

Risk Scores for Death in Patients with Cancer-related Venous Thromboembolism: Still a Long Road Ahead

Daniele Pastori¹ Giancarlo Agnelli²

¹Emergency Medicine Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

²Internal Vascular and Emergency Medicine - Stroke Unit, University of Perugia, Perugia, Italy

Address for correspondence Daniele Pastori, MD, PhD, FESC, Department of Clinical, Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Viale del Policlinico 155, Rome 00161, Italy (e-mail: daniele.pastori@uniroma1.it).

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Patients with cancer have an increased risk of venous thromboembolism (VTE) compared with non-cancer patients.¹ In these patients, the risk of VTE is variable and seems to be related to several factors including cancer site and extension, anti-cancer treatment and several intrinsic patient characteristics.^{2,3} Low-molecular-weight heparin (LMWH) has been for many years the treatment of choice for cancer-related VTE. The European Society of Cardiology (ESC) guidelines published in 2019 opened to the use of direct oral anticoagulants (DOACs) for treatment of cancer-related VTE.⁴

More recently, based on three major studies (► **Table 1**), the American Society of Hematology guidelines for management of VTE in patients with cancer published in 2021 recommend considering the oral factor Xa inhibitors apixaban, edoxaban, or rivaroxaban for the initial treatment of VTE.⁵ Regarding the clinical benefit of DOACs, recent meta-analyses showed that these agents reduce the risk of recurrent VTE at 6 months (risk ratio [RR]: 0.62; 95% confidence interval [CI]: 0.43–0.91) without a significant increase in major bleeding compared with LMWH.⁶ Other studies are also supportive of the use of DOACs in these patients.^{7–9} Results from these studies are likely to influence the next guidelines for the management of VTE in patients with cancer.

Patients with VTE and cancer show an increase in the mortality compared with patients with cancer without VTE or VTE alone.¹⁰ For this reason, the identification of high-risk patients is of clinical relevance.¹¹

In this issue of *Thrombosis and Haemostasis*, Li et al¹² found that 18.0% of 460 patients with active cancer and PE died within 30 days, 2.0% suffered major bleeding and 0.2% a recurrence of VTE. The authors tested the predictive perfor-

mance of some clinical risk scores, both generic (Pulmonary Embolism Severity Index [PESI] and Hestia) and cancer specific (modified Ottawa, Registro Informatizado de la Enfermedad TromboEmbólica [RIETE] and POMPE-C). All scores showed a good predictive performance for predicting 30-day overall mortality with c-indexes above 0.70 except for the modified Ottawa (0.74 for PESI, Hestia and RIETE scores, 0.78 for POMPE-C and 0.64 for modified Ottawa). Similar predictive performances were found for 30-day PE-related death and overall adverse outcomes with the use of these scores.

Looking at risk stratifications, the authors reported that patients classified as low risk for mortality according to the PESI, Ottawa and Hestia still suffered a high mortality, which exceeds 5%. Conversely, low-risk patients according to RIETE and POMPE-C presented a low overall mortality (1.4 and 3.5%, respectively).

Considering the growing use of clinical risk scores to predict clinical outcomes of patients with cancer in different cardiovascular settings,¹³ some issues should be considered and these also apply to the interpretation of this article.

First, it is important to evaluate clinical scores in the same patient population they were derived from. In particular, concerning outcomes in patients with VTE and cancer, only the two scores evaluated in this study were developed in cohorts of cancer patients with VTE (► **Table 2**). Indeed, PESI¹⁴ and Hestia¹⁵ were originally derived from non-cancer cohorts.

Second, it is important to evaluate clinical scores in the prediction of the specific outcomes identified in the derivation cohort. Indeed, the modified Ottawa score was developed to predict the risk of VTE recurrence in cancer patients and not overall death, and the Hestia score is intended to

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Table 1 Randomized clinical trials investigating direct oral anticoagulants in patients with cancer and VTE

Study	No. of patients	DOAC used	Recurrent VTE (%)		Major bleeding (%)	
			DOAC	Dalteparin	DOAC	Dalteparin
Hokusai VTE Cancer ¹⁷	1,050	Edoxaban	7.9	11.3	6.9	4
SELECT-D ¹⁸	203	Rivaroxaban	3.9	8.9	5.4	3
ADAM VTE ¹⁹	300	Apixaban	0.7	6.3	0.0	1.4
Caravaggio ^{20,21}	1,155	Apixaban	5.6	7.9	3.8	4.0

Abbreviations: DOAC, direct oral anticoagulant, VTE, venous thromboembolism.

Table 2 Risk scores for mortality in VTE patients

Score (year)	Derivation setting	Original outcome	Variables
PESI (2005) ¹⁴	PE	Mortality	Age, male sex, cancer, heart failure, chronic lung disease, pulse ≥ 110 bpm, systolic blood pressure < 100 mm Hg, respiratory rate ≥ 30 /min, temperature $< 36^\circ\text{C}$, altered mental status, $\text{SaO}_2 < 90\%$
POMPE-C (2012) ²²	Active cancer and PE	Mortality	Body mass, heart rate > 100 , respiratory rate, $\text{SaO}_2\%$, respiratory distress, altered mental status, do not resuscitate status and unilateral limb swelling
RIETE (2013) ²³	Active cancer and PE	Mortality	Age > 80 y, heart rate ≥ 110 /min, systolic blood pressure < 100 mm Hg, body weight < 60 kg, recent immobility and presence of metastases
Hestia (2011) ¹⁵	Acute PE	Outpatients management	Haemodynamically unstable, thrombolysis or embolectomy needed, active bleeding or high risk of bleeding, > 24 h on supplemental oxygen required to maintain $\text{SaO}_2 > 90\%$, PE while on anticoagulation, severe pain needing IV pain medication > 24 h, medical or social reason for admission > 24 h (infection, malignancy, no support system), creatinine clearance < 30 mL/min by Cockcroft–Gault formula, severe liver impairment, pregnant, documented history of heparin-induced thrombocytopenia

Abbreviations: IV, intravenous; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RIETE, Registro Informatizado de la Enfermedad TromboEmbólica; VTE, venous thromboembolism.

identify patients to be managed in an out-of-hospital setting and not to predict clinical outcomes.

Third, the application of risk scores to retrospective cohorts of patients with some missing patients and variables may further lower the accuracy of the validation. In the study by Li et al, ~25% of the patients of the retrospective cohort were excluded from the analysis.

Fourth, the evaluation of the usefulness of the risk scores for the prediction of fatal outcomes, as mortality in patients with VTE and cancer, should take into account the improvement in quality of life or clinical management of high-risk patients.

Finally, the limitations of clinical risk scores need to be recognized. All clinical risk scores have modest predictive value for identifying high-risk patients that sustain events, which will be improved by the addition of biomarkers (whether urine, blood or imaging). Nonetheless, biomarkers tend to be non-specific and are often predictive of other adverse outcomes beyond what they were proposed for.¹⁶

In conclusion, there are several risk scores to predict mortality in patients with VTE and cancer, but if their use translates into a better care or improved quality of life for patients needs further investigation.

Conflict of Interest

None declared.

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