



# Five steps for the use and interpretation of D-dimer in the Emergency Department

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Received: 7 October 2018 / Accepted: 29 January 2019 / Published online: 7 February 2019  
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## Introduction

D-dimer is one of the major fibrin clot degradation products, released from cleavage of crosslinked fibrin by plasmin during fibrinolysis process. Since its introduction in 1990, D-dimer dosage has been proposed and used as a marker for several acute pathologies in which thrombosis or fibrinolysis processes are involved. Blood D-dimer's values rise in several situations such as inflammation, neoplastic disease, autoimmune and rheumatic diseases, trauma, liver disease, pregnancy and age [1]. The purpose of this paper, part of a series of articles on biomarkers in the emergency medicine setting [2], is to provide a few practical steps that we think should be followed by the physician to correctly test and interpret D-dimer levels when evaluating patients.

## Step 1: knowledge of the available assays

Several kinds of D-dimer assays are available.

First, they can differ for technical method of measure of the D-dimer concentration in blood. The most diffuse are ELISA and ELISA-related assays, quantitative latex-derived assays and whole-blood agglutination assays. These different types of test have different sensitivities and specificities for several pathologies. For example, in the case of suspected venous thromboembolism (VTE—pulmonary embolism and

deep venous thrombosis), ELISA and ELISA related assays are considered to be highly sensitive (95% sensitivity or better), while latex-derived assays and whole-blood agglutination assays are considered to be intermediately sensitive. The diagnosis is the result of a Bayesian process that combines the pre-test clinical probability of a disease and the results and diagnostic accuracy of a test [3]. This fact implies that knowing the sensitivity of the available test is necessary to evaluate the post-test probability of a clinical condition, given the pre-test probability.

Second, similar kind of tests could have different positivity thresholds (i.e. international accepted threshold for positive D-dimer is 500 µg/L but some tests use different values).

The first thing to do in approaching D-dimer is asking your laboratory which kind of assay is available and which positivity threshold it uses.

## Step 2: ask yourself why you are ordering D-dimer test (rule-out, rule-in)

D-dimer test should not be ordered as a routine test but only if a particular disease is suspected. Because of the general characteristics of the test (relatively high sensitivity, low specificity), D-dimer should be considered as an assay able only to rule-out such diseases, basing on the pre-test probability. On the other hand, a positive test result should not be considered as a confirmation test, but only as a threshold for carrying out the next investigation.

## Step 3: ask yourself what you will do depending on the result

Before ordering D-dimer is important asking ourselves how we would manage the patient depending on the result.

A test that will not modify our patient management is unnecessary and confounding and therefore should not be

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ordered. Thus, if none D-dimer related pathology is suspected in that patient, D-dimer test should not be requested. In the typical condition of the emergency department, if a patient is thought to have high pre-test probability of VTE basing on his medical history and clinical features—and none of the available types of test are sufficiently sensitive and therefore able to exclude VTE on these bases -D-dimer test should not be tested and the patient should be referred directly to an imaging investigation able to exclude with high grade of certainty this kind of disease.

In the remaining cases of low-intermediate pre-test probability of disease we should ask ourselves how would we manage the patient in the case of a negative or positive test. If the result of the D-dimer test will not modify our actions, the test should not be ordered.

#### **Step 4: ask yourself what to do if someone else has ordered it**

A particularly difficult condition in the Emergency Department is the case in which you take charge of a patient to whom the physician of the previous shift has ordered D-dimer test.

In this setting it is essential to start over the reasoning, asking ourselves if we would have ordered the test, if the request is appropriate, consider the characteristics of the patient (pre-test probability, symptoms, clinical context) and if any other causes of positivity may be present.

A positive result deriving from an inappropriate request of the D-dimer test should be considered an accidental finding and does not need to be explained.

Several different physiologic or para-physiologic causes can determine an elevation in the D-dimer blood levels, and if the pre-test probability of the cited pathologies is assumed to be 0%, a positive D-dimer itself does not increase the probability of the disease.

#### **Step 5: clinical situations and other considerations**

##### **D-dimer in VTE**

In the Emergency Department setting, the most common situation in which D-dimer test can be useful is suspected VTE. Considering the test characteristics and the pre-test probability of the patient, D-dimer test should be requested only in conditions of low pre-test probability if an intermediate-test is available or in low-intermediate probability if a high sensitivity test is available (see the proposed algorithm in Fig. 1).

##### **D-dimer in the elderly, pregnant woman and neoplastic patient**

D-dimer test is considered positive above a standard cut-off value of 500 µg/L. Because of its very low specificity in several situations (in particular in the elderly, during pregnancy and in neoplastic patient), some considerations have been made in the last years for special situations. Age-adjusted cut-off values for high-sensitive assays (age ×10 mg/L above 50 years instead of the usual 500 mg/L cut-off) have been proposed and validated [4]. Similarly, higher cut-off values have been proposed also for pregnant patients but are still under validation [1].

In neoplastic patients, plasmatic D-dimer levels can rise due to the malignancy, thus a positive test could result to have very low specificity, raising the proportion of CT scan performed and the risk of overdiagnosis of subsegmental PE (frequent in this kind of patient although its meaning and indication to anticoagulant treatment have not yet been established). At the moment few studies exist on this topic and results are conflicting [1].

##### **Disseminated intravascular coagulation, aortic dissection, cerebral venous thrombosis**

Disseminated intravascular coagulation (DIC) is a serious and life-threatening condition, associated with various acute states of disease (ie sepsis, acute promyelocytic leukemia, birth complications). D-dimer is part of the set of laboratory indexes that need to be analyzed in the case of this clinical suspicion.

The finding of high D-dimer values, consumption of coagulation factors (low fibrinogen, elongated PT and aPTT) and thrombocytopenia together with compatible clinical features and in the absence of an alternative diagnosis are suggestive for DIC.

Other discussed uses of the D-dimer test is in the diagnosis of acute aortic syndrome [5] and cerebral venous thrombosis, but at the moment further studies are needed before recommending it in the diagnostic pathway of such pathologies.

#### **Final conclusions**

In conclusion, physicians should ask themselves whether D-dimer results can affect the patient management, and proceed with measurement only when the answer to the question is positive (Table 1). Clinicians should also know which kind of test is available in their setting. It is important to know pathologies in which D-dimer test could really

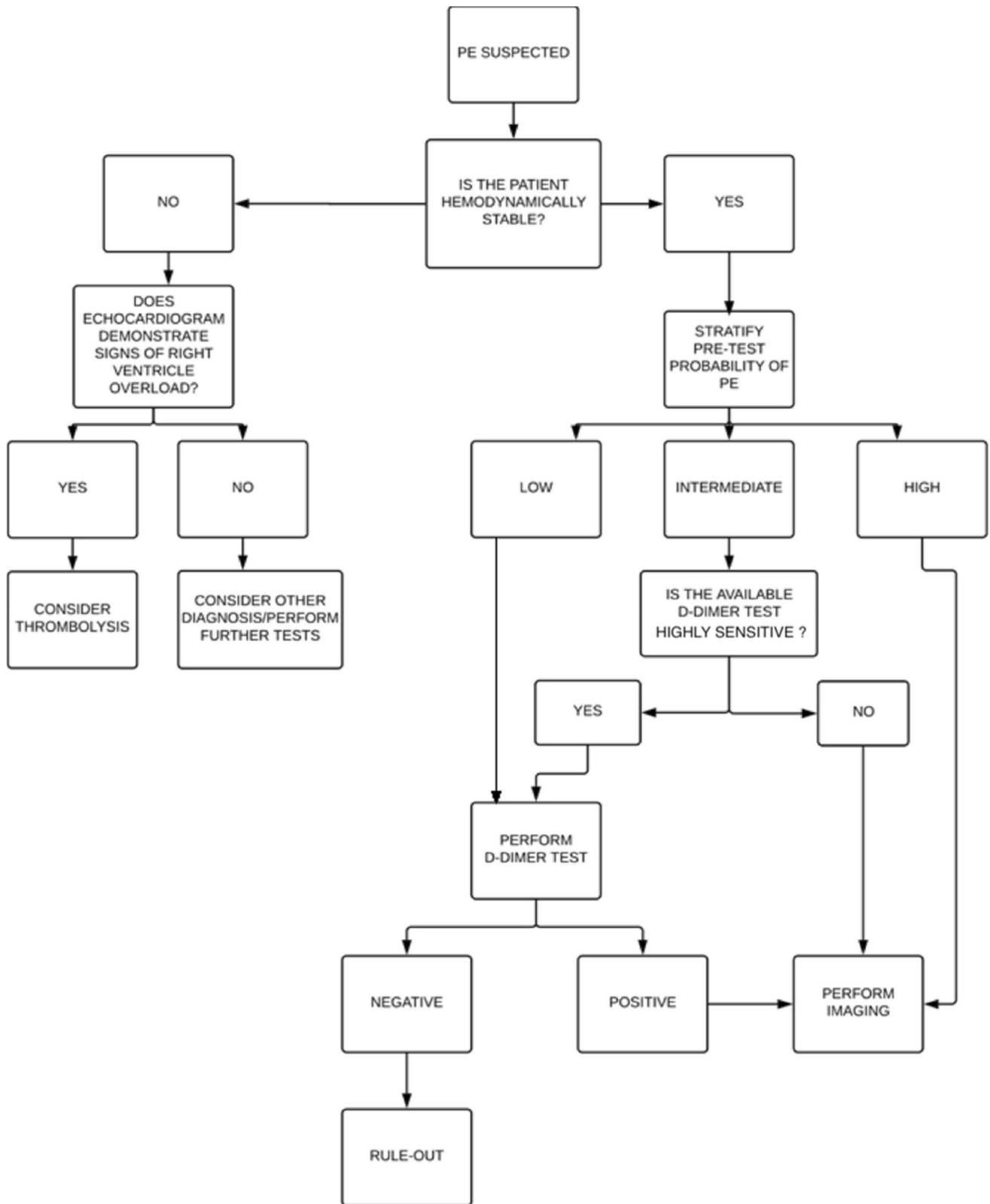


Fig. 1 Diagnostic flow-chart and use of D-dimer in suspected pulmonary embolism

**Table 1** Dos and don'ts in approaching D-dimer test

Do	Don't
Ask yourself which kind of test is available in your clinical setting (high or intermediate sensitivity)	Do not order D-dimer as a routine test
Assess the pre-test probability of pathology	Do not repeat D-dimer test unless a laboratory mistake is suspected
Consider the test's characteristics (in particular sensitivity) and order D-dimer only if able to actually affect the post-test probability	Do not consider D-dimer as a confirmation test

be useful and proceed in ordering it only if one of them is suspected taking into consideration test characteristics and pre-test probability of the disease for that patient.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Statement of human and animal rights** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** None.

**Funding** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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