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肾癌患者凝血指标的临床分析*

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摘要 目的:探讨肾癌患者异常增高的凝血指标、静脉血栓栓塞症(VTE)发生率与临床分期的关系,分析肾癌患者血液高凝状态的临床特征。**方法:**对2010年至2012年335例住院的肾癌患者Fib、D-D、BPC水平进行检测并筛查发生VTE的患者。**结果:**335例肾癌患者中,异常Fib、D-D、BPC的发生率分别为20.6%、9.9%、6.6%,且随着肾癌分期的增加,凝血指标异常的发生率逐渐升高,各分期之间比较有统计学差异($P<0.05$);VTE的发生率为2.2%,Ⅳ期肾癌患者最高为1.2%,且各分期之间比较有统计学意义($P<0.05$)。年龄 ≥ 60 岁、肿瘤最大径 >10 cm、临床分期晚、伴有远处转移的肾癌患者血液高凝的发生率分别显著高于年龄 <60 岁、肿瘤最大径 <10 cm、临床分期早、不伴有远处转移的肾癌患者($P<0.05$)。**结论:**年龄 ≥ 60 岁、肿瘤最大径 >10 cm、临床分期晚、伴有远处转移可能是肾癌患者发生血液高凝状态和VTE的危险因素,应引起临床重视。

关键词:肾癌;高凝状态;静脉血栓栓塞症;临床特征

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Clinical Analysis of Coagulation Indexes in Renal Cell Carcinoma Patients*

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ABSTRACT Objective: To investigate the relationship between abnormal coagulation indexes, incidence rate of venous thromboembolism (VTE) and clinical stages of RCC patients and analyze the clinical features of RCC patients in hypercoagulable state. **Methods:** The coagulation index (Fib, D-D, BPC) of 355 RCC patients admitted from January 2010 to March 2012 in our hospital were detected and the incidence of VTE was analyzed. **Results:** In 355 RCC patients, Fib, D-D, and BPC were abnormally high, the incidence rates of abnormally high Fib, D-D, and BPC levels were respectively 20.6%, 9.9%, and 6.6%. With the increase of stage, the incidence rate of abnormal coagulation indexes also significantly increased ($P<0.05$). The incidence of VTE was 2.2%, which was 1.2% of patients at Stage IV, and there was statistical difference between different stages ($P<0.05$). The incidence rates of hypercoagulability in RCC patients with age ≥ 60 years, tumor size > 10 cm, advanced stage, distant metastasis metastases were significantly higher than those RCC patients with aged <60 years, tumor size <10 cm, early stage and without distant metastasis($P<0.05$). **Conclusion:** Age ≥ 60 years, tumor size > 10 cm, advanced stage, and distant metastasis may be the risk factors which lead to hypercoagulability and VTE in RCC patients and should be paid attention to.

Key words: Renal cell carcinoma; Hypercoagulable state; Venous thromboembolism(VTE); Clinical features

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前言

相关文献报道,恶性肿瘤患者尤其是晚期患者具有一项或一项以上凝血指标异常的约占95%^[1],恶性肿瘤患者合并血液高凝状态易导致静脉血栓栓塞症(venous thromboembolism, VTE)发生,约4%~12%的VTE患者确诊时发现伴随恶性肿瘤^[2]。因此,早期发现血液高凝状态对于防止肿瘤患者并发血栓性疾病具有重要意义。迄今为止,有关肾癌患者血液高凝状态的系统研究较少。本研究通过回顾性分析肾癌患者的临床和随访资料,旨在探讨肾癌患者凝血指标的变化、VTE的发生率及其临床特征,为肾癌患者的临床诊治提供参考依据。

1 资料与方法

1.1 一般资料

2010年01月至2012年3月哈尔滨医科大学附属肿瘤医院经手术后病理确诊的肾细胞癌患者335例,其中男性186例,女性149例;年龄范围19~81岁,平均年龄53.40岁。根据2004年世界卫生组织(World Health Organization, WHO)肾细胞癌病理分类标准:肾透明细胞癌284例,乳头状肾细胞癌16例,透明细胞癌伴肉瘤样变6例,肾嫌色细胞癌11例,肾Bellini集合管癌5例,囊性肾细胞癌11例,未分类癌2例。据PET-CT、增强CT和MRI、骨ECT、胸部正侧位片、胸部CT及手术患者的病理结果及手术记录进行分期,采用2009年美国癌症联合委员会(American Joint Committee on Cancer, AJCC)的TNM分期标准:I期211例、II期48例、III期45例、IV期31

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例。治疗方法:以手术治疗为主,其中接受根治性肾癌切除术 278 例,接受保留肾单位的肾癌切除术 35 例。排除标准:血液系统疾病、血栓栓塞性疾病、近期使用抗凝或抗血小板治疗、急慢性炎症反应、既往恶性肿瘤病史,无法界定是否有转移的患者。

1.2 VTE 的诊断

患者就诊过程中 D-二聚体(D-D)值如在正常范围内,可首先排除 VTE。根据 VTE 的临床表现出临床诊断,并行影像学检查进一步证实。下肢深静脉血栓(DVT)表现为下肢疼痛、麻木、皮肤颜色变化等,行下肢彩色多普勒超声检查确诊。肺栓塞(PTE)患者可出现呼吸困难、胸闷、胸痛等,行胸部 CT 或肺动脉造影确诊。

1.3 血液标本采集、测定、凝血指标参考范围及评价标准

1.3.1 凝血指标测定 采集患者术前空腹静脉血 2.7 mL 加入含有固定抗凝剂枸橼酸钠 0.3 mL 的采血管中,2 小时内用日本 Sysmex CA-1500 全自动凝血纤溶分析仪及其配套实际测定纤维蛋白原(Fib)、D-二聚体(D-D)、血小板计数(BPC)。

1.3.2 凝血指标参考范围及评价标准 根据我院化验指标参考范围:Fib:2~4 g/L,D-D:0~0.55 mg/L,BPC:100×10⁹/L~300×10⁹/L。上述三个凝血指标任何一个指标大于参考范围上限值我们认为肾癌患者为血液高凝状态,且将高纤维蛋白原血

症定义为:Fib>44.0 g/L。

1.4 统计学分析

统计数据采用 SPSS17.0 统计软件,计数资料采用 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 肾癌患者凝血指标异常增高的发生率

在 335 例肾癌患者中,Fib 值 (4.07 ± 1.15) g/L,D-D 值 (1.26 ± 0.85) mg/L,BPC(366.5 ± 25.6)×10⁹/L。Fib、D-D、BPC 异常增高的病人例数分别为 69、33、22 例,发生率分别为 20.6%、9.9%、6.6%,其中高纤维蛋白血症 18 例,发生率为 5.4%,见图 1。I、II、III、IV 期肾癌患者凝血指标异常增高的发生例数分别为 10、12、18、22 例,VTE 发生率分别为 2.82%、3.38%、5.07%、6.2%,且各分期之间比较差异有统计学意义($P<0.05$),见表 1。

2.2 肾癌患者 VTE 的发生率

335 例肾癌患者中,I、II、III、IV 期 VTE 的发生例数分别为 1、2、1、4 例,VTE 在各分期中的发生率分别为 0.5%、4.2%、2.2%、12.9%,且各分期之间比较有统计学意义($P<0.05$)。

2.3 肾癌患者血液高凝状态的临床特征分析

335 例肾癌患者血液高凝状态的临床特征分析,见表 1。

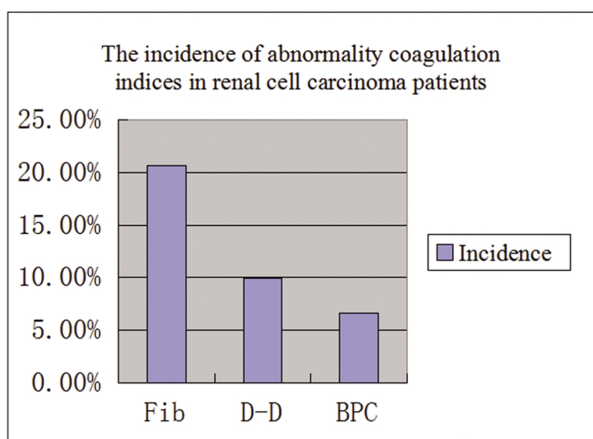


图 1 肾癌患者凝血指标异常增高的发生率

Fig. 1 The incidence rate of abnormal increase of coagulation indexes in renal cell carcinoma patients

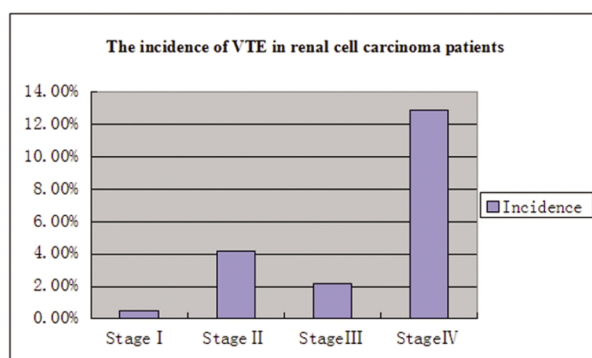


图 2 各期肾癌患者 VTE 的发生率

Fig. 2 The incidence rate of VTE in renal cell carcinoma patients at different stages

表 1 肾癌患者血液高凝状态的临床特征分析

Table 1 The analysis of clinical characteristics of renal cell carcinoma patients in hypercoagulable state

Clinical characteristics	n	Renal cell carcinoma patients in hypercoagulable state		P value
		n	Abnormal coagulation indexes percentage(%)	
Age				
≥ 60 years old	124	42	12.54	P< 0.05
< 60 years old	211	37	11.04	
Gender				
Male	186	41	12.24	P> 0.05
Female	14*	38	11.34	
Maximum tumor diameter(cm)				
>10 cm	197	56	16.72	P< 0.05
7 cm-10 cm	138	23	6.87	

Clinical stage				
I	231	10	2.99	P<0.05
II	48	12	3.58	
III	45	18	5.37	
IV	31	22	6.57	
Metastasis				
Yes	31	22	6.57	P<0.05
No	304	31	9.25	

3 讨论

血液高凝状态是肾癌常见的副肿瘤综合征之一,近年来逐渐受到重视。本研究通过 Fib、D-D、BPC 三项结果分析肾癌患者血液的高凝状态,结果显示 Fib、D-D、BPC 三者在肾癌患者中均有异常增高,且随着临床分期增加发生率也显著增高,Fib 异常增高发生率最高,为 20.6%。研究表明,Fib 与恶性肿瘤的关系如下:1)恶性肿瘤细胞浸润、转移、破坏使大量促凝物质入血,导致 Fib 转化成纤维蛋白,血浆 Fib 水平升高可导致凝血紊乱,促进肿瘤转移^[3];2)恶性肿瘤患者 Fib 及其降解产物的血浆含量增高,增强了血小板对癌细胞的黏附利于癌细胞转移^[4,5];3)Fib 可构成瘤核的基质保护肿瘤细胞不被自身抗体、化疗药物、免疫细胞等的杀伤。肾癌患者血浆 Fib 异常增高的发生率较高,且 Fib 水平的变化与肾癌的转移、临床分期密切相关^[6,7],检测肾癌患者的 Fib 水平可能对于辅助诊断血栓性并发症、判断肿瘤是否转移、评估预后均有一定的临床意义。国外也有研究认为肾癌患者的血清 Fib 水平为理想的肾癌标记物,其水平变化与肾癌分期及生物学行为相关^[8-11]。通过降低肾癌患者的血浆 Fib 水平,改善患者血液的高凝状态,可能是防治肾癌的重要措施之一。目前,临床上已有学者开始使用抗凝药物预防肿瘤转移^[12,13],但对于肾癌的临床试验尚未开展。此外,D-D、BPC 也与恶性肿瘤如肺癌、胃癌、肝癌有着密切关系^[14],其检测结果可对疾病疗效观察及预后分析提供依据,但与肾癌的研究需进一步探讨。

恶性肿瘤易导致凝血指标的异常,促进 VTE 的发生,给患者带来严重的后果,但临床医生目前重视不足。VTE 是恶性肿瘤的严重并发症之一,有研究发现 VTE 的发生率与恶性肿瘤的临床分期有关,远处转移的肿瘤患者 VTE 的发生率明显高于局限者^[15]。本研究中,肾癌患者 VTE 的总体发生率较低,但 IV 期肾癌患者 VTE 的发生率较其他分期肾癌患者明显增高,且经统计学比较,各分期肾癌之间比较有统计学意义 ($P<0.05$),这与上述观点一致。因此,临床上通过监测高分期肾癌患者的凝血指标,可能对于防治 VTE 有一定的指导意义。

本研究结果显示,肾癌患者血液高凝状态的临床特征包括年龄 ≥ 60 岁、肿瘤最大径 >10 cm、临床分期晚、伴有远处转移,可能是导致肾癌患者血液高凝状态的原因。高龄本身就是促血栓形成的高危因素,高龄患者运动量的减少、肿瘤压迫、长期卧床等可使血流减慢,易促发凝血级联反应导致凝血功能改变。肿瘤较大、临床分期晚、伴有远处转移对肿瘤凝血功能的影响可能是肿瘤自身的特点所决定,这些因素可能与肿瘤长期发生、发展及转移有关。高龄和肿瘤自身因素可能共同作用促进肾癌患者血液高凝状态的发生。

综上所述,肾癌患者伴凝血指标异常增高并不罕见,尤其是高分期肾癌患者凝血指标异常增高的发生率更高,VTE 发生率有着同样的规律。因此,监测凝血指标水平和抗凝治疗可能对防治 VTE、延长肾癌患者的生存期有益。此外,年龄 ≥ 60 岁、肿瘤最大径 >10 cm、临床分期晚、伴有远处转移,可能是导致肾癌患者血液高凝状态的危险因素,应引起临床重视。

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