., Papavassiliou I. Effect of aging and diffuse chronic pancreatitis on pancreas elasticity evaluated using semiquantitative EUS elastography. *Ultraschall. Med*. 2014; 35: 253–258. DOI: 10.1055/s-0033-1355767.

36. Chantarojanasiri T., Hirooka Y., Ratanachu-Ek T. Evolution of pancreas in aging: degenerative variation or early changes of disease? *J. Med. Ultrason*. 2015; 42: 177–183. DOI: 10.1007/s10396-014-0576-2.

37. Seicean A., Vultur S. Endoscopic therapy in chronic pancreatitis: current perspectives. *Clin. Experim. Gastroenterol*. 2015; 8: 1–11. DOI: 10.2147/CEG.S43096.

38. Tantau A., Mandrutiu A., Leucuta D.C., Ciobanu L., Tantau M. Prognostic factors of response to endoscopic treatment in painful chronic pancreatitis. *World J. Gastroenterol*. 2017; 23 (37): 6884–6893. DOI: 10.3748/wjg.v23.i37.6884.

39. Conwell D.L., Wu B.U. Chronic pancreatitis: making the diagnosis. *Clin. Gastroenterol. Hepatol*. 2012; 10: 1088–1095. DOI: 10.1016/j.cgh.2012.05.015.

40. Anaizi A., Hart P.A., Conwell D.L. Diagnosing chronic pancreatitis. *Dig. Dis. Sci*. 2017; 62 (7): 1713–1720. DOI: 10.1007/s10620-017-4493-2.

41. Issa Y., Kempeneers M.A., van Santvoort H.C., Bollen T.L., Bipat S., Boermeest M.A. Diagnostic performance of imaging modalities in chronic pancreatitis: a systematic review and meta-analysis. *Eur. Radiol*. 2017; 27 (9): 3820–3844. DOI: 10.1007/s00330-016-4720-9.

42. Martinez J., Laveda R., Trigo C., Frasquet J., Palazon J.M., Perez-Mateo M. Fecal elastase-1 determination in

the diagnosis of chronic pancreatitis. *Gastroenterol. Hepatol.* 2002; 25: 377–382. DOI: 10.1016/S0210-5705(02)70269-0.

43. Stevens T., Dumot J.A., Parsi M.A., Zuccaro G., Vargo J.J. Combined endoscopic ultrasound and secretin endoscopic pancreatic function test in patients evaluated for chronic pancreatitis. *Dig. Dis. Sci*. 2010; 55: 2681–2687. DOI: 10.1007/s10620-009-1084-x.

44. Yin Q., Zou X., Zai X., Wu Z., Wu Q., Jiang X., Chena H., Miao F. Pancreatic ductal adenocarcinoma and chronic mass-forming pancreatitis: Differentiation with dual-energy MDCT in spectral imaging mode. *Eur. J. Radiol*. 2015; 84: 2470–2476. DOI: 10.1016/j.ejrad.2015.09.023.

45. Sankaran S.J., Xiao A.Y., Wu L.M., Windsor J.A., Forsmark C.E., Petrov M.S. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. *Gastroenterology*. 2015; 149: 1490–1500. DOI: 10.1053/j.gastro.2015.07.066.

46. Whitcomb D.C., Shimosegawa T., Chari S.T., Forsmark C.E., Frulloni L., Garg P., Hegyi P., Hirooka Y., Irisawa A., Ishikawa T., Isaji S., Lerch M.M., Levy P., Masamune A., Wilcox C.M., Windsor J., Yadav D., Sheel A., Neoptolemos J.P.; Working Group for the International (IAP — APA — JPS — EPC) International consensus statements on early chronic pancreatitis: recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, Pancreas Fest Working Group and European Pancreatic Club. *Pancreatology*. 2018; 18 (5): 516–527. DOI: 10.1016/j.pan.2018.05.008.