Original Article

Venous Thromboembolism at the National Healthcare Group, Singapore

Joseph Antonio D Molina,[1] *MD, MSc (PH)*, Zhiwei Jiang Gabriel,[2] *BS*, Bee Hoon Heng,[1] *MSc (PH), FAMS*, Benjamin KC Ong,[3] *MBBS, M Med, FRCP (Edin)*

Abstract

Introduction: Venous thromboembolism (VTE), including its most serious clinical subtype, pulmonary embolism (PE), is a potentially preventable disease. While current assessment tools do not include ethnicity as a risk factor, studies suggest that Asians have lower risk of VTE compared to Caucasians. This study aims to describe 2006 in-hospital and projected population-based incidence rates of VTE and PE in Singapore. Materials and Methods: Data on 2006 admissions at 3 major NHG hospitals, cases of VTE and their demographics were obtained from the ODS, a large administrative database of the National Healthcare Group (NHG). Demographic characteristics of the 2006 Singapore resident population were obtained from the 2006 Singapore Statistics website. Results: In 2006, there were 860 cases of VTE out of 98,121 admissions in these 3 hospitals. Overall and secondary VTE age adjusted in-hospital burden was 73 and 54 per 10,000 patients, respectively. Caucasians and Eurasians had VTE rates in excess of 100 per 10,000 while Chinese, Malays and Indians each had rates below 100 per 10,000. Assuming that 42.5% of the 2006 Singapore population was served by NHG, the estimated population-based incidence of VTE and PE is 57 and 15 per 100,000, respectively. Conclusions: As patterns across ethnic groups point to lower VTE rates among Asians compared to Caucasians and Eurasians, analytic studies should be considered to test this hypothesis. There may be a need to develop locally applicable risk assessment tools which can be used to support local guidelines for VTE prophylaxis, thus leading to more acceptable and cost-effective care.

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Introduction

Venous thromboembolism (VTE) is a potentially fatal disease which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). About 30% of patients with VTE die within 30 days while 20% suffer sudden death from pulmonary embolism.[1] Risk factors commonly seen in hospitalised patients, include immobilization, acute medical illness and increasing age. Despite its serious nature, VTE is potentially preventable particularly in a hospital setting. The availability of prophylactic measures has prompted health professionals to develop protocols which effectively risk-stratify hospitalised patients. While VTE control measures have been aggressively implemented in the West, the condition has attracted much less attention in Asian countries given the apparent lower risk.

Studies in Massachusetts and Minnesota revealed an incidence of one per thousand[2] which is an alarmingly high occurrence. In 2 other population-based studies conducted in the US, the incidence rates were 0.80 and 2.15, or a combined rate of 1.08 per 1000 person-years.[3] Data from the US National Institute of Health (NIH) revealed that in 2004, there were 10,956 deaths from PE and DVT combined.[4] This figure is more than 3 times the number of deaths from asthma and congenital heart disease in the US. In a study conducted in 6 European Union countries, it was estimated that there are over one million VTE events or deaths annually[5] and that many of these could have been prevented.

With these rates, countries such as the US have established standards for the prevention and care of VTE. These standards are part of performance measurement initiatives of the Joint Commission and the National Quality Forum.[6] While the magnitude of the problem in the West has been well documented, results of epidemiologic studies among

[1] Health Services & Outcomes Research, National Healthcare Group, Singapore
[2] Formerly with Health Services & Outcomes Research, National Healthcare Group, Singapore
[3] National University Health System, Singapore
Address for Correspondence: Dr Joseph Antonio D. Molina, Health Services and Outcomes Research, National Healthcare Group Headquarters, 6 Commonwealth Lane, #04-01/02 GMTI Building, Singapore 149547.
Email: Joseph_Antonio_MOLINA@nhg.com.sg

Asians have thus far been conflicting. Some studies suggest that ethnicity is a significant risk factor, and that Asians are at much lower risk of VTE than Caucasians, African-Americans and Hispanics.[7] This appears to downplay the need for routine VTE prophylaxis among Asians.

Our paper describes the in-hospital incidence of VTE in 2006 and estimates the population rates in Singapore. It also describes the distribution of VTE according to selected demographic characteristics. The study uses administrative data from a large sample, and offers a perspective of the burden of VTE in an Asian context that is unique and should serve to inform local policies and decisions regarding VTE control strategies.

Materials and Methods

The proposal for this study underwent ethics review and was approved by the National Healthcare Group (NHG) Domain Specific Review Board. This study reflects the number of incident cases obtained from the Operations Data Store (ODS), a large administrative database containing data from all health facilities within the NHG family of acute care hospitals. Cases of VTE were identified from all patients admitted to the Alexandra Hospital (AH), the National University Hospital (NUH) and Tan Tock Seng Hospital (TTSH). Cases were identified on the basis of diagnosis codes assigned according to the International Classification of Disease (ICD) version 9 CM. A case was considered as VTE if any of the following ICD codes was assigned:

453.2 – Venous embolism and thrombosis of vena cava
453.8 – Venous embolism and thrombosis of other specified veins
453.9 – Venous embolism and thrombosis of unspecified site
415.1 – Pulmonary embolism and infarction

Patients were further classified as to whether VTE was a primary diagnosis, secondary diagnosis or both primary and secondary VTE. Patients admitted with a primary diagnosis of VTE were considered as primary cases, while those whose VTE was considered as a co-morbid illness or whose condition occurred during hospitalisation, were considered as secondary cases. Patients who had both a primary and secondary diagnosis of VTE comprised a third group of cases. Examples of this third group were patients admitted for DVT and who subsequently developed PE during hospitalisation.

The total number of admissions, including their age, gender and ethnic group distribution in the 3 NHG hospitals in 2006 was likewise obtained from the ODS. Population data including age, gender and ethnic group distributions in Singapore were obtained from the 2006 Singapore Statistics website. As NHG forms one of two clusters of restructured hospitals in the country, the proportion of the total Singapore resident population served by NHG hospitals was estimated using data from the 2006 NHG Annual Statistics Bulletin, an administrative reference material which contains data intended for institutional and cluster-wide evaluation and planning.

The following results were generated from the data:

i) In-hospital burden of VTE (total VTE and secondary VTE)

$I_{H\text{-}VTE}$ (per 10000 in-patients) = (n_{VTE} / N_H) x 10,000, where

$I_{H\text{-}VTE}$ = Proportion of in-patients with VTE in Singapore for 2006

n_{VTE} = Number of new cases of VTE among patients admitted to the 3 NHG hospitals in 2006

N_H = Total admissions to the 3 NHG hospitals in 2006

The in-hospital burden of VTE is adjusted for age by applying the age-specific VTE proportions to the combined NHG-SingHealth age-distribution of admissions for 2006.

ii) In-hospital age, gender and ethnic group-specific proportion of VTE

iii) Population-based incidence of VTE and PE using the following formula:

$I_{P\text{-}VTE(P\text{-}PE)}$ (per 100000 population) = $[n_{VTE(PE)} / (N_p \times 0.425)]$ 100000, where

$I_{P\text{-}VTE(P\text{-}PE)}$ = Population-based incidence of VTE in Singapore, 2006

$n_{VTE(PE)}$ = Number of new cases of VTE among patients admitted to the 3 NHG hospitals, 2006

N_p = Total population of Singapore, 2006

0.425 = the proportion of the total Singapore resident population served by NHG hospitals, as estimated in the 2006 NHG Annual Statistics Bulletin

iv) Population-based age, gender and ethnic group-specific incidence of VTE and PE: Age, gender and ethnic group-specific numbers of patients with VTE were divided by 35%, 42.5% and 50% (NHG service coverage) of the corresponding base population, based on the 2006 Singapore population distribution (from the 2006 Singapore statistics). For example, incidence in the 65 to 74 years age group was obtained by dividing the number of VTE cases among those 65 to 74 years old by 35%, 42.5% and 50% of the total population of 65 to 74 years old in Singapore.

v) Sensitivity analysis was carried out by providing interval estimates for population-based overall and group-specific incidence of VTE and PE. In addition to the

point estimate of VTE incidence which was based on the assumption that 42.5% of the Singapore population is served by NHG, interval estimates were computed based on the assumption that NHG serves as little as 35.0% and as much as 50.0% of the population of Singapore.

The computations of this study made the following assumptions:

- All patients who were hospitalised in Singapore in 2006 were admitted to either of the 2 clusters of restructured government hospitals (NHG or Singhealth hospitals only)
- Within NHG, all patients who developed VTE in 2006 were hospitalised at AH, NUH and TTSH
- Within NHG, all cases of VTE in 2006 were captured by the 4 ICD codes enumerated above
- All patients with primary VTE were assumed to have been hospitalised and thus captured in the database

Results

Baseline Characteristics

In 2006, 860 patients were admitted to AH, NUH and TTSH with a diagnosis of VTE. Of these, 636 (73.95%) had deep vein thrombosis, while 224 (26.05%) had pulmonary embolism (Table 1). Except for those ≥75 years old, the number of patients admitted for all VTE increased with age. There were more females than males diagnosed with DVT and PE. Majority of patients admitted for VTE were Chinese, followed by Malays and Indians.

In-hospital Burden

The 860 VTE cases identified in the database were among the 98,121 patients admitted at AH, NUH and TTSH in 2006. This represented a crude overall in-hospital VTE rate of 88 per 10,000 admissions (Table 2). After adjusting for age, the estimated VTE rate was 73 per 10,000 admissions.

Table 1. Demographic Characteristics of Patients with Venous Thromboembolism

Characteristics	All Cases of VTE		DVT		PE	
	Number	%	Number	%	Number	%
Age						
0-14	3	0.35	3	0.47	0	0.00
15-24	14	1.63	9	1.42	5	2.23
25-34	62	7.21	44	6.92	18	8.04
35-44	86	10.00	60	9.43	26	11.61
45-54	118	13.72	91	14.31	27	12.05
55-64	124	14.42	82	12.89	42	18.75
65-74	184	21.40	138	21.70	46	20.54
75-84	181	21.05	134	21.07	47	20.98
85+	88	10.23	75	11.79	13	5.80
Total	860	100.00	636	100.00	224	100.00
Gender						
Male	387	45.00	279	43.87	108	48.21
Female	473	55.00	357	56.13	116	51.79
Total	860	100.00	636	100.00	224	100.00
Ethnicity						
Chinese	579	67.33	426	66.98	153	68.30
Eurasian	4	0.47	4	0.63	0	0.00
Indian	75	8.72	59	9.28	16	7.14
Malay	145	16.86	108	16.98	37	16.52
Caucasian	6	0.70	3	0.47	3	1.34
Sikh	6	0.70	5	0.79	1	0.45
Others	45	5.23	31	4.87	14	6.25
Total	860	100.00	636	100.00	224	100.00

Apart from an increase in rates for VTE with increasing age, VTE rates appeared higher for females than males. By ethnic group, Caucasians, Sikhs and Eurasians had VTE rates in excess of 100 per 10,000 in-patients. Indians, Chinese, Malays and those belonging to "Other" ethnicities had lower rates. However, it must be pointed out that estimates for Caucasians, Sikhs and Eurasians were based on considerably smaller sample sizes of 249,327 and 329 respectively.

Cases of VTE presented above included patients with primary, secondary, and both primary and secondary VTE. As prevention of VTE during a patient's hospital stay is of major concern for healthcare providers, the risk of secondary VTE was specifically determined for subsets of patients (Table 3). The age-adjusted rate for secondary VTE was 54 per 10,000 in-patients.

Table 2. Age, Gender and Ethnic Group-specific In-hospital Rates of VTE

Characteristics	Number of in-patients with VTE	Number of in-patients	Rate per 10,000 in-patients (95%CI)
Age (y)			
0-14	3	6430	5 (0, 10)
15-24	14	9888	16 (7, 21)
25-34	62	12558	50 (37, 61)
35-44	86	11800	73 (58, 88)
45-54	118	14085	84 (69, 99)
55-64	124	135 10	92 (76, 108)
65-74	184	13573	136 (117, 155)
75-84	181	11436	159 (135, 181)
85+	88	5441	162 (128, 196)
Gender			
Male	387	53881	72 (65, 79)
Female	473	44238	107 (97, 117)
Ethnicity	579	62601	93 (85, 99)
Chinese	4	329	122 (3, 241)
Eurasian	75	12234	62 (47, 75)
Indian	145	14618	100 (83, 115)
Malay	6	249	241 (51, 431)
Caucasian	6	327	184 (38, 328)
Sikh	45	7763	58 (41, 75)
Others			
All patients (unadjusted)	860	98121	88 (82, 94)
All patients (age-adjusted)*			73 (68, 78)

*Adjustment is based on age distribution of admissions in the two hospital clusters in Singapore

Age, gender and ethnic group-specific rates for secondary VTE generally followed the same pattern observed for all cases of VTE. Age-specific rates increased with age, and were higher for females, Caucasians, Sikhs and Eurasians.

Population-based Incidence of VTE

The population estimates of VTE incidence for 2006 were computed by applying the number of cases of VTE from the ODS database onto Singapore population data obtained from the 2006 Singapore Statistics. Based on data from the 2006 NHG Annual Statistics Bulletin, NHG hospitals cater to approximately 42.5% of the total population of Singapore. Of the 3 main ethnic groups in Singapore, Malays have the highest risk for VTE followed by Indians and Chinese (Table 4). Incidence of VTE among Eurasians and Caucasians residing in Singapore could not

Table 3. Age, Gender and Ethnic Group-specific In-hospital Rates of Secondary VTE

Characteristics	Number of in-patients with secondary VTE	Number of in-patients	Rate per 10,000 in-patients (95%CI)
Age (y)			
0-14	3	6430	5 (0, 10)
15-24	9	9888	10 (3, 15)
25-34	35	12558	28 (19, 37)
35-44	57	11800	49 (36, 60)
45-54	82	14085	59 (45, 71)
55-64	93	13510	69 (55, 83)
65-74	148	13573	110 (92, 126)
75-84	145	11436	127 (106, 148)
85+	71	5441	131 (100, 160)
Gender			
Male	287	53881	54 (47, 59)
Female	356	44238	81 (72, 88)
Ethnicity			
Chinese	439	62601	71 (63, 77)
Eurasian	4	329	122 (3, 241)
Indian	52	12234	43 (31, 55)
Malay	107	14618	74 (59, 87)
Caucasian	5	249	201 (27, 375)
Sikh	5	327	153 (20, 286)
Others	31	7763	40 (26, 54)
All patients (unadjusted)	643	98121	66 (61, 71)
All patients (age-adjusted)*			54 (50, 58)

* Adjustment is based on age distribution of admissions in the two hospital clusters in Singapore

Table 4. Age, Gender and Ethnic Group-specific Population-based Rates of VTE

Characteristics	Number of in-patients with VTE	2006 Singapore population distribution	Singapore population served by NHG (at 42.5% coverage)	Rate per 100,000 Population (assuming 42.5% coverage)
Age (y)				
0-14	3	698100	296692	1
15-24	14	472300	200728	7
25-34	62	560000	238000	27
35-44	86	640100	272042	32
45-54	118	591500	251388	47
55-64	124	340000	144500	86
65-74	184	192100	81642	226
75-84	181	89700	38123	475
85+	88	24600	10455	842
Gender				
Male	387	1787600	759730	51
Female	473	1820800	773840	62
Ethnicity				
Chinese	579	2713200	1153110	51
Indian	75	319100	135618	56
Malay	145	490500	208463	70
Total	860	3608400	1533570	57

be ascertained as the sizes of their populations are not available.

Sensitivity analysis was performed by computing for interval estimates of risk. Age, gender and ethnic group-specific interval estimates are presented (Figs. 1-3). Increasing risk with increasing age was again demonstrated. Wide, but non-overlapping interval estimates for the older age groups was evident. The interval estimate for the risk of VTE was slightly higher for females than males. Malays had the highest risk of VTE, followed by Indians and Chinese. Widths of interval estimates were almost equal for the three ethnic groups. Trends for lower and upper estimates of risk by ethnic group were consistent with trends for their corresponding point estimates.

Population-based Estimated Incidence of PE

Out of all patients with VTE, cases of PE were identified. The risk of PE increased with age, and was highest among Malays (Table 5). Incidence of PE among Eurasians and Caucasians residing in Singapore could not be ascertained as the sizes of their populations are not available.

Interval estimates for risk of PE were computed based on the assumption that NHG serves as little as 35.0% and as much as 50.0% of the population of Singapore. Age, gender and ethnic group-specific interval estimates are presented (Figs. 4-6). Except for the higher risk of PE in Chinese compared to Indians, demographic-specific patterns of PE incidence follow those for VTE.

Discussion

The controversy of applying Western standards and guidelines for VTE prophylaxis in the Asian context stems from conflicting views on the magnitude of the problem in Asian populations. If ethnicity is a risk factor for the development of VTE, there is a need to review current risk assessment tools. Various international groups including the UK Department of Health, the Australian National Institute of Clinical Studies, the American College of Chest Physicians and the Bavarian Thromboembolic Risk Study have identified risk factors for VTE and have developed VTE risk assessment tools.[8-11] None of the risk factors cited in these resources include ethnicity. On the other hand, there is growing evidence that there is a racial predisposition to the disease. Two reviews which compared rates of VTE among various ethnic groups found that African-Americans and Caucasians had higher disease burdens compared to Asians.[7,12] This finding is supported by a primary study conducted in the US which demonstrates that African-Americans have the highest incidence of VTE, and that Caucasians and Hispanics have the 2nd and 3rd highest rates. Asians and Pacific Islanders were found to have the lowest risk of VTE.[13] One study suggests that

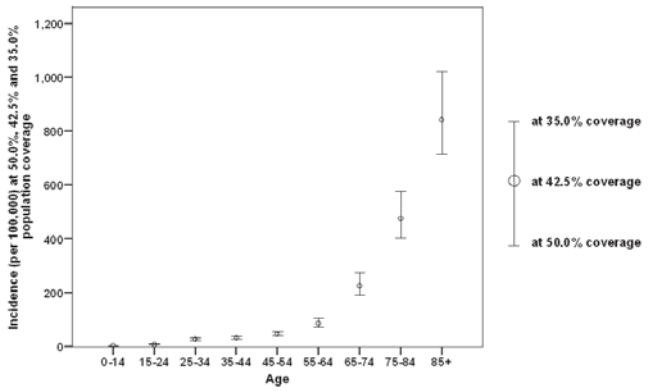

Fig. 1. Interval estimates for risk of VTE by age group, assuming 50.0%, 42.5% and 35.0% Singapore population coverage by NHG, 2006.

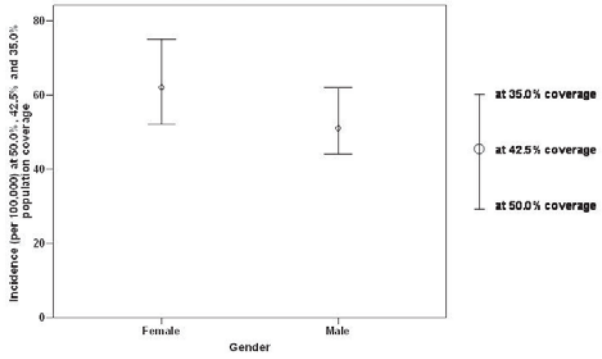

Fig. 2. Interval estimates for risk of VTE by gender, assuming 50.0%, 42.5% and 35.0% Singapore population coverage by NHG, 2006.

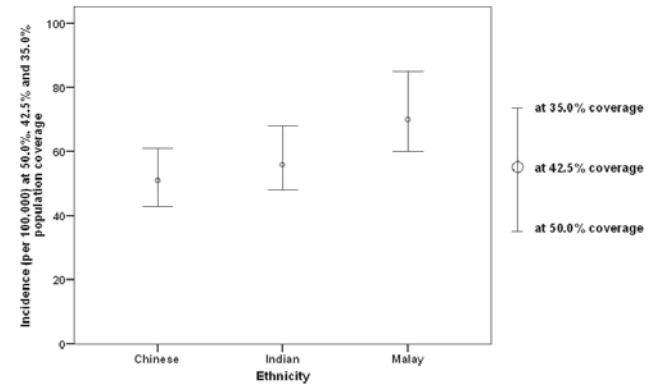

Fig. 3. Interval estimates for risk of VTE by ethnic group, assuming 50.0%, 42.5% and 35.0% Singapore population coverage by NHG, 2006.

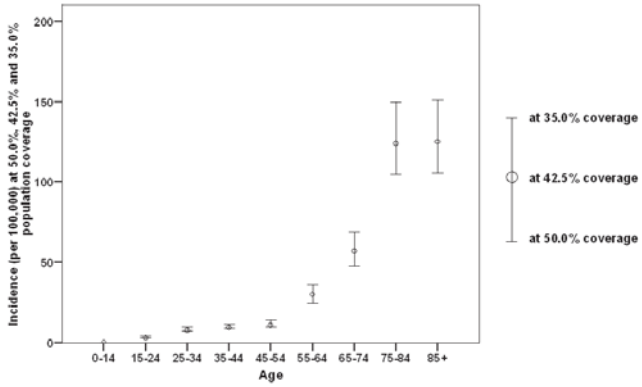

Fig. 4. Interval estimates for risk of PE by age group, assuming 50.0%, 42.5% and 35.0% Singapore population coverage by NHG, 2006.

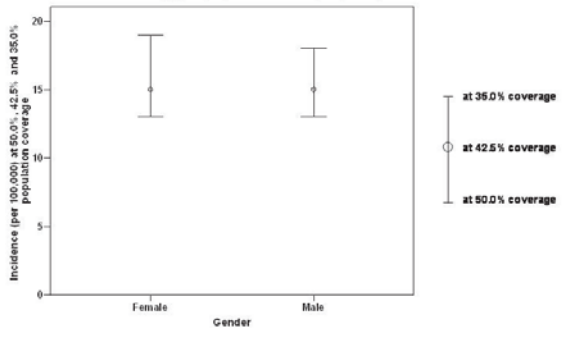

Fig. 5. Interval estimates for risk of PE by gender, assuming 50.0%, 42.5% and 35.0% Singapore population coverage by NHG, 2006.

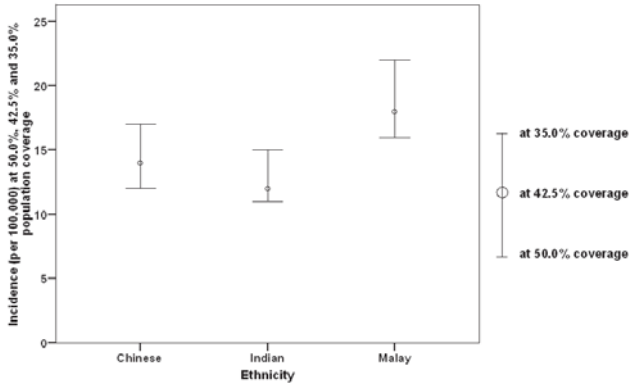

Fig. 6. Interval estimates for risk of PE by ethnic group, assuming 50.0%, 42.5% and 35.0% Singapore population coverage by NHG, 2006.

the difference in risk between ethnic groups may be due to the absence of hazardous mutations or unspecified PE/DVT protective traits in Asians.[14] A population-based study conducted in Hong Kong revealed low VTE rates of 17.1 and 3.7 per 100,000, for DVT and PE, respectively.[15]

While numerous studies point to ethnicity as a risk factor, there are others which suggest otherwise. A review of studies on the incidence of DVT and VTE concludes that these conditions are not rare in Asians.[16] This view is supported by findings of a study conducted in Asian patients undergoing orthopedic surgery.[17] Results revealed a rate of 2.3% for symptomatic VTE after adjudication. In 1997, a study done in Singapore showed that the incidence of sonographically confirmed DVT was 15.8 per 10,000 hospital admissions. This was higher than the previously reported rate of 2.8 and 7.9 per 10,000 in 1990 and 1992, respectively.[18]

Table 5. Age, Gender and Ethnic Group-specific Population-based Rates of PE

Characteristics	Number of in-patients with PE	2006 Singapore population distribution	Singapore population served by NHG (at 42.5% coverage)	Rate per 100,000 population (assuming 42.5% coverage)
Age (y)				
0-14	0	698100	296692	0
15-24	5	472300	200728	3
25-34	18	560000	238000	8
35-44	26	640100	272042	10
45-54	27	591500	251388	11
55-64	42	340000	144500	30
65-74	46	192100	81642	57
75-84	47	89700	38123	124
85+	13	24600	10455	125
Gender				
Male	108	1787600	759730	15
Female	116	1820800	773840	15
Ethnicity				
Chinese	153	2713200	1153110	14
Indian	16	319100	135618	12
Malay	37	490500	208463	18
Total	224	3608500	1533570	15

Results of another study conducted in Singapore revealed low rates of VTE prophylaxis for surgical patients. In that study, the 2 patients who developed DVT post-operatively received mechanical VTE prophylaxis.[19] In another study conducted in the US, the low rate of pulmonary embolism observed among Asians/Pacific Islanders led to the recommendation that risk assessment be adjusted based on ethnic differences.[20] If indeed Asians are at lower risk of VTE, applying risk assessment tools which fail to take ethnicity into consideration may result in unnecessary use of prophylactic measures which may increase costs as well as be associated with some treatment risks.

In the many primary studies which describe the incidence of VTE in various populations, there is wide variation in the range of designs utilised, heterogeneity of the procedures performed and the application of different diagnostic criteria.[16] This lack of uniformity in study characteristics makes it difficult to make cross country comparisons. In this study, hospital-based incidence of VTE and PE was assessed in several ethnic groups. The absolute magnitude of VTE and PE incidence in this study may be very different from those reported by other authors. Not withstanding the descriptive nature of this study, the findings are consistent with those from elsewhere particularly with regard to the apparently higher risk of VTE among Caucasians compared to Asians.[7,12,13,15] Consistency in this observed pattern suggests the potential need to evaluate the relevance of existing international guidelines for VTE prophylaxis.

As is typical of health services research which deals with real world scenarios, the use of administrative data in this study introduced a number of limitations. Whether or not a diagnosis of VTE was confirmed by imaging studies could not be ascertained. The final diagnosis rested entirely on the judgment of attending physicians who may have used different criteria for patient assessment. It is hoped that data captured in the database reflects the actual diagnosis as written by the attending physician, and that the attending physician is confident of the final diagnosis. In this study, a diagnosis of VTE was only made for hospitalised patients. It was not possible to identify those who were diagnosed as out patients. While age-adjustment was done, inter-cluster differences in ethnic distribution and case mix were not controlled for due to the lack of data. Despite the smaller volume of patients admitted to private hospitals compared to restructured hospitals, the lack of data on VTE cases admitted to private hospitals may affect population-based estimates of VTE. To partly compensate for this degree of uncertainty, a sensitivity analysis which assumes a range of service coverage by NHG hospitals was performed. A prospective study with specifically designed data collection methods and tools, and which controls for the effects of

confounders would sufficiently test the hypothesis of a possible association between ethnicity and VTE. Owing to the descriptive nature of this study, it must be emphasised that the results obtained cannot really address the hypothesis of an association between ethnicity and VTE. These results merely sign-post the issues and lay the groundwork for further studies which should lead to the development of locally applicable risk assessment tools.

Conclusions and Recommendations

The applicability of a healthcare intervention depends not only on its acceptability, safety and effectiveness, but also on the cost of its adoption relative to the benefit it imparts. The cost-effectiveness of VTE prophylaxis for various risk categories in Caucasian populations has been well established. However, there appears to be a need to review existing risk assessment tools in light of evidence pointing to ethnicity as a risk factor for the development of VTE.

In our study, the incidence of secondary in-hospital VTE for Chinese, Indians and Malays was 71, 43 and 74 per 10,000 admissions respectively, while that for Eurasians and Caucasians was 122 and 201 per 10,000 admissions. These findings appear to support the hypothesis of a possible association between ethnicity and VTE.

Results of multivariate analysis may be used to device a scoring system for the prediction of VTE. This tool may in turn, serve as the basis for the creation of local guidelines on VTE prophylaxis. Ultimately, an economic evaluation should provide a composite measure of the value of these guidelines and the assessment tools which served to inform them.

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