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Clinical and Laboratory Characteristics of Kawasaki Disease in Iran: A Systematic Review and Meta-analysis

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Abstract

Background

Kawasaki Disease (KD) is a common systemic vasculitis, which mostly develops in children under five years. Based on our knowledge no meta-analysis, studies have been conducted to evaluate the clinical and laboratory findings of KD in Iran. We aimed to evaluate these characteristics in Iranian children with KD.

Materials and Methods: In this Systematic review, online databases, including Medline, Scopus, Web of Science, EMBASE, Medlib, SID, Magiran, and Irandoc were searched until February 2020. The keywords of KD and characteristics were combined and searched. Search, and extraction of papers were performed by two authors independently. The prevalence rates of all clinical and laboratory characteristics of KD and involvement of other organs were analyzed by the random effect model using the STATA software (version 11.0).

Results: Twenty studies were included. In clinical findings among KD patients fever was 100%, change in oral cavity and lips was 82%, bilateral conjunctiva was 78%, rash was 74%, change in extremities was 62%, agitation was 53%, and cervical lymphadenopathy was 50%. In laboratory findings, ESR was 86%, CRP was 67%, leukocytosis was 62%, Hb<10 g/dl was 59%, thrombocytosis was 55%, SGOT elevated was 34%, sterile pyuria was 33%, albuminuria was 31%, and SGPT elevated was 30%. In involvement of other organ, desquamation was 57%, vomiting was 30%, arthritis was 28%, diarrhea was 24%, coronary complication was 17%, coronary aneurysm was 17%, arthralgia was 16%, cardiac involvement was 10%, aseptic meningitis was 6%, gallbladder hydrops was 5%, and BCG inoculation site was 3%.

Conclusion

The fever, erythrocyte sedimentation rate, and desquamation are the most prevalent clinical, laboratory, and involvement of other organ characteristics respectively.

Key Words: Children, Iran, Kawasaki disease, Meta-analysis.

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1- INTRODUCTION

Kawasaki Disease (KD) is a common systemic vasculitis, which mostly develops in children under five years (1). This disease is a cause of vascular inflammation, especially in coronary arteries (2). In recent decades, KD was replaced with rheumatic fever as the first heart disease in developed countries (3). The mean age of onset of KD overall is 2-3 years and men are more prone than women to developing it (2). According to KD described by Kawasaki in Japan in 1967, this disease is associated with fever, mucosal change, bilateral conjunctive injection, swelling or redness of hands and feet, and palm and sole erythema (4).

In addition to permanent fever, there are five clinical characteristics for KD diagnosis: pharyngeal erythema, oral mucus, cervical lymphadenopathy, hand and feet edema, and rash (4). Due to unknown causes of KD, diagnosis of this disease is based on clinical findings. A classic form of KD diagnosis is based on permanent fever (five days or more), and four out of five KD diagnostic criteria. However, the permanent fever and less than four items of five diagnostic criteria are used for the diagnosis of aseptic KD and an incomplete form of KD (2-5).

Along with these clinical findings, there are also important laboratory and echocardiography findings in diagnosis of KD such as leukocytosis, thrombocytosis, anemia, pyuria, increased erythrocyte sedimentation rate (ESR), increased serum levels of C-reaction protein (CRP), and abnormality of coronary arteries (in one quadrant of children) (6-8). Several studies have been conducted in Iran to evaluate the clinical and laboratory findings of KD in various regions such as Kermanshah (9), West Azerbaijan (10), Mazandaran (11), and Markazi provinces (12), and also Kashan city (13). Fever and mucocutaneous complications were reported in all these studies, but there is no agreement between the studies regarding other clinical and laboratory findings. Despite the importance of clinical and laboratory findings for the diagnosis of the KD, there was no meta-analysis study to evaluate these findings in Iran. So, this gap was addressed in this study. This study aimed to evaluate the most important clinical, laboratory, and involvement of other organ characteristics.

2- MATERIALS AND METHODS

2-1. Eligibility criteria

Participants, interventions, comparison, outcomes, and study (PICOS) was used to formulate the review objective and inclusion criteria. Participants**:** children with KD under five years in Iran. Intervention: there was no intervention in this study. Comparison: there was no comparison in this study. Outcomes: clinical findings (fever, bilateral conjunctiva, change in oral cavity and lips, change in extremities, agitation, cervical lymphadenopathy, rash, vomiting, and diarrhea); 2) all studies that assessed the laboratory findings (ESR>40 mm/h, CRP>3.0+, albuminuria, leukocytosis >15000 WBC/mm^3, thrombocytosis (platelet>450000 per microliter), and Hb<10g/dL); and 3) all studies that assessed the involvement in other organs (sterile pyuria, cardiac involvement, BCG inoculation site, arthralgia, desquamation, arthritis, and coronary aneurysm). Study: all cross sectional studies that assessed the findings of KD.

2-2. Included studies

This meta-analysis study was conducted with no restrictions regarding the year and language of publication (all Persian and English studies were included). Other studies that were conducted in other countries, case report studies, and studies that assessed the risk factors of KD were excluded from this meta-analysis.

2-3. Search strategy

All relevant keywords were used to search the databases. Search terms and search strategy are shown in **Table.1**. Electronic databases including PubMed, Scopus, ISI Web of Science, Medlib, SID, Iranmedex, Magiran, and Irandoc were searched by the two authors of the present study (YGH and MB) until February 2020. In addition, the reference list of the selected studies was screened for additional studies. We contacted authors of the selected studies to obtain further studies.

Table-1: Search strategy and search terms.

(Kawasaki[Title/Abstract] OR KD[Title/Abstract] OR Kawasaki diseases[Title/Abstract] OR mucocutaneous lymph node syndrome[Title/Abstract] OR Kawasaki diseases[MeSH Terms]) AND (clinical findings [Title/Abstract] OR laboratory findings[Title/Abstract] OR involvement[Title/Abstract] OR fever[Title/Abstract] OR bilateral conjunctiva[Title/Abstract] OR change in oral cavity[Title/Abstract] OR change in extremities[Title/Abstract] OR agitation[Title/Abstract] OR cervical lymphadenopathy[Title/Abstract] OR rash[Title/Abstract] OR ESR[Title/Abstract] OR CRP[Title/Abstract] OR albuminuria[Title/Abstract] OR leukocytosis[Title/Abstract] OR thrombocytosis[Title/Abstract] OR Hb[Title/Abstract] OR sterile pyuria[Title/Abstract] OR SGOT[Title/Abstract] OR SGPT[Title/Abstract] OR vomiting[Title/Abstract] OR diarrhea[Title/Abstract]) OR cardiac involvement[Title/Abstract] OR BCG inoculation site[Title/Abstract] OR arthralgia[Title/Abstract] OR desquamation[Title/Abstract] OR arthritis[Title/Abstract] OR coronary aneurysm[Title/Abstract] OR coronary complication[Title/Abstract] OR aseptic meningitis[Title/Abstract] OR gallbladder hydrops[Title/Abstract]) AND (Iran [Title/Abstract]).

2-4. Data collection

Two authors (YGH and MB) selected the studies and entered their data into the EndNote Software for assessment. Then, extraction of data was conducted by two authors independently. All disagreements were resolved through discussion with a third party. Extracted data were recorded in electronic form using STATA software (v.11). The Kappa coefficient statistic was calculated to determine agreement between two authors (88.7%). The extracted data were entered into the STATA software (v.11).

2-5. Quality assessment

The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) was used to assess the quality of the studies (14). The following items were evaluated for each study by the two authors (YGH and MB): 1) inclusion and exclusion criteria, 2) methods of selection of participants, 3) definition of outcome, 4) definition of exposure, and 5) calculation of the sample size. Studies with all items were considered as high quality study. The studies with five star-items were considered high-quality studies and those with four star-items or less were considered low quality studies.

2-6. Effect size, heterogeneity, publication bias, and analysis

In this meta-analysis, the prevalence rates of clinical and laboratory findings were synthesized using the random effect model. The I^2 statistic test was used to assess the heterogeneity (15). Publication bias was assessed by Begg's (16), and Egger's (17) tests and also by a visualized funnel plot. All analyses were performed at 95% Confidence Interval (CI) using the STATA software, version 11.0 (StataCorp, College Station, TX, USA).

3- RESULTS

3-1. Clinical characteristics

We achieved a total of 252 studies including 239 studies through searching the electronic databases and 13 studies through screening the reference list of the selected studies until February 2020. At first, we excluded a number of 113 duplicate studies. The number of 115 clearly irrelevant studies was excluded through screening their titles and abstracts. Also, we excluded four studies after

reading their full-text, because they were case report studies. Finally, 20 studies were included in this meta-analysis (**Figure.1**). A total of 1,141 participants were included in this meta-analysis from 2000 to 2019. All studies were cross-sectional and reported the prevalence of clinical and laboratory findings, and findings regarding the involvement of other organs in patients with KD. Quality assessment of 17 studies was performed using the STROB checklist. Eight studies had a high quality (12, 18-22), and assessing the quality of three other studies was not possible, because their full-texts were not available. We extracted the data from the abstracts of these three studies (9, 23, 24). Other studies had a low quality (10, 11, 25-33) (**Table.2**).

The mean age of the participants was 42.09±14.17 months. The male/female sex ratio was 1.63 and 62% of the KD patients were male. Most of the KD cases were diagnosed in winter (29.6%), and then in spring (26.8%) season.

Table-2: General **c**haracteristics of included studies.

1st Author, Year	Province	Mean age (month)	Duration of studies (year)	Gender	Sample	Quality	Reference
Ghandi, 2019	Markazi	42.5	5	Both	69	*****	(12)
Sharif, 2001	Tehran	40	5	Both	63	***	(33)
Ghini, 2002	Kermanshah	50.9	5	Both	23	Abstract	(9)
Kordi Darian, 2007	Isfahan	24	5	Both	45	**	(28)
Mansouri, 2008	Kurdistan	42	5	Both	20	***	(29)
Emami-Moghadam, 2010	Khuzestan	30	4	Both	25	****	(26)
Mosayebi, 2010	Kashan	24	10	Both	69	***	(30)
Sadeghi, 2001	Fars	36	3	Both	50	*****	(32)
Safar, 2003	Mazandaran	38	5	Both	25	***	(11)
Tavasoli, 2005	Tehran	40	5	Both	30	Abstract	(24)
Asadi-Pouya, 2006	Fars	46.6	12	Both	113	*****	(18)
Ayazi, 2007	Qazvin	59.4	10	Both	29	****	(25)
Moradinejad, 2007	Tehran	24	10	Both	159	*****	(20)
Golestan, 2009	Yazd	49	10	Both	48	***	(27)
Mahmudzadeh, 2007	East Azerbaijan	24	6	Both	42	**	(10)
Ghotbi, 2011	Kurdistan	56.4	5	Both	20	Abstract	(23)
Rahmati, 2012	Hormozgan	79.5	3	Both	83	***	(31)
Sedighi, 2014	Hamadan	54	10	Both	73	****	(21)
Shamsizadeh, 2014	Khuzestan	33.6	10	Both	104	*****	(22)
Cheraghali, 2018	Golestan	48	7	Both	51	*****	(19)

3-5. Accuracy of prediction of PRISM III

The results indicated that the PRISM III model in the study therapeutic center has high diagnostic power and differentiation for mortality of children with influenza with the area under the curve of 0.881 (**Figure. 2**). In addition, considering the cut-off point 14, the sensitivity and specificity of the PRISM III model in estimating the mortality of children with influenza are equal to 87.5% and 85.7%, respectively. The mortality estimation models provide excellent visibility of disease progression for medical staff such that the obtained results are significantly

effective for making the decision by the medical staff and the patient. In addition, children with a mean age of 46.22 months who were admitted to Tabriz Children's Hospital with a diagnosis of influenza were examined for short-term outcome based on the PRISM III model.

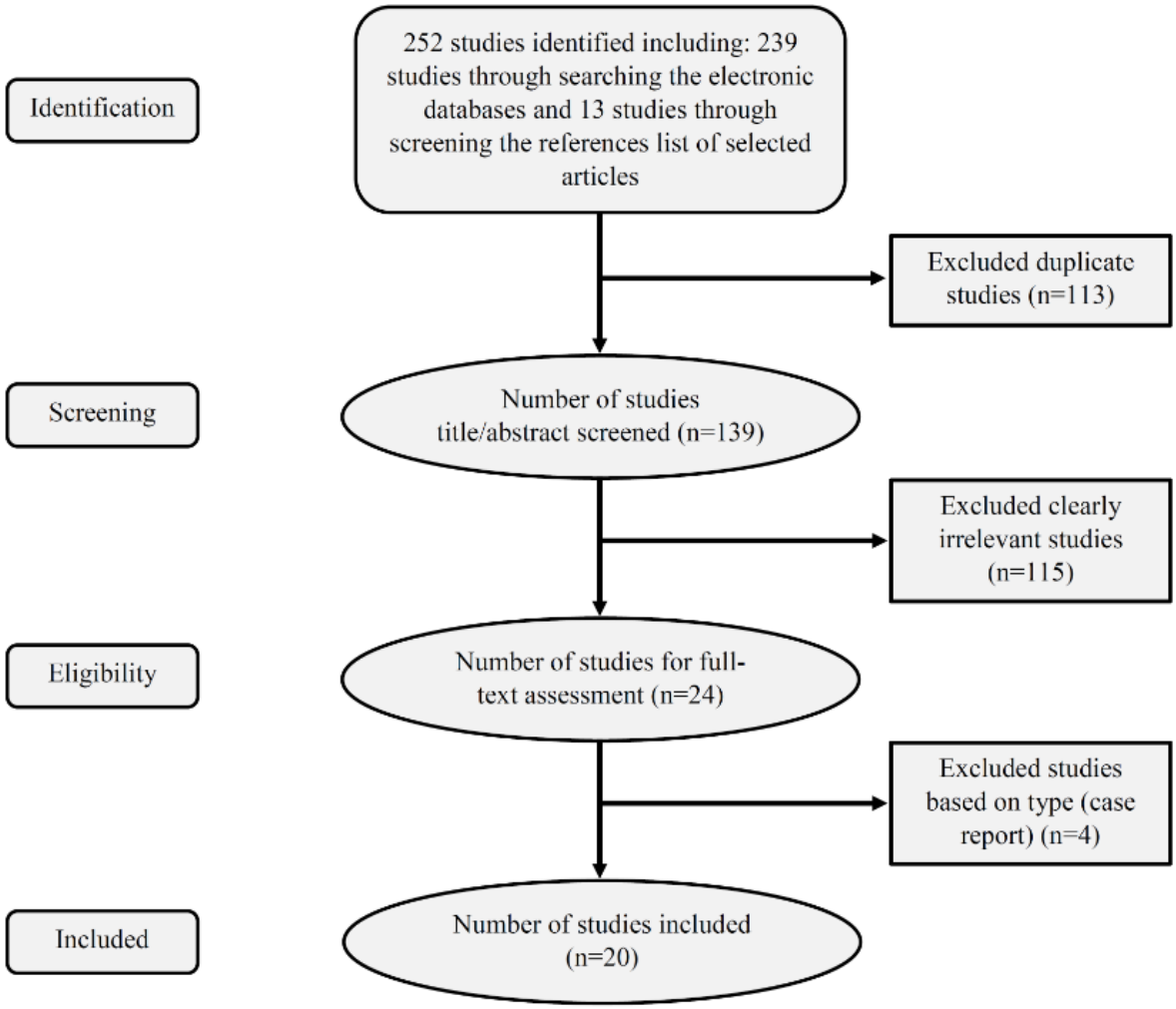

Fig. 1: Flow of information through the different phases of the systematic review.

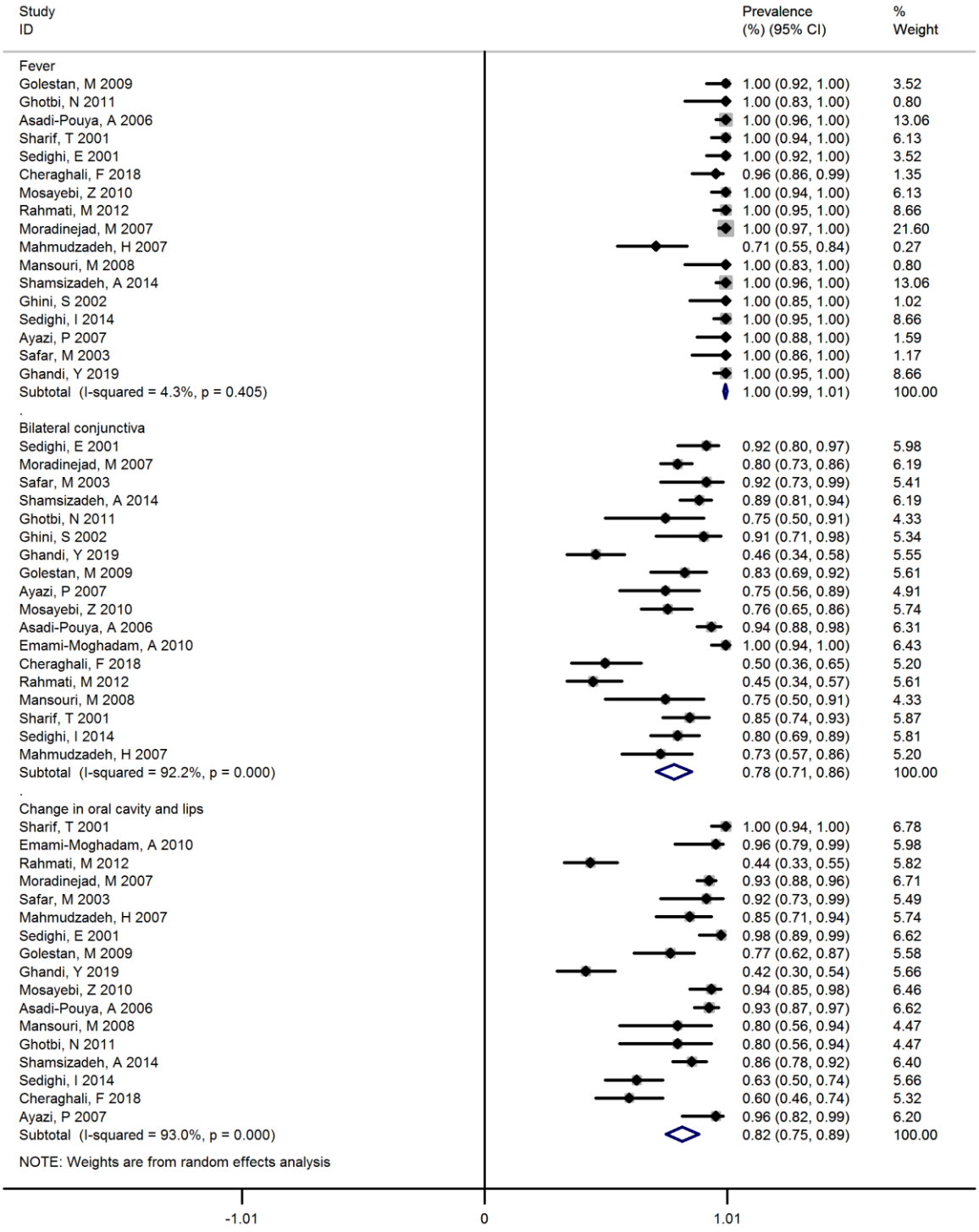

Fig. 2(a): Forest plot of the clinical findings of KD.

3-2. Synthesis of the results

The prevalence rates of clinical findings among patients with KD are shown in **Figure.2 a, b**. According to these forest plots, the prevalence of fever was 100% (95% CI: 99%, 100%, I^2=4.3%, 17

studies); prevalence of change in oral cavity and lips was 82% (95% CI: 75%, 89%, I^2=93%, 17 studies); prevalence of bilateral conjunctiva was 78% (95% CI: 71%, 86%, I^2=92.2%, 18 studies); prevalence of rash was 74% (95% CI: 69%, 79%, I^2=65.2%, 16 studies); prevalence of change in extremities was 62% (95% CI: 50%, 74%, I^2=90.8%, 10 studies); prevalence of agitation was 53% (95% CI: 24%, 81%, I^2=98%, 5 studies); and the prevalence of cervical lymphadenopathy was 50% (95% CI: 41%, 60%, I^2=88.2%, 16 studies).

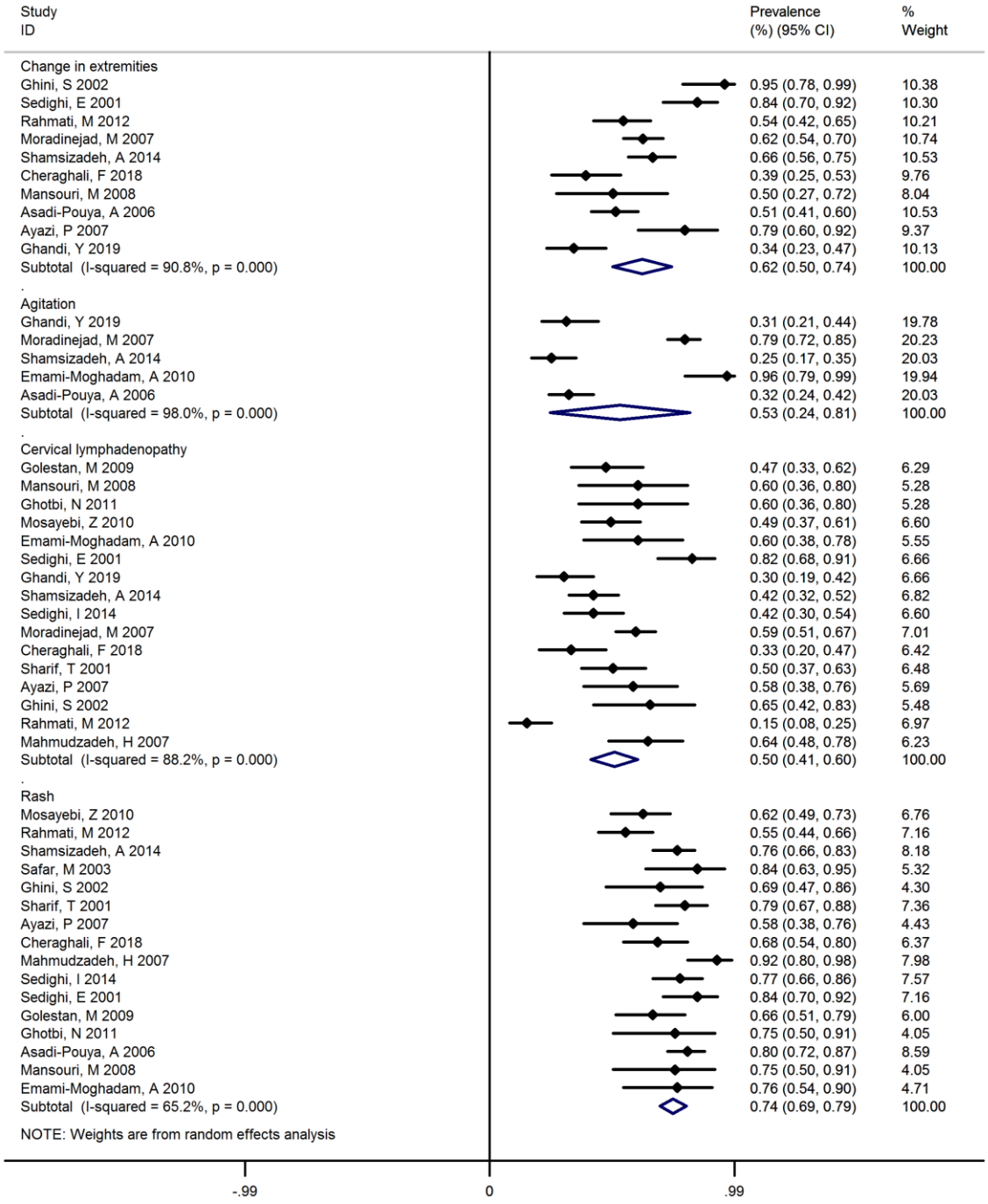

Fig. 2(b): Forest plot of the clinical findings of KD.

Furthermore, the prevalence rates of laboratory findings among patients with KD are shown in **Figure.3**. According to these results, the prevalence of ESR>40 mm/h was 86% (95% CI: 81%, 91%, I^2=88.5%, 15 studies); prevalence of CRP>3.0+ was 67% (95% CI: 53%, 81%, I^2=92.6%, 9 studies); prevalence of leukocytosis (>15000 WBC/mm^3) was 62% (95% CI: 47%, 76%, I^2=96.0%, 11 studies); prevalence of Hb<10g/dL was 59% (95% CI: 29%, 89%, I^2=99.0%, 5 studies); prevalence of thrombocytosis (platelet>450000 per microliter) was 55% (95% CI: 42%, 69%, I^2=91.1%, 8 studies); prevalence of serum glutamic oxaloacetic transaminase (SGOT) elevated was 34% (95% CI: 18%, 49%, I^2=88.6%, 5 studies); prevalence of sterile pyuria was 33% (95% CI: 23%, 43%, I^2=86.5%, 9 studies); prevalence of albuminuria was 31% (95% CI: 12%, 49%, I^2=96.2%, 5 studies); and the prevalence of serum glutamic pyruvic transaminase (SGPT) elevated was 30% (95% CI: 23%, 37%, I^2=26.4%, 4 studies) among the KD patients.

The prevalence rates of involvement of other organs among patients with KD are shown in **Figure.4**. Prevalence of desquamation was 57% (95% CI: 40%, 74%, I^2=91.3%, 6 studies); prevalence of vomiting was 30% (95% CI: 16%, 44%, I^2=88.3%, 5 studies); prevalence of arthritis was 28% (95% CI: 17%, 40%, I^2=90.3%, 7 studies); prevalence of diarrhea was 24% (95% CI: 19%, 30%, I^2=58.8%, 8 studies); prevalence of coronary complication was 17% (95% CI: 12%, 22%, I^2=0.0%, 4 studies); prevalence of coronary aneurysm was 17% (95% CI: 2%, 33%, I^2=91.3%, 5 studies); prevalence of arthralgia was 16% (95% CI: 10%, 22%, I^2=48.2%, 4 studies); prevalence of total cardiac involvement was 10% (95% CI: 6%, 15%, I^2=0.0%, 4 studies); prevalence of aseptic meningitis was 6% (95% CI: 3%, 9%, I^2=0.0%, 3 studies); prevalence of gallbladder hydrops was 5% (95% CI: 2%, 8%, I^2=38.4%, 6 studies); and the prevalence of BCG inoculation site was 3% (95% CI: 0%, 6%, I^2=0.0%, 3 studies).

3-3. Publication bias and heterogeneity assessment

According to the results of I^2 statistics, there was no heterogeneity in the prevalence rates of fever, cardiac involvement, BCG inoculation site, and arthralgia. There was heterogeneity for other results. Also, the results of Begg's (P=0.042), and Egger's tests (P=0.047) indicate the presence of publication bias in the studies.

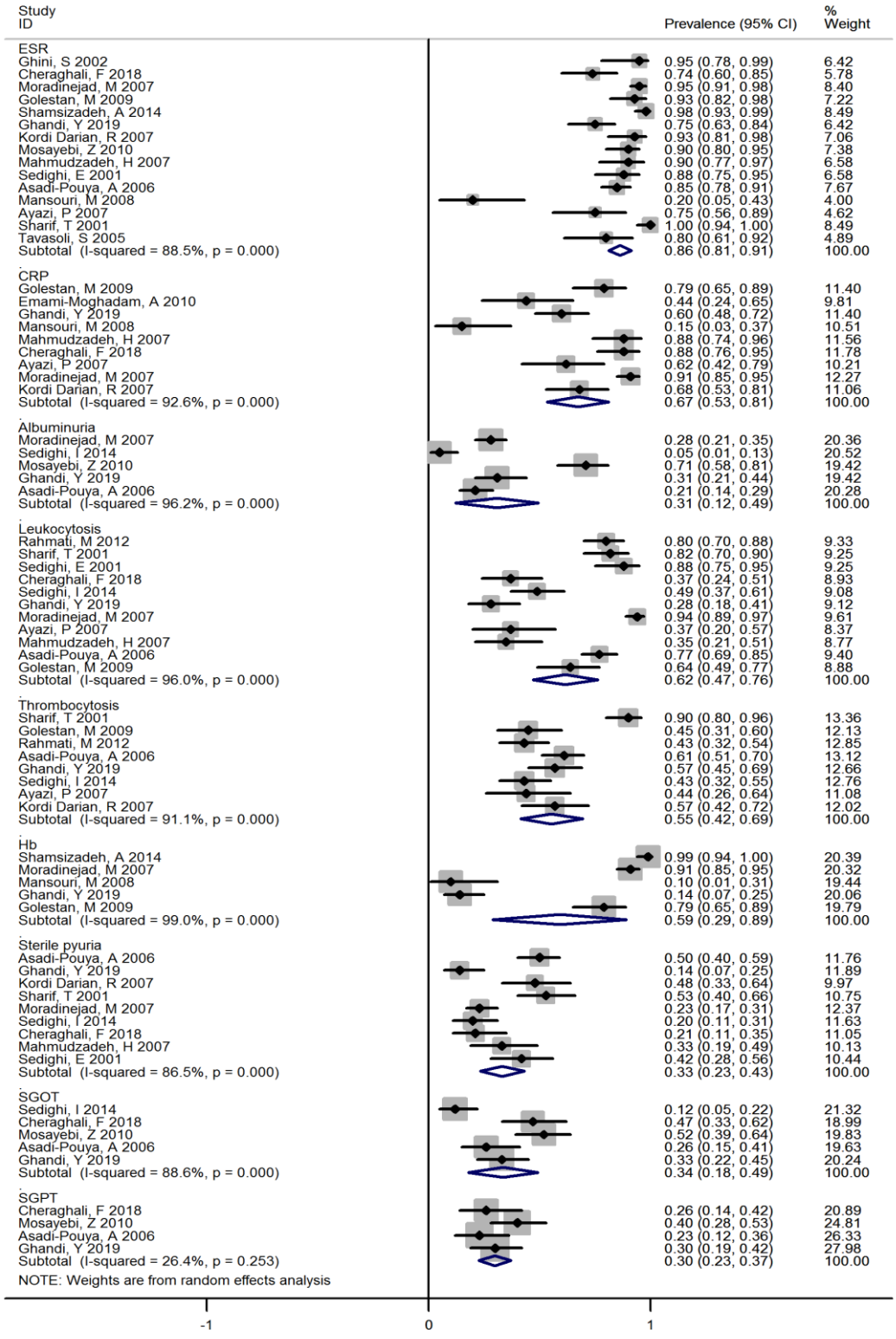

Fig. 3: Forest plot of the laboratory findings of KD.

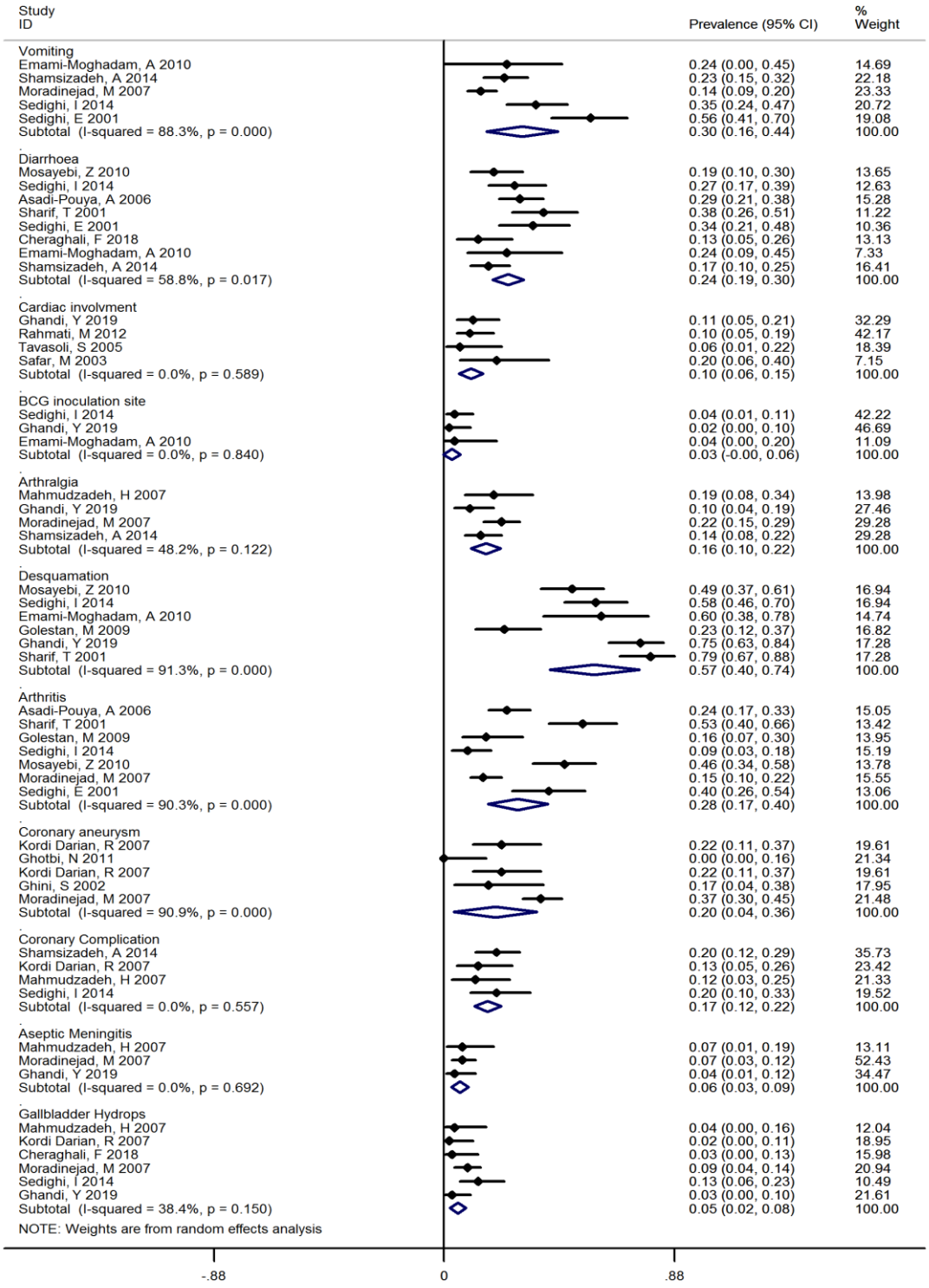

Fig.4: Forest plot of the other organ involvement in KD.

4- DISCUSSION

The present study evaluated the characteristics of KD. Main finding of this study was associated with the most prevalent findings of KD including clinical and laboratory findings. Also we found the most prevalent involvement of other organs in KD. Among KD patients, fever, change in oral cavity and lips, bilateral conjunctiva, rash, change in extremities, agitation, and cervical lymphadenopathy were most prevalent clinical findings respectively. Also, ESR, C-reactive protein (CRP), leukocytosis, Hb<10 g/dl, thrombocytosis, SGOT elevated, sterile pyuria, albuminuria, and SGPT (Significantly elevated levels of ALT) elevated were the most prevalent laboratory findings respectively.

In addition, desquamation, vomiting, arthritis, diarrhea, coronary complication, coronary aneurysm, arthralgia, cardiac involvement, aseptic meningitis, gallbladder hydrops, and BCG inoculation site were the most prevalent involvement respectively. KD is described as a vasculitis with unknown causes (1). This disease mostly involves children. KD diagnosis is based on clinical findings and there is no specific diagnostic test for it (6). Therefore, identifying the clinical findings is important for this disease. According to various primary studies in Iran, this meta-analysis was performed to obtain the estimated clinical and laboratory findings regarding the KD disease.

In our study, the mean age of participants was 42.09 months, which is different from the results of other studies conducted in some countries. Most reported age range of participants with KD was 12-24 months in USA and India (34, 35). Results of different studies conducted in China (36), and Turkey (37) show that the most reported age range of participants with KD was from 3 to 5 years. These findings are in line with the findings of the present study. The sex ratio was 1.63 in the present study and the prevalence of KD in male was more than in female. This finding is in accordance with the findings of a study conducted in Holland (M/F ratio=1.6) (38), a similar study in Spain (M/F ratio=1.5) (39), a study in China (M/F ratio=1.9) (36), and a study in Turkey (M/F ratio=1.4) (37). The KD may occur in all seasons; however, in Japan (40), and USA (34) studies, the highest prevalence was in winter and spring, which is confirmed based on the findings of the present study. Based on the results of previous studies, infectious factors such as Rota virus have a role in this increased prevalence rate (41). Fever was the most prevalent clinical finding in this meta-analysis. In addition, some clinical findings such as bilateral conjunctiva and oral and extremities change were the most prevalent findings of the present study. In a study conducted on KD in Saudi Arabia, the oral change and cervical lymphadenopathy were the most prevalent findings in KD (42).

Their findings confirmed the findings of the present study. According to the high prevalence of fever in KD patients and the high prevalence of infectious diseases in Iran, the diagnosis of KD can be difficult and problematic in this country. Studies conducted in other countries such as Japan (40), Turkey (37), China (36), Korea (43), and Thailand (44), show that fever and conjunctiva were the most prevalent clinical findings in KD and cervical lymphadenopathy had a low prevalence. The prevalence of cervical lymphadenopathy was 50% in the present study. Also, the oral cavity change was an obvious clinical finding in the present study. Rash was one of the most common findings in this study, which was concordant with studies conducted in Australia (45), Oman (46), and India (35).
Some laboratory findings of KD were assessed in this meta-analysis. The highest prevalence of these findings was related to ESR. Also, the prevalence of CRP>3+ was

considerable. However, the prevalence of albuminuria, thrombocytosis, SGPT, and SGOT were low. A study conducted in Japan showed that the level of albumin was low in KD (40); this result was different from the results of the present study. Results of some studies are similar to the result of this meta-analysis. Some immunologic changes such as decreasing the lymphocyte or CD8+ are observed in the acute phase of KD. This issue was shown in our study and was similar to the results of the Spanish study (39).

Evaluation of the involvement of other organs in KD was one of the results of this meta-analysis. Based on these findings, the most common prevalence rates were related to desquamation and arthritis. In addition, the prevalence rates of all of the cardiac involvement and coronary artery aneurysms were 10% and 17%, respectively. The follow-up of KD patients with coronary aneurysms is important, especially when inflammatory markers are high, fever is long, and albumin is low. All of these items were observed in this study. Cardiac involvement is the most expensive complication of KD and had a considerable prevalence in this study. The prevalence of coronary aneurysm in KD patients was 21% in India (35).

Also, the prevalence of coronary involvement in KD patients was 33% and 27% in Turkey (37), and China (36), respectively. These findings were lower than that of the present study, which is probably because of the earlier diagnosis of these complications. The prevalence rates of coronary involvement were 11% and 12.5% in Spain (39), and Oman (46), respectively; this finding was in line with that of the current study. Unlike the present study, the prevalence range of coronary involvement was 15-25% in Japan (40). Due to the high rate of abnormal echocardiography, more precision is necessary to perform it in developed countries.

The results of this meta-analysis in Iran is in agreement with those of most of the studies conducted around the world. In case of the differences, there are some causes as follows: 1) this meta-analysis was conducted on different studies with various characteristics; 2) the prevalence of infectious diseases (as one of the probable risk factors for KD) is different in various places of the world; 3) age difference can be effective in different KD studies; 4) genetic factors can be different in various places of the world; and 5) time of diagnosis, and time of treatment onset may affect clinical findings of KD. There was heterogeneity in some findings of this meta-analysis. One of the important causes of observed heterogeneity is the various populations with different sample sizes in the included studies (47). These studies also have a different quality.

According to quality assessment in this meta-analysis, most of the included studies have a low quality and this issue can cause the heterogeneity. Furthermore, when there are many studies included in a meta-analysis, like the present study, the sensitivity of statistic tests is increased in order to detect the smallest heterogeneity. Low quality of the entered studies to this meta-analysis and the high heterogeneity of the results are the most important limitations of this meta-analysis. In addition, because of the low number of studies in some subgroups, such as convulsion, organ gangrene, and Beau's line, we were unable to analyze them.

5- CONCLUSION

Based on our findings, fever, ESR, and desquamation are the most prevalent clinical, laboratory, and involvement of other organ characteristics respectively. To the best of our knowledge, this study is a first, and the most comprehensive meta-analysis conducted to evaluate clinical and laboratory findings and findings regarding the involvement of other organs in KD

patients in Iran. This meta-analysis is a good evidence for assessing the findings of KD patients in Iran and can be effective in earlier diagnosis of KD.

6- CONFLICT OF INTEREST: None.

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