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Burden of Deep Venous Thrombosis in Gastric and Pancreatic Adenocarcinoma

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ABSTRACT

Objective: To determine the burden of deep venous thrombosis (DVT) in patients with gastric and pancreatic adenocarcinoma, to identify associated risk factors, and to distinguish modifiable risk factors.

Material and Methods: Between January 2016 and November 2022, data from 318 patients with pancreatic adenocarcinoma and 522 patients with gastric adenocarcinoma were retrospectively analyzed; 77 patients (42 with gastric and 35 with pancreatic adenocarcinoma) were included in the study.

Results: The mean age was 62.1±11.5 years; 28 (36.4%) were female. The patients were divided into two groups according to the presence of DVT. Risk factors were compared between the groups. No significant differences were found between the groups in baseline characteristics, except for immobility and venous insufficiency. In univariate analyses, metastasis, higher Khorana score, immobility, previous venous insufficiency, and prior surgery for the primary tumour were associated with DVT. In multivariable models, immobility and pre-existing venous insufficiency remained independently associated with DVT, whereas prior surgery and metastasis did not retain statistical significance. However, tumor stages were similar between the groups. Tumor regimens were compared between groups, and no statistically significant differences were observed.

Conclusion: In patients with gastric and pancreatic adenocarcinoma who undergo Doppler ultrasonography for suspected DVT, immobility and pre-existing venous insufficiency appear to be the main risk factors associated with confirmed DVT. These findings may help refine risk stratification beyond the Khorana score in this high-risk population.

Keywords: Deep venous thrombosis; cancer; chemotherapy; gastric cancer; pancreatic cancer

INTRODUCTION

Venous thromboembolism (VTE) is commonly seen in cancer patients. This condition, cancer-associated VTE, is associated with a 4- to 6-fold higher incidence of deep venous thrombosis (DVT) in patients with cancer than in the general population.[1] In addition to the hypercoagulable state associated with malignancy, oncologic treatments such as chemotherapy may further increase the risk of DVT.[2]

Patient-related risk factors such as venous insufficiency, immobility, and hereditary thrombophilia;[3] tumor-related risk factors such as tumor location, stage, and metastasis;[4,5] and treatment-related risk factors such as chemotherapy agents (especially platinum-based chemotherapy), hormonal therapy, radiotherapy, and surgery play a role in VTE.[6] Cancer-associated thrombosis results from tumor-, host, and treatment-related factors reflecting Virchow's triad: hypercoagulability, venous stasis, and endothelial injury. Gastrointestinal adenocarcinomas overexpress tissue factor and release procoagulant microparticles and mucins, while inflammation and anticancer treatments such as chemotherapy, central venous catheters, major surgery and immobility further promote stasis and endothelial damage.[7] These mechanisms are particularly prominent in pancreatic and gastric cancers and contribute to their high rates of VTE.[8]

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Large cohort and trial data report VTE incidence of approximately 10-20% in patients with advanced gastric cancer receiving systemic therapy, and 20-30% or higher in pancreatic cancer, particularly during chemotherapy. These malignancies also carry a poor overall prognosis; therefore, thrombotic events represent an additional and potentially modifiable source of morbidity and mortality in this population.[9] Identification of risk factors for DVT in patients with gastric and pancreatic adenocarcinoma and management of modifiable risk factors are essential to reducing mortality and morbidity.[6,10]

Since anticoagulant use in oncology patients increases the risk of major bleeding, studies aimed at preventing VTE rather than treating it are particularly important.[11] To identify the risk of VTE in cancer patients, several risk assessment models have been defined. The Khorana scoring system is one of the validated methods for VTE risk assessment. It consists of five parameters: cancer type, body mass index (BMI), pre-chemotherapy platelet, hemoglobin, and leucocyte counts.[12]

The aim of this study was to determine the burden of DVT and its risk factors in patients with gastric and pancreatic adenocarcinoma, and to identify modifiable risk factors.

MATERIAL AND METHODS

This study was carried out at Bezmialem Vakıf University Hospital. It is a retrospective observational case-control study. Ethical approval was obtained from the Bezmialem Vakıf University Ethical Board (approval number: E-54022451-050.05.04-128722, date: 06.11.2023). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data from 318 pancreatic and 522 gastric adenocarcinoma patients were analyzed between January 2016 and November 2022. Doppler ultrasonography was performed in 77 patients with a clinical suspicion of DVT. Patients older than 18 years who underwent Doppler ultrasound for suspected DVT were included in the study. Patients with previous DVT and genetic thrombophilia were excluded from the study.

Patient data were obtained from the hospital's software system. Patients were divided into two groups based on the presence of DVT on Doppler ultrasound. The groups were compared with respect to baseline characteristics (age, gender, BMI, immobility) and clinical characteristics (tumor location, tumor stage, metastasis, treatment with chemotherapy and/or radiotherapy, Eastern Cooperative Oncology Group Performance Status (ECOG), and Khorana score). Chemotherapy regimens were also compared between the groups.

A chemotherapy regimen containing fluorouracil or capecitabine was defined as fluoropyrimidine-containing chemotherapy. Platinum-based chemotherapy is a regimen that include oxaliplatin, carboplatin, and cisplatin. Statistically significant risk factors identified in univariate between-group analyses, together with risk factors reported in the literature were included in the multivariate analysis. An investigation was undertaken to identify the risk factors for DVT among patients with gastric and pancreatic adenocarcinoma.

Statistical Analysis

Statistical analysis was conducted using Jamovi software (version 2.3.28). The Shapiro-Wilk test, along with skewness and kurtosis values, was used to assess the normality of data distribution. Descriptive statistics for continuous variables were presented as mean ± standard deviation, while categorical variables were summarized using frequencies and percentages. The chi-square test was used to compare groups for nominal variables. The Student's t-test was used for the analysis of parametric data, while the Mann-Whitney U test was used for non-parametric data. Variables identified as statistically significant in univariate analysis or recognized in the literature as risk factors for DVT were included in the multivariate analysis. The statistical significance level was set at $p<0.05$.

RESULTS

Of the 77 patients, 42 had gastric adenocarcinoma, and 35 had pancreatic adenocarcinoma. Among the 77 patients who underwent lower-extremity Doppler ultrasonography for suspected DVT, 37 (48%) had confirmed DVT. The mean age was 62.1±11.5, and 28 (36.4%) were female. Three patients had hypothyroidism, two had atrial fibrillation, one had rheumatoid arthritis, and one had a history of bariatric surgery. Among DVT-positive patients who died during follow-up, the mean time from DVT diagnosis to death was 4.09±5.08 months. The groups were similar in terms of gender, diabetes, hypertension, cigarette use, and BMI (Table 1). Metastasis, previous surgery for the primary tumor, pulmonary embolism, and mortality were more common in the DVT-positive group, and the Khorana score was higher. However, tumor stages were similar between the groups (Table 2).

No statistically significant differences in tumor regimens were observed between groups (Table 3). Fluoropyrimidine-containing chemotherapy (fluorouracil and capecitabine) and platinum-based chemotherapy (oxaliplatin, carboplatin, and cisplatin) were similar between groups.

Variables that were statistically significant in the univariate analysis for DVT (venous insufficiency, metastatic disease,

immobility, Khorana score, and previous surgery for the primary tumor) were entered into the multivariate logistic regression model (Table 4). In the regression analysis, no significant associations were observed between the variables and DVT.

A second regression analysis was conducted using immobility, venous insufficiency, and previous surgery as variables; these variables are risk factors for DVT (Table 5). Immobility and venous insufficiency were found to be associated with DVT in patients with pancreatic or gastric adenocarcinoma.

Kaplan-Meier analysis demonstrated that patients with DVT had significantly worse overall survival compared with those without DVT; median overall survival was 9.43 months (95% confidence interval, 6.57-12.30) versus 16.50 months (95% confidence interval, 8.34-24.66) (p<0.001; Figure 1).

DISCUSSION

In this study, we investigated the incidence of DVT among patients with gastric and pancreatic adenocarcinomas and the association of demographic, baseline, and clinical characteristics, as well as anti-tumor regimens, with the risk of DVT. Gastric adenocarcinoma is associated with VTE at a rate of approximately 10% and with a 4- to 7-fold increased risk of VTE.[13,14] However, this rate can reach 27-50% in pancreatic adenocarcinomas.[10,15] The prevalence of confirmed lower-extremity DVT among patients undergoing Doppler ultrasonography for suspected DVT was 48% in our study, which is higher than rates reported in unselected cancer populations.

Although factors such as advanced age, obesity, and medical comorbidities (hypertension, diabetes mellitus) have been associated with an increased risk of DVT in cancer patients,[1,14] no statistically significant associations were observed between the groups in our study.

TABLE 1: Baseline characteristics.

	DVT-negative group (n=40)	DVT-positive group (n=37)	P
Age (mean ± SD)	62.0±10.8	62.1±12.4	0.968
Gender (male)	25 (63.5%)	24 (64.9%)	0.829
Diabetes mellitus	19 (47.5%)	18 (48.6%)	0.920
Hypertension	15 (37.5%)	18 (48.6%)	0.323
Hyperlipidemia	6 (15.0%)	4 (10.8%)	0.585
Chronic pulmonary disease	2 (5.0%)	1 (2.7%)	0.603
Heart failure	1 (2.5%)	2 (5.4%)	0.510
Stroke	1 (2.5%)	3 (8.1%)	0.268
Cigarette use	17 (42.5%)	22 (59.5%)	0.137
Cigarette (pack-year, mean ± SD)	39.4±23.6	30.9±15.6	0.184
Alcohol	4 (10.0%)	5 (13.5%)	0.632
BMI (mean ± SD)	21.6±4.3	21.2±3.6	0.589
Immobility	10 (25.0%)	19 (51.4%)	**0.017**
Venous insufficiency (previous)	4 (10.0%)	11 (29.7%)	**0.029**
Albumin (mean ± SD)	3.15±0.72	3.05±0.56	0.493

BMI: Body mass index; DVT: Deep venous thrombosis; SD: Standard deviation.

TABLE 2: Clinical characteristics between groups.

	DVT-negative group (n=40)	DVT-positive group (n=37)	p
Tumor location			
Gastric adenocarcinoma	22 (55.0%)	20 (54.1%)	0.934
Pancreatic adenocarcinoma	18 (45.0%)	17 (45.9%)	
Stage of adenocarcinoma			
Stage 1	2 (5.0%)	0 (0.0%)	0.099
Stage 2	4 (10.0%)	0 (0.0%)	
Stage 3	4 (10.0%)	3 (8.1%)	
Stage 4	30 (75.0%)	34 (91.9%)	
Metastasis	30 (75.0%)	34 (91.9%)	**0.048**
Site of metastasis			
Peritoneal	9 (22.5%)	13 (35.1%)	0.220
Liver	20 (50.0%)	22 (59.5%)	0.405
Ovarian	0 (0.0%)	2 (5.4%)	0.136
Bone	3 (7.5%)	3 (8.1%)	0.921
Lung	5 (12.5%)	8 (21.6%)	0.286
Recent chemotherapy (<90 days)	34 (85.0%)	29 (78.4%)	0.452
Previous radiotherapy	7 (17.5%)	2 (5.4%)	0.099
Previous surgery for primary tumor	12 (30.0%)	22 (59.5%)	**0.046**
Recent hospitalization (<90 days)	12 (30.0%)	17 (45.9%)	0.149
Central venous catheter	27 (67.5%)	20 (54.1%)	0.227
ECOG-PS grade			
Grade 0-1	22 (61.1%)	14 (38.9%)	0.132
Grade 2-3	18 (43.9%)	23 (56.1%)	
Khorana score	2.7±0.8	3.2±0.9	**0.011**
Pulmonary embolism	2 (5.0%)	10 (27.0%)	**0.008**
Mortality	33 (82.5%)	36 (97.3%)	**0.033**

DVT: Deep venous thrombosis; ECOG-PS: Eastern Cooperative Oncology Group Performance Status.

TABLE 3: Tumor regimens and deep venous thrombosis.			
	DVT-negative group (n=34)	DVT-positive group (n=29)	p
Folinic acid-fluorouracil-oxaliplatin	12 (35.3%)	12 (41.4%)	0.494
Folinic acid-fluorouracil-irinotecan	7 (20.3%)	3 (10.3%)	
Gemcitabine	4 (11.8%)	3 (10.3%)	
Gemcitabine-capecitabine	4 (11.8%)	2 (6.9%)	
Paclitaxel	1 (2.9%)	3 (10.3%)	
Folinic acid-fluorouracil-oxaliplatin-irinotecan	2 (5.9%)	1 (3.4%)	
Capecitabine	2 (5.9%)	0 (0.0%)	
Carboplatin-paclitaxel	1 (2.9%)	1 (3.4%)	
Gemcitabine-cisplatin	0 (0.0%)	2 (6.9%)	
Docetaxel-cisplatin	0 (0.0%)	1 (3.4%)	
Folinic acid-fluorouracil-irinotecan- bevacizumab	1 (2.9%)	0 (0.0%)	
Folinic acid-fluorouracil-oxaliplatin- bevacizumab	0 (0.0%)	1 (3.4%)	
Fluoropyrimidine-containing chemotherapy	28 (59.6%)	19 (40.4%)	0.094
Platin-based chemotherapy	15 (45.5%)	18 (54.5%)	0.323
DVT: Deep venous thrombosis.			

TABLE 4: Multivariable logistic regression analysis of factors associated with DVT (model 1).					
			p-value	OR (95% CI)	
Immobility			0.173	2.1 (0.7-6.2)	
Venous insufficiency (previous)			0.091	3.2 (0.8-12.5)	
Metastasis			0.404	2.0 (0.4-9.7)	
Khorana score			0.177	1.6 (0.8-3.0)	
Previous surgery for primary tumor			0.296	0.6 (0.2-1.7)	
Accuracy	Specificity	Sensitivity	AUC	R^2 Nagelkerke	p
0.675	0.725	0.622	0.751	0.248	**0.007**
AUC: Area under curve; CI: Confidence interval; OR: Odds ratio; DVT: Deep venous thrombosis.					

TABLE 5: Multivariable logistic regression analysis restricted to immobility, pre-existing venous insufficiency and prior surgery (model 2).					
			p-value	OR (95% CI)	
Immobility			**0.043**	2.8 (1.0-7.8)	
Venous insufficiency (previous)			**0.048**	3.8 (1.0-14.2)	
Previous surgery for adenocarcinoma			0.091	0.4 (0.2-1.1)	
Accuracy	Specificity	Sensitivity	AUC	R^2 Nagelkerke	p
0.662	0.775	0.541	0.718	0.207	**0.005**
AUC: Area under curve; CI: Confidence interval; OR: Odds ratio.					

Tumor stage and metastasis are among the reported risk factors for DVT. The association we observed between metastatic disease, immobility, pre-existing venous insufficiency, and DVT is consistent with current concepts of cancer-associated thrombosis. Metastatic tumors increase tissue factor expression and release procoagulant microparticles and mucins, which activate the coagulation cascade. Immobility and chronic venous disease cause venous stasis and endothelial dysfunction, completing Virchow's triad when combined with tumor-related hypercoagulability. In pancreatic and gastric adenocarcinomas, tumor-derived mucins and inflammatory cytokines further enhance platelet activation and fibrin formation, which may contribute to the high DVT rates in our cohort.[7,8] Rollins et al.[16] observed an increased risk of VTE from tumor stage T1 to T3 (3% to 9%). No similar relationship was found at the T4 stage. In their review

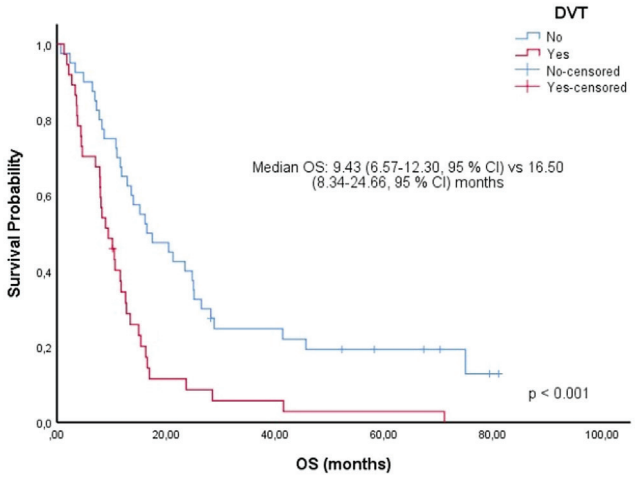

FIGURE 1: Overall survival of patients with and without deep vein thrombosis: Kaplan-Meier analysis.

CI: Confidence interval; OS: Overall survival; DVT: Deep venous thrombosis.

articles, Marshall-Webb et al.[17] and Prouse et al.[18] observed that advanced tumor stage is associated with an increased risk of VTE. However, no significant association was observed between tumor stages and DVT in our study. The increased risk of DVT was only observed in patients with tumor stage 4.

Immobility has been associated with an increased risk of DVT, which can lead to pulmonary embolism.[17,18] However, the relationship between chronic venous disease and DVT, as stated in existing vascular surgery guidelines, has not been sufficiently investigated in oncologic publications.[3] In our study sample, all three risk factors increased the risk of DVT.

Prior surgery for the primary tumor is associated with an increased risk of DVT, and studies have therefore recommended prophylactic anticoagulation.[10,19] The present study is consistent with the literature and demonstrates an association between surgery and the risk of DVT.

The Khorana score is a scoring system that uses tumor type, BMI, and pre-chemotherapy blood counts in oncology patients. A high Khorana score has been reported to predict VTE in some studies.[19,20] In contrast, van Es et al.[12] 2017 reported that the Khorana score failed to predict VTE. In our study group, a high Khorana score was more frequent in the DVT-positive group, suggesting a possible association.

It is controversial whether DVT in patients with gastric and pancreatic cancer is caused by tumor type or by the chemotherapy regimen.[7] However, the literature reports that cisplatin-based chemotherapy is associated with an increased risk of DVT.[21] In our study, we compared the relationship between chemotherapy regimens and DVT in each group separately. However, we did not observe a statistically significant association between chemotherapy regimens and DVT.

Development of DVT in patients with pancreatic cancer has been associated with increased mortality.[10] Likewise, DVT has been associated with increased mortality in gastric cancer patients.[17] Although mortality was high in both groups in our study population, it was significantly higher in the DVT-positive group.

Study Limitations

The major limitations of our study are its retrospective, single-centre design and the relatively small sample size, which may have limited the power to detect modest associations, particularly for individual chemotherapeutic agents and for the Khorana score. Only patients for whom Doppler ultrasonography was requested because of a clinical suspicion of DVT were included in the analysis (77 of 840 screened cases of gastric or pancreatic cancer), introducing a selection bias toward symptomatic events and precluding estimation of the true incidence of asymptomatic DVT in this population. Patients with hereditary thrombophilia were excluded, and their effects could not be evaluated. It is difficult to investigate the effects of chemotherapeutic agents in studies with small sample sizes. In addition, although all patients with confirmed DVT were receiving therapeutic anticoagulation, we lacked complete information on the duration or timing of anticoagulant use, which may have influenced risk estimates and confounded some observed associations.

CONCLUSION

Gastric and pancreatic adenocarcinoma patients have a high mortality rate. Among patients with gastric and pancreatic adenocarcinoma who undergo Doppler ultrasonography for suspected DVT, almost half have confirmed lower-extremity DVT. In our cohort, immobility and pre-existing venous insufficiency were the main factors independently associated with DVT, whereas prior surgery and metastatic disease did not retain significance in multivariable analyses. These findings highlight the importance of careful assessment of functional status and chronic venous disease when evaluating thrombotic risk in this high-risk population. We hope that our research will inform further studies.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Bezmialem Vakıf University Ethical Board (approval number: E-54022451-050.05.04-128722, date: 06.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.S.İ., A.Ö., Concept: Z.S.İ., A.Ö., Design: A.Ö., Data Collection or Processing: Z.S.İ., Analysis or Interpretation: A.Ö., Literature Search: Z.S.İ., A.Ö., Writing: Z.S.İ., A.Ö.

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