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Evaluation and Improvement of Oncologists' Adherence to NCCN Guideline for Prevent and Treatment of Cancer Associated Venous Thromboembolism

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Abstract

Objective: The aim of this study is asses the adherence of physician to NCCN guideline recommended anticoagulant therapy in patient with cancer associated venous thromboembolism.

Methods: Study was designed with two phases an observational phase and an interventional prospective phase with the educational program, was conducted at Middle Euphrates cancer center/An-Najaf governorate/Iraq. Ten oncologists who agreed to participate in the study. Used validated questionnaire include (25 items) where distributed to 10 oncologists who were working at the Middle Euphrates cancer center then all questionnaires were collected from participated oncologists over two months. Subsequently, an educational part including a lecture and posters was submitted in cancer center to in raising awareness of seriousness of this disease and how prevention and treatment.

Results: The overall mean total score of oncologists for prevention and management of cancer associated VTE (out of 25 items) of all questionnaire parts was remarkably increased from (0.54) to (0.72) after the intervention therefore the level of oncologist's adherence to NCCN guideline improved to 70% with large effect size (1.04).

Conclusion: According to the final evaluation of responses of oncologists showed improvement in adherence toward the NCCN guideline. In addition, there were several barriers that mainly reduce the adherence like sever side effect, increase cost and Lack of awareness of guidelines.

Keywords: Cancer, venous thromboembolism, anticoagulant therapy, NCCN guideline, adherence

Introduction

The earliest mention of a connection between cancer and thrombosis was made by Bouillaud in 1823, which marks the beginning of the relationship between the two diseases.[1] Trousseau noted a connection between thrombophlebitis that is moving and possible malignancy in 1865.[2] cancer-associated thromboembolism cases have been steadily rising around the globe.[3] Malignancies and the hemostatic system have a complex relationship that has long been understood. Because thromboembolic illness is the second most prevalent cause of mortality after cancer progression and has a reported incidence of 4–20% in cancer patients, it is critical that these patients receive sufficient treatment.[4,5] By secreting procoagulant substances by tumor cell that eventually activate platelets and inflammatory cells, which in turn encourage angiogenesis and clot formation, cancer cells bypass the coagulation route in order to improve their diffusion. In fact, thrombotic events may reveal a hidden malignancy as its initial symptom.[6] The synthesis of plasminogen activator inhibitor-1 (PAI-1), the release of tissue factors, and the production of cytokines by tumor cells all have a role in the development of thrombosis.[7,8] In addition to venous thrombosis, these intricate pathways may also result in artery thrombosis.[9] The primary site of the cancer, the presence of metastatic disease, the use of antineoplastic therapies like chemotherapy and hormonal therapy, surgery, disturbances to venous flow caused by extravascular tumor compression, intravenous tumor invasion, long-term bedridden status, and intravenous catheterization are just a few of the significant risk factors for cancer-associated VTE that previous studies have identified.[4,10,11] A cancer diagnosis increases the risk of venous thromboembolism (VTE) by more than four times than non-patients, while active chemotherapy patients see an increase of up to 6.5 times.[12] The likelihood of having VTE during cancer treatment may be influenced by patient-related factors (such as age, body mass index, performance status, smoking, and concurrent medical comorbidities), tumor-related factors (such as cancer type and stage), and treatment-related factors (such as surgery, use of chemotherapy, hormone therapy or immune-checkpoint inhibitor and placement of a venous catheter).[13,14]

Methodology

Between November 2022 and March 2023, a study was designed with two phases an observational phase and an interventional prospective phase with the educational program, was conducted at Middle Euphrates cancer center/An-Najaf governorate/Iraq to assess the knowledge and practice followed by oncologists in the prevention and treatment of cancer-associated venous thromboembolism disease to evaluate adherence to the National Comprehensive Cancer Network (NCCN) guideline recommended anticoagulant therapy in patients with cancer-associated venous thromboembolism. Ten oncologists who agreed to participate in the study were included. A validated questionnaire was used to evaluate the knowledge and practice of oncologists that followed in the prevention and treatment of venous thromboembolism. This questionnaire was validated before the start of the study was conducted by experts and through performing a pilot study. used questionaries that include 25 questions have two parts the first part contains 14 questions inquiring about risk and NCCN recommended to

Questionnaire about cancer-associated VTE

	Part I: questionnaire about risks and NCCN recommended management of cancer-associated VTE	Never	Some-times	Always
1	How often do you use risk scores to identify patients at high risk of VTE?			
2	How often do you talk to your patients with risk of blood VTE?			
3	How familiar are you with recommendations for VTE risk assessment and primary prophylaxis?			
4	How familiar are you with the Khorana score?			
5	How often do you do you prescribe mechanical or pharmacologic thromboprophylaxis during chemo-therapy or Perioperatively in cancer patients?			
6	Concerned about the risk of bleeding, when use thromboprophylaxis agents in cancer patients			
7	Considered patient factors when deciding on thromboprophylaxis during chemotherapy			
8	Clinical risk factors, biomarkers or both are used to estimate VTE risk			
9	Thromboprophylaxis in cancer patients are highly recommended when • Hemoglobin level less than 10 g/dl or use of red cell growth factors • Pre-chemotherapy leukocyte count >11,000/mm^3			
11	In outpatient thromboprophylaxis, oral anticoagulants preferred than low molecular weight heparin (LMWH)			
12	For hospitalized oncology patients Low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or fondaparinux with or without pneumatic compression (PCD) used for patients with no contraindication to anticoagulation or bleeding			
13	Thromboprophylaxis in patients undergoing cancer surgery a Prophylactic dose LMWH, UFH, or fondaparinux with or without PCD is recommended			
14	For prevention of VTE in high-risk ambulatory medical oncology patients starting a new chemotherapy regimen, apixaban or rivaroxaban are prescribed for up to 6 months			
15	Out-of-hospital VTE prophylaxis is recommended for up to 4 weeks after surgery for high risk patients with abdominal or pelvic cancer			

	Part II: For treatment of cancer-associated VTE	Never	Some-times	Always
1	Apixaban, edoxaban or rivaroxaban preferred over LMWH for patients without GI malignancies.			
2	LMWH preferred over oral anticoagulants in patients with GI malignancies.			
3	Unfractionated heparin (UFH) is preferred for patients with Creatinin clearence (CrCl) of <30 mL/min			
4	Recommended duration of anticoagulation therapy is for as long as the patient's cancer is active or under treatment			
5	For recurrent VTE on warfarin, switching to LMWH, UFH, fondaparinux, or oral anticoagulants			
6	In Patients with Extremes of weight BMI ≥40			
7	In Patients with BMI ≥40, prophylactic dalteparin (7500 units daily or 5000 units every 12 hours,or 40–75 units/kg daily)			
8	In patients with Renal impairment and CrCl < 30 ml/min oral anticoagulants are recommended			
9	In patients with Hepatic dysfunction Apixaban and edoxaban or oral anticoagulants are recommended			
10	In patients with Thrombocytopenia oral anticoagulants are preferred than LMWH			
11	In pregnant cancer patients, no specifc thromboprophylaxis recommended by NCCN guideline			
12	Training sessions for health professionals regarding VTE prevention are conducted			

manage cancer-associated venous thromboembolism and the second part has11 questions about assessing the treatment of cancer associated venous thromboembolism. To assess the responses of oncologist and their adherence to the NCCN guideline, the mean score for each questionnaire was categorized as correct or neutral, or incorrect. When the oncologist adheres to a specified item within a questionnaire he was considered "correct" adherence and given a score of one, when he did not adhere, assigned as "incorrect", oncologist who did not respond or did not know the optimal response he was assigned as neutral, however, both incorrect and neutral responses scored zero. the intervention phase includes the lecture and posters to enhance the knowledge and improve the practice of participants about how prevention and treatment of venous thromboembolism disease according to NCCN guideline.

The study was approved by the Ethical and Scientific Committee of the Faculty of Pharmacy/Kufa University (September 2022) in addition to the Scientific Committee of Research of Najaf Health Directorate (September 2022) registration number 3055 dated 4/9/2022.

Statistical Analysis

Data of oncologists and cancer-patients before and after education program were entered managed and analyzed using the statistical package for social sciences, SPSS, version 28. Descriptive statistics presented as frequencies and percentages for categorical variables and as mean and standard deviation or standard error with 95% confidence interval for scale (continuous) variables.

The statistical tests used in comparisons based on the type of variables, paired t test used to compare means within group, before vs. after. When a scale variable did not follow the normal statistical distribution, alternatively, non-parametric tests where applied; Mann Whitney U test to compare two groups (between groups) while Wilcoxon Signed Rank Test used to compare within group (before vs. after). For categorical variables, chi square test used in comparison. As an alternative, Fisher's exact test used when chi-square test was inapplicable (when small numbers or zero frequency are found). All statistical procedures were performed at a level of significance of 0.05.

Results

As shown in (Table 1), 10 oncologists were included in this study. the mean age of participant oncologist was 40.8 ± 8.9 (range: 28–58) years. They had a duration in practice of oncology of 8 months to 20 years with a mean of 8.4 ± 6.6 years. Majority of the participant oncologists, 7/10 had board graduation of specialty, one with master degree and two with MBChB degree, (Table 2) Regarding following specific guideline for anticoagulant therapy, three oncologists did not follow any guideline and depend their practice and experience, however, 4/10 followed NCCN and ESMO guidelines, one oncologist did follow NCCN and ASCO, one followed NCCN and NEJM and only one oncologist followed the NCCN guideline only, (Table 2).

The comparison of mean scores before and after the education program revealed significant change in the overall mean score of the oncologist compared to their scores before education program, where the mean score was 0.65 ± 0.06 and it was significantly increased to 0.78 ± 0.5 after the education program, with a large effect size of 0.76, (*P*. value <0.05), (Table 3). Almost similar trend of changes was observed after the education program regarding the 11 items of the questionnaire about treatment of cancer-associated VTE as shown in the (Table 4). Further comparisons were performed for the total questionnaire items which included 25 items, and significant changes were also reflected in total scores for the 25 items (Table 5) and (Figure 1).

To assess the possible effect of the baseline characteristics (age, duration in practice and degree of specialty) on the changes in the adherence scores for the 14 items, 11 items and overall, 25 items, we performed bivariate correlation test which revealed that neither age nor the years in practice significantly affect the change in adherence score, ($P > 0.05$). Conversely, the and Degree of Specialty was significantly associated with changes in the adherence score, ($P < 0.05$), (Table 6), to clarify this correlation, further comparison was performed for the mean adherence scores of oncologists with board graduation versus those with MBChB\master degree (Table 7).

Table 1. **Descriptive statistics of age and years in practice in oncology field of participated doctors (*N* = 10)**

Variables	Mean	SD	Range
Age	40.8	8.9	28–58
Duration of Practice in oncology (year)	8.4	6.6	0.8–20

Table 2. **Distribution of oncologists according to Degree of Specialty and guideline for anticoagulant therapy they did follow (*N* = 10)**

Variables		No.	%
Degree of Specialty	Board	7	70.0
	Master	1	10.0
	MBChB	2	20.0
Total		10	100.0
Follow specific guideline for anticoagulant therapy	NCCN and ESMO	4	40.0
	NCCN and ASCO	1	10.0
	NCCN and NEJM	1	10.0
	NCCN	1	10.0
	None*	3	30.0
Total		10	100.0

*None: They depended their clinical experience, practice and judgment.

Table 3. **Comparison of mean scores of oncologists for the 14 items of questionnaire about risks and NCCN recommended management of cancer-associated VTE**

Item (Q)	Before		After		
	Mean	SE	Mean	SE	*P*. value
Q1	0.60	0.16	0.80	0.13	0.168
Q2	0.30	0.15	0.70	0.15	0.037
Q3	0.90	0.10	0.90	0.10	1.000
Q4	0.60	0.16	0.70	0.15	0.343
Q5	0.40	0.16	0.60	0.16	0.168
Q6	0.80	0.13	0.80	0.13	1.000
Q7	0.80	0.13	0.90	0.10	0.343
Q8	0.90	0.10	0.90	0.10	1.000
Q9	0.40	0.16	0.70	0.15	0.041
Q10	0.60	0.16	0.80	0.13	0.168
Q11	0.80	0.13	0.80	0.13	1.000
Q12	0.80	0.13	0.90	0.10	0.343
Q13	0.40	0.16	0.60	0.16	0.168
Q14	0.80	0.13	0.80	0.13	1.000
Overall mean score out of 1	0.65	0.06	0.78	0.05	0.011
Overall Mean Percent score	65.0%	5.8%	77.9%	5.0%	0.011
Overall mean total score out of 14	9.10	0.81	10.90	0.71	0.002

Effect size for overall change in overall mean score = 0.76 (large effect).

Table 4. **Comparison of mean scores of oncologists for the 11 items of questionnaire about treatment of cancer-associated VTE before and after education program**

Q11	Before		After		*P*. value
	Mean	SE	Mean	SE	
Q1	0.50	0.17	0.70	0.15	0.157
Q2	0.80	0.13	0.80	0.13	1.000
Q3	0.70	0.15	0.80	0.13	0.317
Q4	0.40	0.16	0.60	0.16	0.157
Q5	0.80	0.13	0.90	0.10	0.317
Q6	0.40	0.16	0.60	0.16	0.157
Q7	0.00	0.00	0.50	0.17	0.025
Q8	0.00	0.00	0.40	0.16	0.046
Q9	0.30	0.15	0.70	0.15	0.046
Q10	0.10	0.10	0.60	0.16	0.022
Q11	0.30	0.15	0.60	0.16	0.083
Overall mean score out of 1	**0.39**	**0.06**	**0.65**	**0.08**	**0.005**
Overall Mean Percent score	**39.1%**	**6.1%**	**65.5%**	**8.3%**	**0.005**
Overall mean total score out of 11	**4.30**	**0.67**	**7.20**	**0.92**	**0.005**

Effect size for overall change in overall mean score = 1.15 (large effect).

Table 5. **Comparison of overall mean scores of oncologists for the total questionnaire (25 items) of NCCN guideline risk assessment, management and treatment of VTE before and after education program**

	Mean score		Level of adherence		
Oncologist	Before	After	Before	After	Change
1	0.28	0.52	Inadequate	Inadequate	None
2	0.32	0.64	Inadequate	Partial	Yes
3	0.32	0.44	Inadequate	Inadequate	None
4	0.52	0.72	Inadequate	Partial	Yes
5	0.52	0.64	Inadequate	Partial	Yes
6	0.56	0.88	Partial	Adequate	Yes
7	0.64	0.72	Partial	Partial	None
8	0.72	1.00	Partial	Adequate	Yes
9	0.72	0.84	Partial	Adequate	Yes
10	0.76	0.88	Partial	Adequate	Yes
All oncologists	0.54	0.72	Inadequate	Partial	Yes
Total change	Improved	7			
	None	3			
Percentage of improved		70%			
P. value	0.001				

Effect size for overall change in overall mean score = 1.04 (large effect).

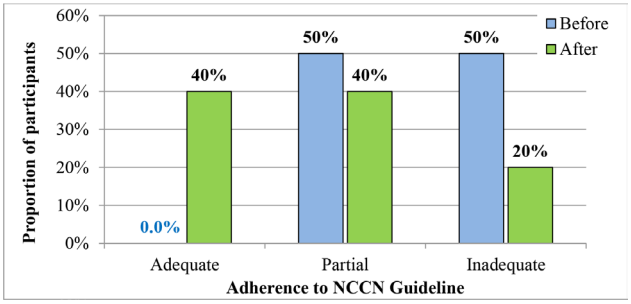

Fig. 1 **Overall levels of adherence to NCCN guideline before and after education program of the 10 participant oncologists.**

The reasons for non-adherence according to the oncologists opinion are shown in (Table 8), where 5 oncologists stated that non adherence , under use or Noncompliance with Guidelines could be attributed to lack of awareness of guidelines , 7/10 concern about adverse effects, 2/10 stated that guidelines are difficult or inconvenient to use in our patients, 4/10 need for new resources or facilities that are not available in our center, 2/10 due to disagreement between guidelines and clinical practice/experience and 6/10 attributed the non-adherence to the increased costs.

Discussion

In this study, Regarding the knowledge of participant oncologists toward NCCN guideline for prevention and treatment of cancer-associated VTE guideline, in the present study found that mean total scores of oncologists about prevention and treatment of cancer-associated VTE increased after intervention (educational program) particularly in the questions concerned with the significant knowledge and practice of oncologist about cancer-associated VTE risks and management of cancer-associated VTE according to NCCN guideline this is due to the fact that before intervention the overall mean total score for oncologists about that it (9.1) compared to (10.9) after intervention and with large effect size (0.76) as shown in the Table 3.

Almost similar trends of changes were found regarding other parts of knowledge and practice. Concerning the knowledge and practice of oncologists about treatment of cancer-associated VTE, it was show that after intervention program the knowledge and practice of oncologists was significantly enhanced especially in the correct identification of patient with comorbidities and the need for anticoagulant prophylaxis for patients with risk for VTE. This was reflected by that the overall mean total score for prescribing anticoagulant agents which showed a notable elevated after intervention from (4.3) before to (7.2) after the intervention with large size effect (1.15) as shown in the Table 4. This study is comparable to one from the Kingdom of Saudi Arabia that was reported by Al-Tawfiq and Saadeh, which found that the use of several educational intervention enhanced the compliance rate for VTE prevention.[15] The overall mean total score of oncologists for prevention and management of cancer associated VTE (out of 25 items) of all questionnaire parts was remarkably increased from (0.54) to (0.72) after the intervention therefore, the level of oncologist's adherence to NCCN guideline

Table 6. **Results of bivariate correlation analysis between general baseline characteristics and adherence questionnaire scores of oncologists**

		Dependent variable		
Independent variable	**Correlation parameter**	**Risk assessment and management questionnaire (14 items)**	**Treatment questionnaire (11 items)**	**Overall (25 items)**
Age	*R*	−0.308	−0.232	−0.380
	P. value	0.387	0.519	0.279
Duration of Practice in oncology	*R*	0.110	−0.305	−0.186
	P. value	0.763	0.392	0.608
Degree of Specialty	*R*	0.427	0.513	0.708
	P. value	**0.030 sig**	**0.021 sig**	**0.001 sig**

R: Correlation coefficient, sig: significant.

Table 7. **Comparison of mean adherence scores of oncologists according to the degree of specialty**

Questionnaire		**Degrees**				***P*. value between group**
		Board		**MBChB\Master**		
		Mean	**SD**	**Mean**	**SD**	
Risk and management (14 items)	Pre	10.1	2.0	6.7	2.1	**0.049 sig**
	Post	11.5	1.9	9.3	2.5	**0.039 sig**
	Mean difference	1.4	0.79	2.6	0.92	**0.005 sig**
	% change	13.9%	6.8%	38.8%	9.9%	**0.022 sig**
P. value within group		**0.039 sig**		**0.032 sig**		
Treatment (11 items)	Pre	4.9	2.1	3.0	1.7	**0.041 sig**
	Post	7.1	3.1	7.0	3.1	**1.000**
	Mean difference	2.2	1.04	4.0	0.96	**0.003 sig**
	% change	44.9%	14.6%	133.3%	13.7%	**0.001 sig**
P. value within group		**0.016 sig**		**0.005 sig**		
Overall 25 items	Pre	15.0	3.92	9.7	3.79	**0.006**
	Post	18.7	4.54	16.7	4.73	**0.347**
	Mean difference	3.7	1.69	7.0	1.70	**0.007 sig**
	% change	24.7%	9.0%	72.2%	10.2%	**0.001 sig**
P. value within group		**0.017 sig**		**0.011 sig**		

Table 8. **Reasons for under-use of or noncompliance with guidelines**

Reasons	**No.**	**%**
Lack of awareness of guidelines	5	50.0
Concern about adverse effects	7	70.0
Guidelines are difficult or inconvenient to use in our patients	2	20.0
Need for new resources or facilities that are not available in our center	4	40.0
Disagreement between guidelines and clinical practice and experience	2	20.0
Increased costs	6	60.0

improved to 70% with large effect size (1.04) as shown in the Table 5. Previously, an ambulatory and inpatient oncology setting conducted prospective research between September and December 2018. Utilizing eight criteria created based on the NCCN Guideline on Cancer Associated Venous Thromboembolic Disease. For five of the eight pre-defined criteria, the rate of adherence to the guidelines varied from 59 to 100%, while the rate for the remaining two remained at 0–1%. The rates of adherence for initiating prophylaxis at admission and determining the appropriate anticoagulant dose increased significantly after recommendations were followed.[16]

The Degree of Specialty was significantly associated with changes in the adherence score, ($P < 0.05$), (Table 6), to clarify this correlation, further comparison was performed for the

mean adherence scores of oncologists with board graduation versus those with MBChB\master degree , this comparison revealed that board certified oncologist had higher scores before education program, and therefore, the effect of the education program was more obvious in those with MBChB and master graduation, this reflected by the mean differences and percentage change reported in the Table 7.

Furthermore, we reported many barriers that reduce the oncologists adherence to the guideline (Table 8). Adverse effects (bleeding) and increase cost constitute 70% and 60% respectively from barriers. This study Similar to a multicenter study in Canada and united state that included medical staff, research coordinators, and patients in 27 intensive care units, it was discovered that there are some barriers to the use of thromboprophylaxis. These include, in descending order of frequency: the cost of drugs, concern over patient bleeding, and lack of resident information.[17] Accordingly, the next barriers that constitute 50% lack of awareness of guideline. There are a number of knowledge gaps among oncologists, including the current guidelines for treating symptomatic calf-vein thrombosis, according to a survey of physicians' knowledge and practices in managing thrombosis conducted in the United States. Another possibility is that oncologists are unaware of currently recommended VTE management strategies.[18] In addition, need for new resources or facilities that are not available in the center by 40%. In previous study the use of prophylaxis increased as a result of the adoption of a hospital-wide computer alert tool that alerted oncologists to patients at risk for DVT, and rates of DVT and PE among hospitalized patients were markedly decreased.[19] In a different study, the adoption of a formal CME program for VTE prevention did result in some increase in adherence.[20] According to an Italian study, a teaching hospital saw an increase in the appropriate use of VTE prophylaxis among surgical patients from 64% to 97% after implementing several interventions, such as pocket guidelines, presentations, and working groups to identify barriers to change.[21]

Guidelines are difficult or inconvenient to use in our patients and Disagreement between guidelines and clinical practice and experience reason constitute 20% of barriers according the opinion of the participants. Several physician-related factors were identified as potential barriers to adherence in a general survey of clinical practice guideline uptake barriers, including lack of familiarity, disagreement with the guidelines, lack of confidence in doing so, belief that doing so will not improve outcomes, and overcoming resistance to altering established practice patterns.[22]

This study has some limitations, including the fact that it was conducted exclusively at the Middle Euphrates Cancer Center in the Iraqi governorate of An-Najaf because of time constraints and the short duration required to complete a single-center study. This restricts generalizability in other Oncology centers in Iraq.

Conclusion

According to the final evaluation of responses of oncologists showed improvement in adherence toward the NCCN guideline. In addition, there were several barriers that mainly reduce the adherence like sever side effect, increase cost and Lack of awareness of guidelines.

Competing Interests

According to the authors, no conflicts of interest exist.

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References

1. Bouillaud, S., & Bouillaud, J. (1823). De l'Obliteration des veines et de son influence sur la formation des hydropisies partielles: consideration sur la hydropisies passive et general. Arch Gen Med, 1(2), 188–204.
2. Trousseau, A. (1865). Phlegmasia alba dolens. Clinique Medicale de l'Hotel-Dieu de Paris., 94.
3. Ikeda, S., Koga, S., Yamagata, Y., Eguchi, M., Sato, D., Muroya, T., Yonekura, T., Tsuneto, A., Yoshimuta, T., & Koide, Y. (2018). Comparison of the effects of edoxaban, an oral direct factor Xa inhibitor, on venous thromboembolism between patients with and without cancer. Journal of Cardiology, 72(2), 120–127.
4. Lyman, G. H., Khorana, A. A., Falanga, A., Clarke-Pearson, D., Flowers, C., Jahanzeb, M., Kakkar, A., Kuderer, N. M., Levine, M. N., & Liebman, H. (2007). American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. Journal of Clinical Oncology, 25(34), 5490–5505.
5. Khorana, A. A., Francis, C. W., Culakova, E., Kuderer, N. M., & Lyman, G. H. (2007b). Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. Journal of Thrombosis and Haemostasis, 5(3), 632–634.
6. Carrier, M., Le Gal, G., Wells, P. S., Fergusson, D., Ramsay, T., & Rodger, M. A. (2008). Systematic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? Annals of Internal Medicine, 149(5), 323–333.
7. Mukai, M., & Oka, T. (2018). Mechanism and management of cancer-associated thrombosis. Journal of Cardiology, 72(2), 89–93.
8. Hisada, Y., & Mackman, N. (2017). Cancer-associated pathways and biomarkers of venous thrombosis. Blood, The Journal of the American Society of Hematology, 130(13), 1499–1506.
9. Varki, A. (2007). Trousseau's syndrome: multiple definitions and multiple mechanisms. Blood, The Journal of the American Society of Hematology, 110(6), 1723–1729.
10. Horsted, F., West, J., & Grainge, M. J. (2012). Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med, 9(7), e1001275.
11. Khorana, A. A., Francis, C. W., Culakova, E., Kuderer, N. M., & Lyman, G. H. (2007a). Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer: Interdisciplinary International Journal of the American Cancer Society, 110(10), 2339–2346.
12. Mansfield, A. S., Tafur, A. J., Wang, C. E., Kourelis, T. V, Wysokinska, E. M., & Yang, P. (2016). Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. Journal of Thrombosis and Haemostasis, 14(9), 1773–1778.
13. Streiff, M. B., Holmstrom, B., Angelini, D., Ashrani, A., Elshoury, A., Fanikos, J., Fertrin, K. Y., Fogerty, A. E., Gao, S., & Goldhaber, S. Z. (2021). Cancer-associated venous thromboembolic disease, version 2.2021, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network, 19(10), 1181–1201.
14. Fernandes, C. J., Morinaga, L. T. K., Alves, J. L., Castro, M. A., Calderaro, D., Jardim, C. V. P., & Souza, R. (2019). Cancer-associated thrombosis: the when, how and why. European Respiratory Review, 28(151).

15. Al-Tawfiq, J. A., & Saadeh, B. M. (2011). Improving adherence to venous thromoembolism prophylaxis using multiple interventions. Annals of Thoracic Medicine, 6(2), 82.
16. Kandemir, E. A., Bayraktar-Ekincioglu, A., & Kilickap, S. (2021). Assessment of adherence to cancer-associated venous thromboembolism guideline and pharmacist's impact on anticoagulant therapy. Supportive Care in Cancer, 29, 1699–1709.
17. Cook, D., Duffett, M., Lauzier, F., Ye, C., Dodek, P., Paunovic, B., Fowler, R., Kho, M. E., Foster, D., & Stelfox, T. (2014). Barriers and facilitators of thromboprophylaxis for medical-surgical intensive care unit patients: a multicenter survey. Journal of Critical Care, 29(3), 471–e1.
18. Zierler, B. K., Meissner, M. H., Cain, K., & Strandness Jr, D. E. (2002). A survey of physicians' knowledge and management of venous thromboembolism. Vascular and Endovascular Surgery, 36(5), 367–375.
19. Kucher, N., Koo, S., Quiroz, R., Cooper, J. M., Paterno, M. D., Soukonnikov, B., & Goldhaber, S. Z. (2005). Electronic alerts to prevent venous thromboembolism among hospitalized patients. New England Journal of Medicine, 352(10), 969–977.
20. Anderson, F. A., Wheeler, H. B., Goldberg, R. J., Hosmer, D. W., Forcier, A., & Patwardhan, N. A. (1994). Changing clinical practice: prospective study of the impact of continuing medical education and quality assurance programs on use of prophylaxis for venous thromboembolism. Archives of Internal Medicine, 154(6), 669–677.
21. Scaglione, L., Piobbici, M., Pagano, E., Ballini, L., Tamponi, G., & Ciccone, G. (2005). Implementing guidelines for venous thromboembolism prophylaxis in a large Italian teaching hospital: lights and shadows. Haematologica, 90(5), 678–684.
22. Cabana, M. D., Rand, C. S., Powe, N. R., Wu, A. W., Wilson, M. H., Abboud, P.-A. C., & Rubin, H. R. (1999). Why don't physicians follow clinical practice guidelines?: A framework for improvement. Jama, 282(15), 1458–1465.