Assessing IgG4-related autoimmune pancreatitis with contrast-enhanced ultrasonography based on time-intensity curve: a single-centre prospective study

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Abstract

Objective

The aim of this study was to investigate the changes in various parameters of contrast-enhanced ultrasound (CEUS) before and after treatment in patients with IgG4-related autoimmune pancreatitis (IgG4-AIP), and to identify potential indicators that can assist in evaluating disease activity.

Methods

In this prospective study, we enrolled patients diagnosed with IgG4-AIP from June 2021 to November 2022. Demographic characteristics, clinical features, laboratory tests were recorded. Baseline and follow-up, conventional ultrasound and CEUS were conducted. Additionally, a region of interest (ROI) within lesions, pancreatic head, pancreatic body, and pancreatic tail was taken to draw time-intensity curves (TIC) and parameters of TIC were recorded and analysed.

Results

Seventy-three active IgG4-AIP patients were enrolled. Follow-up, a notable decrease in the size of the pancreatic lesion was observed with a reduction in the maximum diameter from 4.3 ± 2.0 cm to 1.7 ± 1.6 cm ($p=0.01$). The results revealed a statistically significant increase in peak intensity (PI) in the head, body, and tail regions of the pancreas ($p<0.001$), along with a significant rise in the area under the curve (AUC) in the tail region of the pancreas ($p=0.029$) after treatment compared to baseline. In contrast, no statistically significant differences were observed in other parameters of TIC. A significant increase of PI was observed in 12 patients with diffuse IgG4-AIP following treatment. Following treatment, there was a significant increase in PI in the focal area among the 12 patients with focal lesions.

Conclusion

CEUS based on TIC holds great potential for assessing response to treatment in patients with IgG4 AIP.

Key words

contrast-enhanced ultrasound, IgG4-related disease, autoimmune pancreatitis, time-intensity curve

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Introduction

Autoimmune pancreatitis (AIP) is a chronic disorder of the pancreas characterised by fibroproliferative changes and inflammatory infiltration, predominantly distinguished by obstructive jaundice, abdominal pain, weight loss, and fatigue. In 2011, the International Consensus Diagnostic Criteria (ICDC) for AIP placed significant emphasis on the differences between type I and type II AIP (1). The histopathological manifestations observed in type I AIP include pancreatic fibrosis, infiltration of lymphocytes and plasma cells, with a predominance of $IgG4^+$ plasma cells, which are classified as the manifestations of IgG4-RD (2).

Presently, the imaging modalities employed for IgG4-AIP encompass ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose positron emission tomography (PET/CT). Each imaging modality possesses distinct drawbacks. Marked changes in size of the pancreas detected by conventional ultrasound can directly reflect the therapeutic effect of AIP. Whereas sometimes the use of conventional ultrasound alone is not enough to assess the treatment effect of patients with IgG4-AIP because of the remained hypoechoic of lesions, especially in focal IgG4-AIP. ERCP can detect the narrowing of interlobular septa and the main pancreatic duct, but is unsuitable for long-term evaluation as its invasive nature (3, 4). PET/CT proves to be an efficient tool for the selection of biopsy site, evaluation of treatment effectiveness, surveillance for recurrence, and assessment of extra-pancreatic involvement (3, 5, 6). However, PET/CT is not routinely used for follow-up monitoring due to high costs and the use of radioisotopes. MRI is not suitable for regular monitoring of IgG4-AIP because of its complex operation and the risk of contrast agent allergy in enhanced MRI. For CT, patients may have potential damage from repeated radiation exposure. Consequently, it is imperative to investigate alternative imaging modalities characterised as safer, more convenient and effective that can facilitate the monitoring of disease activity in IgG4-AIP to better guide therapeutic decisions.

CEUS is a real-time imaging modality, wherein microbubble contrast agents are administered intravenously to facilitate enhanced visualisation. CEUS integrates diverse ultrasound imaging methodologies, including low mechanical index imaging, contrast harmonic imaging, and energy contrast harmonic imaging, which enable the real-time assessment of microbubble distribution within the microcirculatory system depending on the non-linear signals from blood-pooling ultrasound contrast agents. CEUS allows continuous and dynamic observation of blood flow perfusion within lesions, which is not available in conventional ultrasound. This technique presents a greater abundance of blood flow information and microvascular insights compared with conventional ultrasound. Currently, CEUS has been utilised in the diagnosis and evaluation of hepatic, thyroid and gynaecological conditions (7, 8). Nevertheless, the evidence on the utilisation of CEUS technology in IgG4-AIP is scant. The objective of this study is to identify indicators of CEUS that can assist in evaluating IgG4-AIP disease activity.

Methods

Patients

This study enrolled patients from the Rheumatology and Immunology Department of the First Medical Center of the Chinese PLA General Hospital between June 2021 and November 2022. The diagnosis of IgG4-RD was based on the 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD (9). There were several exclusion criteria for this study. Firstly, individuals with contraindications to contrast agents, including acute heart failure, unstable angina, known right-to-left shunt, and acute endocarditis, as well as those with a known allergy to contrast agents, were excluded. Secondly, patients with other serious organic diseases such as cardiovascular diseases, tumours, and infections were also excluded. Lastly, obese patients with a body mass index (BMI) exceeding 30

kg/m^2 were not included in the study. The study was approved by the Ethics Committee at Chinese PLA General Hospital and all patients provided written informed consent.

Data collection

Patient data collection includes gathering information on gender, age, disease duration, initial symptoms, involvement of additional organs, and medications administered to the patients.

Various parameters such as eosinophil percentage (Eos%), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bilirubin (TBIL), indirect bilirubin (DBIL), amylase, lipase, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), immunoglobulin IgG, IgG4, IgE, complement C3, complement C4 were measured.

Ultrasound examination

All participants underwent supine ultrasound examination and were provided with instructions to engage in slow breathing. Ultrasound examinations were conducted utilising Resona R7 and R9 ultrasound machines (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.), along with a C5-1 convex array transducer operating at a frequency range of 1–5MHz. Prior to the implementation of CEUS, conventional ultrasound was performed to evaluate the size, margins, shape of the lesions, and the presence of pancreatic duct dilation. Following the completion of the conventional ultrasound, a rapid bolus injection of 2.2 mL sulfur hexafluoride microbubbles contrast agent (SonoVue@, manufactured by Bracco, Italy) was conducted followed by a flush of 5 mL of saline solution through the left elbow vein. Following that, the ultrasound probe was fixed for 2 minutes, while images were continuously and automatically recorded. During the observation period of contrast, the patterns of enhancement were noticed, encompassing the arterial phase (10 to 30 seconds) and the venous phase (30 to 120 seconds). The lesions were classified according to the lesional enhancement in the enhanced phases as hypoechoic (lesions almost without enhancement or with enhancement lower than that of the adjacent parenchyma), isoechoic (lesions with slight continuous enhancement or enhancement similar to that of the adjacent parenchyma) and hyperechoic (lesions with bright enhancement or enhancement superior to that of the adjacent parenchyma) (10). By implementing meticulous ultrasound examination and following strict assessment procedures, the reliability and accuracy of the data were effectively ensured which provided the basis to assess the effectiveness of CEUS in evaluating IgG4-AIP before and after treatment.

We utilised the built-in software (Contrast QA) of the Resona R7 and R9 ultrasound machines for further analysis of the CEUS images. Firstly, ROI was selected with meticulous attention to maintaining uniformity in terms of depth, size, shape and ensuring the exclusion of any potential interference arising from large vessels or necrotic areas. In the case of diffuse lesions, three ROIs were established in the pancreatic head, pancreatic body, and pancreatic tail. For focal lesions, an additional ROI was chosen within the lesion itself. Following this, TIC for CEUS were drawn for subsequent analysis (Supplementary Fig. S2). TIC exhibiting a Goodness of Fit (GOF) exceeding 70% were considered effective and filtered out for to further analysis. The quantitative parameters of TIC were generated, including Peak Intensity (PI) which meant the maximal contrast enhancement observed within the ROI, indicating the highest intensity attained by the contrast agent within the lesion, Baseline intensity (BI) which meant the initial intensity observed prior to the arrival of the contrast agent, serving as a representation of the background intensity within the lesion, Arise Time (AS), the duration between the administration of the contrast agent and the initiation of increased intensity, determined by the point at which the actual intensity surpasses 110% of the initial baseline, time to peak (TTP), the duration between the administration of the contrast agent and the attainment of maximal enhancement within the lesion, DT/2 (time to half peak intensity), the time point at which the intensity decreases to half of the peak value after reaching the peak, AS (ascending slope), the slope of the curve from the onset of lesion perfusion to the peak, DS (descending slope), the rate of decline in the curve, AUC (area under the curve), which represented the total blood flow within the lesion.

Treatment

All participants in this study received prednisone at an initial dosage of 0.5–1.0 mg/kg/day (equivalent to 30–60 mg/day) for one month. Subsequently, a gradual reduction in dosage was implemented, leading to a final maintenance dosage of 5–10 mg/day. Among the cohort, a total of 26 patients were administered immunosuppressive therapy, including leflunomide (n=13), mycophenolate mofetil (n=6), methotrexate (n=4), and Iguratimod (n=3). Besides, 2 patients underwent treatment with rituximab.

Statistical analysis

The mean ± standard deviation (SD) or median (interquartile range, IQR) were used to describe the quantitative variables. Proportions were employed to present the categorical variables. To analyse the differences between groups, two independent samples t-test or Wilcoxon rank sum test were utilised for quantitative variables, while the chi-square test or Fisher's exact test were employed for categorical variables. Furthermore, the degree of the association between two continuous variables was conducted. In cases where the data adhered to a normal distribution, the Pearson correlation analysis was employed. Otherwise, the Spearman correlation analysis was utilised. All the data were processed by the IBM SPSS Statistics v. 23.0 software and GraphPad Prism 9. Significant differences were defined as $p<0.05$.

Results

Demographic features

Seventy-three IgG4-AIP patients were enrolled into the cohort (Fig. I). The median age of the patients was 60.1 years, with a range of 22 to 79 years.

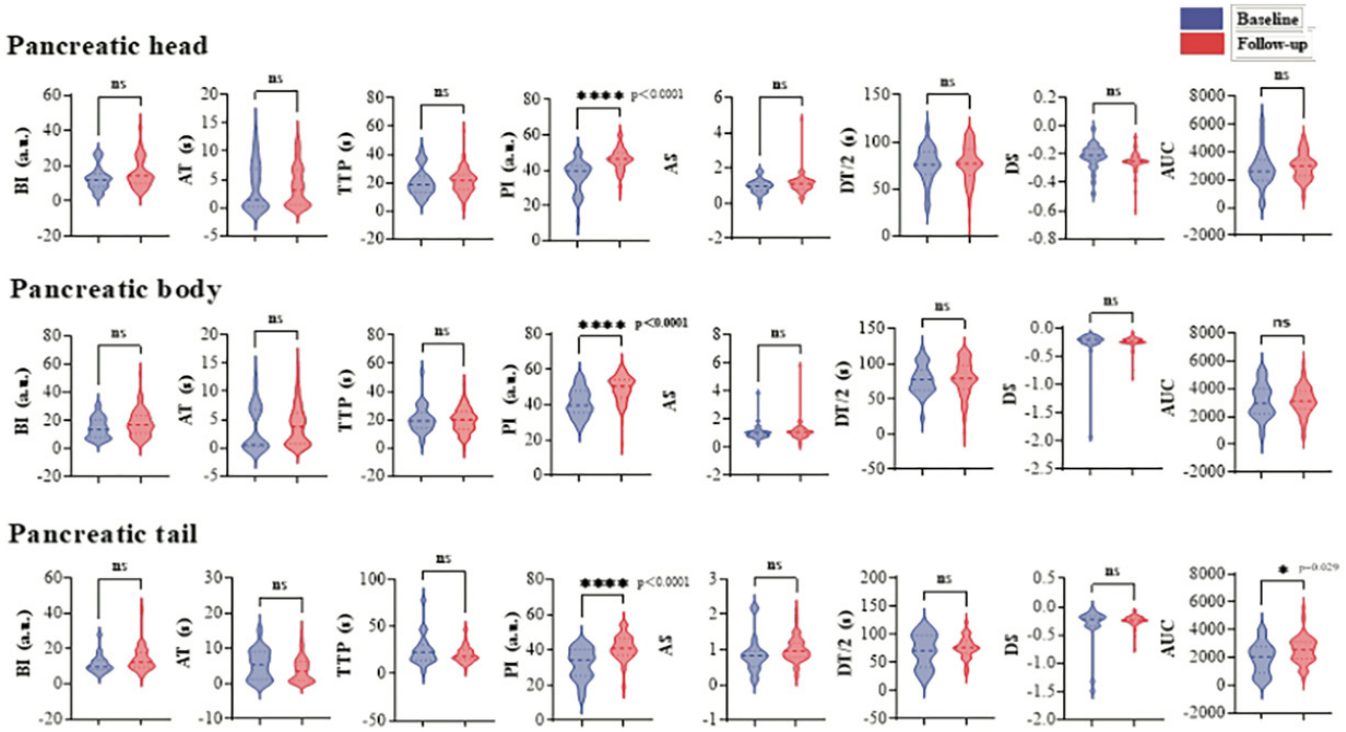

Fig. 1. Changes in contrast-enhanced ultrasound parameters during baseline and follow-up.
PI: peak intensity; BI: baseline intensity; AT: arise time; TTP: time to peak; DT/2: half time of peak intensity; AS: ascending slope; DS: descending slope; AUC: area under the curve.

Table I. Baseline characteristics of patients with IgG4-AIP (n=73).

Variable	Value
Sex (male:female)	1.8:1
Age (years) median (IQR)	60.1 (52,67)
Diagnosis, n (%)	
Definite	27 (37%)
Probable	26 (35.6%)
Possible	20 (27.4%)
Disease duration (months), median (IQR)	3.0 (1.0,6.1)
Follow-up time (months), median (IQR)	5.2 (3.5,7.5)
Clinical manifestation, n (%)	
Weight loss	38 (52.1%)
Fatigue	31 (42.5%)
Abdominal pain	36 (49.3%)
Jaundice	38 (52.1%)
Allergy history	
Rhinallergosis	27 (37.0%)
Allergic asthma	5 (6.8%)
Urticaria	6 (8.2%)
Diabetes, n (%)	25 (34.2%)
Smoke, n (%)	24 (32.8%)
Treatment, n (%)	
GCs	45 (61.6%)
GC+IMs	26 (35.6%)
GC+RTX	2 (2.8%)

GCs: glucocorticoids; Ims: immunosuppressants; RTX: rituximab; IQR: interquartile range.

Table II. CEUS characteristics of IgG4-AIP patients during baseline and follow-up periods.

Characteristics	Baseline (n=56)	Follow-up (n=56)	*p*-value
Echogenicity			0.679
Hypoechoic	52 (92.8%)	54 (96.4%)	
Isoechoic	4 (7.2%)	2 (3.6%)	
Arterial phase			0.070
Hypo-enhancement	23 (41.1%)	14 (25.0%)	
Iso-enhancement	19 (33.9%)	22 (39.3%)	
Hyper-enhancement	14 (25.0%)	20 (35.7%)	
Venous phase			0.058
Hypo-enhancement	41 (73.2%)	32 (57.1%)	
Iso-enhancement	13 (23.2%)	23 (41.1%)	
Hyper-enhancement	2 (3.6%)	1 (1.8%)	

p-value of <0.05 was considered statistically significant.

The male-to-female ratio was 1.8:1. The median (IQR) duration of follow-up was 5.2 (3.5, 7.5) months. Other baseline clinical characteristics are shown in Table I.

We conducted a comparative analysis of clinical and laboratory parameters among patients diagnosed with IgG4-AIP at the baselines and during subsequent follow-ups. Our findings revealed notable disparities in multiple indicators between the baseline group and follow-up group, including PGA score, IgG4-RD RI score, Eos%, ALT, AST, ALP, GGT, TBIL, DBIL, ESR, IgG, and IgG4 levels ($p<0.001$). Nevertheless, the comparison between baseline and follow-up did not yield any statistically significant difference in the levels of CRP, complement C3, complement C4, amylase, and lipase. Supplementary Table S1 provides further details.

Conventional ultrasound examination findings at baseline and follow-up

A total of 73 patients underwent conventional ultrasound examinations, with 61 patients exhibiting diffuse pattern and 12 patients presenting focal or multifocal pattern. On conventional ultrasound, hypoechoic masses within the affected segments were shown in

Table III. Comparison of ultrasound parameters between baseline and follow-up in 12 patients with diffuse IgG4-AIP.

	Pancreatic head			Pancreatic body			Pancreatic tail		
	Baseline	Follow-up	*p*	Baseline	Follow-up	*p*	Baseline	Follow-up	*p*
BI (a.u.)	15.76 ± 7.85	13.03 ± 7.22	0.399	16.99 ± 8.82	17.64 ± 6.88	0.856	12.25 ± 8.24	12.48 ± 2.78	0.345
AT (s)	2.60 ± 3.50	4.58 ± 4.31	0.214	3.22 ± 4.70	5.46 ± 5.14	0.248	6.13 ± 6.44	7.10 ± 5.30	0.917
TTP (s)	22.50 ± 10.16	23.11 ± 7.05	0.897	22.04 ± 7.84	21.93 ± 7.98	0.976	31.60 ± 13.02	25.95 ± 12.24	0.346
PI (a.u.)	38.37 ± 7.42	45.35 ± 5.24	0.006	40.36 ± 7.47	50.70 ± 5.01	0.001	29.38 ± 8.07	38.46 ± 6.20	0.028
AS	0.90 ± 0.39	1.16 ± 0.24	0.083	0.96 ± 0.25	1.12 ± 0.34	0.167	0.58 ± 0.24	0.89 ± 0.17	0.043
DT/2 (s)	80.21 ± 10.84	84.38 ± 15.59	0.499	84.43 ± 20.71	85.20 ± 16.30	0.923	90.74 ± 14.95	82.28±14.49	0.249
DS	-0.19 ± 0.07	-0.25 ± 0.04	0.047	-0.18 ± 0.05	-0.24 ± 0.07	0.065	-0.16 ± 0.05	-0.21 ± 0.03	0.027
AUC	3577.93 ± 1340.82	3085.15 ± 968.85	0.147	3604.40 ± 1285.75	3143.14 ± 1131.73	0.152	2278.27 ± 1003.89	1982.39 ± cc787.07	0.463

PI: peak intensity; BI: baseline intensity; AT: arise time; TTP: time to peak; DT/2: half time of peak intensity; AS: ascending slope; DS: descending slope; AUC: area under the curve.

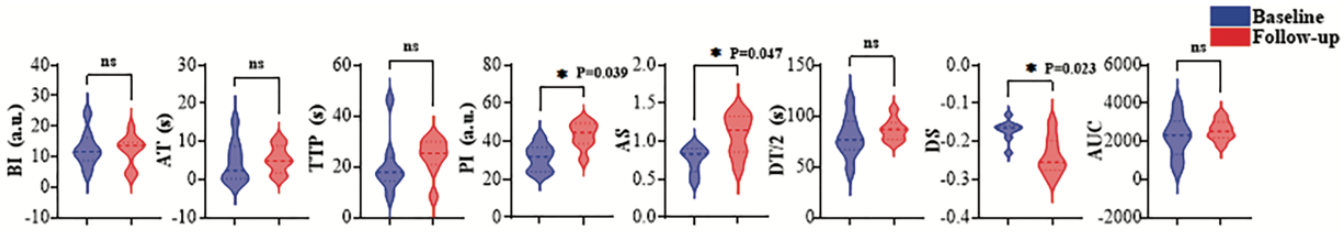

Fig. 2. Changes of contrast-enhanced ultrasound parameters in nodule area during baseline and follow-up.
PI: peak intensity; BI: baseline intensity; AT: arise time; TTP: time to peak; DT/2: half time of peak intensity; AS: ascending slope; DS: descending slope; AUC: area under the curve.

patients with focal or multifocal lesions. These echoes exhibited similarity with pancreatic parenchyma, characterised by indistinct boundaries, irregular shape, and the presence of internal hyperechoic spots. Of the observed lesions, 50% were situated in the pancreatic head, 8.3% in the pancreatic body, and 41.7% in the pancreatic tail. The lesions exhibited a maximum diameter of 4.3±2.0 cm in baseline (range: 2.0–7.3 cm), whereas following treatment, the lesions displayed a maximum diameter of 1.7±1.6 cm (range: 0–5.1 cm). Furthermore, among patients with diffuse IgG4-AIP, there was an evident a pancreatic enlargement accompanied by a diminished parenchymal echogenicity and a heightened echogenicity. Hyperechoic spots in pancreas were observed in 21.3% of patients. Additionally, thirteen patients displayed dilation of the main pancreatic duct, with a range of dilation from 2 to 7 mm.

A total of fifty-six AIP patients underwent CEUS examinations both at the initial and subsequent follow-up assessment. The evaluation of enhancement intensity grading during the arterial and venous phases revealed no statistically significant differences as presented in Table II. The results of the enhancement intensity grading for patients with focal AIP in both the arterial and venous phases did not exhibit any statistically significant differences, as indicated in Supplementary Table S2.

TIC and quantitative analysis of contrast-enhanced ultrasound at baseline and follow-up

TIC was generated for 28 patients at the initial assessment and for 60 patients during the subsequent follow-up (Suppl. Fig. S1). A comparison of ultrasound contrast parameters between lesions and normal pancreatic tissue at baseline demonstrated notable disparities in the PI (22.93±7.38 *vs*. 37.41±14.42, p=0.043) and AUC (1304.59±956.22 *vs*. 2730.78±1689.31, p=0.043). No significant differences were observed in other parameters (Suppl. Fig. S3). PI at baseline in the pancreatic head, body, and tail exhibited a statistically significant decrease compared to the follow-up group. Furthermore, the AUC in the pancreatic tail at baseline also demonstrated a significantly lower value than that observed at follow-up, with a statistically significant distinction. No statistical differences were observed in other parameters (Fig. 1).

Fifteen IgG4-AIP patients underwent TIC analysis both before and after treatment, with 12 cases classified as diffuse type (9 of which also had concomitant focal lesions) and 3 cases classified as focal type. Significant differences were observed in the TIC parameters of 12 patients with diffuse IgG4-AIP, specifically in the PI at the head, body, and tail of the pancreas, as well as DS at the head and tail. However, no significant differences were found in the other parameters (Table. III). Significant differences in PI, AS, and DS were observed before and after treatment in the 12 IgG4-AIP patients with nodular lesions (including 9 diffuse type and 3 focal type), whereas no significant differences were found in other parameters (Fig. 2).

Correlational analyses showed that some parameters of TIC at various anatomical locations were significantly positively correlated with some laboratory indicators at baseline. Specifically, in the pancreatic head, there was a positive correlation between PI and AST levels (r=0.311, p=0.047). In the pancreatic body, PI exhibited positive correlations with AST, ALT, and GGT levels (r=0.324, p=0.038; r=0.356, p=0.024; r=0.327, p=0.033). Similarly, in the

Table IV. Correlation analysis of ultrasonic parameters and clinical indicators.

	AST(U/L)	ALT(U/L)	GGT(U/L)	TBIL(μmol/L)	DBIL(μmol/L)
Pancreatic head PI	0.331*	0.299	0.368	0.437	0.531
Pancreatic body PI	0.324*	0.356*	0.327*	0.398	0.566
Pancreatic tail PI	0.601*	0.433	0.561	0.578*	0.562*

* $p<0.05$, ** $p<0.01$. PI: peak intensity.

pancreatic tail, PI displayed positive correlations with AST, TBIL, and DBIL levels (r=0.601, p=0.024; r=0.578, p=0.029; r=0.562, p=0.032) (Table. IV). The findings indicate a potential correlation between distinct parameters of TIC and laboratory indicators.

Discussion

It was observed in the present study that on conventional ultrasound, diffuse AIP typically presents as diffuse pancreatic enlargement with parenchymal hypoechogenicity, coarse echotexture, and presence of hyperechoic spots, whereases focal AIP exhibits hypoechogenic nodules in lesions with similar echogenicity and unclear boundaries of normal pancreatic tissue (11). AIP lesions frequently displayed diminished enhancement during both the arterial and venous phases, occasionally presenting iso-enhancement or hyper-enhancement. Owing to no obvious patterns observed in semi-quantitative grading and no apparent changes in the grade of lesions before and after treatment, it is hard to assess the change of lesions by semi-quantitative grading. Li *et al*. (12) observed that IgG4-AIP, particularly the mass-forming subtype, demonstrates heterogeneous hypo-enhancement during both the arterial and venous phases in the initial stages of the disease. Following treatment, there was no substantial enhancement intensity improvement; however, the mass-like lesions exhibited noticeable reduction in size. Numata *et al*. (13) found that in patients with IgG4-AIP, the intensity of arterial phase enhancement manifested as iso-enhancement or hyper-enhancement, whereas the intensity of venous phase enhancement remained consistent with iso-enhancement or hyper-enhancement. Following corticosteroid treatment, both arterial and venous phase enhancement intensities exhibited a significant enhancement alteration. The two studies both reached the conclusion that semi-quantitative enhancement intensity in CEUS was inadequate for evaluating pancreatic lesions, aligning with the findings of this study.

In our research, we discovered that parameters derived from the TIC could reflect microvascular perfusion in pancreatic lesions and assist the evaluation of treatment efficacy. Following treatment, there was a notable increase in the PI across the head, body, and tail of the pancreas. Additionally, AUC exhibited an increase in the pancreatic tail. In patients with pancreatic nodules, both the PI and AS levels demonstrated an increase, whereas the DS exhibited a decrease within the nodular region following treatment. These changes may be attributed to the resolution of vascular inflammation and fibrosis within pancreatic lesions following treatment, resulting in improved microcirculation of the affected areas(14). Faccia *et al*. (15) proposed that TIC analysis on CEUS images had the potential to detect microvascularisation in hepatocellular carcinoma (HCC) and could be served as a valuable tool for monitoring the therapeutic response in HCC patients. Jung *et al*. (16) proposed that the utilisation of CEUS parameter imaging in conjunction with TIC analysis held potential for assessing the effectiveness following benign prostatic artery embolisation. The utilisation of CEUS in conjunction with TIC analysis allows for the observation of microcirculatory alterations in tissue and organs, thereby assisting in assessing disease severity, the progression of disease and the response to treatment.

While biomarker research in IgG4-RD has recently improved, disease management cannot rely on single indicators and should be complemented by established laboratory analysis and diagnostic imaging (17). Both CT and MRI imaging techniques offer superior spatial resolution and are capable of providing detailed anatomical information. Manfredi *et al*. (18) reported that typical IgG4-AIP appeared as diffuse or focal pancreatic swelling on CT, with the diffuse form also known as 'sausage-like appearance' and delayed enhancement in the venous phase. The lesions in pancreas exhibits low signal intensity on T1-weighted MRI images and slightly high signal intensity on T2-weighted images. There are different patterns of enhancement in the early phase of enhancement and delayed enhancement changes in the later phase1. Irie *et al*. (19) have documented that IgG4-AIP exhibited a low-attenuation 'capsule-like rim' surrounding the pancreas on contrast-enhanced CT scans which is a characteristic imaging feature of IgG4-AIP, indicative of fibrotic and inflammatory alterations in the adjacent adipose tissue. Despite the potential limitations of conventional ultrasound in detecting these characteristics, CEUS imaging effectively identifies these regions as hypoechoic areas in the corresponding location. The administration of steroids results in a noticeable amelioration of these abnormalities (20). PET/CT relies on the functional metabolic information of lesions, thereby allowing accurate identification and localisation of lesions. Nakajo *et al*. (21) conducted a study wherein they observed that pancreatic lesions exhibited augmented metabolic uptake in PET/CT scans initially, but subsequent to steroid treatment, the heightened metabolic uptake of lesions gradually subsided. Consequently, PET/CT imaging can serve as a valuable tool for monitoring disease activity. Nevertheless, PET/CT exhibits low spatial resolution and is deemed inadequate for evaluating microvascular perfusion. Around 33% of individuals with IgG4-AIP are concomitantly diagnosed with diabetes, while following glucocorticoid therapy, 14% of patients develop new onset diabetes (22). Hyperglycaemia could potentially influence the results of SUV values. Furthermore, PET/CT is inappropriate for the dynamic evaluation of IgG4-AIP due to high costs and the risk of radiation exposure. This study has determined that the combination of CEUS and TIC analysis is a

reliable method for evaluating the treatment effect of IgG4-AIP.Furthermore, CEUS is cost-effective, no risk of radiation exposure, and less risk of adverse reactions to contrast agents compared with other contrast agents. Consequently, it can be recommended as a routine follow-up assessment tool for IgG4-AIP, offering a reference for clinicians to make more accurate diagnosis and provide more appropriate treatment.

Future studies could build on and extend this work in several ways to advance the utilisation of CEUS in assessing the efficacy of IgG4-AIP treatment. The sample size employed in the study should be expanded to enhance the reliability of the findings. Furthermore, the refinement of expertise in CEUS imaging technology and the establishment of standardised protocols can effectively mitigate result variability and bolster its reliability as a diagnostic and evaluative instrument. It will be a significant avenue for future investigation to combine CEUS with other imaging modalities, such as CT, MRI, and PET/CT, which help identify their respective merits and drawbacks in assessing the treatment response of IgG4-AIP. Furthermore, the incorporation of artificial intelligence and machine learning algorithms has the potential to augment the precision and efficacy of CEUS analysis when evaluating the therapeutic effect of IgG4-AIP (23). Longitudinal studies over an extended period of time can provide more comprehensive insights into the enduring impacts on the assessment IgG4-AIP treatment and the significance of CEUS in the management of the disease.

This study is a prospective investigation, which provides a more dependable evaluation of disease activity by means of regular follow-up. A total of 73 patients diagnosed with IgG4-AIP were included in this study, making it a quite large sample size considering the rarity of this condition. The utilisation of CEUS in conjunction with TIC analysis for disease monitoring represents a novel and pioneering approach in the assessment of this disease. It shows the advantages of operational simplicity, robust reproducibility, and cost-efficiency. However, it is important to note that this study is conducted at a single centre and has a limited sample size, potentially compromising the statistical power of the research. Therefore, it is imperative to conduct further studies with larger sample sizes in order to validate and substantiate our findings. While CEUS exhibits promising clinical application prospects, the requirements of professional competencies and the lack of standardised guidelines of CEUS for IgG4-AIP, to some extent, limit its widespread adoption. All patients in this study were diagnosed based on the RCD criteria rather than the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria. Giovanni Costanzo *et al*. reported that both the RCD criteria and ACR/EULAR Classification Criteria show good sensitivity and specificity in IgG4 RD, especially in patients with pancreatic involvement (24). The disease activity of IgG4-AIP could be affected by several factors, such as treatment regimens and individual differences. Our study was unable to entirely exclude the interference of these factors, and further research to elucidate the role of the factors in IgG4-AIP is needed.

In summary, conventional ultrasound only shows the reduction of pancreatic lesions after treatment. Quantitative analysis based on TIC contrast-enhanced ultrasound can illustrate the difference in microcirculation between lesion sites and normal sites with more straightforwardness and sensitivity. Therefore, CEUS can effectively evaluate disease activity by accurately and promptly assessing alterations in microvascular perfusion among patients with IgG4-AIP following treatment. The microcirculation recovery of pancreatic lesions in patients can be determined by analysing the PI of CEUS, which would provide important guidance for subsequent treatment.

Take home messages

- Precision with CEUS-TIC in IgG4-AIP treatment response assessment.
- PI and AUC for detailed IgG4-AIP treatment evaluation.
- CEUS-TIC offers economical follow-up assessment for IgG4-AIP.

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