

Table S1. Detailed Clinical features of the enrolled IgG4-RD patients and the matched healthy controls.

	IgG4-RD (n=136)	HC (n=73)
Demography		
Sex (male, %)	77 (56.6%)	38 (52.1%)
Age at onset (years, mean \pm SD)	54.30 \pm 11.48	52.30 \pm 10.67
Disease duration (months, median, IQR)	12(6-36)	NA
Affected organ numbers (mean \pm SD)	2.79 \pm 1.56	NA
Serology (Median, IQR)		
IgG (g/L)	18.19 (13.94-23.42)	NA
IgG1 (mg/L)	8640.00 (7310.00-10625.00)	NA
IgG2 (mg/L)	5300.00 (3915.00-6805.00)	NA
IgG3 (mg/L)	398.00 (235.50-790.75)	NA
IgG4 (mg/L)	8460.00 (3260.00-18475.00)	NA
IgA (g/L)	1.79 (1.25-2.54)	NA
IgM (g/L)	0.73 (0.53-1.08)	NA
IgE (KU/L)	255.00 (90.38-672.00)	NA
RF (IU/L)	12.45 (5.50-26.90)	NA
ESR (mm/h)	17.00 (8-33)	NA
CRP (mg/L)	1.57 (0.73-5.48)	NA
C3 (g/L)	0.96 (0.74-1.17)	NA
C4 (g/L)	0.15 (0.10-0.23)	NA
Eosinophils ($10^9/L$)	0.23 (0.12-0.42)	NA
ALT (g/L)	19.50 (13.00-31.00)	NA
AST (g/L)	21.00 (16.00-35.25)	NA
Tbil (μ mol/L)	11.55 (8.85-19.33)	NA
Dbil (μ mol/L)	3.33 (2.60-6.50)	NA
ALP (U/L)	87 (60-140.75)	NA
GGT (U/L)	22.9 (15.50-96.00)	NA
BUN (mmol/L)	5.38 (4.50-6.53)	NA
Cr (μ mol/L)	67.00 (59.00-79.00)	NA
TG (mmol/L)	1.03 (0.69-1.34)	NA
TC (mmol/L)	4.66 (4.12-5.76)	NA
LDL (mmol/L)	2.84 (2.48-3.73)	NA
HDL (mmol/L)	1.34 (1.17-1.51)	NA
UA (μ mol/L)	341.00 (275.70-435.00)	NA
Organ involvements (n%)		
Lacrimal gland	60 (44.12%)	NA
Parotid gland	17 (12.50%)	NA
Submandibular gland	69 (50.74%)	NA
Pancreas	44 (32.35%)	NA
Bile duct	18 (13.24%)	NA

Lung	32 (23.53%)	NA
Kidney	9 (6.62%)	NA
Retroperitoneum	13 (9.56%)	NA
Paranasal sinus	33 (24.26%)	NA
Thyroid	4 (2.94%)	NA
Pituitary	3 (2.21%)	NA
Lymph node	32 (23.53%)	NA

S.D. represented for Standard deviation, IQR represented for interquartile range.

IgG, IgA, IgM, IgE were immunoglobulin G, A, M and E. ESR was Erythrocyte Sedimentation Rate, CRP was C-reactive protein, RF was rheumatoid factor and C3/4 represented for complement 3/4.

ALT represented for alanine aminotransferase; AST represented for aspartate aminotransferase; Tbil was Total bilirubin; Dbil was direct bilirubin; ALP was Alkaline Phosphatase; GGT was gamma-glutamyl transpeptidase; BUN was blood urea nitrogen; Cr was Creatinine; TG was triglyceride; TC was total cholesterol; LDL was Low Density Lipoprotein; HDL was High Density Lipoprotein; UA was Uric Acid.

(*P<0.05, **P<0.01, *P<0.001)**

Table S2. Comparison the clinical features between HE4 positive patients and HE4 negative patients.

	HE4 positive (n=100)	HE4 negative (n=36)	P-value
Demography			
Sex (male, %)	64 (64%)	13 (36.11%)	**0.004
Age at onset (years, mean \pm SD)	56.64 \pm 10.66	47.81 \pm 11.33	***<0.001
Disease duration (months, median, IQR)	12 (6-36)	24 (6-48)	0.148
Affected organ numbers (mean \pm SD)	2.78 \pm 1.58	2.83 \pm 1.50	0.861
Serology (Median, IQR)			
IgG (g/L)	18.72 (13.94-26.83)	17.63 (13.08-20.67)	0.162
IgA (g/L)	1.42 (1.14-2.34)	2.24 (1.79-2.92)	***<0.001
IgM (g/L)	0.69 (0.48-0.97)	0.93 (0.56-1.23)	*0.048
IgE (KU/L)	345 (98.95-811.75)	200 (51.58-609)	0.102
IgG4 (mg/L)	9142 (3390-20675)	4330 (2462.5-13475)	*0.012
RF (IU/L)	15.45 (7.75-31.58)	8.7 (5-24.8)	0.099
ESR (mm/h)	23 (11.25-48.5)	10 (6.5-14)	***<0.001
CRP (mg/L)	2.1 (0.77-7.28)	1.02 (0.54-2.77)	*0.021
C3 (g/L)	0.92 (0.66-1.12)	1.06 (0.9-1.21)	*0.028
C4 (g/L)	0.15 (0.08-0.23)	0.17 (0.13-0.24)	0.252
Eosinophils (10 ⁹ /L)	0.24 (0.12-0.51)	0.15 (0.1-0.31)	*0.036
ALT (g/L)	21 (13-42)	17 (12.5-23)	0.222
AST (g/L)	21 (16-47)	20 (14.5-22)	0.166
Tbil (μ mol/L)	11.45 (8.85-24.18)	11.85 (8.93-15.43)	0.739
Dbil (μ mol/L)	3.4 (2.55-9.5)	3.1 (2.7-4.95)	0.610
ALP (U/L)	89 (60-158)	79 (58-94)	0.349
GGT (U/L)	27 (15.5-118.5)	17 (15.25-24.5)	0.186
Cr (μ mol/L)	72 (61.9-84)	58.55 (54-64)	***<0.001
Organ involvements (n%)			
Lacrimal gland	38 (38%)	22 (61.11%)	*0.017
Parotid gland	13 (13%)	4 (11.11%)	0.796
Submandibular gland	46 (46%)	23 (63.89%)	0.066
Pancreas	37 (37%)	7 (19.44%)	0.054
Bile duct	16 (16%)	2 (5.55%)	0.154
Lung	27 (27%)	5 (13.89%)	0.112
Kidney	7 (7%)	2 (5.55%)	0.765
Retroperitoneum	10 (10%)	3 (8.33%)	0.771
Paranasal sinus	23 (23%)	10 (27.78%)	0.566
Thyroid	3 (3%)	1 (2.78%)	0.946
Pituitary	2 (2%)	1 (2.78%)	0.785
Lymph node	23 (23%)	9 (25%)	0.808

S.D. represented for Standard deviation, IQR represented for interquartile range.

IgG, IgA, IgM, IgE were immunoglobulin G, A, M and E. ESR was Erythrocyte Sedimentation Rate, CRP was C-reactive protein, RF was rheumatoid factor and C3/4 represented for complement 3/4.

ALT represented for alanine aminotransferase; AST represented for aspartate aminotransferase; Tbil was Total bilirubin; Dbil was direct bilirubin; ALP was Alkaline Phosphatase; GGT was gamma-glutamyl transpeptidase; BUN was blood urea nitrogen; Cr was Creatinine; TG was triglyceride; TC was total cholesterol; LDL was Low Density Lipoprotein; HDL was High Density Lipoprotein; UA was Uric Acid. (*P<0.05, **P<0.01, ***P<0.001)

Table S3. Comparison of the HE4 levels between patients with or without the corresponding organ involvements.

Organ involvements (Median, IQR)	HE4 value of patients without organ involvements (pmol/L)	Number of patients without organ involvements	HE4 value of patients with organ involvements (pmol/L)	Number of patients with organ involvements	P-value
Pancreas	56.1 (48.075-79.525)	n=92	68.45 (53.3-92.15)	n=44	*0.011
Bile duct	57.25 (49.575-79.825)	n=118	72.65 (54.075-105.15)	n=18	*0.042
Submandibular gland	68.4 (51.5-92.2)	n=67	55 (48.15-71.9)	n=69	*0.016
Lacrimal gland	69.85 (52.825-92.15)	n=76	52.85 (45.475-62.325)	n=60	***0.00009
Parotid gland	57.6 (50.2-80.2)	n=119	66.8 (50.6-109.5)	n=17	0.407
Retroperitoneum	57.6 (50.2-76.5)	n=123	101 (50.55-204)	n=13	*0.019
Lung	56.95 (49.35-78.15)	n=104	67.25 (51.525-96.65)	n=32	0.06
Kidney	58.2 (50.2-80.2)	n=127	69.6 (51.75-701.5)	n=9	0.119
Lymph node	57.9 (50.25-79.9)	n=104	63 (49.925-102.5)	n=32	0.425
Paranasal sinus	63.2 (50.4-92)	n=103	52.6 (47.95-59)	n=33	**0.005
Thyroid	58.4 (50.25-82.225)	n=132	73.1 (46.9-127.875)	n=4	0.589

IQR represented for interquartile range.

(*P<0.05, **P<0.01, ***P<0.001)

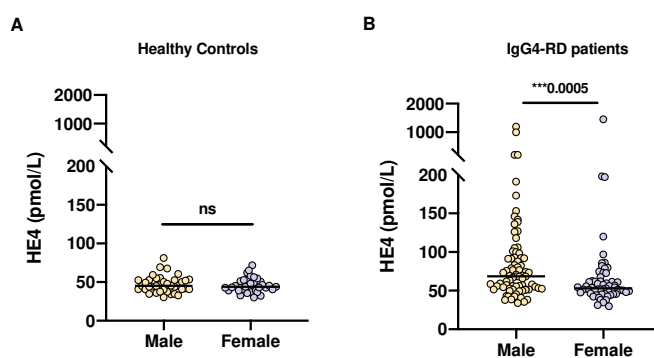


Figure S1. Results of comparing HE4 levels between different genders in healthy controls and IgG4-RD patients (*P-value <0.05).

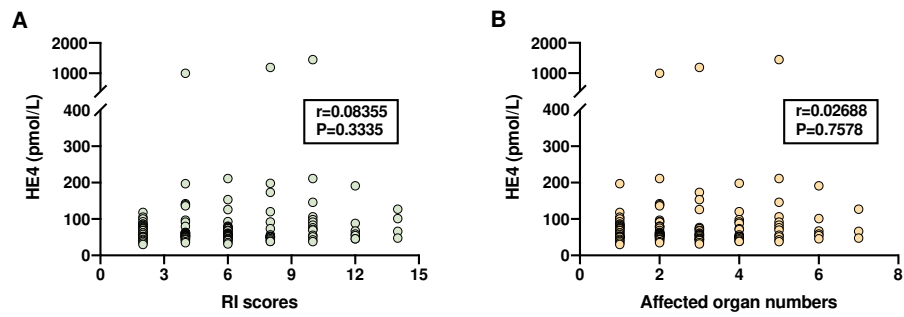


Figure S2. The correlations between plasma HE4 levels and (A) IgG4-RD RI scores or (B) affected organ numbers.

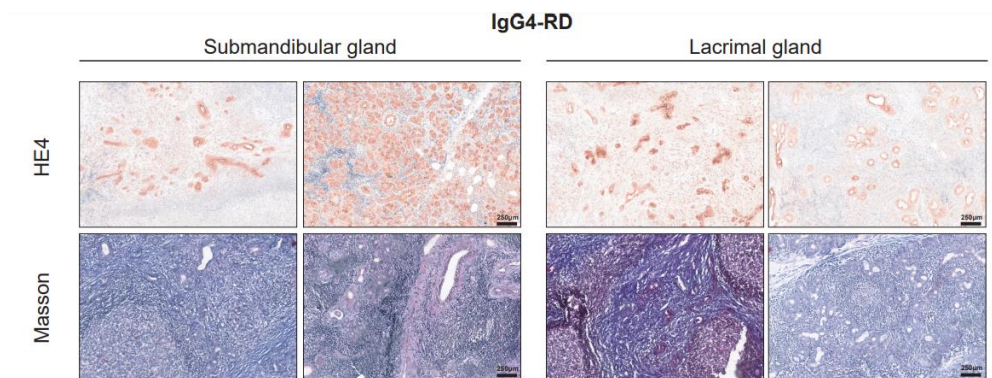


Figure S3. Immunohistochemistry and Masson trichrome stain for HE4 expression and fibrosis degree in the submandibular and lacrimal glands of IgG4-RD patients.

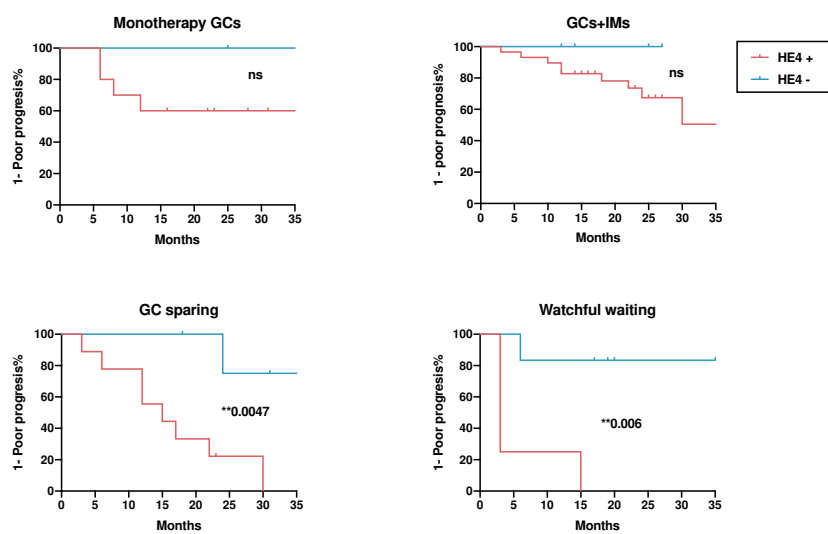


Figure S4. Comparison of the poor prognosis rate between HE4+ and HE4- patients under the different treatment regime: (A) GCs monotherapy; (B) GCs+IMs; (C) GC sparing; (D) Watchful waiting.