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MAINTENANCE CORTICOSTEROIDS THERAPY REDUCING THE RISK OF RELAPSE FOR IGG4-RELATED DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objectives: To estimate the efficacy of maintenance corticosteroids therapy in patients with IgG4- related disease (IgG4-RD). **Methods:** Medical databases of MEDLINE/PubMed, EMBASE and Web of Science were systematically searching by using "IgG4 related disease" or "IgG4 related diseases" or "Autoimmune pancreatitis" or "Immunoglobulin G4 related disease" AND "Glucocorticoids" or "adrenal cortex hormones " or prednisone " or "methylprednisolone" or "Hydrocortisone " or " Dexamethasone used Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines during the preparation of this review. **Results:**11 studies 907 IgG4 -RD patients were included in our studies. The overall effect estimates favored maintenance therapy in term of relapse episodes (RR 1.92, 95% CI [1.63, 2.26]; p <0.001;). The pooled effect estimate was homogenous (p >0.1). Similarly, the overall effect estimates favored maintenance therapy in term of improvement rate (RR 0.75, 95% CI [0.70, 0.80]; p <0.001;). The pooled analyses were highly heterogeneous (p <0.1). However, no significant difference was detected between both groups in terms of number of organs with relapse episodes (RR 1.10 [0.71, 1.70]; p =0.066;) and IgG4 elevation levels (SMD 0.01, 95% CI [-0.77, 0.79]; p =0.99;). The pooled analyses were highly heterogeneous (p <0.1). **Conclusion:** Maintenance corticosteroid therapy plays an essential role in reducing the risk of relapse in IgG4-RD. The heterogeneity of the studies published until now means that more studies are needed to evaluate its necessity better.

KEYWORDS: IgG4 related disease, corticosteroids, maintenance therapy, induction therapy, Relapse.

INTRODUCTION

Immunoglobulin(Ig)G4-related disease (IgG4-RD) is a rare systemic fibro-inflammatory disease characterized by extensive spread lesions with specific histological features.[1] These features include plasma cells infiltration and fibrosis at many sites. It may be accompanied by serum IgG4 levels elevation and IgG4-positive plasma cells infiltration in the involved organs and tissues.[2] Since IgG4-RD began to be recognized as a distinct clinical entity, the clinical field of IgG4-RD severely expanded. It combined with different organs involvement including pancreas, bile ducts, retroperitoneum, salivary glands, lacrimal glands, lymph nodes, thyroid gland, pituitary gland, lung and kidney.[3] The lack of awareness about IgG4-RD and the defect of facilities to measure serum IgG4 levels in a lot of medical centers are the most common causes for delay and or miss the best time to diagnosis of this disease.

Besides, being a new entity, treatment protocols for this illness are not standardized.[2]

Corticosteroid is the standard first-line treatment for IgG4-RD[4], as it showed a dramatically strong response when used in the therapy.[5] Rapid response to the corticosteroid treatment is included in the International Consensus Diagnostic Criteria (ICDC) for Autoimmune pancreatitis (AIP)[5]. As relapse of the disease developed in many patients either during tapering of the steroid or after steroid cessation[6], the requirement for maintenance therapy is controversial, and the benefit of universal and prolonged maintenance corticosteroid therapy has not been established yet.[4]

In our study, we defined the "induction therapy" as a high dose of glucocorticoids taken for a short time, which is required to produce improvement and remission

of the disease. We mean by the "maintenance therapy" the small dose of steroid taken for a long time to prolong the period of remission and prevent the relapse. Herein, we performed this meta-analysis focusing on maintenance corticosteroid treatment to help clinicians care for patients with IgG4-RD and to help make an ideal treatment protocol of it.

MATERIALS AND METHODS
Data search and search strategies
A comprehensive literature search in biomedical databases of Medline (via PubMed), EMBASE and WEB OF SCIENCE were carried out. Both databases were searched from the inception to March 2018. Medical subject headings (MeSH) and free text words were combined to retrieve all the potential studies. MeSH were modified based on the specifications of each database. The following search strategy was used for the literature search with different combination: "IgG4-related disease" or "IgG4 related diseases" or "Autoimmune pancreatitis" or "immunoglobulin G4 related disease" AND "Glucocorticoids" or "adrenal cortex hormones" or "prednisone" or "methylprednisolone" or "hydrocortisone" or "dexamethasone". Retrieved citations were downloaded and duplicates of retrieved records were removed using EndNote version 7. We followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines during the preparation of this review.

Inclusion and Exclusion Criteria for Study selection
Primary studies that fulfilled the following criteria: 1) studies included patients with IgG4-related disorders (IgG4-RD); 2) studies compared glucocorticoid maintenance therapy versus induction therapy alone; and 3) studies reported the frequency of relapse episodes in each group were included. The conference abstracts and studies which were not written in the English language were excluded. In the case of multiple reports, we analyzed data from the complete dataset.

Data extraction and management
The authors extracted the raw data independently from each included study using a standardized online data extraction form. The extracted data included the characters of study design and outcomes. Here in we used relapse episodes, improvement rate, full resolution rate and igG4 level as a parameter for measuring the outcome of IgG4 RD patients among the studies comparing glucocorticoid maintenance versus induction therapy alone. Relapse was defined as a new evolution or return of abnormal findings on physical examination, laboratory tests that showed IgG4-RD activity through specific organs, or radiological studies. The time of relapse was either the time of symptom beginning or new or worse physical examination, laboratory or imaging findings. Increasing in the serum IgG4 concentration alone did not constitute a disease relapse.[7]

Data Synthesis
Dichotomous data were pooled as a relative risk (RR) using the Mantel-Haenzel (M-H) method. Continuous data were pooled as a standardized mean difference (SMD). We used Review Manager 5.3 for windows. In the case of missing Standard error (SE) of mean difference, it was calculated from a 95% confidence interval (CI) according to Altman.[7] In the case of a significant heterogeneity (Chi-Square P<0.1), a random effect model was used. Otherwise, a fixed-effect model was used.

Assessment of heterogeneity
Heterogeneity was assessed by visual inspection of the forest plots and measured by I-square and Chi-Square tests. Chi-square test was used to test the existence of significant heterogeneity while I-square quantifies of the variability of effect estimates that are due to heterogeneity if present. I-Square test was interpreted according to recommendations of Cochrane Handbook of Systematic Reviews and meta-analysis (0% to 40%: might not be necessary; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity).

RESULTS
Database Search
We retrieved unique 1694 citations from online databases search. After title and abstract screening, 61 potentially relevant articles were retained for full-text screening. Finally, after detailed review 11 studies[5, 6][8–16] met the selection criteria and were included with a total of 1907 IgG4-RD patients. The detailed process of selection is shown in **figure1.**
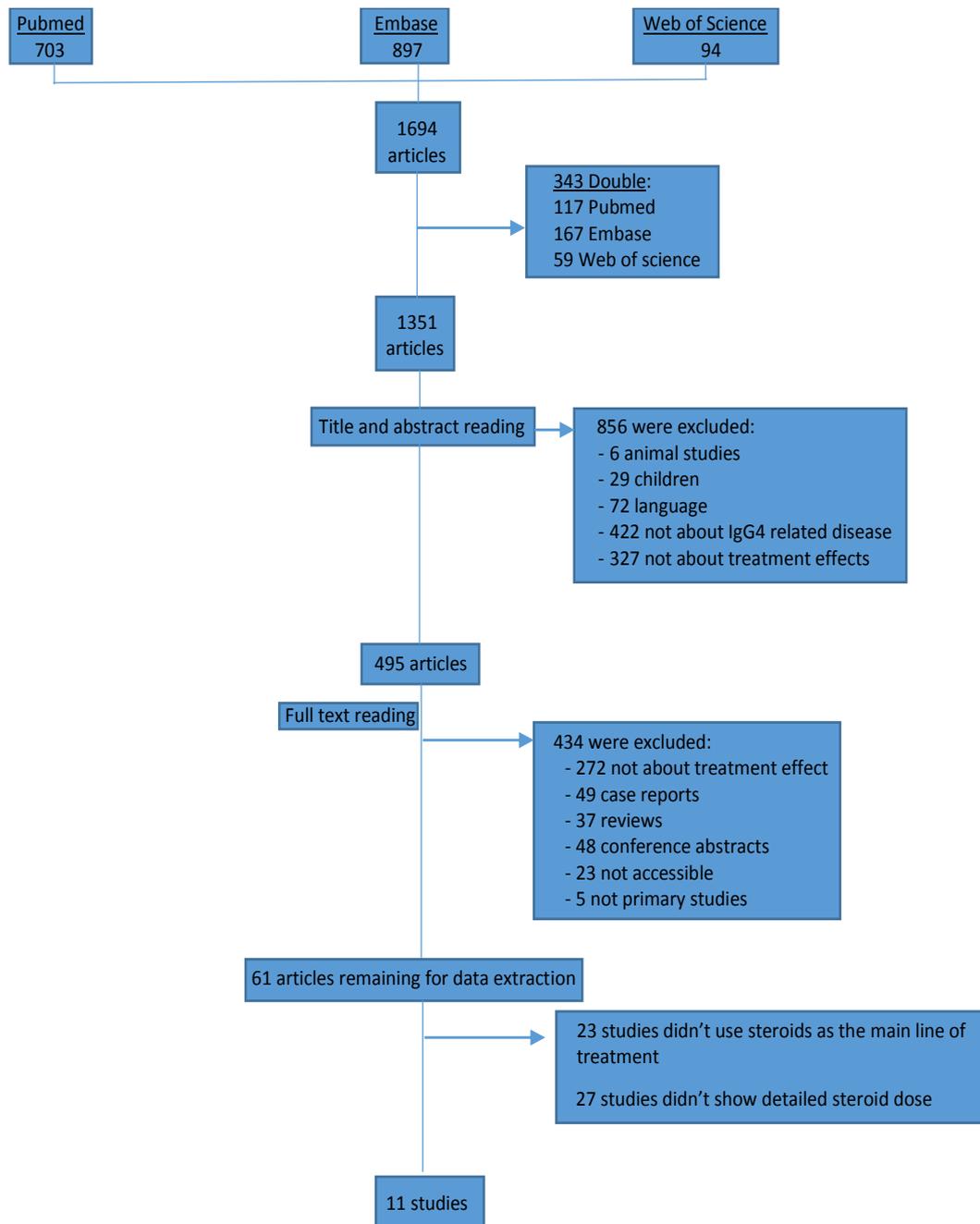
Figure 1: Prisma checklist of the process of selection.

Study Characteristics and Quality Assessment

Among the 11 included studies, six studies were retrospective reviews, four studies were prospective studies, and only one study was a randomized controlled trial. Eight studies included patients with autoimmune pancreatitis, while the rest of the included studies enrolled patients with a wide variety of IgG4 related conditions. The sample size of the included studies ranged from 19 to 978 patients. Moreover, the included studies administrated different doses of induction and maintenance regimens. Quality assessment was done with the Newcastle-Ottawa Quality Assessment Scale; studies are classified to be of good quality as all the

reviews had a score of 6 – 8 Table.1 shows the summary characteristics of the included studies.

Table 1: The summary characteristics of the included studies

Study ID	Study Design	Region	Type of Patients	Sample Size	Quality	Age ratio (years)	M/F ratio	Regimen	Conclusion
Masamune 2016	Randomized Controlled Study	Japan	AIP	49	8	20 -79	2.7:1	0.6 mg /kg/day as induction therapy then 5-7.5 mg /day for 3 years	Three years maintenance steroid therapy reduce AIP relapse
kubota 2011	A Retrospective Review	Japan	AIP	70	8	40-93	2.6: 1	30-40 mg /day as induction then 5 mg /day for more than 12 months	High IgG4 level with jaundice are the predictors of relapse in AIP
Sekiguchi 2016	A Retrospective Review	USA	IgG4-RD	66	8	61	3:1	0.4-0.6mg/kg /day as induction therapy then.11 mg/kg /day for at least one year	Multiple organs affected is a predictor sign for relapse
Kamisawa 2009	A retrospective Review	Japan	AIP	459	8	63	3.5:1	20-60mg/day as induction therapy then 2.5-10mg/day 3 year	. Maintenance steroid treatment reduces relapse in AIP
Kamisawa 2008	A retrospective Review	Japan	AIP	41	7	63.5	2.7:1	20-60 mg /day as induction therapy then 2.5-5 mg for two year	Steroid maintenance therapy indicated if an incomplete resolution
Hart 2013	A retrospective Review	Japan	AIP	978	6	61.4	2.3:1	30-40 mg/day as induction therapy then 2.5-5 mg for six months to 3years	The most common relapse sites are the pancreases and biliary tree suggesting maintenance therapy to decrease relapse
Nishino 2006	Prospective study	Japan	AIP	12	7	56-57	1:1	30-40mg /day as in therapy then 2.5-5 mg for one year	AIP treated with PSL has a favorable long-term outcome
Hirano 2007	A retrospective Review	Japan	AIP	19	6	64	4.7:1	30-40mg /day as in therapy then 2.5-5 mg for 41 months	CST could reduce AIP-related unfavorable events.
Shimizu 2015	A retrospective Review	Japan	AIP	65	7	65.5	4.3: 1	0.6mg/kg/day as induction then 2.5-10mg/day for 6 months-3 year	Side effects of Steroid maintenance therapy open a way for searching alternative maintenance therapy
Campochiaro 2015	Prospective study	Japan	IgG4-RD	36	7	62	1.73: 1	0.6mg/kg/day as induction then 2.5-10mg/day for 6 months-3 year	Combined corticosteroids and DMARDs maintenance therapy control the disease in the long run.
Yamamoto 2014	Prospective study	Japan	IgG4-RD	112	6	23-81	1.03: 1	0.6mg/kg/day as induction then 4.5mg/day for more than three years	Most cases need maintenance steroid therapy to prevent relapse.

Meta-analysis

With regard to the results of the meta-analysis, the overall effect estimates favored maintenance therapy in term of relapse episodes (RR 1.92, 95% CI [1.63, 2.26]; p <0.001; Figure 2), the pooled effect estimate was homogenous (p >0.1). Similarly, the overall effect estimates favored maintenance therapy in term of improvement rate (RR 0.75, 95% CI [0.70, 0.80]; p <0.001; Figure 3). The pooled analyses were highly heterogeneous (p <0.1). However, no significant difference was detected between both groups in terms of

number of organs with relapse episodes (RR 1.10 [0.71, 1.70]; p =0.066; Figure 4) and IgG4 elevation level (SMD 0.01, 95% CI [-0.77, 0.79]; p =0.99; Figure 5). The pooled analyses were highly heterogeneous (p <0.1). Our finding Demonstrate that Maintenance corticosteroids therapy plays an important role in decreasing the relapse episodes and increasing the improvement rate in IgG4 -RD patients, While It did not show an obvious effect in decreasing the number of organs affected nor the IgG4 level.
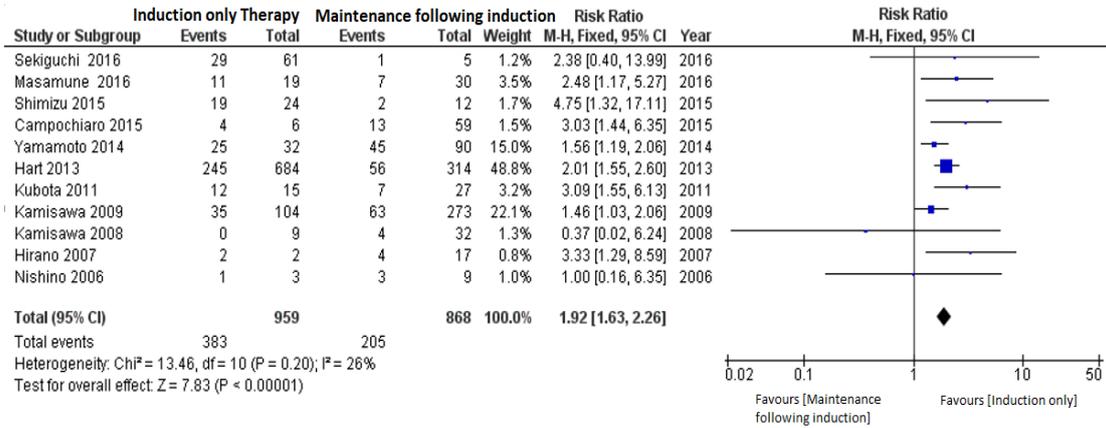

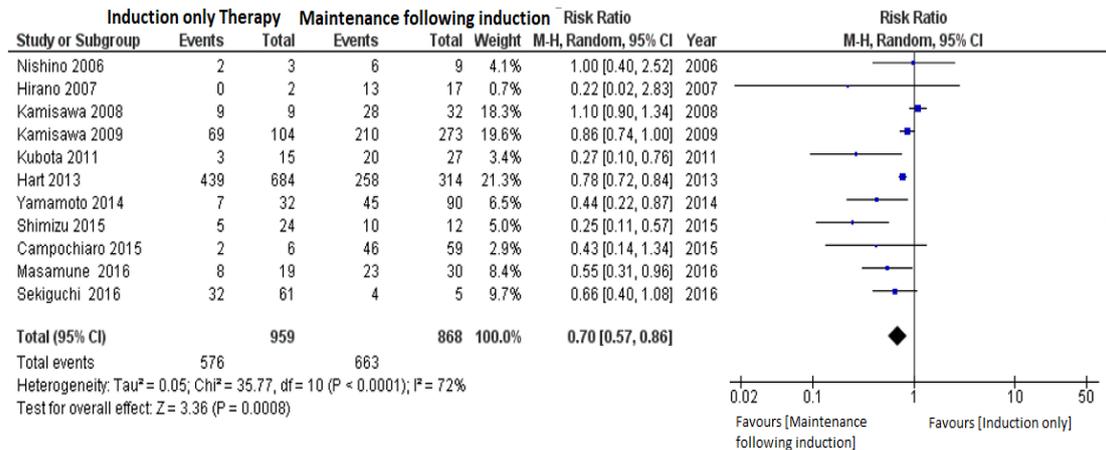**Figure2: Forest plot shows the pooled effect estimates of relapses episodes.**

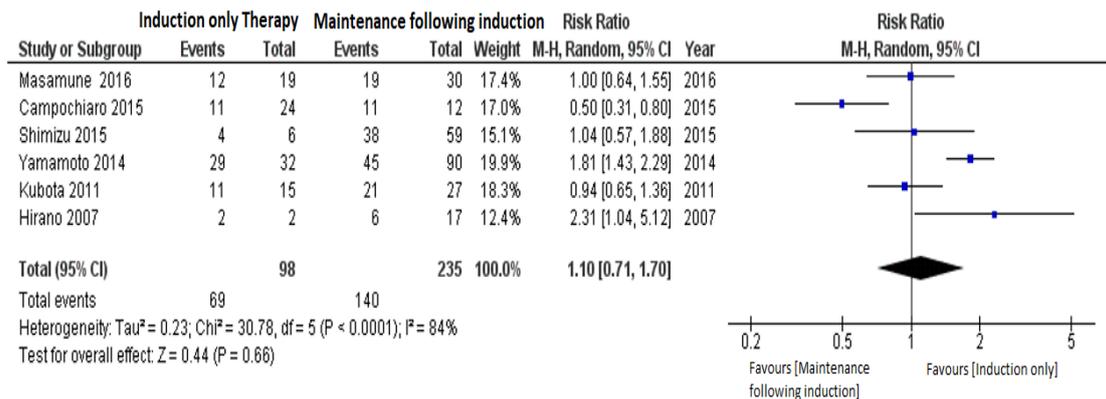**Figure 3: Forest plot shows the pooled effect estimates of improvement rate.**

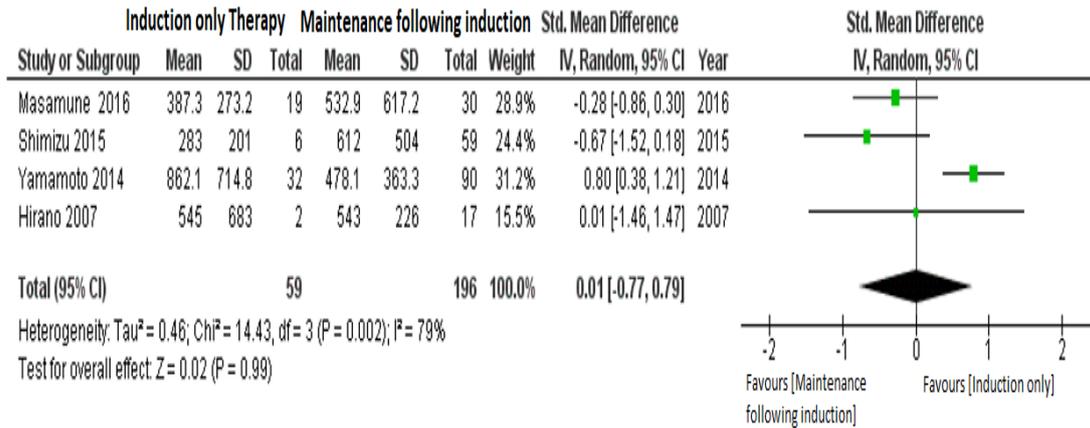**Figure 4: Forest plot shows the pooled effect estimates of no. of organs affected in both groups.**

Figure 5: Forest plot shows the pooled effect estimates of IgG4 level elevation.

Publication bias

About the publication bias, the funnel plot showed no evidence of publication bias for the pooled of effect estimates in terms of relapse rate **(Figure.5)**, improvement rate **(Figure.6)**, no. of an organ with relapse **(Figure.7)**, and IgG4 level **(Figure.8)**.
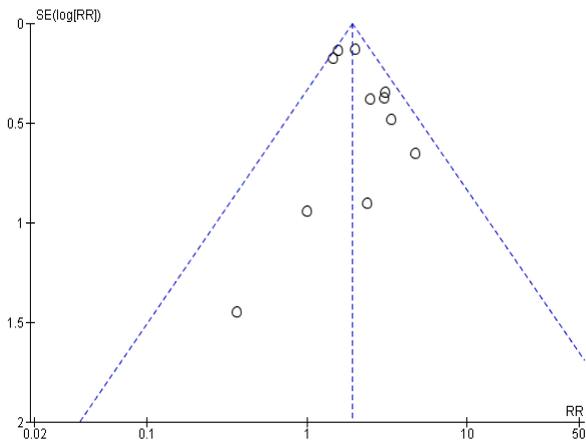

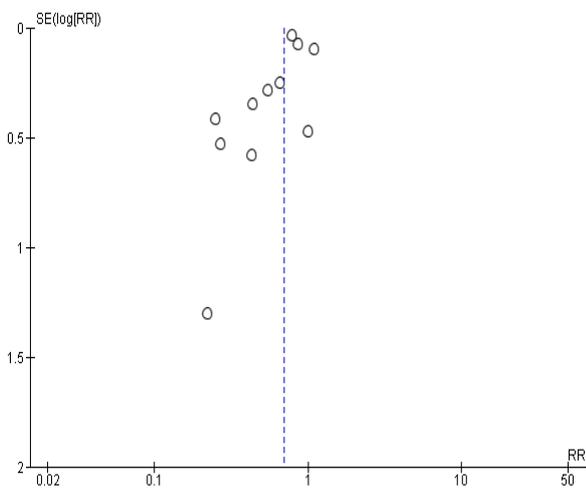**Figure 6: Funnel plot shows the pooled effect estimates of relapses episodes.**

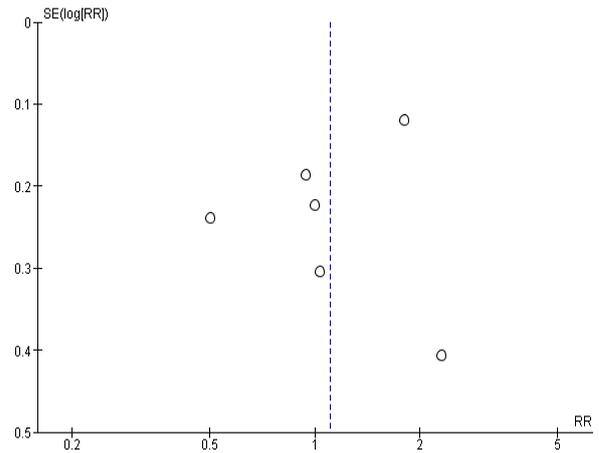**Figure 7: Funnel plot shows the pooled effect estimates of improvement rate.**

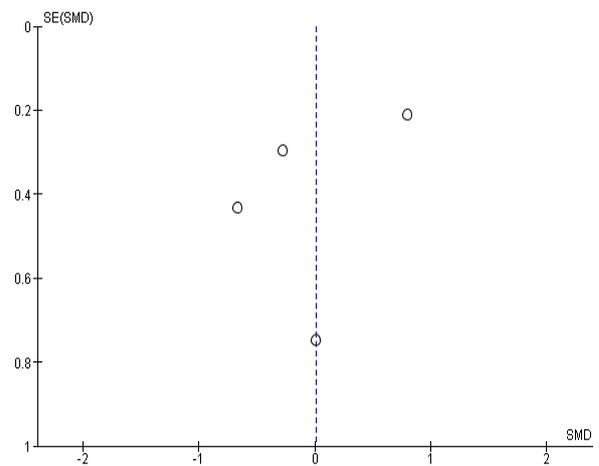**Figure 8: Funnel plot shows the pooled effect estimates of no. of organs with relapse.**

Figure9: Funnel plot shows the pooled effect estimates of IgG4 elevation level.

DISCUSSION

Corticosteroids are considered as the cornerstone of IgG4-RD treatment due to the rapid remission of the disease associated with this drug. That is why the response to it was mentioned as one of the diagnostic criteria for IgG4 -RD[17] In most studies clinicians were using glucocorticoids as the initial therapy for induction

of IgG4-RD and some of them prefer using a low dose of prednisone equivalent for maintenance therapy.[18] However, the dose, the duration of treatment and the need for maintenance therapy remains controversial. The aim of using corticosteroids in the IgG4 -Rd treatment is to improve the symptoms, Delay disease progression(including organ failure or additional involvement of other organs) and achieving long term maintenance of treatment benefits.[19] The IgG4 -Rd patients are usually old and more susceptible for corticosteroids side effects from here came to the importance of determining a specific treatment regimen to protect the patient from unnecessary complications and achieve the best results.

Recently, several studies aimed to detect the use of corticosteroids maintenance therapy in IgG4 related disease. We summarized these studies to perform our meta-analysis which includes 11 studies with the total number of 1907 patients. To our knowledge, this is the first meta-analysis trying to estimate the benefit of maintenance therapy in the outcome of IgG4 related disease. The main finding in our meta-analysis is that the maintenance therapy for three years reduces the risk of relapse in IgG4 -RD and increases the improvement rate. All IgG4 -RD patients who had a clinical response to treatment are at risk of developing relapse[20], As without short follow-ups, between 40–76% of patient who had successful treatment with glucocorticoids will relapse in the same organ or another, requiring several induction treatments and long taper[21] Despite that the need for maintenance therapy in IgG4 related disease is still not approved, some studies are supporting its essential role in decreasing the relapse episodes.

In 2017, the last International Consensus on AIP treatment concluded That using a low dose of steroids or disease-modifying antirheumatic drugs as maintenance therapy may be helpful in some patients with type 1 AIP.[22] A randomized controlled trial made by **Masamune et al**.[5] showed that The Kaplan-Meier measure of the relapse rate at three years was 23.8% in the maintenance therapy group and 60.9% in the cessation group this the only randomized controlled trial in our analysis. These results were comparable to another multi-center study in Japan showing that 10/38 (26.3%) cases relapsed during the maintenance corticosteroid therapy and 12/26 (46.2%) cases did after stopping the therapy.[23] On the other side this Results were different from those of **Hirano and colleagues** who found that 10 of 21 (47.6%) patients with AIP complained of disease relapse after treatment with a 3-year course of steroids, with a median of 43 months follow-up[24] Previous studies showed that most patients who were in remission relapsed soon after the cessation of corticosteroid treatment.[25,26] In a retrospective study from Pittsburgh, (60%) patients who were in complete remission developed relapses within 8–12 weeks after stopping of corticosteroids.[25] In a prospective study reported from the UK, 48/96 (50%) relapsed at a median time of 4.6 months after cessation of the first course of corticosteroids, with two of these patients developed relapse while taking steroids.[26]

These studies support Our results which favored maintenance therapy in term of relapse episodes (RR 1.92, 95% CI [1.63, 2.26]; p <0.001; Figure.1), the pooled effect estimate was homogenous (p >0.1) and the improvement increased markedly with patients using the maintenance therapy (RR 0.75, 95% CI [0.70, 0.80]; p <0.001;).

We thought that with steroid treatment there would be marked lowering in the IgG4 level an indicator of disease remission putting its important role in the diagnosis in consideration. As its role in detecting the use of maintenance steroid therapy is still doubtful. However, surprisingly we did not find a prominent role of steroid therapy on this factor. Now Studies have shown that high IgG4 levels do not approve and low IgG4 serum levels do not exclude IgG4-RD. Great mimickers of IgG4-RD like, lymphoma, pancreatic adenocarcinoma, and ANCA associated vasculitis could appear with elevated serum IgG4 levels while biopsy that confirms The IgG4-RD patients can have normal IgG4 concentrations.[21] Also studies like **Kamisawa et al**.[20] did not support a significant relationship between maintenance steroid therapy and IgG4 level. On the other hand, Some studies found that the decrease in IgG4 concentration following steroid treatment is significant like **Hamano et al**.[17] (P = 0.002) and **Umemura et al**. (P = 0.016).[18] **Also, Culver et al**.[27] observed a marked decrease in IgG4 level after steroid treatment especially after 8 -12 week of treatment. Our meta-analysis also showed an insignificant decrease in IgG4 level with maintenance steroid therapy (SMD 0.01, 95% CI [-0.77, 0.79]; p =0.99; the pooled analyses were highly heterogeneous (p <0.1).

Organ involvement was defined as single if only one organ system was affected and multiple if more than one organ system was affected (confirmed radiologically and histologically)[11] during follow-up. 60% of patients with IgG4-RD have more than one single organ involvement at the time of diagnosis. A complete history and physical examination can show another asymptomatic organ involvement. It is essential to estimate for multiorgan involvement in patients who present with single organ disease because deficiency of rapid treatment of specific organs can cause irreversible damage[10] corticosteroids treatment aiming to save other healthy organs from being affected by the disease but in our meta-analysis. We found no significant difference between both groups as regards the number of organs affected (RR 1.10 [0.71, 1.70]; (p =0.066). This is supported by other studies like **Ghazali et al**[19] and **Khosroshahi et al**.[28] showing that multi-organ involvement and elevated serum IgG4 levels are not good predictors for treatment response and they also did not increase the risk of areas.

This gives us questions about the appropriate duration of corticosteroid treatment in IgG4 RD patients. Now, there is no international consensus on the dose regimen and the treatment duration of steroids for IgG4-RD. Prolonged steroid treatment can affect patients negatively like worsening glycemic control, bone resorption, weight gain, infections, and cataracts. Choosing the treatment for relapse of disease (immunosuppressants vs. low-dose steroids) and the maximum duration of the treatment have to be estimated in clinical trials to make fixed clinical guidelines for the management of this disease.[12] Our meta-analysis has some limitations: Firstly, there was heterogeneity in the included studies because of the different doses of steroids and different duration of maintenance therapy between the studies. Secondly, the types of included studies are different; as there are six retrospective studies, four prospective studies and one randomized clinical trial.

CONCLUSION
There is a distinct role of maintenance corticosteroids therapy in reducing the relapse episodes in patients with IgG4 related disease. Additional studies are required to prove the effectiveness of maintenance therapy, the appropriate dose of steroids and the duration of treatment.

CONFLICT OF INTEREST
The authors confirm that this article content has no conflict of interest.

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