

96例肺腺癌伴发静脉血栓栓塞症危险因素分析

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[摘要] 目的:研究肺腺癌伴发静脉血栓栓塞症(venous thromboembolism, VTE)的危险因素,提高对肺腺癌伴发VTE的认识。方法:回顾分析2012年1月—2016年12月南京医科大学第一附属医院住院的2 930例肺腺癌患者临床资料,发现96例伴发VTE。将伴发VTE肺腺癌患者纳入VTE组,未发生VTE患者纳入非VTE组,对肺腺癌伴发VTE的危险因素进行分析。结果:96例(3.3%)肺腺癌伴发VTE。VTE患者中,男57例,女39例,平均年龄(60.8±10.1)岁;非VTE组中男1 477例,女1 357例,平均年龄(61.0±10.5)岁。两组比较发现,吸烟、中心静脉置管、合并有慢性肺部疾病、肺腺癌分期的差异有统计学意义($P < 0.05$)。多因素 Logistic 回归分析示肺腺癌Ⅲ~Ⅳ期、合并慢性肺部疾病是肺腺癌伴发VTE的高危因素。96例中,单独发生肺血栓栓塞(pulmonary thromboembolism, PTE)26例(27.1%),单独发生深静脉血栓(deep vein thrombosis, DVT)51例(53.1%),同时存在DVT和PTE 19例(19.8%)。45例PTE患者中,37例(82.2%)出现明显临床症状,8例(17.8%)无明显症状。70例DVT患者中,66例(94.3%)表现为患侧肢体肿胀或疼痛。96例中,71例为肺癌治疗后伴发VTE,0~3个月、3~6个月、6~9个月、9~12个月、>12个月VTE发生例数分别为37、8、8、4、14例。截至随访时间,52例(54.17%)死亡,伴发VTE的中位生存时间为5个月。结论:肺腺癌Ⅲ~Ⅳ期、合并有慢性肺部疾病与肺腺癌伴发VTE显著相关。肺腺癌诊断后的前3个月内最容易发生VTE。

[关键词] 肺腺癌;静脉血栓栓塞症;肺血栓栓塞症;深静脉血栓形成

[中图分类号] R563.5

[文献标志码] A

[文章编号] 1007-4368(2018)09-1234-06

doi: 10.7655/NYDXBNS20180913

Analysis of risk factors for 96 cases of pulmonary adenocarcinoma with venous thromboembolism

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[Abstract] **Objective:** To study the risk factors of pulmonary adenocarcinoma with venous thromboembolism (VTE), and to improve the understanding of lung adenocarcinoma with VTE. **Methods:** The clinical data of 2 930 patients with lung adenocarcinoma admitted to the First Affiliated Hospital of NMU from January 2012 to December 2016 were retrospectively analyzed, and 96 cases were found to have VTE. Patients with VTE were included in the VTE group. Patients without VTE were included in the non-VTE group. The risk factors of VTE in lung adenocarcinoma were analyzed. **Results:** Among the 2 930 cases of lung adenocarcinoma, 96 cases/2 930 cases (3.3%) were associated with VTE. In the VTE group, there were 57 males and 39 females, with an average age of (60.8 ± 10.1) years. In the non-VTE group, there were 1 477 males and 1 357 females, the average age was (61.0 ± 10.5) years old. There were significant differences in smoking, central venous catheterization, chronic pulmonary diseases and stage of lung adenocarcinoma between two groups ($P < 0.05$). Multiple factor analysis suggested that the chronic pulmonary disease and Ⅲ~Ⅳ stage of lung adenocarcinoma were high risk factors for lung adenocarcinoma associated with VTE. Of the 96 patients with VTE group, 26 cases (27.1%) occurred in pulmonary thromboembolism (PTE) only, 51 cases (53.1%) occurred in deep vein thrombosis (DVT) only, and 19 cases (19.8%) occurred in PTE and DVT. Among 45 patients with PTE, 37 cases (82.2%) showed obvious clinical symptoms, and 8 cases (17.8%) had no obvious symptoms. Among 70 patients with DVT, 66 cases (94.3%) showed swelling or pain on the affected side. Seventy-one patients in VTE group were accompanied by VTE after treatment of lung cancer. For 0-3 months, 3~6 month, 6-9 months, 9-12 months and >12 months, the number of VTE cases was 37, 8, 8, 4 and 14, respectively. At the end of follow-up, 52 cases/96 cases (54.17%) died, and the median survival time of patients with VTE was 5 months. **Conclusion:** There was a significant correlation between Ⅲ-Ⅳ

[基金项目] 江苏省卫生厅重点项目(H201601);国家科技重大专项(2018ZX10722301-002)

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stage of lung adenocarcinoma, chronic pulmonary disease and lung adenocarcinoma with VTE. VTE was the most likely to occur in the first 3 months of the diagnosis of lung adenocarcinoma.

[Key words] lung adenocarcinoma; venous thromboembolism; pulmonary thromboembolism; deep vein thrombosis

[Acta Univ Med Nanjing, 2018, 38(09): 1234-1239]

静脉血栓栓塞症(venous thromboembolism, VTE)是恶性肿瘤患者常见的并发症之一^[1],也是除肿瘤外的第二大致死原因。VTE的发生可以增加肿瘤患者死亡风险和医疗费用,同时显著降低患者生活质量^[2]。不同类型恶性肿瘤中,VTE的发生率存在差异。胃癌、胰腺癌、肺癌、卵巢癌、恶性淋巴瘤等伴发VTE的风险更高^[3]。目前肺癌仍是我国发病率及病死率最高的恶性肿瘤,其中最常见病理类型是腺癌。因此,加强临床医师对肺腺癌伴发VTE的认识十分必要。本研究回顾分析住院的2 930例肺腺癌患者,了解肺腺癌伴发VTE的危险因素,以提高临床医生对肺腺癌伴发VTE的认识。

1 对象和方法

1.1 对象

收集2012年1月—2016年12月在本院住院的2 930例肺腺癌的患者临床资料,发现其中96例伴发VTE。将伴发VTE患者纳入VTE组,未发生VTE患者纳入非VTE组。

非VTE组纳入标准:①经组织病理学或细胞学确诊的肺腺癌;②初诊肺腺癌;③年龄>18岁;排除标准:①既往发生血栓;②合并其他恶性肿瘤。

VTE组纳入标准:肺腺癌患者通过血管彩色多普勒诊断深静脉血栓形成(deep vein thrombosis, DVT),螺旋CT肺血管造影(computed tomographic pulmonary angiography, CTPA)诊断肺动脉栓塞(pulmonary thromboembolism, PTE)。排除标准:合并其他恶性肿瘤。PTE的诊断参照2014年欧洲心脏病学会《急性肺栓塞诊治指南》^[4]。DVT的诊断参照美国胸科医师学会《静脉血栓栓塞症抗栓治疗指南》第10版^[5]。肺腺癌的临床分期标准参照2017版美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)非小细胞肺癌指南^[6]。

1.2 方法

在本院电子病历系统中以出院诊断为“肺腺癌”“肺癌”“非小细胞肺癌”“支气管肺泡癌”进行搜索。选取肺腺癌并记录患者的性别、年龄、体重指数(body mass index, BMI)、吸烟史、合并疾病、肺癌

分期、表皮生长因子受体(epidermal growth factor receptor, EGFR)突变情况、是否伴发VTE及发生部位。VTE组与非VTE组进行危险因素比较。将单因素分析差异有统计学意义的变量再进行多因素回归分析。记录伴发VTE患者肺癌治疗情况,统计VTE累计发生时间。截至2017年12月,对96例伴发VTE的患者进行电话或门诊随访,收集随访资料。

1.3 统计学方法

本研究运用SPSS 24.0统计学软件处理。计量资料用均数±标准差($\bar{x} \pm s$)表示,组间比较运用 t 检验或秩和检验;计数资料用数值或百分比表示,组间比较运用 χ^2 检验;应用单因素分析评估肺腺癌伴发VTE的相关临床危险因素,将其中 $P \leq 0.05$ 的变量纳入二分类多因素Logistic回归分析(因变量:肺腺癌未发生VTE=0;肺腺癌伴发VTE=1),确定肺腺癌伴发VTE的高危因素;用Kaplan-Meier法绘制生存曲线,Log-rank检验方法进行检验。 $P \leq 0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料比较

VTE组96例,其中男57例,女39例,年龄35~85岁,平均年龄(60.8 ± 10.1)岁;非VTE组2 834例,男1 477例,女1 357例,年龄22~93岁,平均年龄(61.0 ± 10.5)岁。VTE组与非VTE组比较,两组性别、年龄、EGFR基因突变状态差异无统计学意义。吸烟、中心静脉置管、合并有慢性肺部疾病、肺癌分期在两组间差异具有统计学意义($P < 0.05$,表1)。100例肺腺癌患者合并慢性肺部疾病,其中VTE组8例,非VTE组92例,以慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)多见(表2)。

2.2 多因素的Logistic回归分析

将以上单因素分析结果中有统计学差异的变量(吸烟状态、肺癌分期、中心置管、合并肺部慢性疾病)进行多因素的Logistic回归分析(表3、4)。肺腺癌Ⅲ~Ⅳ期(OR: 2.698, 95% CI: 1.579~4.612, $P < 0.001$)、合并有慢性肺部疾病(OR: 2.327, 95% CI: 1.075~5.035, $P=0.032$)与肺腺癌伴发VTE显著相关。

表1 两组患者一般资料比较

Table 1 Comparison of general data between two groups of patients

| 指标 | VTE组 (n=96) | 非VTE组 (n=2 834) | P值 |
|---|-----------------|--------------------|--------|
| 性别[n(%)] | | | 0.161 |
| 男 | 57(59.4) | 1 477(52.1) | |
| 女 | 39(40.6) | 1 357(47.9) | |
| 年龄(岁, $\bar{x} \pm s$) | 60.8 \pm 10.1 | 61.0 \pm 10.5 | 0.902 |
| > 65岁[n(%)] | 30(31.3) | 970(34.2) | 0.545 |
| \leq 65岁[n(%)] | 66(68.8) | 1 864(65.8) | |
| BMI(kg/m ² , $\bar{x} \pm s$) | 24.1 \pm 2.7 | 23.6 \pm 4.8 | 0.934 |
| 吸烟[n(%)] | | | 0.044 |
| 是 | 39(40.6) | 877(31.0) | |
| 否 | 57(59.4) | 1 957(69.1) | |
| 同时合并基础疾病[n(%)] | | | |
| 高血压 | 30(31.3) | 774(27.3) | 0.395 |
| 糖尿病 | 12(12.5) | 266(9.4) | 0.306 |
| 冠心病 | 6(6.3) | 158(5.6) | 0.777 |
| 脑血管疾病 | 6(6.3) | 113(4.0) | 0.269 |
| 心力衰竭 | 2(2.1) | 41(1.4) | 0.610 |
| 肝脏疾病 | 3(3.1) | 34(1.2) | 0.097 |
| 慢性肺部疾病 | 8(8.3) | 92(3.3) | 0.007 |
| 中心静脉置管[n(%)] | 67(69.8) | 1 641(57.9) | 0.020 |
| 化疗[n(%)] | 53(55.2) | 1 800(63.5) | 0.095 |
| 肺癌分期[n(%)] | | | <0.001 |
| I~II | 18(18.8) | 1 171(41.3) | |
| III~IV | 78(81.3) | 1 663(58.7) | |
| EGFR突变[n(%)] | | | 0.393 |
| 阳性 | 27(28.1) | 952(33.6) | |
| 阴性 | 25(26.0) | 693(24.5) | |

2.3 肺腺癌伴发VTE患者的临床特点

96例患者中,单独发生PTE 26例(27.1%),单独发生DVT 51例(53.1%),同时存在DVT和PTE 19例(19.8%),其中1例(1.0%)因D-二聚体明显增高,予以低分子肝素预防抗凝1周,余患者未采用预防性抗凝治疗。45例患者伴发VTE,其中表现为呼吸困难 29例(64.4%),胸痛 5例(11.1%),咯血 1例(2.2%),发热 1例(2.2%),晕厥 1例(2.2%),无明显临床症状 8例(17.8%)。伴发DVT的70例患者中,66例(94.3%)表现为患侧肢体肿胀或疼痛,3例(4.3%)表现为颜面部水肿,1例(1.4%)无明显临床表现。96例VTE患者,住院期间都予以低分子肝素进行急性期抗凝治疗,5例住院治疗期间死亡,2例放弃治疗,89例出院后选择口服抗凝药。25例(26.0%, 25/96)为肺癌治疗前发生VTE,其中7例(28.0%, 7/25)以VTE为首发症状入院;71例(74.0%, 71/96)为肺癌治疗后发现VTE。71例中,12例接受肺癌手术,22例化疗,12例手术+化疗,5例靶向治疗,13例化疗+靶向治疗,5例化疗+放疗,1例手术+靶向治疗,1例手术+化疗+放疗。手术、化疗、手术+化疗组、靶向治疗组间3、6、9、12个月VTE累积发生率差异无统计学意义($\chi^2=1.820, P=0.611$,表5)。

2.4 肺腺癌伴发VTE患者的生存分析

截至随访日期,96例患者中共有52例(54.2%)死亡,失访12例(12.5%),32例(33.3%)存活。伴发VTE的死亡患者,中位生存时间为5个月。死亡患者中,仅发生DVT 23例,仅发生PTE 16例。仅发生

表2 合并慢性肺部疾病的肺腺癌患者的疾病类型

Table 2 Types of chronic lung diseases in patients with lung adenocarcinoma [n(%)]

| 组别 | COPD | 慢性支气管炎 | 肺间质纤维化 | 支气管哮喘 | 支气管扩张 | 肺动脉高压 | 肺结核 |
|-------------|----------|----------|--------|----------|----------|---------|---------|
| VTE组(n=8) | 3(37.5) | 1(12.5) | 0(0.0) | 0(0.0) | 0(0.0) | 2(25.0) | 2(25.0) |
| 非VTE组(n=92) | 43(46.7) | 13(14.1) | 8(8.7) | 11(12.0) | 14(15.2) | 1(1.1) | 2(2.2) |

表3 变量赋值

Table 3 Variable assignment

| 自变量 | 赋值方式 |
|----------|---------------------|
| 吸烟 | 0=否; 1=是 |
| 肺癌分期 | 0= I~II期; 1=III~IV期 |
| 中心静脉置管 | 0=无; 1=有 |
| 合并慢性肺部疾病 | 0=无; 1=有 |

PTE的患者中位生存时间为2个月,明显短于仅发生DVT的患者(8个月,图1)。

3 讨论

恶性肿瘤患者合并VTE约占所有VTE的18.0%,其发生风险是健康人的4~20倍^[7-8]。本研究发现肺腺癌伴发VTE的发生率为3.3%,较其他研究肺腺癌合并VTE的发生率(5.0%~18.6%)低^[9-12],可能与以下因素有关:①本研究中,肺癌分期III~IV患者为59.4%(1 741/2 930),较其他研究晚期肺癌(70.0%)比例低^[9],接受放化疗治疗少;②还可能与

表4 肺腺癌伴发VTE危险因素Logistic回归分析

Table 4 Logistic regression analysis of VTE risk factors associated with lung adenocarcinoma

| 影响因素 | B | 标准误差 | P值 | OR(95%CI) |
|----------|-------|-------|--------|--------------------|
| 吸烟 | 0.238 | 0.218 | 0.274 | 1.269(0.828~1.944) |
| 肺癌Ⅲ~Ⅳ期 | 0.993 | 0.273 | <0.001 | 2.698(1.579~4.612) |
| 中心静脉置管 | 0.256 | 0.234 | 0.274 | 1.292(0.816~2.046) |
| 合并慢性肺部疾病 | 0.844 | 0.394 | 0.032 | 2.327(1.075~5.035) |

表5 治疗方案与VTE发生时间

Table 5 Treatment plan and the time of VTE occurred

| 时间 | 例数 | 手术 | 化疗 | 手术+化疗 | 靶向治疗 |
|--------|-----------|-----------|-----------|-----------|----------|
| 0~3个月 | 37(52.1) | 9(75.0) | 13(59.1) | 6(50.0) | 3(60.0) |
| 3~6个月 | 8(11.3) | 0(0.0) | 3(13.6) | 2(16.7) | 0(0.0) |
| 6~9个月 | 8(11.3) | 1(8.3) | 2(9.1) | 2(16.7) | 1(20.0) |
| 9~12个月 | 4(5.6) | 0(0.0) | 2(9.1) | 0(0.0) | 0(0.0) |
| >12个月 | 14(19.7) | 2(16.7) | 2(9.1) | 2(16.7) | 1(20.0) |
| 合计 | 71(100.0) | 12(100.0) | 22(100.0) | 12(100.0) | 5(100.0) |

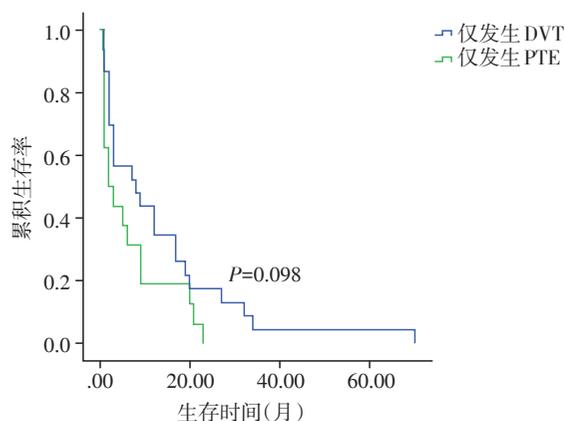


图1 死亡患者中仅发生PTE组(16例)与仅发生DVT组(23例)的生存曲线

Figure 1 Survival curves of patients with PTE alone (16 cases) and DVT alone (23 cases)

亚裔人种合并VTE的发病率较欧美国家低,与基因易感差异性有关^[11]。

本研究单因素分析发现吸烟、中心静脉置管、肺癌Ⅲ~Ⅳ期、合并慢性肺部疾病与肺腺癌伴发VTE相关($P < 0.05$)。Logistic多因素回归分析中肺癌Ⅲ~Ⅳ期、合并慢性肺部疾病与肺腺癌伴发VTE显著相关。其他研究发现肺癌伴发VTE的危险因素还包括:化疗、放疗、D-二聚体 ≥ 0.50 mg/L等^[8,13-14]。本研究中吸烟患者更容易伴发VTE($P < 0.05$)。Pomp等^[15]研究发现吸烟患者伴发VTE的风险是非吸烟患者的1~2倍,其机制可能是吸烟引起血管内皮损伤和纤维蛋白原(fibrinogen, FIB)水平增高,导致血

液黏稠。本研究中,VTE组中心静脉置管比例(69.8%)高于非VTE组(57.9%)($P < 0.05$),与文献报道中心静脉置管可增加相关血栓风险相符^[16]。

多因素分析发现晚期肺癌是伴发VTE的高危因素。本研究中,I~II期患者VTE发生率为1.5%(18/1189),Ⅲ~Ⅳ期患者发生率为4.5%(78/1741),晚期肺癌更容易发生VTE,与先前研究结果一致^[10]。这与晚期肺癌患者促凝血物质(组织因子等)增多^[17],同时接受放疗等损伤血管内皮有关。本研究发现肺腺癌合并慢性肺部疾病中,以COPD最为多见,并且合并慢性肺部疾病(包括COPD、慢性支气管炎、肺纤维化等)是肺腺癌伴发VTE的高危因素,可能与以下原因有关:①由于肺部基础疾病导致部分患者的肺功能难以耐受手术,丧失手术根治机会,从而晚期肺癌数量增多,VTE的发生事件增多;②部分患者肺功能受损,活动耐量下降,卧床时间增加,更易导致血流瘀滞,增加DVT发生风险^[16];③患有肺部基础疾病,例如COPD,容易急性发作合并感染,增加VTE发生风险^[18]。

对96例患者研究发现,性别、年龄和EGFR突变状态与VTE无关。Walker等^[12]研究发现老年患者伴发VTE的风险呈下降趋势($P=0.016$),而王燕玲等^[19]研究中年龄 ≥ 65 岁是肺癌伴发VTE的危险因素,这可能与研究样本大小、临床特点及地区差异有关。Davidsson等^[20]报道,患有EGFR突变的肺腺癌患者的VTE风险更低。本研究中VTE和非VTE组EGFR突变情况差异无统计学意义,可能与本研

究中突变患者数量少有关。由于中国人非小细胞肺癌患者EGFR突变率较高^[21],可行大样本前瞻性研究进一步探讨基因突变状态与VTE发生率间的关系。本研究VTE和非VTE组化疗患者比例差异无统计学意义,可能由于VTE组中,25例VTE是发生在肺癌治疗之前,未接受相关治疗,使得两组间差异减少。

VTE为肺癌的常见并发症,亦可成为肺癌的驱表现,影响患者生存时间^[22]。本研究中,7例是以VTE为首发症状入院,对于突发VTE的患者应同时注重恶性肿瘤的排查。94.3%(66/70)伴有DVT患者以患侧肢体疼痛及红肿多见。在伴发PTE患者中,有17.8%(8/45)无明显症状,为检查过程中发现,存在漏诊可能,症状性PTE患者主要表现为呼吸困难(64.4%)和胸痛(11.1%),以上表现易与肺炎、胸腔积液和肿瘤进展造成的呼吸困难及肿瘤骨转移、神经侵犯所致的胸痛混淆,所以对于具有高风险的PTE患者更需要临床医生提高警惕,加以甄别。DVT是VTE最常见的首发症状。96例患者中,单独发生PTE 26例(27.1%),单独发生DVT 51例(53.1%),同时发现DVT和PTE 19例(19.8%)。71例(74.0%)患者为肺癌治疗后伴发VTE,其中超过半数的肺腺癌患者是在肺癌治疗的前3个月内发生VTE,与既往研究一致^[23]。本研究中,不同治疗方式下,VTE的累积发生率差异无统计学意义($P < 0.05$),由于本研究治疗例数少,仍需扩大样本量探讨其关系。

本研究中,52例(54.2%)患者死亡,合并VTE的中位生存时间为5个月。其中单独发生PTE的患者中位生存时间明显短于单独发生DVT的患者,与既往研究结果(56 d vs. 156 d)相似^[24]。本研究中两组间生存时间无差异($P=0.098$),考虑在单独伴发DVT的23例患者中,有3例由于肿瘤进展,在血栓发生后的30 d内死亡,造成DVT与PTE组间差异无统计学意义。

本研究探讨了肺腺癌伴发VTE的危险因素,发现吸烟、中心静脉置管、肺腺癌Ⅲ~Ⅳ期、慢性肺部疾病是肺腺癌伴发VTE的相关危险因素,其中肺腺癌Ⅲ~Ⅳ期、合并慢性肺部疾病与肺腺癌伴发VTE更为重要。VTE多出现在肺癌治疗后的前3个月,伴发VTE患者病死率高。因此,对于具有高危因素的肺腺癌患者要随时警惕VTE的发生,减少患者病死率,改善患者预后。

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