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Address: 1 Kraljice Natalije Street, 11000 Belgrade, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

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Original Article / Оригинални рад

Dragan Marković[1,2], Dragan Vasić[1,2,†], Jelena Bašić[3], Slobodan Tanasković[1,4], Slobodan Cvetković[1,2], Zoran Rančić[5,6]

Sensitivity and specificity of D-dimer tests comparing to the ultrasound examination of deep vein thrombosis

Компарација *D-dimer* теста са ултразвучним прегледом код дијагностике дубоке венске тромбозе

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Clinical Centre of Serbia, Clinic for Vascular and Endovascular Surgery, Belgrade, Serbia;
[3]Rudolfstiftung, Department of Cardiology, Vienna, Austria;
[4]Institute for Cardiovascular Diseases "Dedinje", Clinic for Vascular Surgery, Belgrade, Serbia;
[5]University Hospital Zurich, Department of Cardiovascular Surgery, Zurich, Switzerland;
[6]University of Zurich, Faculty of Medicine, Zurich, Switzerland

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†**Correspondence to:**
Dragan VASIĆ
Clinic for Vascular and Endovascular Surgery, Clinical Centre of Serbia
Koste Todorovica 8
11000 Belgrade, Serbia
dr_dragan_vasic@yahoo.com

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SUMMARY

Introduction/Objective Untreated deep vein thrombosis (DVT) is associated with a high risk of pulmonary embolism (PE) and false diagnosis of DVT results in unnecessary anticoagulant therapy, with a risk of bleeding. Accurate diagnosis of DVT and prompt therapy are essential to reduce the risk of thromboembolic complications. The aim of our study was to evaluate the sensitivity and specificity of three D-dimer tests (DD PLUS, HemosIL and VIDAS) comparing to compression ultrasonography examination.

Methods We have observed 350 patients, some with different risk factors. The patients have undergone through the same protocol (evaluation of patient's history, physical examination and D-dimer testing) and compression ultrasonography (CUS) was used as reference for all patients. According to Wells score patients have been divided in groups with low, moderate and high pretest probability (PTP).

Results The most of the examined patients were with moderate PTP. The CUS has showed that there was the highest number of examined patients without DVT. The most of the examined patients with positive CUS finding had proximal - iliac and femoral DVT. VIDAS test was positive in the highest percent in the group of patients with CUS documented thrombosis.

Conclusion All three D-dimer tests (DD PLUS, HemosIL i VIDAS) used in our study were with similar sensitivity and specificity. However, VIDAS test had higher levels of positive and negative predictive values comparing to the others. The comparison of the three D-dimer tests by ROC curve has showed that the highest overall statistical accuracy of all three D-dimer tests had VIDAS test.

Keywords: D-dimer test; compression ultrasonography; deep vein thrombosis

САЖЕТАК

Увод/Циљ Нелечена дубока венска тромбоза (ДВТ) је повезана са увећаним ризиком плућне емболије (ПЕ), а погрешно дијагностикована ДВТ доводи до сувишне антикоагулационе терапије и тако до повећаног ризика крварења. Тачна дијагностика и брза терапија ДВТ су круцијалне за редукцију ризика од тромбоемболичких компликација. Циљ наше студије је да процени сензитивност и специфичност три *D-dimer* теста (*DD PLUS*, *HemosIL* и *VIDAS*) у поређењу са ултразвучним испитивањем.

Методе У студију је било укључено 350 пацијената за различитим факторима ризика. Пацијенти су подвргнути истом протоколу (евалуација историје пацијента, физички преглед и контрола D-dimera), а ултразвучни преглед (УЗ) је коришћен као акредитив за све пацијенте.

Резултати Пацијенти су подељени по Велсовој скали у групе са ниском, средњом и високом предтест вероватноћом (претест пробабилиту ПТП). Већина прегледаних пацијената је било у групи са средњом ПТП. На УЗ је показано да највећи број пацијената није имао ДВТ. Већина пацијената са позитивним УЗ прегледом је имало проксималну – илијачну или феморалну ДВТ. *VIDAS* тест је у највећем проценту био позитиван у групи пацијената са доказаном ДВТ на УЗ. Поређење сва три D-dimer теста на *ROC* криви је показало највишу статистичку тачност VIDAS теста.

Закључак Сва три *D-dimer* теста која смо користили у нашој студији су имала сличне вредности сензитивности и специфичности, с тим сто је *VIDAS* тест имао виши ниво позитивне и негативне предиктивне вредности него *DD PLUS* и *HemosIL* тестови.

Кључне речи: *D-dimer* тест; компресивна ултрасонографија; дубока венска тромбоза

INTRODUCTION

Venous thromboembolism (VTE) is a common disorder associated with significant morbidity and mortality, with annual incidence in developed countries of 1 in 1000 [1].

That might be a problem, because untreated deep vein thrombosis (DVT) is associated with a high risk of pulmonary embolism (PE) and false diagnosis of DVT results in unnecessary anticoagulant therapy, with increased risk of bleeding. Accurate diagnosis of DVT and prompt therapy are essential to reduce the risk of thromboembolic complications. DVT also predisposes patients to post-thrombotic or post-phlebitic syndrome in 40-75% cases. The lower extremity DVT is responsible for 90-95% of PEs [2, 3].

In the past, contrast venography has been the gold standard for the diagnosis of DVT, but nowadays it has been replaced in most centers by color duplex ultrasonography. Venography is invasive and associated with small, but significant risk of complications [4].

The recommended protocol for the diagnosis of DVT consists of:

1. Wells score used for diagnosing DVT [5],
2. D-dimer assay for DVT and
3. Compression ultrasonography (CUS).

A careful history has to be taken considering risk factors. Physical examination is inadequate for establishing the diagnosis of VTE. In recent years, usage of D-dimer tests has been increased because testing is fast and non-invasive [6, 7]. The fragments of the disintegrating fibrin in the clot are fibrin degradation products (FDP). One of the FDPs produced is D-dimer, which consists of variously sized pieces of cross-linked fibrin. D-dimer levels are normally very low in the blood and concentrations are raised by thrombolysis. D-dimer tests generally have a high negative predictive value (NPV) and should not be used in isolation as screening tests. Therefore they are often used in conjunction with clinical probability scoring or CUS to reduce the need for further imaging.

There are four types of D-dimer assays commercially available: enzyme linked immunosorbent assay (ELISA), latex agglutination assay, whole-blood agglutination assay (SimpliRED) and immunochromatographictest (Simplify). Many quantitative latex agglutination and ELISA tests are available and the conventional ELISA is considered to be the gold standard for determination of D-dimer concentration.

CUS, due to its high sensitivity, specificity and reproducibility, has replaced venography as the most widely used test in the evaluation of this disease. In symptomatic patients, CUS has shown to be highly specific and sensitive for both proximal and distal DVT. The sensitivity has ranged from 90 to 100% for the diagnosis of symptomatic deep vein thrombosis. The specificity has ranged from 95 to 100%. In high-risk asymptomatic patients it has sensitivity ranged from 50-80% and specificity ranged from 95-100%.The safety, availability and well-documented accuracy of this technique justify its widespread use [8, 9].

D-dimer tests should not be used as stand-alone tests nor are they useful in situations of concurrent anticoagulant use, malignancies, post-surgery, pregnancy or severe infections. Problem can occur, as well, because 30% patients with PE will have normal D-dimer. The aim of our study was to evaluate the sensitivity and specificity of three D-dimer tests (DD PLUS, HemosIL and VIDAS) comparing to compression ultrasonography examination.

METHODS

This study has been performed over the June 2016 - October 2017 period at the Clinic for vascular and endovascular surgery, Clinical Centre of Serbia (Belgrade, Serbia).

All the patients have undergone through the same protocol that consisted of patient's history evaluation and physical examination, as well as, D-dimer testing as a second step. Finally, compression ultrasonography of the symptomatic leg was used as reference test in all patients.

Physicians in Vascular department filled in a questionnaire (modified Wells score) comprising details of history (risk factors) and physical examination (clinical signs). Pretest probability score models for predicting the probability of DVT, based on history and examination, were used in order to help clinicians to improve the accuracy of diagnosis of DVT (Table 1).

According to Wells score all patients have been divided in three groups: patients with a score 0 or less than 0 had low, patients with a score one or two were considerate as moderate and patients with score that equals 3 or more were with high pretest probability [5].

Three D-dimer assays were used: DD PLUS - a latex-enhanced immunoturbodimetric assay (Dade-Behring, Marburg, Germany) on the BCT analyzer, HemosIL - a latex enhanced immunoassay (Instrumentation laboratory, Milan, Italy) on the ACLTM 7000 analyzer and VIDAS (ELISA) DD Exclusion (DD2) (bioMérieux, Marcy L'Etoile, France) on the VIDAS analyzer. D-dimer tests were performed within an hour of admission to the vascular ambulance. D-dimer test was considered positive if the values were >149-196 μg/L for DD PLUS, >268 μg/L for HemosIL and >650-676 μg/L for VIDAS test.

Compression ultrasonography of the veins of the symptomatic leg was used as reference test in all patients. All examinations were performed on a single ultrasoundmachine (Siemens-Acuson Antares), using a linear array 7 MHz scan head (7540) with standardized image settings, including resolutionmode, depth of field, gain, and transmit focus. CUS examinations were made according to a standardized protocol and report form, performed within 3 hours of admission to the vascular ambulance. Patients were classified as DVT positive if they had DVT confirmed with CUS or as DVT negative if they had no CUS confirmed DVT. Patients with unclear CUS findings were excluded from the data analysis. The results of the D-dimer assay were unknown to the ultrasonographer.

Data analysis was assessed using statistical evaluation in addition to various descriptive and analytic statistical methods (T-test, χ^2 test, McNemar's test and others).

RESULTS

We have observed 350 patients, 168 male and 182 female. Average age of our patients was 62.5 ±8.4 years (range, 18-85 years).

Several risk factors were present in our patients with different frequency. Malignant diseases were previously diagnosed in 24 patients (6.8%) that were included in our study (active cancer, either previously surgically treated, on chemo- or radio-therapy). There were 6 female patients with gynecologic cancers (cervical, ovarian, uterine, vaginal and vulvar), 5 patients with cancer of gastrointestinal tract and liver, 4 patients with leukaemias and lymphomas and 2 female patients with breast carcinoma. Previous episodes of VTE had 26 (7,4%) patients and 7 patients (2.0%) were with known and documented primary thrombophilia (3 patients with activated protein C resistance (factor V Leiden), 3 patients with protein C and protein S deficiency and 1 patient with prothrombin gene mutation).

DVT had 13 patients (3.7%) with lower-extremity plaster immobilization in the moment when diagnosis was established. Lower-extremity paresis and paralysis were present in 9 patients (2.6%) - either as a result of spinal cord trauma (3 patients), cerebrovascular insult (3 patients), progressive myelitis (1 patient) or cerebral tumor (2 patients). Fifteen patients (4.3%) with CUS documented DVT were bedridden (7 patients in end-stage of malignant diseases, 2 patients with end-stage of renal failure, 2 patients with AIDS and 4 patients with sequelae of cerebrovascular disease).

Major surgery procedures (orthopedic, vascular/cardiac, abdominal, gynecological or neurosurgical procedures) were performed in 23 patients (6.6%) - 2 days to 12 weeks before CUS examination.

The patients in our study had the following clinical signs' distribution: entire leg swelling was present in 59 (16.9%) and calf swelling was present in 48 (13.7%) patients, unilateral pitting edema had 36 (10.3%) patients and alternative clinical signs (i.e. muscle pain, chronic venous insufficiency, isolated joint pain, cellulitis etc.) had 52 (14.9%) patients.

Most of the examined patients (56.8%) were with moderate PTP according to the modified Wells score used.

For all three PTP groups CUS examination results are presented in Figure1. The highest number of examined patients in all PTP groups was without DVT (59.2%). Proximal DVT localization (iliac and femoral DVT) has been found in 60.5% and distal DVT localization (popliteal and crural DVT) in 39.5% patients with DVT.

The comparison of D-dimer test results and CUS examination is presented in Table 2. The results show that VIDAS test was positive in the highest percent in the group of patients with CUS documented thrombosis. In the group without CUS documented thrombosis HemosIL test was negative in the highest percent.

Important statistical parameters of D-dimer tests compared in our study are presented in Table 3. VIDAS had the highest sensitivity and HemosIL had the highest specificity. Comparing to the other tests, VIDAS had the highest levels of both positive and negative predictive values.

The comparison of three D-dimer tests by Receiver Operating Characteristic (ROC) curve is represented in Figure 2. In this curve the sensitivity is plotted in function of the specificity for different cut-off points, where each point represents a pair corresponding to a particular decision threshold and test with perfect discrimination has a plot that passes through the upper left corner. Therefore, the closer the ROC plot is to the upper left corner - the higher the overall accuracy of the test. In our study it was the case with VIDAS test.

DISSCUSION

Patients with acute VTE require clinical assessment and objective testing to be accurately diagnosed. Almost all patients with acute VTE have an elevated D-dimer level, but an elevated D-dimer can be associated with many illnesses, and therefore, is not specific for VTE. However, D-dimer tests can have a high sensitivity that is useful because a normal test excludes the diagnosis of VTE. D-dimer testing is the most appropriate in the assessment of outpatients because the prevalence of disease and the likelihood of comorbidity are lower than in inpatient populations, making a test of exclusion particularly valuable [10, 11].

The role of the pretest clinical probability score and/or the D-dimer concentration in the diagnostic management of DVT has been the objective in many different studies. Thus, while reviewing management outcome studies Carrier et al. have found that the three-month PTE risk in patients left untreated on the basis of a low/intermediate or unlikely PTP and a negative D-dimer test was very low and that the combination of a negative VIDAS D-dimer result and a non-high PTP effectively and safely excludes PE [12]. The results of the study of Van der Graaf suggest that the VIDAS and Tinaquant D-dimer assays have the highest sensitivity for the exclusion of DVT in outpatients. In outpatients that have a low or moderate pretest probability for DVT these tests may be used in management studies where anticoagulation is withheld on the basis of D-dimer testing alone [13].

Vermeer and co-workers have tested samples, from 274 consecutive symptomatic patients with suspected PE, DVT or suspected for both complications, with DD PLUS assay. The conclusion of their study shows that this appears to be safe when implemented in an algorithm based on clinical assessment, D-dimer concentration and radiological diagnostic techniques to stratify the risk for PE or DVT [14].

The objective of Legnani and co-workers' study was to evaluate the possible advantage of using quantitative D-dimer assays (VIDAS, Innovance, HemosIL and STA Liatest)

performed in plasma aliquots sampled after cessation of vitamin K-antagonism in 321 patients enrolled in the PROLONG study. Their conclusion was that quantitative D-dimer assays may provide information useful for evaluating the individual risk of recurrent venous thromboembolism and they seem particularly advantageous since they allow the selection of different cut-off levels according to the age and other patients' characteristics [15].

Djurabi et al. have studied the VTE-failure rate of 2206 consecutive patients with an unlikely clinical probability where VIDAS or Tinaquant D-dimer tests were performed. Their conclusion was that both tests perform equally well in combination with an unlikely clinical probability in excluding PE but the VIDAS test was shown to be more efficient [16].

Gardiner et al. have evaluated the performance of eight D-dimer assays, including VIDAS, DD PLUS and HemosIL, evaluated both as stand-alone tests and in combination with pretest probability. Their conclusion was that the highly variable diagnostic performance of these D-dimer assays means that some assays can be unsuitable for certain diagnostic strategies, but the combination of sensitive D-dimer assays with an assessment of PTP may be used to exclude a diagnosis of DVT [17].

Bogavac-Stanojevic et al. have analyzed the total cost of three D-dimer assays (VIDAS, DD Plus and HemosIL). Total cost of diagnostic procedure was calculated on the basis of the consumed resources for diagnostic tests, laboratory time and consumables). Their study group consisted of 96 outpatients with clinically suspected DVT. In the selection of patients for CUS they have used one diagnostic algorithm for the entire patients group and another for the patients selected for CUS according to clinical PTP. The conclusion was that a diagnostic algorithm using PTP assessment, DD assay and CUS could effectively diagnose DVT and also reduce CUS utilization and costs per patient [18].

Lots of authors emphasize the advantages of other non-invasive diagnostic procedures in for establishing diagnosis of DVT. In combination with CUS they can estimate the diagnostic accuracy, clinical- and cost-effectiveness.

CUS, due to its high sensitivity, specificity and reproducibility has replaced venography as the most widely used test in the evaluation of this disease. The safety, availability and well-documented accuracy of this technique justify its widespread use.In symptomatic patients, CUS has shown to be highly specific and sensitive for both proximal and distal DVT. Michiels et al. have found that pulmonary angiography can be the gold standard for segmental PE and that normal pulmonary ventilation/perfusion scan and normal rapid ELISA VIDAS D-dimer test safely exclude PE. The combination of clinical assessment and a rapid ELISA VIDAS D-dimer, followed by CUS, will reduce the need for helical spiral CT by 40% to 50% [19].

Le Gal et al. have showed that the presence of a clot, even asymptomatic, in the proximal lower limb veins of a patient with clinically suspected PE, confirmed by CUS, provides evidence for VTE and indicates anticoagulant therapy in such patients. Their experience is that invasive tests are often unavailable and their use is therefore limited to selected patients and non-invasive management (clinical probability, D-dimer and multislice CT) is feasible in most patients with suspected PE [20].

Goodacre et al. have sought from electronic searches of electronic medical databases and additional data from the bibliographies of articles. Their conclusion was that old techniques as plethysmography and rheography have modest sensitivity for proximal DVT, poor sensitivity for distal DVT and modest specificity. Ultrasound has 94% sensitivity for proximal DVT, 64% sensitivity for distal DVT and 94% specificity. Computed tomography scanning has 95% sensitivity for all DVT (proximal and distal combined) and 97% specificity. Magnetic resonance imaging has 92% sensitivity and 95% specificity [21].

Diagnostic algorithms based on a combination of Wells score, D-dimer and ultrasound (with repeat if negative) are feasible at most worldwide hospitals and are among the most cost-effective. Pretest probability and D-dimer tests can decrease the need of CUS in patients with suspicion on DVT who are young and healthy. D-dimer tests should not be used as a stand-alone test or in situations as usage of anticoagulants, presence of malignant diseases, post surgical procedures, in pregnancy, in patients with severe infections etc.

CONCLUSION

All three D-dimer tests used in our study were with similar sensitivity and specificity. However, VIDAS test had higher levels of positive and negative predictive values comparing to the DD plus and HemosIL tests. The comparison of the three D-dimer tests by ROC curve has showed that the highest overall statistical accuracy of all three D-dimer tests has VIDAS test.

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Table 1. Pretest probability scale for deep vein thrombosis used in this study

Risk factors	Score
1. Active cancer: curative or palliative treatment initiated within 6 months.....	2
2. Prior history of idiopathic VTE or known primary thrombophilia.....	2
3. Paralysis, paresis, plaster immobilization within 12 weeks.....	1
4. Bedridden ≥3days or major surgery within 12 weeks.....	1
Clinical Signs	Score
1. Entire symptomatic leg swollen (asymptomatic leg is not swollen).....	2
2. Calf swelling >3cm compared to asymptomatic leg.....	1
3. Pitting edema, greater in symptomatic leg.....	1
4. Alternative diagnosis (usually muscle pain or venous insufficiency).....	-2
-Tenderness or Homan's sign is nonspecific and receives no points -High probability ≥3, Moderate probability 1-2, Low probability ≤0	

Table 2. CUS and D-dimer tests results comparison

	without thrombosis		with thrombosis		whole group	
	positive (%)	negative(%)	positive (%)	negative(%)	positive (%)	negative(%)
DD PLUS	40.3	59.7	93.0	7.0	73.3	26.7
HemosIL	33.8	66.2	88.4	11.6	56.1	43.8
VIDAS	42.6	57.4	95.3	4.7	62.8	37.2

Table 3. Statistical parameters of DD PLUS, HemosIL and VIDAS test

D-dimer test	Sn (%)	Sp (%)	PPV (%)	NPV (%)
DD PLUS	93	40	51	89
HemosIL	84	66	62	89
VIDAS	95	59	64	94

Sn-Sensitivity, Sp-Specificity, PPV-Positive Predictive Value, NPV-Negative Predictive Value

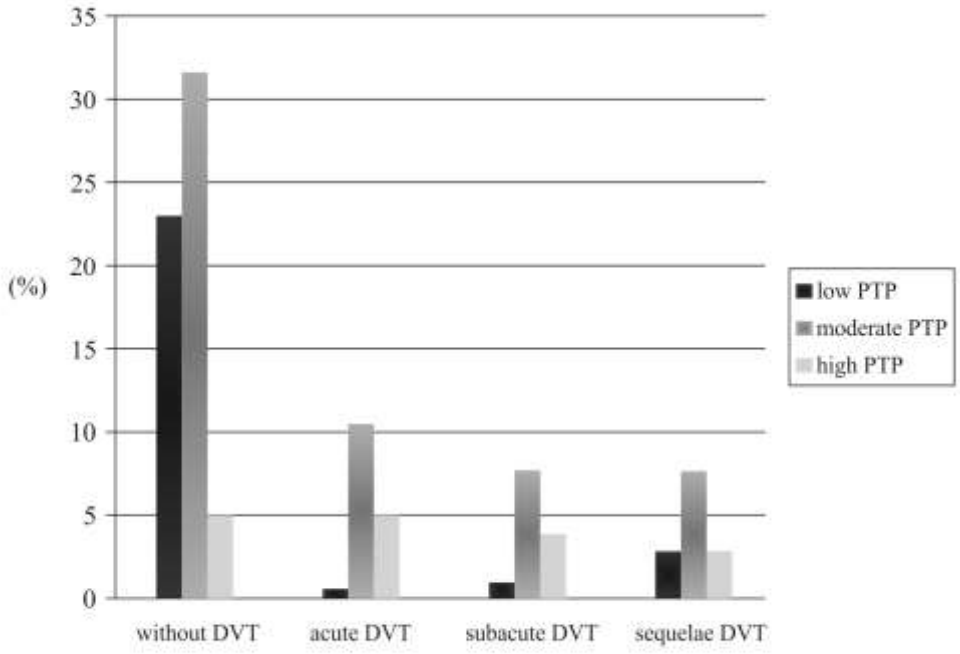

Figure1. Cumulative CUS results for low, moderate and high PTP groups

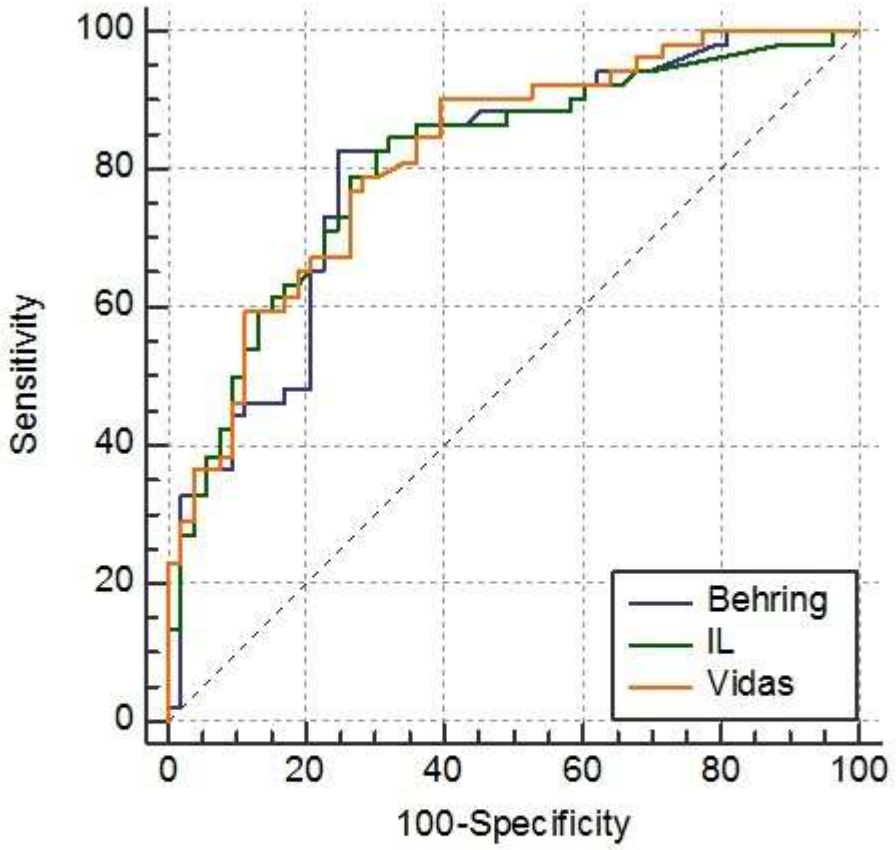

Figure 2. D-dimer tests comparison by sensitivity and specificity (ROC curve)

