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Original Research Article

Clinico-pathological correlation between deep vein thrombosis and malignancy

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ABSTRACT

Background: Cancer is one of the risk factors with estimates suggesting annual incidence of venous thrombo-embolism (VTE) is 0.5% in cancer patients compared to 0.1% in the general population. VTE is the second most common cause of death from cancer. Cancer associated thrombosis (CAT) is the target of intense interest in recent medical literature, including its epidemiology, pathophysiology, challenges in diagnosis, prophylaxis and treatment. Cancer types, stages, treatment and comorbidities are among the risk factors for developing VTE.
Methods: This was a retrospective study based on patient hospital records from May 2017 to Dec 2021. About 50 patient records reportedly having CAT were studied to meet research objectives. Data pertaining to patient age, gender and comorbidity was collected for study purpose. Patients having confirmed diagnosis for deep venous thrombosis (DVT) (Duplex scan) and malignancy (Biopsy) were considered to ensure data completeness for analysis and reporting.
Results: Our study showed that there was no correlation between different types of cancer with deep venous thrombosis, neither with different approach of treatment had it showed any significant results nor with any comorbidity. But we found out a correlation between different cancer with various comorbidity.
Conclusions: Our study aimed at exploring clinical and pathological correlation between DVT and malignancy. Our study was a sincere effort to study clinic-pathological correlation among cancer patients with known cases of venous thrombosis. Further studies are warranted with large sample and more extensive case record format, and preferably long-term follow-up to understand patient outcome.

Keywords: DVT, Cancer, Blood clot, Chemotherapy, Radiotherapy, Comorbidity

INTRODUCTION

Deep vein thrombosis (DVT) is the condition characterized by the formation of a blood clot in a deep vein under the skin, usually in the lower leg and thigh. However, DVT could also occur in the pelvis and arm. Slow blood flow, blood with increased tendency to clot, or injury to the lining of a vein are commonest causes of a thrombus. Common symptoms of DVT may include swelling, warmth, pain or tenderness, and redness of the skin at the site of the clot. Certain long-term medical conditions including heart disease, inflammatory bowel disease, cancer and some genetic blood disorders increase the risk of blood clots. Family or self-history of DVT, being overweight or obese, and older age also increase the risk of DVT.[1]

Cancer is one of the risk factors with estimates suggesting annual incidence of VTE is 0.5% in cancer patients compared to 0.1% in the general population.[2] Its pathophysiology involves the production of tissue factor and pro-coagulant substances which impair the endothelial balance between thrombosis. Haematological, lung, pancreas, brain and stomach cancers are particularly prone to VTE. In case of cancer patients undergoing major surgery, primary prophylaxis with low molecular-weight heparin (LMWH) has shown positive results in VTE recurrence.[3]

Risk assessment models, like Vienna CATS, COMPASS-CAT, can help predict primary and recurrent VTE and support clinical decision making.[4,5] Biomarkers are also widely studied for prediction of primary VTE risk in CAT. Leukocyte count, platelet count, D-dimer, and inflammatory markers are commonly used for diagnostic consideration. D-dimer, a degradation product of plasmin-induced fibrinolysis, is widely studied biomarker for primary VTE in cancer. Research studies have found elevated levels of D-dimer in newly diagnosed cancer patients as the risk factor for primary VTE. Elevated pre-treatment levels of D-dimer is associated with risk of primary VTE in certain gynaecological, colorectal and mixed cancer patients. While tissue factor (TF) and tissue factor–positive extracellular vesicle (TF+ EV) have been well researched, current interest is to understand the role of neutrophil extracellular trap (NET)-related proteins, podoplanin, polyphosphate, and micro RNAs. In addition, research is also warranted to understand role of biomarkers in determining treatment duration and predicting bleeding complications from anticoagulants.[6]

Studies have found that patients on chemotherapy were at 2.2 times greater risk of developing VTE.[7-9] The incidence of post-operative VTE in cancer patients is twice that of post-operative VTE in patients free from neoplasms.[7-9] Cancer-associated thrombosis needs to be managed differently compared to thrombosis in non-cancer patients, given the understanding that thrombosis has an impact on cancer proliferation and extension.[10] CAT resulting from venous stasis can be attributed to prolonged bed rest and compression of vessels by tumours or ascites. The condition due to hypercoagulability can be attributed to factors such as malnutrition, dehydration, transfusions, post-operative conditions as well as coagulation-promoting factors secreted by tumour cells, chemotherapy and platelet activation. Even the placement of venous catheters, direct tumour invasion, injury by substances produced by tumours, radiotherapy and chemotherapy are likely to induce vascular endothelial injury and ultimately leading to CAT.[11]

Leg oedema and chest symptoms, which can be assessed according to the Wells score, are important in the diagnosis of VTE. Diagnostic imaging study contrast-enhanced CT performed to evaluate cancer often accidentally diagnosis VTE. Lower-limb venous ultrasonography and hemostatic activity testing based on D-dimer levels are among the other diagnostic imaging studies.[12]

Treatment for VTE is currently performed as per the guidelines for treating acute pulmonary thromboembolism, as clinical guidelines for VTE treatment in CAT is yet to have consensus.[13] Nearly half of the deaths from pulmonary embolism are clinically preventable through prophylaxis, but there is potential consideration for bleeding risks in cancer patients taking anticoagulants.

Objectives

Objectives were to explore the relation of DVT and malignancy with regards to age, sex, comorbidities, to study the risk of DVT and malignancy according to site of DVT and stage of cancer and to study DVT and malignancy associated with surgical intervention, chemotherapy and radiotherapy.

METHODS

Study design

Retrospective study based on secondary data collection and analysis, pertaining to patient hospital records May 2017 to Dec 2021.

Study site

Patient enrolment was done at a teaching hospital Shree Krishna Hospital affiliated to the Pramukh Swami Medical College, Bhaikaka university, Karamsad, district Anand in the state of Gujarat, India.

Study sample

About 50 patient records reportedly having CAT were studied to meet research objectives. Data pertaining to patient age, gender and comorbidity was collected for study purpose.

Inclusion criteria

Patients having confirmed diagnosis for DVT (Duplex scan) and malignancy (biopsy) were considered.

Exclusion criteria

Patient records having either DVT or malignancy; benign disorder; and incomplete hospital records were not considered for study purpose.

Study variables

Patient records were screened for completeness of data with regards to following study variables-age group, gender, co-morbidities, site of DVT, stage of cancer, mode of intervention.

Plan for analysis

A master chart was prepared to arrange the observed parameters of each and every case in Microsoft excel. Descriptive statistics [Frequency (%), mean (SD)] were used to depict the sociodemographic characteristics and clinical profile of the study population. Associations between the site of DVT, stage of cancer, mode of intervention, and sociodemographic variables were determined using a chi-square test. P value less than 0.05

was considered as statistically significant. STATA (14.2), Stata Corp LLC, Texas, USA was used to analyze the data.

Ethical consideration

Considering this is retrospective study based on patient data, there weren't any direct ethical, cost or treatment implications for patients. While screening and obtaining patient related data from hospital records, due diligence was exercised to ensure privacy and confidentiality of the participants. The patient related information was retrieved with reference to their hospital patient ID and patient name or any such information that my reveal patient identity was omitted during the data collection process. The study proposal was presented to the august meeting of the ethics committee of HM Patel centre for medical care and education, Karamsad. The present study is approved via letter reference number 195/2022 dated 22/08/2022.

RESULTS

Of the total of 50 participants enrolled for this study, majority of them were female (n=33; 66%). Proportion of the male participants was (n=17; 34%). There was only one male participant younger than 30 years of age. In 30-60 years (24 v/s 11) and >60 years (9 v/s 5) age-groups, female participants were close to double the number of male participants. About two third of all the participants (66%) didn't have any comorbidity. Hypertension, diabetes and both of these conditions were reported among 16%, 12% and 6% participants, respectively. Gender-wise distribution of comorbidities was much in line with the proportions of male and female participants enrolled for this study. Majority of the participants with no co-morbidity 30 (90.9%) were ≤60 years of age. Most participants with hypertension were 7 (87.5%) >60 years of age (Figure 1).

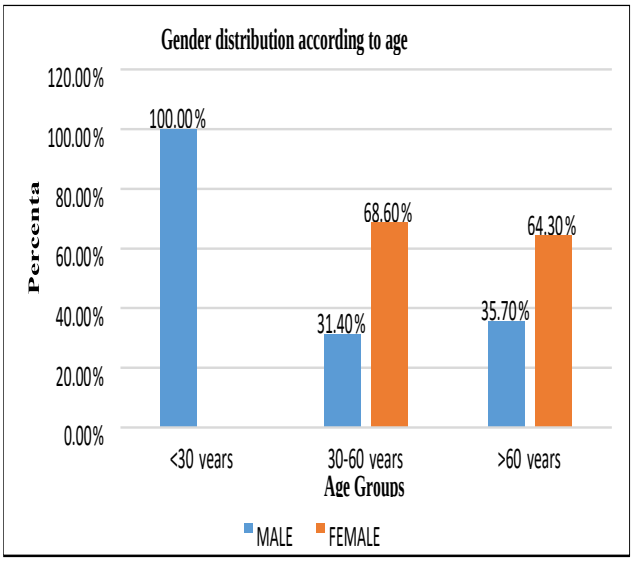

Figure 1: Demographic details.

Majority of the patients (n=46; 92%) had DVT at distal site followed by lower limb-proximal (n=3; 6%) and upper limb (n=1; 2%). Lower limb-proximal and upper limb were the site of DVT for patients under the age of 60 years. About 70% (n=32) as well as the 30% (n=14) patients in the age groups of ≤60 years as well as the >60 years had distal DVT. Fisher's exact test revealed that there is no statistically significant association between age as well as site of DVT ($p>0.05$). The site of DVT was proportional to the overall gender distribution in our study. About two third of females (n=30; 65.2%) were having distal DVT site as compared to the males (n=16; 34.8%). Similar distribution was observed for the DVT of lower limb proximal. Fisher's exact test indicated no relationship between gender as well as the DVT site ($p>0.05$).

Table 1: Type of the cancer or malignancy.

Type of malignancies	N
Adenocarcinoma left lung	1
CA breast	3
CA buccal mucosa	4
CA cervix	12
CA endometrium	1
CA gall bladder	1
CA HCC	1
CA hypopharynx	1
CA lung	2
CA ovary	4
CA pancreases	1
CA prostate	1
CA rectum	1
CA sigmoid colon	1
CA stomach	2
CA testis	2
CA vulva	1
Lip sarcoma	1
Metastatic CA cervix	1
Multiple myeloma	2
NHL B cell	2
Right retroperitoneal mass	1
SC cervix	1
SC lung	1
SC abdominal lymph node	1
Spindle cell carcinoma left thigh	1
Grand total	50

Table 2: Mode of intervention treatment-wise distribution.

Mode of intervention	Frequency	Percentages (%)
Chemotherapy	45	90
Radiotherapy	14	28
Surgical intervention	8	16

Table 3: Distribution and association of mode of intervention and site of DVT.

Site of DVT	Type of intervention, n (%)		
	Chemotherapy, (n=45)	Radiotherapy, (n=14)	Surgical, (n=8)
Lower limb-proximal	3 (6.7)	1 (7.1)	2 (25)
Distal	41 (91.1)	13 (93.9)	6 (75)
Upper limb	1 (2.2)	-	-
P value	0.78, >0.999	0.80, >0.999	0.04-Chi^2 0.11-Exact

Of the 50 participants, about half (n=27; 54%) had stage III cancer; followed by 26% participants having stage II and 20% participants having stage IV cancers. Of the 14 participants aged >60 years, 9 had stage III cancer, 4 had stage IV cancer and one had stage II cancer. Among those ≤60 years of age, about 50% (n=18) had stage III cancer, followed by 12 and 6 participants having stage II and IV cancers, respectively. Fisher's exact test indicated no statistically significant correlation between age and cancer stage (p>0.05). Of 33 female participants, 17 (51.5%), 10 (30.3%) and 6 (18.2%) had stage III, stage II and stage IV cancers, respectively. Among male participants, 10 (59%), 3 (17.6%) and 4 (23.4%) participants had stage III, stage II and stage IV cancers. Fisher's exact test revealed no statistically significant association between cancer stage and gender (p>0.05) in our sample.

The distribution of type of malignancies reveals our sample participants were suffering from various types of malignancies with cancer of cervix being the most common (n=12; 24%); followed by cancers of ovary and buccal mucosa (n=4; 8%) each.

Statistical analysis to explore association of mode of intervention for cancer with age-group, gender, and site of DVT didn't find any significant association.

Analysis of stages of cancer and comorbidities revealed that about 48% (n=16) patients with no-comorbidity and 65% (n=11) patients with comorbidity had stage III cancer. About 36% (n=12) patients with no-comorbidity and 6% (n=1) patients with comorbidity had stage II cancer. Similarly, 15% (n=5) patients with no-comorbidity and 29% (n=5) patients with comorbidity had stage IV cancer. Fisher's exact test revealed statistically significant association between stages of cancer and comorbidities (p<0.05) in our sample.

DISCUSSION

Our study aimed at exploring clinical and pathological correlation between DVT and malignancy. Hence, we included patients having confirmed diagnosis for DVT (Duplex scan) and malignancy (biopsy).

Our study had a total of 50 patients with DVT and malignancy, about 92% (46) patients had distal DVT, 6% and 2% patients had DVT at lower limb and upper limb, respectively. As far malignancy is the concerned, 54% patients had stage III cancer, followed by 26% and 20% patients having stage II and stage IV cancers. The distribution of type of malignancies reveals our sample participants were suffering from various types of malignancies with cancer of cervix being the most com mon (n=12; 24%); followed by cancers of ovary and buccal mucosa (n=4; 8%) each. With regards to cancer treatment, about 60% (30) patients received only chemotherapy, followed by 18% (9) patients who received chemotherapy and radiotherapy. About 16% (8) patients received surgical intervention to treat cancer. Of the 46 patients having distal site of DVT, 26% (12), 52% (24) and 22% (10) were having stage II, stage III and stage IV cancers, respectively. Statistical analysis to explore association of stage of cancer with site of DVT didn't find any significant association (p>0.05). The distribution of age by stage of cancer revealed that 92% (12), 67% (18) and 60% (6) patients with stage II, stage III and stage IV cancer, respectively, were ≤60-year of age. Sex wise 77% (10), 63% (17) and 60% (6) patients with stage II, stage III and stage IV cancer, respectively, were females. The analysis of stages of cancer with age (p>0.1) and sex (p>0.7) didn't reveal any statistically significant association. Further analysis to explore the relationship between mode of intervention with age group, sex and site of DVT also didn't find any statistically significant association.

Alongside type and stages of cancer and site of DVT, we also captured whether patients are suffering from comorbidities such as diabetes and/or hypertension. However, two third (66%; 33) of patients in our study didn't suffer from any of these comorbidities. About 16% (8) patients had hypertension and 12% (6) had diabetes. Just about 6% (3) patients were suffering from both hypertension and diabetes. The distribution of age for underlying comorbidities reveal that 87.5% (7), 33.3% (2) and 66% (2) patients with hypertension, diabetes and both hypertension & diabetes were >60-year of age. Similarly, sex distribution for underlying comorbidities found that about two third of patients suffering with hypertension (5), diabetes (4) and both hypertension and diabetes (2) were females. Our analysis didn't find any statistically significant association between site of DVT and comorbidities (p>0.5) in study sample. However, there statistically significant association between stages of cancer and comorbidities (p<0.05) in our sample.

However, there are studies in hospital setting, which have explored the prevalence of CAT among patients with

incident venous thrombosis. One such study has reported co-occurrence of DVT and malignancy in ~20% patients from a cohort of 21,002 individuals hospitalized with incident venous thrombosis.[18] Similarly, the RIETE registry had enrolled more than 35,000 individuals with symptomatic venous thrombosis between 2001 and 2011. The presence of active cancer was reported in about 17% patients from this cohort.[19] On the other hand, cancer patients are also at risk of developing VTE. The cancer and thrombosis study (CATS), a prospective follow-up of ~850 cancer patients in Vienna found that about 8% of the cancer patients developed VTE within a year from diagnosis/ progression of malignancy.[20]

Site of DVT is also important to study VTE in cancer patients, and there is dearth of literature reporting this aspect. One such study had reported lower limb DVT, upper limb DVT and symptomatic iliocaval thrombosis to be more common among cancer patients compared with noncancer patients.[21] In our study, 92% cancer patients had distal DVT, followed by 6% patients having proximal lower limb DVT and 2% patients having upper limb DVT.

The research has also demonstrated that the risk of VTE incidence is highest in the first few months following the cancer diagnosis, and decreases thereafter.[17] However, our study didn't report the date of first diagnosis for cancer, and hence missed the opportunity to study this aspect of CAT. Risk of VTE is also associated with type of cancer, and it is higher in pancreatic cancer patients, followed by cancers of brain, lung, hematologic, colorectal and bone.[21] In our study, cancer of cervix (24%; 12) was the commonest one, followed by cancers of ovary, buccal mucosa and breast. Pancreatic cancer was reported in just one of the patients (2%). Pancreatic cancer patients are at high risk of CAT, compared with other cancer patients. However, patients with cancers of brain, ovary, cervix, lung, kidney and certain blood cancers also have higher risk of getting CAT.[16] Patients with breast cancer and prostate cancer are at relatively low risks of having CAT, compared to patients with other types of cancers.[17]

The limitation of this study was less resources for proper study, the number of subjects and different modes of treatment approach for same type of cancer.

CONCLUSION

We conducted a retrospective study based on secondary data collection and analysis, pertaining to patient hospital records May 2017 to Dec 2021. About 50 patient records reportedly having CAT were studied to meet research objectives. Patients having confirmed diagnosis for DVT (Duplex scan) and malignancy (biopsy) were considered. Statistical analysis to explore association of stage of cancer with site of DVT didn't find any significant association ($p>0.05$). Alongside type and stages of cancer and site of DVT, we also captured whether patients are suffering from comorbidities such as diabetes and/or hypertension. There was statistically significant association between stages of cancer and comorbidities ($p<0.05$) in our sample. The limitation of this study was less resources for proper study, the number of subjects and different modes of treatment approach for same type of cancer.

Recommendations

Our study was a sincere effort to study clinicopathological correlation among cancer patients with known cases of venous thrombosis. Further studies are warranted with large sample and more extensive case record format, and preferably long-term follow-up to understand patient outcome.

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