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Original Article

Serum carcinoembryonic antigen improves accuracy in differentiating autoimmune pancreatitis from early-stage pancreatic cancer

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Abstract: Background and aims: Autoimmune pancreatitis (AIP) is an IgG4-related disease that is prone to be misdiagnosed as pancreatic cancer (PC) because of similar clinical symptoms and imaging appearance. Serum IgG4 has helped much in the differentiation of the two diseases, but its diagnostic sensitivity and specificity are still not very satisfactory. Methods: In this work, 82 AIP and 160 stage IA and IB PC patients with complete clinical and laboratory data were enrolled and analyzed retrospectively. Serum IgG4, CA19-9, CEA and total bilirubin levels were measured. Mann-Whitney U and Chi-square test were used for statistical analyses, and receiver operating characteristic curve analysis was performed to determine optimal cut-off values and the area under the curve. Results: IgG4 was the best single serum marker, while either serum CA19-9 or CEA alone also help to differentiate AIP and early-stage PC patients. Combination of CA19-9 improved the overall diagnostic efficiency of IgG4 but sacrificed the sensitivity a little. Further incorporation of serum CEA into the combination of IgG4 and CA19-9 in a special pattern, however, produced the best diagnostic performance with intriguing parameters: sensitivity, 86.59%; specificity, 95.63%; positive predictive value, 91.03%; negative predictive value, 93.29%: accuracy, 91.03%; and AUC, 0.911. Conclusions: This article, for the first time, revealed that CEA, in combination with serum CA19-9 and IgG4 in a special pattern, would overwhelmingly enhance the diagnostic performance of serum IgG4 alone or the combination of IgG4 and CA19-9 in differentiating AIP from early-stage PC patients. The new utility of CEA is worthy of further clinical investigation.

Keywords: Autoimmune pancreatitis, CEA, IgG4, CA19-9, pancreatic cancer

Introduction

Sarles and his colleagues first reported a special type of pancreatitis with hypergammaglobulinemia and named it primary inflammatory sclerosis [1]. And the concept of autoimmune pancreatitis (AIP) characterized by elevated IgG4 was established until 1995 [2]. Nearly 20 years after, AIP has now been known well by clinicians. Diffuse enlargement of the pancreas or the presence of a pancreatic head mass and irregular stenosis of the pancreatic duct in imaging examinations are the major clinical manifestations of AIP which make it easy to be misdiagnosed as pancreatic cancer (PC) [3]. In fact, a number of AIP patients have been suffering unnecessary exploratory laparotomy or surgical resection since glucocorticoid therapy could always achieve a satisfactory therapeutic effect for AIP [4]. When undertaking pancreatoduodenectomy for a suspicious lesion in the pancreatic head, there might be at least a 5% chance of resecting a benign, inflammatory lesion masquerading as cancer [5]. AIP is the most common benign lesion which would be suspected of PC and be surgically excised [6]. The proportion of AIP cases in patients who underwent pancreatic resection is 2.2-2.4%, and the proportion dramatically rises to 19.5-28% in patients with benign pancreatic disease who underwent pancreatic resection [7]. Therefore, powerful markers for the differentiation of AIP from early-stage PC patients are urgently needed.

As an important cornerstone of diagnosis of AIP, elevated serum IgG4 is currently included in the International Consensus Diagnostic

Criteria (ICDC) for AIP [8]. However, as a subset of AIP patients have normal IgG4 levels, and IgG4 levels could be elevated non-specifically in some other diseases [9], the diagnostic sensitivity and specificity of serum IgG4 alone for AIP are not very satisfactory [10]. Abnormally high level of carbohydrate antigen 19-9 (CA19-9) has been found in many types of malignant tumors, including PC. Previous studies have assessed the diagnostic performance of IgG4 combined with CA19-9 in differentiating AIP and PC [11, 12], but the diagnostic efficiency was only moderately improved. Other markers that can further improve the differentiation of AIP from PC are still needed.

Carcinoembryonic antigen (CEA) is a traditional gastrointestinal tumor maker. Although the sensitivity and specificity of CEA alone in the diagnosis of PC are low, its addition to the combination of serum IgG4 and CA19-9 might further improve the accuracy of differentiation of AIP from early-stage PC. To test this hypothesis, the present study, with the largest number of patients with confirmed AIP ever reported in Mainland China, investigated the performance of serum CEA, combined with serum IgG4 and CA19-9, in differentiating AIP from early-stage PC.

Materials and methods

Patients

During 2011-2013, a total of 102 patients had a confirmed diagnosis of AIP at our hospital, of whom 82 had complete clinical, imaging and laboratory data non-smokers were enrolled and analyzed retrospectively. Non-smokers in this study were defined as never-smokers and ex-smokers who had stopped smoking more than 6 months prior and had never exceeded 5 pack-years at any time. We compared them with a control group involving 160 non-smokers who were diagnosed with stage IA and IB PC at our hospital. The Asian criteria [13], HISORt criteria [14] and International Consensus Diagnostic Criteria [8] were adopted, and all AIP patients included in this study met at least one of these diagnostic criteria. All AIP patients were treated with oral prednisolone which started at 0.6 mg/kg/day, the dosage of the steroids was gradually tapered over 4-6 weeks. These AIP patients were periodically monitored by serological and imaging tests from the start of therapy. PC diagnosis was confirmed histopathologically or cytologically by two seasoned pathologists. Informed consent was obtained from all the patients. The study was approved by the ethics committee of Changhai Hospital.

Sample collection and measurements

Blood samples were collected from untreated subjects included in our study to measure serum levels of IgG4, CA19-9, CEA and total bilirubin. Serum IgG4 levels were measured by immunological scatting turbidity method on a BNII automatic protein analyzer (SIEMENS, Germany); SIEMENS original reagents were applied in analysis, and N/T Protein Control SL/M and N/T Protein Control SL/H (SIEMENS, Germany) were used as internal quality controls. Serum CA19-9 and CEA levels were measured by immunochemiluminometric assays on an ARCHITECT i2000sr automatic chemiluminescence immunoassay analyzer (Abbott, USA), with Immunoassay Control Level 1 and Level 3 (Randox, UK) as internal quality controls. Serum total bilirubin was measured by vanadate oxidation method (Wako, Japan) on a 7600 automatic biochemical analyzer (HITACHI, Japan), with Synchron@ Control (Beckman Coulter, USA) as an internal quality control.

Statistical analysis

Serum IgG4, CA19-9, CEA and total bilirubin levels are presented as medians with quartiles, and Mann-Whitney U test was used to reveal differences between groups, with P-values < 0.05 considered statistically significant. Two independent sample t-tests were used to detect age differences between groups. Sex and clinical manifestations were analyzed by Chi-square test. Binary logistic regression analyses were performed to disclose the predictive performance of serum IgG4, CA19-9 and CEA levels in the differential diagnosis of AIP and early-stage PC. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-off values and the area under the curve (AUC) of diagnostic tests.

Results

Clinical characteristics of AIP and PC patients

A total of 82 AIP and 160 stage IA and IB PC patients were enrolled in this study, and the

Table 1. Clinical data for AIP and pancreatic cancer patients

	AIP patients (*n* = 82)	PC patients (*n* = 160)	*P*
Age (mean ± SD, years)	57.5 ± 11.1	64.4 ± 11.8	< 0.001
Male-to-female ratio	73:9	92:68	< 0.001
Abdominal pain	37 (45%)	88 (55%)	0.146
Weight loss	9 (11%)	42 (26%)	0.006
Diabetes mellitus	12 (23%)	52 (33%)	0.003
Steatorrhea	2 (3%)	8 (5%)	0.343
IgG4 median (interquatile range, g/L)	8.2 (4.4-14.9)	0.7 (0.3-1.4)	< 0.001
CA19-9 median (interquatile range, U/mL)	14.3 (7.7-33.7)	484.7 (68.2-1200)	< 0.001
CEA median (interquatile range, ng/mL)	2.3 (1.7-3.4)	5.73 (3.4-10.4)	< 0.001
Bilirubin median (interquatile range, μmol/L)	17.5 (11.1-45.1)	25.4 (10.4-109.4)	< 0.001

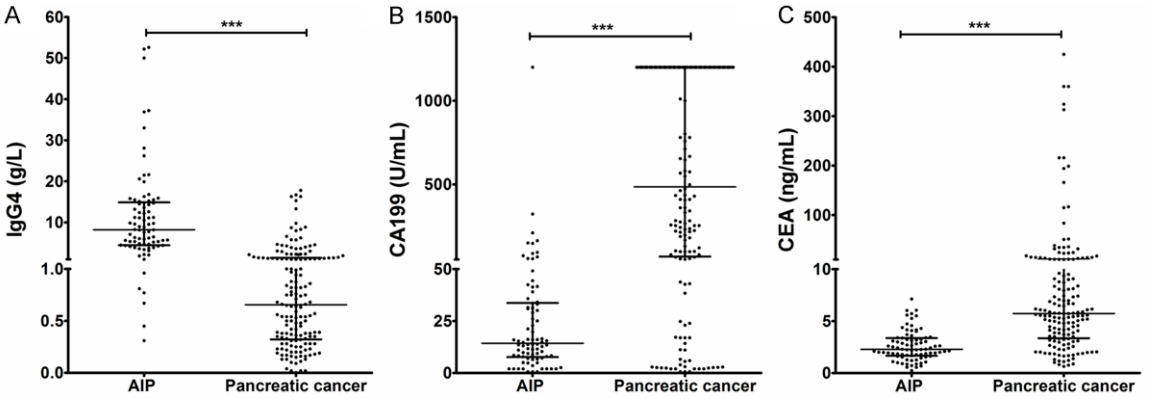

Figure 1. Scatter plots of serum IgG4, CA19-9 and CEA levels in AIP and PC patients. Serum IgG4 (A), CA19-9 (B) and CEA (C) were quantified and analyzed by the Mann-Whitney U test. The horizontal bar denotes the median with interquartile range. Note: Data more than 1200 IU/L of CA19-9 levels were set as 1200 IU/L. AIP: autoimmune pancreatitis; ***$P < 0.0001$.

clinical features and laboratory data were significantly different between the two groups (**Table 1**). A relatively higher ratio of younger male patients was confirmed in AIP compared to PC patients. Abdominal pain was quite common and steatorrhea was rare in both AIP and PC patients. Weight loss and diabetes mellitus seemed more likely to occur in PC patients. As could be expected, serum IgG4 levels were significantly higher and CA19-9 levels were significantly lower in AIP patients than in PC patients (**Table 1**). Further analysis of the data demonstrated that serum IgG4 levels in 57 out of 82 (70%) AIP patients were higher above 1.4 g/L (the cut-off value suggested by multiple previous studies) [10-12], while serum CA19-9 levels in 65 out of 160 (41%) PC patients were above 1200 IU/L (the upper limit of CA19-9 in our laboratory). Although lower serum total bilirubin levels were confirmed in AIP patients, jaundice was also a common clinical symptom in AIP patients compared to PC patients (50% vs. 61%, **Table 1** and **Figure 1**). Serum CEA had a lower positive rate than CA19-9 in PC patients (8.5% vs. 61.3%, cut-off value: < 5 IU/L), but serum CEA levels were statistically higher in PC patients than in AIP patients. The surprisingly different distribution of serum CEA levels in AIP and PC patients suggested that CEA might be a useful marker for helping differentiate AIP from PC patients and is thus worthy of further investigation.

Predictive potential of serum IgG4, CA19-9, CEA and total bilirubin levels for AIP

Binary logistic regression analyses were performed to analyze the predictive potential of serum IgG4, CA19-9, CEA and total bilirubin levels for AIP (**Table 2**). Univariate analysis showed that serum IgG4 was positively while CA19-9 and CEA levels alone were negatively correlat-

Table 2. Logistic regression analyses to evaluate the predictive potential of serum IgG4, CA19-9 and CEA

	Univariate Analysis				Multivariate Analysis			
	B	Wals	OR (95% CI)	*P*	B	Wals	OR (95% CI)	*P*
IgG4	-0.312	49.663	0.732 (0.671-0.798)	< 0.001	-0.388	25.893	0.679 (0.585-0.788)	< 0.001
CA19-9	0.007	20.472	1.007 (1.004-1.01)	< 0.001	0.006	11.445	1.006 (1.002-1.009)	< 0.001
CEA	0.541	35.828	1.718 (1.439-2.05)	< 0.001	0.599	16.657	1.82 (1.365-2.426)	< 0.001

Table 3. Diagnostic performance of IgG4, CA19-9 and CEA with different cut-offs and/or different panels in differentiating AIP from pancreatic cancer

Cut-offs	SEN	SPE	PPV	NPV	Accuracy	LR+	LR-	AUC
IgG4 > 3.08	87.80%	85%	75%	93.15%	85.95%	5.85	0.14	0.9
IgG4 > 1.4	91.46%	76.88%	67%	94.62%	81.82%	3.955	0.111	0.842
CA19-9 < 94.5	92.68%	73.75%	64.41%	95.16%	80.17%	3.53	0.1	0.836
CA19-9 < 43	82.93%	79.38%	67.33%	90.07%	80.58%	4.02	0.22	0.812
CA19-9 < 37	78.05%	80.63%	67.37%	87.76%	79.75%	4.03	0.27	0.793
CEA < 4.02	86.59%	68.75%	58.68%	90.91%	74.79%	2.77	0.2	0.819
IgG4 > 3.08 and CA19-9 < 94.5	80.49%	95.63%	90.41%	90.53%	90.50%	18.4	0.2	0.881
IgG4 > 3.08 and CA19-9 < 43	71.95%	97.50%	93.65%	87.15%	88.84%	28.78	0.29	0.847
IgG4 > 3.08 and CA19-9 < 37	67.07%	97.50%	93.22%	85.25%	87.19%	26.83	0.34	0.823
IgG4 > 3.08 and CEA < 4.02	75.61%	98.13%	95.38%	88.70%	90.50%	40.33	0.25	0.869
IgG4 > 3.08 and CA19-9 < 94.5 and CEA < 4.02	69.51%	100%	100.00%	86.49%	89.67%	∞	0.3	0.848
IgG4 > 3.08 and CA19-9 < 43 and CEA < 4.02	60.98%	100%	100%	83.33%	86.78%	∞	0.39	0.805
IgG4 > 3.08 and CA19-9 < 37 and CEA < 4.02	57.32%	100%	100.00%	82.05%	85.54%	∞	0.43	0.787
IgG4 > 3.08 and (CA19-9 < 94.5 or CEA < 4.02)	86.59%	93.75%	87.65%	93.17%	91.32%	13.85	0.14	0.902
IgG4 > 3.08 and (CA19-9 < 43 or CEA < 4.02)	86.59%	95.63%	91.03%	93.29%	92.56%	19.79	0.14	0.911
IgG4 > 3.08 and (CA19-9 < 37 or CEA < 4.02)	87.80%	85%	75%	93.15%	85.95%	5.85	0.14	0.864
IgG4 > 1.4 and (CA19-9 < 94.5 or CEA < 4.02)	90.24%	90%	82.22%	94.74%	90.08%	9.024	0.1084	0.901
IgG4 > 1.4 and (CA19-9 < 43 or CEA < 4.02)	90.24%	91.88%	85.06%	94.84%	91.32%	11.11	0.1062	0.911
IgG4 > 1.4 and (CA19-9 < 37 or CEA < 4.02)	90.24%	84.38%	74.75%	94.41%	86.36%	5.776	0.1156	0.873

SEN: sensitivity, SPE: specificity, PPV: positive predictive value, NPV: negative predictive value, LR+: likelihood ratio of positive test, LR-: likelihood ratio of negative test, AUC: area under the curve.

ed with AIP ($P < 0.001$), suggesting that these three markers might have predictive power for the diagnosis of AIP when used for the discrimination of AIP and early-stage PC. Multivariate analysis further revealed that all the three serum markers had predictive potential for the diagnosis of AIP. In contrast, serum total bilirubin was not significantly related with AIP ($P = 0.635$).

Performance of serum IgG4, CA19-9 and CEA alone in the differential diagnosis of AIP from early-stage PC

Based on our enrolled AIP and PC patients, we first evaluated the diagnostic sensitivity, specificity and accuracy of serum IgG4, CA19-9 and CEA alone. The diagnostic efficiency of these indexes is shown in **Table 3**; **Figures 1** and **2**. Using an optimal cut-off value of 3.08 g/L for IgG4 derived from ROC analysis, the diagnostic sensitivity, specificity, accuracy and AUC for AIP were 87.8%, 85%, 85.95% and 0.90, respectively. Although this cut-off value seemed better than the cutoff value (1.4 g/L) suggested by most of other studies, there were still 10 (12%) AIP patients who demonstrated "normal" serum IgG4 levels and 24 PC (15%) patients who exhibited "increased" serum IgG4 levels. The diagnostic sensitivity, specificity, accuracy and AUC of CA19-9 were 92.68%, 73.75%, 80.17% and 0.84, respectively, when 94.85 KU/L was chosen as the optimal cut-off value. Remarkably, 6 AIP cases and 42 PC patients were missed because their serum CA19-9 levels were above or under the cut-off value,

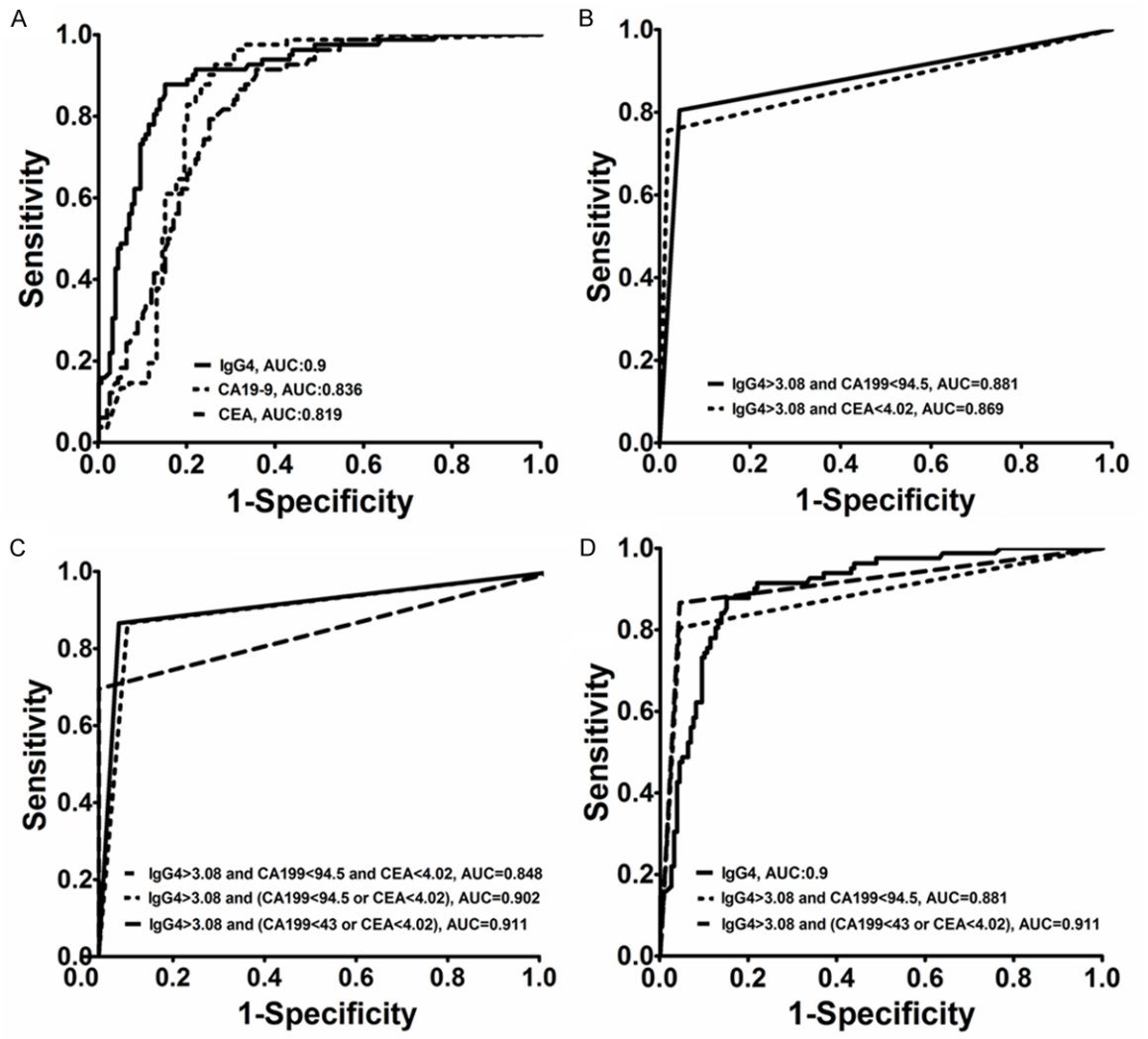

Figure 2. Receiver operating characteristic (ROC) curves for single markers or combined panels in differentiating AIP and PC patients. A. Comparison among three single serum markers; B. Comparison between the combination of IgG4 with CA19-9 or CEA; C. Comparison among different panels composed of IgG4, CA19-9 and CEA simultaneously. D. Comparison among single IgG4, IgG4 combined with CEA, and the best triple combination. CEA efficiently enhances the diagnostic performance of IgG4 with or without CA19-9.

respectively. When CEA was evaluated at 4.02 g/L, the diagnostic sensitivity, specificity, accuracy and AUC were 86.59%, 68.75%, 74.79% and 0.82, respectively. This time we found 11 (13%) AIP patients with serum CEA higher and even more PC (50, 31%) patients with serum CEA lower than the cut-off value. Collectively, IgG4 is the best single serum marker, although CA19-9 and CEA might be able to help differentiate AIP and early-stage PC patients.

Combination with CA19-9 or CEA improves the differential diagnostic performance of IgG4

Since the three markers alone had unsatisfactory performance in the differential diagnosis, we attempted to combine IgG4 with CA19-9 or CEA to improve the diagnostic efficiency of IgG4. As shown in **Table 3** and **Figure 2**, when IgG4 > 3.08 g/L and CA19-9 < 94.85 IU/L were selected as the cut-off values and were combined for the diagnosis of AIP, the diagnostic specificity and accuracy were significantly increased (95.63% and 90.50%, respectively) accompanied by a slight reduction of sensitivity and AUC (80.49% and 0.88%, respectively) compared with serum IgG4 alone (**Table 3**). Combination of IgG4 with other cut-off values of CA19-9 performed even less well (**Table 3**). The combination of serum IgG4 and CEA did not provide more surprising diagnostic perfor-

mance for AIP, either. Therefore, combination with CA19-9 improves the overall diagnostic efficiency of IgG4 but sacrificed the sensitivity a little, which means more AIP patients would be missed.

Serum CEA significantly enhances the diagnostic performance of the combination of IgG4 and CA19-9 in AIP

In order to further improve the sensitivity of IgG4 and CA19-9 combination in differential diagnosis between AIP and PC while retaining their good specificity and accuracy as far as possible, we then attempted to combine all the three markers with different cut-off values together to screen out more powerful serum laboratory proofs for AIP. As shown in **Table 3** and **Figure 2**, when the suggested optimal cut-off values were selected (IgG4 > 3.08 g/L; CA19-9 < 94.85 IU/L and CEA < 4.02 μg/L, respectively) and combined together directly, satisfactory specificity, PPV, accuracy and AUC (100%, 100%, 89.67% and 0.90, respectively) were obtained except for a more disappointing sensitivity (69.51%). Further screening of different combinations identified that the best panel should include serum CEA and the combination pattern should be "IgG4 > 3.08 g/L and (CA19-9 < 43 IU/L or CEA < 4.02 μg/L)". When this panel was adopted, there were only 8 (10%) AIP patients and 13 (8%) PC patients who were not classified into their corresponding groups. The diagnostic performance parameters of the panel were as follows: sensitivity, 86.59%; specificity, 95.63%; PPV, 91.03%; NPV, 93.29%; LR+: 19.79; LR-: 0.14; accuracy, 91.03%; and AUC, 0.911. Therefore, serum CEA further helps to differentiate AIP from early-stage PC patients.

Discussion

AIP is a special type of chronic pancreatitis with complicated etiopathogenesis as well as unknown pathogenesis. It has been recognized that the abnormality of autoimmune system is vital throughout the genesis and development of AIP [15]. AIP can be divided into two types: 1 and 2. Type 1 AIP often offends elderly men. The primary complaint is painless jaundice, followed by abdominal distension and pain, weight loss and steatorrhea, and part of the patients suffer diabetes or acute pancreatitis too [16]. The most valuable indicators for diagnosing type 1 AIP are elevated serum levels of IgG and IgG4. Type 2 AIP tends to affect young patients, the extrapancreatic organ involvement is extremely rare, serum IgG4 levels are often normal, and it is often complicated with inflammatory bowel disease [17]. An international multicenter survey has reported recently that the proportion of type 2 AIP cases was 3.7% in Asia, 12.9% in Europe and 13.7% in North America [6], which means that using serum IgG4 alone might inevitably miss some AIP patients in clinical work.

Actually, AIP is prone to be misdiagnosed as PC because of their similar clinical symptoms and imaging appearance. Although histopathology is always the golden standard for AIP diagnosis, this disease is often difficult to be diagnosed pathologically due to a combination of several reasons. First, the acceptance rate of pathologic biopsy of the pancreas is rather low. Second, although endoscopic ultrasound (EUS)-guided fine needle aspiration biopsy can help to rule out malignancy, the diagnostic accuracy is often restricted by the limited amount of biopsy specimens [18]. Serological examination has long been commonly performed for the diagnosis and differential diagnosis of AIP and PC. Among many serological exceptions of AIP patients, the elevation of IgG4 is the most common one [2, 8, 11-14]. As the only serological marker that was recommended by the ICDC, IgG4 is very efficient in the differential diagnosis of AIP and PC. AIP is reported to be characterized by elevated serum IgG4 levels [19]. In their article where only 20 AIP patients were enrolled, they demonstrated that IgG4 could help to differentiate AIP from PC patients with a sensitivity of 95% and a specificity of 97%. This study opened a new chapter in serological diagnosis markers for AIP. Nevertheless, subsequent studies in European populations reported considerably low diagnostic efficiency of serum IgG4 for AIP because elevated serum IgG4 was also identified in a number of acute/chronic pancreatitis and PC patients. It was reported that if 1.64 g/L was selected as a cut-off value for serum IgG4, there were only 45% of AIP patients with elevated IgG4 [20]. In another separate study, only 44% AIP patients were found to have elevated IgG4 when 1.40 g/L was set as a cut-off value for serum IgG4 [10]. Although many other studies recommended using 1.40 g/Las the

diagnostic cut-off for IgG4, serum IgG4 levels in AIP patients vary significantly due to differences in geographic location, race, type of AIP, and detection systems. Another important factor that affects the objective evaluation of diagnostic performance of serum IgG4 is the very small number of AIP patients included in most of the recent studies [10, 19, 20].

In our work, 102 AIP patients were enrolled, of whom 82 with complete clinical data were further analyzed with 160 stage IA and IB PC patients. In order to differentiate AIP from early-stage PC, we figured out 3.08 g/L as an optimal cut-off value for serum IgG4 according to the specific ROC curve. The diagnostic performance of using 3.08 g/L as a cut-off value for IgG4 was significantly better than 1.40 g/L, the most commonly used cut-off value for serum IgG4 in the literature. Remarkably, the diagnostic specificity was significantly improved. Even so, there were still 12% (10/82) of AIP patients with normal serum IgG4 levels, and 15% (24/160) of PC patients with elevated serum IgG4 levels in our study. AIP and PC are two essentially different diseases, and the treatment measures are completely distinct from each other. When it comes to the differential diagnosis of AIP and early-stage PC, both diagnostic sensitivity and specificity should be taken into account. A low sensitivity or specificity of a detection method could lead to leak-diagnosis or misdiagnosis and the following mistreatments. Therefore, further improvement of the sensitivity and specificity of serum markers for AIP is urgently needed.

CA19-9 has been found to have a relatively satisfying diagnostic sensitivity in PC. Therefore, the combination of serum IgG4 and CA19-9 might help differentiate AIP and PC patients. However, Lewisa-b-individuals (10-15% of our population) do not express CA19-9 [21]. In some benign pancreatic diseases or hepatobiliary diseases, due to inadequate bile drainage, CA19-9 would increase in various degrees, too. Our study group and other researchers have tried to combine IgG4 and other serum markers to diagnose AIP, and the diagnostic efficiency was improved a little but was still not very satisfactory. When combining CA19-9 $\leq$ 74 and 1.0 < IgG4 $\leq$ 2.6 or IgG4 $\geq$ 2.6, the diagnostic sensitivity, specificity and AUC were 93.5%, 100% and 0.97, respectively. It seemed that this study had achieved a perfectly good diagnostic efficiency, but their results were supposed to be inconclusive due to their small size of enrolled AIP and total samples (33 AIP patients). Moreover, another study with larger samples (188 AIP patients) reported that combined serum IgG4 (> 2.80 g/L) and CA19-9 (< 85 U/L) could not obviously improve the diagnostic efficiency in differentiating AIP from PC [12]. The demonstrated sensitivity was only 68.9%, which meant that there would be 31.1% of AIP patients who were difficult to differentiate from PC patients. When combined IgG4 (> 3.08 g/L) and CA19-9 (< 94.5 IU/L) were used in our study where more AIP and PC patients were included, we got a better but also not satisfying sensitivity (80.49%). Taken together, these results demonstrated that CA19-9 could help IgG4 to differentiate AIP from PC patients, but the sensitivity needs further improvement.

CEA is expressed on embryonic gastrointestinal mucosal epithelial cells and some malignant cells. Increased serum CEA has been found in many patients with gastrointestinal tumors and in part of PC patients. Since it has been proven that smoking could also raise the serum CEA level, only non-smokers were enrolled in this study. However, serum CEA alone is not satisfying in diagnosing PC because of lower sensitivity and specificity. Since significantly lower serum CEA levels were identified in AIP patients than in PC patients in our study (shown in **Table 1**), we then probed into its potential value in helping differentiate these two disease. Although combining IgG4 and CEA directly did not provide more surprisingly clinical value than the combination of serum IgG4 and CA19-9, further addition of CEA to the combination of IgG4 and CA19-9 in a special pattern greatly enhanced the sensitivity for differentiation without reducing their specificity and accuracy, and finally got the highest AUC (0.911) among all the attempted combinations.

In summary, for the first time, our work revealed that serum CEA, a traditional gastrointestinal tumor maker, in combination with serum CA19-9 and IgG4 in a special pattern, would overwhelmingly enhance the diagnostic performance of IgG4 alone or the combination of IgG4 and CA19-9 in differentiating AIP from early-stage PC patients. This work is clinically valuable because of the difficult differentiation

of AIP from early-stage PC, the completely different or even conflict therapeutic regimens and the following totally different prognosis of the two diseases. The new utility of CEA is worthy of further clinical investigation.

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Disclosure of conflict of interest

None.

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