

Clinical significance of FABP2 expression in newborns with necrotizing enterocolitis

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Background: This meta-analysis aimed to determine the role of human fatty acid binding protein 2 (FABP2) expression in the diagnosis of necrotizing enterocolitis (NEC) of newborns.

Data sources: Eligible studies for further statistical analysis were identified from various databases including PubMed, Expert Medica Database, Web of Science, Cochrane Library, Google Scholar, China BioMedicine and China National Knowledge Infrastructure. Random effects model was used, and summary standardized mean difference (SMD) with its 95% confidence interval (CI) was calculated to assess the association of FABP2 expression and NEC.

Results: Ten articles which included 572 infants (262 infants with NEC and 310 healthy controls) were included in the current meta-analysis. FABP2 showed a positive relationship with NEC of newborns (SMD=2.88, 95% CI=2.09-3.67, $P<0.001$). And FABP2 expression was higher in patients with advanced stage of NEC (stage III or stage II+III) than in those with early stage of NEC (stage I) (SMD=-0.48, 95% CI=-0.87 to -0.09, $P=0.015$). Ethnicity-stratified analysis yielded significantly different estimates with a high FABP2 expression in NEC in both Caucasians (SMD=3.16, 95% CI=1.90-4.43, $P<0.001$) and Asians (SMD=2.57, 95% CI=1.50-3.64, $P<0.001$). Sample-based subgroup analysis showed that FABP2 expression was positively correlated with neonatal NEC in both urinary- and blood-sample subgroups (all $P<0.05$).

Conclusion: The results prove that the high FABP2 expression is related to the damage to intestinal cells, which may be a possible early detection marker identifying neonatal NEC.

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Key words: fatty acid binding protein 2; meta-analysis; necrotizing enterocolitis of newborn; protein expression

Introduction

Necrotizing enterocolitis (NEC) of newborns is a severe gastrointestinal disorder ranking the second most common cause of death in premature infants.^[1] Preterm infants have a high morbidity of 10%-15% and a mortality of 20%-40%.^[2] It has been proved that the onset of NEC occurs in very low birth weight infants.^[3] Gastrointestinal ischemia and enteral aliments are the risk factors of NEC.^[4] In addition, bacterial colonization and prematurity are also the causes for the development of NEC or intestinal necrosis.^[5] The symptoms of defective intestinal epithelial barrier and gut wall inflammation are characterized by the etiology of NEC.^[6] Because of its sudden onset and rapid progression, NEC is difficult to anticipate, diagnose and treat.^[7] Hence, effective treatments of NEC are warranted and need further research into the molecular mechanisms about the onset of the disease.^[8] Intestinal fatty acid binding protein (FABP) is used as a marker to detect NEC by monitoring the degree of intestinal ischemia and necrosis.^[9,10]

FABPs is a set of widely expressed cytoplasmic proteins with small molecular weight and excellent organ specificity, which are immediately secreted into the systemic circulation upon the damage of cells.^[11] As a member of the FABPs family, FABP2, which is a *FABP2* gene encoding protein, accounts for up to 2% of the cytoplasmic proteins in the mature enterocyte, and it is responsible for the intake alongside with the transport of polar lipids like fatty acids from the lumen of the small

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bowel.^[7,12] FABP2 is a water soluble cytosolic protein with a small molecular weight of 14-15 kDa, and it is initially located in the mature enterocytes of the small intestine. FABP2 is also named as intestinal-type FABP (I-FABP).^[13] More specifically, FABP2 is expressed along the overall length of the entire small intestine, though the majority is found to be abundant in the medial portion.^[14] Because of its small molecular mass, FABP2 is believed to be delivered to the circulation immediately upon the loss of the integrity of cell membrane and the filtering of glomerulus with a renal excretion of 28% and a considerable half-life of 11 minutes. Therefore, it is supposed to be detectable in urine.^[15] Thus, varying FABP2 expressions in the urine could exactly reflect the severity of cell damage to the intestinal epithelia, making it possible to use FABP2 as a candidate indicator of the disease progression.^[16] In addition, increased expression of FABP2 has not yet been reported in intestinal diseases including NEC in humans.^[17-19] Reports^[16,19] described increased FABP2 expression in the NEC progression; but we found some contradictory results which deny the value of high FABP2 expression in NEC prediction.^[13,20] Because of inconsistent results about FABP2 expression in NEC, a meta-analysis was carried out to determine the correlation of FABP2 expression with NEC.

Methods

Data sources and key words

PubMed, Expert Medica Database, Web of Science, Cochrane Library, Google Scholar, China BioMedicine and China National Knowledge Infrastructure databases were searched. The terms or phrases we used in searching were as follows: "fatty acid-b proteins" or "FABP2 protein, human" or "FABP2" or "intestinal fatty acid binding protein 2" or "I-FABP" or "intestinal fatty acid-binding protein 2" or "intestinal fatty acid binding protein" or "intestinal fatty acid-binding protein" for the exposure factors ("enterocolitis, necrotizing" or "necrotizing enterocolitis" or "NEC" or "necrotic enterocolitis"), and "infant, newborn" or "newborn infant" or "newborn infants" or "newborns" or "newborn" or "neonate" or "neonates" or "neonatal" or "new born infant" or "newborn baby" or "newborn babies" for the subjects. There was no restriction of language of the article. Manual searching was done further to identify additional relevant studies.

Selection criteria

Human-associated case-control studies were included in the meta-analysis. All patients should be clinically diagnosed with neonatal NEC. Exclusion criteria were

as follows: 1) summary or abstracts; 2) animal studies; 3) duplicate publications; 4) incomplete data.

Data extraction

Data were independently extracted by two investigators using a standardized form, and consensus was reached on all items for recording. If consensus was not reached, the disagreements in data extraction were resolved by another investigator. The data extracted from each study included name of first author, publication year, country, ethnicity, language, disease, the total number of subjects, age, gender, detection method, stage of neonatal NEC, and FABP2 expression.

Quality assessment

The quality of the enrolled studies was evaluated according to the predefined criteria based on the Critical Appraisal Skill Program (CASP) criteria by the two investigators (<http://www.casp-uk.net/#!casp-tools-checklists/c18f8>). The CASP criteria were scored according to the following ten aspects: the study addressing a clearly focused issue (CASP01); appropriate research problem and research design for the research problem (CASP02); cases recruited appropriately (CASP03); controls selected in a right way (CASP04); measurement of exposure factors for minimizing bias (CASP05); control of other important confounding factors (CASP06); complete research result (CASP07); precise research result (CASP08); reliable research result (CASP09); research result applicable to the local population (CASP10); research result consistent with other evidence (CASP11). The CASP criteria for case-control studies included section A (CASP01-CASP07), B (CASP08-CASP09) and C (CASP10-CASP11).

Statistical analysis

Standardized mean differences (SMDs) and 95% confidence intervals (CI) were calculated to determine their correlation, and Z test was used to examine the significance of the overall effect. A random-effect model was used when heterogeneity was found among studies ($P < 0.05$ or I^2 test exhibited $> 50\%$) or a fixed-effect model was used when no heterogeneity was detected. The Cochran's Q test ($P < 0.05$) and I^2 test (0%, no heterogeneity; 100%, maximal heterogeneity) were also conducted to detect the heterogeneity among the studies.^[21,22] A sensitivity analysis was made to determine whether the individual study results had a significant effect on the overall results by deleting single study one by one. Publication bias was assessed using the funnel plot and Egger test.^[23] All tests were two-sided and $P < 0.05$ indicated the significance of our

results. Investigators inputted all data in version 12.0 STATA software (Stata Corp, College Station, TX, USA).

Results

Included studies

A total of 10 case-control studies published in 2002-2014 were enrolled. They focused on the association of FABP2 expression with neonatal NEC in Asians and Caucasians, including 649 subjects altogether (260 infants with NEC and 389 healthy controls) (Table).^[7,12,13,16,19,20,24-27] The studies were from different countries: USA (1 study), China (3 studies), the Netherlands (3 studies), Turkey (1 study), UK (1 study), and Germany (1 study). Samples were taken from urine (5 studies) and blood (5 studies). Infants with NEC were found in various stages: Bell stage I, Bell stage II, Bell stage III, Bell stage II+III, Bell stage, Walsh and Kliegman I, Walsh and Kliegman II, Walsh and Kliegman III, and Walsh and Kliegman II+III. Enzyme-linked immuno sorbent assay (ELISA) was the only method detecting FABP2 expression in this meta-analysis. The preferred reporting items for systematic reviews and meta-analyses 2009 flow diagram reporting the results of this meta-analysis is shown in Fig. 1. A total of 23 records were identified through databases searching, and subsequently duplicates ($n=1$), non-human studies ($n=2$), letters, reviews or meta-analysis ($n=3$), the records not related to research topics ($n=2$), not case-control or cohort study ($n=1$), not relevant to NEC ($n=1$), not relevant to FABP2 ($n=2$), or not supplying enough information ($n=1$) were excluded. And 10 studies were finally enrolled for selection into our meta-analysis study.

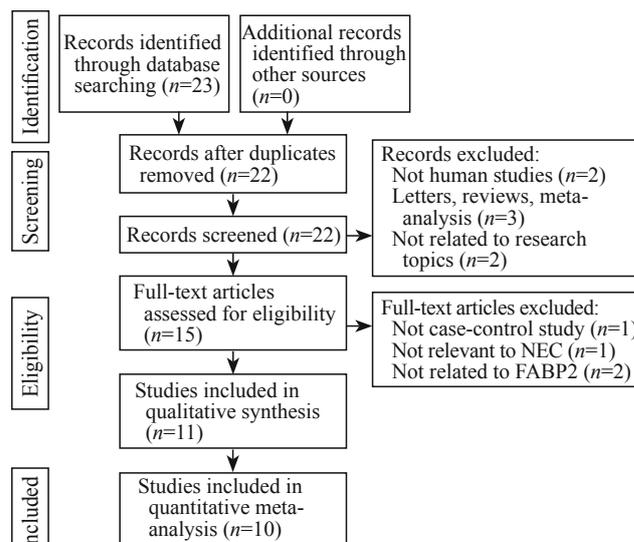


Fig. 1. The PRISMA 2009 flow diagram for reporting this meta-analysis. NEC: necrotizing enterocolitis; FABP2: fatty acid binding protein 2.

	CASP01	CASP02	CASP03	CASP04	CASP05	CASP06	CASP07	CASP08	CASP09	CASP10	CASP11
Gregory (2014) ^[7]	+	+	+	+	?	+	+	+	+	+	?
Qin (2013) ^[24]	+	+	+	+	-	+	+	+	+	+	?
Li (2013) ^[25]	+	+	+	+	?	-	+	+	+	+	+
Ng (2013) ^[19]	+	+	+	+	-	?	+	+	+	+	?
Reisinger (2012) ^[20]	+	+	+	+	-	?	+	+	+	+	?
Aydemir (2011) ^[12]	+	+	+	+	+	?	+	+	+	?	+
Thuijls (2010) ^[16]	+	+	+	+	-	?	+	+	+	+	?
Evennett (2010) ^[13]	+	+	+	+	?	-	+	+	+	+	?
Derikx (2007) ^[26]	+	+	+	+	+	+	+	+	+	?	-
Guthmann (2002) ^[27]	+	+	+	+	?	+	+	+	+	+	?

Fig. 2. The methodological quality of the 10 case-control studies was assessed using the CASP scores. CASP: Critical Appraisal Skill Program. "+": yes; "-": no; "?": unclear.

Table. Characteristics of included studies focused on serum level of FABP2

First author	Year	Ethnicity	Stage	Total	Sample size		Gender (M/F)		Gestational age (wk)		Sample Method
					Case	Control	Case	Control	Case	Control	
Gregory-a ^[7]	2014	Caucasians	Bell stage I	36	18	18	7/11	11/7	26 (25-28)	27 (25-27)	Urinary ELISA
Gregory-b ^[7]	2014	Caucasians	Bell stage II	42	21	21	14/7	14/7	27 (26-28)	27 (26-28)	Urinary ELISA
Gregory-c ^[7]	2014	Caucasians	Bell stage III	62	31	31	22/9	13/12	25 (24-26)	26 (25-27)	Urinary ELISA
Qin-a ^[24]	2013	Asians	Bell stage I	39	13	26	-	-	38.4±2.2	37.7±2.8	Blood ELISA
Qin-b ^[24]	2013	Asians	Bell stage II+III	39	13	26	-	-	37.2±3.2	37.7±2.8	Blood ELISA
Li-a ^[25]	2013	Asians	Bell stage	75	30	45	17/13	25/20	31.0±1.2	31.0±1.9	Blood ELISA
Li-b ^[25]	2013	Asians	Bell stage	65	30	35	17/13	19/16	31.0±1.2	31.0±1.3	Blood ELISA
Ng ^[19]	2013	Asians	Bell stage II+III	60	20	40	13/7	27/13	28.4 (25.6-30.1)	27.8 (26.0-29.1)	Blood ELISA
Reisinger ^[20]	2012	Caucasians	Bell stage II+III	62	29	33	11/18	21/12	215 (184-268)	213 (175-289)	Urinary ELISA
Aydemir-a ^[12]	2011	Asians	Walsh and Kliegman I	53	22	31	10/12	10/21	29.2±2.4	31.4±2.3	Blood ELISA
Aydemir-b ^[12]	2011	Asians	Walsh and Kliegman II	39	8	31	-	10/21	-	31.4±2.3	Blood ELISA
Aydemir-c ^[12]	2011	Asians	Walsh and Kliegman III	42	11	31	-	10/21	-	31.4±2.3	Blood ELISA
Thuijls ^[16]	2010	Caucasians	Bell stage II+III	35	14	21	9/5	12/9	31 (27-38)	31 (25-41)	Urinary ELISA
Evennett ^[13]	2010	Caucasians	Bell stage II+III	22	16	6	-	-	34 (28-41)	36 (32-40)	Urinary ELISA
Derikx ^[26]	2007	Caucasians	Walsh and Kliegman II+III	29	17	12	-	-	-	-	Urinary ELISA
Guthmann-a ^[27]	2002	Caucasians	Walsh and Kliegman I	31	5	26	-	-	-	30 (28-33)	Blood ELISA
Guthmann-b ^[27]	2002	Caucasians	Walsh and Kliegman II	29	3	26	-	-	-	30 (28-33)	Blood ELISA
Guthmann-c ^[27]	2002	Caucasians	Walsh and Kliegman III	30	4	26	-	-	-	30 (28-33)	Blood ELISA

FABP2: fatty acid-binding protein 2; M: male; F: female; ELISA: enzyme linked immunosorbent assay. "-": not reported.

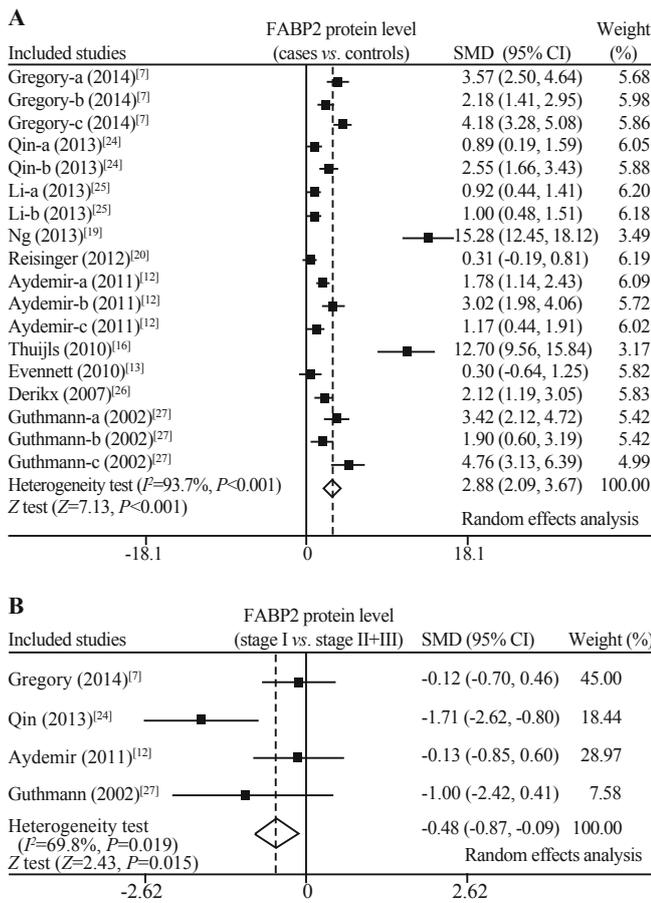


Fig. 3. Forest plots for the differences of FABP2 protein level between necrotizing enterocolitis of newborns and healthy controls. FABP2: fatty acid binding protein 2; SMD: standardized mean differences; CI: confidence interval.

The baseline characteristics and CASP criteria for the 10 studies are shown in Table and Fig. 2, respectively.

Association between FABP2 expression and neonatal NEC

As shown in Fig. 3, a positive association was found between FABP2 expression and neonatal NEC (SMD=2.88, 95% CI=2.09-3.67, $P<0.001$). Additionally, FABP2 expression was much higher in patients with advanced stage of NEC (stage III or stage II+III) than that in the early stages of NEC (stage I), with statistically significance (SMD=-0.48, 95% CI=-0.87 to -0.09, $P=0.015$). Ethnic-based subgroup analysis indicated that high FABP2 expression increased neonatal NEC risk in both Caucasian population (SMD=3.16, 95% CI=1.90-4.43, $P<0.001$) and Asian population (SMD=2.57, 95% CI=1.50-3.64, $P<0.001$). Further subgroup analyses of samples showed that FABP2 expression was positively correlated with neonatal NEC in both urinary- (SMD=3.12, 95% CI=1.55-4.70, $P<0.001$) and blood-samples subgroups

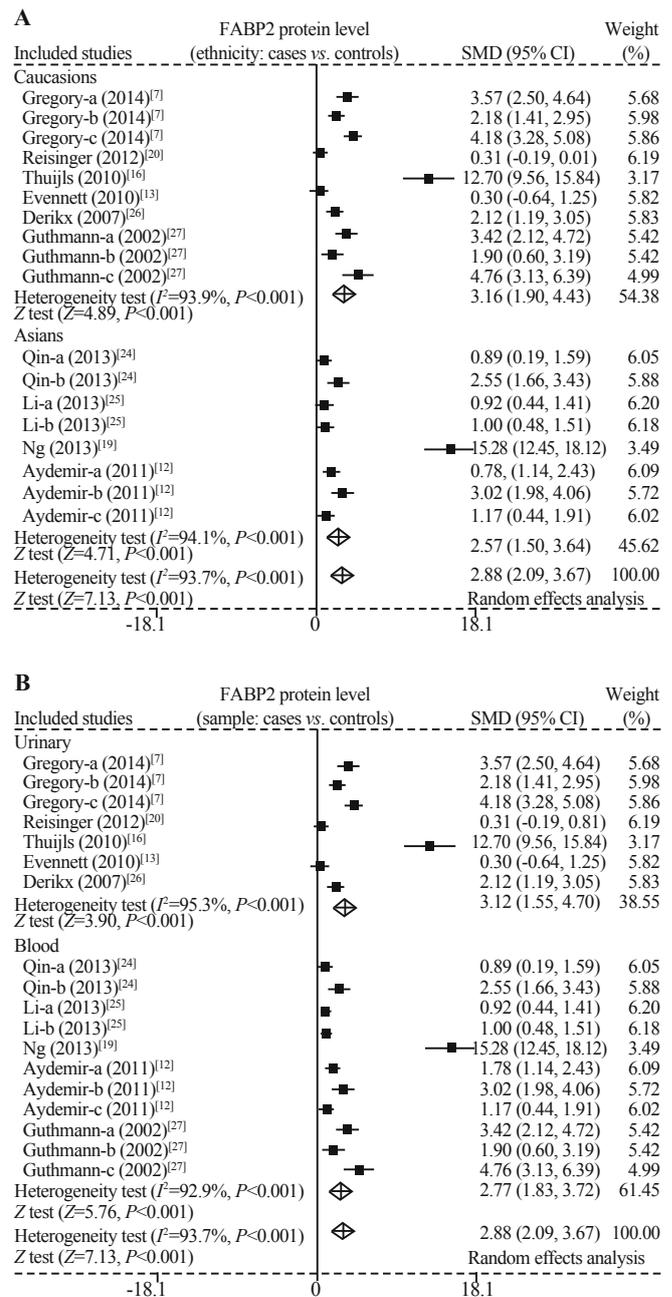


Fig. 4. Subgroup analysis for the differences of FABP2 in necrotizing enterocolitis of newborns and healthy controls. FABP2: fatty acid binding protein 2; SMD: standardized mean differences; CI: confidence interval.

(SMD=2.77, 95% CI=1.83-3.72, $P<0.001$) (Fig. 4).

Sensitivity analysis and publication bias

The results after sensitivity analyses suggested that each study exerted no marked influence on the pooled SMDs of the connections between FABP2 expression and neonatal NEC (Fig. 5). The graphical funnel plots of the 10 studies presented a little asymmetry, and Egger's test showed publication bias ($P<0.001$) (Fig. 6).

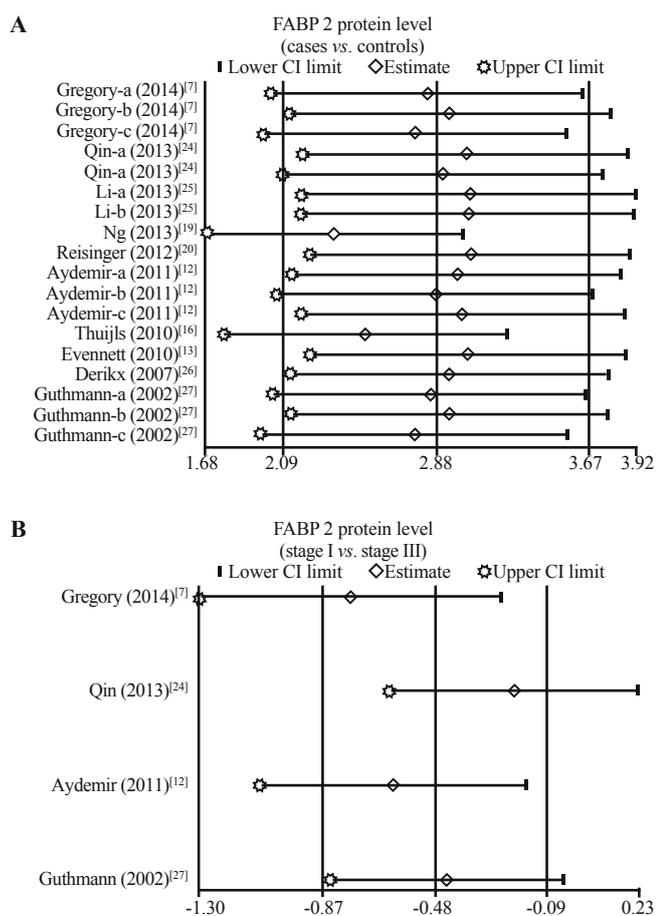


Fig. 5. Sensitivity analysis of the summary odds ratio coefficients for the differences of FABP2 expression in necrotizing enterocolitis of newborns and healthy controls. FABP2: fatty acid binding protein 2; CI: confidence interval.

Discussion

To determine the association of FABP2 expression and NEC, a meta-analysis of the studies was made. The results of the analysis showed that there was a significant relationship between high FABP2 expression and the pathogenesis of NEC. FABPs comprising cytoplasmic proteins with a small molecular mass about 15 kDa and a high specificity and sensibility to organs could be useful for solubilization and trafficking of ligands, affecting the lipid metabolism.^[28] FABP2, a member of FABPs, also known as I-FABP, a water-soluble protein, is expressed from the duodenum to the cecum in the gut which makes up 2% of cytosolic proteins in mature enterocytes, and could be measurable in the blood and urine after mucosal injury of enterocytes resulting in intestinal ischemia.^[27,29] The cytoplasmic content of FABP2 could be delivered into the systematic circulation once the death of enterocyte happens, thus the elevated FABP2 concentration in the blood has been shown in many human intestinal diseases, such

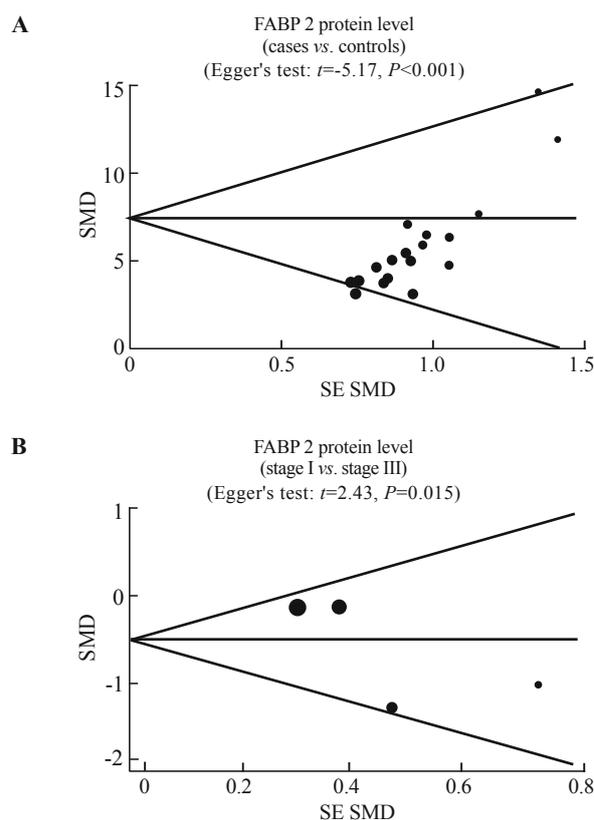


Fig. 6. Funnel plot of publication bias for the differences of FABP2 expression in necrotizing enterocolitis of newborns and healthy controls. FABP2: fatty acid binding protein 2; SMD: standardized mean differences; SE: standard error.

as intestinal ischemia, systemic inflammatory response syndrome, strangulated mechanical, small bowel obstruction, mesenteric infarction and NEC.^[12,13] Most imaging techniques and laboratory tests are reported to be lack of diagnostic accuracy of NEC, whereas the detection of FABP2 could identify the damage of intestinal cell and could sensitively and selectively differentiate NEC from many other diseases, which could be even better if combined with other intestinal inflammation marker such as fecal calprotectin.^[7,20] Additionally, plasma FABP2 with a small molecular weight could pass the glomerular filter and be detected in urine, and as FABP2 could not be expressed in the urinary tract, FABP2 concentration could reflect the extent of intestinal mucosal damage. Even after the clearance of intestinal ischemia in transient time with the bladder as a storage site, urinary FABP2 might be a better biomarker for NEC.^[16] Furthermore, cumulative release of FABP2 could estimate the extent of intestinal damage which is of great importance for treatment, including surgery time, duration of antibiotic treatment, and time of enteral feeding.^[26] We conclude that FABP2 could be a marked biomarker for identification of NEC with a high specificity and sensitivity because of its

special expression site in the intestinal mucosa cilia which is sensible to hypoxia. Blood and urine detection could be used for the diagnosis of NEC with the increased extent of FABP2 in proportion to the length and extent of intestinal lesions. In lines with our study, Schurink et al^[10] found that FABP2 in urine correlates with FABP2 in blood in patients with suspected NEC which could offer a chance to select an appropriate and convenient way for FABP2 measurement.

To evaluate other factors affecting the validity of our overall results, we conducted a meta-analysis as well as a subgroup analysis based on ethnicity and sample size. From the stratified analysis of ethnicity, we could know that there is no obvious influence of races in both Asians and Caucasians, indicating the possible wide application of FABP2 detection. In conclusion, our results are partly in consistent with previous studies that the high expression of FABP2 has a strong association with NEC, suggesting that FABP2 might be a better marker for NEC diagnosis and prognosis.

Case-control studies showed that single urinary FABP2 measurement was not completely accurate in detecting newborns with NEC of different severity. We detected FABP2 expression in blood samples that may ensure the accuracy of results. In addition, a unified detection method (ELISA method in ten trails) was conducted in the methodological analysis, helping to diminish methodologic bias. This study has limitations. First, this research had a small size of samples, i.e. less than 20 patients were enrolled. Second, clinical decision-making cannot be made exclusively on one single or overmuch biomarkers, and coincidentally only FABP2 expression was involved. Third, articles in Chinese and English were included. Publication bias was also discovered, indicating that the data obtained may not reflect the actual results.

In summary, the results of our analysis suggest that FABP2 expression may be a significant indicator for neonatal NEC. We support that FABP2 expression may be used as a possible early detection marker, and that FABP2 provides some meaningful interpretation in identifying the progression of neonatal NEC.

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Ethical approval: Not necessary.

Competing interest: No conflicts of interest.

Contributors: Liu Y proposed the study and wrote the first draft. Jiang LF analyzed the data. All authors contributed to the design and interpretation of the study, and Zhang WT is the guarantor.

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