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Research Article

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The Prevalence of Cardiac Complications among Iranian Kawasaki Patients: A Systematic Review and Meta-analysis

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Abstract

Objective: This study aimed to evaluate the prevalence of cardiac complications in Iranian children with Kawasaki disease.

Methods: The present meta-analysis was performed in keeping with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement. We used the keywords ["Kawasaki disease"], ["cardiac complications"], ["cardiac aneurysm"], ["myocarditis"], and ["vascular ectasia"] to retrieve potentially relevant studies in the Medline, Cochrane Library database, and the Clinicaltrials.gov website until August 2022. Statistical analyses were performed using the Review Manager (RevMan) software package, version 5.0; Cochrane Collaboration; and Comprehensive Meta-Analysis software version 2.2 (BioStat Inc). All P values were 2-tailed, and statistical significance was set at 0.05.

Results:

Our meta-analysis showed that both myocarditis and coronary aneurysms with the same prevalence of 3% are the most frequent cardiac complication among Iranian Kawasaki patients.

Conclusion:

To conclude, it is clear that KD is associated with several cardiovascular outcomes. While aneurysms are the most recognized side effects of this disease, other complications, such as myocarditis, KDSS, valvular abnormalities, and endothelial dysfunction, are now increasingly recognized. Early identification and proper treatment of these complications are of high importance.

Keywords: Kawasaki, Cardiac Complication, Iran

Introduction

Kawasaki disease (KD) refers to an acute vasculitis of unknown etiology seen in all populations (1, 2). In developed countries, it is children's main cause of acquired cardiovascular disease. This disease mostly affects children under five years of age (80%), and the average age of onset is two to three years (1, 2). Also, males are more predisposed to KD than females. Affecting the medium vessels,this disease appears as continuous fever, erythema of the lips and oral mucosa, bilateral non-purulent conjunctivitis, skin outbreaks, swelling and redness of the hands and foot and conjunctivitis, and is usually accompanied by a short period of respiratory or gastrointestinal symptoms (1, 2). Since cardiac side effects are the main cause for concern, it is essential to employ effective proceduresto diagnose and treat this self-limited disease. If no treatment is given, coronary artery aneurysms (CAAs) may occur in 15 to 25% of children with KD (3, 4). Arterial inflammation in coronary arteries is necrotic and might start from the endothelium and infiltrate the walls of the coronary arteries within the first 2 weeks of the disease, andat last, lead to a saccular aneurysm. A type of subacute or chronic vasculitis may occurin lymphocytes, causing that plasma cells and eosinophils to continue for weeks or years and leading to fusiform aneurysms. Next, in vessels affected by subacute or chronic vasculitis, smooth myofibroblast muscle cells expand and cause progressive coronary artery stenosis (5, 6). It appears that myocarditis is an intrinsic part of KD and may be seen in all patients (7, 8). Fujiwara et al. (1978) reported the findings of autopsy studies on 20 patients having KD (9). The authors classified KD pathology into four clinical-pathological phases and noted pancarditis in histology. In the first 9 days of the disease, the main finding was carditis with edema and inflammatory cell infiltration in all three layers of the heart (9). This study explores the prevalence of cardiac complications in Iranian children with Kawasaki disease.

Method

The present meta-analysis was performed in keeping with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement.

Study selection criteria:

The community approach, intervention, comparison, and consequence were adopted for inclusion in the study. The target population was children with KD. 4,11,12 outcome measures encompassed CAA incidence, time until discharge, and complications in both groups.

Literature search strategy and data extraction:

We used the keywords ["Kawasaki disease"], ["cardiac complications"], ["cardiac aneurysm"], ["myocarditis"], and ["vascular ectasia"] to retrieve potentially relevant studies in the Medline, Cochrane Library database, and the Clinicaltrials.gov website until August 2022. Both English and non-English- literature were identified. 2 authors studied titles and abstracts to determine suitability for inclusion. Relevant articles were re-assessed by full-text review. Dispute, as study inclusion, was resolved by compromise.

Statistical analysis:

Heterogeneity between studies was calculated usingthe Q test, and the I2 statistical value was used to show the degree of heterogeneity between studies. Failsafe N test, Begg's regression and Egger's regression were used to estimate the spread bias. Meta-regression was performed to investigate risk factors thatwould introduce potential bias to overall effects, and the rate of studies was assessed with a random-effects regression model. In the meta-regression diagram, the size of the circle reflects the weight that each study gets in this meta-regression. We also used sensitivity (sensitivity analysis by the recurrent exclusion of 1 study at a time to confirm that any single study does not guide our primary results) and subgroup analyses to test the stability of our

meta-analysis. Statistical analyses were performed using the Review Manager (RevMan) software package, version 5.0; Cochrane Collaboration; and Comprehensive Meta-Analysis software version 2.2 (BioStat Inc). All P values were 2-tailed, and statistical significance was set at 0.05.

Results

Characteristics of Included Studies

A total of 4 studies consisting of 423 Iranian Kawasaki patients were included from 4 provinces(Babol, Tehran, Arak, Ahvaz). All the included studies were retrospective and the overall mean age of the patients was 33.5 ± 2.(table 1)

Meta-analysis of the Prevalence of Cardiac Complication of Kawasaki

Our meta-analysis showed that both myocarditis and coronary aneurysms with the same prevalence of 3%(95%CI:1-4%) are the most frequent cardiac complication among Iranian Kawasaki patients.
(figure 2,3)

Table1. Characteristics of the Included Studies Regarding the Prevalence of Cardiac Complication of Kawasaki

Author	year	Province	Design	Sample size	Mean age (month)	Prevalence of cardiac complication				
						Coronary aneurysm	Myocarditis	ectasia	Valvular involvement	Total
Mohammadi	2021	Babol	Retro	60	32±8	N/A	32/60	16/60	N/A	48/60
Sadeghi	2021	Tehran	Retro	190	36	26.3%	1.6%	N/A	0	27.9%
Ghandi	2018	Arak	Retro	69	33.49±24.31	1/69	4/69	N/A	4/69	12%
Shamsizadeh	2014	Ahvaz	Retro	104	33.6 ± 24.2	1/104	0	15/104	5/104	20%

Figure 2. Meta-analysis of the prevalence of coronary aneurysm among Iranian Kawasaki patients

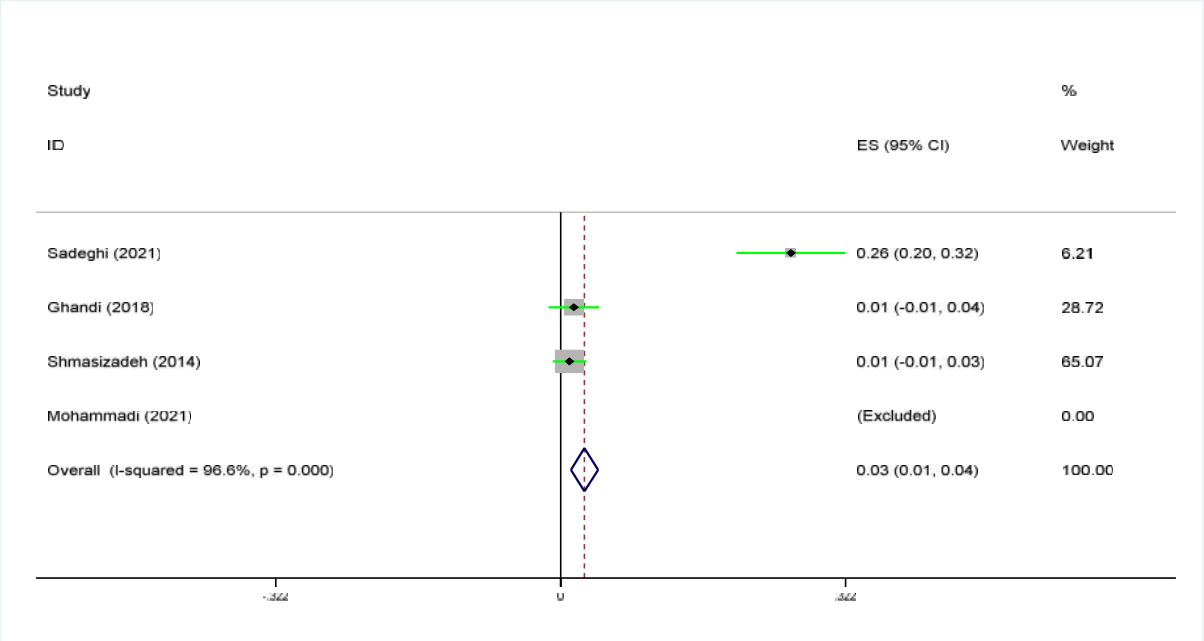
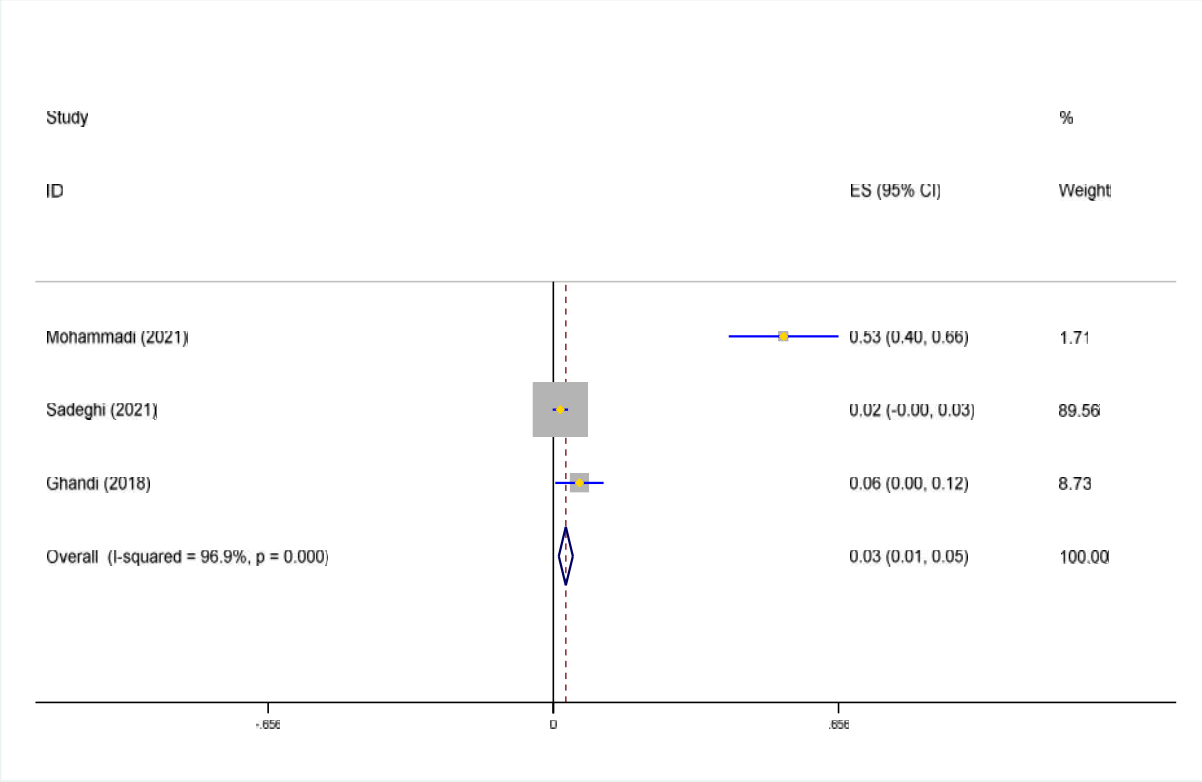


Figure 3. Meta-analysis of the prevalence of myocarditis among Iranian Kawasaki patients



Discussion

With the developments in echocardiography as well as the improvement of diagnostic skills of the physician, cardiac complications, especially CAA, may be detected in the early days of the disease from the inception of KD. Our findings indicated that almost one percentwas infected.Previous studies the world over have found that early detection of CAA helps distinguish KD from other febrile illnesses, indicating that echocardiography should be performed as soon as KD is first suspected (11-16). Second, the number of etiologic factors for KD may have increased over the years of study, ending up with more patients developing KD, although this is only a hypothesis because the chiefcontributorto KD remains unidentified. Some previous studies supported that quite a few unknown infectious agents may cause the onset of KD, even though the genetic history of patients may change the development of the disease (19-17).

Recent advances in treating KD would help to prevent the development of cardiac complications. The early administration of secondary IVIG for the early diagnosis of KD couldaffect the decreasing trend in the ratio of cardiac complications (20-24). CAAs detected on admission indicate the risk of subsequent coronary outcomes and help get patientsup to speedwith early treatment as well as first aid treatments. Our survey data showed that the number of patients receiving standard initial IVIG therapy (2 g/kg/day as a single) infusion increased annually, although mean sick days in IVIG administration barely changed (data not shown). Also, previous studies have reported lower rates of CAA in patients with KD who receive initial adjuvant treatments, as well as additional therapies for unresponsive primary IVIG, such as the use of corticosteroids, infliximab, or cyclosporine (25–35).

KD patients not reacting to initial IVIG treatment are at high risk of developing cardiac complications. Our findings showed that the annual rate of non-responders to initial IVIG

increased slightly after 2015, which isrelated to an increase in the proportion of cardiac complications. It is difficult to find out why the proportion of KD patients who do not react to the initial administration of IVIG has augmented recently. A previous study concentrating on seasonality in KD showed that unknown etiological factors of KD may vary between initial IVIG responders and non-responders, which may support our finding that the percentage of non-responders has increased after 2015. Another possible hypothesis is the latter. Subtle changes in the elements of IVIG because IVIG is derived from human donors, and the action mechanism of IVIG in the treatment of KD is unknown (36-39).

Conclusion

To conclude, it is clear that KD is associated with several cardiovascular outcomes. While aneurysms are the most recognized side effects of this disease, other complications, such as myocarditis, KDSS, valvular abnormalities, and endothelial dysfunction, are now increasingly recognized. Early identification and proper treatment of these complications are of high importance.

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