RESEARCH ARTICLE

Is there an association between intravenous immunoglobulin resistance and coronary artery lesion in Kawasaki disease?—Current evidence based on a meta-analysis

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Abstract

Background
Coronary artery lesion (CAL) caused by Kawasaki disease (KD) is a leading cause of acquired heart disease in children. Initial treatment of intravenous immunoglobulin (IVIG) can reduce the incidence of CAL. Although most of the current studies have shown a certain correlation between CAL and IVIG resistance, the conclusions are not completely consistent. Thus, we performed this meta-analysis to evaluate the association between IVIG resistance and CAL in KD.

Methods
PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and China National Knowledge Infrastructure through April 21, 2020 were searched to detect relevant studies. Data analysis was performed with STATA 15.1.

Results
A total of 53 relevant studies were eligible to this analysis, including 30312 KD patients, of which 4750 were IVIG resistance and 25562 were responders. There was a significant difference found between IVIG resistance and IVIG response groups in the incidence of CAL (P < 0.001, odds ratio (OR), 3.89; 95% confidence interval (CI) (3.18, 4.75)). The heterogeneity test results showed that the I² value was 74.8%. The meta-regression analysis showed that the study regions might be the sources of heterogeneity. The subgroup analysis suggested that the incidence of CAL in the IVIG resistance group was still higher than that in the IVIG response group under different regions, IVIG resistance diagnostic criteria, CAL diagnostic criteria, and study types. Meanwhile, the sensitivity analysis did not find any significant impact from every single study.
Conclusions

This is the first meta-analysis to reveal the incidence of CAL was associated with IVIG resistance in KD patients. Further well-designed studies with uniform criteria are needed to evaluate the incidence of CAL in IVIG resistant patients.

Introduction

Kawasaki disease (KD) is an acute vasculitis of unknown etiology that predominantly affects children, first identified in Japan and now reported worldwide [1]. KD may cause coronary artery lesion (CAL) and is currently the leading cause of acquired heart disease in children in developed countries [2]. The American Heart Association (AHA) recommends the standard treatment regimen for the acute phase of KD involves administering intravenous immunoglobulin (IVIG) 2 g·kg⁻¹ and aspirin [3]. Previous studies have indicated that the incidence of CAL is highly correlated with dose and infusion timing of IVIG, not aspirin [4, 5]. Early use of IVIG in KD can effectively reduce the incidence of CAL from 25% to about 4% [3]. However, up to 20% of KD patients may fail to respond to IVIG [6]. Even though the precise molecular mechanism of CAL and IVIG in KD are still unclear, many clinical studies suggest IVIG resistance has deeply associated with the occurrence of CAL [7–9]. Thus, a great deal of literature have used this as a starting point to study the indicators for predicting IVIG resistance [10–13], with the expectation that additional therapeutic measures can be taken to reduce the incidence of CAL through early diagnosis of IVIG resistance.

Although most of the current studies have shown the association between CAL and IVIG resistance, the conclusions are not completely consistent. Besides, there is still a lack of comprehensive and systematic analysis of this issue. Therefore, we performed this meta-analysis for the first time to evaluate the association between IVIG resistance and CAL in KD.

Materials and methods

Study protocol

We generated this meta-analysis followed a predetermined protocol by the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [14]. The PRISMA checklist could be found in S1 Table. This study was registered with PROSPERO (CRD42020181359).

Search strategy

We searched multiple databases, including PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CCTR), and China National Knowledge Infrastructure (CNKI) through April 21, 2020 to identify relevant studies. We searched the PubMed as follows: (((Mucocutaneous Lymph Node Syndrome [MeSH Terms] OR Kawasaki disease OR Kawasaki syndrome) AND (Immunoglobulins, Intravenous [MeSH Terms] OR IVIG OR Intravenous Immune Globulin OR Immune Globulin, Intravenous OR Intravenous Immunoglobulins)) AND (((resistance) OR (resistant)) OR (nonresponse) OR (refractory))) AND (coronary artery). Search terms and corresponding results of EMBASE, CCTR, and CNKI are shown in S1 Appendix. The language was limited to English.
Study selection
We initially screened researches by the title and abstract. A full-text search that retrieved potentially relevant reports was assessed for compliance using the inclusion and exclusion criteria. Inter-rater reliability for the study selection was calculated using the kappa statistic [15]. Studies that meet all the following criteria were included: 1) All cases were KD patients; 2) non-randomized or randomized controlled clinical trials or cohort studies evaluating the incidence of CAL in KD patients, including IVIG resistance and IVIG response. Meanwhile, researches meeting any of the following criteria were excluded: 1) Initial IVIG treatment is not the AHA recommended standard dose (2 g·kg⁻¹); 2) conference articles, reviews, or abstracts; 3) The sample size included in the study was too small (n < 60); 4) duplicate reports.

Data collection and assessment of study quality
Two investigators (Xiaolan Zheng, Jinhui Li) independently assessed the eligibility of studies by the title and abstract, and a third reviewer (Peng Yue) determining divergence based on the inclusion or exclusion criteria and the quality of literature, and consultation with a fourth reviewer (Yifei Li) if necessary. Besides, we used the Newcastle-Ottawa Scale (NOS) to assess the quality of the included researches [16]. Additionally, literature with a score of fewer than five stars was considered as of low quality and needed to be excluded.

Data synthesis and analysis
We calculated the odds ratio (OR) with 95% confidence intervals (CI) for each outcome of interest then pooled them into an independent meta-analysis. KD children with IVIG resistance were the experimental group, and the control group was the IVIG responders. The outcome was the incidence of CAL in the experimental group or the control group, including coronary artery aneurysm (CAA), coronary artery dilatation (CAD) or ectasia, which was defined according to the diagnostic criteria of the American Heart Association (AHA) Z-score [3] or the Japan Kawasaki Disease Research Committee (JKDRC) [17].

Publication bias
We used Egger’s regression by STATA software version 15.1 to test the publication bias of the include studies. Each study is represented by a dot, and the asymmetrical distribution of dots between the regression line suggested publication bias, where the quantified result showed that P < 0.05 [18]. When publication bias occurs, we use the trim-and-fill method further to evaluate the impact of publication bias on the results. If there is no significant difference between the results before and after the test of the trim-and-fill method, it indicates that the results are stable and reliable even if there is publication bias [19].

Heterogeneity
Heterogeneity was investigated by the Chi-squared test and was considered as statistically significant when P < 0.05 in these tests. The I² values can range from 0 to 100%, higher than 25%, 50%, and 75%, suggesting low, moderate, and high heterogeneity, respectively [20]. When the I² value exceeded 50%, we used the random-effects (M-H method) for analysis; otherwise, the fixed-effects (M-H method) was used.
Meta-regression and subgroup analysis
The meta-regression was conducted to investigate the potential factor of leaded heterogeneity. The subgroups analysis was performed according to the study regions, IVIG resistance diagnostic criteria, CAL diagnostic criteria, and study types.

Sensitivity analysis
Sensitivity analysis was conducted for every study to investigate whether any single study caused undue weight in the results of the meta-analysis.

Statistical analysis
Data analysis was performed with STATA 15.1. The numbers of children who developed CAL in each study were converted to OR. Meanwhile, heterogeneity, publication bias, and sensitivity analysis were also conducted by STATA 15.1.

Results
Search results
Initially, 1232 potentially relevant studies were retrieved by the search method, of which 126 were considered as of interest by titles and abstracts. However, 73 studies were excluded by reading the complete researches due to article type (n = 18), using the modified IVIG dosing as the initial treatment (n = 7), and lacking specific numbers of CAL cases in KD patients with IVIG resistance or response (n = 48). Ultimately, 53 articles [8, 10, 11, 13, 21–69] were included in the meta-analysis. The kappa test showed the kappa value of agreement during the systematic searches was 0.86. The research selection process was shown in Fig 1.

Study characteristics
A total of 30312 KD patients were included, of which 4750 were IVIG resistance, and 25562 were responders. The 53 studies included were from 11 countries in three regions (Asia, North America, and Europe). Besides, the criteria for the diagnosis of KD resistance was not consistent, among them, IVIG resistance of six studies was defined as persistent fever \(\geq 24\)h after the end of the first IVIG infusion, 21 studies to define the time for \(\geq 36\)h, or otherwise, 17 studies was defined as \(\geq 48\)h, and for the remaining nine studies was defined as a second dose of IVIG for persistent or recrudescent fever without mentioning the specific time. Moreover, the CAL diagnostic criteria in all the included literatures were not consistent, among which, JKDRC criteria was used in 29 studies, AHA criteria was used in 14 studies, JKDRC or AHA criteria was both used in eight studies, and the remaining two studies did not report which criteria was used. All included studies were non-randomized trials, including 5 prospective studies and 48 retrospective studies. Moreover, all the included reports were awarded \(\geq six\) stars and qualified as high quality. The characteristics of KD children in all involved studies were illustrated in Table 1.

Data synthesis and analysis
The OR value and 95%CI of the CAL cases of IVIG resistant children in each study were calculated by STATA 15.1, and all the results were pooled into an independent meta-analysis. The results showed a significant difference between IVIG resistance and IVIG response groups in the incidence of CAL (P < 0.001, OR, 3.89; 95%CI (3.18, 4.75)) (Fig 2). Due to the I^2 value was 74.8%, we used the random-effects (M-H method) for analysis.
Publication bias

The result of the Egger’s regression test was shown an asymmetric distribution indicated that publication bias existed (P = 0.002, t = 3.19, 95%CI (0.47, 2.07)) (S1A Fig). Then, we use the trim-and-fill method further to evaluate the impact of publication bias on the results. The funnel plot of publication bias used the trim-and-fill method showed that no significant difference between the results before (P < 0.001, Z = 13.26, 95%CI (1.16, 1.56)) and after filled 13 studies.
| No. | First author | Year | Countries | Study type | Diagnostic criteria of CAL | Diagnostic time of IVIG resistance | Age (years) (IVIG resistance/IVIG response) | Male (%) (IVIG resistance/IVIG response) | KD patients (IVIG resistance/IVIG response) | CAL patients (IVIG resistance/IVIG response) | Follow-up (weeks) | NOS |
|-----|--------------|------|-----------|------------|--------------------------|------------------------------------|------------------------------------------|-----------------------------------------|-------------------------------------------|-------------------------------------------|----------------|-----|
| 1   | Hashino      | 2001 | Japan     | retrospective | JKDRC                  | 48h                                 | N/R                                      | 35/227                                  | 9/0                                     | N/R                                      | 6              |     |
| 2   | Hsieh        | 2004 | China     | retrospective | JKDRC                  | 72h                                 | 2.8/1.7                                  | 9/153                                   | 3/20                                    | 8             |    7 |
| 3   | Sittiwangkul | 2006 | Thailand  | retrospective | JKDRC/ AHA              | 36h                                 | 1.4/1.6                                  | 44.0/50.1                                | 9/61                                    | 7/10                      | 52            |     6 |
| 4   | Sano         | 2006 | Japan     | retrospective | AHA                    | 24h                                 | 2.2/2.3                                  | N/R                                     | 22/90                                   | 17/9          | > 52 6 |
| 5   | Furukawa     | 2007 | Japan     | retrospective | JKDRC                  | 36h                                 | 54.0/60.1                                | 63/348                                  | 7/1                                     | N/R                                      | 7              |     7 |
| 6   | Uehara       | 2008 | Japan     | retrospective | JKDRC                  | N/R                                 | 2.0/1.9                                  | N/R                                     | 1286/5044                              | 333/402       | N/R            | 6       |
| 7   | Tremoulet    | 2008 | USA       | retrospective | AHA                    | 48h                                 | 63.3/60.9                                | 60/302                                  | 29/109                                  | 8             | 4     |
| 8   | Sabharwal    | 2009 | Canada    | retrospective | JKDRC                  | 36h                                 | N/R                                      | 181/1117                                | 54/2046                                | 8–6           |     6 |
| 9   | Mamtani      | 2010 | Japan     | prospective  | JKDRC                  | 36h                                 | N/R                                      | 25/68                                   | 18/5                                    | N/R                                      | 6              |     6 |
| 10  | Weng         | 2010 | China     | retrospective | JKDRC                  | 48h                                 | 50.0/57.4                                | 20/136                                  | 12/44                                   | 8             | 7     |
| 11  | Do           | 2010 | Korea     | retrospective | JKDRC                  | 48h                                 | 1.7/2.5                                  | 61.5/66.7                                | 13/64                                   | 5/7                       | 52            |     7 |
| 12  | Kuo          | 2010 | China     | retrospective | JKDRC                  | 48h                                 | 1.6/1.6                                  | N/R                                     | 20/111                                  | 6/24                      | 4             | 7     |
| 13  | Hwang        | 2011 | Korea     | retrospective | JKDRC                  | 24h                                 | 60.8/54.4                                | 23/206                                  | 14/37                                   | 4             | 6     |
| 14  | Sittiwangkul | 2011 | Thailand  | retrospective | JKDRC                  | N/R                                 | N/R                                      | 18/137                                  | 11/29                                   | 52           |     6 |
| 15  | Iwashima     | 2011 | Japan     | retrospective | JKDRC                  | 48h                                 | N/R                                      | 108/325                                 | 30/23                                   | N/R                                      | 7              |     7 |
| 16  | Kim          | 2011 | Korea     | prospective   | JKDRC                  | 48h                                 | 50.0/53.3                                | 22/107                                  | 7/3                                     | 8             | 6     |
| 17  | Yoshimura    | 2013 | Japan     | retrospective | AHA                    | 24h                                 | 47.0/73.0                                | 17/63                                   | 8/11                                    | 4             | 6     |
| 18  | Ou-Yang      | 2013 | China     | retrospective | JKDRC                  | 48h-72h                             | 40.0/63.8                                | 5/58                                    | 5/7                                     | 12           | 7     |
| 19  | Park         | 2013 | Korea     | retrospective | AHA                    | 36h                                 | 63.3/50.9                                | 30/279                                  | 13/19                                   | N/R                                      | 7              |     7 |
| 20  | Teraguchi    | 2013 | Japan     | prospective   | JKDRC                  | 36h                                 | 58.5/62.2                                | 41/196                                  | 12/5                                    | N/R                                      | 6              |     6 |
| 21  | Cho          | 2014 | Korea     | retrospective | AHA                    | 36h                                 | 52.9/55.6                                | 17/135                                  | 8/29                                   | 10–62         |     6 |
| 22  | Yi           | 2014 | Korea     | retrospective | JKDRC                  | 36h                                 | N/R                                      | 17/47                                   | 7/17                                   | > 4           | 7     |
| 23  | Adjagba      | 2014 | Canada    | prospective   | AHA                    | 36h                                 | N/R                                      | 16/93                                   | 6/16                                   | 12           |     6 |
| 24  | Tajima       | 2015 | Japan     | retrospective | JKDRC                  | N/R                                 | 1.7/2.3                                  | 71.0/66.7                                | 31/60                                  | 10/3                      | 4             | 8     |
| 25  | Loomba       | 2015 | USA       | retrospective | AHA                    | N/R                                 | 3.5/3.5                                  | 58/124                                  | 4/4                                     | 6–8          |     7 |
| 26  | Ha           | 2015 | Korea     | retrospective | JKDRC                  | 48h                                 | 60.4/56.2                                | 222/365                                 | 36/26                                   | 10           |     8 |
| 27  | Maggio       | 2016 | Italy     | retrospective | AHA                    | N/R                                 | 50.0/51.8                                | 14/50                                   | 4/11                                   | 52           |     6 |
| 28  | Lee          | 2016 | Korea     | retrospective | JKDRC/ AHA              | 36h                                 | 55.9/55.3                                | 34/253                                  | 21/9                                   | N/R                                      | 7              |     7 |
| 29  | Xu           | 2016 | China     | retrospective | JKDRC                  | N/R                                 | N/R                                      | 44/378                                  | 18/65                                   | 12           |     6 |
| 30  | Okuma        | 2016 | Japan     | retrospective | JKDRC                  | N/R                                 | 4.5/48                                   | 22/89                                   | 3/5                                    | N/R                                      | 8              |     8 |
| 31  | Kawamura     | 2016 | Japan     | retrospective | JKDRC                  | 24h                                 | 57.6/57.8                                | 85/320                                  | 9/1                                    | N/R                                      | 7              |     7 |
| 32  | Xie          | 2017 | China     | retrospective | JKDRC                  | 48h                                 | N/R                                      | 56/504                                  | 27/126                                  | 4             | 6     |
| 33  | Berdej-Szczot| 2017 | Poland    | retrospective | JKDRC                  | 36h                                 | N/R                                      | 8/65                                    | 1/12                                   | 26           |     6 |
| 34  | Kimura       | 2017 | Japan     | retrospective | JKDRC                  | 48h                                 | N/R                                      | 147/476                                 | 12/1                                   | N/R                                      | 7              |     7 |
| 35  | Chbeir       | 2018 | France    | retrospective | JKDRC/ AHA              | 48h                                 | 53.3/60.7                                | 45/112                                  | 14/17                                   | 52           |     8 |
| 36  | Hua          | 2018 | China     | retrospective | JKDRC/ AHA              | 48h                                 | N/R                                      | 380/1735                                | 118/371                                 | N/R                                      | 6              |     6 |
| 37  | Kim          | 2018 | Korea     | retrospective | JKDRC                  | 48h                                 | 60.5/52.2                                | 524/4627                                | 90/435                                  | N/R                                      | 7              |     7 |
| 38  | Miyakoshi    | 2018 | Japan     | retrospective | JKDRC                  | 24h                                 | 70.0/58.0                                | 98/224                                  | 17/15                                   | N/R                                      | 8              |     8 |
| 39  | Ahn          | 2018 | Korea     | prospective   | JKDRC/ AHA              | 36h                                 | N/R                                      | 38/227                                  | 14/31                                   | 52           |     6 |
| 40  | Fabi         | 2018 | Italy     | retrospective | JKDRC/ AHA              | 36h                                 | 69.8/55.6                                | 43/214                                  | 16/42                                   | N/R                                      | 6              |     6 |

(Continued)
Meta-regression and subgroup analysis

As the results of meta-analysis showed moderate to high heterogeneity, we used the meta-regression to investigate the origins of heterogeneities. According to the results (Fig 3), the study regions might be the sources of heterogeneity (P = 0.012, t = -2.62, 95%CI (0.42, 0.89)) (Fig 3A). Besides, IVIG resistance diagnostic criteria were not the impact factor on the heterogeneity (P = 0.269, t = -1.12, 95%CI (0.63, 1.14)) (Fig 3B). Meanwhile, CAL diagnostic criteria could not impact the homogeneity too (P = 0.473, t = -0.72, 95%CI (0.65, 1.22)) (Fig 3C). Additionally, the meta-regression also suggested the study type was not a dramatic impact factor (P = 0.571, t = 0.57, 95%CI (0.52, 3.18)) (Fig 3D). The subgroup analysis suggested that the incidence of CAL in the IVIG resistance group was still higher than that in the IVIG response group under different regions (OR(95%CI): Asia, 4.80(3.76, 6.13); North America, 2.00(1.56, 2.57); Europe, 2.46(1.82, 3.32)) (S2 Fig), IVIG resistance diagnostic criteria(OR(95%CI): <24h, 7.08(3.31, 15.15); ≥24h, 4.11(2.72, 6.20); ≥48h, 3.40(2.42, 4.76); N/R, 3.34(2.34, 4.77)) (S3 Fig), CAL diagnostic criteria (OR(95%CI): JKDRC, 4.29(3.32, 5.56); AHA, 3.09(2.11, 4.52); JKDRC/AHA, 3.99(2.11, 7.56); N/R, 4.76(0.09, 245.28)) (S4 Fig), and study types (OR(95%CI): retrospective, 3.75(3.06, 4.59); prospective, 5.77(2.16, 15.42)) (S5 Fig).

Sensitivity analysis

Sensitivity analysis was performed by STATA 15.1, and we did not detect any significant impact from every single research in the result (Fig 4).
Discussion

CAL caused by KD is a significant component of acquired heart disease in children in many countries [70, 71]. Although initial IVIG treatment can effectively reduce the incidence of...
CAL, IVIG resistance still exists in some children. This is the first meta-analysis to evaluate the association between IVIG resistance and CAL in KD. A total of 53 relevant studies were involved in our meta-analysis, including 30312 KD patients (4750 IVIG resistant patients and 25562 responders). The results showed a significant difference between IVIG resistance and IVIG response groups in the incidence of CAL in KD patients.

CAL is the major complications to KD, which reveals a poor prognosis. So that, hundreds of researchers had been involved in the studies of risk factors related with CAL in the last decades. IVIG resistance is one of the dominant adverse effects during acute phase treatment, which brought into observations. Even several previous studies [7–9] have suggested that the incidence of CAL was significantly higher in IVIG resistant populations. However, this issue still be debating as a series of researches demonstrated the negative association between IVIG resistance and CAL. So that it is important to draw a clear relationship of IVIG administration effects and CAL based on this meta-analysis. To predict IVIG resistance, a variety of scoring systems have been designed, and Kobayashi and Egami are the most popular ones [72, 73]. Additionally, a lot of researches have been conducted to identify risk factors for IVIG resistant KD [74–78]. Patients’ ages, biomarkers including CRP, ESR, total bilirubin, AST, ALT, and Pro-BNP were identified positively correlation with IVIG resistance. Unfortunately, the

![Image](https://doi.org/10.1371/journal.pone.0248812.g003)
sensitivity and specificity of such indicators are not qualified to be applied alone. So that an integrative scoring system need to be developed to predict IVIG resistance. And the different genetic backgrounds were also considered to be involved in various clinical results. Therefore, our study was intended to conduct subgroup analysis on ethical race. Due to the included literature was mainly divided by region and lacked ethnic information, this paper finally adopted region for subgroup analysis. In addition, some studies have shown that children with younger or elder age are more likely to demonstrate a drug resistance. However, since the included literature in this paper also lacks the segmentation of the age of the included children, further subgroup analysis at different ages cannot be carried out. These questions need to be analyzed in more well-designed studies in the future.

It is worth noting that in our literature search process, we found that majority of studies indicated that IVIG resistance might lead to an increase in the incidence of CAL, while there were few studies with different opinions. In this case, we should be aware of the possibility of publication bias. And then, the Egger’s test turned out publication bias existed. Next, we use the trim-and-fill method to evaluate the impact of publication bias on the results. Finally, the trim-and-fill method suggested the results were relatively robust even with publication bias.

As the heterogeneity test results showed that the $I^2$ value was 74.8%, we conducted the meta-regression analysis to investigate the origins of heterogeneities. The results showed that the study regions might be the sources of heterogeneity. The subgroup analysis suggested that the incidence of CAL in the IVIG resistance group was still higher than that in the IVIG response group under different regions, IVIG resistance diagnostic criteria, CAL diagnostic criteria, and study types. These results indicate that the IVIG resistance group has a higher risk of CAL than the IVIG response group, even under a variety of conditions. Since IVIG was first used in Kawasaki disease in 1982 [79], CAL has decreased significantly. Gradually, the occurrence of IVIG resistance has attracted extensive attention. Research on the prediction and treatment of IVIG resistance has been a research hotspot for many years. Nevertheless, the mechanism by which IVIG reduces the incidence of CAL and IVIG resistance is not yet clear,
and the mechanism by which CAL is also unclear, probably because the etiology of KD is still unknown.

Current follow up drug therapy for KD children with IVIG resistance mainly includes the second dose of IVIG, methylprednisolone (MP), infliximab, interleukin 1 receptor antagonist or cyclosporin [3]. However, KD patients who fail to respond to 2 doses of IVIG present a unique challenge [80]. A meta-analysis comprising 372 refractory KD patients conducted in 2019 by Chan et al. [81] revealed that infliximab, MP, and second IVIG infusion showed no significant differences in the cardioprotective effect or the rate of treatment resistance. So far, there is still no accepted treatment algorithm for refractory KD patients [82]. Among the 53 literatures included in our study, there were few literatures that provided detailed adjunct therapies and outcomes for IVIG resistance, so we could not perform analysis to evaluate the effect of different treatment regimens on the incidence of CAL in IVIG resistance. A meta-analysis [83] focused on this issue showed that steroids were more effective at reducing fever than second dose of IVIG, but was no difference in the incidence of CAL. It should be noted that the current AHA guidelines do not recommend the routine use of steroids [3]. Besides, studies which comparing infliximab with the second dose of IVIG in IVIG resistance indicated that infliximab reduced fever duration, but the outcome of coronary was similar [84, 85]. In general, there have been no robust clinical trials comparing second-line regimens for IVIG resistance in KD [86], further research into adjunct therapies is an area for future work.

Our study has several limitations. First, most studies lacked information about the adjunct therapies of IVIG resistance. Although previous studies suggested that adjuvant therapy had no significant effect on the incidence of CAL in IVIG resistance, it may still cause bias to the results of this study. Second, the follow-up time of many studies was not reported, which may also lead bias to the results. Third, most of the included studies were retrospective trials, which could lead to biased results. Therefore, further well-designed studies with uniform criteria are needed to evaluate the incidence of CAL in IVIG resistant patients and IVIG responders.

Conclusions
This is the first meta-analysis to reveal the incidence of CAL was associated with IVIG resistance in KD patients. Further well-designed studies with uniform criteria are needed to evaluate the incidence of CAL in IVIG resistant patients.

Supporting information
S1 Table. PRISMA checklist.
(DOC)

S1 Appendix. Search strategies for EMBASE, CCRT, and CNKI.
(DOCX)

S1 Fig. The assessment results of potential publication bias. (A) Egger’s publication bias plots for the assessment of potential publication bias. Asymmetry of the dot distribution between regression lines showed potential publication bias, P = 0.002, t = 3.19, 95%CI (0.47, 2.07). (B) The funnel plot of publication bias by the trim-and-fill method. After filled 13 potentially missing studies, the funnel plots were symmetrical. CI, confidence interval.
(PDF)

S2 Fig. The results of subgroup analysis by study regions.
(PDF)
S3 Fig. The results of subgroup analysis by IVIG resistance diagnostic criteria. (PDF)

S4 Fig. The results of subgroup analysis by CAL diagnostic criteria. (PDF)

S5 Fig. The results of subgroup analysis by study types. (PDF)

Author Contributions

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References

1. Newburger JW. Kawasaki disease: State of the art. Congenit Heart Dis. 2017; 12(5):633–5. Epub 2017/06/06. https://doi.org/10.1111/chd.12498 PMID: 28580712.
2. Denby KJ, Clark DE, Markham LW. Management of Kawasaki disease in adults. Heart. 2017; 103(22):1760–9. Epub 2017/07/29. https://doi.org/10.1136/heartjnl-2017-311774 PMID: 28751537.
3. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for healthcare professionals from the American Heart Association. Circulation. 2017; 135(17):e927–e99. https://doi.org/10.1161/CIR.0000000000000484 PMID: 28356445.
4. Durongpisitkul K, Gururaj VJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics. 1995; 96(6):1057–61. Epub 1995/12/01. PMID: 7491221.
5. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr. 1997; 131(6):888–93. Epub 1998/01/15. https://doi.org/10.1016/s0022-3476(97)70038-6 PMID: 9427895.
6. Soni PR, Noval Rivas M, Arditi M. A Comprehensive Update on Kawasaki Disease Vasculitis and Myocarditis. Curr Rheumatol Rep. 2020; 22(2):6. Epub 2020/02/06. https://doi.org/10.1007/s11926-020-0882-1 PMID: 32020498.
7. Lega JC, Bozio A, Cimaz R, Veyrier M, Floret D, Ducreux C, et al. Extracoronary echocardiographic findings as predictors of coronary artery lesions in the initial phase of Kawasaki disease. Archives of disease in childhood. 2013; 98(2):97–102. Epub 2012/12/14. https://doi.org/10.1136/archdischild-2011-301256 PMID: 23235890.
8. Miyakoshi C, Yamamoto Y, Yamakawa M, Fukuhara S. Heart Rate, Responsiveness to Intravenous Immunoglobulin, and Coronary Artery Aneurysms in Kawasaki Disease. J Pediatr. 2018; 200:160–5.e5. Epub 2018/05/26. https://doi.org/10.1016/j.jpeds.2018.04.036 PMID: 29793867.
9. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, et al. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Lancet Child Adolesc Health. 2018; 2(12):855–62. Epub 2018/10/20. https://doi.org/10.1016/S2352-4642(18)30293-1 PMID: 30337183.
10. Yılmazer MM, Özdemir R, Meşe T, Küçük M, Öner T, Devrim İ, et al. Kawasaki disease in Turkish children: a single center experience with emphasis on intravenous immunoglobulin resistance and giant coronary aneurysms. Turk J Pediatr. 2019; 61(5):648–56. Epub 2020/02/28. https://doi.org/10.24953/turkpediatr.2019.05.002 PMID: 32104995.

11. Piram M, Darce Bello M, Tellier S, Di Filippo S, Boralevi F, Madhi F, et al. Defining the risk of first intravenous immunoglobulin unresponsiveness in non-Asian patients with Kawasaki disease. Scientific reports. 2020; 10(1):3125. Epub 2020/02/23. https://doi.org/10.1038/s41598-020-59972-7 PMID: 32080307

12. Liu G, Wang S, Du Z. Risk Factors of Intravenous Immunoglobulin Resistance in Children With Kawasaki Disease: A Meta-Analysis of Case-Control Studies. Frontiers in pediatrics. 2020; 8:187. Epub 2020/05/07. https://doi.org/10.3389/fped.2020.00187 PMID: 32373568

13. Kim MK, Song MS, Kim GB. Factors Predicting Resistance to Intravenous Immunoglobulin Treatment and Coronary Artery Lesion in Patients with Kawasaki Disease: Analysis of the Korean Nationwide Multicenter Survey from 2012 to 2014. Korean Circ J. 2018; 48(1):71–9. Epub 2017/11/25. https://doi.org/10.4070/kcj.2017.0136 PMID: 29171205

14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. 2009; 339:b2535. Epub 2009/07/23. https://doi.org/10.1136/bmj.b2535 PMID: 19622561

15. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012; 22(3):276–82. Epub 2012/10/25. PMID: 23092060

16. Wells G, Shea B, O’connell D, Peterso n J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2008 [cited 2008].

17. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr Int. 2005; 47(2):232–4. Epub 2005/03/18. https://doi.org/10.1111/j.1442-200x.2005.02033.x PMID: 15771703.

18. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol. 2005; 58(9):882–93. Epub 2005/08/09. https://doi.org/10.1016/j.jclinepi.2005.01.016 PMID: 16085191.

19. Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018; 74(3):785–94. Epub 2017/11/16. https://doi.org/10.1111/biom.12817 PMID: 29141096

20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003; 327(7414):557–60. Epub 2003/09/06. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

21. Adjagba PM, Desjardins L, Fournier A, Spigelblatt L, Montigny M, Dahdah N. N-terminal pro-brain natriuretic peptide in acute Kawasaki disease correlates with coronary artery involvement. Cardiol Young. 2015; 25(7):1311–8. Epub 2014/12/30. https://doi.org/10.1017/S1047951114002431 PMID: 25544036.

22. Ahn JG, Bae Y, Shin D, Nam J, Kim KY, Kim DS. HMGB1 gene polymorphism is associated with coronary artery lesions and intravenous immunoglobulin resistance in Kawasaki disease. Rheumatology (Oxford). 2019; 58(5):770–5. Epub 2018/12/12. https://doi.org/10.1093/rheumatology/key356 PMID: 30535242.

23. Amano Y, Akazawa Y, Yasuda J, Yoshino K, Kojima K, Kobayashi N, et al. A low-frequency IL4R locus variant in Japanese patients with intravenous immunoglobulin therapy-unresponsive Kawasaki disease. Pediatr Rheumatol Online J. 2019; 17(1):34. Epub 2019/07/05. https://doi.org/10.1186/s12969-019-0337-2 PMID: 31269967

24. Bar-Meir M, Kalisky I, Schwartz A, Somekh E, Tasher D. Prediction of Resistance to Intravenous Immunoglobulin in Children With Kawasaki Disease. J Pediatric Infect Dis Soc. 2018; 7(1):25–9. Epub 2017/01/08. https://doi.org/10.1093/jpids/pix075 PMID: 28062554.

25. Berdej-Szczot E, Malecka-Tendera E, Gawlik T, Firek-Pedras M, Szydlowski L, Gawlik A. Risk factors of intravenous immunoglobulin resistance and coronary complications in children with Kawasaki disease. Kardiol Pol. 2017; 75(3):261–6. Epub 2016/12/21. https://doi.org/10.5603/KP.a2016.0179 PMID: 27995598.

26. Chantasiriwan N, Silvilarit S, Makonkawkeyoon K, Pongprot Y, Sittiwangkul R. Predictors of intravenous immunoglobulin resistance and coronary artery aneurysm in patients with Kawasaki disease. Paediatr Int Child Health. 2018; 38(3):209–12. Epub 2018/05/18. https://doi.org/10.1080/20469047.2018.147181 PMID: 29768976.

27. Chbér D, Gaschignard J, Bonnefoy R, Beyer C, Melki I, Fayez A, et al. Kawasaki disease: abnormal initial echocardiogram is associated with resistance to IV Ig and development of coronary artery lesions. Pediatr Rheumatol Online J. 2018; 16(1):48. Epub 2018/07/20. https://doi.org/10.1186/s12969-018-0264-7 PMID: 30021610
28. Cho KH, Kang SJ. Clinically useful predictors of resistance to intravenous immunoglobulin and prognosis of coronary artery lesions in patients with incomplete Kawasaki disease. Korean Circ J. 2014; 44(5):328–35. Epub 2014/10/04. https://doi.org/10.4070/kcj.2014.44.5.328 PMID: 25279866

29. Clark DE, Denby KJ, Kaufman LM, Fill MA, Piya B, Krishnaswami S, et al. Predictors of Intravenous Immunoglobulin Nonresponse and Racial Disparities in Kawasaki Disease. Pediatr Infect Dis J. 2018; 37(12):1227–34. Epub 2018/03/24. https://doi.org/10.1097/INF.0000000000002019 PMID: 29570178.

30. Do Y, Kim K, Chun J, Cha B, Namgoong M, Lee H. Predicting Factors for Refractory Kawasaki Disease. Korean Circ J. 2010. https://doi.org/10.4070/kcj.2010.40.5.239 PMID: 20514335

31. Fabi M, Andreozzi L, Corinaldesi E, Bodnar T, Lami F, Cicero C, et al. Inability of Asian risk scoring systems to predict intravenous immunoglobulin resistance and coronary lesions in Kawasaki disease in an Italian cohort. Eur J Pediatr. 2019; 178(3):315–22. Epub 2018/12/01. https://doi.org/10.1007/s00431-018-3297-5 PMID: 30499051.

32. Fernandez-Cooke E, Barrios Tascón A, Sánchez-Manubens J, Antón J, Grasa Lozano CD, Aracil Santos J, et al. Epidemiological and clinical features of Kawasaki disease in Spain over 5 years and risk factors for aneurysm development. (2011–2016): KAWA-RACE study group. PLoS One. 2019; 14(5): e0215665. Epub 2019/05/21. https://doi.org/10.1371/journal.pone.0215665 PMID: 31107862

33. Furukawa T, Kishiro M, Akimoto K, Nagata S, Shimizu T, Yamashiro Y. Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease. Archives of disease in childhood. 2008; 93(2):142–6. Epub 2007/10/27. https://doi.org/10.1136/adc.2007.126144 PMID: 17962370.

34. Gámez-González LB, Hamada H, Cisneros Castro M, Honda T, Yasukawa K, Takanashi JI. Vital Signs as Predictor Factors of Intravenous Immunoglobulin Resistance in Patients With Kawasaki Disease. Clin Pediatr (Phila). 2018; 57(10):1148–53. Epub 2018/03/01. https://doi.org/10.1177/ 0009922818759320 PMID: 29486579.

35. Ha KS, Lee J, Jang GY, Lee J, Lee KC, Son CS, et al. Value of neutrophil-lymphocyte ratio in predicting outcomes in Kawasaki disease. Am J Cardiol. 2015; 116(2):301–6. Epub 2015/05/16. https://doi.org/10.1016/j.amjcard.2015.04.021 PMID: 25975725.

36. Hashino K, Ishii M, Iemura M, Akagi T, Kato H. Re-treatment for immune globulin-resistant Kawasaki disease: A comparative study of additional immunoglobulin and steroid pulse therapy. Pediatrics International 2001; 43:211–7. https://doi.org/10.1111/j.1442-200x.2001.01373.x PMID: 11380911

37. Hsieh KS, Weng KP, Lin CC, Huang TC, Lee CL, Huang SM. Treatment of acute Kawasaki disease: aspirin’s role in the febrile stage revisited. Pediatrics. 2004; 114(6):e689–93. Epub 2004/11/17. https://doi.org/10.1542/peds.2004-1037 PMID: 15545617.

38. Hua W, Ma F, Wang Y, Fu S, Wang W, Xie C, et al. A new scoring system to predict Kawasaki disease with coronary artery lesions. Clin Rheumatol. 2019; 38(4):1099–107. Epub 2018/12/14. https://doi.org/10.1007/s10067-018-4393-7 PMID: 30523553.

39. Hwang JY, Lee KY, Rhim JW, Youn YS, Oh JH, Han JW, et al. Assessment of intravenous immunoglobulin non-responders in Kawasaki disease. Archives of disease in childhood. 2011; 96(11):1088–90. Epub 2010/06/17. https://doi.org/10.1136/adc.2010.184101 PMID: 20551193.

40. Iwashima S, Kimura M, Ishikawa T, Ohtsuki T. Importance of C-reactive protein level in predicting non-response to additional intravenous immunoglobulin treatment in children with Kawasaki disease: a retrospective study. Clin Drug Invest. 2011; 31(3):191–9. https://doi.org/10.1007/s10067-010-0393-7 PMID: 21456105

41. Kawamura Y, Takeshita S, Kanai T, Yoshida Y, Nonoyama S. The Combined Usefulness of the Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios in Predicting Intravenous Immunoglobulin Resistance with Kawasaki Disease. J Pediatr. 2016; 178:281–4.e1. Epub 2016/10/30. https://doi.org/10.1016/j.jpeds.2016.07.035 PMID: 27526622.

42. Kim HK, Oh J, Hong YM, Sohn S. Parameters to guide retreatment after initial intravenous immunoglobulin therapy in Kawasaki disease. Korean Circ J. 2011; 41(7):379–84. Epub 2011/08/24. https://doi.org/10.4070/kcj.2011.41.7.379 PMID: 21860639

43. Kimura M, Harazaki M, Fukuoka T, Asakura I, Sakai H, Kamimaki T, et al. Targeted use of prednisolone with the second IVIG dose for refractory Kawasaki disease. Pediatr Int. 2017; 59(4):397–403. Epub 2016/10/16. https://doi.org/10.1111/ped.13190 PMID: 27743415.

44. Kong WX, Ma FY, Fu SL, Wang W, Xie CH, Zhang YY, et al. Biomarkers of intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. World J Pediatr. 2019; 15(2):168–75. Epub 2019/02/28. https://doi.org/10.1007/s12519-019-00234-6 PMID: 30809758.

45. Kuo HC, Liang CD, Wang CL, Yu HR, Hwang KP, Yang KD. Serum albumin level predicts initial intravenous immunoglobulin treatment failure in Kawasaki disease. Acta Paediatr. 2010; 99(10):1578–83. Epub 2010/05/25. https://doi.org/10.1111/j.1651-2227.2010.01875.x PMID: 20491705.
46. Lee HY, Song MS. Predictive factors of resistance to intravenous immunoglobulin and coronary artery lesions in Kawasaki disease. Korean J Pediatr. 2016; 59(12):477–82. Epub 2017/02/15. https://doi.org/10.3345/kjp.2016.59.12.477 PMID: 28194213

47. Liu FF, Liu HH, Qiu Z, Wang JJ, Samadli S, Wu Y, et al. Clinical observation of noncoronary cardiac abnormalities in Chinese children with Kawasaki disease. Eur J Clin Invest. 2020; 50(4):e13210. Epub 2020/02/16. https://doi.org/10.1111/eji.13210 PMID: 32061097.

48. Loomba R, Raskin A, Gudausky T, Kirkpatrick E. Role of the Egami Score in Predicting Intravenous Immunoglobulin Resistance in Kawasaki Disease Among Different Ethnicities. Am J Ther. 2015; 23(6):e1293–e9. https://doi.org/10.1097/MJT.0000000000000045 PMID: 25611359

49. Maggio MC, Corsello G, Prinzi E, Cimaz R. Kawasaki disease in Sicily: clinical description and markers of disease severity. Ital J Pediatr. 2016; 42(1):92. Epub 2016/11/04. https://doi.org/10.1186/s13052-016-0306-z PMID: 27806720

50. Mamtani M, Matsubara T, Shimizu C, Furukawa S, Akagi T, Onouchi Y, et al. Association of CCR2-CCR5 haplotypes and CCL3L1 copy number with Kawasaki Disease, coronary artery lesions, and IVIG responses in Japanese children. PLoS One. 2010; 5(7):e11458. Epub 2010/07/16. https://doi.org/10.1371/journal.pone.0011458 PMID: 20628649

51. Okuma Y, Suda K, Nakaoka H, Katsube Y, Mitani Y, Yoshikane Y, et al. Serum Tenascin-C as a Novel Predictor for Risk of Coronary Artery Lesion and Resistance to Intravenous Immunoglobulin in Kawasaki Disease—A Multicenter Retrospective Study. Circ J. 2016; 80(11):2376–81. Epub 2016/10/28. https://doi.org/10.1253/circj.CJ-16-0563 PMID: 27746411.

52. Ou-Yang MC, Kuo HC, Lin IC, Sheen JM, Huang FC, Chen CC, et al. Plasma clusterin concentrations may predict resistance to intravenous immunoglobulin in patients with Kawasaki disease. Scientific WorldJournal. 2013; 2013:382523. Epub 2013/08/21. https://doi.org/10.1155/2013/382523 PMID: 23956692

53. Park HM, Lee DW, Hyun MC, Lee SB. Predictors of nonresponse to intravenous immunoglobulin therapy in Kawasaki disease. Korean J Pediatr. 2013; 56(2):75–9. Epub 2013/03/14. https://doi.org/10.3345/kjp.2013.56.2.75 PMID: 23482814

54. Sabhanwai T, Manhioth C, Benseler SM, Tyrrell PN, Chahal N, Yeung RSM, et al. Comparison of Factors Associated With Coronary Artery Dilation Only Versus Coronary Artery Aneurysms in Patients With Kawasaki Disease. American Journal of Cardiology. 2009; 104(12):1743–7. https://doi.org/10.1016/j.amjcard.2009.07.062 PMID: 19962487

55. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr. 2007; 166(2):131–7. Epub 2007/02/08. https://doi.org/10.1007/s00431-006-0223-z PMID: 16896641.

56. Sittiwangkul R, Pongprut Y, Silvilairat S, Phromphutkul C. Management and outcome of intravenous gammaglobulin-resistant Kawasaki disease. Singapore Med J 2006; 47(9):780–4. PMID: 16924360

57. Sittiwangkul R, Pongprut Y, Silvilairat S, Phromphutkul C. Delayed diagnosis of Kawasaki disease: risk factors and outcome of treatment. Ann Trop Paediatr. 2011; 31(2):109–14. Epub 2011/05/18. https://doi.org/10.1186/s13052-011-0005-7 PMID: 21575314.

58. Tajima M, Shiozawa Y, Kagawa J. Early Appearance of Principal Symptoms of Kawasaki Disease is a Risk Factor for Intravenous Immunoglobulin Resistance. Pediatr Cardiol. 2015; 36(6):1159–65. Epub 2015/03/11. https://doi.org/10.1007/s00246-015-1136-2 PMID: 25753685.

59. Tan XH, Zhang XW, Wang XY, He XQ, Fan C, Lyu TW, et al. A new model for predicting intravenous immunoglobulin-resistant Kawasaki disease in Chongqing: a retrospective study on 5277 patients. Scientific reports. 2019; 9(1):1722. Epub 2019/02/12. https://doi.org/10.1038/s41598-019-39330-y PMID: 30742060

60. Teraguchi M, Ogino H, Yoshimura K, Taniuchi S, Kino M, Okazaki H, et al. Steroid pulse therapy for children with intravenous immunoglobulin therapy-resistant Kawasaki disease: A prospective study. Pediatric Cardiology. 2013; 34(4):959–63. https://doi.org/10.1007/s00246-012-0589-9 PMID: 23184018

61. Tremoulet AH, Best BM, Song S, Wang S, Corinladesi E, Eichenfield JR, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. J Pediatr. 2008; 153(1):117–21. Epub 2008/06/24. https://doi.org/10.1016/j.jpeds.2007.12.021 PMID: 18571548

62. Türkçuç S, Yıldız K, Acar C, Dundar HA, Kir M, Ünsal E. Risk factors of intravenous immunoglobulin resistance and coronary arterial lesions in Turkish children with Kawasaki disease. Turk J Pediatr. 2020; 62(1):1–9. Epub 2020/04/08. https://doi.org/10.24953/turkjped.2020.01.001 PMID: 32253860.

63. Uehara R, Delay ED, Maddox RA, Holman RC, Nakamura Y, Yashiro M, et al. Analysis of potential risk factors associated with nonresponse to initial intravenous immunoglobulin treatment among Kawasaki disease patients in Japan. Pediatr Infect Dis J. 2008; 27(2):155–60. Epub 2008/01/05. https://doi.org/10.1097/INF.0b013e31815922b5 PMID: 18174868.
Is there an association between IVIG and CAL in KD?

64. Wang H, Shang J, Tong M, Song Y, Ruan L. Evaluation of left ventricular function in immunoglobulin-resistant children with Kawasaki disease: a two-dimensional speckle tracking echocardiography study. Clin Cardiol. 2019; 42(8):753–9. Epub 2019/06/08. https://doi.org/10.1002/clc.23213 PMID: 31173382

65. Weng KP, Hsieh KS, Ho TY, Huang SH, Lai CR, Chiu YT, et al. IL-1B polymorphism in association with initial intravenous immunoglobulin treatment failure in Taiwanese children with Kawasaki disease. Circ J. 2010; 74(3):544–51. Epub 2010/01/19. https://doi.org/10.1253/circj.cj-09-0664 PMID: 20081319.

66. Xie T, Wang Y, Fu S, Wang W, Xie C, Zhang Y, et al. Predictors for intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. Pediatr Rheumatol Online J. 2017; 15(1):17. Epub 2017/03/23. https://doi.org/10.1186/s12969-017-0149-1 PMID: 28320400

67. Xu H, Fu S, Wang W, Zhang Q, Hu J, Gao L, et al. Predictive value of red blood cell distribution width for coronary artery lesions in patients with Kawasaki disease. Cardiol Young. 2016; 26(6):1151–7. Epub 2015/10/06. https://doi.org/10.1017/S1047951115002140 PMID: 26435202.

68. Yi D, Kim J, Choi E, Choi J, Yang H. Hepatobiliary risk factors for clinical outcome of Kawasaki disease in children. BMC Pediatrics. 2014; 14:51. https://doi.org/10.1186/s12887-014-0511-1 PMID: 24548331.

69. Yoshimura K, Kimata T, Mino K, Uchiyama T, Tsuji S, Kaneko K. N-terminal pro-brain natriuretic peptide and risk of coronary artery lesions and resistance to intravenous immunoglobulin in Kawasaki disease. J Pediatr. 2013; 162(6):1205–9. Epub 2013/01/08. https://doi.org/10.1016/j.jpeds.2012.11.026 PMID: 23290510.

70. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. Archives of disease in childhood. 2015; 100(11):1084–8. Epub 2015/06/27. https://doi.org/10.1136/archdischild-2014-307536 PMID: 26111818.

71. Dietz SM, van Stijn D, Burgner D, Levin M, Kuipers IM, Hutten BA, et al. Dissecting Kawasaki disease: a state-of-the-art review. Eur J Pediatr. 2017; 176(8):995–1009. Epub 2017/06/29. https://doi.org/10.1007/s00431-017-2937-5 PMID: 28656474.

72. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. The Journal of pediatrics. 2006; 149(2):237–40. Epub 2006/08/05. https://doi.org/10.1016/j.jpeds.2006.03.050 PMID: 16887442.

73. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation. 2006; 113(22):2606–12. Epub 2006/06/01. https://doi.org/10.1161/CIRCULATIONAHA.105.592865 PMID: 16735679.

74. Liu L, Luo C, Hua Y, Wu M, Shao S, Liu X, et al. Risk factors associated with progression and persistence of small- and medium-sized coronary artery aneurysms in Kawasaki disease: a prospective cohort study. European journal of pediatrics. 2020; 179(6):891–900. Epub 2020/01/26. https://doi.org/10.1007/s00431-019-03492-8 PMID: 31980953.

75. Liu X, Zhou K, Hua Y, Wu M, Liu L, Shao S, et al. Prospective Evaluation of Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio for Intravenous Immunoglobulin Resistance in a Large Cohort of Kawasaki Disease Patients. The Pediatric infectious disease journal. 2020; 39(10):229–31. Epub 2020/01/10. https://doi.org/10.1097/INF.0000000000002566 PMID: 31917754.

76. Shao S, Luo C, Zhou K, Hua Y, Wu M, Liu L, et al. Predictive value of serum procalcitonin for both initial and repeated immunoglobulin resistance in Kawasaki disease: a prospective cohort study. Pediatric rheumatology online journal. 2019; 17(1):78. Epub 2019/11/30. https://doi.org/10.1007/s12969-019-0379-5 PMID: 31775782.

77. Shao S, Luo C, Zhou K, Hua Y, Wu M, Liu L, et al. The role of age-specific N-terminal pro-brain natriuretic peptide cutoff values in predicting intravenous immunoglobulin resistance in Kawasaki disease: a prospective cohort study. Pediatric rheumatology online journal. 2019; 17(1):65. Epub 2019/09/20. https://doi.org/10.1186/s12969-019-0368-8 PMID: 31533770.

78. Zheng X, Zhang Y, Liu L, Yue P, Wang C, Zhou K, et al. N-terminal pro-brain natriuretic peptide as a biomarker for predicting coronary artery lesion of Kawasaki disease. Scientific reports. 2020; 10(1):5130. Epub 2020/03/22. https://doi.org/10.1038/s41598-020-62043-6 PMID: 32198398.

79. Furusho K, Kamiya T, Nakano H, Kyosawa N, Shinomiya K, Hayashieda T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet. 1984; 2(8411):1055–8. Epub 1984/11/10. https://doi.org/10.1016/s0140-6736(84)90504-6 PMID: 6209513.

80. Song MS. Predictors and management of intravenous immunoglobulin-resistant Kawasaki disease. Korean J Pediatr. 2019; 62(4):119–23. Epub 2019/04/20. https://doi.org/10.3345/kjp.2019.00150 PMID: 30999718.

81. Chan H, Chi H, You H, Wang M, Zhang G, Yang H, et al. Indirect-comparison meta-analysis of treatment options for patients with refractory Kawasaki disease. BMC pediatrics. 2019; 19(1):158. Epub 2019/05/19. https://doi.org/10.1186/s12867-019-1504-9 PMID: 31101091
82. Eun LY. Infliximab, Is It Really a New Horizon for the Treatment of Kawasaki Disease? Korean Circ J. 2019; 49(2):192–3. Epub 2019/01/30. https://doi.org/10.4070/kcj.2018.0460 PMID: 30693682

83. Chandelia S. A meta-analysis of re-treatment for intravenous immunoglobulin-resistant Kawasaki disease. Cardiol Young. 2015; 25(6):1228. Epub 2015/04/24. https://doi.org/10.1017/C1047951115000487 PMID: 25904322.

84. Son MB, Gauvreau K, Burns JC, Corinaldesi E, Tremoulet AH, Watson VE, et al. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. J Pediatr. 2011; 158(4):644–9.e1. Epub 2010/12/07. https://doi.org/10.1016/j.jpeds.2010.10.012 PMID: 21129756.

85. Mori M, Hara T, Kikuchi M, Shimizu H, Miyamoto T, Iwashima S, et al. Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: a phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial. Scientific reports. 2018; 8(1):1994. Epub 2018/02/02. https://doi.org/10.1038/s41598-017-18387-7 PMID: 29386515;

86. Duignan S, Doyle SL, McMahon CJ. Refractory Kawasaki disease: diagnostic and management challenges. Pediatric Health Med Ther. 2019; 10:131–9. Epub 2019/12/06. https://doi.org/10.2147/PHMT.S165935 PMID: 31802968