Real world data on clinical profile, management and outcomes of venous thromboembolism from a tertiary care centre in India

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ABSTRACT

Objectives: Venous thromboembolism (VTE) is a major cause of mortality and morbidity worldwide. This study describes a real-world scenario of VTE presenting to a tertiary care hospital in India.

Methods: All patients presenting with acute VTE or associated complications from January 2017 to January 2020 were included in the study.

Results: A total of 330 patient admissions related to VTE were included over 3 years, of which 303 had an acute episode of VTE. The median age was 50 years (IQR 38–64); 30% of patients were younger than 40 years of age. Only 24% of patients had provoked VTE with recent surgery (56%) and malignancy (16%) being the commonest risk factors. VTE manifested as isolated DVT (56%), isolated pulmonary embolism (PE; 19.1%), combined DVT/PE (22.4%), and upper limb DVT (2.3%). Patients with PE ($n = 126$) were classified as low-risk (15%), intermediate-risk (55%) and high-risk (29%). Reperfusion therapy was performed for 15.7% of patients with intermediate-risk and 75.6% with high-risk PE. In-hospital mortality for the entire cohort was 8.9%; 35% for high-risk PE and 11% for intermediate-risk PE. On multivariate analysis, the presence of active malignancy (OR = 5.8; 95% CI: 1.1–30.8, p = 0.038) and high-risk PE (OR = 4.8; 95% CI: 1.6–14.9, p = 0.006) were found to be independent predictors of mortality.

Conclusion: Our data provides real-world perspectives on the demographic sand management of patients presenting with acute VTE in a referral hospital setting. We observed relatively high mortality for intermediate-risk PE, necessitating better subclassification of this group to identify candidates for more aggressive approaches.

1. Introduction

Venous thromboembolism (VTE) includes both deep venous thrombosis (DVT) and pulmonary thromboembolism (PE), and is a significant contributor to the worldwide healthcare burden. The incidence of VTE is estimated at 0.75 to 2.7 per 1000 population, increasing to 7 per 1000 in those above 70 years of age.[1,2] The incidence of DVT has stayed nearly constant while that of PE has steadily increased, likely as a result of better awareness and diagnostic techniques.[3] VTE imposes significant morbidity due to complications of treatment, recurrent disease, and loss of quality of life.[4] Data on the epidemiology of VTE is available predominantly from Caucasian populations with very little data from India.[5,6] Data on VTE from Indian settings is available from two hospital-based retrospective registries, but no data is available on demographics and treatment outcomes of patients presenting with incident VTE managed with a standardized approach. We conducted this study to describe real-world data on clinico–demographic profile and in-hospital outcomes of patients presenting with VTE (DVT or PE) or associated complications in a referral tertiary care setting.

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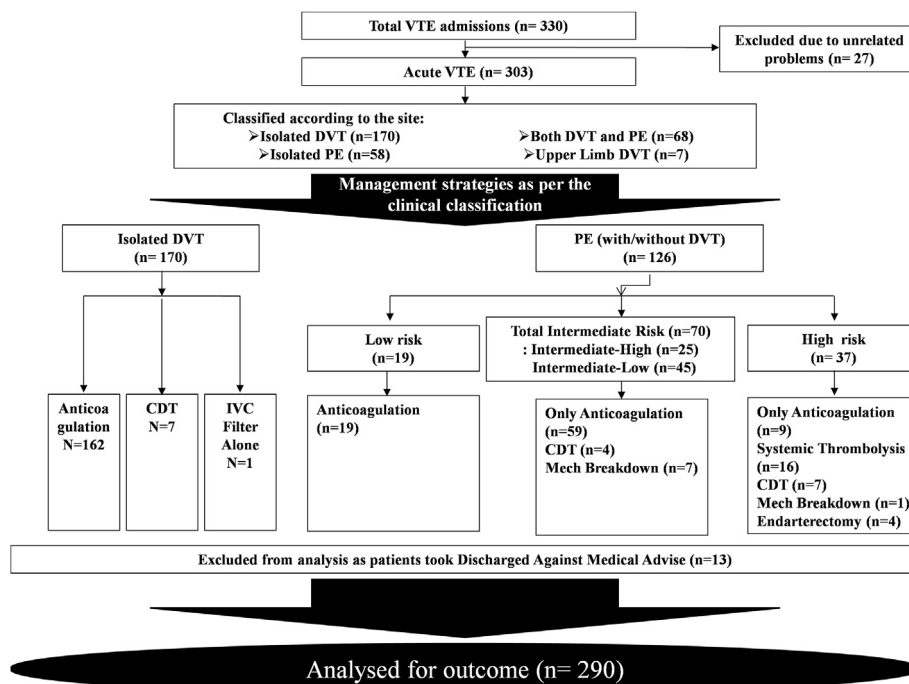E-mail address: bishav_68@yahoo.co.in (B. Mohan).

Fig. 1. Figure showing the study design. VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism, CDT: catheter directed thrombolysis, IVC: inferior vena cava.

2. Methodology

2.1. Study design and setting

This was a retrospective observational study, cleared by the hospital ethics committee. It was conducted in the departments of Cardiology and Clinical Haematology at a high volume tertiary care centre. The study design is shown in Fig. 1.

2.2. Materials and methods

This study was conducted in high volume tertiary care hospital in North India. All patients with confirmed venous thromboembolism (VTE) during 3 years from January 2017 to December 2019 were included in the study. The patients were meeting the diagnostic criteria laid by standard guidelines.[7] For all patients, demographic details and history of known risk factors or medical conditions were recorded as per protocol. As defined by the American Heart Association (AHA) and European Society for Cardiology (ESC) criteria, the patients having pulmonary embolism were risk-stratified into three groups: a) High Risk/Massive, b) Intermediate-Risk/Submassive, and c) Low Risk.[8,9] Treatment related bleeding was defined as significant if it led to a fall in haemoglobin of more than 2 g/dl, requiring transfusion or symptomatic bleeding in critical organs. Patients with missing data were excluded from the study. All the patients received treatment as per standard guidelines.[7]

3. Statistical analysis

Data were described in terms of range; mean ± standard deviation (±SD), frequencies (number of cases), and relative frequencies (percentages) as appropriate. For comparing categorical data, the Chi-square (χ^2) test was performed and the exact test was used when the expected frequency is less than 5. Multivariate logistic regression analysis was used for assessing independent predictors of in-hospital outcome of the patients. A probability value (*p*-value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows. All patients were included in the descriptive analysis but patients discharged against medical advice were excluded from statistical analysis of outcomes.

4. Results

4.1. Baseline data and demographics

Over three years, a total of 333 admissions for VTE and related complications were included, of which 303 were for an episode of acute VTE. The median age at presentation was 50 years (IQR 38.5 to 64.5), and majority were males ($n = 184$, 60.7%). Most common clinical presentation was isolated DVT (Fig. 1). Isolated upper limb DVT was noted in seven patients. Echocardiographic (ECHO) abnormalities were noted in 84% of patients presenting with symptomatic PE. Table 1 summarizes baseline data, demographic profile, and symptomatology of the study cohort.

4.2. Risk factors for VTE

A majority of patients in our cohort (76%) had unprovoked VTE, and a known risk factor was present in only 73 patients (24%). The commonest risk factor was recent surgery, seen in 41 (56%) patients, including seven with a recent caesarean section. The median duration of presentation after surgery was 24 days (range: 8—47). The second commonest risk factor was active malignancy, noted in 11 patients (16%). Other risk factors included prolonged immobilization in 8 patients and recent air travel in two. Remaining risk factors were uncommon and included polycythemia vera, May-Thurner syndrome, oral contraceptive (OCP) usage, lower limb varicose veins, Sjogren Syndrome, recent Olanzapine use, and active gestation in one patient each. Data on genetic thrombophilia

Table 1
Table summarizing the baseline data and demographics of the study cohort.

Clinical parameters		$n = 303$
Age (Years), median (IQR)		50 (IQR 38.5—64.5)
<40 years, n (%)		91 (30%)
40—60 years, n (%)		120(39.6%)
>60 years, n (%)		92 (30.3%)
Male gender, n (%)		184 (60.7%)
Diabetes Mellitus		55 (18%)
Systemic Hypertension		82 (27%)
Classification of VTE, n (%)	Provoked	73 (24.1%)
	Unprovoked	230 (75.9%)
Site, n (%)	Isolated Proximal DVT	170 (56.6%)
	Isolated PE	58 (19.1%)
	Both DVT and PE	67 (22.1%)
	Upper Limb DVT	7 (2.3%)
	Upper Limb DVT and PE	1 (0.3%)
Risk Stratification of PE	Low risk	37 (29.3%)
	Intermediate risk	70 (55.5%)
	High risk	19 (15.1%)
Clinical presentation of DVT (n = 238)	Duration (in days), median (range)	4 (0—180)
	Swelling, n (%)	170 (71.4%)
	Pain, n (%)	34 (14.2%)
	Others, n (%)	3 (1.2%)
	Incidental, n (%)	31 (13%)
Clinical presentation of PE (n = 126)	Duration (in days), median (range)	1 (0—365)
	Dyspnoea, n (%)	92 (73.0%)
	Chest Pain, n (%)	12 (9.5%)
	Haemoptysis, n (%)	6 (4.7%)
	Fever, n (%)	1 (0.7%)
	Syncope, n (%)	6 (4.7%)
	Incidental, n (%)	9 (7.1%)

VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism.

were available for 22 patients, out of which two patients were homozygous and three were compound heterozygous for MTHFR polymorphisms. No Factor V Leiden or Prothrombin gene mutations were detected. Among patients with upper limb DVT, all but one had a provoking risk factor, including two with recent surgery and one each with carcinoma breast, intravenous drug use, Paget-Schroetter syndrome and obstructive sleep apnoea.

Sixty-eight patients in the cohort had a history of at least one previous admission for VTE or related complications. Out of these, 41 (60.2%) patients were admitted now for a recurrent episode of VTE, out of which 21 (51%) were already on anticoagulation at the time of recurrence. This included 15 patients on VKA and 6 on newer oral anticoagulants. No reliable data was available on the frequency of international normalized ratio (INR) monitoring in patients on VKA. The remaining 20 patients had either stopped anticoagulation of their own accord or after finishing a definite prescribed period. A provoking factor was present in only three patients with recurrent VTE, including renal cell carcinoma, Sjogren's syndrome, and recent surgery in one patient each. The next pertinent cause for repeat admission was bleeding secondary to anticoagulation, seen in five (7.3%) patients. Out of these, one patient was on Rivaroxaban and four were on VKAs. Two patients

required surgical intervention for severe bleeding (subdural haemorrhage evacuation and uterine artery ligation, respectively), and none died.

4.3. Treatment details and outcomes

4.3.1. Isolated DVT

All patients with isolated DVT were initiated on anticoagulation therapy either with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) at admission and switched to an oral agent after a median duration of 6 days (range 0—39). For patients with isolated DVT, a majority (96.7%) were treated with anticoagulation alone. A small minority with isolated extensive DVT ($n = 5$, 2.9%) underwent catheter-directed thrombolysis and clot breakdown. Major bleeding was noted in eight patients on the whole and was non-fatal. In the entire subgroup with isolated DVT, seven patients died. All deaths were secondary to a systemic illness, including two patients with stage IV cancer and five with sepsis and multi-organ dysfunction. DVT was detected incidentally in these patients and was not the direct cause of death in any patient. All seven patients with isolated upper limb DVT were managed with anticoagulation alone.

4.3.2. Pulmonary embolism (with or without DVT)

Treatment of pulmonary embolism was based on risk stratification as follows and is summarized in Table 2.

Among low-risk PE, treatment-related bleeding was seen in three patients and no mortality was observed. Among intermediate-risk group, significant bleeding was noted in three patients after anticoagulation and one patient after catheter-directed thrombolysis (CDT). In the CDT group, one patient died with coexistent malignancy and sepsis, while seven patients died in the anticoagulation group due to hemodynamic worsening. The overall mortality with intermediate-risk PE was 11.4% ($n = 8$).

Among high-risk PE, the patients undergoing systemic thrombolysis, non-fatal major bleeding was noted in two patients and three deaths occurred due to hemodynamic worsening. Four patients were taken up for surgical endarterectomy out of which 2 died in-hospital with persistent shock. Nine patients refused or had a contraindication to thrombolysis and were managed with anticoagulation alone. This subgroup had the highest mortality rate of 66% ($n = 6$). No patient had major bleeding or mortality after CDT. Overall, eleven patients (35.4%) with high-risk PE died, all due to hemodynamic worsening.

All patients with VTE were planned for the initiation of oral anticoagulants at discharge. Most patients ($n = 163$, 54.3%) were initiated on Vitamin K antagonists, followed by Apixaban in 13 (4.3%), Dabigatran in 49 (16.3%) and Rivaroxaban in 36 (12%) patients.

4.4. Mortality predictors

Patients with congestive cardiac failure ($p = 0.041$), active malignancy ($p = 0.011$), associated co-morbidities ($p = 0.018$) and the presence of high-risk PE ($p = 0.017$) were found to have

Table 2
Treatment strategy of pulmonary embolism according to risk stratification.

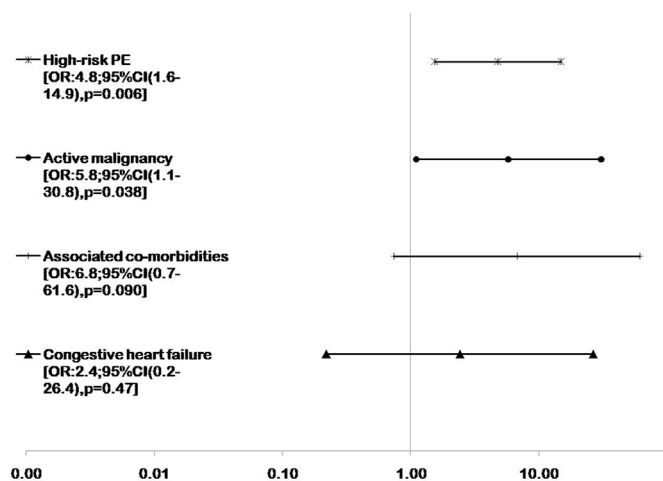|	Low risk $n = 19$	Intermediate risk $n = 70$	High risk $n = 37$
Anticoagulation alone, n (%)	19 (100%)	59 (84.3%)	9 (24.3%)
Systemic Thrombolysis, n (%)	0	0	16 (43.2%)
Catheter directed thrombolysis (CDT), n (%)	0	4 (5.7%)	7 (18.9%)
Pharmaco-mechanical catheter directed thrombolysis (PCDT), n (%)	0	7 (10%)	1 (2.7%)
Surgical endarterectomy, n (%)	0	0	4 (10.8%)

Fig. 2. Forrest chart showing predictors of mortality in patients with venous thromboembolism. PE: pulmonary embolism.

significantly higher mortality. On multivariate logistic regression analysis, the presence of active malignancy (OR = 5.8; 95% CI: 1.1—30.8, p = 0.038) and high-risk PE (OR = 4.8; 95% CI: 1.6—14.9, p = 0.006) were found to be the independent predictors of mortality (Fig. 2).

5. Discussion

Venous thromboembolism is associated with significant morbidity and mortality and is no longer considered uncommon in India.[10] Significant geographic variations in epidemiology and causative risk factors make it necessary to compile and evaluate indigenous data.[11] We present real-world data from a tertiary care setting on patients presenting with VTE (DVT and PE) and associated complications. Our data is distinctive for a high proportion of intermediate and high-risk PE (approximately 85%) and omission of systemic thrombolysis in over 24% patents with high-risk PE due to contraindications or patient refusal. We also document an in-hospital mortality of 8.9%, predominantly due to hemodynamic deterioration in patients with intermediate/high-risk PE.

A majority of patients had unprovoked VTE (76%), which is much higher than that noted by two other Indian studies.[12,13] Our findings are in line with Western data, likely due to a majority of patients having out-of-hospital VTE, which may select for unprovoked disease.[14] It is important to identify a precipitating factor in as many patients as possible to avoid indiscriminate testing for thrombophilia.[15,16]

The commonest major risk factor was recent surgery in the past three months, which is consistent with other published data.[17] In our series, the median time to presentation after surgery was 24 days, with one patient presenting as late as 47 days. This is consistent with a time frame of 22—24 days noted in other large series of postoperative VTE.[18] The second most common provoking factor in published literature is active malignancy, accounting for up to 20% of patients.[19] The absolute risk of VTE attributable to cancer is stratified and comparatively higher for pancreatic, lung, and renal cancers, especially those with metastatic disease.[20] In our cohort, 16% of provoked VTE was due to active malignancy, with a higher representation of stage IV and metastatic cancers.

Proportion of patients with DVT alone or DVT with PE is consistent with previously published data.[21] The presence of DVT and PE together has prognostic significance and is associated with a higher 30-day mortality, making it essential to screen for DVT in a patient with PE and vice-versa.[22] The median duration of symptoms in our cohort was similar to other published studies, but a higher proportion of patients presented with a delay of 7 or more days, including 57.6% patents with isolated DVT and 49% with isolated PE. This is much higher than Western data, and indicates a need for increased awareness in the community and primary care physicians.[23]

Distinct risk factor profiles and long term treatment implications have been identified for younger patients, who constituted 30% of our study population.[24]

A Cochrane review in 2017 noted no difference in long term mortality with either UFH or LMWH used as first line, noting poor quality of evidence.[25] At our institution, UFH with aPTT monitoring is preferred in view of low cost and rapid onset and offset of action. Anticoagulation alone is sufficient for most patients with limb DVT, but select patients with extensive proximal involvement at a high risk of post-thrombotic syndrome may benefit from reperfusion therapies.[26] Five patients with extensive proximal lower limb DVT underwent catheter-directed clot breakdown with no immediate complications.

Reperfusion therapy is of utmost importance for hemodynamically unstable patients with PE to reverse venous obstruction and hemodynamic compromise and is associated with a survival benefit.[27,28]

Systemic thrombolysis is an effective reperfusion therapy for PE and improves short term mortality.[29] Due to a significant increase in risk of major bleeding (OR 2.91, 95% CI: 1.95—4.36), it is justified only for patients with high-risk disease.[30] In a meta-analysis exclusively enrolling patients with high-risk PE (n = 1574) a survival benefit for thrombolysis was most prominent for younger (<65 year old) patients, likely due to the absence of major bleeding.[31] The number needed to treat (NNT) with thrombolysis to prevent one death for high-risk PE has been calculated as 59, with a number needed to harm (NNH) for major bleed of 18, further impressing that bleeding risk is a major determinant of outcomes.[32] Patients who have a contraindication or refuse systemic thrombolysis should be considered for catheter-directed thrombolysis so that a lower dose of the thrombolytic agent can be safely administered locally.[33] Our data included eight such patients with high-risk PE who would otherwise have not received any thrombolytic agent. Patients with high risk PE not receiving thrombolysis had the highest short term mortality (66%).

For patients with intermediate-risk disease (submassive PE), the choice of therapy is more contentious, as certain patients worsen on anticoagulation alone but can be identified based on several clinical parameters.[9] Presence of RV dysfunction is associated with a two-fold higher mortality in this group.[34] We and others have previously shown that patients who have ECG and Echocardiographic changes of RV strain, elevated brain natriuretic peptide, or troponin T or a thrombus in proximal branches of pulmonary artery have a higher risk of mortality and should be managed with more aggressive strategies.[9] A meta-analysis of 28 studies with 2135 patients showed that catheter-directed thrombolysis is safe, effective, and associated with reliable hemodynamic improvement in intermediate risk PE.[35] The safety and efficacy of CDT have also been documented in the OPTALYZE[36] and the SEATTLE II[37] trials. In the present cohort, eleven intermediate-risk patients underwent catheter-directed intervention with no short-term mortality. CDT has also been shown to be safe for sick patients with multiorgan illness.[38]

The major cause of mortality from VTE is attributable to intermediate/high-risk PE because of rapidly worsening haemodynamics. In-hospital mortality rate of approximately 30% in high risk PE is consistent with published data.[8] Mortality rates for intermediate-risk -PE range from 2 to 3% in prospective randomized trials to over 15% in retrospective studies, likely indicating a selection bias in randomized trials.[32] Our study documents a comparatively high mortality rate of 11.4% in patients with intermediate-risk PE. Possible reasons for high mortality rates include late presentation and management without thrombolysis in patients with intermediate risk PE. Forty-one patients (13%) in our cohort presented with recurrent VTE, out of whom approximately half were already on anticoagulation. A prospective follow up of our cohort will lend further insights into the risk of recurrent VTE.

Based on literature search, Indian data on VTE is available from two retrospective studies, RAVS and ARRIVE.[12,13] Our series is one of the largest from India documenting the clinical profile, and short term treatment outcomes with VTE in a hospital setting using a standardized approach. Our study reaffirms the need for indigenous data for VTE in India and documents real-world management strategies for acute VTE. We also demonstrate relatively high mortality with intermediate-risk PE, necessitating identification of high-risk patients in this subgroup so that patients at the highest risk of mortality are identified.

6. Limitations

The absence of long term follow up and single-centre nature of data are possible limitations of our study.

7. Conclusions

Venous thromboembolism is a heterogeneous disease with significant regional differences in presentation and outcomes. Our study highlights high mortality with intermediate and high risk PE, and additionally provides a baseline for a prospective VTE registry in India. It also sets the stage for further studies on genetic thrombophilia, recurrent VTE, and assessment of long-term complications.

Funding source

Declaration of competing interest

None.

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