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Original article

Evaluation of the Khorana Predictive Thrombotic Risk and Thromboprophylaxis Score in Cancer Patients in a Third Level Hospital

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ABSTRACT

Introduction: Current clinical guidelines do not recommend the routine use of thromboprophylaxis in cancer primary unselected patients. Identifying cancer patients who could be beneficiaries of thrombotic prophylaxis is a real challenge. We aimed to analyse the application of Khorana score in cancer patients. We also tried to evaluate the prescription of primary thromboprophylaxis in cancer patients at risk of venous thromboembolic disease (VTED).
Methods: A retrospective observational study of survival of hospitalised patients diagnosed with pulmonary embolism (PE) at the Hospital Central de la Defensa from January 2009 to March 2018. They were stratified into tumour PE (TPE) and non-tumour PE (nTPE). A case-control study was also carried out by TPE patients and non PE cancer patients (nPEC).
Results: 108 patients were diagnosed with TPE, 260 nTPE and 324 nPEC. Gynaecological tumours were the most frequent (23.1%), followed by lung, digestive and urological cancer (20.4% each) in the TPE group. Death risk was 1.9 times higher in cancer patients (95% CI: 1.23–2.8) ($p < 0.001$). Khorana score was ≥3 points in 9.7% of TPE and 3.1% of nPEC compared to 26.2% of TPE and 9.9% of nPEC with Khorana score ≥2 points ($p < 0.001$). 7.4% of TPE patients received thromboprophylaxis. Khorana score in TPE patients without thromboprophylaxis was ≥3 points in the 9% and ≥2 points in the 24%.
Conclusions: There is an underutilisation of thromboprophylaxis in our cancer patients and mainly in those with high risk of VTED, as well as poor adherence to the Khorana score. More studies are needed to validate these findings and to optimise predictive strategies in the management of these patients.

Evaluación de la escala predictiva de riesgo trombótico y de tromboprofilaxis de Khorana en el paciente oncológico en un hospital de tercer nivel

Palabras clave:
Embolia de pulmón
Enfermedad tromboembólica venosa
Cáncer
Escala de Khorana
Tromboprofilaxis

RESUMEN

Introducción: El objetivo del estudio es analizar la aplicación de la escala predictiva de Khorana en el paciente oncológico. Asimismo el estudio trata de evaluar la prescripción de tromboprofilaxis primaria en los pacientes con cáncer en riesgo de enfermedad tromboembólica venosa (ETV).
Métodos: Estudio observacional retrospectivo de supervivencia en pacientes hospitalizados en el Hospital Central de la Defensa diagnosticados de embolia pulmonar (EP) desde el 01 de enero de 2009 al 15 de marzo de 2018, estratificándose en EP tumoral (EPT) y EP no tumoral (EPnT). Se ha realizado también un estudio de casos y controles, con pacientes con EPT y con cáncer sin EP (CsEP).

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Resultados: Se encontró que 108 pacientes presentaron EPT, 260 EPnT y 324 CsEP. En la EPT el tumor ginecológico fue el más frecuente (23,1%), seguido de pulmón, digestivo y urológico (20,4% cada uno). Los pacientes con cáncer presentaron 1,9 veces más riesgo de muerte (IC 95%: 1,23-2,8) ($p < 0,001$). Mediante la escala de Khorana el 9,7% de EPT y el 3,1% de CsEP presentaron ≥3 puntos, frente a 26,2% de EPT y 9,9% de CsEP con ≥2 puntos ($p < 0,001$). Un 7,4% de EPT recibió tromboprofilaxis. De los que no la recibieron el 9% tenía ≥3 puntos y el 24% ≥2 puntos.
Conclusiones: Existe una infrautilización de la tromboprofilaxis en nuestros pacientes oncológicos y fundamentalmente en los de alto riesgo de ETV, así como una escasa adherencia a la escala de Khorana. Son necesarios más estudios para validar estos hallazgos y conseguir optimizar las estrategias predictivas en el manejo de estos pacientes.

Introduction

Thromboembolic disease (VTED) is a frequent event in cancer patients. It is related to cancer treatment interruption, a decrease in quality of life and an increase in comorbidity, morbidity and mortality. It also increases hospital stay and healthcare costs.[1–6]

This relationship between VTED and cancer is bidirectional. The presence of active cancer increases the risk of VTED by 9 times compared to the general population. The incidence of VTED in cancer patients have practically been tripled in the last two decades.[7]

Current clinical guidelines do not recommend the routine use of thromboprophylaxis in cancer primary unselected patients.[8–10] Identifying cancer patients who could be beneficiaries of thrombotic prophylaxis is a real challenge. That is why the Khorana score was developed as a validated tool incorporated into thromboprophylaxis guidelines, which assesses the risk of developing VTED in cancer patients before starting chemotherapy.[9,11] This score evaluates five clinical and analytical parameters prior to chemotherapy (Table 1), classifying patients as low (0 points), intermediate (1–2 points) or high risk (≥3 points) for VTED.[12]

Several authors and guidelines have suggested that primary thromboprophylaxis should be considered only in selected patients in the high risk group (Khorana ≥3).[13–16] Recently, two randomised controlled trials have demonstrated the efficacy and safety of thromboprophylaxis with apixaban and rivaroxaban in cancer patients classified in the intermediate or high risk group of VTED (Khorana score ≥2).[17–20] After that, new guidelines recommend thromboprophylaxis in patients with ≥2 points on this score.[8–11] Although it is currently well known that thromboprophylaxis reduces the risk of VTED,[21] there are certain limitations in the available literature and clinical practice guidelines do not provide solid recommendations in certain situations in cancer patients. Furthermore, the current adherence of clinicians to the predictive risk scores for thrombosis associated with cancer and the prescription of thromboprophylaxis in high risk patients are not well established.

Table 1
Khorana score for predicting VTE in cancer patients.

Characteristics	Score
Cancer location	
- Very high risk (pancreas, stomach)	2
- High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Platelets before chemotherapy ≥350,000/mm^3	1
Hemoglobin before chemotherapy <10 g/dl or use of erythropoiesis-stimulating factors	1
Leukocytes before chemotherapy >11,000/mm^3	1
Body mass index ≥35 kg/m^2	1

0 point: low risk of VTE.
1–2 points: intermediate risk of VTE.
≥3 points: high risk of VTE.

The aim of our study is to analyse the application of the Khorana risk prediction score in cancer patients. Our study also tries to evaluate the prescription of primary thromboprophylaxis in cancer patients at risk of VTED.

Methods

A retrospective observational survival study was carried out from January 2009 to March 2018. There were included those patients admitted at the Hospital Central de la Defensa for any cause diagnosed with acute pulmonary embolism (PE) by computed tomographic pulmonary angiography and/or ventilation perfusion scan, according to the Spanish Pulmonology and Thoracic Surgery Society clinical practice guidelines of 2013[22] and the European Cardiology Society guidelines of 2014.[23] A comprehensive search was performed in the registry of medical records during this period of patients diagnosed with PE in the emergency department or in the hospital ward. A non-probabilistic consecutive sampling was executed.

This population was classified into two groups: tumour PE (TPE) and no tumour PE (nTPE).

In addition, a case-control study was carried out by TPE patients (cases) and no PE cancer patients (nPEC). The registry of medical records was accessed by performing a deep search during this period of the different cancer Committees of the Hospital Central de la Defensa of patients diagnosed of cancer (gynaecological, lung, digestive, urological, haematological, and other tumour types) without VTED. The prevalence was maintained in both groups.

There were excluded from the study: patients diagnosed with an incidental pulmonary embolism (IPE) and incomplete clinical information cases, patients with prior anticoagulant treatment with poor adherence or infratherapeutic blood levels, pregnant women, children, patients with a difficult follow-up and those cases with a doubtful diagnosis.

Study variables

Data from the patient's admission history were determined, such as the presence or absence of cancer and the histological type, death, sociodemographic variables, analytical parameters (biochemistry, blood count, coagulation, ultrasensitive Troponin T, C-reactive protein, NT-ProBNP, D-dimer) and cancer treatment received.

Comorbidity was measured at the time of admission using the Charlson Comorbidity Index (ChI). In addition, VTE risk was evaluated by the Khorana score in cancer patients, classifying them as low (0 points), intermediate (1–2 points) and high risk (≥3 points). Intermediate to high risk was considered when Khorana score was ≥2 points. Mortality was determined in patients with TPE and nTPE and its relationship to cancer and histological type.

A sample size calculation was performed for each of the three categories of the Khorana score, comparing them to each of the groups.

Statistic analysis

The quantitative variables were expressed as mean ± standard deviation (SD) and the qualitative variables as percentages and absolute frequencies. Measures of association between variables were performed using the chi-square test, Student's *t* test, Mann–Whitney *U* test, ANOVA and Kruskal–Wallis. Precision was calculated with their 95% confidence intervals (95% CI). Multiple comparisons were made using the Bonferroni, Levene, Dunett and medians tests. The survival study was carried out using the Kaplan–Meier test. The comparison of survival curves was carried out using a Cox regression model (Log Rank). As a degree of statistical significance, a value of $p < 0.05$ was used and the statistical application was the SPSS version 15.0 packages.

Confidentiality commitment

Throughout the study process, the Organic Law on the Protection of Personal Data and the ethical principles for medical research involving human subjects of the World Medical Association Declaration of Helsinki were respected, as well as the current legislation for observational studies. In addition, the study has the authorisation from the Ethics Committee for Drug Research of the Defense General Health Inspection. Given the required nature of anonymity of this data set, and the non- interventional nature of the study that did not modify clinical practice towards the patients included in the study, it was not necessary to obtain informed consent.

Results

Study population. Demographic and clinical characteristics

368 patients were diagnosed with acute symptomatic PE from January 2009 to March 2018. 29.3% (108 patients) presented an association with tumour, compared to 70.7% (260 patients) of patients without cancer.

TPE patients in our study were more frequently male, older, with a lower body mass index (BMI) and with a higher smoking history than those with nTPE. Demographic and clinical characteristics of the patients with TPE and nTPE are represented in Table 2.

Histological types and cancer treatment received

When analysing the different histological types in patients with TPE, the gynaecological tumour has been the most frequently associated cancers, in 23.1% of patients (16 breast cancer, 6 uterus, 2 ovary, 1 endometrial cancer). It was followed by lung, in 20.4% of patients (22), digestive, in 20.4% of patients (14 colon, 3 pancreatic, 2 gastric, 1 rectal, 2 biliary tract cancer), urological in 20.4% of patients (15 prostate, 5 bladder, 2 kidney cancer), haematological cancer, in 6.5% of patients, and other tumour types in 9.3% of patients (which include head and neck, sarcoma, skin and miscellaneous).

In women, gynaecological tumours were the most common (50%), followed by digestive (21%) and lung cancer (10.5%). In contrast, in men the most frequent tumour was urological (33%), followed by lung cancer (28.5%). Regarding the cancer treatment received in patients with TPE, 41% had received surgical treatment, 30.6% chemotherapy, 22% radiotherapy and 5.6% hormonal treatment.

Table 2
Demographic and clinical characteristics of patients with TPE and nTPE.

	TPE $n = 108$	nTPE $n = 260$	p
Age (years), $\bar{x}$ (SD)	73 (11)	71 (15)	0.140[a]
BMI kg/m^2, $\bar{x}$ (SD)	28.55 (4.26)	29.73 (5.27)	0.063[a]
Sex, n (%)			
Male	60 (55.6)	108 (41.5)	0.014[b]
Female	48 (44.4)	152 (58.5)	
Smoking, n (%)			
Active smoker	9 (10.5)	25 (11.6)	0.040[b]
Non smoker	54 (62.8)	160 (74.1)	
Former smoker	23 (26.7)	31 (14.4)	
Oral contraceptives, n (%)	–	8 (3.1)	0.067[b]
mMRC dyspnea scale, n (%)			
0	3 (2.9)	6 (2.4)	0.973[b]
1	19 (18.1)	44 (17.5)	
2	39 (37.1)	102. (40.5)	
3	42 (40)	94 (37.3)	
4	2 (1.9)	6 (2.4)	
Recent surgery, n (%)	19 (17.6)	13 (5)	<0.001[b]
History of acute stroke, n (%)	4 (3.9)	10 (4)	
Long journey, n (%)	1 (1.2)	3 (1.4)	0.902[b]
History of previous DVP, n (%)	33 (39.3)	96 (45.3)	0.348[b]
Thromboprophylaxis, n (%)	8 (7.4)	10 (3.8)	

[a] ANOVA.
[b] χ^2 Pearson.
TPE: tumour pulmonary embolism; nTPE: no tumour pulmonary embolism. $\bar{x}$ (*SD*): mean (standard deviation); BMI: body mass index; DVP: deep venous thrombosis.

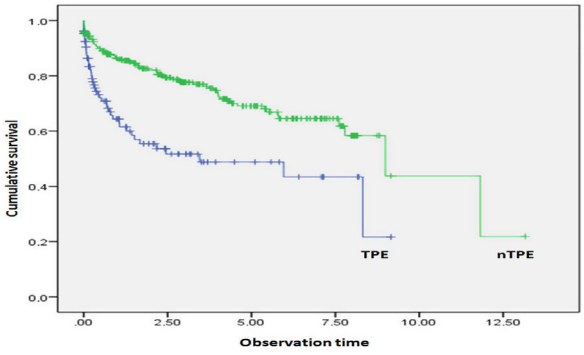

Fig. 1. Representation of survival of TPE and nTPE patients. Kaplan–Meier survival curve. TPE: tumour pulmonary embolism; nTPE: no tumour pulmonary embolism.

Mortality based on the presence of cancer and histological types

When we analyse survival based on the presence of cancer, patients with TPE survived less than those in the nTPE group, with a median survival of 3.4 years (95% CI: 0–7.7) and 8.98 years (95% CI: 6.8–11.1), respectively ($p < 0.001$). When evaluating the cancer staging in patients with TPE, the main prognostic factor for tumour disease, 34 patients (31%) had metastatic cancer, and 74 patients (69%) had nonmetastatic disease.

In the Cox proportional hazards analysis, it was shown that patients with cancer had a 1.9 times higher risk of death than those without associated neoplastic disease (95% CI: 1.23–2.8) ($p = 0.003$). Fig. 1 represents the survival curves in patients with TPE and nTPE. In this analysis it was included other variables such the Pulmonary embolism severity index (PESI) and its simplified version (PESIs), sex, and the ChI. It was also shown in the Cox proportional hazards analysis that PESI was a prognostic factor related to survival [patients with PESI V had 6.5 times higher risk of death than those with PESI I (95% CI: 2–21) ($p = 0.002$)], as well as PESIs [patients with PESIs 4 had a 31 times higher risk than those with PESIs 0 (95% CI:

Table 3
Survival of the TPE group according to the histological type of cancer.

Histology	Mean		95% CI	
	Estimate	Standard error	Lower limit	Upper limit
Gynaecological	7.257	0.760	5.767	8.747
Lung	1.355	0.539	0.298	2.12
Hematological	7.012	1.059	4.936	9.088
Digestive	3.552	0.783	2.017	5.087
Urological	4.99	0.771	3.487	6.51
Others	3.219	1.254	0.76	5.67

95% CI: 95% confidence interval.

4–243) ($p = 0.001$)] and ChI [patients with ICh > 5 had a 10.7 times higher risk of death than those with the lowest ChI score (95% CI: 1.5–77.6) ($p = 0.019$).

When assessing mortality based on the different histological types, in the TPE group, patients with lung cancer survived the least, with a mean survival time of 1.3 years (95% CI: 0.3–2.4). They were followed by other tumour types (3.2 years), digestive (3.55 years), urological (5 years) and haematological (7 years) compared to patients with gynaecological tumours who had a longer survival, with a mean survival of 7.25 years (95% CI: 5.76–8.74) ($p < 0.001$). Table 3 represents survival in TPE, according to the different histological types.

Risk stratification using the Khorana predictive score

We conducted a case–control study on the risk assessment of VTED using the Khorana score with 108 patients in the TPE group and 324 patients in the nPEC group. We observed that 29% of the TPE group had a score of 0 points (low risk) compared to 44% of the nPEC group. 61.2% of the TPE group presented 1 or 2 points (intermediate risk) compared to 52.8% of the nPEC group, and 9.7% of the TPE group presented 3 or 4 points (high risk) compared to 3.1% of the nPEC group.

Indication of thromboprophylaxis in the risk groups of the Khorana score

When we evaluated the history of primary thromboprophylaxis in patients with TPE, we observed that only 8 patients (7.4%) had received it. Of these, four were classified in the low-risk group, 3 in the intermediate group and only one in the high risk group, with 3 patients presenting a score of ≥2.

Of the 100 patients who had not received thromboprophylaxis, 24% had a score ≥2 and 9% belonged to the high risk group (Table 4).

Discussion

VTED has experienced an increase in its incidence in hospitalised patients in recent years, with greater comorbidity and lower mortality over time.[24–26] VTED is the second cause of death in cancer patients.[27] Patients with TPE present greater comorbidity measured by the ChI compared to patients with nTPE,[1] and this consideration is reflected in the present study. Regarding primary thromboprophylaxis in cancer patients, there is currently an open debate on the optimal way to identify cancer patients at high risk of VTED. Because of the recent publication of two trials,[17,18] several guidelines recommend thromboprophylaxis in patients with a score of ≥2 on the Khorana score,[8–11] so indication for thromboprophylaxis in cancer patients would increase significantly.[28]

This study aims to analyse this aspect when evaluating the usefulness of the Khorana predictive score in hospitalised cancer patients and the prescribing of thrombotic prophylaxis in the oncologic patient with high and intermediate-high risk of VTED using this score.

Although it is true that this predictive score was validated as a predictive tool in ambulatory cancer patients, numerous studies have evaluated its predictive capacity in hospitalised patients.[29,30]

When evaluating and comparing the Khorana score in patients with TPE and nPEC in our study, we found that it had predictive capacity, with intermediate risk prevailing in both groups. The high risk group (≥2 points) was more frequent in patients with TPE. The intermediate to high risk group (≥2 points) was also more frequent in the TPE group, both with statistically significant differences. The sensitivity of this score is modest in our series, since 90% and 74% of the thromboembolic events did not occur in the high risk and intermediate to high risk groups, respectively.

These data reflect how our series significantly increases the proportion of cancer patients who could benefit from thromboprophylaxis by prescribing it in patients with 2 points on the Khorana scale based on recent guidelines.[8–11] This increase is comparable to that described by Mulder et al,[28] who observed that the indication for thromboprophylaxis would increase from 17% to 47%[28] when prescribing it in patients with ≥2 points.

Recently, several meta-analyses have analysed this aspect, finding results in the same direction, but with higher percentages in the intermediate to high and high risk groups. According to Mulder et al,[28] 64% of the 35,000 cancer patients were classified as intermediate risk, 17% as high risk, and 47% had ≥2 points. On the other hand, according to Bosch et al,[31] 64% of cancer patients presented ≥2 points.

It is essential to note that in this review one of the six studies analysed, unlike ours, considered very high risk brain tumour and high risk myeloma.[18,28] Another aspect that could explain these striking differences is that in our study the most common tumour was gynaecological, followed by urological (mostly prostate), lung and digestive. On the other hand, in other studies, digestive, lung and gynaecological tumours were more frequent, implying higher score on Khorana score. Taking into account the histological types, in the recent study of the CARAVAGGIO registry, which included 1155 patients with TPE, the most frequent tumour was colorectal,

Table 4
VTE risk assessment using the Khorana score in the TPE and nPEC group. Thromboprophylaxis indication in the PE group based on the Khorana score.

	Khorana score *n* (%)					*p*
	0	1	2	3	4	
TPE, $n = 108$	30 (29.1)	46 (44.7)	17 (16.5)	9 (8.7)	1 (1)	
NPEC, $n = 324$	143 (44.1)	149 (46)	22 (6.8)	8 (2.5)	2 (0.6)	<0.001[a]
Total, $n = 432$	173 (40.5)	195 (45.7)	39 (9.1)	17 (4)	3 (0.7)	
Thromboembolic prophylaxis, $n = 8$	3 (10)	2 (4.3)	2 (11.8)	1 (11.1)	0 (0)	
No thromboembolic prophylaxis, $n = 100$	27 (90)	44 (95.7)	15 (88.2)	8 (88.9)	1 (100)	0.815[a]
Total, $n = 108$	30 (100)	46 (100)	17 (100)	9 (100)	1 (100)	

TPE: tumour pulmonary embolism; nPEC: no pulmonary embolism cancer patient.
[a] χ^2 Pearson.

followed by lung and breast.[32] Similar results were obtained in the TESEO registry, with colon cancer being the most frequent followed by lung and breast.[33] In contrast, in the RIETE registry, the most frequent associated cancer was lung, followed by breast and colorectal.[34]

Our TPE patients with lung cancer survived less than those with gynaecological tumours, who had the longest survival. The RIETE registry[35] has described similar results, with survival being lower in patients with lung and digestive cancer, and higher in neoplasms of mammary origin. It should be mentioned that neoplasms with a high capacity to produce PE have recently been described, such as biliary tumour and non-small cell lung carcinoma.[7] Furthermore, it is worth noting the growing importance of molecular biology in cancer (specifically the rearrangements of the ROS1 and ALK biomarkers in non-small cell lung cancer) due to its increased risk of producing PE.[7,36]

Continuing with our work and the history of thromboprophylaxis, only 7.4% of the TPE group had received it, corresponding to 8 patients. Of these, half, four patients were classified in the low risk group on the Khorana score and only one patient in the high risk group, with 3 patients scoring ≥2 points on the Khorana score. Of the 100 patients who had not received thromboprophylaxis, 9% had an indication of thromboprophylaxis with a score of ≥3 points and 24% had an indication based on the most recent guidelines with ≥2 points. This reflects a low prescription of thrombotic prophylaxis and limited adherence to this predictive score in our experience.

Evidence of this underutilisation of thromboprophylaxis in our series and poor adherence to this predictive score are other studies in cancer patients,[37] such as that of Parker et al.,[29] in which out of 1398 hospitalised cancer patients, 34.5% received thrombotic prophylaxis. In this study, unlike ours, patients with high risk of VTED on the Khorana score received more thromboprophylaxis than those at low risk (46.4% vs 23.9%).[29]

The present study has several limitations as it is a single-centre study and its design. It would require validation in future prospective studies. In addition, our sample with TPE is small, 108 patients, which could limit finding conclusions. Furthermore, in this study we have applied broad exclusion criteria, which could lead to a selection bias in the sampling. Likewise, the relative scarcity of similar studies that analyse the Khorana score in patients with TPE and nPEC limits the possibility of establishing large comparisons and parallels. Another limitation of this work is that we have not included certain treatments that are involved in the development of VTED, such as immunotherapy, protein kinase inhibitors, and angiogenic therapy.[7]

We have not analysed the Khorana score in the incidental pulmonary embolism (IPE). Numerous studies have not distinguished between IPE and TPE,[7] or have not evaluated the usefulness of the Khorana score in the IPE, although this aspect could have been studied since the clinical characteristics do not differ significantly with respect to TPE.[38] Regarding survival in this population, there are discordant results in this aspect, because while some studies have reported a similar prognosis in IPE and TPE,[39] in a recent study by the RIETE registry have shown a lower mortality in IPE than in clinically suspected PE.[40]

Although we have not been able to conclude that the Khorana score constitutes a prognostic factor for VTED, based on the obtained results, thromboprophylaxis should be indicated in patients with intermediate (1–2 points) risk of VTED.

In conclusion, this study reflects the underutilisation of thromboprophylaxis in cancer patients and mainly in patients at high risk of VTED. Furthermore, there is little adherence to the Khorana score in our series, indicating the need for greater application and knowledge of this predictive score in clinical practice. More studies are needed to validate these findings and to optimise predictive strategies in the management of these patients.

Authors contributions

Each of the authors of the article has contributed substantially to the elaboration of the manuscript: the design of the study or acquisition data, or analysis and interpretation of data, drafting the article or revising it deeply and critically for important intellectual content, final approval of the version to be submitted.

Conflict of interest

The authors declare that they have no conflict of interest directly or indirectly related to the contents of the manuscript.

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