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REVIEW ARTICLE

Matrix Metalloproteinase-7 as a Diagnostic Marker for Biliary Atresia: a Systematic Review and Meta-analysis

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Abstract

The matrix metalloproteinase-7 (MMP-7) is a promising marker for identification of biliary atresia. We assessed the accuracy and clinical value of MMP-7 for diagnosis of biliary atresia in infants. We searched MEDLINE, Embase, ISI Web of Knowledge, and the Cochrane Library, from inception to December 30, 2020. We included articles written in English, Chinese, or French that investigated MMP-7 for differentiation of biliary atresia infants from those with other form of cholestasis. Two review authors independently assessed eligibility for inclusion, evaluated the methodological quality of included studies, and extracted data to estimate diagnostic accuracy. We calculated individual and pooled sensitivities and specificities. We used I^2 to test heterogeneity and investigated the source of heterogeneity. Our search identified 4 studies (593 infants). Risk of bias in the included studies was generally low. Bivariate analysis yielded a mean sensitivity of 0.96 (95% CI: 0.93–0.98) and specificity of 0.91 (95% CI: 0.85–0.95). The area under the receiver operating characteristic curve was 0.97 (95% CI: 0.95–0.98). A moderate heterogeneity was found among the included studies as the I^2 values for sensitivity and specificity were 8.6% (95% CI: 1.5–19.04) and 56.7% (95% CI: 28.91–70.07), respectively. After a sensitivity analysis, there was no change in sensitivity and MMP-7 specificity ranged from 0.91 to 0.93. The serum MMP-7 is a helpful biomarker for diagnosis of biliary atresia in cholestasis infants. Nevertheless, it cannot be recommended as the single definitive test for biliary atresia diagnosis; further primary clinical research is mandatory.
Trial registration: prospero230839

Keywords MMP-7 · Biliary atresia · Cholestasis

Introduction

Biliary atresia (BA) is a disease that involves the biliary tract both inside and outside the liver, causing progressive fibrous obstruction of the bile ducts, leading to severe cholestasis and cirrhosis [1]. Because of the many causes of neonatal jaundice and similar clinical manifestations, it is difficult to distinguish BA from other neonatal cholestasis in the early stages, and how to diagnose BA quickly and accurately is a recent research hotspot. Delay in the diagnosis of BA can greatly affect quality of life of the child, but the gold standard for the diagnosis of BA is intraoperative cholangiography and liver biopsy, an invasive test that is prone to

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serious complications [2]. Finding a non-invasive indicator for early preoperative diagnosis of BA is crucial.

MMP-7, a member of the MMP family, is expressed in both bile duct epithelial cells and liver cells, and it can promote hepatic fibrosis in BA children [3]. In an earlier microarray study, MMP-7 mRNA expression was significantly higher in biliary atresia than in non-biliary atresia liver tissue [4]. MMP-7 was experimentally confirmed to be associated with biliary epithelial damage and had been termed the excellent biomarker for identification of biliary atresia because it has several advantages over other potential biomarkers [5]. However, there are no meta-analyses about the accuracy of MMP-7 for the diagnosis of biliary atresia.

Currently, most diagnostic studies on MMP-7 have been performed in single medical centers with small sample sizes and lack of strong evidence, the use of serum MMP-7 in the clinical diagnosis of biliary atresia is limited, and clinical practice varies widely [5]. A systematic review to identify, quality-appraise, and synthesize the data in meta-analyses could help clarify the evidence base to inform practice and future research. So, we did a systematic review to evaluate the diagnostic efficacy of MMP-7 in the diagnosis of biliary atresia in infants with cholestasis.

Methods

Search Strategy

The literature on the accuracy of MMP-7 in diagnosing biliary atresia was searched in PubMed, EMBASE, Web of Science, and Cochrane Library databases, respectively. Our medical subject heading terms were "matrix metalloproteinase 7" OR MMP-7 AND "Biliary atresia" OR "Intrahepatic bile duct atresia" OR "Extrahepatic bile duct atresia" OR "BA". We searched the databases between inception and June 30, 2021.

Selection Criteria

Inclusion criteria: tests to assess the accuracy of serum MMP-7 for the diagnosis of biliary atresia, with sufficient information in the literature to warrant its use for analysis. The studies had to provide sufficient information to construct the two-by-two contingency table, for example, false positives, true positives, false negatives, and true negatives. The gold standard for the diagnosis of biliary atresia was intraoperative cholangiography and liver pathology consistent with the pathology of biliary atresia. Exclusion criteria: animal experiments, correspondence, reviews, case reports, conference abstracts, journal reviews, expert opinions, literature with obvious errors in the data, and literature of a screening nature. Inclusion and exclusion of literature was performed by two individuals independently, and if two individuals reached inconsistent conclusions, they were resolved by discussion. If no agreement could be reached after the discussion, a third party should be asked to judge whether to be included.

Data Extraction and Management

Two investigators independently extracted data, and they solved disagreements by discussion or by consulting a third author. Data extracted from the studies included the following items: title; year of publication; country; study inclusion and exclusion criteria; study site; diagnostic gold standard; MMP-7: child characteristics, test specimen type, diagnostic kit type, and diagnostic cutoff value; number of true positive, false negative, false positive, and true negative. We contacted the corresponding authors if further information was needed. If no response was received after sending a reminder, the study was excluded.

Assessment of Methodological Quality

We assessed the methodological quality of the studies with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist [6], including the risk of bias and clinical applicability, which in turn consists of case selection, trials to be evaluated, gold standard, case flow, and progression. To limit the influence of different biases, the whole process was done independently by two evaluators, and inconsistencies were resolved after discussion and consultation with a third reviewer.

Statistical Analysis

We used Review Manager 5 software and STATA version 14.0 for analyses and plots. We built two-by-two tables for each primary study and for all the index tests considered. We used the numbers to calculate sensitivity and specificity and a corresponding CI. We used the bivariate model for diagnostic meta-analysis [7]. We then construct a hierarchical summary receiver operating curve for MMP-7 with summary operating points for sensitivity and specificity on the curves [8]. We calculated I^2 to assess heterogeneity and we consider heterogeneity between articles when $I^2 > 50\%$, and no heterogeneity when $I^2 \leq 50\%$. We planned to examine the effect of subgroup in meta-regression analyses. If sufficient data were available, we planned to explore whether study heterogeneity affected the results by removing studies considered at higher heterogeneity. In addition, Deeks' funnel plot was applied to assess publication bias ($P \leq 0.05$ indicates significant publication bias, $P > 0.05$ indicates no significant publication bias) [9].

Results

Literature Selection and Quality Assessment

A total of 87 records related to the searched keywords were initially found through electronic search. Finally, a total of 4 literatures met the inclusion criteria in this meta-analysis [10–13]. The flowchart of study selection is shown in Fig. 1. The prevalence of biliary atresia among studies ranged between 36 and 65% (mean 52%). The cutoff for MMP-7 concentration differed substantially between studies (median 5.9 ng/mL, IQR 1.2–52.8). The characteristics of included studies are shown in Table 1. Four papers were published between 2017 and 2019, including three in China and one in the USA. The populations tested were confirmed BA and neonatal hepatitis in the USA and jaundiced infants from newborn to 150 days postnatal in China. The number of children with BA diagnosed by the gold standard was 333 (35–187). The risk of bias for each study across each QUADAS-2 domain is shown in Fig. 2A. The overall risk of bias assessment for all included studies across each QUADAS-2 domain is shown in Fig. 2B.

Overall Diagnostic Value of MMP-7 for Biliary Atresia

The sensitivity and specificity of MMP-7 for diagnosing biliary atresia is shown in Fig. 3A. Pooled sensitivity was 0.96 (95% CI: 0.93–0.98) and pooled specificity was 0.91 (95% CI: 0.85–0.95). The I^2 values of sensitivity and specificity were 8.60% (95% CI: 1.50–19.04) and 56.70% (95% CI: 28.91–70.07), respectively, indicating a moderate heterogeneity among the enrolled studies. The Spearman correlation coefficient was − 0.2; p value was 0.8, indicating no threshold effect. The summary receiver operating characteristics (SROC) curve is illustrated in Fig. 3B. The area under the curve (AUC) for MMP-7 detection in diagnosing biliary atresia was 0.97 (95% CI: 0.95–0.98).

Investigation of Heterogeneity and Publication Bias

We were unable to perform a meta-regression analysis because only four studies reported the diagnostic efficiency of MMP-7 for biliary atresia, and we were unable to perform a subgroup analysis because of the small number of included studies. The bivariate boxplot showed that one study (Wu 2019) was an outlier (Fig. 4A), and we explored

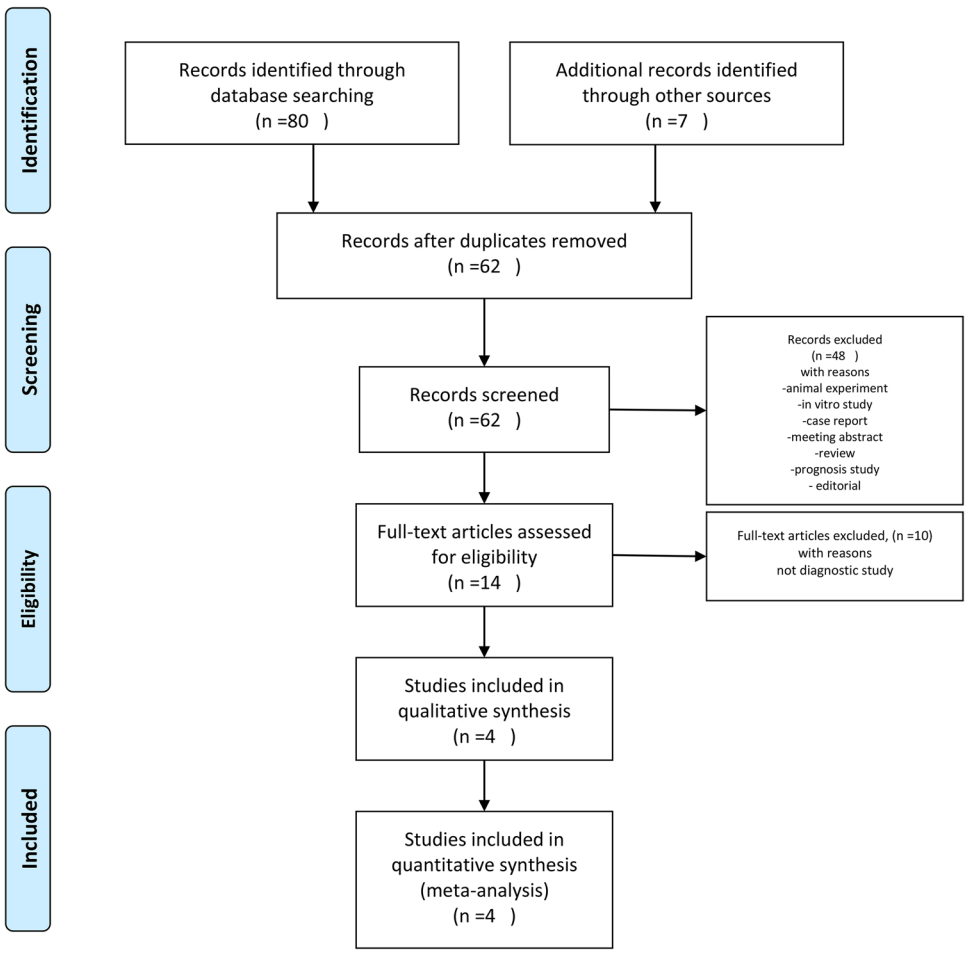


Fig. 1 Study flow diagram

Table 1 The characteristics of included studies

Author	Year	Country	Total	BA	Control	Gender	Age at diagnosis (days)	Assay type	Kit name	Cutoff (ng/mL)	TP	FP	TN	FN
Jiang	2019	China	288	187	Obstructive jaundice	81 M, 106 F	61.5 SD 19.0	ELISA	Cloud-Clone Corp	10.37	178	7	94	9
Wu	2019	China	100	36	Cholestasis	14 M, 22 F	42.36 SD 3.56	ELISA	DuoSet	1.43	35	11	53	1
Yang	2018	China	135	75	Obstructive jaundice	34 M, 41 F	54 (43–67)	ELISA	Cloud-Clone Corp	52.85	74	3	57	1
Chatmanee	2017	US	70	35	Intrahepatic cholestasis	19 M, 16 F	62 SD 28	ELISA	MILLIPLEX Multiplex	0.49	34	3	32	1

BA, biliary atresia; *TP*, true positive; *FP*, false positive; *TN*, true negative; *FN*, false negative; *US*, United States; *M*, male; *F*, female; *ELISA*, enzyme-linked immunosorbent assay

the source of heterogeneity by sensitivity analysis and reran the meta-analysis after excluding relatively poor-quality literature from the included studies, with no significant difference after combined effects, and the overall sensitivity and specificity were 0.96 (95% CI: 0.93–0.98) and 0.93 (95% CI: 0.89–0.96), respectively. We used funnel plots and the Deeks test to assess publication bias and found no significant asymmetry and no statistical significance (Fig. 4B). Both likelihood ratio and posttest probability were high (Fig. 5). A positive likelihood ratio of 11 implies that a person with disease is eleven-times more likely to have a positive test result than is a healthy person. Given a pretest probability of 50%, the posttest probability for a positive test result is 91%. Likewise, a negative likelihood ratio of 0.04 reduces the posttest probability to 4% for a negative test result.

Discussion

We present the first systematic review of studies of serum MMP-7 as a diagnostic tool for biliary atresia, with a total of 4 studies reporting the diagnostic accuracy of serum MMP-7 in infant biliary atresia. Our meta-analysis showed a pooled sensitivity of 96%, specificity of 91%, and SROC of 0.97 for MMP-7. These data suggest that serum MMP-7 may be useful in the diagnosis of biliary atresia, and to our knowledge, this systematic review is the first assessment of the value of MMP-7 as a diagnostic tool for biliary atresia.

The most important characteristic of a biomarker is its potential to alter clinical decision, and serum MMP-7 is gradually gaining attention as an auxiliary diagnostic tool. The four studies did not predefine a threshold for positivity, and the investigators selected the cutoff value that maximized the area under the ROC curve as the optimal cutoff for serum MMP-7 by post hoc analysis. However, the cutoff values that distinguished infants with biliary atresia from those without biliary atresia varied widely in the four studies, and none of these cutoffs were later further validated. In the diagnosis of biliary atresia, a false-negative results can prevent a BA child from undergoing Kasai surgery in a timely manner, which can be fatal for the child [14]. However, it is important to note that an indicator alone that increases its diagnostic sensitivity necessarily decreases its diagnostic specificity; in other words, reducing the number of missed diagnoses necessarily increases the number of misdiagnoses and vice versa, and in order to prevent the development of cholestasis and liver fibrosis, other forms of cholestatic infants without biliary atresia should also be correctly identified. Therefore, a reasonable threshold needs to be chosen and we suggest testing the diagnostic accuracy at different ages and we should further investigate the validity of MMP-7 in infants of different days to find a reasonable threshold for daily clinical practice needs.

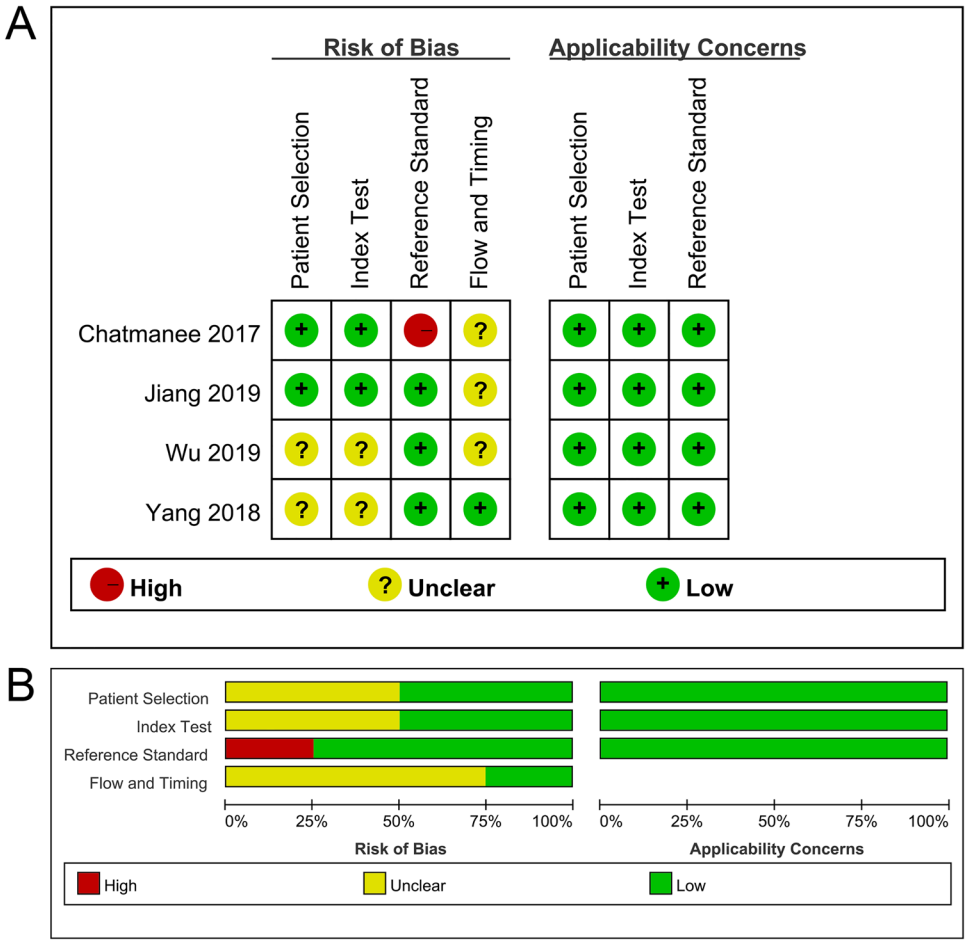
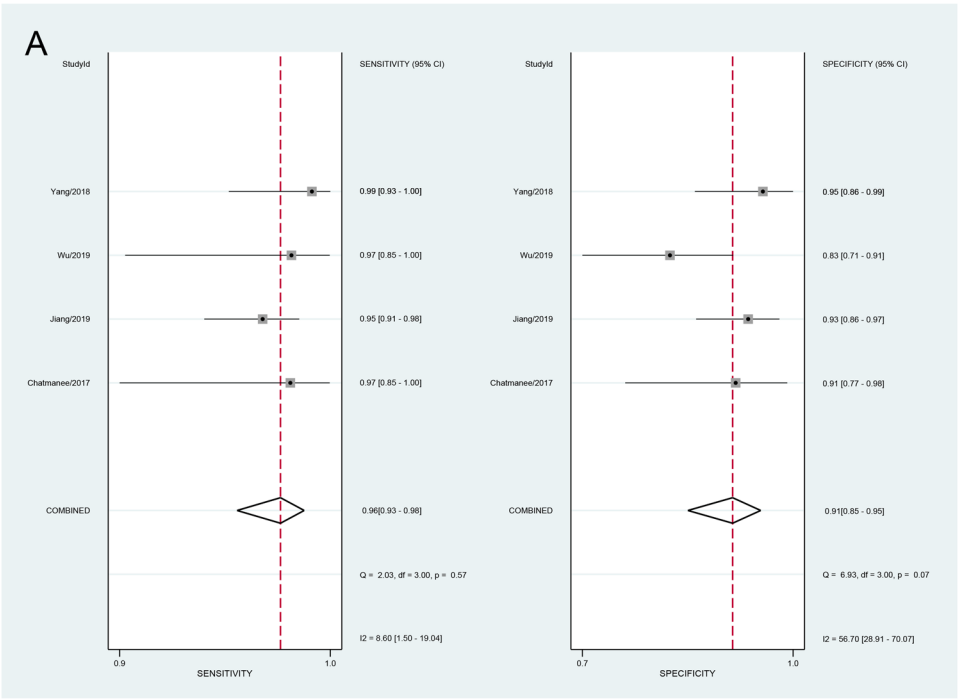


Fig. 2 Risk of bias and applicability concerns plot. **A** Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study. **B** Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

We detected heterogeneity between studies and identified one study [12] as the main cause of this heterogeneity, and differences between studies included the clinical spectrum of patients, admission category, and ELISA test kits. The use of a more homogeneous population could address this issue, but it also has the potential to cause selection bias. In addition, some studies lacked key information on experimental design and full reporting, which became an obstacle for us to clarify the sources of heterogeneity, and further well-designed studies with large sample sizes are needed to assess the diagnostic accuracy of MMP-7. Studies with desirable results are more likely to be published, which may lead to an overestimation of overall diagnostic accuracy. In our meta-analysis, we did not find publication bias, and we again searched for literature by searching databases and reference lists of major studies and failed to find more relevant articles. Likelihood ratios and posttest probabilities are also extremely important for clinicians, as they provide information about the likelihood that a patient with a positive or negative test result actually has biliary atresia. In our study, both likelihood ratios and posttest probabilities were high. We applied the likelihood ratios derived from the meta-analysis to a hypothetical group of infants with suspected biliary atresia and showed that the test would yield the relatively best diagnostic results. For example, if the estimated pretest probability of biliary atresia in a given infant is 50% (the median of the included studies); then, adding serum MMP-7 levels to the assessment results in a 4% posttest probability for a negative test and a 91% posttest probability for a positive test.

The MMP-7 may be a perfect marker for the diagnosis of biliary atresia, but the ideal marker does not exist and biliary atresia is not a simple disease with a very complex pathogenesis that cannot be diagnosed with a single indicator [15]. Serum MMP-7 showed good accuracy in the diagnosis of BA, but the heterogeneity in the meta-analysis prevents us from drawing clear conclusions and making recommendations, and no convincing evidence was found to recommend the routine use of serum MMP-7 in clinical practice for the diagnosis of BA, and MMP-7 cannot be used as a reliable and unique marker for the diagnosis of BA in infants for the time being. We recommend that pediatricians use the level of MMP-7 only as a reference and should consider all possible differential diagnoses of BA and use other laboratory tests and imaging, and consult with a pediatric surgeon if necessary, to assist in the



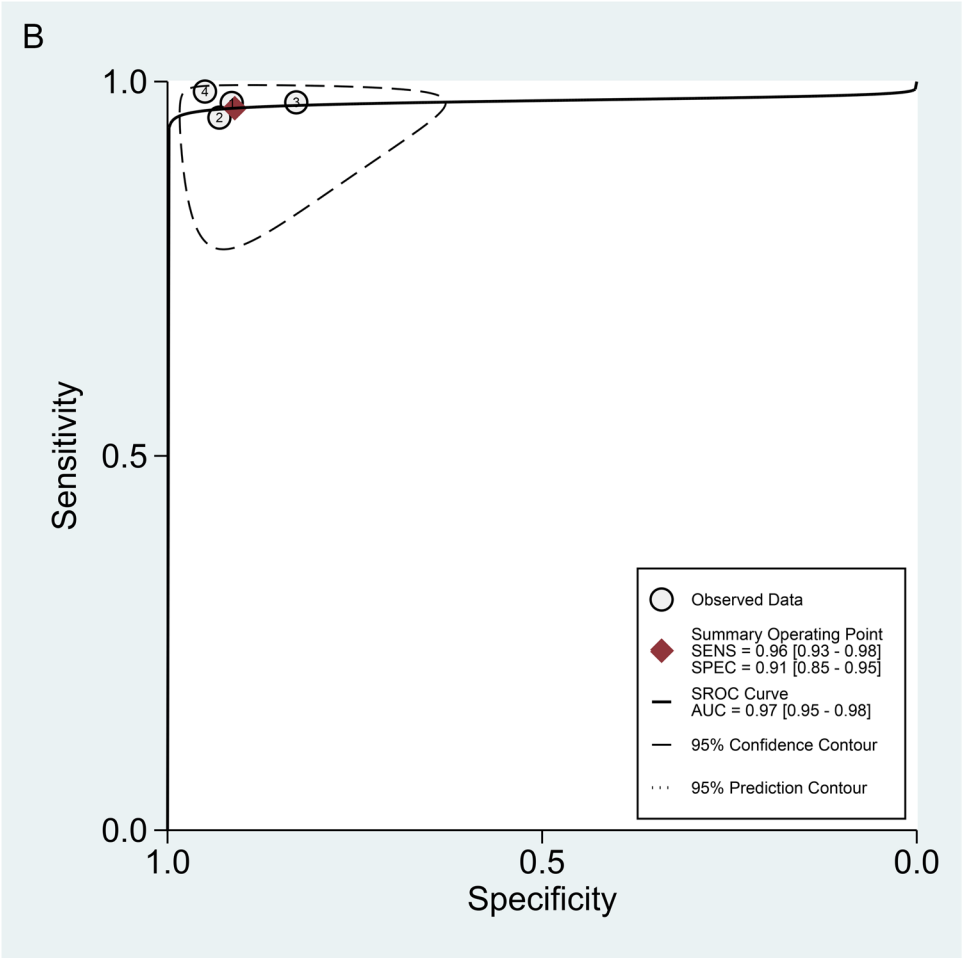


Fig. 3 Forest plot and SROC curve. **A** Sensitivity and specificity of serum MMP-7 assay for diagnosis of biliary atresia. **B** Summary receiver operating characteristic curve

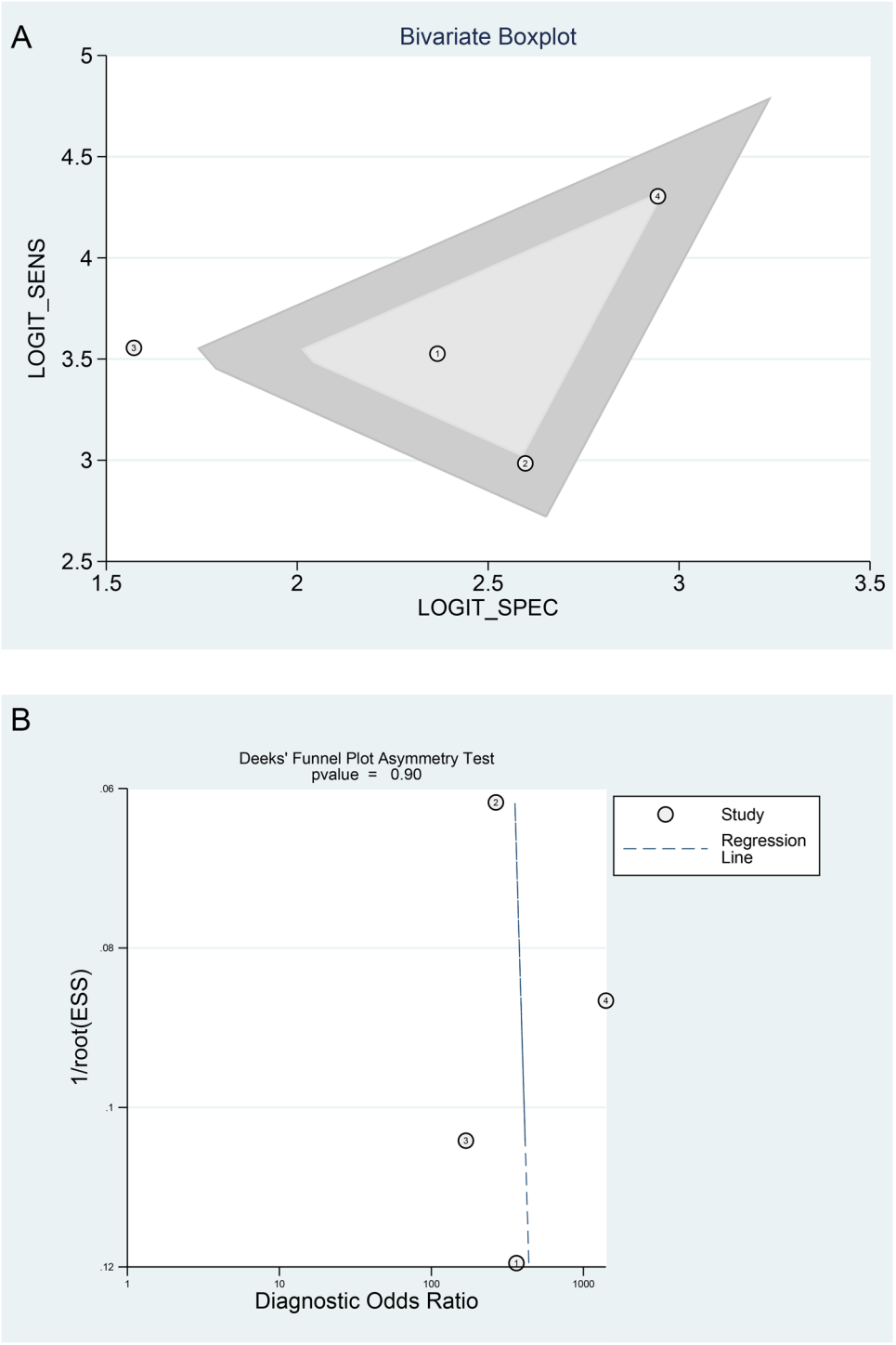


Fig. 4 Bivariate boxplot and funnel plot. **A** The bivariate boxplot. **B** Deeks' funnel plot asymmetry test

diagnosis of BA. Nevertheless, MMP-7 is one of the most promising serum markers for BA. There is a lack of serum diagnostic markers for biliary atresia in infants, and we need ongoing basic clinical research to explore the possible mechanisms of MMP-7 in the pathogenesis of biliary atresia that may help us identify more accurate biomarkers for the disease. We need well-designed diagnostic studies to assess the diagnostic accuracy of these tests, and these studies should be reported in accordance with the STARD statement [16].

The limitation in this meta-analysis was that the number of included literatures was small, especially only 4 literatures reported the diagnostic performance of MMP-7 in biliary atresia.

In conclusion, MMP-7 is a helpful marker for diagnosis of biliary atresia in cholestasis infants. However, it cannot be

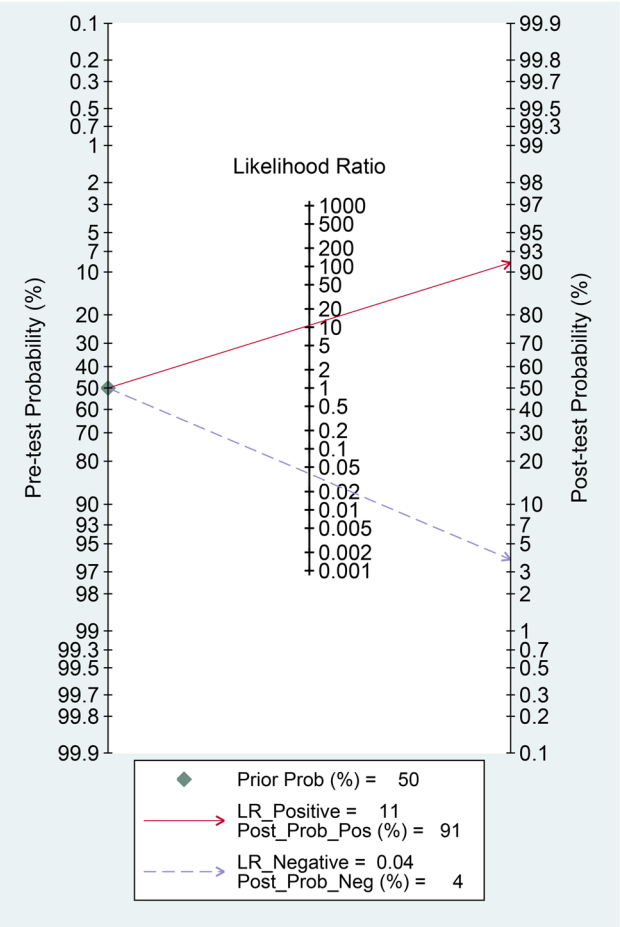


Fig. 5 Fagan nomogram of the serum MMP-7 test for diagnosis of biliary atresia

recommended as the single definitive test for biliary atresia diagnosis. Moreover, continuing re-evaluation during the course of disease is advisable. Further large-scale studies are warranted to validate our findings.

Author Contribution Xiaojie Tang and Yong Lv: studied the concept, drafted of the manuscript, and did the analysis.

Lihui Pu: helped the acquisition and interpretation of data.

Jingyu Ma: revised the article and optimized the language.

Shuguang Jin and Bo Xiang: studied the concept and critical revision of the manuscript for important intellectual concept.

Declarations

Conflict of Interest The authors declare no competing interests.

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