***Original Research Article***

**Incidence and risk factors of postoperative venous thromboembolism in patients undergoing colorectal cancer surgery: A prospective cross-sectional study**

**Abstract:**

**Background:** Among the most prevalent malignant neoplasms worldwide, colorectal cancer (CRC) is a major threat to human life and health. The second most common cause of death for cancer patients receiving medical and surgical treatment is venous thromboembolism (VTE). Patients with colorectal cancer who have radical surgery run the risk of developing venous thromboembolism (VTE).The current study analyzes the incidence and risk factors associated with post-operative VTE after colorectal cancer surgery(CRC) within 90 days of postoperative period.

**Methods and materials:** This was a prospective cross sectional study conducted in a tertiary medical college and hospital of Dhaka, Bangladesh from January 2021 to December 2023.There was no VTE prophylaxis guideline in the institute. None of the patient received any standard VTE prophylaxis in the perioperative period. Statistical analysis was performed using IBM SPSS version 26.0. Statistical significance was defined as a p-value of < 0.05. Multivariable analysis using a binary logistic regression model was used to verify the independent risk factors for VTE in the post-operative patients. Variables identified as having a potential association (p < 0.05) in a univariate analysis were entered into each multivariable analysis model.

**Results:** A total of 86 patients who underwent surgery for CRC were included in the study. The included patients were divided into two groups: VTE and non-VTE group. Out of 86 patients, 7(8.13%) patients presented with DVT. Two patients (2.3%) had pulmonary embolism and both of them died in the post-operative period. Advanced age (OR-1.876 95% CI: 1.765–1.975) elevated Caprini score (OR-1.564, 95%CI: 0.85-1.72), elevated d-dimer (OR-1.446,95% CI: 1.130-0.1.849), advanced stage of disease (OR-1.94, 95% CI: 1.87-1.213), prolong duration of surgery OR-1.277,95% CI;0.87-1.312) and presence of inflammatory bowel disease(OR-1.34,95% CI:1.29-1.41) were independent predictors of postoperative VTE (P<0.05).

**Conclusion:** The current study showed post-operative VTE is a grave complication after malignant colorectal surgery. There were several factors for development of post-operative VTE in CRC patients. So further large scale multicenter study should be conducted to identify the predictors of post-surgical VTE.

Key words:*incidence, risk factors, venous thromboembolism, colorectal cancer surgery*

**Introduction:**

Among the most prevalent malignant neoplasms worldwide, colorectal cancer (CRC) is a major threat to human life and health.1 There are little treatment options for colorectal cancer (CRC), and for individuals with resectable tumors, surgery in conjunction with chemotherapy and radiation therapy has been deemed a crucial strategy.2 Patients with colorectal cancer are increasingly being treated using robotic and laparoscopic surgery as a result of the rapid advancements in technology.3 Because it produces less trauma than open surgery, laparoscopic and robotic surgery are referred to as minimally invasive surgery. Nevertheless, complications may arise with any kind of surgery.

The second most common cause of death for cancer patients receiving medical and surgical treatment is venous thromboembolism (VTE).4 Deep vein thrombosis (DVT) and its sequelae, pulmonary embolism (PE), make up VTE. Treatment of venous thromboembolism in cancer patients is difficult because of the increased risk of bleeding and recurrent thrombosis.5 Additionally, surgery is thought to have a pro-inflammatory influence on VTE incidence. During the procedure, the patient's hypercoagulable condition, venous blood pooling, and vessel wall damage are all likely to happen. Another significant factor contributing to the development of VTE following surgery is tissue factor exposure at the operative site.5 Prior research has demonstrated that red blood cell transfusions are linked to a higher incidence of VTE in surgical patients.6 Additionally, through platelet G protein-coupled (GPCR) and immune-receptor tyrosine-based activation motif (ITAM) receptor signaling, platelets contribute to venous thrombosis and are necessary for hemostasis.6 It has been demonstrated that biochemical measures related to platelets can predict DVT in patients with breast cancer, and biochemical parameters related to thromboelastography (TEG) can predict VTE in patients with gynecologic oncology.7

Patients with colorectal cancer who have radical surgery run the risk of developing venous thromboembolism (VTE).8 Chronic leg swelling, ulceration, and discomfort (post thrombotic syndrome) or even mortality can be caused by a pulmonary embolism (PE) or a VTE.8 In the absence of preventive interventions, the risk of thrombosis following abdominal surgery is 15–40%, and the rate of perioperative DVT following general surgery is 10–40%.9 Compared to abdominal surgery, the risk of PE is three times higher and the incidence of DVT is twice as high following colorectal surgery.10 Surgery itself is an independent risk factor for the development of VTE, according to different studies.11.12 Patients undergoing colon surgery have a higher risk of developing VTE following surgery than those undergoing other abdominal surgeries because of the unique position and prolonged operation time, especially after radical colorectal surgery, which has been reported as high as 37–46%.12 Postoperative VTE can be a grave complication following CRC surgery. Never the less, VTE also had a major impact on surgical patients' prognosis and decreased their quality of life. Within a month following surgery, VTE is the leading cause of death for individuals undergoing oncological surgery. About one-third of patients with DVT will experience post-thrombotic syndrome (PTS) in the long run, and thirty percent of patients with VTE will experience a recurrence within eight years following surgery.13 There are several known factors that raise the likelihood of a postoperative VTE. A history of prior VTE, cancer, inflammatory bowel disease, thrombophilia, advanced age, obesity, smoking, acute sickness, wound infection, and prolonged immobility are among them, in addition to the actual surgical procedure.14 Consequently, there is interest in more accurately describing the specific risk factors for a VTE, especially a PE, in patients undergoing colorectal surgery. This could assist in establishing strategies for VTE and PE prevention for these patients. In addition, the appropriate risk stratification can provide the actual benefits of VTE prophylaxis.

**Materials and methods:**

This was a prospective cross sectional study conducted in a tertiary medical college and hospital of Dhaka, Bangladesh from January 2021 to December 2023.There was no VTE prophylaxis guideline in the institute. None of the patient received any standard VTE prophylaxis in the perioperative period. The inclusion criteria were as follows:

1. Patient age>18 years

2. Patient underwent surgery for colorectal malignancy

3. Patient diagnosed with DVT within 90 days after operation

Following patients were excluded from study

1. Recurrent DVT

2. Past history of venous thromboembolism (VTE)

3. Incomplete medical records

4. Age< 18 years

5. Patient underwent surgery for benign colorectal conditions

6. Emergency surgery

DVT was diagnosed according to the clinical examination findings like unilateral swollen limb with pain and erythema of lower extremity aided ultrasonography, performed by trained ultrasound physicians. DVT was defined based on the following ultrasonic findings:

• Heterogeneous thrombus was present inside any of the screened veins on B-mode

• Presence of a non-compressible segment

• Flow impairment on color Doppler imaging.

PE was identified with lung ventilation/perfusion scans or chest computed tomography.

Demographic variables including age, sex, BMI, history of smoking, co-morbidities (hypertension, diabetes, coronary heart disease) were obtained. Laboratory data like complete count, serum albumin, CRP, blood glucose level, post-operative d-dimer and pre-operative CEA level were collected. Disease profile like stage of malignancy, histopathological type, location, history of chemo-radiotherapy and associated inflammatory bowel disease (IBD) were also included in the study. Operative data like type of surgery, mode of surgery (open vs laparoscopic) duration of surgery, amount of blood transfusion were also identified. Caprini risk assessment model (RAM) score of VTE was also calculated. Originally developed for surgical patients, the Caprini RAM facilitates the derivation of VTE risk by summing individual risk factors so as to place patients into four categories: “low risk” (0-1 points), “moderate risk” (2 points), “high risk” (3-4 points), and “highest risk” (≥5 points). Post-operative data including rate of infection (wound infection, pneumonia, urinary tract infection) anastomotic leak, early mobilization, hospital mortality and length of hospital stay were also observed.

An ethical clearance was taken from institutional ethical committee. Data was collected in a preformed questionnaire. Incidence of VTE among the patients who underwent surgery for CRC was investigated up to 90 days after surgery. Then, the clinical characteristics and laboratory results were compared between those with and without VTE. Statistical analysis was performed using IBM SPSS version 26.0. Continuous variables were analyzed in the form of the means with standard deviations (Mean ± SD). Categorical variables were shown as numbers and proportions. Continuous data were analyzed using the independent samples t-test. Categorical data were analyzed using the chi-squared test. Statistical significance was defined as a p-value of < 0.05. Multivariable analysis using a binary logistic regression model was used to verify the independent risk factors for VTE in the post-operative patients. Variables identified as having a potential association (p < 0.05) in a univariate analysis were entered into each multivariable analysis model.

**Results:**

A total of 86 patients who underwent surgery for CRC were included in the study. The included patients were divided into two groups: VTE and non-VTE group. Out of 86 patients, 7(8.13%) patients presented with DVT. Two patients (2.3%) had pulmonary embolism and both of them died in the post-operative period. The general characteristics of the patients are demonstrated in Table 1. There was no significant difference in BMI, smoking, comorbidities, between the two groups. Patients with VTE were older than those without VTE (66.7 ± 11.6 vs. 46.5 ± 13.9 years, p < 0.05). Females were more affected by VTE (77.77% vs. 22.07%, p<0.05).Caprini score was more in VTE group (8±1.62 vs 3±1.2,p<0.05)

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Non-VTE(n=77) | VTE(n=9) | P-value |
| Age (years) | 46.5 ± 13.9 | 66.7 ± 11.6 | 0.003 |
| Male n (%) | 60(77.92%) | 2(22.22%) | 0.067 |
| Female n (%) | 17(22.07%) | 7(77.77%) | 0.002 |
| BMI (kg/m2) | 22±1.2 | 25±4.2 | 0.137 |
| Smoking, n (%) | 21(27.27%) | 1(11.11%) | 0.076 |
| Comorbidities |  |  |  |
| Hypertension, n (%) | 19(24.67%) | 4(44.44%) | 0.125 |
| Hyperlipidemia (%) | 22(28.57%) | 4(44.44%) | 0.132 |
| Diabetes, n (%) | 23(29.87%) | 5(55.56%) | 0.098 |
| Coronary heart disease n(%) | 16(77.77%) | 3(33.33%) | 0.436 |
| Caprini RAM score | 3±1.2 | 8±1.62 | 0.001 |

Table-1 demographic characteristics of patients

Table-2 Disease profile of study population

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | VTE(n=9) | Non-VTE(n=77) | P value |
| Stage of malignancy |  |  |  |
| Stage-I | 0 | 5(6.49%) |  |
| Stage-II | 1(11.11%) | 32(41.55%) | 0.086 |
| Stage-III | 2(22.22%) | 28(36.37%) | 0.094 |
| Stage-IV | 6(66.67%) | 12(15.58%) | 0.003 |
| location |  |  |  |
| Right colon | 1(11.11%) | 16(29.87%) | 0.176 |
| Left Colon | 3(33.33%) | 20(25.97%) | 0.165 |
| Rectum | 5(55.56%) | 41(53.24%) | 0.114 |
| Histopathological type |  |  |  |
| Adenocarcinoma  Poorly Differentiated  Moderately differentiated  Well Differentiated | 6(66.67%)  1(11.11%)  2(22.22%) | 16(20.77%)  10(12.98%)  51(66.23%) | 0.003  0.126  0.063 |
| Others |  |  |  |
| New adjuvant chemo-radiotherapy | 7(77.79%) | 28(36.37%) | 0.001 |
| Presence of inflammatory bowel disease (IBD) | 5(55.56%) | 11(14.28%) | 0.002 |

Table-3 laboratory variables of the patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **VTE** | **Without VTE** | **p-value** |
| WBC (10*∧*9/L) | 6.6 *±* 5.8 | 7.7 *±* 3.6 | 0.128 |
| Hb(gm/dl) | 10*±*2.3 | 12*±*1.4 | 0.214 |
| Platelet(10∧3 /L) | 460*±*24 | 320*±*32 | 0.086 |
| Alb (g/L) | 28.3 *±* 3.9 | 36.5 *±* 4.5 | 0.076 |
| Random Blood glucose (mmol/L) | 8.8 *±* 1.9 | 7.45 *±* 2.4 | 0.627 |
| CRP | 16±4.3 | 10±1.6 | 0.127 |
| CEA(ng/ml) | 24±4.6 | 5±2.1 | 0.023 |
| D-dimer (ug/mL) | 3.2 ± 1.6 | 0.35 ± 1.2 | 0.002 |
| FDP | 12.3 *±* 1.4 | 8.0 *±* 1.3 | 0.083 |

Table 3 shows the results of laboratory factors in patients with VTE vs. those without VTE. In the VTE group, the level of D-dimer was significantly higher than that in the non- DVT group (3.2 ± 1.6 vs. 0.35 ± 1.2, p < 0.05) and low serum albumin level (28.3 *±* 3.9 vs 36.5 *±* 4.5) were observed in VTE group which was statistically significant (p<0.05).Pre-operative high CEA level was also significantly associated post-operative VTE (24±4.6 vs 5±2.1, p<0.05).

Table-4 per-operative variables of the patients

|  |  |  |  |
| --- | --- | --- | --- |
|  | VTE(n=9) | Non VTE(n=77) | P- value |
| Type of surgery  Right hemicolectomy  Left hemicolectomy  Anterior resection  Abdominoperineal resection  Palliative loop Sigmoid/ileostomy | 1(11.11%)  2(22.22%)  1(11.11%)  5(55.56%)  1(11.11%) | 16(20.77%)  18(23.37%)  23(29.87%)  10(12.98%)  10(12.98%) | 0.128  0.342  0.437  0.167  0.084 |
| Mode of surgery  open  laparoscopic | 6(66.67%)  3(33.33%) | 51(66.23%)  16(20.77%) | 0.192  0.427 |
| Duration of surgery(hrs) | 4*±*2.3 | 2*±*1.4 | 0.002 |
| Amount of blood Transfusion(ml) | 600±80 | 400±55 | 0.004 |

Table-4 shows increased duration of surgery (4*±*2.3hrs vs 2*±*1.4hrs) and increased per-operative blood transfusion(600±80 ml vs 400±55 ml) was significantly associated with post-operative VTE(p<0.05)

Table-5 Multivariate logistic regression model correlated to VTE

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Odd ratio** | **95% Cl** | **P value** |
| Age | 1.876 | 1.765–1.975 | 0.004 |
| Female sex | 0.852 | 0.713–0.993 | 0.071 |
| D dimer | 1.446 | 1.130–1.849 | 0.004 |
| Duration of surgery(Hrs) | 1.277 | 0.87-1.312 | 0.001 |
| Amount of blood Transfusion(ml) | 0.754 | 0.678-0.923 | 0.414 |
| Serum Albumin | 0.876 | 0.613-0.934 | 0.064 |
| Caprini RAM score | 1.564 | 0.85-0.1.72 | 0.001 |
| New adjuvant chemo-radiotherapy | 0.065 | 0.054-0.71 | 0.189 |
| Presence of inflammatory bowel disease (IBD) | 1.34 | 1.29-1.41 | 0.003 |
| Stage –IV malignancy | 1.94 | 1.87-1.213 | 0.001 |
| Poorly differentiated adenocarcinoma | 0.114 | 0.110-0.121 | 0.634 |
| Pre-operative high CEA  Level | 0.218 | 0.212-0.312 | 0.567 |

Odds ratio for advanced age, elevated d-dimer, elevated Caprini score were 1.876(1.765–1.975, p=0.004),1.446(1.130-0.1.849,p=0.004),1.564(0.85-1.72,p=0.001) respectively. Besides, stage-

IV disease, presence of IBD and prolong duration of surgery were independent predictors of postoperative VTE (P<0.05).

**Discussion:**

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) or pulmonary embolism (PE) represents a frequent complication amongst the patients suffering from cancer. There is at least twice more risk for cancer patients undergoing surgical procedures to get postoperative DVT or PE, the likelihood increases more than threefold compared with non-cancer patients receiving similar procedures.15 The percentage of patients developing DVT following colorectal surgery in patients who did not receive thromboembolic prophylaxis is about 30%, and the likelihood of death due to PE in these patients is 1%.15 The pelvic dissection carries very high risk of thromboembolic complications on account of the patient's positioning during the surgery plus other associated risk factors such as cancer, old age, heart or respiratory failure which places the patient in a hypercoagulable state.16 In our study, there were 8.13% patients who had DVT and 2.3% who had PE. The low incidence of DVT in our study as because many patients did not undergo significant pelvic dissection during surgery, which being a major contributory factor for post-operative DVT; is not routinely carried out in the current center.

Elderly patients (over 60 years) and females were at higher risk for developing post-operative VTE. A recent systematic review indicated that age acted as an independent risk factor for both DVT and PE.17 In our study, age was an independent risk factor (OR=1.876, 95%Cl 1.765–1.975, p<0.05) for both DVT and PE. Moreover, the female sex might also affect the personal risk for venous thromboembolism (VTE). A recent investigation involving patients with VTE who participated in the Hokusai-VTE trial and case-control MEGA study showed that the occurrence of PE was greater in women compared to men.18 In our research, we had 2 patients who experienced PE, and both were women who died in the postoperative period.

A low concentration of albumin is recognized as a comprehensive indicator of inflammation, increased clotting tendency, or medical conditions that make patients more susceptible to thrombosis.19 Numerous prior studies have indicated a link between low albumin levels and venous thromboembolism (VTE).19,20 In our research, we discovered that a decreased albumin level had a notable correlation with postoperative VTE. However, the logistic regression analysis indicated no significant relationship between DVT and serum albumin, with a p-value of 0.064.

Relatively longer surgeries (> 4 hours) were associated with an increased risk of VTE (OR = 1.277, 95% CI 1.168-1.312, p = 0.001) in the present study. Tran et al. in a case series also found that surgeries lasting longer than 3 hours had an increased risk of VTE (OR = 4.36, 95% CI 3.02‒6.30, p < 0.001).21On the other hand advanced disease stage was significantly associated (p<0.05) with post-operative VTE which was showed in the study of Jung et al..22

A key consequence of blood transfusion is the introduction of large quantities of redox-active iron, which has been associated with wide spread inflammatory changes due to heightened oxidative stress from iron-catalyzed free radicals leading to prothrombotic state.23 Donated red blood cells are notably lacking in nitric oxide, potentially resulting in vasoconstriction and elevating the risk of thrombosis due to alterations in the vascular system and heightened platelet activation.23 The current research indicated a significant correlation between venous thromboembolism (VTE) and increased blood transfusions but failed establish a significant link through the multivariate logistic regression analysis (p<0.05).

Among individuals with inflammatory bowel disease (IBD), those with ulcerative colitis (UC) might have a greater likelihood of developing cancer compared to patients with Crohn's disease (CD).24 In the analysis of the Swiss IBD patient cohort, Alatri et al. discovered that undergoing surgery for IBD-related colorectal cancer was an independent risk factor for venous thromboembolism (VTE), which aligns with the findings of our research.24 The activation of both inflammatory and coagulation pathways creates a prothrombotic environment that involves the coagulation cascade, natural anticoagulants, the fibrinolytic system, the endothelium, the immune response, and platelets, leading to VTE.24,25

The Caprini RAM score is a well-established tool for evaluating the risk of post-operative VTE.26 A recent retrospective study conducted in China analyzed the Caprini RAM in patients who experienced VTE and discovered that a score above 6 was significantly correlated with post-surgical DVT, which coincides with our findings.26 Elevated levels of D-dimer are a known risk factor for DVT. Prior research indicated that raised D-dimer level had a sensitivity range of 85–95% and specificity of 25–50% for detecting post-operative VTE.27 In our study, patients underwent D-dimer testing during the post-surgical phase which was an independent predictor of VTE (OR-1.446, 95% CI 1.130–1.849, p=0.04).

The present study had some limitations. This was a single centre study with a small number of patients. Never the less no standard protocol for VTE prophylaxis existed in the centre; so results obtained from this study may not reflect the true picture of VTE burden of the patients undergoing CRC surgery.

**Conclusion:**

The current study showed post-operative VTE is a grave complication after malignant colorectal surgery. Longer duration of surgery, advanced disease stage, high Caprini RAM score, synchronous presence of IBD, raised post-operative D-dimer and advanced age were independent predictors of post-operative VTE. So every center should adopt a VTE prophylaxis protocol to prevent post-surgical VTE in patients undergoing CRC surgery.

**CONSENT:**

Patient’s informed written consent was taken to publish her/his case for academic purpose.

**ETHICAL APPROVAL:**

As per international standards or university standards written ethical approval has been collected from Institutional ethical committee and preserved by the authors.

**DISCALIMER (ARTIFICIAL INTELLEGENCE):**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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