Clues to Mortality Trends and Their Related Factors in IgG4-related Disease: a Japanese Single-center Retrospective Study

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Research Article

Keywords: IgG4-related disease, mortality, standardized mortality ratio, malignancy

Posted Date: November 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1063841/v1>

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Abstract

Background: Few observations on the long-term prognosis have been conducted in immunoglobulin G4-related disease (IgG4-RD) patients with various organ involvement, not limited to autoimmune pancreatitis. Especially, mortality and its related factors in patients with IgG4-RD with various organ involvement are not well known. This study aimed to clarify mortality trends and its related factors in IgG4-RD with various organ involvement.

Methods: We retrospectively reviewed the medical records of patients with IgG4-RD at a single center in Japan. We calculated the crude mortality rate and the standardized mortality ratio (SMR) using national Japan mortality statistics and investigated the cause of death. We performed Cox regression analyses to assess mortality-related factors.

Results: A total of 179 patients with IgG4-RD were included and the median follow-up from diagnosis was 47 months (IQR 19-96). Ten patients (5.6%) in our cohort died during the follow-up period. The crude mortality rate was 11.1 per 1,000 person-years. According to national Japan mortality statistics, 11.6 age- and sex-matched deaths would have been expected to occur within the follow-up period, resulting in an SMR of 0.86 (95% confidence interval [CI] 0.41-1.59). Univariate Cox regression analyses indicated that the number of affected organs at diagnosis (hazard ratio [HR] 1.45, 95% CI 1.02-2.05), eGFR <45 mL/min/1.73m² at diagnosis (vs. ≥45, HR 8.48, 95% CI 2.42-29.79), and the presence of malignancy during the clinical course (HR 3.93, 95% CI 1.10-14.02) had a significant impact on the time to death.

Conclusions: Our findings suggested that IgG4-RD does not significantly affect long-term patient survival. On the other hand, multi-organ involvement and renal dysfunction as well as malignancy might be associated with higher mortality trends in IgG4-RD. Early detection and appropriate management of risk factors may improve the long-term prognosis of IgG4-RD.

Background

Immunoglobulin G4-related disease (IgG4-RD) is a multi-organ, fibro-inflammatory condition with mass-forming lesions, organ-swelling, and/or hypertrophic lesions due to dense lymphoplasmacytic infiltrates with IgG4 positive plasma cells¹). In this disease, an elevation of serum IgG4 levels is a characteristic serological finding, seen in most cases. Generally, patients with this disease respond well to glucocorticoid therapy, but frequently relapse.

Despite a good response to glucocorticoid, the long-term prognosis of IgG4-RD is not always favorable. As mentioned above, relapses are common, with past reports describing relapse rates of 21-46%²⁻⁴). If not treated early and appropriately, progressive fibrosis in the affected organs causes persistent organ dysfunction, such as chronic salivary and lacrimal gland dysfunction due to IgG4-related dacryoadenitis and sialadenitis⁵) and diabetes mellitus and pancreatic exocrine insufficiency due to type 1 autoimmune pancreatitis (AIP)^{6,7}). Particularly, serious complications in IgG4-RD include biliary obstruction, cirrhosis, and portal hypertension due to IgG4-related sclerosing cholangitis (IgG4-SC)^{6,7}), renal dysfunction due to IgG4-related kidney disease^{8,9}) or IgG4-related retroperitoneal fibrosis causing ureteral obstruction¹⁰), and aortic aneurysm formation and/or aortic dissection due to IgG4-related periaortitis¹¹). Furthermore, some recent studies have focused on the

potential risk of malignancy in IgG4-RD patients which also can worsen the long-term prognosis of patients. In fact, the mortality is reported to be significantly higher in AIP/IgG4-SC than that in the general population, with an estimated odds ratio of 2.07⁶⁾. In addition, cardiovascular events are more common in the elderly and affect their prognosis. Because IgG4-RD generally occurs in the elderly¹⁾, cardiovascular events may also affect the prognosis of patients with this disease. However, an impact of cardiovascular events on the prognosis of patients with IgG4-RD has not been sufficiently investigated.

Few observations on the long-term prognosis have been conducted in IgG4-RD patients with various organ involvement, not limited to autoimmune pancreatitis. Especially, mortality trends and its related factors in patients with IgG4-RD are not well known. Therefore, we undertook the present study to clarify mortality trends compared to the general population in Japan and to identify factors associated with mortality in IgG4-RD with various organ involvement.

Methods

Patients and Materials

Between January 1, 2014, and December 31, 2020, we included 179 consecutive patents with IgG4-RD. The diagnosis of IgG4-RD was made by experts based on fulfillment of the Japanese comprehensive diagnostic criteria¹²⁾ and/or the 2019 ACR/EULAR classification criteria for IgG4-RD¹³⁾.

Retrospectively reviewing the medical records, we determined the following clinical factors at the time of diagnosis: age; gender; presence or absence of allergy, dyslipidemia, hypertension, diabetes mellitus, smoking history, and cardiovascular diseases; serum levels of IgG, IgG4, IgE, CH50, C3, C4, C-reactive protein (CRP), and creatinine; estimated glomerular infiltration rate (eGFR) calculated on the basis of a 3-variable Japanese equation¹⁴⁾; peripheral blood eosinophil counts; presence or absence of rheumatoid factor (RF), anti-nuclear antibody (ANA), and various disease-specific autoantibodies including SSA/Ro antibody, anti-neutrophil cytoplasmic antibody (ANCA), double-stranded DNA antibody, and anti-citrullinated protein antibody (ACPA); number of affected organs; involvement of pancreas, salivary glands, lacrimal glands, kidney, aorta/artery, retroperitoneum, and lung. We also determined presence or absence of malignancy, relapse, and death during the observation periods. Presence of malignancy during the observation periods was defined as having malignancy at or after the diagnosis of IgG4-RD.

Using the collected data, we calculated the all-cause and malignancy-related mortality rate and the standardized mortality ratio (SMR) using national Japan mortality statistics and investigated the cause of death. Incidence of malignancy during the clinical course and standardized incidence ratio (SIR) were also calculated using Cancer Statistics provided by Cancer Information Service, National Cancer Center, Japan (Vital Statistics of Japan, Ministry of Health, Labour and Welfare).

Statistical Analysis

Statistical analysis was performed using SPSS V.25 (IBM Corp., Armonk, NY, USA). Data are presented as median (interquartile range [IQR1, IQR3]) for continuous variables.

The significance of differences between groups was determined using Mann-Whitney U test, while the significance of differences in frequencies was analyzed with Fisher's exact probability test. Factors related to mortality were assessed by Cox regression analysis. For the time-to-event analysis, we considered that the follow-up of the patients started at the time of diagnosis and was terminated at the time of the end of the observation period (December 31, 2020), loss of follow-up, or death. In these Cox regression analyses, for continuous variables, units for increments to calculate hazard ratios were set at 1 year for age; 100 mg/dL for serum IgG4 levels; 1 mg/dL for serum creatinine and CRP levels; 10 mL/min/1.73m² for eGFR. Receiver operating characteristic (ROC) curve analyses were performed to test the usefulness of certain parameters for the prediction of mortality and to determine the appropriate cut-off values. According to the presence or absence of the detected risk factors, survival rates were calculated using the Kaplan-Meier method. Log-rank test was used to compare survival times of patients with and without malignancies. Significant differences were recognized at $P < 0.05$.

Results

One hundred and seventy-nine patients with IgG4-RD were included. Patients' characteristics were listed in Table 1. One hundred and twenty-four were male (69.3%); the median age was 68 years (interquartile range [IQR] 60-75 years); and the median follow-up period from diagnosis was 47 months (IQR 19-96). Median number of involved organs was 2.0 (IQR 1.0-4.0). Involved organs were predominantly salivary glands (56.4%), lacrimal glands (50.2%), kidney (29.6%), pancreas (29.5%), aorta/artery (28.4%), and retroperitoneum (5.0%). Median serum IgG4 and CRP levels were 434 mg/dL (IQR 224-916) and 0.10 mg/dL (IQR 0.04-0.30), respectively. Malignancy and relapse during the clinical course were found in 23 (12.8%) and 27 cases (15.1%), respectively.

Ten patients (5.6%) in our cohort died during the follow-up period (Table 2). Five died of malignancy, one of respiratory failure, two of infectious pneumonia, one of sudden cardiac event, and one of suspected aortic aneurysmal rupture. Median period from diagnosis to death was 44 months (IQR 28-79). The crude all-cause mortality rate was 11.1 per 1,000 person-years. According to national Japan mortality statistics, 11.6 age- and sex-matched deaths would have been expected to occur within the follow-up period, resulting in an SMR of 0.86 (95% confidence interval [CI] 0.41-1.59). The cancer-related mortality was not significantly increased compared with the general population (4.42 expected deaths versus 5 observed deaths; SMR 1.13, 95%CI 0.36-2.64). On the other hand, according to the Cancer Statistics in Japan, the expected number of cases of age- and sex-matched malignancies to occur within the follow-up period would be 12.7. The actual number of cases with malignancies was 23 in this cohort. Therefore, there was an increased SIR of 1.81 (95%CI 1.14-2.71) for all malignancies compared with the general population.

To clarify the characteristics of the non-surviving group, we compared various clinical features of the surviving and non-surviving groups using Mann-Whitney U test and Fisher's exact probability test (Table 1). The serum levels of IgE, CRP, and creatinine as well as the frequency of malignancy in the non-surviving group were significantly higher than those in the surviving group, whereas eGFR was significantly lower in the non-surviving group.

Factors related to mortality trends were assessed by univariate Cox regression analysis (Table 3), which indicated that the number of affected organs at diagnosis (hazard ratio [HR] 1.45, 95% CI 1.02-2.05), involvement of ≥ 4 organs at diagnosis (vs. ≤ 3 organs, HR 3.87, 95% CI 1.09-13.75), serum creatinine levels at diagnosis (HR 1.82, 95% CI 1.06-3.12), eGFR at diagnosis (HR 0.68, 95% CI 0.51-0.91), eGFR of less than 45 mL/min/1.73m² at diagnosis (vs. ≥ 45 mL/min/1.73m², HR 8.48, 95% CI 2.42-29.79), and the presence of malignancy during the clinical course (vs. absence, HR 3.71, 95% CI 1.05-13.02) all had a significant impact on the time to death, whereas the other factors including age at diagnosis (HR 1.06, 95% CI 0.99-1.12) and serum CRP (HR 1.19, 95% CI 0.79-1.79) and IgG4 levels (HR 1.02, 95% CI 0.93-1.11) at diagnosis did not. Presence of dyslipidemia (HR 1.16, 95% CI 0.33-4.12), hypertension (HR 1.68, 95% CI 0.47-5.96), diabetes mellitus (HR 0.33, 95% CI 0.07-1.55), smoking history (HR 2.50, 95% CI 0.53-11.82), and cardiovascular diseases (HR 2.08, 95% CI 0.54-8.06) did not have a significant impact on the time to death either.

To help determine the extent to which the number of affected organs and eGFR can contribute to the reliable prediction of mortality during the clinical course, and to identify their appropriate cut-offs, we used ROC curves (Figure 1). Concerning the number of affected organs, the area under the ROC curve was 0.640 (95% CI: 0.433–0.846, P=0.137), suggesting that this parameter does not accurately predict mortality. However, we found that multiple organ involvement in more than 4 organs was the most appropriate cut-off and yielded a sensitivity of 60.0% and specificity of 72.7% in predicting mortality (Figure 1A). Concerning eGFR, the area under the ROC curve was 0.717 (95% CI: 0.544–0.889, P=0.021). We found that eGFR of less than 73.6 mL/min/1.73m² was a sensitive cut-off that yielded a sensitivity of 90.0% and specificity of 47.6% and eGFR of less than 38.9 mL/min/1.73m² was a specific cut-off that yielded a sensitivity of 50.0% and specificity of 91.7% in predicting mortality (Figure 1B).

According to the presence or absence of malignancy, ≥ 4 affected organs or ≤ 3 at diagnosis, and eGFR of <45 or ≥ 45 mL/min/1.73m² at diagnosis, survival rates were calculated using the Kaplan-Meier method. Kaplan-Meier analyses also showed significant differences in the cumulative rates of death between patients with and without malignancy during the clinical course (P=0.028) (Figure 2A), ≥ 4 affected organs at diagnosis (P=0.024) (Figure 2B), and eGFR of <45 mL/min/1.73m² at diagnosis (P<0.01) (Figure 2C).

Discussion

The present study analyzing 179 patients with IgG4-RD showed that the all-cause mortality trends of patients with IgG4-RD did not significantly differ from those of the age- and sex-matched Japanese population. The malignancy-related mortality was not increased compared with the matched Japanese population, but the incidence of malignancy was increased. Multi-organ involvement and renal dysfunction at diagnosis as well as malignancy developing during the clinical course were associated with higher mortality trends. Especially, the cumulative survival rate was significantly lower in the patients with malignancy compared with those without. These new findings may provide clues to better long-term management and screening of IgG4-RD.

Although several studies have analyzed the long-term prognosis of IgG4-RD, it has not been fully elucidated because of its rarity. The nationwide epidemiological survey of 1,370 Japanese patients with AIP in 2016¹⁵⁾ reported that 37 (2.7%) patients died within approximately two years of the diagnosis. Huggett et al⁶⁾ studied 115 patients with AIP/IgG4-SC and found that 11 patients (10%) died during a mean follow-up of 33 months.

Using National UK mortality statistics, the authors suggested that there was an increased all-cause mortality ratio of 2.07 (95%CI 1.07–3.55). In our study of 179 patients with IgG4-RD, 10 patients (5.5%) died during the follow-up. There was no significant increase in the mortality trends compared to the age- and sex-matched population in Japan. This result was contrary to the previous report by Huggett et al⁶⁾, but this might be due to the fact that our cases, unlike the cases of Huggett et al⁶⁾, had not only AIP/IgG4-SC but also various affected organs including mainly salivary and lacrimal gland lesions. On the other hand, these results suggest that, with proper management, the prognosis of patients with IgG4-RD may be similar to that of the general population.

Some recent studies have focused on the potential risk of malignancy in patients with IgG4-RD. Conflicting studies have noted both an increased occurrence of malignancies in this group^{6,15-22)} and no such increase in others^{23,24)}, making the association between IgG4-RD and malignancy controversial even now. In our study, the risk of any malignancy at diagnosis or during follow-up was increased (SIR 1.81, 95%CI 1.14-2.71) when compared with the matched national population. In addition, Cox regression analysis indicated that malignancy during the clinical course had a significant impact on the time to death. The Kaplan–Meier survival curve also showed that all-cause mortality increased during the clinical course in the patients with malignancy as compared to those without. These results suggest that the periodical screening of systemic organs in patients with IgG4-RD may lead to a further improvement of their prognosis through the early detection and treatment of malignancy.

Furthermore, we found that the number of affected organs and renal dysfunction at diagnosis were associated with mortality trends in IgG4-RD. The number of affected organs is recognized as one of the factors reflecting disease activity in general, and it may also be related to long-term prognosis. Accordingly, the periodical screening of systemic organs is also important for the early detection of subclinical new or recurrent organ involvement. On the other hand, acute kidney injury^{25,26)} and chronic kidney disease²⁷⁾ are known to be associated with patient mortality, and this study also suggested that renal dysfunction was an important prognostic factor in IgG4-RD. Our ROC analysis demonstrated eGFR <73.6 mL/min/1.73m² to be a sensitive cut-off and eGFR <38.9 mL/min/1.73m² a specific cut-off for prediction of mortality. Of note, IgG4-RKD was not diagnosed in 2 of the 5 non-surviving patients with <38.9 mL/min/1.73m² in this study (Table 2), meaning that renal dysfunction due to not only IgG4-RKD but also any other causes may be associated with a poor prognosis. In patients with IgG4-RD, therefore, it is necessary to also pay attention to the presence of these factors. On the other hand, further studies are necessary to clarify which therapeutic interventions improve the prognosis of patients with multiple organ involvement and/or renal dysfunction.

In this study, cardiovascular events and their classical risk factors, an important cause and risk factors of death in the general population, respectively, were not clearly associated with the mortality trends in patients with IgG4-RD despite glucocorticoid maintenance therapy. Cardiovascular events and their classical risk factors are more common in the elderly irrespective of having IgG4-RD or not and affect their prognosis. Although IgG4-RD is more prevalent in the elderly¹⁾, an impact of cardiovascular events and their risk factors on the prognosis of patients with IgG4-RD was not evident in the present cohort. However, in IgG4-related periarteritis, aneurysm or rupture of the affected aorta/artery and/or ischemic events in the coronary arterial lesions are recognized as fatal complications¹¹⁾, suggesting that cardiovascular events may be an important

cause of death depending on the affected organ in IgG4-RD. It is important to further investigate and clarify the impact of cardiovascular events on the long-term prognosis of this disease in multicenter studies with a larger number of patients.

There are some limitations in this study. First, it was designed as a single-center cohort study. We should confirm the results in populations with different characteristics such as race, affected organ, and treatment. Second, in assessing the incidence of malignancy, this study had a possible risk of ascertainment bias because the incidence of malignancy may be elevated by earlier detection in patients receiving various radiological examinations for follow-up of IgG4-RD. Finally, we should treat conclusions drawn from a comparison with national statistics with caution, because the analysis was not adjusted for other risk factors such as smoking, alcohol intake, and obesity. The cohort size was relatively large for this rare disease, but the number of the patients who died was not sufficient to perform multivariate analysis. Further studies involving more patients are needed.

In conclusion, our findings suggested that IgG4-RD does not significantly affect long-term patient survival. On the other hand, multi-organ involvement and renal dysfunction at diagnosis as well as malignancy during the clinical course might be associated with higher mortality trends in IgG4-RD. Early detection of risk factors and appropriate management and intervention are considered to be necessary to improve the long-term prognosis of IgG4-RD.

Abbreviations

ACPA: Anti-citrullinated protein antibody; ACR/EULAR: the American College of Rheumatology and the European League Against Rheumatism; AIP: type 1 autoimmune pancreatitis; ANA: Anti-nuclear antibody; ANCA: Anti-neutrophil cytoplasmic antibody; CH50: 50% hemolytic unit of complement; CI: Confidence interval; CRP: C-reactive protein; CVD: Cardiovascular disease; DL: Dyslipidemia; DM: Diabetes mellitus; eGFR: estimated glomerular filtration rate; HR: Hazard ratio; HT: Hypertension; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IgG4: Immunoglobulin G4; IgG4-RD: Immunoglobulin G4-related disease; IgG4-SC: IgG4-related sclerosing cholangitis; IQR: Interquartile range; RF: Rheumatoid factor; ROC: Receiver operating characteristic; SMR: Standardized mortality ratio; s/o: Suspect of.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics board of the Medical Ethics Committee of Kanazawa University, and informed consent for the use of all data was obtained from each patient. The research was conducted in compliance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The data used and/or analyzed during the present study will be available on reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by Health and Labour Sciences Research Grants for the Study of Intractable Diseases from the Ministry of Health, Labor and Welfare, Japan.

Authors' contributions

HK and IM designed the research, acquired data, contributed to analysis and interpretation of data, and drafted and revised the manuscript. ST, SS, TY, RH, RN, TZ, SH, and KI acquired data and provided intellectual content of critical importance to the work described. MK designed the research, acquired data, contributed to analysis and interpretation of data, provided intellectual content of critical importance to the work described, and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank John Gelblum for his critical reading of the manuscript.

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Tables

Table 1. Patient characteristics.

	All patients (n=179)	Non-surviving group (n=10)	Surviving group (n=169)	P- value
Characteristics and clinical course				
Male	124 (69.3%)	8 (80.0%)	116 (68.6%)	0.449
Age	68.0 (60.0-75.0)	68.5 (61.0-79.5)	68.0 (59.5-74.5)	0.318
Allergy (%)	95 (53.1%)	3 (30.0%)	92 (54.4%)	0.193
Diabetes Mellitus (%)	70 (39.1%)	2 (20.0%)	68 (40.2%)	0.203
Hypertension (%)	80 (44.7%)	6 (60.0%)	74 (43.8%)	0.316
Dyslipidemia (%)	62 (34.6%)	4 (40.0%)	58 (34.3%)	0.714
Smoking history (%)	111 (62.7%)	8 (80.0%)	103 (61.6%)	0.244
Cardiovascular disease (%)	32 (18.4%)	3 (30.0%)	29 (17.6%)	0.329
Observation periods (month)	47 (19-96)	44.0 (16-79)	47 (19-99)	0.676
Number of affected organs	2.0 (1.0-4.0)	4.0 (1.8-5.5)	2.0 (1.0-4.0)	0.128
Presence of malignancy at or after diagnosis (%)	23 (12.8%)	5 (50.0%)	18 (10.7%)	0.004*
Relapse (%)	27 (25.1%)	1 (10.0%)	26 (15.4%)	0.644
Laboratory Findings				
Serum IgG level (mg/dL)	1951 (1556-2572)	2235 (1960-2757)	1932 (1538-2572)	0.219
Serum IgG4 level (mg/dL)	434 (224-916)	717 (274-1093)	409 (224-864)	0.400
Serum IgE level (IU/mL)	501 (213-1125)	1055 (518-2477)	467 (180-1068)	0.026*
Serum C3 level (mg/dL)	94 (80-110)	105 (84-114)	94 (79-111)	0.442
Serum C4 level (mg/dL)	22 (15-27)	24 (16-39)	22 (15-27)	0.419
Serum CH50 level (U/mL)	53(40-60)	58 (44-60)	53 (39-60)	0.578
Serum CRP level (mg/dL)	0.10 (0.04-0.30)	0.40 (0.18-1.20)	0.10 (0.03-0.30)	0.004*
Serum creatinine level (mg/dL)	0.79 (0.65-1.00)	1.20 (0.65-1.72)	0.77 (0.64-0.99)	0.046*
eGFR (mL/min/1.73m ²)	70.9 (54.8-85.4)	46.6 (32.1-71.0)	72.7 (56.4-85.7)	0.021*
Eosinophil count (/μL)	201 (113-342)	160 (106-486)	208 (115-340)	0.523
RF (%)	28 (18.8%)	1 (11.1%)	27 (19.2%)	0.543

ANA (%)	41 (24.0%)	3 (30.0%)	38 (23.6%)	0.625
Disease-specific antibodies (%)	21 (13.2%)	0 (0%)	21 (13.2%)	1.00
Affected organs				
Salivary gland (%)	101 (56.4%)	7 (70.0%)	94 (55.6%)	0.759
Lacrimal glands (%)	90 (50.2%)	4 (40.0%)	86 (50.8%)	0.512
Kidney (%)	53 (29.6%)	4 (40.0%)	49 (29.0%)	0.315
Pancreas (%)	52 (29.5%)	3 (30.0%)	49 (29.0%)	0.991
Aorta/artery (%)	51 (28.4%)	5 (50.0%)	46 (27.2%)	0.290
Lung/pleura (%)	34 (19.0%)	4 (40.0%)	30 (17.8%)	0.121
Retroperitoneum (%)	17 (9.5%)	1 (10.0%)	16 (9.4%)	0.991

Note: Conversion factor for creatinine: mg/dL to $\mu\text{mol/L}$, $\times 88.4$. Data are presented as median (IQR), or n/N (%). p values were calculated by Mann-Whitney U test or Fisher's exact test, as appropriate.

Abbreviations: IgG: immunoglobulin G; IgG4: immunoglobulin G4; IgE: immunoglobulin E; CH50: 50% hemolytic unit of complement; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; RF: rheumatoid factor; ANA: anti-nuclear antibody; DM: diabetes mellitus; HT: hypertension; DL: dyslipidemia; CVD history: cardiovascular disease history.

Table 2. Characteristics of the 10 non-surviving patients

No	Age	Affected organ	Serum IgG4 level (mg/dL)	eGFR (mL/min/1.73m ²)	Presence of malignancy at or after diagnosis	Cause of death	Time after diagnosis of IgG4-RD (month)
1	77	salivary glands, lacrimal glands, kidney, lung, lymph nodes	984	73.4	Absent	Sudden cardiac event	91
2	70	pancreas, biliary tract, salivary glands, aorta	1420	32.5	Present	Pancreatic cancer	140
3	62	salivary glands, lacrimal glands	204	70.3	Present	Malignant lymphoma	2
4	60	aorta	354	95.8	Present	Colon cancer	75
5	61	salivary glands, lung	944	69.4	Absent	Respiratory failure	20
6	61	salivary glands, lacrimal glands, kidney, lymph nodes	886	31.0	Absent	Severe pneumonia	75
7	81	salivary glands, kidney, aorta, pleura, paravertebral lesion in the thorax, prostate, lymph nodes	548	33.6	Absent	Recurrent gastric cancer	3
8	79	pancreas	10.7	26.4	Present	Sepsis, pneumonia	50
9	67	lacrimal glands, orbits, lung, liver, aorta, retroperitoneum, pituitary gland, submucosal lesion in the stomach, lymph nodes	2090	54.5	Present	Cancer of unknown primary	38
10	89	salivary glands, kidney, pancreas, aorta	297	38.8	Absent	s/o aortic aneurysmal rupture	30

Abbreviations: eGFR, estimated glomerular filtration rate; s/o, suspect of.

Table 3. Univariate Cox regression analysis of factors associated with mortality

	HR	95%CI	P value
Age	1.06	0.99-1.12	0.08
Male gender	1.99	0.42-9.38	0.38
Presence of malignancy at or after diagnosis	3.71	1.06-13.03	0.04*
Number of affected organs at diagnosis	1.45	1.02-2.05	0.04*
Involvement of ≥ 4 organs at diagnosis (vs. ≤ 3 organs)	3.87	1.09-13.75	0.04*
Serum creatinine level (mg/dL)	1.82	1.06-3.12	0.03*
eGFR (per 10 mL/min/1.73m ²)	0.68	0.51-0.91	0.01*
eGFR <45 mL/min/1.73m ² (vs. ≥ 45 mL/min/1.73m ²)	8.48	2.42-29.79	<0.01*
Serum CRP level (mg/dL)	1.19	0.79-1.79	0.41
Serum IgG4 level (per 100mg/dL)	1.02	0.93-1.11	0.70
Dyslipidemia	1.16	0.33-4.12	0.82
Hypertension	1.68	0.47-5.96	0.42
Diabetes Mellitus	0.33	0.07-1.55	0.16
Smoking History	2.50	0.53-11.81	0.25
CVD History	2.08	0.54-8.06	0.29

Abbreviations: CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HR: hazard ratio; 95%CI: 95% confidence interval.

Figures

Figure 1

Receiver operating characteristic curve analysis. (A) Receiver operating characteristic (ROC) curves to identify the appropriate cut-offs of the number of involved organs for the prediction of mortality show that involvement of more than 3.5 organs yields a sensitivity of 60.0% and a specificity of 72.8% (circle). (B) ROC curves to identify the appropriate eGFR cut-offs for the prediction of mortality show that eGFR of less than 38.9 mL/min/1.73m² yields a sensitivity of 50.0% and a specificity of 91.7% (square) and eGFR of less than 73.6 mL/min/1.73m² yields a sensitivity of 90.0% and a specificity of 47.6% (circle).

Figure 2

Kaplan–Meier event curves. Kaplan–Meier event curves demonstrated the mortalities in the groups with and without the risk factors. Malignancy (A), multiple organ involvement in ≥ 4 organs (B), and renal dysfunction with eGFR < 45 mL/min/1.73m² (C) were significantly associated with lower survival rates.