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ORIGINAL ARTICLE

Management of venous thromboembolism in cancer patients: the economic burden of hospitalizations

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Abstract
Purpose Venous thromboembolism (VTE) is one of the most frequent events associated with cancer, requiring hospitalization and generating additional healthcare costs. To date, no studies analyzing the additional costs resulting from VTE associated with cancer in France have been published. The objective of this study was to provide an estimation of the additional cost induced by VTE with cancer by analyzing hospital stays reported in the 2013 PMSI French Hospital Database ("Programme de Médicalisation des Systèmes d'Information", a national hospital administrative database) for four cancer types (breast, lung, hepatocellular carcinoma, and colon).
Methods The analysis is divided into three parts: a descriptive evaluation of hospitalizations for VTE with cancer, an analysis by severity level of diagnosis-related groups (DRG), and an estimation of the hospital costs based on the National Reference Costs (ENC). The French public ATIH ("Agence Technique de l'Information sur l'Hospitalisation", a national Agency for Data on Hospital Care) database was used. The critical approach of this study is based on analysis of the distribution of stays according to levels of severity of DRG.
Results A total of 14,251 hospitalizations were analyzed combining VTE and cancer. Hospitalizations of the two highest levels of severity (levels 3 and 4) for VTE with cancer represented 81.7 % of all hospitalizations in this population. Increased costs were seen for all four cancer types evaluated, with cost coefficients ranging from 1.34 to 2.01. For example, the average cost of lung cancer in cancer patients with VTE in the PMSI database was 7296 € versus 4647 € in the ATIH database. Cost coefficients were calculated, ranging from 1.34 in colon cancer, 1.50 for breast cancer, 1.57 in lung cancer, and 2.01 for hepatocellular carcinoma.
Conclusion As discussed in the article, the current costs are high. Better physician adherence to clinical practice guidelines could potentially reduce these costs by lowering the number of recurrent VTE in patients with cancer.

Keywords Cancer · Economic burden · Hospitalization · Venous thromboembolism

Data were collected and analyzed by Bourguignon S, health economist. From the "Stratégique Santé" company, Evry

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Introduction

Venous thromboembolism (VTE) is a complication commonly linked to active cancers, and which is furthermore exacerbated by the associated treatments. Patients with cancer have a six- to sevenfold higher risk of VTE than those without [1]. Progressing cancers account for almost 20 % of all new VTE cases [2], and the occurrence of VTE increases the risk of death in cancer patients (hazard ratios, 1.6–4.2; $P < 0.01$) [3, 4]. According to Geerts et al., Cancer patients who undergo surgery have a risk of developing postoperative DVT two times higher than non-cancer patients, and three times more likely to make a fatal PE [5]. In addition, VTE is a major cause

of morbidity and mortality in hospitalized patients, including those with acute medical illnesses like cancer. [6, 7].

The risk of VTE varies according to both tumor type and location [1–8]. With an odds ratio (OR) of 28.0 (95 % CI 4.0–199.7), hematologic cancers are associated with the highest risk, followed by lung cancers (OR=22.2; 95 % CI 3.6–136.1), and gastrointestinal cancers (OR=20.3; 95 % CI 4.9–83.0), while breast cancer patients have a much lower risk of VTE (OR=4.9; 95 % CI 2.3–10.5) [9].

Considering changes of organization of care, of medical practices, and of costs of care, the economic study results cannot be transposed to others countries. It is therefore relevant to conduct the study in French context to validate the results of Khorana in France.

Further exacerbating this problem, cancer patients experiencing VTE are at an increased risk of recurrence with recent studies showing a tendency towards the greatest risk of recurrence during the first few days after the initial event [10–12]. Low-molecular-weight heparins (LMWH) have been shown to be effective in preventing the risk of VTE recurrences without increasing the risk of bleeding in cancer patients. Specifically, the CLOT study showed that the use of dalteparin was more favorable than utilization of VKA in treating and preventing VTE recurrence in cancer patients [8]. Thus, LMWH are recommended by national and international guidelines [13–15].

The value of proactively managing VTEs in cancer patients is clearly twofold; for the patient, it lowers the risk of potentially fatal complications associated with their cancer and a likely worsening of general status, while for healthcare payers (government and private health insurers), it avoids costs associated with the management of thrombosis, notably hospital costs; indeed, hospital costs weight heavily on the healthcare system, accounting for 42 % of the expected French national objective of healthcare expenditure in 2015 (ONDAM—national target for health insurance spending 2015).

Despite the known increased risk of an initial VTE and recurrences in cancer patients, along with the associated costs, few analyses on the economic impact of VTE in this patient population have been performed. Khorana et al. reported that in the USA, VTE in a cancer patient entails substantially increased additional hospital costs and more extensive and longer patient care than for a cancer patient without VTE, with average hospital costs 2.9 times higher [9]. In another US study, a general population experiencing VTE was compared with a population without VTE in a real-life setting from 2004 to 2008 [16]. This study showed an annual cost differential per patient, all costs combined, of more than $15,941 (95 % CI, $14,819–$17,012).

To date, no studies evaluating incremental costs associated with VTEs in cancer patients in France have been published. The current study aimed to address this in the context of the French healthcare system in 2013. In light of the varying risk of VTEs according to tumor type, selected cancer types were included in our analysis, lung, hepatocellular, and colon cancers, which have a high risk of VTE, and breast cancer with a lower risk of VTE, representing a population with fewer comorbidities and care requirements.

Materials and methods

Data sources and patient populations

The French PMSI database ("Programme de Médicalisation des Systèmes d'Information", a national hospital administrative database) of medicine, surgery, and obstetrics (MCO) for 2013 was used to identify all inpatient hospitalizations in public and private institutions for patients classified as being hospitalized with a concomitant diagnosis of cancer and VTE according to CIM-10 coding. The French public ATIH MCO database ("Agence Technique de l'Information sur l'Hospitalisation", a national Agency for Data on Hospital Care) for 2013 was used in a subsequent comparative analysis. Patients had to have either cancer or VTE as the primary diagnosis, with the other diagnosis considered a comorbidity or complication. Both first VTE events and recurrences are captured in the PMSI extraction. The average cost included the number of readmissions for 1 year. All cancer types were included. For DVTs, the CIM-10 codes I801, I802, and I803 were used, and I260 and I269 were used for PE.

Study design

The analysis was performed in several steps. First, a descriptive evaluation of hospitalizations for a primary diagnosis of VTE associated with a cancer or for a primary diagnosis of cancer associated with a VTE was performed using the PMSI; second, the economic cost of hospitalizations for four cancer types (lung, breast, colon, and hepatocellular carcinoma) was evaluated using the PMSI; third, the prevalence of hospitalizations according to their level of severity (coded according to diagnosis-related groups (DRG)) were evaluated; and fourth, hospital costs in terms of the incremental costs for these hospitalizations according to the National Reference Costs (ENC; "Echelle Nationale des Coûts"), which are determined from a real-life sample of private and public institution costs, were estimated.

The economic cost of hospitalization was determined in a two-step process. For each hospitalization (with both diagnoses of cancer and VTE), the mean costs for lung, breast, hepatocellular, and colon cancer patients were calculated using the PMSI according to the Standardized Diagnosis-Related Hospitalizations (GHS; "Groupes Homogènes de Séjour"), taking into account the mean duration of hospitalization (adjusted according to the maximum and minimum set values) as

well as any additional costs due to any emergency or intensive care stays, or ongoing observation. Mean hospitalization costs were then compared with data for costs of hospitalizations in all institutions using the ATIH MCO database.

An analysis using a comparative population from the PMSI database for each cancer type was not performed given that the validity of such a population is questionable in light of associated comorbidities (e.g., infections) which can generate substantial incremental costs which cannot be distinguished from costs generated by VTE. For the ATIH population, the population was not identified on the basis of VTE or any other comorbidity. We thus analyzed the distribution of the diagnosis-related groups (DRG; "Groupe Homogène de Malades in French"), with costs calculated according to the National Reference Costs (ENC; v11f) for public MCO institutions for 2012. Within a given DRG, several levels of severity of hospitalization are defined according to the complexity of the hospitalization which is dependent on patient age, comorbidities, and complications, from level 1, the least severe through to level 4 with the highest severity.

Finally, a cost coefficient was calculated for incremental costs associated with VTE using the ratio of the mean costs of hospitalizations for the population from the PMSI database (with VTE) versus the costs of hospitalizations of the ATIH population (with or without VTE). To ensure a valid comparison and minimize bias, costs for each DRG were adjusted according to the National Reference Costs (ENC) for data from both the PMSI and ATIH databases.

Results

Characteristics of patients and hospitalizations

Using the PMSI database, the two hospitalization groups identified were 6683 hospitalizations (6398 patients) for a primary diagnosis of cancer and 7368 hospitalizations (7223 patients) for a primary diagnosis of DVT or PE, with a concomitant diagnosis of VTE or cancer, respectively. The majority (71.5 %) of hospitalizations were in public institutions. Patients had a mean age of 71.5 years (median also at 71.5 years), and the male/female ratio was even with 53 % of male patients. There were no differences across patient characteristics (age and sex ratio) in the two groups (primary diagnosis of cancer versus VTE). The PMSI database does not authorize individual statistical analyses; data are by GHM and hospitals. The PMSI database includes no clinical results and so do not allow directly an analysis of the stages of cancer. Moreover, the initial extraction was done on all types of cancer; it was not appropriate to look for acts characteristics of metastatic phases. This subgroup analysis should be performed on only a single type of cancer that was not the objective of this study.

The mean cost per hospitalization was 7743 € for a primary diagnosis of cancer and 3470 € for a primary diagnosis of VTE. Among all hospitalizations in 2013 for patients with a primary diagnosis of either a tumor or a VTE in the PMSI database, the most common causes were for PE alone, accounting for 19.6 % of hospitalization costs, followed by 5.9 % for DVTs alone.

Hospitalizations for cancer were evaluated in terms of severity of hospitalization in the PMSI database. For patients with a primary diagnosis of cancer, the highest level of severity (3 and 4) accounted for the majority of hospitalizations in public institutions (81.7 %; Fig. 1a); by definition, level 3 and 4 hospitalizations are more costly and as a consequence accounted for a greater proportion of costs in our sample (Fig. 1a, 1b).

Comparison of hospitalization costs from two national databases

Data from the PMSI database, which represent the amount an institution receives per hospitalization based on the published costs in the Official Journal, were then compared with data from the public ATIH database—which represent the real hospitalization costs to the institution based on the National Reference Costs. This comparison was performed to identify incremental costs for hospitalizations in patients with a diagnosis of cancer (lung, hepatocellular, colon, and breast). The public ATIH database does not distinguish between the presence or not of VTEs or other complications. For the majority of hospitalizations, the comparative analysis of the ATIH and PMSI databases did not reveal a differential in costs according to DRG, for any of the four cancers analyzed. Figure 2 shows results for hepatocarcinoma and breast—similar results were seen for lung and colon cancers.

The distribution of hospitalizations by severity for these two databases was compared for these four cancers. The results show a significantly different distribution by level of severity between data from the ATIH and PMSI databases (Table 1; Fig. 3). Overall, for all four cancer types, there were more severe-level hospitalizations according to the data sample from the PMSI database for patients with cancer or VTE as a primary diagnosis than in the ATIH database. While the ATIH database shows a distribution leaning towards levels 1 and 2 for hospitalizations with or without VTE annual report [17]), the PMSI database shows a tendency towards a higher level of severity for hospitalizations due to cancer with a VTE (Fig. 3). Equivalent distributions were observed for the other three cancers types.

The costs and cost coefficients of PMSI hospitalizations (with VTE) compared with ATIH hospitalizations (with or without VTE) are shown by cancer type in Table 2. The ratio varied from 1.34 to 2.01 depending on cancer type.

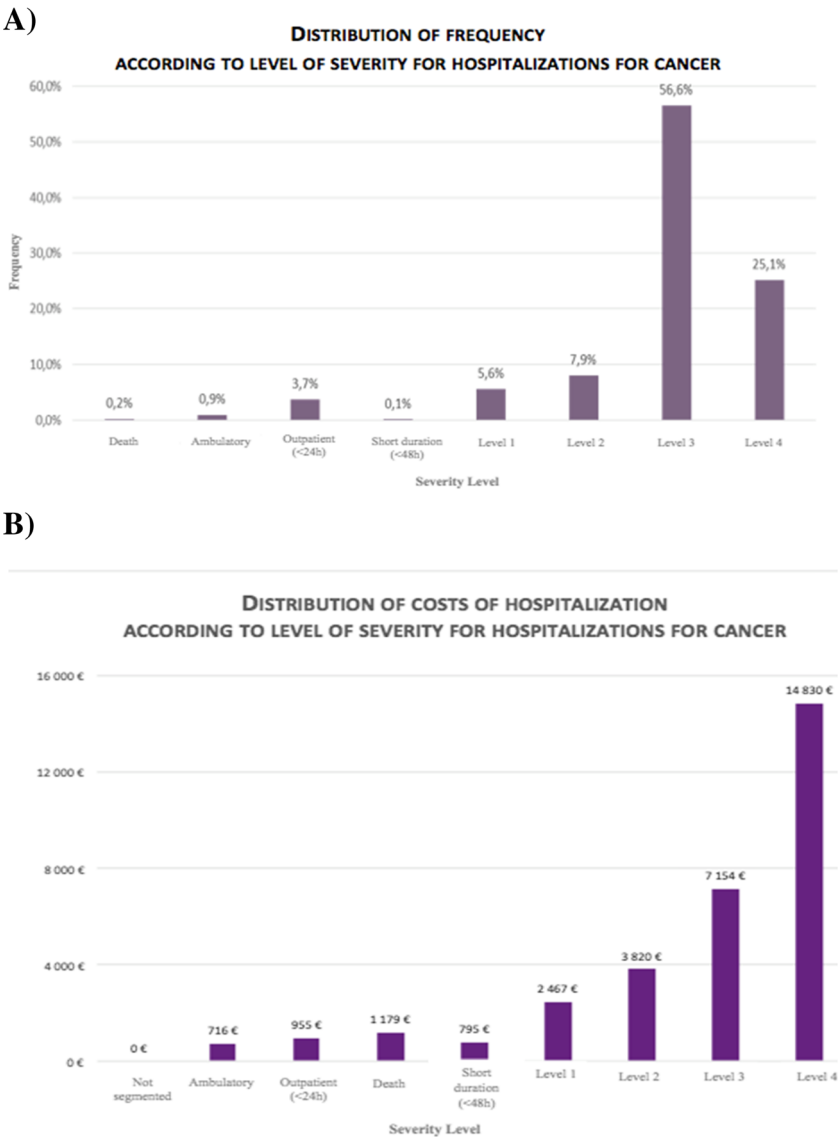

Fig. 1 Distribution of **a** frequency and **b** costs of hospitalizations according to level of severity for hospitalizations for cancer

Discussion

The current analysis validates the hypothesis of incremental costs of hospitalization due to VTE associated with a cancer in France and presents an estimation of this cost. The estimation is likely to be low as the study uses a conservative approach comparing a large population by cancer type. This study raises two key points: on the one hand the economic costs for the society of VTEs in the context of cancer and on the other hand the avoidable part of this cost.

Scotte et al. performed a study in two relatively homogenous populations, prostate and breast cancer patients, based on an analysis of the French PMSI database from 2012 [18]. In the absence of a comparison arm, the extra costs were not estimated—which is a key aspect of the current study.

Only hospital costs could be measured with exhaustivity. There is no study on the allocation between outpatient and inpatient costs in this pathology, neither on the part of self-injection use by patients.

The descriptive part of our study and the calculation of hospitalization costs are coherent with the study by Scotte et al. which reports a mean cost of 3261 € for breast cancer patients experiencing VTE and 3584 € for prostate cancer patients with VTE. Their study demonstrated that these costs are not linked to VTE recurrence. However, an earlier study reported that the frequency of re-hospitalization for PE or DVT is 14.3 % after 1 year, and that re-hospitalizations occur within 90 days for 58.6 % of PEs and 50.7 % of DVTs [19]. According to a recently published study by Lang et al. [20], the rate of re-hospitalization may be even higher, with reports of 12 to 32 % for PE and 6 to 16 % for DVTs, with higher rates of hospitalization reported in the Medicare population (i.e., the public healthcare system) indicating an increased

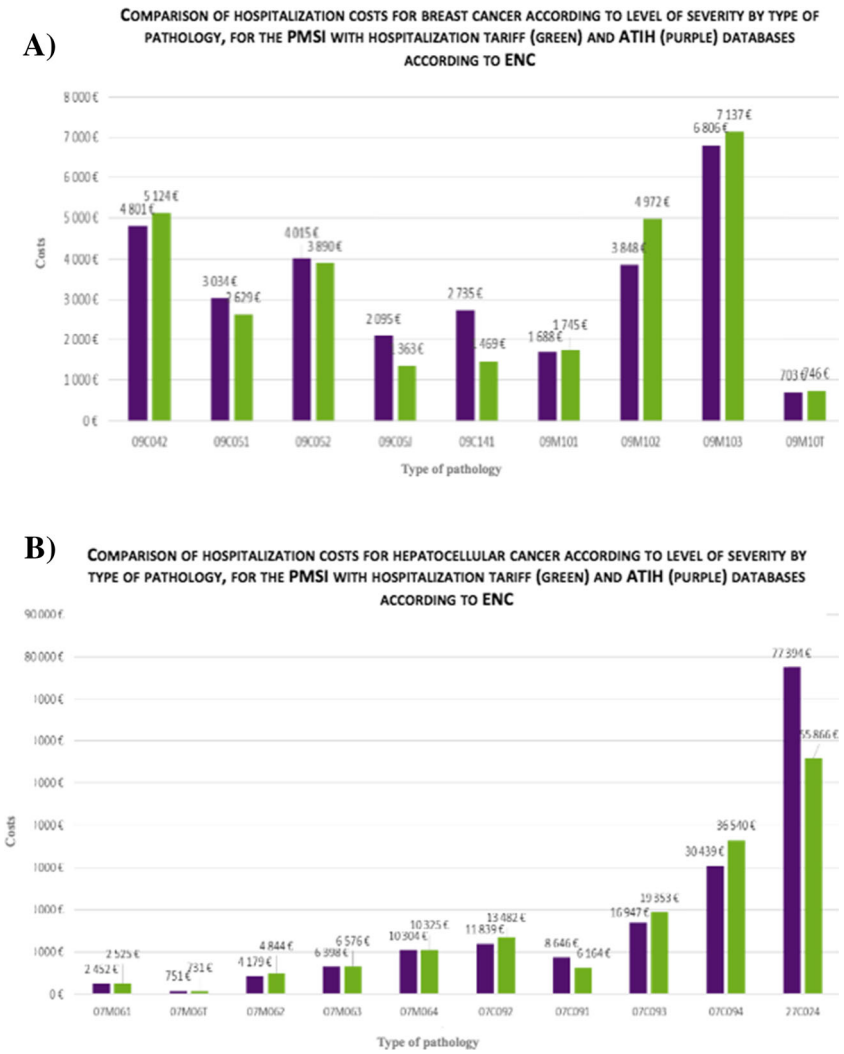

Fig. 2 Comparison of hospitalization costs for **a** breast and **b** hepatocellular cancer according to level of severity by type of pathology, for the PMSI with hospitalization tariff (*green*) and ATIH (*purple*) databases according to the ENC

risk of re-hospitalization in more fragile populations. The authors also highlight an increased duration of hospitalizations for patients experiencing VTE. From the broad perspective of the budgetary impact of VTE in France, the study by Scotte estimated the total costs of VTE for two pathologies, prostate and breast cancer, over 2 years as 3.4 million euros in 2012.

The value of a cost coefficient for the French healthcare system as determined in this study highlights the importance of the fact that VTEs can, at least in part, be prevented with anticoagulant treatment. This point is particularly relevant given the report from the French observational study CARMEN showing that compliance with Good Practices recommendations (ANSM recommendations and GFTC

Table 1 Distribution by frequency of hospitalizations by level of severity and cancer type for the PMSI and ATIH databases

Level of hospitalization[a]	Lung		Breast		Colon		Hepatocellular	
	PMSI[b]	ATIH (public)[c]	PMSI[b]	ATIH (public)[c]	PMSI[b]	ATIH (public)[c]	PMSI[b]	ATIH (public)[c]
1	4.09 %	18.37 %	13.53 %	63.15 %	2.82 %	19.37 %	3.30 %	35.04 %
2	4.74 %	20.68 %	28.57 %	16.06 %	5.22 %	24.90 %	6.94 %	22.57 %
3	73.72 %	29.70 %	53.38 %	9.27 %	69.25 %	34.77 %	68.37 %	17.78 %
4	12.72 %	6.33 %	0	0	19.89 %	9.25 %	18.20 %	4.91 %

[a] Level 1 (least severe) to level 4 (greatest severity), according to complexity of the case (age, comorbidities, etc.)

[b] Patients with cancer and VTE from the PMSI database

[c] Cancer for all patients (including all comorbidities) from the public ATIH database

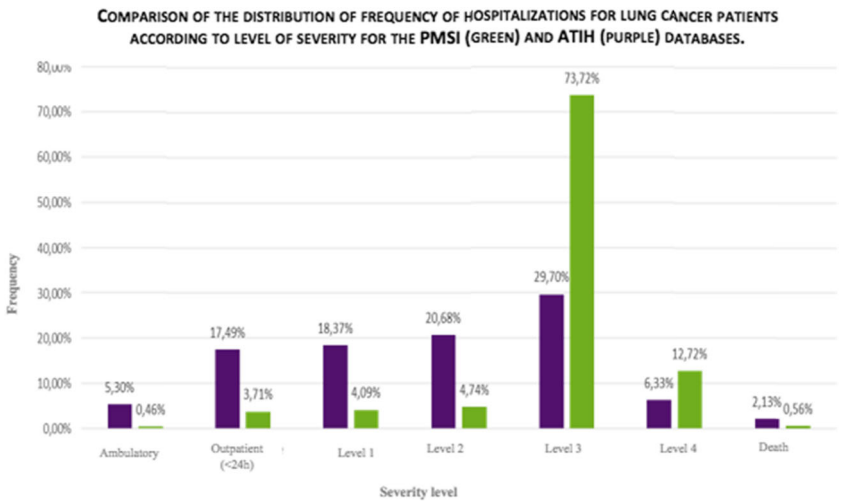

Fig. 3 Comparison of the distribution of frequency of hospitalizations for lung cancer patients according to level of severity for the PMSI (*green*) and ATIH (*purple*) databases

expert opinion) designed to avoid recurrences is partial, with only 57.8 % of patients treated for 10 days with LMWH followed by maintenance treatment for 3 months [21].

This point was also analyzed in a US study using a decision-tree cost-efficacy model, based on a retrospective analysis of two national databases, ENDORSE 2006/2007 (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) and NIS (Nationwide Inpatient Sample) [22]. The model estimates a global reduction at 0.5 % of mortality with the correct use of prophylactic LMWH, which was associated with avoided death costs of $50,637. Extrapolation of this data in the primary analysis of the model to the entire US population estimates the number of avoided deaths as 15,875 per year and a reduction in costs of $803 million. A 1 % improvement in adhering to LMWH recommendations by the American College of Chest Physicians (ACCP) would reduce the number of deaths annually by between 139 and 193, generating a cost saving of between $7.0 and $9.8 million. However, this study, while interesting, was focused only on prophylaxis in surgery and medical environment, in case of acute medical infections. [23].

This is the first study performed in the French setting designed to estimate the costs associated with VTEs in an oncology context. However, only direct hospital medical costs were considered. Transport costs and loss of productivity [24] were not included in the analysis as these data are not reported in the PMSI database. To ensure an exhaustive analysis from an economic perspective, costs generated from non-hospital follow-up of VTE patients should be taken into consideration. The choice of treatment and its impact on the cost of non-hospital follow-up should not be overlooked in the therapeutic decision-making process. Over the last few years in France, filling hospital prescriptions in non-hospital pharmacies has become an important means of cost saving. In the short term, all healthcare institutions will have to implement healthcare savings, and the choice of treatments will play a critical role in reducing non-hospital treatment costs. Furthermore, in some cases, uncomplicated VTEs are not managed by hospitals and are thus not included in this analysis (despite generating healthcare costs). This estimation of the cost from this study should thus be considered conservative in terms of the economic burden of VTEs in cancer.

Life expectancy is expected to increase in patients with cancer, and consequently the incidence of cancer-associated thrombosis in those patients. The implications of our results are numerous. It is of utmost importance to improve the guidelines implementation in patients with VTE and cancer to reduce the risk of recurrence and also the duration of stay at hospital [25]. The ambulatory management of VTE in patients with cancer should be encouraged, especially in patients who have other frequent reasons to be hospitalized.

Table 2 Mean cost of hospitalization by cancer type, according to ENC value and estimation of the cost coefficient for hospitalizations for VTE

	Mean cost of hospitalization (€ ENC)		
	Patients with cancer and VTE (PMSI)	All cancer patients (ATIH)	Coefficient
Lung	7296	4647	1.57
Breast	5268	3515	1.50
Hepatocellular	9525	4744	2.01
Colon	11,693	8716	1.34

The choice of treatment and its impact may change between countries, and it is not possible to generalize this result to other countries than France. However, the results of the Khorana study and the French study should encourage other countries to conduct a similar reflection and to think about the respect of the good practice recommendations.

conclusion

This French study supports the concept that VTE associated with cancer generates incremental financial costs which could be lowered by the proper management of VTE, which is of high clinical interest in terms of patient mortality and avoidable hospitalizations.

This assessment highlights the economic value of following the Good Practice Guidelines which recommend anticoagulant therapy to treat, and to avoid recurrence of, VTE in patients with cancer.

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Conflict of interest The authors declare that they have no conflict of interest.

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