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肿瘤患者静脉血栓栓塞症的风险评估模型及其应用

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• 综　述 •

肿瘤患者静脉血栓栓塞症的风险评估模型及其应用

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Risk Assessment Models of Venous Thromboembolism for Cancer Patients and Their Applications

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Abstract: Venous thromboembolism (VTE) is a common complication and death cause of cancer patients. Some studies have shown that effective VTE risk assessment model and appropriate preventive anticoagulation therapy can reduce the risk of thrombosis in cancer patients. But before patients start preventive anticoagulant treatment, they need an effective VTE risk assessment model to carry out VTE risk stratification. For the high-risk group of VTE patients, preventive anticoagulation should be carried out after eliminating the contraindications of anticoagulation. However, tumor diseases have complexity, different pathological types and stages are with different risks and characteristics of VTE. The current VTE risk assessment models for cancer patients are still limited. This paper mainly reviews the current situation and application of VTE risk assessment model for cancer patients.

Key words: Risk assessment model; Venous thromboembolism; Cancer; Thrombosis prevention

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摘　要：静脉血栓栓塞症（VTE）是肿瘤患者常见的并发症和死亡原因。多项研究显示，有效的VTE风险评估模型和恰当的预防性抗凝治疗可以降低肿瘤患者的血栓发生风险。但哪些肿瘤患者需要进行预防性抗凝治疗，需要有效的VTE风险评估模型，对肿瘤患者进行VTE风险分层。对血栓高危人群，在排除抗凝禁忌证后进行预防性抗凝。但肿瘤疾病存在复杂性，不同的病理类型和分期，VTE风险和特点不同，而目前专门针对肿瘤患者的VTE风险评估模型仍然有限，本文将对肿瘤患者的VTE风险评估模型的现状及其应用进行综述。

关键词：风险评估模型；静脉血栓栓塞症；肿瘤；血栓预防

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0　引言

静脉血栓栓塞症（venous thromboembolism, VTE）包括肺栓塞和深静脉血栓，是肿瘤患者常见的并发症[1-2]。首次发生VTE的病例中20%~30%与肿瘤相关[3]。VTE的发生提示肿瘤患者的预后较差，VTE是肿瘤患者第二大死亡原因[4]。因此，VTE的预防得到越来越多的关注。预防性抗凝治疗可以降低肿瘤患者VTE的发生风险，但并不是所有的肿瘤患者都需要进行预防性抗凝治疗。哪些肿瘤患者需要进行预防性抗凝治疗，需要应用有效的VTE风险评估模型对肿瘤患者进行风险分层，对其中的血栓高危人群，在排除抗凝禁忌后进行预防性抗凝。但肿瘤疾病存在复杂性，手术患者和非手术患者、不同的病理类型和分期、不同的抗肿瘤治疗方案、住院化疗患者和门诊化疗患者的VTE的发生风险和发生特点均可能不同，

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而目前专门针对肿瘤患者的VTE风险评估模型仍然有限，本文对目前国内外比较认可的几种VTE风险评估模型进行综述，并介绍各自适用的肿瘤患者人群、模型的局限性和发展前景。

1 VTE风险评估模型的发展

在了解VTE风险评估模型之前，须明确两方面内容：（1）VTE发生的危险因素；（2）建立VTE风险评估模型的目的和意义。

1.1 VTE发生的危险因素

既往研究[5]表明，许多因素与VTE的发生存在相关性，例如：年龄、长期制动、恶性肿瘤、外科大手术、多发性创伤、既往VTE病史和慢性心力衰竭等，见表1。活动性肿瘤是发生VTE的重要危险因素，但是肿瘤患者的情况复杂，肿瘤存在自身疾病特点。例如，多发性骨髓瘤（multiple myeloma, MM）与VTE发生的关系尤为密切[6]。治疗MM的免疫调节剂，如沙利度胺和来那度胺等药物可明显增加VTE的发生率，特别是在与化疗和大剂量皮质类固醇联合使用时[7-8]。另外，所有住院化疗的肿瘤患者均为VTE的高危人群[9]。

1.2 建立VTE风险评估模型的目的

在了解VTE危险因素的基础上，需要评估患者发生VTE的风险大小，因此引入了风险评估模型。这种模型的建立，可以帮助区分不同情况下患者发生VTE的风险，从而更加有针对性的采取预防措施，降低VTE的发生风险。基于肿瘤患者的不同特征，并没有一个统一的标准的风险评估模式适用于所有患者，而是要根据不同的情况，分别建立不同的VTE血栓风险评估模型。

2 临床常用的VTE风险评估模型及应用

2.1 Caprini血栓风险评估模型

Caprini风险评估模型由Caprini评分量表和VTE风险分层组成，见表2，该评估量表由美国Caprini等[10]基于临床经验和研究结果设计。第9版ACCP（American College of Chest Physicians）指南推荐使用Caprini风险评估模型对外科手术患者进行血栓风险评估[11]。Caprini评估量表已被广泛验证，纳入验证的患者群包含内科和外科住院患者[12-13]，即Caprini评估量表适用于外科住院患者，也适用于内科住院患者。但对于内科患者Caprini评估量表相对较为复杂，并且其中有些危险因素并不适用于内科患者。

2.2 Padua风险评估模型

由意大利Padua（帕多瓦）大学多学科协同完成，主要针对以往的内科住院患者VTE风险评估模

表1 VTE的危险因素

Table 1 Risk factors of venous thromboembolism (VTE)

Groups	Risk factors
High risk	Fracture(pelvis or lower limb), pelvic or knee replacement, major surgical operation, severe trauma, spinal cord injury
Intermediate risk	Arthroscopic knee surgery, central venous catheterization, chemotherapy, congestive heart failure or respiratory failure, hormone replacement therapy, malignant tumors, oral contraceptives, stroke hemiplegia, pregnancy/postpartum, history of thrombosis, thrombocytosis
Low risk	Bedridden≥3 days, sedentary, increasing age, laparoscopic surgery, obesity, pregnancy/prenatal phase, varicose veins

表2 Caprini评分量表

Table 2 Caprini risk assessment model

Risk factors	Caprini score
41-60 years old; minor surgery (<30 min); body mass index >25 kg/m^2; lower extremity edema; varicose veins; pregnancy or postpartum; unexplained or history of secondary spontaneous abortion; oral contraceptives or hormone replacement therapy; Sepsis (within 1 month); severe lung disease, including pneumonia (within 1 month); abnormal lung function; acute myocardial infarction; congestive heart failure (within 1 month); history of enteritis; bed rest	1
61-74 years old; arthroscopic surgery; large open surgery (>45 min); laparoscopic surgery (>45 min); malignant tumor; bed rest or immobilization (>72 h); plaster fixation; central venous catheterization	2
≥75 years old; VTE medical history; VTE family history; positive factor V Leiden; positive prothrombin 20210A; positive lupus anticoagulant; positive anticardiolipin antibody; elevated serum homocysteine; heparin-induced thrombocytopenia; Other congenital or acquired thrombophilia	3
Stroke (within 1 month); elective joint replacement; hip, pelvic or lower limb fracture; acute spinal cord injury (within 1 month)	5

Notes: VTE risk classification:Very low risk:Caprini score 0, the incidence of VTE is <0.5%; Low risk: Caprini score 1-2, the incidence of VTE is 1.5%; Intermediate risk: Caprini score 3-4, the incidence of VTE is 3.0%; High risk: Caprini score 5-8, the incidence of VTE is 6.0%; Very high risk: Caprini score >8, the incidence of VTE is 6.0%.

型进行回顾，并在其基础上发展而来[14]，见表3。该模型经临床验证显示有很好的VTE预测价值。一项前瞻性队列研究纳入1 180例内科患者，根据Padua评估量表将总体人群分为VTE高危组（评分≥4分）和低危组（评分<4分），随访90天统计患者症状性VTE发生率。结果显示高危组中11%的患者发生VTE，而低危组0.3%的患者发生VTE[15]。国内有研究对Padua风险评估模型进行验证，结果显示Padua风险评估模型简单易用，对内科住院患者VTE的早期筛查和预防具有重要意义[16]。虽然Padua评估模型更适合内科患者，但并不是专门针对肿瘤患者设计的血栓风险评估模型。

表3　Padua风险评分量表

Table 3　Padua risk assessment model

Risk factors	Padua score
Active cancer[a]	3
Previous VTE (superficial vein thrombosis excluded)	3
Reduced mobility[b]	3
Known thrombophilia[c]	3
Trauma and/or surgery (within one month)	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity（BMI≥30 kg/m^2）	1
Ongoing hormonal treatment	1

Notes: a: Patients with local or distant metastases and/or chemoradiotherapy within 6 months; b: Bed rest ≥3 days (either due to patient's limitations or on physicians advice); c: inherited anticoagulation deficiency, inherited protein C (PC), protein S (PS) deficiency, factor V Leiden (FVL) mutation, G20210A prothrombin mutation, antiphospholipid syndrome. VTE risk classification: Low risk: Padua score<4, the incidence of VTE is 0.3%; High risk: Padua score≥4, the incidence of VTE is 11%.

2.3　Khorana血栓风险评估模型

由美国医生Khorana博士等[17]共同设计，评估化疗相关的门诊患者VTE风险。2013年调整后被美国临床肿瘤学会采用，评估化疗相关VTE风险，见表4。该模型主要针对门诊化疗的肿瘤患者设计。

2.4　以Khorana评估模型为基础的改良模型

为进一步提高肿瘤患者VTE风险预测的准确性，在Khorana评估模型基础上产生许多新的评估模型。例如，PROTECT评估模型[18]在Khorana评估模型基础上增加了化疗药物的因素。Vienna CATS评估模型[19]在Khorana评估模型基础上增加了P-选择素和D-二聚体的化验指标因素。ONKOTEV评估模型[20]在Khorana评估模型基础上增加了VTE病史、肿瘤远处转移和血管/淋巴管受压等因素。Tic-ONCO评估模型[21]在Khorana评估模型基础上增加了基因风险评分。这些VTE风险评估模型对于不同情况的肿瘤患者针对性更强，但是评估系统变得越来越复杂，并且尚有待大规模的临床数据进行验证。

2.5　其他的VTE风险评估模型

CATS风险评估模型只包括两个因素：原发肿瘤部位和D-二聚体的水平[22]。COMPASS-CAT风险评估模型纳入的因素包括：蒽环类或激素治疗、癌症诊断后的时间、中心静脉导管、肿瘤分期、存在的心血管危险因素、最近急性疾病住院治疗、既往VTE病史和血小板计数[23]。

3　VTE风险评估模型的应用价值

因为预防VTE的原则是推荐高危风险的患者进行预防性抗凝治疗，而低风险患者无须进行常规的预防性抗凝治疗。例如，行动不便需要住院化疗的肿瘤患者均属于VTE高危患者，因此应该进行VTE的一级预防。而门诊化疗的患者VTE发生风险不同，如何识别门诊化疗的高危人群，是目前研究的热点。Khorana风险评估模型中，评分≥3分的肿瘤患者是VTE的高危人群，应考虑进行VTE的一级预防，以此为基础进行了一些大规模的临床试验[24-25]。其中CASSINI研究[24]显示，对于血栓高风险的门诊癌症患者（Khorana评分≥2分），服用利伐沙班10 mg，每日1次，与安慰剂相比能显著减少VTE和VTE相关死亡的

表4　Khorana血栓风险评估模型

Table 4　Khorana thrombosis risk assessment model

Patient's characteristics	Khorana score
Site of primary cancer	
Very high risk (stomach, pancreas, primary brain tumor)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal tumors)	1
Pre-chemotherapy leukocyte count>11×10^9/L	1
Pre-chemotherapy Hemoglobin level<100 g/L or use of hemopoietin	1
Pre-chemotherapy blood platelet count≥350×10^9/L	1
Body mass index≥35 kg/m^2	1

Notes: VTE risk classification: Low risk: Khorana score 0; Intermediate risk: Khorana score 1-2; High risk: Khorana score ≥3.

发生（2.6% *vs*. 6.4%, *HR*=0.40, 95%*CI*: 0.2~0.8, *P*=0.007）。基于CASSINI研究，2019年的ASCO（The American Society of Clinical Oncology）肿瘤血栓指南和ISTH（International Society on Thrombosis and Haemostasis）指南均推荐对起始化疗、Khorana评分≥2分、无药物间相互作用且无出血高风险（如胃肠道肿瘤）的门诊肿瘤患者，在起始化疗时可应用利伐沙班作为血栓一级预防[26]。另一项AVERT研究[25]也是将Khorana评分≥2分的中高危患者作为研究对象，探讨阿哌沙班对于VTE的预防作用，研究显示阿哌沙班与安慰剂相比明显降低门诊化疗患者的VTE发生风险（4.2% *vs*. 10.2%, *P*<0.001）。但是，也有研究表明Khorana评估模型用于某些类型的肿瘤患者时敏感度较低，例如肺癌和胰腺癌[27-29]。因此，需要更为精准的VTE风险评估模型指导肿瘤患者VTE的一级预防。

4 VTE风险评估模型的前景

随着“大数据”时代的到来，患者的健康档案和电子病历系统能够提供许多可供分析的数据，因此VTE风险评估模型可与人工智能/机器学习结合起来，产生新的甚至是互联网上的在线VTE风险计算器。在不久的将来，VTE风险预测和分层的自动预测模型可能为临床决策提供巨大支持[30-32]。

综上所述，VTE是肿瘤患者常见的并发症和死亡原因，预防性抗凝治疗可以减低肿瘤患者的血栓发生风险。VTE风险评估模型有助于从不同情况的肿瘤患者中筛选出高危患者，从而指导临床干预措施。合理选择VTE风险评估模型，建立更加准确和简便易行的风险评估模型，有利于对肿瘤患者进行个体化全程抗凝管理，尽可能降低肿瘤患者VTE的发生、改善肿瘤患者的预后。

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