

doi: 10.13241/j.cnki.pmb.2017.16.016

脑室出血合并脑积水行脑室外引流高危因素的临床分析*

郭迎喜 贺世明 陆 丹 赵兰夫 王 元 薛亚飞 张玉富 赵天智[△]

(第四军医大学唐都医院神经外科 陕西 西安 710000)

摘要 目的:探讨脑室出血后未立即行脑室外引流术发生脑积水的指征和时机。**方法:**回顾性分析 2009 年 1 月到 2015 年 9 月我院收治的 98 例脑室内出血患者的临床资料。**结果:**98 例患者中,28 例(28.6%)患者需要行脑室外引流术。全脑室出血是最常见的类型(49 例,50%),这些患者中 24 例(49%)需要行脑室外引流术。在脑室外引流术组和非脑室外引流术组平均 mGS 分别是 17 ± 5.1 (12-28)和 8 ± 4.2 (2-20)($P < 0.001$)。与脑室外引流术相关的因素包括影像学表现为脑积水、中线移位 > 5 mm、GCS 评分 < 8 分、mGS > 13 分、三脑室 mGS=5 及四脑室 mGS=5 分。多因素回归分析中,mGS > 13 分、GCS 评分 < 8 分和四脑室 mGS=5 分仍是重要的影响因素。大部分患者(24 例,85.7%)在有脑积水症状时很快行脑室外引流术,有 4 例患者在 48 小时后行脑室外引流术。**结论:**昏迷、mGS > 13 分和四脑室扩大使行脑室外引流术的风险增大。大部分患者在脑室出血后一天内行脑室外引流术,很少一部分患者在 48 小时后行脑室外引流术。

关键词: 脑室内出血;脑积水;脑室外引流术;脑出血

中图分类号:R743.34 文献标识码:A 文章编号:1673-6273(2017)16-3064-04

Clinical Analysis of Risk Factors for Hydrocephalus Patients after Intraventricular Hemorrhage in Exerting External Ventricular Drainage*

WU Ying-xi, HE Shi-ming, LU Dan, ZHAO Lan-fu, WANG Yuan, XUE Ya-fei, ZHANG Yu-fu, ZHAO Tian-zhi[△]

(Department of Neurosurgery, Tangdu Hospital of The Fourth Military Medical University, Xi'an, Shaanxi, 710000, China)

ABSTRACT Objective: To discuss and examine the indicators and time for hydrocephalus patients who were not immediately treated with external ventricular drainage (EVD) after intraventricular hemorrhage (IVH). **Methods:** Retrospective analysis of clinical data of 98 cases of IVH from January 2009 to september 2015. **Results:** Ninety-eight patients met the criteria; twenty-eight (28.6%) received EVD. Paraventricular hemorrhage was the most common pattern (49.5%), with twenty-four in these patients requiring EVD. The median mGS in the EVD group was 17 ± 5.1 (12-28) and was 8 ± 4.2 (2-20) ($p < 0.001$) in the No-EVD group. Hydrocephalus diagnosed by imaging, midline shift > 5 mm, Glasgow Coma Scale (GCS) score < 8 , mGS > 13 , third ventricle mGS = 5, and fourth ventricle mGS = 5 were associated with EVD. On multivariate regression analysis, mGS > 13 , GCS score < 8 and fourth ventricle mGS = 5 were still significant factors. Most patients (24, 85.7%) who were symptomatic hydrocephalus received EVD soon. Only four patients received EVD after forty-eight hours. **Conclusions:** Coma, mGS > 13 and a dilated fourth ventricle increased the risk of EVD. Most patients experienced EVD within 24 hours after IVH, and a minority required EVD after 48 hours.

Key words: Intraventricular hemorrhage; Hydrocephalus; External ventricular drainage; Intracerebral hemorrhage

Chinese Library Classification (CLC): R743.34 **Document code:** A

Article ID: 1673-6273(2017)16-3064-04

前言

脑室内出血(intraventricular hemorrhage, IVH)主要或常发生于颅内出血(ICH)、蛛网膜下腔出血、创伤和肿瘤出血。脑积水是 IVH 常见的并发症。许多研究表明 IVH 后脑室出血和脑积水是预后不良的独立危险因素^[1-3]。脑室外引流术 (IVD)是 IVH 有效的治疗方法,最新来自于美国心脏协会和脑卒中协会的治疗颅内出血指南指出脑室外引流 " 作为治疗脑积水引起的意识障碍是合理的 " 的^[4]。但当患者临床症状恶化,影像学表现脑积水诊断不明确或影像学表现脑积水诊断明确但临床症状

良好的情况下是有争议的^[2,5]。当 IVH 伴有大量脑出血时,无论有无脑积水,脑出血,脑室内出血和脑积水都能引起恶心、呕吐和嗜睡的症状,这就更加难以评估。因此,本研究通过回顾性分析脑室内出血的患者的临床资料,旨在明确与脑积水症状相关需要行脑室外引流的影响因素和实施脑室外引流的临床时机。

1 资料和方法

1.1 入选和排除标准

回顾性分析 2009 年 1 月到 2015 年 9 月 IVH 患者的临床资料。入选标准:年龄 ≥ 18 岁,有脑出血,创伤,肿瘤或血管病

* 基金项目:陕西省自然科学基金项目(S2015YFJQ1250)

作者简介:郭迎喜(1982-),硕士研究生,主治医师,主要研究方向:颅脑肿瘤和创伤,电话:13572868554, E-mail:476620343@qq.com

[△] 通讯作者:赵天智,博士研究生,主治医师,主要研究方向:颅底肿瘤, E-mail:ares1102@126.com

(收稿日期:2016-11-03 接受日期:2016-11-30)

合并 IVH 的患者。排除标准:IVH 合并微量的蛛网膜下腔出血,CT 扫描表现仅有一层 IVH,CT 扫描后立即行脑室外引流的患者和出血量很大仅能行姑息治疗的患者。初期结果是患者有脑积水症状需要行 EVD,包括需要行 EVD 但因为保守治疗而没有干预的患者。有症状的脑积水定义为影像学表现患者意识障碍主要由脑积水引起。EVD 管的放置符合当前的 AHA 指南。患者表现为昏睡但影像学表现没有脑积水,如果连续 CT 扫描证实脑室扩大需要行 EVD。

1.2 观察指标

符合入选标准的患者记录其年龄、合并症(包括高血压、糖尿病、高脂血症、中风和抗凝治疗)、出血原因、出血位置、ICH 评分、出血开始的时间、GCS 评分、CT 扫描结果(包括出血量、中线移位程度)、脑室出血量、脑积水程度、脑室外引流位置、脑室分流位置、死亡率、致残使用改良 Rankin 量表。不良结果定义为 mRS 评分 ≥ 3 分,改良的 Graeb 评分(mGS)用来测量 IVH 的程度^[6]。mGS 是一个半定量评分从 0 到 32,右侧和左侧颞角和枕角评分各 1 分代表脑室出血 $\leq 50\%$,右侧和左侧颞角和枕角评分各 2 分代表脑室出血 $> 50\%$;右侧和左侧脑室从 1 分到 4 分每增加 1 分脑室出血增加 25%;三脑室和四脑室评分 2 分代表脑室出血 $\leq 50\%$,三脑室和四脑室评分 4 分代表脑室出血 $> 50\%$ 。当 IVH 扩大到其他部位时会增加评分。因此,在颞极和枕极 mGS 评分 3 分和在侧脑室,3 脑室和 4 脑室评分 5 分表明整个脑室扩大。3 脑室和 4 脑室的扩大通过和以前的 CT 扫描对比获得。如果没有以前的 CT 扫描结果对比,通过测量 3 脑室宽度 >6.6 mm 和 4 脑室宽度 >19 mm 或前后径 >12 mm 表明脑室扩大^[7]。ABCD/2 方法用来评价出血量^[8]。脑积水评分使用 Stein 等提出的方法(22):0 分,无脑积水;1 分,轻度脑积水,1 个颞角轻度扩大;2 分,中度脑积水,1 个颞角中度扩大,至少在前角有 1 个脑叶的脑沟消失;3 分,重度脑积水,超过 2 个区域脑沟消失或双侧压迫基底池。通过连续的 CT 扫描分析进行评分。对于在住院期间存活的患者进行随访 1-12 个月。

1.3 统计学分析

所有统计学资料用 Graphpad prism 分析。统计学分析使用卡方检验,Student's t-test 和 Mann-Whitney test 来分析两组之间的差异。多变量回归分析决定单变量的重要性。以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 术前合并症

98 例患者符合入选标准。这些患者中,41 例患者(41.8%) 在初期的影像学结果中表现为脑积水且 28 例(26.7%)发展为有症状的脑积水,需要行 EVD(表 1)。28 例(50%)患者中 14 例拒绝行第二次 EVD 来达到治疗目标。

2.2 脑室出血的程度

在 EVD 组和非 EVD 组患者合并症间无统计学差异。大部分的患者(82,83.7%)的 IVH 继发于自发性脑出血,深部血肿(55, 56.1%)超过了脑叶出血(35, 35.7%)。表 2 对比了 EVD 组和非 EVD 组患者 IVH 的程度,这与 IVH 位置和 IVH 原因有关。大部分不需要行 EVD 的患者 IVH 仅局限于一侧侧脑室(29, 29.6%),而大部分需要行 EVD 的患者有全脑室出血(24,

24.5%)。然而,25/98 例有全脑室出血的患者(25.5%)并不需要行 EVD。在全脑室出血的患者中(49/98,50%),与不需要行 EVD 的患者相比 $[12\pm 2.8(8-19)]$, $p<0.001$,需要行 EVD 的患者 $[19\pm 4.2 (13-28)]$ mGS 评分明显升高。与脑叶出血的患者(6/37; 16.2%)相比深部血肿(18/48; 37.5%)和幕下血肿(4/7; 57.1%)的患者行 EVD 的比率更高。随着 GCS 评分的减少和 mGS 评分增加行 EVD 的可能性也增加。

2.3 行 EVD 的影响因素

在单变量分析中,脑积水表现为:中线偏移 >5 mm,GCS 评分 <8 分,全脑室出血,mGS >13 分,三脑室 mGS=5 分和四脑室 mGS=5 分均需要行 EVD。在多变量分析中,mGS >13 分 [OR 3.98 (CI 1.12-15.02), $P=0.034$], GCS <8 分 [OR 3.98(CI 1.12-15.02), $P=0.044$] 和四脑室 mGS = 5 分 [OR 5.21 (CI 1.24-23.08) $P=0.024$]需要行 EVD(表 3)。

2.4 并发症和行 EVD 的时机

住院患者死亡率为 20.4%(20 例),对于行 EVD 组和未行 EVD 组分别是 53.6% (15 例) 和 8.6% (7 例)($p<0.01$)。预后不良的患者有 52 例(53.1%),而对于行 EVD 组和未行 EVD 组分别是 78.6% (22 例)和 40% (28 例)($p<0.01$)。仅两例患者需行脑室腹腔分流术。行 EVD 的平均时间是 16 ± 24.0 小时 (1.4-96.5 小时)。大部分患者(24/28, 85.7%)需在 24 小时之内行 EVD,脑室恢复正常的时间间隔为 6.2 ± 3.1 小时(1.4-13 小时)。有 4 例患者在 68.6 ± 21.5 小时 (52-102.6 小时)行 EVD。在 24 小时内行 EVD 的患者 mGS 平均为 17.8 ± 4.9 分,在 24 小时后行 EVD 的患者 mGS 平均为 12.5 ± 5.1 分,但两组间无统计学差异。

表 1 脑室出血患者临床特征

Table 1 The clinical characteristics of patients with IVH

Vabriable	NO EVD(70)	EVD(28)
Age in year	65.4(20-85)	66.2(24-86)
Female	32(45.7)	14(50.0)
Hypertension	36(51.4)	15(53.6)
Diabetes	8(11.4)	3(10.7)
Hyperlipidemia	27(38.6)	10(35.7)
Stroke history	6(8.6)	2(7.1)
Anticoagulation	20(28.6)	7(25.0)
Spontaneous ICH	58(82.9)	26(92.9)
Trauma	6(8.6)	0
Tumor	2(2.9)	1(3.6)
Vascular anomalies	2(2.9)	1(3.6)

3 讨论

既往对于 IVH 和脑积水主要集中在对发病率、影像学评估、治疗和预后的研究^[9-11],很少直接观察 IVH 的位置、体积。Young 等^[12]对 47 例患者 CT 扫描出血量体积分析的方法研究了幕上 IVH 对预后的意义,他们发现脑积水、脑室出血的数量、脑室的出血量和四脑室出血与患者预后不良密切相关,但

表 2 基于脑室出血的位置和出血来源对比接受 EVD 和没有接受 EVD 患者脑室出血的程度(mGS)

Table 2 Comparison of IVH extent (mGS) in patients requiring and not requiring EVD based on IVH location and hemorrhage origin

Variables	No EVD		EVD		NoEVDvsEVD mGS
	Median mGS± SD		Median mGS± S		p Value
	No. (%)	(range)	No. (%)	(range)	
IVH location					
RLV or LLV only	29(29.6)	5± 2.1(2-9)	-	-	-
RLV and/or LLV+3rd	7(7.1)	11± 2.6(5-12)	-	-	-
RLV and/or LLV+4th	2(2.0)	11(8,14)	-	-	-
3rd+4th only	-	-	1(1.0)	9	-
4th only	2(2.0)	4.5(4,5)	1(1.0)	5	-
RLV or LLV +3rd+4th	5(5.1)	13± 3.1(8-15)	2(2.0)	18± 2.4 (16, 20)	0.1
Panventricular	25(25.5)	12± 2.8(8-19)	24(24.5)	19± 4.2 (13-28)	<0.001
Hemorrhage origin					
IVH only	6(6.1)	7± 4.1(2-13)	-	-	-
Caudate	9(9.2)	12± 4.8(3-20)	4(4.1)	19.1± 2.6 (16-23)	0.02
Basal ganglia	13(13.3)	8± 2.9(4-14)	7(7.1)	21± 4.6 (16-30)	<0.001
Thalamic	8(8.2)	9± 3.6 (5-15)	7(7.1)	16± 2.7 (11-19)	0.001
Lobar	31(31.6)	7.5± 4.3 (3-18)	6(6.1)	18± 5.3(9-26)	<0.001
Infratentorial	3(3.1)	8± 3.6 (4-11)	4(4.1)	10± 4.4(5-15)	0.55

LLV = left lateral ventricle; RLV = right lateral ventricle; - = no patients in category.

表 3 行脑室外引流术的影响因素

Table 3 Factors resulting in EVD placement

Factors	Univariate Analysis			Multivariate Analysis	
	No EVD(n=70)	EVD(n=28)	P Value	OR(95%CI)	P Value
Age in year	65.4(20-85)	66.2(24-86)	0.680	-	
Hydrocephalus	20(28.6)	21(0.75)	<0.001	-	
Midline shift>5 mm	16(22.9)	18(64.3)	<0.001	-	
GCS<8	11(14.1)	19(67.9)	<0.001	3.98(1.12-15.02)	0.034
ICH volume, mean± SD (range)	28.9± 35.6(0-185)	43.2± 42.4(2-208)	0.093	-	
Panventricular hemorrhage	25(32.1)	24(85.7)	<0.001	-	
mGS >13	9(12.9)	22(78.6)	<0.001	3.76(0.98-15.13)	0.044
mGS=5 for 3rd ventricle	2	9(32.1)	<0.001	-	
mGS=5 for 4th ventricle	3	16(57.1)	<0.001	5.21(1.24-23.08)	0.024

- = no patients in category

没有直接分析 IVH 和脑积水症状之间的关系。患者脑室出血量越多,脑积水越严重,这使我们注意到在脑室出血量、脑室出血的数量、四脑室出血和脑积水的程度之间可能具有重要的联系^[12]。

Diringer 等^[13]观察了 81 例自发性幕上脑出血患者中合并脑积水的 40 例患者脑积水对预后的影响。在多变量分析中脑积水是患者死亡率的独立预测因素[OR 1.63, CI 1.20-2.31 (p=0.001)],超过血肿大小和脑室内出血对死亡率的影响。合并脑积

水的患者比无脑积水的患者平均 IVH 评分高[5.0± 3.5(0-11)/0.8± 1.6(0-6), p<0.005]。Nishikawa 等^[14]通过观察 100 例中 35 例合并 IVH 的脑出血患者,确定了 IVH 对于脑积水和临床效果的影响。在 IVH 的患者中,8 例发展为脑积水,且 GS≥ 6 是发生急性脑积水的高危因素[OR 23.99,CI 3.24-177.38 (p=0.002)]。在最近的研究中,Herrick 等^[15]验证了 183 例自发性颅内出血患者放置脑室外引流管的确定因素,在多元变量分析中发现 GCS

评分 ≤ 8 分,未改良的GS >5 分,非脑叶出血 ≤ 30 mL是独立的预测因素。其中,67例患者需要行EVD,需要行EVD的患者出血量高于那些不需要行EVD的患者(31.8 ± 3.3 mL/ 12.7 ± 2.0 mL, $p=0.03$)。

对比以上的研究,我们排除了有明显的脑积水症状立即行EVD的患者,旨在确定对导致迟发的放置脑室外引流管的因素。除此之外,本研究探讨了IVH的类型和IVH在脑积水中的作用,并且用改良的mGS替代原来的GS。在我们的研究中,脑积水发展到需要行EVD与IVH的位置和出血量密切相关。行EVD的患者并不限定在侧脑室引流,仅有两个患者在三脑室和四脑室引流或单独行四脑室引流。行EVD风险最大的患者是那些脑室内出血 ≥ 3 个脑室。几乎一半的全脑室出血的患者不需要行EVD。需要行EVD的患者mGS评分高,意味着脑室内出血量是行EVD的关键因素。然而,脑室内出血量在需要行EVD的患者中变化很大(mGS:6-28分)。

发展为有症状脑积水的时间是不确定的,我们通过天而不是小时来记录发展为脑积水的时间,这表明IVH后发展为有症状的脑积水是一个动态的过程,在个例上是很难预测的,包括脑积水发展的时间和发生风险的时间。可能有促凝固的,分子的和解剖的因素^[16]相互作用影响脑脊液的循环。在脑室内出血的动物模型也支持上面的观点,因为向脑室内注射血液并不会产生凝血块。但如果改变血液的形式,如注射凝固的血块或带有凝血酶的血液,会使脑室铸型导致脑室扩张和脑脊液循环的阻塞^[17,18]。

目前,AHA和美国卒中协会并没有赞同EVD,除非有进行性的意识障碍^[9]。然而,有一些基于出血位置和出血量更激进的研究。Naff^[19]表明IVH并不会促使脑积水除非明显地堵塞了一侧或两侧室间孔或三脑室才应该行EVD,因为梗阻性脑积水可能进展很快。尽管IVH对于神经功能的恢复是有害的,但没有明确的证据表明EVD对没有脑积水症状的患者有有益的影响^[20,21]。我们的结果表明只要患者无脑积水症状就可以先观察,但这些患者必需密切的监护,特别是如果患者脑室内出血量增加,昏迷但无脑积水或四脑室扩大可能行EVD。此外,将来进一步的研究如脑室内出血治疗的临床实验可能为我们提供更多的证据。

总之,在我们的研究中,大部分IVH但没有脑积水症状的患者入院后不需要行EVD。单侧脑室出血的患者也不需要行脑室外引流术,有全脑室出血的患者中一半需要行EVD,且那些接受EVD的患者脑室出血量较未接受EVD的多。合并昏迷,mGS >13 分和四脑室扩大的患者最有可能行EVD。大部分患者(84.5%)在24小时内接受了EVD。然而,有一些有广泛脑室内出血和临床效果较好的患者没有接受EVD,有少数患者48小时后需要行EVD。

参考文献(References)

- [1] Guo R, Ma L, Shrestha BK, et al. A retrospective clinical study of 98 adult idiopathic primary intraventricular hemorrhage cases [J]. *Medicine (Baltimore)*, 2016, 95(42): e5089
- [2] Radic JA, Vincer M, McNeely PD. Outcomes of intraventricular hemorrhage and posthemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010[J]. *J Neurosurg Pediatr*, 2015, 15(6): 580-588
- [3] Tully HM, Wenger TL, Kukull WA, et al. Anatomical configurations associated with posthemorrhagic hydrocephalus among premature infants with intraventricular hemorrhage [J]. *Neurosurg Focus*, 2016, 41(5): E5
- [4] Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association[J]. *Stroke*, 2010, 41(9): 2108-2129
- [5] Dey M, Jaffe J, Stadnik A, et al. External ventricular drainage for intraventricular hemorrhage [J]. *Curr Neurol Neurosci Rep*, 2012, 12(1): 24-33
- [6] Morgan TC, Dawson J, Spengler D, et al. The Modified Graeb Score: an enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome[J]. *Stroke*, 2013, 44: 635-641
- [7] Calayag M, Paul AR, Adamo M. Intraventricular hemorrhage after ventriculoperitoneal shunt revision: a retrospective review [J]. *J Neurosurg Pediatr*, 2015, 16(1): 42-45
- [8] Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes[J]. *Stroke*, 1996, 27(8): 1304-1305
- [9] Chan E, Anderson CS, Wang X, et al. Early Blood Pressure Lowering Does Not Reduce Growth of Intraventricular Hemorrhage following Acute Intracerebral Hemorrhage: Results of the INTERACT Studies [J]. *Cerebrovasc Dis Extra*, 2016, 6(3): 71-75
- [10] Hwang BY, Bruce SS, Appelboom G, et al. Evaluation of intraventricular hemorrhage assessment methods for predicting outcome following intracerebral hemorrhage [J]. *J Neurosurg*, 2012, 116(1): 185-192
- [11] Mukerji A, Shah V, Shah PS. Periventricular/Intraventricular Hemorrhage and Neurodevelopmental Outcomes: A Meta-analysis[J]. *Pediatrics*, 2015, 136(6): 1132-1143
- [12] Young WB, Lee KP, Pessin MS, et al. Prognostic significance of ventricular blood in supratentorial hemorrhage: a volumetric study[J]. *Neurology*, 1990, 40(4): 616-619
- [13] Diringer MN, Edwards DF, Zazulia AR. Hydrocephalus: a previously unrecognized predictor of poor outcome from supratentorial intracerebral hemorrhage[J]. *Stroke*, 1998, 29(7): 1352-1357
- [14] Nishikawa T, Ueba T, Kajiwara M, et al. A priority treatment of the intraventricular hemorrhage (IVH) should be performed in the patients suffering intracerebral hemorrhage with large IVH [J]. *Clin Neurol Neurosurg*, 2009, 111(5): 450-453
- [15] Herrick DB, Ullman N, Nekoovaght-Tak S, et al. Determinants of external ventricular drain placement and associated outcomes in patients with spontaneous intraventricular hemorrhage [J]. *Neurocrit Care*, 2014, 21(3): 426-434
- [16] Strahle J, Garton HJ, Maher CO, et al. Mechanisms of hydrocephalus after neonatal and adult intraventricular hemorrhage[J]. *Transl Stroke Res*, 2012, 3 (Suppl 1): 25-38
- [17] Lodhia KR, Shakui P, Keep RF. Hydrocephalus in a rat model of intraventricular hemorrhage [J]. *Acta Neurochir Suppl*, 2006, 96: 207-211

- carcinogen exposure[J]. *Nicotine Tob Res*, 2011, 13(9): 772-783
- [13] Park S L, Kotapati S, Wilkens LR, et al. 1,3-Butadiene Exposure and Metabolism among Japanese American, Native Hawaiian, and White Smokers [J]. *Cancer Epidemiology Biomarkers & Prevention*, 2014, 23(11): 2240-2249
- [14] Gannon A M, M R Stampfli, W G Foster. Cigarette smoke exposure leads to follicle loss via an alternative ovarian cell death pathway in a mouse model[J]. *Toxicol Sci*, 2012, 125(1): 274-284
- [15] Karpathiou G, Sivridis E, Koukourakis M, et al. Autophagy and Bcl-2 /BNIP3 death regulatory pathway in non-small cell lung carcinomas [J]. *APMIS*, 2013, 121(7): 592-604
- [16] Lv ZQ, Han JJ, Liu YQ, et al. Expression of beclin 1 in non-small cell lung cancer: an immunohistochemical study[J]. *Clin Respir J*, 2015, 9 (3): 359-365
- [17] Wael H, Yoshida R, Kudoh S, et al. Notch1 signaling controls cell proliferation, apoptosis and differentiation in lung carcinoma[J]. *Lung Cancer*, 2014, 85(2): 131-140
- [18] Zhou M, Jin WY, Fan ZW, et al. Analysis of the expression of the Notch3 receptor protein in adult lung cancer [J]. *Oncol Lett*, 2013, 5 (2): 499-504
- [19] Cheng Z, Tan Q, Tan W, et al. Cigarette smoke induces the expression of Notch3, not Notch1, protein in lung adenocarcinoma[J]. *Oncol Lett*, 2015, 10(2): 641-646
- [20] Galluzzo P, M Bocchetta. Notch signaling in lung cancer [J]. *Expert Rev Anticancer Ther*, 2011, 11(4): 533-540
- [21] Rosenberg L, Boggs DA, Bethea TN, et al. A prospective study of smoking and breast cancer risk among African-American women[J]. *Cancer Causes Control*, 2013, 24(12): 2207-2215
- [22] Catsburg C, A B Miller, T E Rohan. Active cigarette smoking and risk of breast cancer[J]. *International Journal of Cancer*, 2015, 136(9): 2204-2209
- [23] Gaudet M M, Gapstur SM, Sun J, et al. Active smoking and breast cancer risk: original cohort data and meta-analysis [J]. *J Natl Cancer Inst*, 2013, 105(8): 515-525
- [24] van Duijnhoven, F J Botma A, Winkels R, et al. Do lifestyle factors influence colorectal cancer risk in Lynch syndrome? [J]. *Fam Cancer*, 2013, 12(2): 285-293
- [25] Tanakaya K, Furukawa Y, Nakamura Y, et al. Relationship between smoking and multiple colorectal cancers in patients with Japanese Lynch syndrome: a cross-sectional study conducted by the Japanese Society for Cancer of the Colon and Rectum [J]. *Japanese Journal of Clinical Oncology*, 2015, 45(3): 307-310
- [26] Coffey K, Beral V, Green J, et al. Lifestyle and reproductive risk factors associated with anal cancer in women aged over 50 years[J]. *Br J Cancer*, 2015, 112(9): 1568-1574
- [27] Wu X C, Zheng YF, Tang M, et al. Association Between Smoking and p53 Mutation in Oesophageal Squamous Cell Carcinoma: A Meta-analysis[J]. *Clinical Oncology*, 2015, 27(6): 337-344
- [28] Kayamba, V Bateman AC, Asombang AW, et al. HIV infection and domestic smoke exposure, but not human papillomavirus, are risk factors for esophageal squamous cell carcinoma in Zambia: a case-control study[J]. *Cancer Medicine*, 2015, 4(4): 588-595
- [29] Fagan P, Moolchan ET, Pokhrel P, et al. Biomarkers of tobacco smoke exposure in racial/ethnic groups at high risk for lung cancer[J]. *Am J Public Health*, 2015, 105(6): 1237-1245
- [30] Chaffer C L, R A Weinberg. A perspective on cancer cell metastasis [J]. *Science*, 2011, 331(6024): 1559-1564
- [31] Sharma J, Young DM, Marentette JO, et al. Lung endothelial cell platelet-activating factor production and inflammatory cell adherence are increased in response to cigarette smoke component exposure[J]. *Am J Physiol Lung Cell Mol Physiol*, 2012, 302(1): 47-55
- [32] Kispert S E, J O Marentette, J McHowat. Enhanced breast cancer cell adherence to the lung endothelium via PAF acetylhydrolase inhibition: a potential mechanism for enhanced metastasis in smokers [J]. *AJP: Cell Physiology*, 2014, 307(10): 951-956
- [33] Perumal D, Pillai S, Nguyen J, et al. Nicotinic acetylcholine receptors induce c-Kit ligand/Stem Cell Factor and promote stemness in an ARRB1/ beta-arrestin-1 dependent manner in NSCLC[J]. *Oncotarget*, 2014, 5(21): 10486-10502
- [34] Lee CH, Chang JS, Syu SH, et al. IL-1 β Promotes Malignant Transformation and Tumor Aggressiveness in Oral Cancer[J]. *Journal of Cellular Physiology*, 2015, 230(4): 875-884
- [35] Chen L C, Wang LJ, Tsang NM, et al. Tumour inflammasome-derived IL-1 β recruits neutrophils and improves local recurrence-free survival in EBV-induced nasopharyngeal carcinoma [J]. *EMBO Mol Med*, 2012, 4(12): 1276-1293
- [36] Xie D, Lan L, Huang K, et al. Association of p53/p21 expression and cigarette smoking with tumor progression and poor prognosis in non-small cell lung cancer patients[J]. *Oncol Rep*, 2014, 32(6): 2517-2526
- [37] Hsu, C L, Chen JH, Chen KY, et al. Advanced non-small cell lung cancer in the elderly: The impact of age and comorbidities on treatment modalities and patient prognosis [J]. *Journal of Geriatric Oncology*, 2015, 6(1): 38-45
- [38] Miyata Y, Kanda S, Mitsunari K, et al. Heme oxygenase-1 expression is associated with tumor aggressiveness and outcomes in patients with bladder cancer: a correlation with smoking intensity[J]. *Translational Research*, 2014, 164(6): 468-476

(上接第 3067 页)

- [18] Chen Q, Tang J, Tan L, et al. Intracerebral Hematoma Contributes to Hydrocephalus After Intraventricular Hemorrhage via Aggravating Iron Accumulation[J]. *Stroke*, 2015, 46(10): 2902-2908
- [19] Naff NJ. Intraventricular hemorrhage in adults[J]. *Curr Treat Options Neurol*, 1999, 1(3): 173-178
- [20] Wang S, Liao C, Liang S, et al. Ultrasound findings of mild neonatal periventricular-intraventricular hemorrhage after different treatments [J]. *Int J Clin Exp Med*, 2015, 8(4): 5085-5093
- [21] Ziai WC, Tuhim S, Lane K, et al. A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III)[J]. *Int J Stroke*, 2014, 9(4): 536-542