·临床研究·

早产儿脑白质损伤核磁共振成像定量评估与血细胞参数和围产期因素的相关性分析

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摘　要：【目的】探讨早产儿脑白质损伤(WMD)的围产期高危因素及血细胞参数的相关性，为早期发现并规避早产儿 WMD 的发生提供科学依据。【方法】采用回顾性病例对照研究设计，收集南方医科大学附属深圳市妇幼保健院新生儿科 2018 年 1 月 1 日至 2020 年 12 月 31 日经核磁共振检查诊断为 WMD 的早产儿 85 例为病例组，并以胎龄为匹配条件选取同期 115 例经核磁共振检查未诊断 WMD 患者作为对照组。采用 SPSS22.0 统计学软件进行围产期相关因素的单因素分析、血细胞参数单因素分析、构建多因素 Logistic 回归模型分析 WMD 的相关因素，并对其中有意义的连续性变量进行接受者操作特性曲线分析，以获得 WMD 危险因素截断值，最后进行有序 Logistic 回归分析 WMD 严重程度的影响因素。【结果】①围产期相关因素单因素分析显示，两组在孕期贫血率、产前足疗程激素使用率、早发败血症发生率、机械通气(≥7 d)比例、低血压发生率、早产儿脑室周围-脑室内出血(PIVH)Ⅲ-Ⅳ级及有血流动力学意义的动脉导管未闭(hsPDA)发生率之间的差异均有统计学意义(均 P <0.05)。②生后第 1 周的两组血细胞参数单因素分析显示，两组在生后第 1 周的白细胞(WBC)、中性粒细胞(NEUT)、单核细胞(MONO)、平均红细胞体积(MCV)、平均血红蛋白量(MCH)、血小板(PLT)、血小板压积(PCT)、平均血小板体积(MPV)、血小板分布宽度(PDW)之间的差异均有统计学意义(均 P <0.05)。③Logistic 回归模型显示，机械通气(≥7 d)是 WMD 发生的独立危险因素，而生后 1 周内较高的 MCH 和 PLT 以及产前足疗程激素治疗是 WMD 发生的保护因素。④MCH 诊断 WMD 的 AUC 为 0.708，95%CI 为(0.595，0.820)，截断值为 37.10 pg。PLT 诊断 WMD 的 AUC 为 0.669，95%CI 为(0.551，0.787)，截断值为 227.50×10^9/L。⑤有序 Logistic 回归分析，结果显示：早发型败血症是 WMD 严重程度的危险因素，而胎龄和血小板分布宽度则是其保护因素及血细胞学指标。【结论】早产儿机械通气(≥7 d)、生后 1 周血细胞 MCH 和 PLT 减低可能是预测早产儿 WMD 发生的独立危险因素及相关血细胞学指标，而产前应用足疗程的糖皮质激素则是其保护因素；早发型败血症及越小的胎龄及 PDW 可能是 WMD 严重程度的危险因素。

关键词：早产儿；脑白质损伤；高危因素；血细胞参数
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Correlation Analysis of MRI Quantitative Assessment of White Matter Damage with Blood Cell Parameters and Perinatal Factors in Premature Infants

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Abstract:【Objective】To explore the correlation between perinatal risk factors and blood cell parameters of white matter damage (WMD) in premature infants and to provide scientific basis for early detection and avoidance of WMD in

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premature infants.【Methods】This is a retrospective study performed at the Neonatal Department, Affiliated Shenzhen Maternity & Child Healthcare Hospital, from January 1st 2018 to December 31st 2020. The case group included 85 premature infants diagnosed as WMD by MRI, and 115 premature infants without WMD matched by gestational age and admission date constituted the control group. SPSS 22.0 statistical software was used to conduct univariate analysis of perinatal related factors and blood cell parameters, and to construct a multivariate Logistic regression model to analyze WMD related factors. Meaningful continuous variables were analyzed by the receiver operating characteristic curve to obtain the cut-off value of WMD risk factors. Then ordinal Logistic regression was used to analyze the influencing factors of WMD severity.【Results】① There were no significant differences in sex ratio, twins rate, gestational age, birth weight, cesarean section rate, assisted reproductive technology pregnancy rate, Apgar score at 1 and 5 minutes after birth, and age at diagnosis between the two groups (P>0.05). ② Univariate analysis of perinatal factors showed that there were significant differences between the two groups in the rate of anemia during pregnancy, antenatal glucocorticoid treatment, the incidence of early-onset sepsis, neonatal hypotension, PIVH (grade Ⅲ-Ⅳ) and hsPDA, the proportion of mechanical ventilation (≥7 d)(P<0.05). ③ Univariate analysis of blood cell parameters in the first week after birth showed that there were significant differences in WBC, Neut, Mono, MCV, MCH, PLT, PCT, MPV and PDW between the two groups(P<0.05). ④ Logistic regression model showed that mechanical ventilation (≥7 d) was an independent risk factor for WMD, while higher MCH and PLT within one week after birth and antenatal glucocorticoid treatment were protective factors for WMD. ⑤ The AUC of MCH in the diagnosis of WMD was 0.708, 95% CI was (0.595-0.820), and the cut-off value was 37.10 pg. The AUC of WMD diagnosed by PLT was 0.669, 95% CI was (0.551-0.787) and the cut-off value was 227.50×10^9/L. ⑥ Ordered Logistic regression showed that early-onset sepsis was a risk factor for the severity of WMD, while gestational age and platelet distribution width were its protective factors and hematology indicators.【Conclusions】Mechanical ventilation (≥7 d) decreased MCH and PLT counts may be independent risk factors for WMD in preterm infants, and antenatal glucocorticoids treatment is a protective factor.Early-onset sepsis, smaller gestational age and PDW may be risk factors for the severity of WMD.

Key words: preterm infants; white matter damage; high risk factors; blood cell parameters

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随着现代诊疗技术的发展,越来越多的新生儿特别是早产儿得以存活。但是,现代技术的使用下的早产儿脑发育易受缺氧缺血、感染及炎症等影响,导致早产儿脑损伤的发病率和病死率增高,特别是脑白质损伤(white matter damage, WMD)[1-2]。WMD可造成小儿神经系统后遗症,如脑瘫、视听功能异常、认知障碍等,给家庭和社会带来巨大的负担[3]。李新等[4]探讨了早产儿WMD后神经系统发育障碍的围产期影响因素。曹一翀等[5]探讨了脂肪干细胞生物活性分泌物在防治早产儿WMD的安全性及早期疗效。然而,早产儿WMD与血细胞的关系尚未有系统的研究报道。本研究回顾性分析我院早产儿WMD与围产期因素和血细胞学参数的关系,旨在探索与WMD相关的血液学预测指标,以期早期识别高危人群,预防并降低WMD的发生。

1 材料与方法

1.1 一般资料

采用回顾性病例对照研究设计,收集南方医科大学附属深圳市妇幼保健院新生儿科,在2018年1月1日至2020年12月31日期间收治的早产儿患者(出生胎龄小于37周)。纳入标准:经核磁共振成像(magnetic resonance imaging, MRI)检查诊断为WMD的早产儿85例为病例组,并以胎龄为匹配条件选取同期住院的115例经核磁共振检查未诊断WMD患者作为对照组。排除标准:①未接受MRI检查的新生儿;②在产前检查中发现脑部异常或其他先天性异常;③化脓性脑膜炎,遗传性代谢性脑病。本研究经过医院伦理委员会批准,伦理审批号为[2019]-119。所有患儿监护人知情同意。

1.2 研究方法

1.2.1 早产儿脑白质损伤的核磁共振成像诊断及

量化评分　做好MRI检查前准备，包括喂养、保暖，以及口服水合氯醛镇静。使用1.5特斯拉通用电气Signa系统（Philips Achieva Nova Dual）进行了MRI扫描。在整个扫描过程中监测脉搏血氧饱和度，温度和心电图，并使用护耳器。扫描参数：常规t1-se序列：TR 450 ms，TE 10~20 ms，矩阵225×200；T2WI：TR 4 500 ms，TE120 ms，矩阵320×224；T2 flair：TR 10 000 ms，TE 140ms，矩阵225×220；所有序列层的厚度均为5 mm，层间距为0.5 mm，FOV为180 mm × 160 mm）。根据WMD诊断标准[6]：①局灶性WMD MRI表现为半卵圆中心、侧脑室旁点状或线状高信号，伴或不伴短T1短T2信号。②脑白质弥漫性损伤DWI表现为弥漫性高信号改变，表现为侧脑室旁白质大片状高信号，常规MRI通常无信号改变。满足其中任何一条即诊断为WMD。量化评分见表1。评分5-6分为无WMD，7-9分为轻度WMD，10-12分为中度WMD，13-15分为重度WMD[7]。

1.2.2　血细胞参数测定　出生后第1周从新生儿的静脉中采集血样，并在迈瑞5390血细胞分析仪（中国深圳）上进行检验，获得血细胞参数，如果1周内有两次以上的血常规检查结果则取其平均值。

1.2.3　分析变量　一般临床资料及混杂因素包括：性别、体质量、受孕方式、单双胎、分娩方式、1 min和5 min Apgar评分[8]、诊断日龄、是否孕期贫血、妊娠期高血压、产前应用足疗程糖皮质激素、早发型败血症、机械通气（≥7 d）、新生儿低血压、中心静脉置管、Ⅲ-Ⅳ级早产儿脑室周围-脑室内出血（periventricular-intraventricuar hemorrhage，PIVH）、有血流动力学意义的动脉导管未闭（hemodynamically significant patent ductus arteriosus，hsPDA）等。血细胞学指标包括血常规各细胞参数。影像学资料收集及评分及分度如前述。产前应用足剂量、足疗程糖皮质激素定义为：产妇分娩前，完成地塞米松6 mg肌肉注射，1次/12h，共4次[9]；早发型败血症定义为：生后7 d内发生的新生儿感染（特指细菌感染）；新生儿低血压定义为：目前学界暂无统一的界定值，本研究以平均动脉压（mean arterial pressure，MAP）低于胎龄定义为低血压[10]。hsPDA定义见参考文献[11]。

1.3　统计学方法

采用SPSS 22.0统计软件对数据进行统计学分析。本研究中计量资料数据呈偏态分布，以$M(P_{25}\sim P_{75})$描述，组间比较采用Mann-Whitney U检验。计数资料采用频数和率进行描述，组间比较采用χ^2检验。在Logistic回归分析中计算优势比（OR）和95%置信区间（CI）然后，采用线性回归分析MRI评分与WMD危险因素之间的关系，并对其中有意义的连续性变量进行接受者操作特性（ROC）曲线分析，以获得WMD危险因素截断值。P<0.05为组间差异有统计学意义。

2　结 果

2.1　研究中脑白质损伤代表性核磁共振成像扫描影像

本研究中WMD代表性MRI影像的不同序列见图1。

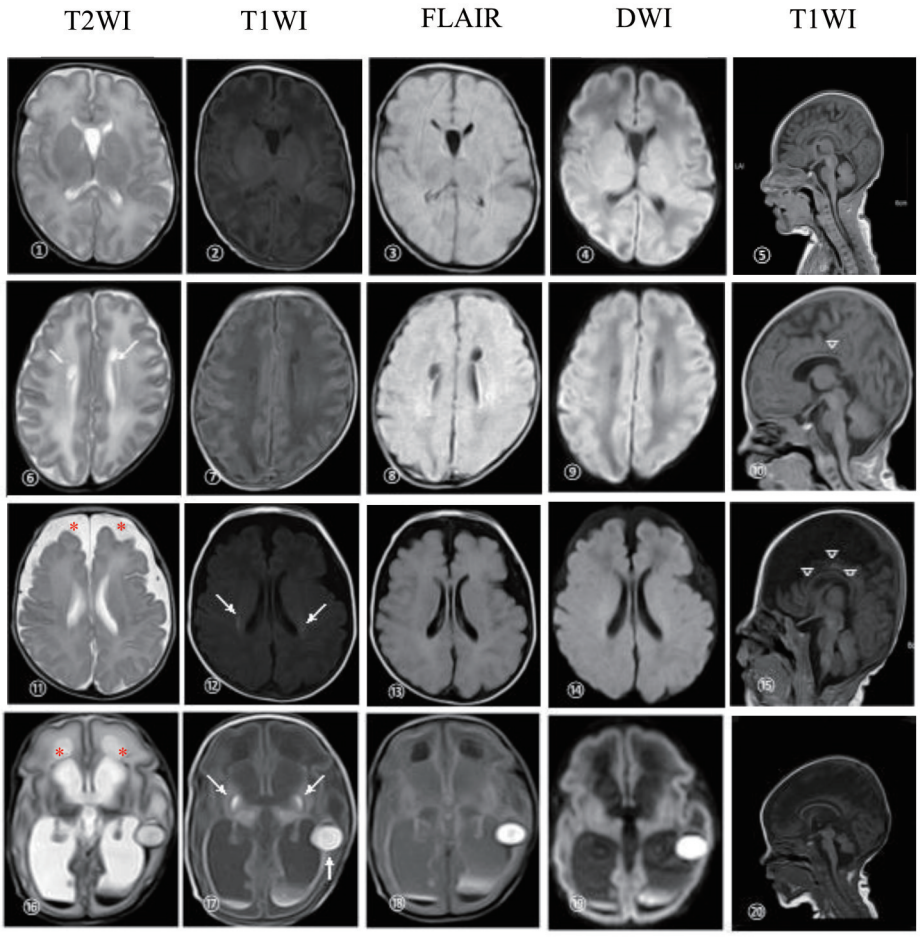
2.2　病例组核磁共振成像评分后脑白质损伤各分度的占比图情况

分度为正常（5-6分）8例（9.4%），轻度WMD（7-9分）46例（54.1%），中度WMD（10-12分）27例（31.8%），重度WMD（13-15分）4例（4.7%）。

表1　早产儿WMD的量化MRI评分系统

Table 1　Quantitative MRI scoring system for WMD in premature infants

	1	2	3
Cystic lesion	Non	Focal，≤ 2 mm	Multifocal，≥ 2 mm
Ventricular enlargement	Non	Moderate	Significantly expanded（all）
Corpus callosum	Normal	Local thinning	Overall thinning
White matter（lesion，signal）	Normal	Focal，≤2 lesions/hemisphere	Multifocal，≥2 lesions/hemisphere
White matter volume	Normal	Mild-moderate reduction	Significantly reduced，usually with enlarged ventricle and widened extracerebral space



Case 1, MRI of normal premature infant:picture ①–⑤ GA 32^{+2} week, 31 d, PMA 36^{+5}week MRI examination, Every sequence of MRI examination shows normal. MRI scores: 1 for white matter (no lesions and normal signals) +1 for white matter volume (normal) +1 for cystic lesions (none) +1 for dilated ventricle (none) +1 for corpus callosum (no thinning) =5. Case2, MRI of mild WMD: picture ⑥–⑩ GA 32^{+3} week, 49 d, PMA 39^{+3} week MRI examination, bilateral pariventricular multiple cystic lesions. MRI scores: 1 for white matter (no lesions and normal signals) +1 for white matter volume (normal) +3 for cystic lesions (multifocal lesions) +1 for dilated ventricle (none) +2 for corpus callosum (genu of corpus callosum thinning) =8. Case 3, MRI of moderate WMD: picture ⑪–⑮ GA 28^{+5} week, 85 d, PMA 40^{+6} week MRI examination, Widening of extracerebral space(*) , T1WI high signal near the posterior horn of bilateral ventricle (arrow) and corpus callosum (all thinning)(▽) . MRI scores: 3 for white matter (multifocal signal anomalies) +3 for white matter volume (significantly reduced) + 1 for cystic lesions (none) +1 for dilated ventricle (none) +3 for corpus callosum (overall thinning) =11. Case 4, MRI of severe WMD: picture ⑯–⑳ GA 28^{+1} week, 73 d, PMA 38^{+4} week MRI examination, white matter showed homogeneous edema, bleeding lesions at the junction of bilateral basal ganglia and the left temporal occipital lobe (arrows) , softening lesions seen at the bilateral frontal lobe (*), bilateral ventricles significantly dilated, hemorrhage seen inside the subventricular and ventricular system, global thinning of the corpus callosum. MRI score: 3 for white matter (multifocal signal anomalies) +3 for white matter volume (significantly reduced) +3 for cystic lesions (multifocal lesions) +3 for dilated ventricle (significantly dilated) +3 for corpus callosum (overall thinning) =15. Abbreviations: GA:gestational age; PMA: postmenstrual age.

图1 研究中WMD代表性MRI扫描影像

Fig.1 Representative MRI scans of WMD in the study

2.3 两组的一般情况比较

病例组与对照组在性别构成比、双胎率、胎龄、出生体质量、剖宫产率、辅助生殖技术受孕率、生后1 min和5 min Apgar评分和诊断时日龄之间的差异均无统计学意义(均P>0.05),具有可比性(表2)。

2.4 脑白质损伤影响因素分析

2.4.1 两组的临床围产期单因素分析比较 对两组早产儿的临床围产期单因素分析比较,显示两组在孕期贫血率、产前足疗程激素使用率、早发败血症发生率、机械通气(≥7d)比例、低血压发生率、PIVH(Ⅲ–Ⅳ级)及hsPDA发生率之间的差异均有

表2　病例组与对照组基本临床情况比较

Table 2　Comparison of basic clinical situation between case group and control group　[$M(P_{25}\sim P_{75})$]

Items	Case group	Control group	χ^2/Z	P
Male/Female	45/40	61/54	0	0.989
Twins	38.82%(33/85)	37.39%(43/115)	0.043	0.837
GA/weeks	30.05(26.18～35.39)	29.31(26.62～34.35)	−0.343	0.731
BW/g	1 430(815～2 275)	1 165(910～1 893)	−0.325	0.745
Cesarean section delivery	45.88%(39/85)	51.30%(59/115)	0.575	0.448
Conception by IVF-ET	23.53%(20/85)	21.74%(25/115)	0.090	0.764
Apgar score at 1 min	7(5～10)	9(5～10)	−1.416	0.157
Apgar score at 5 min	10(9～10)	10(9～10)	−0.067	0.947
Age at diagnosis	37(12.5～70.5)	30.0(13.0～61.0)	−0.729	0.466

GA：gestational age；BW：birth weight；IVF-ET：in vitro fertilization-embryo transfer.

统计学意义(均P<0.05)。而两组在妊娠期高血压率及中心静脉置管使用率之间的差异均无统计学意义(均P>0.05；表3)。

2.4.2　两组的血细胞参数单因素分析　生后第1周的两组血细胞参数单因素分析显示，两组在生后第1周的白细胞(white blood cell，WBC)、中性粒细胞(neutrophils，NEUT)、单核细胞(monocyte，MONO)、平均红细胞体积(mean corpuscular volume，MCV)、平均血红蛋白量(mean hemoglobin，MCH)、血小板(platelet，PLT)、血小板压积(plateletcrit，PCT)、平均血小板体积(meanplateletvolume，MPV)、血小板分布宽度(plateletvolumedistribution-width，PDW)之间的差异均有统计学意义(均P<0.05)。而两组在红细胞(red blood cell，RBC)、淋巴细胞(lymphocyte，LYMPH)、嗜酸性粒细胞(eosinophils，EO)、嗜碱性粒细胞(basophils，BASO)、血红蛋白(hemoglobin，HGB)、红细胞压积(Hematocrit，HCT)、平均血红蛋白浓度(mean hemoglobin concentration，MCHC)、红细胞分布宽度(red blood cell distribution width，RDW)之间的差异均无统计学意义(均P>0.05；表4)。

表3　病例组与对照组围产期相关因素的单因素分析

Table 3　Univariate analysis of related factors in perinatal period between case group and control group　[%，(n/N)]

	Case group	Control group	χ^2	P
Pregnancy anaemia	11.76%(10/85)	3.48%(4/115)	5.155	0.023
Pregnancy IDA/MA	9.41%(8/85)	3.48%(4/115)	3.051	0.081
Gestational hypertension	7.06%(6/85)	6.96%(8/115)	0.001	0.978
Antenatal glucocorticoid treatment	65.88%(56/85)	81.74%(94/115)	6.554	0.010
Intrauterine growth retardation	11.8%(10/85)	7.8%(9/115)	0.882	0.348
Early-onset sepsis	31.76%(27/85)	19.13%(22/115)	4.218	0.040
Mechanical ventilation(≥7 d)	43.53%(37/85)	20%(23/115)	12.885	0.000
PICC	38.82%(33/85)	32.17%(37/115)	0.950	0.330
Neonatal hypotension	23.53%(20/85)	6.96%(8/115)	11.150	0.001
PIVH(Ⅲ-Ⅳ)	15.29%(13/85)	3.48%(4/115)	10.686	0.001
HsPDA	32.94%(28/85)	14.78%(17/115)	9.242	0.002

IDA：iron deficiency anemia；MA：mediterranean anemia；PICC：peripherally inserted central catheter；PIVH：periventricular-intraventricular hemorrhage；HsPDA：hemodynamically significant patent ductus arteriosus.

2.4.3 脑白质损伤影响因素的Logistic回归分析 将单因素分析筛选有统计学意义的影响因素作为自变量,以是否发生WMD作为因变量,构建Logistic回归模型。结果显示,机械通气(≥7 d)OR=8.987[95%CI为(2.083, 38.770)]是WMD发生的独立危险因素。而生后1周内相对较高的MCH OR=0.679[95%CI为(0.507, 0.910)]和PLT OR=0.989[95%CI为0.981,0.998)]以及产前足疗程激素治疗OR=0.224[95%CI为(0.057,0.877)]是WMD发生的保护因素(表5)。

2.4.4 平均血红蛋白量和血小板计数诊断脑白质损伤的ROC曲线 以MCH和PLT的原始数据构建诊断WMD的ROC曲线。MCH诊断WMD的AUC为0.708,95% CI为(0.595,0.820),截断值为37.10 pg。PLT诊断WMD的AUC为0.669,95% CI为(0.551,0.787),截断值为227.50×10⁹/L(图2)。

2.4.5 平均血红蛋白量及血小板计数分层后的Logistic回归分析 根据最佳截断值,将MCH和PLT各分为两层,MCH≤37.10pg与MCH>37.10、PLT≤227.50×10⁹/L与PLT>227.50×10⁹/L,在调整两者可能的混杂因素(孕期贫血、胎龄、双胎妊娠、早发型

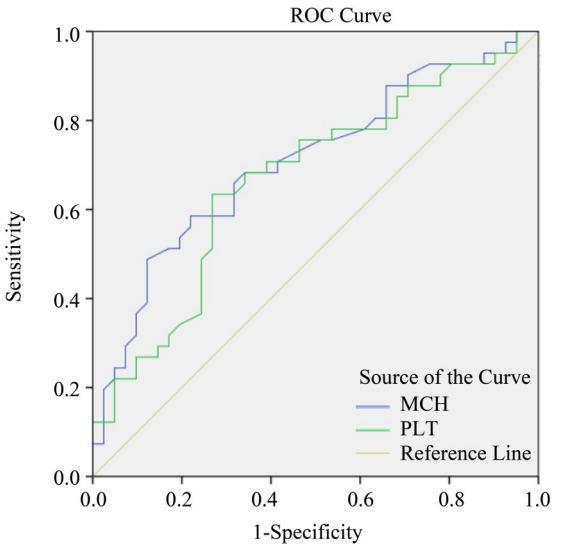


图2 MCH和PLT诊断WMD的ROC曲线

Fig. 2 ROC curve of MCH and PLT to diagnose WMD

表4 两组间血细胞参数的单因素分析

Table 4 Univariate analysis of blood cell parameters between the two groups [$M(P_{25}\sim P_{75})$]

Blood cell parameters	Case group	Control group	Z	P
WBC/(×10⁹/L)	12.86(9.66 ~ 21.09)	10.32(6.70 ~ 14.48)	−2.597	0.009
RBC/(×10¹²/L)	4.29(3.86 ~ 4.84)	4.33(4.09 ~ 4.77)	−0.742	0.458
NEUT/(×10⁹/L)	6.94(5.31 ~ 12.45)	5.39(2.84 ~ 8.34)	−3.042	0.002
LYMPH/(×10⁹/L)	3.80(2.77 ~ 6.32)	4.19(2.59 ~ 5.87)	−0.116	0.908
EO/(×10⁹/L)	0.18(0.06 ~ 0.40)	0.09(0.07 ~ 0.25)	−0.942	0.346
BASO/(×10⁹/L)	0.04(0.01 ~ 0.09)	0.03(0.02 ~ 0.06)	−0.331	0.740
MONO/(×10⁹/L)	1.16(0.87 ~ 1.50)	0.86(0.51 ~ 1.32)	−2.435	0.015
HGB/(g/L)	157.00(142.00 ~ 171.00)	170.00(153.50 ~ 179.00)	−1.856	0.064
HCT/%	53.05(42.00 ~ 53.30)	53.05(47.33 ~ 56.23)	−1.762	0.078
MCV/fl	111.60(103.60 ~ 116.90)	115.70(108.95 ~ 122.55)	−2.731	0.006
MCH/pg	35.70(33.95 ~ 37.90)	38.00(37.05 ~ 39.58)	−3.237	0.001
MCHC/(g/L)	324.00(317.50 ~ 332.50)	323.50(316.50 ~ 335.25)	−0.831	0.406
RDW/%	15.70(15.25 ~ 16.85)	16.20(15.35 ~ 16.85)	−0.534	0.593
PLT/(×10⁹/L)	192.00(161.00 ~ 251.50)	252.00(161.00 ~ 293.50)	−2.639	0.008
PCT/%	18.40(15.55 ~ 23.85)	21.95(16.93 ~ 27.10)	−2.207	0.027
MPV/fl	9.80(9.05 ~ 10.30)	9.40(8.85 ~ 10.00)	−1.964	0.049
PDW/%	16.80(16.30 ~ 17.20)	16.60(16.00 ~ 16.80)	−2.374	0.018

WBC: white blood cell; RBC: red blood cell; NEUT: neutrophils; LYMPH: lymphocytes; EO: eosinophils; BASO: basophils; MONO: monocyte; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; PLT: platelet; PCT: plateletcrit; MPV: mean platelet volume; PDW: platelet distribution width.

表5　WMD影响因素的Logistic回归分析结果

Table 5　Multivariate Logistic regression analysis of selected variables associated with WMD

Factors	b	S_b	Wald χ^2	P	OR	95% Confidence interval
Constant	16.758	5.810	8.319	0.004	–	–
Mechanical ventilation(≥7 d)	2.196	0.746	8.667	0.003	8.987	(2.083,38.770)
Antenatal glucocorticoid treatment	−1.495	0.696	4.618	0.032	0.224	(0.507,0.877)
MCH	−0.386	0.149	6.722	0.010	0.679	(0.507,0.910)
PLT	−0.011	0.004	6.133	0.013	0.989	(0.981,0.998)

MCH: mean corpuscular hemoglobin; PLT: platelet

败血症、PIVH(Ⅲ-Ⅳ级)、新生儿低血压、检查时日龄等)后进行Logistic回归分析，结果显示高MCH(>37.10 pg)、高PLT(>227.50×10⁹/L)是早产儿WMD的保护因素(表6)。

2.4.6　脑白质损伤评分分度后相关影响因素的有序Logistic回归分析　根据MRI评分后将WMD分为轻、中、重度，拟定为因变量，将可能影响其分度的可能的影响因素拟定为自变量，进行有序Logistic回归分析，结果显示：早发型败血症是WMD严重程度的危险因素，而胎龄和血小板分布宽度则是其保护因素及血细胞学指标(表7)。

3　讨论

3.1　早产儿脑白质损伤的现况

WMD是一类严重威胁新生儿生命健康的疾病。Blencowe[12]研究报道小于33周的早产儿WMD的发生率为4%~10%。而Hinojosa-Rodríguez等[13]研究发现小于28周的极早产儿甚至高达50%~80%。国内学者金越等[14]报道WMD在早产儿的总体发生率为8%~26%，且发生率呈逐年升高趋势。因此，早产儿WMD应该得到重点关注和高度的重视。

表6　MCH及PLT分层后的Logistic回归分析

Table 6　Logistic regression analysis after stratification of MCH and PLT

Factors	b	S_b	Wald χ^2	P	OR	95% Confidence interval
Constant	1.124	0.481	5.461	0.019	–	–
H-MCH	−1.494	0.538	7.724	0.005	0.224	(0.078,0.644)
H-PLT	−1.309	0.539	5.897	0.015	0.270	(0.094,0.777)
PIVH(Ⅲ-Ⅳ)	20.725	12868.472	0.000	0.999	1.001×10⁹	(0.000,-)

H-MCH: high mean corpuscular hemoglobin(>37.10 pg); H-PLT: high platelet (227.50×10⁹/L); PIVH: periventricular-intraventricuar hemorrhage.

表7　WMD严重程度影响因素的有序Logistic回归分析

Table 7　Ordinal Logistic Regression Analysis on the Influencing Factors of WMD Severity

Factors	b	S_b	Wald χ^2	P	95% Confidence interval
Early-onset sepsis	14.435	7.251	3.963	0.047	(0.224,28.646)
GA	−5.216	2.654	3.861	0.049	(0.013,10.418)
PDW	−7.820	3.940	3.939	0.047	(0.097,15.542)
Antenatal glucocorticoid treatment	−10.918	6.264	3.037	0.081	(−23.196,1.360)

GA: Gestational age; PDW: Platelet distribution width.

3.2 早产儿脑白质损伤的围产期高危影响因素

WMD目前被认为是早产儿在自身生理特点的基础上遭受缺氧缺血、感染、炎症反应等损伤后的结局。本研究选择了包括生后缺氧窒息、早发型败血症、机械通气(≥7 d)、新生儿低血压、中心静脉置管、PIVH(Ⅲ-Ⅳ级)、hsPDA,以及产妇围产期可能的影响因素比如孕期贫血、妊娠期高血压疾病、胎儿宫内生长发育迟缓等指标进行探讨。从本研究的单因素分析来看,病例组与对照组的差异有统计学意义的指标有:孕期贫血率、产前足疗程激素使用率、早发败血症发生率、机械通气(≥7 d)比例、低血压发生率、PIVH(Ⅲ-Ⅳ级)及hsPDA发生率。与Pietracupa等[15]和Kaur等[16]的研究结论相一致。此外,本研究结论与影像学研究中的发现一致:感染和炎症不仅增加了脑损伤的易感性,而且还认为与白质扩散张量成像(diffusion tensor imaging,DTI)序列的分数各向异性(fractional anisotropy,FA)值的降低有关(在脑白质中,FA值与髓鞘的完整性、纤维致密性和平行性呈正相关)。

本研究中病例组机械通气(≥7 d)比例明显高于对照组,并且研究结论认为其是早产儿WMD的独立危险因素,与既往研究一致[17-18]。我们在与MRI成像相关的研究中,还发现胼胝体、扣带回中的FA值与机械通气天数呈负相。推测可能的原因最有可能是机械通气容易引起脑血流和颅内压波动,进而导致脑室内出血。而Park等[19]研究发现的高氧应激是白质损伤的独立危险因素。Resch等[20]研究认为机械通气容易引起二氧化碳分压(partial pressure of carbon dioxide, PCO_2)的波动,过低的PCO_2会导致脑血流减少,与本研究结论吻合。

本研究结果显示,分娩前给予足剂量、足疗程的地塞米松治疗是早产儿WMD的保护因素。其保护作用可能与降低感染相关的免疫反应,减轻细胞因子对少突胶质细胞的损伤,显著促进脑血管的成熟,从而减少出生后脑损伤的发生有关[9]。但在本研究中,孕期贫、低血压、中心静脉置管、hsPDA、PIVH(Ⅲ-Ⅳ级)5个因素并未进入多因素回归分析模型中,仍需扩大样本量进一步确认研究确认。

3.3 血细胞学参数与脑白质损伤

本研究的病例组MCV、MCH显著低于对照组,而Silva等[21]的研究结论:早产儿WMD的有核红细胞计数显著增加。English等[22]研究认为较高的血红蛋白水平与较少的脑缺血和较好的临床结局相关。我们的研究认为,可能是因为较高的血红蛋白含量可能有利于氧气或其他脑营养素的运输,减少了脑缺氧缺血性损伤。胎儿在宫内的特定环境下MCV、MCH、MCHC等各项指标往往均高于生后的相应值,但在临床中缺铁、地中海贫血或地中海贫血基因携带这些因素可能影响这些指标。在本研究中,这些因素在两组病例的构成比无统计学差异的情况下通过Logistic回归分析发现减低的MCH作为WMD发生的相关血细胞指标,确认这一结论需要扩大样本量进一步探讨分析。

此外,病例组的PLT计数、PCT明显低于对照组,而MPV和PDW高于对照组,在临床中,新生儿的红细胞、血小板易受感染、宫内生长发育迟缓、母体疾病等因素的影响,严重的颅内出血也可能影响血小板及红细胞的数值变化,本研究将早发型败血症、胎儿宫内生长发育迟缓、母体炎症或免疫相关疾病、PIVH(Ⅲ-Ⅳ级)纳入Logistic回归模型进行混杂因素调整,经分析后显示MCH减少及PLT计数是多因素分析中WMD的危险因素相关的血细胞指标,且按WMD的严重程度分度后进行有序Logistic回归分析后显示早发型败血症和越小的胎龄是其危险因素,而PDW则是其保护因素。事实上,血小板在机体内除了凝血止血功能外,还参与了大脑微血管的形成与修复、神经组织的再生与保护,并介导了脑细胞间的通讯[23-24]。因此,血小板可能有助于早产儿脑白质区域微血管形成,以保证血供。在发育中的大脑,sonic hedgehog(shh)反应干细胞的增殖依赖于血小板,血小板将上皮shh转运到齿状回,表明血小板与围产期血管壁的胶质细胞直接相互作用[25]。此外,血小板还在致密的颗粒中储存了大量的神经发生促进分子,如5-羟色胺和组胺[26]。外泌体已被证明是包括神经干细胞在内的不同类型的成体干细胞的细胞通讯的重要机制。结合临床,我们推测血小板可能在脑白质的损伤与修复中起着重要作用。

其他血细胞学参数如第一周的白细胞总数、中性粒细胞计数、单核细胞计数在单因素分析中显示病例组均明显高于对照组,但基于新生儿白细胞在生后6 d内变化较大的生理特点,进行多因素回归分析意义不大。

3.4 本研究新的发现及对临床的指导意义

由于新生儿生后早期的血液学被认为容易受母体及生后感染、炎症及免疫因素影响,本研究已

对其相关的混杂因素加以控制，并利用单因素、多因素 Logistic 回归分析、ROC 曲线、有序 Logistic 回归分析等统计学研究方法来探讨早产儿脑白质损伤的围产期高危因素及血细胞指标的相关性。如果能用简便的血细胞指标加传统的围产期高危因素来预测或者指导 WMD 患者的诊治，将能减轻患者痛苦，减少社会经济负担。

3.5　结论性意见及不足

我们的研究结论认为：早产儿机械通气（≥7 d）、生后1周平均血红蛋白含量和血小板数目减低可能是早产儿 WMD 发生的独立危险因素，而产前应用足疗程的糖皮质激素则是其保护因素；早发型败血症及较小的胎龄及较小的血小板分布宽度可能是 WMD 严重程度的危险因素。然而，由于研究时间的限制，我们仅收集了近3年85例发生了 WMD 的早产儿作为研究对象，样本量可能比较小，研究结论可能存在一定的误差。在此，我们呼吁更多的专科和学者，在今后的诊治工作中，能在前瞻性大样本量中去验证 WMD 与血细胞参数的相关性，为 WMD 患儿的早发现早诊治提供更可靠的依据。

参考文献

[1] Sozmen EG, Rosenzweig S, Ditullio DJ, et al. White matter stroke induces a unique oligo-astrocyte niche that inhibits recovery[J]. J Neurosci, 2019, 39(47): 9343-9359.

[2] 王诗男，王金芳，石庆丽，等. 脑白质高信号合并认知障碍患者脑白质损伤程度的评价[J]. 中华行为医学与脑科学杂志, 2020, 29(6): 546-550.
Wang SHN, Wang JF, Shi QL, et al. Evaluation of the degree of white matter damage in patients with white matter hypertensities and cognitive impairment [J]. Chin J Behav Med & Brain Sci, 2020, 29(6): 546-550.

[3] 刘亚龙，李洁，王颖，等. 基于精细化残差U-Net的新生儿局灶性脑白质损伤分割模型[J]. 计算机应用, 2019, 39(12): 3456-3461.
Liu YL, Li J, Wang Y, et al. Segmentation model of neonatal focal white matter injury based on refined residual u-net[J]. J Comp Appl, 2019, 39(12): 3456-3461.

[4] 李新，李彤. 晚期早产儿脑白质损伤后神经系统发育障碍影响因素分析[J]. 中国中西医结合儿科, 2020, 12(6): 511-515.
Li X, Li T. Analysis of the influencing factors of neurodevelopmental disorder after brain white matter injury in late preterm infants[J]. Chin Pediatr Integr Tradit Western Med, 2020, 12(6): 511-515.

[5] 曹一翀，刘卫鹏，王凤，等. 脂肪干细胞生物活性分泌物防治早产儿脑白质损伤的安全性及早期疗效[J]. 中华实用儿科临床杂志, 2018, 33(19): 1503.
Cao YC, Liu WP, Wang F, et al. Safety and early curative efficacy of lipocytebioactive secretion in preventing white matter injury of premature infants[J]. Chin J Appl Clin Pediatr, 2018, 33(19): 1503.

[6] Sanz AB, José Vicente Mollá-Torró, López-CeladaSusana, et al. MRI evidence of brain atrophy, white matter damage, and functional adaptive changes in patients with cervical spondylosis and prolonged spinal cord compression [J]. Eur Radiol, 2020, 30(1): 357-369.

[7] Woodward LJ, Anderson PJ, Austin NC, et al. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants [J]. N Engl J Med, 2006, 355(7): 685-694.

[8] 邵肖梅，叶鸿瑁，丘小汕. 实用新生儿学[M]. 北京：人民卫生出版社, 2019: 393.
Shao XM, Ye HM, Qiu XS. Practical Neonatology [M]. People's Health Publishing House, Beijing 2019:393.

[9] Yagi M, Uchiumi T, Sagata N, et al. Neural-specific deletion of mitochondrial p32/C1qbp leads to leukoencephalopathy due to undifferentiated oligodendrocyte and axon degeneration [J]. Sci. Rep, 2017, 7(1): 15131.

[10] Barrington KJ, Janaillac M.Treating hypotension in extremely preterm infants. The pressure is mounting[J]. Arch Dis Child Fetal Neonatal Ed, 2016, 101(3): 188-189.

[11] Guler Kazanci E, Buyuktiryaki M, Unsal H. Useful platelet indices for the diagnosis and follow-up of patent ductus arteriosus [J]. Am J Perinatol, 2019, 36

(14):1521-1527.

[12] Blencowe H, Lee AC, Cousens S, et al. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010[J]. Pediatr Res,2013 ,74,(1): 17-34.

[13] Hinojosa-Rodríguez M, Harmony T, Carrillo-Prado C, et al. Clinical neuroimaging in the preterm infant: Diagnosis and prognosis[J]. Neuroimage Clin, 2017, 14 (16): 355-368.

[14] 金越,张敏,鲍星星,等. S100B 蛋白和行为神经评分对早产儿脑白质损伤的诊断价值[J].中华实用儿科临床杂志, 2015, 30(7): 1110-1112.
Jin Y, Zhang M, Bao XX, et al. Diagnostic value of S100B protein and behavioral nerve score in premature infants with white matter injury[J]. Chin J Appl Clin Pediatr, 2015, 30(7): 1110-1112.

[15] Pietracupa S, Bologna M, Bharti K, et al. White matter rather than gray matter damage characterizes essential tremor[J]. Eur Radiol, 2019, 29 (12): 6634-6642.

[16] Kaur C, Rathnasamy G, Ling EA. Roles of activated microglia in hypoxia induced neuroinflammation in the developing brain and the retina[J]. J Neuroimmune Phar, 2012, 8(1): 66-78.

[17] Isabella, Panfoli, Giovanni, et al. Oxidative stress as a primary risk factor for brain damage in preterm newborns[J]. Front Pediatr, 2018, 29(6): 369.

[18] Chang JL, Bashir M, Santiago C, et al. Intrauterine growth restriction and hyperoxia as a cause of white matter injury [J]. Dev Neurosci, 2018, 40 (4): 344-357.

[19] Park YW, Joers JM, Guo B, et al. Assessment of cerebral and cerebellar white matter microstructure in spinocerebellar ataxias 1, 2, 3, and 6 using diffusion MRI[J]. Front Neurol, 2020, 4(11): 411.

[20] Resch B, Neubauer K, Hofer N, et al. Episodes of hypocarbia and early-onset sepsis are risk factors for cystic periventricular leukomalacia in the preterm infant [J]. Early Hum Dev,2012, 88(1): 27-31.

[21] Silva AM, Smith RN, Lehmann CU, et al. Neonatal nucleated red blood cells and the prediction of cerebral white matter injury in preterm infants[J]. Am J Obstet Gynecol, 2006, 107(3): 550-556.

[22] English SW, McIntyre L. Is hemoglobin good for cerebral oxygenation and clinical outcome in acute brain injury? [J]. Curr Opin Crit Care, 2018, 24 (2): 91-96.

[23] Stellos K, Gnerlich S, Kraemer B, et al. Platelet interaction with progenitor cells: Vascular regeneration or injury? [J]. Pharmacol Rep, 2008, 60 (1): 101-108.

[24] Massberg S, Konrad I, Schurzinger K, et al. Platelets secrete stromal cell-derived factor 1 alpha and recruit bone marrow-derived progenitor cells to arterial thrombi in vivo[J]. J Exp Med, 2006, 203 (5): 1221-1233.

[25] Choe Y, Huynh T, Pleasure SJ. Epithelial cells supply Sonic Hedgehog to the perinatal dentate gyrus via transport by platelets[J]. Elife, 2015, 12(4): 7834.

[26] Wasielewska JM, Gronnert L, Rund N, et al. Mast cells increase adult neural precursor proliferation and differentiation but this potential is not realized in vivo under physiological conditions[J]. Sci Rep, 2017, 7 (1): 17859.

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