

· 临床研究 ·

老年原发性肝癌介入手术后胆汁瘤发生的危险因素

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【摘要】目的 探讨老年原发性肝癌介入手术后胆汁瘤发生的危险因素。**方法** 选取长治医学院附属长治市人民医院 2021 年 1 月至 2023 年 3 月收治的 632 例行肝动脉化疗栓塞术 (TACE) 治疗的老年原发性肝细胞癌 (HCC) 患者为研究对象, 随访 6 个月, 14 例失访。以 TACE 术后是否发生胆汁瘤将患者分为胆汁瘤组 ($n=46$) 与非胆汁瘤组 ($n=572$), 比较两组性别、年龄、Child-Pugh 分级、 γ -谷氨酰基转移酶 (GGT)、碱性磷酸酶 (ALP) 等临床资料, 并记录老年原发性 HCC 患者 TACE 术后胆汁瘤的预后转归情况。采用 SPSS 24.0 统计软件进行数据分析。根据数据类型, 分别采用 t 检验、 χ^2 检验或 Fisher 精确概率法检验进行组间比较。使用 logistic 回归分析评估老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素。**结果** 618 例患者 TACE 术后胆汁瘤发生率为 7.44% (46/618), 胆汁瘤组术前胆道扩张发生率、术中使用聚乙烯醇颗粒占比及术后 1 周 GGT 异常升高、ALP 异常升高率均高于非胆汁瘤组, 差异有统计学意义 ($P<0.05$)。46 例胆汁瘤患者中 36 例 (78.26%) 无症状, 无症状胆汁瘤患者中有 1 例随访增大, 行经皮胆汁瘤引流术治疗后缩小, 其他胆汁瘤无变化或缩小; 10 例 (21.74%) 有发热、黄疸症状, 行经皮胆汁瘤引流术, 8 例胆汁瘤缩小, 1 例消失, 1 例因引流效果不佳行经皮肝穿刺胆道引流后缩小。logistic 回归分析显示, 术前胆道扩张 ($OR=2.542$, 95% CI 1.503~4.300; $P<0.05$)、术中使用聚乙烯醇颗粒 ($OR=3.391$, 95% CI 2.145~5.360; $P<0.05$)、术后 1 周 GGT 异常升高 ($OR=2.056$, 95% CI 1.049~4.031; $P<0.05$) 及术后 1 周 ALP 异常升高 ($OR=2.450$, 95% CI 1.380~4.350; $P<0.05$) 均为老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素。**结论** 术前胆道扩张、使用聚乙烯醇颗粒栓塞、术后 1 周 GGT 及 ALP 异常升高是老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素, 临床可依此制定防控对策, 改善患者预后。

【关键词】 老年人; 原发性肝癌; 肝细胞癌; 肝动脉化疗栓塞术; 胆汁瘤

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Risk factors of biloma after interventional surgery for primary hepatocellular carcinoma in the elderly

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【Abstract】Objective To explore the risk factors of biloma in elderly patients with primary hepatocellular carcinoma after interventional surgery. **Methods** A total of 632 elderly patients who underwent transcatheter arterial chemoembolization (TACE) for primary hepatocellular carcinoma (HCC) in Changzhi People's Hospital affiliated to Changzhi Medical College from January 2021 to March 2023 were selected as the study subjects. They were followed up for 6 months, and 14 cases were lost to follow-up. According to whether they developed biloma after TACE, the patients were divided into biloma group ($n=46$) and non-biloma group ($n=572$). The general data such as gender, age, Child-Pugh grading, gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) were compared between groups. SPSS 24.0 was used for data analysis. According to the data type, t test, χ^2 -square test or Fisher exact probability method was used for data comparison. Logistic regression analysis was used to evaluate the risk factors of biloma after TACE in elderly patients with primary HCC. **Results** The incidence of biloma after TACE was 7.44% (46/618) in 618 elderly patients with primary HCC. The incidence rate of preoperative biliary tract dilatation, the proportion of intraoperative use of polyvinyl alcohol particle, and the abnormal increase rates of GGT and ALP at one week after surgery in the biloma group were higher than those in the non-biloma group ($P<0.05$). Among the 46 patients with biloma, 36 (78.26%) were asymptomatic, among whom one had enlarged bilioma during follow-up and shrank after percutaneous biloma drainage. The other asymptomatic patients had no change or did not shrink. Ten (21.74%)

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patients had fever and jaundice. After percutaneous biloma drainage, biloma shrank in eight patients, disappeared in one, and shrank in one after percutaneous transhepatic biliary drainage due to poor drainage effect. Logistic regression analysis showed that preoperative biliary tract dilatation ($OR=2.542$, $95\%CI$ 1.503–4.300; $P<0.05$), intraoperative use of polyvinyl alcohol particle ($OR=3.391$, $95\%CI$ 2.145–5.360; $P<0.05$), abnormal increase of GGT at one week after surgery ($OR=2.056$, $95\%CI$ 1.049–4.031; $P<0.05$), and abnormal increase of ALP at one week after surgery ($OR=2.450$, $95\%CI$ 1.380–4.350; $P<0.05$) were risk factors of biloma in elderly patients with primary HCC after TACE. **Conclusion** Preoperative biliary tract dilatation, embolization with polyvinyl alcohol particle, and abnormal increases of GGT and ALP at one week after surgery are risk factors of biloma in elderly patients with primary HCC after TACE. Accordingly, it is necessary to formulate clinical prevention and control measures in order to improve the prognosis of patients.

【Key words】 aged; primary hepatocellular carcinoma; hepatocellular carcinoma; transhepatic arterial chemoembolization; biloma
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原发性肝癌在全球实体瘤发病率中排名第五,其中肝细胞癌(hepatocellular carcinoma, HCC)为最常见的病理类型,约占 80%~90%^[1]。有研究指出,原发性 HCC 发病风险随年龄的升高而增加,60 岁及以上老年人发病风险是 40 岁以下人群的 4 倍^[2]。对于中晚期原发性 HCC,外科手术及介入栓塞为主要治疗手段,而老年患者身体素质差,耐受能力低,外科根治性切除治疗难以使患者获益,肝动脉化疗栓塞术(transcatheter arterial chemoembolization, TACE)是此类患者的主要治疗方式^[3]。但 TACE 治疗可引起胆道损伤,诱发胆汁瘤等并发症,影响患者生存质量^[4]。然而,TACE 术后胆汁瘤的相关报道少见,其危险因素及防控对策尚在探索阶段。基于此,本研究调查本院近年老年原发性 HCC 患者 TACE 术后胆汁瘤发生情况及其危险因素,为临床防控对策的制定提供参考数据。

1 对象与方法

1.1 研究对象

选取 2021 年 1 月至 2023 年 3 月长治医学院附属长治市人民医院收治的 632 例行 TACE 治疗的老年原发性 HCC 患者为研究对象。纳入标准:经病理活检证实为原发性 HCC,肝癌巴塞罗那临床分期系统 B 期,且诊断符合《原发性肝癌诊疗规范(2019 年版)》^[5];年龄 ≥ 60 岁;肝功能 Child-Pugh 分级为 A~B 级;美国东部肿瘤协作组体力状况评分为 0~2 分;首次行 TACE 治疗。排除标准:既往肝胆手术史;存在肝肾功能衰竭、栓塞相关药物过敏等 TACE 治疗禁忌;门静脉主干癌栓、下腔静脉癌栓;合并全身感染性疾病或血液系统、免疫系统疾病;联合射频、微波、消融治疗或二期手术切除治疗。剔除标准:TACE 术后随访不足 6 个月。随访期间,14 例失访,予以剔除。患者及家属对研究内容知情并签署知情

同意书。本研究获得长治医学院附属长治市人民医院伦理委员会审批(批号:20210781)。

1.2 方法

1.2.1 资料收集 所有患者在术前 1 d、术后 1 周采集空腹外周肘静脉血,使用自动生化分析仪(日本 OLYMPUS 公司,型号:AU2700)检测丙氨酸氨基转移酶(alanine aminotransferase, ALT)、门冬氨酸氨基转移酶(aspartate aminotransferase, AST)、 γ -谷氨酰基转移酶(gamma-glutamyl transferase, GGT)、碱性磷酸酶(alkaline phosphatase, ALP)及白蛋白水平,其中 $GGT \leq 50$ U/L、 $ALP \leq 130$ U/L 为正常,术前 GGT、ALP 正常者术后异常,或术前 GGT、ALP 异常者术后 GGT、ALP 较术前进一步升高,定义为术后 GGT、ALP 异常升高。人口学资料、实验室数据及手术相关资料等均来自患者电子病例。

1.2.2 TACE 治疗方法 618 例老年原发性 HCC 患者均采用 Seldinger 技术在右侧股动脉插管,使用 5F RH 导管行腹腔肝动脉造影,使用 3F 微导管行超选择肿瘤动脉栓塞,栓塞药物为 6~10 mg 丝裂霉素+30~50 mg 盐酸吡柔比星+1 g 5 氟尿嘧啶+40 mg 奈达铂碘化油混合液,并根据肿瘤供血动脉管径使用明胶海绵颗粒($150 \sim 1\,000 \mu m$)或聚乙烯醇颗粒($100 \sim 1\,000 \mu m$)栓塞供血动脉近端;术毕加压包扎穿刺点,术后行止吐、护胃、保肝等常规治疗;TACE 术后 4~6 周行影像学检查,若供血动脉未完全栓塞则重复 TACE 治疗。

1.2.3 胆汁瘤诊断 所有患者 TACE 术后 1~2 周门诊随访 1 次,行影像学检查,若术区或周围肝实质见新发类圆形的囊状水样信号灶,或沿 Glisson 纤维鞘排列的新发柱状水样信号灶,或肝包膜下胆汁样信号聚集,在排除结石等引起的胆管扩张后即可确诊胆汁瘤^[6]。术后随访观察 6 个月,以 TACE 术后 6 个月是否发生胆汁瘤将患者分为胆汁瘤组($n=46$)

与非胆汁瘤组($n=572$)。

1.2.4 胆汁瘤治疗 随访期间若胆汁瘤增大或出现黄疸、发热等典型症状时,行经皮胆汁瘤引流术治疗,临床症状消失或引流量减少可拔除引流管。记录老年原发性 HCC 患者 TACE 术后胆汁瘤的预后转归情况。

1.3 统计学处理

采用 SPSS 24.0 统计软件进行数据分析。符合正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验。计数资料以例数(百分率)表示,组间比较采用 χ^2 检验或 Fisher 精确概率法。使用 logistic 回归分析评估老年原发性 HCC 患者

TACE 术后发生胆汁瘤的危险因素。 $P<0.05$ 为差异有统计学意义。

2 结 果

2.1 两组患者临床资料比较

618 例老年原发性 HCC 患者 TACE 术后胆汁瘤发生率为 7.44%(46/618),其中 42 例(91.30%)发生于术后 0.5~3 个月,4 例(8.70%)发生于术后 3~6 个月。胆汁瘤组术前胆道扩张发生率、术中使用聚乙烯醇颗粒占比及术后 1 周 GGT 异常升高、ALP 异常升高率均高于非胆汁瘤组($P<0.05$;表 1)。

表 1 两组老年原发性 HCC 患者临床资料比较

Table 1 Comparison of clinical data between two groups of elderly patients with primary HCC

Item	Biloma group($n=46$)	Non-biloma group($n=572$)	χ^2/t	P value
Gender[$n(\%)$]			0.291	0.589
Male	40(86.96)	512(89.51)		
Female	6(13.04)	60(10.49)		
Age[$n(\%)$]			1.054	0.305
60–70 years	35(76.09)	470(82.17)		
>70 years	11(23.91)	102(17.83)		
Child-Pugh grading[$n(\%)$]			0.358	0.550
Grade A	36(78.26)	468(81.82)		
Grade B	10(21.74)	104(18.18)		
Preoperative abnormal GGT[$n(\%)$]			1.099	0.294
Yes	25(54.35)	265(46.33)		
No	21(45.65)	307(53.67)		
Preoperative abnormal ALP[$n(\%)$]			2.746	0.097
Yes	29(63.04)	288(50.35)		
No	17(36.96)	284(49.65)		
Preoperative albumin level(g/L, $\bar{x}\pm s$)	31.25±7.55	33.05±8.24	1.434	0.152
Maximum tumor diameter[$n(\%)$]			1.072	0.301
<5 cm	22(47.83)	229(40.03)		
≥5 cm	24(52.17)	343(59.97)		
Tumor blood supply type[$n(\%)$]			1.599	0.206
Abundant blood supply	35(76.09)	477(83.39)		
Poor blood supply	11(23.91)	95(16.61)		
Preoperative biliary tract dilatation[$n(\%)$]			13.490	<0.001
Yes	14(30.43)	66(11.54)		
No	32(69.57)	506(88.46)		
Drug-loaded microspheres[$n(\%)$]			34.118	<0.001
Intraoperative use of polyvinyl alcohol particle	22(47.83)	82(14.34)		
Intraoperative use of gelatin sponge particle	24(52.17)	490(85.66)		
TACE frequency[$n(\%)$]			0.333	0.564
≤2 times	41(89.13)	524(91.61)		
>2 times	5(10.87)	48(8.39)		
Abnormal increase of GGT at 1 week after surgery[$n(\%)$]			10.405	0.001
Yes	33(71.74)	269(47.03)		
No	13(28.26)	303(52.97)		
Abnormal increase of ALP at 1 week after surgery[$n(\%)$]			15.517	<0.001
Yes	36(78.26)	275(48.08)		
No	10(21.74)	297(51.92)		

HCC: hepatocellular carcinoma; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; TACE: transcatheter arterial chemoembolization.

2.2 老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素

以 TACE 术后 6 个月是否发生胆汁瘤为因变量,将单因素分析中有统计学意义的指标作为自变量赋值(表 2),代入二元 logistic 回归方程,结果显示,术前胆道扩张、术中使用聚乙烯醇颗粒、术后 1 周 GGT 异常升高及术后 1 周 ALP 异常升高均为老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素($P<0.05$;表 3)。

表 2 自变量赋值

Table 2 Assignment of independent variables

Independent variable	Assignment
Preoperative biliary tract dilatation	No=0, Yes=1
Intraoperative use of polyvinyl alcohol particle	No=0, Yes=1
Abnormal increase of GGT at 1 week after surgery	No=0, Yes=1
Abnormal increase of ALP at 1 week after surgery	No=0, Yes=1

GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase

2.3 老年原发性 HCC 患者 TACE 术后胆汁瘤的预后转归情况

46 例胆汁瘤患者中 36 例无症状(78.26%),平均胆汁瘤直径为(2.94±0.56)cm,其中 1 例随访增大,行经皮胆汁瘤引流术治疗后缩小,其他无症状者随访见胆汁瘤无变化或缩小;10 例有发热、黄疸症状(21.74%),平均胆汁瘤直径为(7.04±1.25)cm,均行经皮胆汁瘤引流术,8 例胆汁瘤缩小,1 例消失,1 例因引流效果不佳行经皮肝穿刺胆道引流后缩小。

3 讨论

TACE 作为中晚期老年原发性 HCC 的常用介入治疗手段,具有微创、短期疗效好等优点,但栓塞引起的缺血及化疗药物毒性损伤易造成胆管坏死,胆汁漏至周围肝组织形成胆汁瘤^[7]。目前报道的 TACE 术后胆汁瘤发生率波动在 0.9%~9.6%,这可能与入组病例的差异及随访时间不同等有关^[8]。本研究结果显示,老年原发性 HCC 患者 TACE 术后 6 个月的胆汁瘤发生率为 7.44%,处于稍高水平,可

能与本研究观察期较长且入组的为耐受力较差的老年人群有关。另外,发生胆汁瘤患者中 91.30%发生于术后 3 个月内,8.70%发生于术后 3~6 个月,提示老年原发性 HCC 患者的胆汁瘤多发生于 TACE 术后早期,与目前的报道相似^[9]。

本研究结果显示,术前胆道扩张是老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素,分析其原因为 HCC 肿瘤侵及肝门部胆管时,导致胆管微循环受阻、胆管扩张,增加胆汁淤积风险,造成 TACE 术后更易发生胆汁瘤^[10]。本研究发现,术中使用聚乙烯醇颗粒也是老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素,这可能与聚乙烯醇颗粒直径更小,更易阻塞胆管周围毛细血管丛,TACE 术后早期易发生胆管坏死,胆汁瘤发生风险升高有关^[11]。也有研究指出,非超选择性插管及多次 TACE 治疗是 TACE 术后胆汁瘤的高危因素^[12]。由于近年 TACE 治疗普遍采用超选择性插管,本研究中均采用 3F 微导管超选择性插管,且胆汁瘤组与非胆汁瘤组 TACE 治疗次数并无显著差异,考虑与超选择性插管使 TACE 操作对胆管损伤降低有关^[13]。

此外,本研究结果显示术后 1 周 GGT 异常升高、术后 1 周 ALP 异常升高均为老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素。其中,GGT 是一种肝功能指标,在胆管梗阻性疾病中显著升高^[14],ALP 不仅能用于评估肝功能损伤,也可评估胆汁淤积及胆管损伤^[15]。因此,上述结果提示 TACE 术后发生胆汁瘤的患者在术后 1 周即存在胆管梗阻及损伤,使 GGT、ALP 异常升高,而胆汁瘤的明确诊断普遍在术后 2 周以后,存在滞后性。因此,TACE 术后 1 周 GGT、ALP 异常升高的患者发生胆汁瘤的风险较高,临床应注意监测,及时予以穿刺置管引流治疗,避免治疗延误造成的胆汁瘤感染等严重后果。由于相关报道少见,该推测还需后续多中心大样本量研究的论证。本研究中,TACE 术后胆汁瘤患者经对症处理后,大部分患者胆汁瘤能缩小,未发生恶化,预后良好。

表 3 老年原发性 HCC 患者 TACE 术后发生胆汁瘤的 logistic 回归分析

Table 3 Logistic regression analysis of risk factors of biloma after TACE in elderly patients with primary HCC

Factor	β	SE	Wald χ^2	OR	95%CI	P value
Preoperative biliary tract dilatation	0.933	0.244	14.621	2.542	1.503–4.300	<0.001
Intraoperative use of polyvinyl alcohol particle	1.221	0.304	16.132	3.391	2.145–5.360	<0.001
Abnormal increase of GGT at 1 week after surgery	0.721	0.227	10.088	2.056	1.049–4.031	0.001
Abnormal increase of ALP at 1 week after surgery	0.896	0.254	12.444	2.450	1.380–4.350	<0.001

HCC: hepatocellular carcinoma; TACE: transcatheter arterial chemoembolization; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase.

综上所述,肝脏背景因素的术前胆道扩张、TACE 操作因素的术中使用聚乙烯醇颗粒是老年原发性 HCC 患者 TACE 术后发生胆汁瘤的危险因素,且术后 1 周 GGT 异常升高、术后 1 周 ALP 异常升高者术后胆汁瘤风险更高,可为胆汁瘤的临床防控提供参考依据。

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