ORIGINAL ARTICLE

The incidence of deep venous thrombosis in Chinese medical Intensive Care Unit patients

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Objective To evaluate the incidence of deep venous thrombosis in critically ill, Intensive Care Unit patients of Chinese ethnicity.

Design Prospective, observational study.

Setting Intensive Care Unit in a Hong Kong teaching hospital.

Patients Consecutive adult Chinese medical patients not receiving pharmacological or mechanical prophylaxis for deep venous thrombosis.

Main outcome measures Compression and duplex Doppler ultrasound examinations of the lower limbs within 24 hours of admission and twice weekly thereafter during their Intensive Care Unit stay. After discharge, a 1-week follow-up investigation was also performed. Demographic data and risk factors for deep venous thrombosis were prospectively recorded.

Results Over a 9-month study period, 80 patients were investigated. Deep venous thrombosis was detected by ultrasound examination in 15 (19%) of the patients (95% confidence interval, 14-23%). Nine of 15 had isolated below-knee deep venous thrombosis, and of these, five had bilateral involvement. Characteristics of patients with or without deep venous thrombosis were similar. Of the 15 patients who had a positive ultrasound examination, only four (27%) had clinical signs of deep venous thrombosis. Of the 65 patients without a positive ultrasound examination, only two (3%) had positive clinical signs (P=0.01). This yielded a moderate positive likelihood ratio of 9 (95% confidence interval, 2-43) and a small negative likelihood ratio of 0.76 (95% confidence interval, 0.56-1.03). There were no cases of pulmonary embolism. Hospital mortality in those with and without deep venous thrombosis was 33% and 28%, respectively.

Conclusions In the absence of prophylaxis, the incidence of deep venous thrombosis in Chinese medical Intensive Care Unit patients is lower than that reported in similar Caucasian patients, but higher than expected. As clinical features are not able to reliably exclude the presence of deep venous thrombosis, early routine prophylaxis for deep venous thrombosis in Chinese medical Intensive Care Unit patients should be considered.

Key words
Critical care; Pulmonary embolism; Thromboembolism; Ultrasonography; Venous thrombosis

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Introduction

Venous thromboembolic disease is common in hospitalised patients and leads to significant morbidity and mortality.[1] Studies of hospitalised patients in North America and Hong Kong have suggested that Asian patients, including those of Chinese origin, have a much lower incidence of deep venous thrombosis (DVT) than other ethnic groups.[2,3] Among high-risk surgical patients, several studies have shown a lower incidence of DVT in subgroups of Chinese patients than in Caucasian patients,[4-7] while other studies have demonstrated a similar incidence in high-risk surgical groups.[8,9] Therefore, while the weight of evidence suggests a generally lower rate of DVT in Chinese patients, for many subgroups the situation is not clear.

Two systematic reviews of DVT in non-Chinese critically ill adults have reported high rates in general intensive care unit (ICU) patients not receiving prophylaxis.[10,11] In studies published since 1990, this rate was approximately 30% (range, 25-32%).[12-15] The rate in patients receiving DVT prophylaxis was recently reported to be lower (approximately

10%).[16] Although routine DVT prophylaxis in ICU patients is recommended by several guidelines and individual experts,[10-12] its use in such patients is variable and ranges from 33 to 100%.[17-19]

Because of the common perception that DVT is infrequent in Chinese patients, routine prophylaxis is less commonly practised in Hong Kong.[3,9] At the time of this study, the use of DVT prophylaxis was not routine for medical patients in the ICU of our hospital. Although the risk of DVT in surgical and postoperative patients in particular has been well described and prophylaxis generally regarded as indicated, to date, there are no published data on the incidence of DVT in critically ill Chinese medical ICU occupants. The aim of this study was to prospectively determine the incidence of DVT in critically ill adult Chinese medical patients not receiving routine DVT prophylaxis.

深切治療部華籍病人的深靜脈血栓形成的發病率

目的 探討深切治療部危重的華籍病人的深靜脈血栓發病率。

設計 前瞻性研究。

安排 香港一所教學醫院的深切治療部。

患者 並未因深靜脈血栓而接受藥物或機械預防的連續入診的成年華籍病人。

主要結果測量 入院24小時內及入住深切治療部期間每星期兩次為下肢進行壓迫超聲和複式多普勒超聲測試。出院後一星期再進行隨訪研究。記錄有關人口學數據及深靜脈血栓的風險因素。

結果 9個月內對80名病人進行了研究。超聲測試發現15名病人（19%）有深靜脈血栓（95%置信區域：14-23%）；其中9名有個別的膝下深靜脈血栓，5名更涉及雙肢。有深靜脈血栓和沒有深靜脈血栓的病人特徵相似。15名呈陽性超聲測試結果的病人中，只有4名（27%）有深靜脈血栓的臨床徵兆；而65名呈陰性超聲測試結果的病人中，只有2名（3%）有深靜脈血栓的臨床徵兆（P=0.01）；產生溫和的陽性似然比（9；95%置信區域：2-43）及小值的陰性似然比（0.76；95%置信區域：0.56-1.03），也未有肺栓塞的案例。住院死亡率方面，有深靜脈血栓和沒有深靜脈血栓的病人分別為33%及28%。

結論 沒有預防措施的情況下，深切治療部華籍病人的深靜脈血栓形成的發病率比外國文獻報告的低，但比預期為高。由於臨床徵兆不能準確排除深靜脈血栓，應考慮盡早為深切治療部華籍病人進行深靜脈血栓的常規測試。

Methods

The study was performed in the 15-bed general medical and surgical ICU of a university teaching hospital. Approval for the study was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong. Informed consent was obtained from each patient or a senior relative if the patient's condition precluded obtaining consent. Consecutive patients were recruited over a 9-month period.

All Chinese medical patients aged 18 years or older with an anticipated minimum stay of 48 hours were eligible for enrolment. A medical patient was defined as one admitted from a medical parent team with a medical diagnosis as the reason for ICU admission. Patients were excluded if the clinical team considered that they were too unstable for an ultrasound examination to be performed safely, or if there was a diagnosis of DVT or pulmonary embolism (PE). Patients were also excluded if they were pregnant, required placement of a femoral venous catheter (we have previously demonstrated individuals with femoral catheters have an increased risk of lower limb DVT[20]), or were already receiving full anticoagulation therapy. Patients with pre-existing DVT defined as a positive ultrasound on the first screening examination within 24 hours of admission were also excluded.

Investigation and diagnosis of DVT depended on ultrasound examination. The first screening examination was undertaken within 24 hours of admission. During the ICU stay ultrasound examination was performed twice weekly (Mondays and Thursdays), and a follow-up study was performed 1 week after discharge from the ICU. Patient participation in the study was terminated if a study for DVT was reported positive. In which case, the finding was communicated to the physician-in-charge of that patient, who decided the treatment and follow-up plan of that patient. Investigation for PE was undertaken on the basis of clinical suspicion and in keeping with the routine clinical practice of the physician-in-charge.

The deep venous systems of both lower extremities were examined from the external iliac veins proximally to the posterior tibial, peroneal, gastrocnemius and soleal veins distally. The veins were evaluated in the transverse and longitudinal planes using the compression technique of Cronan et al,[21] supplemented with duplex and colour Doppler capability.[22,23] Deep venous thrombosis was diagnosed when there was visualisation of thrombus, non-compressibility of the vein, abnormal Doppler flow, phasicity and augmentation, and Doppler and colour spectral flow void. The site of the DVT was recorded. Scans were performed with a diagnostic ultrasound system (Brüel and Kjaer, B-K Medical, Denmark) using either a high-resolution 5-MHz curved or 8-MHz linear array probe depending on the depth

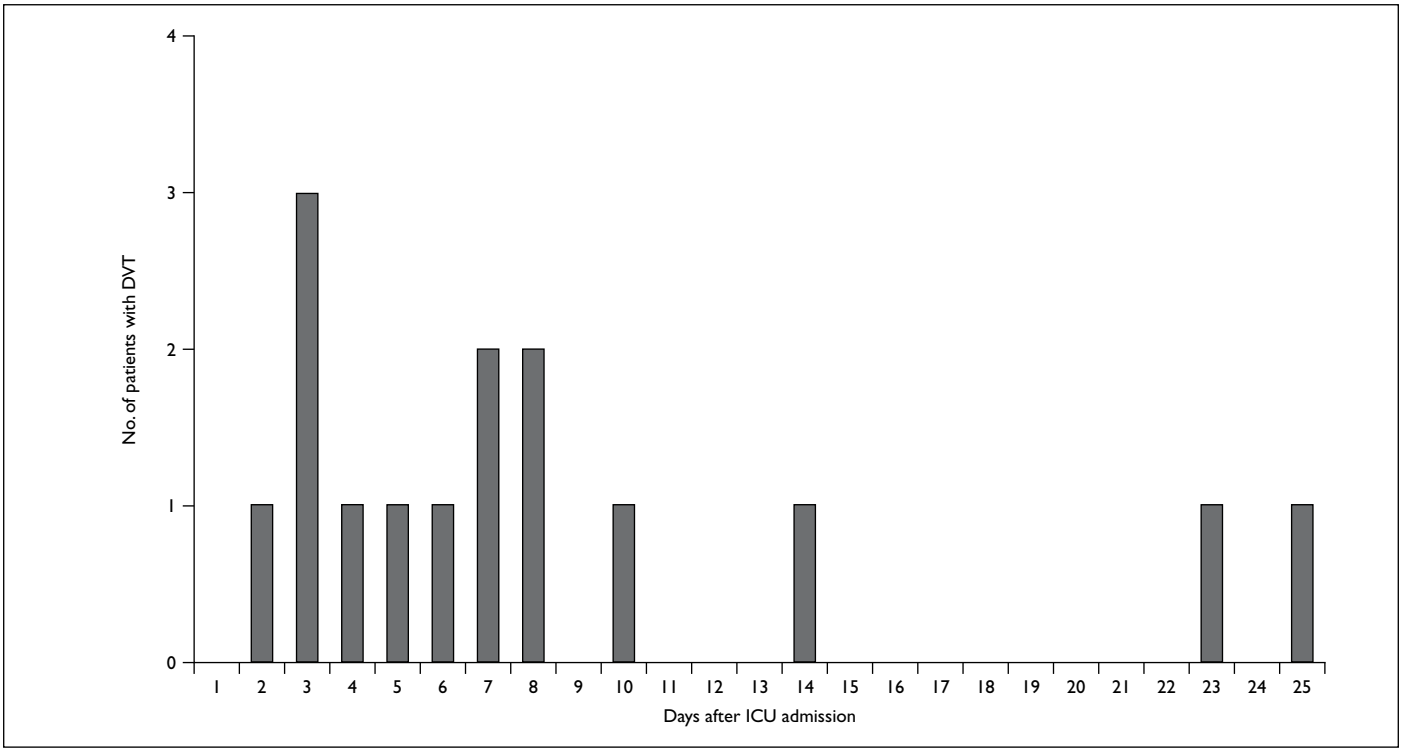

FIG. Days of deep venous thrombosis (DVT) diagnosis in critically ill Chinese medical patients following admission to the Intensive Care Unit (ICU)

of view under interrogation. All examinations were completed by one of two sonographers, both of whom had over 7 years of experience with vascular ultrasound, and were unaware of patient characteristics or risk factors. Examinations were recorded and reviewed by a specialist radiologist, who was also fully blinded to patient characteristics and risk factors.

The following patient demographic data and known risk factors for venous thromboembolism were prospectively recorded: age, sex, weight, height, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, clinical diagnosis, history of DVT or PE, number of days in hospital prior to ICU admission, presence of malignancy, and the need for operation after admission (eg exploratory laparotomy, cholecystectomy). Although not routinely prescribed for DVT prophylaxis, anticoagulation for other indications (eg acute coronary syndrome, arrhythmia) during the ICU admission, in a dose equal to or greater than that given for routine prophylaxis, was prospectively recorded. The presence or absence of a clinical diagnosis of DVT prior to each ultrasound screening was also recorded.

Results were presented as means (standard deviations) or medians (ranges), as appropriate. The Student's *t* test, Chi squared and Fisher's exact tests were used, where appropriate. A P value of less than 0.05 was considered significant. Confidence intervals (CIs) were calculated using Wilson's method.[24]

Results

There were 774 admissions to the ICU during the study period. Among these, 282 were general surgical, 154 neurosurgical, 27 orthopaedic, 47 paediatric, 37 obstetric or gynaecological, 14 were burns cases, and 213 medical patients. Of the 213 medical patients, exclusions per protocol included: history of thromboembolic disease (n=14), receipt of full anticoagulation therapy (n=21), femoral line insertion (n=14), moribund unstable status (n=3), non-Chinese ethnicity (n=3), being pregnant (n=2), having a positive initial ultrasound (n=4), and anticipated ICU stay of less than 48 hours (n=37). Eighteen patients refused consent, a study radiologist/radiographer was unavailable for nine patients, and eight were wrongly considered ineligible.

Deep venous thrombosis was detected by ultrasound examination in 15 (19%; 95% CI, 14-23%) of the 80 medical patients considered eligible. Nine of 15 patients with DVT had isolated below-knee (distal) DVT. In two of the latter, the DVT was non-occlusive. Five of these nine patients with distal DVT had bilateral involvement. All proximal DVTs were occlusive (n=6). In all patients with bilateral DVT, at least one side was occlusive. Nine of the 15 patients had DVT diagnosed within a week of ICU admission (Fig).

Baseline characteristics of the 80 recruited patients are shown in Table 1. Factors known to be

predictive of DVT were similar in patients with or without DVT (Table 2). A small number of medical patients underwent surgical procedures requiring anaesthesia as a consequence of complications related to their underlying medical condition. These procedures included: tracheostomy, cholecystostomy for acalculous cholecystitis, bedsore debridement, and intra-abdominal abscess drainage. Most patients had short hospital stays prior to ICU admission (median pre-ICU hospital stay, 0 days).

The majority of patients with positive ultrasound findings for DVT demonstrated no clinical signs. More patients with ultrasound-documented DVT showed clinical signs of DVT than those who were ultrasound negative (P=0.01). Four (27%) of 15 of the former patients had clinical features of a DVT (unilateral leg swelling, with or without redness), compared to only two (3%) of the 65 patients with negative ultrasound findings. Using the positive ultrasound as an indicator of the presence of a DVT, the likelihood ratio (LR) for the presence of clinical features was 9 (95% CI, 2-43) and the LR for the absence of clinical features was 0.76 (95% CI, 0.56-1.03). In more traditional nomenclature, presence of clinical features had a sensitivity of 0.27 and their absence a specificity of 0.97. For the prevalence noted in this study, the positive predictive value of clinical features amounted to 0.68, and the negative predictive value was 0.85.

Treatment of DVT in patients with a positive ultrasound diagnosis was decided by the physician-in-charge of each case. The characteristics and outcome of the 15 patients with DVT are shown in Table 3. Of those diagnosed with DVT, three patients received full anticoagulation with low-molecular-weight heparin and three received full anticoagulation with intravenous unfractionated heparin. Two had severe coagulopathy precluding the use of anticoagulants, and in one other anticoagulation was withheld because of severe gastro-intestinal bleeding. The remaining patients were observed and not treated with full anticoagulation because the DVT was asymptomatic and below-knee (Table 3). The overall hospital mortality of the cohort was 29%, being 33% and 28% in those with and without DVT, respectively. There was no documented PE in these patients.

TABLE 1. Baseline characteristics of 80 consecutive critically ill Chinese medical Intensive Care Unit patients with and without deep venous thrombosis (DVT)*

Characteristic	With DVT (n=15)	Without DVT (n=65)	Total (n=80)
No. of patients			
Males	7	22	29
Females	8	43	51
Median APACHE II† score (range)	21 (9-29)	20 (11-32)	20 (9-32)
Diagnosis			
Acute pulmonary oedema	2	9	11
Primary respiratory failure	5	10	15
Haemoptysis/bronchiectasis	0	2	2
Cardiovascular disease	1	15	16
Neurological disease	3	2	5
Renal failure	0	3	3
Hepatosplanchnic disease	1	8	9
Multiple organ failure	1	6	7
Metabolic abnormality	2	10	12

* No statistically significant differences
† APACHE II denotes Acute Physiology and Chronic Health Evaluation II

TABLE 2. Potential risk factors and outcomes in critically ill Chinese medical Intensive Care Unit (ICU) patients with and without deep venous thrombosis (DVT)

Risk factor/outcome	With DVT (n=15)	Without DVT (n=65)	P value
No. of patients			
Males	7	22	0.35
Females	8	43	
Median age (range) [years]	64 (18-78)	60 (17-79)	0.87
Median body mass index (range) [kg/m^2]	24 (21-34)	22 (15-41)	0.10
Clinical signs of DVT	4	2	0.01
History of DVT	1	3	0.11
Malignancy	1 (7%)	6 (9%)	1.00
Operative procedure during ICU stay	0 (0%)	7 (11%)	0.34
Mechanical ventilation while in ICU	14 (93%)	57 (88%)	1.00
Median duration of mechanical ventilation (range) [days]	4 (0-14)	2 (0-46)	0.81
Anticoagulation in ICU	0 (0%)	4 (6%)	0.58
In-hospital mortality	5 (33%)	18 (28%)	0.75
Median hospital days prior to ICU (range)	0 (0-24)	0 (0-57)	0.73
Median ICU days (range)	4 (5-21)	3 (2-61)	0.89

Discussion

Using compression and Doppler ultrasound, this study documented that in the absence of DVT prophylaxis, the rate of DVT in Chinese medical ICU patients was 19%, of which the majority (60%) were isolated below the knee. Characteristics of patients with or without DVT were similar, as were hospital length of stay and mortality. In the majority of patients, DVT was detected within the first week of ICU admission. Although the majority of patients with DVT diagnosed by ultrasound demonstrated no clinical signs, a significantly greater number of patients with clinical signs of DVT prior to screening had a positive ultrasound examination.

The DVT rate documented in this study (19%) was lower than that previously reported in Caucasian medical ICU patients not receiving prophylaxis (28-32%).[12-14] Genetic differences may partly explain this

TABLE 3. Characteristics and outcomes of patients with ultrasound findings of deep venous thrombosis (DVT)

Patient No.	Sex/age (years)	Diagnosis	Clinical feature	DVT site	DVT therapy	Survive?
1	F/73	Chronic obstructive pulmonary disease exacerbation	-	Bilateral soleal veins	Intrinsic coagulopathy	No
2	F/45	Pneumonia and multiple organ failure	-	Right proximal popliteal vein	Intrinsic coagulopathy	No
3	F/65	Pulmonary oedema	Unilateral leg swelling	Bilateral soleal, proximal popliteal veins	Low-molecular-weight heparin anticoagulation	Yes
4	F/59	Pulmonary oedema	-	Right popliteal and posterior tibial veins	Compressive stockings	No
5	F/67	Pneumonia	-	Bilateral soleal veins	No specific therapy	No
6	F/64	Guillain-Barré syndrome	-	Left soleal vein	Unfractionated heparin infusion	Yes
7	F/28	Hyperglycaemic coma	Unilateral leg swelling	Left leg-left common iliac vein	Unfractionated heparin infusion	Yes
8	M/18	Meningitis	-	Left proximal popliteal vein	Unfractionated heparin infusion	No
9	M/48	Bronchopneumonia	-	Left soleal and long saphenous veins	No specific therapy	Yes
10	M/66	Status epilepticus	-	Bilateral soleal veins	Compressive stockings	Yes
11	M/47	Post-cardiac arrest	Unilateral leg swelling and fever	Bilateral soleal veins	No specific therapy	Yes
12	M/69	Drug overdose	-	Right soleal vein	No specific therapy	Yes
13	M/34	Pneumonia	-	Right common femoral vein	Low-molecular-weight heparin anticoagulation	Yes
14	M/78	Pneumonia	Unilateral leg swelling and tenderness	Right soleal and left peroneal veins	Low-molecular-weight heparin anticoagulation	Yes
15	M/77	Gastro-intestinal bleeding	-	Right calf to proximal popliteal vein	Anticoagulation therapy contra-indicated	Yes

observation. Thus, in Chinese there is a very low rate of factor V Leiden (a factor known to increase venous thromboembolism risk substantially).[25,26] Also, Asians may have lower mean fibrinogen, factor VIIc and VIIIc concentrations, and other as yet poorly explored factors (such as the prevalence of thrombin gene *G20210A*) that may play a synergistic protective role.[27] Other factors such as Asian diets and lifestyles may also affect venous thrombosis rates.[28,29]

Many risk factors for DVT in ICU patients have been identified. They include: recent surgery or trauma, sepsis, malignancy, stroke, advanced age, cardiac or respiratory failure (especially associated with mechanical ventilation), immobilisation (particularly with sedation and paralysis), the use of lower limb central venous catheters, previous venous thromboembolism, and pregnancy.[11,16,19] Because of the relatively small numbers of patients in this study, we were unable to demonstrate any strong associations between known risk factors and the incidence of DVT. Patients who had femoral central venous catheters inserted were excluded from the study, as we had already demonstrated an approximately six-fold increase of risk in this group.[20]

While DVT prevention has received much attention, few comparative studies have directly assessed the effect of routine DVT prophylaxis in ICU patients.[13,14] However, prospective data documenting the high rate of DVT in ICU patients, as well as data demonstrating the efficacy of prophylaxis in reducing thromboembolic complications in non-ICU patients at high risk, have led to the recommendations that most ICU patients should receive routine DVT prophylaxis.[11] The low rate and predominantly distal location of DVT demonstrated in our study suggest that Chinese patients are possibly at lower risk of thromboembolic complications and further studies are needed to clarify the benefit of prophylaxis in this population. Nevertheless, at present we are of the opinion that a DVT rate of 19%, with a 7.5% rate of proximal occlusive DVT, is sufficient to justify the introduction of routine DVT prophylaxis. However, this opinion should be viewed in the context of other potentially important factors. There are some suggestions that the dose of intravenous heparin or oral warfarin required for full intravenous anticoagulation therapy in Chinese

patients may be lower than that in corresponding Caucasian patients.[30,31] On this basis it is possible that smaller prophylactic doses may also be sufficient, but to date there are no published data exploring optimal prophylactic heparin dosage in Chinese patients. In keeping with the lower thrombosis rates, it is also possible that complications related to bleeding as a result of DVT prophylaxis in Chinese patients might be more frequent than in Caucasian patients, although we are unaware of any published data confirming this suspicion.

The time of onset of DVT in our series was early, sometimes within 48 hours of admission and within 1 week in the majority. This finding indicates that there should be no unnecessary delay if prophylaxis is to be initiated.

Even with the relatively few ultrasound-positive patients in our series, there was an association between the presence of the clinical features (unilateral swollen leg) and a subsequent positive Duplex compression ultrasound study. The LR of 9 suggests that the impact on likelihood is moderate to good, supporting the practice of examining for signs of DVT at least daily. Moreover, all patients with clinical signs of DVT should undergo a confirmatory ultrasound study. However, the absence of clinical signs does not exclude the presence of DVT as the negative LR of 0.76 suggests a small-to-moderate impact on likelihood.[32] A recent cost-effectiveness analysis suggested that prospective screening for DVT in patients with femoral venous catheters in situ—a technique such as Doppler ultrasound—would fall within acceptable willingness to pay thresholds.[33] However, the cost-effectiveness of similar screening for all ICU patients is unknown. Current expert recommendation, therefore, continues to stress universal prophylaxis rather than screening.[34]

A limitation of this study was that Doppler ultrasound is operator-dependent. To maximise accuracy, the investigations were performed by two experienced, but blinded radiographers with expertise in the detection of venous thrombosis. All studies were recorded and independently reviewed for accuracy by a blinded radiologist. Venography is still considered the gold standard for the detection of DVT and a detailed comparison of techniques in observational studies has shown Doppler ultrasound to be good for detecting DVT in symptomatic patients (mean sensitivity 97% and specificity 94%) and moderate in asymptomatic patients (mean sensitivity 62% and specificity 94%).[35] However, venography is invasive, may induce nephrotoxicity, and is time-consuming and difficult to perform in sick ICU patients. By contrast, ultrasound with duplex Doppler can be performed safely at the bedside in almost all cases. For this reason the vast majority of ICU studies investigating DVT have used Duplex ultrasound as the imaging technique.[12,13,15,16,36] Therefore, whilst comparison with other ICU studies and populations was likely to be valid, the absolute number of events reported in our study may be underestimated.

The calculations of LR, sensitivity and specificity, and positive and negative predictive values should be interpreted with caution in a clinical setting, as our study was not designed or powered to specifically evaluate clinical signs and CIs were wide. Moreover, the prevalence of the condition in a given population may have important effects on both predictive values and LRs. In addition, a positive ultrasound examination is not yet a universally established gold standard. Lastly, study numbers and DVT events were too infrequent to allow robust multivariate analyses to evaluate associations with risk factors.

Conclusions

In the absence of routine prophylaxis, the incidence of DVT in Chinese medical ICU patients was lower than that reported in similar Caucasian patients, but higher than expected. Clinical features were not able to reliably exclude the presence of DVT. Therefore in Chinese medical ICU patients, early routine prophylaxis for DVT should be considered. Clinical features of DVT should always be followed with further testing to confirm the diagnosis.

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