

早产儿脑损伤产前影响因素统计

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收稿日期: 2025年5月19日; 录用日期: 2025年6月13日; 发布日期: 2025年6月23日

摘 要

目的: 本研究旨在统计临床早产儿脑损伤现状及母亲产前影响因素。方法: 收集住院治疗的133例早产儿病例, 对早产儿一般资料、床旁超声表现及分级、复查超声表现及分级、母亲产前因素进行分析。结果: 133例早产儿病例中, 初次床旁超声提示单纯脑白质回声增强78.9%, 单纯脑室周围-脑室内出血2.4%。脑白质回声增强伴脑室周围-脑室内出血18.8%。复查超声提示脑损伤82例, 其中单纯脑白质回声增强65.9%, 单纯脑室周围-脑室内出血12.2%, 进展为脑室周围白质软化2.4%, 脑室周围白质软化合并脑室周围-脑室内出血19.5%。早产儿母亲产前因素中, 妊娠期高血压42.9%、妊娠期糖尿病24.1%、妊娠期贫血14.3%、先天性心脏病29.1%、未足月胎膜早破32.3%、脐绕颈29.3%、羊水污染16.5%、胎盘早剥12.8%。结论: 早产儿脑损伤的主要诱因是缺血缺氧及感染。

关键词

早产儿脑损伤, 产前因素

Statistics of Prenatal Influencing Factors of Brain Injury in Premature Infants

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Received: May 19th, 2025; accepted: Jun. 13th, 2025; published: Jun. 23rd, 2025

Abstract

Objective: This study aims to statistically analyze the current status of brain injury in clinical

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文章引用: 王妮娜, 董奕辰, 雷哲, 王银, 马乾凤. 早产儿脑损伤产前影响因素统计[J]. 临床医学进展, 2025, 15(6): 1368-1377. DOI: 10.12677/acm.2025.1561861

preterm infants and the maternal prenatal influencing factors. Methods: A total of 133 cases of premature infants hospitalized for treatment were collected, including general information, bedside ultrasound findings and grades of brain injury, follow-up ultrasound findings and grades of brain injury, and maternal prenatal factors. **Results:** Among the 133 preterm infants, 78.9% had simple cerebral white matter echogenicity on initial bedside ultrasound, 2.4% had simple intraventricular hemorrhage. 18.8% had simple cerebral white matter echogenicity with intraventricular hemorrhage. 82 of the infants had brain injury on follow-up ultrasound, with 65.9% having simple cerebral white matter echogenicity, 12.2% having simple intraventricular hemorrhage, 2.4% having progressive white matter softening around the ventricles, and 19.5% having ventricular white matter softening with intraventricular hemorrhage. Among the maternal prenatal factors, 42.9% had gestational hypertension, 24.1% had gestational diabetes, 14.3% had maternal anemia, 29.1% had congenital heart disease, 32.3% had premature rupture of membranes, 29.3% had umbilical cord entanglement, 16.5% had fetal membrane contamination, and 12.8% had placental abruption. **Conclusion:** The main inducing factors of brain injury in preterm infants are hypoxia and ischemia and infection.

Keywords

Brain Injury in Premature Infants, Prenatal Factors

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1. 引言

临床研究发现,增加早产风险的因素有很多,比如吸烟[1]或感染性疾病(如尿路感染、细菌性阴道病、沙眼衣原体感染、绒毛膜羊膜炎、HBV、HIV、疟疾和梅毒)[2]-[9]。妊娠期母体疾病包括妊娠期高血压、糖尿病、宫颈病变,及妇产科之外的疾病如贫血、肥胖、母体 VitD 低等[10]-[17]。系统性红斑狼疮、多囊卵巢综合征、癫痫、双相情感障碍等问题也会增加早产的可能性[18]-[22]。胎儿附属结构包括胎盘、羊水状况也与早产相关[23][24]。有研究表明,室外空气污染($PM \geq 2.5 \mu m$)与早产增加相关[25]。

患有早产儿脑白质损伤(preterm white matter injury, PWMI)的婴儿因弥漫性白质损伤和局灶性囊性坏死病变所致的全能性髓鞘退化有长期神经功能缺陷的风险,包括脑瘫、认知和视觉缺陷以及学习障碍[26][27]。目前还没有针对 PWMI 的具体治疗方法。

2. 材料与方法

2.1. 研究对象

宁夏医科大学总医院新生儿科 2023 年 11 月~2024 年 6 月收入院的早产儿 133 例。所有操作规程均按照相关指南进行。临床数据已获得参与者和/或其监护人知情同意,并获得宁夏医科大学总医院伦理审批(伦理编号: KYLL-2022-0649)。

2.2. 纳排标准及资料收集

纳入标准: (1) 出生胎龄 < 258 日; (2) 住院期间行床旁颅脑超声且报告完整。排除标准: (1) 患有先天性神经系统发育畸形; (2) 非本院出生,孕产史不全; (3) 缺少超声复查报告。资料收集: 胎龄、性别、出生时体重、单/双胎、妊娠期合并症、床旁超声表现。

2.3. 诊断标准

脑室周围脑白质回声增强(PVE 分级及超声表现)，见表 1。

Table 1. PVE graded ultrasound manifestations
表 1. PVE 分级超声表现

类型	分级	超声表现
PVE	I	脑室旁脑白质回声增强，比正常脉络丛稍低
	II	脑室旁脑白质会将较强，与正常脉络丛相仿
	III	脑室周围白质回声比正常脉络丛回声强

依据 Papile 分级法对 PIVH 进行分级，见表 2。

Table 2. Papile graded ultrasound manifestations
表 2. Papile 分级法超声表现

类型	分级	超声表现
PIVH	I	单侧/双侧室管膜下出血
	II	脑室内出血但无脑室增大
	III	脑室内出血伴脑室增大
	IV	脑室内出血伴脑室周围出血性梗死

2.4. 研究定义

参照人民卫生出版社第 10 版《妇产科学》相关定义。

- (1) 早产：妊娠达到 28 周但早于 37 周的分娩者娩出的新生儿成为早产儿。
- (2) 妊娠期高血压：是妊娠与血压升高并存的一组疾病。
- (3) HELLP：是在子痫前期 - 子痫基础上发生的以溶血、转氨酶升高以及血小板减少为特点的一组综合征。
- (4) 妊娠期糖尿病：指妊娠前血糖正常，妊娠期才出现的糖代谢异常。
- (5) 妊娠合并心脏病：包括妊娠前已患心脏病以及妊娠后新发生的心脏病。
- (6) 病毒性肝炎：由肝炎病毒引起的以肝脏病变为主的传染性疾病。
- (7) TORCH 综合征：T 是弓形虫，O 指其他如梅毒螺旋体，R 指风疹病毒，C 指巨细胞病毒，H 指单纯疱疹病毒。
- (8) 贫血：外周血血红蛋白 $< 110\text{ g/L}$ 及血细胞比容 < 0.33 为妊娠期贫血。
- (9) 甲状腺疾病：妊娠合并甲状腺功能亢进和甲状腺功能减退。
- (10) 未足月胎膜早破： < 37 周发生胎膜自然破裂。
- (11) 胎盘早剥：妊娠满 20 周位置正常的胎盘在胎儿娩出前部分/全部剥离。
- (12) 羊水过多/过少：妊娠期间羊水量超过 2000 mL /少于 300 mL 。
- (13) 脐带过短/单脐动脉：脐带短于 30 cm /脐带内只有 1 条动脉。
- (14) 脐带扭转：胎儿活动可使脐带顺其纵轴扭转呈螺旋状。可引起血管闭塞或伴血栓形成。
- (15) 前置胎盘：胎盘位置低于胎先露部位。
- (16) 脐带帆状附着：脐带附着于胎膜上，脐血管通过羊膜与绒毛膜间进入胎盘。

(17) 球拍状胎盘：脐带附着于胎盘边缘。

(18) 绒毛膜羊膜炎：① 母体体温 $\geq 38^{\circ}\text{C}$ ；② 阴道分泌物异味；③ 胎心率增快(胎心率基线 ≥ 160 次/分)或母体心率增快(心率 ≥ 100 次/分)；④ 母体外周血白细胞计数 $\geq 15 \times 10^9/\text{L}$ ；⑤ 子宫呈激惹状态、宫体有压痛。母体体温升高的同时伴有上述②~⑤任何一项表现可考虑绒毛膜羊膜炎，并排除其他感染性疾病。

3. 结果

3.1. 早产儿出生时胎龄(日)、体重较足月儿下降

本研究共纳入早产儿 133 人，其中男婴 73 例(54.9%)，女婴 60 例(45.1%)。单胎 92 例(69.2%)，双胞胎 41 例(30.1%)。出生时平均胎龄(211.7 ± 18.9)日(见图 1(A))，其中极早产儿(<223 日) 110 例(82.7%)，中度早产儿(224~237 日) 13 例(9.8%)，晚期早产儿(238~258 日) 7 例(5.34%)。出生时体重男婴(1338.7 ± 420.9) g，女婴(1393.4 ± 432.7) g。其中极低出生体重儿(<1500 g) 92 例(69.2%)，低出生体重儿(1500~2499 g) 38 例(28.6%)，正常体重出生儿(2500~4000 g) 3 例(2.2%)，平均体重明显低于足月儿(见图 1(B))。参照人民卫生出版社《儿科学(第十版)》，足月儿出生时体重男婴(3380 ± 400) g，女婴(3260 ± 400) g (见表 3)。

Table 3. General clinical information
表 3. 临床一般信息

基本信息		例数(例)	构成比(%)
胎儿数	单胎	92	69.2
	双胞胎	41	30.1
性别	男婴	73	54.9
	女婴	60	45.1
出生时胎龄	极早产儿(<223 日)	110	82.7
	中度早产儿(224~237 日)	13	9.8
	晚期早产儿(238~258 日)	7	5.34
出生时体重	极低出生体重儿(<1500 g)	92	69.2
	低出生体重儿(1500~2499 g)	38	28.6
	正常体重儿(2500~4000 g)	3	2.2

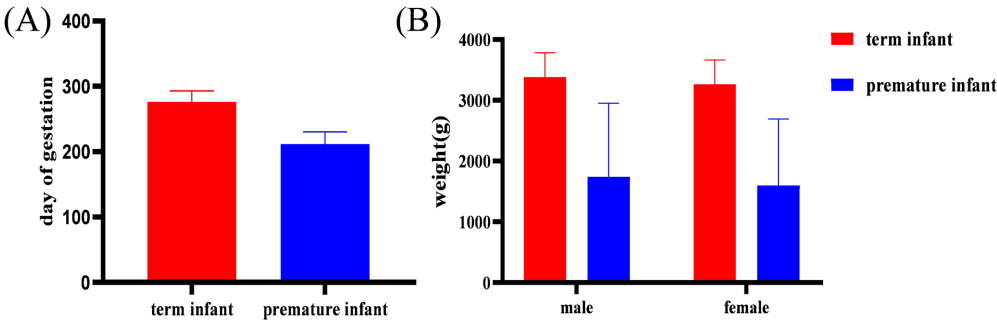


Figure 1. The gestational age (days) and weight of premature infants at birth are lower than those of full-term infants. (A) Average gestational age at birth of premature infants; (B) The birth weight of premature infants is significantly lower than that of full-term infants

图 1. 早产儿出生时胎龄(日)、体重较足月儿下降。(A) 早产儿平均出生胎龄；(B) 早产儿出生时体重明显低于足月儿

3.2. 早产儿脑损伤发生率及分级

本研究纳入的早产儿床旁超声提示出现脑损伤共 133 例，其中单纯 PVE105 例 78.9%，单纯 PIVH 3 例 2.3%，PVE-PIVH 25 例 18.8% (见表 4、图 2)。

Table 4. Brain injury of infants
表 4. 早产儿脑损伤

类型		例数(例)	构成比(%)
PVE	I	105	78.9
	I	1	0.8
PIVH	II	1	0.8
	III	0	0
	IV	1	0.8
PVE-PIVH		25	18.8

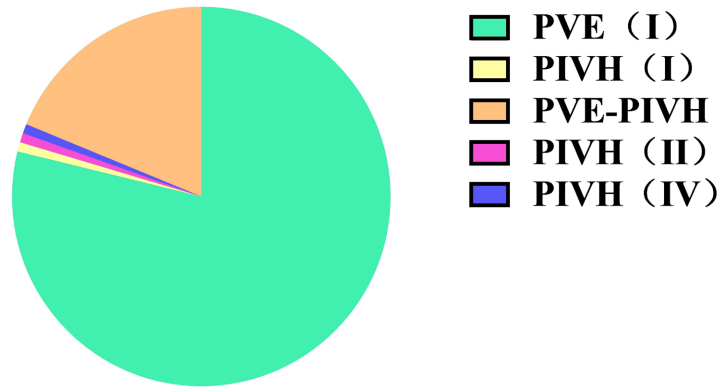


Figure 2. Composition ratio of pathological injury type
图 2. 病理损伤类型构成比

3.3. 超声复查早产儿损伤发生率级分级

本研究纳入的早产儿床旁超声复查提示出现脑损伤共 82 例，其中单纯 PVE 54 例(65.9%)，单纯 PIVH 10 例(12.2%)，PVL2 例(2.4%)，PVL-PIVH 16 例(19.5%) (见表 5、图 3)。

Table 5. Ultrasound reexamination of brain injury in premature infants
表 5. 早产儿超声复查脑损伤

类型		例数(例)	构成比(%)
PVE	I	54	65.9
	I	9	11.0
PIVH	II	0	0
	III	0	0
	IV	1	1.2
PVL		2	2.4
PVL-PIVH		16	19.5

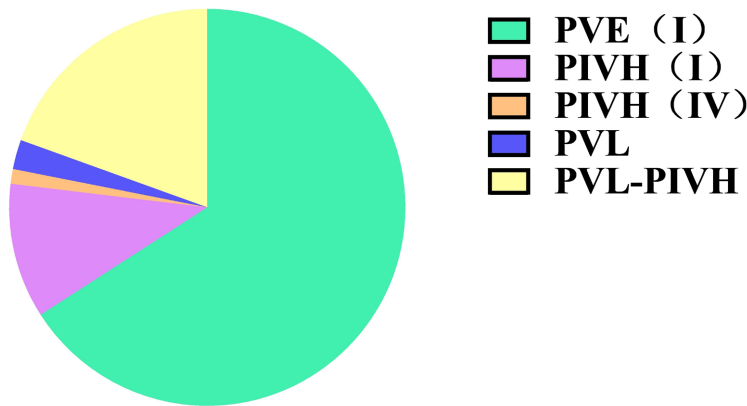


Figure 3. Ultrasound reexamination of the composition ratio of pathological injury types
图 3. 超声复查病理损伤类型构成比

3.4. 产前因素统计

超声提示脑损伤的早产儿中，母亲患妊娠期高血压疾病的有 38 例、妊娠期糖尿病 14 例、妊娠期甲状腺疾病 9 例、先天性心脏病 4 例、免疫系统疾病 3 例、贫血 16 例、感染性疾病 7 例、脐带异常 22 例、胎盘异常 21 例、羊水异常 30 例、胎膜早破 20 例、宫内窘迫 21 例、其他因素 9 例(包括子宫肌瘤、双角子宫、纵膈子宫、染色体异常等)。在早产儿的母亲产前因素中，同时合并两种及以上的有 69 例(见表 6)。

Table 6. Statistics of prenatal factors
表 6. 产前因素统计

产前因素	例数(例)	构成比(%)	产前因素	例数(例)	构成比(%)
妊娠期高血压疾病	57	42.9	单脐动脉	2	1.5
HELLP	3	2.3	脐带扭曲	11	8.3
妊娠期甲状腺疾病	11	8.3	胶质脐带	5	3.8
妊娠期糖尿病	32	24.1	脐绕颈	39	29.3
妊娠期贫血	19	14.3	脐带过短	1	0.8
先天性心脏病	28	21.1	羊水过多	8	6.0
病毒性肝炎	9	6.8	羊水过少	16	12.0
上呼吸道感染	11	8.3	羊水污染	22	16.5
肥胖	10	7.5	血性羊水	7	5.2
盆腔炎	2	1.5	无羊水	2	1.5
阴道炎	5	3.8	脐带帆状附着	8	6.0
人乳头瘤病毒	2	1.5	球拍状胎盘	7	5.2
TORCH	1	0.8	胎盘梗死	1	0.8
未足月胎膜早破	43	32.3	胎盘血池	2	1.5
先兆子宫破裂	2	1.2	胎盘早剥	17	12.8
宫腔感染	4	3.0	绒毛膜羊膜炎	4	3.0
过敏性哮喘	1	0.8	前置胎盘	8	6.0

3.5. 早产儿脑损伤超声表现

在新生儿出生后行颅脑超声。正常超声提示：脑实质回声未见明显增强，脑内结构清晰；脑室脑池系统未见扩张，中线结构无移位(见图 4(A))。早产儿床旁超声提示：脑实质回声增强。超声下显示 PVE 提示早产儿发生脑白质损伤，并可发展为 PVL (见图 4(B))。

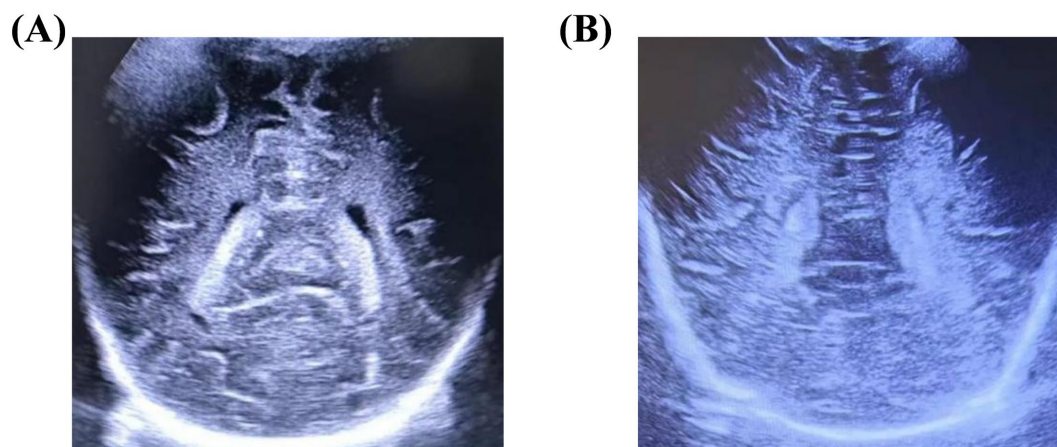


Figure 4. Ultrasound manifestations of brain injury in premature infants. (A) Normal cranial ultrasound; (B) Brain injury cranial ultrasound (coronal position)

图 4. 早产儿脑损伤超声表现。(A) 正常颅脑超声；(B) 脑损伤颅脑超声(冠状位)

3.6. 早产儿脑损伤诱因分析

通过对超声表现有脑损伤的 133 例早产儿母亲进行产前因素总结归纳，发现主要有两大重要影响因素，一个是缺血缺氧，另一个是感染。其中可导致胎儿急性缺氧的因素包括：胎盘异常(前置胎盘、胎盘早剥)；脐带异常(脐带扭转、脐带脱垂)；母体严重血液循环障碍导致胎盘灌注急剧减少(失血性休克)。可导致胎儿发生慢性缺氧的因素包括：母体血氧量不足(先天性心脏病/心功能不全、呼吸道感染、哮喘、贫血)；子宫胎盘血管硬化，狭窄，梗死，绒毛间隙血液灌注不足(妊娠期高血压疾病、慢性肾炎、糖尿病、过期妊娠)；胎儿运输及利用氧能力弱等。可导致胎儿发生感染的因素包括：羊水污染、胎膜早破等。综合以上因素分析导致早产儿发生脑损伤的主要原因是缺血缺氧及感染。

4. 讨论

在统计临床早产儿母亲产前产时影响因素时发现，早产儿的母亲大多患有一种或多种妊娠合并症。在本研究的统计结果中，超过 40%的早产儿母亲患有妊娠期高血压疾病，其中最常见的是慢性高血压合并子痫前期重度和早发子痫前期重度。发病机制可能是与子宫螺旋动脉重塑不足有关，子宫螺旋动脉重塑不足会导致胎盘灌注减少，从而使胎儿发生慢性缺氧。还有少数母亲患有先天性心脏病。多数先天性心脏病有遗传因素，除能增加胎儿患先天性心脏病的风险外，孕期母亲心功能异常也会增加胎儿缺血缺氧的风险。妊娠期糖尿病在早产儿母亲产前疾病当中占比较高，约有 24.1%，胎儿长期处于高胰岛素血中增加发展为巨大儿的危险，且易导致羊水过多而发生胎膜早破，另外可使胎儿宫内耗氧量增加，发生慢性缺氧。孕期贫血也是早产儿母亲常见的合并症，不管是中度还是重度的贫血，都可导致胎盘供养不足，胎儿在宫内出现慢性缺氧状态，提高了早产的发生率。胎盘和脐带在整个妊娠期发挥重要作用。而胎盘和脐带疾病也常常发生。胎盘早剥在统计中占比 12.8%，胎盘早剥常会引发胎儿缺氧，而隐形胎盘早剥极易并发胎儿窘迫并导致产妇产后失血性休克。在脐带疾病当中有导致急性缺氧的脐带扭转、脐绕颈，也有不

常见的单脐动脉和脐血管断裂。

除可导致急/慢性缺血缺氧的因素外,感染也是诱发早产的重要原因。在早产儿母亲的常见合并症中,感染性疾病,包括 HBV、梅毒,都可通过垂直传播导致胎儿发生宫内感染。另外生殖道感染是常见胎膜早破的病因,也是早产的主要原因之一,而随着胎膜早破时间的延长,宫内感染风险也增加,易诱发早产,并可能出现羊水污染。胎儿宫内缺氧可促使胎儿排出胎粪从而出现羊水胎粪污染。

围产期脑白质损伤指多相的、普遍的脑白质损伤,包括灶性坏死(囊性和非囊性 PVL)与弥漫性损伤。弥漫性脑白质损伤主要分布于脑白质,累及少突胶质细胞及其前体细胞(oligodendrocyte precursor cell, OPC)。若不及时干预,最终将发展为髓鞘化障碍与脑室扩大,是导致认知障碍、癫痫、智力低下等神经功能障碍的基础。白质病变以髓鞘减少和成熟 OLs 数量不足为主要特征,可通过再髓鞘化加以干预[26]。目前,弥漫性白质损伤在早产儿脑损伤中最为常见。皮质髓鞘化大约在妊娠 34 周开始,并以尾端到头端的方式进展[27][28]。因此,若出生时间小于 34 周,早产破坏了重要的子宫内脑成熟[29][30],则会出现明显髓鞘化不足。通过调查临床早产儿的出生胎龄和体重,发现早产儿的体重明显低于足月儿,意味着其器官系统及各项功能的发育较足月儿也会有差异。

目前中重度缺血缺氧性脑病足月儿的标准治疗以低温治疗为主。临床指南建议在出生后 6 小时内尽早开始低温治疗,并持续 72 小时,目标脑温为 $33.5 \pm 0.5^{\circ}\text{C}$ [31]。治疗性低温与免疫抑制性改变相关[32]。但对于早产儿的治疗暂无相关指南。

OPC 出生前位于神经管的脑室下区,在整个大脑和脊髓中迁移,并分化为 OL,直至出生后发育[33]。尽管 OL 的产生率随着大脑的成熟而大幅下降,但在 7 月龄小鼠(相当于人类的 40 岁)的脑内通过免疫荧光进行 PDGFRa 染色,发现大量 OPC 的存在。OPC 极易受到氧化损伤,当 OPC 因氧化损伤出现死亡时,周边的 OPC 便可进行增殖和迁移,以保证 OPC 池的相对稳定。值得注意的是,白质损伤区域 OPC 增殖有所增加,但是这些 OPC 却停滞于分化成熟前[34],这可能是由于其损伤后的抑制性环境所致。因此,如何促进损伤后 OPC 的正常分化,对于白质修复至关重要。目前对此类疾病常见的治疗方法包括基因疗法、药理学干预、干细胞移植等,主要聚焦于 Notch、Wnt/ β -catenin 和乙酰透明质酸介导的信号通路。但是到目前为止,所有在动物实验中尝试的损伤疗法均未能实现临床转化,仅低温治疗可用[35]。因此,对此类疾病的预防干预成为围产医学的重中之重。

通过对临床病例的分析,本研究总结早产儿发生脑白质损伤的主要诱因为缺血缺氧和感染。

基金项目

宁夏自然科学基金(2023AAC03238, 2023AAC03547)。

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