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**Retrospective cohort study of venous
thromboembolism rates in ambulatory cancer
patients, association with Khorana score and other
risk factors**

Venous thromboembolism in ambulatory cancer patients

Austin Keziah,¹ *George Jessica,^{1*} Robinson Emily J,² Scully
Marie,^{1,3} Thomas Mari R^{†1,3}

1. UCH Department of Haematology, 3rd Floor West, 250
Euston Road, London, NW1 2PG
2. King's College London Department of Biostatistics &
Health Informatics, Institute of Psychiatry, De
Crespigny Park, Denmark Hill, London, SE5 8AF
3. Department of Haematology & Cardiometabolic BRC,
1st Floor, Maple House, 149 Tottenham Court Road,
London, W1T 7DN

*joint first authors

[†] corresponding author: mari.thomas@nhs.net

Summary

Background & Aims Guidelines do not recommend that cancer outpatients receive thromboprophylaxis unless at high VTE risk, with the Khorana score suggested for risk stratification. This study investigated VTE incidence in outpatients with pancreatic, endometrial, colorectal, ovarian and cervical cancer, the role of Khorana score in risk assessment, and potential risk factors. **Methods** Data was retrospectively collected 1 year after cancer diagnosis. VTE associated with inpatient admissions was excluded. **Results** 746 patients were included. VTE rates varied: 26.8% pancreatic; 5.7% endometrial; 9.8% colorectal; 10.2% ovarian, 0.0% cervical cancer. Excluding VTE at diagnosis, potentially preventable VTE rates were 16.5% pancreatic; 3.8% endometrial; 9.8% colorectal and 8.7% ovarian cancer. Khorana score was associated with VTE in endometrial cancer only [high-risk:16.7% vs. low-risk:1.5%; $p<0.001$]. VTE rates for patients with central venous catheters (CVC) were 22.6-34.8% in pancreatic, endometrial, colorectal, and ovarian cancers. VTE was associated with CVC in endometrial, colorectal, and ovarian; chemotherapy and Hb<100g/L in pancreatic; surgery in endometrial and ovarian, and BMI>35 in ovarian cancers following adjusted analysis ($p<0.05$). **Conclusions** VTE is a significant burden in

pancreatic, endometrial, colorectal and ovarian cancers. Khorana score was not predictive in most cancers. The major VTE-associated variable was CVC. Our data suggests a role for clinical trials of thromboprophylaxis in targeted cancer outpatients.

Keywords

Venous thromboembolism, Khorana score, ambulatory cancer, thromboprophylaxis

Introduction

Venous thromboembolism (VTE) causes significant morbidity and mortality in patients with malignancy. The MEGA study (2005) demonstrated that the risk of VTE increased seven-fold in patients with cancer, and that the highest risk was immediately after diagnosis, in patients with metastatic disease, and in those with haematological malignancy.¹ Cancer VTE is the second leading cause of death in cancer patients, and it is a recognised independent risk factor for mortality.² Patients with cancer-associated thrombosis have an increased risk of VTE recurrence, and of major bleeding.^{3,4}

Risk assessment for VTE is now routine for both medical and surgical inpatients in the UK. International guidelines recommend thromboprophylaxis in surgical inpatients with a moderate VTE risk of 3%, provided bleeding risk is not high, and also in medical inpatients at a high risk (11%) of VTE.^{5,6} However, the role of thromboprophylaxis in outpatients with cancer is less clear, with guidance recommending that prophylaxis is not used routinely, but considered for those at high thrombotic risk.^{5,7} Some guidelines suggest risk stratification using the Khorana score (Table 1) with thromboprophylaxis considered in patients with a high risk score (≥ 3).^{8,9}

We undertook a retrospective cohort study to investigate VTE incidence in the first year of diagnosis in outpatients diagnosed with pancreatic, endometrial, colorectal, ovarian or cervical cancer, at a large tertiary cancer centre. We reviewed the association with Khorana score at cancer diagnosis and investigated the role of other risk factors in development of cancer VTE.

Methods

Patient selection

Retrospective identification of patients with a multidisciplinary team (MDT) diagnosis of pancreatic, endometrial, colorectal, ovarian or cervical cancer, between 1st December 2012 – 31st December 2014, or 1st December 2009 – 31st December 2014 for pancreatic cancer patients (to ensure sufficient data). Cases were excluded from analysis if: VTE occurred whilst an inpatient or within 90 days of discharge (NHS England, 2013); pre-existing anticoagulation at the time of VTE; patients who had incomplete data available to calculate a Khorana score; concurrent primary cancer or patients who did not receive all of their oncology care at the tertiary centre and therefore with insufficient follow-up data. For the main analysis, patients with VTE diagnosed at or before cancer diagnosis were also excluded, as the aim was to calculate the role of the Khorana score in identifying patients at risk of a VTE which could have potentially been prevented with thromboprophylaxis (Figure 1).

Data collection

For each patient, clinician reports (including clinic letters, chemotherapy planning documents, discharge summaries and MDT discussions), radiology reports, pathology results, electronic VTE risk assessments,

chemotherapy regime and electronically stored patient demographics were reviewed. Information on the following variables was collected: patient age, ethnicity, BMI, cancer type and stage, details of cancer therapy including chemotherapy, radiotherapy, and surgical intervention, indwelling central venous catheters as well as details relating to any VTE events including date, site, clinical presentation and treatment. VTEs were recorded if documented by radiology report or clinician report of confirmed VTE event. Baseline/pre-chemotherapy blood tests were collated including haemoglobin level, leukocyte count, platelet count, C-reactive protein and creatinine level, and the Khorana score calculated. Cancer stage was divided into early and advanced for the purpose of analysis. Early stage was defined as attempt at curative resection in pancreatic cancer, FIGO stages 1-3 in colorectal cancer and FIGO stages 1-2 in both endometrial and ovarian cancer.

Statistical analysis

Descriptive statistics were reported for patient demographics and treatment variables, stratified by cancer type to compare the different cohorts. For continuous variables statistics were reported in means (SD) or medians (IQR), where appropriate, and

categorical variables were reported by n (%). Clinical measures that are included in the Khorana score were grouped into high and low risk categories, corresponding to the thresholds when calculating the score. Similarly, patients were split into low risk (Khorana score <3) vs. high risk (Khorana score $\geq$ 3) for each cancer cohort. Abdominal VTE events were not included in the Khorana score analysis as such events were not included in the derivation of the score.

For the inferential analyses, a binary variable was created for VTE development (any vs. none). Univariate associations were tested between VTE development and clinical measures that were agreed *a priori* as potential risk factors of VTE using Pearson's chi-squared. Results were reported using the corresponding p-values.

Stepwise logistic regression using backward elimination was then performed for each cancer type, using a significance level for removal from the model of $\alpha=0.05$. This tested which of the VTE risk factors remained statistically significant after adjusting for the other factors. All analysis was completed using Stata version 14.0 (StataCorp, 2015).

Results

There were 878 new diagnoses of pancreatic, endometrial, colorectal, ovarian and cervical cancer between 01/12/2012 (or 01/12/2009 for pancreatic) and 31/12/2014 (Figure 1, STROBE diagram). 113 patients were excluded from the study due to pre-existing anticoagulation or incomplete data. 19 further patients were excluded as the thrombotic event occurred during patient admission or within 90 days of discharge or surgery (hospital acquired thrombosis, HAT). 746 patients were therefore included in the study: 97 pancreatic cancer diagnoses, 157 endometrial cancer, 205 colorectal cancer, 196 ovarian cancer, and 91 cervical cases. Patients who presented with a VTE at time of cancer diagnosis (n=16) were excluded from the subsequent VTE risk factor analysis. Patient and treatment characteristics of patients included in the VTE risk factor analysis are shown in Table 2.

VTE incidence

Rates of total VTEs and potentially preventable VTEs (Figure 2) were recorded for each cancer group.

VTE demographics

Pancreatic cancer 26 patients with VTE diagnosed during the first year of cancer diagnosis developed 31 individual clots (9 lower limb deep vein thrombosis (LL-DVT), 3 upper limb DVT (UL-DVT) [all central venous catheter (CVC) associated], 5 pulmonary emboli (PE), 1 inferior vena cava (IVC), and 13 intra-abdominal thromboses comprising of portal, splenic, hepatic, superior mesenteric and renal vein thromboses). Of these patients, 13/26 had symptomatic VTE, whilst the remaining patients had VTE incidentally found on staging scans – the majority of these were intra-abdominal VTE (5 portal vein, 4 splenic vein, 1 hepatic vein, 1 renal vein, 1 superior mesenteric vein) as well as 2 incidental PEs. 14/26 patients were treated with low molecular weight heparin (LWMH). Untreated patients were asymptomatic or had contraindication to anticoagulation.

Endometrial cancer 9 patients with VTE diagnosed during the first year of diagnosis developed 10 individual clots (2 LL-DVT, 1 UL-DVT [CVC associated], 7 PE). 6/9 were symptomatic, with 3 incidental PEs found on staging CT scans. All received treatment dose LMWH.

Colorectal cancer 20 patients with VTE diagnosed within the first year developed 21 individual VTE episodes (5

LL-DVT, 5 UL-DVT [all CVC associated], 8 PE, 1 neck, 2 portal vein thromboses). 9/20 patients were asymptomatic (7 incidentally found PE and 2 incidentally found portal vein thromboses on staging scans). The majority of patients (18/20) were treated with LMWH. Of the remaining 2 patients, 1 died prior to treatment commencing, and the other had a small non-occlusive CVC-associated DVT which was managed by removal of the line only.

Ovarian cancer 20 patients with VTE diagnosed within the first year developed 23 individual clots (5 lower limb DVT, 4 upper limb DVT [all PICC-associated], 12 pulmonary emboli, 2 inferior vena cava thromboses). 14/21 patients had symptomatic VTE, 7 asymptomatic, 1 patient had 3 individual events (1 symptomatic PE, followed by separate lower limb and IVC thromboses incidentally found on staging scans). 20/21 patients received LMWH. In the remaining patient anticoagulation was contraindicated due to high bleeding risk outweighing benefit for treating small incidental PEs.

Cervical cancer None of the 91 patients diagnosed with cervical cancer had a VTE unrelated to an inpatient stay or surgery in the first year following diagnosis.

Association with Khorana score

Patients were divided into high risk (≥ 3) and low risk (< 3) groups by Khorana score at diagnosis (excluding those with abdominal VTE). In all groups except for endometrial cancer, a high risk Khorana score was not associated with a higher VTE rate (Figures 3A-D).

Association with other variables

The association between the development of VTE in the first year of cancer diagnosis with background and treatment variables were analysed (Table 3). In all cancer groups (excluding cervical cancer where no patient developed a VTE), VTE development was univariately associated with indwelling central venous catheters (CVC) ($p < 0.05$). In endometrial and colorectal cancers chemotherapy use was significantly associated with VTE development; and in pancreatic, endometrial and ovarian cancers surgical intervention was significantly associated, even after exclusion of VTE occurring within 90 days of surgery. BMI was only associated with VTE development in ovarian cancer; and full blood count parameters used in the calculation of the Khorana score (platelet count $\geq 350 \times 10^9$, Hb level $< 100\text{g/l}$, leukocyte count $> 11 \times 10^9$) were only associated with VTE development in

endometrial cancer. Finally, advanced stage of cancer was univariately associated with VTE development in endometrial and ovarian cancer.

Risk factors that remained statistically significant after stepwise logistic regression were indwelling CVC for endometrial, colorectal and ovarian cancers; chemotherapy for pancreatic cancer only; surgery for endometrial and ovarian cancers; Hb <100g/L for pancreatic cancer; BMI>35 for ovarian cancer; and surgical intervention for endometrial and ovarian cancers.

The VTE rate for patients with indwelling lines were: 34.8% (8/23) for pancreatic; 25.0% (2/8) for endometrial; 22.6% (14/62) for colorectal and 22.7% (5/22) for ovarian. The VTE rate for patients having chemotherapy were: 23.2% (13/56) for pancreatic; 9.1% (4/44) for endometrial; 16.4% (19/116) for colorectal and 10.1% (15/148) for ovarian. Numbers were too small for further subgroup partitioning within subgroups.

The number of days between cancer and potentially preventable VTE diagnosis was calculated. The median (IQR) time to VTE was 24 days in endometrial cancer (7-62 days); 61 days (14-153) in ovarian cancer; 90 days

(42-191) in pancreatic cancer and 122 days (64-153) in colorectal cancer.

Discussion

This retrospective cohort study of ambulatory cancer patients demonstrates a significant burden of VTE in the first year of diagnosis in four out of five cancer groups analysed. The exception to this is cervical cancer in which there were no VTE unrelated to an inpatient stay or surgery. However, 4/91 cervical cancer patients developed VTE which were all associated with short day-case surgical procedures (3 EUA and 1 laparoscopic EUA) defined as “low risk” on local VTE risk assessment and thus did not receive post-operative thromboprophylaxis

The total rates of VTE were 26.8%, 5.7%, 9.8%, 10.2% and 0.0% for pancreatic, endometrial, colorectal, ovarian and cervical cancers respectively. Even excluding those patients who presented with VTE or had thrombosis diagnosed on initial staging scans, the majority of patients with these cancers had a VTE that was potentially preventable with thromboprophylaxis. However, this is not routine clinical practice for outpatients, despite being a quality standard in hospitalised patients.¹⁰ International

ACCP guidelines currently recommend that clinicians should not routinely offer pharmacological VTE prophylaxis to outpatients with cancer, but recommend prophylactic LMWH for patients with low bleeding risk and additional risk factors including previous VTE, immobilisation, hormonal therapies, angiogenesis inhibitors, thalidomide and lenalidomide.⁵ More recent guidelines suggest the use of the Khorana score for risk stratification.⁸

However, our data suggests that the Khorana score is not valuable in risk stratifying patients with pancreatic, colorectal, and ovarian cancers, although a higher Khorana score was predictive of 1-year VTE development in endometrial cancer. Furthermore, use of the Khorana score to define who may benefit from prophylactic anticoagulation in the cervical cancer cohort would have potentially meant all 25 patients with a high-risk score were unnecessarily anticoagulated, since none developed a VTE which was not associated with an inpatient admission or surgery.

We investigated other variables associated with VTE development in ambulatory cancer patients. Risk factors which remained statistically significant after stepwise

logistic regression were indwelling CVC for endometrial, colorectal, and ovarian cancers; chemotherapy for pancreatic cancer only; surgery for endometrial and ovarian cancers; Hb<100g/L for pancreatic cancer and BMI>35 for ovarian cancer. The VTE rate for patients with indwelling lines were particularly high, with around a quarter of endometrial, colorectal and ovarian; and over a third of pancreatic cancer patients with CVC developing VTE, either local or systemic.

Improving risk stratification in ambulatory cancer patients is likely to have an impact on morbidity due to the high burden of VTE incidence demonstrated in this study. The VTE risk in patients with malignancy is greatest in the first year following diagnosis, so it is important to develop simple and reliable methods to risk stratify in the MDT or outpatient department soon after diagnosis.¹¹ Despite some studies suggesting that bleeding rates with use of anticoagulants in cancer patients are higher than in patients without malignancy, large studies have refuted this and there is no evidence suggesting this is the case with primary thromboprophylaxis.^{7,12}

An obvious limitation is that this is a retrospective study. However, it includes a large cohort and provides

important information to guide future prospective investigations of thromboprophylaxis in ambulatory cancer patients, in particular, factors to identify those at high risk. Oncology care was delivered at our tertiary centre but some patients may have consulted their local hospitals with acute presentations, including of VTE. Thus, our data may in fact underestimate the incidence of VTEs and this may explain in part why there were no VTE diagnoses in the cervical cancer cohort. Future multicentre prospective studies looking at additional tumour groups would be of value in further evaluating the extent of the clinical problem.

In summary, this retrospective cohort study at a tertiary oncology centre has identified a significant burden of VTE in pancreatic, endometrial, colorectal, and ovarian cancer cohorts. Khorana score did not predict risk of VTE development in pancreatic, colorectal, ovarian or cervical cancer groups, although it was predictive in patients with endometrial cancer. The major variable associated with VTE development was indwelling CVC with VTE rates of 23-35% depending on tumour type. Our data suggests a role for clinical trials of routine thromboprophylaxis in targeted groups of cancer outpatients, such as those with

pancreatic cancer, or with endometrial, colorectal and ovarian cancers and indwelling central venous catheters.

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Dr Jessica George (joint first author) - performed research including data collection, and wrote the paper.

Dr Keziah Austin (joint first author) - performed research including data collection, and wrote the paper.

Miss Emily Robinson - statistically analysed the data, created tables and wrote the 'statistical analysis' section of the paper.

Dr Marie Scully - designed research, study and provided expert clinical knowledge to revise critically.

Dr Mari Thomas - designed research study and provided expert clinical knowledge to revise critically.

Competing interests: the authors have no competing interests

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