Original Article

Evaluation of white matter microstructural alterations in premature infants with necrotizing enterocolitis

Chunxiang Zhang[1,2], Xin Zhao[1,2], Zitao Zhu[3], Kaiyu Wang[4], Brianna F. Moon[5], Bohao Zhang[2], Sayed Noman Sadat[6], Jinxia Guo[4], Jieaoxue Bao[1,2], Ding Zhang[1,2], Xiaoan Zhang[1,2]

[1]Department of Radiology, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [2]Institute of Neuroscience, Zhengzhou University, Zhengzhou, China; [3]Medical College, Wuhan University, Wuhan, China; [4]GE HealthCare, MR Research China, Beijing, China; [5]Institute for Innovation in Imaging, Department of Radiology, Massachusetts General Hospital, Boston, MA, USA; [6]University of Central Lancashire, London, UK

Contributions: (I) Conception and design: C Zhang, X Zhao, Z Zhu; (II) Administrative support: X Zhang; (III) Provision of study materials or patients: B Zhang; (IV) Collection and assembly of data: J Bao, D Zhang; (V) Data analysis and interpretation: K Wang, BF Moon, SN Sadat, J Guo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xiaoan Zhang, MD. Department of Radiology, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Institute of Neuroscience, Zhengzhou University, No. 7 Kangfuqian Street, Zhengzhou 450015, China. Email: zxa@zzu.edu.cn.

Background: Preterm infants with necrotizing enterocolitis (NEC) are at high risk of adverse neurodevelopmental outcomes. The aim of this study was to explore the value of diffusion tensor imaging (DTI) combined with serum C-reactive protein (CRP) and procalcitonin (PCT) in evaluating alterations of white matter (WM) microstructure in preterm infants with NEC.

Methods: A retrospective cross-sectional study was conducted in which all participants were consecutively enrolled at The Third Affiliated Hospital of Zhengzhou University from June 2017 and October 2021. Data from 30 preterm infants with NEC [mean gestational age at birth 31.41±1.15 weeks; mean age at magnetic resonance imaging (MRI) 37.53±3.08 weeks] and 40 healthy preterm infants with no NEC were recorded (mean gestational age at birth 32.27±2.09 weeks; mean age at MRI 37.15±3.23 weeks). WM was used to obtain the fractional anisotropy (FA) and mean diffusivity (MD) values of the regions of interest (ROIs). Additionally, serum levels of CRP and PCT were determined. Spearman correlation analysis was performed between the WM-derived parameters, CRP level, and the PCT serum index.

Results: Preterm infants with NEC had reduced FA values and elevated MD values in WM regions [posterior limbs of the internal capsule (PLIC), lentiform nucleus (LN), frontal white matter (FWM)] compared to the control group ($P<0.05$). Additionally, the FA of the PLIC was negatively correlated with serum CRP ($r=-0.846$; $P<0.05$) and PCT ($r=-0.843$; $P<0.05$). Meanwhile, the MD of PLIC was positively correlated with serum CRP ($r=0.743$; $P<0.05$) and PCT ($r=0.743$; $P<0.05$, respectively). The area under the curve (AUC) of FA and MD combined with CRP and PCT in the diagnosis of WM microstructure alterations with NEC was 0.968, representing a considerable improvement in predicted efficacy over single indicators, including FA [AUC: 0.938; 95% confidence interval (CI): 0.840–0.950], MD (AUC: 0.807; 95% CI: 0.722–0.838), CRP (AUC: 0.867; 95% CI: 0.822–0.889), and PCT (AUC: 0.706; 95% CI: 0.701–0.758).

Conclusions: WM can noninvasively and quantitatively assess the WM microstructure alterations in preterm infants with NEC. WM combined with serum CRP and PCT demonstrated superior performance in detecting and evaluating WM microstructure alterations in preterm infants with NEC.

Keywords: Necrotizing enterocolitis (NEC); white matter (WM); microstructure alterations; diffusion tensor imaging (DTI)

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Introduction

Necrotizing enterocolitis (NEC) remains one of the most common complications of prematurity (1), with white matter (WM) microstructure alterations being common among survivors with NEC. In an acute process, intestinal barrier dysfunction and injury allow bacteria and inflammatory mediators to enter the systemic circulation. The cytokines which are produced in the acute phase may disrupt the development of the vulnerable preterm brain (2). Therefore, infants with NEC have a higher risk of WM microstructure alterations.

For infants with microstructure alterations, diffusion tensor imaging (DTI) is more helpful in investigating an underlying WM microstructure abnormality in comparison to conventional structural magnetic resonance imaging (MRI) scan protocols such as the T_1-weighted imaging (T_1WI), T_2-weighted imaging (T_2WI), and T_2-fluid attenuated inversion recovery (T_2-FLAIR) (3,4). Fractional anisotropy (FA) is derived from DTI and is a measurement of the anisotropy of water diffusion in fiber bundles and allows for the detection of the degree of fiber myelination. Furthermore, DTI can aid in identifying the location of WM microstructure alterations. Neuroinflammation causes disruption of the cell membrane, which leads to water flowing into the extracellular environment, thus directly increasing mean diffusivity (MD) values in the brain. Moreover, the inflammatory response causes myelin damage, which manifests as reduced diffusion heterogeneity, causing reduced FA. In a study of DTI, Barnett *et al.* report lower FA values in the posterior limbs of the internal capsule (PLIC) and the corpus callosum of preterm infants with NEC (5). DTI has also shown sensitivity in detecting delayed cerebral maturation, which appears more commonly in preterm infants with NEC (6). Known areas of aberrant development that have been assessed include the PLIC, frontal white matter (FWM), and parietal white matter (PWM), while suspected areas include the caudate nucleus (CN), thalamus (TH), and cerebral peduncle (CP) (7-9). In addition, the C-reactive protein (CRP) and procalcitonin (PCT) are sensitive and convenient indicators of inflammation (10,11). Various biomarkers for early diagnosis of NEC have been studied, including inflammation and neutrophil biomarkers. A relationship between higher cytokine levels, such as CRP and PCT, and worse neurodevelopmental has also been demonstrated in neonates with NEC (12-14). These studies have illustrated that the inflammatory cascade plays an important role in the WM microstructure development of NEC. CRP is a sensitive marker of inflammation in preterm infants with NEC, and PCT is a biomarker that is elevated during a bacterial infection (15). A study conducted by Cetinkaya *et al.* found that white blood cell, CRP, and PCT levels are increased in infants with NEC (16). This suggests that CRP and PCT are valuable for detecting and monitoring NEC.

NEC survivors are at higher risk of WM microstructure alterations. Therefore, there is an urgent need to find effective methods to predict WM microstructure alterations at an early stage. Thus far, DTI, serum CRP, and PCT have been investigated as it relates to their efficacy in detecting WM microstructure alterations of premature infants with NEC (17,18). However, the value of their combination has not been extensively reported. The purpose of this study was thus to determine the value of DTI combined with serum CRP and PCT in assessing the alterations of WM microstructure in preterm infants with NEC. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-195/rc).

Methods

Participants

This retrospective, cross-sectional study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University (No. 2022-253-01). Written informed consent was obtained from each participating infant's legal guardian. We collected imaging datasets from 250 infants between June 2017 and October 2021. The inclusion criteria for the preterm infants in the NEC group were the following: (I) with at least stage 2a of NEC (i.e., presence of pneumatosis intestinalis on abdominal X-ray films based on the

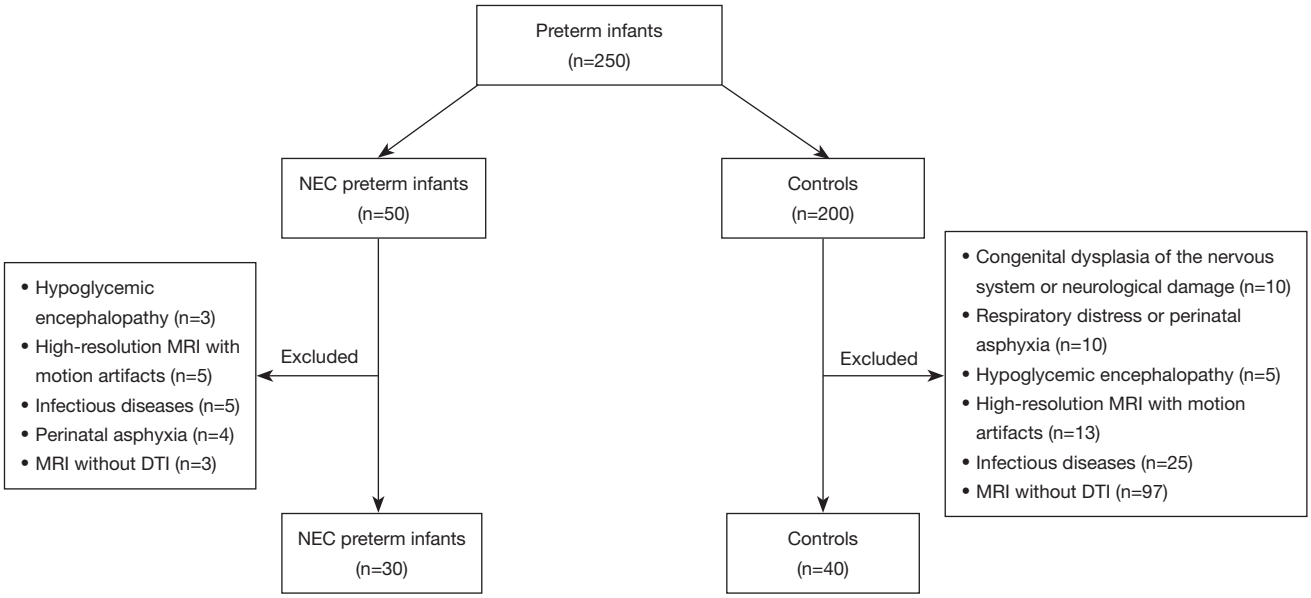

Figure 1 Flowchart of the study. NEC, necrotizing enterocolitis; MRI, magnetic resonance imaging; DTI, diffusion tensor imaging.

modified Bell's classification of NEC) (19); (II) absence of perinatal asphyxia, hypoglycemic encephalopathy, bilirubin encephalopathy, and other encephalopathy; and (III) high-resolution MRI without motion artifacts. Meanwhile, the exclusion criteria were the following: (I) chromosomal mutation or hypotension; (II) genetic or structural defects can be seen; (III) septicemia among newborn, neonatal infectious pneumonia, bronchopulmonary dysplasia, and other infectious diseases; (IV) MRI without DTI; and (V) an unstable clinical condition unsuitable for MRI. For the control group, the exclusion criteria were the following: (I) congenital dysplasia of the nervous system or neurological damage; (II) respiratory distress or perinatal asphyxia; (III) hypoglycemic encephalopathy; (IV) high-resolution MRI with motion artifacts; (V) with infectious diseases; (VI) MRI without DTI; and (VII) NEC. In total, a group of 70 preterm infants (39 boys and 31 girls) were recruited, including 30 preterm infants with NEC (mean gestational age at birth 31.41±1.15 weeks; mean age at MRI 37.53±3.08 weeks; birth weight 1,678.67±449.39 g) and 40 healthy preterm infants with no NEC (mean gestational age at birth 32.27±2.09 weeks; mean age at MRI 37.15±3.23 weeks; birth weight 1,756.95±523.16 g). MRI and serum examinations were collected from the recruited preterm infants (*Figure 1*).

MRI acquisition procedure

The MRI acquisition procedure began with an intravenous injection of 5 mg/kg of phenobarbital, an antiepileptic medicine that also helps patients with insomnia, thus, causing the infant to fell asleep, 30 minutes prior to the MRI scan. A neonatologist was present during each scan. A pulse oximeter was used to monitor heart rate and oxygen saturation throughout the scanning process. The infant was taken to the MRI scan bed, and cotton balls were placed in the external auditory canal to reduce the noise. Magnetic resonance (MR) images with a low signal to contrast ratio or artifacts were excluded from the study.

All MR scans were carried out on a 3.0 T MR scanner with a 16-channel head coil and the infants in a supine position. The parameters for DTI sequence were as follows: repetition time (TR) =2,000 ms, time to echo (TE) =2.32 ms, directions =25, b value =0 and 1,000 s/mm^2; slice thickness =3.0 mm (without a gap), field of view =256 mm × 256 mm, matrix =256×256, and acquisition time =20 min.

DTI data were analyzed in preprocessing with motion artifact-correction methods. FMRIB's Diffusion Toolbox (FDT; FMRIB Analysis Group, University of Oxford, Oxford, UK) module was used for eddy current correction and parameter calculation to obtain the FA and MD. Then, 10 regions of interest (ROIs) were manually outlined, including the splenium of the corpus callosum (SCC), lentiform nucleus (LN), CN, TH, FWM, PWM, occipital

Table 1 Demographic and baseline characteristics of neonates

Characteristic	NEC group (n=30)	Control group (n=40)	P value
GA (weeks)	31.41±1.15	32.27±2.09	0.051
PMA at MRI (weeks)	37.53±3.08	37.15±3.23	0.106
Birth weight (g)	1,678.67±449.39	1,756.95±523.16	0.513
Birth weight at MRI (g)	2,520.11±120.22	2,690.71±630.08	0.193
Apgar score (1 min)	7.10±1.729	7.75±1.515	0.099
Apgar score (5 min)	7.67±1.52	8.38±1.51	0.057
Male	20 (66.7)	19 (47.5)	0.110
Cesarean delivery	14 (46.7)	21 (52.5)	0.285

Data are expressed as the mean ± SD and n (%). There were no significant differences between the 2 groups (P>0.05). NEC, necrotizing enterocolitis; GA, gestational age; PMA, postmenstrual age; MRI, magnetic resonance imaging; SD, standard deviation.

Table 2 Interobserver consistency of measurements

Parameter	Intraclass correlation coefficient (95% CI)
FA	0.926 (0.814–0.972)
MD	0.862 (0.620–0.932)

CI, confidence interval; FA, fractional anisotropy; MD, mean diffusivity.

white matter (OWM), cerebellum (CERE), PLIC, and CP. The area of each ROI was 10±2 mm^2, and the ROI outlines were independently assessed by 2 radiologists (one with 8 years of experience in radiology and another with 7 years of experience in radiology). The results were reviewed by a third radiologist with over 15 years of experience in neuroradiology.

Serum CRP and PCT detection

To detect serum CRP and PCT levels, 5 mL of peripheral venous blood was collected from each infant and was analyzed with enzyme-linked immunosorbent assay method. All tests were safely conducted according to the operating procedures of the test kit to ensure test results were precise.

Statistical analysis

Statistical analysis was performed on SPSS 26.0 software (IBM Corp., Armonk, NY, USA). Results are reported as the mean ± standard deviation (SD). After the normality of the datasets was assessed, either an independent samples *t*-test or Mann-Whitney test was used for comparison between the 2 groups. Intraclass correlation coefficients (ICCs) were calculated to assess the interobserver reliability of DTI measurements. The relationships between DTI-derived parameters, CRP levels, and the PCT serum index were analyzed using Spearman correlation analysis. A logistic regression model was then built to test the ability of the combined indicators (FA + MD + CRP + PCT) in diagnosing preterm infants with NEC. The established Logistic regression model is shown as: Logit(p) = 23.605 + 35.469 × FA + 5.694 × MD + 12.581 × CRP – 1.508 × PCT.

Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of each indicator for alterations of WM structure. Statistical significance was set a P<0.05.

Results

Study participants

This study included 70 preterm infants, and details of the demographic and baseline neonate characteristics are shown in *Table 1*. There was no statistically significant difference in baseline neonate characteristics between the 2 groups. The DTI parameter value of ROIs measured by the 2 radiologists showed good consistency. For FA, the ICC was 0.926 [95% confidence interval (CI): 0.814–0.972], while for MD it was 0.862 (95% CI: 0.620–0.932) (*Table 2*).

Measurement of DTI parameters in cerebral WM

An image sample of a patient with NEC is shown in *Figure 2*. ROIs among the selected patients for SCC, LN, CN, TH, FWM, PWM, OWM, CERE, PLIC, and CP in the FA and MD maps were measured, and the ROI measurements

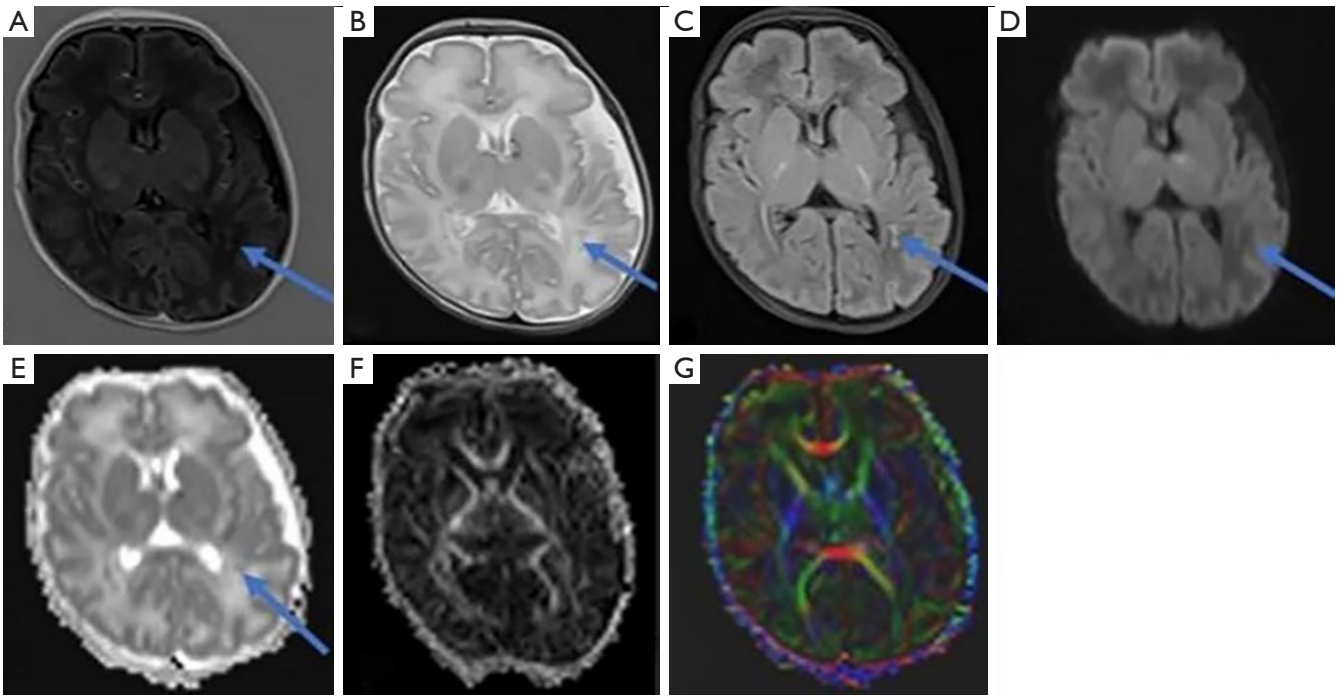

Figure 2 Male, premature infant with necrotizing enterocolitis and a corrected gestational age of 34 weeks. There is punctate lesion near the posterior corner of the left lateral ventricle (blue arrows). (A) T_1WI shows a slightly high signal. (B) T_2WI shows a slightly low signal. (C) T_2-FLAIR shows a slightly high signal. (D) DWI shows a slightly high signal shadow. (E) The MD map is a low signal, (F,G) FA image and color FA image. T_1WI, T_1-weighted image; T_2WI, T_2-weighted image; T_2-FLAIR, T_2 fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; MD, mean diffusivity; FA, fractional anisotropy.

were compared between the group of preterm infants with NEC and the control group, as shown in *Table 3*. In comparison with the control group, the NEC group had significantly lower FA values for the SCC (P<0.001), PLIC (P<0.001), LN (P<0.001), FWM (P=0.005), and CP (P=0.047). Meanwhile, the MD values for the LN (P=0.028), FWM (P=0.040), and PLIC (P<0.001) were significantly higher in the NEC group than in the control group.

Diagnostic performance of DTI parameters in different ROIs

The ROC analysis of DTI parameters in differentiating between the preterm infants with NEC and those without NEC are shown in *Figure 3*, and the area under the curve (AUC) was calculated (*Table 4*). FA for the PLIC showed the best performance, while FA and MD for the PLIC and FA for the SCC showed higher AUC values. The ability to diagnose NEC in preterm infants using DTI measurements (FA, MD) was assessed using AUC, with AUC values of 0.920, 0.938, and 0.807 for FA for the SCC, FA for the PLIC, and MD for the PLIC, respectively.

Comparison of CRP and PCT levels between the 2 groups

The CRP (P=0.038) and PCT (P=0.046) levels for the premature infants in the NEC group were all significantly higher than those in the control group (*Figure 4*).

Comparison of the AUC between single indicator and combined indicators

Between-group comparisons of FA and MD in the PLIC were significantly different, and the PLIC was selected as a representative region for preterm infants with NEC (*Figure 3*). The AUC of the model with combined indicators (FA + MD + CRP + PCT) for the diagnosis of preterm infants with NEC was 0.968, representing a considerable improvement in predicted efficacy over single indicators,

Table 3 Comparison of FA and MD values between the 2 groups

ROI	Parameter	NEC group (n=30)	Control group (n=40)	t or Z value	P value	Q value
SCC	FA	0.44±0.07	0.62±0.07	−8.214	<0.001*	0.02**
	MD	1.102±0.076	1.074±0.080	−1.482	0.143	0.26
LN	FA	0.09±0.02	0.14±0.04	−4.932	<0.001*	0.01**
	MD	1.059±0.112	0.999±0.108	2.246	0.028*	0.093**
CN	FA	0.05±0.02	0.06±0.02	−1.908	0.063	0.14
	MD	1.148±0.133	1.114±0.155	−0.984	0.329	0.47
TH	FA	0.16±0.02	0.17±0.04	−0.792	0.443	0.554
	MD	1.062±0.084	1.045±0.084	−0.826	0.412	0.549
FWM	FA	0.06±0.02	0.08±0.03	−2.965	0.005*	0.02**
	MD	1.194±0.115	1.138±0.108	−2.090	0.040*	0.114
PWM	FA	0.10±0.03	0.11±0.04	−0.691	0.493	0.548
	MD	1.187±0.236	1.053±0.538	−1.278	0.209	0.322
OWM	FA	0.11±0.03	0.11±0.03	−0.176	0.861	0.861
	MD	1.299±0.251	1.218±0.216	1.453	0.151	0.252
CERE	FA	0.09±0.02	0.11±0.03	−1.539	0.131	0.262
	MD	0.944±0.273	0.912±0.962	−0.692	0.492	0.579
PLIC	FA	0.37 (0.31–0.48)	0.56 (0.52–0.61)	−5.071	<0.001*	0.01**
	MD	1.182±0.116	1.017±0.179	4.394	<0.001*	0.005**
CP	FA	0.13 (0.10–0.17)	0.16 (0.14–0.18)	−1.987	0.047*	0.1175
	MD	1.083±0.121	1.072±0.277	0.229	0.820	0.863

Data are expressed as the mean ± SD or median (range). The NEC group had significantly lower FA values for the SCC (P<0.001), PLIC (P<0.001), LN (P<0.001), FWM (P=0.005), and CP (P=0.047). *, P value <0.05; **, Q value <0.1. FA, fractional anisotropy; MD, mean diffusivity; ROI, region of interest; NEC, necrotizing enterocolitis; SCC, splenium of the corpus callosum; LN, lentiform nucleus; CN, caudate nucleus; TH, thalamus; FWM, frontal white matter; PWM, parietal white matter; OWM, occipital white matter; CERE, cerebellum; PLIC, posterior limbs of the internal capsule; CP, cerebral peduncle; SD, standard deviation.

including FA (AUC: 0.938; 95% CI: 0.840–0.950), MD (AUC: 0.807; 95% CI: 0.722–0.838), CRP (AUC: 0.867; 95% CI: 0.822–0.889), and PCT (AUC: 0.706; 95% CI: 0.701–0.758).

Correlation between DTI quantifications and serum indicators in the NEC group

In the ROC analysis, the regions (PLIC, LN, SCC, CP, FWM) and parameters (FA, MD) demonstrated the diagnostic value for NEC differentiation. The Spearman correlation analysis was based on these regions, and the correlation between the parameters and serum indicators was also examined. The parameters that negatively correlated with serum CRP and PCT included the FA value of the PLIC (CRP: r=−0.846; PCT: r=−0.843; P<0.05) and the FA value of the LN (CRP: r=−0.549; PCT: r=−0.634; P<0.05). Meanwhile, the parameters that positively correlated with serum CRP and PCT included the MD value of PLIC (CRP: r=0.743; PCT: r=0.743; P<0.05) and the MD value of the LN (CRP: r=0.605; PCT: r=0.711; P<0.05). Additionally, the FA value of the SCC was negatively correlated with serum CRP and serum PCT (CRP: r=−0.464; PCT: r=−0.483; P<0.05). The FA and MD for the PLIC, LN, and SCC regions all showed moderate correlations with serum indicators. Other brain regions were not correlated with serum markers or DTI parameters (*Figure 5*).

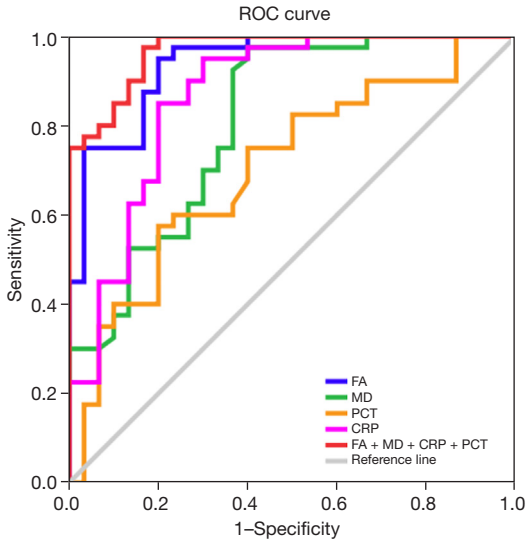

Figure 3 Diagnostic manifestations of different parameters. ROC curve analyses of FA + MD + CRP + PCT combined and each of FA, MD, CRP, and PCT alone in the diagnosis of premature infants with NEC yielded AUCs of 0.968, 0.938, 0.807, 0.867, and 0.706, respectively. The differences were statistically significant. ROC, receiver operating characteristic; FA, fractional anisotropy; MD, mean diffusivity; PCT, procalcitonin; CRP, C-reactive protein; NEC, necrotizing enterocolitis; AUCs, areas under the curve.

Table 4 Diagnostic performance of DTI parameters in different ROIs

ROI	Parameter	AUC	95% CI
SCC	FA	0.920	0.823–0.934
LN	FA	0.571	0.530–0.612
	MD	0.742	0.702–0.784
FWM	FA	0.581	0.551–0.611
	MD	0.762	0.744–0.791
PLIC	FA	0.938	0.840–0.950
	MD	0.807	0.722–0.838
CP	FA	0.601	0.591–0.611

The AUCs of FA in the SCC, LN, FWM, PLIC, and CP were 0.920, 0.571, 0.581, 0.938, and 0.601. The AUCs of MD in the LN, FWM, and PLIC were 0.742, 0.762, and 0.807. DTI, diffusion tensor imaging; ROIs, regions of interest; AUC, area under the curve; CI, confidence interval; SCC, splenium of the corpus callosum; FA, fractional anisotropy; LN, lentiform nucleus; MD, mean diffusivity; FWM, frontal white matter; PLIC, posterior limbs of the internal capsule; CP, cerebral peduncle.

Discussion

There is a higher risk of WM microstructure alterations in premature infants with a history of NEC. Our study found that the FA values of SCC, PLIC, LN, PWM, and CP of preterm infants with NEC were significantly lower than those of the control group. Meanwhile, the MD values of PLIC, LN, and PWM in preterm infants with NEC were higher than those of the control group. It was also discovered that the levels of CRP and PCT inflammation indicators in preterm infants with NEC were significantly increased. In the NEC group, the FA and MD values of PLIC were correlated with CRP and PCT level. The combination of FA and MD combined with serum CRP and PCT levels was more effective than was a single indicator in evaluating the WM microstructure alterations in preterm infants with NEC.

NEC is a relatively common disease among premature infants and is characterized by inflammation, degeneration, and necrosis of the deep intestinal mucosa (20,21). Intestinal injury and intestinal mucosal dysfunction allow the inflammatory mediators to enter into the systemic circulation, resulting in a systemic inflammatory response. Consequently, inflammatory cells or cytokines enter the brain through the blood, which leads to an inflammatory response in the brain and the disruption of WM microstructures (22-25). Near-term infants have progressive fibrosis of the WM fibers, which inhibits water diffusion. However, the inflammatory state of the brain leads to abnormal myelination, which reduces diffusion restriction (26). The FWM develops in the late period and is easily damaged by an inflammatory reaction (27). In addition, research suggests that the inflammatory response in the brain causes the cell membrane to rupture, leading water to flow into the extracellular environment (28), thus directly increasing the MD values in the brain (29-31). Moreover, the inflammatory response causes myelin damage, which manifests as reduced diffusion heterogeneity or even reduced FA (32). Our study revealed that the changes of FA and MD were consistent with the WM microstructure alterations in preterm infants with NEC.

In addition, CRP and PCT levels were examined in all participants. Both of these inflammation indicators were significantly increased in the preterm infants with NEC. Moreover, blood testing revealed elevated white blood cell, CRP, and PCT levels. These findings are in line with those from animal experiments. For instance, in a mouse model of NEC, levels of tumor necrosis factor (TNF)-α and platelet

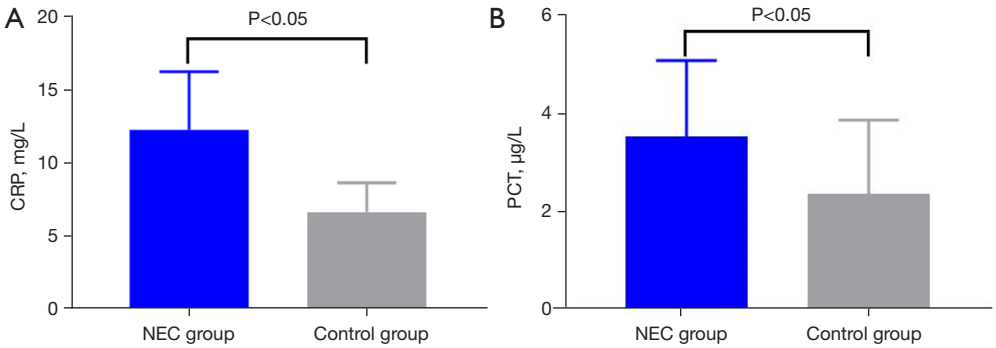

Figure 4 The comparison of the CRP and PCT levels between the between the 2 groups. (A) The CRP levels of the preterm infants with the necrotizing enterocolitis were significantly higher than those in the controls (P=0.038). (B) The PCT levels of the preterm infants with the necrotizing enterocolitis were significantly higher than those in the controls (P=0.046). NEC, necrotizing enterocolitis; CRP, C-reactive protein; PCT, procalcitonin.

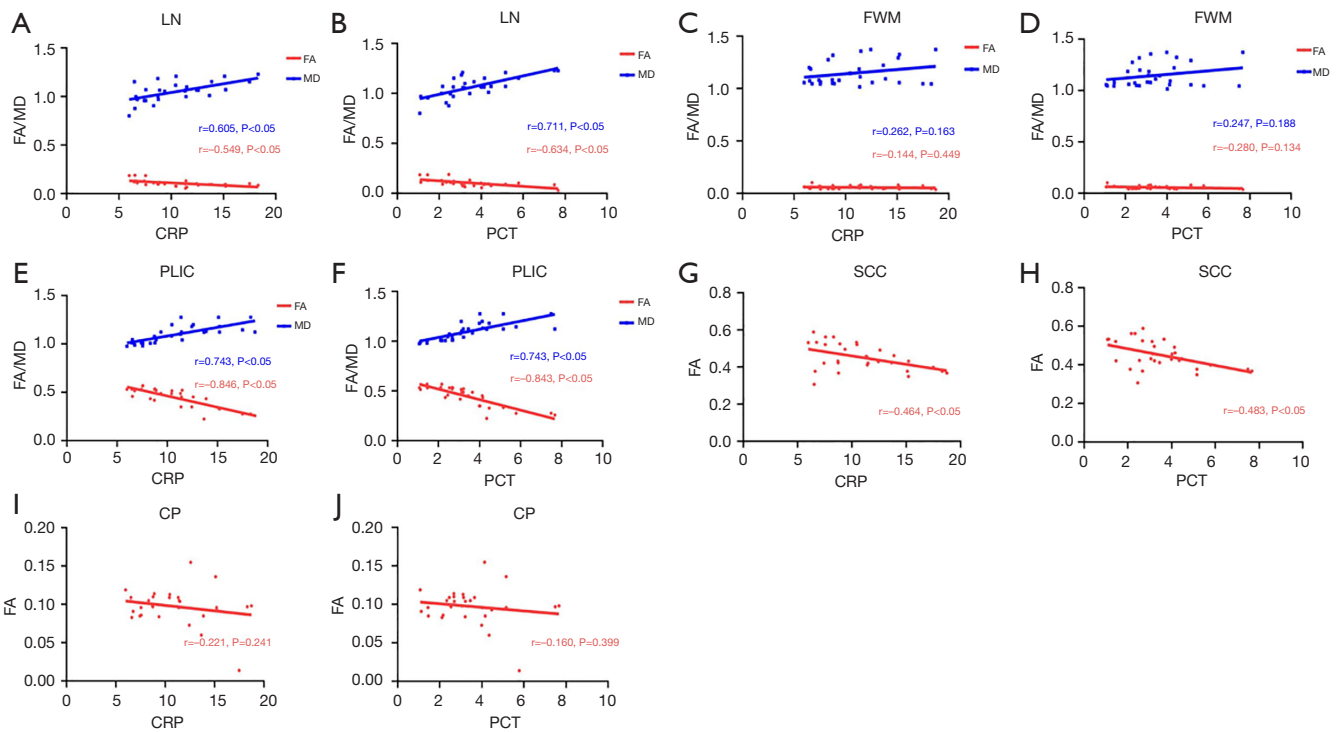

Figure 5 Correlation between DTI parameters and serum indicators. (A) The FA value of the LN was negatively correlated with the serum CRP level (r=–0.549; P<0.05); the MD value of the LN was positively correlated with the serum CRP level (r=0.605; P<0.05). (B) The FA value of the LN was negatively correlated with serum the PCT level (r=–0.634; P<0.05); the MD value of the LN was positively correlated with serum the PCT level (r=0.711; P<0.05). (C,D) There was no correlation in CRP with FA/MD and PCT with FA/MD (P>0.05). (E) The FA value of the PLIC was negatively correlated with serum CRP (r=–0.846; P<0.05); the MD value of the PLIC was positively correlated with the serum CRP level (r=0.743; P<0.05). (F) The FA value of the PLIC was negatively correlated with the serum PCT level (r=–0.843; P<0.05); the MD value of the PLIC was positively correlated with the serum PCT level (r=0.743; P<0.05). (G) The FA value of SCC was negatively correlated with the serum CRP level (r=–0.464; P<0.05). (H) The FA value of SCC was negatively correlated with the serum PCT level (r=–0.483; P<0.05). (I,J) There was no correlation in CRP with FA and PCT with FA (P>0.05). LN, lentiform nucleus; CRP, C-reactive protein; FA, fractional anisotropy; MD, mean diffusivity; PCT, procalcitonin; FWM, frontal white matter; PLIC, posterior limbs of the internal capsule; SCC, splenium of the corpus callosum; CP, cerebral peduncle; DTI, diffusion tensor imaging.

excitons were found to be elevated, with their interaction promoting intestinal mucosal damage (33) and subsequently leading to an increase in the level of inflammatory mediators [interleukin (IL)-6, IL-8, and IL-11]. In another study, the degree of ileum damage in mice with NEC was found to be correlated with the level of inflammatory cells in the brain (34). Piglet studies revealed that NEC could precipitate systemic inflammation, leading to blood-brain barrier disruption and region-specific neuronal degeneration (35). We believe that the systemic inflammatory response of NEC may lead to damage in specific neurons and may therefore change the dispersion characteristics of water molecules in brain.

In neonatal infections, such as early-onset sepsis and NEC, there is an association between elevated levels of inflammatory cytokines and WM microstructure alterations (36). As FA and MD values of PLIC were found to have diagnostic significance, FA and MD values of PLIC and serum inflammatory levels were selected for a correlation study (6). Our results showed that the FA value of PLIC was negatively correlated with serum CRP and PCT levels, while the MD value of the PLIC was positively correlated with CRP and PCT levels. Brunse *et al.* reported that systemic inflammation leads to the destruction of the blood-brain barrier, thus causing WM microstructure alterations (37). As the serum CRP and PCT levels increase, the FA value decreases and the MD value increases. The increase in serum CRP levels in preterm infants with NEC causes neurodevelopmental abnormalities (38). In a recent study, it was reported that the increase of intestinal proinflammatory cytokine was correlated with WM microstructure alterations in the mice with NEC (39). Therefore, we can conclude that the values of FA, MD, CRP, and PCT may have a certain predictive value for WM microstructure alterations.

DTI imaging has been previously used to detect the alterations of WM microstructures (40), while the inflammatory indicators have been used to reflect the level of systemic inflammation (41). The present study analyzed the value of combining these indicators in the evaluation of WM microstructure alterations. It was found that the diagnostic specificity of FA and MD combined with CRP and PCT was higher than that of any single indicator used alone. We found the alterations of WM microstructures in preterm infants with NEC were affected by the systemic inflammatory response. The model of FA and MD combined with CRP and PCT may serve as an early biomarker for WM microstructure alterations in preterm infants with NEC and may thus help clinicians improve the early detection and intervention of WM microstructure alterations in preterm infants with NEC.

Some limitations of this study should be noted. First, the results were derived from a small sample size from a single hospital. To mitigate the effect of this, we completed calibration curves with bootstrapping (1,000 resamplings; Figure S1), and the curves indicated the stability of the established regression model with DTI parameters and the blood inflammatory indicators. However, it is still necessary to collect additional data to confirm the generalizability of our results. Another limitation would be the use of a single system, and it is necessary to collect data from different systems and time points in the future and to increase the data volume and variety. Following this, we can combine these approaches, which could minimize batch variation and increase the robustness and generalization of the results (39). We also need to consider the feasibility of collecting data from multiple sites and potentially use variable data collection systems in future research. Finally, the manual extraction of brain areas is time-consuming, so we will consider machine learning segmentation to delineate the ROIs in subsequent studies.

Conclusions

NEC infection after birth in premature infants may cause inflammation-mediated WM microstructure alterations. DTI can noninvasively and quantitatively assess the abnormal change of the WM in preterm infants with NEC. Serum CRP and PCT levels can reflect the systemic inflammation of preterm infants with NEC. The combination of DTI, PCT, and CRP markers improves the ability to detect the WM microstructure alterations in preterm infants with NEC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-195/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-195/coif). KW and JG are employed by GE HealthCare. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University (No. 2022-253-01). Written informed consent was obtained from each participating infant's legal guardian.

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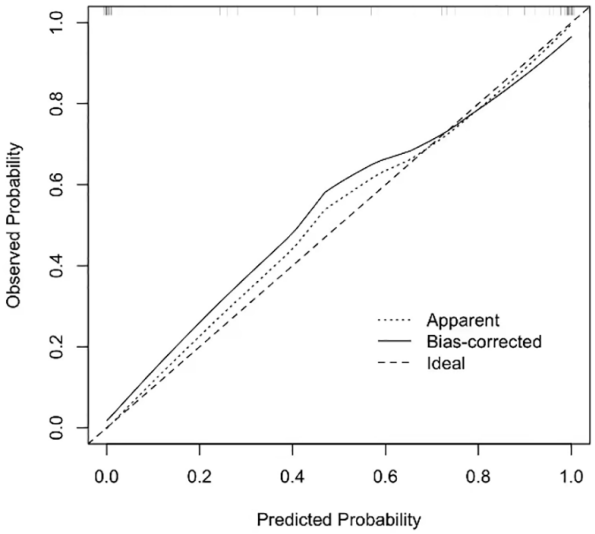

Figure S1 The calibration curves with bootstrapping indicated the stability of the established regression model with DTI parameters and the blood inflammatory indicators. DTI, diffusion tensor imaging.

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