Validation of International Consensus Diagnostic Criteria For Diagnosis of Autoimmune pancreatitis From Pancreatic Cancer in a Taiwanese Cohort

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<td>Chang, Ming-Chu; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Internal Medicine Liang, Po-Chin; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Radiology Jan, I-Shiow; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Laboratory Medicine Yang, Ching-Yao; National Taiwan University Hospital, College of Medicine, Department of Surgery Tien, Yu-Wen; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Surgery Wei, Shu-Chen; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Internal Medicine Wong, Jau-Min; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Internal Medicine Chang, Yu-Ting; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Internal Medicine</td>
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Validation of International Consensus Diagnostic Criteria For Diagnosis of

Autoimmune pancreatitis From Pancreatic Cancer in a Taiwanese Cohort

Ming-Chu Chang¹, M.D., Ph.D., Po-Chin Liang², M.D., I-Shiow Jan³, M.D., Ching-Yao Yang⁴, M.D., Ph.D., Yu-Wen Tien⁴, M.D., Ph.D., Shu-Chen Wei¹, M.D., Ph.D., Jau-Min Wong¹, M.D., Ph.D., Yu-Ting Chang¹, M.D., M.S., Ph. D.

¹Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

²Department of Radiology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

³Department of Laboratory Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

⁴Department of Surgery, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

Correspondence Author: Yu-Ting Chang, M.D., M.S., Ph. D.

Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan;

No.7 Chung Shan South Road, Taipei, Taiwan.

Tel: 886-2-23123456 ext 63563
Fax: 886-2-23633658

e-mail: yutingchang@ntu.edu.tw

Running title: evaluation of diagnostic criteria in AIP and focal AIP

Keywords: autoimmune pancreatitis (AIP), pancreatic cancer (PC), HISORt, Asian; ICDC, focal type, diffuse type

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Abstract

Objectives: The International Consensus Diagnostic Criteria (ICDC) for diagnosed autoimmune pancreatitis (AIP) has been proposed recently. The diagnostic performance of ICDC has not been evaluated in diffuse and focal type AIP respectively in comparison of the revised HISORt criteria and Asian criteria before.

Design: Prospective, consecutive patient cohort.

Setting: Largest tertiary referred center hospital managing pancreatic disease in Taiwan.

Participants: One hundred and eighty-eight patients with autoimmune pancreatitis and one hundred and thirty of tissue proofed pancreatic adenocarcinoma were consecutively recruited.

Interventions: The ICDC, revised HISORt criteria and Asian criteria were applied for each participant. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in diffuse and focal type of AIP.

Outcomes: Sensitivity, specificity, and accuracy. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in AIP and focal type of AIP.

Results: The sensitivity, specificity and accuracy of ICDC for all AIP were the best: 89.4% 100.0% and 93.7%, respectively in these 3 criteria. The sensitivity, specificity
and accuracy of ICDC for focal AIP (84.9% 100.0% and 93.8%) were also the best among these 3 criteria. The area under curve of ROC of ICDC was 0.95 (95% CI:0.92-0.97) in all AIP and 0.93 (95% CI:0.88-0.97) in focal type AIP.

**Conclusions:** The sensitivity, specificity and accuracy of ICDC are higher than revised HISORt and Asian criteria. The sensitivity, specificity and accuracy of each criterion are higher in diffuse type of AIP compared to focal type AIP. Under the same specificity, the sensitivity and accuracy of ICDC are higher than other diagnostic criteria in focal type AIP. ICDC has better diagnostic performance compared to previous proposed diagnostic criteria, in both diffuse and focal type AIP.
ARTICLE SUMMARY

Article focus

1. There are several criteria proposed for diagnosis of autoimmune pancreatitis (AIP) in different countries. Revised HISROT criteria and Asian criteria are the two most common used diagnostic criteria in our Asian country. The International Consensus Diagnostic Criteria (ICDC) is the newest diagnostic criteria proposed in 2011 in a consensus meeting. One major goal of these criteria is to avoid “over” diagnosis of AIP in patient with pancreatic cancer, especially in focal type AIP. The diagnostic performance of ICDC has not been evaluated compared to previous criteria in the aspect of differentiating diffuse and focal type AIP before.

2. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in AIP and focal type of AIP.

3. Sensitivity, specificity, and accuracy of the revised HISROT criteria, Asian criteria and ICDC are compared.

Key messages:

1. The sensitivity, specificity and accuracy of ICDC are all higher than revised HISROT and Asian criteria.

2. The sensitivity, specificity and accuracy of each criterion are higher in diffuse type of AIP compared to focal type AIP.
3. Under the same specificity, the sensitivity and accuracy of ICDC are higher than other diagnostic criteria in focal type AIP. ICDC has better diagnostic performance compared to previous proposed diagnostic criteria, in both diffuse and focal type AIP.

**Strengths and limitations of this study**

1. This is the first study to determine the diagnostic accuracy of ICDC of AIP from pancreatic cancer with focus on “focal” type AIP.

2. The study focus on only type 1 AIP in our study owing to the prevalence of type 2 AIP are relatively low in us eastern countries. The role of ICDC in type 2 AIP needs further study.

3. The diagnostic performance of ICDC compared to other diagnostic criteria proposed in other regions or countries, other than revised HISORT and Asian criteria, are needed to confirm the universalization of diagnosis of AIP.
INTRODUCTION

Autoimmune pancreatitis (AIP) is a unique type of chronic pancreatitis characterized by elevated serum immunoglobulin G4 (IgG4), swelling of pancreas, irregular narrowing of main pancreatic duct, histological evidence of lymphoplasmacytic inflammation, and a good response to steroid therapy[1]. Although some advance has been made in the diagnosis and treatment of AIP over the past years[2], the diagnosis of AIP is still a great clinical challenge, especially in the differential diagnosis from pancreatic cancer[3-5]. Correct diagnosis could avoid unnecessary resection of pancreas and vice versa, to avoid delay treatment of pancreatic cancer. In 2002, the Japan Pancreas Society proposed diagnostic criteria for AIP based on imaging, serology, and histology. At that time, the serological criteria included elevated γ-globulin, immunoglobulin G (IgG), and auto-antibodies[6]. In 2006, the revised Japanese criteria were modified and added IgG4 to the serological criteria [7]. In 2008, the Asian diagnostic criteria was established according to modification of Japanese diagnostic criteria and Korean diagnostic criteria[8]. In western countries, the HISORt criteria was proposed from America[9]. In 2011, the international consensus diagnostic criteria (ICDC) was proposed which classified AIP into type 1 and type 2. Type 1 is featured histologically by lymphoplasmacytic sclerosing pancreatitis (LPSP) and type 2 by idiopathic duct-centric pancreatitis (IDCP).
ICDC included 5 cardinal features of AIP including parenchymal imaging, ductal imaging, serology, other organ involvement (OOI), histology of pancreas, and response to steroid therapy. Each criterion was further classified into two levels (level 1 and level 2). The aim of the proposal of ICDC was intended to improve the diagnosis of AIP [10]. AIP could be also classified into focal type and diffuse type AIP according to the involvement of pancreatic enlargement. In clinical settings, it is more important and also difficult in differentiating focal type AIP from pancreatic cancer. Till now, it still lacks a simple parameter with absolute diagnostic value. Therefore, use of combined parameters according to different diagnostic criteria in different countries exists.

The objective of this study is to evaluate the diagnostic performance (sensitivity, specificity and accuracy) of ICDC from differentiating pancreatic cancer in a prospectively collected cohort[11-13], compared to the two most commonly used two criteria in our country before ICDC made (revised HISROT criteria and Asian criteria). The diagnostic role of each cardinal features of ICDC will be compared to revised HISORT and Asian criteria in diffuse AIP and focal type AIP respectively.
METHODS

Study participants

Between Jan 1996 and Dec 2013, we consecutively collected 188 patients with AIP (95 men and 93 women) at National Taiwan University Hospital, a tertiary referred center also the largest medical center for management of pancreatic diseases in Taiwan. All the patients with AIP fulfilled at least one of the HISORt criteria (158/188, 84.0 %), or Asian diagnostic criteria (162/188, 86.2%), or the ICDC criteria (168/188, 89.4%) for AIP. All patients were followed up for at least 12 months. A total of consecutive 130 patients (65 men and 65 women) with cytological or/and pathologically confirmed adenocarcinoma of pancreas were enrolled as a control group. The patients' mean age was 51.4 years (range, 33-78 years) and 60.9 years (range, 32-78 years) in patient with AIP and pancreatic cancer. The institutional ethics committee approved this study. All the patients' medical charts were reviewed and the patients' demographic data, including age, gender, serological studies, image studies, and clinical manifestations etc. were collected.

Findings of Diagnostic criteria of ICDC

We categorized all patients with AIP and PC as to level 1 finding, level 2 findings or neither for each of 5 criteria ( parenchymal imaging, ductal imaging, serology, other OOI, histology of pancreas, and response to steroid therapy) according to ICDC. For
parenchymal imaging, the frequencies of diffuse enlargement, focal enlargement and atypical imaging (pancreatic duct dilatation or calcification or atrophy) were evaluated. Enlargement of pancreas was defined as when the width of the pancreatic body or tail exceeds two-thirds of the transverse diameter of the vertebral body or if the width of the pancreatic head exceeds the full transverse diameter of the vertebral body[14]. For ductal imaging, main pancreatic duct diameter was measured by use of abdominal computed tomography (CT) or/and magnetic resonance cholangiopancreatography (MRCP) or/and endoscopic retrograde pancreatography (ERP). The frequencies of long stricture without marked upstream dilatation, multiple strictures without marked upstream dilatation, segmental/focal narrowing without marked upstream dilatation, and marked upstream dilatation of the MPD were evaluated. Pancreatic duct dilatation was defined as the diameter of the main pancreatic duct (MPD) exceeding 5mm. Parenchymal and ductal imaging scans were analyzed by 3 experts (MC Chang, YT Chang and PC Liang).

For OOI, the frequencies of segmental/multiple proximal bile duct stricture, retroperitoneal fibrosis, symmetrically enlarged salivary/lachrymal glands, and radiologic evidence of renal involvement were evaluated. Bile duct stricture was evaluated by MRCP or ERC, or percutaneous transhepatic cholangiography (PTC.) Retroperitoneal fibrosis was evaluated by contrast enhanced CT or MRI.
Symmetrically enlarged salivary/lachrymal glands was evaluated by physical examination or/and CT.

For histology of pancreas in AIP, there were 25 patients received pancreatectomy. There were 6 patients received biopsy of pancreas. Pancreatic histology were evaluated by an experienced pathologist (YM Jeng) blinded to the other data.

For steroid therapy, 126 patients (67.0%) received corticosteroid therapy as the initial treatment of AIP. The dose for induction therapy was started from 30-40 mg/day for 2 week -4 week and then tapered 5 mg/week gradually. The treatment response of steroid was nearly 98%.

We evaluated of the frequencies of level 1 findings, level 2 finding and neither of each criterion in all patients with AIP and PC. Sensitivity, specificity and accuracy were compared between ICDC, revised HISORt, and Asian criteria. We also evaluated the cases which did not fit the diagnosis with AIP according to each criterion.

**Statistical analysis**

We calculated the sensitivity, specificity, and accuracy of each diagnostic criterion.

The between-group demographic data were compared by the Student unpaired t test for continuous data and by the $\chi^2$ test for categorical data. Receiver-operator characteristic (ROC) curves and area-under-the-curves (AUCs) were estimated after logistic regressions in different criteria in all AIP and focal AIP subgroups and
presented with corresponding 95% confidence intervals (CIs). The statistical
calculations were carried out using SPSS 17 statistical software (SAS Institute, Cary,
NC). All reported P value was 2-sided. Differences with a P value less than 0.05 were
considered to be statistically significant.
RESULTS

Parenchymal imaging

Of the 188 patients, 90 (50.5%) and 93 (49.5%) with AIP were categorized as level 1 and 2, respectively. All patients with PC were classified as level 2 (Table 1).

Ductal Imaging

Ductal imaging was evaluated by at least one of the ERC or MRCP in all patients. Among them, 93 (49.5%) of 188 patients with AIP and no any patients with PC were categorized as level 1. There were 68 (36.2%) of 188 patients with AIP and 13 (10.0%) of 130 patients with PC were categorized as level 2 (Table 1). Marked MPD dilatation was observed significantly frequent in patient with PC (n=117; 90.0%) than in those with AIP (n=27; 14.4%, P<0.001). Among the 27 patients with AIP with MPD dilatation, narrowing of the downstream MPD was observed in 3 patients and the others with normal downstream appearance.

Serology

Forty seven (36.7%) of 188 patients with AIP and 4 (4.8%) of 84 patients with PC were categorized as level 1 respectively (Table 1). The mean serum IgG4 level was 346.6±56.2 mg/dL, statistically significantly higher than those in patients with pancreatic cancer, 119.2±23.9 mg/dL. The frequencies of serum level above 280 mg/dl (level 1) and 140 mg/dl (level 2) were significantly higher in AIP patients (P<0.001).
Table 1. Frequencies of level 1 and 2 findings in international consensus diagnostic criteria (ICDC) for autoimmune pancreatitis (AIP) and pancreatic cancer (PC)

<table>
<thead>
<tr>
<th>Features</th>
<th>AIP (n=188)</th>
<th>PC (n=130)</th>
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<tbody>
<tr>
<td><strong>Parenchymal imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>95 (50.5%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>93 (49.5%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>188 (100.0%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>0 (0.0%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td><strong>Ductal imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>93 (49.5%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>68 (36.2%)</td>
<td>13 (10.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>161 (85.6%)</td>
<td>13 (10.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>27 (14.4%)</td>
<td>117 (90.0%)</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>47/128 (36.7%)</td>
<td>4/84 (4.8%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>55/128 (42.9%)</td>
<td>3/84 (3.6%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>102/128 (79.7%)</td>
<td>7/84 (8.3%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>26/128 (20.3%)</td>
<td>77/84 (91.7%)</td>
</tr>
<tr>
<td><strong>OOI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>63 (33.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>64 (34.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>127 (92.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>61 (32.4%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td><strong>Histology of pancreas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>28 (14.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>3 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>31 (16.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>157 (83.5%)</td>
<td>130 (100.0%)</td>
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</tbody>
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AIP: autoimmune pancreatitis; PC: pancreatic cancer; OI: other organ involvement

Other organ involvement (OOI)

Sixty-three (33.5%) of 188 patients with AIP was categorized as level 1 and no any one of 130 patients with PC were categorized as level 1 or 2 (Table 1). Proximal bile duct stricture was observed in 53 patients (28.2%) with AIP, and retroperitoneal
fibrosis was observed in 5 patients (2.7%) with AIP both level 1 findings. Enlarged salivary/lacrimal glands were observed in 58 patients (27.6%) with AIP and renal involvement in 9 (4.8%), these met level 2 criteria. Neither enlarged salivary/lacrimal glands nor renal involvement was observed in any patients with PC.

**Histology of pancreas**

There were 31 (16.4%) patients with AIP were categorized as level1 or level 2 criteria and none of 130 patients with PC were categorized as level1 or level 2 (Table 1). There were 28 patients (14.9%) with level 1 evidence and 3 patients (1.6 %) with level 2 evidence in histologically LPSP. No any patients with PC fulfilled the level 1 or 2 criteria.

**Response to steroid therapy**

Of the 128 patients who received steroid treatment as the initial treatment (induction therapy), 126 patient (98.4 %) showed steroid response with improvement clinically, serologically and morphologically. Two of the patients with diffuse pancreatic enlargement and narrowing of MPD received steroid but no morphologically response. Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) were performed and no malignancy was detected. These two patients discontinued steroid after 3 months of steroid and was follow up regularly. These two patients were followed up for 18 months and 20 months and no any malignancy were documented although the
pancreatic enlargement did not subside.

**Diagnosis on the basis of ICDC, revised HISORt and Asian criteria**

Of the 188 patients with AIP, 116 patients were diagnosed as definite AIP; 35 patients were diagnosed as probable AIP and 17 were classified as not otherwise specified (NOS). Among these patients, the primary basis for diagnosis was histology in 31 patients, response to steroid therapy in 126 patients and imaging in 188 patients.

There were 20 patients in this study deniable for type 1 AIP. All patients with PC were deniable for type 1 AIP on the basis of ICDC. The sensitivity, specificity and accuracy of the ICDC for type 1 AIP were 89.4%, 100/0% and 93.7% (Table 2).

Using revised HISORt criteria, 158 patients (84.0%) were diagnosed as definitive AIP. Among these 158 patients, the primary basis of diagnosis was diffuse type in 95 patients (60.1%), histology based diagnosis in 31 patients (19.6%). There were 30 patients were deniable for AIP based on revised HISORt criteria in this study. All of the PC patients were deniable for AIP based on the revised HISORt criteria. The sensitivity, specificity and accuracy of the revised HISORt criteria were 84.0%, 100.0% and 90.5% (Table 2). Using Asian criteria, 162 patients (86.2%) were diagnosed as AIP. There were 143 patients (88.3%) were diagnosed based on Imaging plus serology; 143 patients (88.3%) were diagnosed based on Imaging plus serology; 31 patients (19.1%) diagnosed based on histopathology and 126 patients(77.8%)
Table 2. Comparison of diagnostic criteria for autoimmune pancreatitis from pancreatic cancer

<table>
<thead>
<tr>
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<th>Case number</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
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<tr>
<td>All AIP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit Asian</td>
<td>162</td>
<td>86.2</td>
<td>100.0</td>
<td>91.8</td>
</tr>
<tr>
<td>Fit revised</td>
<td>158</td>
<td>84.0</td>
<td>100.0</td>
<td>90.5</td>
</tr>
<tr>
<td>HISORt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit ICDC</td>
<td>168</td>
<td>89.4</td>
<td>100.0</td>
<td>93.7</td>
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<tr>
<td>Focal AIP</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit Asian</td>
<td>68</td>
<td>73.1</td>
<td>100.0</td>
<td>99.6</td>
</tr>
<tr>
<td>Fit revised</td>
<td>73</td>
<td>78.5</td>
<td>100.0</td>
<td>95.6</td>
</tr>
<tr>
<td>HISORt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit ICDC</td>
<td>79</td>
<td>84.9</td>
<td>100.0</td>
<td>97.3</td>
</tr>
</tbody>
</table>

ICDC: international consensus diagnostic criteria

diagnosed based on steroid treatment response. Here were 26 patients were deniable for AIP based on Asian criteria in this study. All of the PC patients were deniable for AIP based on the Asian criteria. The sensitivity, specificity and accuracy of the revised HISORt criteria were 86.2%, 100.0% and 91.8% (Table 2).

Deniable cases on the basis of ICDC

There were 20 patients who were deniable for ICDC in this study. All these 20 patients could be diagnosed by Asian criteria. Among them, there were 2 patients could be diagnosed both by HISORt criteria and Asian criteria. They included 6 cases and 14 cases with level 1 or 2 parenchymal imaging; 6 cases and 12 cases with level 1 or 2 ductal imaging; 9 cases with level 2 serology; 11 patients with level 1 OOI.

There was 1 patient with steroid treatment response. The most common factor which
lead to deniable of ICDC or revised HISORt criteria was the serology criterion. There were 18 out of 20 patients had antoantibodies which could be one of the item in Asian serology criterion. The ICDC and HISORt only adapted IgG4 level alone as the serology criterion.

**ICDC criteria in Focal type AIP and diffuse type AIP**

The comparisons of frequencies of level 1 and 2 findings in ICDC in focal type and diffuse AIP were shown in Table 3. The frequencies of level 1 or level 2 features in ductal imaging were significantly lower in focal type AIP (73.1% vs. 97.9%, p<0.001, Table 3). The frequencies of level 1 or 2 features in serology was also lower in focal type (55.4% vs. 69.3%, p=0.075). The frequencies of any level of OOI in focal type AIP was higher than diffuse type (81.7% vs. 53.7%, p<0.0001). The frequencies of any histological evidence of LPSP in our focal type AIP was higher than diffuse type (23.7% vs. 9.5%, p=0.01) in our study (Table 3).

**Sensitivity, Specificity and Accuracy of ICDC, revised HISORt criteria and Asian criteria**

The sensitivity, specificity and accuracy of the ICDC were 84.9%, 100.0% and 93.8% (Table 2). The sensitivity, specificity and accuracy of the revised HISORt criteria were 78.5%, 100.0% and 91.0% (Table 2). The sensitivity, specificity and accuracy of the Asian criteria were 73.1%, 100.0% and 88.8% (Table 2).
Table 3 Frequencies of level 1 and 2 findings in international consensus diagnostic criteria (ICDC) for focal and diffuse type autoimmune pancreatitis (AIP)

<table>
<thead>
<tr>
<th>Features</th>
<th>Focal AIP (n=93)</th>
<th>Diffuse AIP (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>0(%)</td>
<td>93(97.9%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>68(73.1%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>68(73.1%)</td>
<td>93(97.9%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>25(26.9%)</td>
<td>2(2.1%)</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>16/74(21.6%)</td>
<td>31/88(35.2%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>25/74(33.8%)</td>
<td>30/88(34.1%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>41/74(55.4%)</td>
<td>61/88(69.3%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>33/74(44.6%)</td>
<td>27/88(30.7%)</td>
</tr>
<tr>
<td>OOI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>31(33.3%)</td>
<td>32(33.7)</td>
</tr>
<tr>
<td>Level 2</td>
<td>45(48.4%)</td>
<td>19(20.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>76(81.7%)</td>
<td>51(53.7%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>17(11.3%)</td>
<td>44(46.3%)</td>
</tr>
<tr>
<td>Histology of pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>20(21.5%)</td>
<td>8(8.4%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>2(2.2%)</td>
<td>1(1.1%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>22(23.7%)</td>
<td>9(9.5%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>71(76.3%)</td>
<td>86(90.5%)</td>
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</table>

AIP: autoimmune pancreatitis; OI: other organ involvement

The ROC was calculated in AIP (Fig 1) and focal type AIP (Fig 2). The area under the curve was 0.95 (95% CI: 0.92-0.97) of ICDC (Fig 1a), 0.91(95% CI: 0.92-0.97) of revised HISORt criteria (Fig 1b), and 0.93(95% CI: 0.92-0.97) of Asian criteria (Fig 1c). For focal type AIP, the area under the curve was 0.93(95% CI: 0.88-0.97) of ICDC (Fig 2a), 0.89(95% CI: 0.84-0.94) of revised HISORt criteria (Fig. 2b), and 0.87(95% CI: 0.81-0.92) of Asian criteria( Fig 2c).
Discussion

The sensitivity, specificity and accuracy of ICDC for all AIP were 89.4% 100.0% and 93.7%. The sensitivity, specificity and accuracy of ICDC for focal AIP were 84.9% 100.0% and 93.8%. Among the three criteria, the sensitivity and accuracy of ICDC were the best one compared to revised HISORt criteria and Asian criteria with the same specificity (Table 2). There were 12 patients with deniable revised HISORt criteria were diagnosed as AIP in ICDC (10 definite, 1 probable and 1 NOS of ICDC). There were 26 patients with deniable Asian criteria were diagnosed as AIP in ICDC (11 definite, 14 probable and 1 NOS in ICDC). The ICDC showed higher sensitivity the revised HISORt and Asian criteria. The reason why patients deniable for revised HISORt or Asian criteria but fit ICDC diagnosis was partially caused by the different definition of parenchymal imaging between these criteria. ICDC includes atypical imaging and classifies atypical imaging as S2 level in parenchymal imaging criterion. That's one reason why ICDC had higher sensitivities in diagnosis of AIP in general. The wider range of imaging criteria improved the diagnostic sensitivity but did not decreased neither the specificity nor the accuracy of ICDC. All the three criteria showed high specificity (Table 2). The ICDC showed higher accuracy than Asian criteria and revised HISORt criteria.

In ductal imaging criterion, 161 (92.5%) of 188 patients with AIP and 13 (1.0%) of 130 patients with PC were categorized as level 1 or 2, respectively. The specificity
of ductal imaging is high. One of the reasons for this high specificity is that patients with marked upstream MPD dilatation (>5 mm) were excluded from level 1 or 2. In the present study, 28 of 31 patients with PC who showed focal MPD stricture were excluded from level 2 because of marked upstream MPD dilatation. On the other hand, 27 (14.4%) of 188 patients with AIP showed marked upstream MPD dilatation. The frequency of any level 1 or 2 evidence in ductal imaging is close to the recently reported on (7/62, 11.3%) by Nishino et al.[15]. Naitoh et al also reported that a maximal diameter of the upstream MPD less than 5 mm was an appropriate cutoff point to differentiate mass-forming AIP from PC[16]. In our study, we also use the 5mm as a cutoff point to differentiating focal type AIP and PC. Therefore, we consider that a 5-mm diameter of the upstream MPD is appropriate to discriminate AIP from PC. In the present study, 4 patients with PC fulfilled the level 1 serological criterion. Marked upstream MPD dilatation (5 mm) was observed in these patients. If this exclusion criterion (marked upstream MPD) did not exist, this patient would have fulfilled level 2 criteria for ductal imaging, and we would have misdiagnosed these 4 patients with PC as definitive type 1 AIP under the ICDC. Therefore, we consider that this exclusion criterion of ductal imaging is useful for excluding out PC.

The value of serum IgG4 as a serological marker of AIP was first established in 2001[17] [18]. Hamano et al. reported that sensitivity and specificity for
differentiating AIP from PC were 90.2% and 97.5%[18]. In the present study, those
sensitivity and specificity of serum IgG4 (>140 mg/dL) were 79.6% and 92.6%,
respectively. The cause of the wide range of sensitivity in the reported series might be
caued by the combined analysis of types 1 and 2 in these studies. The distribution
between types 1 and 2 AIP might affect the value of IgG4. Ghazale et al [4] reported
that the sensitivity of elevated serum IgG4 (>140 mg/dL) for PC was 10%, and that of
2-fold elevation (level 1 ICDC serology criteria) was 1%. Our present study showed
that the sensitivity and specificity of 2-fold elevation of serum IgG4 were 36.7% and
95.2% in out type 1 AIP. Serum IgG4 is the only used serology marker in ICDC. In
Asian criteria, they adapted IgG, IgG4 and presence of antoantibody as the serological
criteria. In our patients with type 1 AIP, if we add the presence of autoantibody as
also a surrogate marker in serology, thus all of the patients deniable for ICDC could
be diagnosed by this modification.

IgG4-related disease (IgG4-RD) is a new I disease entity characterized by elevated
serum IgG4 concentration and /or tissue infiltration by IgG4-positive cells[19]. Type
1 AIP is regarded as a part (pancreatic manifestation) of IgG4-RDs. In the present
study, level 1 or 2 OOI was observed in 127 (67.6%) of the patients with AIP and in
none of those with PC. Therefore, this OOI criterion has high specificity for type 1
In the present study, all resection specimens (27 patients) and fulfilled level 1 criteria. One of four biopsied specimens guided by computed tomography fulfilled level 1, with the rest diagnosed as level 2. The present findings suggest obtaining histopathologic evidence of type 1 AIP by biopsied specimen is difficult. Endoscopic ultrasonography-guided FNA was considered useful for the differentiation from PC but might be insufficient for tissue collection to diagnosis as level 1. Kanno et al[20] reported that 14 and 6 of 25 patients were judged to have level 1 and level 2 histological findings by trucut biopsy under endoscopic ultrasound (EUS) guidance respectively. We did not perform EUS-trucut biopsy in this study owing to the needle is not available and the cost is not covered by our health insurance. Further studies for the feasibility and necessarily of EUS-FNA in diagnosing type 1 AIP in ICDC histological need to be studied.

Diffuse and focal enlargement of the pancreas is a characteristic feature of AIP in parenchymal imaging. ICDC included patients with atypical parenchymal imaging as level 2. For diffuse type AIP, the diagnostic accuracy of ICDC, Asian, and HISORt criteria were over 95%, much better than that in focal type AIP. This observation is
reasonable for us to understand because of it is very rare to have pancreatic cancer involving whole pancreas in clinical practice. The diagnosis sensitivity in diffuse type AIP were also higher than those in focal type in these three diagnostic criteria (Table 2). In diffuse type AIP, Asian criteria was most sensitive with sensitivity 98.9%, followed by ICDC (93.7%) and the HISORt criteria (89.5%). There were 4 patients with diffuse AIP who did not have elevated was the least sensitive criteria in the diagnosis of diffuse type with sensitivity only 89.5%. The were 4 diffuse type AIP deniable for HISROT but fit ICDC NOS owing to these 4 patients did not have any collateral evidence. These 4 patients could be diagnosed by Asian criteria as they have presence of autoantibodies which made they fit the serology criteria in Asian diagnosis setting but not fit the serology criteria in ICDC and HISORt criteria. These 4 patients had received steroid response as the initial treatment and they all had disease relapse in their follow up. The increase of sensitivity in Asian criteria in diagnosing diffuse type AIP is relevant to the wide range of definition in serology criterion (IgG, IgG4 or/and autoantibodies), compared to use IgG4 alone as serology criterion in HISORt and ICDC.

It is a greater challenge to differentiate focal type AIP with pancreatic cancer, compare to differentiate diffuse type AIP from PC. In this study, we have 93 patients with focal AIP. The ductal imaging, serology and OOI were different from diffuse
type. Focal type AIP had less frequency of level 1 or 2 presentations of ductal imaging and serology. In contrast, focal type AIP had higher frequencies of level 1 or 2 presentations of OOI. These clinical observations remind us that the collateral evidence of AIP in focal type AIP is mostly in OOI, but not serology. Detailed physical examination and history taking and imaging interpretation imaging other than pancreas could give some hint to increase the sensitivity of diagnosis of focal AIP.

In focal type of AIP, the diagnostic sensitivity of ICDC (84.9%) was higher than revised HISORt criteria (78.5%) and Asian criteria (73.1%). There were 14 (15.1%) focal type AIP patients deniable for ICDC criteria. All these 14 patients could be diagnosed by Asian criteria. There were 12 patients with presence of autoantibodies and 9 patients with serum IgG4 level above 140 mg/dl. Among them, they were 12 patients with level 2 and 2 patients without any level 1 or 2 criteria in ductal imaging. In OOI, there were 9 patients with level 2 criteria and 5 patients without any level 1 or 2 criteria. All the focal type AIP patients deniable Asian criteria could be diagnosed by ICDC criteria.

In conclusion, the ICDC shows high sensitivity, specificity and accuracy in the
diagnosis of type 1 AIP. In focal type AIP, ICDC is still the best one in sensitivity, specificity and accuracy. The diagnostic sensitivity in focal type AIP not as good as diffuse type AIP in all the three adapted criteria (ICDC, Asian and revised HISORt criteria). How to improve the sensitivity of diagnosis of focal AIP is the issue need to be resolved in the future.
AUTHOR CONTRIBUTION

Ming-Chu Chang and Yu-Ting Chang have full access to the data take responsibility for the integrity of the data, and the accuracy of the data analysis.

Conception and design, or analysis and interpretation of data: Ming-Chu Chang, Po-Chin Liang, I-Shiow Jan, Ching-Yao Yang, Yu-Wen Tien, Shu-Chen Wei, Jau-Min Wong, Yu-Ting Chang

Drafting the article or revising it critically for important intellectual content: Ming-Chu Chang, Yu-Ting Chang

Final approval of the version to be published: Ming-Chu Chang, Yu-Ting Chang

Obtained funding: Ming-Chu Chang and Yu-Ting Chang, Jau-Min Wong

Administrative, technical, or material support: Ming-Chu Chang and Yu-Ting Chang,

Jau-Min Wong

Study supervision: Yu-Ting Chang

Yu-Ting Chang had the final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST DISCLOSURE

The authors report no conflict of interest.

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The funding source had no role in study design, data collection, analysis, or interpretation, report writing or the decision to submit this paper for publication.

PATIENT CONSENT

Signed informed consent was obtained from each study subject prior to participation in the study.

ETHICS APPROVAL

The study protocol was approved by the institutional review board of National Taiwan University Hospital.

DATA SHARING STATEMENT

No additional data are available.
ACKNOWLEDGEMENTS

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The authors express their deep sense of gratitude to all of the individuals for agreeing to participate in the study.
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13. JI Chang MC, Liang PC, Jeng YM, Yang CY, Tien YW, Wong JM, Chang YT, PRSS1 But not SPINK1 Variants Increase the Risk of Type 1 Autoimmune Pancreatitis; *J GASTROEN HEPATOL*. accepted

15. T Nishino, H Oyama, F Toki, et al., Differentiation between autoimmune pancreatitis and pancreatic carcinoma based on endoscopic retrograde cholangiopancreatography findings; *J Gastroenterol* 2010. 45:988-96.


Figure 1. Receiver-operator characteristics curves of International Consensus Diagnostic Criteria (ICDC), revised HISORT and Asian criteria in diagnosis of 188 patients with autoimmune pancreatitis (AIP) from 130 patients.

1a. ICDC diagnostic criteria

![ICDC ROC curve]

Area under ROC curve = 0.95 (0.92-0.97)

1b. revised HISORT criteria
1c. Asian criteria
Figure 2. Receiver-operator characteristics curves of International Consensus Diagnostic Criteria (ICDC), revised HISORT and Asian criteria in diagnosis of 93 patients with focal autoimmune pancreatitis (AIP) from 130 patients with pancreatic cancer.

2a. ICDC diagnostic criteria
2b. revised HISORT criteria

![Graph showing sensitivity and specificity for revised HISORT criteria]

Area under ROC curve = 0.87 (95% CI 0.81-0.92)

2c. Asian criteria

![Graph showing sensitivity and specificity for Asian criteria]

Area under ROC curve = 0.87 (95% CI 0.81-0.92)
### STARD checklist for reporting of studies of diagnostic accuracy
*(version January 2003)*

<table>
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<tr>
<th>Section and Topic</th>
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<tr>
<td><strong>TITLE/ABSTRACT/KEYWORDS</strong></td>
<td>1</td>
<td>Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
<td>2</td>
<td>State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.</td>
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<td><strong>METHODS</strong></td>
<td>3</td>
<td>The study population: The inclusion and exclusion criteria, setting and locations where data were collected.</td>
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<td>Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?</td>
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<td>Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.</td>
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<td>Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?</td>
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<td><strong>Test methods</strong></td>
<td>7</td>
<td>The reference standard and its rationale.</td>
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<td>Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.</td>
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<td>Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.</td>
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<td>The number, training and expertise of the persons executing and reading the index tests and the reference standard.</td>
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<td>Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.</td>
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<td><strong>Statistical methods</strong></td>
<td>12</td>
<td>Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).</td>
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<td><strong>RESULTS</strong></td>
<td>13</td>
<td>Methods for calculating test reproducibility, if done.</td>
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<td><strong>Participants</strong></td>
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<td>When study was performed, including beginning and end dates of recruitment.</td>
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<td>Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).</td>
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<td>16</td>
<td>The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).</td>
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<tr>
<td><strong>Test results</strong></td>
<td>17</td>
<td>Time-interval between the index tests and the reference standard, and any treatment administered in between.</td>
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<td>18</td>
<td>Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.</td>
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<td>19</td>
<td>A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.</td>
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<td>Any adverse events from performing the index tests or the reference standard.</td>
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<td><strong>Estimates</strong></td>
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<td>Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).</td>
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<td>How indeterminate results, missing data and outliers of the index tests were handled.</td>
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<td>Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.</td>
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<td>24</td>
<td>Estimates of test reproducibility, if done.</td>
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**DISCUSSION**
25 Discuss the clinical applicability of the study findings.  
23,24,25
Comparison and Validation of International Consensus Diagnostic Criteria For Diagnosis of Autoimmune pancreatitis From Pancreatic Cancer in a Taiwanese Cohort

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| Complete List of Authors: | Chang, Ming-Chu; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Internal Medicine
Liang, Po-Chin; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Radiology
Jan, I-Shiow; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Laboratory Medicine
Yang, Ching-Yao; National Taiwan University Hospital, College of Medicine, Department of Surgery
Tien, Yu-Wen; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Surgery
Wei, Shu-Chen; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Internal Medicine
Wong, Jau-Min; National Taiwan University Hospital, College of Medicine, National Taiwan University, Department of Internal Medicine
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| Primary Subject Heading: | Gastroenterology and hepatology |
| Secondary Subject Heading: | Diagnostics, Gastroenterology and hepatology, General practice / Family practice |
| Keywords: | Pancreatic disease < GASTROENTEROLOGY, GASTROENTEROLOGY, Adult gastroenterology < GASTROENTEROLOGY |
Comparison and Validation of International Consensus Diagnostic Criteria For Diagnosis of Autoimmune pancreatitis From Pancreatic Cancer in a Taiwanese Cohort

Ming-Chu Chang¹, M.D., Ph.D., Po-Chin Liang², M.D., I-Shiow Jan³, M.D., Ching-Yao Yang⁴, M.D., Ph.D., Yu-Wen Tien⁴, M.D., Ph.D., Shu-Chen Wei¹, M.D., Ph.D., Jau-Min Wong¹, M.D., Ph.D., Yu-Ting Chang¹, M.D., M.S., Ph.D.

¹Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

²Department of Radiology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

³Department of Laboratory Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

⁴Department of Surgery, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

Correspondence Author: Yu-Ting Chang, M.D., M.S., Ph.D.

Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan;

No.7 Chung Shan South Road, Taipei, Taiwan.
Tel: 886-2-23123456 ext. 63563

Fax: 886-2-23633658

e-mail: yutingchang@ntu.edu.tw

Running title: evaluation of diagnostic criteria in AIP and focal AIP

Keywords: autoimmune pancreatitis (AIP), pancreatic cancer (PC), HISORt, Asian; ICDC, focal type, diffuse type

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Abstract

Objectives: The International Consensus Diagnostic Criteria (ICDC) for diagnosis autoimmune pancreatitis (AIP) has been proposed recently. The diagnostic performance of ICDC has not been evaluated in diffuse and focal type AIP respectively in comparison of the revised HISORt criteria and Asian criteria in Taiwan before.

Design: Prospective, consecutive patient cohort.

Setting: Largest tertiary referred center hospital managing pancreatic disease in Taiwan.

Participants: One hundred and eighty-eight patients with autoimmune pancreatitis and one hundred and thirty of tissue proofed pancreatic adenocarcinoma were consecutively recruited.

Interventions: The ICDC, revised HISORt criteria and Asian criteria were applied for each participant. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in diffuse and focal type of AIP.

Outcomes: Sensitivity, specificity, and accuracy. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in AIP and focal type of AIP.
Results: The sensitivity, specificity and accuracy of ICDC for all AIP were the best: 89.4% 100.0% and 93.7%, respectively in these 3 criteria. The sensitivity, specificity and accuracy of ICDC for focal AIP (84.9% 100.0% and 93.8%) were also the best among these 3 criteria. The area under curve of ROC of ICDC was 0.95 (95% CI:0.92-0.97) in all AIP and 0.93 (95% CI:0.88-0.97) in focal type AIP.

Conclusions: The sensitivity, specificity and accuracy of ICDC are higher than revised HISORt and Asian criteria. The sensitivity, specificity and accuracy of each criterion are higher in diffuse type of AIP compared to focal type AIP. Under the same specificity, the sensitivity and accuracy of ICDC are higher than other diagnostic criteria in focal type AIP. ICDC has better diagnostic performance compared to previous proposed diagnostic criteria, in both diffuse and focal type AIP.
ARTICLE SUMMARY

Article focus

1. There are several criteria proposed for diagnosis of autoimmune pancreatitis (AIP) in different countries. Revised HISORt criteria and Asian criteria are the two most common used diagnostic criteria in our Asian country including Taiwan.

The International Consensus Diagnostic Criteria (ICDC) is the newest diagnostic criteria proposed in 2011 in a consensus meeting. One major goal of these criteria is to improve the accuracy of autoimmune pancreatitis and to avoid “over” diagnosis of AIP in patient with pancreatic cancer, especially in focal type AIP.

The diagnostic performance of ICDC has not been evaluated compared to previous criteria in the aspect of differentiating diffuse and focal type AIP in Taiwan before.

2. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in AIP and focal type of AIP.

3. Sensitivity, specificity, and accuracy of the revised HISORt criteria, Asian criteria and ICDC are compared.

Key messages:

1. The sensitivity, specificity and accuracy of ICDC are all higher than revised HISORt and Asian criteria.
2. The sensitivity, specificity and accuracy of each criterion are higher in diffuse type of AIP compared to focal type AIP.

3. Under the same specificity, the sensitivity and accuracy of ICDC are higher than other diagnostic criteria in focal type AIP. ICDC has better diagnostic performance compared to previous proposed diagnostic criteria, in both diffuse and focal type AIP.

**Strengths and limitations of this study**

1. This is the first study to determine the diagnostic accuracy of ICDC of AIP from pancreatic cancer with focus on “focal” type AIP in Taiwan.

2. The study focus on only type 1 AIP in our study owing to the prevalence of type 2 AIP are relatively low in eastern countries including Taiwan. The role of ICDC in type 2 AIP needs further study.

3. The diagnostic performance of ICDC compared to other diagnostic criteria proposed in other regions or countries, other than revised HISORt and Asian criteria, are needed to confirm the universalization of diagnosis of AIP.
INTRODUCTION

Autoimmune pancreatitis (AIP) is a unique type of chronic pancreatitis characterized by elevated serum immunoglobulin G4 (IgG4), swelling of pancreas, irregular narrowing of main pancreatic duct, histological evidence of lymphoplasmacytic inflammation, and a good response to steroid therapy[1]. Although some advance has been made in the diagnosis and treatment of AIP over the past years[2], the diagnosis of AIP is still a great clinical challenge, especially in the differential diagnosis from pancreatic cancer[3-5]. Correct diagnosis could avoid unnecessary resection of pancreas and vice versa, to avoid delay treatment of pancreatic cancer. In 2002, the Japan Pancreas Society proposed diagnostic criteria for AIP based on imaging, serology, and histology. At that time, the serological criteria included elevated γ-globulin, immunoglobulin G (IgG), and auto-antibodies[6]. In 2006, the revised Japanese criteria were modified and added IgG4 to the serological criteria [7]. In 2008, the Asian diagnostic criteria was established according to modification of Japanese diagnostic criteria and Korean diagnostic criteria[8]. In western countries, the HISORt criteria was proposed from America[9]. In 2011, the international consensus diagnostic criteria (ICDC) was proposed which classified AIP into type 1 and type 2. Type 1 is featured histologically by lymphoplasmacytic sclerosing pancreatitis (LPSP) and type 2 by idiopathic duct-centric pancreatitis (IDCP). The
ICDC included 5 cardinal features of AIP including parenchymal imaging, ductal imaging, serology, other organ involvement (OOI), histology of pancreas, and response to steroid therapy. Each criterion was further classified into two levels (level 1 and level 2). The aim of the proposal of ICDC was intended to improve the diagnosis of AIP [10]. AIP could be also classified into focal type and diffuse type AIP according to the involvement of pancreatic enlargement. In clinical settings, it is more important and also difficult in differentiating focal type AIP from pancreatic cancer. Till now, it still lacks a simple parameter with absolute diagnostic value. Therefore, use of combined parameters according to different diagnostic criteria in different countries exists.

The objective of this study is to evaluate the diagnostic performance (sensitivity, specificity and accuracy) of ICDC from differentiating pancreatic cancer in a prospectively collected cohort in Taiwan[11-13], compared to the two most commonly used two criteria in our country before ICDC made (revised HISORt criteria and Asian criteria). The diagnostic role of each cardinal features of ICDC will be compared to revised HISORt and Asian criteria in diffuse AIP and focal type AIP respectively.
METHODS

Study participants

Between Jan 1996 and Dec 2013, we consecutively collected 188 patients with AIP (95 men and 93 women) at National Taiwan University Hospital, a tertiary referred center also the largest medical center for management of pancreatic diseases in Taiwan[11]. All the patients with AIP fulfilled at least one of the HISORt criteria (158/188, 84.0 %), or Asian diagnostic criteria (162/188, 86.2%), or the ICDC criteria (168/188, 89.4%) for AIP. All patients were type 1 AIP. All patients were followed up for at least 12 months. A total of consecutive 130 patients (65 men and 65 women) with cytological or/and pathologically confirmed adenocarcinoma of pancreas were enrolled as a control group. The patients' mean age was 51.4 years (range, 33-78 years) and 60.9 years (range, 32-78 years) in patient with AIP and pancreatic cancer. The institutional ethics committee approved this study. All the patients' medical charts were reviewed and the patients' demographic data, including age, gender, serological studies, image studies, and clinical manifestations etc. were collected.

Findings of Diagnostic criteria of ICDC

We categorized all patients with AIP and PC as to level 1 finding, level 2 findings or neither for each of 5 criteria ( parenchymal imaging, ductal imaging, serology, other OOI, histology of pancreas, and response to steroid therapy) according to ICDC. For
parenchymal imaging, the frequencies of diffuse enlargement, focal enlargement and atypical imaging (pancreatic duct dilatation or calcification or atrophy) were evaluated. Enlargement of pancreas was defined as when the width of the pancreatic body or tail exceeds two-thirds of the transverse diameter of the vertebral body or if the width of the pancreatic head exceeds the full transverse diameter of the vertebral body[14]. For ductal imaging, main pancreatic duct diameter was measured by use of abdominal computed tomography (CT) or/and magnetic resonance cholangiopancreatography (MRCP) or/and endoscopic retrograde pancreatography (ERP). The frequencies of long stricture without marked upstream dilatation, multiple strictures without marked upstream dilatation, segmental/focal narrowing without marked upstream dilatation, and marked upstream dilatation of the MPD were evaluated. Pancreatic duct dilatation was defined as the diameter of the main pancreatic duct (MPD) exceed 5mm. Parenchymal and ductal imaging scans were analyzed by 3 experts (MC Chang, YT Chang and PC Liang).

For OOI, the frequencies of segmental/multiple proximal bile duct stricture, retroperitoneal fibrosis, symmetrically enlarged salivary/lachrymal glands, and radiologic evidence of renal involvement were evaluated. Bile duct stricture was evaluated by MRCP or ERC, or percutaneous transhepatic cholangiography (PTC.) Retroperitoneal fibrosis was evaluated by contrast enhanced CT or MRI.
Symmetrically enlarged salivary/lachrymal glands was evaluated by physical examination or/and CT.

For histology of pancreas in AIP, there were 25 patients received pancreatectomy. There were 6 patients received biopsy of pancreas. Pancreatic histology were evaluated by an experienced pathologist (YM Jeng) blinded to the other data.

For steroid therapy, 126 patients (67.0%) received corticosteroid therapy as the initial treatment of AIP. The dose for induction therapy was started from 30-40 mg/day for 2 week -4 week and then tapered 5 mg/week gradually. The treatment response of steroid was nearly 98%.

We evaluated of the frequencies of level 1 findings, level 2 finding and neither of each criterion in all patients with AIP and PC. Sensitivity, specificity and accuracy were compared between ICDC, revised HISORt, and Asian criteria. We also evaluated the cases which did not fit the diagnosis with AIP according to each criterion.

Statistical analysis

We calculated the sensitivity, specificity, and accuracy of each diagnostic criterion. The between-group demographic data were compared by the Student unpaired t test for continuous data and by the χ² test for categorical data. Receiver-operator characteristic (ROC) curves and area-under the-curves (AUCs) were estimated after logistic regressions in different criteria in all AIP and focal AIP subgroups and
presented with corresponding 95% confidence intervals (CIs). The statistical
calculations were carried out using SPSS 17 statistical software (SAS Institute, Cary,
NC). All reported P value was 2-sided. Differences with a P value less than 0.05 were
considered to be statistically significant.
RESULTS

Parenchymal imaging

Of the 188 patients, 90 (50.5%) and 93 (49.5%) with AIP were categorized as level 1 and 2, respectively. All patients with PC were classified as level 2 (Table 1).

Ductal Imaging

Ductal imaging was evaluated by at least one of the ERC or MRCP in all patients. Among them, 93 (49.5%) of 188 patients with AIP and no any patients with PC were categorized as level 1. There were 68 (36.2%) of 188 patients with AIP and 13 (10.0%) of 130 patients with PC were categorized as level 2 (Table 1). Marked MPD dilatation was observed significantly frequent in patient with PC (n=117; 90.0%) than in those with AIP (n=27; 14.4%, P<0.001). Among the 27 patients with AIP with MPD dilatation, narrowing of the downstream MPD was observed in 3 patients and the others with normal downstream appearance.

Serology

Forty seven (36.7%) of 188 patients with AIP and 4 (4.8%) of 84 patients with PC were categorized as level 1 respectively (Table 1). The mean serum IgG4 level was $346.6\pm56.2$ mg/dL, statistically significantly higher than those in patients with pancreatic cancer, $119.2\pm23.9$ mg/dL. The frequencies of serum level above 280 mg/dl (level 1) and 140 mg/dl (level 2) were significantly higher in AIP patients (P<0.001.)
Table 1. Frequencies of level 1 and 2 findings in international consensus diagnostic criteria (ICDC) for autoimmune pancreatitis (AIP) and pancreatic cancer (PC)

<table>
<thead>
<tr>
<th>Features</th>
<th>AIP (n=188)</th>
<th>PC (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenchymal imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>95 (50.5%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>93 (49.5%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>188 (100.0%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>0 (0.0%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td><strong>Ductal imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>93 (49.5%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>68 (36.2%)</td>
<td>13 (10.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>161 (85.6%)</td>
<td>13 (10.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>27 (14.4%)</td>
<td>117 (90.0%)</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>47/128 (36.7%)</td>
<td>4/84 (4.8%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>55/128 (42.9%)</td>
<td>3/84 (3.6%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>102/128 (79.7%)</td>
<td>7/84 (8.3%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>26/128 (20.3%)</td>
<td>77/84 (91.7%)</td>
</tr>
<tr>
<td><strong>OOI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>63 (33.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>64 (34.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>127 (92.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>61 (32.4%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td><strong>Histology of pancreas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>28 (14.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>3 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>31 (16.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>157 (83.5%)</td>
<td>130 (100.0%)</td>
</tr>
</tbody>
</table>

AIP: autoimmune pancreatitis; PC: pancreatic cancer; OI: other organ involvement

**Other organ involvement (OOI)**

Sixty-three (33.5%) of 188 patients with AIP was categorized as level 1 and no any one of 130 patients with PC were categorized as level 1 or 2 (Table 1). Proximal bile duct stricture was observed in 53 patients (28.2%) with AIP, and retroperitoneal
fibrosis was observed in 5 patients (2.7%) with AIP both level 1 findings. Enlarged salivary/lacrimal glands were observed in 58 patients (27.6%) with AIP and renal involvement in 9 (4.8%), these met level 2 criteria. Neither enlarged salivary/lacrimal glands nor renal involvement was observed in any patients with PC.

**Histology of pancreas**

There were 31 (16.4%) patients with AIP were categorized as level 1 or level 2 criteria and none of 130 patients with PC were categorized as level 1 or level 2 (Table 1). There were 28 patients (14.9%) with level 1 evidence and 3 patients (1.6%) with level 2 evidence in histologically LPSP. No any patients with PC fulfilled the level 1 or 2 criteria.

**Response to steroid therapy**

Of the 128 patients who received steroid treatment as the initial treatment (induction therapy), 126 patient (98.4%) showed steroid response with improvement clinically, serologically and morphologically. Two of the patients with diffuse pancreatic enlargement and narrowing of MPD received steroid but no morphologically response. Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) were performed and no malignancy was detected. These two patients discontinued steroid after 3 months of steroid and was follow up regularly. These two patients were followed up for 18 months and 20 months and no any malignancy were documented although the
pancreatic enlargement did not subside.

**Diagnosis on the basis of ICDC, revised HISORt and Asian criteria**

Of the 188 patients with AIP, 116 patients were diagnosed as definite AIP; 35 patients were diagnosed as probable AIP and 17 were classified as not otherwise specified (NOS). Among these patients, the primary basis for diagnosis was histology in 31 patients, response to steroid therapy in 126 patients and imaging in 188 patients.

There were 20 patients in this study deniable for type 1 AIP. All patients with PC were deniable for type 1 AIP on the basis of ICDC. The sensitivity, specificity and accuracy of the ICDC for type 1 AIP were 89.4%, 100/0% and 93.7% (Table 2).

Using revised HISORt criteria, 158 patients (84.0%) were diagnosed as definitive AIP. Among these 158 patients, the primary basis of diagnosis was diffuse type in 95 patients (60.1%), histology based diagnosis in 31 patients (19.6%). There were 30 patients were deniable for AIP based on revised HISORt criteria in this study. All of the PC patients were deniable for AIP based on the revised HISORt criteria. The sensitivity, specificity and accuracy of the revised HISORt criteria were 84.0%, 100.0% and 90.5% (Table 2). Using Asian criteria, 162 patients (86.2%) were diagnosed as AIP. There were 143 patients (88.3%) were diagnosed based on Imaging plus serology; 143 patients (88.3%) were diagnosed based on Imaging plus serology; 31 patients (19.1%) diagnosed based on histopathology and 126 patients (77.8%)
Table 2. Comparison of diagnostic criteria for autoimmune pancreatitis from pancreatic cancer

<table>
<thead>
<tr>
<th></th>
<th>Case number</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AIP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit Asian</td>
<td>162</td>
<td>86.2</td>
<td>100.0</td>
<td>91.8</td>
</tr>
<tr>
<td>Fit revised HISORt</td>
<td>158</td>
<td>84.0</td>
<td>100.0</td>
<td>90.5</td>
</tr>
<tr>
<td>Fit ICDC</td>
<td>168</td>
<td>89.4</td>
<td>100.0</td>
<td>93.7</td>
</tr>
<tr>
<td>Focal AIP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit Asian</td>
<td>68</td>
<td>73.1</td>
<td>100.0</td>
<td>99.6</td>
</tr>
<tr>
<td>Fit revised HISORt</td>
<td>73</td>
<td>78.5</td>
<td>100.0</td>
<td>95.6</td>
</tr>
<tr>
<td>Fit ICDC</td>
<td>79</td>
<td>84.9</td>
<td>100.0</td>
<td>97.3</td>
</tr>
</tbody>
</table>

ICDC: international consensus diagnostic criteria

diagnosed based on steroid treatment response. Here were 26 patients were deniable for AIP based on Asian criteria in this study. All of the PC patients were deniable for AIP based on the Asian criteria. The sensitivity, specificity and accuracy of the revised HISORt criteria were 86.2%, 100.0% and 91.8% (Table 2).

Deniable cases on the basis of ICDC

There were 20 patients who were deniable for ICDC in this study. All these 20 patients could be diagnosed by Asian criteria. Among them, there were 2 patients could be diagnosed both by HISORt criteria and Asian criteria. They included 6 cases and 14 cases with level 1 or 2 parenchymal imaging; 6 cases and 12 cases with level 1 or 2 ductal imaging; 9 cases with level 2 serology; 11 patients with level 1 OOI.

There was 1 patient with steroid treatment response. The most common factor which
lead to deniable of ICDC or revised HISORt criteria was the serology criterion. There were 18 out of 20 patients had antoantibodies which could be one of the item in Asian serology criterion. The ICDC and HISORt only adapted IgG4 level alone as the serology criterion.

**ICDC criteria in Focal type AIP and diffuse type AIP**

The comparisons of frequencies of level1 and 2 finings in ICDC in focal type and diffuse AIP were shown in Table 3. The frequencies of level1 or level2 features in ductal imaging were significantly lower in focal type AIP (73.1% vs. 97.9%, p<0.001, Table 3). The frequencies of level 1 or 2 features in serology was also lower in focal type (55.4% vs.69.3%, p=0.075). The frequencies of any level of OOI in focal type AIP was higher than diffuse type (81.7% vs. 53.7%, p<0.0001). The frequencies of any histological evidence of LPSP in our focal type AIP was higher than diffuse type (23.7% vs. 9.5%, p=0.01) in our study (Table 3).

**Sensitivity, Specificity and Accuracy of ICDC, revised HISORt criteria and Asian criteria**

The sensitivity, specificity and accuracy of the ICDC were 84.9%, 100.0% and 93.8% (Table 2). The sensitivity, specificity and accuracy of the revised HISORt criteria were 78.5%, 100.0% and 91.0% (Table 2). The sensitivity, specificity and accuracy of the Asian criteria were 73.1%, 100.0% and 88.8% (Table 2).
Table 3 Frequencies of level 1 and 2 findings in international consensus diagnostic criteria (ICDC) for focal and diffuse type autoimmune pancreatitis (AIP)

<table>
<thead>
<tr>
<th>Features</th>
<th>Focal AIP (n=93)</th>
<th>Diffuse AIP (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>0(%)</td>
<td>93(97.9%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>68(73.1%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>68(73.1%)</td>
<td>93(97.9%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>25(26.9%)</td>
<td>2(2.1%)</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>16/74(21.6%)</td>
<td>31/88(35.2%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>25/74(33.8%)</td>
<td>30/88(34.1%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>41/74(55.4%)</td>
<td>61/88(69.3%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>33/74(44.6%)</td>
<td>27/88(30.7%)</td>
</tr>
<tr>
<td>OOI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>31(33.3%)</td>
<td>32(%33.7)</td>
</tr>
<tr>
<td>Level 2</td>
<td>45(48.4%)</td>
<td>19(20.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>76(81.7%)</td>
<td>51(53.7%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>17(11.3%)</td>
<td>44(46.3%)</td>
</tr>
<tr>
<td>Histology of pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>20(21.5%)</td>
<td>8(8.4%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>2(2.2%)</td>
<td>1(1.1%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>22(23.7%)</td>
<td>9(9.5%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>71(76.3%)</td>
<td>86(90.5%)</td>
</tr>
</tbody>
</table>

AIP: autoimmune pancreatitis; OI: other organ involvement

The ROC was calculated in AIP (Fig 1) and focal type AIP (Fig 2). The area under the curve was 0.95 (95% CI: 0.92-0.97) of ICDC (Fig 1a), 0.91 (95% CI: 0.92-0.97) of revised HISORt criteria (Fig 1b), and 0.93 (95% CI: 0.92-0.97) of Asian criteria (Fig 1c). For focal type AIP, the area under the curve was 0.93 (95% CI: 0.88-0.97) of ICDC (Fig 2a), 0.89 (95% CI: 0.84-0.94) of revised HISORt criteria (Fig. 2b), and 0.87 (95% CI: 0.81-0.92) of Asian criteria (Fig 2c).
Discussion

The sensitivity, specificity and accuracy of ICDC for all AIP were 89.4% 100.0% and 93.7%. The sensitivity, specificity and accuracy of ICDC for focal AIP were 84.9% 100.0% and 93.8%. Among the three criteria, the sensitivity and accuracy of ICDC were the best one compared to revised HISORt criteria and Asian criteria with the same specificity (Table 2). There were 12 patients with deniable revised HISORt criteria were diagnosed as AIP in ICDC (10 definite, 1 probable and 1 NOS of ICDC).

There were 26 patients with deniable Asian criteria were diagnosed as AIP in ICDC (11 definite, 14 probable and 1 NOS in ICDC). The ICDC showed higher sensitivity the revised HISORt and Asian criteria. The reason why patients deniable for revised HISORt or Asian criteria but fit ICDC diagnosis was partially caused by the different definition of parenchymal imaging between these criteria. ICDC includes atypical imaging and classifies atypical imaging as S2 level in parenchymal imaging criterion. That's one reason why ICDC had higher sensitivities in diagnosis of AIP in general.

The wider range of imaging criteria improved the diagnostic sensitivity but did not decreased neither the specificity nor the accuracy of ICDC. All the three criteria showed high specificity (Table 2). The ICDC showed higher accuracy than Asian criteria and revised HISORt criteria in our population. Recently, studies from Japanese population also demonstrated better accuracy of ICDC compared to other criteria, including the Japanese pancreatic society criteria[15-18]. Though ICDC is
considered to be superior to other various criteria, ICDC seems to be too complicated to handle for clinician. Japanese has proposed revised diagnostic criteria by Japanese pancreatic society very recently[19]. It would be interest to whether the performance could even be better or easlily to use in clinical practice compared to ICDC criteria.

Type 1 AIP composed of a heterogenous population, at this time moment, we did not have suitable simple amendment for ICDC for clinical use in our country. With the advance of better understanding the pathogenesis of the disease, to simplify the diagnostic criteria might be feasible and needed for clinician.

In ductal imaging criterion, 161 (92.5%) of 188 patients with AIP and 13 (1.0%) of 130 patients with PC were categorized as level 1 or 2, respectively. The specificity of ductal imaging is high. One of the reasons for this high specificity is that patients with marked upstream MPD dilatation (>5 mm) were excluded from level 1 or 2. In the present study, 28 of 31 patients with PC who showed focal MPD stricture were excluded from level 2 because of marked upstream MPD dilatation. On the other hand, 27 (14.4%) of 188 patients with AIP showed marked upstream MPD dilatation. The frequency of any level1 or 2 evidence in ductal imaging is close to the recently reported on (7/62, 11.3%) by Nishino et al.[20]. Naitoh et al also reported that a maximal diameter of the upstream MPD less than 5 mm was an appropriate cutoff point to differentiate mass-forming AIP from PC[21]. In our study, we also use the
5mm as a cutoff point to differentiating focal type AIP and PC. Therefore, we consider that a 5-mm diameter of the upstream MPD is appropriate to discriminate AIP from PC. In the present study, 4 patients with PC fulfilled the level 1 serological criterion. Marked upstream MPD dilatation (5 mm) was observed in these patients. If this exclusion criterion (marked upstream MPD) did not exist, this patient would have fulfilled level 2 criteria for ductal imaging, and we would have misdiagnosed these 4 patients with PC as definitive type 1 AIP under the ICDC. Therefore, we consider that this exclusion criterion of ductal imaging is useful for excluding out PC.

The value of serum IgG4 as a serological marker of AIP was first established in 2001[22] [23]. Hamano et al. reported that sensitivity and specificity for differentiating AIP from PC were 90.2% and 97.5%[23]. In the present study, those sensitivity and specificity of serum IgG4 (>140 mg/dL) were 79.6% and 92.6%, respectively. The cause of the wide range of sensitivity in the reported series might be caused by the combined analysis of types 1 and 2 in these studies. The distribution between types 1 and 2 AIP might affect the value of IgG4. Ghazale et al [4] reported that the sensitivity of elevated serum IgG4 (>140 mg/dL) for PC was 10%, and that of 2-fold elevation (level 1 ICDC serology criteria) was 1%. Our present study showed that the sensitivity and specificity of 2-fold elevation of serum IgG4 were 36.7% and 95.2% in out type 1 AIP. Serum IgG4 is the only used serology marker in ICDC. In
Asian criteria, they adapted IgG, IgG4 and presence of autoantibody as the serological criteria. In our patients with type 1 AIP, if we add the presence of autoantibody as also a surrogate marker in serology, thus all of the patients deniable for ICDC could be diagnosed by this modification.

IgG4-related disease (IgG4-RD) is a new disease entity characterized by elevated serum IgG4 concentration and/or tissue infiltration by IgG4-positive cells[24]. Type 1 AIP is regarded as a part (pancreatic manifestation) of IgG4-RDs. In the present study, level 1 or 2 OOI was observed in 127 (67.6%) of the patients with AIP and in none of those with PC. Therefore, this OOI criterion has high specificity for type 1 AIP.

In the present study, all resection specimens (27 patients) and fulfilled level 1 criteria. One of four biopsied specimens guided by computed tomography fulfilled level 1, with the rest diagnosed as level 2. The present findings suggest obtaining histopathologic evidence of type 1 AIP by biopsied specimen is difficult. Endoscopic ultrasonography–guided FNA was considered useful for the differentiation from PC but might be insufficient for tissue collection to diagnosis as level 1. Kanno et al[25] reported that 14 and 6 of 25 patients were judged to have level 1 and level 2
histological findings by trucut biopsy under endoscopic ultrasound (EUS) guidance respectively. We did not perform EUS-trucut biopsy in this study owing to the needle is not available and the cost is not covered by our health insurance. Further studies for the feasibility and necessarily of EUS-FNA in diagnosing type 1 AIP in ICDC histological need to be studied.

Diffuse and focal enlargement of the pancreas is a characteristic feature of AIP in parenchymal imaging. ICDC included patients with atypical parenchymal imaging as level 2. For diffuse type AIP, the diagnostic accuracy of ICDC, Asian, and HISORt criteria were over 95%, much better than that in focal type AIP. This observation is reasonable for us to understand because of it is very rare to have pancreatic cancer involving whole pancreas in clinical practice. The diagnosis sensitivity in diffuse type AIP were also higher than those in focal type in these three diagnostic criteria (Table 2). In diffuse type AIP, Asian criteria was most sensitive with sensitivity 98.9%, followed by ICDC (93.7%) and the HISORt criteria (89.5%). There were 4 patients with diffuse AIP who did not have elevated was the least sensitive criteria in the diagnosis of diffuse type with sensitivity only 89.5%. The were 4 diffuse type AIP deniable for HISORt but fit ICDC NOS owing to these 4 patients did not have any collateral evidence. These 4 patients could be diagnosed by Asian criteria as they have
presence of autoantibodies which made they fit the serology criteria in Asian

diagnosis setting but not fit the serology criteria in ICDC and HISORt criteria. These

4 patients had received steroid response as the initial treatment and they all had
disease relapse in their follow up. The increase of sensitivity in Asian criteria in
diagnosing diffuse type AIP is relevant to the wide range of definition in serology
criterion (IgG, IgG4 or/and antoantibodies), compared to use IgG4 alone as serology
criterion in HISORt and ICDC.

It is a greater challenge to differentiate focal type AIP with pancreatic cancer,
compare to differentiate diffuse type AIP from PC. In this study, we have 93 patients
with focal AIP. The ductal imaging, serology and OOI were different from diffuse
type. Focal type AIP had less frequency of level 1 or 2 presentations of ductal
imaging and serology. In contrast, focal type AIP had higher frequencies of level 1 or
2 presentations of OOI. These clinical observations remind us that the collateral
evidence of AIP in focal type AIP is mostly in OOI, but not serology. Detailed
physical examination and history taking and imaging interpretation imaging other
than pancreas could give some hint to increase the sensitivity of diagnosis of focal
AIP.

In focal type of AIP, the diagnostic sensitivity of ICDC (84.9%) was higher than
revised HISORt criteria (78.5%) and Asian criteria (73.1%). There were 14 (15.1%) focal type AIP patients deniable for ICDC criteria. All these 14 patients could be diagnosed by Asian criteria. There were 12 patients with presence of autoantibodies and 9 patients with serum IgG4 level above 140 mg/dl. Among them, they were 12 patients with level 2 and 2 patients without any level 1 or 2 criteria in ductal imaging.

In OOI, there were 9 patients with level 2 criteria and 5 patients without any level 1 or 2 criteria. All the focal type AIP patients deniable Asian criteria could be diagnosed by ICDC criteria.

In conclusion, the ICDC shows high sensitivity, specificity and accuracy in the diagnosis of type 1 AIP. In focal type AIP, ICDC is still the best one in sensitivity, specificity and accuracy. The diagnostic sensitivity in focal type AIP not as good as diffuse type AIP in all the three adapted criteria (ICDC, Asian and revised HISORt criteria). How to improve the sensitivity of diagnosis of focal AIP is the issue need to be resolved in the future.
AUTOHOR CONTRIBUTION

Ming-Chu Chang and Yu-Ting Chang have full access to the data take responsibility for the integrity of the data, and the accuracy of the data analysis.

Conception and design, or analysis and interpretation of data: Ming-Chu Chang, Po-Chin Liang, I-Shiow Jan, Ching-Yao Yang, Yu-Wen Tien, Shu-Chen Wei, Jau-Min Wong, Yu-Ting Chang

Drafting the article or revising it critically for important intellectual content: Ming-Chu Chang, Yu-Ting Chang

Final approval of the version to be published: Ming-Chu Chang, Yu-Ting Chang

Obtained funding: Ming-Chu Chang and Yu-Ting Chang, Jau-Min Wong

Administrative, technical, or material support: Ming-Chu Chang and Yu-Ting Chang, Jau-Min Wong

Study supervision: Yu-Ting Chang

Yu-Ting Chang had the final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST DISCLOSURE

The authors report no conflict of interest.

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The funding source had no role in study design, data collection, analysis, or interpretation, report writing or the decision to submit this paper for publication.

**PATIENT CONSENT**

Signed informed consent was obtained from each study subject prior to participation in the study.

**ETHICS APPROVAL**

The study protocol was approved by the institutional review board of National Taiwan University Hospital.

**DATA SHARING STATEMENT**

No additional data are available.
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Figure Legend

Figure 1. Receiver-operator characteristics curves of International Consensus Diagnostic Criteria (ICDC), revised HISORT and Asian criteria in diagnosis of 188 patients with autoimmune pancreatitis (AIP) from 130 patients

1a. ICDC diagnostic criteria

1b. revised HISORT criteria

1c. Asian criteria
Figure 2. Receiver-operator characteristics curves of International Consensus Diagnostic Criteria (ICDC), revised HISORT and Asian criteria in diagnosis of 93 patients with focal autoimmune pancreatitis (AIP) from 130 patients with pancreatic cancer.

2a. ICDC diagnostic criteria

2b. revised HISORT criteria

2c. Asian criteria
Comparison and Validation of International Consensus Diagnostic Criteria For Diagnosis of Autoimmune pancreatitis From Pancreatic Cancer in a Taiwanese Cohort

Ming-Chu Chang¹, M.D., Ph.D., Po-Chin Liang², M.D., I-Shiow Jan³, M.D., Ching-Yao Yang⁴, M.D., Ph.D., Yu-Wen Tien⁴, M.D., Ph.D., Shu-Chen Wei¹, M.D., Ph.D., Jau-Min Wong¹, M.D., Ph.D., Yu-Ting Chang¹, M.D., M.S., Ph.D.

¹Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

²Department of Radiology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

³Department of Laboratory Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

⁴Department of Surgery, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

Correspondence Author: Yu-Ting Chang, M.D., M.S., Ph.D.

Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan;

No.7 Chung Shan South Road, Taipei, Taiwan.

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Tel: 886-2-23123456 ext. 63563

Fax: 886-2-23633658

e-mail: yutingchang@ntu.edu.tw

Running title: evaluation of diagnostic criteria in AIP and focal AIP

Keywords: autoimmune pancreatitis (AIP), pancreatic cancer (PC), HISORt, Asian; ICDC, focal type, diffuse type

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abstract, figure/table legends, and references.)

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Abstract

Objectives: The International Consensus Diagnostic Criteria (ICDC) for designing the diagnosis of autoimmune pancreatitis (AIP) has been proposed recently. The diagnostic performance of ICDC has not been evaluated in diffuse and focal type AIP respectively in comparison of the revised HISORt criteria and Asian criteria in Taiwan before.

Design: Prospective, consecutive patient cohort.

Setting: Largest tertiary referred center hospital managing pancreatic disease in Taiwan.

Participants: One hundred and eighty-eight patients with autoimmune pancreatitis and one hundred and thirty of tissue proofed pancreatic adenocarcinoma were consecutively recruited.

Interventions: The ICDC, revised HISORt criteria and Asian criteria were applied for each participant. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in diffuse and focal type of AIP.

Outcomes: Sensitivity, specificity, and accuracy. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in AIP and focal type of AIP.
Results: The sensitivity, specificity and accuracy of ICDC for all AIP were the best: 89.4% 100.0% and 93.7%, respectively in these 3 criteria. The sensitivity, specificity and accuracy of ICDC for focal AIP (84.9% 100.0% and 93.8%) were also the best among these 3 criteria. The area under curve of ROC of ICDC was 0.95 (95% CI:0.92-0.97) in all AIP and 0.93 (95% CI:0.88-0.97) in focal type AIP.

Conclusions: The sensitivity, specificity and accuracy of ICDC are higher than revised HISORt and Asian criteria. The sensitivity, specificity and accuracy of each criterion are higher in diffuse type of AIP compared to focal type AIP. Under the same specificity, the sensitivity and accuracy of ICDC are higher than other diagnostic criteria in focal type AIP. ICDC has better diagnostic performance compared to previous proposed diagnostic criteria, in both diffuse and focal type AIP.
ARTICLE SUMMARY

Article focus

1. There are several criteria proposed for diagnosis of autoimmune pancreatitis (AIP) in different countries. Revised HISORt criteria and Asian criteria are the two most common used diagnostic criteria in our Asian country including Taiwan. The International Consensus Diagnostic Criteria (ICDC) is the newest diagnostic criteria proposed in 2011 in a consensus meeting. One major goal of these criteria is to improve the accuracy of autoimmune pancreatitis and to avoid “over” diagnosis of AIP in patient with pancreatic cancer, especially in focal type AIP.

The diagnostic performance of ICDC has not been evaluated compared to previous criteria in the aspect of differentiating diffuse and focal type AIP in Taiwan before.

2. Each diagnostic criterion of ICDC was validated with special reference to levels 1 and 2 in AIP and focal type of AIP.

3. Sensitivity, specificity, and accuracy of the revised HISORt criteria, Asian criteria and ICDC are compared.

Key messages:

1. The sensitivity, specificity and accuracy of ICDC are all higher than revised HISORt and Asian criteria.
2. The sensitivity, specificity and accuracy of each criterion are higher in diffuse type of AIP compared to focal type AIP.

3. Under the same specificity, the sensitivity and accuracy of ICDC are higher than other diagnostic criteria in focal type AIP. ICDC has better diagnostic performance compared to previous proposed diagnostic criteria, in both diffuse and focal type AIP.

Strengths and limitations of this study

1. This is the first study to determine the diagnostic accuracy of ICDC of AIP from pancreatic cancer with focus on “focal” type AIP in Taiwan.

2. The study focus on only type 1 AIP in our study owing to the prevalence of type 2 AIP are relatively low in eastern countries including Taiwan. The role of ICDC in type 2 AIP needs further study.

3. The diagnostic performance of ICDC compared to other diagnostic criteria proposed in other regions or countries, other than revised HISORt and Asian criteria, are needed to confirm the universalization of diagnosis of AIP.
INTRODUCTION

Autoimmune pancreatitis (AIP) is a unique type of chronic pancreatitis characterized by elevated serum immunoglobulin G4 (IgG4), swelling of pancreas, irregular narrowing of main pancreatic duct, histological evidence of lymphoplasmacytic inflammation, and a good response to steroid therapy[1]. Although some advance has been made in the diagnosis and treatment of AIP over the past years[2], the diagnosis of AIP is still a great clinical challenge, especially in the differential diagnosis from pancreatic cancer[3-5]. Correct diagnosis could avoid unnecessary resection of pancreas and vice versa, to avoid delay treatment of pancreatic cancer. In 2002, the Japan Pancreas Society proposed diagnostic criteria for AIP based on imaging, serology, and histology. At that time, the serological criteria included elevated γ-globulin, immunoglobulin G (IgG), and auto-antibodies[6]. In 2006, the revised Japanese criteria were modified and added IgG4 to the serological criteria [7]. In 2008, the Asian diagnostic criteria was established according to modification of Japanese diagnostic criteria and Korean diagnostic criteria[8]. In western countries, the HISORt criteria was proposed from America[9]. In 2011, the international consensus diagnostic criteria (ICDC) was proposed which classified AIP into type 1 and type 2. Type 1 is featured histologically by lymphoplasmacytic sclerosing pancreatitis (LPSP) and type 2 by idiopathic duct-centric pancreatitis (IDCP). The
ICDC included 5 cardinal features of AIP including parenchymal imaging, ductal imaging, serology, other organ involvement (OOI), histology of pancreas, and response to steroid therapy. Each criterion was further classified into two levels (level 1 and level 2). The aim of the proposal of ICDC was intended to improve the diagnosis of AIP [10]. AIP could be also classified into focal type and diffuse type AIP according to the involvement of pancreatic enlargement. In clinical settings, it is more important and also difficult in differentiating focal type AIP from pancreatic cancer. Till now, it still lacks a simple parameter with absolute diagnostic value. Therefore, use of combined parameters according to different diagnostic criteria in different countries exists.

The objective of this study is to evaluate the diagnostic performance (sensitivity, specificity and accuracy) of ICDC from differentiating pancreatic cancer in a prospectively collected cohort in Taiwan[11-13], compared to the two most commonly used two criteria in our country before ICDC made (revised HISORt criteria and Asian criteria). The diagnostic role of each cardinal features of ICDC will be compared to revised HISORt and Asian criteria in diffuse AIP and focal type AIP respectively.
METHODS

Study participants

Between Jan 1996 and Dec 2013, we consecutively collected 188 patients with AIP (95 men and 93 women) at National Taiwan University Hospital, a tertiary referred center also the largest medical center for management of pancreatic diseases in Taiwan[11]. All the patients with AIP fulfilled at least one of the HISORt criteria (158/188, 84.0 %), or Asian diagnostic criteria (162/188, 86.2%), or the ICDC criteria (168/188, 89.4%) for AIP. All patients were type 1 AIP. All patients were followed up for at least 12 months. A total of consecutive 130 patients (65 men and 65 women) with cytological or/and pathologically confirmed adenocarcinoma of pancreas were enrolled as a control group. The patients' mean age was 51.4 years (range, 33-78 years) and 60.9 years (range, 32-78 years) in patient with AIP and pancreatic cancer. The institutional ethics committee approved this study. All the patients' medical charts were reviewed and the patients' demographic data, including age, gender, serological studies, image studies, and clinical manifestations etc. were collected.

Findings of Diagnostic criteria of ICDC

We categorized all patients with AIP and PC as to level 1 finding, level 2 findings or neither for each of 5 criteria ( parenchymal imaging, ductal imaging, serology, other OOI, histology of pancreas, and response to steroid therapy) according to ICDC. For
parenchymal imaging, the frequencies of diffuse enlargement, focal enlargement and atypical imaging (pancreatic duct dilatation or calcification or atrophy) were evaluated. Enlargement of pancreas was defined as when the width of the pancreatic body or tail exceeds two-thirds of the transverse diameter of the vertebral body or if the width of the pancreatic head exceeds the full transverse diameter of the vertebral body [14]. For ductal imaging, main pancreatic duct diameter was measured by use of abdominal computed tomography (CT) or/and magnetic resonance cholangiopancreatography (MRCP) or/and endoscopic retrograde pancreatography (ERP). The frequencies of long stricture without marked upstream dilatation, multiple strictures without marked upstream dilatation, segmental/focal narrowing without marked upstream dilatation, and marked upstream dilatation of the MPD were evaluated. Pancreatic duct dilatation was defined as the diameter of the main pancreatic duct (MPD) exceeding 5mm. Parenchymal and ductal imaging scans were analyzed by 3 experts (MC Chang, YT Chang and PC Liang).

For OOI, the frequencies of segmental/multiple proximal bile duct stricture, retroperitoneal fibrosis, symmetrically enlarged salivary/lachrymal glands, and radiologic evidence of renal involvement were evaluated. Bile duct stricture was evaluated by MRCP or ERC, or percutaneous transhepatic cholangiography (PTC). Retroperitoneal fibrosis was evaluated by contrast enhanced CT or MRI.
Symmetrically enlarged salivary/lachrymal glands was evaluated by physical examination or/and CT.

For histology of pancreas in AIP, there were 25 patients received pancreatectomy. There were 6 patients received biopsy of pancreas. Pancreatic histology were evaluated by an experienced pathologist (YM Jeng) blinded to the other data.

For steroid therapy, 126 patients (67.0%) received corticosteroid therapy as the initial treatment of AIP. The dose for induction therapy was started from 30-40 mg/day for 2 week -4 week and then tapered 5 mg/week gradually. The treatment response of steroid was nearly 98%.

We evaluated of the frequencies of level 1 findings, level 2 finding and neither of each criterion in all patients with AIP and PC. Sensitivity, specificity and accuracy were compared between ICDC, revised HISORt, and Asian criteria. We also evaluated the cases which did not fit the diagnosis with AIP according to each criterion.

**Statistical analysis**

We calculated the sensitivity, specificity, and accuracy of each diagnostic criterion.

The between-group demographic data were compared by the Student unpaired t test for continuous data and by the $\chi^2$ test for categorical data. Receiver-operator characteristic (ROC) curves and area-under the-curves (AUCs) were estimated after logistic regressions in different criteria in all AIP and focal AIP subgroups and
presented with corresponding 95% confidence intervals (CIs). The statistical
calculations were carried out using SPSS 17 statistical software (SAS Institute, Cary,
NC). All reported P value was 2-sided. Differences with a P value less than 0.05 were
considered to be statistically significant.
RESULTS

Parenchymal imaging

Of the 188 patients, 90 (50.5%) and 93 (49.5%) with AIP were categorized as level 1 and 2, respectively. All patients with PC were classified as level 2 (Table 1).

Ductal Imaging

Ductal imaging was evaluated by at least one of the ERC or MRCP in all patients. Among them, 93 (49.5%) of 188 patients with AIP and no any patients with PC were categorized as level 1. There were 68 (36.2%) of 188 patients with AIP and 13 (10.0%) of 130 patients with PC were categorized as level 2 (Table 1). Marked MPD dilatation was observed significantly frequent in patient with PC (n=117; 90.0%) than in those with AIP (n=27; 14.4%, P<0.001). Among the 27 patients with AIP with MPD dilatation, narrowing of the downstream MPD was observed in 3 patients and the others with normal downstream appearance.

Serology

Forty seven (36.7%) of 188 patients with AIP and 4 (4.8%) of 84 patients with PC were categorized as level 1 respectively (Table 1). The mean serum IgG4 level was 346.6±56.2 mg/dL, statistically significantly higher than those in patients with pancreatic cancer, 119.2±23.9 mg/dL. The frequencies of serum level above 280 mg/dl (level 1) and 140 mg/dl (level 2) were significantly higher in AIP patients (P<0.001.)
Table 1. Frequencies of level 1 and 2 findings in international consensus diagnostic criteria (ICDC) for autoimmune pancreatitis (AIP) and pancreatic cancer (PC)

<table>
<thead>
<tr>
<th>Features</th>
<th>AIP (n=188)</th>
<th>PC (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenchymal imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>95 (50.5%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>93 (49.5%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>188 (100.0%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>0 (0.0%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td><strong>Ductal imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>93 (49.5%)</td>
<td>0.0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>68 (36.2%)</td>
<td>13 (10.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>161 (85.6%)</td>
<td>13 (10.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>27 (14.4%)</td>
<td>117 (90.0%)</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>47/128 (36.7%)</td>
<td>4/84 (4.8%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>55/128 (42.9%)</td>
<td>3/84 (3.6%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>102/128 (79.7%)</td>
<td>7/84 (8.3%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>26/128 (20.3%)</td>
<td>77/84 (91.7%)</td>
</tr>
<tr>
<td><strong>OOI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>63 (33.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>64 (34.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>127 (92.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>61 (32.4%)</td>
<td>130 (100.0%)</td>
</tr>
<tr>
<td><strong>Histology of pancreas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>28 (14.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>3 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>31 (16.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>157 (83.5%)</td>
<td>130 (100.0%)</td>
</tr>
</tbody>
</table>

AIP: autoimmune pancreatitis; PC: pancreatic cancer; OI: other organ involvement

Other organ involvement (OOI)

Sixty-three (33.5%) of 188 patients with AIP was categorized as level 1 and no any one of 130 patients with PC were categorized as level 1 or 2 (Table 1). Proximal bile duct stricture was observed in 53 patients (28.2%) with AIP, and retroperitoneal
fibrosis was observed in 5 patients (2.7%) with AIP both level 1 findings. Enlarged salivary/lacrimal glands were observed in 58 patients (27.6%) with AIP and renal involvement in 9 (4.8%), these met level 2 criteria. Neither enlarged salivary/lacrimal glands nor renal involvement was observed in any patients with PC.

**Histology of pancreas**

There were 31(16.4%) patients with AIP were categorized as level1or level 2 criteria and none of 130 patients with PC were categorized as level1 or level 2 (Table 1). There were 28 patients (14.9%) with level 1 evidence and 3 patients (1.6 %) with level 2 evidence in histologically LPSP. No any patients with PC fulfilled the level 1 or 2 criteria.

**Response to steroid therapy**

Of the 128 patients who received steroid treatment as the initial treatment (induction therapy), 126 patient (98.4 %) showed steroid response with improvement clinically, serologically and morphologically. Two of the patients with diffuse pancreatic enlargement and narrowing of MPD received steroid but no morphologically response. Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) were performed and no malignancy was detected. These two patients discontinued steroid after 3 months of steroid and was follow up regularly. These two patients were followed up for 18 months and 20 months and no any malignancy were documented although the
pancreatic enlargement did not subside.

**Diagnosis on the basis of ICDC, revised HISORt and Asian criteria**

Of the 188 patients with AIP, 116 patients were diagnosed as definite AIP; 35 patients were diagnosed as probable AIP and 17 were classified as not otherwise specified (NOS). Among these patients, the primary basis for diagnosis was histology in 31 patients, response to steroid therapy in 126 patients and imaging in 188 patients. There were 20 patients in this study deniable for type 1 AIP. All patients with PC were deniable for type 1 AIP on the basis of ICDC. The sensitivity, specificity and accuracy of the ICDC for type 1 AIP were 89.4%, 100.0% and 93.7% (Table 2).

Using revised HISORt criteria, 158 patients (84.0%) were diagnosed as definitive AIP. Among these 158 patients, the primary basis of diagnosis was diffuse type in 95 patients (60.1%), histology based diagnosis in 31 patients (19.6%). There were 30 patients were deniable for AIP based on revised HISORt criteria in this study. All of the PC patients were deniable for AIP based on the revised HISORt criteria. The sensitivity, specificity and accuracy of the revised HISORt criteria were 84.0%, 100.0% and 90.5% (Table 2). Using Asian criteria, 162 patients (86.2%) were diagnosed as AIP. There were 143 patients (88.3%) were diagnosed based on Imaging plus serology; 143 patients (88.3%) were diagnosed based on Imaging plus serology; 31 patients (19.1%) diagnosed based on histopathology and 126 patients (77.8%)


Table 2. Comparison of diagnostic criteria for autoimmune pancreatitis from pancreatic cancer

<table>
<thead>
<tr>
<th></th>
<th>Case number</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All AIP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit Asian</td>
<td>162</td>
<td>86.2</td>
<td>100.0</td>
<td>91.8</td>
</tr>
<tr>
<td>Fit revised HISORt</td>
<td>158</td>
<td>84.0</td>
<td>100.0</td>
<td>90.5</td>
</tr>
<tr>
<td>Fit ICDC</td>
<td>168</td>
<td>83.4</td>
<td>100.0</td>
<td>96.7</td>
</tr>
<tr>
<td><strong>Focal AIP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit Asian</td>
<td>68</td>
<td>73.1</td>
<td>100.0</td>
<td>99.6</td>
</tr>
<tr>
<td>Fit revised HISORt</td>
<td>73</td>
<td>78.5</td>
<td>100.0</td>
<td>95.6</td>
</tr>
<tr>
<td>Fit ICDC</td>
<td>79</td>
<td>84.9</td>
<td>100.0</td>
<td>97.3</td>
</tr>
</tbody>
</table>

ICDC: international consensus diagnostic criteria

diagnosed based on steroid treatment response. Here were 26 patients were deniable for AIP based on Asian criteria in this study. All of the PC patients were deniable for AIP based on the Asian criteria. The sensitivity, specificity and accuracy of the revised HISORt criteria were 86.2%, 100.0% and 91.8% (Table 2).

**Deniable cases on the basis of ICDC**

There were 20 patients who were deniable for ICDC in this study. All these 20 patients could be diagnosed by Asian criteria. Among them, there were 2 patients could be diagnosed both by HISORt criteria and Asian criteria. They included 6 cases and 14 cases with level 1 or 2 parenchymal imaging; 6 cases and 12 cases with level 1 or 2 ductal imaging; 9 cases with level 2 serology; 11 patients with level 1 OOI. There was 1 patient with steroid treatment response. The most common factor which
lead to deniable of ICDC or revised HISORt criteria was the serology criterion. There were 18 out of 20 patients had antoantibodies which could be one of the item in Asian serology criterion. The ICDC and HISORt only adapted IgG4 level alone as the serology criterion.

**ICDC criteria in Focal type AIP and diffuse type AIP**

The comparisons of frequencies of level1 and 2 finings in ICDC in focal type and diffuse AIP were shown in Table 3. The frequencies of level1 or level2 features in ductal imaging were significantly lower in focal type AIP (73.1% vs. 97.9%, p<0.001, Table 3). The frequencies of level 1 or 2 features in serology was also lower in focal type (55.4% vs.69.3%, p=0.075). The frequencies of any level of OOI in focal type AIP was higher than diffuse type (81.7% vs. 53.7%, p<0.0001). The frequencies of any histological evidence of LPSP in our focal type AIP was higher than diffuse type (23.7% vs. 9.5%, p=0.01) in our study (Table 3).

**Sensitivity, Specificity and Accuracy of ICDC, revised HISORt criteria and Asian criteria**

The sensitivity, specificity and accuracy of the ICDC were 84.9%, 100.0% and 93.8% (Table 2). The sensitivity, specificity and accuracy of the revised HISORt criteria were 78.5%, 100.0% and 91.0% (Table 2). The sensitivity, specificity and accuracy of the Asian criteria were 73.1%, 100.0% and 88.8% (Table 2).
Table 3 Frequencies of level 1 and 2 findings in international consensus diagnostic criteria (ICDC) for focal and diffuse type autoimmune pancreatitis (AIP)

<table>
<thead>
<tr>
<th>Features</th>
<th>Focal AIP (n=93)</th>
<th>Diffuse AIP (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>0(0%)</td>
<td>93(97.9%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>68(73.1%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>68(73.1%)</td>
<td>93(97.9%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>25(26.9%)</td>
<td>2(2.1%)</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>16/74(21.6%)</td>
<td>31/88(35.2%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>25/74(33.8%)</td>
<td>30/88(34.1%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>41/74(55.4%)</td>
<td>61/88(69.3%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>33/74(44.6%)</td>
<td>27/88(30.7%)</td>
</tr>
<tr>
<td>OOI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>31(33.3%)</td>
<td>32(33.7)</td>
</tr>
<tr>
<td>Level 2</td>
<td>45(48.4%)</td>
<td>19(20.0%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>76(81.7%)</td>
<td>51(53.7%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>17(11.3%)</td>
<td>44(46.3%)</td>
</tr>
<tr>
<td>Histology of pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>20(21.5%)</td>
<td>8(8.4%)</td>
</tr>
<tr>
<td>Level 2</td>
<td>2(2.2%)</td>
<td>1(1.1%)</td>
</tr>
<tr>
<td>Level 1+2</td>
<td>22(23.7%)</td>
<td>9(9.5%)</td>
</tr>
<tr>
<td>Nonlevel 1,2</td>
<td>71(76.3%)</td>
<td>86(90.5%)</td>
</tr>
</tbody>
</table>

AIP: autoimmune pancreatitis; OI: other organ involvement

The ROC was calculated in AIP (Fig 1) and focal type AIP (Fig 2). The area under the curve was 0.95 (95% CI: 0.92-0.97) of ICDC (Fig 1a), 0.91(95% CI: 0.92-0.97) of revised HISORt criteria (Fig 1b), and 0.93(95% CI: 0.92-0.97) of Asian criteria (Fig 1c). For focal type AIP, the area under the curve was 0.93(95% CI: 0.88-0.97) of ICDC (Fig 2a), 0.89(95% CI: 0.84-0.94) of revised HISORt criteria (Fig. 2b), and 0.87(95% CI: 0.81-0.92) of Asian criteria( Fig 2c).
Discussion

The sensitivity, specificity and accuracy of ICDC for all AIP were 89.4% 100.0% and 93.7%. The sensitivity, specificity and accuracy of ICDC for focal AIP were 84.9% 100.0% and 93.8%. Among the three criteria, the sensitivity and accuracy of ICDC were the best one compared to revised HISORt criteria and Asian criteria with the same specificity (Table 2). There were 12 patients with deniable revised HISORt criteria were diagnosed as AIP in ICDC (10 definite, 1 probable and 1 NOS of ICDC). There were 26 patients with deniable Asian criteria were diagnosed as AIP in ICDC (11 definite, 14 probable and 1 NOS in ICDC). The ICDC showed higher sensitivity the revised HISORt and Asian criteria. The reason why patients deniable for revised HISORt or Asian criteria but fit ICDC diagnosis was partially caused by the different definition of parenchymal imaging between these criteria. ICDC includes atypical imaging and classifies atypical imaging as S2 level in parenchymal imaging criterion. That's one reason why ICDC had higher sensitivities in diagnosis of AIP in general. The wider range of imaging criteria improved the diagnostic sensitivity but did not decreased neither the specificity nor the accuracy of ICDC. All the three criteria showed high specificity (Table 2). The ICDC showed higher accuracy than Asian criteria and revised HISORt criteria in our population. Recently, studies from Japanese population also demonstrated better accuracy of ICDC compared to other criteria, including the Japanese pancreatic society criteria[15-18]. Though ICDC is
considered to be superior to other various criteria, ICDC seems to be too complicated to handle for clinician. Japanese has proposed revised diagnostic criteria by Japanese pancreatic society very recently[19]. It would be interest to whether the performance could even be better or easlily to use in clinical practice compared to ICDC criteria.

Type 1 AIP composed of a heterogenous population, at this time moment, we did not have suitable simple amendment for ICDC for clinical use in our country. With the advance of better understanding the pathogenesis of the disease, to simplify the diagnostic criteria might be feasible and needed for clinician.

In ductal imaging criterion, 161 (92.5%) of 188 patients with AIP and 13 (1.0%) of 130 patients with PC were categorized as level 1 or 2, respectively. The specificity of ductal imaging is high. One of the reasons for this high specificity is that patients with marked upstream MPD dilatation (>5 mm) were excluded from level 1 or 2. In the present study, 28 of 31 patients with PC who showed focal MPD stricture were excluded from level 2 because of marked upstream MPD dilatation. On the other hand, 27 (14.4%) of 188 patients with AIP showed marked upstream MPD dilatation. The frequency of any level1 or 2 evidence in ductal imaging is close to the recently reported on (7/62, 11.3%) by Nishino et al.[20]. Naitoh et al also reported that a maximal diameter of the upstream MPD less than 5 mm was an appropriate cutoff point to differentiate mass-forming AIP from PC[21]. In our study, we also use the
5mm as a cutoff point to differentiating focal type AIP and PC. Therefore, we consider that a 5-mm diameter of the upstream MPD is appropriate to discriminate AIP from PC. In the present study, 4 patients with PC fulfilled the level 1 serological criterion. Marked upstream MPD dilatation (5 mm) was observed in these patients. If this exclusion criterion (marked upstream MPD) did not exist, this patient would have fulfilled level 2 criteria for ductal imaging, and we would have misdiagnosed these 4 patients with PC as definitive type 1 AIP under the ICDC. Therefore, we consider that this exclusion criterion of ductal imaging is useful for excluding out PC.

The value of serum IgG4 as a serological marker of AIP was first established in 2001[22] [23]. Hamano et al. reported that sensitivity and specificity for differentiating AIP from PC were 90.2% and 97.5%[23]. In the present study, those sensitivity and specificity of serum IgG4 (>140 mg/dL) were 79.6% and 92.6%, respectively. The cause of the wide range of sensitivity in the reported series might be caused by the combined analysis of types 1 and 2 in these studies. The distribution between types 1 and 2 AIP might affect the value of IgG4. Ghazale et al [4] reported that the sensitivity of elevated serum IgG4 (>140 mg/dL) for PC was 10%, and that of 2-fold elevation (level 1 ICDC serology criteria) was 1%. Our present study showed that the sensitivity and specificity of 2-fold elevation of serum IgG4 were 36.7% and 95.2% in out type 1 AIP. Serum IgG4 is the only used serology marker in ICDC.
Asian criteria, they adapted IgG, IgG4 and presence of antoantibody as the serological criteria. In our patients with type 1 AIP, if we add the presence of autoantibody as also a surrogate marker in serology, thus all of the patients deniable for ICDC could be diagnosed by this modification.

IgG4-related disease (IgG4-RD) is a new l disease entity characterized by elevated serum IgG4 concentration and/or tissue infiltration by IgG4-positive cells[24]. Type 1 AIP is regarded as a part (pancreatic manifestation) of IgG4-RDs. In the present study, level 1 or 2 OOI was observed in 127 (67.6%) of the patients with AIP and in none of those with PC. Therefore, this OOI criterion has high specificity for type 1 AIP.

In the present study, all resection specimens (27 patients) and fulfilled level 1 criteria. One of four biopsied specimens guided by computed tomography fulfilled level 1, with the rest diagnosed as level 2. The present findings suggest obtaining histopathologic evidence of type 1 AIP by biopsied specimen is difficult. Endoscopic ultrasonography-guided FNA was considered useful for the differentiation from PC but might be insufficient for tissue collection to diagnosis as level 1. Kanno et al[25] reported that 14 and 6 of 25 patients were judged to have level 1 and level 2
histological findings by trucut biopsy under endoscopic ultrasound (EUS) guidance respectively. We did not perform EUS-trucut biopsy in this study owing to the needle is not available and the cost is not covered by our health insurance. Further studies for the feasibility and necessarily of EUS-FNA in diagnosing type 1 AIP in ICDC histological need to be studied.

Diffuse and focal enlargement of the pancreas is a characteristic feature of AIP in parenchymal imaging. ICDC included patients with atypical parenchymal imaging as level 2. For diffuse type AIP, the diagnostic accuracy of ICDC, Asian, and HISORt criteria were over 95%, much better than that in focal type AIP. This observation is reasonable for us to understand because of it is very rare to have pancreatic cancer involving whole pancreas in clinical practice. The diagnosis sensitivity in diffuse type AIP were also higher than those in focal type in these three diagnostic criteria (Table 2). In diffuse type AIP, Asian criteria was most sensitive with sensitivity 98.9%, followed by ICDC (93.7%) and the HISORt criteria (89.5%). There were 4 patients with diffuse AIP who did not have elevated was the least sensitive criteria in the diagnosis of diffuse type with sensitivity only 89.5%. The were 4 diffuse type AIP deniable for HISORt but fit ICDC NOS owing to these 4 patients did not have any collateral evidence. These 4 patients could be diagnosed by Asian criteria as they have
presence of autoantibodies which made they fit the serology criteria in Asian
diagnosis setting but not fit the serology criteria in ICDC and HISORt criteria. These
4 patients had received steroid response as the initial treatment and they all had
disease relapse in their follow up. The increase of sensitivity in Asian criteria in
diagnosing diffuse type AIP is relevant to the wide range of definition in serology
criterion (IgG, IgG4 or/and antoantibodies), compared to use IgG4 alone as serology
criterion in HISORt and ICDC.

It is a greater challenge to differentiate focal type AIP with pancreatic cancer,
compare to differentiate diffuse type AIP from PC. In this study, we have 93 patients
with focal AIP. The ductal imaging, serology and OOI were different from diffuse
type. Focal type AIP had less frequency of level 1 or 2 presentations of ductal
imaging and serology. In contrast, focal type AIP had higher frequencies of level 1 or
2 presentations of OOI. These clinical observations remind us that the collateral
evidence of AIP in focal type AIP is mostly in OOI, but not serology. Detailed
physical examination and history taking and imaging interpretation imaging other
than pancreas could give some hint to increase the sensitivity of diagnosis of focal
AIP.

In focal type of AIP, the diagnostic sensitivity of ICDC (84.9%) was higher than
revised HISORt criteria (78.5%) and Asian criteria (73.1%). There were 14 (15.1%) focal type AIP patients deniable for ICDC criteria. All these 14 patients could be diagnosed by Asian criteria. There were 12 patients with presence of autoantibodies and 9 patients with serum IgG4 level above 140 mg/dl. Among them, they were 12 patients with level 2 and 2 patients without any level 1 or 2 criteria in ductal imaging. In OOI, there were 9 patients with level 2 criteria and 5 patients without any level 1 or 2 criteria. All the focal type AIP patients deniable Asian criteria could be diagnosed by ICDC criteria.

In conclusion, the ICDC shows high sensitivity, specificity and accuracy in the diagnosis of type 1 AIP. In focal type AIP, ICDC is still the best one in sensitivity, specificity and accuracy. The diagnostic sensitivity in focal type AIP not as good as diffuse type AIP in all the three adapted criteria (ICDC, Asian and revised HISORt criteria). How to improve the sensitivity of diagnosis of focal AIP is the issue need to be resolved in the future.
AUTOHOR CONTRIBUTION

Ming-Chu Chang and Yu-Ting Chang have full access to the data take responsibility for the integrity of the data, and the accuracy of the data analysis.

Conception and design, or analysis and interpretation of data: Ming-Chu Chang, Po-Chin Liang, I-Shiow Jan, Ching-Yao Yang, Yu-Wen Tien, Shu-Chen Wei, Jau-Min Wong, Yu-Ting Chang

Drafting the article or revising it critically for important intellectual content: Ming-Chu Chang, Yu-Ting Chang

Final approval of the version to be published: Ming-Chu Chang, Yu-Ting Chang

Obtained funding: Ming-Chu Chang and Yu-Ting Chang, Jau-Min Wong

Administrative, technical, or material support: Ming-Chu Chang and Yu-Ting Chang, Jau-Min Wong

Study supervision: Yu-Ting Chang

Yu-Ting Chang had the final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST DISCLOSURE

The authors report no conflict of interest.

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The funding source had no role in study design, data collection, analysis, or interpretation, report writing or the decision to submit this paper for publication.

PATIENT CONSENT

Signed informed consent was obtained from each study subject prior to participation in the study.

ETHICS APPROVAL

The study protocol was approved by the institutional review board of National Taiwan University Hospital.

DATA SHARING STATEMENT

No additional data are available.
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Figure Legend

Figure 1. Receiver-operator characteristics curves of International Consensus Diagnostic Criteria (ICDC), revised HISORT and Asian criteria in diagnosis of 188 patients with autoimmune pancreatitis (AIP) from 130 patients

1a. ICDC diagnostic criteria

1b. revised HISORT criteria

1c. Asian criteria
Figure 2. Receiver-operator characteristics curves of International Consensus Diagnostic Criteria (ICDC), revised HISORT and Asian criteria in diagnosis of 93 patients with focal autoimmune pancreatitis (AIP) from 130 patients with pancreatic cancer.

2a. ICDC diagnostic criteria

2b. revised HISORT criteria

2c. Asian criteria
Figure 1. Receiver-operator characteristics curves of International Consensus Diagnostic Criteria (ICDC), revised HISORT and Asian criteria in diagnosis of 188 autoimmune pancreatitis (AIP) from 130 pancreatic cancer.

1a. ICDC diagnostic criteria

Area under ROC curve = 0.95 (0.92-0.97)

173×200mm (300 x 300 DPI)
1b. revised HISORT criteria

173x182mm (300 x 300 DPI)
Fig 1c. Asian criteria

173x186mm (300 x 300 DPI)
Figure 2. Receiver-operator characteristics curves of International Consensus Diagnostic Criteria (ICDC), revised HISORT and Asian criteria in diagnosis of 93 focal autoimmune pancreatitis (AIP) from 130 pancreatic cancer.

2a. ICDC diagnostic criteria

Area under ROC curve = 0.93 (0.88-0.97)
2b. revised HISORT criteria

Area under ROC curve = 0.87 (0.81-0.92)
2c. Asian criteria

Area under ROC curve = 0.87 (0.81 - 0.92)

173x189mm (300 x 300 DPI)
# Validation of International Consensus Diagnostic Criteria For Diagnosis of Autoimmune pancreatitis From Pancreatic Cancer in a Taiwanese Cohort

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Comparison and validation of International Consensus Diagnostic Criteria for diagnosis of autoimmune pancreatitis from pancreatic cancer in a Taiwanese cohort

Ming-Chu Chang, Po-Chin Liang, I-Shiow Jan, Ching-Yao Yang, Yu-Wen Tien, Shu-Chen Wei, Jau-Min Wong and Yu-Ting Chang

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