

## Clinical Update on Deep Vein Thrombosis in Singapore

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### Abstract

*Venous thromboembolism (VTE) is thought to be a rare occurrence in Asian patients. The clinical features of VTE are elusive and the disease often unsuspected. Objective testing such as the duplex ultrasound scans and pulmonary imaging are necessary as clinical diagnosis alone is inaccurate. Fatality can occur in untreated patients not suspected of the disease as shown by our post-mortem studies. Indeed VTE is one of the leading causes of maternal mortality in Singapore. There is a rising trend in the incidence of VTE in Asia. Initial studies found an incidence of about 3 per 10,000 hospital admissions in Hong Kong and Malaysia in 1988 and 1990, respectively; rising to 8 and 15.8 per 10,000 hospital admissions in Singapore 1992 and 2000, respectively. The major risk factors for developing deep vein thrombosis (DVT) in our patients are immobilisation, surgery and malignancy. While Factor V Leiden mutation and mutation at position 20210 in the prothrombin gene are found to be extremely rare in Chinese, the rest of the thrombophilia has not been formally studied. Studies in Singapore reported rates of 3% to 7% of DVT after general surgery, 9.7% after hip surgery and 14% after total knee replacement surgery. It is difficult to compare with studies from other centres because of differences in patient selection and diagnostic criteria. Studies in Singapore showed that the use of prophylactic low molecular weight heparin completely abolished the occurrence of DVT for patients undergoing total knee replacement and colorectal surgery without an increase in bleeding complications. In conclusion, VTE is not an uncommon problem here. Major acquired risk factors do not differ from the Caucasian populations. VTE is a preventable disease and a better understanding of its epidemiology, patient-risk factors and biological factors will allow better management of this condition.*

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**Key words:** *Rising incidence, Risk factors, Thromboembolism*

### Introduction

Deep vein thrombosis (DVT), and its acute complication—pulmonary embolism (PE), is one of the most important preventable causes of death in hospital patients. It also contributes to significant morbidity in terms of post-phlebotic syndrome and chronic venous ulcers. In Caucasian populations, venous thromboembolism (VTE) is an established entity. In the Scottish population, VTE or PE occurs in about 2 in 10,000 persons each year.<sup>1</sup> The Worcester study in England estimated the annual incidence of DVT to be 48 per 100,000 population, with a prevalence of 0.9% among hospitalised patients.<sup>2</sup> In the USA, the annual incidence of VTE is approximately 0.1%.<sup>3</sup> As a result, there is a high level of diagnostic awareness and the widespread application of consensus group guidelines on thrombosis risk, thrombosis prevention and thrombosis management.<sup>3</sup>

In contrast, VTE is perceived to be absent or a rare occurrence in Asian and Oriental patients since 40 years ago<sup>4,5</sup> and that VTE is a mostly ‘Caucasian’ problem. This view is bolstered when studies show that Factor V Leiden

mutation and prothrombin gene mutation at position 20210 are extremely rare in Chinese<sup>6-8</sup> although common in the Caucasian patients with thrombosis.<sup>9-13</sup> Therefore, the study of VTE in Asian populations has attracted limited attention. The true incidence of VTE in the Asian populations is unknown.

Literature pertaining to VTE in Singapore is reviewed and compared with published data from other countries. A MEDLINE search from 1980 to 2001, using the search terms DVT, PE and Singapore was done. There were 22 case reports of VTE,<sup>14-35</sup> 22 papers directly addressing issues on VTE,<sup>7,36-56</sup> and 7 other papers involving other conditions with VTE<sup>57-63</sup> as a complication. Of the papers directly addressing the issues of VTE, there were 7 papers on diagnostic modalities,<sup>36-42</sup> 3 post-mortem studies,<sup>43-45</sup> 4 involving a clinical series of hospitalised patients,<sup>46-49</sup> 6 on DVT post-surgery,<sup>50-55</sup> 1 on the use of vena cava filter<sup>56</sup> and 1 on the study of Factor V Leiden.<sup>7</sup>

The studies directly addressing the issues of VTE as well as two abstracts on large-scale studies on prevalence of DVT<sup>64,65</sup> are discussed in this paper.

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### Studies on Diagnostic Modalities

While venography remains the “gold standard” in the diagnosis of DVT, studies found that duplex ultrasound is very sensitive and specific for patients with symptomatic DVT. Studies done in Singapore showed good results. The reported sensitivity and specificity was 100% and 91.7%, respectively, with an overall accuracy of 95.1%.<sup>38</sup> This compares favourably with published studies done overseas, with sensitivity ranging from 88% to 100% and specificity ranging from 88% to 100%.<sup>66-70</sup> In our local studies,<sup>36-42</sup> clinical features of DVT and PE were unreliable if used alone to make a diagnosis of DVT, this is in agreement with previous findings that clinical diagnosis of VTE is notoriously inaccurate. None of the clinical features of DVT is unique to VTE as they can be present in numerous non-thrombotic disorders.

Similarly, for PE, the clinical diagnosis is unreliable as the clinical features are non-specific and can be present in many chest disorders. Pulmonary angiography remains the gold standard for establishing the diagnosis of PE but it is invasive and not suitable for ill patients. The V/Q lung scan is the most frequently requested test for PE,<sup>40</sup> the results are reported in terms of probabilities of the patient having PE and there are considerable problems in interpreting intermediate probability lung scans. Since its introduction in the 1990s, the spiral computed tomographic angiography (CTA) has emerged as a useful tool for the diagnosis of PE as it is not invasive and accurate.<sup>41</sup> Indeed, there were suggestions that the CTA should replace the V/Q lung scan as the first-line investigation for PE.<sup>41,42</sup>

The clinical features of VTE are elusive and the disease often unsuspected. Objective testing is a necessity as clinical diagnosis alone is inaccurate and fatality can occur in untreated patients.

### Post-mortem Studies

There are 3 studies on mortality associated with VTE and they revealed very interesting and important data.<sup>43-45</sup> A 1993 study compared the clinical cause of death with the autopsy cause of death in 623 coroners' cases.<sup>43</sup> Of those patients who suffered a PE, only 33% had agreement between the ante-mortem clinical diagnosis on cause of death and the autopsy diagnosis. Therefore, 67% of patients who perished from fatal PE had failed to be diagnosed while alive and were thought to have died from acute myocardial infarction (AMI) or acute pulmonary problems. Another study published in 1995 examined approximately 11,000 autopsies over 5 years.<sup>44</sup> In this study, there were 116 patients with fatal PE, 77% of whom were not suspected to have PE at all. This again re-emphasised the fact that clinical signs and symptoms are not reliable for diagnosis of VTE. Its first presentation can be fatal in individuals who may be otherwise healthy. These data also reflect the

low level of diagnostic awareness among the physicians who did not have a high index of suspicion then. In 1997, Chen et al<sup>45</sup> conducted a retrospective analysis of maternal deaths from January 1992 to December 1995. There were 7 maternal deaths during this period and autopsies revealed 3 out of 7 patients died from PE, making PE the leading cause of maternal mortality at 4.9 per 100,000 maternities.

Studies involving Caucasian populations reported rates of in-hospital deaths due to PE ranging from 4% to 13%,<sup>71-75</sup> which are substantially higher than the 1% (116 fatal PE in 11,044) reported in Singapore.<sup>44</sup> However, these studies are not really comparable as the studies on Caucasian populations were based on in-hospital patients and the study in Singapore was based on all autopsies done. Besides, autopsy studies in hospital patients in Caucasian populations are much more common than in Asian populations due to cultural and religious differences; autopsies performed in this region are mainly for coroner's cases and those with unnatural causes of death. The difference in the type of patients subjected to autopsies may account for the difference in rate of fatal PE.

### Hospital Series Studies

The true incidence of DVT in the local population is not known. VTE has always been perceived to be rare in Asians but the incidence of DVT is noticeably on the rise. In 1988, a paper from Hong Kong reported a rate of 2.7 per 10,000 patient admissions;<sup>46</sup> similar to the rate of 2.8 per 10,000 hospital admissions reported in Kuala Lumpur, Malaysia in 1990.<sup>47</sup> In 1992, Kueh et al<sup>48</sup> from Singapore reported a rate of 7.9 per 10,000 hospital admissions at the National University Hospital (NUH). Most of these cases were identified on clinical grounds with confirmatory tests performed in the minority. Between 1996 and 1997, the Singapore General Hospital (SGH) diagnosed 388 cases of DVT; all these cases had DVT confirmed on duplex ultrasound examination.<sup>65</sup> There were 332 cases of acute DVT and 63 cases of previous DVT. This study reported frequency rates of all DVTs and acute DVT at 19.3 and 15.8 per 10,000 patient admissions, respectively. This is substantially higher than previously reported. Conversely, if all symptomatic patients were included, we expect the reported incidence of acute DVT in the SGH to be higher than 15.8 per 10,000 admissions. Results of these hospital studies clearly show an increasing incidence of acute DVT in Asians from 2.7 to 15.8 per 10,000 admissions from 1988 to 1999. Notwithstanding differences in patient characteristics and admission policies, the rate of DVT is likely to be increasing among Asians. Part of this rising trend may be related to an ageing population, increased life expectancy and increased numbers of patients undergoing surgical procedures and suffering from malignant conditions. However, this figure is still considerably lower

than the 0.9% reported in the Worcester study.<sup>2</sup> Importantly, 8% to 18% of our patients were complicated by potentially fatal PE.

The risk stratification for DVT depends on the patient population base. The major risk factors for developing DVT in our local patients are increasing age, immobilisation, surgery and malignancy.<sup>46-48,65</sup> These are also the major risk factors for VTE in Caucasian populations.<sup>3</sup> Reported local studies were based on an older cohort of patients bringing with them more of the problems of advancing age and less of inherited risk factors. A study on younger patients will naturally select genetically related risk factors; but to date, no such study has been done in Singapore.

Attempts have been made to study the incidence of DVT in specific patients groups. One such study was conducted by Pek et al<sup>49</sup> on 33 patients with chronic obstructive pulmonary disease. None of these patients developed DVT and the authors concluded a low prevalence of DVT in this group of patients.

### The Role of Thrombophilia

In Caucasians, the commonly known inherited thrombophilia include deficiencies in antithrombin, protein C, protein S as well as mutations in Factor V Leiden and prothrombin 20210.<sup>3</sup> Thrombophilic factors such as antithrombin, protein C and protein S have not been well studied in Asians. A Taiwanese study involving 85 Chinese patients, reported protein C and protein S deficiency rates of 17.2% and 33.6%, respectively.<sup>6</sup> The authors concluded that protein C and protein S deficiencies were the most important risk factors for thrombosis in Chinese venous thrombophilic patients. A few Taiwanese studies have also shown that Factor V Leiden and mutation at position 20210 in the prothrombin gene are extremely rare in Chinese;<sup>6,8</sup> however, they are common in the Caucasian populations with thrombosis.<sup>9-13</sup>

There is no systematic large-scale study done in Singapore to address the role of thrombophilia in DVT. Most data here are in the form of sporadic case reports and findings from studies done to address other issues of DVT.<sup>26,28,48,65</sup> A small local study on Factor V Leiden drew similar conclusions that it is rare or absent in Chinese.<sup>7</sup> In a study on patients with DVT at the NUH, 4/39 patients had either protein C and protein S deficiency, but no antithrombin deficiency or anticardiolipin antibody (ACA) was detected.<sup>48</sup> In the 388 patients with DVT at the SGH, not all patients were subjected to thrombophilia testing but among those who were tested, 12.1% had protein C deficiency, 12.2% had protein S deficiency and 9.9% had antithrombin deficiency.<sup>65</sup> The small numbers involved, as well as the methodology of these studies, do not allow any definitive conclusions and direct comparisons with other studies.

### DVT and Surgery

Similarly, in the surgical setting, thromboembolism occurring post-surgery is thought to be uncommon and thromboprophylaxis is not routinely practised locally. Several studies have documented DVT following surgery in which patients were not given thromboprophylaxis. In a 1989 post-hip surgery study conducted in Singapore, 9.7% of patients suffered a DVT, all of which were distal and diagnosed by venography.<sup>50</sup> The authors concluded that the incidence of DVT was low and complications were negligible. They suggested that prophylaxis of DVT in this group of patients was not essential. A 1993 study examined the incidence of DVT in a high-risk subgroup of Chinese patients undergoing colorectal operations<sup>51</sup> and found that DVT only occurred in those with malignancy and it affected 5 out of the 107 patients. Of these 5 cases, 3 developed PE with 1 death as a result. A large prevalence study on post-surgical DVT in Asians was undertaken at the SGH. One thousand and thirteen patients who did not receive any form of thromboprophylaxis underwent a routine duplex scan before surgery and on the fifth day after surgery.<sup>64</sup> Deep venous thrombosis occurred in 75 (7%) patients of whom 48 had distal DVT and 27 had proximal. Five patients progressed to PE, with one fatality. While the incidence of DVT is low compared to the Caucasian data, these data called for further evaluation to determine the role of thromboprophylaxis in surgical patients.

The increasing awareness of DVT led to recent studies on VTE prophylaxis in Singapore. A study was conducted where 320 patients undergoing colorectal surgery were randomly assigned to either the perioperative enoxaparin group or the control group.<sup>54</sup> In the control group, 3% experienced DVT compared to 0% in the enoxaparin group ( $P = 0.045$ ). Of the DVT patients, 3/5 had PE and 1 patient died. The authors suggested that DVT prophylaxis is required in Asian patients undergoing major colorectal surgery. On patients who underwent total knee replacements, the Department of Orthopaedic Surgery, SGH showed that 14% of patients who underwent total knee replacements developed DVT without prophylaxis and the use of prophylactic low molecular weight heparin (LMWH) completely abolished the occurrence of DVT.<sup>53</sup> Among the patients who developed a DVT, 64% were distal DVT and many were asymptomatic. These studies showed that DVT is easily preventable by prophylactic LMWH without increase in bleeding complications.

It is difficult to compare data from Asian populations with data from Caucasian populations due to differences in study designs, patient selection criteria and particularly diagnostic tools. Studies on general surgery patients conducted in other Asian centres between 1974 and 1993 reported DVT rates ranging from 3% to 19.1%,<sup>76-80</sup> which

appears to be lower than in Caucasian populations where post-surgical DVT rates ranged from 6% to 35%.<sup>3,81</sup> However, there is a considerable overlap between these 2 sets of values. In Asian patients undergoing orthopaedic surgery, there are huge variations in the reported DVT rates between different Asian centres ranging from 0% in Thailand,<sup>82</sup> to 64.3% in Malaysia<sup>83</sup> for DVT post total hip replacement. Regarding DVT developing post total knee replacement, the reported rates range from 11.3% in Korea,<sup>84</sup> 14% in Singapore<sup>52</sup> and 76.5% in Malaysia.<sup>83</sup> Perhaps further studies using similar study designs and diagnostic tools may make more meaningful comparisons with western data where this area is concerned.

## Conclusion

Clinical observations have shown that while DVT may not be as common in the Asian populations as in the Caucasian populations, it is certainly not rare and is indeed on the rise. This is more commonly seen than thought and is seen across all disciplines of clinical practice from post-surgical patients, cancer patients, pregnant women to healthy individuals. VTE is a preventable disease and a better understanding of its epidemiology, patient risk factors and biological risk factors will enable better preventive measures.

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