Healthcare costs of patients with cancer stratified by Khorana score risk levels

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ABSTRACT

Aims: Patients with cancer are at high risk of venous thromboembolism (VTE), which entails a high economic burden. The risk of cancer-associated VTE can be assessed using the Khorana score (KS), a validated VTE risk prediction algorithm. This study compared healthcare costs associated with different KS in a population of patients newly diagnosed with cancer.

Methods: The Optum Clinformatics DataMart database (01/01/2012–09/30/2017) was used to select adult patients with ≥1 hospitalization or ≥2 outpatient claims with a cancer diagnosis (index date) initiated on systemic therapy or radiation therapy. Patients were classified in mutually exclusive cohorts based on KS (i.e. KS = 0, 1, 2 or ≥3). The observation period spanned from index to the earliest among the end of data availability, death, end of insurance coverage, or 12 months.

Results: In total 6,194 patients (KS = 0: 2,488; KS = 1: 2,125; KS = 2: 1,074; KS ≥ 3: 507) were included. On average, patients were aged 68 years, 48–52% were female, and the Quan–Charlson comorbidity index ranged between 1.1 and 1.4. Over the observation period, all-cause total healthcare costs per patient per month (PPPM) were $8,826 (KS = 0), $11,598 (KS = 1), $14,028 (KS = 2), and $16,211 (KS ≥ 3). Using the KS = 0 cohort as a reference, adjusted PPPM costs were $2,506, $4,775, and $6,452 higher in the KS = 1, KS = 2, and KS ≥ 3 cohorts, respectively. Hospitalization and outpatient costs were the main drivers of these differences. Similar results were found for VTE-related costs, which represented 4–11% of the total all-cause cost difference between KS cohorts.

Limitations: Residual confounders; results may not be generalized to patients with other insurance plans or those who received treatments other than systemic therapy or radiation therapy.

Conclusions: This real-world analysis found that cancer patients at higher risk of VTE (based on KS) incurred significantly greater all-cause and VTE-related healthcare costs compared with cancer patients at lower risk of VTE.

Introduction

Cancer is a major risk factor for venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism.1–3 Specifically, the risk of VTE is increased by four to seven-fold in patients with cancer.1,3, and those with cancer and treated with systemic therapy are at even higher risk.1,3 In addition to causing high morbidity and mortality, cancer-associated VTE imposes a substantial cost burden for healthcare systems.4–9

The Khorana score (KS) is a validated clinical risk assessment tool10–24 endorsed by current guidelines25,26 to predict the risk of VTE in patients with cancer. This score is derived from different risk factors for VTE, including the tumor’s primary site, pre-chemotherapy platelet count, hemoglobin levels <100 g/L, or use of red blood cell growth factors, pre-chemotherapy leukocyte count >11 x 10^9/L, and body mass index (BMI) ≥35 kg/m^2.27 Several previous studies used this score to identify patients with cancer at high risk of VTE (i.e. KS ≥2 or ≥3) and assess the efficacy and safety of primary thromboprophylaxis in this subgroup.24,28–31

Patients with cancer at high risk of VTE may incur higher healthcare costs than those at lower risk due to increased risk of early mortality and cancer progression,32–34 along with greater burden of VTE-related expenses and ensuing complications, including VTE recurrences, post-thrombotic syndrome, and pulmonary hypertension.35 However, among studies that assessed the economic burden of cancer-associated VTE, none stratified patients into different VTE risk cohorts. Such information may provide preliminary insight into the economic impact that may ensue from VTE prophylaxis in patients at high risk of VTE. Therefore, this study sought to compare healthcare costs in newly diagnosed.
cancer patients treated with various cancer treatments stratified by risk of VTE using the KS clinical algorithm.

Methods

Data source

The Optum Clinformatics Data Mart database was used with data from January 2012 to September 2017. The database covers 12–14 million annual lives in all census regions of the United States. It contains more than 36 months of historical data on patients (claims from commercial and Medicare Advantage plans, including patients’ demographics, dates of eligibility, inpatient, outpatient, and pharmacy claims, laboratory tests and results, and date of death). Data from the Optum Clinformatics Data Mart database are de-identified and fully compliant with the confidentiality requirements of the Health Insurance Portability and Accountability Act.

Study design

This study used a retrospective cohort study design, with the index date defined as the date of the first diagnosis of cancer with at least six months of continuous eligibility before the index date (i.e. baseline period). Cancer treatment initiation was assessed during the 45 days following the index date to avoid including patients for whom treatment initiation was inappropriately delayed. Laboratory values required for the calculation of the KS were collected and assessed during the 28 days prior to the initiation of cancer treatment (i.e. the risk stratification period), and this period may overlap with the baseline period. The observation period covered the period from the index date up to the earliest among the end of data availability, death, 12 months post-index, or end of insurance coverage.

Study population

Patients were included if they met the following criteria: (1) ≥18 years of age on the index date; (2) ≥1 hospitalization or ≥2 outpatient visits with a diagnosis of cancer (i.e. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 140–209; ICD-10-CM: C00–C7A); (3) treated with systemic therapy (based on the list from the National Cancer Institute) or radiation therapy within 45 days post-index date (i.e. index cancer treatment); (4) ≥6 months of continuous eligibility during the baseline period; and (5) ≥1 laboratory test result for hemoglobin, platelet, and leukocyte counts during the 28-day risk stratification period (Figure 1).

The following exclusion criteria were applied: (1) a VTE event during the baseline period; (2) used anticoagulants any time prior to the index date or up until a VTE event during the follow-up period; or (3) had an inpatient surgery after the index date, defined as a procedure code for major surgery, abdominopelvic surgery, and neurosurgery or orthopedic surgery during an inpatient stay (Figure 1). Note that major surgery did not include surgical resection of cancer.

Study outcomes

All-cause and VTE-related healthcare costs were evaluated and broken down into medical (i.e. hospitalization, emergency room [ER] visit, outpatient visit, and other visit costs) and pharmacy costs. Other visits included visits such as home service and hospice. VTE-related costs were defined as costs associated with medical claims with a primary or secondary diagnosis of VTE. VTE-related pharmacy costs were defined as costs associated with anticoagulant dispensing.

Statistical analysis

Baseline characteristics, overall and stratified by KS risk cohorts, were reported using descriptive statistics. More specifically, frequencies and proportions were used to summarize categorical variables; means, standard deviations, and medians were used to summarize continuous variables.

All-cause and VTE-related healthcare costs were evaluated during the observation period for each KS cohort and reported per-patient-per-month (PPPM). Moreover, costs were inflation-adjusted to 2018 USD. Cost differences between KS cohorts were computed using multivariable linear regression models adjusting for age, sex, insurance type, region, year and month of the index date, Quan-Charlson comorbidity index (CCI) score, Elixhauser comorbidities with a proportion ≥5%, and healthcare resource utilization and costs. p-values and 95% confidence intervals (CIs) were obtained using non-parametric bootstrap procedures with 499 replications.

Results

A total of 6,194 cancer patients were selected, including 2,488 (40.2%) classified in the KS = 0 cohort, 2,125 (34.3%) in the KS = 1 cohort, 1,074 (17.3%) in the KS = 2 cohort, and 507 (8.2%) in the KS ≥3 cohort (Figure 1).

Baseline characteristics

The mean age of patients was 68.0 years (range, 18 to 90 years) and 48.8% were female (Table 1). The study population had good geographical representation across the four US census regions. Lung (16.8%), breast (14.3%), and prostate cancer (10.2%) were the most common malignancies at the index date, and systemic therapy was the index cancer treatment for 62.3% of patients. The mean CCI was 1.2, which did not vary substantially across KS cohorts. In each KS cohort, the top three most common Elixhauser comorbidities were hypertension (range: 62.3%–71.8%), chronic pulmonary disease (range: 22.1%–41.6%), and hypothyroidism (range: 19.8%–22.9%), with higher rates in the higher KS cohorts. The mean all-cause total healthcare costs were $8,689 among all patients and ranged between $7,864 and $9,542 in the KS cohorts. Hospitalization costs and outpatient visit costs accounted for the majority of the baseline cost differences between KS cohorts.
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The observation period, which was truncated at 12 months following the index date, lasted an average of 9.6 months in the KS = 0 cohort, 8.7 months in the KS = 1 cohort, 8.0 months in the KS = 2 cohort, and 6.9 months in the KS ≥3 cohort (Table 1). Over this period, total all-cause healthcare costs averaged $8,826 PPPM for patients in the KS = 0 cohort, $11,598 for those in the KS = 1 cohort, $14,028 for those in the KS = 2 cohort, and $16,211 for those in the KS ≥3 cohort (Figure 2). The main drivers of the total all-cause healthcare costs PPPM were outpatient visit costs (KS = 0: $5,855, KS = 1: $6,860, KS = 2: $7,380, KS ≥3: $7,671), which accounted for 47.3%–66.3% of total costs (Table 2). Hospitalization costs (KS = 0: $1,217, KS = 1: $2,118, KS = 2: $3,633, KS ≥3 $4,915) accounted for 13.8%–30.3% of total costs.

After adjusting for baseline covariates, costs PPPM were $2,506 higher in the KS = 1 cohort, $4,775 higher in the KS = 2 cohort, and $6,452 higher in the KS ≥3 cohort relative to the KS = 0 cohort (all p < .05; Figure 2). Across all comparisons, hospitalization costs were the primary drivers of the total cost differences, representing 35.3%, 48.3%, and 52.9% of the total cost difference for the comparison of KS = 1, KS = 2, and KS ≥3 versus KS = 0, respectively (Table 2). The second most important driver was outpatient visit costs, representing 36.7%, 28.4%, and 22.9% of the total cost difference for the comparison of KS = 1, KS = 2, and KS ≥3 versus KS = 0, respectively.

VTE-related costs increased with increasing risk and were significantly higher among patients with KS = 1, KS = 2, or KS ≥3 compared to those with KS = 0 (all p < .05; Figure 3). Similar to all-cause costs, VTE-related hospitalization (49.1%–78.0%) and VTE-related outpatient costs (9.5%–21.8%) accounted for the majority of the difference in healthcare costs (Table 2 and Figure 3).

Discussion

In this retrospective cohort study of patients newly diagnosed with cancer, healthcare costs were evaluated and stratified by patients’ risk of VTE. All-cause total healthcare costs increased with increasing risk of VTE, with a cost difference of $6,452 PPPM between the KS ≥3 and KS = 0 cohorts up to 12 months of follow-up. Hospitalization costs were the main driver of the observed cost differences, and outpatient visit costs also accounted for a substantial portion of the cost differences. Similar patterns were observed for VTE-related costs, which were $708 PPPM higher in the KS ≥3 cohort versus the KS = 0 cohort. Altogether, these results emphasize that patients with cancer at risk of VTE incur substantial incremental healthcare costs.

Previous studies that assessed the healthcare costs of cancer-associated VTE compared the costs of cancer patients with versus without VTE. These studies invariably found higher total healthcare costs in cancer patients with VTE relative to those without VTE. Nonetheless, the populations
Eligibility post-index, months, mean ± SD (median)  
Observation period\textsuperscript{a}, months, mean ± SD (median)

Demographics

| Age\textsuperscript{d}, mean ± SD (median) | Gender\textsuperscript{d}, female, n (%) | Year of the index date, n (%) |
|----------------------------------------|-------------------------------------|-------------------------------|
| 68.0 ± 12.2 [70]                       | 3,021 (48.8)                       | 2012                           |
| 67.6 ± 12.2 [69]                       | 1,185 (47.6)                       | 2013                           |
| 68.2 ± 12.5 [70]                       | 1,032 (46.8)                       | 2014                           |
| 68.2 ± 12.2 [70]                       | 553 (51.5)                         | 2015                           |
| 68.2 ± 12.2 [70]                       | 251 (49.5)                         | 2016                           |

Region\textsuperscript{e}, n (%)  

| Region | Total healthcare costs \textsuperscript{f}, mean ± SD [median] | All-cause HRU\textsuperscript{g}, mean ± SD [median] |
|--------|---------------------------------------------------------------|-----------------------------------------------------|
| South  | 8,689 ± 17,848 [12.1]                                        | 1.225 (19.8)                                        |
| West   | 7,864 ± 18,334 [12.0]                                        | 0.96 (7.6)                                           |
| Midwest| 9,352 ± 17,999 [12.2]                                        | 0.87 (5.0)                                           |
| Northeast| 9,542 ± 16,564 [12.4]                                      | 0.80 (4.9)                                           |
| Unknown| 8,147 ± 17,254 [12.6]                                        | 0.69 (3.6)                                           |

Insurance plan type\textsuperscript{h}, n (%)  

| Type of index cancer treatment, n (%) | Systemic therapy | Radiation therapy |
|--------------------------------------|------------------|-------------------|
| Solid cancers                        | 1,439 (23.2)     | 2,025 (32.7)      |
| Lung                                 | 4,737 (76.5)     | 787 (12.8)        |
| Prostate                             | 1,042 (16.8)     | 543 (21.8)        |
| Breast                               | 630 (10.2)       | 543 (21.8)        |
| Colorectal                           | 885 (14.3)       | 486 (20.9)        |
| Other solid cancer                   | 1,251 (21.8)     | 213 (9.8)         |

Charlson comorbidity index\textsuperscript{d}, mean ± SD (median)  

| Hypertension                         | 4,100 (66.2)     | 436 (5.6)         |
| Chronic pulmonary disease            | 1,884 (30.4)     | 147 (5.6)         |
| Hypothyroidism                       | 1,251 (21.8)     | 13 (0.5)          |
| Peripheral vascular disorder         | 1,223 (19.7)     | 6 (0.2)           |
| Depression                           | 1,223 (19.7)     | 255 (4.1)         |

All-cause HRU\textsuperscript{i}, mean ± SD (median)  

| All-cause healthcare costs\textsuperscript{j}, NUS 2018, mean ± SD |
|---------------------------------------------------------------|-----------------------------------------------------|
| Total healthcare costs                                       | 8,689 ± 17,848 [12.1]                               |
| Hospitalization costs                                        | 1,554 ± 8,943 [12.0]                               |
| ER visit costs                                               | 1,174 ± 5,702 [12.0]                               |
| Outpatient visit costs                                       | 3,850 ± 11,161 [12.0]                              |
| Other medical costs                                          | 914 ± 3,148 [12.0]                                 |
| Pharmacy costs                                               | 1,197 ± 5,019 [12.0]                               |
assessed in these studies often differed relative to that of the current study with regards to the location of the primary tumor (i.e. only patients with lung cancer\textsuperscript{5} or specific cancer types\textsuperscript{6,7} rather than any cancer type) and patient disease history (i.e. prevalent cancer cases\textsuperscript{4,5} rather than newly diagnosed patients); one study focused on the costs of hospitalization\textsuperscript{9}. There was also substantial heterogeneity in the reporting of healthcare costs; prior studies reported costs incurred after a first VTE event\textsuperscript{4,6}, after the initiation of chemotherapy\textsuperscript{5,7}, or after the initiation of anticoagulation\textsuperscript{8} as opposed to post-cancer diagnosis in the current study. Further, some studies reported costs over follow-up that extended up to three or five years\textsuperscript{4,8}, as opposed to 12 months in the current study. Among studies that reported healthcare costs over 12 months (i.e. post-VTE or post-chemotherapy initiation), total all-cause healthcare costs ranged from $6,246 to $9,227 PPPM among patients with VTE\textsuperscript{5–7}, which is lower than the estimate in our study (weighted average across KS cohorts: $11,283 PPPM). This may be due to the aforementioned differences in study design and study population, as well as the study periods assessed (current study: 2012–2017, prior studies [range]: 2004–2009). Furthermore, differences in the proportion of patients with an advanced cancer stage, which is associated with a higher risk of VTE\textsuperscript{38}, might also partially explain the difference in costs between the current study versus prior studies\textsuperscript{10}; however, information on cancer stage was not available in this and most previous studies. These differences highlight that the current study builds on the existing literature by evaluating healthcare costs among newly diagnosed patients with cancer stratified by the risk of subsequent VTE, as assessed by the KS.

In the current study, both all-cause and VTE-related healthcare costs significantly increased with KS. All-cause healthcare costs were predominantly driven by non-VTE-related costs across all KS cohorts in the current study, which aligns with previous studies that have found KS to be predictive of early mortality and cancer progression during the first four cycles of outpatient chemotherapy, independent from other major prognostic factors including VTE itself\textsuperscript{22–34}. The VTE-related healthcare cost findings suggest that VTE and associated complications (e.g. post-thrombotic syndrome, and pulmonary hypertension\textsuperscript{35}) entail higher costs among patients at high risk compared with those at low risk. Notably, hospitalization costs were the main driver of the difference in VTE-related and all-cause costs, highlighting the substantial costs associated with the inpatient management of VTE. In addition, VTE may have translated into higher costs related to the management of cancer, where VTE can delay or interrupt adjuvant chemotherapy\textsuperscript{39} and other comorbidities. In addition to the management of the VTE event itself, the occurrence of VTE may complicate the management of comorbidities, which are highly prevalent in the cancer population\textsuperscript{40–42}. For example, potential drug–drug interactions with anticoagulants may necessitate the modification or temporary withdrawal of medications used to treat certain comorbidities, leading to adverse health outcomes and higher costs. Further studies are needed to better understand how VTE may affect comorbidities and healthcare costs among patients with cancer.

The population analyzed in the current study has been evaluated by our group in a previous study that assessed patients’ risk of VTE and death stratified by KS\textsuperscript{43}. In that study, patients with KS = 1, KS = 2, and KS ≥3 had a 1.72, 2.46, and 4.99 times greater risk of VTE, respectively, relative to those with KS = 0 up to 12 months of follow-up. This increased risk of VTE was also associated with significantly greater all-cause mortality. Notably, patients with VTE were approximately seven times more likely to die prematurely relative to those who did not develop VTE among the KS = 0 cohort. Therefore, the higher rates of VTE and mortality

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**Figure 2.** All-cause total healthcare costs per patient per month up to 12 months of follow-up. Abbreviation. KS, Khorana score. \textsuperscript{a}Defines p-value < .05. \textsuperscript{1}Calculated using linear regressions. \textsuperscript{p}-values were obtained using nonparametric bootstraps with 499 replications. \textsuperscript{2}Adjusted for the following variables: sex, age, index year, region, insurance type, Charlson comorbidity index, baseline healthcare resource use and costs, and comorbidities with proportions ≥5% at baseline (e.g. hypertension and chronic pulmonary disease).
documented in our previous study corroborate the higher costs found in this study for patients at high risk of VTE. Recent results from the CASSINI (rivaroxaban vs. placebo) and AVERT (apixaban vs. placebo) trials have shown that primary VTE prophylaxis with the direct oral anticoagulants rivaroxaban or apixaban reduces the risk of VTE in patients with cancer and a KS ≥ 2. This evidence led the American Society of Clinical Oncology and the International Society on Thrombosis and Haemostasis to formulate a new recommendation to offer rivaroxaban or apixaban for primary VTE prophylaxis in ambulatory patients with cancer. By assessing healthcare costs stratified by KS, the present study provides insights for future studies to assess the potential savings that might ensue from interventions to reduce VTE rates in high-risk patients.

**Limitations**
The current study is subject to important limitations. First, included patients were treated with either systemic therapy or radiation therapy, and results may not apply to patients...
receiving other cancer treatments, such as newer therapies (e.g. CAR-T) or surgical procedures. Second, this claims-based study may also be subject to residual confounding due to unrecognized or unmeasured potential confounding factors. Third, BMI was evaluated using ICD codes on health insurance claims, which may have led to an underestimation of the KS. Fourth, these results may have limited generalizability to the uninsured US population, patients with health insurance plans that differ from those of the population analyzed in this study, or non-US populations. Finally, there is the potential for health insurance claims to have coding omissions and inaccuracies.

Conclusions
In this large real-world retrospective claims analysis, patients newly diagnosed with cancer who were at higher risk of VTE incurred significantly greater all-cause and VTE-related healthcare costs compared to patients with a lower risk of VTE. VTE-related costs represented 4% to 11% of the total costs difference for KS = 0 to KS ≥3 cohorts and were mainly driven by VTE-related hospitalization costs. Even though VTE-related costs may appear to be a modest proportion of the total cost difference among this high burden population, primary VTE prophylaxis in cancer patients with a KS ≥2 could potentially reduce the costs and consequences of VTE in the higher risk subgroups.

Notes
i. Overall, 67.7% of VTE-related hospitalizations during follow-up (up to 12 months) had a primary diagnosis of VTE (KS = 0: 69.8%; KS = 1: 65.6%; KS = 2: 65.0%; KS ≥3: 72.4%).
ii. Using secondary neoplasm ICD codes as a proxy for metastasis, 13.8% of patients in the present study had metastasis on the index date (KS = 0: 10.4%; KS = 1: 12.4%; KS = 2: 18.3%; KS ≥3: 27.0%). When extending to within one month after the index date, 28.3% of patients had metastasis (KS = 0: 21.3%; KS = 1: 26.9%; KS = 2: 36.5%; KS ≥3: 50.9%).

Transparency
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Declaration of financial/other relationships
G.G., F.L., S.D.M., and P.L. are employees of Groupe d’Analyse, Ltee, a consulting company that provided paid consulting services to Janssen Scientific Affairs, LLC, for the conduct of the present study.
D.M. is an employee of Janssen Scientific Affairs and a shareholder of Johnson & Johnson.
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Author contributions
All authors were involved in the conception and design, or analysis and interpretation of the data; the drafting of the paper or revising it critically for intellectual content; and approved the version to be published; all authors agree to be accountable for all aspects of the work.

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