# Immunoglobulin G4–related disease in Hong Kong: clinical features, treatment practices, and its association with multisystem disease

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## ABSTRACT

**Introduction:** Immunoglobulin G4–related disease remains an under-recognised and evolving disease. Local data are sparse and previous publications have been limited to individual case reports or case series only. We conducted this study to review the clinical features, treatment practices, and factors associated with multisystem involvement in Hong Kong. We described the clinical features and treatment modalities of the largest cohort of immunoglobulin G4–related disease in our locality thus far.

**Methods:** We retrospectively evaluated all patients with immunoglobulin G4–related disease between January 2003 and December 2015 in Queen Mary Hospital and combined this with patient data extracted from previous local publications. We analysed the clinical features, treatment practices, and factors associated with the number of organ systems involved.

**Results:** A total of 104 patients (55 from Queen Mary Hospital and 49 from literature review) were identified. Patients were predominantly older men (mean [standard deviation] age, 61.9 [12.7] years; male-to-female ratio=3:1) and 94.4% had elevated pre-treatment serum immunoglobulin G4 levels. Hepatobiliary and pancreatic system (40.4%), salivary gland (33.7%), lymph node (29.8%), and eye (19.2%) were the most common organ systems involved. Lymphadenopathy was associated with glucocorticoid use (odds ratio=2.65; 95% confidence interval, 1.08-6.54; P=0.034). Pre-treatment serum immunoglobulin G4 levels correlated with the number of organ systems involved (ß=0.347; P=0.004) and, specifically, more associated with patients having salivary gland involvement than those without (mean, 1109 mg/dL vs 599 mg/dL; P=0.012).

**Conclusion:** We identified pre-treatment serum immunoglobulin G4 to be associated with multisystem disease, especially with salivary gland involvement, highlighting its potential for disease prognostication and monitoring. Increased physician awareness and multidisciplinary efforts are required for early diagnosis and optimal management of this masquerading disease.


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**New knowledge added by this study**

- Hepatobiliary and pancreatic system, salivary gland, lymph node, and eye were the most common organ systems involved in immunoglobulin (Ig) G4–related disease in Hong Kong.
- Pre-treatment serum IgG4 levels were associated with salivary gland involvement and multisystem disease.
- Glucocorticoids were most frequently used, but local experience with other immunomodulatory agents was limited and varied across different centres.

**Implications for clinical practice or policy**

- Serum IgG4 should be used for disease prognostication and monitoring of treatment response.
- Salivary gland involvement should be screened in patients with IgG4-related disease, especially in the presence of higher level of serum IgG4.
- Future studies on treatment strategies within the contexts of different epidemiology and patient characteristics are urgently needed.

## 香港免疫球蛋白G4相關性疾病：臨床特徵、治療方法以及與多系統疾病的關聯

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**引言：**免疫球蛋白G4（IgG4）相關性疾病不斷進化，可惜仍然未被廣泛認識。有關IgG4相關性疾病的本地數據較少，出版的文獻亦僅限於個別病例報告或病例系列。本研究旨在回顧此疾病的臨床特徵和治療方法，以及探討與香港患者多個受影響組織和器官相關的因素。這是迄今有關IgG4相關性疾病最大型的本地隊列研究，我們針對患者的臨床表現及治療方式加以描述。

**方法：**回顧分析2003年1月至2015年12月期間瑪麗醫院內所有IgG4相關性疾病患者，將他們與過往本地出版文獻取得的患者資料結合。並分析此疾病的臨床特徵和治療方法，以及與多個受影響組織和器官相關的因素。

**結果：**研究了共104例（瑪麗醫院55例，文獻綜述49例）。患者多數為年長男性（平均〔標準差〕年齡：61.9〔12.7〕歲；男女比例為3：1），有94.4%的患者治療前血清IgG4水平升高。最常見受影響的器官有肝膽和胰腺（40.4%）、唾液腺（33.7%）、淋巴結（29.8%）和眼部（19.2%）。淋巴結病與使用糖皮質激素有關（比值比=2.65；95%置信區間1.08-6.54；P=0.034）。治療前血清IgG4水平與受影響的器官數目相關（ß=0.347；P=0.004），尤其與唾液腺受影響相關（唾液腺受影響患者與非患者的平均IgG4水平：1109 mg/dL比599 mg/dL；P=0.012）。

**結論：**本研究發現治療前血清IgG4水平與多系統疾病相關，尤其是唾液腺，可見治療前血清IgG4水平可作為對此疾病的預後和監測。增加醫生對此病的認識和跨專科參與是針對此疾病的早期診斷和最佳管理的關鍵。


## Introduction

Immunoglobulin (Ig) G4–related disease (IgG4-RD) is a systemic immune-mediated disease unifying what were previously considered to be unrelated individual organ disorders. This characteristic fibroinflammatory condition continues to be increasingly recognised but is still an evolving concept. The disease, IgG4-RD, was first described in 2003 when extra-pancreatic lesions with IgG4-positive plasmacytic infiltration were identified in patients with autoimmune pancreatitis (now known as IgG4-related pancreatitis).[1] Involvement of almost every anatomical site has been reported since. In addition to IgG4-related hepatobiliary disease, other examples of previous disease entities now under the diagnostic umbrella of IgG4-RD include Riedel's thyroiditis, Ormond's disease (idiopathic retroperitoneal fibrosis), Mikulicz's disease (lymphoepithelial sialadenitis), Küttner's tumour (chronic sclerosing sialadenitis), and other 'idiopathic' pseudotumours.[2] Regardless of the organ involved, patients share similar clinical, serological, and histopathological features.[2,3] According to the 'comprehensive diagnostic criteria for IgG4-RD', the diagnosis of IgG4-RD is based on the constellation of clinical, serological and, especially, histopathological findings.[4] The recommended cut-off value for serum IgG4 level is >135 mg/dL. The characteristic histopathological findings include dense lymphoplasmacytic infiltrates, 'storiform' or swirling fibrosis, and obliterative phlebitis. Immunostaining for IgG4 should show >10 IgG4-positive plasma cells per high-power field and an IgG4-positive–to–IgG-positive ratio (IgG4:IgG) plasma cell ratio of >0.4.

Despite continued advances in our understanding of the disease and the various multinational guidance now available,[4,5] few studies have examined factors to predict disease severity or disease prognostication. The bulk of IgG4-RD–related research originates from Caucasian or Japanese studies, and local regional data are sparse. Publications from Hong Kong have been limited to individual case reports or case series only. In this study, we performed a retrospective review of all our IgG4-RD patients between January 2003 and December 2015. To the best of our knowledge, this is the largest cohort reported in our locality at the time of writing. By combining our data with all other available publications from Hong Kong, we examined the clinical features and treatment practices of IgG4-RD, as well as its clinical factors associated with multisystem involvement.

## Methods

### Retrospective study at Queen Mary Hospital

All available case records of IgG4-RD patients from Queen Mary Hospital—under the care of the Hong Kong West Cluster serving a population of 0.53 million—between January 2003 and December 2015 were reviewed. Cases were identified by the compilation of various databases of multiple specialist divisions (Rheumatology and Clinical Immunology, Gastroenterology and Hepatology, Otorhinolaryngology–Head and Neck Surgery, and Hepatobiliary and Pancreatic Surgery), in addition to cluster-wide screening of all patients with laboratory requests for serum IgG4 within the study period. Case records were reviewed according to the 'comprehensive diagnostic criteria for IgG4-RD' and all patients with definite, probable, or possible IgG4-RD were recruited.[4] In accordance with these criteria, patients could also be diagnosed with a definite diagnosis of IgG4-RD if they fulfilled organ-specific criteria.[6]

All data were extracted from patient records, including sex, age (at onset), organ manifestations, pre-treatment serum IgG4 and IgG levels,

pathology reports, and treatment modalities. Organ manifestations were classified into bone, central nervous system (CNS), hepatobiliary and pancreatic (HBP) system, lung, lymph node, eye (including lacrimal gland, extraocular muscles, and other intraorbital involvement), renal system, retroperitoneum, salivary glands (parotid and submandibular glands), and skin/soft tissue involvement. Treatment modalities were classified into surgical intervention (including resection and other mechanical interventions such as biliary or ureteric stenting), use of glucocorticoids (GCs), or other specified immunomodulatory therapy. This study was done in accordance with the principles outlined in the Declaration of Helsinki. Clinicians involved in data extraction were unaware of the studied associations.

### Literature review of existing local publications

We searched PubMed, PubMed Central, and MEDLINE databases without language restrictions from 1 January 2003 to 31 December 2016 using the terms 'Hong Kong' and 'immunoglobulin G4' or 'IgG4' or 'IgG4-related disease' or 'IgG4-associated disease' or 'IgG4 sclerosing disease'. All patient data available from local IgG4-RD publications were reviewed against the 'comprehensive diagnostic criteria for IgG4-RD'[4] and extracted for analysis. Patients from publications originating from Queen Mary Hospital, who were already present in our database, were excluded. Parallel with the retrospective analysis, data regarding patients' age, organ manifestations, pre-treatment serum IgG4 and IgG levels, pathology reports, treatment modalities, and medication regimens were recorded. Clinicians involved in data extraction were unaware of the studied associations.

### Statistical analysis

Potential factors associated with multisystem disease, reflected by the number of involved organ systems, were investigated. Univariate analysis was performed first using the independent samples *t*-test to compare categorical variables (such as sex) and linear regression was used to compare between continuous variables (such as age). Variables with a P value of ≤0.1 from univariate analysis were included in a multivariate linear regression to determine which were independently associated with the number of involved organ systems. The two-sided Fisher's exact test was used to evaluate the association between treatment modalities and presence of organ manifestations. A P value of <0.05 was considered statistically significant. Statistical Package of the Social Sciences (Windows version 20.0; IBM Corp, Armonk [NY], US) was used for all analyses. The Venn diagram was created using jvenn.[7]

## Results

### Demographics, clinical features, and treatment modalities

Between January 2003 and December 2015, a total of 55 patients with IgG4-RD were identified at Queen Mary Hospital. Patients were under the care of a variety of medical and surgical subspecialties, including Rheumatology and Clinical Immunology, Gastroenterology and Hepatology, Otorhinolaryngology–Head and Neck Surgery, and Hepatobiliary and Pancreatic Surgery, in addition to multidisciplinary care between other departments and disciplines. Baseline demographics, clinical features, and treatment modalities are summarised in Table 1.[8-21] Pre-treatment serum IgG4 level, total IgG level, and IgG4:IgG ratio were available for 48, 43, and 43 patients, respectively. A total of 46/48 (95.8%) patients had a serum IgG4 level of >135 mg/dL, and 39/43 (90.7%) patients had a IgG4:IgG ratio of >8%. Of the 55 patients, 40 (72.7%) had histopathological confirmation, of which 32 samples had immunohistochemical staining with anti-IgG4 monoclonal antibodies. All treatment modalities were primarily used for the treatment of IgG4-RD except for one patient who was treated with COPP chemotherapy (cyclophosphamide, vincristine, procarbazine, and prednisone) because of concomitant lymphoma. Of the patients, 19 (34.5%) underwent surgical treatment, including sialoadenectomy (n=7), pancreaticoduodenectomy (n=6), orbitotomy (n=2), cholecystectomy (n=2), and excision of musculoskeletal lesions (n=2).

We identified an additional 49 IgG4-RD patients from 11 published case reports and case series from Hong Kong.[8-18] Only those reporting pre-treatment serum IgG4 and IgG levels were included in our study. Treatment modalities were not reported in four patients. A summary of patient demographics, clinical features, and treatment modalities is shown in Table 2.[8-18]

As a result, a total of 104 patients were identified from Queen Mary Hospital and literature review. For patients with pre-treatment results available, 68/72 (94.4%) patients had a serum IgG4 level of >135 mg/dL, and 58/63 (92.1%) patients had an IgG4:IgG ratio of >8%. A summary of the demographics, clinical features, and treatment modalities in comparison to other cohorts is shown in Table 1.[8-21] The most common organ systems involved were HBP system (40.4%), salivary gland (33.7%), lymph node (29.8%), and eye (19.2%). A Venn diagram of these most common involved systems from the combined cohort is shown in the Figure.

### Treatment practices: associations between organ manifestations and treatment modalities

The associations between various organ

TABLE 1. Comparison of immunoglobulin G4–related disease cohorts from Hong Kong,[8-18] Beijing (Mainland China),[19] Massachusetts (US),[20] and Milan (Italy)[21]

| | No. (%) of patients, mean ± SD (range), or median (IQR) | | | | |
|---|---|---|---|---|---|
| | **Current cohort, Hong Kong (n=55)** | **Combined cohort (current cohort + cases from literature review[8-18]), Hong Kong (n=104)** | **Beijing, Mainland China[19] (n=118)** | **Massachusetts, US[20] (n=125)** | **Milan, Italy[21] (n=41)** |
| Male | 42 (76.4) | 78 (75.0) | 82 (69.5) | 76 (60.8) | 26 (63.4) |
| Age (years) | 62 ± 12 (27-86) | 62 ± 13 (26-89) | 53 (19-80) | 55 (24-83) | 62 (55-67) |
| Serum IgG4 (mg/dL) | 660.5 ± 488.1 (116-2100) [n=48] | 790 ± 717.5 (110-3450) [n=72] | 1521.8 | NA | 284 (132-545) |
| Total IgG (mg/dL) | 2202.1 ± 1108.6 (1080-5900) [n=43] | 2611.1 ± 1436.7 (1080-7750) [n=69] | 2300 | NA | NA |
| IgG4:IgG ratio | 0.29 ± 0.18 (0.04-0.65) [n=43] | 0.31 ± 0.18 (0.04-0.70) [n=63] | 0.38 | NA | NA |
| Histopathological confirmation | 40 (72.7) | 85 (81.7) | 64 (54.2) | 125 (100) | 30 (73.2) |
| Organ involvement | | | | | |
| Hepatobiliary and pancreatic system | 26 (47.3) | 42 (40.4) | Autoimmune pancreatitis: 45 (38.1); sclerosing cholangitis: 21 (17.8) | 24 (19.2) | Pancreas: 17 (41.5); biliary tree: 4 (9.8) |
| Salivary gland | 24 (43.6) | 35 (33.7) | 76 (64.4) | Submandibular: 35 (28.0); parotid: 21 (16.8) | 8 (19.5) |
| Lymph node | 8 (14.5) | 31 (29.8) | 77 (65.3) | 34 (27.2) | 5 (12.2) |
| Eye | 8 (14.5) | 20 (19.2) | 60 (50.8) | 28 (22.4) | Orbit: 3 (7.3); lacrimal glands: 2 (4.9) |
| Lung | 7 (12.7) | 7 (6.7) | 32 (27.1) | 22 (17.6) | 1 (2.4) |
| Retroperitoneum | 7 (12.7) | 8 (7.7) | 31 (26.3) | 23 (18.4) | 8 (19.5) |
| Renal system | 2 (3.6) | 3 (2.9) | 29 (24.6) | 15 (12.0) | 1 (2.4) |
| Central nervous system | 1 (1.8) | 7 (6.7) | NA | NA | 3 (7.3) |
| Skin/soft tissue | 1 (1.8) | 8 (7.7) | 5 (4.2) | 2 (1.6) | NA |
| Other | 1 (1.8)* | 8 (7.7)† | NA | NA | NA |
| No. of involved organ systems | 1.7 (1-5) | 1.6 (1-5) | NA | NA | NA |
| Treatment | | | | | |
| Glucocorticoids | 37 (67.3) | 57 (54.8) | NA | 64 (51.2) | 36 (87.8) |
| Surgery | 19 (34.5) | 46 (44.2) | NA | NA | NA |
| Other | 12‡ | 18§ | NA | NA | NA |

Abbreviations: COPP = cyclophosphamide, vincristine, procarbazine, and prednisone; Ig = immunoglobulin; IQR = interquartile range; NA = not available; SD = standard deviation

* Other organ systems include bone (n=1)

† Other organ systems include bone (n=1), breast (n=4), nasopharynx (n=1), pericardium (n=1), and prostate (n=1)

‡ Other treatments include azathioprine (n=6), mycophenolate mofetil (n=4), cyclophosphamide (n=1), and COPP (n=1)

§ Other treatments include azathioprine (n=8), mycophenolate mofetil (n=4), chlorambucil (n=2), cyclophosphamide (n=1), COPP (n=1), radiation therapy (n=2), and thalidomide (n=1); some patients received more than one form of treatment

manifestations and treatment modalities are shown in Table 3. Lymphadenopathy was associated with GC use (odds ratio [OR]=2.65; 95% confidence interval [CI], 1.08-6.54; P=0.034). Involvement of CNS was negatively associated with GC use (OR=0.12; 95% CI, 0.01-1.05; P=0.044).

## Associations of serum immunoglobulin G4 with multisystem disease and specific organ manifestations

Age, sex, pre-treatment serum IgG4, total IgG, and IgG4:IgG ratio were used in univariate analysis. Both age (P=0.021) and pre-treatment serum IgG4 levels

TABLE 2. Characteristics and treatment of 49 patients with IgG4-related disease in Hong Kong based on literature review[8-18]

| Study | Sex | Age (years) | Organ manifestations | IgG4 (mg/dL) | IgG (mg/dL) | Histological confirmation | Treatment |
|---|---|---|---|---|---|---|---|
| Wong et al,[8] 2007 | M | 77 | CNS, HBP | 720 | 1330 | Yes | NA |
| Cheung and Lo,[16] 2008 | M | 59 | HBP | NA | 1930 | Yes | Surgery |
| | F | 68 | HBP | NA | 2890 | Yes | Surgery |
| | M | 69 | HBP | NA | 4330 | NA | Biliary stenting only |
| | M | 63 | HBP | NA | NA | Yes | GC |
| | M | 61 | HBP | 950 | 2180 | Yes | GC |
| Cheuk et al,[15] 2008 | M | 63 | HBP, LN | 180 | NA | Yes | Surgery |
| | M | 59 | HBP, LN | NA | 2290 | Yes | Surgery |
| | F | 68 | HBP, LN | NA | 2887 | Yes | Surgery |
| | M | 77 | LN, orbital, salivary | NA | 2830 | Yes | Surgery |
| | M | 67 | LN, orbital | 580 | 1660 | Yes | GC, azathioprine |
| | M | 71 | LN, orbital, soft tissue | NA | 2533 | Yes | GC, chlorambucil, RT |
| | M | 47 | HBP, LN | 1383 | 5940 | Yes | GC |
| | M | 74 | LN | NA | NA | Yes | Refused steroid therapy |
| | M | 73 | LN, orbital, salivary | 3200 | 5620 | Yes | GC |
| | M | 70 | LN | 2150 | 3667 | Yes | GC |
| | M | 69 | LN | 260 | 2606 | Yes | No treatment |
| | M | 37 | LN | NA | 5790 | Yes | GC |
| Cheuk et al,[14] 2008 | F | 69 | Orbital | NA | NA | Yes | NA |
| | M | 69 | Nasopharynx | NA | NA | Yes | NA |
| | M | 60 | Orbital, LN | NA | NA | Yes | NA |
| Cheuk et al,[11] 2009 | F | 48 | Breast | 350 | NA | Yes | Surgery |
| | F | 51 | Breast | NA | NA | Yes | Surgery |
| | F | 37 | Breast, LN | NA | NA | Yes | Surgery |
| | F | 54 | Breast | NA | NA | Yes | Surgery |
| Chan et al,[10] 2009 | M | 37 | CNS | NA | NA | Yes | Surgery |
| Lui et al,[9] 2009 | F | 60 | CNS | NA | NA | Yes | Surgery, RT |
| | F | 52 | CNS | NA | NA | Yes | Surgery |
| | M | 45 | CNS | NA | NA | Yes | Surgery |
| | F | 26 | CNS | NA | NA | Yes | GC, thalidomide |
| Cheuk et al,[12] 2009 | M | 76 | Orbital, soft tissue | 1060 | 2340 | Yes | GC |
| | F | 74 | LN, orbital, renal, salivary, soft tissue | 1320 | 4540 | Yes | GC, chlorambucil |
| Chung et al,[17] 2010 | M | 51 | HBP | NA | NA | Yes | Surgery |
| Cheuk et al,[13] 2010 | M | 42 | Soft tissue | NA | NA | Yes | Surgery |
| | M | 60 | LN, soft tissue | 125 | NA | Yes | GC |
| | M | 89 | LN, orbital, salivary, soft tissue | NA | 2350 | Yes | Surgery, GC |
| | M | 71 | LN, salivary, soft tissue | NA | NA | Yes | Surgery |
| Ng et al,[18] 2011 | M | 48 | HBP | 340 | 1440 | Yes | Surgery, GC |
| | M | 51 | HBP | 200 | 2240 | Yes | Surgery, GC, azathioprine |
| | M | 50 | HBP, LN | 800 | 2430 | NA | Surgery, GC |
| | M | 72 | HBP, LN | 920 | 4880 | NA | GC |
| | M | 50 | HBP, LN, orbital, salivary | 1450 | 2200 | Yes | GC |
| | F | 80 | HBP | 300 | 1490 | Yes | Surgery |
| | M | 67 | Salivary, pericardium | 1250 | 2850 | Yes | Surgery, GC |
| | M | 55 | LN, orbital, salivary | 400 | 3560 | Yes | GC |
| | M | 83 | Salivary, prostate | 3450 | 7750 | Yes | Surgery, GC |
| | M | 71 | Salivary | 480 | NA | NA | Surgery |
| | M | 74 | Orbital, salivary | 3150 | 4520 | Yes | GC |
| | F | 77 | Retroperitoneal | 110 | 1400 | Yes | Surgery |

Abbreviations: CNS = central nervous system; F = female; GC = glucocorticoids; HBP = hepatobiliary and pancreatic; Ig = immunoglobulin; LN = lymph node; M = male; NA = not available; RT = radiation therapy

(P=0.020) significantly correlated with the number of involved organ systems in univariate analysis. Other variables did not reach statistical significance (data not shown). Only pre-treatment serum IgG4 levels remained statistically significant in subsequent multivariate analysis (ß=0.347; P=0.004). For specific organ manifestations, pre-treatment serum IgG4 level was more associated with patients having salivary gland involvement than those without (mean, 1109 mg/dL vs 599 mg/dL; P=0.012). No associations of serum IgG4 with other organ manifestations were found (P>0.1; data not shown).

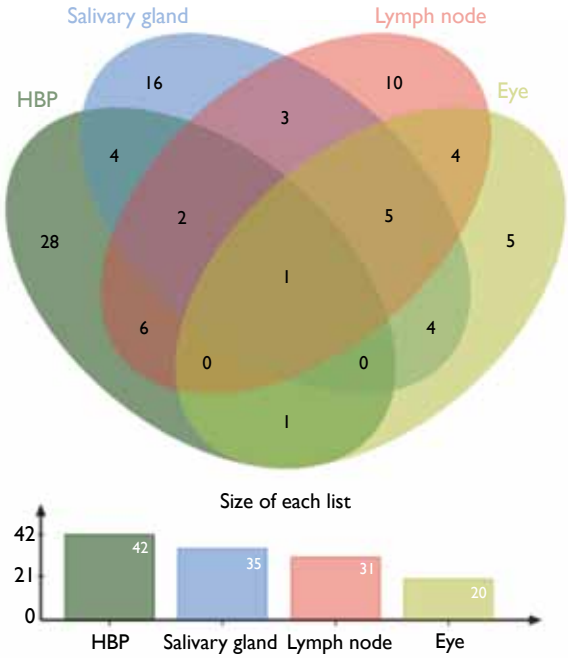


FIG. Venn diagram of the four most commonly involved organ systems (n=89)
Abbreviation: HBP = hepatobiliary and pancreatic system

## Discussion

In this study, we describe the clinical features and treatment practices of the largest cohort of IgG4-RD in our locality. After combination of our patients with all other published cases of IgG4-RD from Hong Kong, we analysed 104 cases comprising predominantly older men (mean age, 62 ± 13 years; male-to-female ratio=3:1), which is consistent with other reports.[19-22] Over 95% of patients had serum IgG4 level of >135 mg/dL and an IgG4:IgG ratio of >8%. Although these cut-offs are often quoted in the diagnostic criteria for IgG4-RD,[4,23] it is important to note that elevated serum IgG4 levels can be seen in a variety of other conditions such as malignancies, infections, or autoimmune disorders. Serum IgG4 level and IgG4:IgG ratio alone have poor specificity and low positive predictive value. The specificity and positive predictive value of serum IgG4 and IgG4:IgG ratio have been reported to be approximately only 0.6 and 0.3, respectively.[24] Of note, 4/72 (5.6%) of our patients with biopsy-proven IgG4-RD had normal serum IgG4 levels (ie false negatives). The gold standard for diagnosis of IgG4-RD in most cases therefore remains biopsy with histopathological confirmation. Over 70% of patients in Queen Mary Hospital had positive histopathological confirmation, in comparison to 54.2% in a large Mainland Chinese cohort.[19] Although this proportion increased to 81.7% in the combined analysis, this could be an over-estimation of real clinical practice with potential publication and selection bias from literature review. Similar to other reported populations, HBP system, salivary gland, lymph node, and eye were the most

TABLE 3. Associations between organ manifestations and treatment modalities

| Organ manifestation | No. (%) of patients | | | | | |
|---|---|---|---|---|---|---|
| | Glucocorticoid treatment | | | Surgical intervention | | |
| | Yes (n=57) | No (n=47) | P value | Yes (n=46) | No (n=58) | P value |
| Hepatobiliary and pancreatic system | 27 (47.3) | 15 (31.9) | 0.160 | 17 (37.0) | 25 (43.1) | 0.552 |
| Salivary gland | 21 (36.8) | 14 (29.8) | 0.331 | 15 (32.6) | 20 (34.5) | 1.000 |
| Lymph node | 22 (38.6) | 9 (19.1) | 0.034* | 10 (21.7) | 21 (36.2) | 0.133 |
| Eye | 13 (22.8) | 7 (14.9) | 0.331 | 5 (10.9) | 15 (25.9) | 0.079 |
| Lung | 6 (10.5) | 1 (2.1) | 0.125 | 0 | 7 (12.1) | 0.017 |
| Retroperitoneum | 6 (10.5) | 2 (4.3) | 0.289 | 2 (4.3) | 6 (10.3) | 0.297 |
| Renal system | 2 (3.5) | 1 (2.1) | 1.000 | 0 | 3 (5.2) | 0.253 |
| Central nervous system | 1 (1.7) | 6 (12.8) | 0.044† | 5 (10.9) | 2 (3.4) | 0.079 |
| Skin/soft tissue | 4 (7.0) | 4 (8.5) | 1.000 | 4 (8.7) | 4 (6.9) | 0.730 |

* Odds ratio = 2.65
† Odds ratio = 0.12

common organ systems involved in both Queen Mary Hospital and the combined analysis. Although involvement of HBP system seemed more prevalent in the Queen Mary Hospital and Mainland China cohorts, the rate of HBP involvement is similar to other studies dedicated to IgG4-related hepatobiliary disease (approximately 40%-60%).[25]

We also examined the treatment practices employed in our locality. Treatment of IgG4-RD is typically individualised because of substantial disease heterogeneity—even subclinical disease can lead to irreversible organ damage and not all manifestations require immediate treatment. For example, a watchful 'wait and see' approach may be an appropriate option for mild disease or after surgical debulking. However, there is currently no high-quality evidence-based guidance for the management of IgG4-RD and practices often vary significantly across different countries. In the combined analysis, GCs were the most popular treatment option and over half of the patients had received GCs either alone or in combination with other treatment modalities. In the combined analysis, use of GCs was significantly associated with lymphadenopathy, which may reflect their preferential use, especially in patients with systemic involvement. This is consistent with the general consensus and recommendations made by most experts because of their good initial efficacy.[26] The opposite was seen with an inverse association between CNS involvement and GC use. This was expected because most of these patients with CNS involvement had localised disease and the diagnosis of IgG4-RD was not readily established prior to surgical resection. Only one case was diagnosed by open brain biopsy and subsequently treated with GCs and thalidomide.[9]

Local experience with other immunomodulatory agents was limited and choices for steroid-sparing agents varied between different centres. Conventional agents such as azathioprine, cyclophosphamide, methotrexate, mycophenolate, and tacrolimus have all demonstrated similar efficacy, although head-to-head comparisons are not available.[27] B-cell depletion with rituximab has also gained much popularity in recent years and proven to be effective as induction and maintenance therapy, even without concomitant GCs.[27,28] Nonetheless, we were unaware of any published experience with its use for IgG4-RD in Hong Kong at the time of writing. The advent of this ground-breaking treatment will likely require multidisciplinary expertise as well as further research, especially in the context of the high prevalence of chronic hepatitis B infection and subsequent risk of viral reactivation in Hong Kong.

Finally, we also recommend the utility of pre-treatment serum IgG4 in disease prognostication and treatment monitoring. Pre-treatment serum IgG4 levels (but not IgG4:IgG ratios) significantly correlated with the number of organ systems involved. The correlation with age did not remain statistically significant after multivariate regression. Interestingly, Wallace et al[20] also described elevated serum IgG4 levels associated with both age and number of organs involved, but analysis with multivariate regression was not reported in their study. Specifically, serum IgG4 levels also correlated with salivary gland involvement, but not with other individual organ systems. The reason for this particular correlation remains uncertain, but highlights the importance of screening for salivary gland involvement in all IgG4-RD patients, especially in the presence of higher serum IgG4 levels.

The main limitations of this study included its retrospective nature and restrictions of literature review. Limited clinical data were available and we were unable to determine or standardise for the disease duration of each patient. There were substantial missing data for some key variables, reducing the effective number of patients suitable for analysis. The nature of a literature review also harbours risk of publication or selection bias, although it was reassuring that findings from the combined analysis were similar to those obtained from Queen Mary Hospital. Some indefinite findings, such as lower prevalence of renal involvement, highlight the necessity of future prospective and multicentre studies. Specifically, we advocate the need for more uniform international diagnostic criteria and the establishment of a region-wide registry with longitudinal data collection.

In conclusion, we found that pre-treatment serum IgG4 significantly correlated with the number of organ systems involved, highlighting its potential for disease prognostication and guiding treatment. We also describe the clinical characteristics, treatment practices, and factors associated with multisystem disease in IgG4-RD in Hong Kong. There is vast disease and patient heterogeneity, making local research and expertise exchange imperative. Increased physician awareness and a multidisciplinary approach will be required for early diagnosis and optimal management of this masquerading disease. Further studies, especially focusing on treatment strategies within the contexts of different epidemiology and patient characteristics, are urgently needed.

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## Declaration

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