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重度颅脑损伤开颅术后早期颅内压与CRP和D-二聚体的相关性

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[摘要] 目的: 探讨重度颅脑损伤患者接受开颅术后早期颅内压(intracranial pressure, ICP)与患者脑脊液及外周血CRP和D-二聚体(D-dimer, D-D)的相关性, 为判断重度颅脑损伤病情发展提供参考。方法: 纳入2015年1月至2017年12月于航天中心医院神经外科接受治疗的37例重度颅脑损伤、接受开颅术患者, 均于术后留置颅内测压导管, 持续监测ICP。术后3 d内, 每12 h采集患者脑脊液及外周血标本, 采用免疫比浊法检测CRP和D-D水平, 并统计对应时点ICP指标。结果: 37例患者共获得6组、222份数据, 其中105份ICP>20 mmHg, 117份ICP≤20 mmHg。ICP>20 mmHg时患者血清CRP、血清D-D、脑脊液CRP、脑脊液D-D水平均明显高于ICP≤20 mmHg时的水平($P<0.05$)。血清CRP、血清D-D、脑脊液CRP、脑脊液D-D与ICP均呈明显正相关($\rho=0.742, 0.884, 0.805, 0.886$; 均 $P<0.001$)。血清CRP、血清D-D、脑脊液CRP、脑脊液D-D对诊断ICP>20 mmHg均有较可靠的价值, 其曲线下面积分别为0.854, 0.943, 0.870, 0.951。脑脊液D-D是ICP>20 mmHg的独立影响因素($OR=4.115, P=0.001$)。结论: 重度颅脑损伤开颅术后, 患者早期ICP与脑脊液及外周血CRP, D-D均呈明显的正相关, 且与脑脊液D-D的关系最密切。联合检测脑脊液及外周血CRP及D-D有助于反映患者ICP变化情况, 从而对患者术后治疗提供参考。

[关键词] 颅脑损伤; 颅内压; 外周血; 脑脊液; C反应蛋白; D-二聚体

Relationship of early intracranial pressure with C-reactive protein and D-Dimer in patients with severe traumatic brain injury after craniotomy

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Abstract **Objective:** To investigate the correlation of early intracranial pressure with CRP and D-dimer (D-D) in cerebrospinal fluid and peripheral blood in patients with severe traumatic brain injury after craniotomy, and to provide reference for the judgment of severe craniocerebral injury disease. **Methods:** Thirty-seven patients with severe craniocerebral injury treated by craniotomy in the Department of Neurosurgery from January 2015 to December 2017 was involved. Postoperative ICP of all patients were detected by

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intracranial pressure catheter. The cerebrospinal fluid and peripheral blood samples of patients were collected at each 12 h within 3 days after surgery, CRP and D-D were detected, and the corresponding ICP index at the time point was statistically analyzed. **Results:** A total of 222 copies of the data were obtained, in which 105 copies showed ICP >20 mmHg and 117 showed \leq 20 mmHg. When ICP >20 mmHg, CRP and D-D in both serum and cerebrospinal fluid were higher than when ICP \leq 20 mmHg ($P < 0.05$). ICP was positive correlated with CRP in serum, D-D in serum, CRP in cerebrospinal fluid and D-D in cerebrospinal fluid ($\rho = 0.742, 0.884, 0.805, 0.886$; all $P < 0.001$). CRP in serum, D-D in serum, CRP in cerebrospinal fluid and D-D in cerebrospinal fluid were all reliable values for the diagnosis of ICP >20 mmHg. The area under ROC were 0.854, 0.943, 0.870, and 0.951, respectively. D-D in cerebrospinal fluid was an independent factor of ICP >20 mmHg (OR=4.115, $P = 0.001$). **Conclusion:** The early postoperative ICP has positive correlation with serum and peripheral blood CRP and D-D in both cerebrospinal fluid and peripheral blood, and it is most closely related to CSF D-D. The combined detection of CRP and D-D in cerebrospinal fluid and peripheral blood can help to reflect the change of ICP in patients, so as to provide reference for postoperative treatment.

Keywords traumatic brain injury; intracranial pressure; peripheral blood; cerebrospinal fluid; C reactive protein; D-dimer

重度颅脑损伤为神经外科常见疾病, 具有较高的致死及致残率^[1], 准确检测患者颅内压 (intracranial pressure, ICP), 积极防治颅内压升高, 是提升患者预后的关键^[2]。开颅期间放置有创ICP探头有助于实时测定ICP, 但此类探头价格昂贵, 同时可能带来额外的并发症, 因此有一定局限性。颅脑损伤后外周血及脑脊液D-二聚体(D-Dimer, D-D)和CRP水平均明显上升, 且上升程度与颅脑损伤的严重程度及患者预后密切相关^[3-4], 但针对性分析上述指标与ICP相关性的研究较少。本研究纳入37例重度颅脑损伤开颅术患者, 于术后3 d内采用颅内测压导管持续监测ICP, 并通过免疫比浊法检测脑脊液及外周血CRP和D-D水平, 旨在探讨脑脊液及外周血中CPR和D-D与ICP的相关性。

1 对象与方法

1.1 对象

纳入2015年1月至2017年12月于航天中心医院神经外科接受治疗的37例重度颅脑损伤患者, 开展前瞻性非随机对照研究。纳入患者及其家属均知情且签署同意书, 本研究已获得航天中心医院医学伦理委员会批准。纳入标准: 近期闭合性头部外伤史, 术前Glasgow昏迷量表评分 \leq 8分, 经CT证实存在脑损伤, 参考《中国颅脑创伤外科手术指南》^[5], 需要接受开颅手术; 受伤至手术时间 \leq 12 h; 术后于神经重症监护病房接受监护, 存活时间 $>$ 3 d; 病历资料完整。排除标准: 术前应用

抗凝药物; 院前及院内感染患者; 心、肝、肺、肾等重要脏器功能不全; 合并严重复合伤、多发伤; 合并肿瘤。纳入患者中男22例, 女15例, 年龄18~78(55.7 \pm 12.7)岁, 术前GCS评分3~8(4.8 \pm 1.1)分, 交通伤27例、打击伤7例、其他损伤3例。

1.2 方法

1.2.1 治疗方法

所有患者入院后立即开展对症治疗, 包括脱水、机械通气、镇静等, 及时评估手术可行性, 并接受手术治疗, 术中留置基本型或脑室型ICP探头(美国Codman公司), 并接配套监护仪。37例患者中21例探头置入脑实质, 12例置入硬膜下, 4例置入脑室内。术后患者转入神经重症监护病房, 持续监测ICP。发现患者ICP $>$ 20 mmHg (1 mmHg=0.133 kPa), 且持续 $>$ 5 min后, 采用阶梯疗法控制ICP, 如无法在30 min内控制ICP, 或ICP \geq 30 mmHg, 立即复查头颅CT, 积极准备再次手术。

1.2.2 CRP及D-D监测

患者转入神经重症监护病房后3 d内, 每12 h采集1次脑脊液及静脉血标本各5 mL, 其中静脉血标本均离心分离血清, 每位患者共获得6组标本。标本均置于 -80 °C冰箱冻存。采用免疫比浊法测定CRP及D-D水平, 其中CRP检测试剂盒购自德国罗氏, 检测仪器为德国罗氏生产的cobas C501型全自动电化学发光免疫分析仪, D-D检测试剂盒购自德国西门子, 检测仪器为日本希森美康生产的Sysmex CA-7000全自动血凝仪, 检测方案均参

照检测参考仪器及试剂说明书。在采集检测标本时, 同时统计对应时点ICP指标, 各时点按 $T_1 \sim T_6$ 标记。如在设定的数据采集时间, 患者处于无法采集标本的情形, 如正在接受二次手术等, 则标本采集时间按需延后, 以能够获得可靠的数据监测指标为准。

1.3 统计学处理

采用SPSS 19.0软件进行数据分析。计量资料采用Shapiro-Wilk验证正态性。非正态分布资料统计中位数(M)、第1四分位数(Q_1)、第3四分位数(Q_3), 按 $M(Q_1 \sim Q_3)$ 表示。按 $ICP > 20$ mmHg与否分组, 采用Mann-Whitney法对比组间血清及脑脊液CRP, D-D的差异。采用Spearman相关性分析血清及脑脊液CRP, D-D与ICP的相关性, 对具备相关性的指标, 采用ROC曲线分析该指标诊断 $ICP > 20$ mmHg的效能。 $ICP > 20$ mmHg的影响因素采用二分类logistic逐步回归方法分析。 $P < 0.05$ 为差异有

统计学意义。

2 结果

2.1 重度颅脑损伤患者开颅术后ICP与血清及脑脊液CRP, D-D描述性统计

共获得数据222份, 经Shapiro-Wilk检验, 各指标均不符合正态分布($P < 0.05$)。对222组数据总体描述性统计: 血清CRP [23.8 (18.4~31.1) mg/L], 血清D-D [770.8 (337.2~2 156.6) mg/L], 脑脊液CRP [2.2 (1.5~3.2) mg/L], 脑脊液D-D [689.3 (242.8~2 677.2) mg/L], ICP [19.2 (14.4~27.3) mmHg]。按统计时间分组后, 患者ICP在 $T_1 \sim T_6$ 时刻取值范围分别为18.2 (15.7~22.6), 17.3 (12.7~25.5), 17.9 (14.2~27.2), 19.2 (15.5~28.9), 20.7 (13.4~30.2)及21.3 (14.4~28.8) mmHg, 血清及脑脊液CRP, D-D的统计结果如图1所示。

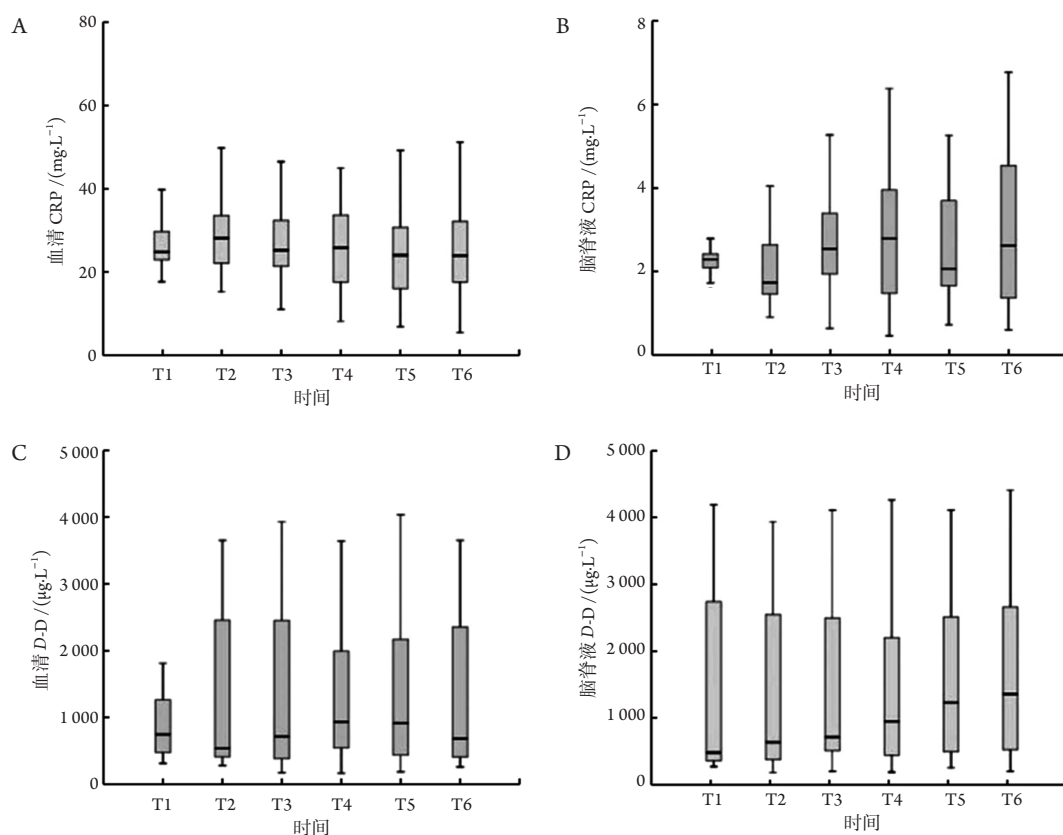


图1 重度颅脑损伤患者开颅术后不同时间点血清及脑脊液CRP, D-D描述性统计

Figure 1 Levels of CRP and D-D in cerebrospinal fluid and peripheral blood in patients with severe traumatic brain injury after craniotomy at different time points

(A)血清CRP水平; (B)脑脊液CRP水平; (C)血清D-D水平; (D)脑脊液D-D水平。

(A) Levels of CRP in serum; (B) Levels of CRP in cerebrospinal fluid; (C) Levels of D-D in serum; (D) Levels of D-D in cerebrospinal fluid.

2.2 重度颅脑损伤患者开颅术后 ICP>20 mmHg 组与 ICP ≤ 20 mmHg 组指标差异

222份数据中, 105份ICP>20 mmHg, 117份 ICP ≤ 20 mmHg。经Mann-Whitney检验, 2组间 ICP、血清CRP、血清D-D、脑脊液CRP、脑脊液 D-D差异均有统计学意义($P<0.05$, 表1)。

2.3 重度颅脑损伤患者开颅术后血清及脑脊液 CRP, D-D 与 ICP 的相关性分析

血清CRP、血清D-D、脑脊液CRP、脑脊液 D-D与ICP均呈明显正相关($\rho=0.742, 0.884, 0.805, 0.886$; P 均 <0.001 ; 图2)。

表1 ICP>20 mmHg组与ICP ≤ 20 mmHg组血清及脑脊液CRP、D-D对比

Table 1 Compare of the levels of CRP and D-D in cerebrospinal fluid and peripheral blood between ICP >20 mmHg group and ICP ≤20 mmHg group

| 组别 | <i>n</i> | ICP/mmHg | 血清 CRP/(mg·L ⁻¹) | 血清 D-D/(μg·L ⁻¹) | 脑脊液 CRP/(mg·L ⁻¹) | 脑脊液 D-D/(μg·L ⁻¹) |
|---------------|----------|---------------------|---------------------------------|---------------------------------|----------------------------------|----------------------------------|
| ICP>20 mmHg | 105 | 27.7 (23.0~30.8) | 31.0 (25.8~36.6) | 2115.6 (1259.8~3151.7) | 3.1 (2.3~4.0) | 2633.7 (1552.8~3369.3) |
| ICP ≤ 20 mmHg | 117 | 14.7 (12.3~17.3) | 19.8 (14.6~23.8) | 371.8 (230.7~587.8) | 1.6 (1.2~2.0) | 279.4 (136.2~513.5) |
| Z | | -12.856 | -9.114 | -11.382 | -9.509 | -11.604 |
| P | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

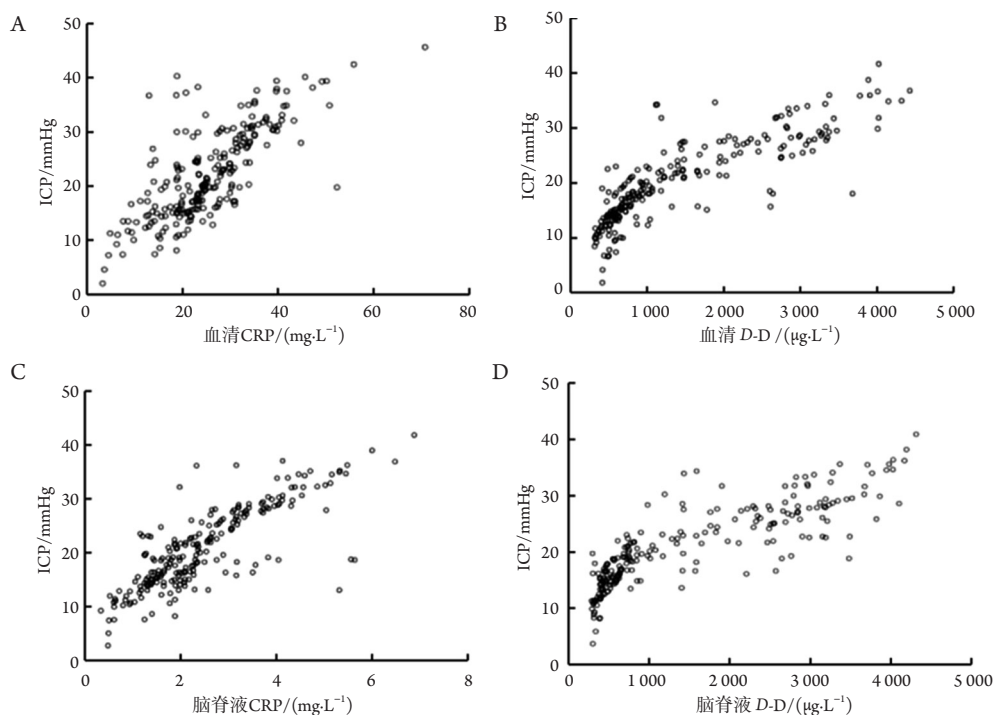


图2 ICP与血清及脑脊液CRP和D-D的散点分布图

Figure 2 Scatter diagram of the levels of ICP and the levels of CRP and D-D in serum and cerebrospinal fluid

(A) ICP与血清CRP的散点分布图; (B) ICP与血清D-D的散点分布图; (C) ICP与脑脊液CRP的散点分布图; (D) ICP与脑脊液 D-D的散点分布图。

(A) Scatter diagram of the levels of ICP and the levels of CRP in serum; (B) Scatter diagram of the levels of ICP and the levels of D-D in serum; (C) Scatter diagram of the levels of ICP and the levels of CRP in cerebrospinal fluid; (D) Scatter diagram of the levels of ICP and the levels of D-D in cerebrospinal fluid.

2.4 重度颅脑损伤患者开颅术后血清及脑脊液CRP, D-D对诊断ICP>20 mmHg效能分析

血清CRP、血清D-D、脑脊液CRP、脑脊液D-D对诊断ICP>20mmHg均有较可靠的价值,其曲线下面积分别为0.854(95%CI 0.804~0.905, $P<0.001$)、0.943(95%CI 0.911~0.974, $P<0.001$)、0.870(95%CI 0.821~0.918, $P<0.001$)、0.951(95%CI 0.925~0.978, $P<0.001$),见图3。根据ROC曲线,血清CRP诊断ICP>20 mmHg的最佳界值为26.4 mg/L,此时敏感度0.743,特异性0.880,约登指数0.623;血清D-D诊断ICP>20 mmHg的最佳界值为906.3 $\mu\text{g/L}$,此时敏感度0.886,特异度0.932,约登指数0.818;脑脊液

CRP诊断ICP>20 mmHg的最佳界值为2.3 mg/L,此时敏感度0.781,特异性0.863,约登指数0.644;血清D-D诊断ICP>20 mmHg的最佳界值为1 111.4 $\mu\text{g/L}$,此时敏感度0.848,特异度0.915,约登指数0.763。

2.5 重度颅脑损伤患者开颅术后ICP>20 mmHg影响因素分析

采用逐步进入的二分类logistic回归分析方案,结果显示仅脑脊液D-D是ICP>20 mmHg的独立影响因素,脑脊液D-D每上升1 mg/L,患者出现ICP>20 mmHg的风险上升3.115倍(表2)。

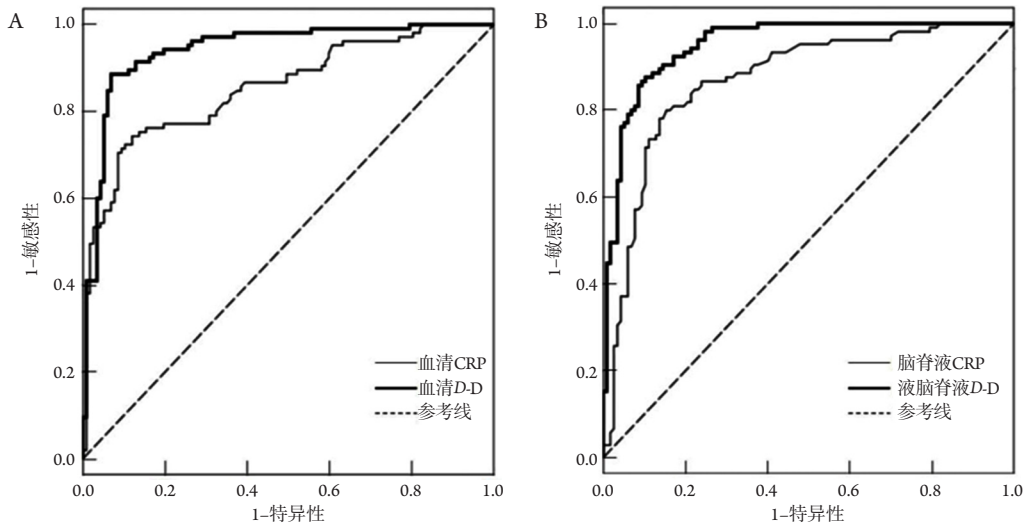


图3 血清及脑脊液CRP、D-D对诊断ICP>20 mmHg的ROC曲线

Figure 3 ROC curves of the levels of CRP and D-D in serum and cerebrospinal fluid used to diagnose ICP > 20 mmHg

(A)血清CRP、D-D对诊断ICP>20 mmHg的ROC曲线;(B)脑脊液CRP、D-D对诊断ICP>20 mmHg的ROC曲线。

(A) ROC curves of the levels of CRP and D-D in serum were used to diagnose ICP > 20 mmHg; (B) ROC curves of the levels of CRP and D-D in cerebrospinal fluid were used to diagnose ICP > 20 mmHg.

表2 ICP>20 mmHg影响因素的logistic回归分析

Table 2 Logistic regression analysis of influencing factors of ICP > 20 mmHg

| 指标 | β | Wals | P | OR | 95% CI |
|---------|---------|--------|--------|-------|-------------|
| 血清 CRP | 0.025 | 0.362 | 0.548 | 1.025 | 0.945~1.112 |
| 血清 D-D | 0.940 | 3.339 | 0.068 | 2.560 | 0.934~7.018 |
| 脑脊液 CRP | -0.083 | 0.071 | 0.789 | 0.920 | 0.500~1.694 |
| 脑脊液 D-D | 1.415 | 10.622 | 0.001 | 4.115 | 1.758~9.634 |
| 常数项 | -3.237 | 16.091 | <0.001 | 0.039 | |

3 讨论

随社会急救系统、治疗技术等的发展,目前已能有效控制颅脑损伤的病死率,但重度颅脑损伤的致残率仍居高不下。目前研究认为控制和减少继发性脑损伤是提升患者预后的关键,而继发性脑损伤又多与ICP升高有关^[6],这提示实时监测患者ICP,有助于指导治疗并提升患者预后。Yuan等^[7]行Meta分析,纳入2012年后的7份研究资料,证实ICP检测能够显著减少颅脑损伤患者的病死率,合并OR=0.56(95%CI 0.41~0.78);Ferreira等^[8]纳入来自巴西圣保罗的299例颅脑损伤患者,结果虽提示ICP检测可能无法改善患者病死率,但亦指出在当地医院接受ICP监护的多为重度颅脑损伤患者,因此其结论提示经ICP监护的重度颅脑损伤患者的病死率可下降至与未接受ICP监护的轻度患者相近。ICP升高对患者的危害可能包括:引起脑血管自动调节功能失调、降低脑灌注、加重脑组织缺氧性损伤、引发脑移位和脑疝等。Kawoos等^[9]认可了ICP监测的重要性,并指出目前以放置监测探头为主的有创ICP检测方案是最精确、可靠的监测方案,但该方案在国内尚未普及,因此探寻其他能够反映ICP变化的实验室检测指标有重要意义。

D-D是反映机体高凝状态和激发纤溶亢进的敏感指标;CRP则是临床常见的炎症细胞因子,能够反映创伤和感染的严重程度,且其快速上升往往先于临床症状的出现。本研究观察到患者术后血清CRP、血清D-D、脑脊液CRP、脑脊液D-D多处于异常升高区间,提示重度颅脑损伤患者术后多伴随D-D及CRP的异常升高。赵飞等^[10]纳入60例老年颅脑损伤患者,研究证实颅脑损伤患者血清D-D和CRP水平均明显上升,且损伤程度越严重,上升水平越高;Foaud等^[11]纳入埃及吉萨的46例颅脑损伤儿童,证实术后1~14 d,外周血D-D对预测死亡的诊断敏感度从89.5%下降至73.7%,特异度从100.0%下降至81.5%,但均处于较高水平,提示D-D是患儿预后的重要预测指标;王佳等^[12]证实颅脑损伤程度、脑出血量及脑水肿体积均与血清CRP表达水平单峰性升降有关;Gyoneva等^[13]研究也证实炎症损伤是导致患者预后不良的主要因素。上述结论均表明血清及脑脊液CRP和D-D的异常升高与患者不良预后有关,机制^[14-17]可能包括:1)脑组织富含组织因子,损伤后大量组织因子释放入血及脑脊液,进而激活凝血瀑布。同时颅脑损伤继发炎症反应,导致脑血管内皮受损,激活内源性

凝血途径并活化血小板。颅脑损伤时合并出现的低体温、低氧血症、酸中毒等均可能加重凝血功能紊乱。上述均可能导致脑脊液及外周血D-D水平升高;2)炎症则是机体对损伤性刺激所造成的损伤的正常反应,重度颅脑损伤后炎症反应本质上属于机体抗损伤保护性反应,但CRP等炎症因子的过度表达又会加重脑细胞损伤,甚至导致全身炎症反应,形成恶性循环。

ICP升高是导致继发性颅脑损伤的主要原因,这进一步提示血清及脑脊液CRP,D-D与ICP升高的直接相关性。本研究观察到血清及脑脊液CRP,D-D均与ICP呈正相关。赵鹏洲等^[18]也观察到重度颅脑损伤患者外周血D-D及CRP与ICP呈正相关;谢昌纪等^[19]纳入65例患者,证实脑脊液CRP含量的变化与ICP变化正相关;Neklyudov等^[20]报道脑脊液D-D与ICP变化有关;齐艳艳等^[21]则利用右美托咪啶抑制CRP等炎症因子水平降低ICP,其结论也提示CRP与ICP呈正相关。本研究进一步构建了以外周血及脑脊液CRP,D-D预测ICP>20 mmHg的ROC曲线,显示4项指标均具备良好的诊断及预测价值,其ROC曲线下面积均在0.85以上。但在logistic回归分析中,外周血CRP、外周血D-D、脑脊液CRP均不是ICP>20 mmHg的独立危险因素,提示脑脊液D-D最能反映ICP的变化,这可能是由于ICP升高直接导致脑灌注下降、脑血流减慢,使脑血管形成局部微血栓,激活纤溶系统,同时局部脑损伤导致D-D大量释放入脑脊液,因此脑脊液D-D对ICP的变化更为敏感。

总之,本研究发现重度颅脑损伤术后ICP>20 mmHg较常见,且ICP与外周血、脑脊液CRP及D-D呈正相关,尤其与脑脊液D-D的关系最为密切。术后积极检测外周血及脑脊液上述指标,可能有助于及时发现ICP升高,开展针对性治疗,进而提升患者预后。

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