

· 肝纤维化及肝硬化 ·

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## 内镜下曲张静脉套扎术/组织胶注射术治疗肝硬化食管胃静脉曲张的安全性及术后出血的影响因素分析

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**摘要:** **目的** 分析内镜下曲张静脉套扎术(EVL)和内镜下组织胶注射术(ECI)治疗肝硬化食管胃静脉曲张术后5 d和2周内出血的影响因素,探讨血小板计数减少患者接受EVL/ECI的安全性。**方法** 选取2018年1月—2023年12月于广州医科大学附属市八医院接受EVL/ECI治疗的489例肝硬化食管胃静脉曲张患者为研究对象,根据术后是否出血分为术后出血组和术后未出血组,分析术后5 d和2周出血的危险因素。计量资料两组间比较采用成组 *t* 检验或 Mann-Whitney *U* 检验,计数资料两组间比较采用  $\chi^2$  检验或连续校正  $\chi^2$  检验;通过受试者操作特征曲线(ROC曲线)确定终末期肝病模型(MELD)评分的截断值。采用 Logistic 多因素回归分析术后出血的独立危险因素。**结果** 血小板计数  $\geq 50 \times 10^9/L$  患者( $n=386$ )与血小板计数在  $25 \times 10^9/L \sim 49 \times 10^9/L$  的患者( $n=103$ )EVL/ECI术后5 d出血率(1.94% vs 2.85%,  $P=0.870$ )和术后2周出血率(2.91% vs 4.92%,  $P=0.544$ )比较,差异均无统计学意义。EVL/ECI术后5 d和2周的总体出血率分别是2.66%(13/489)和4.50%(22/489)。Logistic 多因素回归分析显示,MELD评分是EVL/ECI术后5 d出血[比值比(*OR*)=3.726,95%置信区间(*CI*):1.214~11.429,  $P=0.021$ ]和术后2周出血的独立危险因素(*OR*=5.760,95%*CI*:1.779~18.651,  $P=0.003$ ),血红蛋白是术后5 d(*OR*=0.972,95%*CI*:0.948~0.996,  $P=0.025$ )和术后2周(*OR*=0.976,95%*CI*:0.957~0.995,  $P=0.016$ )出血的保护因素,门静脉癌栓是术后2周出血的独立危险因素(*OR*=2.667,95%*CI*:1.000~7.117,  $P=0.050$ ),血小板计数( $25 \times 10^9/L \sim 49 \times 10^9/L$ )不是术后出血的危险因素( $P>0.05$ )。**结论** 对于伴有三级血小板减少的肝病患者,EVL和ECI治疗安全性较好;MELD评分是术后5 d和2周出血的独立危险因素,血红蛋白为保护因素;门静脉癌栓是术后2周出血的独立危险因素。

**关键词:** 血小板减少;食管和胃静脉曲张;内窥镜检查**基金项目:** 广东省医学科研基金项目(A2022491)

### Safety of endoscopic variceal ligation and endoscopic cyanoacrylate injection in treatment of esophagogastric varices in patients with liver cirrhosis and influencing factors for postoperative bleeding

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**Abstract: Objective** To investigate the risk factors for bleeding within 5 days and 2 weeks after endoscopic variceal ligation (EVL) or endoscopic cyanoacrylate injection (ECI) for the treatment of esophagogastric varices in patients with liver cirrhosis, as well as the safety of EVL/ECI in patients with thrombocytopenia. **Methods** A total of 489 patients with liver cirrhosis and esophagogastric varices who underwent EVL/ECI in Guangzhou Eighth People's Hospital, Guangzhou Medical University, from January 2018 to December 2023 were enrolled as subjects, and according to the presence or absence of bleeding after surgery, they were divided into bleeding

group and non-bleeding group. The risk factors for bleeding within 5 days and 2 weeks after surgery were analyzed. The independent-samples *t* test or the Mann-Whitney *U* test was used for comparison of continuous data between groups, and the chi-square test or the continuity-corrected chi-square test was used for comparison of categorical data between groups; the receiver operating characteristic (ROC) curve was plotted to determine the cut-off value of MELD score; a multivariate logistic regression analysis was used to identify the independent risk factors for postoperative bleeding. **Results** There were no significant differences in the bleeding rates within 5 days and 2 weeks after EVL/ECI between the 386 patients with a platelet count of  $\geq 50 \times 10^9/L$  and the 103 patients with a platelet count of  $(25-49) \times 10^9/L$  (5 days: 1.94% vs 2.85%,  $P=0.870$ ; 2 weeks: 2.91% vs 4.92%,  $P=0.544$ ). The overall bleeding rate was 2.66% (13/489) and 4.50% (22/489), respectively, within 5 days and 2 weeks after EVL/ECI. The multivariate logistic regression analysis showed that MELD score was an independent risk factor for bleeding within 5 days (odds ratio [OR]=3.726, 95% confidence interval [CI]: 1.214—11.429,  $P=0.021$ ) and 2 weeks (OR=5.760, 95%CI: 1.779—18.651,  $P=0.003$ ) after EVL/ECI, while hemoglobin (Hb) was a protective factor against bleeding within 5 days (OR=0.972, 95%CI: 0.948—0.996,  $P=0.025$ ) and 2 weeks (OR=0.976, 95%CI: 0.957—0.995,  $P=0.016$ ) after surgery; portal vein tumor thrombus (OR=2.667, 95%CI: 1.000—7.117,  $P=0.050$ ) was an independent risk factor for bleeding within 2 weeks after surgery, while platelet count [ $(25-49) \times 10^9/L$ ] was not a risk factor for postoperative bleeding ( $P>0.05$ ). **Conclusion** Both EVL and ECI have good safety in patients with liver diseases and grade 3 thrombocytopenia. MELD score is an independent risk factor for bleeding within 5 days and 2 weeks after EVL/ECI, while Hb is a protective factor; portal vein tumor thrombus is an independent risk factor for bleeding within 2 weeks after surgery.

**Key words:** Thrombocytopenia; Esophageal and Gastric Varices; Endoscopy

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食管胃静脉曲张破裂出血(esophagogastric variceal bleeding, EVB)是肝硬化失代偿期严重及致命的并发症,其规范诊疗至关重要。内镜下曲张静脉套扎术(endoscopic variceal ligation, EVL)和内镜下组织胶注射(endoscopic cyanoacrylate injection, ECI)是常用的治疗策略<sup>[1-2]</sup>。通常认为,血小板计数低于 $50 \times 10^9/L$ 时存在皮肤、黏膜出血风险,但此类患者接受EVL或ECI治疗的安全性尚有争议<sup>[3]</sup>。中国指南建议食管胃静脉曲张(gastroesophageal varices, GOV)的内镜下治疗参考血小板阈值 $\geq 50 \times 10^9/L$ <sup>[4]</sup>,然而Baveno VII共识指出尚无证据表明血小板与止血失败或再出血相关<sup>[5]</sup>。本研究通过回顾本院行EVL/ECI治疗的病例,旨在探讨血小板计数为 $25 \times 10^9/L \sim 49 \times 10^9/L$ 的患者接受EVL/ECI治疗的安全性,并分析术后5 d和2周内出血的危险因素,以期为临床实践提供参考依据。

## 1 资料与方法

**1.1 研究对象** 回顾性收集2018年1月—2023年12月于广州医科大学附属市八医院就诊的肝硬化合并GOV并接受EVL/ECI治疗的497例患者。纳入标准:(1)符合肝硬化临床、实验室或影像学等诊断;(2)本中心接受EVL或EVL联合ECI治疗的患者,且术后随访时间 $\geq 2$ 周。排除标准:(1)非肝硬化门静脉高压所致GOV;(2)入院资料不全,拒绝随访或失访患者。主要观察指标为术后2周内是否发生上消化道出血。所有患者均签署内镜治疗知

情同意书。根据术后是否出血分组:术后5 d出血组和术后5 d未出血组、术后2周出血组和术后2周末出血组。

**1.2 定义** 三级血小板减少判定标准:血小板计数为 $25 \times 10^9/L \sim 49 \times 10^9/L$ <sup>[6]</sup>;治疗失败:EVL/ECI术后5 d内发生活动性出血事件;术后2周出血:EVL/ECI术后2周内发生活动性出血事件。活动性出血事件定义为呕血、黑便或便血,伴收缩压下降 $>20$  mmHg或心率增加 $>20$ 次/min,或未输血状况下血红蛋白(hemoglobin, HGB)下降 $>30$  g/L<sup>[2]</sup>。

**1.3 器械及药物** 器械包括日本Olympus H290型电子胃镜、美国Wilson-Cook公司套扎器以及Olympus NM-200L-0423黏膜注射针,药物包括聚桂醇(陕西天宇制药有限公司)和组织胶(北京康派特医疗器械有限公司)。

**1.4 治疗方法** 一般治疗:常规予以质子泵抑制剂、生长抑素持续静脉泵入48~72 h、预防性抗生素、扩容等对症处理,HGB $<60$  g/L时输注红细胞。内镜治疗:食管静脉曲张在齿状线上方1~2 cm处螺旋式套扎、胃底静脉曲张采用“聚桂醇+组织胶+聚桂醇”三明治注射治疗。

**1.5 统计学方法** 采用SPSS 23.0软件进行统计学处理。符合正态分布的计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用成组*t*检验;非正态分布的计量资料以 $M(P_{25} \sim P_{75})$ 表示,两组间比较采用Mann-Whitney *U*检验。计数资料两组间比较采用 $\chi^2$ 检验或连续校正 $\chi^2$ 检验。通过MedCalc软件绘制受试者操作特征曲线(receiver operator characteristic, ROC曲线),确定终末期肝病模型(model for end-stage liver

disease, MELD)评分的截断值。采用二元 Logistic 单因素和多因素分析危险因素。 $P < 0.05$ 为差异有统计学意义。

## 2 结果

2.1 一般资料 共收集497例患者,其中资料缺失8例,最终共489例患者纳入研究,平均年龄( $53.04 \pm 10.62$ )岁,男性占85.07%(416/489)。全组EVL/ECI术后随访2周,术后中位出血时间为2(1~8)d,术后5d出血共13例(2.66%),术后2周出血共22例(4.50%)。血小板计数为 $25 \times 10^9/L \sim 49 \times 10^9/L$ 的患者103例,术后5d和2周的出血率分别为1.94%、2.91%;血小板计数 $\geq 50 \times 10^9/L$ 的患者386例,术后5d和2周的出血率分别为2.85%、4.92%,两组患者的术后5d出血率和术后2周出血率差异均无统计学意义( $P$ 值均 $> 0.05$ )。

2.2 EVL/ECI术后5d出血危险因素分析 根据术后5d是否出血分组,术后5d出血组13例,术后5d未出血

组476例。两组患者的基线HGB和MELD评分比较差异均有统计学意义( $P$ 值均 $< 0.05$ )(表1)。

单因素 Logistic 回归分析显示,MELD评分是EVL/ECI术后5d出血的危险因素,基线HGB是保护因素( $P$ 值均 $< 0.05$ )。ROC曲线分析显示,MELD评分最佳截断值是14.39分,约登指数为0.325,根据截断值将MELD评分转化为计数资料,将2个因素纳入 Logistic 多因素回归分析,MELD评分( $> 14.39$ 分)是EVL/ECI术后5d出血的独立危险因素,基线HGB是保护因素( $P$ 值均 $< 0.05$ )(表2,图1a)。

2.3 EVL/ECI术后2周出血危险因素分析 单因素 Logistic 回归分析显示,MELD评分、Child-Pugh评分、凝血酶原时间和门静脉癌栓是EVL/ECI术后2周出血的危险因素,基线HGB是保护因素( $P$ 值均 $< 0.05$ )。ROC曲线分析显示,MELD评分最佳截断值是14.39分,约登指数为0.387,根据截断值将MELD评分转化为计数资料,将5个因素纳入 Logistic 多因素回归分析,MELD评分( $> 14.39$ 分)

表1 EVL/ECI术后5d出血组和未出血组的基线特征比较

Table 1 Comparison of baseline characteristics between bleeding group and non bleeding group after 5-day EVL/ECI

项目	术后5d出血组 ( $n=13$ )	术后5d未出血组 ( $n=476$ )	统计值	$P$ 值
男性[例(%)]	12(92.3)	404(84.9)	$\chi^2=0.121$	0.728
年龄(岁)	$51.54 \pm 9.33$	$53.09 \pm 10.66$	$t=-0.519$	0.604
肝硬化病因[例(%)]			$\chi^2=0.182$	0.670
HBV相关	9(69.2)	372(78.2)		
无HBV	4(30.8)	104(21.8)		
合并肝癌[例(%)]	6(46.2)	145(30.5)	$\chi^2=0.817$	0.366
门静脉血栓[例(%)]	1(7.7)	38(8.0)	$\chi^2=0.000$	$> 0.05$
门静脉宽度(cm)	14(12~16)	13(12~14)	$Z=-1.730$	0.080
门静脉癌栓[例(%)]	5(30.8)	59(12.4)	$\chi^2=2.345$	0.126
内镜治疗方式[例(%)]			$\chi^2=1.318$	0.251
EVL	9(68.2)	404(84.9)		
EVL+ECI	4(30.8)	72(15.1)		
血小板计数( $\times 10^9/L$ )	72(54~153)	77(52~116)	$Z=-0.373$	0.709
血小板计数[例(%)]			$\chi^2=0.027$	0.870
$\geq 50 \times 10^9/L$	11(84.6)	375(78.8)		
$25 \times 10^9/L \sim 49 \times 10^9/L$	2(15.4)	101(21.2)		
HGB(g/L)	63(52~77)	87(65~111)	$Z=-2.640$	0.008
PTA(%)	55(49~68)	63(52~72)	$Z=-1.405$	0.160
INR	1.49(1.28~1.62)	1.35(1.21~1.58)	$Z=-1.357$	0.175
PT(s)	18.20(16.10~19.55)	16.7(15.4~18.8)	$Z=-1.388$	0.165
APTT(s)	42.10(39.35~58.15)	41.15(37.57~45.39)	$Z=-1.411$	0.158
TBil( $\mu\text{mol/L}$ )	24.68(13.75~96.71)	22.48(14.87~37.90)	$Z=-0.787$	0.431
Alb(g/L)	$31.85 \pm 5.52$	$32.95 \pm 5.58$	$t=-0.702$	0.483
MELD评分(分)	14.43(10.33~20.02)	10.90(8.93~3.63)	$Z=-2.410$	0.016
Child-Pugh评分(分)	8(7~10)	7(6~9)	$Z=-1.210$	0.226

注:EVL,内镜下曲张静脉套扎术;ECI,内镜下组织胶注射术;HBV,乙型肝炎病毒;HGB,血红蛋白;PTA,凝血酶原活动度;INR,国际标准化比值;PT,凝血酶原时间;APTT,活化部分凝血活酶时间;TBil,总胆红素;Alb,白蛋白;MELD,终末期肝病模型;Child-Pugh评分,蔡尔德-皮尤评分。

和门静脉癌栓是EVL/ECI术后2周出血的独立危险因素( $P$ 值分别为0.003、0.050),基线HGB是保护因素( $P=0.016$ )(表3,图1b)。

### 3 讨论

传统观点认为血小板减少可能增加出血风险,加重外科手术或创伤性出血,甚至取消治疗,因此,血小板计数 $\geq 50 \times 10^9/L$ 被认为侵入性操作的前提条件<sup>[6]</sup>。然而,国外指南的演变对血小板计数预测术后出血的价值提出了质疑<sup>[3]</sup>。本研究结合本院GOV内镜治疗病例,探讨血小板减少是否与EVL/ECI治疗失败及术后2周出血相关,以期为临床实践提供循证依据。

本研究纳入489例患者,血小板计数范围为 $25 \times 10^9/L \sim 447 \times 10^9/L$ ,其中三级血小板减少患者占21.1% (103例),总体术后5d出血率为2.66%,表明EVL及ECI术后5d治疗成功率较高,总体安全性良好。血小板计

数 $\geq 50 \times 10^9/L$ 的患者与血小板计数为 $25 \times 10^9/L \sim 49 \times 10^9/L$ 的患者术后5d出血率和术后2周出血率比较,差异均无统计学意义( $P$ 值均 $>0.05$ );单因素分析也提示,血小板并非术后出血的危险因素。这说明血小板计数为 $25 \times 10^9/L \sim 49 \times 10^9/L$ 的患者接受EVL/ECI可能是安全的,并未增加出血风险。既往研究同样显示,血小板计数 $< 50 \times 10^9/L$ 患者EVL术后出血率为0.6%~5.6%,且血小板减少并非EVL术后出血的危险因素<sup>[7-10]</sup>,与本研究结论一致。此外,凝血指标(凝血酶原时间、活化部分凝血活酶时间和国际标准化比值)亦不能预测术后出血,这与Vieira da Rocha等<sup>[7]</sup>和Pfisterer等<sup>[9]</sup>研究结论,以及欧美指南的意见一致<sup>[11-12]</sup>。MELD评分常用评估肝脏疾病严重程度,Pfisterer等<sup>[9]</sup>研究提示MELD评分越高,EVL术后出血风险似乎也越高;de Oliveira Souza等<sup>[8]</sup>研究提示EVL术后出血患者的MELD评分更高。本研究亦提示术后出血患者的MELD评分更高,且多因素分析

表2 EVL/ECI术后5d出血的单因素和多因素Logistic回归分析

Table 2 Univariate and multivariate Logistic regression analysis of bleeding 5-days after EVL/ECI

影响因素	单因素分析		多因素分析				
	OR(95%CI)	P值	B值	SE	Wald	OR(95%CI)	P值
HGB(g/L)	0.971(0.949~0.994)	0.015	-0.029	0.013	4.996	0.972(0.948~0.996)	0.025
MELD评分>14.39分	4.278(1.407~13.009)	0.010	1.315	0.572	5.289	3.726(1.214~11.429)	0.021
Child-Pugh评分(分)	1.186(0.931~1.511)	0.168					
PT(s)	1.075(0.966~1.195)	0.184					
APTT(s)	1.000(0.997~1.003)	0.983					
INR	1.689(0.749~3.810)	0.207					
血小板计数( $25 \times 10^9/L \sim 49 \times 10^9/L$ )	0.675(0.147~3.095)	0.613					
内镜治疗方式	2.494(0.748~8.315)	0.137					
门静脉癌栓	3.141(0.938~10.523)	0.063					

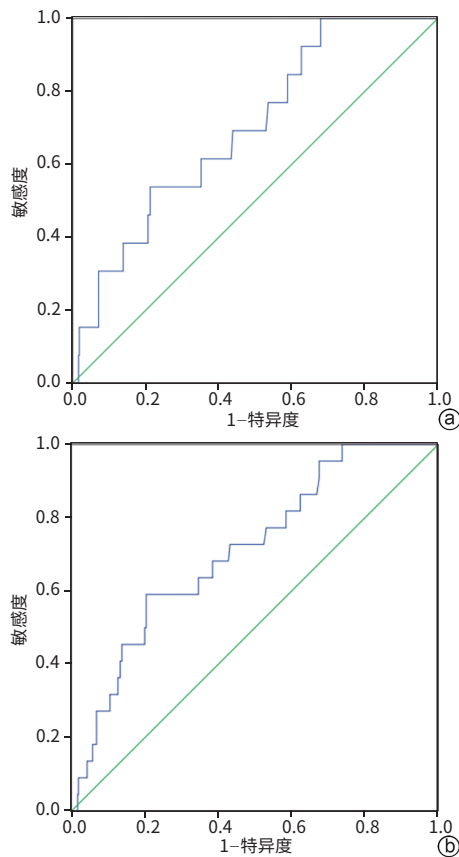
注: EVL,内镜下曲张静脉套扎术;ECI,内镜下组织胶注射术;HGB,血红蛋白;MELD,终末期肝病模型;Child-Pugh评分,蔡尔德-皮尤评分;PT,凝血酶原时间;APTT,活化部分凝血活酶时间;INR,国际标准化比值;OR,比值比;CI,置信区间。

表3 EVL/ECI术后2周出血的单因素和多因素Logistic回归分析

Table 3 Univariate and multivariate Logistic regression analysis of bleeding 2-weeks after EVL/ECI

影响因素	单因素分析		多因素分析				
	OR(95%CI)	P值	B值	SE	Wald	OR(95%CI)	P值
HGB(g/L)	0.976(0.959~0.993)	0.006	-0.024	0.010	5.777	0.976(0.957~0.995)	0.016
MELD评分>14.39分	4.919(2.046~11.825)	<0.001	1.751	0.599	8.533	5.760(1.779~18.651)	0.003
Child-Pugh评分(分)	1.280(1.062~1.542)	0.010					
PT(s)	1.092(1.004~1.187)	0.040					
APTT(s)	1.000(0.997~1.003)	0.926					
INR	1.909(0.984~3.702)	0.056					
血小板计数( $25 \times 10^9/L \sim 49 \times 10^9/L$ )	1.726(0.501~5.949)	0.388					
内镜治疗方式	1.304(0.428~3.970)	0.640					
门静脉癌栓	4.281(1.718~10.66)	0.002	0.981	0.501	3.837	2.667(1.000~7.117)	0.050

注: EVL,内镜下曲张静脉套扎术;ECI,内镜下组织胶注射术;HGB,血红蛋白;MELD,终末期肝病模型;Child-Pugh评分,蔡尔德-皮尤评分;PT,凝血酶原时间;APTT,活化部分凝血活酶时间;INR,国际标准化比值;OR,比值比;CI,置信区间。



注:a,5 d;b,2周。MELD,终末期肝病模型;EVL,内镜下曲张静脉套扎术;ECI,内镜下组织胶注射术;ROC曲线,受试者操作特征曲线。

**图1 MELD评分预测EVL/ECI术后出血的ROC曲线**  
**Figure 1 ROC curve of MELD scoring in predicting of bleeding after EVL/ECI**

证实MELD评分是术后5 d、术后2周出血的独立危险因素,提示EVL术后出血与肝脏疾病的严重程度有关。HGB水平较低是EVB内镜治疗后早期再出血的独立危险因素<sup>[13]</sup>,其降低程度可直接反映急性出血的严重程度,与疾病的预后呈正相关,同时还与肝硬化患者常合并的脾功能亢进和骨髓造血抑制有关<sup>[14]</sup>。本研究提示,HGB是保护因素,应警惕HGB显著降低患者的术后出血风险。门静脉癌栓可加重门静脉高压,增加静脉曲张出血风险,是高危GOV及内镜治疗失败的危险因素<sup>[15-16]</sup>,本研究显示,门静脉癌栓是EVL/ECI术后2周出血的独立危险因素,提示门静脉高压与术后出血有关,应重视门静脉高压的管理和诊治。

高出血风险操作是指出血风险 $\geq 1.5\%$ ,或轻微出血也可造成永久损伤或死亡的操作。中国指南将GOV内镜下治疗纳入高风险操作<sup>[17]</sup>。然而,国外仅欧洲指南将其纳入高风险操作<sup>[11]</sup>,另有4项国外指南将其纳入低风险操作<sup>[12,18-20]</sup>。2023年中国指南仍推荐接受GOV内镜

下治疗的血小板阈值为 $\geq 50 \times 10^9/L$ <sup>[4]</sup>。早期英国、意大利及奥地利指南也曾推荐肝硬化侵入性操作前血小板计数为 $\geq 50 \times 10^9/L$ <sup>[21-23]</sup>。然而,最新美国与欧洲指南均未使用血小板来识别出血风险<sup>[11-12]</sup>。Baveno VII共识亦指出,无证据表明血小板计数与控制出血失败或再出血的风险相关<sup>[5]</sup>。本研究为“三级血小板减少不能预测EVL/ECI术后出血”提供了循证学证据。

从病理生理机制看,血小板生理性止血通过与血管性血友病因子(von Willebrand factor, vWF)相互作用黏附到受损血管壁,促进聚集并形成初级止血栓<sup>[24]</sup>。Lisman等<sup>[25]</sup>研究提示,vWF蛋白水平升高可抵消低血小板计数,de Oliveira Souza等<sup>[8]</sup>研究提示,血小板计数 $< 50 \times 10^9/L$ 肝硬化患者的vWF活性和vWF裂解酶活性并未降低,血小板功能得以保留。这或许可以解释血小板减少的肝硬化患者在接受侵入性操作后出血事件少见,且无法通过血小板预测<sup>[26]</sup>。

综上所述,各国指南与共识的演变刷新了人们对血小板阈值的刻板印象,并对血小板计数预测肝硬化EVL/ECI术后出血提出了质疑。本研究提示,血小板计数为 $25 \times 10^9/L \sim 49 \times 10^9/L$ 并非EVL/ECI术后5 d治疗失败和术后2周出血的危险因素。基线HGB是保护因素,MELD评分是术后5 d治疗失败和术后2周出血的独立危险因素,门静脉癌栓是术后2周出血的独立危险因素。因此,将血小板计数 $< 50 \times 10^9/L$ 作为EVL/ECI的禁忌证,可能延误部分危重患者的救治,临床更应该关注基线MELD评分、贫血程度和门静脉高压。本研究为单中心、回顾性研究,随访时间短,可能存在一定偏倚,有待多中心前瞻性队列研究进一步论证。

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