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SYSTEMATIC REVIEW

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Treatment approaches for idiopathic retroperitoneal fibrosis: a systematic review with meta-analysis

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Abstract

Background Currently, there is no standard therapy for idiopathic retroperitoneal fibrosis, so a systematic review was undertaken to assess the effectiveness of different treatment approaches.

Methods A comprehensive search of English and German literature from 1980 to 2021 was conducted using PubMed, Embase, and PreMedline. To be included, studies must have had a minimum of two patients employing the same treatment approach and reporting relevant treatment outcomes. A meta-analysis with a subgroup analysis was conducted for the primary outcomes "regression of fibrosis," "freedom from ureteric stents" and "relapse rate," and the secondary outcome "clinical improvement." The lack of homogeneous data prevented a subgroup analysis for the primary outcome "improvement in renal function."

Results The search resulted in a total of 3818 articles, of which 108 were selected for qualitative analysis involving a total of 1408 patients. For the meta-analysis 83 studies were included involving 1044 patients. The summary effect size of the outcomes "regression of fibrosis," "freedom from ureteric stent" and "clinical improvement" was high with values between 80–97.9%. The summary relapse rate across studies was 18.1%. Subgroup analysis revealed no statistically significant differences in the effectiveness of treatment approaches for the outcomes "regression of fibrosis" (QM = 2.72, $p = 0.74$), "freedom from ureteric stent" (QM = 7.21, $p = 0.13$), "relapse rate" (QM = 11.34, $p = 0.08$) and "clinical improvement" (QM = 9.54, $p = 0.15$).

Conclusions Considering the lack of clear evidence indicating that one drug is more effective than the other, the treatment choice should depend on factors such as the potential side effects of different drug therapies, patient comorbidities, and clinician expertise. The review protocol is registered on PROSPERO under the identification number CRD42019115744.

Keywords Idiopathic retroperitoneal fibrosis, Systematic review, Meta-analysis, Treatment

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Background

Idiopathic retroperitoneal fibrosis (IRF) is presumed to be a systemic disease with an autoimmune origin [1]. The condition is categorized within the group of chronic periaortitis, alongside other entities such as inflammatory abdominal aortic aneurysm, and perianeurysmal fibrosis [1, 2]. It is a very rare disorder that has been estimated to have an incidence of about 1.3 in 100,000 by a single centre study from the Netherlands [3]. A connection with the HLA-DRB1 gene has been identified [4]. Furthermore, IRF is associated with various other autoimmune diseases such as autoimmune thyroiditis [1]. It is crucial to highlight that it can manifest with or without the typical features of immunoglobulin G4-related disease (IgG4-RD). These include lymphoplasmacytic infiltration with IgG4 positive plasma cells, elevated serum IgG4 levels and the fibro-inflammatory affection of various organs (e.g. pancreas, salivary glands, thyroid gland) [5, 6]. The development of retroperitoneal fibrosis is not exclusive to idiopathic causes; it can be secondary to other conditions: these include infectious diseases, post-radiotherapy scarring, major abdominal surgery, trauma, Erdheim-Chester disease, other histiocytosis and drugs [1]. Additionally, malignancies such as retroperitoneal lymphoma or retroperitoneal metastases accompanied by a desmoplastic reaction may mimic the presence of retroperitoneal fibrosis [1, 7]. Patients frequently complain of flank or back pain, along with fatigue and weight loss [8, 9]. In some cases the disorder may lead to deep venous thrombosis and hypertension [9]. Laboratory findings often show elevated inflammatory markers and impaired renal function [10]. IRF can be managed through either surgical or conservative treatment approaches [1]. For the acute relief of ureteric obstruction, a commonly employed strategy involves combining drug therapy with the insertion of a double pigtail stent (DJ stent) or a percutaneous nephrostomy (PCN) [11]. Conservative treatment options for IRF include immunosuppressive drugs (corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, rituximab, ciclosporin, tocilizumab), immunomodulators (colchicine), and anti-hormonal agents (tamoxifen) [12–22]. In case of treatment failure, surgical interventions are possible. A frequently employed treatment approach is ureterolysis, which involves the release of the ureters and can be performed either laparoscopically or through open surgery [11]. There is no standardized treatment regime at present [11]. To assess the response to drug therapy and detect potential relapses, follow-up imaging of retroperitoneal fibrosis through MRI or CT is typically conducted [1, 10]. Consequently, regression of fibrosis is expected to lead to clinical improvement. The objective of this systematic review is to evaluate the effectiveness of the mentioned treatment approaches in managing IRF. This assessment will consider the primary outcomes of "regression of fibrosis," "freedom from ureteric stent," "improvement in renal function," "relapse rate," and the secondary outcome "clinical improvement."

Methods

Protocol

The review protocol is registered on the Prospective Register of Systematic Reviews (PROSPERO) under the identification number CRD42019115744 [23]. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used to write this review [24].

Literature search

A literature search spanning from 1980 to 2021 using Embase, PubMed, and Premedline was conducted, covering both English and German literature. For the search Medical Subject Headings (MeSH) terms, Emtrees, and different synonyms were used. The detailed search strategy is provided in the supplement (Supplemental File 1). The initial search was executed on October 30, 2018, followed by a subsequent search, conducted on February 13, 2021. In addition to the database search, a manual consultation of references of the selected studies and reviews on the topic was done [1, 10, 11, 25–28]. Furthermore, searches for existing systematic reviews and meta-analyses on IRF were performed using Embase, PubMed, PROSPERO, and the Cochrane database; this search was last repeated on October 19, 2021. It is noteworthy that only one extensive qualitative, nonsystematic review authored by Cristian et al. (2015) was identified. This review summarizes the literature on IRF from 1998–2013 [11]. Notably, the sole systematic review registered on PROSPERO concentrates on the relief of ureteric obstruction in cases of secondary retroperitoneal fibrosis due to malignancy [29].

Eligibility criteria

Studies including at least two patients with IRF treated with the same therapy with an outcome of effectiveness were considered. As the focus of this review is IRF, studies focusing on secondary retroperitoneal fibrosis, inflammatory abdominal aortic aneurysm, perianeurysmal fibrosis, and IgG4-related IRF were excluded. However, studies with at least 70% IRF patients and studies without evidence for secondary causes were included. In studies investigating idiopathic and secondary retroperitoneal fibrosis patients, individual data was exclusively extracted from IRF participants when available. Patients treated with more than one IRF-specific drug simultaneously were excluded, as the outcome could not reliably be associated with one treatment approach. The sole exception was posed by patients taking both corticosteroids

and an additional IRF-specific drug. This exception was accepted due to the combination of corticosteroids and a corticosteroid-sparing immunosuppressive drug being common practice [1, 11].

Furthermore, the review protocol was adapted from originally including studies with at least five patients to including studies with at least two patients, as most case series found during the literature search only treated two patients the same way. To exclude arriving at a different result with the adaptation from the primary review protocol, a sensitivity analysis was conducted, including only studies with a minimum of five patients.

Data extraction and study outcomes

Data were collected using a data extraction sheet in SPSS Statistics 25 [30]. The outcomes were assessed after initial treatment success. Patients with an initial treatment response and a subsequent worsening, were subsumed under relapsed patients. All primary and secondary outcomes were assessed categorically (outcome achieved/outcome not achieved, patient relapsed/not relapsed). The primary and secondary outcomes were defined as follows:

"Regression of fibrosis" was met in all patients, which regressed either partially or completely during the follow-up period as confirmed by an imaging technique. No minimum regression of fibrosis was predefined, as many papers did not report the exact values. If there was an increase of the fibrosis or it stayed the same during follow-up this was counted as no regression of fibrosis.

"Relapse rate" involved either a clinically or radiologically diagnosed relapse after initial treatment success. Patients who relapsed after treatment discontinuation were also included.

"Freedom from ureteric stent" in patients with bilateral stenting was only considered as such if both ureters were free from stents. Certain papers only reported summarized outcomes for "freedom from ureteric stents," and "freedom from nephrostomies." These papers are outlined in the meta-analysis.

For "improvement in renal function" the improvement in laboratory values (creatinine, estimated glomerular filtration rate), the relief of ureteric obstruction, the improvement of hydronephrosis, and the improvement in renal scintigraphy was considered. No specific cut-off value was determined for the improvement in renal function concerning laboratory values (creatinine, estimated glomerular filtration rate) given the absence of precise laboratory data in the studies selected. Consequently, any amelioration in these laboratory values was deemed an improvement in renal function.

The secondary outcome "clinical improvement" was defined as any improvement in symptoms without specific criteria, as the symptoms for IRF vary widely and are frequently non-specific. If the author of the paper reported the patient improved clinically or became symptom-free this was subsumed under "clinical improvement." If the patient reported persistent symptoms or persistent pain until the end of the study follow-up this was not seen as an amelioration. In larger studies, the same approach was chosen. The number of patients with "clinical improvement" was the one stated as such by the author.

Quality assessment

The included studies were analysed for biases with the Quality in Prognostic Studies Tool (QUIPS). This tool contains the following categories: study participation, study attrition, outcome measurement, study confounding, and statistical analysis and reporting. The category of prognostic factor measurement was excluded, as most studies were retrospective. Each category was rated with a low, moderate, or high possibility of bias. If at least one category had a high risk of bias, the whole study was set at high overall risk [31]. The bias tool is depicted as a summary of all the studies included in the analysis.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used to assess the evidence of the different outcomes. As most studies were observational, the evidence is rated low [32, 33].

Statistical analysis

The primary outcomes "regression of fibrosis," achieving "freedom from ureteric stent," "relapse rate," and the secondary outcome "clinical improvement" were analysed with a forest plot of proportion with subgroup analysis. For this quantitative analysis only studies with two patients with the same treatment method and the same outcome measurement were included. A sensitivity analysis was also conducted, which only included the studies involving at least five patients, as defined in the review protocol. The different treatment approaches (azathioprine, colchicine, corticosteroids, cyclophosphamide, mycophenolate mofetil, tamoxifen, rituximab, ureterolysis) were defined as subgroups and compared to each other. However, ureterolysis as a subgroup was removed from the subgroup analysis for the outcome "regression of fibrosis" and "freedom from ureteric stent." This was done due to the assumption that in the case of ureterolysis the fibrosis is removed during the surgery and the obstruction of the ureters is released so those outcomes should always be reached in 100 % of the patients. Furthermore, for a subgroup to be included in the meta-analysis it had to contain at least two studies. It is important to notice that some studies are mentioned more than once in the subgroup analysis, as they include different treatment approaches, whose data were analysed separately.

Additional subgroup analyses were done comparing treatment categories. The definition of the subgroups for the meta-analysis was as follows: Subgroups in main analysis: azathioprine, colchicine, corticosteroids, cyclophosphamide, mycophenolate mofetil, tamoxifen, rituximab, ureterolysis. Patients with corticosteroids in addition to an immunosuppressive, immunomodulatory, hormonal therapy or surgery, are counted under the respective subgroup. The subgroup of corticosteroids only encompasses patients who had corticosteroids as their sole treatment.

Subgroups in the first additional analysis with treatment categories: hormonal therapy (tamoxifen), immunomodulators (colchicine), and immunosuppressive drugs (corticosteroids, mycophenolate mofetil, azathioprine, cyclophosphamide, rituximab), ureterolysis.

Subgroups in the second additional analysis with treatment categories: hormonal therapy (tamoxifen), immunomodulators (colchicine), and immunosuppressive drugs p.o. (corticosteroids, mycophenolate mofetil, azathioprine), immunosuppressive drugs i.v. (cyclophosphamide, rituximab).

Subgroups in the third additional analysis with treatment categories: medical treatment (azathioprine, colchicine, corticosteroids, cyclophosphamide, mycophenolate mofetil, tamoxifen, rituximab), surgery (ureterolysis).

All statistical calculations were conducted in RStudio with R Version 4.2.2 employing the packages metafor and meta as well as tidyverse [34–37]. The code is shown in the supplement (Supplemental File 2). The forest plot of proportion was created with a random-effects model with the estimator restricted maximum likelihood method (REML) for the between-study variance [38]. The Freeman-Tukey double arcsine transformation was used for the transformation of proportions [39, 40]. The subgroup analysis was performed with a mixed effects model [41].

The heterogeneity was quantified with the Q-statistic and the I^2-Test and was calculated per subgroup [42]. Publication bias was assessed with a Funnel plot and Egger's test [43]. Influential studies were searched for with a Baujat plot [44].

The primary outcome "improvement in renal function" was not analysed in the meta-analysis as the documentation for this outcome was very heterogeneous across different studies and no statistical analysis was possible. As such, it is only reported descriptively in a chart. Some studies reported laboratory values, whereas others reported the improvement in renal function with imaging techniques. The primary outcome "freedom from ureteric stent" indirectly depicts an improvement in renal function as stents can only be removed if the obstructive uropathy improves.

Results

Identification of relevant studies

The study selection and screening process can be seen in the flow diagram in Fig. 1. Out of 3171 records screened in total from different sources (mainly EMBASE and PubMed), 157 full-text articles were included, of which 108 were used for a qualitative synthesis and 83 could be used for a quantitative meta-analysis.

Specific reasons for exclusion of studies are shown in the supplement (Supplemental Tables 1–3).

The chart with all studies included with their main treatment and number of patients treated, as well as the study design and publication year, are shown in the supplement (Supplemental Table 4).

Quality assessment of the included studies

In Fig. 2 the risk of bias across different categories is depicted for all included studies. The assessment of the statistical analysis was often not applicable, as many small case series did not use statistical calculations. Highest risks for bias were attributed to confounding and outcome measurements. In total, there was a rather high risk of overall bias.

Table 1 presents the grade of evidence for each outcome. Most studies were retrospective case series and are therefore observational. The risk of bias was serious in most studies, as assessed by the QUIPS bias tool. Heterogeneity was substantial in two subgroups for each of the outcomes and hence inconsistency was rated as serious. "Regression of fibrosis" and "freedom from ureteric stent" are surrogate outcomes, as they measure patient-important outcomes not directly. Thus, these outcomes are indirect evidence for the effectiveness of the treatment. The outcomes "relapse rate" and "clinical improvement" measure a patient-important outcome and therefore are not rated down for indirectness. Most studies were very small, leading to a wide confidence interval.

Even though the funnel plot with Egger's test did not show a significant publication bias except for the outcome "clinical improvement," it is still strongly suspected due to different classifications of the disease by different authors. Furthermore, many studies reported a very high success rate, which might be due to positive results being reported more frequently.

Improvement in renal function

For this outcome 80 studies including 816 patients were available. The improvement of renal function varied largely between treatment approaches and measurement methods. Many studies reported high success rates between 70–100%. There were also studies which did not have any improvement in renal function or only in a small part of the patients. These studies often used surgical approaches such as ureterolysis. Details for the outcome

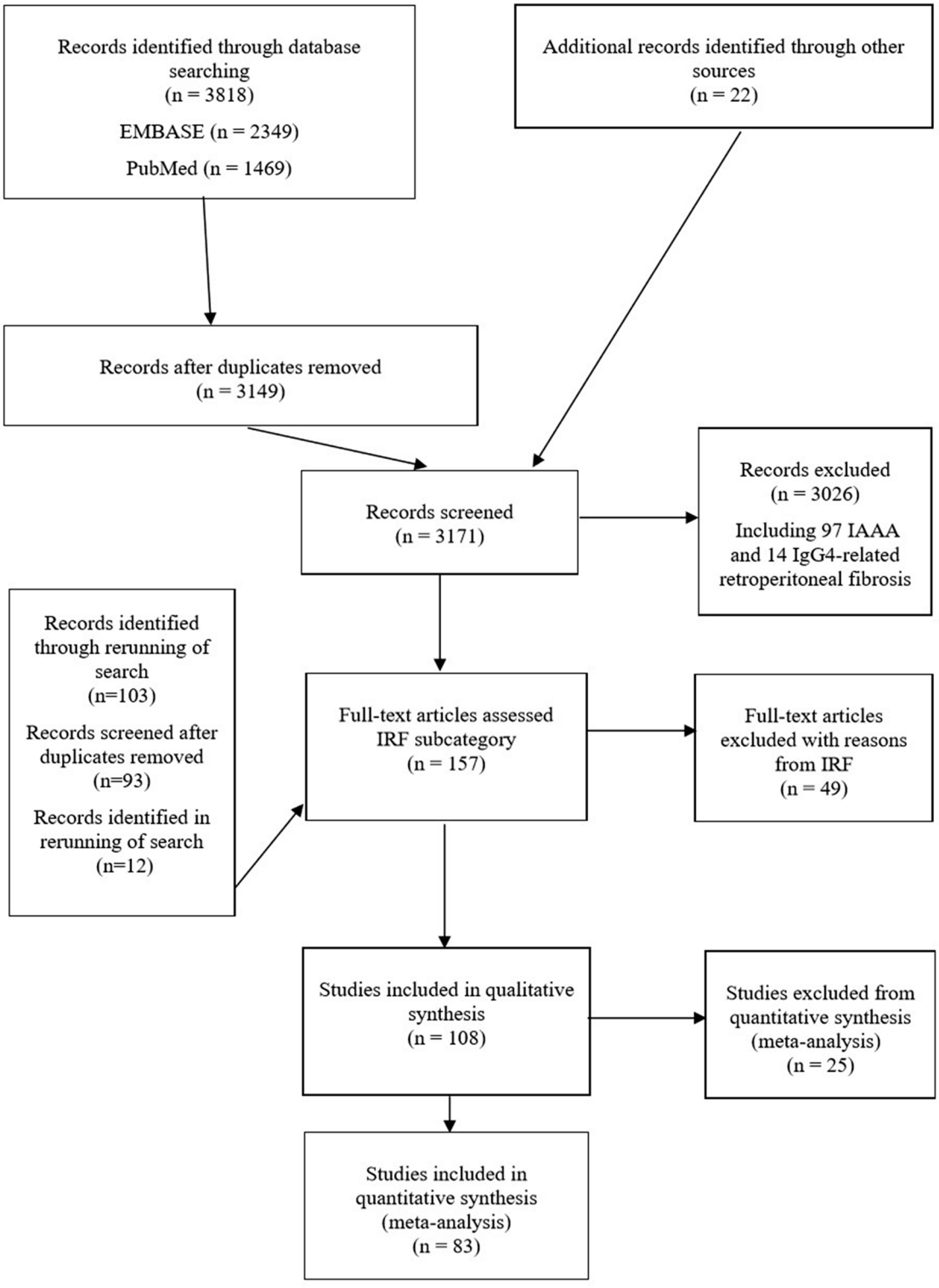

Fig. 1 Flow diagram of the literature search. *IAAA* Inflammatory abdominal aortic aneurysm, *IRF* Idiopathic retroperitoneal fibrosis, *IgG4-related* Immunoglobulin G4-related

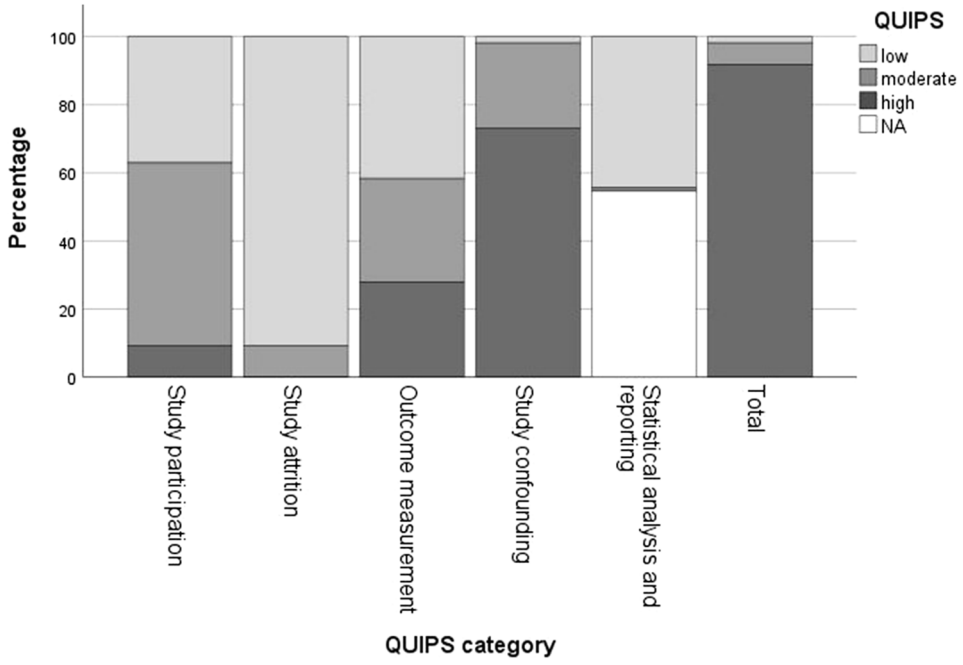

Fig. 2 Quality in prognostic studies (QUIPS) tool. *NA* Not applicable

Table 1 Grading of recommendations, assessment, development and evaluation (GRADE)

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty
ROF	Observational studies	serious	serious	serious	serious	publication bias	very low
FUS	Observational studies	serious	serious	serious	serious	publication bias	very low
Relapse rate	Observational studies	serious	serious	not serious	serious	publication bias	very low
Clinical improvement	Observational studies	serious	serious	not serious	serious	publication bias	very low

ROF, Regression of fibrosis; FUS, Freedom from ureteric stent

"improvement in renal function" are shown in the supplement (Supplemental Table 5), as measured with different methods: either improvement of laboratory values (creatinine, estimated glomerular filtration rate), the relief of ureteric obstruction, the improvement of hydronephrosis or the improvement in renal scintigraphy.

Adverse drug reactions

Adverse drug reactions for the different medications are shown in the supplement (Supplemental Tables 6–14).

Meta-analysis with subgroup analysis

No statistically significant difference between the different treatment approaches for the four outcomes "regression of fibrosis," "freedom from ureteric stent," "relapse rate," and "clinical improvement" could be found in the subgroup analysis. The sole analysis that detected a statistically significant result was for the outcome "freedom from ureteric stent" with drugs separated into treatment categories (hormonal, immunosuppressive p.o., immunosuppressive i.v.). However, this result is skewed due to a major outlier (Boyeva et al. 2020) and hence should be interpreted with caution [45]. The plots for the subgroup analyses for the treatment categories as well as for the sensitivity analysis are shown in the supplement (Supplemental Figs. 1–18).

Regression of fibrosis

For this outcome 35 studies including 423 patients were available. The summary effect size for "regression of fibrosis" across all subgroups was 94.7% (CI95% 88.7 to 98.9%). The subgroup analysis for the outcome "regression of fibrosis" is represented in Fig. 3 and was not statistically significant with the test of moderator (QM) = 2.72 ($p = 0.74$). The mean follow-up period is documented in months. Furthermore, the number of patients with either additional ureterolysis or corticosteroids is mentioned, as is the imaging technique used for the follow-up [12–18, 46–73]. The number of patients refers to the number of patients for whom the outcome "regression of fibrosis" was reported for.

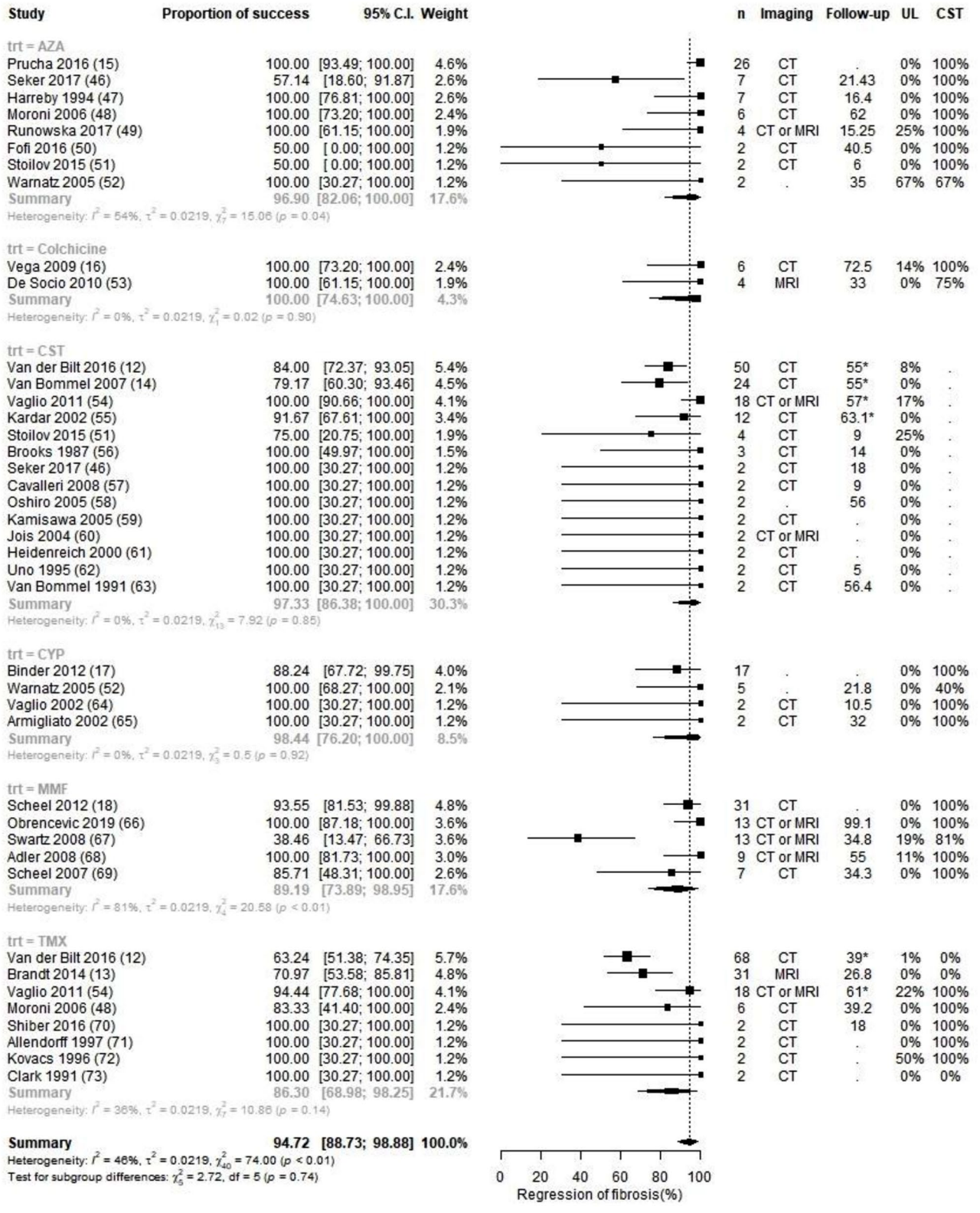

Fig. 3 Forest plot for the outcome "regression of fibrosis". *Follow-up months as a median; *Trt* treatment, *n* patient number, *AZA* Azathioprine, *CST* Corticosteroids, *CYP* Cyclophosphamide, *MMF* Mycophenolate Mofetil, *TMX* Tamoxifen, *UL* Ureterolysis, *CT* Computed Tomography, *MRI* Magnetic Resonance Imaging

Freedom from ureteric stent

For this outcome 18 studies including 191 patients were available. The summary effect size for "freedom from ureteric stent" across all subgroups was 80.4% (CI95% 68.5 to 90.6%). The subgroup analysis for the outcome "freedom from ureteric stent" is represented in Fig. 4 and was not statistically significant with QM = 7.21 ($p = 0.13$). The mean follow-up period is documented in months. The number of patients with either additional ureterolysis or corticosteroids is also mentioned [13, 14, 19, 45, 47, 48, 51, 52, 55, 61, 66–69, 72, 74, 75, 76]. The number of patients refers to the number of patients for whom the outcome "freedom from ureteric stent" was reported for.

Relapse rate

For this outcome 52 studies including 746 patients were available. The overall relapse rate across all subgroups was 18.1% (95% CI 12.8 to 24.0%). The subgroup analysis for the outcome "relapse rate" is represented in Fig. 5 and was not statistically significant with "relapse rate" QM = 11.34 ($p = 0.08$). The mean follow-up period is documented in months. The number of patients with either additional ureterolysis or corticosteroids is also mentioned [12–16, 18, 47, 48, 53–55, 59–63, 65–103]. The number of patients refers to the number of patients for whom the outcome "relapse rate" was reported for.

It was not possible to assess clinical or serological predictors statistically due to the heterogeneity of the involved studies. Three studies mentioned the investigation of predictive markers. Morin et al. found persistent

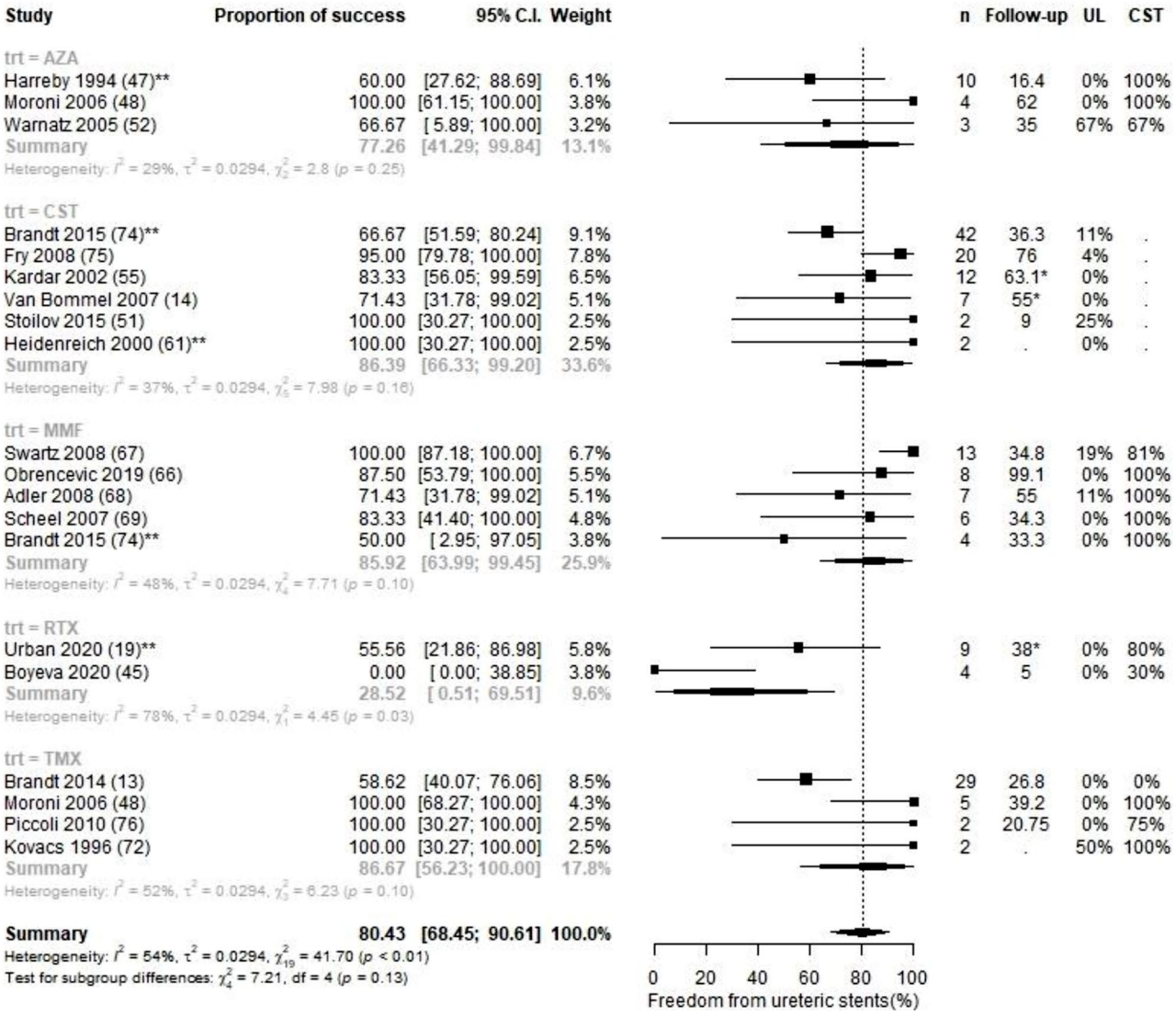

Fig. 4 Forest plot for the outcome "freedom from ureteric stent". *Follow-up months as a median; **Stent or percutaneous nephrostomy; *Trt* treatment, *n* patient number, *AZA* Azathioprine, *CST* Corticosteroids, *MMF* Mycophenolate Mofetil, *RTX* Rituximab, *TMX* Tamoxifen, *UL* Ureterolysis

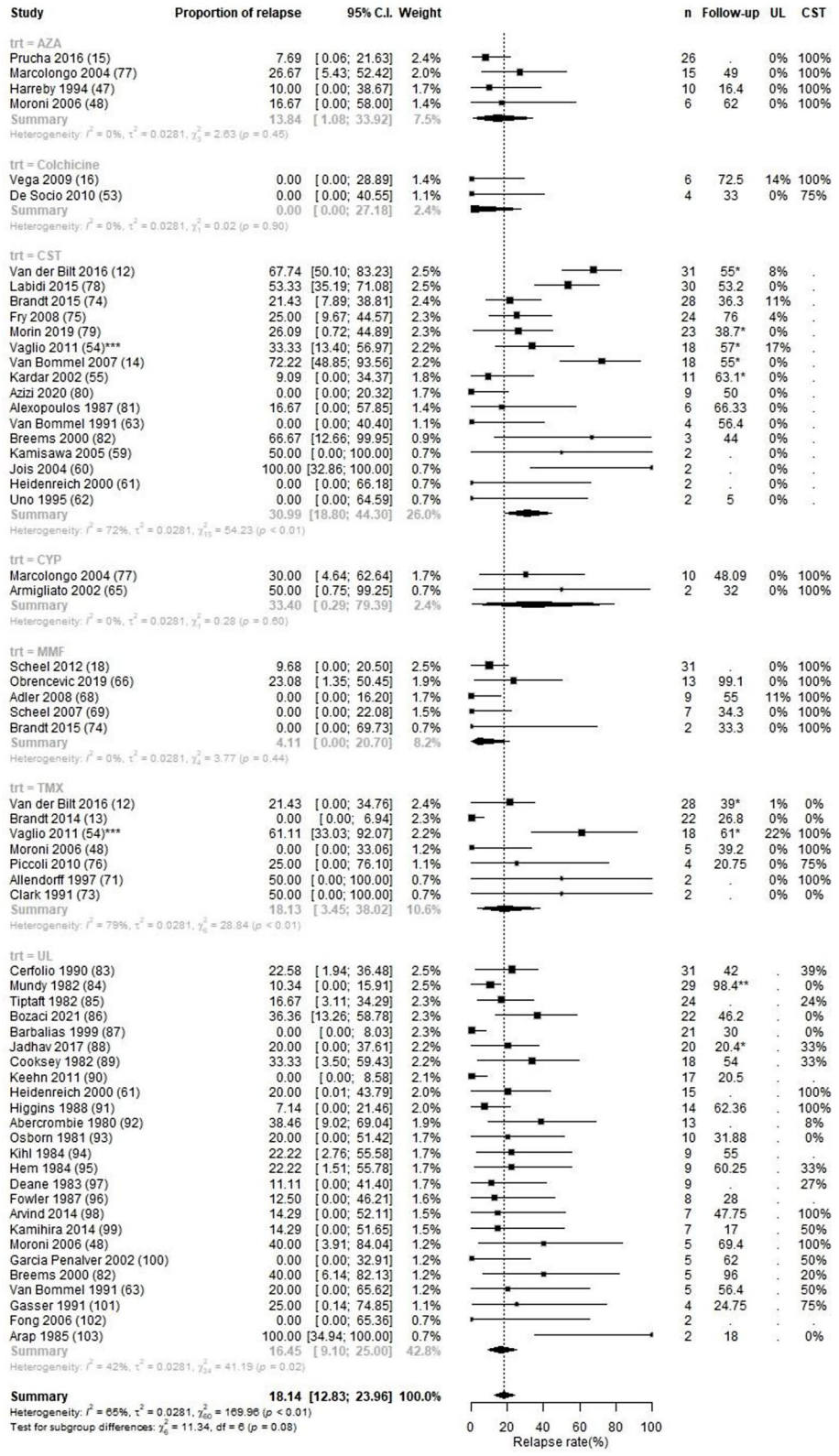

Fig. 5 Forest plot for the outcome "relapse rate". *Follow-up months as a median; **Follow-up months includes follow-up from patients treated with a different treatment method; *** Relapse rate at last follow-up after treatment discontinuation. Relapse rate at primary endpoint after 8 months was 6% for the prednisone group and 39% for the tamoxifen group; *Trt* treatment, *n* patient number, *AZA* Azathioprine, *CST* Corticosteroids, *CYP* Cyclophosphamide, *MMF* Mycophenolate Mofetil, *TMX* Tamoxifen, *UL* Ureterolysis

18 F-Fluorodeoxyglucose (FDG) uptake at second evaluation in IRF patients as a predictor for relapse in a multivariate analysis [79]. The study by Van der Bilt did not find a correlation between relapse rate and acute-phase reactant levels, and also no correlation between relapse rate and drug dosage and duration of corticosteroids [12]. At last, Van Bommel reported no difference in the baseline characteristics of patients who relapsed and patients who did not relapse [14].

Clinical improvement

For this outcome 45 studies including 492 patients were available. The summary effect size for "clinical improvement" across all subgroups was 97.9% (CI95% 94.5 to 99.8%). The subgroup analysis for the outcome "clinical improvement" is represented in Fig. 6 and was not statistically significant with QM = 9.54 ($p = 0.15$). The mean follow-up period is documented in months. The number of patients with either additional ureterolysis or corticosteroids is also mentioned [12, 14, 16, 18, 19, 45, 47–49, 53, 55, 56, 60, 63, 66, 67, 69, 72, 76, 79–81, 88, 90, 91, 93, 97, 98, 103–119]. The number of patients refers to the number of patients for whom the outcome "clinical improvement" was reported for.

Corticosteroid treatment scheme

In Table 2. the corticosteroid dose and tapering schemes of studies with at least ten patients under treatment with corticosteroids are described.

Publication bias

Egger's test was neither statistically significant for the sample size nor the standard error for the outcomes "regression of fibrosis," "freedom from ureteric stent," and "relapse rate." For the outcome "clinical improvement" Egger's test was not statistically significant for the predictor standard error but was statistically significant with $p = 0.02$ for the sample size. This result was confirmed in the sensitivity analysis ($p = 0.009$) for the sample size.

In conclusion, there is a possible publication bias for the outcome "clinical improvement" according to Egger's test. The funnel plots are shown in the supplement (Supplemental Figs. 19–26).

Heterogeneity and influential studies

For the outcome "regression of fibrosis, the study by Swartz et al. (2008) has the most impact on the overall results [67]. The study by Van der Bilt et al. (2016) accounts for most of the overall heterogeneity [12].

For the outcome "freedom from ureteric stent," the study by Boyeva et al. (2020) accounts for most of the overall heterogeneity and has the most impact on the overall results [45].

For the outcome "relapse rate," as well as for the outcome "clinical improvement" the study by Van der Bilt (2016) has the most impact on the overall results and accounts for most of the overall heterogeneity [12].

The Baujat plots are shown in the supplement (Supplemental Figs. 1–18).

Discussion

To date, there has been one large non-systematic review by Cristian et al. (2015) on this topic [11]. However, our systematic review includes more studies over a longer time period and includes more recent data than the review by Cristian et al. (2015). Furthermore, the review by Cristian et al. (2015) did not conduct a statistical analysis of the data but merely created a chart with an overview of the different studies [11].

In our review, there was no statistically significant evidence for a difference in the effectiveness of any drug treatment or surgical procedure over another for the outcomes of effectiveness. This is most likely due to the lack of high-quality data. Most studies were observational and only one study—the one by Vaglio et al. (2011)—was a randomized-controlled study [54]. Thus, although we collect more evidence, we come to the same conclusion as Cristian et al. (2015): there is no standardized treatment protocol with clear evidence for idiopathic retroperitoneal fibrosis [11].

The treatment approaches available each have their advantages and disadvantages. Corticosteroids have been used for many years and their effectiveness is well documented [12, 14, 46, 51, 54–63]. However, long-term treatment with corticosteroids has various known side effects [120, 121].

Other immunosuppressive drugs for long-term treatment of IRF are associated with the risk of opportunistic infections and some immunosuppressive drugs (cyclophosphamide, azathioprine) increase the risk for malignant diseases (non-melanoma skin cancer, lymphoma) [120].

The only treatment approach that involves a hormonal medication is tamoxifen. Tamoxifen does not have the disadvantages of an immunosuppressive drug, and its effectiveness is documented in various studies [12, 13, 48, 54, 70–73, 76]. Currently, there is one randomized controlled study and a comparative study that both analyze the treatment of tamoxifen versus corticosteroids [12, 54]. In the comparative study by Van der Bilt et al. (2016), the patients treated with corticosteroids had a faster improvement of symptoms, a larger decrease in acute phase reactant levels and creatinine, and a more frequent regression of fibrosis in the CT. The relapse rate was lower in the patients treated with tamoxifen [12]. However, in the randomized controlled study by Vaglio et al. (2011) with the primary outcome "relapse rate after

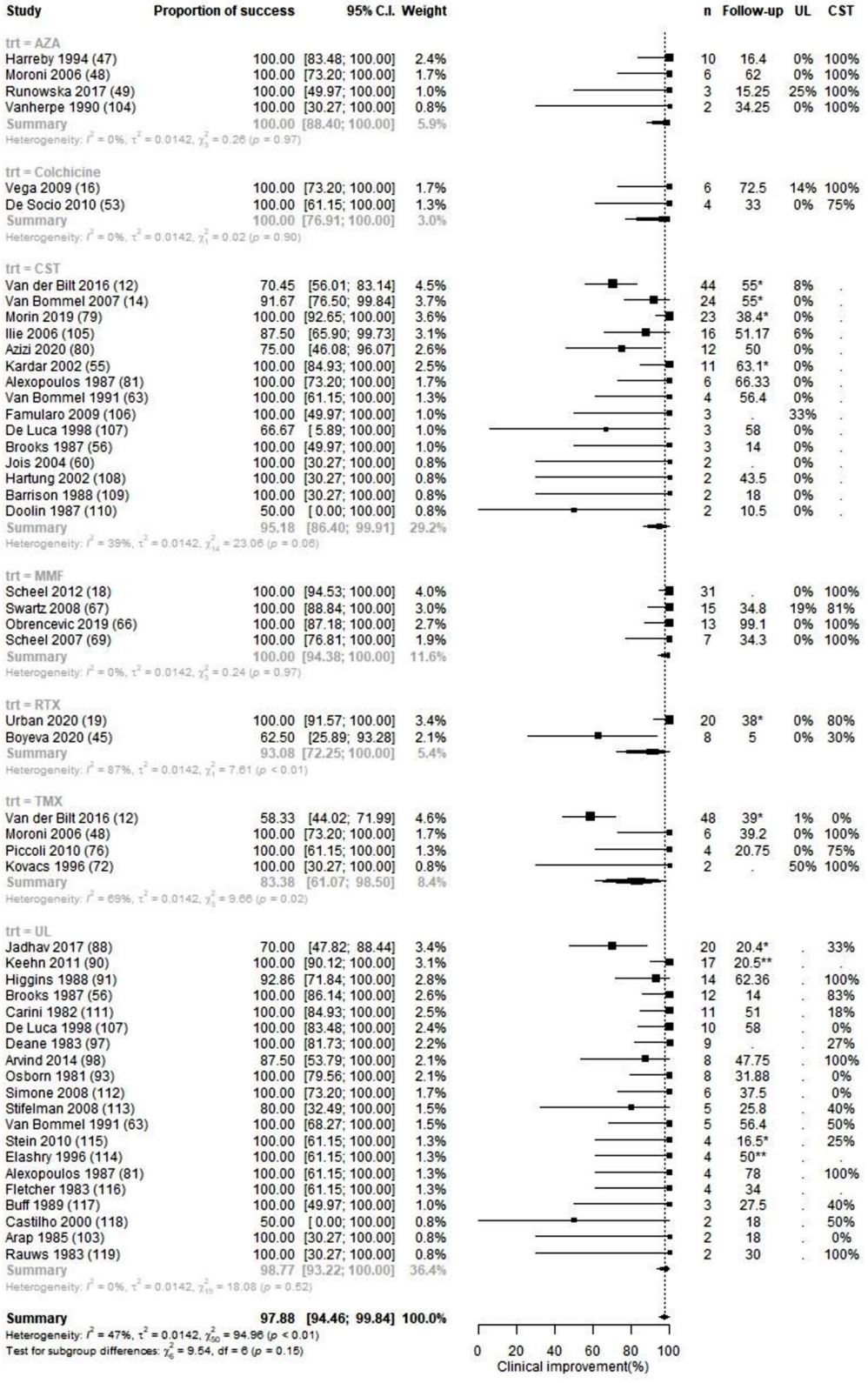

Fig. 6 Forest plot for the outcome "clinical improvement". *Follow-up months as a median; **Follow-up months includes follow-up period from secondary retroperitoneal fibrosis patients (Keehn et al: 85% of patients were idiopathic; Elashry et al: Outcome and baseline characteristics are separately reported for idiopathic retroperitoneal fibrosis patients); *Trt* treatment, *n* patient number, *AZA* Azathioprine, *CST* Corticosteroids, *MMF* Mycophenolate Mofetil, *RTX* Rituximab, *TMX* Tamoxifen, *UL* Ureterolysis

Table 2 Corticosteroid dose and tapering scheme

Study	n	Drug	Dose (per day)	Tapering scheme (per day)
Van der Bilt 2016 [12]	50	PDN or PDNolon	60 mg*	60 mg for median duration of 14 months, detailed tapering scheme not described
Labidi 2015 [78]	30	CST	0.98 mg/kgBW**	At 52.3 months follow-up mean dose 9.5 mg, detailed tapering scheme not described
Brandt 2015 [74]	46	PDNolon	1 mg/kgBW (one alternate days)	1 mg/kgBW/2d for 10 weeks 40 mg for two weeks 20 mg for two weeks 10 mg for two weeks 5 mg for one year
Fry 2008 [75]	24	PDNolon	30 mg**	Reduced during 1–2 months to 10 mg, then gradual reduction to 5 mg (for 2–3 years)
Van Bommel 2007 [14]	24	PDN	60 mg	60 mg for six weeks reduction within 2–3 months to 10 mg 10 mg for one year
Morin 2019 [79]	23	PDN	1 mg/kgBW	1 mg/kgBW for 4 weeks Tapered by 10 mg every 4 weeks until 20 mg Tapered by 5 mg every 4 weeks until 10 mg Tapered by 1 mg every 4 week until 7 mg 7 mg for 12–36 months
Vaglio 2011 [54]	18	PDN	1 mg/kgBW	1 mg/kgBW for one month (max 80 mg) 0.5 mg/kgBW for one month 0.25 mg/kgBW for two months 0.2 mg/kgBW for one month 0.15 mg/kgBW for one month 7.5 mg/d for one month 5 mg/d for half a month 2.5 mg/d for half a month 2.mg/d on alternating days for half a month
Ilie 2006 [105]	16	PDNolon	40 mg	40 mg for mean four weeks (range 1–8 weeks) Reduction 5 mg per week to 1–5 mg
Kardar 2002 [55]	12	PDNolon	60 mg (on alternate days)	60 mg/2d for two months 40 mg for 2 weeks, 20 mg for 2 weeks, 10 mg for 2 weeks, 5 mg maintenance dose (for total two years)
Azizi 2020 [80]	12	CST	0.5–1 mg/kgBW	Tapering scheme and drug duration not mentioned

PDN Prednisone, *PDNolon* Prednisolone, *CST* Corticosteroids, *kgBW* kilogram of bodyweight

*median drug dose

** mean drug dose

regression of fibrosis," the patients treated with tamoxifen relapsed more frequently than the patients treated with prednisone [54]. In some studies, patients relapsed after immunosuppressive treatment discontinuation or after glucocorticoid tapering, suggesting inadequate treatment duration [15, 18, 54, 73].

Ureteric stenting and nephrostomies are sometimes essential in acute treatment and cannot be avoided [15, 55, 66, 74]. However, stents may lead to urinary tract infections which require antibiotic treatment [66].

Whether additional drug therapy is needed after ureterolysis is controversial. However, in the multi-institutional study by Duchene et al. in 2007, no difference was seen between patients with additional drug therapy and those without [122].

There are several limitations for this systematic review. Most of the studies included are small retrospective case series so there may be a recall bias. Furthermore, some patients had already undergone different treatments without success before being referred to the study centre so the study populations between the different studies vary in number with regard to newly diagnosed and refractory patients.

Another potential bias exists due to the challenging nosology. IRF overlaps with inflammatory abdominal aortic aneurysms and perianeurysmal fibrosis, which were not included in this analysis as most patients with aneurysms are treated surgically [123]. Furthermore, some patients with IRF fulfil criteria for IgG4-RD [5]. Specific IgG4-related IRF studies were excluded from the analysis in the end, as knowing which of the older studies

included IgG4-related IRF patients is impossible, as this disease was only defined in 2003 [124].

In addition, the treatment approaches differed between studies. The treatments varied in drug doses and duration, as well as in different interventions in the surgical procedures. Many studies combined various treatment approaches: immunosuppressants with corticosteroids, ureterolysis with medical treatment, and stents with medical treatments. In those cases, it is neither possible to distinguish which treatment led to the achieved outcome nor which treatment resulted in the complications. In addition, the expertise of the operating surgeon and the volume load of a centre influences the outcome of the surgical procedure.

In the subgroup analysis some subgroups were heterogeneous, whereas others were almost completely homogenous. Many studies documented effectiveness of the treatment in 100% of the patients for the outcomes considered. These extreme values might be due to an outcome reporting bias, as positive results might be reported more frequently. Concerning the outcome "freedom from ureteric stent" it is not clear if in all patients the freedom from ureteric stent was attempted so the results for this outcome vary largely. The follow-up period as well as the diagnosis of relapse and regression of fibrosis also varied.

Large prospective, randomized controlled trials are needed, especially for glucocorticoid-sparing drugs with fewer side effects. However, this might be difficult given the rarity of the disease [3]. Breems, Haye and Van der Meulen (2000) calculated that for a sufficiently powered study, 40–50 study centres are needed so a multi-centric trial would be essential [82]. Currently, several studies are registered as clinical trials and are in the recruiting process. These studies evaluate tocilizumab, sirolimus, cyclophosphamide, and methotrexate and compare these drugs to glucocorticoids [125–128]. The Peking Union Medical College Hospital Beijing has also developed a national registry for IRF [129]. The results of these studies and registries are eagerly awaited.

Conclusion

In conclusion, further studies are needed to prove the superiority of one treatment. As there is currently no clear evidence for any drug being more effective than others in treating IRF, the medication most suitable for the patient should be chosen according to comorbidities and possible side effects.

Abbreviations

IRF	Idiopathic retroperitoneal fibrosis
IgG4-RD	Immunoglobulin-G4 related disease
CT	Computed tomography
MRI	Magnet resonance imaging
FDG-PET	18F-Fluorodeoxyglucose positron emission tomography
DJ Stent	Double pigtail stent
PCN	Percutaneous nephrostomy
PROSPERO	Prospective Register of Systematic Reviews
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
MeSH	Medical Subject Headings
QUIPS	Quality in Prognostic Studies
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
REML	Restricted maximum likelihood

Supplementary Information

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Supplementary Material 1: Search strategy

Supplementary Material 2: R Code

Supplementary Material 3: Table 1–3 Reasons for exclusion of articles

Supplementary Material 4: Table 4 Study characteristics

Supplementary Material 5: Table 5 Improvement in renal function

Supplementary Material 6: Table 6–14 Adverse drug reactions

Supplementary Material 7: Figs. 1–18 Forest plot of proportions, Baujat plots

Supplementary Material 8: Figs. 19–26 Publication bias

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AS: literature search, data extraction, statistical analysis, writing. BM: literature search, data extraction, conceptualization, supervision, editing. The authors read and approved the final manuscript.

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