Original Article

# Perspective on the hospital incidence rate of deep venous coagulopathy: Clinical and biochemical diagnostic markers

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## Abstract

**Background:** Identifying factors contributing to the increased risk of deep venous thrombosis (DVT) in each population is vital, because of its life-threatening outcome. The current study aims to find the diagnostic performance of some laboratory coagulation markers for predicting DVT in an Iranian population complaining of DVT in the lower limbs.

**Patients and Methods:** For this study, 66 consecutive patients with documented DVT, admitted to the Al-Zahra Hospital in Isfahan for the first time, were considered as the case group and 33 patients without DVT documentations were included as the control group. DVT was considered when there was visualization of thrombus or non-compressibility of the vein, confirmed by bilateral lower extremity compression Doppler ultrasonographic examination. Homocysteine, antiphospholipid, and anticardiolipin antibodies were measured in both groups by using sensitive ELISA kits. Protein C was measured via a functional clotting method, and prothrombin was measured by a kinetic, enzymatic assay.

**Results:** Multivariable analysis showed that the serum homocysteine levels was potentially associated with the presence of DVT after adjusting for age and gender (OR: 1.038, 95% CI: 1.007-1.070, $P = 0.017$). Comparison of the C statistic showed a partially good discrimination of homocysteine for DVT, with the area under the receiver operating characteristic (ROC) curve being 0.614 and with the optimal cut-off value of 16.5 micromol/L (μmol/L) for men and 14.5 μmol/L for women.

**Conclusion:** Hyperhomocysteinemia could be considered as an independent risk factor for DVT, with an actual acceptable prognostic value, in the Iran population.

**Key Words:** Biochemical diagnostic, deep venous coagulopathy, incidence

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## INTRODUCTION

Deep Venous Thrombosis (DVT) has been known as a common preventable health problem associated with high mortality and co morbidities. The overall risk for this life-threatening event has been reported to be between 14 and 15%, following general surgical



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interventions and 60-80% in patients hospitalized in Critical Care Units as well as in patients with spinal cord injuries.[1,2] Thus, evaluation of the predisposing factors for DVT in each population is vital, because, delay of its prevention and treatment might lead to fatal adverse outcomes such as pulmonary embolism.[3,4] Some of the identified permanent and triggering factors contributing to an increased risk of thrombus formation and the related DVT include, relative immobilization, chronic heart failure, obesity, violent effort, muscular trauma, deterioration in the general condition, immobilization, long-distance travel, infectious disease, brain stroke, pregnancy, trauma-related vascular complications, long bone fractures, malignancies, and severe neurotrauma.[5,6] A survey in northern Iran revealed that the most common risk factors for DVT were age less than 40 years, immobility, pregnancy or puerperium, previous DVT, major surgery, and deep venous insufficiency.[7]

A difference in the predisposing factors of DVT between the western and non-western countries has now been suggested.[6] There are extensive data to support the role of clinical factors for predicting DVT; however, the situation of the crucial role of chemical biomarkers to discriminate DVT, especially coagulation indices, is far less clear, especially in patients with cardiovascular diseases. Hence, in patients with vascular occlusive disease, pathological changes of these biomarkers must be elucidated and treated. In fact, the levels of these chemical markers may actually be of prognostic or predictive value in cases of DVT. Occurrence of DVT is highly dependent on the population. The current study aims to address the predictive role of selected serum laboratory coagulation markers in predicting DVT in an Iranian population complaining of DVT in the lower limbs.

## PATIENTS AND METHODS

### Study population

A case-control study was conducted at a general referral hospital in Isfahan, Iran. Sixty-six consecutive patients, over 20 years of age, with documented DVT, admitted to the Al-Zahra Hospital for the first time, during the period between April 2007 and August 2008 were considered for inclusion in the study, as the case group. Furthermore, 33 patients without manifestations of DVT, who referred due to other complications, were included as the control group and were matched for demographics with the case subjects. Patients who were admitted with prolonged immobility were excluded because of their high-risk for thromboembolic events. Patients were also excluded if they had undergone cardiac surgery, received thrombotic prophylaxis, were pregnant or had an extremely unfavorable prognosis. Approval for the study was obtained from the Research Ethics Committee of the Isfahan University of Medical Sciences, and informed consent was obtained from each patient.

After primary careful physical assessing, the deep venous systems of both lower extremities were examined from the external iliac veins proximally to the posterior tibial, peroneal, gastrocnemius, and soleal veins distally. Deep venous thrombosis was considered when there was visualization of a thrombus or non-compressibility of the vein. Bilateral lower extremity compression Doppler ultrasonographic (US) examination (HDI 5000, Phillip Inc., USA) was performed as the gold standard on patients with suspected DVT, to confirm the diagnosis of DVT in the study subjects. An expert sonographer, unaware of the patients' characteristics or risk factors, performed all the examinations. Those with a final diagnosis of DVT were considered as the case group and others were considered as the control group.

### Study data

The baseline data of the study subjects, including, age, gender, common clinical manifestations, and probable risk factors of DVT, such as, family history of DVT, obesity, cigarette smoking, history of surgery, malignancies, immobility, and oral contraceptive consumption were collected via a face-to-face interview. For measuring the biomarkers, the total homocysteine concentration was measured in citrated plasma by automated high-performance liquid chromatography (HPLC), with reverse-phase separation and fluorescent detection. The antiphospholipids were measured by an enzyme-linked immunosorbent assay (ELISA). Antiphospholipid and anticardiolipin antibodies were measured in both groups by using sensitive ELISA kits. Protein C was measured via a functional clotting method, and prothrombin was measured by a kinetic enzymatic assay.

### Statistical analysis

Data were presented as mean ± SD for continuous variables and as percentages for categorical variables. Comparisons of categorical variables across the groups were performed using an overall chi-square test or the Fisher's exact test if required; while comparisons of continuous variables were performed using an independent t-test or Mann-Whitney U test. For determining the main chemical predictors of DVT, we first evaluated the univariate associations between the study biomarkers and the appearance of DVT. Following this, in the subsequent analysis, factors obtained in the univariate analysis were considered in the multivariable binary logistic regression analyses, for determining the relationship between these predictors and DVT appearance, as dependant variables, in the presence of cofounders such as age,

gender, and total length of stay in the hospital. The discriminatory capacity for each predicting biomarker was also analyzed using the calculation of the area under the receiver operating characteristic (ROC) curve (C statistic) presented with 95% confidence interval. A value of 0.5 indicated that the model was equivalent to pure chance and a value of 1 indicated perfect discrimination. The predictive power analysis was carried out using the STATA statistical package (version 8.0; College Station, TX, USA) and comparative analysis was carried out using the SPSS (version 13.0, SPSS Inc., Chicago, IL, USA). All *P*-values were two-sided, with statistical significance defined by $P \leq 0.05$.

## RESULTS

The baseline characteristics of 122 recruited patients are shown in Table 1. Among these participants, DVT was detected in 66 patients. No significant relationship was found between advanced age and diagnosis of DVT, so 83.3% of the patients in the DVT group and 87.9% of the patients in the control group were more than 40 years old. The majority of patients without positive findings for DVT demonstrated no clinical signs, whereas, 92.4% of those with DVT diagnosis had leg pain and about one-third of them suffered from leg tenderness or leg warmth. Regarding the biochemical parameters, only the serum concentration of homocysteine was significantly higher in the DVT group and no significant differences were observed in the other biomarkers between the two study groups. Comparing the serum level of these biomarkers between men and women in the group with DVT, it was seen that the concentrations of anticardiolipin, antiphospholipid, and prothrombin were higher in women, whereas, men with DVT had a higher serum level of homocysteine than women in the same group [Table 2]. On multivariable analysis, only the serum homocysteine level was potentially associated with the presence of DVT adjusting for patients' age and gender (OR: 1.038, 95% CI: 1.007-1.070, $P = 0.017$).

The discriminatory powers of the laboratory parameters for DVT, using the area under the ROC curve, were different [Table 3]. The informal comparison of the C statistic showed a partially good discrimination of homocysteine for DVT with the area under the ROC curve of 0.614 (95% CI: 0.505-0.723). The discriminative value of homocysteine for DVT in men was higher than in women (with the area under the ROC curve of 0.638 vs. 0.500) [Figure 1]. The optimal cut-off value for homocysteine, for predicting DVT in men, was identified to be 16.5 μmol/L, yielding a sensitivity of 64.3% and a specificity of 64.0%, and in women it was 14.5 μmol/L, yielding a sensitivity of 50.0% and a specificity of 57.1% [Figure 2].

## DISCUSSION

The results of this study showed that hyperhomocysteinemia could be considered as an independent risk factor for DVT, with an actually acceptable prognostic value in the Iran people. Nowadays, clinicians attempt to identify suspected postoperative deep-vein thrombosis (PDVT) by considering the patients' manifestations and associated risk factors. However, recent researches suggested

**Table 1: Baseline characteristics of 99 consecutive patients with and without deep venous thrombosis**

| Characteristics | Group with DVT (*n* = 66) | Group without DVT (*n* = 33) | *P*-value |
|---|---|---|---|
| Male gender | 56 (84.8) | 25 (75.6) | 0.409 |
| Age (years) | 52.20±14.84 | 54.63±15.62 | 0.466 |
| Common manifestations | | | |
| Leg pain | 61 (92.4) | 2 (6.1) | <0.001 |
| Leg tenderness | 24 (36.4) | 1 (3.0) | <0.001 |
| Leg warmth | 22 (33.3) | 1 (3.0) | <0.001 |
| Chemical parameters | | | |
| Abnormal factor V Liden | 2 (3.0) | 0 (0.0) | 0.551 |
| Anticardiolipin | 7.07±14.44 | 3.55±1.86 | 0.181 |
| Antiphospholipid | 5.02±10.65 | 4.60±3.90 | 0.777 |
| Homocysteine | 33.85±36.61 | 17.37±7.73 | 0.014 |
| Antithrombin | 10.75±17.88 | 8.51±3.29 | 0.485 |
| ANA factor | 1.35±2.02 | 0.85±0.20 | 0.170 |
| Prothrombin B | 16.53±39.76 | 7.43±5.44 | 0.195 |
| Protein-C | 104.55±33.43 | 116.16±30.86 | 0.095 |

**Table 2: Comparison of diagnostic biochemical markers between men and women with deep venous thrombosis**

| Biomarker | Men with DVT (*n* = 56) | Women with DVT (*n* = 10) | *P*-value |
|---|---|---|---|
| Anticardiolipin | 5.31±1.24 | 16.93±9.22 | 0.018 |
| Antiphospholipid | 3.61±0.67 | 12.94±7.64 | 0.010 |
| Homocysteine | 36.18±5.19 | 20.80±5.02 | 0.041 |
| Antithrombin | 9.36±1.92 | 18.54±9.81 | 0.136 |
| ANA factor | 1.29±0.25 | 1.67±0.93 | 0.703 |
| Prothrombin B | 12.13±1.95 | 41.15±30.53 | 0.032 |
| Protein-C | 102.82±4.37 | 114.10±12.38 | 0.408 |

**Table 3: Discriminative value of chemical biomarkers for predicting deep venous thrombosis-based on the area under the ROC curve analysis**

| Biomarker | Area | 95% confidence interval | | *P*-value |
|---|---|---|---|---|
| Anticardiolipin | 0.452 | 0.333 | 0.570 | 0.445 |
| Antiphospholipid | 0.305 | 0.185 | 0.424 | 0.002 |
| Homocysteine | 0.614 | 0.505 | 0.723 | 0.056 |
| Antithrombin | 0.278 | 0.180 | 0.377 | <0.001 |
| ANA factor | 0.541 | 0.420 | 0.663 | 0.507 |
| Prothrombin B | 0.595 | 0.478 | 0.712 | 0.129 |
| Protein-C | 0.392 | 0.271 | 0.512 | 0.087 |

that approximately 75% of the patients who are suspected of having PDVT might not have DVT, when formal diagnostic testing is completed.[8,9] Therefore, the tests used by physicians should have a very high sensitivity for identifying patients with DVT. One of the most effective and efficient diagnostic laboratory methods for diagnosing DVT is the use of D-dimer testing, as a simple blood test of fibrin degradation. Although D-dimer levels in the blood have been found to be the most useful as high sensitive markers of fibrinolysis, they have no acceptable specificity for predicting DVT.[10,11] Thus, the discriminative value of other laboratory tests in combination with clinical signs must be considered. In the present study, we have assessed the predictive power of some laboratory coagulation markers for confirming DVT in these patients. Similar studies on hospitalized patients in North America and the eastern Asian populations have suggested a low incidence of DVT in comparison with other ethnic groups.[12,13] This incidence rate is potentially associated with the main cause of a patient's hospitalization as well as with a presence of the DVT prophylaxis regimen. Our study subjects did not receive any prophylaxis regimen. Review of literatures on the incidence of DVT in critically ill adults showed that the incidence rate in patients receiving DVT prophylaxis was approximately 10%, whereas, this rate in those who did not receive these regimens was estimated higher than 25%.[14,15] In a study by Motykie *et al*. found that the prevalence of DVT in the suspected group could be varied in different risk stratification groups, so that the prevalence of DVT was found to be 92.4% in the high-risk category, 11.5% in the moderate-risk category, and 3.2% in the low-risk category.[16] In our study, the appearance of DVT was considerably higher in men; however, age was not an independent predictor for DVT diagnosis. Regarding sex and age distribution, previous studies

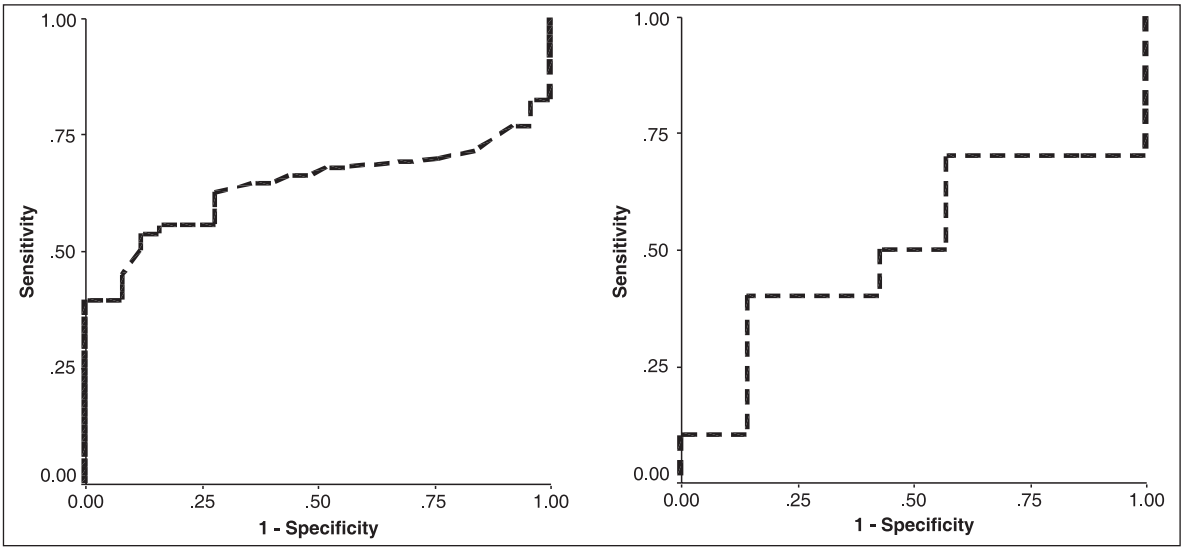


**Figure 1:** The area under the receiver operating characteristic (ROC) curve for determining the discriminatory capacity of homocysteine for predicting DVT in men and women

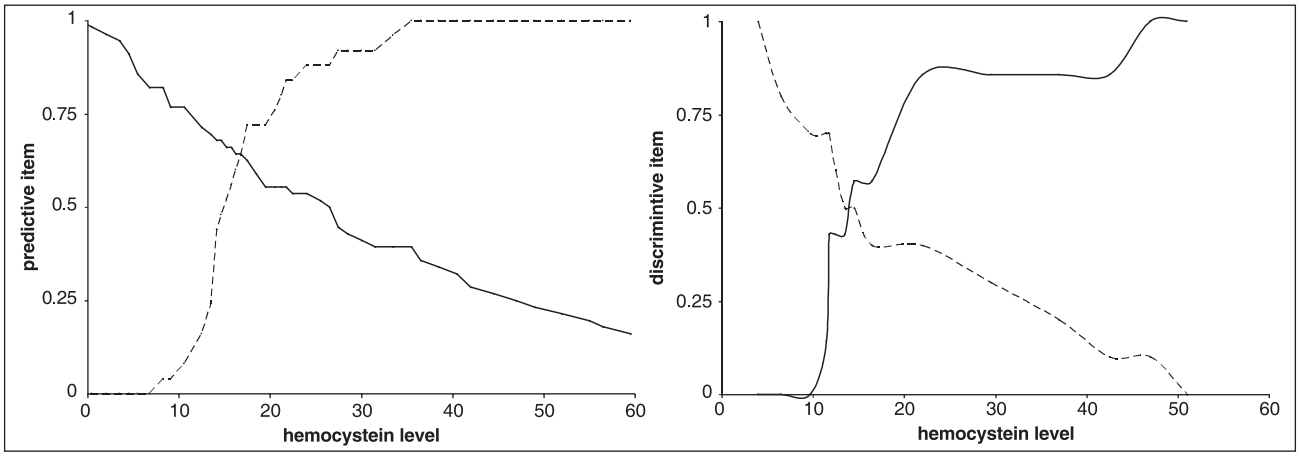


**Figure 2:** Optimal cut-off value of homocysteine for prediction of DVT (best cut-off point for hemocystein in men was 16.5 and in women was 14.5)

had different results. In the Chua study, no significant demographic or clinical predictive factors for DVT were found.[5] In other studies by Wilasrusmee[17] and Joynt,[18] age and gender were not associated with the presence of DVT, and the only independent and significant risk factor for DVT was a longer ICU stay. Anderson introduced increasing age a weak DVT risk factor.[19] Besides, similar to our study, some researches could confirm that advanced age was an important predictor for DVT appearance.[20,21] With respect to the gender reference in the incidence of DVT, it is believed that women are a prime target for complications of DVT such as pulmonary emboli, more often than men.[22]

Another important finding of the current study was confirming the role of hyperhomocysteinemia as one of the main discriminative factors of DVT in suspected patients, as also an Odds Ratio of 1.03, in patients with hyperhomocysteinemia could be an indication of having DVT. In a similar study among Iranians, the association between homocysteine and DVT was not confirmed, especially for men who had a higher level of serum homocysteine than women.[23] However, this relationship was strongly confirmed in several studies.[24-26] It has been demonstrated that hyperhomocysteinemia, even of a mild level is an established risk factor for vascular diseases, especially with an origin in the veins. Some hypotheses could explain the association between DVT appearance and hyperhomocysteinemia. An increased plasma level of homocysteine may result in its toxic effect on the vascular endothelium and on the clotting cascade.[27-29] In addition, a high level of homocysteine can reflect methionine abnormality that leads to destruction of the DNA methylation and cell membranes.[30] As shown in our study, the predictive power of this laboratory parameter in the two genders was different and even its diagnostic cut-points were varied. It seems that by using different cut-off points for hyperhomocysteinemia in men and women, the odds ratio may be roughly twice as high for women as for men. Unlü *et al*. indicated that the association between elevated homocysteine levels and venous thrombosis was stronger among men than among women.[31] Although, Tabrizi *et al*. showed genetic mutation in prothrombin, Factor II [G20210A] is one of the most important genetic variations involved in traumatic patients with DVT, despite the prophylaxis.[32] However, it has been suggested that women may be more susceptible to the pathological effects of elevated homocysteine levels, even though their homocysteine levels are in general lower than those in men,[32] however, as we have noted, the sensitivity and specificity of the changes of this marker can be significantly lower in women than in men. Furthermore, in the present study, the cut-off points of the homocysteine levels for diagnosing DVT in men and women were different (16.5 μmol/L and 14.5 μmol/L, respectively), whereas, in the Castañon *et al*. study, this cut-off was 12 μmol/L.[33-34] We think that the discriminative power of hyperhomocysteinemia can be varied in different nations as well as in the two genders, and thus, further studies, preferably with greater sample size, should be considered for the homocysteine discrimination role in suspected DVT patients.

In summary, the incidence of DVT in suspected hospitalized patients in Iran is notable, especially in men, however, DVT appearance was similarly observed in different age subgroups. Hyperhomocysteinemia has an important discriminative power for DVT in the Iranian population. Therefore, this laboratory parameter can be effectively used for DVT risk stratification in suspected patients. We propose 16.5 μmol/L as the hyperhomocysteinemia cut-off value for men and 14.5 μmol/L as the hyperhomocysteinemia cut-off value for women, but further researches are needed to evaluate the efficacy of these cut-off points in DVT-suspected patients.

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