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# The value of intestinal fatty acid binding protein as a biomarker for the diagnosis of necrotizing enterocolitis in preterm infants: a meta-analysis

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## Abstract

**Background** Necrotizing enterocolitis (NEC) is a serious condition mainly affecting newborns, especially preterm or low birth weight ones, with a poor prognosis. The present study aimed to comprehensively evaluate the diagnostic value of intestinal-type fatty acid-binding protein (I-FABP) in NEC through meta-analysis.

**Methods** Relevant documents on the diagnosis of I-FABP in neonatal NEC were retrieved from PubMed, ScienceDirect, Embase, Cochrane, Wanfang, and CNKI databases. Summary receiver operating characteristic curve (SROC), sensitivity, specificity, and likelihood ratio (LR) were constructed to evaluate the pooled diagnostic value. Meta-regression analysis was conducted to explore the sources of heterogeneity. Sensitivity analysis was performed to detect the robustness of current results.

**Results** The present study encompassed 15 studies. I-FABP had a high diagnostic value for NEC, with a sensitivity at 0.78 (0.70–0.85), a specificity of 0.85 (0.78–0.90), and the area under the curve (AUC) value was 0.89 (0.86–0.91). The combined diagnostic odds ratio (DOR) was 20.33 (10.90–37.90) indicating a high diagnostic potential with strong discriminatory power. Sample source, detection method, and critical value might be the source of heterogeneity. There was no significant publication bias.

**Conclusion** I-FABP played a crucial role in diagnosing NEC in premature infants.

**Keywords** Intestinal fatty acid binding protein (I-FABP), Necrotizing Enterocolitis (NEC), Meta-analysis, Preterm infant

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## Background

Necrotizing Enterocolitis (NEC) is an inflammatory intestinal condition resulting from the interplay of various factors, including prematurity, formula feeding, abnormal colonization of the intestinal tract by gut microbiota, ischemia of the intestinal mucosa, infection, and dysbiosis [1, 2]. Pertinent statistical data indicates that NEC predominantly affects premature infants and those with low birth weight the incidence rate among premature infants is approximately 5–7%, while the rate for extremely low birth weight infants (< 2500 g) ranges from 30–50% [3]. Moreover, children affected by this condition frequently encounter adverse prognostic factors, including neurodevelopmental delays, growth impairments, and intestinal dysfunction, and these complications not only result in significantly increased healthcare costs but also profoundly affect the long-term quality of life for these children [4]. The pathogenesis of NEC remains poorly understood. Clinically, there has been limited advancement in the prevention, diagnosis, and treatment strategies for NEC in premature infants. Currently, the widely accepted diagnostic criteria for NEC are based on a modified version of Bell's classification [5]. Based on this, early diagnosis and intervention for NEC are of paramount importance. In recent years, researchers both domestically and internationally have conducted extensive studies in search of new biomarkers for NEC. Among these, intestinal fatty acid binding protein (I-FABP) has emerged as the most promising candidate biomarker.

I-FABP is a lipid-binding protein primarily located in the epithelial cells of the intestine, demonstrating significant tissue specificity [6]. Research shows that I-FABP is a reliable biomarker for intestinal cell injury, with high sensitivity and specificity to differentiate neonatal NEC from other conditions [7, 8, 9]. Gerald et al. [10] demonstrated that urinary I- FABP serves as a reliable biomarker for intestinal mucosal injury, exhibiting both sensitivity and specificity. In infants diagnosed with NEC, the levels of urinary I- FABP are typically elevated. Abdel-Haie et al. [11] involved 160 preterm infants with a gestational age of less than 35 weeks, and serum I- FABP levels were measured from birth. The findings indicated that when serum I-FABP levels were ≥ 7.75 ng/ml, the sensitivity for predicting neonatal NEC reached 94.4%, accompanied by a specificity of 100%. Furthermore, in instances where the infants presented symptoms such as abdominal distension and feeding intolerance, an I- FABP level exceeding 37.95 ng/ml resulted in both sensitivity and specificity for diagnosing NEC being at 100%. Furthermore, a significant correlation exists between serum I-FABP and urinary I-FABP ($P < 0.0001$) [12]. The levels of I-FABP are relatively low in healthy neonates; however, they demonstrate a significant increase in neonates diagnosed with NEC, particularly among preterm infants. These findings suggest that I-FABP may serve as an optimal biomarker for the diagnosis of NEC.

Currently, there have been numerous domestic and international studies focusing on the application of I-FABP in diagnosing neonatal NEC. However, previous meta-analyses failed to differentiate between premature infants and also exhibited variations in sample sources of I-FABP, resulting in significant disparities in its sensitivity and specificity for NEC diagnosis. To address this issue comprehensively, this study integrated relevant research to evaluate I-FABP's diagnostic efficacy for NEC in preterm infants.

## Materials and methods

### Literature search strategy

Potential articles were selected from PubMed, Embase, EBSCO, Cochrane Library, Wanfang, and China National Knowledge Infrastructure (CNKI) databases. Keywords for selection included: "Infant" or "Newborn" or "Neonates" or "Infant" or "Premature" or "Low-Birth-Weight Infant", and "Enterocolitis" or "Necrotizing" or "Necrotizing Enterocolitis", and "intestinal fatty acid binding protein" or "I-FABP". Manual selection has been performed to select potential articles from reference lists. Disputes were resolved through discussion. The literature search was performed electronically between November and December 2024 (the date of the last search was 12/1/2024).

### Inclusion and exclusion criteria

Inclusion criteria: [1] The study subjects were preterm infants, defined as those with a gestational age (GA) of less than 37 weeks or a low birth weight (LBW) of less than 2500 g; [3] had clear diagnostic criteria of NEC, and the inclusion of Bell stages in the diagnosis of premature infants at all stages of NEC; [4] had the control group with normal neonates or no-NEC neonates; [5] had sufficient data for the calculation of true positive (TP), true negative (TN), false positive (FP), false negative (FN). Excluded criteria contained: [1] study subjects were not premature infants; [2] the study type was not a diagnostic study; [3] had no sufficient data.

### Literature review

Two investigators independently reviewed and assessed each study, extracting relevant data from the included literature. In instances of conflicting opinions, an additional researcher was consulted for evaluation. Initially, duplicate records in the database were screened to eliminate redundancies, thereby ensuring the independence and accuracy of the research process. Subsequently, titles and abstracts of the literature were examined to make a preliminary judgment regarding their potential eligibility

for inclusion. Following this initial assessment, full texts of studies that appeared to meet the criteria were further analyzed to more accurately determine their compliance with inclusion standards. During this process, any uncertainties encountered were addressed through email communication with the authors of the articles to obtain more detailed information. The literature screening process and results were illustrated in Fig. 1.

#### Enhancement of literature data extraction

In the analysis of the 15 included studies, a comprehensive extraction of various information was conducted. This encompassed details such as the authors of the literature, publication dates, countries of origin, diagnostic criteria, sample source for both case and control groups, gestational age at birth, detection methods, area under the ROC curve, cutoff values, sensitivity and specificity of I-FABP in diagnosing NEC in neonates.

#### Assessment of document quality

The quality assessment of the included literature was performed utilizing Review Manager 5.4 software. This evaluation strictly adhered to the standards established by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria for standard assessment [13]. According to this standard, each question was assessed independently by two researchers who provided judgments of "Yes," "No," or "Unclear." In instances of disagreement, a discussion was conducted to achieve consensus.

#### Statistical analysis

Stata 16.0 was utilized for conducting the meta-analysis. Based on the extracted data, we calculated overall sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and their corresponding 95% confidence intervals (CI). The diagnostic discrimination capability was assessed by plotting the summary receiver operating characteristic curve (SROC) and calculating the area under the curve (AUC). Both sensitivity and specificity were reported with 95% credible intervals (CIs). Chi-square tests ($\chi^2$) and $I^2$ statistics were applied to assess heterogeneity among studies, with heterogeneity deemed significant when $P<0.05$ and $I^2 > 50\%$. A random-effects model was implemented in instances of significant heterogeneity, whereas a

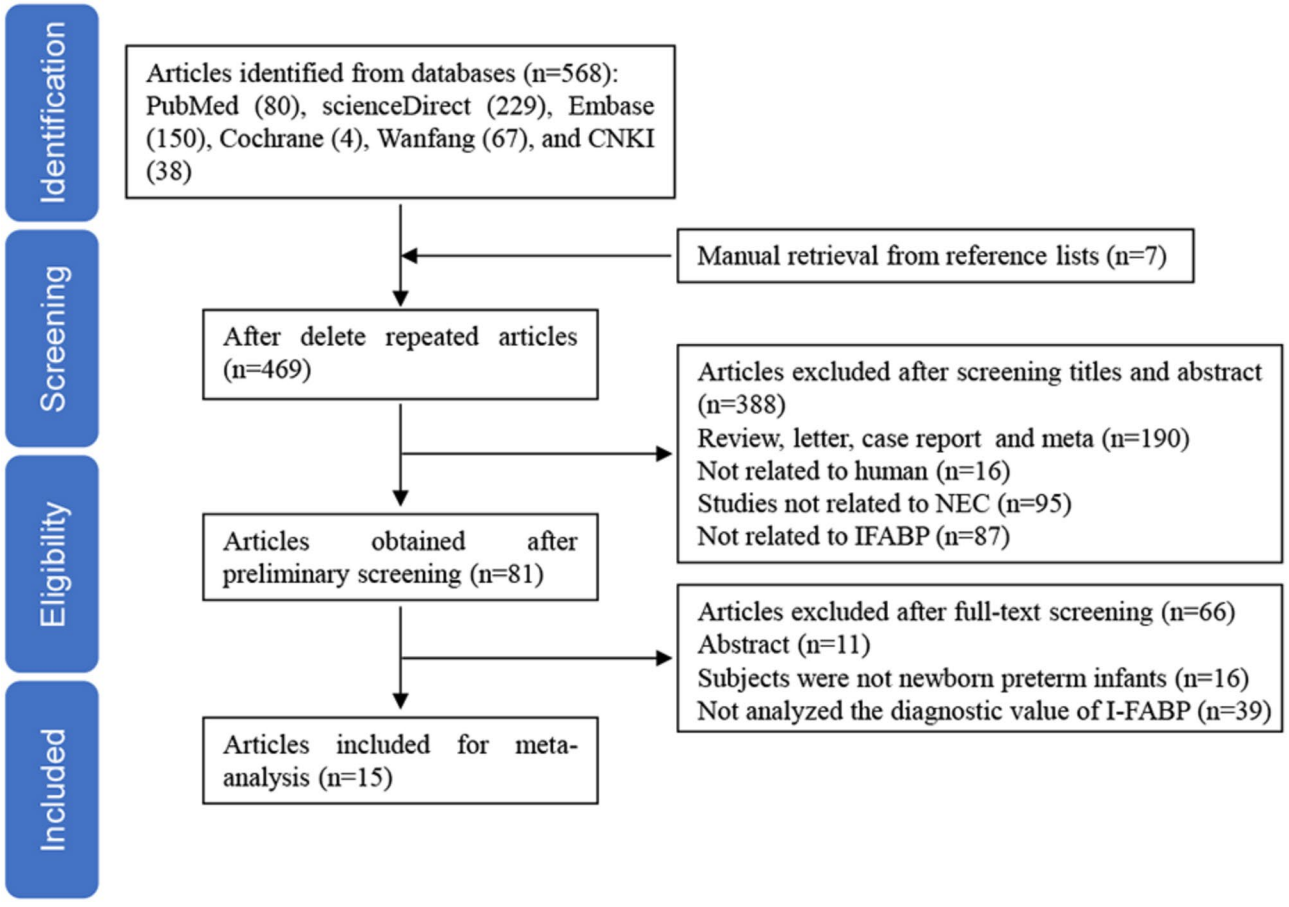


**Fig. 1** Refinement of the selection process for studies included in the meta-analysis

fixed-effects model was adopted when no heterogeneity was present. Subgroup analyses and meta-regressions were conducted for further exploration of sources of heterogeneity. Fagan's nomogram was used to calculate pre-test probabilities as well as post-test probabilities for PLR and NLR. Finally, funnel plots were generated to evaluate publication bias. All statistical tests unless otherwise specified, $P<0.05$ were considered statistically significant.

## Results

### Search outcomes

After conducting a systematic search, a total of 568 articles were identified, comprising 105 Chinese publications (Wanfang (67), CNKI (38)) and 463 English publications (PubMed (80), ScienceDirect (229), Embase (150), Cochrane (4)). Following the screening process detailed in Fig. 1, duplicate publications were excluded, resulting in a remaining total of 469 articles. A preliminary review of titles and abstracts led to the exclusion of an additional 388 articles. There were 190 categorized as reviews, letters, case reports, or meta-analyses; 16 that did not pertain to human subjects; 95 studies unrelated to necrotizing enterocolitis (NEC); and 87 that were not relevant to IFABP. Then 81 relevant studies pass into full text selection. After a comprehensive review of the full texts, 66 articles were excluded from consideration. Among these, 11 articles were classified as abstracts, the subjects of 16 articles were not newborn preterm infants, and 39 articles did not analyze the diagnostic value of I-FABP. Ultimately, 15 studies [7, 10, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26]. Among the 15 reviewed literatures, 7 studies utilized serum samples, 1 study employed plasma samples, 6 studies used urine samples, and 1 study investigated both serum and urine concurrently. The latter was considered as two separate test studies for this analysis, resulting in a total of 16 tests.

A total of 15 studies published between 2002 and 2024 were included in this analysis. The samples analyzed were derived from serum (8 tests), plasma (1 test), and urine (7 test). 15 studies were diagnosed by the Bell stage or the modified Bell staging method. I-FABP assessment in all studies employed enzyme-linked immunosorbent assay (ELISA) (14 tests detected I-FABP and 4 tests detected I-FABP/Cr). The fundamental characteristics of the included literature are summarized in Table 1.

### Results of quality assessment

The QUADAS-2 scale was applied using Cochrane bias risk tool of Revman 5.4 software to evaluate the quality of the included literature. The results indicate that the overall quality of the included studies is high. However, one study exhibited unclear reporting in the patient selection domain [19], another study demonstrated a higher risk of bias in the index test [24], and one study showed bias concerning reference standards [26]. Additionally, two studies presented biases in flow and timing [10, 24] (Fig. 2). Overall, the quality of the included research is considered to be high.

### Results of the meta-analysis

Due to the substantial heterogeneity observed in the sensitivity ($I^2=87.27\%$) and specificity ($I^2=87.88\%$) among these 16 trials, a random-effects model was employed. Sensitivity and specificity reflect the diagnostic accuracy of a method in identifying cases and controls accurately, where values closer to "1" indicate higher accuracy levels. The AUC was used for comprehensive evaluation

**Table 1** Characteristics of studies included in the meta-analysis

| Author | Year | Country | Criteria | Source | Detection method | Case | Control | Cutoff vale | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|---|---|---|
| Yu [14] | 2016 | China | Bell stage | serum | ELISA(I-FABP) | 30 | 60 | 21.25ng/ml | 73.30 | 70.00 |
| Yu [14] | 2016 | China | Bell stage | Urine | ELISA(I-FABP) | 30 | 60 | 8.75ng/ml | 80.00 | 51.70 |
| Lin [16] | 2022 | China | Bell stage | serum | ELISA(I-FABP) | 50 | 50 | / | 98 | 88 |
| Li [18] | 2022 | China | Bell stage | serum | ELISA(I-FABP) | 26 | 58 | / | 92.4 | 88 |
| Ji [19] | 2020 | China | Bell stage | serum | ELISA(I-FABP) | 74 | 74 | / | 81.36 | 93.26 |
| Shang [15] | 2014 | China | Bell stage | Urine | ELISA(I-FABP) | 19 | 55 | 2.567 ng/ml | 89.5 | 72.7 |
| Liu [17] | 2018 | China | Bell stage | Urine | ELISA(I-FABP) | 56 | 60 | 7.75 ng/ml | 85 | 46.3 |
| Wang [20] | 2017 | China | Bell stage | serum | ELISA(I-FABP) | 56 | 30 | 21.8 μg/L | 70 | 81 |
| Liu SJ [21] | 2024 | China | Bell stage | serum | ELISA(I-FABP) | 30 | 40 | 2.54 ng/mL | 76.7 | 87.5 |
| Huo [22] | 2021 | China | Bell stage | serum | ELISA(I-FABP) | 205 | 200 | 12.10 pg/ml | 92.5 | 72.6 |
| Gollin [10] | 2014 | USA | Bell stage | Urine | ELISA(I-FABP/Cr) | 5 | 21 | / | 100 | 95.6 |
| Reisinger [23] | 2012 | UK | Bell stage | Urine | ELISA(I-FABP/Cr) | 29 | 33 | 2.4 pg/nmol | 79 | 85 |
| Aydemir [24] | 2011 | Turkey | Bell stage | serum | ELISA(I-FABP) | 41 | 31 | / | 59.9 | 95 |
| Schurink [25] | 2015 | Netherlands | Bell stage | Urine | ELISA(I-FABP) | 22 | 15 | 687 ng/ml | 67 | 75 |
| Gregory [26] | 2014 | USA | Bell stage | Urine | ELISA(I-FABP) | 70 | 70 | 13.3 ng/ml | 60 | 78 |
| Guthmann [7] | 2002 | Germany | Bell stage | plasma | ELISA(I-FABP) | 14 | 26 | / | 71 | 100 |

Notes: Enzyme-Linked Immunosorbent Assay: ELISA. The classification method used in our included literature is Bell staging or the modified Bell staging method, which is collectively referred to here as Bell staging

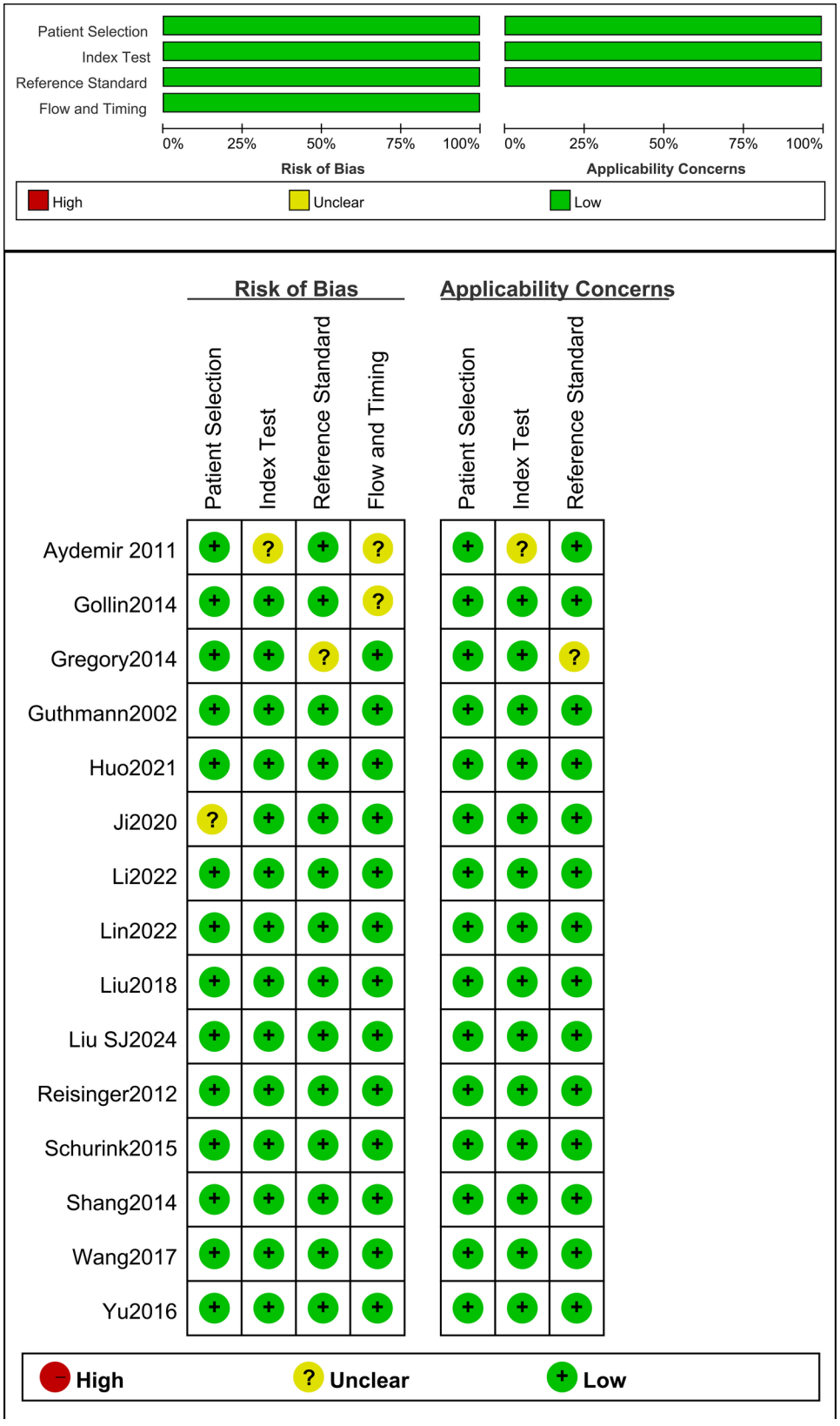


**Fig. 2** Methodological quality graph and methodological quality summary

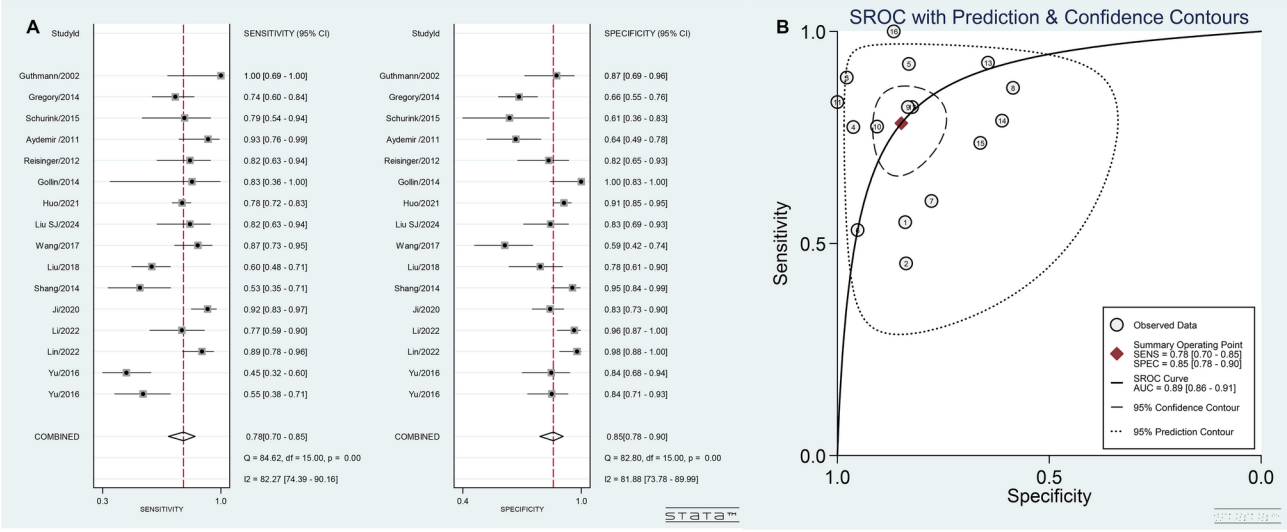


**Fig. 3** Evaluation of the Sensitivity and Specificity of I-FABP in NEC. (**A**) Sensitivity and specificity forest plot. (**B**) Symmetric receiver operating characteristic curve

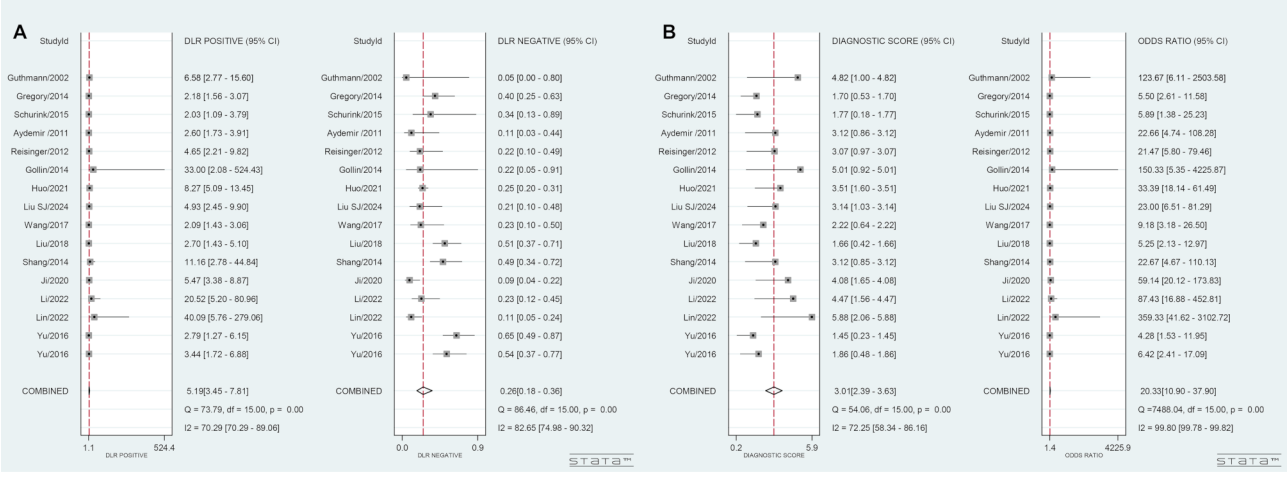


**Fig. 4** (**A**) Likelihood ratio forest figure. (**B**) Diagnostic odds ratio and diagnostic score

of diagnostic performance, with an SROC greater than 0.7 indicating good performance and exceeding 0.9 suggesting excellent performance. Based on our meta-analysis results, I-FABP exhibited a combined sensitivity of 0.78 (0.70–0.85) and specificity of 0.85(0.78–0.90) for diagnosing NEC (Fig. 3A), with an area under the curve of 0.89 ( 0.86 – 0.91) (Fig. 3B). The pooled PLR was 5.19(3.45–7.81), while the pooled NLR was 0.26 (0.18–0.36) (Fig. 4A). In general, a higher DOR was considered more favorable, and the combined DOR of all eligible studies was 20.33 (10.90–37.90) (Fig. 4B). The scatterplot results indicated that most data points were concentrated in the LRP < 10 region, with fewer points appearing in the LRN < 0.1 region, suggesting I-FABP's tendency to yield discriminative outcomes (Fig. 5A).

### Heterogeneity analysis

Based on the sample source, detection method, and cutoff value, meta-regression analysis was conducted to investigate the underlying sources of heterogeneity (Fig. 5B). Subgroup analysis showed that 9 studies had samples from serum and plasma (NO) and the remaining 7 studies had samples from urine (YES), with combined sensitivities of 0.46 (0.38–0.53) and 0.42 (0.32–0.51); combined specificity was 0.45 (0.26–0.65) and 0.71 (0.50–0.93), respectively. In 14 studies using ELISA to detect I-FABP (NO) and 2 studies using ELISA to detect I-FABP/Cr (YES), The comprehensive sensitivity was 0.46 (0.40–0.52) and 0.34 (0.17–0.51), and the comprehensive specificity was 0.55 (0.38–0.72) and 0.61 (0.04-1.00), respectively. In terms of critical value, 10 studies had critical value (NO) and 6 studies did not (YES), and the comprehensive sensitivity was 0.39 (0.30–0.48) and

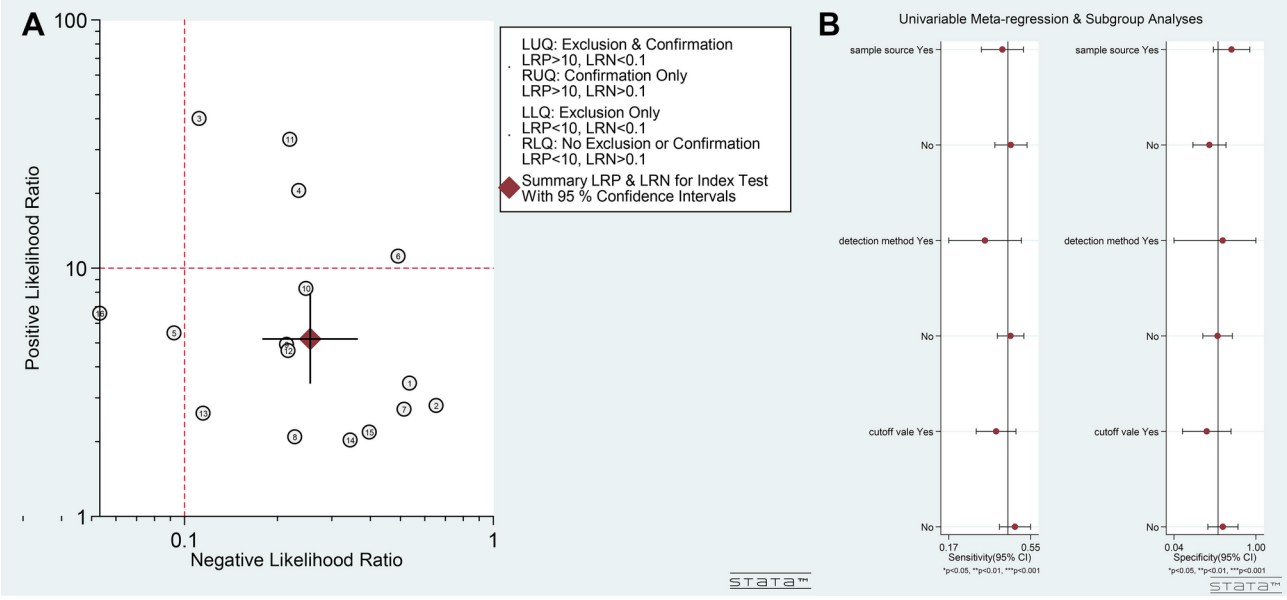


**Fig. 5** (**A**) Distribution scatter diagram. (**B**) Univariable meta-regression analysis

**Table 2** Regression analysis of stratified sensitivity and specificity notes: sample source no = serum or plasma, yes = urine; detection method NO = ELISA, YES = ELISA (I-FABP/Cr); cutoff value no = present, yes = not shown

| Parameter | Category | *N* studies | Sensitivity and Specificity | | | | Joint Model | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sensitivity | P1 | Specificity | P2 | LRTChi2 | *P* value | $I^2$ | $I^2$ low | $I^2$ high |
| Sample source | YES | 6 | 0.42 (0.32–0.51) | 0.73 | 0.71 (0.50–0.93) | 0.24 | 3.01 | 0.22 | 33 | 0 | 100 |
| | NO | 10 | 0.46 (0.38–0.53) | | 0.45 (0.26–0.65) | | | | | | |
| Detection method | YES | 2 | 0.34 (0.17–0.51) | 0.82 | 0.61 (0.04–1.00) | 0.77 | 1.54 | 0.46 | 0 | 0 | 100 |
| | NO | 14 | 0.46 (0.40–0.52) | | 0.55 (0.38–0.72) | | | | | | |
| Cutoff value | YES | 6 | 0.39 (0.30–0.48) | 0.95 | 0.42 (0.14–0.71) | 0.34 | 3.51 | 0.17 | 43 | 0 | 100 |
| | NO | 10 | 0.48 (0.41–0.55) | | 0.61 (0.44–0.79) | | | | | | |

Notes: Sample source NO = serum or plasma, YES=urine; detection method NO= ELISA, YES=ELISA (I-FABP/Cr); cutoff value NO=present, YES= not shown

0.48 (0.41–0.55); specificity was 0.42 (0.14–0.71) and 0.61 (0.44–0.79), respectively (Table 2). The results indicated no significant statistical heterogeneity in this subgroup analysis. It suggested that sample source, detection method, and critical value might be the source of heterogeneity. In contrast, there was minimal disparity between the detection methods. Urine exhibited a high specificity, thus recommending follow-up testing for I-FABP in urine.

### Clinical diagnostic efficiency

The pre-test and post-test probabilities of PLR and NLR were calculated using the Fagan nomogram, reflecting the diagnostic value of I-FABP. The pre-test probability for PLR was 50%, while the post-test probability increased to 84%. For NLR, the pre-test probability remained at 50%, but the post-test probability decreased to 20% (Fig. 6A).

### Publication bias

The Deeks funnel plot asymmetry test was employed to assess the potential publication bias of the included studies. A $P<0.01$ in the asymmetry test indicated a significant result for publication bias. As illustrated in Fig. 6B, the *P*-value from Deeks' funnel plot asymmetry test was 0.9, suggesting that there was no significant publication bias in this meta-analysis (Fig. 6B).

### Sensitivity analysis

The results of the sensitivity analysis indicated that the goodness of fit and bivariate normality reflect the degree to which the regression line aligns with the observed values. The distribution of observed values was centered around the reference line, demonstrating stability. Impact analysis suggested that one study may influence the overall results. Outlier detection confirmed that all studies fall within acceptable limits (Fig. 7a-d).

## Discussion

NEC remains a significant surgical emergency that poses a serious threat to life during the neonatal period [27]. The incidence of NEC has increased over the past two decades and presents a lower survival rate [28].

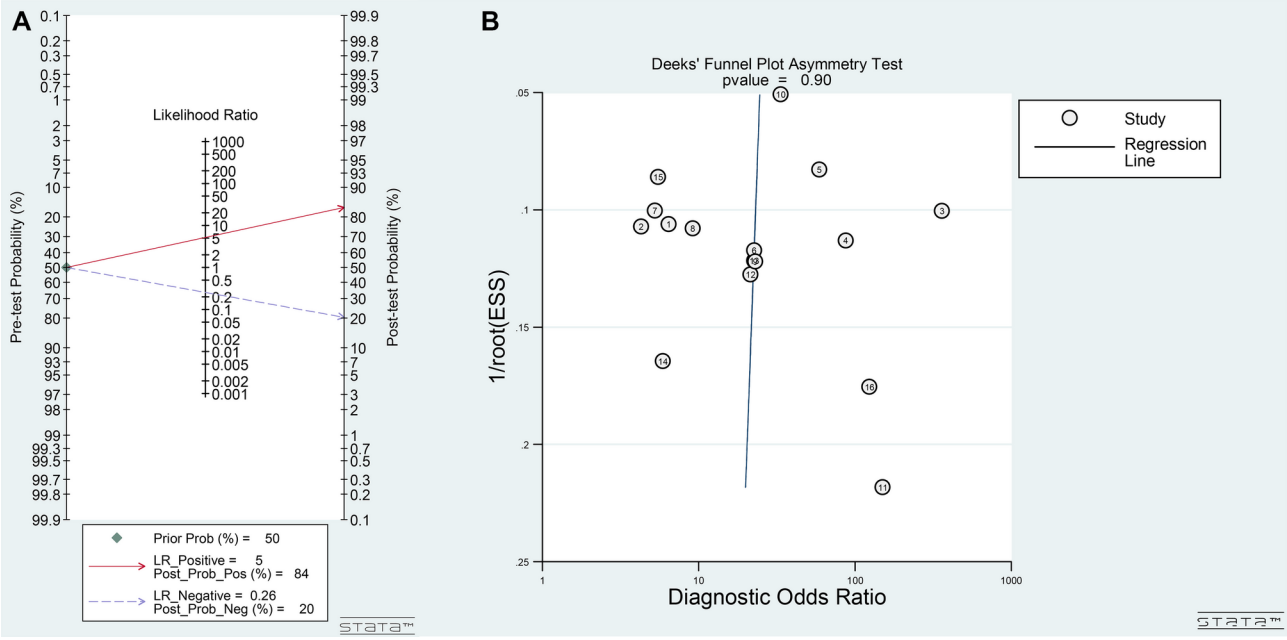


**Fig. 6** (**A**) Fagan Nomogram for Assessing the Diagnostic Accuracy of I-FABP in NEC. (**B**) Deek's funnel plot asymmetrical test

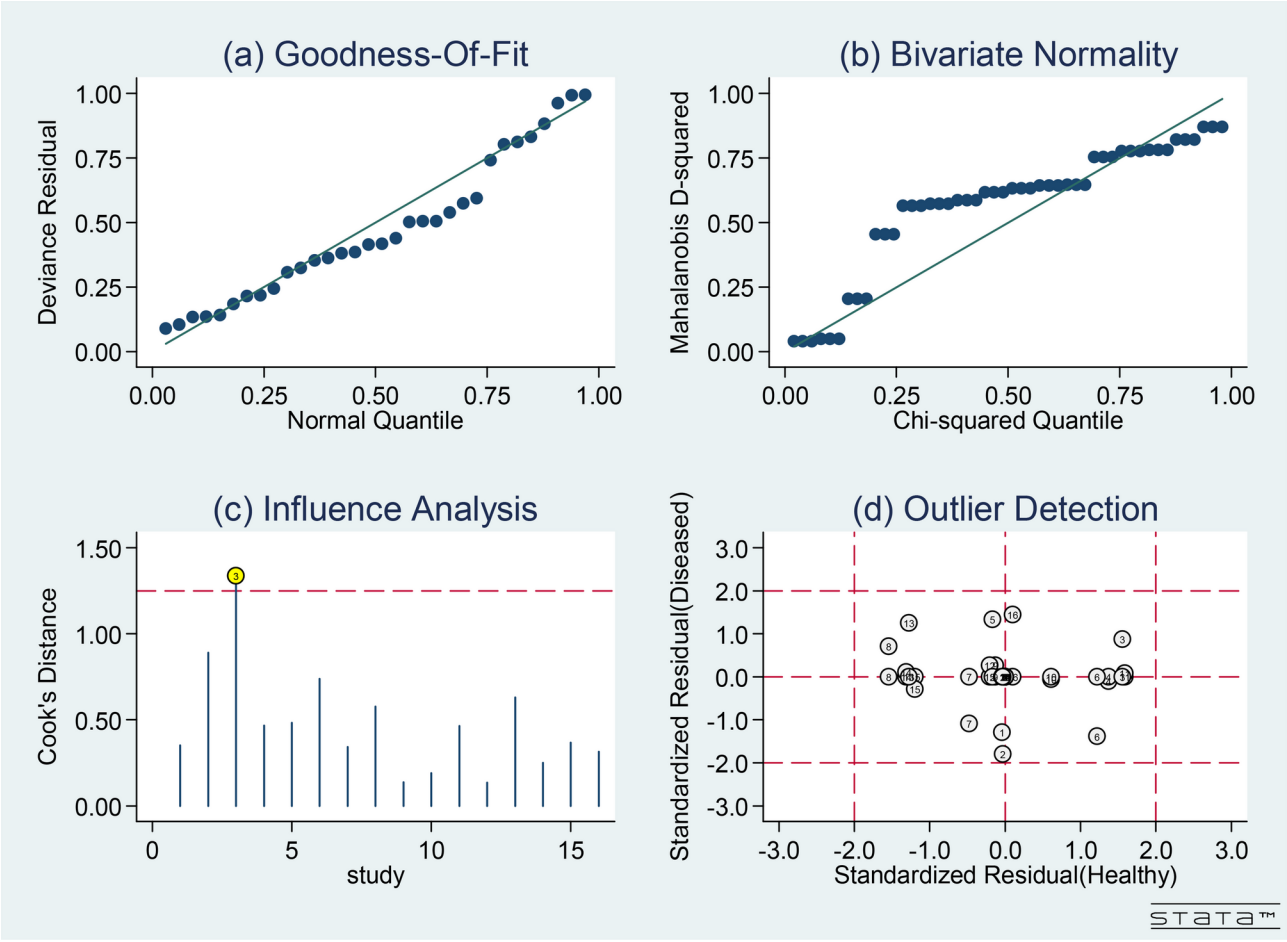


**Fig. 7** Sensitivity analyses: graphical depiction of residual-based (**a**) goodness-of-fit (**b**) bivariate normality (**c**) influence analysis and (**d**) outlier detection analysis

Khasawneh et al. [29] identified that premature infants constitute the primary population at risk for NEC. The pathogenesis of NEC remains unclear to this day. Research indicates that when intestinal epithelial cells undergo apoptosis during ischemia, they release I-FABP [28]. Many scholars generally consider I-FABP to be a promising biomarker for the diagnosis of NEC. Onay et al. [30] found that the levels of I-FABP in patients with NEC were significantly higher than those in the control group. The research on I-FABP for the diagnosis of NEC has been conducted both domestically and internationally. However, previous meta-analyses failed to differentiate between premature infants and also exhibited variations in sample sources of I-FABP, resulting in significant disparities in its sensitivity and specificity for NEC diagnosis. To address this issue comprehensively, this study integrated relevant research from both domestic and international sources using meta-analysis methods to evaluate published findings on I-FABP's diagnostic efficacy for NEC across serum, plasma, and urine samples. Specifically targeting premature infants (gestational age < 37 weeks) and low-birth-weight infants (LBW < 2500 g), a comprehensive analysis was conducted to assess the diagnostic accuracy of I-FABP while providing a scientific foundation for its clinical application in NEC diagnosis. The present meta-analysis encompassed 15 studies. I-FABP demonstrated a high diagnostic value for NEC, indicating significant diagnostic potential with robust discriminatory power. Potential sources of heterogeneity may include sample source, detection method, and critical value thresholds. Additionally, no significant publication bias was detected.

Previous studies have indicated that urinary I-FABP [10, 31] or serum I-FABP [11, 24, 32] might potentially serve as a biomarker for the diagnosis of NEC. Nevertheless, before this, no one has examined the impact of different I-FABP sample sources, cut-off values, and detection methods on the diagnosis of NEC. It has been reported that NEC was more prone to occur in preterm infants and low birth weight infants [3, 12]. However, there have been few studies on the diagnosis of NEC in infants who have been identified as preterm. Therefore, we conducted a meta-analysis specifically concentrating on preterm infants and low birth weight infants.

This meta-analysis enrolled 15 studies (16 tests), encompassing 757 NEC patients and 883 healthy control subjects, and conducted subgroup analysis based on sample source, detection method, and cutoff value to certify the heterogeneity sources. The results demonstrated that these factors were the sources of heterogeneity in the diagnosis of NEC using I-FABP. The results of previous meta-analyses indicated that the pooled sensitivity of I-FABP for NEC I, NEC II, and NEC III was 0.67, 0.74, and 0.83, respectively, while the pooled specificity was consistently 0.84 across all three stages. The overall diagnostic accuracy, as reflected by the AUC value, was 0.75 [33]; another study revealed that the comprehensive sensitivity of urinary I-FABP for the early diagnosis of NEC in newborns was 0.64, the specificity was 0.73, and the AUC value was 0.81 [34]. However, the results of our comprehensive meta-analysis of both serum and urine demonstrate that the comprehensive sensitivity of I-FABP for the diagnosis of NEC was 0.78, the specificity was 0.85, the AUC value was 0.89, and the DOR was 20.33. Moreover, Deeks' asymmetry test for the funnel plot did not reveal any publication bias. Goodness-of-fit and binary normality assessments demonstrated that the regression line closely aligns with the observed values, indicating a stable distribution of observations around the reference line. Sensitivity analysis suggested that one study may have an impact on the overall results. Outlier detection confirmed that all studies fell within acceptable limits for detection. These findings fully validated the significant correlation between I-FABP levels and the diagnosis of necrotizing enterocolitis, highlighting its strong diagnostic potential with high discriminatory power.

Overall, I-FABP played a pivotal role in the diagnosis of NEC in preterm infants. The subgroup analysis demonstrated that the source of I-FABP (serum or urine) exerted no influence on the accuracy of diagnosing NEC. Additionally, the subgroup analysis revealed that urine samples exhibited higher specificity compared to blood samples, and as a non-invasive sample type, urine was more accessible than blood. Based on these discoveries, it was recommended to utilize urine I-FABP as a diagnostic tool for NEC. Furthermore, the diagnostic experiments encompassed in this study were conducted in multiple countries, leading to inconsistencies in medical standards, the utilization of diagnostic equipment, and the timing of specimen collection, which might have an impact on the study results. Hence, further large-scale multicenter clinical trials are requisite to fully validate these findings. In conclusion, I-FABP has played a crucial role in the diagnosis assessment of NEC in preterm infants, and this finding provided novel clinical research evidence for the diagnosis of neonatal NEC.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05687-5.

Supplementary Material 1

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Not Applicable.

**Author contributions**
L. R and M. J conceived and designed the experiments. M.Y. H, H.L. W, D. G, S.Q. L and Q.R. Z performed the experiments. M.Y. H, H.L. W, D. G, S.Q. L and Q.R. Z contributed sample collection and statistical analysis. L. R and M. J wrote the

manuscript. All authors revised it critically for important intellectual content. All authors read and approved the final manuscript.

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**Data availability**
Corresponding authors may provide data and materials.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Conflict of interest**
The authors have declared no conflict of interest.

**Clinical trial number**
Not applicable.

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