Risk Factors for Rate of Relapse and Effects of Steroid Maintenance Therapy in Patients With Autoimmune Pancreatitis: Systematic Review and Meta-analysis

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e64. Learning Objective–Upon completion of this activity, successful learners will be able to choose critically the exams that should be performed to diagnose autoimmune pancreatitis; recognize, diagnose, and describe possible other organ involvement in patients with IgG4-related autoimmune pancreatitis; and select the most appropriate test in the evaluation of suspected exocrine pancreatic insufficiency.

BACKGROUND & AIMS: **Risk for relapse after induction of remission with steroid therapy has been studied extensively in patients with autoimmune pancreatitis (AIP), but findings have been equivocal. We performed a systematic review and meta-analysis to estimate the relapse rate of AIP after initial remission after steroid treatment and to identify factors associated with relapse.**

METHODS: **Three reviewers searched MEDLINE, SCOPUS, and EMBASE until July 2018 to identify studies on rate of relapse of AIP after induction of remission with steroid therapy. A pooled estimate was calculated using the DerSimonian and Laird method for a random-effects model. This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.**

RESULTS: **Thirty-six studies met the inclusion criteria for meta-analysis. The median follow-up time was 40.8 months. Fifty-two percent of patients were classified as having type 1 AIP. The pooled estimate of relapse rate was 33% (95% CI, 30%–37%). A higher proportion of patients with type 1 AIP had a relapse compared with patients with type 2 AIP (37.5% vs 15.9%; $P < .001$). We found significant heterogeneity among studies ($P < .01$). Long-term maintenance therapy with steroids and study quality were associated independently with AIP relapse, after we adjusted for year of publication by multivariate meta-regression.**

CONCLUSIONS: **In a systematic review and meta-analysis, we found that a large proportion of patients with AIP treated successfully with steroid induction therapy had a relapse (33%)—particularly patients with type 1 AIP (37%). Maintenance steroid therapy lasting longer than 1 year could reduce risk of relapse. However, the data characterizing relapse rates are of limited quality, indicating the need for randomized controlled trials and new immunosuppressive drugs.**

Keywords: Pancreas; Inflammation; Response To Treatment; Long-Term Outcome.

Autoimmune pancreatitis (AIP) is a peculiar form of pancreatitis with specific clinical, radiologic, serologic, and histologic features.[1–3] Although the vast majority of AIP patients[4] initially respond to glucocorticoids, a significant proportion of patients relapse once steroid therapy is discontinued or reduced. The clinical course of the disease can be more severe in patients who relapse, with accelerated progression

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Abbreviations used in this paper: AIP, autoimmune pancreatitis; MST, maintenance steroid therapy; RCT, randomized controlled trial.

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toward chronic changes, with development of biliary strictures, pancreatic insufficiency, and extrapancreatic manifestations.[5,6] Therefore, prevention of relapse remains a major issue in the long-term management of AIP.

Several prospective and retrospective studies of steroid-based regimens for treatment of AIP have been published,[4,7–10] with relapse rates ranging broadly from 9.8%[11] to 62%.[12] The results of these studies are inconclusive or conflicting because of the relatively small sample size, short period of follow-up evaluation, and differences in baseline patient characteristics, diagnostic criteria, steroid dose (first course), maintenance protocol, definition of relapse, and re-treatment regimen. Importantly, the rate of relapse is known to be much higher in type 1 AIP, which is more common in Asia, in men, and in the seventh decade of life. Type 1 AIP is characterized by the presence of IgG4 and often involves other organs (60% of cases). Type 2 AIP occurs more frequently in Western countries, equally in younger men and women, is IgG4 negative, and is associated with inflammatory bowel disease.[13] When this distinction is not possible, AIP is defined as not otherwise specified.

In 2014, the Japanese consensus panel on AIP[14] concluded that maintenance steroid therapy (MST) with low-dose steroid should last for up to 3 years, with cessation in cases with radiologic and serologic improvement. In most Western countries, including the United States,[15] steroid treatment is tapered over a period of 12 to 16 weeks, after an induction period of 2 to 4 weeks. In 2017, the last consensus on treatment of AIP concluded that "maintenance therapy with low-dose glucocorticoids or steroid-sparing agents may be useful in some patients with type 1 AIP"[10] after successful induction of remission.

Therefore, questions persist regarding the modality of steroid tapering, MST and its duration, and the use of immunomodulating agents for maintenance.

To increase statistical power and to reduce uncertainty, we propose a systematic review and meta-analysis of the available studies. The aims of this meta-analysis were as follows: (1) to analyze the variability in AIP relapse rates by looking at the heterogeneity among the studies as a means of interpreting this; (2) to assess the efficacy of MST in reducing relapse rate; and, finally, (3) to identify risk factors for AIP relapse.

What You Need to Know

Background

Autoimmune pancreatitis (AIP) is a form of pancreatitis that can have multiple sequelae, such as exocrine and endocrine pancreatic insufficiency or extrapancreatic complications (eg, biliary stricture). Almost 100% of patients respond successfully to glucocorticoids, but data on relapse remain equivocal. Moreover, there is debate on how long maintenance steroid therapy (MST) should last

Findings

This meta-analysis of aggregate data from 31 studies shows that there is significant heterogeneity among relapse rates, which ranged from 9.8% to 59.2%. The pooled relapse rate was 32% (95% CI, 28%–35%) during a median follow-up period of 40.9 months. Subgroup analysis showed that the relapse rate was significantly lower for long-term MST than for short-term MST (27% vs 38%, respectively; $P = .01$). The benefit of long-term MST was confirmed by multivariate meta-regression.

Implications for patient care

This meta-analysis, which included more than 3000 patients with AIP, shows the efficacy of long-term MST in the prevention of disease relapse. In particular, patients with AIP type 1 could benefit from this type of regimen. The results of this meta-analysis are subject to several limitations, such as differences in design, sample size, baseline severity of illness, and maintenance regimens. Further randomized controlled trials are needed to determine the optimal duration and modality (steroid vs immunosuppressant) of maintenance therapy.

Methods

Literature Search and Study Selection

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Table 1).[16]

A systematic search of MEDLINE, EMBASE, and SCOPUS databases was performed including the following terms: "autoimmune pancreatitis," "relapse," "steroid therapy," and "maintenance." The search included reports published until July 2018.

To identify additional studies, the computer search was supplemented with manual searches of the reference lists of all review articles and primary studies retrieved. When the results of a single study were reported in more than one publication, only the most recent and complete data were included in the meta-analysis. Moreover, we performed a search for abstracts presented at main relevant pancreatic conference proceedings (United European Gastroenterology week, Digestive Disease Week, and European Pancreatic Club) during the past 4 years. Abstracts that had been published subsequently as a full-text study were excluded if a full-text study already was included in the meta-analysis.

Studies were included in the meta-analysis if they met the following criteria: (1) patients had a diagnosis of AIP according to International Consensus Diagnostic Criteria[7] for AIP, Mayo Clinic's HiSORT criteria,[17] Japanese Pancreas Society guidelines,[18] or Asian diagnostic criteria[19]; (2) steroid therapy was used for induction at an initial dose of at least 0.5 mg/kg/day or at least 20

mg/day; (3) steroid therapy was used for maintenance of remission; and (4) the proportion of patients with relapse was reported.

Studies were excluded if the patient cohorts included in the studies were overlapping, (in this case, only the more recent study was included), or if the follow-up time was shorter than 6 months.

Literature Review

Study-level variables included the last name of the first author, publication year, region where the study was conducted, study design, number of patients treated with steroids, number of centers (single vs multiple), length of follow-up evaluation, length of MST, definition of relapse, and study quality. Because of the lack of a worldwide accepted definition of relapse, we classified the studies according to their definition of AIP relapse into 3 categories: undefined (studies in which a clear definition of relapse was not reported), radiologic, or clinical and radiologic.

Studies were categorized based on the length of MST as short vs long term (shorter vs longer than 1 year).

Patient-level variables included age, sex, type of AIP (1 or 2), median IgG4 level at baseline, and the number of patients with diffuse enlargement of the pancreas, as shown by imaging. Each study was evaluated and classified by 3 independent investigators (M.T., C.C., and B.M). We performed a systematic review evaluating risk factors for AIP relapse in all the studies included in the meta-analysis.

Discrepancies among reviewers were not frequent (interobserver variation, $<10\%$) and were resolved by discussion.

Assessment of Study Quality

All studies were assessed for study quality according to a checklist based on a modified version of the Newcastle–Ottawa quality assessment scale,[20] with discrepancies resolved by consensus (Supplementary Table 2). Studies were graded using the following parameters: (1) representativeness of the exposed cohort, (2) ascertainment of exposure, (3) demonstration that outcome of interest was not present at the start of the study, (4) assessment of outcome, (5) sufficient period of follow-up evaluation, and (6) adequacy of follow-up evaluation. Each parameter was given a numeric score from 0 to 2. Studies with scores of 9 or greater were classified as high quality, and scores lower than 9 were classified as low quality. In abstract, it was not possible to assess methodologic quality.

Statistical Analysis

The crude relapse rate was extracted as an outcome measure. Pooled estimates were obtained using a random-effects model with the generic inverse variance method. The method of moments estimator, proposed by DerSimonian and Laird, was used to assess between-study variance.[21,22] Heterogeneity was assessed with the Pearson chi-square test and the I^2 statistic. We considered a priori subgroups based on study-level (publication year, region where the study was conducted, study design, number of centers, length of follow-up evaluation, length of maintenance, definition of relapse, and study quality) and patient-level variables (age, sex, AIP type, IgG4 levels, and diffuse pancreatic enlargement on imaging). Univariate and multivariate logistic meta-regression analysis was used to examine associations between patient- or study-level covariates and relapse rate. Variables with a P value less than .1 in univariate meta-regression were included in multivariate meta-regression. For all other analyses, a P value less than .05 was considered statistically significant. The amount of heterogeneity in the outcome explained by risk factors was evaluated with the R^2 index. The Egger regression test was performed to evaluate the asymmetry of the Begg funnel plot and potential publication bias. We used the nonparametric approach reported by Combescure et al[23] to assess the pooled relapse probability over time. R Core Team (2018): A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria) was used to obtain all analyses and graphics.

Results

Literature Search

Our primary search identified 414 titles. After removal of duplicate articles, we identified 176 studies. We excluded 104 articles because they were not consistent with our aim. Finally, 72 studies (62 full-text articles and 10 abstracts) were included in a qualitative synthesis and full-text was reviewed to establish eligibility for quantitative analysis. After review of the studies, 31 full-text articles[6,9,11,12,24–50] and 5 abstracts[51–55] (1 randomized clinical trial, 21 retrospective studies, and 14 prospective studies) fulfilled the inclusion criteria and were selected for meta-analysis (Figure 1).

Study Characteristics

Table 1 reports the features of the studies selected for quantitative analysis. A total of 3595 patients with AIP treated with steroids were included in the meta-analysis. The number of patients treated with steroids varied greatly, ranging from 11[55] to 736.[6] Thirteen studies[24–26,28,32,34,35,37–39,41,49,52,55] included fewer than 30 patients, with wide CIs resulting in inaccurate estimates of relapse rates. Twenty-two studies were performed in Asian countries,[11,24–26,29,32–34,37,39,41,42,44,45,47–50,52

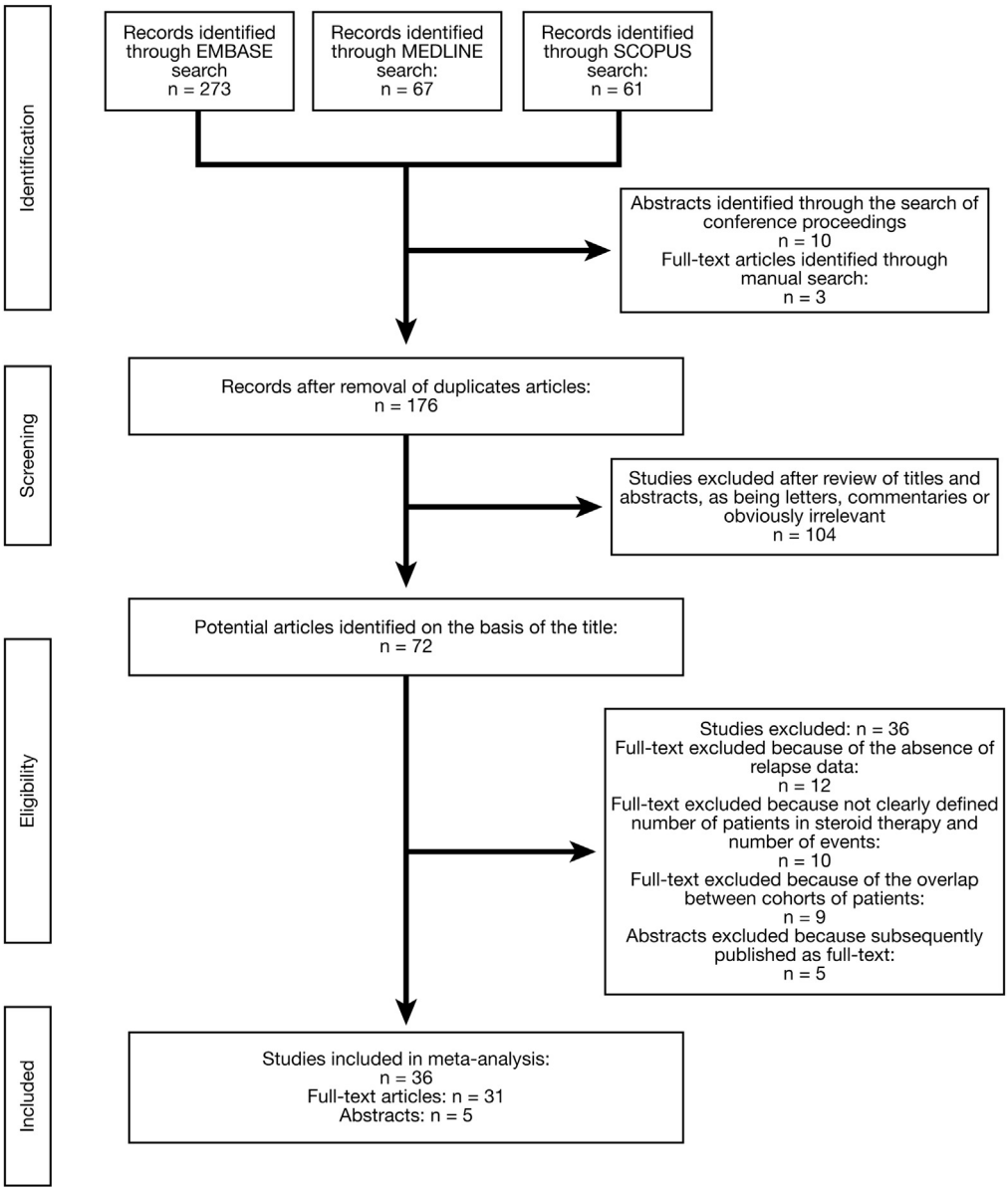

Figure 1. Study flow chart.

and 12 were conducted in Western countries.[5,12,28,30,31,35,38,43,46,51,54,55] Two were multinational studies.[6,40] Twenty-three studies were conducted at single centers.[24–30,33,35,37–39,42,49–55] Thirteen studies were multicentric.[6,9,11,12,31,34,36,40,41,45–48]

In 8 studies[12,24,32–34,36,44,50] relapse was defined radiologically, whereas in 17 studies[9,27–31,35,39–42,45–49,54] it was defined clinically and radiologically. Relapse was not clearly defined in 11 studies (including 4 abstracts).[6,11,25,26,37,38,43,51–53,55] In 16 studies[9,11,24–26,29,32,37,39,41,44,45,47,48,50,55] MST lasted more than 1 year (long-term maintenance). In 13 studies[12,27,28,30,31,33,35,36,38,42,43,46,49] MST was shorter than 1 year (short-term maintenance). The randomized controlled trial (RCT)[34] and the large multinational multicentric study[40] included were split into 2 subgroups according to length of MST. The length of MST was not defined clearly in 1 full-text article[6] and in 4 abstracts.[51–54] The median length of follow-up evaluation differed among studies, ranging from 6[38] to 61.1[48] months, with a median value of 40.8 months (interquartile range, 20.2 mo). In 6 studies[24,36,38,42,43,49] the length of follow-up evaluation was shorter than 2 years. In 27 studies[6,9,11,12,25–30,37,39,41,44–48,50–52,54] the length of follow-up evaluation was longer than 2 years (in 2 studies[53,55] it was not clearly specified). Methodologic quality scores (scale, 0–12) ranged from 5[37,38,43] to 12[27,45] (Supplementary Table 3).

The percentage of men ranged from 45%[35] to 89%.[47] The median age ranged from 30.1[35] to 71 years,[31] with a median age of 63.5 years. The median IgG4 values of patients treated with steroids were available from only 9 studies[25,26,32,34,38,44,47,48,50]; values ranged from 114[38] to 534 mg/dL,[44] with a median of 383 mg/dL. The

Table 1. Study- and Patient-Level Characteristics for Studies Included in the Meta-Analysis

Study	Year of publication	Study design	Country	Type of studies: number of centers	Diagnostic criteria	Total number of patients	Patients treated with steroid, n	Relapse definition	Long-term length of maintenance	Median or mean time of follow-up evaluation (range), *mo*	Quality score	Median age, *y*	Males, %	Median IgG4, *mg/dL*	Diffuse pancreatic enlargement, %
Full-text articles															
Wakabayashi et al[24]	2005	Prospective	Japan	Unicentric	JPS 2002	35	21	Radiologic	Yes	20 (3–44)	6	60.3	76.2	NA	76.2
Nishino et al[25]	2006	Prospective	Japan	Unicentric	JPS 2002	12	12	Undefined	Yes	41 (18–133)	6	65	50	135	100
Hirano et al[26]	2007	Prospective	Japan	Unicentric	HiSORT	42	19	Undefined	Yes	41 (10–114)	9	64	84.2	440	NA
Park et al[27]	2008	Prospective	South Korea	Unicentric	HiSORT	46	40	Clinical and radiologic	No	39 (21–57)	12	58.5	80	NA	NA
Kamisawa et al[11]	2008	Prospective	Japan	Multicentric	JPS 2006 revised	41	41	Undefined	Yes	43.5 (17.4–69.6)	6	63.5	73.2	NA	7.3
Maire et al[28]	2010	Prospective	France	Unicentric	HiSORT	44	26	Clinical and radiologic	No	41 (5–130)	10	NA	NA	NA	NA
Kubota et al[29]	2011	Prospective	Japan	Unicentric	Asian diagnostic criteria	70	42	Clinical and radiologic	Yes	46.9 (NA)	11	NA	NA	NA	NA
Ikeura et al[30]	2013	Prospective	Italy	Unicentric	ICDC	92	74	Clinical and radiologic	No	>24	9	49	NA	NA	64
Huggett et al[12]	2014	Prospective	United Kingdom	Multicentric	ICDC	115	98	Radiologic	No	32.5 (0.8–107)	7	61	NA	NA	43
Buijs et al[31]	2015	Prospective	Holland	Multicentric	ICDC	107	89	Clinical and radiologic	No	74	11	71	87	NA	NA
Hart et al[35]	2016	Prospective	United States	Unicentric	ICDC	43	20	Clinical and radiologic	No	34.8	9	30.1	45	NA	35
Hirano et al[32]	2016	Prospective	Japan	Unicentric	Asian diagnostic criteria	21	21	Radiologic	Yes	43 (19–48)	9	67	85.7	192	NA
Lee et al[33]	2018	Prospective	Korea	Unicentric	ICDC	244	138	Radiologic	No	60 (24–197)	11	59.9	81.2	NA	50
Masamune et al[34] (short)[a]	2017	RCT	Japan	Multicentric	ICDC	19	19	Radiologic	No	36	9	63.2	NA	532.9	46.7
Masamune et al[34] (long)[a]	2017	RCT	Japan	Multicentric	ICDC	30	30	Radiologic	Yes	36	9	63.2	NA	387.3	57.9
Ryu et al[36]	2008	Retrospective	Korea	Multicentric	HiSORT	67	55	Radiologic	No	20 (2–88)	6	56	NA	NA	100
Kamisawa et al[9]	2009	Retrospective	Japan	Multicentric	Asian diagnostic criteria	563	451	Clinical and radiologic	Yes	>12 (NA)	7	62.3	82.9	NA	10
Uchida et al[37]	2009	Retrospective	Japan	Unicentric	JPS 2006 revised	52	12	Undefined	Yes	40.8 (18–130)	5	68.5	83.3	NA	100
Raina [38]	2009	Retrospective	United States	Unicentric	HiSORT	26	19	Undefined	No	6 (NA)	5	62.5	63.2	114	21
Takuma [39]	2011	Retrospective	Japan	Unicentric	Asian diagnostic criteria	50	29	Clinical and radiologic	Yes	50 (12–134)	8	66	NA	NA	10.3
Kamisawa et al[40] (histologic)[b]	2011	Retrospective	Multinational	Multicentric	Diagnostic criteria of each country	268	111	Clinical and radiologic	NA	>24 (NA)	7	NA	NA	NA	NA

Table 1. Continued

Study	Year of publication	Study design	Country	Type of studies: number of centers	Diagnostic criteria	Total number of patients	Patients treated with steroid, n	Relapse definition	Long-term length of maintenance	Median or mean time of follow-up evaluation (range), *mo*	Quality score	Median age, *y*	Males, %	Median IgG4, *mg/dL*	Diffuse pancreatic enlargement, %
Kamisawa et al[40] (nonhistologic)[b]	2011	Retrospective	Multinational	Multicentric	Diagnostic criteria of each country	463	387	Clinical and radiologic	[c]	>24 (NA)	7	54.9	NA	NA	NA
Hart et al[6]	2013	Retrospective	Multinational	Multicentric	Diagnostic criteria of each country	1064	736	Undefined	NA	>24 (NA)	7	NA	NA	NA	NA
Liu et al[41]	2013	Retrospective	China	Multicentric	Asian diagnostic criteria	68	28	Clinical and radiologic	Yes	NA (12–36)	9	62	71.4	NA	60.7
Xin et al[42]	2014	Retrospective	China	Unicentric	ICDC	100	41	Clinical and radiologic	No	16.5 (NA)	8	NA	NA	NA	NA
Rasch et al[43]	2015	Retrospective	Germany	Unicentric	ICDC	53	33	Undefined	No	21 (0.25–72)	5	NA	NA	NA	NA
Shimizu et al[44]	2015	Retrospective	Japan	Unicentric	ICDC	84	65	Radiologic	Yes	54.1 (6.1–178.1)	6	65.6	NA	534	NA
Ohno et al[45]	2016	Retrospective	Japan	Multicentric	ICDC	41	32	Clinical and radiologic	Yes	36 (3–107)	12	63	81.3	NA	100
López-Serrano et al[46]	2016	Retrospective	Spain	Multicentric	ICDC	52	42	Clinical and radiologic	No	45 (NA)	8	64,4	NA	NA	NA
Miyazawa et al[47]	2017	Retrospective	Japan	Multicentric	ICDC	82	82	Clinical and radiologic	Yes	52.9 (13.1–180.4)	10	65.6	89	381.5	65.9
Kubota et al[48]	2017	Retrospective	Japan	Multicentric	ICDC	510	510	Clinical and radiologic	Yes	61.1 (20.2–101.9)	10	65.2	77.1	510	19.4
Rana et al[49]	2018	Retrospective	India	Unicentric	ICDC	18	12	Clinical and radiologic	No	8.5	6	56.25	66.7	NA	50
Suzuki et al[50]	2018	Retrospective	Japan	Unicentric	ICDC	102	73	Radiologic	Yes	>24 (NA)	7	66	72.6	383	NA
Abstracts															
Jimenez et al[51]	2017	Retrospective	Chile	Unicentric	NA	60	60	Undefined	NA	>60 (NA)	NA	47	63	NA	NA
Kato et al[52]	2016	Prospective	Japan	Unicentric	NA	30	30	Undefined	NA	57 (NA)	NA	NA	NA	NA	NA
Blayney et al[53]	2015	Retrospective	United States	Unicentric	NA	52	34	Undefined	NA	NA	NA	49	NA	NA	NA
Sumi[54]	2014	Retrospective	Australia	Unicentric	NA	52	52	Clinical and radiologic	NA	36 (NA)	NA	NA	NA	NA	NA
Storey et al[55]	2014	Retrospective	United Kingdom	Unicentric	NA	17	11	Undefined	Yes	NA	NA	61	82	NA	NA

ICDC, International Consensus Diagnostic Criteria; JPS, Japanese Pancreas Society; NA, data were not available;
[a]The study by Masamune et al35 was split into 2 cohorts (short and long) according to different lengths of maintenance treatment.
[b]The study by Kamisawa et al41 was split into 2 different cohorts (histologic and nonhistologic) because there were no data about the whole cohort.
[c]Regarding length of maintenance, this study was subdivided into 2 cohorts: short term and long term.

percentage of patients with diffuse pancreatic enlargement at imaging ranged from 7.3%[11] to 100%.[25,36,37,45] This information was available in 18 studies.[9,11,12,24,25,30,33–39,41,45,47–49]

Eight studies[12,32,33,39,44,45,47,48] included only patients with type 1 AIP, and 1 study[35] included only type 2 AIP patients. Five studies distinguished between type 1 AIP and type 2 AIP patients treated with steroids, and provided data on their relapse rate (Supplementary Table 4). The remaining studies failed to distinguish between type 1 and type 2 AIP or did not include data on steroid treatment. Only 8 studies[24,26,29,31,32,34,47,48] reported Kaplan–Meier curves of risk for relapse.

Relapse Rate

The pooled estimate for the overall AIP relapse rate among patients treated with steroids was 33% (95% CI, 30%–37%; I^2, 79%; $P < .01$) (Figure 2*A*), ranging from 9.8%[11] to 62%.[31] Relapse curves were extracted from the studies in which Kaplan–Meier curves were available.[24,26,29,31,32,34,47,48] Summary relapse curves are shown in Figure 3. One-year, 2-year, and 3-year actuarial relapse rates were available in 8 studies; the 4-year actuarial relapse rate was available in 5 studies. The pooled actuarial relapse rate was 20% (95% CI, 7%–32%) at 1 year, 37% (95% CI, 14%–54%) at 2 years, 48% (95% CI, 22%–66%) at 3 years, and 53% (95% CI, 27%–69%) at 4 years.

Predictors of Relapse

To identify potential risk factors for AIP relapse, 31 different variables were evaluated among 17 studies, as shown in Table 2. Variables found to be significant risk factors for AIP relapse by univariate analysis in at least 3 studies were as follows: pretreatment IgG4 value, persistently increased IgG4 value, other organ involvement, and induction and maintenance with steroid treatment. Jaundice was the most common significant risk factor for AIP relapse by multivariate analysis.

Subgroup Analysis

The pooled relapse rate was lower in studies with MST treatment for longer than 1 year, compared with studies in which MST lasted less than 1 year (27% vs 39%; $P = .01$) (Figure 2*B*). The relapse rate was lower in studies in which relapse was defined as clinical and radiologic and in studies with undefined relapse criteria than in studies in which relapse was defined radiologically (32% and 32% vs 37%, respectively); however, this difference was not statistically significant ($P = .69$) (Supplementary Figure 1*A*). A sensitivity analysis after exclusion of 11 studies that did not clearly define AIP relapse showed a similar relapse rate (34%; 95% CI, 29%–38%), in comparison to the overall effect (Supplementary Figure 2). The relapse rate was significantly higher in studies classified as high quality,

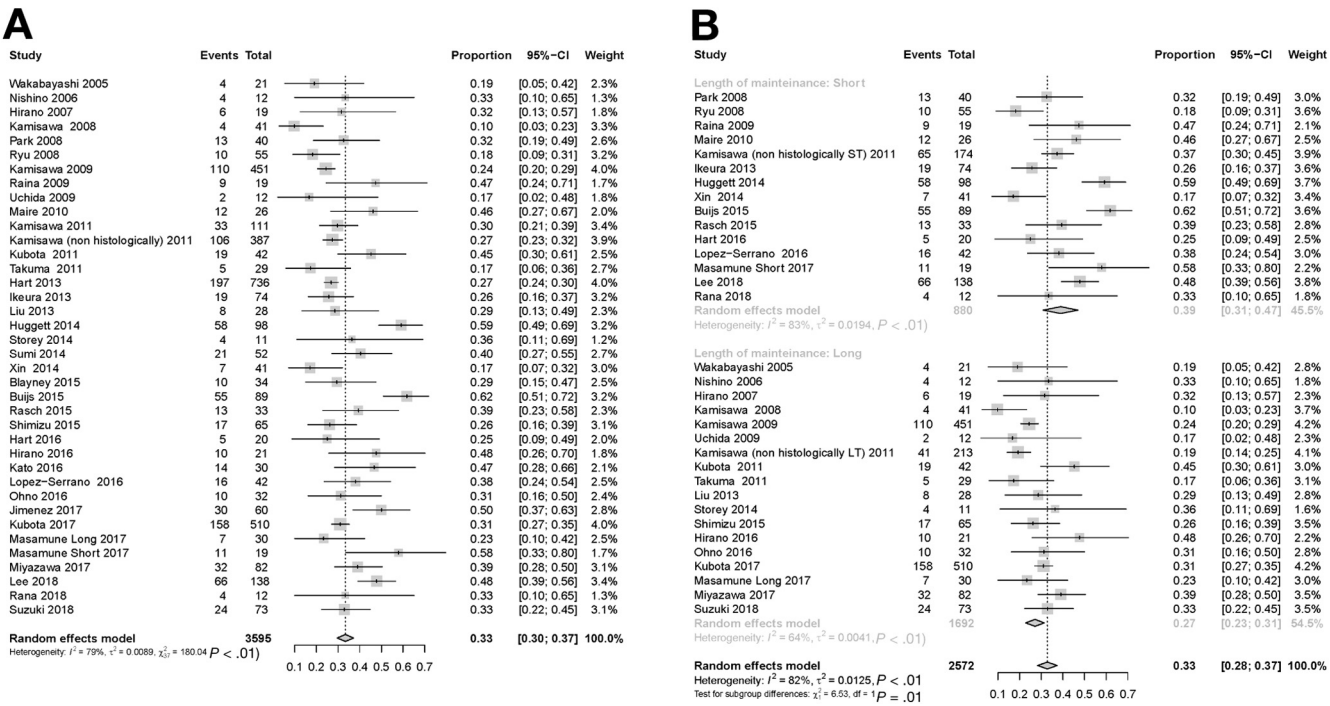

Figure 2. (*A*) Relapse rates of patients with AIP after steroid-induced remission in studies included in the meta-analysis. (*B*) Forest plot of pooled estimates and stratified according to length of maintenance. The Kamisawa[40] cohort of patients with nonhistologic diagnosis was split according to length of maintenance into 2 arms: short-term and long-term. The *squares* show the effect estimates from the single studies; the diamonds show the pooled result.

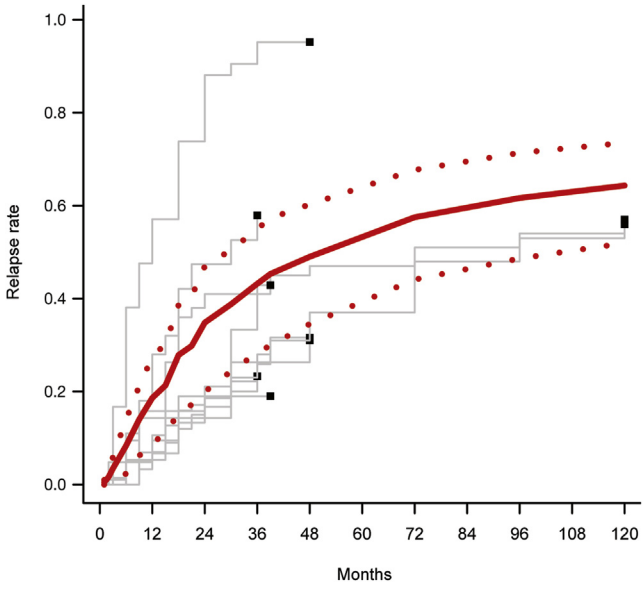

Figure 3. Kaplan–Meier curves of AIP relapse rate. *Grey lines* represent recurrences in each study. *Black squares* indicate the end of follow-up evaluation. *Thick line* represents the summarized relapse rate curve with 95% confidence bands (*dotted lines*) obtained using the approach proposed by Combescure et al[23] with random effects.

compared with studies classified as low quality (39% vs 29%, respectively; $P = .03$) (Supplementary Figure 1*B*). The relapse rate also was significantly higher in studies conducted in Western countries, compared with studies conducted in Asia and multinational studies (42% vs 30% and 27%; $P < .01$) (Supplementary Figure 1*C*). A significant difference also was observed between studies published before vs after 2014 (26% vs 39%; $P < .01$). The relapse rate was similar between prospective and retrospective studies (38% vs 29%, respectively; $P = .08$) (Supplementary Figure 1*D*), between unicentric and multicentric studies (34% vs 33%; $P = .76$), and between studies with a median follow-up evaluation shorter vs longer than 2 years (26% vs 35%; $P = .10$) (Supplementary Figure 3*A–C*). Regarding patient-level variables, there was no significant difference in relapse rate with respect to age, sex, IgG4 values, or the presence of diffuse pancreatic enlargement as shown by imaging. When data were analyzed according to AIP type, the relapse rate was significantly higher in patients with type 1 AIP than in patients with type 2 AIP (37.5% vs 15.9%; $P < .001$; odds ratio, 3.18; 95% CI, 1.86–5.75) (Supplementary Figure 4). The AIP relapse rate was higher in studies in which International Consensus Diagnostic Criteria were used for diagnosis than in studies that used different diagnostic criteria (37% vs 30%; $P = .08$) (Supplementary Figure 3*D*).

Meta-Regression

Univariate logistic meta-regression analysis was performed to identify potential sources of heterogeneity among studies. Among the variables assessed, long-term MST ($P = .007$) was associated significantly with a lower

Table 2. Variables Most Commonly Found to Be Significant Predictors of AIP Relapse in Studies Included in the Meta-Analysis

	Variables that were significant divided by the total number of studies in which the variable was tested by univariate analysis	Variables that were significant divided by the total number of studies in which the variable was tested by multivariate analysis
Pretreatment IgG4 value	3/14	1/3
Other organ involvement	3/12	1/2
Maintenance steroid therapy (protective)	3/7	1/1
Persistently increased IgG4 value	3/7	
Use of steroids (protective)	3/5	1/1
Jaundice	2/7	2/3
Diffuse pancreatic enlargement	2/8	1/4
Biliary stenosis	2/5	0/2
IgG4 sclerosing cholangitis	2/3	0/1
Abdominal pain	1/4	0/1
Pancreatic calcifications	1/1	
Lymphoplasmacytic sclerosing pancreatitis	1/1	
Duodenal papillitis	1/1	0/2
Duration of follow-up evaluation	1/1	
Pancreatic volume after therapy	1/1	1/1
Age	0/11	0/1
Sex	0/11	0/1
Diabetes mellitus type 2	0/5	0/1
IgG value	0/5	
Diffuse pancreatic ductal change	0/3	
Initial steroid dosage	0/2	1/1
AIP type	0/2	

NOTE. The following variables were evaluated in only 1 study and they were not significant: weight loss, amylase/lipase dosage, presence of circulating immune complexes, radiologic alterations, IgG4 immunostaining, type of first-line treatment, surgery, spleen volume reduction after therapy, body mass index.

Table 3. Predictors of Relapse Rate After Steroid Induction Therapy in AIP by Univariate and Multivariate Meta-Regression

	Studies, n	Patients, n	β	CI	*P*	R^2
Univariate						
Year of publication	36	3595				31.2%
After 2014			0.121	0.054–0.188	**<.001**	
Centers, n	36	3595				0.45%
Multicentric			-0.012	-0.087 to 0.063	.753	
Definition of relapse	36	3595				0%
Radiologic			0.045	-0.048 to 0.138	.343	
Undefined			-0.001	-0.096 to 0.095	.992	
Length of follow-up evaluation	33	3052				0.4%
≥2 y			0.083	-0.034 to 0.201	.164	
Length of MST	31	2572				26.89%
≥1 y			-0.114	-0.196 to -0.031	**.007**	
Study quality	31	3348				16.07%
High			0.115	0.036–0.194	**.004**	
Age, *y*	29	2137	0.002	-0.005 to 0.009	.556	0%
Male, %	21	1765	0.224	-0.315 to 0.762	.415	0%
IgG4, *mg/dL*	10	850	-0.001	-0.001 to 0	**.009**	25%
Diffuse enlargement of pancreas	18	1651	0.022	-0.315 to 0.762	.415	0%
Multivariate						
High study quality			0.098	0.018–0.179	**.016**	50.65%
Year of publication after 2014			0.066	-0.013 to 0.146	.103	
Long-term MST			-0.116	-0.192 to -0.004	**.003**	

NOTE. Bolded entries refer to statistically significant associations.

relapse rate, whereas high study quality ($P = .004$) and year of publication after 2014 ($P < .001$) were associated significantly with a higher relapse rate. The length of MST, study quality, and year of publication accounted for 26.9%, 16.1%, and 31.2%, respectively, of overall heterogeneity. Multivariate logistic meta-regression showed that long-term MST was associated significantly with an 11.6% decrease in relapse rate (95% CI, 4.0%–19.2%; $P = .003$), whereas high study quality was associated with a 9.8% increase in relapse rate (95% CI, 1.8%–17.9%; $P = .016$) (Table 3). IgG4 median values were available in only 10 studies and for this reason this variable was not evaluated by multivariate meta-regression.

After excluding studies in which diagnostic criteria for relapse were undefined, year of publication ($P = .013$), length of follow-up evaluation ($P = .02$), length of MST ($P = .08$), study quality ($P = .057$), and male sex ($P = .069$) were associated with relapse by univariate logistic meta-regression analysis. After adjustment for year of publication and study quality, long-term MST was associated with an 11.8% decrease in relapse rate ($P = .008$), while length of follow-up evaluation longer than 2 years was associated significantly with a higher relapse rate ($P = .02$), by multivariate meta-regression (Supplementary Table 5).

Publication Bias

The results of the funnel publication bias plot for relapse rate (Supplementary Figure 5) and the Egger test for publication bias showed that the risk of having missed or overlooked studies was not significant ($P = .06$).

Quality Assessment

A quality assessment of included studies is provided in Supplementary Table 3. Five of 30 studies had cohorts that were appropriately representative. Exposure ascertainment, defined by using international diagnostic criteria[7] or HiSORT,[17] was achieved by 68% of studies. Seventeen studies[9,27–31,35,39–42,45–49,54] ascertained AIP relapse using clinical and radiologic criteria, whereas 8 studies[12,24,32–34,36,44,50] did not report a clear definition of relapse.

Discussion

Evidence regarding the risk of relapse after induction of remission with steroids in patients with AIP is sparse and heterogeneous. A consistent estimation of relapse rate among patients with AIP treated with steroid is essential for assessing the efficacy of new treatment strategies, for calculating sample size, and for interpreting the results of additional RCTs. This systematic review and meta-analysis of aggregate data from 36 studies shows that the clinical course after steroid-induced remission remains highly variable. We found a pooled relapse rate of 33%, although this point estimate must be interpreted in the context of clinical and methodologic limitations of the published data. A significant reduction in the relapse rate was observed in long-term MST studies. The benefit of long-term MST was confirmed by multivariate meta-regression. As expected, we found a high degree of heterogeneity among studies. The inconsistency in relapse rate among studies is not surprising if

one considers differences in design, power, potential biases in the selection of patients with different demographic and clinical characteristics, and, finally, different definitions of relapse and maintenance protocol. Therefore, we performed further analyses to identify groups of studies with consistent rates of relapse. Nevertheless, our subgroup and meta-regression analyses were unable to fully explain the observed heterogeneity. Although the studies included in the meta-analysis used different criteria for AIP relapse, subgroup and meta-regression analyses after exclusion of studies that did not clearly define relapse had similar results. Therefore, a standardized and worldwide accepted definition of AIP relapse is urgently needed. Taking all this in consideration, because of the limited quality of AIP relapse definition, our results seem to be informative but still not conclusive regarding the role of MST. After stratification according to study location, our analysis showed a significant difference in relapse rate between Asian and Western countries (30% vs 42%, respectively). This discrepancy could be related to different approaches in terms of maintenance therapy or to differences in proportions of type 1 and type 2 AIP between Western and Asian countries. Indeed, type 1 AIP is more common in Asian countries, and MST is used commonly in such cases.

One of the current issues in the field of AIP is whether MST may be useful to prevent relapse and, if so, how long MST should be maintained. It is not clear whether all patients with AIP should receive MST, or whether MST should be administered only to a subgroup of patients who clearly stand to benefit. In 2017, the last International Consensus meeting on AIP treatment[10] concluded that maintenance therapy with low-dose glucocorticoids or steroid-sparing agents may be useful in some patients with type 1 AIP. We added further evidence that the relapse rate after MST significantly differs between type 1 and type 2 AIP (37% vs 16%, respectively). However, data on relapse rate according to AIP type are scanty. Identification of potential risk factors for AIP relapse can be useful to select patients who are more likely to benefit from maintenance therapy. According to the last International Consensus for treatment of AIP,[10] we found that IgG4 levels, jaundice, and other organ involvement were the most relevant risk factors associated with AIP relapse.

Our meta-analysis showed considerable variation among studies in dose and length of MST, suggesting that standardized regimens are urgently needed. Pannala and Chari[15] suggested tapering steroids over a period of 12 to 16 weeks, after an induction period of 2 to 4 weeks. By contrast, a large multicentric retrospective study[9] showed that the relapse rate was significantly lower in patients treated with low-dose (2.5–10 mg/day) long-term MST, compared with those who stopped maintenance therapy. Based on these results, Asian experts[14] recommend a maintenance duration of at least 6 months. In 2017, a RCT by Masamune et al[34] showed that the 3-year relapse rate differed significantly between long-term and short-term MST (23.3% vs 57.9%, respectively). This is the only RCT available on the topic, and it had several limitations,[56] such as small sample size and an imbalance in the number of patients treated with long- vs short-term MST. As part of this meta-analysis, we performed multivariate meta-regression to show that the relapse rate was significantly lower (27%) in studies with long-term MST, compared with studies with short-term MST (39%). However, this finding may be biased by the lack of follow-up evaluation of patients with long-term MST after steroid discontinuation.

The pooled actuarial curves of AIP relapse from 8 studies showed that approximately half of all patients experienced relapse after 4 years of follow-up evaluation. Although obtained from a small number of studies, this result supports the clinical rationale to prolong MST and highlights the importance of designing future RCTs with an adequate sample size, stratification by AIP type, and extended length of follow-up evaluation. Recent studies have reported a role for immunosuppressant drugs[57–59] in treatment of the first relapse. RCTs comparing long-term MST vs immunosuppressants (mainly azathioprine) could be useful to substantiate the benefit of immunosuppressant therapy in decreasing the rate of relapse.

The results of this meta-analysis are subject to several limitations. Differences in design, in sample size, in baseline severity of illness, in AIP relapse definition, and in maintenance regimens may limit the accuracy of this quantitative analysis. We attempted to control for these differences by including patient- and study-level covariates. However, there were likely other potentially important confounders for which we did not control and that might have affected the results. Lack of data on the distribution between patients with type 1 vs type 2 AIP, on the pattern of presentation (pancreatic vs extrapancreatic), and on factors associated with the likelihood of relapse in AIP may have affected the accuracy of the results. Furthermore, the results only describe variation between studies, rather than between patients, because they reflect group averages rather than individual data. More detailed comparisons could be achieved with meta-analyses of individual patient data. As with all meta-analyses, this study also has the potential limitation of the generalizability of results to new populations and settings. Meta-analyses are likely to have poor external validity when the included studies all use the same limited patient population or are all conducted in a single setting. Because AIP patients are a heterogeneous population, we decided to include studies with different designs and those that included patients treated with different first steroid courses and re-treated with different maintenance regimens. We believe that this approach may have improved the generalizability of our data to results observed in real clinical practice. A methodologic issue of the current study is the potential

limitation of the generalizability of its results to different populations and settings, given that the benefit of long-term MST was observed particularly in Asian patients, limiting the broad application of the results to a Western population. With our extensive computer search for studies, we are confident that no important published studies were overlooked. Publication bias was not substantial and was considered unlikely to change the magnitude of our pooled estimates.

The available evidence is sufficient to conclude the following: (1) the risk of relapse after induction of remission with steroids in patients with AIP remains high during long-term follow-up evaluation, particularly in patients with type 1 AIP; (2) MST significantly reduces the risk of AIP relapse; and (3) the benefit of long-term MST appears to be observed more consistently in Asian populations. Further large-scale, multicenter RCTs may prove useful to substantiate the benefit of long-term MST and to compare steroid maintenance with steroid-sparing immunosuppressive drug therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.09.051.

References

1. Finkelberg DL, Sahani D, Deshpande V, et al. Autoimmune Pancreatitis. N Engl J Med 2006;355:2670–2676.
2. Kamisawa T, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. Am J Gastroenterol 2003; 98:2811–2812.
3. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 2003; 38:982–984.
4. Kim M-H, Moon S-H. The need for a consensus on the definition of remission of autoimmune pancreatitis after steroid treatment. Gut 2010;59:1730.
5. Ikeura T, Miyoshi H, Shimatani M, et al. Long-term outcomes of autoimmune pancreatitis. World J Gastroenterol 2016; 22:7760–7766.
6. Hart PA, Kamisawa T, Brugge WR, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut 2013;62:1771–1776.
7. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011;40:352–358.
8. Tomiyama T, Uchida K, Matsushita M, et al. Comparison of steroid pulse therapy and conventional oral steroid therapy as initial treatment for autoimmune pancreatitis. J Gastroenterol 2011;46:696–704.
9. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. Gut 2009;58:1504–1507.
10. Okazaki K, Chari ST, Frulloni L, et al. International consensus for the treatment of autoimmune pancreatitis. Pancreatology 2017; 17:1–6.
11. Kamisawa T, Okamoto A, Wakabayashi T, et al. Appropriate steroid therapy for autoimmune pancreatitis based on long-term outcome. Scand J Gastroenterol 2008;43:609–613.
12. Huggett MT, Culver EL, Kumar M, et al. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. Am J Gastroenterol 2014; 109:1675–1683.
13. Sah RP, Chari ST. Autoimmune pancreatitis: an update on classification, diagnosis, natural history and management. Curr Gastroenterol Rep 2012;14:95–105.
14. Kamisawa T, Okazaki K, Kawa S, et al. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013 III. Treatment and prognosis of autoimmune pancreatitis. J Gastroenterol 2014;49:961–970.
15. Pannala R, Chari ST. Corticosteroid treatment for autoimmune pancreatitis. Gut 2009;58:1438–1439.
16. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.
17. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic Experience. Clin Gastroenterol Hepatol 2006;4:1010–1016.
18. Members of the Criteria Committee for Autoimmune Pancreatitis of the Japan Pancreas Society. Diagnostic criteria for autoimmune pancreatitis by the Japan Pancreas Society (2002). J Jpn Pan Soc 2002;17:585–587.
19. Otsuki M, Chung JB, Okazaki K, et al. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol 2008;43:403–408.
20. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed February 1, 2009.
21. Earle CC, Wells GA. An assessment of methods to combine published survival curves. Med Decis Mak 2000;20:104–111.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
23. Combescure C, Foucher Y, Jackson D. Meta-analysis of single-arm survival studies: a distribution-free approach for estimating summary survival curves with random effects. Stat Med 2014; 33:2521–2537.
24. Wakabayashi T, Kawaura Y, Satomura Y, et al. Long-term prognosis of duct-narrowing chronic pancreatitis: strategy for steroid treatment. Pancreas 2005;30:31–39.
25. Nishino T, Toki F, Oyama H, et al. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. Intern Med 2006;45:497–501.
26. Hirano K, Tada M, Isayama H, et al. Long-term prognosis of autoimmune pancreatitis with and without corticosteroid treatment. Gut 2007;56:1719–1724.
27. Park DH, Kim M-H, Oh HB, et al. Substitution of aspartic acid at position 57 of the DQbeta1 affects relapse of autoimmune pancreatitis. Gastroenterology 2008;134:440–446.
28. Maire F, Baleur Y Le, Rebours V, et al. Outcome of patients with type 1 or 2 autoimmune pancreatitis. Am J Gastroenterol 2011; 106:151–156.
29. Kubota K, Watanabe S, Uchiyama T, et al. Factors predictive of relapse and spontaneous remission of autoimmune pancreatitis

patients treated/not treated with corticosteroids. J Gastroenterol 2011;46:834–842.
30. Ikeura T, Manfredi R, Zamboni G, et al. Application of international consensus diagnostic criteria to an Italian series of autoimmune pancreatitis. United European Gastroenterol J 2013;1:276–284.
31. Buijs J, Cahen DL, Heerde MJ van, et al. The long-term impact of autoimmune pancreatitis on pancreatic function, quality of life, and life expectancy. Pancreas 2015;44:1065–1071.
32. Hirano K, Tada M, Isayama H, et al. Outcome of long-term maintenance steroid therapy cessation in patients with autoimmune pancreatitis: a prospective study. J Clin Gastroenterol 2016;50:331–337.
33. Lee HW, Moon S-H, Kim M-H, et al. Relapse rate and predictors of relapse in a large single center cohort of type 1 autoimmune pancreatitis: long-term follow-up results after steroid therapy with short-duration maintenance treatment. J Gastroenterol 2018;53:967–977.
34. Masamune A, Nishimori I, Kikuta K, et al. Randomised controlled trial of long-term maintenance corticosteroid therapy in patients with autoimmune pancreatitis. Gut 2017;66:487–494.
35. Hart PA, Levy MJ, Smyrk TC, et al. Clinical profiles and outcomes in idiopathic duct-centric chronic pancreatitis (type 2 autoimmune pancreatitis): the Mayo Clinic experience. Gut 2016;65:1702–1709.
36. Ryu JK, Chung JB, Park SW, et al. Review of 67 patients with autoimmune pancreatitis in Korea: a multicenter nationwide study. Pancreas 2008;37:377–385.
37. Uchida K, Yazumi S, Nishio A, et al. Long-term outcome of autoimmune pancreatitis. J Gastroenterol 2009;44:726–732.
38. Raina A, Yadav D, Krasinskas AM, et al. Evaluation and management of autoimmune pancreatitis: experience at a large US center. Am J Gastroenterol 2009;104:2295–2306.
39. Takuma K, Kamisawa T, Tabata T, et al. Short-term and long-term outcomes of autoimmune pancreatitis. Eur J Gastroenterol Hepatol 2011;23:146–152.
40. Kamisawa T, Chari ST, Giday SA, et al. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas 2011;40:809–814.
41. Liu B, Li J, Yan L-N, et al. Retrospective study of steroid therapy for patients with autoimmune pancreatitis in a Chinese population. World J Gastroenterol 2013;19:569–574.
42. Xin L, He Y-X, Zhu X-F, et al. Diagnosis and treatment of autoimmune pancreatitis: experience with 100 patients. Hepatobiliary Pancreat Dis Int 2014;13:642–648.
43. Rasch S, Phillip V, Schmid RM, et al. Epidemiology, clinical presentation, diagnosis and treatment of autoimmune pancreatitis: a retrospective analysis of 53 patients. Pancreatology 2016;16:73–77.
44. Shimizu S, Naitoh I, Nakazawa T, et al. Correlation between long-term outcome and steroid therapy in type 1 autoimmune pancreatitis: relapse, malignancy and side effect of steroid. Scand J Gastroenterol 2015;50:1411–1418.
45. Ohno Y, Kumagi T, Yokota T, et al. Early pancreatic volume reduction on CT predicts relapse in patients with type 1 autoimmune pancreatitis treated with steroids. Orphanet J Rare Dis 2016;11:103.
46. López-Serrano A, Crespo J, Pascual I, et al. Diagnosis, treatment and long-term outcomes of autoimmune pancreatitis in Spain based on the International Consensus Diagnostic Criteria: a multi-centre study. Pancreatology 2016;16:382–390.
47. Miyazawa M, Takatori H, Shimakami T, et al. Prognosis of type 1 autoimmune pancreatitis after corticosteroid therapy-induced remission in terms of relapse and diabetes mellitus. PLoS One 2017;12:e0188549.
48. Kubota K, Kamisawa T, Okazaki K, et al. Low-dose maintenance steroid treatment could reduce the relapse rate in patients with type 1 autoimmune pancreatitis: a long-term Japanese multicenter analysis of 510 patients. J Gastroenterol 2017;52:955–964.
49. Rana SS, Gupta R, Nada R, et al. Clinical profile and treatment outcomes in autoimmune pancreatitis: a report from North India. Ann Gastroenterol 2018;31:506–512.
50. Suzuki D, Shimizu K, Tokushige K. Relative rise of serum IgG4 levels after steroid therapy for autoimmune pancreatitis predicts the likelihood of relapse. Pancreas 2018;47:412–417.
51. Jimenez A, Sedano R, Araneda G, et al. Different types of autoimmune pancreatitis. Clinical characteristics and follow-up. Pancreatology 2017;17:S7.
52. Kato Y, Iwasaki A, Sato T, et al. 1116 Clinical differences of IgG4-related sclerosing cholangitis between isolated type and type associated with autoimmune pancreatitis. Gastroenterology 2016;150:S223.
53. Blayney MJ, Irani S, Gluck M. Tu1482 autoimmune pancreatitis: variable response to first-line oral steroid treatment in 52 patients at a tertiary referral center. Gastroenterology 2015;148:S904–S905.
54. Sumi H. P- 506 risk factors for relapse of autoimmune pancreatitis. J Gastroenterol Hepatol 2014;29:51–313.
55. Storey R, Bell R, Young A, et al. Autoimmune pancreatitis, a single centre experience within the United Kingdom. Pancreatology 2014;14:S51.
56. Frulloni L, de Pretis N, Amodio A, et al. Maintenance therapy in autoimmune pancreatitis: a weak light into the darkness. Ann Transl Med 2017;5:367.
57. de Pretis N, Amodio A, Bernardoni L, et al. Azathioprine maintenance therapy to prevent relapses in autoimmune pancreatitis. Clin Transl Gastroenterol 2017;8:e90.
58. Seleznik G, Graf R. Alternatives to steroids?! Beneficial effects of immunosuppressant drugs in autoimmune pancreatitis. Gut 2014;63:376–377.
59. Pezzilli R. Immunosuppressive drugs for the treatment of autoimmune pancreatitis. Immunotherapy 2014;6:477–483.

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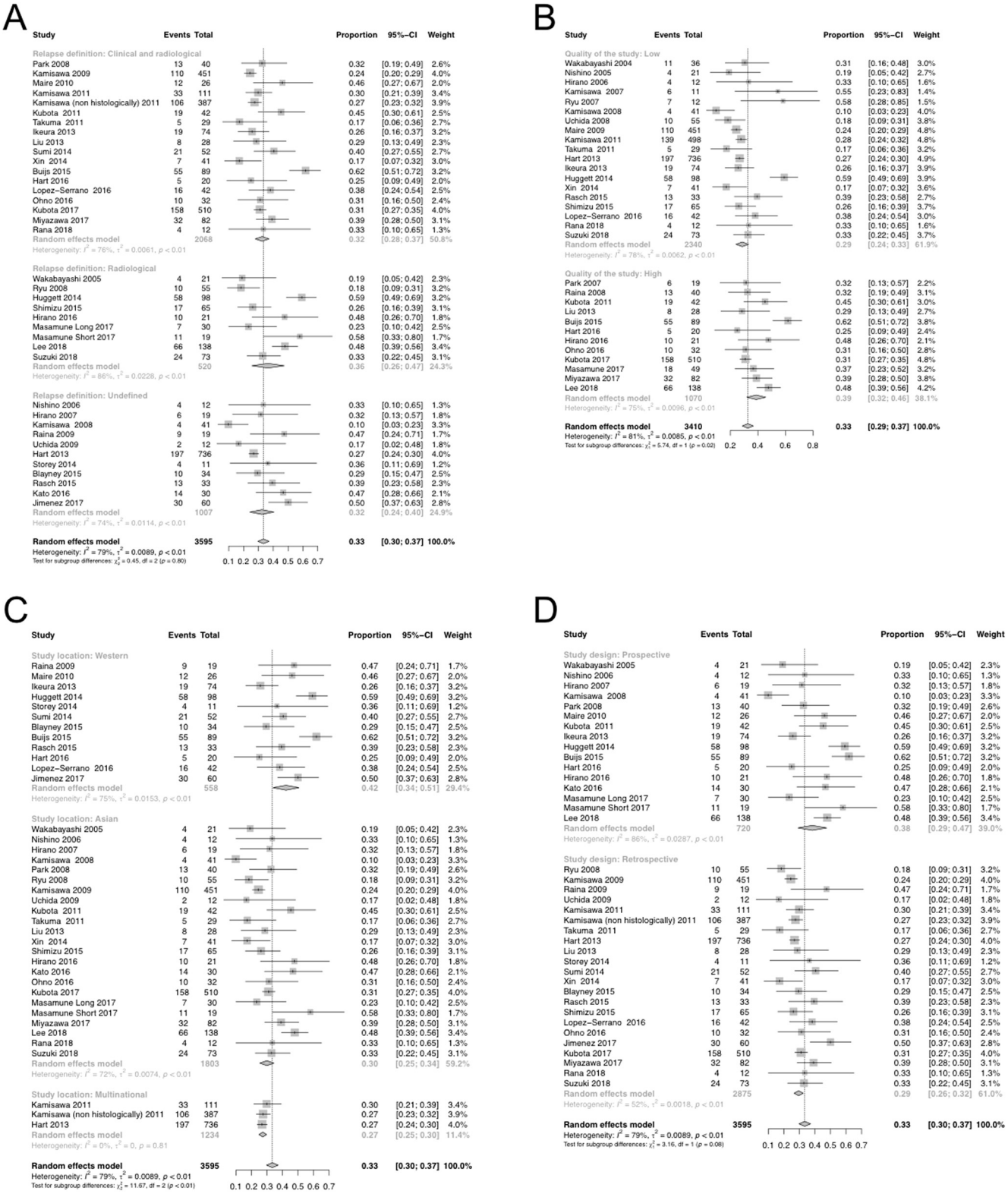
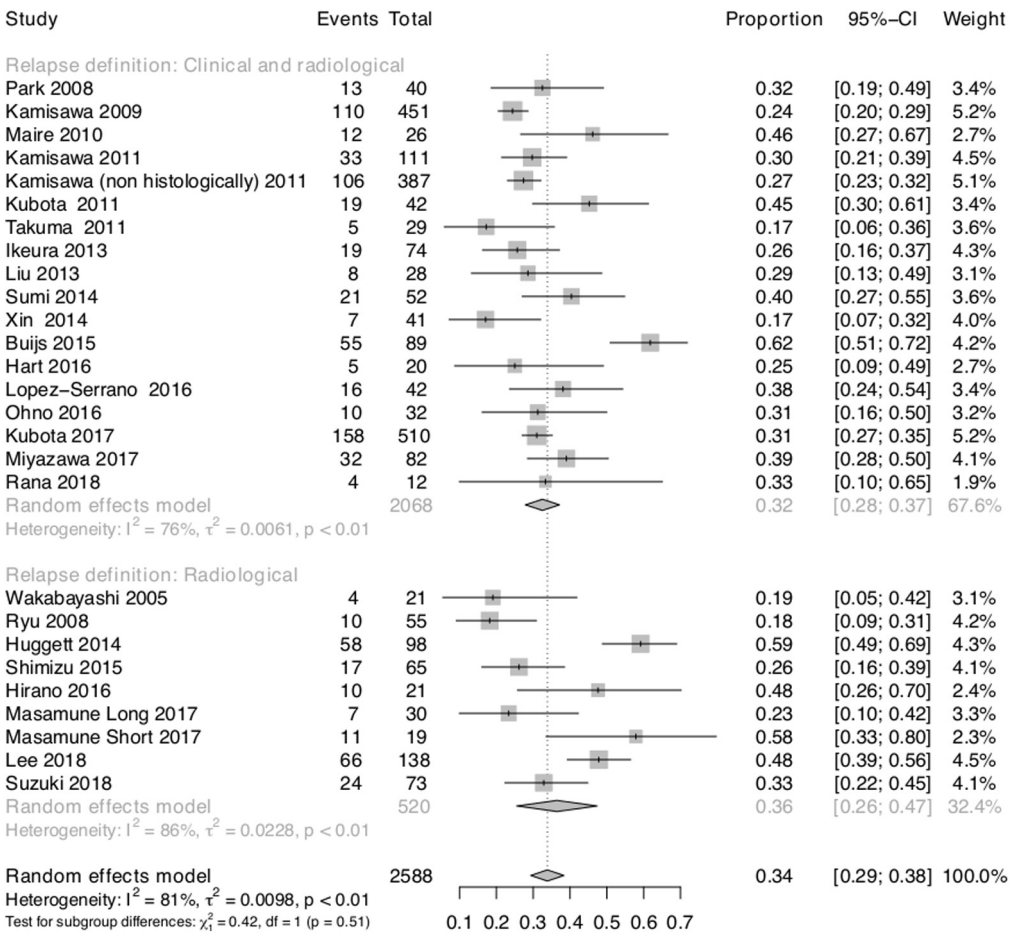
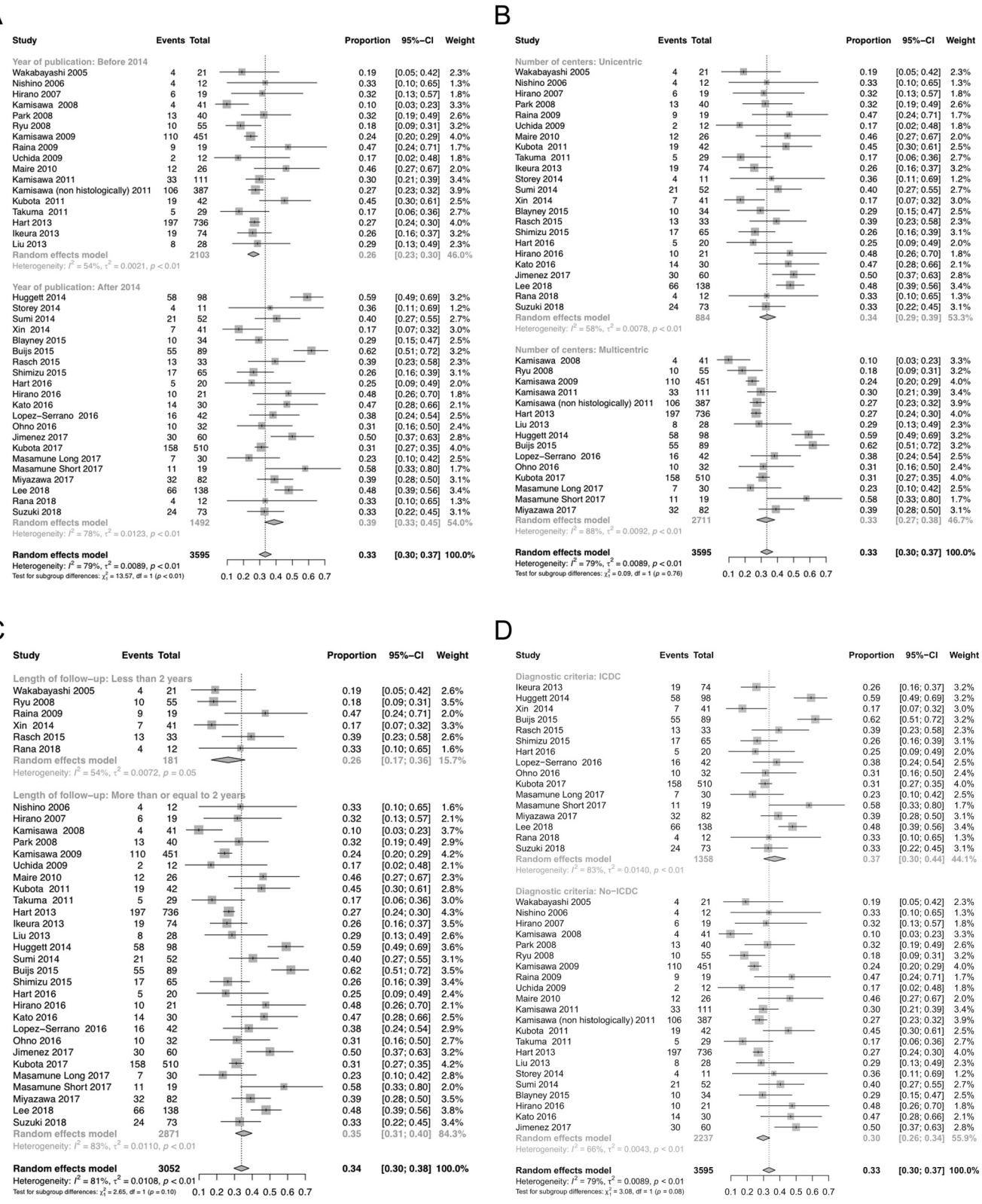
Conflicts of interest
The authors disclose no conflicts.



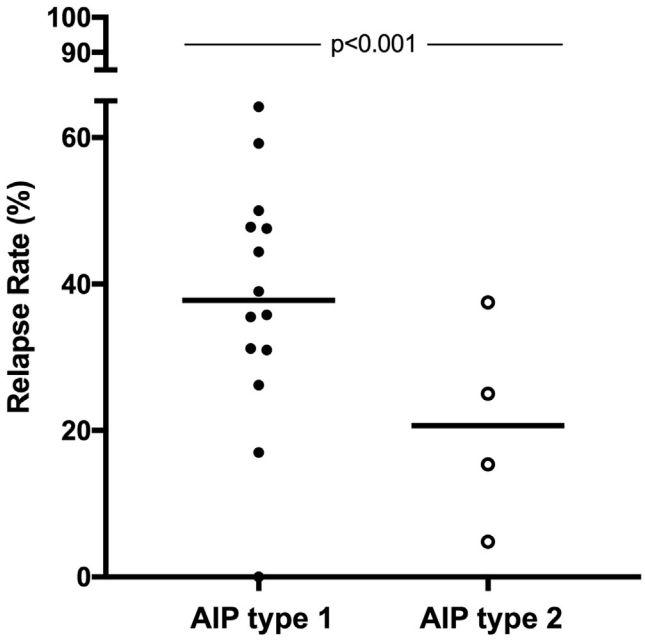
Supplementary Figure 1. Forest plot of relapse rates of patients with AIP after steroid-induced remission stratified according to (*A*) relapse definition, (*B*) study quality, (*C*) study location, and (*D*) study design.



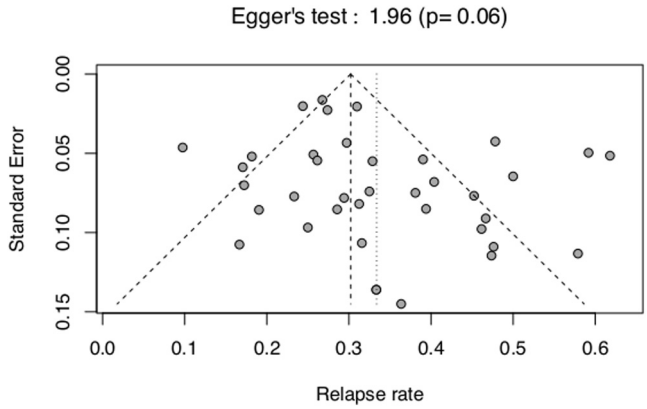
Supplementary Figure 2. Forest plot of relapse rates of patients with AIP after steroid-induced remission, stratified according to relapse definition, after exclusion of studies in which relapse was not defined clearly.



Supplementary Figure 3. Forest plot of relapse rates of patients with AIP after steroid-induced remission stratified according to (*A*) year of publication, (*B*) number of centers, and (*C*) median time of follow-up evaluation. (*D*) diagnostic criteria.



Supplementary Figure 4. Relapse rate according to AIP type.



Supplementary Figure 5. Funnel publication bias for relapse rate.

Supplementary Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Checklist

Section/topic	Number	Checklist item	Reported on page number
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1–2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to PICOS	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number	3–4
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up evaluation) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale	3–4
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	3–4
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated	3–4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	3–4, Figure 1
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	3–4
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made	3–4, Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was performed at the study or outcome level), and how this information is to be used in any data synthesis	Assessment of study quality in method section: pages 4–5 Statistical analyses: page 5 Results section: page 8
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means)	Statistical analyses: page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if performed, including measures of consistency (eg, I^2) for each meta-analysis	Results section: pages 5–7 Figure 1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	8
Additional analysis	23	Provide results of additional analyses, if performed (eg, sensitivity or subgroup analyses, meta-regression [see item 16])	6–7, Figure 4, Table 2
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers)	8–9
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias)	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	10
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review	3–4

PICOS, participants, interventions, comparisons, outcomes, and study design.

Supplementary Table 2. Criteria for Study Quality

Items			Risk of bias	Points
Selection	Representativeness	Patients were consecutively enrolled	[a]	2
		Patients were not consecutively enrolled; study design was prospective	Low	1
		Not consecutive, retrospective	High	0
	Ascertainment of exposure	HiSORT or international diagnostic criteria	[a]	2
		National diagnostic criteria	Low	1
		Diagnostic criteria was not validated	High	0
	Demonstration that outcome of interest was not present	Yes	[a]	2
		No	High	0
Outcome	Assessment of outcome	Clinical and radiologic relapse definition	[a]	2
		Radiologic relapse definition	Low	1
		Not a clear definition of relapse	High	0
	Sufficient follow-up period	Follow-up period >2 y	[a]	2
		Follow-up period <2 y	Low	1
		Undefined time of follow-up evaluation	High	0
	Adequacy of follow-up evaluation	Definite follow-up schedule	[a]	2
		Follow-up schedule was undefined	High	0

High, high risk of bias; Low, low risk of bias.
[a]Very low risk of bias.

Supplementary Table 3. Assessment of Study Quality

Study	Year of publication	Representative cohort	Ascertainment of exposure	Outcome not present at start	Assessment of outcome	Sufficient follow up period	Adequacy of follow up	Quality score	Quality
Wakabayashi et al[24]	2005	Low	Low	[a]	Low	Low	High	6	Low
Nishino et al[25]	2006	Low	Low	[a]	High	[a]	High	6	
Ryu et al[36]	2008	High	[a]	[a]	Low	Low	High	6	
Kamisawa et al[11]	2008	Low	Low	[a]	High	[a]	High	6	
Kamisawa et al[9]	2009	High	Low	[a]	[a]	[a]	High	7	
Uchida et al[37]	2009	High	Low	[a]	High	[a]	High	5	
Raina et al[38]	2009	High	[a]	[a]	High	Low	High	5	
Takuma et al[39]	2011	Low	Low	[a]	[a]	[a]	High	8	
Kamisawa et al[40]	2011	High	Low	[a]	[a]	[a]	High	7	
Hart et al[6]	2013	Low	[a]	[a]	High	[a]	High	7	
Xin et al[42]	2014	Low	[a]	[a]	[a]	Low	High	8	
Huggett et al[12]	2014	High	[a]	[a]	Low	[a]	High	7	
Rasch et al[43]	2015	High	[a]	[a]	High	Low	High	5	
Shimizu et al[44]	2015	High	[a]	[a]	Low	Low	High	6	
López-Serrano et al[46]	2016	High	[a]	[a]	[a]	[a]	High	8	
Rana et al[49]	2018	High	[a]	[a]	[a]	High	High	6	
Suzuki et al[50]	2018	High	[a]	[a]	Low	[a]	High	7	
Hirano et al[26]	2007	Low	[a]	[a]	High	[a]	[a]	9	High
Park et al[27]	2008	[a]	[a]	[a]	[a]	[a]	[a]	12	
Maire et al[28]	2010	[a]	[a]	[a]	[a]	[a]	High	10	
Kubota et al[29]	2011	[a]	Low	[a]	[a]	[a]	[a]	11	
Ikeura et al[30]	2013	Low	[a]	[a]	[a]	High	High	8	
Liu et al[41]	2013	High	Low	[a]	[a]	[a]	[a]	9	
Hart et al[35]	2016	Low	[a]	[a]	[a]	[a]	High	9	
Buijs et al[31]	2015	Low	[a]	[a]	[a]	[a]	[a]	11	
Ohno et al[45]	2016	[a]	[a]	[a]	[a]	[a]	[a]	12	
Hirano et al[32]	2016	Low	Low	[a]	Low	[a]	[a]	9	
Masamune et al[34]	2017	Low	Low	[a]	Low	[a]	[a]	9	
Miyazawa et al[47]	2017	High	[a]	[a]	[a]	[a]	[a]	10	
Kubota et al[48]	2017	High	[a]	[a]	[a]	[a]	[a]	10	
Lee et al[33]	2018	[a]	[a]	[a]	Low	[a]	[a]	11	

High, high risk of bias; Low, low risk of bias.
[a]Very low risk of bias.

Supplementary Table 4. Relapse Rate According to AIP Type

	Patients with relapse/number of patients with AIP1, n	Relapse rate in AIP1	Patients with relapse/number of patients with AIP2, n	Relapse rate in AIP 2	χ^2 test	*P*	OR (95% CI)
Kamisawa et al,[40] 2011	32/90	35.5%	1/21	4.8%	19.56	<.001	3.18 (1.86–5.75)
Takuma et al,[39] 2011	5/29	17%	0	0%			
Hart et al,[6] 2013	245/684	35.8%	8/52	15.4%			
Huggett et al,[12] 2014	58/98	59.2%	0	0%			
Hart et al,[35] 2016	0	0	5/20	25%			
Buijs et al,[31] 2015	52/81	64.2%	3/8	37.5%			
Shimizu et al,[44] 2015	17/65	26.2%	0	0%			
López-Serrano et al,[46] 2016	16/36	44.4%	0/4	0%			
Hirano et al,[32] 2016	9/21	47.6%	0	0%			
Ohno et al,[45] 2016	9/32	31.2%	0	0%			
Kubota et al,[48] 2017	158/510	31%	0	0%			
Miyazawa et al,[47] 2017	32/82	39%	0	0%			
Rana et al,[49] 2018	5/10	50%	0/2	0			
Lee et al,[33] 2018	66/138	47.8%	0	0%			
Total	704/1876	37.5%	17/107	15.9%			

Supplementary Table 5. Predictors of Relapse Rate After Steroid Induction Therapy in AIP by Univariate and Multivariate Meta-Regression After Exclusion of Studies in Which Diagnostic Criteria for Relapse Were Undefined

	Studies, n	Patients, n	β	CI	*P*	R^2
Univariate						
Year of publication	25	2375				21.15%
After 2014			0.106	0.022–0.189	**.013**	
Centers, n	25	2375				0%
Multicentric			0.032	-0.06 to 0.124	.498	
Definition of relapse	25	2375				5.95%
Radiologic			0.045	-0.047 to 0.137	.335	
Length of follow-up evaluation	25	2090				10.2%
≥2 y			0.166	0.026 to 0.305	**.02**	
Length of MST	23	2212				15.8%
≥1 y			-0.084	-0.178 to 0.01	**.08**	
Quality of the study	24	2487				6.99%
High			0.092	-0.003 to 0.187	**.057**	
Age, *y*	20	1929	0.005	-0.002 to 0.013	.144	2.3%
Male, %	14	1591	0.566	-0.045 to 1.177	.069	0%
IgG4, *mg/dL*	7	800	-0.001	-0.001 to 0.0001	**.01**	25%
Diffuse enlargement of pancreas	14	1567	0.012	-0.26 to 0.284	.931	0%
Multivariate						
High study quality			0.058	-0.036 to 0.151	.225	54.1%
Year of publication			0.067	-0.022 to 0.144	.138	
Long-term follow-up evaluation			0.157	0.025 to 0.289	**.02**	
Long-term maintenance			-0.118	-0.205 to -0.031	**0.008**	

NOTE. Bolded entries refer to statistically significant associations.