2 June 2021

Lian-Sheng Ma

World Journal of Gastroenterology

Dear Prof. Lian-Sheng Ma,

We wish to resubmit the manuscript titled “Comprehensive review of the diagnostic modalities for early chronic pancreatitis.” The manuscript ID is 64458.

We would like to thank you and all reviewers for your positive comments and evaluations of our review. We have carefully read all comments and suggestions and have revised the manuscript accordingly. These constructive suggestions to us have helped improve the quality and clarity of this review. We hope that the revised paper is now acceptable for publication in **World Journal of Gastroenterology**. Our point-by-point

responses to the reviewers' comments follow.

Science editors' comments:

(1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Answer: Thank you. We have uploaded related funding document.

Company editor-in-chief:

(1) Before final acceptance, the author(s) must add a figure to the manuscript.

Answer: Thanks for your suggestions, we have added a figure to the manuscript.

Reviewer #1: Some minor editing is required before publication.

Answer: Thanks for your suggestions. I have checked the words and grammar of the whole text and corrected

Modalities	Diagnostic Standards	Sensitivity	Specificity	so

me mistakes.

Reviewer #2:

The tables are not well structured, please make an edit. Please divide the last paragraph "DISCUSSION AND CONCLUSION" into two paragraphs.

Answer:

Thanks for your suggestions. I have reorganized **Table 2** as follow and divided the "DISCUSSION AND CONCLUSION" into two paragraphs.

Aetiology	TIGAR-O classification (version 2)[13]	-	-
Clinical presentation	Three or more of the following features: abnormal serum or urine pancreatic enzyme concentrations; continuous heavy alcohol consumption (>80 g alcohol/day or more than 5 drinks/day), family history of hereditary chronic pancreatitis, or known sporadic high-risk mutations; recurring epigastric abdominal pain; and abnormal exocrine function. Genetic pancreatitis should be suspected in young patients with clinical presentations but without a history of risk factors.	-	-
TA-US	Irregular main pancreatic duct with a diameter >3 mm, hyperechoic pancreatic duct wall, or lobularity with stranding.	69%(95%CI: 54-80)	94%(95%CI: 90-100)
CT	Two or more of the following features: MPD within 2-4 mm; mild organ enlargement; irregular main pancreatic duct with ≥3 pathological side branches; pseudocysts ≤ 10 mm; and heterogeneous parenchyma.	75%(95%CI: 66-83)	91%(95%CI: 81-96)
MRI/MRCP	Two or more of the following features: MPD 2-4 mm; mild organ enlargement; irregular main pancreatic duct with ≥3 pathological side	Single-parametric: 77% Multi-parametric: 91%	Single-parametric: 83% Multi-parametric: 86%

	branches; pseudocysts ≤ 10 mm; and heterogeneous parenchyma.		
ERCP			
	More than three pathological side branches plus a normal MPD.	82% (95% CI: 76-87)	94% (95% CI: 87-98)
EUS			
	More than two of the following seven criteria, including at least one of criteria 1-4: 1. Stranding 2. Hyperechoic foci without shadowing 3. Lobularity with honeycombing 4. Lobularity without honeycombing 5. Cysts 6. Dilated side branches 7. Hyperechoic main pancreatic duct margin	61% (non-fibrosis) 84% (for fibrosis)	75% (non-fibrosis) 100% (for fibrosis)
EUS-EG			
	A strain ratio of >10 or a mean strain histogram value of <50 was associated with malignancy. The mean value can be used to diagnose mild or higher-grade fibrosis.	76.4%	91.7%
FE-1			
	Moderate EPI can be diagnosed based on an abnormal FE-1 level of <200 µg/g, which has a high false-positive rate.	76.5% 45.0% (mild ductal changes and insufficiency)	86.0%

ePFT			
	Peak bicarbonate concentration of < 80 mmol/L is considered abnormal and correlated with early fibrosis.	86% (95 % CI: 67-100)	67% (95 % CI: 13-100)
FNA			
	Ruling out malignancy and staging of CP CEA testing: cut-off value of 192 ng/ml. Molecular analysis: *KRAS* and *GNAS* mutations	85% (pancreatic cancer)	98% (pancreatic cancer)
nCLE			
	A complementary modality for detecting subtle changes in early CP and helpful for distinguishing malignancies.	94.3% (cystic lesions) 90.3% (PDAC)	98.1% (cystic lesions) 89.5% (PDAC)

Abbreviations: Sen: sensitivity; Spec: specificity; TA-US: transabdominal ultrasound; MPD: main pancreatic duct; CT: computed tomography; MRI: magnetic resonance imaging; EUS: endoscopic ultrasound; EUS-EG: endoscopic ultrasound elastography; FE-1: faecal elastase-1; ePFT: endoscopic pancreatic function test; nCLE: endoscopic pancreatic function test; EPI: exocrine pancreatic insufficiency; CP: chronic pancreatitis; CEA: carcinoembryonic antigen; MRCP: magnetic resonance cholangiopancreatography; ERCP: endoscopic retrograde cholangiopancreatography; FNA: fine-needle aspiration; PDAC: pancreatic ductal adenocarcinoma; AIP:

autoimmune pancreatitis; AP: acute pancreatitis; RAP: recurrent acute pancreatitis; CKD: chronic kidney disease; NCCP: non-calcific chronic pancreatitis; ROC: receiver operating characteristic; ROI: region of interest; SD: standard deviation; SR: strain ratio.

Yours sincerely,

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