Original Article

The effectiveness of infliximab for Kawasaki disease in children: systematic review and meta-analysis

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Background: Kawasaki disease (KD) is a self-limited illness that results in coronary artery aneurysms (CAAs) and threatens children's health and lives. The therapeutic effects of single intravenous immunoglobulin gamma (IVIG) *vs.* infliximab (IFX) (with or without IVIG) in young children with KD remain unclear. Thus, we made a meta-analysis and systematic review, including all of the studies which have evaluated the effectiveness and safety of IFX and IVIG KD patients.

Methods: The databases of the Cochrane Library, PubMed and Embase websites were searched for articles appearing from inception until December 31, 2020. Clinical studies that compared IFX either as initial therapy plus IVIG or rescue therapy after IVIG (IFX group) failure compared with IVIG treatment alone (IVIG group) in treating KD patients were included.

Results: The meta-analysis included nine studies characterizing 712 patients. The treatment response was significantly higher in the adjunctive IFX therapy group than in the IVIG therapy group [odds ratio (OR) 2.64; 95% CI: 1.52–4.59; P=0.0005]. Subgroup analysis, the effect of IFX therapy on treatment response is more effectiveness in the group of the high-risk KD patients than IVIG therapy (OR 6.07; 95% CI: 2.30–16.04; P=0.0003; random-effects model). Further analysis showed no difference in the improvement of CAAs in short-term follow-up between the two groups. However, adding IFX either as initial therapy or as additional therapy all showed an advantageous effect regarding the ΔZ score of the left anterior descending (LAD) (MD =0.29; 95% CI: 0.27–0.31; P<0.00001) and right coronary artery (RCA) (MD =0.24; 95% CI: 0.22–0.26; P<0.00001). Further, IFX exhibited significant effect on the treatment response compared with IVIG therapy in the Asian group (OR, 2.84; 95% CI: 1.51–5.36; P=0.001; random-effects model), and the beneficial effects of IFX were given without increasing the risk of AEs.

Conclusions: This meta-analysis emphasizes the importance of IFX on the treatment response in the high-risk KD patients. IFX may play a role in the Asian KD patients and prevention of progressive CAA, and does not increase the risk of AEs in KD patients.

Keywords: Infliximab; Kawasaki disease (KD); children; meta-analysis

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Introduction

Kawasaki disease (KD) is an acute vasculitis mainly presents in children and infants of unknown etiology. It has been increasingly reported worldwide since it was first described in 1967 by Tomisaku Kawasaki in Japan (1). KD is a self-limiting illness that mainly affects the medium-size arteries and results in coronary artery aneurysms (CAAs) in up to 25% of untreated children. It is now the primary reason of children's acquired heart disease, and the patients with CAAs may carry a high risk of coronary artery complications such as coronary artery dilation, coronary artery aneurysms, thrombogenesis, myocardial infarction, and sudden death (2).

The standard therapy for KD patients is intravenous immunoglobulin gamma (IVIG) and aspirin, which reduces the risk of CAAs from 25% to 5% (3). However, studies have shown that 10–38% of the patients fail to react or develop a recrudescent fever. These patients are characterized as IVIG resistant, are at high risk of developing CAAs, and require additional therapy to interrupt the inflammatory reaction (4). We postulate that KD patients may benefit from more intensive initial therapy (5).

Infliximab (IFX) is a novel chimeric monoclonal antibody that produces anti-inflammatory effects through specific blocking of tumor necrosis factor-alpha (TNF-α), the first anti-TNF-α monoclonal antibody treatment validated for pediatric patients. It is safe and well-tolerated and has been used to treat other disease such as spondylitis, rheumatoid arthritis, and Crohn's disease (6). The application of IFX in KD was first reported by Burns *et al.* (7), and since then, research has demonstrated that IFX plays an active role in KD as remedial therapy or initial intensive therapy (8). A prior study by Tremoulet *et al.* (9) showed the use of IFX plus IVIG as initial therapy in KD patients decreased fever duration, inflammation markers, and the Z score of the left anterior descending (LAD) coronary artery. Yamaji *et al.* (10) reported that TNF-α blockers including IFX and etanercept in 5 RCTs that compared TNF-α blockers to placebo or other drugs in children with KD. However, RCT studies are rigorously designed, whether such results are appropriate for other clinical conditions remains unclear. The present study aims to evaluate the effectiveness of IFX either as initial or additional therapy in all studies not only RCTs, but also observational studies and case-control studies in the KD patients.

The study protocol was registered on the PROSPERO database (ID 143267). This meta-analysis was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (11) (available at http://dx.doi.org/10.21037/tp-20-482).

Methods

Study selection criteria

Prospective cohort designs, retrospective observational studies and case-control studies that in comparison IFX (either as initial or rescue therapy) with IVIG treatment for KD were included. Studies were considered to be eligible for inclusion when meeting the following criteria: (I) the included patients were children under the age of 18 years diagnosed with KD (12); (II) the intervention of the IFX group referred to using adjunctive IFX either as initial or additional therapy; (III) a comparison was made between the IFX group and the IVIG group; (IV) the outcome evaluation included the treatment response of IFX, the effectiveness of IFX either as initial and additional therapy, the incidence rate of CAA, hospital stay, and AEs after treatment.

Literature search strategy and data extraction

The PubMed, Medline, Embase, Web of Science, and Cochrane library electronic databases inclusive until December 31, 2020 were searched and the words and MESH terms "Kawasaki disease" OR "Kawasaki syndrome" OR "Mucocutaneous Lymph Node Syndrome,", "TNF-α" OR "Tumor Necrosis Factor-alpha" and "Infliximab" in different forms. A manual and electronic search of references from eligible and relevant studies was performed to find additional trials, and only articles written in the English language were considered eligible (Table S1). The titles and abstracts for the articles identified were assessed by two authors (XL and DL) to determine whether they met the inclusion criteria. Reviews, comments or editorials, conference abstracts, case reports, letters, reviews and meta-analyses were rejected from the analysis. Seventeen articles were reassessed by reviewing the full text, and only studies (with or without randomization) comparing outcomes between two groups (an IFX group and IVIG group) were eligible in the final result. Two independent observers (XL and DL) extracted information from each study, and two other authors (WD and YZ) reviewed the data extraction for completeness and accuracy.

Data collection process

We based the Cochrane recommendation review (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://handbook.cochrane.org/) and evaluated study quality according to study objectives, study design, study performance, outcome evaluation and effectiveness. Study characteristics (study purpose, study design, inclusion, and exclusion criteria); patient characteristics (race, age, sex and severity of disease); interventions (therapeutic method, doses, and treatment duration); and outcomes (incidence of CAA, treatment response, impact, and adverse events) were extracted by two reviewers (XL and DL) from eligible studies. Data was then cross-checked using RevMan Version 5.4 (The Nordic Cochrane Centre Collaboration, Copenhagen, Denmark). The article selection, data abstraction, computation, calculation, evaluation, and synthesis processes were reviewed by two authors (XL and DL), and the other two authors (WD and YZ) resolved disagreements through a joint examination of the articles and discussion until reach a consensus.

Case definition

This meta-analysis investigated randomized controlled trials (RCTs) and non-RCTs comparing IFX and IVIG therapies for KD children. Treatment response refers to the percentage of patients whose fever subsided within 48h with IFX or IVIG therapy with the total patients in each group. Treatment resistance was defined as persistent or recrudescent fever (axillary temperature >37.5 ℃) at 48-hour after the completion of IFX or IVIG infusion, regardless of initial treatment or rescue treatment.

The CAA of KD was defined by the Z score system of the 2017 AHA scientific statement (2) as follows: (I) no involvement: <2; (II) dilation: 2 to <2.5; or if initially <2, a decrease in Z score during follow-up ≥1; (III) small aneurysm: ≥2.5 to <5; (IV) medium aneurysm: ≥5 to <10, or absolute dimension <8 mm; (V) large or giant aneurysm: ≥10, or absolute dimension ≥8 mm. The ΔZ score of the left anterior descending artery (LAD) and right coronary artery (RCA) was the difference between the primary Z score and the follow-up Z score.

Risk of bias

According to the GRADE Working Group, the risk of bias of eligible studies was assessed to assess the risk of bias in studies (13,14). Seven criteria were used to assess the studies' limitation: (I) random sequence generation (selection bias), (II) allocation concealment (selection bias), (III) blinding of participants and personnel (performance bias), (IV) blinding of outcome assessment (detection bias), (V) incomplete outcome data (attrition bias), (VI) selective reporting (reporting bias), (VII) other bias. For each criterion, the risk of bias was categorized as low, unclear, or high, and confidence in the estimates for each outcome in studies was assessed using the GRADE method. Publication bias was assessed by the visual inspection of the funnel plots, and confidence in the estimates was based on three levels; high, moderate, and low.

Statistical analysis

The odds ratios (ORs) were used to estimate the effect and 95% CIs for dichotomous outcomes and mean difference for continuous outcomes. The random-effects model was used to evaluate the effect of our meta-analysis on the intrinsic differences of study design. Heterogeneity among studies was calculated by Q test and estimated by the I^2 statistic (15) and interpreted using the Cochrane Collaboration thresholds. Sensitivity analysis was made to test the stability of the overall results through eliminating individual studies in the presence of significant heterogeneity. Continuous outcome measurements were reported as median and range, and the mean and standard variance was estimated using a simulation formula reported by Hozo *et al.* (16). Statistical analyses were performed with RevMan, all P values were 2-tailed, and the statistical significance was 0.05.

Results

In our study, a total of 440 relevant articles were searched through the preliminary search. With the further assessment of the remaining 18 relevant studies (Table S2), eight noncomparative studies were excluded, and nine full-text studies were enrolled in the meta-analysis resulting in 712 children who met the study criteria and were included in this meta-analysis (7-9,17-22). The PRISMA study selection flow diagram is illustrated in (*Figure 1*). A total of nine randomized and nonrandomized studies were included in the risk of bias assessment, and data were extracted according to each domain (*Figure 2*). Their relevant ethics committees approved the included studies. Methodological quality assessment of included studies is showed in the Table S3.

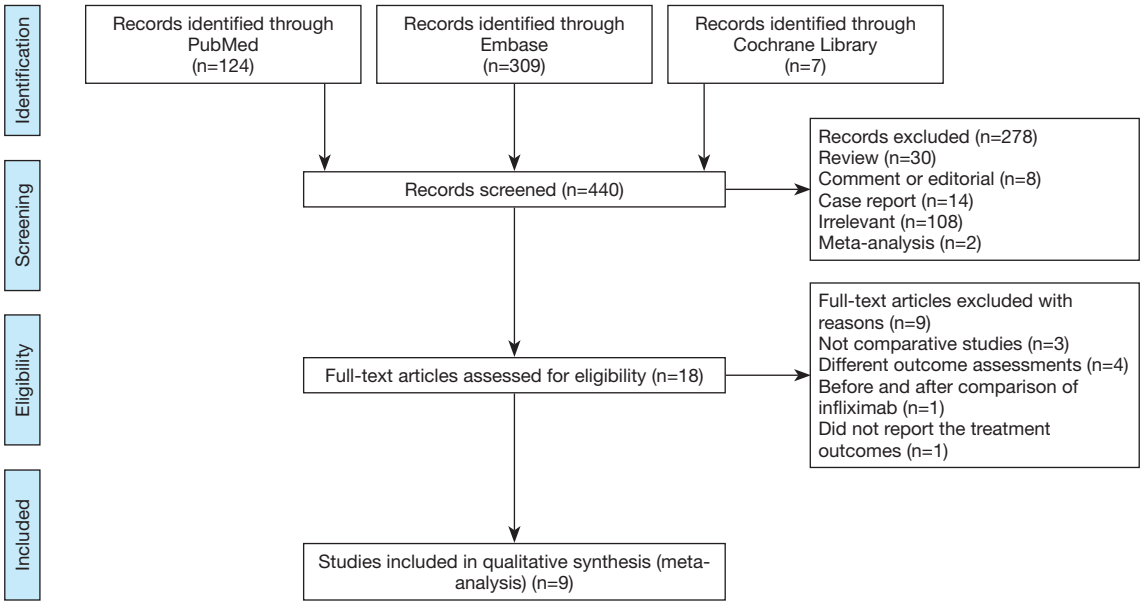

Figure 1 Study selection flow diagram.

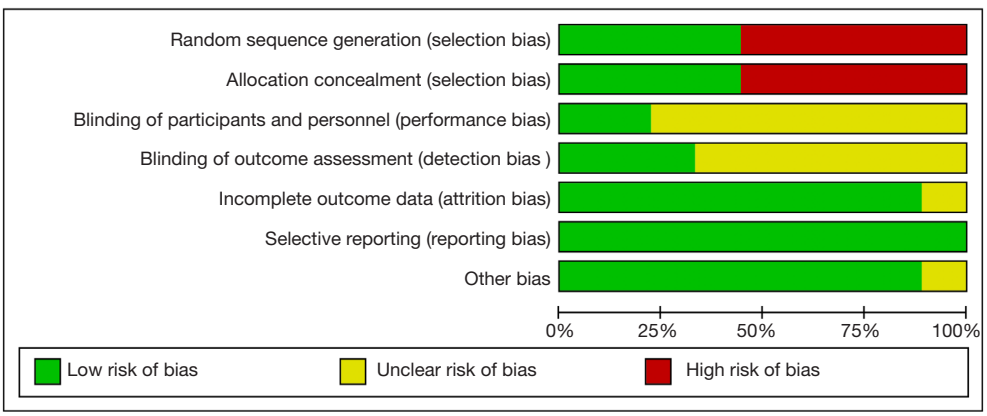

Figure 2 Risk-of-bias graph: authors' judgement of each risk-of-bias item showed as percentages of all studies.

Study characteristics

The clinical profiles and baseline characteristics of the nine studies are presented in *Table 1*. The studies were published in English until December 31, 2020 and included four RCTs (7,9,17,22) and five non-RCT (8,18-21) trials. This study involved 712 cases in total (305 in the IFX group and 407 in the IVIG group). The type of studies, the sample size, sex, mean age, the severity of illness, and hospital stay, are also summarized in *Table 1*. The doses of IFX and IVIG, CAA incidence, and the AEs are detailed in *Table 2*.

Principal outcome: the overall effectiveness of IFX therapy in all studies on treatment response

Studies included in the meta-analysis for the overall effectiveness (IFX either as initial or additional therapy) on KD patients' treatment response are shown in *Figure 3*. We found that the IFX group had a higher treatment response rate (OR, 2.64; 95% CI: 1.52–4.59; P=0.0005; random-effects model) compared with the IVIG group. While there were 256 responders of 305 total patients in the IFX group, and the treatment response rate was 84%, there were 285

Table 1 Baseline characteristics of included studies

Source, year	IFX	Study design	CAA and CAL	Sample size	Female patients (%)	Mean age (months)	Illness severity	Hospital stay (d)
Han *et al.* (17), 2018	Initial treatment	RCT	Included	IFX + IVIG: 77, IVIG: 77	43 (55.8%)	25.2	KD with CAA	Mean (SD): 8.0 (2.0)
Jone *et al.* (18), 2018	Initial treatment	Non-RCT	Included	IFX+IVIG: 35, IVIG: 34	9 (25.7%)	25.2	KD with CAL	Median (range): 3.90 (2.30 to 5.50)
Nagatomo *et al.* (19), 2017	Additional treatment	Non-RCT	Included	IFX: 27, IVIG: 22	4 (11%)	24.0	CAA with IVIG resistance	Median (range): 4 (2 to 11)
Youn *et al.* (20), 2016	Additional treatment	Non-RCT	Included	IFX: 11, IVIG: 32	15 (35%)	3.0-156	Refractory KD	Median (range): 8 (7 to 9)
Tremoulet *et al.* (9), 2014	Initial treatment	RCT	Included	IFX+IVIG: 97, IVIG: 98	37 (38.8%)	33.25	Persistent fever and KD with CAA	Median (range): 3 (4 to 7)
Son *et al.* (21), 2010	Additional treatment	Non-RCT	Included	IFX: 20, IVIG: 86	6 (30%)	23	IVIG resistance	Not reported
Hirono *et al.* (8), 2009	Additional treatment	Non-RCT	Included	IFX: 11, IVIG: 32	6 (45%)	4.0	Refractory KD	Not reported
Burns *et al.* (7), 2008	Additional treatment	RCT	Included	IFX: 12, IVIG: 12	4 (33%)	20	IVIG resistance, KD with CAA	Median (range): 9.5 (7.8 to 10.8)
Mori *et al.* (22), 2017	Initial treatment	RCT	Included	IFX:16, IVIG:15	6 (37.5%)	30	IVIG resistance, KD with CAA	Not reported

IFX, infliximab; IVIG, intravenous immunoglobulin; NR, not reported; RCT, randomized controlled trial.

Table 2 The characteristics of treatment and outcome assessments of included studies

Source, year	Use of Aspirin, mg/kg/d	Use of IFX, mg/kg/d	Use of IVIG, g/kg/d	Criteria of CAA	Incidence of CAA in each group, N (%)	Serious adverse events (SAEs) [MD]
Han *et al.* (17), 2018	80	5	1	Japanese criteria	IFX+IVIG: 77 (3%); IVIG: 77 (4%)	Not reported
Jone *et al.* (18), 2018	80–100	5	2	Z score	IFX+IVIG: 35 (2%); IVIG: 34 (2%)	IFX+IVIG: 35 [1]; IVIG:34 [6]
Nagatomo *et al.* (19), 2017	Not reported	5	1–2	Japanese criteria	IFX+IVIG: 27 (6%); IVIG: 22 (7%)	Not reported
Youn *et al.* (20), 2016	80–100	5	2	Japanese criteria	IFX+IVIG: 11 (1%); IVIG: 32 (4%)	IFX+IVIG: 11 [1]; IVIG:32 [5]
Tremoulet *et al.* (9), 2014	80–100	5	2	American Heart Association case definition (21)	IFX+IVIG: 96 (9%); IVIG: 97 (4%)	IFX+IVIG: 98 [23]; IVIG: 98 [22]
Son *et al.* (21), 2010	80–100	5	2	Z score	IFX+IVIG: 20 (7%); IVIG: 86 (29%)	IFX+IVIG: 20 [0]; IVIG: 86 [2]
Hirono *et al.* (8), 2009	30	5–10	2	Japanese criteria	IFX+IVIG: 11 (4%); IVIG: 32 (10%)	Not reported
Burns *et al.* (7), 2008	80–100	5	2	Z score	IFX+IVIG: 12(2%); IVIG: 12 (2%)	Not reported
Mori *et al.* (22), 2017	Not reported	5	1–2	Z score	IFX+IVIG: 16(1%); IVIG: 15 (3%)	IFX+IVIG: 16 [0]; IVIG: 15 [1]

CAAs, coronary artery abnormalities; IVIG, intravenous immunoglobulin.

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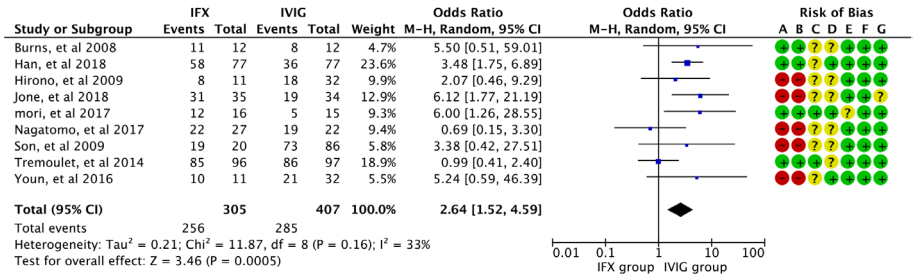

Risk of bias legend
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(G) Other bias

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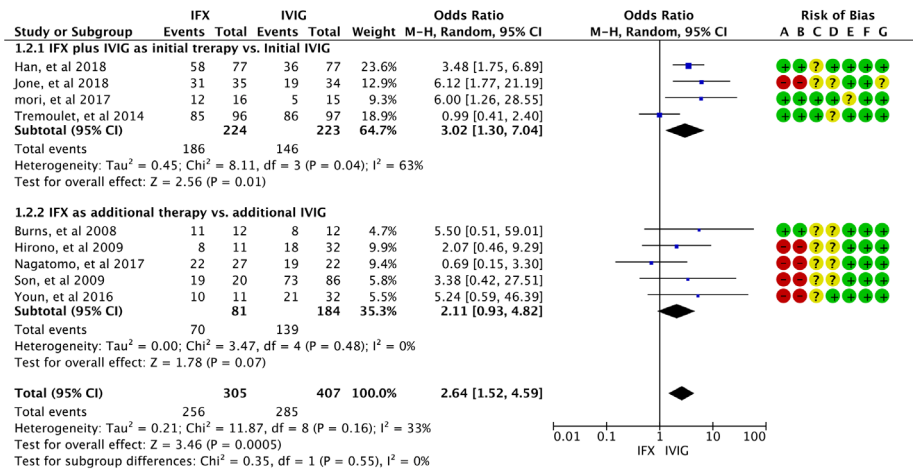

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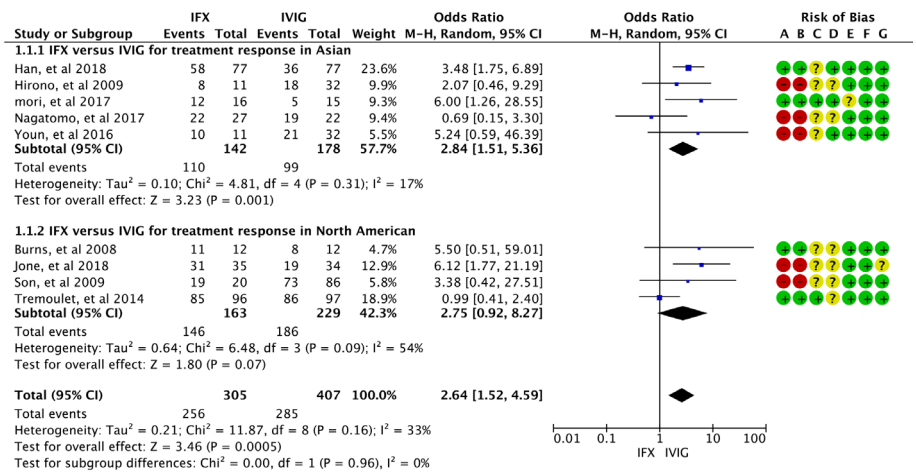

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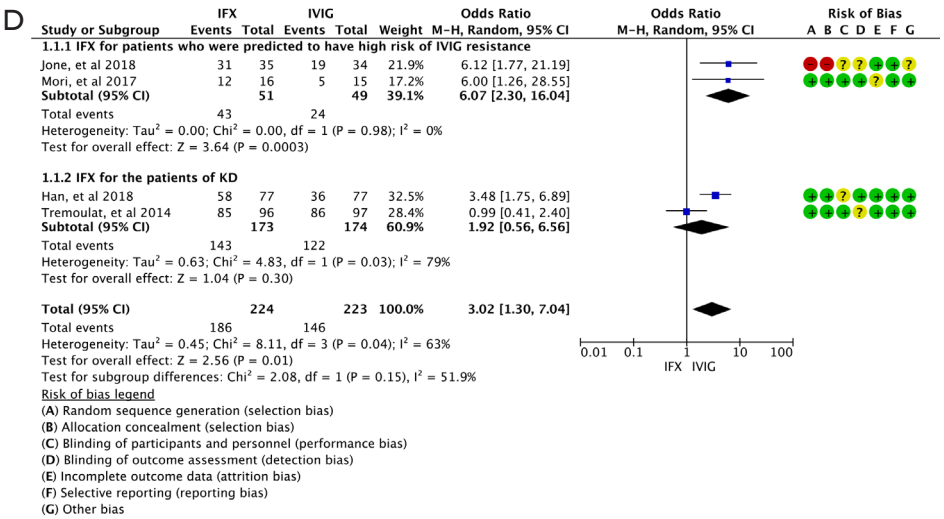


Figure 3 Meta-analysis for the treatment response of KD between the IFX Group and the IVIG Group. (A) The overall effectiveness of IFX therapy in all studies on treatment response. (B) Subgroup 1 shows IFX plus IVIG as initial therapy *vs.* initial IVIG and subgroup 2 shows IFX as additional therapy after the failure of IVIG treatment *vs.* additional IVIG. (C) the effectiveness of IFX versus IVIG therapy on treatment response in Asian and North American group; (D) the effectiveness of IFX as initial therapy on treatment response in different risk stratification KD patients.

responders of 407 total patients in the IVIG group, and the treatment response rate was 70%. There was modest heterogeneity in the included studies (Chi^2 =11.87; df =8; P=0.16; I^2=33%) (*Figure 3*) and funnel plots in the meta-analyses appeared to be nearly symmetrical.

Subgroup analysis: based on the timing of using IFX (subgroup 1 shows IFX plus IVIG as initial therapy *vs.* initial IVIG and subgroup 2 shows IFX as additional therapy after the failure of IVIG treatment *vs.* additional IVIG)

The effect of IFX either as initial or additional therapy is shown in *Figure 3A*,*B*. Subset meta-analysis of using IFX plus IVIG as an initial therapy exhibited a significant effect on the treatment response compared with IVIG therapy alone (OR, 3.02; 95% CI: 1.30–7.04; P=0.01; random-effects model). However, there was medium heterogeneity (we ran a heterogeneity analysis in the supplement) in this subgroup's meta-analysis (Chi^2=8.11; df =3; I^2=63%) (*Figure 3A*). We also make a subgroup meta-analysis of using IFX for treatment response after remove the study of Tremoulet *et al.* and we described in the supplementary (Appendix 1, Figure S1). Subgroup analysis for studies using IFX as an adjuvant therapy after failure of IVIG treatment approached clinical significance compared with additional IVIG therapy (OR, 2.11; 95% CI: 0.93–4.82; P=0.07; random-effects model), and there was no heterogeneity in the subset analysis (Chi^2=3.47; df =4; I^2=0%) (*Figure 3B*).

Subgroup analysis: based on races of using IFX on treatment response (subgroup 1 shows IFX *vs.* IVIG in the Asian group and subgroup 2 shows IFX *vs.* IVIG in the North American group)

The effect of IFX either as initial or rescue therapy on the treatment response for KD patients in Asian and North American population is different as shown in *Figure 3C*. Subset meta-analysis for using IFX either as an initial or rescue therapy strategy exhibited a significant effect on the treatment response compared with IVIG therapy alone in the Asian group (OR, 2.84; 95% CI: 1.51–5.36; P=0.001; random-effects model) and there was modest heterogeneity in this subgroup meta-analysis (Chi^2=4.81; df =4; I^2=17%) (*Figure 3C*). Subgroup analysis for using IFX in the North American population nearly reached a significant level compared with IVIG therapy on the treatment response (OR, 2.75; 95% CI: 0.92–8.27; P=0.07; random-effects model), and there was medium heterogeneity in the subset analysis (Chi^2=6.48; df =3; I^2=54%) (*Figure 3C*).

Subgroup analysis: based on different KD patients of using IFX on the treatment response (subgroup 1 IFX for KD patients who were predicted high-risk of IVIG resistant and subgroup 2 IFX for the normal KD patients)

From the subgroup analysis of the effect of IFX on the treatment response in the two groups of primary therapy, IFX therapy was more effectiveness in the group of the high-risk KD patients than IVIG therapy alone (OR, 6.07; 95% CI: 2.30–16.04; P=0.0003; random-effects model), and there was no heterogeneity in this subgroup meta-analysis (Chi^2=0.00; df =1; I^2=0%) (*Figure 3D*). However, IFX showed little advantage in treatment response in the group of normal KD patients compared with IVIG (OR, 3.02; 95% CI: 1.30–7.04; P=0.3; random-effects model), and there was medium heterogeneity in the subset analysis (Chi^2=4.83; df =1; I^2=79%) (*Figure 3D*).

Secondary outcome

The meta-analysis of KD patients with CAA of KD showed no difference between the IFX group and IVIG group (OR, 1.01; 95% CI: 0.61–1.66; P=0.97; random-effects model) (*Figure 4A*). We have assessed the effect of IFX on KD patients with CAA in rescue therapy and found that it had little significance in rescue therapy compared with IVIG therapy (OR, 0.92; 95% CI: 0.49–1.74; P=0.97; random-effects model), and there was no heterogeneity in included studies (Chi^2=4.10; df =8; I^2=0%) (*Figure 4B*). We also undertook a meta-analysis for the change of Z score (ΔZ) of the LAD and RCA between IFX and IVIG groups. Pooled analysis showed that adding IFX to standard therapy could increase the decrease rate of the Z score for KD patients. The ΔZ score of the LAD was {mean [SD], 1.15 [2] in the IFX group *vs.* 0.47 [1.235] in the IVIG group; mean difference, 0.29; 95% CI: 0.27–0.31; P<0.00001, random-effects model} (*Figure 4C*) and the RCA {mean [SD], 0.72 [1.35] in the IFX group *vs.* 0.39 [1.16] in the IVIG group; mean difference, 0.24; 95% CI: 0.22–0.26; P<0.00001, random-effects model} (*Figure 4D*) was obviously decreased with IFX either as initial therapy or as additional therapy compared with the IVIG alone. There was no heterogeneity in the analysis of ΔZ score (LAD) (Chi^2=0.75; df =2; I^2=0%) and in the analysis of ΔZ score (RCA) (Chi^2=0.08; df =2; I^2=0%).

Subgroup analysis: based on race of using IFX on CAA (subgroup 1 shows IFX *vs.* IVIG in the Asian group and subgroup 2 shows IFX *vs.* IVIG in the North American group)

We also studied the effect of IFX therapy on CAA for KD patients of different races and found that IFX therapy had no clinical significance in either Asian (OR, 0.72; 95% CI: 0.35–1.49; P=0.38; random-effects model) or North American races (OR, 1.36; 95% CI: 0.68–2.72; P=0.38; random-effects model) compared with IVIG therapy, and there was no heterogeneity in the analysis of the Asian group (Chi^2=1.31; df =4; I^2=0%) and North American group (Chi^2=1.25; df =3; I^2=0%) (*Figure 4E*).

Tertiary outcome (meta-analysis for AEs)

We assessed the AEs in both groups by evaluating clinical manifestations and laboratory testing. Meta-analysis for the rate of AEs showed there was no obvious difference between the two groups (15.6% in the IFX group *vs.* 14.3% in the IVIG group; OR, 0.87; 95% CI: 0.49–1.55; P=0.64, random-effects model) (*Figure 5*) and there was no heterogeneity in the analysis (Chi^2=3.99; df =4; I^2=0%). Based on study records, almost all of the AEs were transient and easily recoverable, and no deaths were reported. We also make meta-analysis to evaluate the hospital stays, but because of the different medical system and cost of different country, we analyzed this indicator in the supplement (Appendix 1, Figure S2).

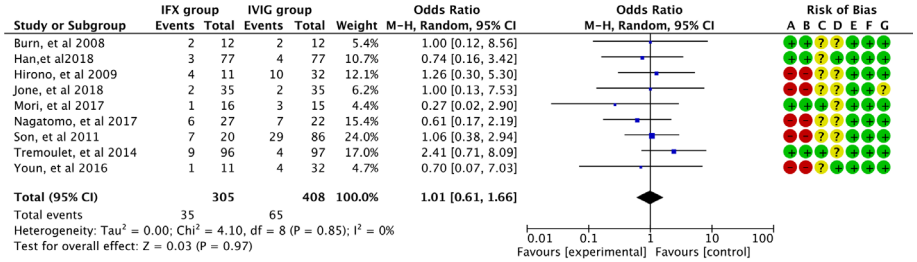
Sensitivity analysis and publication bias

The overall results were not changed after each study was omitted, which confirmed our meta-analysis results (*Figure 3*). Moreover, we calculated the pooled proportion of studies with moderate-poor quality, and the results were not substantially different. Publication bias was assessed for the outcomes by visual inspection of the funnel plots and no obvious publication bias was detected among the publications that reported IFX effectiveness for KD patients (*Figure 6*).

Discussion

This meta-regression demonstrated that adding IFX

A



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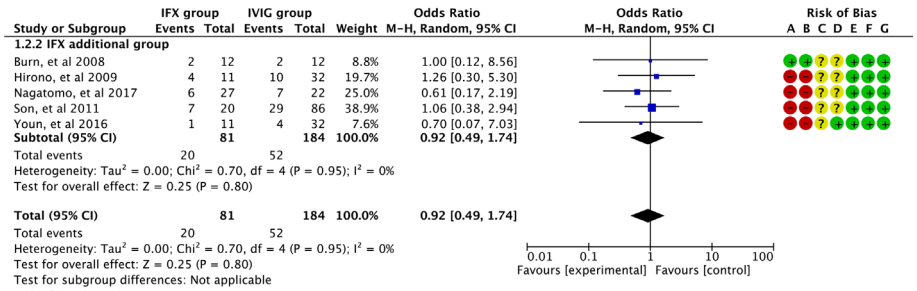

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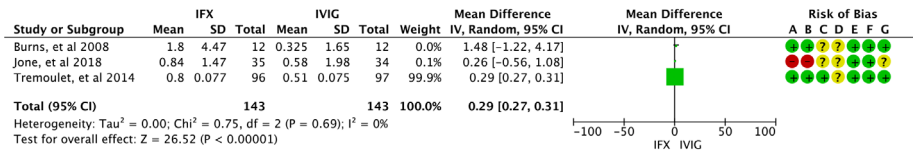

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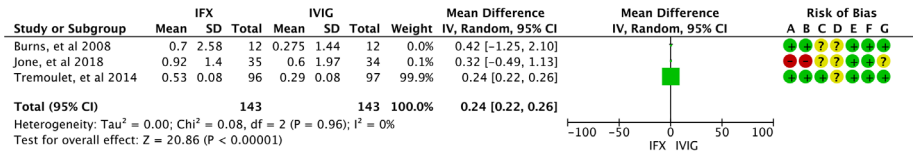
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

D



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

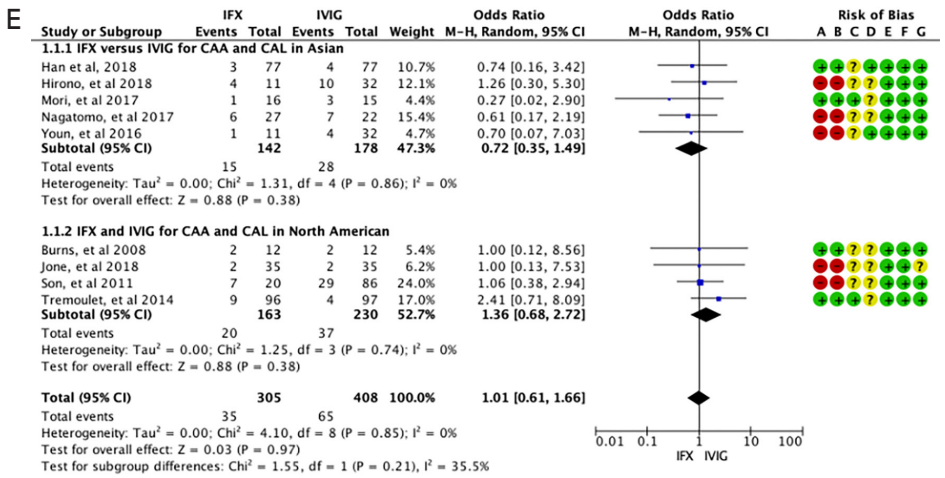


Figure 4 Meta-analysis for the CAA of KD between the IFX Group and the IVIG Group. (A) Meta-analysis for incidence of CAA between the IFX Group and the IVIG group; (B) IFX as rescue therapy versus additional IVIG; (C) meta-analysis for ΔZ score (LAD) between the IFX group and the IVIG group; (D) meta-analysis for ΔZ score (RCA) between the IFX group and the IVIG group; (E) the effectiveness of IFX versus IVIG therapy on CAA in Asian and North American group.

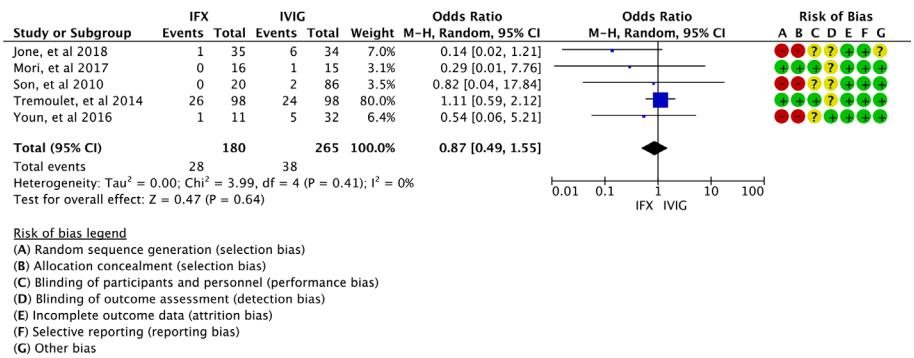


Figure 5 Meta-analysis of AEs.

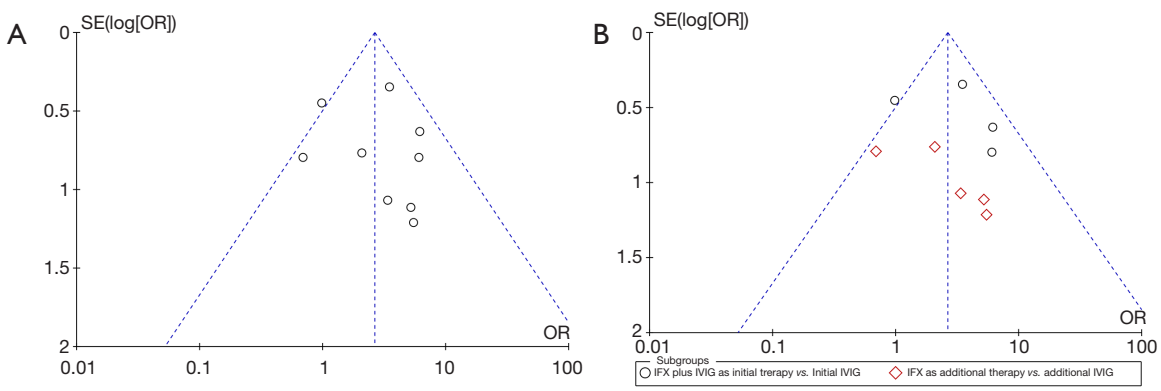


Figure 6 Funnel plots for risk of bias of included studies.

to traditional IVIG therapy is associated with a higher treatment response for KD patients than the standard treatment. The subgroup showed that KD patients benefit the most from initial IFX with IVIG therapy compared to IVIG alone therapy according to the treatment response. Moreover, the IFX rescue therapy may affect the prevention progressive dilatation of LAD and RCA compared with the IVIG alone. What is more, our analysis showed that the treatment of IFX was more beneficial for the Asian KD patients on treatment response than the North American patients.

Subgroup analysis based on different KD patients showed that IFX as initial therapy was more effectiveness in the group of the high-risk KD patients. However, it is a problem to stratify patients with risk. So far, there are at least 4 different scoring systems, such as Kobayashi score, Egami score, Sano score and Formosa score, for the risk stratification of IVIG resistance have been developed (23-26). These models played useful predictive ability in the early identification of high-risk IVIG resistance patients before the start of treatment.

What is more, the third outcome exhibited that the favorable effects of IFX did not have an increased risk of AEs. This study highlights the importance of IFX on treatment response of KD patients. KD patients benefit greatly from an instant and effective adjunctive IFX therapy.

At present, the dominant view is that the occurrence of KD may be related to external infection and internal immune dysfunction. Therefore, modulating immune function and reducing inflammation damage is important in its treatment. TNF-α levels are markedly elevated in the acute phase of KD, and children with CAAs have a higher level of TNF-α. Increased levels of TNF-α can lead to the aggregation and infiltration of monocytes and neutrophils and induce vascular and coronary artery lesions (27). Theoretically, reducing the level of TNF-α or blocking the binding of TNF-α to its receptor can relieve inflammatory reactions.

The present meta-analysis confirmed the significant role of IFX in KD. Han *et al.* (17) investigated the treatment effectiveness of traditional IVIG *vs.* combination therapy of IVIG and IFX during the therapeutic process. They found that body temperature, CRP, WBC, and TNF-α in combined therapy patients all showed an earlier and more obvious reduction than those in the IVIG group and that IFX markedly reduced the incidence of CAA in KD patients compared to traditional IVIG treatment. Furthermore, Jone *et al.* (18) suggested that IVIG plus IFX as primary therapy for KD patients with CAA reduced the need of extra second-line treatment, thus decreasing the number of IVIG-resistant patients. Nagatomo *et al.* (19), showed that the 2-, 4- and 6-year cumulative persistence rate of CAA was 24%, 24% and 24% in IFX-group, whereas 67%, 52%, and 33% in a non-IFX group, respectively. Therefore, IFX treatment in the long-term follow-up of CAA remains a controversial issue, and more studies and trials are needed to test the importance of IFX on CAA for KD patients.

This study has several significant aspects. First, this study included a list of nine clinical studies characterizing 712 cases, making it the most comprehensive IFX treatment analysis in patients with KD. Second, we found that adding IFX therapy to the conditional therapy was associated with improving the treatment response, prevention of progressive CAA, and without increase of the AEs, which may help reduce the suffering and costs of patients and their families. Furthermore, our subgroup analysis found that IFX exerts a beneficial effect when used as initial treatment to high-risk patients.

Limitations

There are limitations in the present study. The current evidence of IFX is mainly based on short-term observations, and the long-term studies investigating the safety and efficacy of IFX in patients with CAAs are of great significance and required. Therefore, more studies with long-term follow-up are needed to provide data on the efficacy and safety of IFX. Second, some of the studies also used other drugs such as prednisolone, cyclosporine, and plasmapheresis, there are 9 studies in this paper, of which 5 studies included not only IFX and IVIG, but also prednisolone, cyclosporine, and plasmapheresis. These drugs were used for the IVIG-resistance after IFX or IVIG treatment, and these drugs considered as confounding factors of analysis the efficacy of IFX, which is effective for the IVIG-resistance KD patients, might influence the results.

Conclusions

In summary, this systematic review and meta-analysis highlight the importance of IFX for KD patients. KD patients benefit greatly from an instant and potent additional IFX therapy to improve the treatment response and prevent coronary artery progressive abnormity.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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