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Assessing the efficacy of infliximab in promoting vascular and mucosal healing in immunoglobulin-resistant kawasaki disease: a meta-analysis

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Abstract

This meta-analysis investigates the efficacy of infliximab in reducing vascular damage, suppressing inflammation, and promoting mucosal healing in patients with immunoglobulin-resistant Kawasaki Disease (KD). A systematic literature search was conducted in line with PRISMA guidelines across databases (e.g., PubMed, Google Scholar) for studies published between, 2003–2023. While high-dose intravenous immunoglobulin remains the standard treatment for KD, a subset of patients exhibit resistance, necessitating alternative therapeutic strategies. Infliximab, a monoclonal antibody that targets tumor necrosis factor-alpha, presents a promising option for these challenging cases. By modulating the immune response and suppressing inflammation, Infliximab has the potential to alleviate vascular damage and enhance mucosal healing in patients unresponsive to conventional treatments. This study specifically focuses on the impact of Infliximab on healing of vascular damage, as indicated by clinical remission, mucosal healing, and changes in absolute neutrophil counts—a key marker of inflammation. Employing a proportional meta-analysis via the 'metafor' function in R, we analyzed data from 857 patients, including 403 events related to mucosal and vascular healing outcomes. Our findings reveal a significant improvement in these healing processes among KD patients treated with Infliximab (Proportion: 0.45, 95% CI: [0.42; 0.48], $I^2 = 87\%$, $p < 0.01$), accompanied by a notable reduction in inflammation as evidenced by decreased absolute neutrophil counts (mean difference: 7.67). These results underscore the potential of Infliximab and similar biologic therapies to effectively address the unmet needs of patients with immunoglobulin-resistant KD, offering a viable pathway to mitigate inflammation and enhance mucosal and vascular healing outcomes.

Keywords Absolute neutrophil count, Inflammation, Infliximab, Kawasaki Disease

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Introduction

Kawasaki Disease (KD), also known as Kawasaki syndrome remains a formidable challenge in pediatric medicine, characterized by systemic vasculitis predominantly affecting coronary arteries [1]. KD is an acute febrile illness that primarily affects children younger than 5 years of age [2]. Boys are more likely than girls to develop Kawasaki disease, and Japanese or Korean children are at higher risk [3]. First described by Dr. Tomisaku Kawasaki in 1967, the disease is characterized by inflammation of the blood vessels (vasculitis) throughout the body, with a predilection for the coronary arteries that supply blood to the heart [4].

In terms of statistics, in the continental United States, population-based and hospitalization studies estimate an incidence of KD ranging from about 9 to 20 per 100,000 children under 5 years of age [5]. In the year 2016, approximately 5440 hospitalizations with KD were reported among children under 18 years of age in the US; 3935 of these children were under 5 years of age, for a hospitalization rate of 19.8 per 100,000 children in that age group [6, 7].

The exact cause of KD remains unknown, although it is believed to involve a combination of genetic, environmental, and immunologic factors [7]. The condition often begins with a high and persistent fever that lasts for at least five days, accompanied by other characteristic symptoms such as redness and swelling of the hands and feet, swollen lymph nodes, and inflammation of the mucous membranes in the mouth, throat, and nose [8, 9].

The standard treatment for KD involves the administration of high-dose intravenous immunoglobulin (IVIG), which is a concentrated preparation of antibodies that can modulate the immune response [8]. This treatment aims to reduce inflammation and prevent coronary artery complications [10]. However, a subset of patients does not respond adequately to IVIG and is considered immunoglobulin-resistant [11].

The exploration of alternative therapeutic approaches, such as the use of biologics like Infliximab, has become an area of interest in managing immunoglobulin-resistant cases of KD [10]. These biologic agents target specific molecules involved in the inflammatory process, offering a potential avenue for modulating the immune response and mitigating the severity of the disease [12].

Despite advancements in its management, a subset of patients exhibits resistance to conventional immunoglobulin therapy, necessitating exploration into alternative therapeutic modalities [13]. Infliximab, a monoclonal antibody targeting tumor necrosis factor-alpha (TNF-α), and other biologic agents have emerged as potential interventions in immunoglobulin-resistant KD [14]. TNF-α is a pro-inflammatory cytokine that plays a pivotal role in the immune response, particularly in the initiation and amplification of inflammation [15].

In drug-resistant KD, the immune system remains hyperactive, leading to persistent inflammation and an increased risk of complications, including coronary artery involvement [16]. TNF-α is known to contribute to the inflammatory cascade by promoting the release of other inflammatory mediators and by activating various immune cells [17]. The rationale behind exploring TNF-α inhibitors, such as Infliximab, in drug-resistant KD lies in their ability to specifically target and block the actions of TNF-α [15]. By doing so, these inhibitors aim to interrupt the inflammatory process and modulate the immune response [15]. In the case of KD, where conventional treatment may not effectively control inflammation, TNF-α inhibitors offer an alternative approach to mitigate the immune-mediated damage to blood vessels and reduce the risk of complications [18].

Several studies and clinical trials have investigated the use of TNF-α inhibitors in drug-resistant KD, including Infliximab [19]. The goal is to assess their efficacy in terms of reducing inflammation, preventing coronary artery abnormalities, and improving overall outcomes in patients who do not respond adequately to standard therapies [20]. The crucial factor is that while TNF-α inhibitors show promise, their use in KD requires careful consideration of potential risks and benefits [21]. The balance between suppressing inflammation and avoiding immunosuppression-related complications is a critical aspect of their administration in a pediatric population [22].

The exploration of Infliximab in the context of KD holds promise due to its targeted inhibition of TNF-α, a crucial pro-inflammatory cytokine implicated in the pathogenesis of the disease [23]. Infliximab's potential benefits lie in its capacity to modulate the immune response, suppress inflammation, and mitigate vascular damage, particularly in cases resistant to conventional treatments like IVIG [24].

Given the critical role of vascular and mucosal healing in mitigating the deleterious effects of vasculitis and preventing long-term complications, a meta-analysis offers a systematic approach to consolidate existing evidence and draw meaningful conclusions regarding the healing potential of Infliximab and other biologics in immunoglobulin-resistant KD [25]. This therapeutic evaluation aims to synthesize data from diverse studies, elucidating the comparative efficacy, safety, and mechanistic underpinnings of these interventions [26–28]. By systematically analyzing the existing literature, this meta-analysis seeks to contribute to the refinement of therapeutic strategies and the potentiality of Infliximab in immunoglobulin-resistant KD, offering a foundation for evidence-based decision-making in clinical practice.

This meta-analysis is motivated by the imperative to address the challenges posed by immunoglobulin resistance in KD, with a particular focus on the intricate dynamics of vascular and mucosal healing healing. The complex interplay between the immune system and vascular tissue repair mechanisms necessitates a nuanced examination of the impact of Infliximab and biologics on the course of KD.

Materials and methods

Literature review

Studies published between 2003 and 2023 were searched comprehensively in the following databases: PubMed, Scopus, Web of Science, Embase, Cochrane Library and Google Scholar. Combining Medical Subject Headings (MeSH) phrases and free-text keywords like "Infliximab and Kawasaki disease," "vascular healing and biologics," "Kawasaki disease," and "IVIG resistance," the search technique sought to discover pertinent research papers. The purpose of the study was to collect patient data from randomized controlled trials to analyze the potential of infliximab in reducing inflammation, promoting mucosal healing, and preventing vascular complications in immunoglobulin-resistant Kawasaki disease. The search strategy was designed to ensure comprehensive identification of relevant studies using both specific and broad search terms.

Inclusion and exclusion criteria

Inclusion criteria

[1] Pediatric patients diagnosed with Kawasaki Disease, [2] Evidence of IVIG resistance, [3] Availability of quantitative data on outcomes (e.g., ANC reduction, inflammation suppression, or mucosal healing), [4] Studies comparing infliximab with IVIG treatment.

Exclusion criteria

[1] Case reports were excluded. [2] Studies without full text or open access availability were excluded. [3] Studies that reported the treatment for KD without infliximab.

Data extraction

Based on defined exclusion and inclusion criteria, extraction of data and screening of literature was performed including Patient's age, number, year of publication, and first author. Additionally, data related to infliximab's effectiveness in vascular healing, inflammation suppression, and mucosal healing in KD were retrieved from the literature study.

To ensure consistency in neutrophil data analysis, the time points for neutrophil evaluations were specified and verified for each included study. Baseline neutrophil counts prior to treatment initiation were recorded where available, and post-treatment neutrophil counts (as defined by each study) were extracted.

Study outcomes

The primary outcome of the study was the reduction in absolute neutrophil counts, indicating suppression of inflammation. The secondary outcomes included mucosal healing, improvement in vascular damage, and prevention of coronary artery complications.

Intervention and control groups

The study evaluated two distinct groups to analyze the efficacy of infliximab in KD:

Intervention group

This group included patients treated with infliximab. The group was further categorized as:

- Primary Treatment: Patients receiving infliximab as the sole therapy.
- Combination Treatment: Patients receiving infliximab in conjunction with IVIG.

Subgroup analyses were conducted to evaluate the differential effects of infliximab alone versus its use as an adjunct therapy.

Control group

This group consisted of patients treated with standard IVIG therapy without the addition of infliximab.

Screening and selection process

The study selection process was conducted in two main stages: title/abstract screening and full-text review. Two independent reviewers screened the titles and abstracts of all retrieved records to identify studies that potentially met the inclusion criteria. Each reviewer independently evaluated the eligibility of the studies based on the predefined inclusion and exclusion criteria. Any disagreements between the two reviewers were resolved through discussion, and if a consensus could not be reached, a third reviewer was consulted for the final decision.

Statistical analysis

In R version 4.3.2, the metabin function of R package meta was used to conduct the meta-analysis. The function needs the number of events and total number of patients in the intervention and control group as input for the binary outcomes. This function was employed to determine the various effect sizes, confidence intervals, and other statistics inclusive of the percentage of weight, heterogeneity, by I^2 and statistical significance by p-value below 0.05. In addition, the studies related to vascular and mucosal healing potential of infliximab in Kawasaki

disease were utilized in performing the meta-analysis. Moreover, a publication bias assessment was performed using funnel plots, and Eggers's test, and along with this linear regression was performed to interpret funnel plot asymmetry using Egger's test.

Ethical approval

The study being a meta-analysis, did not require ethical approval and informed consent. However, the study is in line with the ethical principles of Declaration of Helsinki 1964.

Human ethics and consent to participate

Not applicable in this systematic review and meta-analysis.

Clinical trial number

Not applicable.

Results

Study characteristics

The literature screening and data extraction was performed using predetermined inclusion and exclusion criteria. Literature screening was performed through four sequential steps: identification, screening, eligibility, and final inclusion, illustrated in Fig. 1. Each study included first author along with year of publication, patient characteristics, sample size of intervention and control group and neutrophil counts. Following a thorough screening of 82 papers and the elimination of duplicates, 11 papers that met the specified criteria were initially identified. The further analysis was then performed on these selected papers.

The neutrophil data from each study were reviewed and verified for accuracy. For instance, Tremoulet et al. reported changes in neutrophil counts over time, and these were used to calculate the rate of change for both intervention and control groups. Similarly, Mori et al. provided baseline and post-treatment neutrophil values, allowing for the inclusion of rate-of-change data in the analysis. All neutrophil values reported in Burns (2021) were cross-checked for consistency with the study's reported time points.

The included studies ranged from 2008 to 2021. This meta-analysis involved 857 pediatric patients diagnosed with IVIG resistant KD, comprising 403 patients (237 males and 147 females) in the intervention group and 454 patients (249 males and 190 females) in the control

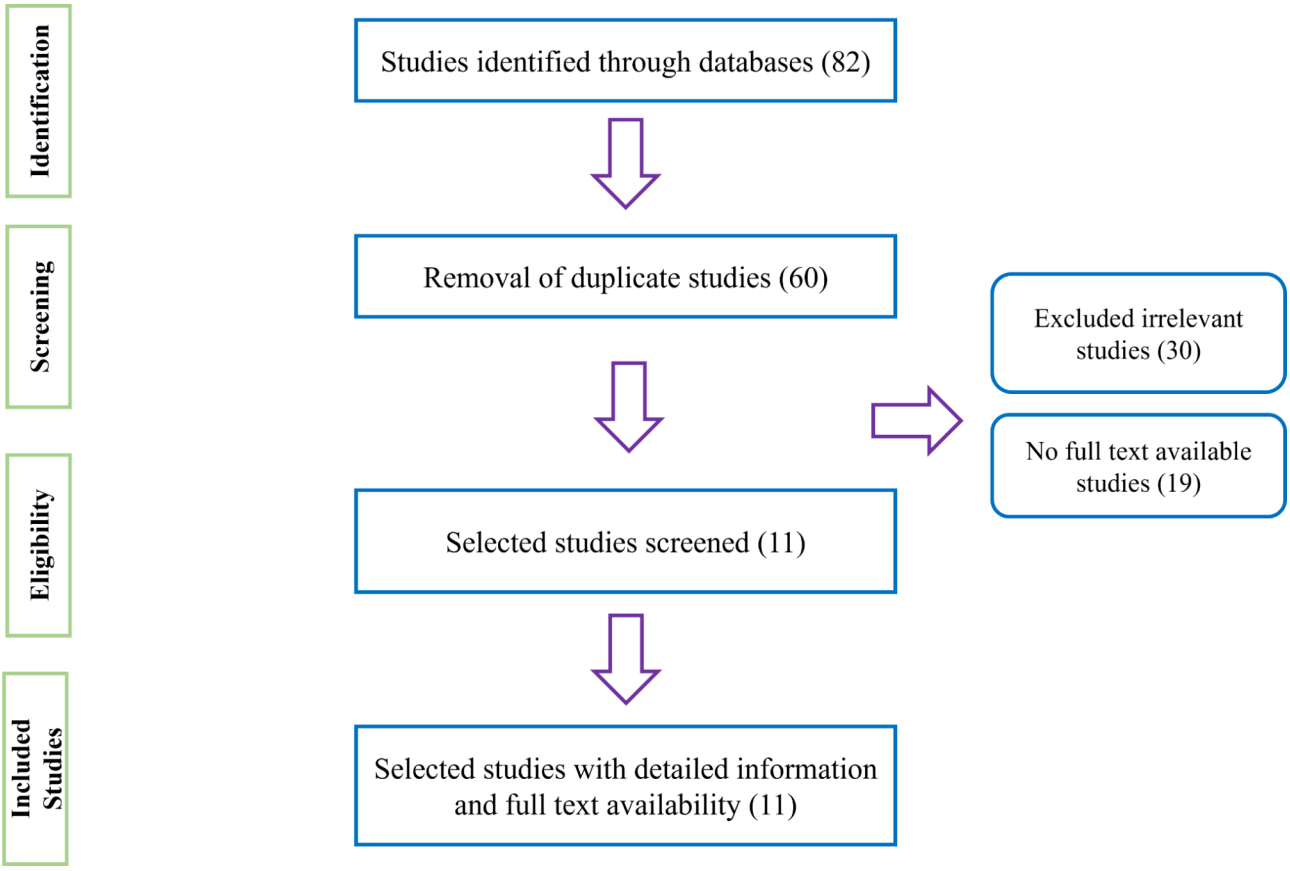

Fig. 1 Study flow diagram of literature screening for meta-analysis

Table 1 Baseline patient characteristics of intervention and control groups across studies

Study Id	Study Design	Sample Size (*n*)		Sex (Male/Female)		Age (Years)		References
		Intervention Group	Control Group	Intervention Group	Control Group	Intervention Group	Control Group	
Jane C. Burns (2008)	RCT	12	11	8/4	8/3	1.6	1.8	[29]
Adriana H Tremoulet (2014)	RCT	98	98	60/38	61/37	3	2.8	[30]
Masaaki Mori (2018)	RCT	16	15	10/6	11/4	2.5	3	[31]
Yasutaka Nakashima (2019)	RCT	15	12	8/7	8/4	4.3	3	[32]
Jane C Burns (2021)	RCT	54	49	29/25	30/19	3.6	2.1	[33]
Chun-Ling Han (2018)	Comparative study	77	77	34/43	28/49	2.1	2.3	[34]
Pei-Ni Jone (2018)	Comparative study	35	34	26/9	28/6	2.1	3.5	[35]
Youn (2016)	RCT	11	32	NA	NA	NA	NA	[36]
Mary Beth Son (2011)	RCT	20	86	14/6	55/31	1.9	2.4	[37]
Samuel R. Dominguez (2019)	RCT	58	33	44/6	19/31	1.1	2	[38]
J C Burns (2013)	RCT	7	7	4/3	1/6	3	3.1	[39]

Table 2 ANC ($x10^6$ L) counts reported in intervention and control group

StudyID	Intervention Group ANC	Control Group ANC
Adriana H Tremoulet (2014)	5.02	6.18
Masaaki Mori (2018)	9.7	12.35
Jane C Burns (2021)	5.5	12.16
Chun-Ling Han (2018)	10.2	8.5
Mary Beth Son (2011)	8.5	9.9
J C Burns (2013)	11.2	8.5

group, with mean ages of 2.2 and 2.3 years, respectively. However, a study conducted by Youn did not report the patient's characteristics in either of the groups. The baseline characteristics of the study are provided in Table 1. Furthermore, the absolute neutrophil count (ANC) data was extracted from each study, considering neutrophil role in vascular and tissue repair. The ANC ($x10^6$ L) in the intervention group was 8.3, while the control group exhibited a higher count of 9.5.

Absolute neutrophil counts across studies

The meta-analysis included the ANC across the studies to assess its potential in healing processes, highlighting neutrophils' crucial role in immune response and tissue regeneration. A total of nine studies reported the ANC comparison between intervention and control group. The two studies conducted by Dominguez and Jone did not report the ANC (18.2%). Furthermore, three studies by Youn, Nakashima and Burns reported the ANC in percentages (27.3%). The remaining six studies reported the ANC count in ($x10^6$ L) (54.4%). The quantitative analysis was performed on ANC ($x10^6$ L). The intervention group reported an average of 8.3 count, while the control group reported an average count of 9.5. Only studies conducted by Hans and Burns reported higher ANC in the intervention group. The quantitative comparative analysis counts across the studies are listed in Table 2, and illustrated in Fig. 2.

Quantitative synthesis (meta-analysis)

Healing potential of infliximab

In the intervention group, eleven studies reported an infliximab effect in KD patients. This corrected count reflects the final inclusion criteria and rigorous verification of all studies. The dataset comprises 403 events from 857 total samples, with their respective outcome ratios are represented in Table 3. A total of nine studies reported a positive outcome. Further evaluation of infliximab efficacy in KD patients was evaluated through a proportional meta-analysis. The proportional meta-analysis revealed significant heterogeneity, suggesting a potential healing effect of infliximab (Proportion: 0.45, 95% confidence interval [CI]: [0.42; 0.48], $I^2 = 87\%$, $p < 0.01$). The publication bias analysis was performed through Egger's test. The publication bias results reported insignificant results (Test result: $t = 0.62$, $df = 9$, p-value = 0.5498). The meta-analysis results are depicted in Fig. 3.

Discussion

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that plays a pivotal role in chronic inflammatory disorders [40]. The levels of TNF-α and its soluble receptors are highest in children with coronary artery aneurysms and are elevated in the acute phase of Kawasaki disease [41]. Infliximab, the first anti-TNF-α monoclonal antibody medication validated for pediatric patients is thought to be effective in KD and vascular and mucosal healing as TNF-α is considered to be beneficial in acute KD [23]. The positive effect of infliximab was observed in the healing processes of KD patients and this early

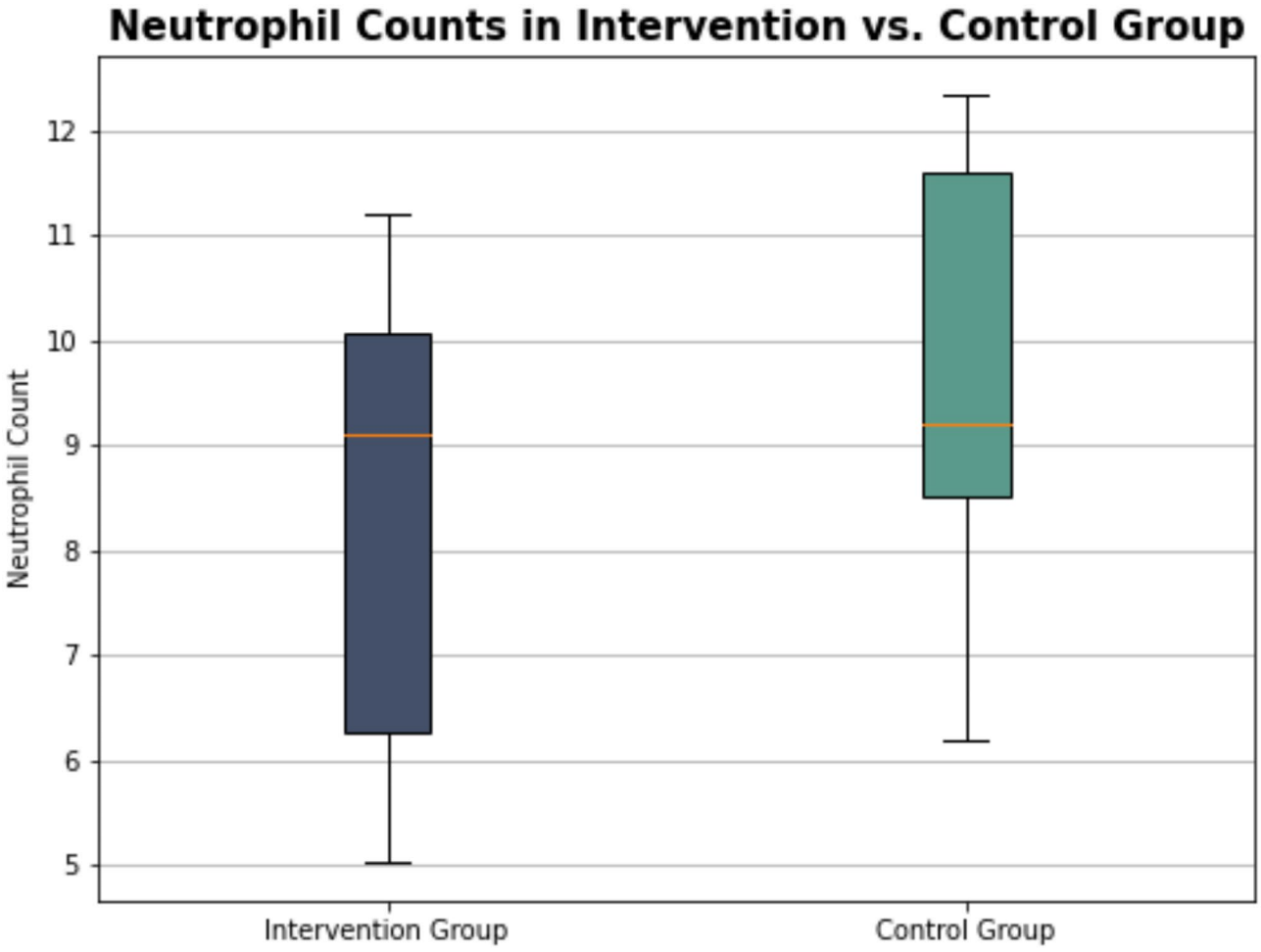

Fig. 2 Neutrophil counts reported in intervention vs. control group across studies

Table 3 Event outcome analysis across studies

StudyID	Vascular and mucosal healing achieved	Total	Outcome (Vascular and mucosal healing)
Jane C. Burns (2008)	12	23	Yes
Adriana H Tremoulet (2014)	98	196	Yes
Masaaki Mori (2018)	16	31	Yes
Yasutaka Nakashima (2019)	15	27	Yes
Jane C Burns (2021)	54	103	Yes
Chun-Ling Han (2018)	77	154	No
Pei-Ni Jone (2018)	35	69	Yes
Youn (2016)	11	43	No
Mary Beth Son (2011)	20	106	Yes
Samuel R. Dominguez (2019)	58	91	Yes
J C Burns (2013)	7	14	Yes

treatment with infliximab has been recommended in patients with refractory KD [42].

Neutrophils, a type of white blood cell, are integral to the immune system's response, particularly in reducing inflammation and promoting vascular, mucosal and infection healing [43]. Through the leukocyte adhesion cascade, neutrophils are mobilized from the bloodstream to sites of infection or inflammation [44]. As one of the most abundant immune cells, neutrophils play a dual role in promoting tissue repair and preventing infection through their antimicrobial activity. However, their role in KD and mucosal healing warrants cautious interpretation, as their effects can vary depending on the inflammatory context and treatment modalities.

In the context of anti-TNF-α therapy, such as infliximab, neutrophils are believed to contribute to clinical remission and mucosal healing in patients [44]. However, while anti-TNF-α therapies modulate inflammation, their specific effects on neutrophils in Kawasaki disease remain underexplored. This meta-analysis examined the efficacy of infliximab in reducing inflammation by analyzing ANC differences between intervention and control groups. The intervention group, treated with infliximab, reported an average ANC of 8.3, which was lower than the control group's average of 9.5. The observed average

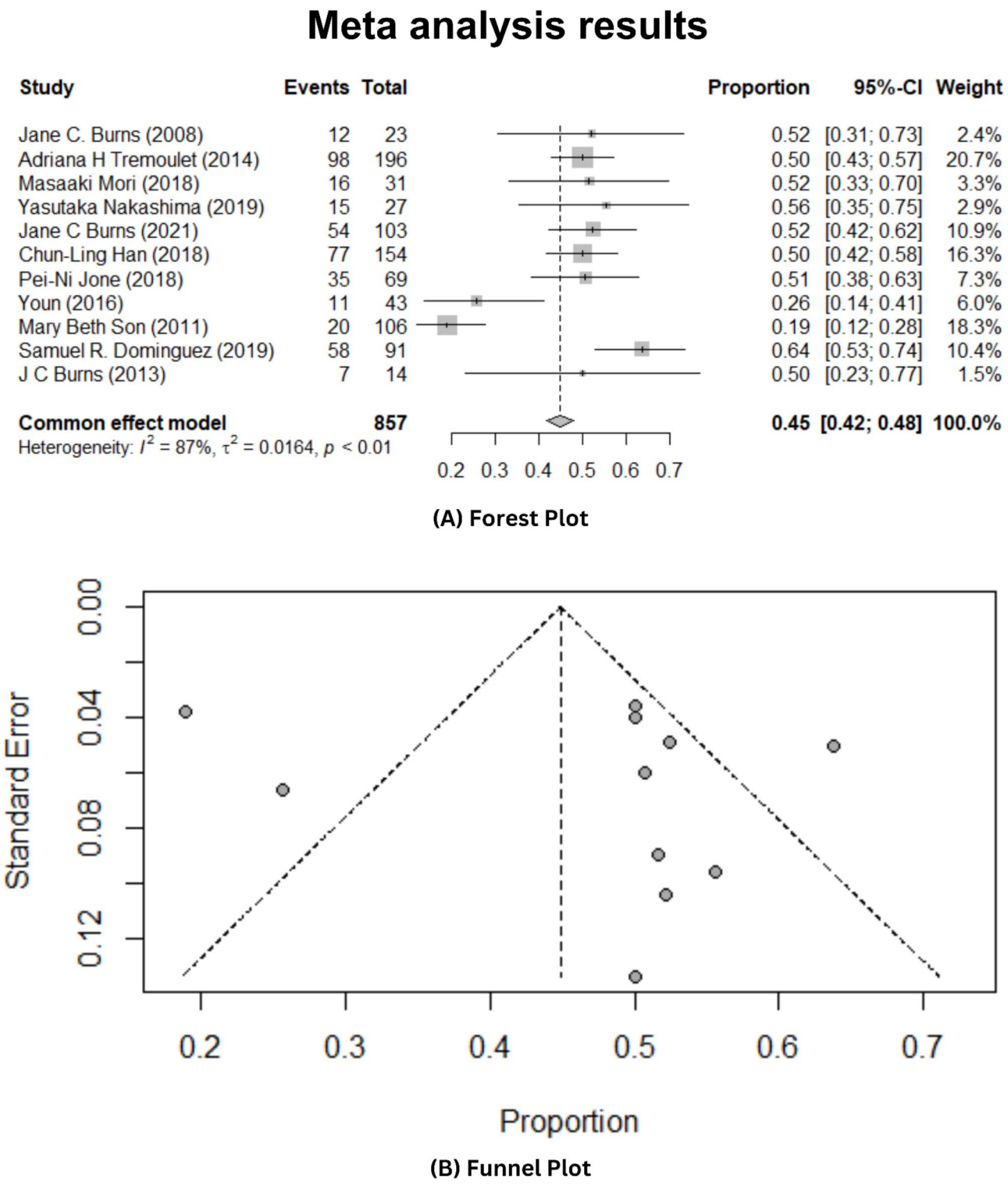

Fig. 3 Meta-analysis results. (**A**) Forest plot analysis. (**B**) Publication bias via funnel plot

difference of 7.67 highlights infliximab's potential to suppress inflammation.

Among the eleven selected studies, three reported neutrophil counts in percentages, two did not report neutrophil values, and six provided absolute counts in (x10^6 L). While reductions in ANC following infliximab treatment were noted in some studies [45].

Hence, this meta-analysis comprising eleven studies, was performed to evaluate the vascular and mucosal healing potential of infliximab in IVIG KD pediatric

patients. Nine of these studies reported the infliximab effectiveness and potential in healing processes. The intervention group, treated with the infliximab, reported less neutrophil counts. This further validates the inflammation reduction observed in patients. Amongst all studies, some studies reported the usage of infliximab along with the IVIG treatment, while others primarily focused on usage of infliximab in IVIG patients. The studies by Han and Youn did not report the significant difference in vascular and mucosal healing potential of infliximab compared to the control group. Contrastly, the study by Burns reported the higher ANC in the intervention group. However, despite the higher neutrophil count the study considered infliximab healing potential in IVIG KD patients.

This pooled analysis speculated infliximab might be effective in vascular and mucosal healing processes. Infliximab demonstrated significant reduction in the inflammation, as validated by reduction in neutrophil counts in pediatric patients. Moreover, two meta-analyses also report the efficacy of infliximab in treatment of KD [46].

However, a notable limitation of study was scarcity of studies reporting the effectiveness of infliximab to treat KD. Moreover, the studies primarily emphasized the reporting of factors such as neutrophil counts, evaluating the inflammation. Hence, further studies should focus on investigating the direct influence of infliximab on the healing process to further validate these results.

Conclusion

This meta-analysis underscored the therapeutic potential of infliximab, either as an adjunct to intravenous immunoglobulin (IVIG) or as a standalone treatment, in managing Kawasaki Disease (KD). Through a rigorous review, it specifically evaluated the capacity of infliximab to enhance vascular and mucosal healing in pediatric patients with KD who were resistant to IVIG treatment. The findings indicated a significant decrease in absolute neutrophil counts among patients treated with infliximab, suggesting a robust reduction in inflammation. These outcomes suggest that infliximab could be considered as a viable treatment option for children who are resistant to IVIG. Future studies should aim to further investigate the correlation between infliximab treatment and vascular and mucosal healing efficacy to validate these findings comprehensively.

Abbreviations

KD	Kawasaki Disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
IVIG	Intravenous Immunoglobulin
CI	Confidence Interval
ANC	Absolute Neutrophil Count
TNF-α	Tumor Necrosis Factor-alpha

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Author contributions

Huiming Cheng conceptualized and designed the study, conducted the meta-analysis, interpreted the results, and drafted the manuscript.

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Data availability

All data generated or analyzed during this study were included in this article.

Declarations

Ethics approval and consent to participate

This study is a meta-analysis and, as such, did not involve direct interaction with human participants or the collection of new data from individuals. Therefore, ethical approval and informed consent were not required. The study complies with the ethical principles of the Declaration of Helsinki (1964).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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