



电子、语音版

·论著·

血小板相关参数对胶质瘤患者预后的影响

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摘要:目的 探讨术前血小板相关参数对胶质瘤患者肿瘤复发的预测作用。方法 分析联勤保障部队第九〇九医院2015—2017年收治的93例胶质瘤患者临床病理资料,根据随访期间肿瘤是否复发分为无复发组($n=52$)和复发组($n=41$),分析血小板相关参数与胶质瘤分级的相关性,采用ROC曲线分析血小板计数(PLT)、血小板体积分布宽度(PDW)、血小板压积(PCT)、平均血小板体积(MPV)、平均血小板体积/血小板计数(MPV/PLT)对肿瘤复发的预测作用,多因素Cox分析肿瘤复发的影响因素,采用Kaplan-Meier曲线分析这些因素对肿瘤复发的影响。结果 胶质瘤Ⅲ、Ⅳ级患者PLT、PCT、高于胶质瘤Ⅰ、Ⅱ级患者($t=-2.388, -2.335$,均 $P<0.05$);胶质瘤Ⅲ、Ⅳ级患者中MPV、MPV/PLT低于胶质瘤Ⅰ、Ⅱ级患者(均 $P<0.05$);无复发组患者PLT和PCT低于复发组(均 $P<0.05$);无复发组患者MPV和MPV/PLT高于复发组(均 $P<0.05$);PLT的ROC曲线下面积(UAC)为0.630(95%CI=0.517~0.743, $P=0.032$),阈值为 $216\times 10^9/L$;MPV的UAC为0.633(95%CI=0.518~0.747, $P=0.029$),阈值为8.65 fL;MPV/PLT的UAC为0.731(95%CI=0.626~0.835, $P<0.001$),阈值为0.040;多因素分析结果发现,肿瘤分级(Ⅲ、Ⅳ)、MPV ≤ 8.65 fL、MPV/PLT ≤ 0.040 是术后肿瘤复发的危险因素(95%CI分别为1.778~3.530、1.730~4.450、1.811~6.067,均 $P<0.05$);肿瘤分级(Ⅲ、Ⅳ)预测术后肿瘤复发曲线下面积为0.679(95%CI=0.569~0.789, $P=0.003$)。Kaplan-Meier曲线分析显示,MPV ≤ 8.65 fL患者术后3年复发率高于MPV > 8.65 fL患者(Long Rank=10.990, $P=0.001$);MPV/PLT ≤ 0.040 患者术后3年复发率高于MPV/PLT > 0.040 患者(Long Rank=6.289, $P=0.012$)。结论 胶质瘤患者术前MPV和MPV/PLT与术后肿瘤复发有关,可以用于肿瘤预后预测,具有一定临床意义。

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关键词: 胶质瘤; 血小板; 预后; 复发; 平均血小板体积/血小板计数

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Influence of platelet-related parameters on the prognosis of patients with glioma

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Abstract: **Objective** To investigate the effect of preoperative platelet-related parameters in predicting tumor recurrence in patients with glioma. **Methods** A retrospective analysis was performed for the clinicopathological data of 93 patients with glioma who were admitted to The 909th Hospital of Joint Logistics Support Force from 2015 to 2017, and according to the presence or absence of tumor recurrence during follow-up, they were divided into non-recurrence group with 52 patients and recurrence group with 41 patients. The correlation between platelet-related parameters and glioma grade was analyzed; the receiver operating characteristic (ROC) curve was used to analyze the effect of platelet count (PLT), platelet distribution width (PDW), plateletcrit (PCT), mean platelet volume (MPV), and MPV/PLT ratio in predicting tumor recurrence, and the Kaplan-Meier curve was used to investigate the influence of these factors on tumor recurrence. **Results** Compared with the patients with grade I/II glioma, the patients with grade III/IV glioma had

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significantly higher PLT and PCT (both $P < 0.05$) and significantly lower MPV and MPV/PLT ratio (both $P < 0.05$). Compared with the recurrence group, the non-recurrence group had significantly lower PLT and PCT (both $P < 0.05$) and significantly higher MPV and MPV/PLT ratio (both $P < 0.05$). The ROC analysis showed that PLT had an area under the ROC curve (AUC) of 0.630 (95% confidence interval [CI]: 0.517–0.743, $P = 0.032$) and a threshold of $216 \times 10^9/L$, MPV had an AUC of 0.633 (95% CI: 0.518–0.747, $P = 0.029$) and a threshold of 8.65 fL, and MPV/PLT ratio had an AUC of 0.731 (95% CI: 0.626–0.835, $P < 0.001$) and a threshold of 0.040. The multivariate analysis showed that tumor grade (III–IV) (95% CI: 1.778–3.530, $P < 0.05$), $MPV \leq 8.65$ fL (95% CI: 1.730–4.450, $P < 0.05$), MPV/PLT ratio ≤ 0.040 (95% CI: 1.811–6.067, $P < 0.05$) were risk factors for postoperative tumor recurrence, and tumor grade (III–IV) had an AUC of 0.679 (95% CI: 0.569–0.789, $P = 0.003$) in predicting postoperative tumor recurrence. The Kaplan–Meier curve analysis showed that the patients with $MPV \leq 8.65$ fL had a significantly higher 3-year recurrence rate than those with $MPV > 8.65$ fL (Long Rank = 10.990, $P = 0.001$), and the patients with $MPV/PLT \leq 0.040$ had a significantly higher 3-year recurrence rate than those with $MPV/PLT > 0.040$ (Long Rank = 6.289, $P = 0.012$). **Conclusions** Preoperative MPV and MPV/PLT ratio are associated with postoperative tumor recurrence in patients with glioma, and therefore, they have a certain clinical significance and can be used for predicting the prognosis of tumor.

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Keywords: glioma; platelet; prognosis; recurrence; mean platelet volume/platelet count ratio

胶质瘤是颅内常见的恶性肿瘤,约占所有颅内原发性肿瘤的45%^[1]。胶质瘤具有手术难度大、恶性程度高、易复发、预后差等特点^[2–3]。研究报道,年龄、肿瘤级别、炎症因子、术前中性粒细胞与淋巴细胞比值等是胶质瘤患者预后的影响因素^[4–5]。血小板计数(platelet count, PLT)、血小板体积分布宽度(platelet volume distribution width, PDW)、血小板压积(Plateleterit, PCT)、平均血小板体积(mean platelet volume, MPV)、平均血小板体积/血小板计数(MPV/PLT)等血小板相关参数与食管癌^[6]、膀胱癌^[7]、肾癌^[8]、卵巢癌^[9]等恶性肿瘤的预后密切相关。但是血小板相关参数与胶质瘤患者的预后关系尚未见报道。

1 资料与方法

1.1 临床资料

选取联勤保障部队第九〇九医院2015—2017年收治的胶质瘤患者93例,收集其临床病理资料,根据随访期间内肿瘤是否复发分为无复发组($n=52$)和复发组($n=41$),两组患者一般资料对比差异无统计学意义(见表1)。胶质瘤分级标准采用世界卫生组织(WHO)关于胶质诊断分级方法^[10]。本研究经我院医学伦理委员会同意并批准。

1.2 纳入标准和排除标准

纳入标准:①经病理组织学证实为胶质瘤并进行手术切除;②临床病理学资料完整;③完成随访者。排除标准:①免疫系统疾病患者;②血液系统疾病患者;③合并其他恶性肿瘤患者;④术前接受放疗患者或其他抗肿瘤治疗患者;⑤围手术期死亡患者;⑥失访患者。

1.3 随访

术后第1天记为随访起始日期,随访3年,随访方式包括电话、门诊和住院随访,随访频率为3个月1次,复查内容包括三大常规、头颅和胸部CT、腹部彩超,若发现肿瘤复发则记录肿瘤复发时间。

1.4 观察指标

性别、年龄、肿瘤大小、肿瘤部位、肿瘤分级、术前Kamofsky功能状态(Kamofsky performancr statue, KPS)评分。术前3 d空腹静脉抽血检验血小板相关参数:PLT、PDW、PCT、MPV、MPV/PLT。

1.5 统计学方法

采用SPSS 22.0统计软件对数据进行分析,计数资料以例(%)表示,比较采用 χ^2 检验或Fisher精确检验;正态分布计量资料以均数 \pm 标准差($\bar{x} \pm s$)表示,比较采用 t 检验;受试者工作特征(ROC)曲线下面积(area under curve, AUC)分析预测价值;单因素和多因素Cox分析肿瘤复发影响因素;Kaplan–Meier曲线分析肿瘤术后复发率;以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 血小板相关参数与胶质瘤分级的相关性

胶质瘤III、IV级患者中PLT、PCT高于胶质瘤I、II级患者($t=-2.388$ 、 -2.335 ,均 $P < 0.05$);胶质瘤III、IV级患者中MPV、MPV/PLT低于胶质瘤I、II级患者($t=2.583$ 、 4.391 ,均 $P < 0.05$);两组患者PDW对比,差异无统计学意义($P > 0.05$)。见表1。

2.2 肿瘤复发单因素分析

复发组中WHO III、IV级所占比例高于无复发组($\chi^2=12.027$, $P < 0.05$);无复发组患者PLT和PCT低于

表1 血小板相关参数与胶质瘤分级相关性 ($\bar{x} \pm s$)

分级	PLT/($\times 10^9/L$)	PDW/fL	PCT/%	MPV/fL	MPV/PLT
I和II级(n=39)	190.24 \pm 51.43	11.35 \pm 2.60	0.16 \pm 0.04	8.69 \pm 1.20	0.042 \pm 0.005
III和IV级(n=54)	208.46 \pm 45.19	11.32 \pm 2.90	0.20 \pm 0.05	8.25 \pm 1.04	0.036 \pm 0.004
t值	-2.388	0.403	-2.335	2.583	4.391
P值	0.012	0.881	0.023	0.029	0.000

复发组($t=-2.490, -2.189$, 均 $P<0.05$);无复发组患者MPV和MPV/PLT高于复发组($t=2.184, 4.252$, 均 $P<0.05$)。见表2。

表2 术后肿瘤复发单因素分析

因素	无复发组(n=52)	复发组(n=41)	t/χ^2 值	P值
性别/例			2.016	0.156
女	19	21		
男	33	20		
年龄/例			1.2370	0.266
≤ 40 岁	31	29		
> 40 岁	21	12		
肿瘤大小/例			0.072	0.789
≤ 3 cm	29	24		
> 3 cm	23	17		
肿瘤部位/例			0.034	0.853
大脑皮层	20	15		
非大脑皮层	32	26		
肿瘤分级/例			12.027	0.001
I、II	30	9		
III、IV	22	32		
术前KPS评分/例			0.002	0.962
≤ 80 分	34	27		
> 80 分	18	14		
PLT/($\times 10^9/L, \bar{x} \pm s$)	187.80 \pm 44.45	210.41 \pm 42.19	-2.490	0.015
PDW/(fL, $\bar{x} \pm s$)	11.33 \pm 2.80	11.31 \pm 3.23	0.037	0.971
PCT/(%, $\bar{x} \pm s$)	0.17 \pm 0.04	0.19 \pm 0.03	-2.189	0.031
MPV/(fL, $\bar{x} \pm s$)	8.64 \pm 1.03	8.22 \pm 0.81	2.184	0.032
MPV/PLT/($\bar{x} \pm s$)	0.041 \pm 0.005	0.036 \pm 0.003	4.252	0.000

2.3 血小板参数预测术后肿瘤复发效能

PLT的AUC为0.630(95%CI=0.517~0.743, $P=0.032$),

阈值为 $216 \times 10^9/L$, 灵敏度为0.610、特异度为0.635;PCT的AUC为0.616(95%CI=0.503~0.729, $P=0.055$), 阈值为0.167%, 灵敏度为0.805、特异度为0.404;MPV的AUC为0.633(95%CI=0.518~0.747, $P=0.029$), 阈值为8.65 fL, 灵敏度为0.519、特异度为0.854;MPV/PLT的AUC为0.731(95%CI=0.626~0.835, $P=0.000$), 阈值为0.040, 灵敏度为0.635、特异度为0.829。

2.4 肿瘤分级预测术后肿瘤复发效能

肿瘤分级(III、IV)的AUC为0.679(95%CI=0.569~0.789, $P=0.003$)。

2.5 肿瘤复发多因素分析

多因素分析结果发现,肿瘤分级(III、IV)、MPV ≤ 8.65 fL、MPV/PLT ≤ 0.040 是术后肿瘤复发的危险因素(均 $P<0.05$)。见表3。

表3 术后肿瘤复发多因素分析

因素	HR	95%CI	P值
肿瘤分级(III、IV)	1.657	1.778~3.530	0.021
PLT $\geq 216 \times 10^9/L$	1.320	0.697~2.449	0.394
PCT $\geq 0.167\%$	1.285	0.871~4.528	0.103
MPV ≤ 8.65 fL	1.803	1.730~4.450	0.011
MPV/PLT ≤ 0.040	1.994	1.811~6.067	0.003

2.6 MPV和MPV/PLT对肿瘤复发的影响

MPV ≤ 8.65 fL患者术后3年复发率高于MPV > 8.65 fL患者(Long Rank=10.990, $P=0.001$);MPV/PLT ≤ 0.040 患者术后3年复发率高于MPV/PLT > 0.040 患者(Long Rank=6.289, $P=0.012$)。见图1。

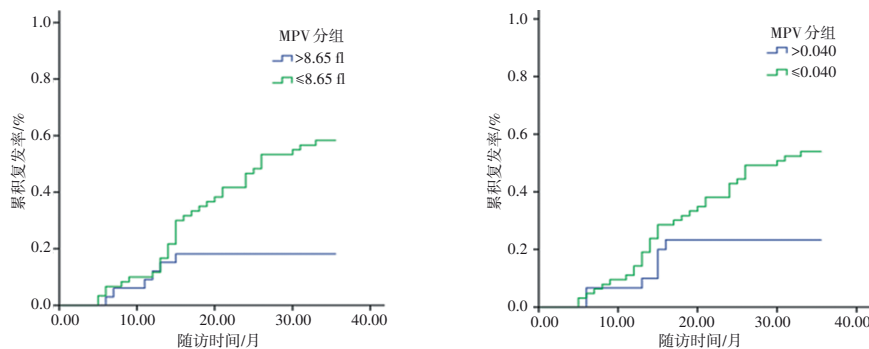


图1 MPV和MPV/PLT对肿瘤复发的影响

3 讨论

近年来,胶质瘤在我国发病率有逐年上升趋势。胶质瘤细胞恶性程度高,生长速度快,术后易出现复发,特别是高级别胶质瘤,中位生存时间仅为1年^[11-12]。尽管针对胶质瘤的手术技术、术后化疗和放疗水平不断取得进展,但是胶质瘤总体治疗效果仍然不理想^[13]。特别是术后对于肿瘤复发的预防和治疗仍缺乏有效手段,虽然Ki-67、O⁶-甲基鸟嘌呤DNA甲基转移酶(MGMT)、P53等分子标志物被证实可以用于胶质瘤预后评估,但是具有检测成本高、流程复杂、临床实用性差等缺点^[14-15]。因此寻找更多简便方法预测胶质瘤复发,是临床研究热点。

研究发现血小板及其相关参数与多种恶性肿瘤的不良预后相关。甲状腺癌中,PLT和PCT升高,且与淋巴结转移和预后呈正相关^[16];在膀胱癌中,MPV和MPV/PLT低于正常人,是预后不良的影响因素^[17];在晚期非小细胞肺癌中,MPV降低,与骨转移、淋巴结转移相关^[18];在直肠癌中,MPV低表达可以作为预测预后指标,并且与化疗效果相关^[19-20]。

血小板及其相关参数可以通过多种途径促进恶性肿瘤进展。首先血小板可以增强肿瘤细胞的侵袭能力,通过上调血管内皮细胞生长因子(VEGF)表达促进新生血管生成,MPV减小进一步加快血小板运动速度,增大与血管内皮细胞黏附机会,新生血管增多,肿瘤细胞氧供和血供得到改善,促进上皮间质化(EMT)^[21]。其次血小板及其衍生物增加肿瘤周围炎症反应和炎症介质释放,炎症因子如白介素、组胺、5-羟色胺等可以促进肿瘤细胞侵袭和转移^[22]。最后血小板可能参与肿瘤细胞免疫逃逸过程,血小板包裹肿瘤细胞形成包被,降低自然杀伤细胞(NK细胞)对肿瘤细胞的识别和杀伤力^[23]。

在本研究中,胶质瘤术后复发的患者PLT和PCT高于无复发的患者,提示在胶质瘤患者中,血小板计数和比容升高可能与术后肿瘤复发有关。同时复发组MPV和MPV/PLT低于无复发组,可能与血小板体积减小,运动速度增快,附着能力增强,促进新生血管生成有关。进一步研究发现PLT、MPV和MPV/PLT可能可以用于预测胶质瘤复发,这与其在肾癌和食管癌中的研究结论相一致^[24-25]。多因素研究发现MPV和MPV/PLT是胶质瘤术后复发的影响因素,并且通过生存曲线分析证实MPV和MPV/PLT较低的患者,胶质瘤术后肿瘤复发的可能性增大。

综上所述,术前血小板及其相关参数水平与胶质瘤术后复发有关,可以用于预测胶质瘤术后复发,并且MPV和MPV/PLT降低是肿瘤复发的影响因素。但是血小板相关指标用于预测肿瘤复发的效能和阈值仍需多中心、大样本验证研究,并且其相关作用机制也仍有待进一步研究。

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