·临床研究·

老年患者肝切除术后谵妄的危险因素分析

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【摘 要】 目的 探讨老年患者肝切除术后谵妄(POD)的危险因素及对预后的影响。**方法** 回顾性分析2018年1月至2022年1月于徐州市中心医院全身麻醉下行肝切除术的314例老年患者的临床资料,根据是否发生POD将患者分为POD组(66例)和非POD组(248例)。采用SPSS软件(美国 Version 26)与R软件(美国 Version 4.1.2)进行数据分析及绘图。根据数据类型,分别采用*t*检验、秩和检验、χ^2检验、*Fisher*确切概率法或*Wilcoxon*秩和检验进行组间比较。采用单因素分析方法和多因素logistic回归方法分析老年患者肝切除术后POD发生的独立危险因素。**结果** 314例老年肝切除患者中,21.0%(66/314)发生POD。高龄(*OR*=1.167,95%*CI* 1.058~1.287;*P*<0.001)、体质量指数<18.5 kg/m^2(*OR*=2.115,95%*CI* 1.124~3.980;*P*=0.018)、术前低简易智力状态检查量表评分(*OR*=1.096,95%*CI* 1.047~1.148;*P*=0.021)、术前高查尔森合并症指数得分(*OR*=1.458,95%*CI* 1.132~1.878;*P*=0.007)、手术时间长(*OR*=1.043,95%*CI* 1.025~1.061;*P*=0.010)、术后入重症监护室(*OR*=2.481,95%*CI* 1.554~3.961;*P*<0.001),术后24 h视觉模拟评分高(*OR*=1.038,95%*CI* 1.017~1.059;*P*=0.014)是老年肝切除患者POD的独立危险因素。该多因素logistic回归模型对POD有良好的区分能力(曲线下面积=0.865,95%*CI* 0.795~0.936),以及较高的拟合程度(Hosmer-Lemeshow拟合优度检验,χ^2=5.199,*P*=0.804)。**结论** 外科医师与麻醉医师可通过术前评估及早识别存在POD风险的老年患者,改善术前状态,优化围术期管理,从而降低老年肝切除患者POD的发生率。

【关键词】 老年人;肝切除术;术后谵妄;危险因素
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Risk factors of postoperative delirium in elderly patients after hepatectomy

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【Abstract】 Objective To investigate the risk factors and prognostic impact of postoperative delirium (POD) in elderly patients after hepatectomy. **Methods** A retrospective observational study was conductd on 314 elderly patients who underwent hepatectomy under general anesthesia in Xuzhou Central Hospital from January 2018 to January 2022. According to whether the patients had POD or not, the patients were divided into POD group (n=66) and non-POD group (n=248). SPSS software Version 26 and R software Version 4.1.2 were used for data analysis and graphing. Depending on data types, student's t test, Rank sum test, *Chi*-square test, *Fisher's* exact test or *Wilcoxon* rank sum test was employed for intergroup comparison. Univariate analysis and multivariate logistic regression were applied to analyze the independent risk factors of POD in elderly patients after hepatectomy. **Results** Among the 314 enrolled elderly patients, 66 (21.0%) developed POD. Advanced age (*OR*=1.167, 95%*CI* 1.058-1.287; *P*<0.001), body mass index< 18.5 kg/m^2(*OR*=2.115, 95%*CI* 1.124-3.980; *P*=0.018), lower preoperative mini-mental state examination score (*OR*=1.096, 95%*CI* 1.047-1.148; *P*=0.021), higher preoperative Charlson comorbidity index (*OR*=1.458, 95%*CI* 1.132-1.878; *P*=0.007), longer operation time (*OR*=1.043, 95%*CI* 1.025-1.061; *P*=0.010), intensive care unit admission after operation (*OR*=2.481, 95%*CI* 1.554-3.961; *P*<0.001), higher postoperative 24 h visual analogue scale score (*OR*=1.038, 95%*CI* 1.017-1.059; *P*=0.014) were independent risk factors for POD in elderly patients after hepatectomy. After calculation, multivariate logistic regression model has good discriminative ability for postoperative POD (area under curve=0.865, 95%*CI* 0.795-0.936) and has a high degree of fit (Hosmer-Lemeshow goodness of fit test, χ^2=5.199, *P*=0.804). **Conclusion** Surgeons and anesthesiologists can identify elderly patients with high risk of POD through preoperative assessment as early as possible. Improvement of preoperative status and optimization of perioperative management can reduce the incidence of POD in elderly patients after hepatectomy.

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【Key words】 aged; hepatectomy; postoperative delirium; risk factors

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肝切除术是目前治疗肝脏良恶性肿瘤的有效方法[1]。由于手术的复杂性,患者术后可发生出血、胆漏、肝功能衰竭、术后谵妄(postoperative delirium, POD)等并发症[2,3]。随着年龄的增加,老年患者肝切除术后更易出现并发症[4]。POD是由手术应激引起的可逆性意识障碍和认知障碍综合征,可交替出现一系列精神症状,如认知功能障碍、睡眠-觉醒周期紊乱、注意力不集中等,是常见的术后神经系统并发症[5,6]。POD可延长住院时间、增加医疗费用、增加患者术后并发症发生率及死亡率,影响患者预后,给临床治疗和护理带来困难[6,7]。因此,预防POD的发生对提高肝切除术生存率至关重要。本研究评估老年患者接受肝切除术后谵妄的发生率及相关危险因素,为预防和治疗肝切除术后谵妄、改善肝切除术预后提供参考。

1 对象与方法

1.1 研究对象

回顾性分析2018年1月至2022年1月于徐州市中心医院全身麻醉下行肝切除术的314例老年患者的临床资料。根据是否发生POD将患者分为POD组(66例)和非POD组(248例)。纳入标准:(1)肝切除术;(2)年龄≥65岁;(3)签署知情同意书。排除标准:(1)既往中枢神经系统感染、头部创伤、癫痫、多发性硬化、精神或意识障碍等其他主要神经系统疾病(如肝性脑病);(2)长期服用精神类药物、类固醇类药物和激素药物;(3)无法配合术后随访工作。

1.2 麻醉管理

所有患者进入手术室后建立心电监护,常规行桡动脉、颈内静脉穿刺并置管,监测有创动脉压及中心静脉压。麻醉诱导使用咪达唑仑0.05 mg/kg,舒芬太尼0.5 μg/kg,依托咪酯0.3 mg/kg,苯磺酸顺式阿曲库铵0.3 mg/kg,麻醉深度(bispectral index, BIS)<60后经口行气管插管。术中维持BIS值在40~60,并根据BIS值调节麻醉深度。根据病情并与外科医师讨论后选择腹腔镜手术或开放手术。术后镇痛采用肋缘下两点法腹横肌平面(transversus abdominis plane, TAP)神经阻滞技术联合自控静脉镇痛(patient controlled intravenous analgesia, PCIA)的多模式镇痛方案。通常情况下,肝切除患者术后如果需要机械通气治疗、存在潜在循环功能障碍和(或)慢性疾病急性加重等情况,术后入重症监护室(intensive care unit, ICU)进行观察和治疗。

1.3 数据收集

由经过专业培训的研究人员进行术前、术后随访并记录相关信息,参与术中管理的临床医师与研究人员互不知情。根据国内外相关研究文献,收集并记录以下指标:患者年龄、性别、美国麻醉医师协会(american society of anesthesiologists, ASA)分级、体质量指数(body mass index, BMI)、术前简易智力状态检查量表(mini-mental state examination, MMSE)评分、术前查尔森合并症指数(Charlson comorbidity index, CCI)得分、既往史(手术史、酗酒史、吸烟史、高血压、糖尿病、心血管疾病、脑血管疾病、呼吸系统疾病等)、肝脏情况(肝炎类型、是否合并肝硬化、肝肿瘤类型、数量及大小、Child-Pugh分级、总胆红素、白蛋白、凝血酶原时间、血小板、谷丙转氨酶、谷草转氨酶等)、手术情况(肿瘤切除部位、手术方式、手术时间、咪达唑仑、舒芬太尼、瑞芬太尼用量、术中低血压发生率、术中失血量、术中输血量等)及术后入ICU比率、术后24 h视觉模拟评分(visual analogue scale, VAS)和术后并发症发生率等。根据相关文献[8],术中低血压的定义为平均动脉压(mean arterial pressure, MAP)低于65 mmHg(1 mmHg=0.133 kPa)。

1.4 POD的评估

术后1~7 d,由经过专业量表评估训练的研究人员采用意识模糊评估法(confusion assessment method, CAM)或ICU患者意识模糊评估法(CAM-ICU)[9]评估患者POD发生情况,每天2次,上午随访时间8:00~10:00,下午随访时间16:00~18:00。术后1~7 d至少出现1次POD的患者纳入POD组,术后1~7 d未发生POD的患者则纳入非POD组。

1.5 统计学处理

采用SPSS软件(美国Version 26)与R软件(美国Version 4.1.2)进行数据分析及绘图。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;不符合正态分布的计量资料使用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,组间比较采用 Mann-Whitney U 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* 确切概率法。等级资料组间比较采用 *Wilcoxon* 秩和检验。将单因素分析中筛选出的潜在的危险因素($P<0.1$)及临床上认为与老年肝切除患者 POD 发生有较大关系的变量纳入多因素 logistic 回归分析,筛选 POD 的独立危险因素。通过受试者工作特征(receiver operating characteristic,ROC)曲线下面积(area under curve,AUC)评价模型的区分能力。采用 Hosmer-Lemeshow 拟合优度检验评估模型拟合值与实际值的拟合程度。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 一般资料

314 例老年肝切除手术患者中,66 例患者出现 POD,POD 发生率为 21.0%(66/314)。66 例 POD 患者中,29 例(43.9%)转出 ICU 后 POD 症状逐渐缓解,32 例(48.5%)服用抗精神药物治疗 POD,5 例(7.6%)术后采用多种方法联合治疗。所有患者出院时 POD 均缓解。

2.2 单因素分析

单因素分析结果显示:患者年龄、BMI、术前 MMSE 评分、术前 CCI 得分、术前白蛋白量、手术时间、术中出血量、术中输红细胞量、术中低血压比例、术后入 ICU 比例,术后 24 h VAS 评分是老年患者肝切除术后谵妄的影响因素($P<0.1$;表 1,表 2)。术后并发症发生情况比较,POD 组腹腔积液、胆漏、术后出血及伤口感染发生率均高于非 POD 组($P<0.05$;表 3)。

2.3 老年肝切除患者 POD 发生的危险因素分析

将单因素分析筛选出的影响因素($P<0.1$)及临床上认为与老年肝切除患者 POD 发生有较大关系的变量纳入多因素 logistic 回归分析,筛选出 POD 的独立危险因素为高龄($OR=1.167$,95%*CI* 1.058~1.287)、BMI < 18.5 kg/m^2($OR=2.115$,95%*CI* 1.124~3.980)、术前低 MMSE 评分($OR=1.096$,95%*CI* 1.047~1.148)、术前高 CCI 得分($OR=1.458$,95%*CI* 1.132~1.878)、手术时间长($OR=1.043$,95%*CI* 1.025~1.061)、术后入 ICU($OR=2.481$,95%*CI* 1.554~3.961),术后 24 h VAS 评分高($OR=1.038$,95%*CI* 1.017~1.059),详见图 1。

2.4 模型区分度及校准度

经计算,该多因素 logistic 回归模型对 POD 有好的区分能力(AUC = 0.865,95%*CI* 0.795~0.936),且具有较高的拟合程度(Hosmer-Lemeshow 拟合优度检验,$\chi^2=5.199$,$P=0.804$;图 2)。

3 讨 论

POD 是一种术后急性波动性的精神状态改变,临床中应注意与肝性脑病的精神症状鉴别,其特征是注意力不集中、意识思维紊乱,多见于老年人,常发生在术后 2~5 d[5,6]。本研究发现大多数老年肝切除患者在术后第 2 天或第 3 天易出现 POD,持续约 3 d,干预或治疗后缓解。本研究老年肝切除患者 POD 发生率为 21.0%,这与 Park 等[7]研究相符。本研究结果显示,高龄、BMI<18.5 kg/m^2、术前低 MMSE 评分、高 CCI 得分、手术时间长、术后入 ICU 及术后 24 h VAS 评分高是 POD 的独立危险因素。Jin 等[6]研究发现,POD 明显增加患者术后并发症发生率及死亡率,影响患者预后,而预防或降低 POD 发生的有效措施包括 BIS 指导下控制麻醉深度[10]、多模式少阿片类镇痛管理、术中使用右美托咪定、术后改变环境因素或使用药物干预等[11-13]。因此对于 POD 高危的老年患者,早期识别并有针对性的进行预防、干预或治疗具有重要意义。

与既往研究一致[14],高龄是 POD 的独立危险因素。老年患者由于神经细胞老化,手术和麻醉的应激,体内调节适应能力下降[15],此外年龄相关的药代动力学和药效学的变化增加了药物相关副作用[16],进而引起 POD。本研究发现,术前低 BMI 患者更容易发生 POD,与 BMI 正常患者相比,BMI < 18.5 kg/m^2 时 POD 的风险会增加 1.115 倍左右。BMI 是反映机体营养状态指标之一,低 BMI 患者常伴有营养不良等情况,这直接或间接导致了 POD 发生率的增加[17]。

MMSE 评分能全面、准确、迅速地反映智力状态及认知功能缺损程度,是最常见的认知功能障碍的筛查表之一。与 Mevorach 等[18]研究一致,术前低 MMSE 评分是发生 POD 的独立危险因素。CCI 是应用较为广泛的合并症评分体系,基于患者所患疾病数目及严重程度,对合并症进行量化,可用于预测疾病的死亡风险[19]。在本研究中,高 CCI 得分是 POD 的独立危险因素,CCI 得分每增加 1 分,风险大概增加 45.8%。

表1 2组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	POD group(n=66)	Non-POD group(n=248)	P value
Age(years, $\bar{x}\pm s$)	72.5±3.1	67.2±2.8	<0.001
Gender[n(%)]			0.440
Male	30(45.5)	126(50.8)	
Female	36(54.5)	122(49.2)	
BMI[n(%)]			0.006
<18.5 kg/m^2	22(33.3)	40(16.1)	
18.5-24.0 kg/m^2	39(59.1)	183(73.8)	
>24.0 kg/m^2	5(7.6)	25(10.1)	
MMSE score[points, $M(Q_1, Q_3)$]	25.0(23.0,29.0)	27.0(26.0,30.0)	0.003
CCI score[points, $M(Q_1, Q_3)$]	5.0(3.0,8.0)	3.0(2.0,4.0)	0.002
Past history[n(%)]			
Surgical history	17(25.8)	50(20.2)	0.324
Alcoholism	17(25.8)	69(27.8)	0.738
Smoking	20(30.3)	82(33.1)	0.670
Hypertension	38(57.6)	124(50.0)	0.274
Diabetes mellitus	14(21.2)	67(27.0)	0.338
Cardiovascular disease	15(22.7)	64(25.8)	0.608
Cerebrovascular disease	7(10.6)	20(8.1)	0.513
Respiratory disease	9(13.6)	37(14.9)	0.793
Type of hepatitis[n(%)]			0.672
NBC	35(53.0)	144(58.1)	
HBV	24(36.4)	72(29.0)	
HCV	5(7.6)	20(8.1)	
HBV+HCV	2(3.0)	12(4.8)	
Cirrhosis[n(%)]	21(31.8)	69(27.8)	0.523
Liver tumor type[n(%)]			0.839
Benign tumor or disease	5(7.6)	15(6.0)	
Primary liver cancer	52(78.8)	203(81.9)	
Metastatic liver tumor	9(13.6)	30(12.1)	
Number of tumors[n(%)]			0.302
Single	54(81.8)	188(75.8)	
Multiple	12(18.2)	60(24.2)	
Tumor size[cm, $M(Q_1, Q_3)$]	2.8(0.9,10.3)	3.2(1.2,12.4)	0.217
Liver function indicators			
Total bilirubin[μmol/L, $M(Q_1, Q_3)$]	26.3(19.6,35.7)	28.2(20.3,34.1)	0.187
Albumin[g/L, $M(Q_1, Q_3)$]	38.5(28.3,55.0)	40.6(29.1,58.4)	0.074
Prothrombin time(g/L, $\bar{x}\pm s$)	13.1±2.2	14.5±3.3	0.542
Platelets[×10^9/L, $M(Q_1, Q_3)$]	147.0(98.0,226.0)	140.5(91.0,217.0)	0.754
Alanine aminotransferase[U/L,$M(Q_1, Q_3)$]	40.0(32.0,53.0)	39.0(31.0,52.0)	0.126
Aspartate aminotransferase[U/L,$M(Q_1, Q_3)$]	38.5(31.0,52.0)	40.0(29.0,48.0)	0.335
Child-Pugh score[n(%)]			0.652
A	61(92.4)	233(94.0)	
B	5(7.6)	15(6.0)	
C	0(0.0)	0(0.0)	
ASA classification[n(%)]			0.540
Class Ⅰ-Ⅱ	48(72.7)	171(69.0)	
Class Ⅲ	16(24.2)	67(27.0)	
Class Ⅳ	2(3.0)	10(4.0)	

BMI: body mass index; MMSE: mini-mental state examination; CCI: Charlson comorbidity index; NBC: negative for both hepatitis B and C virus; HBV: hepatitis B virus; HCV: hepatitis C virus; ASA: American Society of Anesthesiologists; POD: postoperative delirium.

表 2 2 组患者术中及术后资料比较

Table 2 Comparison of intraoperative and postoperative data between two groups

Item	POD group(n=66)	Non-POD group(n=248)	P value
Type of anesthesia[n(%)]			0.634
Inhalation anesthesia	9(13.6)	37(14.9)	
Intravenous anesthesia	45(68.2)	154(62.1)	
Intravenous inhalation anesthesia	12(18.2)	57(23.0)	
Tumor resection site[n(%)]			0.988
Liver lobe	13(19.7)	45(18.2)	
Liver segment	14(21.2)	54(21.8)	
Left liver	22(33.3)	87(35.0)	
Right liver	17(25.8)	62(25.0)	
Surgical approach[n(%)]			0.782
Laparoscopic surgery	30(45.5)	108(43.5)	
Open surgery	36(54.5)	140(56.5)	
Intraoperative hypotension[n(%)]	13(19.7)	28(11.3)	0.072
Midazolam[mg, $M(Q_1, Q_3)$]	3.0(2.0,5.0)	3.0(2.0,4.0)	0.375
Sufentanil[μg, $M(Q_1, Q_3)$]	45.0(40.0,50.0)	40.0(35.0,50.0)	0.861
Remifentanil[mg, $M(Q_1, Q_3)$]	5.0(2.0,8.0)	4.0(2.0,7.0)	0.577
Postoperative ICU admission[n(%)]			<0.001
No	37(56.1)	212(85.5)	
Yes	29(43.9)	36(14.5)	
Operation time[min, $M(Q_1, Q_3)$]	298.0(133.0,450.0)	245.0(129.0,375.0)	<0.001
Intraoperative blood loss[ml, $M(Q_1, Q_3)$]	750.0(350.0,1 200.0)	475.0(250.0,800.0)	0.043
Intraoperative blood transfusion			
Red blood cell suspension(U, $\bar{x}\pm s$)	3.3±2.1	1.9±1.5	0.059
Frozen plasma(ml, $\bar{x}\pm s$)	416.2±60.5	375.1±43.8	0.552
Postoperative VAS score[points, $M(Q_1, Q_3)$]	6.0(3.0,8.0)	3.0(2.0,4.0)	<0.001

ICU: intensive care unit; VAS: visual analogue scale; POD: postoperative delirium.

表 3 2 组患者术后并发症情况比较

Table 3 Comparison of postoperative complications between two groups [n(%)]

Item	POD group(n=66)	Non-POD group(n=248)	P value
Ascites	21(31.8)	36(14.5)	0.001
Pleural effusion	7(10.6)	19(7.7)	0.440
Bile leakage	3(4.6)	1(0.4)	0.030
Postoperative bleeding	5(7.6)	2(0.8)	0.005
Infection	4(6.1)	3(1.2)	0.038
Renal insufficiency	2(3.0)	3(1.2)	0.283
Liver insufficiency	2(3.0)	1(0.4)	0.113

POD: postoperative delirium.

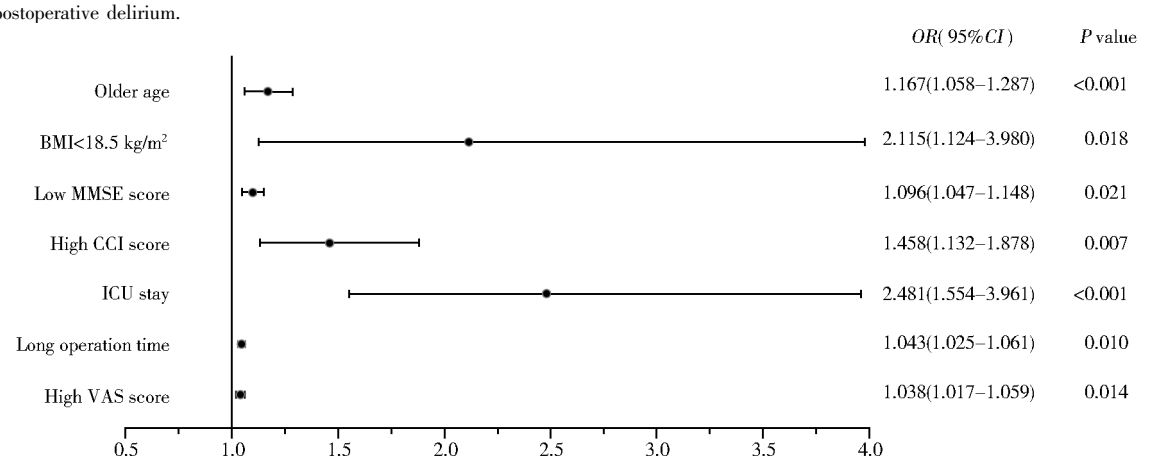

图 1 老年肝切除患者术后谵妄的危险因素

Figure 1 Risk factors for postoperative delirium in elderly patients with liver resection

BMI: body mass index; MMSE: mini-mental state examination; CCI: Charlson comorbidity index; ICU: intensive care unit; VAS: visual analogue scale.

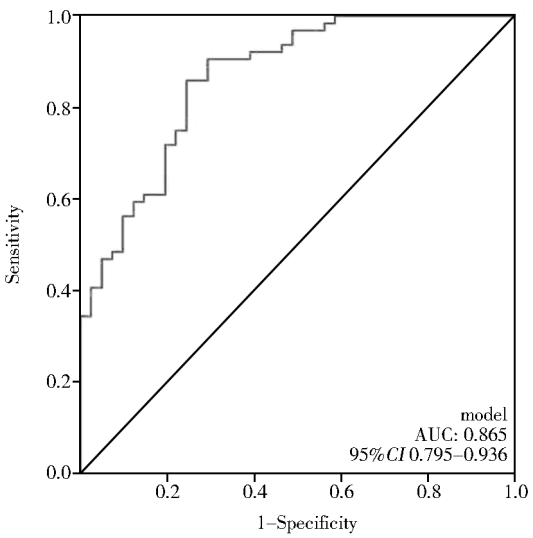

图2 预测模型的ROC曲线

Figure 2 ROC curve of prediction model

ROC: receiver operating characteristic.

本研究发现手术时间每延长1 min,POD风险大概增加4.3%,这可能与手术时间延长,需要更多的苯二氮䓬类和阿片类药物有关,进而导致POD的高发生率。Whitlock等[20]发现苯二氮䓬类药物和阿片类药物可能是老年患者POD的诱发因素。本研究与既往研究一致,术后入ICU增加POD的风险[21]。老年患者术后入ICU一般代表病情较重,此外ICU中各种仪器报警、日夜灯光照明、各种导管及约束带等影响患者睡眠质量,而睡眠质量差也是POD发生的危险因素[22]。疼痛是诱发POD的另一个危险因素,多项观察性研究证实,术后VAS评分与患者POD的发生率存在相关关系[23,24]。Eckenhoff等[25]研究表明,疼痛对个体心理的影响首先表现在认知功能上,所以疼痛刺激与患者POD的发生相关。术后镇痛使用的TAP神经阻滞技术已被证明可以显著改善肝切除患者术后疼痛[26]。在本研究中,术后24 h VAS评分高是POD发生的独立危险因素,VAS评分每增加1分,POD风险大概增加3.8%。

本研究具有以下局限性:(1)本研究为单中心研究,危险因素的分析有待多中心进行验证;(2)本研究从术后第1天开始每日固定时间点评估谵妄发生,可能检测不到1 d中其他时间点发生的轻度、短暂的谵妄,这可能会导致结果的偏倚;(3)肝脏储备功能与POD发生在发病机制上有一定的关系,因此测量残余肝体积、残肝功能、术前肝功能储备等具有重要意义。由于本研究为回顾性观察性研究,当时临床尚未开展残余肝体积、残肝功能、术前肝功能储备等监测工作,这在一定程度上存在缺陷。

综上,外科医师与麻醉医师可通过术前评估及早识别存在POD风险的老年患者,改善患者术前状态,优化患者围术期管理,从而降低老年肝切除患者POD的发生率。

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