Predictive Factors for Autoimmune Pancreatitis Relapse After 3 Years of Maintenance Therapy

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Abstract

Objectives: Oral corticosteroid treatment is the standard therapy for autoimmune pancreatitis (AIP) and is highly effective. However, relapse may occur during maintenance therapy (MT). We aimed to clarify the predictive factors for relapse after 3 years of MT for use in deciding on the continuation of long-term MT.

Methods: Among 56 retrospectively recruited AIP patients who received corticosteroid remission induction therapy followed by MT for a minimum of 5 years, 38 subjects were enrolled after exclusion criteria and divided into the relapse group of patients who experienced relapse after 3 years of MT and the non-relapse group of patients who did not.

Results: According to multivariate analysis, ≥ 4 other organ involvement number at diagnosis (hazard ratio, 5.82; 95% confidence interval, 1.203-28.192) and IgG ≥ 1400 mg/dL at 3 years of MT (hazard ratio, 4.41; 95% confidence interval, 1.096-17.790) were predictive factors for relapse after MT for 3 years, with patients exhibiting both predictive factors having a higher cumulative relapse rate than those with ≤ 1 predictive factor.

Conclusions: We uncovered two predictive factors for AIP relapse after 3 years of MT. These findings will assist in deciding corticosteroid therapy regimens at 3 years of MT to minimize AIP relapse risk and adverse corticosteroid effects.

Key Words: autoimmune pancreatitis, relapse, other organ involvement, IgG4, IgG

Introduction

Autoimmune pancreatitis (AIP) was established based on a pathological background of lymphoplasmacytic sclerosing pancreatitis,[1] high serum IgG4 concentration,[2] and abundant IgG4-bearing plasma cell infiltration.[3] The characteristic clinical features of AIP, such as elderly male preponderance, obstructive jaundice, and mass-forming lesions in the pancreas, often mimic those of pancreatic cancer.[4] Oral corticosteroid treatment is the standard therapy for AIP and is considered highly effective.[5,6] The indications for corticosteroids include obstructive jaundice due to a pancreatic head mass lesion, persistent abdominal or back pain, and symptoms due to extra-pancreatic vital organ lesions.[7-9] In the Japanese Consensus Guidelines for Management of AIP 2013, it is recommended that corticosteroids be administered at an initial dose of 0.6 mg/kg/day for 2-4 weeks as remission induction therapy and then tapered to a maintenance dose of 5-7.5 mg/day over a period of 3-6 months.[10] However, relapse may still occur after remission induction; relapse rates are reportedly 40-60% after corticosteroid cessation and 20-30% during maintenance therapy (MT).[9,11-13] Recurrent relapses have been identified as a major risk factor for pancreatic stone formation in AIP.[6,14,15] which appears to be closely associated with pancreatic insufficiency due to transition to chronic pancreatitis.[16] Maintenance corticosteroid therapy may prevent relapse and is recommended for a period of at least for 3 years,[17] although relapse can occur afterwards. Thus, it is preferable to continue MT for longer than 3 years in some cases despite the possible adverse effects of long-term corticosteroid use.[18] There is therefore debate on whether MT should be extended past 3 years or not. Many reports on AIP have been published to date, but it is difficult to gain objective evidence on AIP relapse risk due to discrepancies in study design, such as patients continuing MT, those without remission induction or MT, and those with

interruption of MT. Moreover, many investigations mainly dealt with relapse at the time of initial treatment, with few focusing on relapse during the long-term course after 3 years of MT. The present study investigated relapse after 3 years of MT and aimed to clarify its predictive factors for use in deciding on whether to continue long-term MT.

Materials and Methods

We recruited 56 patients with type 1 AIP who were treated at our clinic or affiliated hospitals for at least 5 years from the time of diagnosis by December 31, 2015. AIP was diagnosed based on the International Consensus Diagnostic Criteria (ICDC) for AIP 2011 or the Japanese Diagnostic Criteria for AIP 2011.[19,20] Ultimately, 38 patients (male ratio: 82%, median age at AIP diagnosis: 62 years) were selected for further study, with 18 patients being excluded based on the exclusion criteria of a non-definite AIP diagnosis for 5 patients, no corticosteroid therapy for 5 patients, insufficient clinical records of long-term follow-up at another hospital for 1 patient, and discontinued corticosteroid therapy for 7 patients, among whom 2 patients suffered from severe adverse effects (fracture and femur head necrosis) and 5 patients attempted corticosteroid cessation. All patients received prophylactic treatment for pathological fracture, gastric ulcer and pneumocystis carini infection. These 38 AIP patients were administered corticosteroids as remission induction therapy, which were tapered to a maintenance dose over 3-6 months based on the Japanese Consensus Guidelines for Management of AIP 2013,[10] and continued MT for the standard 3 years and then an additional 2 years. These periods included remission induction therapy term and dose up term for relapse. None of the 38 patients attempted corticosteroid discontinuation during the clinical course.

Median follow-up period was 10.9 years (range: 5.2-23.4 years). The subjects were divided into 2 groups for analysis: the relapse group for patients experienced relapse after 3 years of MT and the non-relapse group those who did not. Relapse during the 3 years immediately following corticosteroid introduction was ignored in this group selection.

Previous reports have adopted different definitions for AIP relapse, including reappearance of symptoms after remission induction therapy or after interruption of MT,[21] reappearance of pancreatic swelling or narrowing of the main pancreatic duct (MPD) and resumption or dose increase of corticosteroids for extra-pancreatic lesions,[12] reappearance of symptoms with pancreatic and/or extra-pancreatic abnormalities in imaging studies,[13,22] and pancreatic swelling or narrowing of the MPD and new or worsening extra-pancreatic lesions.[23] To obtain objective evidence, we defined relapse as the reappearance or exacerbation of pancreatic or extra-pancreatic organ lesions recognized by imaging at diagnosis or during MT that had initially improved by remission therapy.

We evaluated medical records retrospectively and recorded clinical features at diagnosis, serum activity markers, and imaging findings at diagnosis and at 3 years of MT, as described below.

1. Clinical features

Clinical features at diagnosis included age, sex, body mass index (BMI), history of alcohol intake, smoking, or allergy, past treatment for diabetes mellitus (DM), jaundice at diagnosis, follow-up period and duration of corticosteroid therapy, reason for corticosteroid induction, and corticosteroid dose at 3 years of MT.

2. Laboratory findings

Laboratory findings included such serum activity markers as serum IgG, IgG4, soluble interleukin 2 receptor

(sIL2-R), beta-2 microglobulin (β2MG), C3, C4, and immune complex (IC) monoclonal rheumatoid factor (ICmRF), at diagnosis and at 3 years of MT. The reduction rates of IgG and IgG4 values at 3 years of MT relative to those at diagnosis were also evaluated.

3. Imaging findings

We evaluated imaging findings of pancreatic lesions (swelling pattern at the head, body, and tail) and other organ involvements (OOIs), as well as the number of OOIs at diagnosis. In this study, OOIs were defined as lacrimal/salivary lesions, lung lesions, pulmonary hilar or mediastinal lymph node lesions, bile duct lesions, kidney lesions, and retroperitoneal fibrosis showing swelling or wall thickening that responded well to corticosteroid therapy. Extrapancreatic bile duct lesions were evaluated based on endoscopic retrograde cholangiography. Lung lesions and hilar lesions included mild lesions responding well to corticosteroid therapy. Lung lesions were evaluated for mass, nodularity, ground-glass opacity, thickening of bronchovascular bundles, and interlobular septae by chest computed tomography (CT) images. We also measured the anteroposterior diameter of affected pancreatic parenchyma at diagnosis and at 3 years of MT for calculations of reduction rate. The pancreatic head was defined as the right-side portion from the left-side edge of the superior mesenteric and portal veins. The pancreatic body and tail were separated by a line equally dividing the remaining portion. The anteroposterior diameter of pancreatic parenchyma was measured as the maximum diameter of each head, body, and tail parts of cross-sectional enhanced CT images. Pancreatic head diameter was measured by a line through the center of the superior mesenteric vein and vertical to the spinous processes of the vertebrae. The diameters of the pancreatic body and tail were measured by a line vertical to the MPD. We also assessed for pancreatic stone formation and calcification

after AIP diagnosis.

4. Relapse

We evaluated the number and organs of relapses occurring during the 3 years after corticosteroid introduction and searched for relationships with those after 3 years of MT.

Statistical analysis

In univariate analysis, the Mann-Whitney U test was used for continuous variables and the Chi-squared and Fisher's exact tests were adopted for qualitative variables. Receiver operating characteristic (ROC) curves were calculated to establish cutoff values for the continuous variables exhibiting significant differences. The Cox proportional hazards model was employed for multivariate analysis. The Kaplan-Meier survival method and log-rank test were used for determining cumulative relapse rate. *P* values of less than 0.05 were considered statistically significant. Analyses were performed using Statflex software, version 6.0 (Artech CO., Ltd., Osaka, Japan).

Ethics

The present study was approved by the ethics committee of Shinshu University School of Medicine (approval number: 3596).

Results

The risk factors associated with relapse after 3 years of MT were assessed as described below.

1. Parameters at diagnosis

1.1 Clinical features

Relapse patients had significantly less frequent jaundice than did non-relapse patients at diagnosis (P = 0.005), with no other significant differences between the groups (Table 1).

1.2 Laboratory findings

The relapse group had significantly higher serum IgG and significantly lower serum C3 values than did the non-relapse group (P = 0.005 and 0.022) (Table 1).

1.3 Imaging findings

There were no significant differences in the locations of pancreatic swelling or bile duct lesions between the groups. The relapse group had significantly more frequent lacrimal/salivary gland lesions (P = 0.003), lung lesions (P = 0.042), kidney lesions (P = 0.020), and retroperitoneal fibrosis (P = 0.011) than did the non-relapse group. Patients with ≥ 4 OOI lesions at diagnosis were also significantly more likely to relapse than those without (P = 0.002) (Table 2).

2. Relationships with corticosteroid therapy

2.1 Observation and corticosteroid administration periods

There were no significant differences in observation period, corticosteroid administration period, or daily corticosteroid dose at 3 years of MT between the relapse and the non-relapse groups after 3 years of MT. There were no statistical differences in relapse rate after 3 years of MT for corticosteroid doses of ≤ 2.5 mg/day vs. > 2.5 mg/day or ≤ 5 mg/day vs. > 5 mg/day (data not shown). The indication for corticosteroid

therapy in the relapse group favored extra-pancreatic lesions apart from bile duct lesions more frequently than in the non-relapse group ($P = 0.038$) (Table 3).

2.2 Relapse during the 3 years after corticosteroid introduction

There were no significant differences in the frequency or distribution of relapse during the 3 years after corticosteroid introduction between the groups (data not shown).

2.3 Relapse organs after 3 years of MT

The pancreas was the most prevalent relapse organ after 3 years of MT (Table 4).

3. Laboratory findings at 3 years of MT

The relapse group had significantly higher serum IgG and IgG4 values at 3 years of MT than those of the non-relapse group ($P = 0.018$ and 0.020) (Table 5). At 3 years of MT, normalization of IgG4 (< 135 mg/dL) was found in 1 of 12 patients (8.3%) and normalization of IgG (< 1700 mg/dl) was seen in 8 of 13 patients (61.5%) in the relapse group. IgG4 and IgG normalization was detected in 5 of 18 patients (27.8%) and 13 of 17 (76.4%) patients, respectively, in the non-relapse group. There were no significant differences in the reduction rate of IgG or IgG4 values between the time of 3 years of MT and at diagnosis between the groups. In ROC curve analysis, serum IgG of 1400 mg/dL and IgG4 of 330 mg/dL at 3 years of MT were the optimal cutoff values to predict relapse after 3 years of MT, with a sensitivity of 84.6%, specificity of 70.8%, and area under the ROC curve (AUC) of 0.739 for a serum IgG cutoff of 1400 mg/dL and a sensitivity of 75.8%, specificity of 71.4%, and AUC of 0.746 for a serum IgG4 cutoff value of 330 mg/dL.

4. Relationship with pancreatic imaging findings

4.1 Anteroposterior diameter of pancreatic parenchyma

There was no significant difference in the anteroposterior diameter of pancreatic parenchyma at diagnosis between the groups. At 3 years of MT, the relapse group had a significantly thicker pancreatic head and tail than did the non-relapse group ($P = 0.045$ and 0.024) (Table 6). The optimal cutoff values predicting relapse after 3 years of MT were 15 mm for pancreatic head and 20 mm for pancreatic tail at 3 years of MT, with sensitivities of 85.7% and 62.5%, specificities of 77.8% and 83.4%, and AUCs of 0.778 and 0.781.

4.2 Reduction rate of anteroposterior diameter of pancreatic parenchyma

The relapse group had a significantly lower reduction rate of anteroposterior diameter of the pancreatic head at 3 years of MT compared with diagnosis than did the non-relapse group ($P = 0.025$) (data not shown). A reduction rate of 45% provided the optimal cutoff value to predict relapse after 3 years of MT, with a sensitivity of 83.3%, specificity of 83.3%, and AUC of 0.810.

4.3 Pancreatic stone formation and calcification

At AIP diagnosis, there were 3 patients each with pancreatic calcification in the relapse and non-relapse groups. After AIP diagnosis, 1 patient with pancreatic stone formation and 1 patient with calcification were found in the relapse group, while in the non-relapse group, 2 patients with calcification were detected. There were no significant differences in pancreatic stone or calcification rates (data not shown).

5. Multivariate analysis

5.1 Predictive factors of relapse after 3 years of oral corticosteroid MT

Cox proportional hazards regression analysis was conducted to confirm the optimal parameters for predicting relapse after 3 years of MT. Candidate variables were selected from the clinical and imaging findings at diagnosis and serological variables at 3 years of MT showing significant differences in univariate analysis. Predictive variables were selected using the bidirectional elimination method. According to multivariate analysis, ≥ 4 OOI number at diagnosis (hazard ratio [HR], 5.82; 95% confidence interval [CI], 1.203-28.192, $P = 0.029$) and IgG ≥ 1400 mg/dL at 3 years of maintenance therapy (hazard ratio [HR], 4.41; 95% confidence interval [CI], 1.096-17.790, $P = 0.037$) were predictive factors of relapse following MT for 3 years (Table 7).

5.2 Analysis of relapse prediction factors after 3 years of MT

We divided the cohort into groups with and without individual relapse prediction factors and examined the cumulative relapse rate after 3 years of MT by Kaplan-Meier testing and the log-rank test. The groups with ≥ 4 OOI number at diagnosis or serum IgG ≥ 1400 mg/dL at 3 years of MT showed significantly higher cumulative relapse rates than counterpart groups ($P = 0.001$ and $P < 0.001$) (Figure 1a and 1b). Fourteen patients without either predictive factor showed relapse in one patient (7.1%), 12 patients with one predictive factor exhibited relapse in three patients (25%), and 11 patients with two predictive factors showed relapse in nine patients (81.8%). Based on these results, the group with both predictive factors had a significantly higher cumulative relapse rate than the group with none or one predictive factor ($P < 0.001$) (Figure 1c).

Discussion

The present study revealed a close association between specific risk factors and relapse after 3 years of oral corticosteroid MT. These parameters may provide useful information in deciding whether to continue long-term treatment and in constructing therapeutic strategies for extended periods.

1. Predictive factors for relapse after 3 years of oral corticosteroid maintenance therapy

1.1 Clinical features

Univariate analysis of clinical features at diagnosis showed less frequent jaundice in the relapse group, which was in contrast to previous reports indicating jaundice at diagnosis to be a risk factor for relapse.[24-26] One reason for this unexpected result may be that the indication for corticosteroid therapy in the relapse group favored extra-pancreatic lesions other than bile duct lesions compared with the non-relapse group, resulting in a lower incidence of jaundice.

1.2 Laboratory findings

The relapse group had higher serum IgG at diagnosis and higher serum IgG and IgG4 at 3 years of MT than did the non-relapse group. Previous studies have reported elevated serum IgG4 at diagnosis,[24,27,28] persistently high IgG4 after corticosteroid induction,[29] and a low reduction rate of IgG4 after corticosteroid induction [23] as predictive factors for relapse, suggesting that cases under insufficient disease activity control by corticosteroids could easily relapse during treatment. Hirano et al. focused on changes in serum IgG and IgG4 before and after corticosteroid therapy and found that 46 of 48 AIP patients (96%) exhibited normal serum IgG (i.e., under 1800 mg/dL) after remission induction therapy. ROC curve analysis revealed the optimal cutoff value in distinguishing between aggravation and remission phases to be 1600 mg/dL (77% sensitivity, 94% specificity, and 85% accuracy). In the same way, 13 of 42 AIP patients showed normal

serum IgG4 (i.e., under 135 mg/dL) after remission induction therapy, with an optimal cutoff value for this differentiation of 244 mg/dL (81% sensitivity, 67% specificity, and 74% accuracy).[30] These proposed cutoff values are in agreement with the IgG and IgG4 cutoff values at 3 years of MT in our cohort. Based on the above studies, serum IgG and IgG4 values under 1400 mg/dL and 330 mg/dL, respectively, have been approved as suitable benchmarks for disease control under MT. However, IgG, and not IgG4, appeared to be a more reliable marker for relapse in this study based on a multivariate model. Shiokawa et al. found that in a neonatal mouse model, pancreatic injury was induced by injecting human AIP IgG1 or IgG4, with more destructive changes induced by the former. The potent pathogenic activity of IgG1 was significantly inhibited by simultaneous injection of IgG4.[31] These results suggested that pathogenic autoantibodies of AIP are included in the IgG1 subclass, a major part of IgG, and not in the IgG4 subclass, and indicated that IgG was a more reliable predictor of relapse than IgG4. The relapse group also had significantly lower serum C3 at diagnosis than did the non-relapse group. Muraki et al. reported that active phase AIP patients exhibited high serum IC values, and those with high serum IC determined by C1q assays had a tendency for low serum C3, significantly low serum C4, and high serum IgG1.[32] Accordingly, complement levels before corticosteroid therapy might be reflected in disease activity during treatment.

1.3 Imaging findings

The relapse group was significantly more frequently complicated with lacrimal/salivary gland lesions, lung lesions, kidney lesions, retroperitoneal fibrosis, and ≥ 4 OOIs at diagnosis compared with the non-relapse group. Extra-pancreatic lesions of the lacrimal/salivary glands [33,34] and bile duct [6,11,26,28] are reported risk factors for relapse. Taken together, AIP cases with multi-organ lesions at diagnosis may possess high disease

activity and be more predisposed to relapse after 3 years of MT. A shortcoming of this study was that imaging analysis of lacrimal/salivary gland and other head lesions were not evaluated in all non-relapse group patients, which may have accounted for no significant associations in multivariate analysis. Another shortcoming is that the number of OOIs may have varied according to the observer or individual institution. Pancreatic imaging analysis showed that the relapse group had significantly thicker pancreatic head and tail regions and a lower reduction rate of the pancreatic head region at 3 years of MT than did the non-relapse group. Ohno et al. reported that AIP patients with a large pancreatic volume or less pancreatic volume reduction after treatment were more predisposed to relapse,[22] indicating that post-treatment pancreatic thickness might reflect disease activity in the remission phase of AIP. We believe that anteroposterior diameter measurement of pancreatic parenchyma is simpler than volume measurement and represents a useful way to predict relapse in daily clinical care. However, an insufficient number of cases was analysed for lesions among pancreatic sections, which might have been a reason why multivariate analysis did not show these factors as predictive of relapse. We observed no significant differences in the location or extent of pancreatic lesions between the two groups. Some studies reported diffuse pancreatic swelling [13,35] and diffuse pancreatic duct lesions [33] as risk factors of relapse, whereas another found no significant difference in relapse rate between diffuse and localized pancreatic swelling.[6] The results of the present investigation support the latter notion; there were no significant differences in the incidence of pancreatic calcification between the relapse and non-relapse groups, although our previous study had indicated that pancreatic calcification was significantly associated with relapse.[36] This discrepancy may have been due to insufficient patient number and differences in the definition of relapse.

1.4 Relationships with corticosteroid therapy

There were no significant differences in daily corticosteroid dose at 3 years of MT between the relapse and the non-relapse groups, possibly because the corticosteroid dose might have been insufficient in the relapse group.

2. Strategy for long-term AIP treatment based on proposed predictive factors of relapse

Using multivariate analysis, we identified ≥ 4 OOI number at diagnosis and IgG ≥ 1400 mg/dL at 3 years of MT as predictive factors of relapse after 3 years of MT in AIP. Kubota et al. described the relapse rate of AIP patients under MT in a large-scale retrospective cohort study of 510 cases to be 10% within a year, 25.8% within 3 years, 35.1% within 5 years, and plateauing at 43% at 7 years; relapse rate increased over 7 years of MT, indicating that persistent therapy was needed even after 3 years.[13] AIP patients with both relapse prediction factors may have a considerable risk of relapse after 3 years of MT and are therefore advised to continue treatment to prevent recurrence and undergo careful follow-up for early detection and management of subclinical relapse. Shimizu et al. reported over 8694 mg of cumulative corticosteroid administration to be a risk factor for severe adverse drug effects.[18] In accordance with these results, Kubota et al. concluded that MT of 5 mg/day for 3 years would be comparatively safe, because of that total corticosteroid dose would be 4625 mg of cumulative corticosteroids at 2 years and 6425 mg at 3 years.[13] Patients with none or one predictive factor are regarded to be at low risk for relapse after 3 years of MT owing to low disease activity and may be candidates for corticosteroid discontinuation to avoid adverse effects. Accordingly, patients with IgG < 1400 mg/dL at 3 years of MT and/or < 4 OOIs at diagnosis may be candidates for cessation of corticosteroids, but the unpredictability of an IgG increase after stopping MT remains a risk.

Conclusion

In the present study, we revealed two predictive factors for AIP relapse after 3 years of corticosteroid MT: ≥ 4 OOI number at diagnosis and IgG ≥ 1400 mg/dL at 3 years of MT. Relapse was associated with the number of these predictive factors, which will provide useful information in deciding corticosteroid therapy regimens at 3 years of MT to minimize AIP relapse and adverse drug effects.

Abbreviations

AIP - autoimmune pancreatitis, BMI - body mass index, β2MG - beta-2 microglobulin, CT - computed tomography, DM - diabetes mellitus, IC - immune complex, ICDC - International Consensus Diagnostic Criteria, ICmRF - immune complex by monoclonal rheumatoid factor, MPD - main pancreatic duct, sIL2-R - soluble interleukin 2 receptor, MT - maintenance therapy, OOI - other organ involvement.

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Table 1. Clinical Characteristics and Laboratory Data at AIP Diagnosis

	Relapse after 3 years of MT		
	(+)	(-)	***P***
	n = 13	n = 25	
Clinical characteristic			
Age, years	59.0 (49–67)	63 (47–81)	0.054
Male	12 (92)	19 (76)	0.385
BMI, kg/m^2	21.22 (17.44–25.48)	20.72 (14.65–24.64)	0.451
Alcohol intake	9 (69)	11 (44)	0.140
Smoking	9 (69)	14 (n = 24, 58)	0.725
Allergy	6 (n = 12, 50)	6 (24)	0.146
DM treatment	2 (15)	6 (24)	0.689
Jaundice	3 (23)	17 (n = 24, 71)	0.005
Laboratory data			
IgG, mg/dL	2741 (1629–7550)	1930 (1167–4538)	0.005
IgG4, mg/dL	758 (245–3890)	600 (4–1910)	0.095
sIL2-R, IU/mL	1210 (439–4695)	862 (390–2788)	0.191
β2MG, mg/dL	2.7 (1.5–6.4)	2.2 (1.4–4.2)	0.182
C3, mg/dL	73 (29–126)	107 (40–215)	0.022
C4, μg/mL	14.3 (1.1–47.3)	22.5 (0.8–40.1)	0.140
ICmRF, μg/mL	6.3 (3.5 – 41.6)	6.1 (2.0 – 53.0)	0.108

Data are expressed as the median (range) or number of patients (%).

Table 2. Imaging Findings at AIP Diagnosis

	Relapse after 3 years of MT		*P*
	(+)	(-)	
AIP			
Diffuse	10/13 (77)	21/25 (84)	0.672
Head	10/13 (77)	24/25 (96)	0.107
OOI			
IgG4-SC *	9/12 (75)	23/24 (96)	0.098
Extra-pancreatic bile duct	6/9 (67)	14/23 (61)	1.000
Lacrimal or salivary gland	10/10 (100)	4/10 (40)	0.003
Lung	8/11 (73)	9/25 (36)	0.042
Pulmonary hilar or mediastinal lymph node	11/11 (100)	21/25 (84)	0.29
Kidney	7/12 (58)	4/24 (17)	0.020
Retroperitoneum	10/13 (77)	6/25 (24)	0.002
Total number of OOI			
≥ 4	10/13 (77)	6/25 (24)	0.002

Data are expressed as the number of patients/evaluable patients (%).

*** Intra- and/or extra-pancreatic bile duct lesion.**

Table 3. Corticosteroid Administration Characteristics

	Relapse after 3 years of MT		
	(+)	(-)	***P***
	n = 13	n = 25	
Observation period, years	9.5 (5.6–18.9)	11.4 (5.2–23.4)	0.498
Dosage period of PSL, years	9.4 (5.6–8.8)	11.3 (5.2–21.2)	0.712
Dose of PSL *, mg/day	2.5 (2.5–12.5)	2.5 (1.25–15)	0.865
Reason for PSL induction			
Pancreas and/or bile duct	9 (69)	22 (88)	0.203
OOI other than bile duct	4 (31)	1 (4)	0.038
Other	0 (0)	2 (8)	0.538

Data are expressed as the median (range) or number of patients (%). *At 3 years of maintenance therapy. PSL, prednisolone

Table 4. Relapse Organ After 3 Years of MT	
	n
Pancreas	8/13 (62)
Bile duct	3/9 (33)
Lacrimal or salivary gland	3/10 (30)
Lung	4/8 (50)
Pulmonary hilar or mediastinal lymph node	5/11 (45)
Kidney	2/7 (29)
Retroperitoneum	3/10 (30)
Data are expressed as patients/patients with organ lesion at diagnosis (%).	

Table 5. Laboratory Data at 3 Years of MT

	Relapse after 3 years of MT		
	(+)	(-)	***P***
	n = 13	n = 25	
IgG, mg/dL	1553 (848–3073)	1332 (727–1924)	0.018
IgG4, mg/dL	487 (122–1720)	245 (6–928)	0.020
sIL2-R, IU/mL	477 (188–663)	400 (148–2184)	0.477
β2MG, mg/dL	1.9 (1.2–5.5)	1.6 (1.2–3.5)	0.299
C3, mg/dL	91.5 (72–114)	98.0 (51–144)	0.266
C4, μg/mL	21.9 (13.6–28.7)	22.2 (10.2–30.4)	0.972
ICmRF, μg/ml	3.5 (2.0–7.7)	2.4 (2.0–5.3)	0.538

Data are expressed as the median (range).

Table 6. Anteroposterior Diameter of Pancreatic Lesions

	Relapse after 3 years of MT					
	(+)	(-)	***P***	(+)	(-)	***P***
	At diagnosis			At 3 years of MT		
Head lesion: +	n = 9	n = 21		n = 7	n = 18	
Diameter, mm	30.9 (20.0–42.0)	31.0 (16.0–45.0)	0.717	26.0 (9.0–32.0)	12.0 (6.0–32.0)	0.045
Body lesion: +	n = 10	n = 20		n = 8	n = 19	
Diameter, mm	27.0 (17.0–35.0)	28.0 (12.0–38.0)	0.692	21.5 (7.0–33.0)	15.0 (9.0–25.0)	0.070
Tail lesion: +	n = 11	n = 22		n = 8	n = 18	
Diameter, mm	27.0 (20.0–57.1)	27.0 (13.0–49.0)	0.592	22.5 (12.0–36.5)	15.0 (8.0–25.0)	0.024

Excluding patients without enhanced CT at diagnosis or during 2 - 4 years from corticosteroid induction. Data are expressed as the median (range).

Table 7. Predictive Factors of Relapse After 3 Years of MT in Multivariate Analysis

	Hazard ratio (95% CI)	*P*
≥ 4 OOI number at diagnosis	5.82 (1.203–28.192)	0.029
IgG ≥ 1400 mg/dL at 3 years of MT	4.41 (1.096–17.790)	0.037

CI, confidence interval

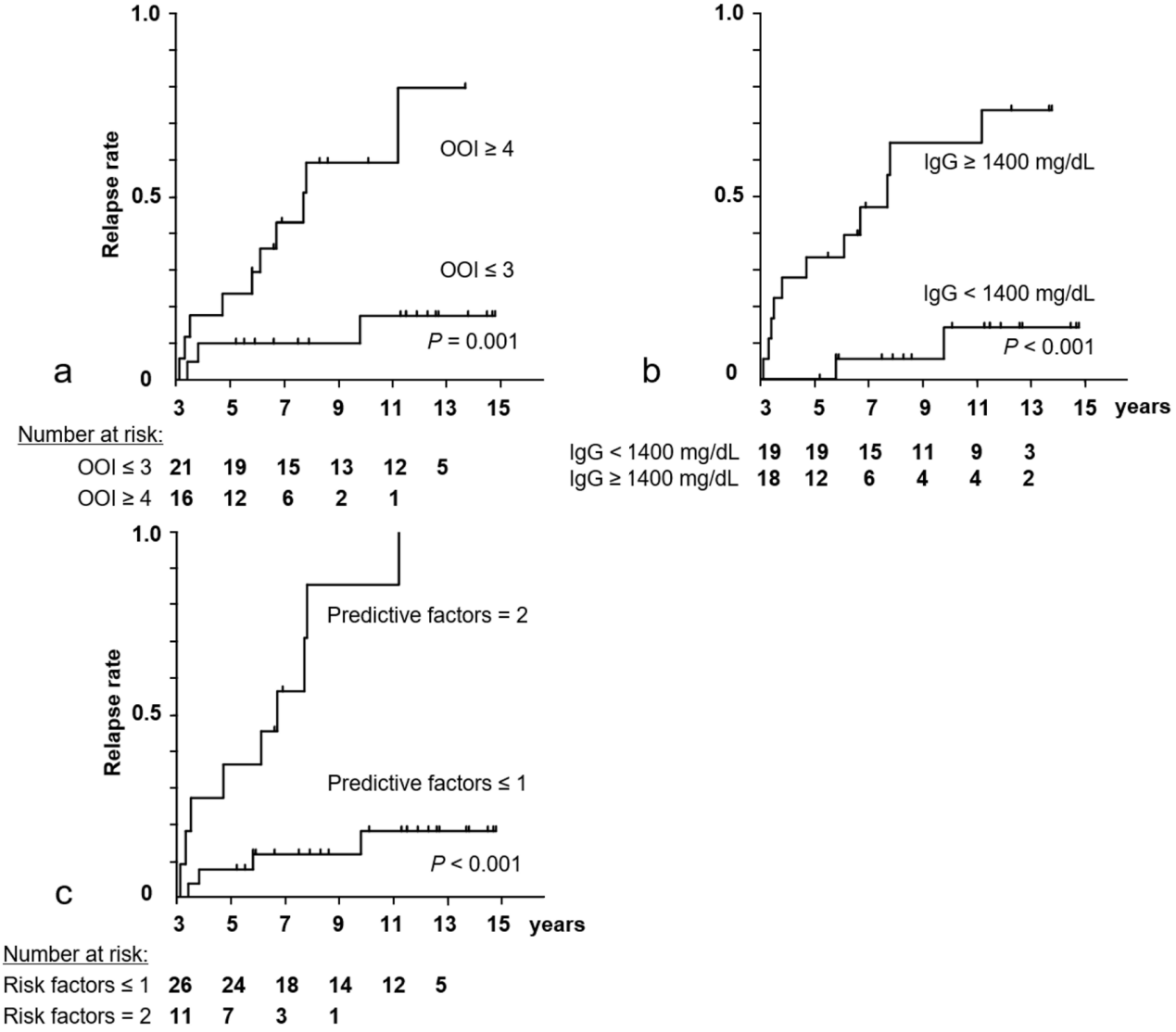

Figure. 1 Cumulative relapse rate after 3 years of MT. (a) Patients with OOI ≥ 4 at diagnosis showed a significantly higher cumulative relapse rate. (b) Patients with serum IgG ≥ 1400 mg/dL at 3 years of MT exhibited a significantly higher cumulative relapse rate. (c) Patients with both predictive factors had a significantly higher cumulative relapse rate than those with none or one predictive factor.