Pulmonary Embolism in Ambulatory Oncologic Patients

Tromboembolismo Pulmonar no Doente Oncológico em Ambulatório

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ABSTRACT

Introduction: The association between cancer and venous thromboembolism is known, and oncology patients present a risk six to seven times higher than the general population of a thrombotic event. Pulmonary embolism is an important cause of morbidity and mortality in this patients group, presenting an underestimated prevalence.

Material and Methods: Retrospective study of all episodes of pulmonary embolism referenced in the last five years. We only selected oncologic outpatients and studied their demographics characteristics, risk factors associated with venous thromboembolism, presence of symptoms at diagnosis, risk stratification of venous thromboembolic events by the Khorana model, probability of mortality at 30 days and overall survival. The study is in accordance with the Helsinki declaration.

Results: From the 186 patients under evaluation, 55.9% were female, with median age of 64 years. The most prevalent cancers were colorectal (24.2%) and lung (17.7%), most of which had metastases (66.1%) or underwent chemotherapy (69.4%). Pulmonary embolism was a radiological finding in 69.4%, whereas no clinical variable was relevant for the presence or absence of symptoms. Mortality at 30 day resulting from pulmonary embolism was 7.5%, and it was found that symptomatic patients had a lower median survival relative to asymptomatic (12 *vs*. 20 months, $p = 0.029$). The retrospective application of the Khorana model to those undergoing chemotherapy identified 11% of individuals at high risk.

Discussion: Pulmonary thromboembolism was an imagiological finding in most patients, with no clinical variable able to predict the presence or absence of symptoms. Asymptomatic patients had a higher survival.

Conclusions: In our study pulmonary embolism was apparently asymptomatic in most study patients. These data reinforce the need to evaluate the risk of venous thromboembolism in cancer outpatients and consider conducting antithrombotic prophylaxis.

Keywords: Ambulatory Care; Neoplasms; Pulmonary Embolism.

RESUMO

Introdução: A associação entre a doença oncológica e a doença tromboembólica venosa é conhecida. O doente oncológico apresenta um risco de evento trombótico seis a sete vezes superior à população em geral. O tromboembolismo pulmonar é uma importante causa de morbilidade e mortalidade neste grupo de doentes, encontrando-se a sua prevalência subestimada.

Material e Métodos: Estudo retrospetivo de todos os episódios de tromboembolismo pulmonar referenciados num período de cinco anos. Selecionaram-se os doentes oncológicos em regime de ambulatório, tendo sido revistos os dados demográficos, fatores de risco, presença de sintomatologia ao diagnóstico, estratificação de risco de doença tromboembólica venosa pelo modelo de Khorana, probabilidade de mortalidade aos 30 dias e sobrevivência global. O trabalho elaborado está de acordo com a declaração de Helsínquia.

Resultados: Avaliaram-se 186 doentes, 55,9% do sexo feminino, mediana de idade de 64 anos. As neoplasias mais prevalentes foram a colo-rectal (24,2%) e a pulmonar (17,7%), sendo que a maioria apresentava metástases (66,1%) ou realizaram quimioterapia (69,4%). O tromboembolismo pulmonar foi um achado imagiológico em 69,4%, sendo que nenhum dado clínico analisado no nosso estudo mostrou ter significado estatístico na apresentação de tromboembolismo pulmonar com sintomatologia clínica evidente. Observou-se uma mortalidade aos 30 dias resultante do tromboembolismo pulmonar de 7,5%, tendo-se verificado que os doentes sintomáticos apresentaram uma sobrevivência média inferior relativamente aos assintomáticos (12 *vs*. 20 meses; $p = 0,029$). A aplicação retrospetiva do modelo preditivo de Khorana para doença tromboembólica venosa nos doentes sob quimioterapia permitiu identificar 11% dos indivíduos em alto risco

Discussão: O tromboembolismo pulmonar foi um achado imagiológico na maioria dos doentes, sendo que nenhuma variável clínica se associou à presença ou ausência de sintomas. Apesar disso, os doentes assintomáticos apresentaram uma sobrevida superior.

Conclusões: O tromboembolismo pulmonar é frequentemente assintomático no doente oncológico em ambulatório. Estes dados reforçam a necessidade de avaliar o risco de doença tromboembólica venosa destes doentes e ponderar a realização de profilaxia anti-trombótica.

Palavras-chave: Cuidados em Ambulatório; Neoplasias; Tromboembolismo Pulmonar.

INTRODUCTION

The association between venous thromboembolism (VTE) and cancer is well established and ranked as the second most common cause of death in patients with cancer.[1,2] When compared to the general population, these patients have a six to seven times higher risk of developing a thrombotic event.[3] A risk of VTE above 20% is estimated in certain subgroups of patients with cancer.[4,5]

Pulmonary embolism (PE) is one of the major forms of presentation of VTE and an important cause for morbidity and mortality. Its real prevalence in patients with

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cancer is probably undervalued.[6] In some clinical series, approximately half of these patients were incidentally diagnosed with PE in imaging; one of the possible causes for this fact may eventually relate to the advances in radiological techniques.[7-9]

Decisions regarding prophylactic outpatient therapy in a patient with cancer are not consensual. As regards risk stratification, a previously validated tool should be used. Prophylaxis is not recommended except in patients with multiple myeloma on thalidomide or lenalidomide.[10-12] Some authors also suggest prophylaxis should be considered in high-risk outpatient patients and in patients on chemotherapy according to the Khorana's predictive model and eventually in patients with locally-advanced pancreatic or pulmonary cancer.[2] It should also be considered when additional risk factors are found, namely previous PE, patient immobilization, hormone therapy and the use of angiogenesis inhibitors.[10] Currently, VTE prophylaxis should therefore be decided on a case-by-case basis.

Our study aimed to characterise a group of patients with cancer diagnosed with VTE.

MATERIAL AND METHODS

This was a retrospective study of all the VTE episodes occurring in patients diagnosed with cancer over a five-year period (2009-2013). From the 234 reported VTE episodes, only those presented by outpatients were selected for inclusion (n = 186).

The clinical records were reviewed and our group of patient's demographic characteristics were determined. VTE events were classified as symptomatic or incidental, based on a patient's clinical record and/or on clinical information that led to imaging. The following risk factors for VTE were analysed, namely: neoplasm location, locally-advanced disease, chemotherapy, recent surgery and the presence of a central venous catheter.

VTE risk stratification was retrospectively established in patients on chemotherapy according to the model by Khorana et al,[13,14] who found an association between clinical findings (tumour location and body mass index above 35 Kg/m^2), pre-chemotherapy complete blood count (leucocyte count above 11 x 10^9/L, platelet count above 350 x 10^9/L and haemoglobin below 10 g/dL) and the use of erythropoiesis-stimulating agents and VTE occurring in outpatients with cancer on chemotherapy. This model established three groups of risk: low, intermediate and high, each group with a 0.3%, 2% and 6.7% probability of VTE development, respectively.[13,14]

VTE-related 30-day mortality probability was also assessed according to the PESI (Pulmonary Embolism Severity Index)[15] score into five probability classes: class I – 1.1%; class II- 3.1%; class III- 6.5%; class IV- 10.4%; class V- 24.5%. This ranking is based on the evaluation of eleven clinical criteria related to the patient's age and gender, as well as to the clinical history (tumour, heart failure, chronic pulmonary disease) and signs, at the time when the VTE was diagnosed (heart and respiratory rate, oxygen saturation, systolic blood pressure, body temperature and altered state of consciousness). VTE-related mortality in our group of patients was based on clinical data, other causes of mortality being excluded.

The SPSS version 20.0 software was used for statistical analysis, chi-square (X^2) applied and global survival calculated using the Kaplan-Meier's method.

RESULTS

A 64-year median age (17-84 rank) was found in our group of patients with a slightly higher PE prevalence in female patients (55.9%).

Table 1 – Characteristics of our group of patients

Characteristics	Number of patients (n = 186)
Gender	
Female	104 (55,9%)
Male	82 (44,1%)
Age (years)	
Median	64 (17 - 84)
History of VTE	3 (1,6%)*
Cancer	
Present	100%
Locally-advanced disease	
Yes	123 (66,1%)
No	49 (26,4%)
Non-classifiable	14 (7,5%)
Cancer location	
Colorectal	45 (24,2%)
Pulmonary	33 (17,7%)
Breast	30 (16,1%)
Stomach	26 (14,0%)
Gynaecological	15 (8,1%)
Haematological	13 (7,0%)
Sarcoma	5 (2,7%)
Pancreas	4 (2,2%)
Oesophagus	4 (2,2%)
Biliary tract	3 (1,6%)
Head	3 (1,6%)
Prostate	2 (1,1%)
Skin	1 (0,5%)
Kidney	1 (0,5%)
Unknown primary	1 (0,5%)

VTE- Venous thromboembolism

* These patients were on anticoagulant therapy at the time when PE was diagnosed

Table 2 – PE risk factor assessment and its relationship to the presence of symptoms when PE is diagnosed

		Symptoms (n = 186)		χ^2
		Yes	No	*p*
Locally-advanced disease	Yes	40 (21.5%)	83 (44.6%)	0.536
	No	12 (6.4%)	37 (19.9%)	
	Unclassified	5 (2.7%)	9 (4.8%)	
Surgery over the previous 3 months	Yes	4 (2.1%)	3 (1.6%)	0.121
	No	53 (28.5%)	126 (67.7%)	
Central venous catheter	Yes	22 (11.8%)	42 (22.6%)	0.424
	No	35 (18.8%)	87 (46.8%)	
Hormonal therapy*	Yes	2 (1.1%)	8 (4.3%)	0.453
	No	55 (29.6%)	121 (65.1%)	
Chemotherapy	Yes	35 (18.8%)	94 (50.5%)	0.118
	No	22 (11.8%)	35 (18.8%)	

χ^2 – Chi-square test
* These patients had breast cancer

Colorectal (24.2%) and pulmonary (17.7%) were the most prevalent cancer locations (Table 1). Locally-advanced cancer was found in most patients (66.1%).

Most patients were incidentally diagnosed with VTE in CT-scan (69.4%). Only three patients (1.6%) were on anticoagulant therapy due to a previous VTE event.

Cancer-related VTE predisposing factors were found in our group of patients: 69.4% were on chemotherapy, 66.1% had locally-advanced disease, 34.4% had a central venous catheter, 5.4% were on hormonal therapy for breast cancer and 3.8% had undergone major surgery over the previous three months. The presence of symptoms when VTE was diagnosed did not correlate to any of these variables (X^2 test; $p > 0.05$) (Table 2).

A VTE risk stratification using Khorana's model was carried out in the 129 patients on chemotherapy at the time when VTE was diagnosed. Most patients had an intermediate (46%) or a low VTE risk (43%) in the 2.5 months following chemotherapy (Fig. 1).[14]

The PESI score revealed that 19% of the patients showed a 24.5% or above 30-day mortality probability (class V) (Fig. 2).

A 7.5% (n = 14) PE-related mortality rate was found. The patients with symptoms showed a lower average survival when compared to the apparently asymptomatic patients incidentally diagnosed with PE (12 months *vs.* 20 months; $p = 0.029$) (Fig. 3).

DISCUSSION

This was a population study involving a group of outpatients with cancer diagnosed with PE.

VTE is a common complication in patients with cancer. However, its incidence depends on several factors.[16] Tumour location is one of these factors and a higher VTE prevalence is described in lymphoma and in gastrointestinal, pulmonary, bone, gynaecological, brain, pancreatic, testis and bladder cancer.[13,17] In our study, PE events were more frequently associated to colorectal and pulmonary cancer (24.2% and 17.7% respectively). This result reflects cancer location as a VTE predisposing factor, as well as the high number of patients with these types of cancer followed in our institution, ranking second and fourth most frequent, respectively. Breast cancer ranked third with more PE

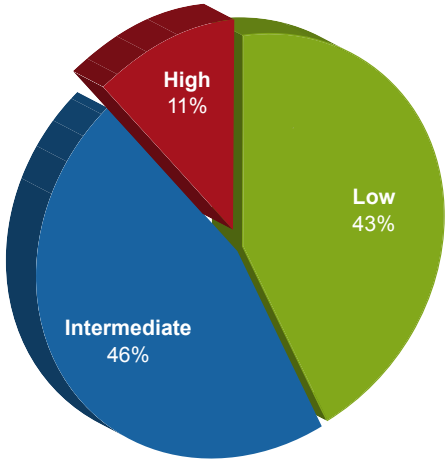

Figure 1 - Chart representing the risk of VTE in patients on chemotherapy according to the Khorana's model (n = 129)

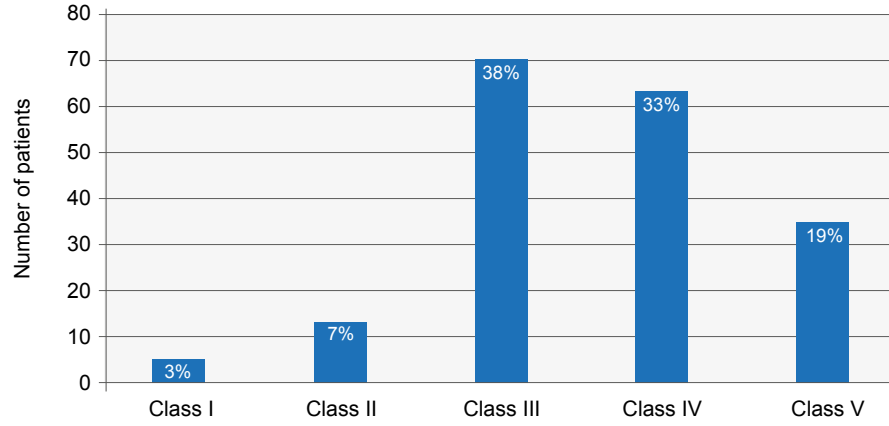

Figure 2 - Chart representing the risk of PE-related 30-day mortality probability according to the PESI score (n = 186)

events (16.1%) in our group of patients, despite not being one of the most VTE-predisposing cancers. This fact was explained by the high number of patients followed in our hospital with this pathology and the most frequently followed and treated cancer.

In our group of patients, 66.1% presented with locally-advanced disease when PE was diagnosed. The presence of locally-advanced disease corresponds to a 20-times higher VTE risk in patients with cancer[16,18] and 58-times higher risk when compared to the general population.[18] This may be explained by a state of hypercoagulability associated to locally-advanced disease, as well as the involvement of haemostatic mechanisms related to solid-tumour locally-advanced disease.[18,19]

Most of our patients (69.3%, n = 129) were on chemotherapy, which represents a 6.5-times higher risk of a thrombotic event.[20] Patient's retrospective stratification according to Khorana's VTE predictive model[13,14] classified 11% of the patients as included in the VTE high-risk group and most patients were classified with low or intermediate risk. Khorana's model is currently being reviewed and the inclusion of biomarkers like P-selectin and D-dimer is expected to occur, allowing for a more reliable predictive value to be obtained.[21,22]

In our group, 69.4% of the patients were incidentally diagnosed with PE by imaging. In a study by Gladish et al, involving a group of 403 patients with cancer, 4% of the patients presented with PE found on CT-scan. However, an image review showed that 25% of the tests initially described as normal had findings consistent with a PE diagnosis, reinforcing the notion that the real number of these events in patients with cancer is underestimated.[7] Several recent studies confirm that half of the patients with cancer are incidentally diagnosed with PE by imaging.[8,23]

In our group of patients, none of the following factors showed to be significantly associated to the presence of symptoms at the time when PE was diagnosed: tumour location, locally-advanced disease, presence of central venous catheter, chemotherapy or hormone therapy and recent surgery ($p > 0.05$). The presence of symptoms when a PE was diagnosed was associated to an approximately eight-month decreased survival when compared to incidental PE ($p = 0.029$). This result may be empirically explained by the presence of more extensive thromboembolic disease in patients with more advanced disease and in a weakened general condition. However, the involvement of both larger and bilateral emboli is frequent in apparently asymptomatic patients[8,23-25] and no differences seem to exist regarding the anatomical distribution of the blood vessel affected by PE between these patients and those with symptoms.[24,25] Other studies have also shown a similar rate of recurrent VTE, haemorrhagic complications and mortality between these two groups of patients.[26-28] Treatment of patients with both incidental or symptomatic PE is currently recommended.[10,12]

Finally, the 30-day mortality risk following the PE event was calculated by the PESI score.[15] Most patients presented with class III or above and a significant percentage (19%) had a 24.3% risk (class V). The application of this model was correlated to the mortality percentage calculated for our group of patients (7.5%).

Prophylactic use of low molecular weight heparin (LMWH) has been recommended in studies involving

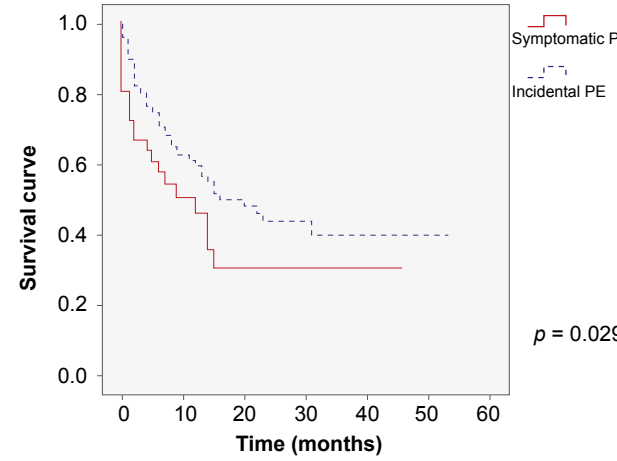

Figure 3 – Survival curve according to the presence of symptomatic *vs.* incidental PE

outpatients with cancer, whether or not ranked according to the risk of VTE. These studies seem to show a reduction in thrombotic events.[22,29-31] However, the patients without prophylactic treatment show a relatively low probability of symptomatic VTE and therefore prophylaxis is only recommended in selected patients.[10,12]

Finding biomarkers or strategies for VTE risk stratification in patients with cancer is currently challenging due to its multifactorial pathogenesis.[32] D-dimer and other biomarkers such as soluble P-selectin, thromboplastin, coagulation factor VIII and prothrombin fragments 1 and 2 are those with the greatest potential for the identification of those patients with cancer that may benefit from a prophylactic treatment.[33]

This study presents some limitations. This was a retrospective study and therefore it may contain some biased information.

Further prospective studies involving new stratification strategies are crucial for the selection of high-risk patients who may benefit from VTE prophylaxis.

CONCLUSIONS

PE was an incidental finding in 69.4% of our group of patients and this diagnosis showed the association of the thromboembolic disease with cancer further supporting the need to reliably assess such patients, in order to stratify and consider the use of anti-thrombotic prophylaxis in outpatients at high risk of VTE.

HUMAN AND ANIMAL PROTECTION

The authors declare that the procedures followed were in accordance to the regulations established by the responsible body of the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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