Internal and Emergency Medicine (2019) 14:941–947
https://doi.org/10.1007/s11739-019-02066-8

IM-ORIGINAL

Proximal and isolated distal deep vein thrombosis and Wells score accuracy in hospitalized patients

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Received: 7 January 2019 / Accepted: 4 March 2019 / Published online: 12 March 2019

Abstract
Deep vein thrombosis (DVT) is an important cause of morbidity and mortality in hospitalized patients. The Wells score for DVT pretest probability (PTP) was validated in outpatients, but its utility for inpatients is unclear. The aim of this study was to establish the prevalence of inpatient proximal and distal DVT and the Wells score performance in inpatients. A single-center cross-sectional study was conducted in a university hospital. During 183 days, all inpatients with suspected lower-extremity DVT were evaluated with the Wells score and whole-leg ultrasound. Among 634 inpatients (age 77.5 ± 13.8 years, males 39.3%), 507 (80.0%) were from medical wards and 127 (20.0%) from surgical wards. During the study period, there were 11,662 hospital admissions in the surgical/medical services. Whole-leg ultrasound detected 128 DVTs (20.2%); 51 (39.8%) were proximal and 77 (60.1%) were isolated distal DVTs. Estimated DVT prevalence in hospital setting was 1.09% (95% CI 0.93–1.31), and isolated distal DVT prevalence was 0.66% (95% CI 0.53–0.82). DVT frequency in low-, moderate-, and high-PTP groups was 9.8%, 24.3%, and 41.5%, respectively ($p = 0.001$). The area under the receiver operating characteristic curve for the Wells score was 0.67 ± 0.03 for all DVTs and 0.75 ± 0.04 for only proximal DVTs. A high PTP had a sensitivity of 24% (95% CI 14–37%) and a specificity of 93% (95% CI 91–95%) for proximal DVT diagnosis. In hospitalized patients, isolated distal DVT has a higher incidence than expected, and the Wells score accuracy for proximal DVT is similar to that found in outpatients.

Keywords Deep vein thrombosis · Diagnosis · Inpatients · Isolated distal deep vein thrombosis · Calf deep vein thrombosis

Introduction

Venous thromboembolism (VTE), either deep vein thrombosis (DVT) or pulmonary embolism (PE), is a major health problem in the European Union, with 370,000 VTE-related deaths per annum, of which almost three-quarters are from hospital-acquired VTE [1]. Lower-extremity DVT incidence in hospitalized patients varies according to different reports. In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial [2] and in the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) [3], the incidence of symptomatic DVT was 1.5% and 0.95% in the 2 trials' placebo arms, respectively. A retrospective study showed that the prevalence of lower-extremity DVT during the hospital stay was less than 0.2% [4], whereas other studies suggested that the incidence of DVT among inpatients is 100 times greater than the incidence among community residents [5].

Since untreated DVT may lead to fatal PE, DVT diagnosis should be therefore timely and accurate. Diagnosing DVT by physical examination is inaccurate, and several diagnostic algorithms have been developed [6]. Compression ultrasonography in combination with a clinical decision rule and/or D-dimer testing has been widely investigated for the diagnosis of DVT of the lower limbs [7]. Wells and colleagues developed a diagnostic rule to estimate DVT pretest clinical probability (PTP) [8]. Recently, it has been reported that such PTP score is associated with a high failure rate and a low efficiency in the inpatient setting [9], while hospital-related VTE is a major cause of long-term morbidity, functional disability, and mortality [10].

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To our knowledge, no large prospective study to specifically record the prevalence of hospital-related DVT has been conducted. The purpose of this study was to evaluate the prevalence of lower limb DVT in inpatients and to evaluate the accuracy of the Wells rule for suspected lower limb DVT in hospitalized patients.

Methods

Study setting

This was an observational cross-sectional study performed in a tertiary care academic hospital (University Hospital S. Orsola-Malpighi, Bologna, Italy) from October 2016 to March 2017. The study was approved by the local Ethics Committee.

Study population

Symptomatic patients with at least one of the following symptoms: acute leg pain, acute leg swelling, calf cramps, acute calf redness, acute calf warmth, were eligible for the study if hospitalized in the surgical, medical, and hematology/oncology wards and referred to the vascular emergency room for suspected acute DVT of the lower limbs. In our academic hospital, hospitalized patients with clinical suspicion of DVT proceed directly to whole-leg ultrasonography. Patients were excluded if they had symptom of DVT before admission and if they were younger than 18 years, pregnant, or in puerperium. Patients with a diagnosis of DVT in the previous 3 months were excluded. Moreover, we excluded patients from the emergency department and patients that were receiving anticoagulant agents as vitamin K antagonists or direct oral anticoagulant. Patients receiving pharmacologic thromboprophylaxis were enrolled. Pharmacologic thromboprophylaxis was defined as the use of subcutaneous heparin calcium, 5000 U, 2 or 3 times daily, or subcutaneous enoxaparin sodium, 40 mg/day, or subcutaneous fondaparinux, 1.5/2.5 mg/day, between the time of hospital admission and whole-leg ultrasound. All consecutive eligible patients were enrolled. Diagnosis of proximal and isolated distal DVT was based on whole-leg ultrasound. For patients with multiple ultrasonographies during the study period, only the first examination was considered if all were negative, otherwise the positive one. For patients with multiple hospitalizations, only the first was considered.

Pretest clinical probability score

We enrolled symptomatic inpatients referred by ward clinician to the vascular emergency room for suspected lower leg DVT. Within 24 h, they were screened by a separate clinician that performed the pretest clinical probability score and filled the PTP questionnaire at the vascular emergency room. Then, a third clinician performed and interpreted the ultrasound. The physician interpreting the ultrasound was blinded to the PTP, and the physician that filled the PTP questionnaire was blinded to the ultrasound results. PTP for DVT was assessed using a questionnaire developed by Wells and associates [7]. One point was added for each of the following positive finding: (a) active cancer treatment ongoing or within previous 6 months or palliative; (b) paralysis, paresis, or recent plaster immobilization of the lower legs; (c) recent immobilization for more than 3 days or major surgery within last 4 weeks; (d) localized tenderness/pain along the distribution of the deep venous system; (e) entire leg swollen; (f) calf swelling by more than 3 cm when compared with the asymptomatic leg; (g) pitting edema greater in the symptomatic leg; (h) collateral superficial veins; (i) previously documented DVT. Two points were subtracted from the total points if an alternative diagnosis as likely as or more likely than DVT was found. Based on such checklist, PTP for DVT could be estimated to be low (score = 0 or less), moderate (score = 1 or 2), or high (score = 3 or more).

Whole-leg ultrasonography investigation

Patients underwent a complete real-time B-mode and color Doppler compression ultrasonography examination of both legs as previously described [11]. Ultrasonography investigation was carried out with an EnVisor C HD instrument (Philips Medical System S.p.A, Monza, Italy) and was performed by board-certified vascular medicine physicians using a standardized examination protocol. The proximal deep veins were examined first, and then, the calf veins were evaluated. The following veins were scanned in the transverse plane over their entire length: common femoral vein, deep femoral vein, femoral vein, popliteal vein, posterior tibial veins, fibular veins, medial and lateral gastrocnemius veins, and soleal veins. DVT diagnosis was confirmed if there was lack of compression of the vein.

Statistical analysis

Analysis was carried out using the SPSS™software package (version 21; IBM Corp., USA). Estimated DVT prevalence in inpatients was calculated as the ratio between the number of DVTs during the study period (180 days) and the number of total hospital admissions in the surgical, medical, and hematology/oncology wards during the study period. A sample size of 644 patients was calculated with an expected prevalence of 20% for lower limb DVT (both proximal and distal) and with 95% confidence intervals (CI) ± 3% (OpenEpi, version 3). Relationships between variables were assessed using Pearson correlation for continuous variables

and Chi-square or Fisher's exact test for categorical variables. Student *t* test was used to compare means among groups for normally distributed variables. Receiver operating characteristic (ROC) curves were prepared by plotting the sensitivity versus 1-specificity. The area under the ROC curves (AUCs) for the discriminatory accuracy of the PCP were calculated. Categorical variables were expressed as frequency and percentage with 95% CI; continuous variables were expressed as mean ± SD, inter-quartile range (IQR) is also reported. The significance level was set at < 0.05.

Table 1 Characteristics of the study population

Age, mean (SD), year	77.5 (13.8)
Female sex	385 (60.7)
BMI mean (SD), kg/m^2	25.4 (4.8)
Active cancer	129 (20.3)
Bedridden	346 (54.6)
Previously documented DVT	84 (13.2)
Hospitalization days at the time of LEUS, mean (SD), d	5.5 (6.2)
Pharmacologic thromboprophylaxis used[a]	371 (58.5)
Ward	
Surgery	127 (20.0)
Medicine[b]	507 (80.0)

Data are presented as number (percentage) of patients unless otherwise indicated

LEUS lower-extremity ultrasound study, *BMI* body mass index, *DVT* deep vein thrombosis

[a]Use of subcutaneous heparin calcium , 5000 U, 2 or 3 times daily, or subcutaneous enoxaparin sodium, 40 mg/day, or subcutaneous fondaparinux, 1.5/2.5 mg/day

[b]Including hematology/oncology

Results

Characteristics of 634 patients enrolled with suspected lower limb DVT during the study period are summarized in Table 1. Among the 634 inpatients (age 77.5 ± 13.8 years, females 60.7%), 476 (75.1%) were hospitalized in medical wards, 127 (20.0%) in surgical wards, and 31 (4.9%) in hematology/oncology wards. For the purpose of analysis, patients were divided into two groups: patients from surgical wards ($n = 127$) and patients from non-surgical wards, i.e., from medical and oncology/hematology wards ($n = 507$). Active cancer was present in 129 (20.3%) patients. Most of the patients were recently bedridden (54.6%). Whole-leg ultrasound was performed after 5.5 ± 6.2 days from hospitalization. Pharmacologic thromboprophylaxis was used in 371 (58.5%) patients. The patient baseline characteristics, such as hospital length of stay, comorbidities, thromboprophylaxis use, and Wells score distribution according to the two different hospital services (surgical ward vs. non-surgical ward) are reported in Table 2. Cancer was more frequent in patients from non-surgical ward vs. patients from surgical wards; 70% of the patients from surgical ward were on pharmacologic thromboprophylaxis vs. 56% of patients from non-surgical wards.

Whole-leg ultrasound detected 128 DVTs (20.2%); 51 (39.8%) were proximal and 77 (60.1%) were isolated distal

Table 2 Characteristics of inpatients with suspected deep vein thrombosis (DVT) by hospital ward

	Non-surgical wards $n = 507$	Surgical wards $n = 127$	*p*-value
Age, mean (SD), year	77.9 (13.3)	75.6 (15.7)	0.087
Male/female (%)	207/300 (59.2)	42/85 (66.9)	0.109
Hospitalization days at the time of LEUS, mean (SD), day	5.1 (6.2)	7.2 (6.1)	0.001
Pharmacologic thromboprophylaxis use[a]	283 (55.6)	89 (70.1)	0.003
Active cancer	113 (22.3)	16 (12.6)	0.015
Previous DVT	70 (13.8)	14 (11.0)	0.408
Wells score, mean (SD)	0.9 (1.4)	0.7 (1.4)	0.077
Wells score risk category			
Low	180 (35.5)	64 (50.4)	0.002
Moderate	284 (56.0)	53 (41.7)	0.004
High	43 (8.5)	10 (7.9)	0.825
Proximal DVT	47 (9.3)	4 (3.1)	0.023
IDDVT	65 (12.8)	12 (9.4)	0.298

Data are presented as number (percentage) of patients unless otherwise indicated

DVT deep vein thrombosis, *IDDVT* isolated distal DVT

[a]Use of subcutaneous heparin calcium , 5000 U, 2 or 3 times daily, or subcutaneous enoxaparin sodium, 40 mg/day, or subcutaneous fondaparinux, 1.5/2.5 mg/day

DVT. The prevalence of proximal DVT was 3 times higher among patients hospitalized in the medical/hematology/oncology services (47 of 507; 9.3%, 95% CI 7.0–12.1%) compared with those hospitalized in the surgical service (4 of 127; 3.2%, 95% CI 1.2–7.8%). Overall, the DVT prevalence was 22% (95% CI 18.7–25.9) among patients from no-surgical wards vs. 14.1% (95% CI 9.2–21.93) among patients from surgical wards. There were 11,662 total hospital admissions in the surgical/medical/hematology/oncology services during the study period. The estimated DVT prevalence in hospital setting was 1.09 per 100 patients (95% CI 0.93–1.31). Isolated distal DVT prevalence was 0.66 per 100 patients (95% CI 0.53–0.82). As shown in Table 3, DVT frequency in low-, moderate-, and high-PTP groups was 9.8%, 24.3%, and 41.5%, respectively ($p=0.0001$). The percentage of subjects receiving pharmacologic thromboprophylaxis was similar in low-, moderate-, and high-pretest probability groups (58.2%, 59.3%, and 54.7%, respectively, $p=0.810$). The area under the receiver operating characteristic curve (AUC) for the discriminatory accuracy of the Wells score for risk of all DVTs identified on whole-leg ultrasound was 0.67 ± 0.03 $p<0.001$. A moderate/high PTP (score ≥ 1) had a sensitivity of 81% (95% CI 74–87%) and specificity of 43% (95% CI 39–47%), with negative and positive predictive values of 90% (95% CI 86–93%), and 27% (95% CI 23–31%), respectively, for the diagnosis of DVT. A high PTP (score ≥ 3) had a sensitivity of 17% (95% CI 12–25%) and a specificity of 94% (95% CI 91–96%), with a negative predictive value of 82% (95% CI 78–85%) and a positive predictive value of 42% (95% CI 29–55%) for the diagnosis of DVT. The failure rate of the low probability score (< 1) to rule out DVT was 9.8% (95% CI 6.7–14.2%), and the efficiency was 38.5% (95% CI 34.8–42.3%).

When only proximal DVTs were considered, the AUC for the discriminatory accuracy of the Wells score was 0.75 ± 0.04; $p=0.0001$. Proximal DVT frequency in low-, moderate-, and high-pretest probability groups was 2.0%, 10.1%, and 23.6%, respectively ($p=0.0001$). A moderate/high PTP (score ≥ 1) had a sensitivity of 90% (95% CI 79–96%) and specificity of 41% (95% CI 37–45%), with negative and positive predictive values of 98% (95% CI 95–99%) and 12% (95% CI 9–15%), respectively, for the diagnosis of proximal DVT. A high PTP (score ≥ 3) had a sensitivity of 24% (95% CI 14–37%) and a specificity of 93% (95% CI 91–95%), with a negative predictive value of 93% (95% CI 91–95%) and a positive predictive value of 23% (95% CI 13–36%) for the diagnosis of proximal DVT. The failure rate of the low probability score (< 1) to rule out proximal DVT was 2.0% (95% CI 0.9–4.7%), and the efficiency was 38.5% (95% CI 34.8–42.3%).

When only isolated distal DVTs were considered, the AUC for the discriminatory accuracy of the Wells score was 0.58 ± 0.03, $p=0.012$. Isolated distal DVT frequency in low-, moderate-, and high-pretest probability groups was 7.8%, 14.2%, and 18.9%, respectively ($p=0.019$). A moderate/high PTP (score ≥ 1) had a sensitivity of 75% (95% CI 64–84%) and specificity of 40% (95% CI 36–45%), with negative and positive predictive values of 92% (95% CI 88–95%), and 15% (95% CI 12–19%), respectively, for the diagnosis of isolated distal DVT. A high PTP (score ≥ 3) had a sensitivity of 13% (95% CI 7–22%) and a specificity of 92% (95% CI 89–94%), with a negative predictive value of 88% (95% CI 86–91%) and a positive predictive value of 19% (95% CI 11–31%) for the diagnosis of isolated distal DVT.

Table 3 Prevalence of deep vein thrombosis (DVT) by pretest clinical probability risk classification

Pretest clinical probability	*n* (%)	Proximal DVT *n* (%)	IDDVT *n* (%)	All DVTs *n* (%)
> 3	19 (3.0)	5 (26.3)	5 (26.3)	10 (52.6)
3	34 (5.4)	7 (20.6)	5 (14.7)	12 (35.3)
2	156 (24.6)	26 (16.7)	22 (14.1)	48 (30.8)
1	181 (28.5)	8 (4.4)	26 (14.4)	34 (18.8)
0 or less	244 (38.5)	5 (2.0)	19 (7.8)	24 (9.8)
Total	634 (100)	51 (8.0)	77 (12.1)	128 (20.2)

IDDVT isolated distal deep vein thrombosis

Discussion

Our data show that, in hospitalized patients, isolated distal DVT is more prevalent than proximal DVT. The accuracy of the Wells score for proximal DVT is similar to that found in the outpatient validation studies.

Hospitalization is one of the most important factors influencing the risk of VTE [5, 12], even in our region [13]. In the Olmsted County, the overall VTE incidence rate was of 9.6 and 4.6 per 100 person-years for DVT [5]. In our series, DVT prevalence was 1.1% that is in line with the data from a large population of US medical patients, among whom 2.0% of all patients experienced a DVT during their hospitalization [14]. All these data suggest the hospital-related DVT is at least ten times more frequent than community DVT. Previous studies that included inpatients suggested that 80% of all diagnosed DVTs are proximal DVT and 20% are isolated distal DVT [8, 15]. We demonstrated that more than half DVTs in a hospitalized population are confined to the infra-popliteal veins of the lower limbs. The prevalence of DVT in hospitalized patients is higher than the prevalence of community-acquired DVT, and such difference is mainly due to an elevated prevalence of isolated distal DVT.

The Wells score was developed in ambulatory patients referred to a tertiary care center for a suspected first episode

of lower limb DVT [8, 16]. More recently, Wells and colleagues published a modified score, adding an item for previously documented DVT [17]. This modified Wells score has been validated in outpatients [17, 18]. When performed in inpatients, it did not appear to be particularly useful [19]. Recently, Silveira et al. [9] have shown that it performed only slightly better than chance for discrimination of risk for DVT in hospitalized patients, being 0.60 the AUC for the discriminatory accuracy of the Wells score for risk of proximal DVT. Our study shows that the AUC for the discriminatory accuracy of the Wells score for risk of all DVTs was 0.67, and this might be in line with the findings of Silveira et al. [9]. However, we found that 0.75 was the AUC for risk of proximal DVT and such result is much better in comparison with what was found by Silveira et al. It should be noted that we enrolled more patients with low PCP in comparison with the population of aforementioned study (38.5% vs. 10.6%, respectively); our population was older, and there were fewer patients with active cancer in comparison with the population of Silveira et al. [9]. Moreover, the frequency of patients from surgery wards was 20% in our study vs. 38% in the aforementioned study [9]. Such differences in the study population may, at least partially, explain the difference between the two studies. Our results are similar to the reported accuracy of the Wells score in outpatients. A meta-analysis on the value of clinical assessment in the diagnosis of DVT has demonstrated that sensitivity and specificity of the Wells score (high vs. intermediate and low threshold) were 0.56 and 0.88, respectively [20]. In our population, the sensitivity and specificity of the Wells score (high vs. intermediate and low threshold) for proximal DVT were 0.24 and 0.93, respectively. Regarding moderate/high vs. low PTP, sensitivity and specificity in the aforementioned meta-analysis were 0.89 and 0.47, respectively [20], and in our population were 0.90 and 0.41, respectively, for proximal DVT. Our series suggests that in hospitalized patients mainly in medical wards, Wells score for proximal DVT performs similarly to outpatients with suspected DVT.

We have already demonstrated that the Wells score poorly predicts isolated distal DVT in outpatients [21]. Other previous small studies enrolling less than 40 isolated distal DVTs showed a poor correlation between PTP and isolated distal DVT diagnosis [19, 22]. The present study confirms that the Wells rule has a low diagnostic accuracy for isolated distal DVT also in inpatients. In fact, the Wells score was developed mainly on patients with suspected proximal DVT, and the clinical benefit of diagnosing and treating isolated distal DVT is still a matter of controversy [23, 24].

We found that the Wells score failure rate of the low probability score (< 1) was much higher in our study compared with that in the original outpatient validation study (9.8% vs. 3.0%) [16]. When only proximal DVTs were considered, the failure rate was 2.0% and it is similar to that in aforementioned study [16]. The efficiency was slightly lower compared with that in the original study (39% vs. 55.5%) [16]. It has been clearly established for many years that even in patients with the lowest score, DVT cannot be excluded without adding D-dimer testing to the rule [6]. Our results confirm that low probability of the Wells score risk stratification is not sufficient to rule out DVT. However, our series suggests that some of the diagnostic strategies for proximal DVT recommended by current guidelines could apply even for inpatients. The utility of the Wells score lies in combining it with D-dimer to avoid unnecessary imaging, and we did not evaluate this aspect of management. It has been suggested that patients with a low clinical suspicion of acute VTE should not be treated with parenteral anticoagulants while awaiting the results of diagnostic tests, if test results are expected within 24 h [25]. In our study, whole-leg ultrasound was performed within 24 h and the failure rate for proximal DVT was low in patients with score < 1. Thus, our results suggest that in inpatients setting, the Wells score risk stratification may influence management decisions as starting anticoagulation while awaiting ultrasound results.

Some limitations of the present study should be acknowledged. No inter-observer variability was assessed for isolated distal DVT diagnosis and we did not follow up patients with negative whole-leg ultrasonography examination, but several studies have shown that anticoagulant therapy can be safely withheld after negative complete compression ultrasound without further testing [26–28] also in inpatients [28]. Since whole-leg ultrasound was performed only in symptomatic patients, our study does not provide information on the prevalence of asymptomatic DVT in this setting and the real prevalence of DVT in hospitalized patients may be underestimated. However, our service performs whole-leg ultrasound within 24 h from the request and routinely no patient is discharged when a DVT is suspected. We excluded patients who had symptom of DVT before hospital admission, but we cannot exclude to have enrolled some DVTs acquired before hospitalization. The study was conducted in a single academic institution and may not be representative of population in different types of hospitals.

In conclusion, isolated distal DVT is more frequent than proximal DVT in inpatient setting. The Wells score seems able to stratify for the risk of proximal DVT in inpatients acceptably well, whereas stratification for isolated distal DVT is poor.

Highlights

- Deep vein thrombosis (DVT) is an important cause of morbidity and mortality in hospitalized patients.
- A single-center cross-sectional study was conducted in a university hospital.

- Distal DVT is more frequent than proximal DVT in inpatient setting.
- The Wells score stratifies patients only for the risk of proximal DVT in the inpatient setting.

Funding None.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all patients.

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