Artigo original

Cancer searching after unprovoked Thromboembolism – still a clinical controversy

Investigação paraneoplásica após um tromboembolismo idiopático – Uma controvérsia clínica

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Abstract

Introduction: *Several trials failed to demonstrate the benefits of extensive screening for the diagnosis of cancer after unprovoked venous thromboembolism (VTE). The RIETE investigators recently proposed a score aimed to identify a subgroup of patients at higher risk of occult cancer in this setting, that would benefit from more extensive workup.*

Methods: *We performed a prospective and observational clinical study, that aimed to validate the RIETE score in patients with unprovoked VTE. We calculated the RIETE score to all patients, and the high-risk patients performed a CT scan of the thorax, abdomen and pelvis, an upper gastrointestinal endoscopy and a colonoscopy. All patients had clinical visits every three months for one year.*

Results: *We included 34 patients between November 2020 and April 2022. Eight patients (23,5%) had a high-risk RIETE score. After a median follow-up of 21 months no cancer diagnosis was found.*

Discussion and Conclusion: *These results do not allow us to conclude about the RIETE score power to distinguish high from low-risk patients of having a cancer diagnosis after VTE, and further research is needed.*

Key-words: *Thromboembolism; cancer; RIETE score.*

Resumo

Introdução: Vários ensaios não conseguiram demonstrar os benefícios do rastreio extenso para o diagnóstico de cancro após um tromboembolismo venoso idiopático (TEV). Os investigadores do RIETE propuseram recentemente um score para identificar um subgrupo de doentes com maior risco de cancro oculto neste contexto, que beneficiaria de uma investigação mais extensa.

Métodos: Foi realizado um estudo clínico prospetivo e observacional, que teve como objetivo validar o score RIETE em doentes com TEV idiopático. Calculamos o score RIETE, e os doentes de alto risco realizaram tomografia computadorizada (TC) do tórax, abdómen e pélvis, endoscopia digestiva alta e colonoscopia. Todos os doentes foram avaliados em consulta de três em três meses durante um ano.

Resultados: Foram incluídos 34 doentes entre novembro de 2020 e abril de 2022. Oito doentes (23,5%) tinham um score de RIETE de alto risco. Após um seguimento médio de 21 meses não houve qualquer diagnóstico oncológico.

Discussão e Conclusão: Estes resultados não permitem concluir acerca da capacidade do score de RIETE apara distinguir os doentes de alto e baixo

risco de vir a ter um diagnóstico oncológico após TEV, pelo que é necessário continuar a investigação.

Palavras-chave: Tromboembolismo; cancro; score de RIETE.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is defined as unprovoked when no risk factors, as trauma, prolonged immobility, pregnancy or thrombophilia can be identified.

VTE is a common complication of cancer, described for the first time in 1865 by Trousseau. Unprovoked VTE may be the first sign of cancer, and approximately 5%-10% of patients will have a cancer diagnosis in the first year following the thrombotic event, there after the risk seems to be like the general population.[1-5] Cancers more often diagnosed in this context are pancreatic, liver, ovarian lung and non-Hodgkin lymphoma, however it has been described with many more.[1-2,6-9] The principle behind this phenomenon is that when the VTE occurs, the patient has already a cancer that is occult at the time. These cancers are thought to be more aggressive, and it's expected that they become apparent in a shortly after the thrombotic event.[10] The goal is to diagnose the occult cancer at an earlier stage, that could allow treatment.

The initial approach to patients diagnosed with unprovoked VTE should include a careful clinical history and physical examination that could point the underlying cause. There's an agreement, that cancer screening exams, suitable to the patient sex and age, should be carried out. Beyond that, the scientific community haven't been able to establish which exams should be included in the investigation to reach a cancer diagnosis. Several prospective randomized trials failed to demonstrate the benefit of an extensive screening, and adding computed tomography (CT) of abdomen/pelvis[1-2] or 18F-Fluorodesoxyglucose Positron Emission Tomography/Computed Tomography (FDG PET/CT)[6] did not yield more cancer diagnoses or a survival advantage.

To identify VTE patients with increased risk of cancer, that would have grater benefit from an extensive screening, a prediction score was developed from the Registro Informatizado Enfermedad TromboEmbólica (RIETE) database.[11] They recognized five positive (male gender, age > 70 years, chronic lung disease, anaemia, elevated platelet count) and two negative (prior VTE and recent surgery) risk factors for cancer after VTE that composed the RIETE score, which divides the patients into a low risk (score≤2) or high risk (score≥3) group. Three validations of the RIETE score have been published –an internal validation from the RIETE registry, and two post hoc analyses of the MVTEP and Hokusai-VTE trials.[10,12,13] One study couldn't show its dictomization value.[14]

We conducted a retrospective study in the Internal Medicine ward of Senhora da Oliveira Hospital (SOH) with the inclusion of 116 patients, from which 17 had a new cancer diagnosis. The RIETE score was able to identify 13 (36,1%) patients as high-risk of cancer diagnosis after an unprovoked VTE, showing a good discriminative power, evident by the area under the ROC curve of 0.81 (0.67-0.94 CI 95%). However, we identified several limitations, mostly because of its retrospective nature.[15]

To confirm these good results and with the goal of introducing this helpful and much needed tool in the clinical practice, we designed an unicentric prospective trial at SOH. We aimed to evaluate the RIETE score performance in identifying the patients at a high-risk of a cancer diagnosis after a VTE and validate its clinical use.

Material and Methods

We performed a prospective and observational clinical study, that aimed to validate the RIETE score in patients with unprovoked VTE.

Patients were identified by the doctors who made the VTE diagnosis in the emergency room (mainly internists and vascular surgeons), who then made an appointment for oncology-thrombosis consultation.

All patients with 18 years and older and an acute and symptomatic DVT or PE, proven by a complementary diagnostic exam (lower limbs ecodoppler and/or angiography computed tomography of the thorax) were eligible. From the beginning, we excluded patients with active cancer diagnosis, immobilization (defined as non-surgical patients who were bed restricted for at least 4 consecutive days in the last 2 months), recent plane travel, pregnancy, or puerperium. Later, we also included COVID-19 diagnosis as an exclusion criterion.

RIETE score was calculated in the first appointment. High-risk patients performed a CT scan of the thorax, abdomen and pelvis, an upper gastrointestinal endoscopy and a colonoscopy. All patients had age adjusted cancer screening tests and had follow-up consultations with clinical evaluation every three months for one year.

We had approval from or hospital ethical board, and all subjects signed a written consent.

Results

We included 34 patients between November 2020 and April 2022, 21 were women and the median age was 57 years. DVT was diagnosed in 47,1% (n=15) of the patients and PE in 41,2% (n=13), while 11,8% (n=6) had both events.

Eight patients (23,5%) had a high-risk RIETE score and you can see their score punctuations in **table 1**.

After a median follow-up of 21 months no cancer diagnosis was found.

Table 1. RIETE score variables from patients with a high risk score

Patient inclusion number	5	8	10	14	16	20	23	31
Age > 70 years (2 points)	2	2	2	2	0	2	2	2
Male sex (1 point)	1	0	1	1	0	0	0	0
Chronic Lung Disease (1 point)	1	0	0	0	0	0	0	0
Anemia* (2 points)	0	0	0	0	2	2	2	2
Platelets > 350000/L (2 points)	0	2	0	0	2	2	0	0
Prior VTE (-1 point)	-1	0	0	0	0	0	0	0
Recent Surgery (-1 point)	0	0	0	0	0	0	0	0
RIETE Score	**3**	**4**	**3**	**3**	**4**	**6**	**4**	**4**

* Hb <13 in men and Hb<12 in women.

Discussion and Conclusion

These results aren't the expected and do not allow us to clearly state on the RIETE score power to distinguish high from low-risk patients of having a cancer diagnosis after VTE. This is mainly because the recruitment goals weren't reached, which we attribute to the COVID-19 pandemic period, that altered the clinical practice. Also knowing of the high association between COVID-19 infection and PE, we had to include this infection as an exclusion criterion.

A common criticism to this score, which we clearly verified, is that its distinguishing power is largely anchored on the age factor. Of the eight patients with high-risk score in our study, only one didn't have more than 70 years of age. The question raised is if the distinguishing factor could be age alone.

Giving the controversial results of the RIETE score, there is also the need to find some new variables that could help in the selection of higher risk patient, and furthermore, identify other markers that could point out a cancer diagnosis during the follow-up of patients in the low-risk group, who didn't undergo extensive screening tests, and in the high-risk group that didn't get a diagnosis after the initial screening tests. D--dimer and neutrophil lymphocyte ratio.

We still think these is a relevant work that tries to solve an important clinical question, that could impact physicians and patients that deal with VTE, and so we hope to achieve a greater population number so that we can get meaningful results and establish the RIETE score ability to identify a group of patients at higher risk of cancer diagnosis after an unprovoked VTE. We are waiting the results of another work, looking to validate the RIETE score, with open recruitment until December 2023 (NCT03937583).

Contributorship Statement / Declaração de Contribuição

JCM: Bibliographic review, methodology, data harvesting, statistical analyses, writing of the original manuscript

ALC: Bibliographic review, methodology, data harvesting

JM: Bibliographic review, methodology, data harvesting, statistical analyses

AB: Bibliographic review, methodology, data harvesting

ASR: Conceptualization, data harvesting, Review

LO: Conceptualization, data harvesting, Review

CCar: Conceptualization, data harvesting, Review and Editing

IF: Conceptualization, data harvesting, Review

AT: Conceptualization, data harvesting, Review

AM: Conceptualization and Review

CCou: Conceptualization, data harvesting, Review

JCM: Pesquisa bibliográfica, metodologia, colheita de dados, análise estatística, escrita do manuscrito original

ALC: Pesquisa bibliográfica, metodologia, colheita de dados

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AB: Pesquisa bibliográfica, metodologia, colheita de dados,

ASR: Conceptualização, colheita de dados, Revisão

LO: Conceptualização, colheita de dados, Revisão

CCar: Conceptualização, colheita de dados, Revisão e Edição

IF: Conceptualização, colheita de dados, Revisão

AT: Conceptualização, colheita de dados, Revisão

AM: Conceptualização e revisão

CCou: Conceptualização, colheita de dados, Revisão

Ethical Disclosures / Responsabilidades Éticas

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Data confidentiality: Throughout the investigation process, the confidentiality of patient data was ensured.

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