

The Clinical Diagnosis of Deep Venous Thrombosis

Integrating Incidence, Risk Factors, and Symptoms and Signs

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Symptoms and clinical signs suggestive of deep venous thrombosis (DVT) are common and have numerous possible causes. Studies have shown that symptoms and clinical signs in themselves are inaccurate for the diagnosis of DVT. However, clinicians have other information at hand, such as data on risk factors for DVT, that may help improve their ability to predict a diagnosis of DVT in the individual patient. Epidemiological data on DVT incidence and risk factors were reviewed, as were published data on the accuracy of clinical diagnosis of DVT, with the use of both symptoms and signs in isolation and symptoms and signs combined with other clinical information in the form of clinical prediction indexes. Symptoms and clinical signs, when combined with other patient information such as the presence or absence of known risk factors for DVT, can improve clinical prediction considerably. Further study is needed to determine whether clinical prediction indexes have a role in improving the diagnostic process in patients with suspected DVT.

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Symptoms and clinical signs suggestive of deep venous thrombosis (DVT) are common in the general population and have numerous possible causes. With the advent of contrast venography as a means of objectively diagnosing DVT, it became evident that symptoms and clinical signs were extremely inaccurate for the diagnosis of DVT.¹ Studies during the last 30 years have shown that among symptomatic patients with suspected DVT referred by clinicians for diagnostic testing, the diagnosis is usually confirmed in only 20% to 40% of patients, a figure that has not changed with time.¹⁻³ Hence, 60% to 80% of referred patients do not have DVT but are nonetheless subjected to diagnostic testing.

There has been interest recently in the use of clinical prediction indexes to help physicians improve their estimates of diagnostic or prognostic outcomes.^{4,5} Clinical prediction indexes are usually derived from multivariate mathematical models, which are then simplified for use by clinicians in individual patients. Their use may improve the efficiency and accuracy of physicians' judgments. Accurate

clinical prediction indexes for DVT diagnosis could improve estimation of the pretest probability of DVT in the individual patient with leg symptoms. This, in turn, could help to direct the choice and interpretation of diagnostic tests and subsequent decision making regarding treatment, and could promote the rational and cost-effective use of these tests.

The aim of this article is to review the accuracy of clinical examination and of clinical prediction indexes for DVT diagnosis in symptomatic patients with suspected DVT. First, however, it is instructive to review the epidemiological data on DVT incidence and risk factors, because estimation of the probability of DVT is influenced by its incidence in the population from which the patient derives, which in turn is influenced by the prevalence of underlying risk factors for DVT in the same population.

INCIDENCE OF DVT

Methodological Difficulties

The true incidence of DVT in the population is difficult to assess. Autopsy studies have been of little use, since DVT in itself is not often fatal. Also, autopsy rates in general are low and overrepresent unusual cases. Most

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incidence studies have been conducted in hospitalized patients, which overestimates the general incidence for 2 main reasons: hospitalized patients are at higher risk for DVT (which will be illustrated) and, in many of these studies, screening tests were used to diagnose DVT in the absence of symptoms suggestive of DVT. It is uncertain how many of these subclinical DVTs would have become symptomatic and reached medical attention. Older community-based studies relied on clinical symptoms and signs to diagnose DVT, without objective testing. This was problematic because less than half of patients suspected of having DVT had the diagnosis confirmed when objective tests were performed.¹ Conversely, since symptoms can be vague or even absent, DVT may be underdiagnosed, especially among outpatients. Thus, clinical diagnosis may both overestimate and underestimate the true incidence. Incidence studies that relied solely on clinical diagnosis of DVT will not be reviewed here.

Incidence Studies

In the United States, data from Vital Statistics and the National Hospital Discharge survey based on hospital discharge diagnoses from 1970 through 1985 showed an age-adjusted rate for DVT of 79 per 100 000 and for pulmonary embolism (PE) of 51 per 100 000.⁶ It is not known how many of these were objectively verified with diagnostic testing. A community-wide study of patients in 16 short-stay hospitals in Worcester, Mass (catchment area of 400 000) retrospectively examined the incidence and case-fatality rates of DVT and PE during an 18-month period.⁷ Ascertainment of outcome was via *International Classification of Disease* codes that included most hospital-diagnosed venous thromboembolic conditions. Objective diagnosis was documented in 84% of cases with DVT codes and 61% of cases with PE codes. The annual incidence of DVT was 48 per 100 000, while the incidence of PE with or without DVT was 23 per 100 000. Rates were higher in men than women, and they increased with age. In-hospital case-fatality rates for DVT and PE were 5% and 23%, respectively. Since data from short-stay hos-

pitals only were examined, cases arising from other facilities and the general outpatient community were not considered. Anderson et al⁷ estimated that there are approximately 170 000 patients with first-time DVT and/or PE and 90 000 cases of recurrent DVT and/or PE treated in short-stay hospitals in the United States each year, resulting in a minimum of 13 000 deaths each year. By extrapolation, and taking into account the almost certain underestimation of the true incidence of venous thromboembolism, this likely represents 600 000 cases in the general population overall.

A similar survey examined the incidence of DVT in the region served by Malmö General Hospital in Malmö, Sweden, a population base of 281 000 people.⁸ This study also relied on hospital-based diagnoses and was oriented to symptomatic DVT, so it cannot be called a true population survey. However, venography was performed at only 1 department of 1 hospital, and the patient population included both inpatients and referred outpatients; hence, the figures for symptomatic DVT were likely quite accurate. The incidence of DVT was 160 cases per 100 000 per year, which included recurrent cases and cases associated with PE. Incidence rates increased with increasing age, but there was no difference in incidence between men and women.

Finally, in a population-based study of 855 men followed up prospectively from 50 to 80 years of age, the incidence of objectively confirmed DVT and PE was 182 and 205 per 100 000, respectively.⁹ The cumulative probability of these events increased with age, a trend that was also noted in a study of a random 5% sample of US Medicare claims during a 3-year period that identified all cases of DVT and PE in the elderly by means of *International Classification of Diseases* codes.¹⁰ Annual incidence rates of DVT were 180 per 100 000 at age 65 to 69 years, which increased to 310 per 100 000 at age 85 to 89 years.

Magnitude of the Problem

The studies already described considered mostly hospital-related cases. It is not possible from the data provided to accurately estimate the in-

cidence of DVT in the general population. However, these studies convincingly show that venous thromboembolic disease is a major health problem that affects all ages and that exacts considerable morbidity and mortality. It is also a costly problem. The total cost per patient for objective diagnosis and treatment of acute DVT has been estimated at approximately US \$4000,^{11,12} a figure that does not include costs incurred by the estimated 40% to 50% of patients with DVT who develop long-term sequelae such as the postphlebotic syndrome.¹³

RISK FACTORS FOR DVT

Virchow Triad

The cause of DVT can still best be conceptualized by the Virchow triad, described in 1860, which delineated the pathophysiological factors that alone or in combination promote the development of venous thrombosis, namely vein wall damage, stasis, and hypercoagulability.¹⁴ For example, knee surgery can result in vein wall damage. Prolonged immobility, via insufficient pumping of the calf muscles, can lead to stasis of venous blood. Certain cancers and inherited abnormalities of the intrinsic blood anticoagulant system can cause hypercoagulability. In some cases, DVT may be promoted by combinations of these factors, while in other cases, no risk factor for the development of DVT can be identified.

Methodological Considerations

Most studies on risk factors for DVT have been conducted in hospitalized patients, in whom the incidence of DVT and patient characteristics are more easily determined than in the community, since objective tests are more readily available and clinical and laboratory information is closer at hand. Much epidemiological information has been provided by the numerous published clinical trials on primary prevention of DVT in high-risk situations, which have prospectively assessed the risk of DVT in selected hospital populations with the use of strict diagnostic criteria. However, there has been difficulty in identi-

lying individual risk factors. Hospitalized patients are a disparate group with numerous potential risk factors for DVT, some iatrogenic, which may interact with or confound one another. Nonetheless, among hospitalized patients, certain populations have been identified as being at increased risk for DVT.

Surgical Patients

Orthopedic Surgery Patients. Patients undergoing major orthopedic surgery of the lower extremity represent the highest operative risk group for DVT and PE. Pooled data from prospective clinical trials of thromboprophylaxis that required mandatory postoperative venography showed that among patients in the untreated or placebo arms, there was a 51% incidence of DVT after total hip replacement, a 71% incidence after total knee replacement, and a 48% incidence after hip fracture surgery. The rates of proximal DVT in the above groups were 23% to 36%, 9% to 20%, and 17% to 36%, respectively, and of fatal PE, 3.4% to 6%, 0.7%, and 3.6% to 12.9%, respectively.¹⁵ The high rates in these patients reflect the presence of numerous underlying factors that promote the development of DVT, namely immobility, vessel injury, and activation of coagulation pathways.

Patients Undergoing General Abdominal and Other Surgery. Approximately 25% to 30% of patients undergoing elective major abdominal surgery show postoperative evidence of DVT when surveyed by serial fibrinogen I 125 leg scanning (FLS), a technique that is sensitive to calf and low proximal DVT but insensitive to high proximal DVT. In pooled data from trials in which DVT diagnosed by FLS was confirmed with venography, this incidence rate was closer to 20%.¹⁵ Patients undergoing surgery for malignant disease have higher DVT rates than those without malignant disease.¹⁵ Among patients undergoing urologic surgery, data collated from 7 trials documented a 41% incidence of DVT.¹⁶ Vascular surgery conferred a 23% to 34% risk of DVT, as shown by 2 prospective screening studies that used FLS.^{17,18} Deep venous thrombosis de-

veloped by FLS also occurred in 17.5% of patients after major gynecological surgery. Among these women, rates were highest in those with malignant neoplasms, a history of thrombophlebitis, or previous radiation therapy.¹⁹

Type of Anesthesia. For a given type of surgery, the type of anesthesia administered can influence the incidence of DVT. McKenzie²⁰ noted among patients with hip fracture undergoing orthopedic procedures that 75% who received general anesthesia developed venographically proved DVT, compared with 40% who received subarachnoid blocks. Similarly, for urologic procedures, a 12% rate of DVT was noted in patients undergoing retropubic prostatectomy who were randomly allocated to receive lumbar epidural analgesia, compared with 52% of those who received general anesthesia.²¹

Trauma Patients. Interpretation of the incidence literature in trauma patients is difficult because of the high proportion with hip or lower-extremity fractures and the overall heterogeneity of this group of patients. In a large prospective study of patients admitted to a regional trauma unit in Toronto,²² DVT was diagnosed by venography in 201 (57.6%) of 349 patients, only 3 of whom had suggestive clinical features. The rate of DVT was 69% in those with lower-extremity fractures, but there was still a 50% incidence in trauma patients whose injury involved only the chest, face, or abdomen. Independent risk factors for DVT among the study group were greater age, blood transfusion, surgery, fracture of the femur or tibia, and spinal cord injury.

Medical Patients

Overall, the risk of DVT in various categories of medical patients has been less well studied than for surgical patients.

Patients With Malignant Neoplasms. Trousseau, in 1865, first suggested the association between DVT and abdominal malignant neoplasms.²³ Since then, numerous studies have confirmed the association be-

tween venous thromboembolism and malignant neoplasms in general; however, precise rate estimates are not available. The risk is also increased among cancer patients undergoing active treatment with chemotherapy. A randomized clinical trial comparing 2 adjuvant chemotherapy regimens clearly showed that all thrombotic events occurred during months that the patients were receiving chemotherapy.²⁴

Myocardial Infarction and Ischemic Stroke. As diagnosed by FLS, the overall incidence of DVT was approximately 24% in patients with myocardial infarction and 42% in the weak or paralyzed limb of patients with stroke. These rates are derived from the pooled placebo arms of trials evaluating preventive antithrombotic therapy in these patient groups.¹⁵

Other Groups at Risk for DVT

Other important risk factors for DVT affecting both hospitalized and ambulatory patients have been recognized.

Age. Deep venous thrombosis is extremely rare in children. Its incidence increases sharply after age 40 years.⁷⁻⁹ Age, however, may not be an independent risk factor for DVT, since comorbid medical and surgical conditions also increase with age.

Immobility. The association between immobility, its duration, and venous thromboembolism has been confirmed in a number of studies. An autopsy study of 253 patients demonstrated DVT in 15% of patients immobilized for less than 1 week, compared with 80% in those with longer periods of immobility.²⁵ Kierkegaard et al²⁶ found that from the second to the eighth day of immobility, 13% of bedridden, non-surgical patients developed DVT diagnosed by daily FLS. More than half of these developed by the fifth hospital day. Hence, even short periods of immobility increase risk.²⁶

Pregnancy and Postpartum. Pregnancy and postpartum are high-risk periods for DVT. Interpretation of existing data in this area is made difficult by the small number of patients

studied, an overreliance on clinical diagnosis because of the adverse effects of radiation on the developing fetus, and varying definitions of the peripartum period. One large retrospective study using limited contrast venography in pregnant women found 11 documented cases of DVT among 14869 women, 9 of which occurred post partum, which represents antepartum and postpartum rates of 10 and 61 per 100 000, respectively.²⁷ In a prospective study during pregnancy using objective diagnostic criteria, the occurrence of 60 episodes of DVT were equally distributed during the 3 trimesters.²⁸

The risk of pregnancy-related venous thromboembolism is much higher in women with inherited thrombophilic disorders, such as activated protein C resistance and deficiencies of protein C, protein S, and antithrombin III, compared with women without these disorders.^{29,30}

Oral Contraception and Hormone Replacement Therapy. Although early studies had various methodological flaws, mostly related to reliance on clinical signs to diagnose DVT, the weight of the evidence points to a 2- to 8-fold increased risk for DVT in women using oral contraceptives.^{31,32} A recent matched case-control study of 471 women with venous thromboembolism and 1772 controls found an odds ratio of 4.0 with use of oral contraceptives vs nonuse, and a 4-fold probability of death from venous thromboembolism.³³ Recent studies showed a 2- to 4-fold increased risk for DVT in women who used hormone replacement therapy compared with those who did not.^{34,35}

Previous DVT. Objectively confirmed previous DVT is associated with an increased risk of future DVT, especially in high-risk settings such as surgery, where studies with FLS have shown a 2- to 3-fold increased risk.³⁶ This risk likely results from persisting venous obstruction and valve damage from the previous DVT, as well as perpetuation of individual risk factors that promoted the development of the first episode of DVT. Of interest, most prevention and treatment studies have excluded such patients, presumably because they

represent a group at different risk than those without previous DVT, and because diagnostic tests do not perform as reliably as a result of altered venous anatomy and function.

Blood Abnormalities. Congenital deficiencies of protein C, protein S, and antithrombin III have been described frequently in association with recurrent DVT and DVT occurring at a young age or in unusual locations. However, the risk of DVT in individuals with these deficiencies has yet to be clarified. Overall, since these deficiencies are rare, DVT in the general population is rarely associated with these disorders. Activated protein C resistance is the most common inherited cause of DVT. It is usually caused by a mutation that alters the binding site of factor V for activated protein C (factor V Leiden) and occurs in 5% of the general population and in 20% to 40% of unselected patients with DVT.³⁷ Other blood abnormalities that result in an increased risk of DVT include the lupus anticoagulant, hyperhomocysteinemia, dysplasminogenemias, and dysfibrinogenemias.^{38,39}

Risk Factors in Combination. The presence of more than 1 risk factor in the individual patient is not uncommon and may lead to additive or even multiplicative risk for DVT. For example, the use of oral contraceptives augments 4-fold the risk for DVT associated with the factor V Leiden mutation.⁴⁰

Other Risks. A number of other links have been made in the literature between certain clinical factors and the risk for DVT, for which sound data on causal and/or independent association are not available. These include obesity, varicose veins, infection, inflammatory bowel disease, nephrotic syndrome, polycythemia, paroxysmal nocturnal hemoglobinemia, and Behçet disease.

IMPORTANCE OF ACCURATE DIAGNOSIS OF DVT

Accurate and timely diagnosis and treatment of DVT are essential. Early treatment of DVT with anticoagulants has been demonstrated to (1) reduce the incidence of pulmonary em-

bolism and its associated mortality, (2) relieve acute symptoms in the leg, and (3) prevent extension of DVT from calf veins to more proximal veins.^{41,42} Rapid achievement of therapeutic anticoagulation⁴³ and ensuring an adequate duration of treatment (eg, 3-6 months) prevents early recurrence of DVT⁴⁴ and may decrease the incidence of the postphlebotic syndrome, probably by limiting the extent of vein wall damage. Failure to diagnose and treat DVT can lead to postphlebotic syndrome, chronic pulmonary thromboembolic disease, and pulmonary hypertension.

As important as diagnosing DVT in patients with the disease is correctly identifying those who do not have DVT. The implication of a diagnosis of DVT is generally a 5- to 7-day course of parenteral heparin (either intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin) followed by oral anticoagulation for at least 6 to 12 weeks and sometimes for life. Parenteral heparin anticoagulation is associated with a 5% risk of bleeding.⁴⁵ Oral anticoagulation is associated with a 5% to 20% risk of bleeding⁴⁵ and requires frequent blood test monitoring and clinic visits. Also, because previous DVT is widely known to be an important risk factor for future DVT, falsely labeling a patient with this diagnosis can result in needless anxiety and unnecessary tests each time leg symptoms occur. Furthermore, a false-positive diagnosis in women of childbearing age has special implications, for it is considered prudent to offer thromboprophylaxis with injected heparin during pregnancy to women who have had DVT. This is inconvenient and uncomfortable; it can also be associated with short-term complications, such as bleeding, and long-term complications, such as osteoporosis.⁴⁶ One can appreciate, therefore, that correct classification of patients with symptoms of DVT is crucial.

CLINICAL PREDICTION OF DVT BY MEANS OF SYMPTOMS AND SIGNS

Because of the unavailability of safe and reliable diagnostic tests, until the 1960s DVT was diagnosed clini-

cally, with poor accuracy. With the advent of contrast venography, Haeger⁷ showed in 1969 that the venous system was completely normal in 46% of patients receiving treatment for DVT. Conversely, autopsy studies have demonstrated consistent underdiagnosis of DVT. In 1 series, among 195 patients who died of autopsy-proved PE, 162 (83.1%) had coexisting DVT. In only one fifth of these was DVT suspected ante mortem, and only 3.1% had an objective test to confirm the diagnosis.⁴⁷ Hence, clinical overdiagnosis and underdiagnosis of DVT are both recognized problems, leading to a consensus in the medical literature that the clinical diagnosis of DVT is inaccurate and cost-ineffective.

Common Symptoms and Signs

Typical symptoms of DVT are pain, warmth, redness, and swelling of the lower extremity. These symptoms may occur in various combinations and commonly evolve over a few days, but both more rapid (over hours) and more chronic (over weeks) evolution can occur. Symptoms may also be absent, as shown by autopsy studies and surveillance studies in high-risk surgical patients.

Signs of DVT on physical examination include tenderness, warmth, erythema, cyanosis, edema, palpable cord (a palpable thrombotic vein), superficial venous dilation, and signs named for the physicians who first described them. The Homans sign, the best known of these, is present if sudden dorsiflexion of the ankle joint with the knee flexed to 30° produces discomfort in the upper part of the calf. The Louvel sign denotes worsening of pain along the course of a thrombotic vein by coughing or sneezing. The Lowenberg sign is present if, after inflation of a sphygmomanometer cuff around each calf, pain is experienced in the affected calf at a lower pressure than in the unaffected one.⁴⁸

Differential Diagnosis

The differential diagnosis of a swollen, painful lower extremity is extensive and includes cellulitis, arthritis, neuropathy, arterial occlusion,

lymphedema, ruptured Baker cyst, muscle tear, varicose veins, superficial thrombophlebitis, and chronic venous insufficiency. Some of these can be easily diagnosed at the time of initial examination, avoiding further testing, whereas others can be inferred only after DVT has been objectively excluded. In a follow-up study of 87 consecutive patients who were clinically suspected to have DVT but who had normal venogram results, the final cause of their symptoms was muscle related in 35 patients (40%), cellulitis in 3 (3%), leg swelling in a paralyzed leg in 8 (9%), venous reflux in 6 (8%), lymphatic in 6 (8%), Baker cyst in 4 (5%), abnormality of the knee in 2 (2%), and unknown in 23 (26%).⁴⁹

Methodological Considerations

A number of studies have examined the accuracy of symptoms and signs in diagnosing DVT. Various methodological flaws affect the interpretation of some of these studies. These include inadequate description of selection criteria, highly selected populations with poor generalizability, lack of information regarding blinding of the clinician to the patient's ultimate diagnosis, use of retrospective clinical data gathered from charts after DVT was diagnosed, failure to provide criteria for positive results of a diagnostic test, and inadequate description of guidelines used to determine the presence or absence of clinical signs, which in themselves are often poorly defined and have untested reliability. Nevertheless, it is possible from the more methodologically robust studies to estimate the sensitivities and specificities of various clinical symptoms and signs for the diagnosis of DVT. The specificities of many of these are low by design, since the primary criterion for entry into these studies was clinical suspicion of DVT.

Accuracy of Individual Symptoms and Signs

Haeger¹ studied 72 consecutive patients examined at his vascular clinic with suspected DVT. All patients were examined by 1 or 2 experienced vascular surgeons, who documented the presence or absence of

selected symptoms and signs before the patient had contrast venography. Patients with 4 or more positive signs were classified as "highly suspected." Overall, 46% of the sample (33 of 72 patients) had DVT proved by contrast venography. Among the individual signs, calf pain and tenderness had the highest sensitivities (0.90 and 0.84, respectively), whereas superficial venous dilation and Lowenberg sign had the highest specificities (0.82 and 0.85, respectively). No individual sign had both high sensitivity and specificity, and even in the highly suspected group, positive and negative predictive accuracies for DVT were 0.55 and 0.66, respectively. Haeger concluded that "clinical signs cannot be trusted" to diagnose DVT.

A later study by Richards and colleagues⁵⁰ prospectively compared the diagnostic accuracy of 4 noninvasive techniques, including physical examination, for the diagnosis of DVT. The study population consisted of 85 unselected patients referred for clinically suspected DVT or PE. Clear-cut criteria for positive contrast venography were provided. All physicians performing noninvasive examinations and those performing and interpreting contrast venography were blinded to each other's findings. After exclusion of technically inadequate venograms, 60 DVTs were found among 150 extremities, a prevalence of 40.0%. With the exclusion of 3 of 11 physical examination maneuvers that are not well known and rarely used (Moses, Ramirez, and Peabody signs), leg tenderness had the highest sensitivity (0.62). Difference in calf circumference, Homans sign, Lowenberg sign, warmth, superficial venous dilation, and palpable cord all had specificities of greater than 0.80, with palpable cord being both the most highly specific (0.98) and poorly sensitive (0.10) sign. However, because of the 40.0% DVT prevalence, the positive predictive accuracy of these signs was poor. Overall, all signs, whether taken individually or in combination, had poor predictive accuracy.

Sandler and colleagues⁵¹ studied 50 patients with suspected DVT referred by various physi-

cians, mostly general practitioners. A standardized clinical examination was carried out in each patient. The reference test was contrast venography, with well-described criteria for positive results of a study and independent review by 2 radiologists. It was not stated whether those performing the clinical examination were blinded to the diagnosis. In addition to sensitivity and specificity, the κ index for each clinical feature was reported to correct for chance agreement. Deep venous thrombosis was diagnosed by contrast venography in 29 (58%) of patients, a higher prevalence than that noted in most studies of symptomatic patients. Pain, edema, and temperature difference did not have good specificity, but they appeared to be reasonably sensitive (0.86, 0.97, and 0.72, respectively). However, after taking into account chance agreement, only the sensitivity for edema remained robust (0.78). There was a large overlap of differences in leg circumference between those with and those without thrombosis. If clinical signs alone had been used to make the diagnosis of DVT, 42% of the patients would have received anticoagulation unnecessarily.

Hence, symptoms and signs in themselves do not appear to be useful in discriminating between patients with and without DVT. The overall poor specificities and positive predictive accuracies of the various symptoms and signs are not surprising, considering that patients are referred for testing because of these features and that the prevalence of diagnosed DVT in symptomatic patients is typically only 20% to 40%. The poor sensitivities of individual factors could indicate that combinations of these factors would be more helpful in predicting DVT. In any case, focusing solely on symptoms and signs is artificial, since clinicians typically have other data at hand that aid clinical judgment when assessing the individual patient, namely the presence or absence of risk factors such as demographic features, concurrent disease status, medical and surgical history, and medication use. Combining these data in the form of clinical prediction indexes may have better predictive accuracy for the di-

agnosis of DVT than do individual symptoms and signs.

CLINICAL PREDICTION INDEXES FOR DVT

Methodological Considerations

Referral of patients with suspected DVT for diagnostic testing is determined by clinical suspicion, namely the use and interpretation of clinical findings to predict the likelihood of DVT. Clinicians traditionally make diagnostic predictions informally and nonquantitatively, using some combination of clinical experience and published evidence.⁵² Studies have shown that clinicians generally overestimate the probability of disease,⁵³ as evidenced by the 60% to 80% of patients with suspected DVT who have normal results of objective tests.

Clinical prediction indexes or rules are statistical models that quantitatively estimate the probability of a diagnostic outcome on the basis of data procured from numerous patients. Methodological standards have been described for the development and validation of clinical prediction indexes.^{4,5,52} The definition of the event to be predicted should be clear and free of ascertainment bias. The predictive findings should be precisely defined, easily available to the clinician, and ideally have proved reliability. Assessment of outcome and predictive findings should be blinded, and both should be clinically relevant. The patient selection process should be described. The population should include a wide spectrum of patients and should be representative of the clinical practice in which the prediction index is to be used. The margin of error in the point estimate of probability and the misclassification rate should be provided as a measure of the accuracy of the prediction index. Cross-validation techniques or, ideally, testing of the prediction index prospectively in a new clinical setting should be done. The mathematical techniques for developing the prediction index should be identified. Finally, the ultimate test of the effectiveness of a clinical prediction index is its effect on patient care, such that even if the above

methodological standards have been met, a prediction index may have little clinical utility.

Published Clinical Prediction Indexes for DVT

Four published prediction indexes have been developed for use in symptomatic patients who are examined because of suspected DVT. Prediction indexes that have been developed specifically for use in asymptomatic high-risk surgical patients will not be reviewed here.

Vine et al⁵⁴ in 1981 retrospectively studied 150 consecutive patients who underwent contrast venography, one third of whom had DVT. Various elements of the clinical history, examination, and laboratory results were collected via retrospective chart review, and likelihood ratios for each variable were calculated. Nine risk factors (malignant neoplasm, recent blood transfusion, recent surgery, congestive heart failure, immobilization, infection, erythema of legs, anemia, and leg swelling) and 4 protective factors (normal cholesterol levels, leg operation, outpatient, and female sex) were identified. Receiver operating characteristic curves were constructed to assess the additive contribution to the risk for DVT of the baseline variables with the highest likelihood ratios. The authors recommended that clinicians select what they believe to be the best cutoff point for their own patient populations. Weaknesses of this study include inadequate information on patient selection, retrospective data collection without information on the amount of missing data, receiver operating characteristic curves developed for this patient population only and not validated in other populations, and inability of the average clinician to use these curves in daily practice.

Landefeld et al⁵⁵ also used retrospective methods to identify clinical findings that might be useful in estimating the probability of acute proximal DVT in a population of 355 consecutive patients who underwent contrast venography during a 2-year period and for whom medical records were available.⁵⁵ Data on 76 clinical items, including symptoms, signs, comorbid conditions,

and laboratory tests, were gathered retrospectively from chart review. To avoid ascertainment bias, ie, the chance that knowledge of venographic results would affect the observation or recording of data, an attempt was made to gather only data recorded before venography was performed. Venogrants were normal in 185 patients (52.1%), showed proximal DVT in 96 patients (27.0%), and were equivocal in 74 patients (20.8%), ie, were either nondiagnostic because of inadequate filling of the deep veins (45 patients) or showed only calf DVT (29 patients).

A derivation group and a validation group were randomly selected from within the study population. Linear discriminant analysis was used to identify independent predictors of the venographic diagnosis. Swelling above and below the knee, recent immobility, cancer, and fever were independent predictors of proximal DVT. Patients in the validation group were classified according to the number of independent predictors present. The risk for proximal DVT was 5% among patients with none of the 5 predictors, 15% among patients with 1 predictor, 50% in those with 2 predictors, and 30% in patients with 3 or more predictors. In patients with at least 1 of the 5 predictors, the sensitivity of the index was 0.97 and the specificity was 0.26. In patients with more than 3 predictors, sensitivity fell to 0.20 but specificity rose to 0.85.

Although this index would be easy to apply in clinical practice, there were methodological flaws in its development and validation. Symptoms and signs were recorded as "present" or "not known to be present," so that an absent finding was treated in the same manner as one not recorded. This could have underestimated the diagnostic value of certain findings. Data were collected retrospectively, and despite the authors' assurances, ascertainment bias likely occurred. Variables were considered for multivariate analysis primarily on the basis of a *P* value cutoff point, without consideration of clinical relevance for those variables not achieving this cutoff point. Deep venous thrombosis was more likely in those with 2 predictors than in those with 3 or more predictors, which is not logical and could result from peculiari-

ties in the data resulting from small patient numbers or from a general lack of validity of this index. Also, in patients with 2 or more predictors, the probability of DVT was 42%, indicating that this index adds little to predictions based simply on the prior probability of DVT in symptomatic patients, ie, prevalence of 20% to 40%. Finally, the index has yet to be validated in other patient populations who may be at different risk for DVT than Landefeld and coworkers' study population.

The third index for DVT prediction was that published by Wells and colleagues.⁵⁶ Before the study the authors developed a clinical model, based on literature review and clinical expertise, that stratified patients into 3 pretest probability categories for DVT: high, moderate, and low. The study was conducted at 3 centers in Canada and Italy. Those eligible for participation were outpatients with clinically suspected DVT who had had symptoms for less than 60 days and who had no obvious alternative cause for their symptoms. Patients were excluded if they had previous venous thromboembolism, could not tolerate contrast dye, had suspected PE, were pregnant, or were taking anticoagulants. Deep venous thrombosis was diagnosed by contrast venography, which was interpreted by readers blinded to the patient's clinical history. Of 887 consecutive patients, 358 were ineligible, mostly because of previous DVT, alternative diagnosis, or inability to perform or evaluate contrast venography.

Table 1 shows the clinical model used. The major and minor points include both risk factors for

DVT and clinical signs of DVT, which more closely emulates the process of clinical judgment than does consideration of either of these in isolation.

With the use of the model, the study patients were assigned to a clinical probability group before undergoing contrast venography. Among the 529 study patients, 135 (25.5%) had abnormal results of venograms. The probability of DVT among patients in the high, moderate, and low clinical probability groups was 85%, 33%, and 5%, respectively. Combining the clinical probability rating with noninvasive diagnostic testing allowed more precise estimation of the predictive accuracy of noninvasive testing (here, ultrasonography) for the diagnosis of DVT, such that the positive predictive accuracy of abnormal results of an ultrasound scan was 100%, 96%, and 63% in the high, moderate, and low clinical probability groups, respectively, and the negative predictive accuracy of normal results of an ultrasound scan was 98%, 84%, and 68% in the low, moderate, and high clinical probability groups, respectively.

The accuracy of the clinical model was similar in all 3 hospital centers despite differences in DVT prevalence in the centers. The model was found to have excellent interobserver reliability. It uses readily available data and could be combined with noninvasive testing to improve the efficiency of the diagnostic process in patients with DVT, especially in cases where pretest probabilities and noninvasive test results are discordant. The authors

Table 1. Original Clinical Model for Predicting DVT*

Major Points	Minor Points
Active cancer	Recent trauma to symptomatic leg
Paralysis, paresis, or recent cast of lower extremities	Pitting edema in symptomatic leg
Recent immobilization or surgery	Dilated superficial veins in symptomatic leg
Tenderness along deep vein distribution	Hospitalization in last 6 mo
Swollen thigh and calf (measured)	Erythema
Strong family history of DVT	

* Pretest probability of DVT is scored as follows: high probability: 3 or more major points present, or 2 or more major and 2 or more minor points present, without an alternative diagnosis; low probability: 1 major point and 2 or fewer minor points and an alternative diagnosis, or 1 major point and 1 or fewer minor points and no alternative diagnosis, or 3 or fewer minor but no major points and an alternative diagnosis; or 2 or fewer minor points but no major points and no alternative diagnosis; and moderate probability: all other combinations. Adapted from Wells et al.⁵⁶ DVT indicates deep venous thrombosis.

suggested that practical use of the clinical model in combination with ultrasonography could decrease the number of inaccurate diagnoses if venography, the criterion standard but more invasive test, were done only when the ultrasound result and clinical probability estimate were discordant.

Wells et al⁵⁷ further tested the practicality of their model in a second study, in which they first refined and simplified the clinical model by means of logistic regression analysis of the original data. Each of the 9 clinical features that were found to independently predict DVT was assigned an integer value, the sum of which provided a summary score for each patient that categorized patients as being at low, moderate, or high risk for DVT (Table 2). They then assessed its value in clinical management by applying the model prospectively to 593 patients with suspected DVT to estimate pretest probability of DVT. Frequency of DVT among patients assigned high, moderate, and low pretest probability was 74.6%, 16.6%, and 3.0%, respectively. Wells et al showed that it was safe and feasible to use a single normal result of a noninvasive test (ultrasound) to exclude DVT in the low-probability group, and abnormal results of an ultrasound scan to rule in DVT in the high-probability group. For patients with moderate pretest probability of DVT, the strategy used and shown to be safe was abnormal results of an ultrasound scan to rule

in DVT and normal results of an ultrasound scan on 2 tests, 1 week apart, to rule out DVT.

Potential limitations of the Wells et al index are that other clinical risk factors not included in the model could also be useful in predicting DVT, and its accuracy in patient groups excluded from the study (eg, recurrent DVT, suspected coexisting PE) cannot be estimated. Nonetheless, Wells et al demonstrated that the use of a clinical model for DVT prediction could have a favorable impact on patient care and resource utilization. Its ultimate utility can be assessed only after prospective validation of the model on other populations.

CONCLUSIONS

Deep venous thrombosis is a condition with high incidence and important morbidity and mortality. Many patient characteristics that increase the risk for DVT have been identified. Nevertheless, clinicians, using clinical judgment, do not accurately predict the presence or absence of DVT in patients with suspected DVT, as shown by the 20% to 40% abnormal test result rate (and corresponding 60%-80% normal test result rate) in patients referred for diagnostic testing for DVT. Individual symptoms and signs in isolation are inaccurate for the diagnosis of DVT. There are 4 published clinical prediction indexes for DVT. None replaces the need for diagnostic testing in the individual patient with suspected DVT. Of the 4, however, the revised index developed by Wells and colleagues was methodologically the strongest and has the most potential to be useful, in addition to diagnostic testing, in estimating the probability of DVT in the individual patient with suspected DVT. Future testing of the use of this index in a variety of clinical practice settings will establish whether it has an impact on physicians' practices and, ultimately, patient care and outcomes, which is the definitive objective of any clinical prediction index.

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Table 2. Revised Prediction Model*

Clinical Feature	Score
Active cancer	1
Paralysis, recent plaster cast	1
Recent immobilization or major surgery	1
Tenderness along deep veins	1
Swelling of entire leg	1
>3-cm difference in calf circumference compared with other leg	1
Pitting edema	1
Collateral superficial veins	1
Alternative diagnosis likely	-2

* Pretest probability of deep venous thrombosis is scored as follows: high probability, ≥ 3 ; moderate probability, 1-2; and low probability, ≤ 0 . Adapted from Wells et al.⁵⁷

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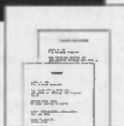
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