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· 文献综述 ·

肝切除术后急性门静脉血栓形成的诊疗进展

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摘要

门静脉血栓(PVT)是产生于门静脉和(或)其分支的血栓,肝切除术后急性PVT指术后30 d内发生的,或在门静脉形成侧支循环之前的血栓状态。PVT形成后,若不及时干预,血栓会沿着门静脉系统蔓延扩展,导致入肝血流急剧减少,发展为肝衰竭等严重并发症的风险高,病死率高。国内外文献对于肝切除术后PVT发生率和病死率的报道存在较大差异,国内文献报道的发生率低,但病死率高。肝切除术后PVT成因复杂,危险因素众多,包括非手术因素(肝硬化、肝细胞癌、高龄)和手术因素(术中频繁的肝门阻断和长时间的肝门阻断、合并门静脉重建、右三肝或右半肝切除、大范围肝切除、尾状叶切除、合并脾切除、手术时间长、胆汁漏、合并肝外胆管切除等)。患者的临床表现无特异性,部分患者无任何症状体征,导致早期诊断难度大,术后D-二聚体明显变化和肝功能指标好转过程中突然急剧恶化有一定的诊断意义,但肝切除术后PVT主要由影像学检查确诊,腹部增强CT检查敏感度和特异度高。对于存在血栓形成危险因素的患者,术后测定血中凝血酶-抗凝血酶III复合物、D-二聚体、抗凝血酶III和可溶性糖蛋白VI等的浓度对预测PVT形成有一定的价值,通常建议肝切除术后常规行增强CT检查以筛查PVT形成。其治疗方式包括抗凝、溶栓和手术取栓等,应通过对病情的准确评估选择个体化的治疗方式。对于肝切除术后PVT,目前尚无明确的防治方案和指南,早发现、早治疗是改善患者预后的关键。笔者通过检索国内外关于肝切除术后PVT形成相关的文献,总结肝切除术后PVT形成的危险因素、临床表现、诊治、预测和预防的最新研究成果,作一综述。

关键词

肝肿瘤; 肝切除术; 血栓形成; 门静脉; 手术后并发症; 综述

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Progress in diagnosis and treatment of acute portal vein thrombosis after hepatectomy

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Abstract

Portal vein thrombosis (PVT) refers to thrombosis that occurs in the portal vein system and (or) its branches. Acute PVT after hepatectomy refers to the thrombotic state that occurs within 30 d after operation, or before the formation of collateral circulation of the portal vein. If there is no timely intervention, the thrombus will spread along the portal vein system, resulting in a sharp decrease in hepatic blood flow, high risk of serious complications such as liver failure and high mortality. There are great differences in the incidence and mortality rates for PVT after hepatectomy in domestic and foreign literature. The incidence reported in domestic literature is low, but the mortality is high. Acute PVT after hepatectomy have complex etiologies, and there are many risk factors, including non-operative factors (liver cirrhosis, hepatocellular carcinoma, advanced age) and surgical factors (frequent and prolonged inflow occlusion, combination with portal vein reconstruction, right trisectionectomy or right hemihepatectomy, major hepatectomy, caudate lobectomy, synchronous splenectomy, long operative time, bile leakage, extrahepatic bile duct resection, etc.). The clinical manifestation of the patients is unspecific, and some patients do not have any symptoms and signs, which leads to the difficulty of early diagnosis. The obvious changes of D-dimer as well as the sudden and sharp deterioration of liver function indexes during their improvements after hepatectomy have diagnostic significance, but PVT after hepatectomy is mainly diagnosed by imaging examination, and abdominal enhanced CT have high sensitivity and specificity. At present, there is no clear prophylaxis and treatment guidelines. For patients with risk factors for thrombosis, the blood determination of thrombin-antithrombin III complex, D-dimer, antithrombin III and soluble form of glycoprotein VI has a certain value in predicting postoperative PVT. For patients with risk factors for PVT, it is recommended that enhanced CT should be performed routinely to screen PVT. The treatment methods include anticoagulation, thrombolysis and thrombectomy, and individualized treatment should be selected through accurate evaluation of patients. There are no clear prevention and treatment guidelines for PVT after hepatectomy. Early detection and early treatment are the keys to improve the prognosis of patients. By searching the literature concerning PVT after hepatectomy at home and abroad, the authors summarize the latest research results on risk factors, clinical manifestations, diagnosis, treatment and prophylaxis of PVT after hepatectomy.

Key words

Liver Neoplasms; Hepatectomy; Thrombosis; Portal Vein; Postoperative Complications; Review

CLC number: R735.7

门静脉血栓 (portal vein thrombosis, PVT) 是指产生于门静脉系统和 (或) 其分支的血栓^[1], 是腹部手术后需警惕的严重并发症之一。以往的研究多聚焦在肝移植、脾切除和胰腺术后, 近年来, 肝切除术后 PVT 开始在临床上引起注意, 它通常起源于手术操作区域^[2]。肝切除术后急性与慢性 PVT 是同一疾病的连续阶段^[3], 有研究^[4-5]提出术后 30 d 内发生的为急性 PVT, 也有文献^[3, 6]将 PVT 发生后, 门静脉没有形成侧支循环定义为急性 PVT。其发病隐匿, 临床表现不典型, 早期诊断困难, 然而病情进展迅速, 若无及时干预血栓会沿着门静脉系统蔓延扩展, 入肝血流急剧减少, 可能导致肝衰竭、肠道瘀血坏死、多器官功能衰竭等严重的并发症甚至死亡, 且目前尚未形成诊疗共识。

笔者以 (“肝切除” 或 “肝脏术后”) 和 (“门静脉血栓” 或 “血栓”) 为关键词在中国知网、维普和万方数据库检索中文文献, 以 “hepatectomy” OR “hepatic resection” OR “hepatic surgery” OR “liver, resection” OR “liver, surgery” AND “portal vein” OR “portal, vein” AND “thrombosis” 为关键词在 Web of Science、ScienceDirect、Springer、PubMed、Medline、Wiley Online Library 和 Ovid 等数据库检索英文文献, 发现国内外报道的肝切除术后 PVT 的发生率和病死率存在较大差异 (表 1), 国内的文献报道较少, 发生率为 0.21%~24.72%, 病死率高达 50% 以上, 大部分死于肝衰竭; 国外, 尤其是日本学者的研究较多, 发生率为 2.1%~20.0%, 病死率低于 10%,

甚至没有死亡病例。对比发现,国内对肝切除术后PVT的预防和诊疗还需进一步规范,以提高患者存活率,改善患者预后。现对肝切除术后PVT

的病因、临床表现、诊断、治疗、预防和预后进行探索和研究。

表1 国内外关于肝切除术后PVT形成的文献报道

Table 1 Chinese and foreign literature on PVT after hepatectomy

文献	原发病	门静脉重建 ¹⁾	PVT数	发生率(%)	病死率[n(%)]
王征,等 ^[7] 2010	原发性肝癌	未报道	5	0.39	3(60.00)
施建设,等 ^[8] 2013	肝内胆管结石	未报道	22	24.72	未报道
廖方,等 ^[9] 2016	原发性肝癌	未报道	8	2.06	5(62.50)
段纪成,等 ^[10] 2016	原发性肝癌	未报道	13	0.21	7(53.80)
李鹏鹏,等 ^[11] 2017	肝细胞癌	未报道	10	未报道	7(53.80)
许志营,等 ^[12] 2021	原发性肝癌	未报道	8	未报道	2(25.00)
Yamashita,等 ^[13] 2014	肝细胞癌	未报道	24	8.54	0(0.00)
Yoshiya,等 ^[14] 2014	肝癌	未报道	19	9.10	0(0.00)
Kuboki,等 ^[15] 2015	所有	90(5)	25	2.10	2(8.00)
Miyazaki,等 ^[16] 2017	所有	74(16)	16	21.60	未报道
Matsui,等 ^[17] 2018	所有	未报道	6	13.04	未报道
Han,等 ^[18] 2019	所有	18(4)	19	3.60	0(8.00)
Uchida,等 ^[19] 2019	肝门部胆管癌	22(1)	9	11.10	1(11.10)
Onda,等 ^[2] 2020	所有	未报道	57	14.30	0(0.00)
Mori,等 ^[20] 2020	肝癌	2(0)	21	3.38	1(4.76)
Cao,等 ^[21] 2021	肝门部胆管癌	53(5)	6	3.40	0(0.00)
Takata,等 ^[22] 2021	肝细胞癌	未报道	13	20.00	0(0.00)
Okuno,等 ^[23] 2021	所有	18(1) ²⁾	19	6.40	0(0.00)

注:1)括号内为PVT患者门静脉重建例数;2)Okuno的研究中血管重建包括但不限于门静脉

Note: 1) The numbers in the parentheses are cases undergoing portal vein reconstruction; 2) Vascular reconstruction without limitation of portal vein in Okuno's study

1 病因

肝切除术后PVT发生的危险因素包括非手术因素和手术因素。非手术因素包括术前存在肝硬化^[2,23]、肝细胞癌^[13]、高龄(>70岁)^[20]和D-二聚体升高^[8,23]等;手术因素包括:术中频繁的肝门阻断和长时间的肝门阻断^[2,14,18-19,22,24]、合并门静脉重建^[16,18,21,25-26]、右三肝或右半肝切除^[14-15]、大范围肝切除^[2,14,20]、尾状叶切除^[15]、合并脾切除^[15]、手术时间长^[2,13-14]、胆汁漏^[2,15]、合并肝外胆管切除^[15]等。肝切除术后PVT形成与门静脉高压、血流缓慢、手术导致血管内皮损伤、凝血功能紊乱等多方面因素相关^[27]。据报道^[28],70%的肝硬化患者术前即存在血栓形成倾向。术中行肝门阻断会损伤血管内皮细胞,使内皮下胶原暴露,促使PVT形成^[24],Onda等^[2]发现,肝切除术中行选择性或全肝门间断性阻断(阻断15 min,再灌注5 min,重复进行),总阻断时间超过75 min是PVT形成的独立

危险因素。Miyazaki等^[16]发现肝胆胰手术合并不同的门静脉重建术式,术后PVT发生率有显著差异($P<0.05$)。右侧肝切除术后PVT发生率高,与术后残肝体积小、腹腔内位置不固定,导致门静脉扭曲、血流瘀滞有关^[16,20],术后超声监测门静脉血流速度 <15 cm/s是预测PVT发生的独立危险因素^[29-30]。Cao等^[21]研究显示术后门静脉夹角 $<100^\circ$;残余肝内门静脉直径 <5.77 mm是PVT发生的危险因素(图1),而Uchida等^[19]进行同样的研究显示术后门静脉夹角 $<90^\circ$;残余肝内门静脉与门静脉主干直径比 $<45\%$ 是PVT形成的危险因素,这些研究解释了术后门静脉扭曲导致PVT发生,但两者的研究都受限于病例数量,无法得出一致临界值。手术时间越长,肝缺血和门静脉受牵拉的时间越久,也增加了腹腔感染的机会,手术时间超过360~430 min是PVT形成的独立危险因素^[2,13]。有报道^[31]称多次手术增加了腹腔感染的机会,从而导致术后PVT形成。

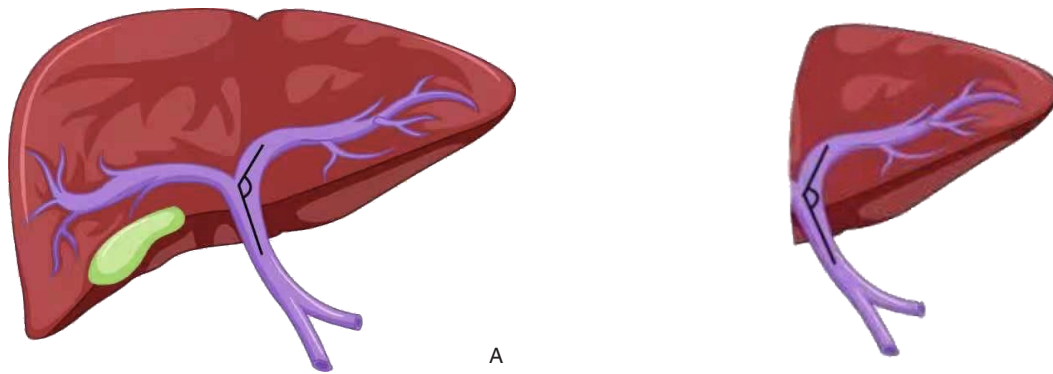


图1 肝切除术前及术后门静脉夹角 A: 术前门静脉夹角; B: 右半肝切除术后门静脉夹角(改画自Cao, 等^[21])

Figure 1 The portal vein angle before and after hepatectomy A: The portal vein angle before surgery; B: The portal vein angle after right hepatectomy (adapted from Cao, et al. ^[21])

2 诊断

肝切除术后PVT平均在术后第7天被发现^[12, 20, 22, 24, 32],患者无任何症状体征或临床表现缺乏特异性,常不能引起临床医生的重视。Kuboki等^[15]总结急性肝切除术后25例PVT患者显示:20.0%无症状,80.0%出现发热,60.0%出现腹痛、腹胀等症状,32.0%的患者出现肝衰竭。Onda等^[2]目前最大样本量的研究发现,肝切除术后42.0%($n=24$)的PVT患者无任何症状,主要由术后影像学检查发现。Takata等^[22]对13例肝切除术后PVT患者的研究显示,62.0%的PVT患者无任何症状,38.0%的患者出现Clavien-Dindo 1~2级与PVT相关的腹水,无Clavien-Dindo 3级以上的并发症。Okuno等^[23]发现肝切除术后100%的PVT患者($n=19$)无任何症状体征,全部由术后第7天腹部增强CT确诊。因此,单纯依靠临床表现诊断PVT不具备可行性。术后D-二聚体明显变化^[8, 15, 22-23]和肝功能指标丙氨酸氨基转移酶(ALT)、天门冬氨酸氨基转移酶(AST)和胆红素等好转过程中突然急剧恶化^[9, 11-12]提示PVT形成,但在某些病例中会有延迟,仅通过实验室检验诊断PVT可能会错失最佳治疗时机。

肝切除术后PVT主要通过影像学检查确诊(图2)。超声对PVT的敏感度为89.0%,特异度为92.0%^[33],但研究发现超声对肝切除术后PVT的诊断易受腹部手术的影响,如肠气的干扰、解剖位置的改变等,其敏感度仅为56%^[15],相比之下,腹部增强CT具有较高的敏感度(90.0%)和特异度(99.0%)^[34],因此在临床高度怀疑PVT而超声检查阴性时,应立即行增强CT检查。超声和CT检查并不能发现所有的PVT,文献^[22]报道即使术后超声或CT未发现PVT,增强CT显示有肝坏死表现,也应按PVT处理。磁共振血管成像受到费用和耗时的限制,不适合应用于术后急性PVT形成检查。门静脉造影是诊断PVT的金标准,现已不作为常规检查,但其可在确诊后同期行溶栓治疗。对于肝癌肝切除术后PVT形成,影像学上须与肿瘤复发导致的门静脉癌栓相鉴别^[35]。为了在肝切除术后尽早诊断PVT, Kuboki等^[15]建议术后每日超声监测门静脉血流直至术后第3天或更久,术后第7天复查腹部增强CT筛查; Onda等^[2, 14]建议肝切除术后第7天常规行增强CT检查以筛查PVT,而不是出现肝功能异常的临床表现后才进行CT检查^[36]。

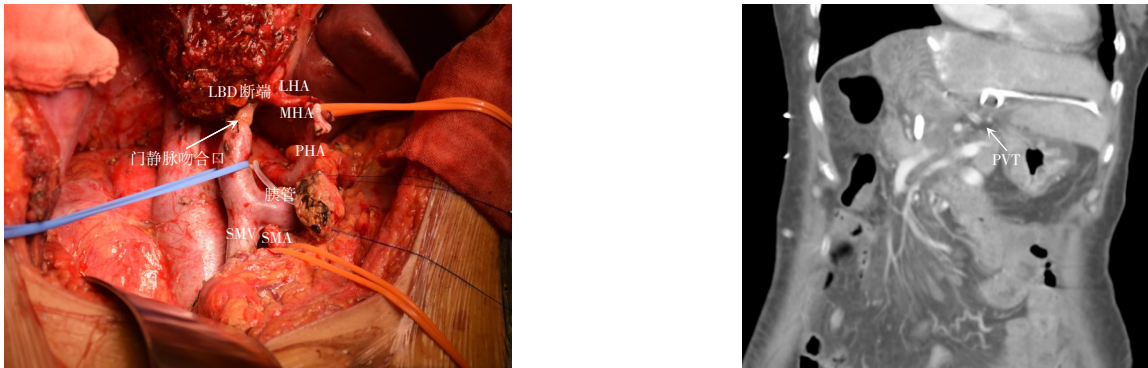


图2 69岁女性肝门部胆管癌患者，行右半肝联合胰十二指肠切除，术中行门静脉重建，术后第9天增强CT提示PVT（图片来自北京清华长庚医院收治的1例急性肝切除术后PVT患者的术中照片和术后CT图像）

Figure 2 A 69-year-old women with hilar cholangiocarcinoma undergoing right hepatectomy and pancreaticoduodenectomy with intraoperative portal vein reconstruction and the Enhanced CT showing PVT (from the intraoperative photos and postoperative CT images of a patient with acute PVT after hepatectomy in Beijing Tsinghua Changgung Hospital)

3 治疗和预后

肝切除术后PVT患者的预后差异很大，从血栓完全消失到血栓沿门静脉系统蔓延直至死亡。在未接受任何治疗的患者自然病程中，48.0%的患者PVT蔓延扩大，可导致肠系膜缺血、肠梗死、脓毒症和消化道大出血而危及生命，45.0%的患者临床症状自发改善，7.0%的患者血栓长期稳定^[14]。肝切除术后PVT的治疗目标为清除血栓、门静脉再通和阻止血栓蔓延，其主要治疗方式包括：抗凝、溶栓和手术等，主要依靠经验进行个体化治疗。总结抗凝治疗对于肝切除术后PVT的再通率和并发症发生率的文献报道（表2），抗凝治疗有较好的有效性和安全性，由于部分再通的门静脉有血栓复发的风险，文献认为抗凝时间至少3个月，对于有血栓形成遗传倾向的患者，抗凝时间至少6个月，甚至需要终身抗凝^[3,37]。但文献中抗凝方案不一，而且小的PVT无需抗凝即可自发消退，这些因素限制了研究结果的可靠性，因此需要更大样本量的研究来验证抗凝治疗的价值。目前尚无肝切除术后PVT溶栓治疗价值及时机方面的研究，肝切除术后PVT的溶栓治疗只见于极少数的病例报道。Kuboki等^[15]比较了抗凝治疗和手术治疗的疗效，对于肝切除术后5d及以内发生的新鲜血栓，手术取栓门静脉再通率显著高于抗凝治疗[100% (n=7) vs. 80.0% (n=4), P=0.013]；但对术后6d及以后发生的血栓，手术取栓效果较差

[50.0% (n=2) vs. 88.9% (n=9), P=0.891]，此时建议首选抗凝治疗。Miyazaki等^[16]的研究同样证实，肝切除术后3d以内比5d以后施行手术能更有效地恢复门静脉血流[83.3% (5/6) vs. 0 (0/3), P<0.02]。血栓机械抽吸和血管球囊扩张也被用于PVT的治疗^[38-39]，Woo等^[40]总结了数例肝移植后使用介入技术（包括溶栓、球囊扩张、机械抽吸等）治疗PVT的病例，提示效果良好，但尚无应用于肝切除术后文献报道。

Han等^[18]提出肝切除术后PVT患者只要没有抗凝禁忌证应立即开始抗凝治疗，对于合并门静脉重建的患者，应先手术取栓，然后抗凝治疗。Onda等^[2]提出了以PVT分类（图3）为导向的新治疗策略，建议门静脉外周和主干1级血栓仅观察即可，门静脉主干2级和肝门部血栓行抗凝治疗，门静脉主干3级血栓行血栓切除术，该治疗策略在其研究中显示较高的血栓清除率（91.0%）。总结目前已有的研究结果，对于肝切除术后早期（3~5d内）发现的门静脉主干完全或接近完全阻塞的PVT患者，多项研究已形成基本共识，即立即手术取栓，结合抗凝和/或溶栓治疗；而对于术后较晚期（3~5d后）发现的患者，一般手术取栓效果不佳，建议采取抗凝、溶栓等治疗方式；门静脉主干未完全阻塞的PVT患者，可暂观察，或结合患者个体情况，选择抗凝、溶栓，对于这一部分患者的治疗，还需进一步探索旨在改善预后的治疗组合和模式。

表2 关于肝切除术后PVT抗凝治疗的文献报道

Table 2 Reports about the anticoagulant therapy for PVT after hepatectomy

文献	抗凝药物	样本量(n)		再通率和时间			出血率(%)		
		抗凝组	对照组	抗凝组	时间	对照组	时间	抗凝组	对照组
Han, 等 ^[18] 2019	低分子肝素、华法林	11	8	100%	未报道	100%	未报道	0	0
Yoshiya, 等 ^[14] 2014	低分子肝素、华法林	9	10	100%	(1.6±0.5)个月	60%	3.0±0.6个月	未报道	未报道
Takata, 等 ^[22] 2021	达那普钠, 华法林、新型口服抗凝剂和AT-III	8	5	100%	2.4(1~5)个月	100%	5.6(4~6)个月	未报道	未报道
Mori, 等 ^[20] 2020	肝素、华法林、抗凝血酶III、达纳肝素和阿司匹林	15	5	80.0%	1年内	100%	1年内	未报道	未报道
Okuno, 等 ^[23] 2021	华法林、新型口服抗凝剂和AT-III	16	3	15例(78.9%) ¹ 血栓在14(3~20)周后消失			未报道	未报道	

注: 1) Okuno 的研究中有 3 例 PVT 形成后未行 CT 随访

Note: 1) Follow-up not obtained in 3 cases with PVT in Okuno's study

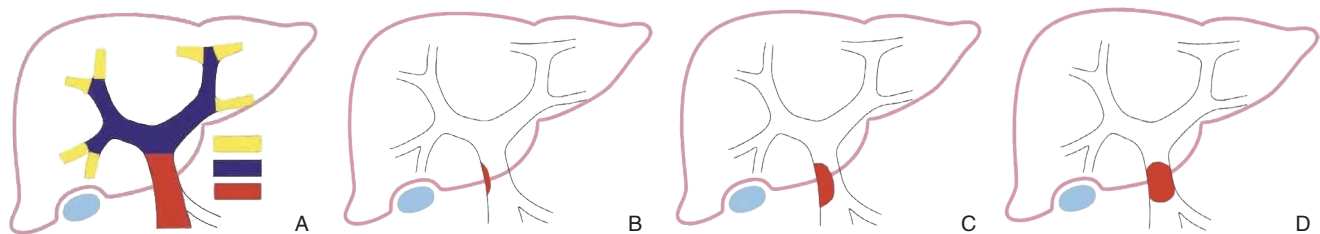


图3 PVT的分类和分级 A: 红色示门静脉主干血栓, 紫色示肝门部PVT, 黄色示外周PVT; B: 门静脉主干1级血栓; C: 门静脉主干2级血栓; D: 门静脉主干3级血栓(改画自Onda, 等^[2])

Figure 3 Classification and grading of PVT A: Red color showing the thrombus in main truck of the portal vein, purple color showing the hilar PVT, and yellow color showing the peripheral PVT; B: Grade 1 thrombus in main truck of the portal vein; C: Grade 2 thrombus in main truck of the portal vein; D: Grade 3 thrombus in main truck of the portal vein (adapted from Onda, et al.^[2])

4 预测和预防

Takata 等^[22]提出肝癌肝切除术后第1天血清凝血酶-抗凝血酶III复合物(thrombin-antithrombin III complex, TAT)水平和第3天D-二聚体水平分别是术前的5.73倍和7.22倍以上时,即可怀疑为PVT。Okuno 等^[23]发现肝切除术后第3天血浆抗凝血酶III(antithrombin III, AT-III)活性 $\leq 60\%$ 预测PVT形成的灵敏度和特异度分别为74%和59%,但预防性补充AT-III对降低术后PVT发生率无显著意义[5.4% ($n=3$) vs. 10.7% ($n=6$), $P=0.489$]。Matsui 等^[17]发现可溶性糖蛋白VI(soluble form of glycoprotein VI, sGPVI)是血小板活化的特异性标志物,血管性假血友病因子(Von Willebrand factor, VWF)和血管性假血友病因子前肽(VWF

propeptide, VWFpp)是血管内皮细胞损伤的标志物,可以通过检测血清sGPVI/血小板的比值和VWF、VWFpp水平来预测肝切除术后PVT形成。

对于存在肝切除术后PVT风险的患者,目前没有公认的预防方案,有研究^[13, 15, 20]认为预防性抗凝、改善术中操作、改进手术器械能降低PVT发生率。预防性抗凝对降低肝切除术后PVT发生率的价值尚存在争议(表3)。Kuboki 等^[15]术中将冗长的门静脉后壁与下腔静脉前壁缝合,以减轻门静脉扭曲,血栓发生率有所降低但差异无统计学意义。Onda 等^[2]提出术中在门静脉周围柔和的拉伸和仔细的解剖可预防PVT形成。Mori 等^[20]发现腹腔镜肝切除术后PVT发生率高,可能与止血器械对门静脉壁的热损伤有关,改用短时间的软凝系统进行止血后,PVT发生率由3.4%下降到1.9%。

表3 肝切除术后预防性抗凝对PVT发生的影响的文献报道

Table 3 Reports about influence of prophylactic anticoagulant therapy on occurrence of PVT after hepatectomy

文献	抗凝药物	样本量(n)		PVT发生率(%)			出血率(%)		
		抗凝组	对照组	抗凝组	对照组	P	抗凝组	对照组	P
Yamashita,等 ^[13] 2014	依诺肝素	53	228	2	10	0.04	1.9	0.4	0.79
Vivarelli,等 ^[25] 2010	那屈肝素钙、依诺肝素钠	157	72	0.63	1.38	0.530	3.18	1.38	0.38
Okuno,等 ^[23] 2021	AT-III	56	56	5.4	10.7	0.489	未报道	未报道	未报道

5 总结

肝切除术后PVT成因复杂,危险因素众多,包括非手术因素(肝硬化、肝细胞癌、高龄)和手术因素(术中频繁的肝门阻断和长时间的肝门阻、合并门静脉重建、右三肝或右半肝切除、大范围肝切除、尾状叶切除、合并脾切除、手术时间长、胆汁漏、合并肝外胆管切除等)。其临床表现无特异性、部分患者无任何临床表现,早期诊断困难,肝切除术后D-二聚体和胆红素等实验室指标有诊断意义,但主要由腹部增强CT确诊。PVT形成后,若不及时干预,发展为肝衰竭等严重并发症的风险高,病死率高。对于肝切除术后PVT,目前尚无明确的防治方案和指南,需要引起肝胆胰外科医生的重视。早发现、早治疗是改善患者预后的关键,关于肝切除术PVT的诊疗还需进一步研究和探索。

利益冲突:所有作者均声明不存在利益冲突。

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