doi: 10.13241/j.cnki.pmb.2015.07.029

肾癌患者凝血指标的临床分析 *

王志超 戴洪双 丁德鑫 王文涛 乔忠杰△

（哈尔滨医科大学附属第三医院泌尿外科 黑龙江 哈尔滨 150081）

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

中图分类号:R737.11 **文献标识码:**A **文章编号:**1673-6273(2015)07-1310-03

Clinical Analysis of Coagulation Indexes in Renal Cell Carcinoma Patients*

WANG Zhi-chao, DAI Hong-shuang, DING De-xin, WANG Wen-tao, QIAO Zhong-jie△

(Department of Urology, The Third Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, 150081, China)

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 deteced 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

Chinese Library Classification(CLC): R737.11 Document code: A

Article ID: 1673-6273(2015)07-1310-03

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 (vascular 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

* 基金项目:黑龙江省自然科学基金项目(D200659);黑龙江省卫生厅科研课题(2006-185)

作者简介:王志超(1987-),男,硕士研究生,主要从事泌尿系肿瘤的研究

△通讯作者:乔忠杰,E-mail:zhongjieqiao@hotmail.com

(收稿日期:2014-07-18 接受日期:2014-08-13)

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的临床表现作出临床诊断,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:100×10^9/L～300×10^9/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x^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)×10^9/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。

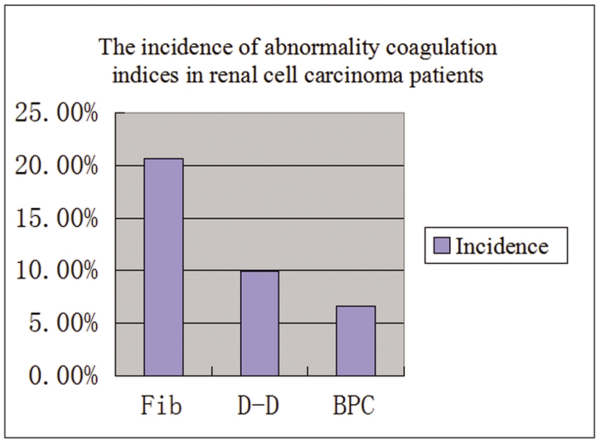

图1 肾癌患者凝血指标异常增高的发生率

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

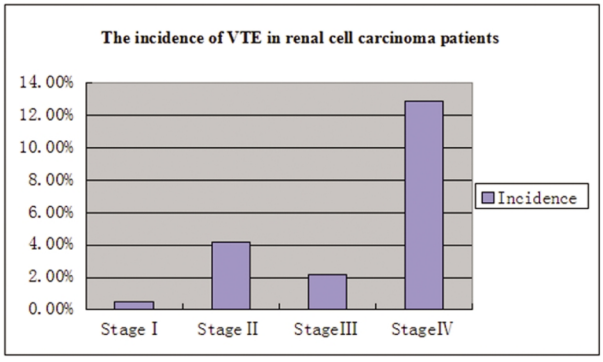

图2 各期肾癌患者VTE的发生率

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。

参 考 文 献（References）

[1] 曹勇军, 钱进军, 刘春风. 纤维蛋白(原)、纤维蛋白(原)降解产物基序拮抗剂与动脉粥样硬化 [J]. 国际脑血管病杂志, 2006, 14(4): 290-293
Cao Yong-jun, Qian Jin-jun, Liu Chun-feng. Fibrin (ogen), Its degradation products and their motif antagonist and atherosclerosis [J]. International Journal of Cerebrovascular Diseases, 2006, 14(4): 290-293

[2] Sorensen HT, Svaerke C, Farkas DK, et al. Superficial and deep venous thrombosis, pulmonary embolism and subsequent risk of cancer [J]. Eur J Cancer, 2012, 48(4): 586-593

[3] 樊锡凤, 冯忠军, 赵文军, 等. 恶性肿瘤患者检测血浆纤维蛋白原的临床意义[J]. 河北医科大学学报, 2005, 26(3): 215-216
Fan Xi-feng, Feng Zhong-jun, Zhao Wen-jun, et al. Clinical significance of detecting serum fibrinogen in patients with carcinoma [J]. Journal of Hebei Medical University, 2005, 26(3): 215-216

[4] 朱武凌, 范秉琳. 肝癌患者高纤维蛋白原血症及其原因分析 [J]. 中华血液杂志, 2004, 25(3): 180
Zhu Wu-ling, Fan Bing-lin. Hyperfibrinogenemia and its etiology analysis in patients with hepatocarcinoma [J]. Chinese Journal of Hematology, 2004, 25(3): 180

[5] 肖博, 马潞林, 黄毅, 等. 肾癌患者凝血功能与肿瘤分期及转移的关系[J]. 中华泌尿外科杂志, 2010, 31(12): 806-809
Xiao Bo, Ma Lu-lin, Hu Yi, et al. Correlation of coagulation function to tumor stage and metastasis status in patients with renal cell carcinoma[J]. Chin J Urol, 2010, 31(12): 806-809

[6] 雪来提·派祖拉, 哈木拉提·吐送, 王文光, 等. 凝血功能与肾癌肿瘤分期转移的相关性研究[J]. 现代泌尿科杂志, 2013, 18(4): 362-364
Xue Lai Ti·Pai Zu La, Ha Mu La ti·Tu Song, Wang Wen-guang, et al. Correlation of coagulation function with tumor stage and metastasis status in patients with renal cell carcinoma [J]. J Mod Urol, 2013, 18(4): 362-364

[7] Yamashita H, Kitayama J, Nagawa H, et al. Hyperfibrinogenemia is a useful predictor for lymphatic metastasis in human gastric cancer[J]. Jpn J Clin Oncol, 2005, 35(10): 595-600

[8] Xiao B, Ma LL, Zhang SD, et al. Correlation between coagu1ation function, tumor stage and metastasis in patients with renal cell carcinoma a retrospective study [J]. Chin Med J (Engl), 2011, 124(8): 1205-1208

（下转第 1364 页）

[2] Drel VR, Pacher P, Ali TK, et al. Aldose reductase inhibitor fidarestat counteracts diabetes-associated cataract formation, retinal oxidative-nitrosative stress, glial activation, and apoptosis [J]. Int J Mol Med, 2008, 21(6): 667-676

[3] Kador PF, Betts D, Wyman M, et al. Effects of top- ical administration of an aldose reductase inhibitor on cataract formation in dogs fed a diet high in galactose[J]. Am J Vet Res, 2006, 67(10): 1783-1787

[4] 崔金丽,徐国兴,陈瑞庆. 糖尿病性白内障发病机制的研究进展[J]. 国际眼科杂志, 2012, 12(2): 246-248
Cui Jin-li, Xu Guo-xing, Chen rui-qing. Research progress in pathogenesis of diabetic cataract[J]. Guoji Yanke Zazhi (Int Eye Sci), 2012, 12(2): 246-248

[5] Hamada Y, Nakashima E, Naruse K, et al. A copper chelating agent suppresses carbonyl stress in diabetic rat lenses [J]. J Diabetes Complications, 2005, 19(6): 328-334

[6] Ranjan M, Nayak S, Rao BS. Immunochemical detection of glycated beta- and gamma-crystallins in lens and their circulating autoantibodies (IgG) in streptozocin induced diabetic rat [J]. Mol Vis, 2006, 12: 1077-1085

[7] Kim YS, Kim NH, Lee SW, et al. Effect of protocatechualdehyde on receptor for advanced glycation end products and TGF-beta1 expression in human lens epithelial cells cultured under diabetic conditions and on lens opacity in streptozotocin-diabetic rats [J]. Eur J Pharmacol, 2007, 569(3): 171-179

[8] Zhang J, Yan H, Harding JJ, et al. Identification of the primary targets of carbamylation in bovine lens proteins by mass spectrometry [J]. Curr Eye Res, 2008, 33(11):963-976

[9] Obrosova IG. Increased sorbitol pathway activity generates oxidative stress in tissue sites for diabetic complications [J]. Antioxid Redox Signal, 2005, 7(11-12): 1543-1552

[10] Obrosova IG, Fathallah L. Evaluation of an aldose reductase inhibitor on lens metabolism, ATPases and antioxidative defense in streptozotocin-diabetic rats: an intervention study [J]. Diabetologia, 2000, 43 (8): 1048-1055

[11] Lou MF. Redox regulation in the lens [J]. Prog Retin Eye Res, 2003, 22(5): 657-682

[12] Qiao F, Xing K, Lou MF. Modulation of lens glycolytic pathway by thioltransferase[J]. Exp Eye Res, 2000, 70(6): 745-753

[13] Kyselova Z, Gajdosik A, Gajdosikova A, et al. Effect of the pyridoindole antioxidant stobadine on development of experimental diabetic cataract and on lens protein oxidation in rats: comparison with vitamin E and BHT[J]. Mol Vis, 2005, 11: 56-65

[14] Srivastava SK, Yadav U, Reddy A. Aldose Reductase Inhibition Suppresses Oxidative Stress Induced Inflammatory Disorders [J]. Chem Biol Interact, 2011, 191(1-3): 330-338

[15] Oates PJ. Aldose reductase, still a compelling target for diabetic neuropathy[J]. Curr Drug Targets, 2008, 9(1): 14-36

[16] Drel VR, Pacher P, Ali TK, et al. Aldose reductase inhibitor fidarestat counteracts diabetes-associated cataract formation, retinal oxidative-nitrosative stress, glial activation, and apoptosis [J]. Int J Mol Med, 2008, 21(6): 667-676

[17] Nambu H, Kubo E, Takamura Y, et al. Attenuation of aldose reductase gene suppresses high-glucose-induced apoptosis and oxidative stress in rat lens epithelial cells [J]. Diabetes Res Clin Pract, 2008, 82 (1): 18-24

[18] Biswas S, Harris F, Singh J, et al. Role of calpains in diabetes mellitus-induced cataractogenesis: a mini review [J]. MolCell Biochem, 2004, 261(1-2): 151-159

[19] Ettl A, Daxer A, Gottinger W, et al. Inhibition of experimental diabetic cataract by topical administration of RS-verapamil hydrochloride[J]. Br J Ophthalmol, 2004, 88(1): 44-47

[20] Obrosova IG, Kador PF. Aldose reductase / polyol inhibitors for diabetic retinopathy[J]. Curr Pharm Biotechnol, 2011, 12(3):373-385

[21] Ramunno A, Cosconati S, Sartini S, et al. Progresses in the pursuit of aldose reductase inhibitors: the structure-based lead optimization step [J]. Eur J Med Chem, 2012, 51:216-226

(上接第 1312 页)

[9] Du J, Zheng JH, Chen XS, et al. High preoperative plasma fibrinogen is an independent predictor of distant metastasis and poor prognosis in renal cell carcinoma [J]. Int J Clin Oncol, 2013, 18(3): 517-23

[10] Tsimafeyeu IV, Demidov LV, Madzhuge AV, et al. Hypercoagulability as a prognostic factor for survival in patients with metastatic renal cell carcinoma[J]. J Exp Clin Cancer Res, 2009, 28: 30

[11] Verheul HM, Vaner K, Homs MY, et al. The relationship of vascular endothelial growth factor and coagulation factor (fibrin and fibrinogen)expression in clear cell renal cell carcinoma [J]. Urology, 2010, 75(3): 608-614

[12] Rickles FR. Mechanisms of cancer-induced thrombosis in cancer[J]. Pathophysiol Haemost Thromb, 2006, 35(1-2): 103-110

[13] Mousa SA, Petersen LJ. Anti-cancer properties of low-molecular-weight heparin: preclinical evidence [J]. Thromb Haemost, 2009, 15 (2): 258-267

[14] 戴庆忠, 谭瑜. 恶性肿瘤患者凝血指标检测的临床意义[J]. 检验医学与临床, 2009, 3(5): 347-348
Dai Qing-zhong, Tan Yu. Clinical significance of hemagglutination index detection in patients with malignant tumor [J]. Lab Med Clin, 2009, 3(5): 347-348

[15] Wun T, White R H. Epidemiology of cancer related venous thromboembolism [J]. Best Pract Res Clin Haemtol, 2009, 22(1): S3-16