Predictors of post-gastrectomy venous thromboembolism in patients with gastric adenocarcinoma: A retrospective study

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Predictors of post-gastrectomy venous thromboembolism in patients with gastric adenocarcinoma: A retrospective study

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Abstract

Background and Objectives: This study aimed to delineate perioperative risk factor of venous thromboembolism (VTE) after gastrectomy in patients with gastric adenocarcinoma.

Materials and Methods: 170 patients with gastric adenocarcinoma underwent gastrectomy at general surgery, Benha university hospital and 60 patients with elevated D-dimer levels on postoperative day 1 (POD1) who received Duplex of lower and upper extremity veins were involved. Data on clinical and pathological factors were collected, and variances in these factors between the postoperative VTE negative (-) and positive (+) cohorts were examined. Both univariate and multivariate logistic regression models were employed to determine predictors of venous thromboembolism following gastrectomy.

Results: Among 60 individuals exhibiting elevated D-dimer levels, 19 patients were diagnosed with deep venous thrombosis (DVT) affecting both lower and upper extremity veins, with 55 patients (91.7%) experiencing DVT in the lower extremities and 5 patients (8.3%) in the upper extremities. Significant preoperative differences were noted in the VTE (+) group for the following parameters: age (P = 0.01), BMI (P = 0.04), WBC count (P = 0.03), D-dimer levels (P = 0.03), blood glucose concentrations (P = 0.01), and Caprini score (P = 0.03). Postoperative observations showed a substantial reduction in hemoglobin levels (P = 0.02) within the VTE (+) group. Pathological assessments indicated greater tumor invasion depth (P = 0.02) and more advanced tumor, node, and TNM stages (P = 0.01), reflecting increased tumor burden in the VTE (+) cohort. Univariate logistic regression identified age, preoperative blood glucose levels, preoperative Caprini scores, postoperative hemoglobin levels, invasion depth, and TNM stage as independent predictors of postoperative VTE in patients undergoing gastrectomy for gastric adenocarcinoma. Multivariate analysis confirmed age, TNM stage, and preoperative Caprini score as independent predictors of VTE post-gastrectomy in patients with gastric cancer.

Conclusion: Our research indicated that age, preoperative blood glucose levels, and Caprini scores, alongside postoperative reductions in hemoglobin, invasion depth, and TNM stage, serve as independent prognostic indicators for post-gastrectomy VTE in individuals with gastric adenocarcinoma. Consequently, perioperative evaluation,

surveillance, and management of these risk elements are crucial for preventing VTE following gastrectomy.

Keywords: Gastric cancer, VTE, gastrectomy, thromboprophylaxis

Abbreviations:

VTE: Venous Thromboembolism
POD: Postoperative Day
DVT: Deep Venous Thrombosis
CAT: Cancer Associated Thrombus
GC: Gastric Cancer
G-CSF: Granulocyte Colony Stimulating Factor
GMCSF: Granulocyte Macrophage Colony Stimulating Factor
IL-6: Interleukin-6
DOAG: Direct Oral Anticoagulant
BMI: Body Mass Index
TNM: Tumor, Node and Metastasis
PE: Pulmonary Embolism
IRB: Institutional Review Board
CTPA: Computed Tomography Pulmonary Angiography
SPSS: Statistical Package for Social Sciences
SD: Standard Deviation

INTRODUCTION

VTE encompasses the acute development of thrombi within the deep veins and pulmonary arteries, including DVT and PE [1]. Typically, DVT manifests in the veins of the lower extremities, though it can infrequently appear in the upper extremities, as well as cerebral, visceral, and splanchnic veins [2].

Major abdominal surgery, active malignancy, neurological disorders characterized by immobilization of the lower extremities, prolonged hospital stays, multiple traumas or fractures, and the administration of specific medications such as estrogen and progestin therapies are all independent risk factors for VTE. Additional predictors comprise elevated BMI, as well as conditions related to pregnancy and the postpartum period [3]. Within these risk factors, active malignancy accounts for roughly 10-20% of all VTE cases. Patients with active malignancy encounter a 4-7-fold increase in the incidence of VTE compared to those without malignancy. The association between malignancy and a hypercoagulable state has been extensively investigated [4-6].

Cancer-associated thrombosis (CAT) stands as a primary cause of mortality among patients with advancing malignancies, closely linked to intricate systemic treatments, especially with the advent of novel molecular targeted therapies. This condition also correlates with adverse outcomes and significant increases in healthcare expenditures [7-9]. The propensity for VTE is predominantly influenced by the type of cancer involved. Pancreatic and gastric cancers are the most frequently associated with CAT, followed by lung, ovarian, and primary brain malignancies [2, 6, 10]. The mechanisms underlying CAT differ based on the type of cancer. Changes in the host's hematologic profile, such as alterations in WBCs, platelets, and tumor-secreted procoagulant proteins like tissue factors and

podoplanin, constitute known oncogenic triggers for VTE [10]. In lung and colorectal malignancies, an elevated WBC count is closely associated with an upsurge in cytokines secreted by the tumors, such as G-CSF, GM-CSF, and IL-6. Neutrophils, in turn, release extracellular traps that ensnare platelets and microvesicles, thus precipitating thrombus formation [11, 12]. Thrombocytosis is frequently observed in gastrointestinal, pulmonary, breast, and ovarian cancers, primarily due to increased hepatic production of thrombopoietin in the circulatory system. Moreover, procoagulant proteins secreted by tumors may directly activate the coagulation cascade [13-14]. The use of heparin and direct oral anticoagulants (DOACs) is recommended as a potent therapeutic strategy for high-risk patients, especially in the perioperative period of major open or laparoscopic oncological procedures.

However, the management of CAT necessitates a nuanced approach that carefully balances the potential risk of hemorrhage with the patient's individual preferences and values [2, 6, 9, 15].

GC, distinguished by its significant thrombogenicity, stands as the fifth most prevalent malignancy and the fourth most common cause of cancer-related mortality on a global scale. In 2020 alone, there were more than 1 million newly diagnosed cases, with nearly 800,000 deaths attributed to GC worldwide [16]. Surgical intervention remains the primary curative strategy for GC, aimed at achieving remission and enhancing prognosis. Research consistently demonstrates that VTE serves as an autonomous mortality risk factor in GC patients. Notable risk predictors of VTE in this demographic include age, gender, performance status, advanced diagnostic stages, T-stage, metastasis, chemotherapy utilization, and reduced hemoglobin and albumin levels [17-26].

Comprehensive evaluations of the preoperative and postoperative clinical and pathological factors influencing VTE in GC patients are scant, leaving the perioperative VTE risk factors poorly defined. This investigation seeks to elucidate the perioperative clinical and pathological variables linked to VTE in individuals undergoing gastrectomy for GC, while also striving to pinpoint the determinants of postoperative VTE in this patient population.

MATERIALS AND METHODS

Study design, setting and period

In this retrospective analysis, 170 patients who underwent radical gastrectomy for gastric adenocarcinoma, stages TNM I-III, at the General Surgery Department of Benha University Hospital from January 2020 to June 2024 were examined. D-dimer levels were assessed on the first postoperative day (POD1) to screen for VTE.

Only individuals presenting with D-dimer levels of ≥ 0.5 mg/mL were deemed eligible for further assessment, which comprised Duplex ultrasonography of both upper and lower extremity veins to identify VTE. Among the patients who underwent gastrectomy, 60 individuals (39 males and 21 females) with D-dimer concentrations meeting the threshold of ≥ 0.5 mg/mL were enrolled in our study. Based on the results of Duplex ultrasonography, these patients were divided into two distinct groups: those without VTE (n = 41) and those with VTE (n = 19), as illustrated in Figure 1. The clinical and pathological characteristics of the participants are summarized in [Table 1].

Ethical approval

This data collection was approved by the Ethical Committee of faculty of medicine, Benha university (RC 16-2-2024).

Diagnosis of VTE

In this investigation, VTE was characterized by the acute development of thrombi within the deep venous system, specifically excluding thromboses related to medical devices. The diagnosis and precise localization of DVT in patients presenting with elevated D-dimer levels were determined through Duplex scanning of the lower and upper extremities, conducted by two seasoned sonographers. These examinations utilized a 3-7.5 MHz transducer on a Voluson E8 Machine (General Electric, Boston, MA, USA). Following the emergence of pulmonary embolism (PE) symptoms—such as shortness of breath, dyspnea, chest discomfort or pain, and reduced oxygen saturation—computed tomography pulmonary angiography (CTPA) was employed to substantiate the diagnosis.

VTE prophylaxis

Based on Caprini score assessment [27], all patients were classified as moderate (3-4) to high risk (≥ 5) for VTE, so each patient subjected to combined mechanical (intermittent pneumatic compression, IPC) and chemical prophylaxis in the form of enoxaparin (40mg) started 12 hours before the surgery and regained 24 hours after surgery (every 24 hour) till ambulation of the patient.

Statistical analysis

Statistical analyses were executed using the Statistical Package for Social Sciences (SPSS), version 16 (SPSS Inc., Chicago, Illinois, USA), complemented by resources from Bristol University, UK. Quantitative variables were articulated as mean ± SD and subjected to analysis through a one-way unpaired t-test for parametric data, where SD constituted less than 50% of the mean. For the comparison of categorical variables between VTE (-) and VTE (+) cohorts, Fisher's exact test or the chi-square test was employed as appropriate. To elucidate the influence of diverse clinical and pathological variables on the development of VTE following gastrectomy, univariate and multivariate logistic regression models were systematically applied. The relative risk associated with each factor was represented by the calculated odds ratio with 95% confidence intervals. Statistical significance was attributed to a P-value of less than 0.05, whereas P-values exceeding this threshold were interpreted as statistically non-significant.

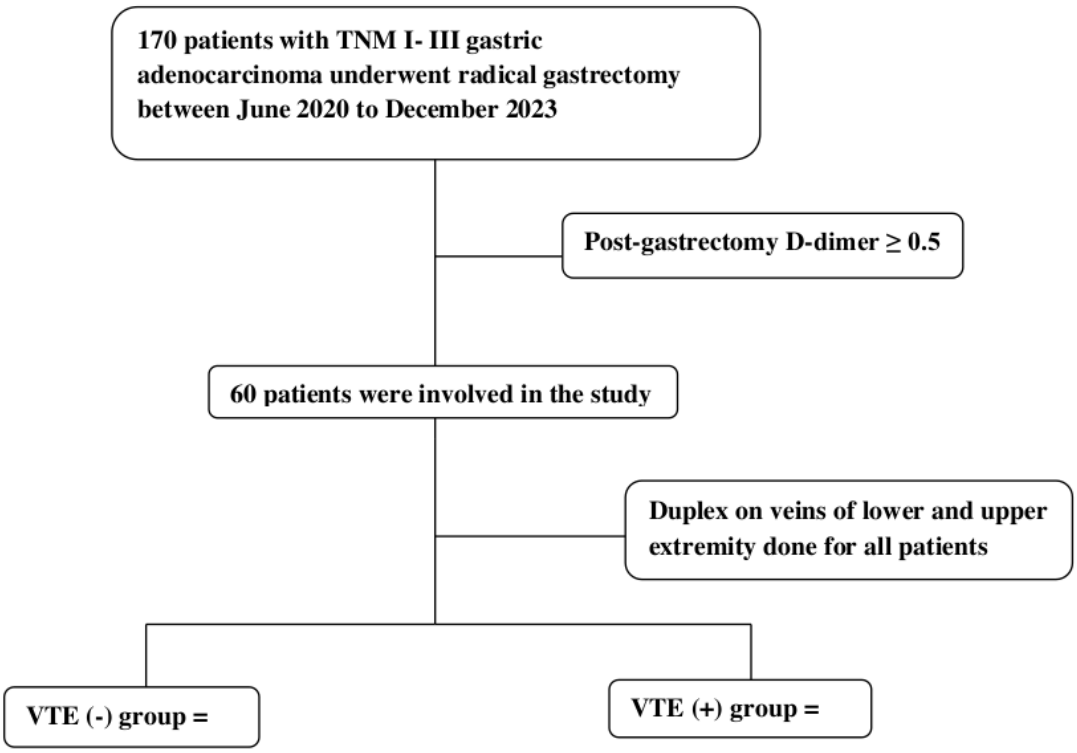

Figure 1: Flowchart demonstrating the patients enrolled in this study.

RESULTS

Patients' demographic, clinical, laboratory and pathological factors:

This study includes 60 patients with D-dimer ≥ 0.5 mg/mL. The median age of the involved patients was 65.4 years (range, 45-82 years), and the median preoperative BMI before surgery was 23.6 kg/m2 (range, 16.8-33.6 kg/m2). The median operative duration was 247.9 min (range, 120-550 min), and the median volume of hemorrhage was 161.8 mL (range, 150-1000 mL). There were 44 patients (73.3%) underwent open gastrectomy while 16 patients (26.7%) underwent laparoscopic gastrectomy, and 49 (81.7%) had a negative history of smoking. Pulmonary disease, cardiovascular disease, hypertension, diabetes mellitus, cerebrovascular disease, past history of cancer (excluding gastric cancer), and peripheral venous disease were detected in 6 (10%), 11 (18.3%), 23 (38.3%), 8 (13.3%), 5 (8.3%), 4 (6.7%), and 2 (3.3%) patients, respectively. 49 patients (81.7%) received neoadjuvant chemotherapy. The sites of tumor were the fundus [7 patients, (11.7%)], body [12 patients, (20%)], and antrum [41 patients, (68.3%)]. The median size of tumor was 5.8

cm (range, 5-8.5 cm). TNM classification identified as TNM I, II and III in 11 (18.3%), 18 (30%) and 31 (51.7%) patients, respectively.

Based on Duplex ultrasonography findings, the cohort was stratified into VTE (-) and VTE (+) groups. Within the VTE (+) group, 55 patients (91.7%) exhibited thrombus formation in the lower extremity veins, while 5 patients (8.3%) were affected in the upper extremity veins. For those manifesting symptoms indicative of PE, CTPA was conducted, revealing that PE occurred in 4 patients. Notably, these individuals, who were all part of the VTE (+) group, demonstrated elevated Caprini scores.

Demographic, clinical, laboratory and pathological factors that were significantly higher in VTE (+) group

Preoperatively, the VTE (+) group demonstrated significantly elevated levels of age (P = 0.01), BMI (P = 0.04), WBC count (P = 0.03), D-dimer concentration (P = 0.03), blood glucose levels (P = 0.01), and Caprini scores (P = 0.03) [Table 2]. Postoperatively, hemoglobin levels were notably lower in the VTE (+) cohort (P = 0.02) [Table 2]. Pathologically, this group also exhibited greater tumor burden, evidenced by increased depth of invasion (P = 0.02) and higher TNM staging (P = 0.01) [Table 3].

Analysis of the factors that were associated with VTE:

Univariate logistic regression analysis identified that patient age (P = 0.03), preoperative blood glucose levels (P = 0.02), preoperative Caprini score (P = 0.04), postoperative hemoglobin levels (P = 0.04), depth of tumor invasion (P = 0.03), and TNM staging (P = 0.01) were independent predictors of postoperative VTE in individuals with gastric adenocarcinoma who underwent radical gastrectomy. In contrast, multivariate logistic regression analysis underscored that age (P = 0.02), TNM staging (P = 0.03), and preoperative Caprini score (P = 0.03) remained the key independent risk factors for post-gastrectomy VTE in patients with gastric cancer [Table 4].

Table 1: Demographic, clinical and laboratory factors of the patients (n=60)

Age (years)		65.4 ± 11.2(45-82)
Gender	**male**	39 (65%)
	female	21 (35%)
Preoperative BMI	23.6 ± 2.9(16.8-33.6)	
Smoking	-	48 (80%)
	+	12 (20%)
Operation	**Duration(min)**	247.9 ± 71.3 (120-550)
	Bleeding (ml)	161.8 ± 169.7 (150-1000)
Approach	**Open**	44 (73.3%)
	Laparoscopic	16 (26.7%)
Pulmonary disease	-	54 (90%)
	+	6 (10%)
Cardiovascular disease	-	49 (81.7%)
	+	11 (18.3%)
Hypertension	-	37 (61.7%)
	+	23 (38.3%)
Diabetes mellitus	-	52 (86.7%)
	+	8 (13.3%)
Cerebrovascular disease	-	55 (91.7%)
	+	5 (8.3%)
Past history of cancer	-	56 (93.3%)
	+	4 (6.7%)
Peripheral venous disease	-	57 (95%)
	+	3 (5%)
Preoperative chemotherapy	-	11 (18.3%)
	+	49 (81.7%)
Tumor markers	**CEA**	45.8 ± 107.9 (6.0-591.0)
	CA19-9	468.8 ± 911.6 (37-3762)
Albumin (g/L)	**35.7 ± 4.9 (19.2-46.4)**	
Preoperative	**Hemoglobin (g/L)**	116.6 ± 28.3 (67-171)
	WBCs (×10^9/L)	7.2 ± 2.1 (3.3-24.8)
	PLT (×10^9/L)	232.4 ± 79.1(64-553)
	D-dimer(mg/mL)	1.3 ± 2.2 (0.2-18.1)
	INR	1.1 ± 0.1 (0.8-1.7)
	Blood glucose (mmol/L)	5.5 ± 1.8 (3.4-21.3)
	Caprini score	4 ± 1.6 (3-7)
Postoperative (POD1)	**Hemoglobin (g/L)**	107.3 ± 21.9 (60-161)
	WBC ($\times 10^9$/L)	10.4 ± 2.9 (2.8-25.3)
	PLT ($\times 10^9$/L)	179.4 ± 84.5 (51-480)
	D-dimer(mg/mL)	4.9 ± 4.5 (0.5-18.3)
	Blood glucose (mmol/L	7.9 ± 2.6 (3.8-16.2)
	INR	1.3 ± 0.6 (1.0-9.8)
	Caprini score	6 ± 1.6 (4-14.0)

Table 1 (continued)

Pathology	**Tumor Site**	**Fundus**	7 (11.7%)
		Body	12 (20%)
		Antrum	41 (68.3%)
	Tumor Size	5.8 ± 1.4 (5-8.5)	
	Differentiation	**Well**	8 (13.3%)
		Moderate	23 (38.3%)
		Poor	29 (48.3%)
	Depth of invasion	**Submucosa**	9 (15%)
		musculosa	4 (6.7%)
		Penetrate musculosa	6 (10%)
		serosa	19 (31.7%)
		Penetrate serosa	22 (36.7%)
	Vessel Invasion	-	29 (48.3%)
		+	31 (42.7%)
	LN metastasis	-	22 (36.7%)
		+	38 (63.3%)
	Distant Metastasis	-	60 (100%)
		+	0 (0%)
	TNM Stage	**I**	11 (18.3%)
		II	18 (30%)
		III	31 (51.7%)
		IV	0 (0%)

CEA: *Carcinoembryonic antigin,* ***WBCs:*** *White Blood Cells,* ***PLT:*** *Platelet,* ***INR:*** *International Normalized Ratio,* ***TNM:*** *Tumor, Node and Metastasis* ***LN:*** *Lymph Node,* ***POD1:*** *Postoperative day one*

Table 2: Analyses of clinical and laboratory factors in both VTE (-) and VTE (+) groups (n =60)

Clinical and laboratory factors		VTE (-), *n* = 41 (68.3%)	VTE (+), n=19(31.7%)	P-Value
Age (years)	< 70	29 (48.3%)	6 (10%)	0.01
	≥ 70	12 (20%)	13(21.7%)	
Sex	Male	28 (46.7%)	11 (18.3%)	0.56
	Female	13(21.3%)	8 (13.3%)	
Preoperative BMI	< 25	34 (56.7%)	14 (23.3%)	0.04
	≥ 25	7 (11.7%)	5 (8.3%)	
Smokings	-	33 (55%)	15 (25%)	0.35
	+	8 (13.3%)	4 (6.7%)	
Operative duration (min)	≤250	10 (16.7%)	4 (6.7%)	0.27
	>250	31 (51.7%)	15 (25%)	
Operative bleeding (ml)	<200	24 (40%)	11 (18.3%)	0.48
	≥200	17 (28.3%)	8 (13.3%)	
Approach	Open	36 (60%)	8 (13.3%)	0.83
	Laparoscopic	5 (8.3%)	11 (18.3%)	
Respiratory disease	-	37 (61.7%)	17 (28.3%)	0.55
	+	4 (6.7%)	2 (3.3%)	
Cardiovascular disease	-	35 (58.3%)	14 (23.3%)	0.28
	+	6 (10%)	5 (8.3%)	
Hypertension	-	25 (41.7%)	12 (20%)	0.51
	+	16 (26.7%)	7 (11.7%)	
Diabetes mellitus	-	36 (60%)	16 (26.7%)	0.89
	+	5 (8.3%)	3 (5%)	
Cerebrovascular disease	-	38 (63.3%)	17 (28.3%)	0.55
	+	3 (5%)	2 (3.3%)	
Past history of cancer	-	37 (61.7%)	19 (31.7%)	0.15
	+	3 (5%)	1 (1.7%)	
Peripheral venous disease	-	39 (65%)	18 (30%)	0.23
	+	2 (3.3%)	1 (1.7%)	
Neoadjuvant chemotherapy	-	3 (5%)	8 (13.3%)	0.97
	+	38 (63.3%)	11 (18.3%)	
Hypoalbuminemia (<35 g/L)	-	29 (48.3%)	11 (18.3%)	0.86
	+	12 (20%)	8 (13.3%)	
Preoperative				
Hemoglobin (g/l)	< 120	20 (33.3%)	11 (18.3%)	0.19
	≥ 120	21 (35%)	8 (13.3%)	
WBC ($\times 10^9$/L)	< 10	38 (63.3%)	4 (6.7%)	0.03
	≥ 10	3 (5%)	15 (25%)	
PLT ($\times 10^9$/L)	< 350	37 (61.7%)	16 (26.7%)	0.76
	≥350	4 (6.7%)	3 (5%)	
D-dimer (mg/mL)	< 0.5	18 (30%)	5 (8.3%)	0.03
	≥ 0.5	23 (38.3%)	14 (23.3%)	
Blood glucose (mmol/L)	< 6	34 (56.7%)	11 (18.3%)	0.01
	≥ 6	7 (11.7%)	8 (13.3%)	
INR	< 1.1	33 (55%)	13 (21.7%)	0.25
	≥ 1.1	8 (13.3%)	6 (10%)	

Table 2: (continued)

Clinical and laboratory factors		VTE (-), n= 41 (68.3%)	VTE (+), *n*=19 (31.7%)	P-Value
Caprini score	0-2 (low risk)	0 (0%)	0 (0%)	0.03
	3-4 (medium risk)	27 (45%)	11 (18.3%)	
	≥5 (high risk)	14 (23.3%)	8 (13.3%)	
Postoperative				
Hemoglobin (g/l)	< 120	30 (50%)	15 (25%)	0.02
	≥ 120	11(18.3%)	4 (6.7%)	
WBC ($\times 10^9$/L)	< 10	20 (33.3%)	8 (13.3%)	0.33
	≥ 10	21(35%)	11(18.3%)	
PLT ($\times 10^9$/L)	< 350	36 (60%)	17 (28.3%)	0.66
	≥350	5 (8.3%)	2 (3.3%)	
D-dimer (mg/mL)	< 0.5	0 (0%)	0(0%)	0.54
	≥ 0.5	41 (68.3%)	19 (31.7%)	
Blood glucose (mmol/L)	< 6	6 (10%)	4 (6.7%)	0.87
	≥ 6	35 (58.3%)	15 (25%)	
INR	< 1.1	13 (21.3%)	5 (8.3%)	0.07
	≥ 1.1	28 (46.7%)	14 (23.3%)	
Caprini score	0-2 (low risk)	0 (0%)	0 (0%)	0.69
	3-4 (medium risk)	9 (15%)	5 (8.3%)	
	≥5 (high risk)	32 (53.3%)	14 (23.3%)	

Table 3: Analyses of pathological factors in both VTE (-) and VTE (+) groups (n =60)

Pathological factors		**VTE (-) 41**	**VTE (+) 19**	P-Value
Tumor site	**Fundus**	5 (8.3%)	2 (3.3%)	0.633
	Body	8 (13.3%)	4 (6.7%)	
	Antrum	30 (50%)	11 (18.3%)	
Tumor size	**< 5**	18 (30%)	6 (10%)	0.113
	≥ 5	23 (38.3%)	13 (21.7%)	
Differentiation	**well**	5 (8.3%)	3 (5%)	0.484
	moderate	14 (23.3%)	9 (15%)	
	poor	22 (36.7%)	7 (11.7%)	
Depth of invasion	**submucosa**	7 (11.7%)	2 (3.3%)	0.02
	musculosa	3 (5%)	1 (1.7%)	
	Penetrate musculosa	4 (6.7%)	2 (3.3%)	
	serosa	11 (18.3%)	8 (13.3%)	
	Penetrate serosa	16 (26.7%)	6 (10%)	
Vessel invasion	**-**	22 (36.7%)	7 (11.7%)	0.171
	+	19 (31.7%)	12 (20%)	
LN metastasis	**-**	16 (26.7%)	6 (10%)	0.881
	+	25 (41.7%)	13 (21.7%)	
Number of LN metastasis	**< 7**	32 (53.3%)	14 (23.3%)	0.426
	≥ 7	9 (15%)	5 (8.3%)	
TNM classification	**I**	9 (15%)	2 (3.3%)	0.01
	II	10 (16.7%)	8 (13.3%)	
	III	22 (36.7%)	9 (15%)	

Table 4: Predictors of post-gastrectomy VTE

	Variables	Odds ratio	95% CI	P-value
Univariate	Age	1.032	1.013-1.056	0.03
	Gender	0.793	1.106-1.124	0.42
	Preoperative BMI	1.004	0.937-1.153	0.85
	Smoking	0.604	0.349-1.327	0.17
	Operative duration	1.003	0.975-1.008	0.21
	Operative bleeding	1.002	0.956-1.009	0.19
	Approach	0.822	0.347-2.186	0.71
	Pulmonary disease	0.773	0.268-2.262	0.68
	Cardiovascular disease	0.758	0.244-1.671	0.23
	Hypertension	0.836	0.548-1.521	0.82
	Diabetes Mellitus	0.891	0.323-1.662	0.53
	Cerebrovascular disease	0.675	0.239-2.503	0.43
	Past history of cancer	0.438	0.112-1.367	0.12
	Peripheral venous disease	0.917	0.183-4.796	0.63
	Neoadjuvant chemotherapy	2.425	0.339-7.129	0.35
	Albumin	0.851	0.947-1.125	0.31
	Preoperative			
	Hemoglobin	0.983	0.993-1.008	0.14
	WBC	1.106	0.986-1.322	0.18
	PLT	1.004	0.977-1.016	0.78
	D-dimer	1.121	0.971-1.326	0.12
	Blood glucose	1.150	1.021-1.446	0.02
	INR	6.532	0.727-9.229	0.49
	Caprini score	1.146	0.966-1.378	0.04
	Postoperative			
	Hemoglobin	0.875	0.955-0.985	0.04
	WBC	1.054	0.976-1.127	0.28
	PLT	0.988	0.984-1.016	0.41
	D-dimer	0.961	0.966-1.135	0.45
	Blood glucose	0.800	0.781-1.038	0.15
	INR	1.114	0.679-1.630	0.87
	Caprini score	1.137	0.859-1.294	0.52
	Pathology			
	Tumor site	1.249	0.667-1.875	0.43
	Tumor size	1.070	0.984-1.262	0.16
	Differentiation	1.028	0.734-1.652	0.93
	Depth of invasion	1.344	1.025-1.671	0.03
	LN metastasis	0.932	0.621-1.772	0.73
	Number of LN metastasis	1.035	0.993-1.036	0.35
	TNM classification	1.614	1.087-2.311	0.01
Multivariate	Age	0.974	0.947-0.988	0.02
	TNM classification	0.326	0.168-0.972	0.03
	Caprini score (Preoperative)	0.413	0.966-0.951	0.03

DISCUSSION

Compared to other solid malignancies, gastric cancer demonstrates a significantly higher occurrence of VTE [6, 10]. Although gastric cancer is the fifth most common cancer and the fourth leading cause of cancer-related mortality globally, it continues to be a major factor in the development of CAT, a severe complication and a predominant cause of non-cancer-related mortality [28]. Research has demonstrated that VTE serves as an independent prognostic factor for mortality in gastric cancer patients [19], with surgical intervention further exacerbating the risk of CAT. Individuals with cancer who undergo major surgical procedures exhibit a heightened susceptibility to CAT [29]. Therefore, recognizing the risk factors linked to VTE is of paramount importance and develop strategies to predict and prevent these events in gastric cancer patients' post-gastrectomy, with the goal of enhancing postoperative outcomes and overall survival.

In this retrospective study, we analyzed clinical data from GC patients who underwent radical gastrectomy and demonstrated elevated D-dimer levels ($n = 60$) to identify risk factors associated with post-gastrectomy VTE. As detailed earlier, the diagnosis of VTE in our study was confirmed using Duplex ultrasonography of both lower and upper extremity veins. Based on the ultrasonography results, patients were categorized into two groups: those without VTE (VTE (−), n = 41) and those with VTE (VTE (+), n = 19). Among the VTE (+) group, most thromboembolic events occurred in the lower extremity veins, with a smaller proportion found in the upper extremity veins. Consistent with our results, Li et al. conducted a retrospective analysis aimed at identifying both preoperative and postoperative risk factors for venous thromboembolism (VTE) in gastric cancer patients who had undergone gastrectomy. This study included 246 patients with elevated postoperative D-dimer levels, all of whom subsequently underwent Doppler ultrasonography to evaluate the veins of both lower and upper extremities. Detailed clinicopathological data were collected, and comparisons were made between the postoperative VTE-positive and VTE-negative groups. Out of the 246 patients with increased D-dimer levels after gastrectomy, 74 were diagnosed with thrombosis in the veins of the lower and/or upper extremities [30].

In the current investigation, neoadjuvant chemotherapy was administered to 49 patients, accounting for 81.7% of the study cohort. The role of neoadjuvant chemotherapy in the management of gastric cancer has gained increasing prominence. Research has demonstrated that administering neoadjuvant chemotherapy prior to surgical intervention can substantially enhance survival outcomes for patients with gastric adenocarcinoma, gastroesophageal junction adenocarcinoma, and lower esophageal adenocarcinoma, respectively [28, 31].

In our analysis, elevated preoperative blood glucose levels were identified as a significant risk factor for postoperative VTE, implying that hyperglycemia may elevate the risk of thrombogenesis by contributing to a hypercoagulable state. Thus, meticulous blood glucose management prior to surgery could be instrumental in reducing the incidence of VTE in patients with gastric cancer. Additionally, D-dimer levels were noted in the VTE (+) group. While normal D-dimer levels can rule out VTE, elevated levels are not confirmatory, indicating the need for further research into the predictive value of preoperative D-dimer

concentrations for post-gastrectomy VTE in GC patients [2]. In a recent Chinese study, the authors reported that D-dimer concentration was significantly higher in the postoperative VTE (+) group [30].

In this study, univariate logistic regression analysis identified several independent risk factors for postoperative VTE in patients with gastric adenocarcinoma undergoing radical gastrectomy, including patient age, preoperative blood glucose levels, preoperative Caprini score, postoperative hemoglobin levels, depth of invasion, and TNM stage. Multivariate logistic regression analysis further refined these findings, indicating that age, TNM stage, and preoperative Caprini score were the most significant independent predictors of post-gastrectomy VTE in patients with GC.

Advancing age is universally recognized as a significant risk factor among cancer patients and has been specifically reported as a contributor to VTE in those with gastric cancer [21, 32, 33]. Within our study, age was identified as a critical independent risk factor for postoperative VTE in individuals undergoing radical gastrectomy for gastric adenocarcinoma. The elevated risk in older patients is likely attributable to a combination of factors, including a higher incidence of comorbid conditions, decreased physical activity, and age-related alterations in the coagulation system, all of which collectively enhance the propensity for thrombosis.

According to the Japanese Circulation Society guidelines, individuals over 40 years of age undergoing major oncological surgery are classified as being at a heightened risk for VTE. Consequently, anticoagulation therapy is advised as a prophylactic measure, particularly for those undergoing abdominal surgical procedures [34].

Furthermore, research has demonstrated that the aging process is linked to alterations in blood composition, notably the elevation of fibrinogen and factor VIII levels, which contribute to a hypercoagulable state [35- 37]. Hence, coagulation in the elderly can be exacerbated post-surgery, particularly in major operations like gastrectomy, thereby increasing the risk of VTE [38].

Our findings align with research conducted among elderly adults in the United States, which reported a significant association between older age and an increased risk of VTE in cancer patients [39].

Li et al. performed a univariate logistic regression analysis focused on postoperative clinical and pathological factors, aligning with the findings of the present study. This analysis identified postoperative hemoglobin levels, tumor stage, depth of tumor invasion, and TNM classification as independent risk factors for the development of postoperative VTE in gastric cancer patients. However, when a multivariate analysis was conducted, only the tumor stage persisted as a significant predictor of postoperative VTE after gastrectomy [30].

In our study, the TNM stage was identified as an independent risk factor for post-gastrectomy VTE in patients with gastric cancer. This correlation can be explained by the fact that advanced TNM stages signify a greater tumor burden and increased disease severity, which are often associated with a hypercoagulable state due to heightened

procoagulant activity, systemic inflammation, and the complexity of surgical procedures. Supporting this, a study conducted in Korea by Kim et al. demonstrated that tumor stage significantly influenced VTE development, with incidence rates of 1.4% in stage I, 2.4% in stages II/III, and 9.7% in stage IV (P = 0.008). In their multivariate analysis, stage IV patients were found to have a markedly higher likelihood of developing postoperative VTE [odds ratio, 8.18 (95% CI, 1.54-43.42)] compared to those in stage I [28].

Regarding the Caprini score, while its effectiveness in predicting VTE risk is established in various surgical fields, its application and significance in gastric adenocarcinoma surgeries are not as extensively documented. Our study's emphasis on this score fills a crucial gap, especially considering the complex interplay of cancer-related and surgical risk factors in these patients.

Limitations of the study

we had some limitations in our study. First, its retrospective, single-institution design limits the generalizability of our findings and may introduce selection bias. Second, by including only patients with elevated post-gastrectomy D-dimer levels, we potentially missed VTE events in patients with normal D-dimer concentrations, coupled with the variability in D-dimer testing methods and cutoff values [8]. Third, our focus was primarily on VTE events during hospitalization, without long-term follow-up data for postoperative VTE in outpatients. Lastly, certain risk assessments like performance status were not evaluated, and the comprehensive impact of different chemotherapy regimens on VTE risk was not explored. To effectively tackle these challenges, there is a pressing need for additional prospective studies.

CONCLUSIONS

In conclusion, gastric cancer ranks among the most thrombogenic malignancies, underscoring the critical importance of identifying risk factors associated with post-gastrectomy VTE in this patient population. Our study has determined that age, preoperative blood glucose levels, Caprini score, and TNM stage serve as independent risk factors for the development of VTE following gastrectomy. Thus, meticulous perioperative surveillance, thorough evaluation, and proactive management of these risk factors are crucial to foresee and prevent VTE incidents in gastric cancer patients following surgery.

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Figure 1: Flowchart demonstrating the patients enrolled in this study.

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Availability of data and material:

All data generated or analyzed during this study are included in this published article and it is available from the corresponding author on reasonable request.

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Mohamed S. Essa: Study concept, design, literature review and writing.
Mohamed E. Zayed: Study design, data collection and Literature review.
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References:

1-Nakamura M, Yamada N, Oda E, Matsubayashi D, Ota K, Kobayashi M, et al. Predictors of venous thromboembolism recurrence and the bleeding events identified using a Japanese healthcare database. Journal of cardiology.2017;70(2):155-62.

2-Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. Lancet. 2021 ;398(10294):64-77.

3-Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. The Lancet. 2016;388(10063):3060-73.

4-Connolly GC, Francis CW. Cancer-associated thrombosis. Hematology 2013, the American Society of Hematology Education Program Book. 2013;2013(1):684-91.

5-Donnellan E, Kevane B, Bird BR, Ni Ainle F. Cancer and venous thromboembolic disease: from molecular mechanisms to clinical management. Current Oncology. 2014;21(3):134-43.

6- Gervaso L, Dave H, Khorana AA. Venous and arterial thromboembolism in patients with cancer: JACC: CardioOncology state-of-the-art review. Cardio Oncology. 2021;3(2):173-90.

7-Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer. 2013;119(3):648-55.

8-Sørensen HT, Mellemkjær L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. New England Journal of Medicine. 2000;343(25):1846-50.

9-Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. The Lancet Oncology. 2019;20(10): e566-81.

10-Khorana AA, Mackman N, Falanga A, Pabinger I, Noble S, Ageno W, et al. Cancer-associated venous thromboembolism. Nature Reviews Disease Primers. 2022;8(1):11.

11-Mukai M, Oka T. Mechanism and management of cancer-associated thrombosis. Journal of Cardiology. 2018;72(2):89-93.

12-Olsson AK, Cedervall J. NETosis in cancer–platelet–neutrophil crosstalk promotes tumor-associated pathology. Frontiers in Immunology. 2016; 7:373.

13-Hisada Y, Mackman N. Cancer-associated pathways and biomarkers of venous thrombosis. Blood, The Journal of the American Society of Hematology. 2017 ;130(13):1499-506.

14-Suzuki-Inoue K. Platelets and cancer-associated thrombosis: focusing on the platelet activation receptor CLEC-2 and podoplanin. Hematology 2014, the American Society of Hematology Education Program Book.2019(1):175-81.

15-Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. Journal of Clinical Oncology. 2020;38(5):496-520.

16-Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021;71(3):209-49.
17-Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. The Lancet. 2020;396(10251):635-48.
18-Majmudar K, Golemi I, Tafur AJ, Toro JD, Visonà A, Falgá C, et al. Outcomes after venous thromboembolism in patients with gastric cancer: Analysis of the RIETE Registry. Vascular Medicine. 2020;25(3):210-7.
19-Fuentes HE, Oramas DM, Paz LH, Wang Y, Andrade XA, Tafur AJ. Venous thromboembolism is an independent predictor of mortality among patients with gastric cancer. Journal of gastrointestinal cancer. 2018; 49:415-21.
20-Tanizawa Y, Bando E, Kawamura T, Tokunaga M, Makuuchi R, Iida K, et al. Prevalence of deep venous thrombosis detected by ultrasonography before surgery in patients with gastric cancer: a retrospective study of 1140 consecutive patients. Gastric Cancer. 2017; 20:878-86.
21-Suzuki K, Shibasaki S, Nakauchi M, Nakamura K, Akimoto S, Tanaka T, et al. Impact of routine preoperative sonographic screening with early intervention for deep venous thrombosis in lower extremities on preventing postoperative venous thromboembolism in patients with gastric cancer scheduled for minimally invasive surgery. Langenbeck's Archives of Surgery. 2022;407(2):597-608.
22-Lee KW, Bang SM, Kim S, Lee HJ, Shin DY, Koh Y, et al. The incidence, risk factors and prognostic implications of venous thromboembolism in patients with gastric cancer. Journal of Thrombosis and Haemostasis. 2010;8(3):540-7.
23-Abdel-Razeq H, Mustafa R, Sharaf B, Al-Tell A, Braik D, Ashouri K, et al. Patterns and predictors of thromboembolic events among patients with gastric cancer. Scientific Reports. 2020;10(1):18516.
24-Wada T, Fujiwara H, Morita S, Fukagawa T, Katai H. Incidence of and risk factors for preoperative deep venous thrombosis in patients undergoing gastric cancer surgery. Gastric Cancer. 2017; 20:872-7.
25-Osaki T, Saito H, Fukumoto Y, Kono Y, Murakami Y, Shishido Y, et al. Risk and incidence of perioperative deep vein thrombosis in patients undergoing gastric cancer surgery. Surgery today. 2018; 48:525-33.
26-Takayoshi K, Kusaba H, Aikawa T, Koreishi S, Sagara K, Nakano M, et al. Hypoalbuminemia for the prediction of venous thromboembolism and treatment of direct oral anticoagulants in metastatic gastric cancer patients. Gastric Cancer. 2019 5; 22:988-98.
27-Golemi I, Adum JP, Tafur A, Caprini J. Venous thromboembolism prophylaxis using the Caprini score. Disease-a-Month. 2019;65(8):249-98.
28-Iwu CD, Iwu-Jaja CJ. Gastric Cancer Epidemiology: Current Trend and Future Direction. Hygiene. 2023;3(3):256-68.

29- Fernandes CJ, Morinaga LT, Alves JL, Castro MA, Calderaro D, Jardim CV, et al. Cancer-associated thrombosis: the when, how and why. European Respiratory Review. 2019;28(151).
30- Li XP, Wang YY, Sun YS, Zhang LJ, Zhao XY, Liu ZQ, et al. Preoperative and postoperative clinical signatures of postgastrectomy venous thromboembolism in patients with gastric cancer: A retrospective cohort study. Asian Journal of Surgery. 2023;46(4):1556-63.
31- Hartgrink HH, Van de Velde CJ, Putter H, Songun I, Tesselaar ME, Kranenbarg EK, et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. European Journal of Surgical Oncology (EJSO). 2004 Aug 1;30(6):643-9.
32- Berben L, Floris G, Wildiers H, Hatse S. Cancer and aging: two tightly interconnected biological processes. Cancers. 2021;13(6):1400.
33- Tanizawa Y, Bando E, Kawamura T, Tokunaga M, Makuuchi R, Iida K, et al. Prevalence of deep venous thrombosis detected by ultrasonography before surgery in patients with gastric cancer: a retrospective study of 1140 consecutive patients. Gastric Cancer. 2017;20:878-86.
34- Ando M, Fukuda I, Ito M, Kobayashi T, Masuda M, Miyahara Y, et al. Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (JCS 2009)-Digest Version. CIRCULATION JOURNAL. 2011;75(5):1258-81.
35- Abbate R, Prisco D, Rostagno C, Boddi M, Gensini GF. Age-related changes in the hemostatic system. International Journal of Clinical and Laboratory Research. 1993;23:1-3.
36- Kamphuisen PW, Eikenboom JC, Bertina RM. Elevated factor VIII levels and the risk of thrombosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2001;21(5):731-8.
37- Basaric D, Saracevic M, Bosnic V, Vlatkovic A, Tomic B, Kovac M. Factor VIII Activity in Relation to the Type of Thrombosis and Patient's Risk Factors for Thrombosis, Age, and Comorbidity. The Eurasian Journal of Medicine. 2023;55(1):9.
38- Laryea J, Champagne B. Venous thromboembolism prophylaxis. Clin Colon Rectal Surg. 2013;26:153-9.
39-Marks MA, Engels EA. Venous thromboembolism and cancer risk among elderly adults in the United States. Cancer epidemiology, biomarkers & prevention. 2014;23(5):774-83.