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HEPATOBILIARY-PANCREAS

Native T1 mapping of autoimmune pancreatitis as a quantitative outcome surrogate

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Abstract

Objectives To investigate the ability of T1 mapping to visualize and quantify the short-term and mid-term response of autoimmune pancreatitis (AIP) to corticosteroid treatment (CST) and to correlate T1 relaxation time of the pancreas with clinical status and serum IgG4 level.

Methods The institutional review board approved this prospective study, and all patients provided written informed consent. Pancreatic MRI including native T1 mapping was performed in 39 AIP patients before and during CST, and 40 patients without pancreatic diseases served as control. T1 relaxation time of the pancreatic head, body, and tail was measured in each patient. Clinical symptoms and serum IgG4 level of the patients were recorded.

Results The native T1 relaxation time of AIP was significantly elongated compared to normal pancreatic tissue (1124.5 ms ± 95.7 ms vs 784.3 ms ± 41.8 ms, $p < 0.001$). After short-term CST (4 weeks), T1 relaxation time of AIP already shortened significantly (957.2 ms ± 97.3 ms, $p < 0.001$). After mid-term CST (12 weeks), the T1 relaxation time further shortened towards normalization (844.2 ms ± 71.6 ms, $p < 0.001$). In 33 AIP patients with elevated serum IgG4 at baseline, T1 relaxation time demonstrated a significant positive correlation with serum IgG4 level ($r = 0.329$, $p = 0.011$). In six AIP patients with normal serum IgG4 level at baseline, T1 relaxation time shortening preceded or was in accordance with symptom relief.

Conclusions Native T1 mapping can be used to assess parenchymal inflammation of AIP and to quantify response to treatment. It provides a quantitative outcome surrogate for AIP.

Key Points

- *Parenchymal inflammation in autoimmune pancreatitis results in T1 relaxation time elongation, which shortens after effective treatment.*
- *T1 relaxation time of the pancreas correlates with serum IgG4 level, and in serum IgG4-negative AIP patients, T1 relaxation time shortening predicts clinical improvement.*
- *T1 mapping provides a quantitative outcome surrogate for AIP.*

Keywords Pancreatitis · IgG4 · Inflammation · Treatment · Magnetic resonance imaging

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Abbreviations

ADC	Apparent diffusion coefficient
AIP	Autoimmune pancreatitis
ANOVA	Analysis of variance
CST	Corticosteroid treatment
ICC	Intraclass correlation coefficient
ICDC	International consensus diagnostic criteria
IgG4	Immunoglobulin G4
MRCP	MR cholangiopancreatography
ROC	Receiver operating characteristic
ROI	Region of interest
SI	Signal intensity
T1WI	T1-weighted image

Introduction

Autoimmune pancreatitis (AIP) has been recognized in the past few decades as a type of chronic pancreatitis primarily characterized by an autoimmune inflammatory process [1]. Its incidence has substantially increased in recent years [2, 3]. As a benign disease entity, AIP shares common clinical and imaging features with pancreatic cancer. One of the characterizing features of AIP is that it responds to steroid therapy, and radiological appearance could change dramatically during follow-up. For patients with suspected AIP, a short-term diagnostic steroid trial could provide collateral evidence for the diagnosis [4, 5].

A measurable, objective outcome surrogate for treatment response is crucial for clinical decision making. Currently, the most appropriate treatment regimen for AIP is still under debate. Maintenance steroid treatment has been recommended, especially by the Asian scholars [6, 7]. However, it is not universally accepted, due to the concern of the short-term and long-term complications from steroid exposure [8]. Ancillary immunomodulators or alternative treatment has been suggested in patients with relapsing AIP [9, 10]. Therefore, there is an increasing need to evaluate the effectiveness of those treatment strategies. Immunoglobulin G4 (IgG4) was recently suggested as a serum biomarker for disease activity [11], but for patients with type 2 AIP and a subgroup of patients with type 1 AIP, serum IgG4 can be normal [12]. There is currently no established imaging biomarker for monitoring treatment effects. Although size and signal change of the pancreas has been noted in serial observations of the same individual under therapy [13–15], substantial overlap exists.

To the best of our knowledge, no previous study has evaluated the potential of native T1 mapping as a quantitative imaging biomarker for assessing the inflammation status in AIP patients and quantifying improvement after effective therapy. Therefore, this prospective study was performed to determine whether T1 mapping of the pancreas could reflect the short-term and mid-term treatment effects of AIP under steroid therapy. Pancreas size and apparent diffusion coefficient (ADC) value of the pancreas was also investigated to determine the optimal MR biomarker for treatment outcome in AIP patients.

Materials and methods

Patient collection

This study was approved by the local institutional review board, and all patients gave written informed consent. From August 2016 to April 2018, patients with suspected or diagnosed AIP were prospectively enrolled. Inclusion criteria were the following: (1) diagnosis of AIP based on the international consensus diagnostic criteria (ICDC); (2) patient received a standard pancreatic MRI protocol and native T1 mapping of the pancreas before starting treatment (baseline study); (3) patient received pancreatic MRI with the same imaging protocol during corticosteroid treatment (CST), including short-term follow-up at 4 weeks after initiation of CST and mid-term follow-up at 12 weeks after initiation of CST; and (4) patient had blood test for serum IgG4 level at the same time (± 3 days) of baseline and follow-up MR scans. Clinical symptoms were recorded by an experienced gastroenterologist at baseline, and symptom improvement, persistence, or exacerbation was documented at follow-up.

Patients were excluded from the study if they had a final diagnosis other than AIP, if they were unable to receive an MR scan, or if the baseline/follow-up imaging and clinical data were not available.

A control group was also prospectively enrolled. Those patients received abdominal MRI with indications other than suspected pancreatic diseases (e.g., follow-up of focal liver lesions). With informed consent, patients agreed to receive an additional native T1 mapping of the pancreas and laboratory tests for exocrine and endocrine function of the pancreas. Inclusion criteria were the following: (1) patient had no clinical evidence of pancreatic diseases, (2) laboratory tests showed normal pancreas function, and (3) imaging findings did not reveal any focal pancreatic lesions, pancreatic duct abnormality, or pancreatic parenchyma signal abnormality.

Imaging technique

MRI examination was performed on a 3-T MR imaging system (MAGNETOM Skyra, Siemens Healthcare). An 18-channel phased-array surface coil and part of a 32-channel spine coil were used in combination for signal reception. The sequences and parameters are listed in Table 1. A native T1 mapping sequence was performed in addition to the routine sequences, before an intravenous contrast agent was

Table 1 Sequence parameters of the pancreatic MRI protocol

Sequence	Plane	Acquisition	TR/TE (ms)	FA (°)	Section thickness (mm)	FOV (mm)	Acquisition time (s)
T1W-VIBE-Dixon	Axial	BH	4.11/1.31–2.54	12	3	380 × 380	17
T2W-TSE FS	Axial	NT	2390/81	90	6	400 × 400	300–400
T2W-HASTE	Axial	NT	2000/92	90	4	300 × 300	120–180
T2W-HASTE	Coronal	NT	2000/92	90	4	300 × 300	120–180
ss-EPI-DWI ($b = 0$ and 800 mm^2/s)	Axial	NT	2500/61	–	4	400 × 400	180–240
2D thick-slab MRCP	Para-coronal	BH	4500/735	180	60	400 × 400	3 × 3–6 orientations
3D MRCP	Coronal	NT	1700/425	105	1	384 × 384	120–180
T1 mapping	Axial	BH	3/1.32	8	4	380 × 380	17/slab × 4~5 consecutive slabs
TWIST-VIBE DCE	Axial	BH	3.89/1.23–2.46	10	3	400 × 400	600, including multiple arterial and portal venous-phase and delayed-phase imaging

T1W T1-weighted images, *VIBE* volumetric interpolated breath-hold examination, *T2W* T2-weighted images, *TSE* turbo spin echo, *FS* fat-saturated, *HASTE* half-Fourier acquisition single-shot turbo spin echo, *ss-EPI* single-shot echo-planar imaging, *DWI* diffusion-weighted imaging, *MRCP* MR cholangiopancreatography, *TWIST* time-resolved imaging with interleaved stochastic trajectories, *DCE* dynamic contrast-enhanced, *BH* breath-hold, *NT* navigator-triggered, *TR* repetition time, *TE* echo time, *FA* flip angle, *FOV* field of view

administered. The T1 parametric maps were acquired using an inversion-recovery snapshot FLASH prototype sequence (WIP 838D, Siemens Healthcare), which performs a 180° inversion at the beginning, followed by continuous FLASH excitations with 16 inversion time sampling points. A parallel imaging factor (GRAPPA) of 2 was used. A slab of five consecutive slices was obtained within each breath-hold, which took 17 s. A total of four to five slabs were taken to cover the entire pancreas. The total acquisition time including audio instruction and the patient's respiratory adjustment took less than 2 min. The reproducibility of T1 mapping was tested by performing the sequence twice during the same examination.

Image analysis

Image evaluation was performed in a retrospective manner. One experienced radiologist reviewed baseline MR images (without T1 maps) of all patients and decided whether the patient had a diffuse or focal form of AIP [16, 17]. For patients with a focal form of AIP, the location of the focal lesion was marked.

Two other radiologists (13 years and 6 years of experience in interpreting abdominal MR, respectively) performed independent measurements of T1 relaxation time by drawing region of interest (ROI) manually on the T1 parametric maps, on a commercially available post-processing workstation (syngo MMWP, VE36A, Siemens Healthcare). Clinical information other than the diagnosis and the result of laboratory tests were blinded to the readers. For both AIP and control groups, circular ROIs with an area of 0.6–1.5 cm^2 were drawn in a homogenous region of the parenchyma. Care was taken to avoid inclusion of the pancreatic duct, peripheral vessels, and retroperitoneal fat. The other MR sequences were displayed alongside to facilitate the recognition of anatomical structures. For each patient, ROIs were drawn in the pancreatic head, body, and tail regions, separately. The T1 relaxation time was measured three times in each region and averaged. When a focal lesion was marked in the region to be measured, the ROI was confined to the lesion only. For paired before- and after-treatment images from the same patient, care was taken to draw the ROIs in the same region of the pancreas.

Statistical analysis

Continuous data was tested for normal distribution with a Kolmogorov-Smirnov test.

Descriptive data was displayed in terms of percentages and means with standard deviations if they were normally distributed. Pearson's correlation and intraclass correlation coefficients (ICCs) were used to test reproducibility. The Bland-Altman analysis was used to assess inter-observer agreement in T1 relaxation time measurement. One-way analysis of variance (ANOVA) was used to compare T1 relaxation time of pancreatic head, body, and tail. The independent *t* test was used to compare T1 relaxation time of AIP and normal pancreas. The paired *t* test was used to compare T1 relaxation time of AIP before and after CST. Receiver operating characteristic (ROC) curve was used to determine the accuracy of T1 relaxation time for differentiating AIP and normal pancreas. Pearson's correlation was used to assess the relationship between T1 relaxation time and serum IgG4 level. Statistical analyses were performed using SPSS 17.0 (IBM Corp.) and MedCalc 16.20 (MedCalc Software). A double-sided *p* value

< 0.05 was considered indicating a statistically significant difference.

Results

Fifty-five patients were prospectively enrolled, and 16 of them were excluded, because of a final diagnosis other than AIP ($n = 2$), inability to receive or tolerate an MR scan ($n = 3$), and missing baseline/follow-up imaging or clinical data ($n = 11$). Nine patients received only one MR follow-up instead of twice (three at 4 weeks and six at 12 weeks), and their data was not excluded. All the other patients had both short-term and mid-term MR follow-up.

The AIP group had 39 patients (29 male; median age, 58 years; range, 32–84 years), and the control group had 40 patients (25 male; median age, 51 years; range, 24–80 years). There was no significant difference concerning gender and age between the groups ($p = 0.257$ and 0.194, respectively). In the AIP group, two patients had a history of pancreatic surgery for suspected malignancy, and 11 patient had underwent previous CST (one to four episodes; median, 2) and experienced disease relapse. Clinical and laboratory data of those patients are shown in Table 2. All patients responded to CST. Six patients had normal serum IgG4 level at baseline (median, 415; range, 282–910 mg/L), all of whom were negative for pancreatic biopsy and achieved clinical remission after CST.

T1 relaxation time of AIP and normal pancreas

The reproducibility of T1 mapping measurement in AIP patients at baseline and follow-up, as well as in the control group, was all satisfactory. Pearson's correlation coefficient was 0.78–0.84, with ICCs 0.87–0.91.

T1 relaxation time did not differ significantly among the pancreatic head, body, and tail for normal pancreas and AIP at baseline ($p = 0.607$ and $p = 0.654$, respectively). T1 relaxation time of AIP at baseline was 1124.5 ms ± 95.7 ms, which was significantly elongated compared to that of normal pancreas (784.3 ms ± 41.8 ms, $p < 0.001$). There was no significant difference in baseline T1 relaxation time, in patients who had the first attack and in patients with relapsed AIP ($p = 0.538$).

ROC curve analysis identified a threshold value of 846.5 ms, with a sensitivity of 97.7% and specificity of 93.7%, for differentiating AIP from normal pancreas (area under the curve (AUC) = 0.973).

T1 relaxation time, pancreas size, and ADC value change of AIP under treatment

T1 relaxation time, size, and ADC values of the pancreas in AIP patients are shown in Fig. 1 and Table 3, in comparison with the values of the normal pancreas.

After 4 weeks of CST, the T1 relaxation time of the affected pancreatic parenchyma in AIP shortened significantly

Table 2 Clinical and laboratory data of patients with AIP

	Diffuse AIP ($n = 24$)	Focal AIP ($n = 15$)	p value
Gender (M:F)	19:5	10:5	0.384
Age (years) type	56 (range 32–79)	60 (range 46–84)	
Type 1	22	13	0.617
Type 2	2	2	
Asymptomatic	16.7% (4/24)	40.0% (6/15)	0.104
Symptoms			
Pain	29.2% (7/24)	6.7% (1/15)	0.156
Jaundice	83.3% (20/24)	20.0 (3/15)	< 0.001
Malaise	50.0% (12/24)	13.3% (2/15)	0.020
Weight loss	33.3% (8/24)	13.3% (2/15)	0.164
Diabetes mellitus	20.8% (5/24)	6.7% (1/15)	0.233
Serum IgG4 level			
At baseline*	5280 (range 463–23,100)	5790 (range 282–21,200)	0.911
At short-term follow-up*	2730 (range 310–11,800)	2580 (range 348–12,600)	0.539
At mid-term follow-up*	1650 (range 275–5520)	1620 (range 304–5850)	0.673
Regional involvement of the pancreas			
Head	100% (22/22)	40.0% (6/15)	–
Body	100% (24/24)	33.3% (5/15)	–
Tail	100% (24/24)	46.7% (7/15)	–

*The normal range of serum IgG4 level is 80–1400 mg/L

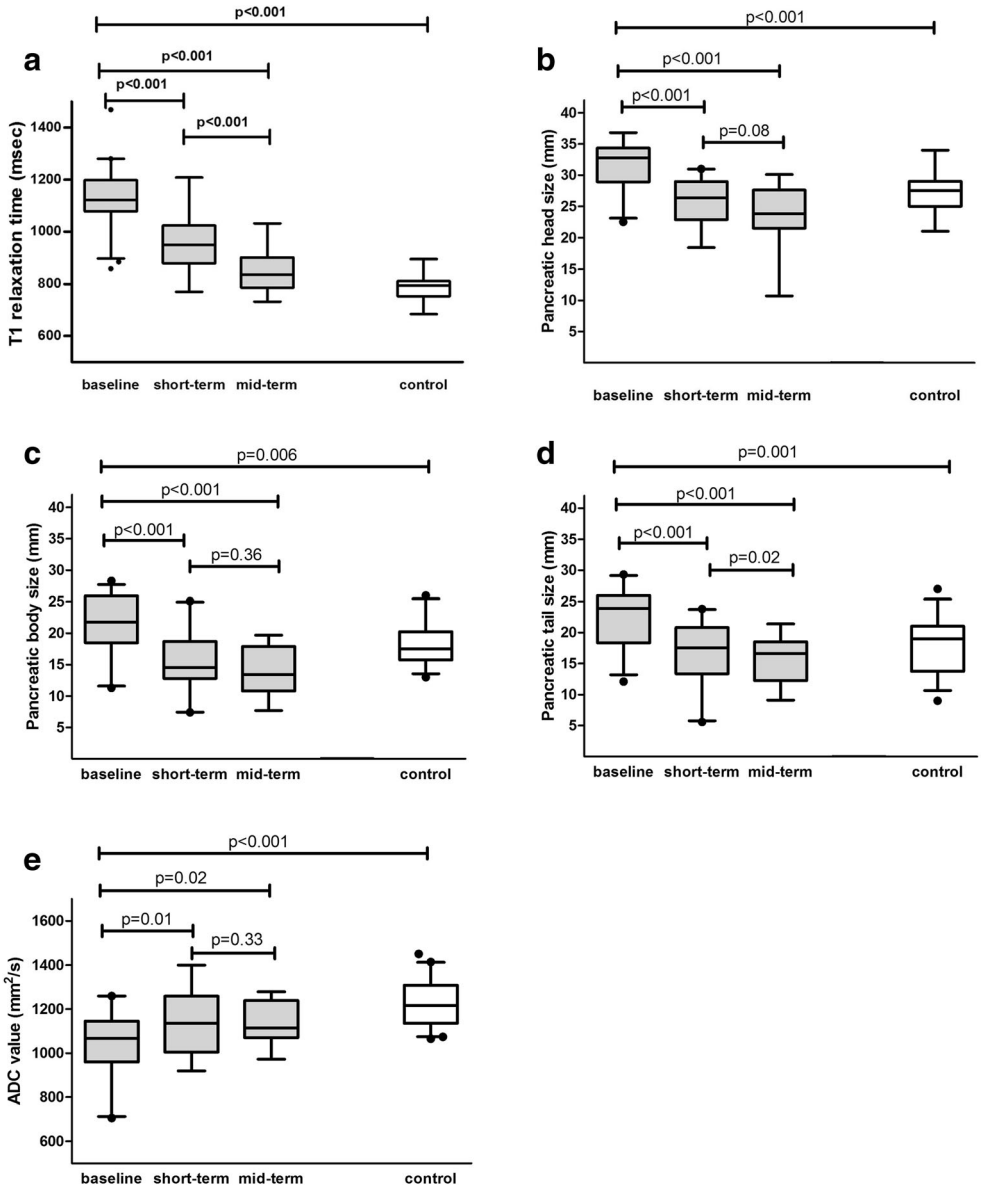

Fig. 1 **a**–**e** Box and whisker plots of T1 relaxation times, pancreas size, and ADC values of the pancreas in AIP patients at baseline short-term and mid-term follow-up, as well as in the normal pancreas

compared to baseline value. After 12 weeks of CST, the T1 relaxation time further shortened but was still slightly longer than the normal value ($p = 0.016$) (Fig. 2).

For patients with a focal form of AIP, the visually unaffected pancreatic parenchyma also demonstrated significantly longer T1 relaxation time compared to the normal pancreas

Table 3 T1 relaxation time, pancreas size, and ADC value change of AIP under treatment

	AIP at baseline	AIP at short-term follow-up	AIP at mid-term follow-up	Normal pancreas (control)	$p_{\text{baseline-control}}$	$p_{\text{short-term-control}}$	$p_{\text{mid-term-control}}$
T1 relaxation time (ms)	1124.5 ± 95.7	957.2 ± 97.3	844.2 ± 71.6	784.3 ± 41.8	< 0.001	< 0.001	0.016
Pancreas size (mm)							
Head	32.6 ± 4.1	26.1 ± 4.1	23.9 ± 4.8	27.2 ± 3.4	< 0.001	0.12	< 0.001
Body	21.0 ± 5.1	15.0 ± 4.3	14.6 ± 4.3	18.3 ± 3.4	< 0.001	0.02	0.014
Tail	22.2 ± 4.9	16.7 ± 4.6	15.2 ± 4.5	18.0 ± 4.3	< 0.001	0.04	0.01
ADC ($\times 10^{-3}$ mm^2/s)	1.052 ± 0.176	1.145 ± 0.176	1.132 ± 0.147	1.225 ± 0.138	< 0.001	0.012	0.002

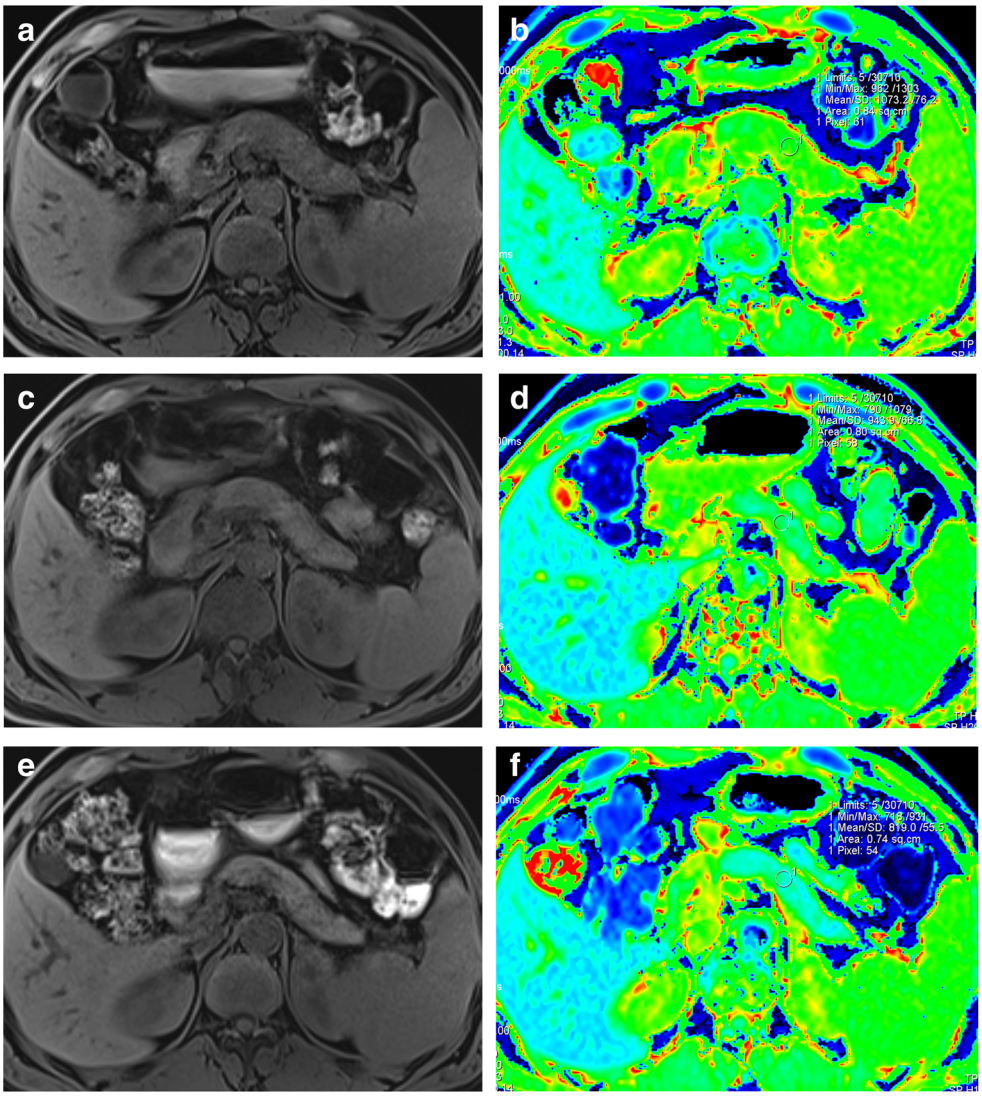

Fig. 2 A 46-year-old male patient with upper abdominal pain and jaundice for the last 2 months. Imaging revealed diffuse pancreas enlargement and distal common bile duct stricture. Serum IgG4 level was normal (485 mg/L; normal range, 80–1400 mg/L). Baseline study: **a** axial fat-saturated T1-weighted image (fs-T1WI) shows slightly enlarged pancreas with loss of lobulation. The signal of the pancreatic parenchyma was heterogeneous and hypointense compared to that of the liver. The size of the pancreatic body and tail was 23.0 mm and 21.8 mm, respectively. **b** The measured T1 relaxation time of the pancreatic body was 1073.2 ms. Short-term follow-up after 4 weeks of corticosteroid therapy (CST): **c** axial fs-T1WI demonstrates a decrease in the size of the pancreatic body and tail, while the parenchyma signal increased and became less heterogeneous. The size of the pancreatic body and tail was 16.8 mm and 17.8 mm, respectively. **d** The measured T1 relaxation time of the pancreatic body was 943.9 ms. Mid-term follow-up after 12 weeks of CST: **e** axial fs-T1WI shows the little change of the pancreas size, while the parenchyma signal increased. The size of the pancreatic body and tail was 15.8 mm and 16.8 mm, respectively. **f** The measured T1 relaxation time of the pancreatic body was 819.0 ms

(918.7 ms ± 128.9 ms, $p < 0.001$), which also shortened significantly during CST (857.3 ms ± 84.5 ms at short-term and 824.1 ms ± 73.6 ms at mid-term follow-up; $p = 0.019$ and $p < 0.001$, respectively) (Fig. 3).

The size of the pancreatic head, body, and tail differs significantly in the normal pancreas and in AIP (both $p < 0.001$). For AIP at baseline, the size in all regions was significantly larger than that of normal pancreas (all $p < 0.001$). On the contrary, the pancreas size became smaller than the normal pancreas at short-term and mid-term follow-up ($p = 0.01$–0.04 in all regions). Short-term follow-up demonstrates a significant size reduction in all regions compared to baseline (all $p < 0.001$). During mid-term follow-up, the pancreatic head showed a further reduction in size ($p = 0.02$), whereas the pancreatic head and body did not change significantly in size ($p = 0.08$ and 0.36, respectively).

ADC value did not differ significantly among the pancreatic head, body, and tail for normal pancreas and AIP at baseline ($p = 0.557$ and $p = 0.473$, respectively). ADC of AIP at baseline was significantly lower than the normal pancreas

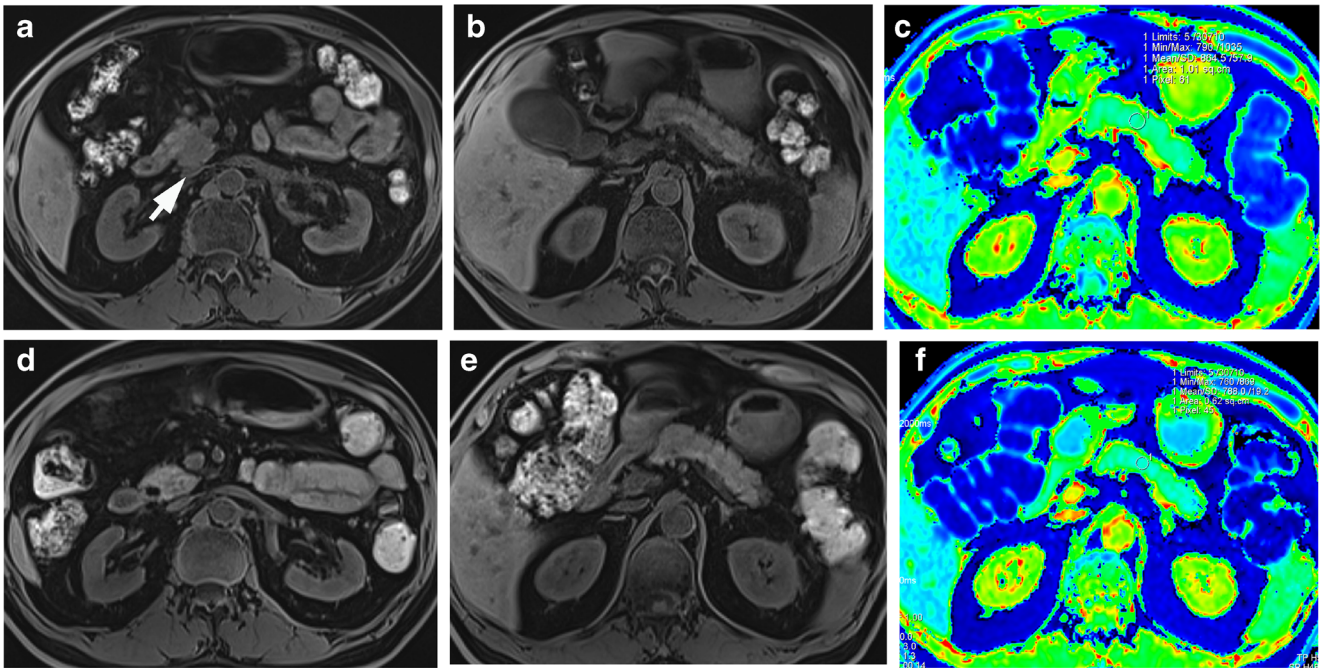

Fig. 3 A 72-year-old male with 3 months of malaise, palpable multiple peripheral lymph node enlargement and increased serum bilirubin level. Imaging revealed solitary pancreas *mass* in the pancreatic head. Serum IgG4 level was 15,000 mg/L. Baseline study: **a**, **b** axial fs-T1WI shows pancreatic head enlargement (size, 36.8 mm) with a solitary mass-like lesion (white arrow), which demonstrated lower signal than the rest of the pancreas. The size of the pancreatic body appeared normal (18.5 mm), and the lobulation was preserved. **c** T1 relaxation time of the pancreatic body measured 864.5 ms at baseline. Short-term follow-up after 4 weeks of CST: **d**, **e** axial fs-T1WI shows the pancreatic head decreased significantly in size (29.7 mm), and the mass-like lesion was no longer evident. The pancreatic body changed little in size (17.2 mm), but the parenchymal signal became more homogeneous and increased compared to the previous scan. **f** T1 relaxation time of the pancreatic body measured 788.0 ms at short-term follow-up

($p < 0.001$). After 4 weeks of CST, ADC value increased compared to baseline ($p = 0.01$). After 12 weeks of CST, no further change was observed ($p = 0.33$). Both were still lower than normal ($p = 0.012$ and $p = 0.002$, respectively).

Correlation of T1 relaxation time of the pancreas with serum IgG4 level

In 33 serum IgG4-positive AIP patients, a positive correlation was found between the serum IgG4 level and the T1 relaxation time of the pancreas ($r = 0.329$, $p = 0.011$). The serial change of serum IgG4 level and T1 relaxation time of the pancreas at baseline and during CST is shown in Fig. 4. Serum IgG4 level dropped significantly at short-term follow-up (median from 6190 to 2850 mg/L, $p < 0.001$) and decreased further at mid-term follow-up (median, 1730 mg/L; $p < 0.001$). However, in serum IgG4-negative AIP patients ($n = 6$), no significant change of serum IgG4 level was observed during follow-up ($p = 0.753$ and $p = 0.647$, respectively). In contrast, T1 relaxation time of the pancreas decreased significantly at short-term and mid-term follow-up, respectively (both $p < 0.001$). The serial change of clinical symptoms and serum biomarkers as well as that of T1 relaxation times in the serum IgG4-negative AIP patients are listed in Table 4.

Inter-reader agreement

The results from the Bland-Altman analysis are shown in Fig. 5. The systematic difference for the T1 relaxation time measured by the two readers was small (−5.6 ms; 95% CI, −11.5 to −0.4), indicating an excellent inter-reader agreement.

Discussion

This study demonstrated the potential of native T1 mapping to evaluate parenchymal inflammation status of AIP and to quantify response to treatment. In AIP patients, the T1 relaxation time of the pancreas was significantly prolonged. As a response to effective treatment, the T1 relaxation time shortened significantly already at short-term follow-up. It further shortened at mid-term follow-up, getting closer but still slightly longer than the normal value from the disease-free pancreas. The significant improvement after CST indicates that T1

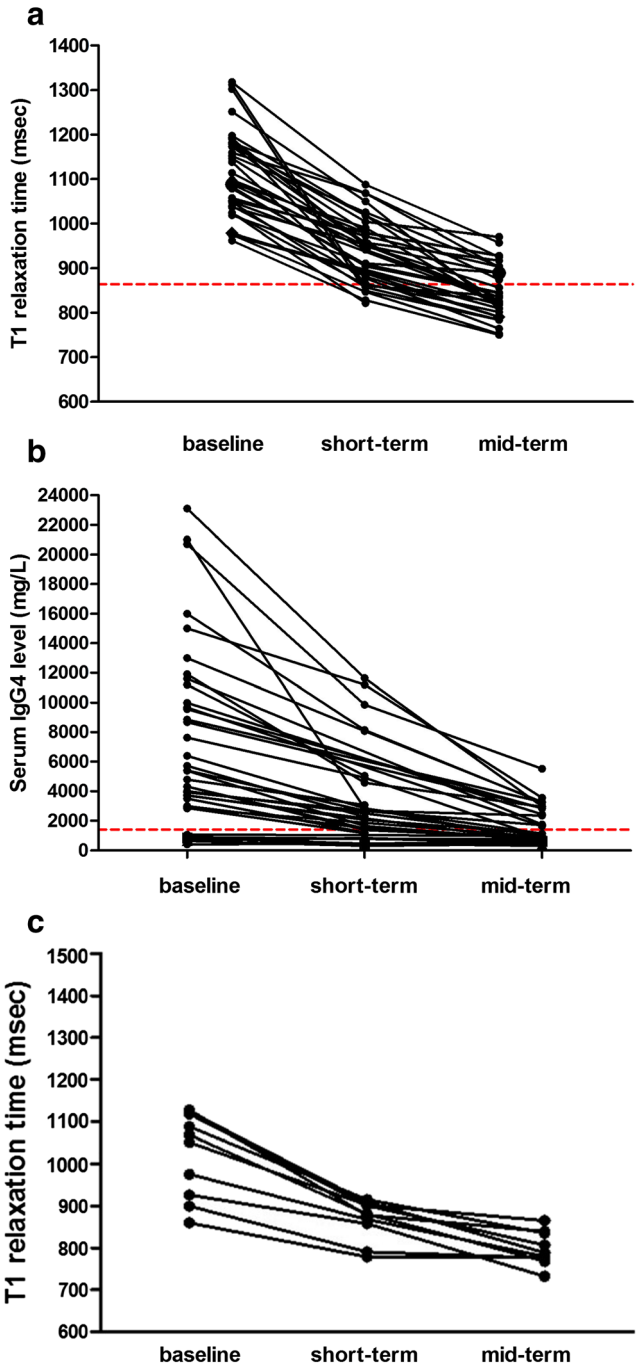

Fig. 4 Graphs of parameters of AIP patients at baseline and follow-up. **a** T1 relaxation time of the pancreas. The reference line represents the cutoff value from ROC curve analysis (846.5 ms). **b** Serum IgG4 level. The reference line represents the upper limit of normal serum IgG4 level (1400 mg/L). **c** T1 relaxation time of the pancreas in serum IgG4-negative AIP patients

mapping provides a sensitive outcome measure in AIP patients under therapeutic intervention.

It is known that pancreas size and parenchyma signal intensity change dramatically after steroid therapy [13, 16, 18]. However, the early changes of pancreas size during CST have not been described. In our study, pancreas size reduced markedly during the first 4 weeks of CST, which already became smaller than that of normal pancreas, indicating that pancreas atrophy can occur very soon with treatment. Further size reduction in the next 8 weeks was smaller and insignificant in the pancreatic head and body. In the meantime, however, clinical improvement and serum IgG4 drop-down was evident. Therefore, pancreas size may only reflect the instant treatment response of AIP but does not indicate treatment effect in later stages. ADC value has been postulated to be a potential MR biomarker for AIP disease activity [18, 19]. In this study, the ADC value of AIP at baseline was lower than that of normal pancreas. We have observed an increase in ADC value at 4 weeks, but no further change at 12 weeks. Therefore, ADC does not fully reflect the treatment effect either. Besides, Braithwaite et al [20] have evaluated the short- and mid-term reproducibility of pancreatic ADC measurement at 3 T and concluded that the treatment effect of less than 27% will not be detectable. This further limits the use of ADC to monitor the treatment effect of AIP.

Fast volumetric T1 mapping sequences have been recently developed, which can be obtained in one breath-hold, increasing its robustness and precision for evaluating small abdominal organs. In this study, the reproducibility and inter-reader agreement of pancreas T1 time measurement were both satisfactory. Pancreatic signal intensity (SI) on T1-weighted images (T1WIs) is useful for determining disease status. A healthy pancreas usually demonstrates a higher signal than a liver, whereas pancreatitis or pancreatic neoplasm often demonstrates a decreased SI [21]. However, the tissue contrast on T1WIs could not be directly compared between different scans, because the measured SI depends on technical factors inherent to the acquisition. What is more, mild diffuse disease might be difficult to detect with visual inspection. In contrast, T1 mapping is defined by the pixel-to-pixel illustration of absolute T1 relaxation times, circumventing confounding factors and enabling a reliable T1 quantification, directly reflecting underlying pathophysiological processes [22, 23].

AIP is characterized by abundant lymphoplasmacytic cell infiltration with associated fibrosis (type 1) or duct-centric pancreatitis (type 2). The pathological change of the parenchyma is a mixed reaction of inflammation and fibrosis, both leading to an increased T1 relaxation time. Manfredi et al [16] noted that in AIP patients, the affected pancreatic parenchyma appeared hypointense on T1WIs, and after CST, the parenchyma became hyperintense in 56% (15/27) of patients, whereas in the rest of patients, the pancreas remained isointense or hypointense than the liver. The main drawback without a quantitative measure is that without a baseline MR study, the treatment response cannot be reliably determined, especially for patients whose pancreatic signal remains abnormal after treatment. Also, by subjective comparison of non-quantitative images, the subtle signal change could be missed. Our study supports the use of T1 mapping as a quantitative outcome

Table 4 Clinical data, laboratory data, and T1 relaxation time of the six patients with serum IgG4-negative AIP at baseline and follow-up

Patient information	Form	Serum IgG4 level (mg/L)	Clinical symptoms					T1 relaxation time of the pancreas (ms)
			Abdominal pain	Jaundice	Malaise	Weight loss	Glucose intolerance	
1, M/37	Diffuse							
Baseline		418	+	++	+	–	+	1230.7
Short-term follow-up		386	–	+	–	–	+	976.5
Mid-term follow-up		404	–	–	–	–	–	870.3
2, M/46	Diffuse							
Baseline		559	–	+++	+	+	–	1124.6
Short-term follow-up		535	–	++	–	–	–	913.4
Mid-term follow-up		527	–	+	–	–	–	823.5
3, F/67	Focal							
Baseline		941	+++	+	++	+	–	979.7
Short-term follow-up		825	++	+	+	–	–	804.5
Mid-term follow-up		871	–	–	–	–	+	800.6
4, F/63	Focal							
Baseline		463	–	–	++	+	–	1062.1
Short-term follow-up		507	–	–	+	–	–	837.5
Mid-term follow-up		492	–	–	–	–	–	810.6
5, M/56	Focal							
Baseline		328	+++	+++	++	+	–	1045.5
Short-term follow-up		330	+	++	+	–	+	927.8
Mid-term follow-up		317	–	–	–	–	+	875.5
6, M/59	Focal							
Baseline		748	–	+	–	–	++	1063.4
Short-term follow-up		910	–	–	–	–	+	914.5
Mid-term follow-up		805	–	–	–	–	+	845.6

+: symptom positive, mild; ++: symptom positive, moderate; +++: symptom positive, severe; – : sympotom negative

measure for treatment responsiveness. After 12 weeks of CST, the T1 relaxation time come close to normal value, and in relapsed AIP, the T1 relaxation time is elongated again, which had a similar value compared to the initial attack. Therefore, T1 mapping could monitor the reversible pathologic change of AIP and could indicate the recurrence.

There is an additional novel finding with a focal form of AIP, which presents a particular diagnostic challenge. Although the lesion appears *focal* visually, T1 relaxation time measurement suggested that the apparently uninvolved part of the pancreas was also affected. Focal AIP might represent a diffuse pancreatic tissue inflammation with uneven distribution. Histological analysis of resected specimens of AIP showed that the inflammatory change was often heterogeneous and patchy, with some areas showing fibrosis and inflammation, alternating with better preserved areas [24, 25]. It has been suggested that focal and diffuse AIP share the same clinical spectrum and the focal/diffuse distribution seems to be related to the stage or extent of the disease [26]. Native T1 mapping could quantify the inflammatory status of the entire pancreas, depict the regional distribution, and measure the severity

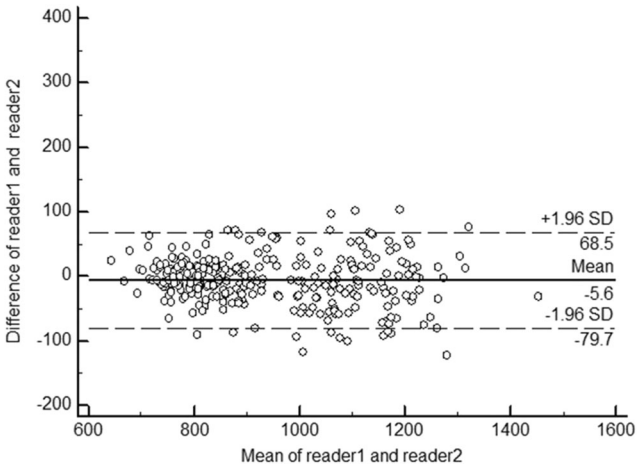

Fig. 5 Bland-Altman plot for inter-reader agreement. Dashed lines show the 95% limits of agreement (± 1.96 standard deviations), and solid line shows the mean of differences. This demonstrates the high inter-reader reproducibility of this technique

of the disease. The *diffuse-and-uneven* pattern of pancreatic tissue involvement might be an additional diagnostic clue against pancreatic cancer.

In this study, a positive correlation was observed between serum IgG4 and T1 relaxation time of the pancreas. Serum IgG4 concentration has been recognized as a biomarker for IgG4-related AIP, both for differential diagnosis and monitoring treatment effect [27]. From the clinical point of view, T1 mapping represents a new imaging biomarker for AIP. Its role might be ancillary in serum IgG4-positive patients. However, in serum IgG4-negative patients, T1 mapping might play a more essential role as a treatment outcome measure.

Our study has several limitations. First, the patients were collected from a single Asian center. The number of serum IgG4-negative AIPs was limited. Multicenter, international studies with non-Asian population are needed to consolidate these findings. Second, since AIP is a benign disease entity, we were not able to obtain a direct radiological-pathological correlation in those patients. AIP is featured by a combination of inflammation and fibrosis. A combination of MR biomarkers reflecting diffusion, perfusion, and fibrosis might better depict the true pathological tissue changes. This interesting hypothesis might be tested in animal models in the future. Third, the effect of novel treatments other than CST was not evaluated. In our cohort, all patients responded to CST and showed clinical improvement, in keeping with the T1 relaxation time change of the pancreas. T1 mapping might have the potential to stratify patients into responders and non-responders to novel treatments, which merits further studies.

In conclusion, native T1 mapping reflects the short-term and mid-term treatment effects of AIP under CST, providing a quantitative outcome surrogate for AIP.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Professor Zheng-yu Jin, the department chair of radiology, Peking Union Medical College Hospital.

Conflict of interest Tian-yi Qian and Marcel Dominik Nickel are employees from Siemens Healthcare Company, who provided technical support with the T1 mapping prototype sequence and were not involved in the data collection and analysis. The other authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
- prospective
- observational
- performed at one institution

References

1. Finkelberg DL, Sahani D, Deshpande V, Brugge WR (2006) Autoimmune pancreatitis. N Engl J Med 355(25):2670–2676
2. Nishimori I, Tamakoshi A, Otsuki M, Research Committee on Intractable Diseases of the Pancreas, Ministry of Health, Labour, and Welfare of Japan (2007) Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. J Gastroenterol 42(Suppl 18):6–8
3. Kanno A, Nishimori I, Masamune A et al (2012) Nationwide epidemiological survey of autoimmune pancreatitis in Japan. Pancreas 41(6):835–839
4. Moon SH, Kim MH, Park DH et al (2008) Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. Gut 57(12):1704–1712
5. Shimosegawa T, Chari ST, Frulloni L et al (2011) International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 40(3):352–358
6. Kamisawa T, Shimosegawa T, Okazaki K et al (2009) Standard steroid treatment for autoimmune pancreatitis. Gut 58(11):1504–1507
7. Kubota K, Kamisawa T, Okazaki K et al (2017) Low-dose maintenance steroid treatment could reduce the relapse rate in patients with type 1 autoimmune pancreatitis: a long-term Japanese multicenter analysis of 510 patients. J Gastroenterol 52(8):955–964
8. Hart PA, Chari ST (2017) Preventing disease relapses in autoimmune pancreatitis with maintenance steroids: are we there yet? Gut 66(3):394–396
9. Hart PA, Kamisawa T, Brugge WR et al (2013) Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut 62(12):1771–1776
10. Hart PA, Topazian MD, Witzig TE et al (2013) Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. Gut 62(11):1607–1615
11. Morselli-Labate AM, Pezzilli R (2009) Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: a systematic literature review and meta-analysis. J Gastroenterol Hepatol 24(1):15–36
12. Chari ST, Smyrk TC, Levy MJ et al (2006) Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol 4(8):1010–1016 quiz 934
13. Sahani DV, Kalva SP, Farrell J et al (2004) Autoimmune pancreatitis: imaging features. Radiology 233(2):345–352
14. Sahani DV, Sainani NI, Deshpande V, Shaikh MS, Frinkelberg DL, Fernandez-del Castillo C (2009) Autoimmune pancreatitis: disease evolution, staging, response assessment, and CT

features that predict response to corticosteroid therapy. Radiology 250(1):118–129
15. Manfredi R, Graziani R, Cicero C et al (2008) Autoimmune pancreatitis: CT patterns and their changes after steroid treatment. Radiology 247(2):435–443
16. Manfredi R, Frulloni L, Mantovani W, Bonatti M, Graziani R, Pozzi Mucelli R (2011) Autoimmune pancreatitis: pancreatic and extrapancreatic MR imaging-MR cholangiopancreatography findings at diagnosis, after steroid therapy, and at recurrence. Radiology 260(2):428–436
17. Frulloni L, Scattolini C, Falconi M et al (2009) Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients. Am J Gastroenterol 104(9):2288–2294
18. Liang W, Xu S (2012) Radiologic evaluation of autoimmune pancreatitis. Radiology 262(2):731–732 author reply 732
19. Oki H, Hayashida Y, Oki H et al (2015) DWI findings of autoimmune pancreatitis: comparison between symptomatic and asymptomatic patients. J Magn Reson Imaging 41(1): 125–131
20. Braithwaite AC, Dale BM, Boll DT, Merkle EM (2009) Short- and midterm reproducibility of apparent diffusion coefficient measurements at 3.0-T diffusion-weighted imaging of the abdomen. Radiology 250(2):459–465
21. Winston CB, Mitchell DG, Outwater EK, Ehrlich SM (1995) Pancreatic signal intensity on T1-weighted fat saturation MR images: clinical correlation. JMRI 5(3):267–271
22. Schelbert EB, Messroghli DR (2016) State of the art: clinical applications of cardiac T1 mapping. Radiology 278(3):658–676
23. Yoon JH, Lee JM, Kim E, Okuaki T, Han JK (2017) Quantitative liver function analysis: volumetric T1 mapping with fast multisection B1 inhomogeneity correction in hepatocyte-specific contrast-enhanced liver MR imaging. Radiology 282(2):408–417
24. Youssef N, Petitjean B, Bonte H, Terris B, de Saint Maur PP, Fléjou JF (2004) Non-alcoholic duct destructive chronic pancreatitis: a histological, immunohistochemical and in-situ apoptosis study of 18 cases. Histopathology 44(5):453–461
25. Wreesmann V, van Eijck CH, Naus DC, van Velthuysen ML, Jeekel J, Mooi WJ (2001) Inflammatory pseudotumour (inflammatory myofibroblastic tumour) of the pancreas: a report of six cases associated with obliterative phlebitis. Histopathology 38(2):105–110
26. Wakabayashi T, Kawaura Y, Satomura Y et al (2002) Clinical study of chronic pancreatitis with focal irregular narrowing of the main pancreatic duct and mass formation: comparison with chronic pancreatitis showing diffuse irregular narrowing of the main pancreatic duct. Pancreas 25(3):283–289
27. Kawa S, Ito T, Watanabe T et al (2012) The utility of serum IgG4 concentrations as a biomarker. Int J Rheumatol 2012:198314