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Review Article

The Value of the Alvarado Score for the Diagnosis of Acute Appendicitis in Children: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Relevant guidelines recommend the use of the Alvarado score (AS) to assist in the diagnosis of acute appendicitis (AA) in children. To provide reference evidence for the clinical application of AS, we performed a meta-analysis of studies related to the diagnostic accuracy of AS in children with AA.
Methods: We searched the relevant literature from databases including CNKI, WanFangdata, VIP, CBM, the Cochrane Library, PubMed, Embase, and Web of Science databases from the date of database creation to April 30, 2022, and screened them according to nadir criteria, followed by data extraction and then combined effect sizes to assess the accuracy of AS for diagnosis in children.
Results: Twenty-six studies involving 2579 cases were finally included, including 19 studies with Alvarado score and 8 studies with modified Alvarado Score (1 study included both Alvarado Score and modified Alvarado Score). The combined sensitivity (SE) of AS for diagnosing AA in children was 76.0% (95% CI 74.0–78.0%; $I^2 = 95.1\%$); combined specificity (SP) was 71.0% (95% CI 68.0–74.0%; $I^2 = 86.4\%$); combined positive likelihood ratio (LR+) was 2.43 (95% CI 1.92- 3.07; $I^2 = 78.7\%$); combined negative likelihood ratio (LR-) was 0.28 (95% CI 0.20–0.41; $I^2 = 94.2\%$); combined AUC = 0.8092, Q* = 0.7439; combined diagnostic ratio (DOR) was 8.96 (95% CI 5.65 -14.21; $I^2 = 76.2\%$). The combined effect size I^2 was greater than 50% for all children with a modified AS diagnosis of AA, so all analyses used a random-effects model, which showed a combined SE of 87.0% (95% CI 85.0 - 88.0%; $I^2 = 85.5\%$); the combined SP was 47.0% (95% CI 43.0 - 51.0%. $I^2 = 88.7\%$); combined LR+ was 1.68 (95% CI 1.31–2.17; $I^2 = 85.9\%$); combined LR-was 0.28 (95% CI 0.20–0.39; $I^2 = 74.3\%$); combined AUC = 0.8672 and Q* = 0.7978. The combined DOR was 6.43 (95% CI 3.38–12.26; $I^2 = 80.0\%$).
Conclusion: The results of this meta-analysis suggest that the accuracy of AS in diagnosing AA in children is moderate, and AS can be an auxiliary tool for the diagnosis of AA in children, relying on AS alone for the diagnosis of AA is not recommended; AS can be further improved scientifically to increase its diagnostic value.

1. Introduction

Acute appendicitis (AA) is often caused by nonspecific obstruction of the appendiceal cavity and can be divided into four types, acute simple appendicitis, acute suppurative appendicitis, acute gangrenous or perforated appendicitis, and periappendiceal abscess, depending on the progression of the disease and the type of pathology, with surgical treatment recommended for all except acute simple appendicitis. The most common indication for emergency abdominal surgery in children is appendicitis. However, the clinical presentation varies by age and sex, making the diagnosis of appendicitis more difficult and leading to a higher rate of negative appendectomy in children. The 2020 World Society of Emergency Surgery (WSES) updated guidelines recommend the use of the Alvarado score (Fig. 1) to aid in the diagnosis of acute appendicitis in children, but it shows that the level of evidence is not high enough [1,2]. Therefore, we systematically searched for studies related to the diagnostic value of the Alvarado Score (AS) for acute

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Project	Point
	Alvarado Score
Metastatic right iliac fossa pain	1
Anorexia	1
Nausea/Vomiting	1
Right iliac fossa pressure pain	2
Right iliac fossa rebound pain	1
Elevated body temperature >37.5°C	1
Leukocytosis	2
Left shift of leukocyte nuclei	1
Total score	10

Fig. 1. Alvarado Score (Note: Modified AS is formed by the investigator's discretion to make appropriate modifications to certain entries of the AS based on clinical experience).

appendicitis in children and performed a meta-analysis to develop more informative evidence.

2. Methods

2.1. Literature search

In this paper, “Appendicitis”, “child”, “Alvarado score”, “sensitivity and specificity”, etc. were used as subject terms, and the corresponding free words were added. CNKI, WanFangdata, VIP, CBM, the Cochrane Library, PubMed, Embase, and Web of Science databases were searched for literature from the date of database creation to April 30, 2022, respectively (detailed search strategies appear in Supplementary Appendix 1). The search results were independently screened by 2 investigators based on pre-defined inclusion and exclusion criteria, and a third investigator shared the judgment in case of disagreement.

2.2. Inclusion & exclusion criteria

Inclusion: Study on the diagnostic accuracy of the Alvarado Score for acute appendicitis in children (age≤18 years old); the diagnostic gold standard was pathologic tissue report results; sufficient data could be extracted to determine the sensitivity (SE) and specificity (SP) of the Alvarado Score.

Exclusions: Case reports, case series, animal studies, studies related to non-pediatric populations, duplicate reports, reviews, systematic evaluations, or studies that did not provide sufficient data to calculate sensitivity and specificity values.

2.3. Data extraction

Data were extracted from the included studies, including first author, year of publication, sample size in appendicitis and control groups, sensitivity, specificity, number of true-positive, false-positive, false-negative, and true-negative cases, and diagnostic thresholds. 2 investigators independently assessed the quality of each included study according to the QUADAS-2 tool, and disagreements, if any, were discussed and resolved with a third investigator.

2.4. Statistical analysis

The correlation data extracted from each study were combined as well as analyzed using Meta-DiSc 1.4 software, Revman 5.3 software, and Stata 15.1 software. Heterogeneity of threshold effects was tested by plotting SROC curves and calculating the Spearman correlation coefficient between SE and (1-SP) logarithm, with a correlation coefficient test level of $P = 0.05$; heterogeneity of non-threshold effects was tested by the Cochran-Q test for diagnostic ratio (DOR), with a test level of $P = 0.1$; fixed or random effects models were used depending on the degree of heterogeneity The meta-analysis of the combined effect sizes was followed by sensitivity analysis and DeeKs bias test with a bias test level of $P = 0.05$.

3. Results

A total of 423 articles were retrieved; there were 55 articles after deleting the duplicate records, reviews, comments, animal experiments, other non-compliant research types, non-compliant research contents, etc. After reading the full-text screening, 26 articles were finally included, including 19 [3–21] articles with study content of AS and 8 [14,22–28] articles with modified AS (1 article contained both AS and modified AS), and meta-analysis was performed separately according to different study content, and the flow chart of literature screening is shown in the figure (Fig. 2).

3.1. Characteristics of the included studies

The included cases involved 5985 children from 11 countries, including China, Nigeria, Pakistan, Turkey, Iran, United Kingdom, Tunisia, Canada, Croatia, Portugal, and Serbia, with 3586 cases involved in AS and 2579 cases involved in modified AS (180 children participated in both AS and modified AS studies), and the main characteristics of the studies were as shown (Table 1), and the quality of study evidence was assessed. The results are shown in figures (Fig. 3) (Fig. 4).

3.2. Heterogeneity of threshold and non-threshold effects

A total of 19 studies of AS were included, and the SROC curves plotted were not typically “shoulder-armed” and had a Spearman's correlation of 0.084 ($P = 0.732$), indicating no threshold-effect heterogeneity. The CochranQ test for DOR ($P < 0.1$), plotted on the Galbraith (GALB) plot (Fig. 5), also showed the presence of non-threshold effect heterogeneity, however, the heterogeneity was not reduced when attempts were made to remove the more sensitive studies, so the included studies were not excluded.

A total of 8 studies of modified AS were included, and the SROC curves plotted were not typically “shoulder-armed” and had a Spearman's correlation of 0.024 ($P = 0.955$), indicating no

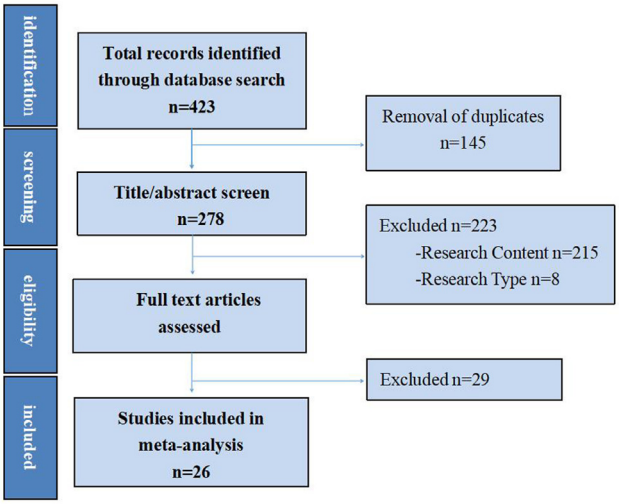

Fig. 2. Flow chart of literature screening.

Table 1
Basic characteristics of included studies.

	Author	Year	AA group	Control group	Sensitivity	Specificity	Threshold value
AS	LU Juan [3]	2021	120	60	94%	76.67%	6
	Ademola Olusegun Talabi [4]	2021	81	19	86.40%	63.20%	7
	Muhammad Adil Iftikhar [5]	2021	97	10	85.57%	70%	–
	Yelda Türkmeno [6]	2020	48	54	77.10%	85.20%	7
	Zhang T [7]	2019	379	18	65.30%	66.70%	7
	Peng DY [8]	2019	170	45	67.06%	53.33%	7
	Ahmet Sami Yazar [9]	2018	170	30	60%	86.67%	7
	Pang L [10]	2017	234	16	73.50%	81.30%	6
	Chen Yu-Feng [11]	2017	151	14	94.04%	64.29%	7
	Joshua Agilinko [12]	2017	94	24	64.89%[a]	54.17%[a]	6
	Mohamed Zouari, MD [13]	2015	148	144	24.24%[a]	91.88%[a]	7
	Ijab Khanafe [14]	2016	55	125	85.20%	43.70%	7
	Chang S. M [15]	2015	77	7	81.80%	71.40%	7
	Zenon Pogorelić [16]	2015	265	46	89%	59%	–
	Peng W [17]	2014	209	11	90.47%	91.21%	6
	Arzu Sencan [18]	2014	42	18	76.19%	38.89%	7
	Tian Hui [19]	2013	–	–	79.30%	66.10%	6
	Jean-Pierre GONÇALVES [20]	2011	123	23	87%	46%	7
	Ana Kostić [21]	2010	68	189	90%	80%	–
Modified AS	JIN Jing [22]	2022	196	34	77%	25.90%	7
	Zhang Yanmei [23]	2021	538	21	83.50%	81%	7
	Liu Na [24]	2017	150	8	85.33%	62.50%	9
	Mehran PEYVASTEH [25]	2017	337	63	91.30%	38.40%	7
	Wu Jialong [26]	2016	–	–	93.00%[a]	47.00%[a]	–
	Ijab Khanafe [14]	2016	55	125	83.30%	36.50%	4
	Hou L-C [27]	2014	114	6	86.80%	33.30%	7
	SONG Weiqiang [28]	2004	153	95	82.30%	77%	7

Note: - is not stated in the literature.
[a] is calculated from extractable data.

threshold-effect heterogeneity. The CochranQ test for DOR ($P < 0.1$), indicating the presence of non-threshold effect heterogeneity, did not reduce heterogeneity when attempts were made to remove studies with higher sensitivity, so all included studies were subjected to meta-analysis.

These results suggest that the diagnostic thresholds of the included studies were approximately the same and that there was no threshold heterogeneity; the potential source of heterogeneity may be from the fact that the cases of children included in the study were from different countries and different settings.

3.3. Diagnostic accuracy

The combined SE for the AS diagnosis of pediatric AA study was 76.0% (95% CI 74.0–78.0%; $I^2 = 95.1\%$); combined SP was 71.0% (95% CI 68.0–74.0%; $I^2 = 86.4\%$); combined positive likelihood ratio (LR+) was 2.43 (95% CI 1.92–3.07; $I^2 = 78.7\%$); combined negative likelihood ratio (LR-) was 0.28 (95% CI 0.20–0.41; $I^2 = 94.2\%$); combined AUC = 0.8092, Q* = 0.7439; combined DOR was 8.96 (95% CI 5.65–14.21; $I^2 = 76.2\%$); random effects model was used for all $I^2 > 50\%$.

The combined effect sizes I^2 for the modified AS diagnosis of pediatric AA studies were all greater than 50%, so the analyses were all performed using a random-effects model, showing that the combined SE was 87.0% (95% CI 85.0–88.0%; $I^2 = 85.5\%$); combined SP was 47.0% (95% CI 43.0- 51.0%; $I^2 = 88.7\%$); combined LR+ was 1.68 (95% CI 1.31–2.17; $I^2 = 85.9\%$); combined LR-was 0.28 (95% CI 0.20–0.39; $I^2 = 74.3\%$); combined AUC = 0.8672, Q* = 0.7978; combined DOR was 6.43 (95% CI 3.38–12.26; $I^2 = 80.0\%$).

3.4. Analysis of sensitivity

The results of the sensitivity analysis of the included studies with AS (Fig. 6) showed that only one study by Mohamed Zouari. MD [13] had a strong sensitivity, probably due to the fact that there were too few true-positive cases in this study and there was a large chance, resulting in a low sensitivity. Other original studies did not contribute to the sensitivity of the results, and overall, the results of this study were stable.

The results of the sensitivity analysis of the included studies with modified AS showed overall good stability of the study results, and only one study by Jin Jing [22] had a strong sensitivity, probably because the included cases were all surgical children with a heavy clinical comprehensive assessment of the disease and too few true-negative cases, resulting in a lower specificity, but with less influence on the stability of the final results.

3.5. DeeKs bias test

As shown in the figure (Fig. 7), the publication bias test on data of the included studies with AS showed $P = 0.69 > 0.05$, indicating that the funnel plot was symmetrical and there was no publication bias.

The publication bias test on the modified AS inclusion study data showed $P = 0.47 > 0.05$, implying that the funnel plot was symmetrical and there was no publication bias.

4. Discussion

In the meta-analysis of 26 studies involving 5985 children in 11 countries, the Alvarado Score had a combined sensitivity of 76.0% and a combined specificity of 71.0% for the diagnosis of acute appendicitis in children; the modified Alvarado Score had a combined sensitivity of 87.0% and a combined specificity of 47.0%. The combined results of this meta-analysis were all stable, and none of data in the studies were subject to publication bias, so it contributed a high degree of confidence.

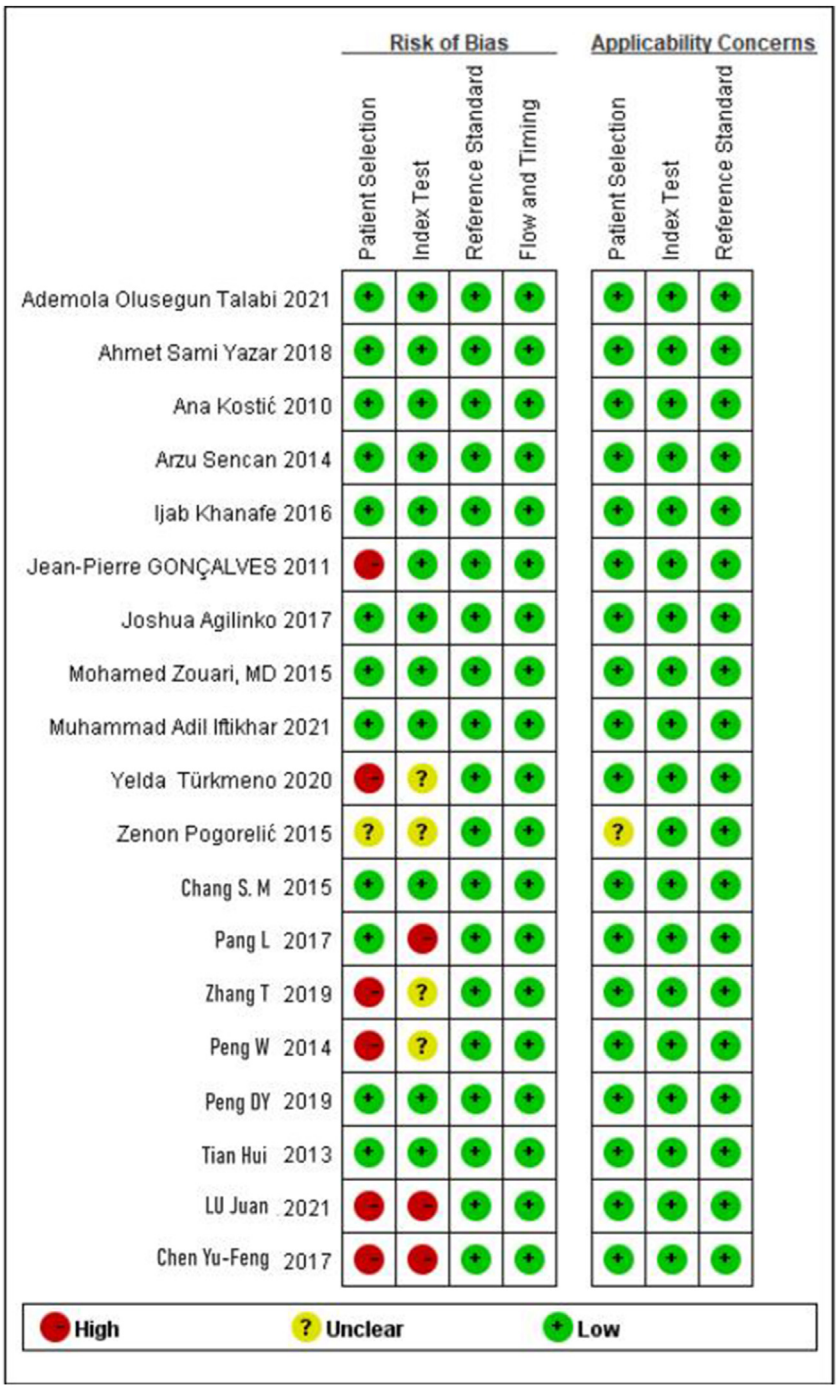

Fig. 3. Summary of risk of bias in the inclusion studies of AS.

From the combined results, the accuracy of AS in diagnosing AA in children still needs to be improved, and it is not recommended to be used alone. However, the meta-analysis results here cannot completely deny the clinical diagnostic significance of AS because the source of control cases was inconsistent and unrepresentative in terms of the original study characteristics. Although the control cases all originated from children who were judged by their physicians to have suspected AA, the patients in the control cases of 2 studies [10,17] were children with acute simple appendicitis confirmed by surgical pathology, and acute simple appendicitis could be considered for conservative treatment as an alternative therapy [1]; the control cases of 7 studies [3,4,6,13,14,18,21] were children with surgical pathology confirmed and not non-AA children diagnosed using surgical modalities; the control cases of 10 studies [5,7–9,11,12,15,16,19,20] were non-AA children diagnosed with surgical pathological tissue confirmation. Different sources of control cases led to the different positioning of the study objectives; if simple AA children were used as the control group, the aim was to assess the accuracy of AS for clinical staging of children with AA; if non-AA children were used as the control group, the study was aimed at assessing the accuracy of AS in diagnosing AA in children. The significance of the results in this study differs

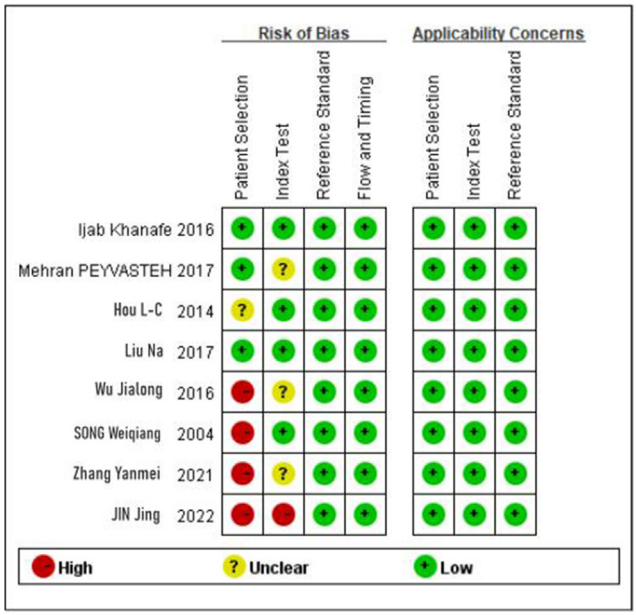

Fig. 4. Summary of risk of bias in the inclusion studies of modified AS.

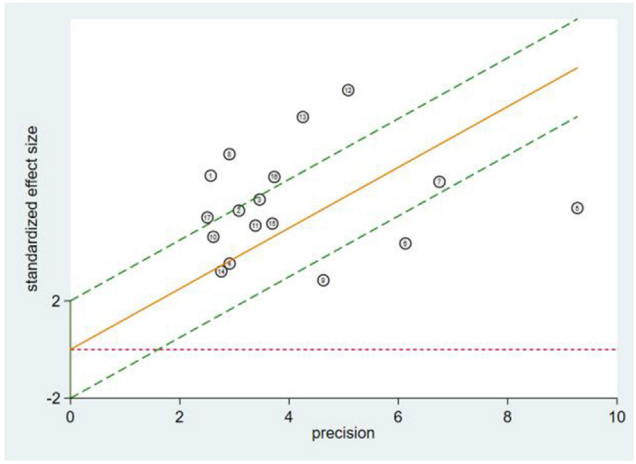

Fig. 5. GALB chart of the included studies with AS.

depending on the targeting of the study. There is no authoritative evidence on the best diagnostic route for pediatric patients with suspected appendicitis, and AS has the advantages of being economical and practical, simple and reproducible, and it has a non-negligible value in the clinical diagnosis of AA in children. AS is a reliable tool for the clinical diagnosis of AA in pediatrics in two situations. One is when imaging is scarce. The other is when a child with suspected AA has difficulty finding the appendix on ultrasound due to obesity. And the use of AS for the diagnosis of AA can reduce radiation exposure examinations in children to a certain extent. For example, if a physician cannot immediately and definitively determine the condition of a child based on the examination results and needs to continue to observe the progression of a child with suspected AA, AS can be used several times to evaluate the condition and observe the progression of the children's condition, which facilitates the physician's clinical diagnosis while avoiding unnecessary multiple imaging examinations. In addition, AS can be tried in combination with other tests to improve the accuracy of diagnosing AA in children. A recent study has shown that AS combined with APPY-1, a biomarker consisting of calprotectin and C-reactive protein (CRP) and leukocyte count, can provide an effective exclusion diagnosis in children with low/intermediate-risk AA [29]; AS combined with CRP can improve the diagnostic accuracy of AA and also help in the exclusion diagnosis [30], in addition, AS combined with thiol/disulfide steady–state parameters or Ultrasound or Pentraxin 3 (PTX3) and IL-6 have also shown the advantage of improving the accuracy of AA [31–34], and these studies provide evidence that AS can be used as a diagnostic aid for children with AA.

The combined results of modified AS showed higher sensitivity and lower specificity compared to AS. Its inclusion also suffers from inconsistent control sources, with 4 studies [22,26–28] aiming to assess the accuracy of modified AS for differentiating clinical staging of AA in children and 4 studies [14,23–25] aiming to assess its accuracy for diagnosing this disease. Moreover, modified AS is a decision of the investigators to modify certain entries of AS based on their own clinical experience and related literature studies, and the items of modified AS included in the studies were varied, contributing to the fact that the results of this meta-analysis do not fully explain their clinical significance. From the trend of single study results, appropriate adjustment of certain entries of AS did improve its diagnostic sensitivity but the specificity was poor, and modifications of certain items could be attempted in conjunction with recent studies. For example, the results of a pediatric study suggest that the specificity of PTX3 for diagnosing AA can be as high as 100% [34], and one study showed that immature granulocyte count may be a predictor for patients with intermediate-risk AA [35], which can be used as a reference for modifying the AS entries, thus making the modified AS of greater clinical diagnostic value. In addition, an attempt could be made to modify the AS into a graded quantitative scale for evaluating the clinical efficacy of conservative treatment of simple AA, so that it could be more fully valued for clinical application. These ideas are all inferred, and more scientific and rigorous clinical studies are needed to verify whether they can be implemented.

5. Study limitations

A total of 26 studies were included in this meta-analysis, with the following shortcomings: (1) the studies were all single-center studies, (2) 9 studies were not circumvented, 2 studies were unclear whether the risk of case selection was circumvented; 4 studies were not circumvented, 7 studies were unclear whether the risk of the trial to be evaluated was circumvented, (3) the studies were inconsistently positioned, 6 studies were designed to assess the clinical staging accuracy of AS to distinguish childhood AA accuracy; the remaining 20 studies aimed to assess the accuracy of AS in diagnosing childhood AA as a disorder, (4) the relevant studies used different modified AS entries. These deficiencies may account for the presence of heterogeneity in non-threshold effects and also contribute to the lack of a high enough level of evidence and representation in this study.

In the future, to provide a more reliable reference basis for clinical application, more rigorous multicenter prospective studies with large samples need to be designed to validate the accuracy of AS a diagnostic or adjunctive diagnostic tool for AA in children. The AS can also be improved by combining the latest research profile and clinical experience, and then scientific studies can be designed to validate the clinical diagnostic value of the improved AS, so that the AS can more fully exploit its advantages in the diagnosis of AA in children.

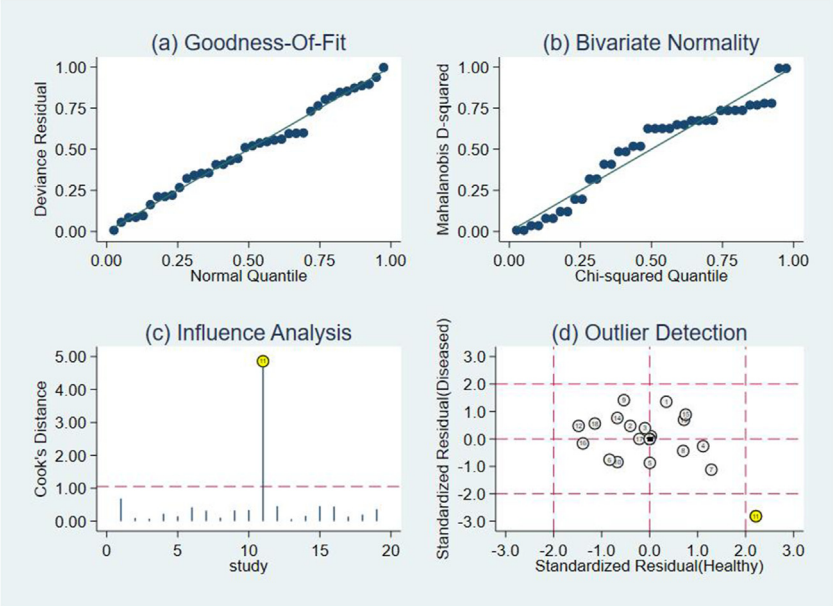

Fig. 6. Results of the analysis of sensitivity for the included studies with AS.

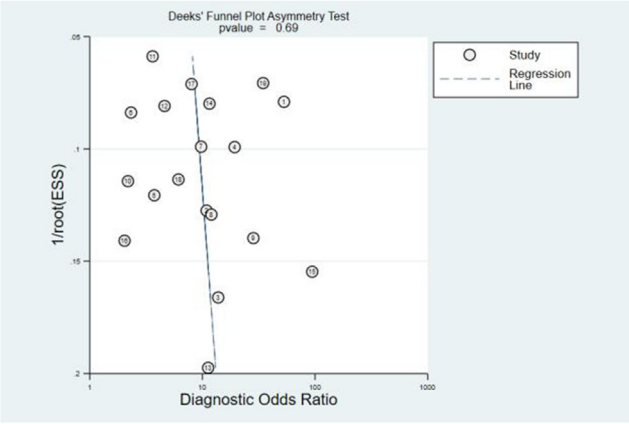

Fig. 7. Results of DeeKs publication bias test for the included studies with AS.

6. Conclusion

The results of this meta-analysis suggest that the accuracy of AS diagnosis of AA in children is moderate and needs further improvement, and AS can be an auxiliary tool for the diagnosis of AA in children, relying on AS alone for the diagnosis of AA is not recommended; AS can be further improved scientifically to increase its diagnostic value.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2023.02.060.

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