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EDITORIAL

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D-dimer for the diagnosis of pulmonary embolism: a call for sticking to evidence

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Critically ill patients are at high risk of venous thromboembolism (VTE). However, the disease is often clinically silent, especially in these patients, and is not associated with any specific clinical sign or biologic marker. It is, therefore, particularly difficult to diagnose this condition in the ICU. D-dimers (DD) are cross-linked fibrin derivatives that are produced upon fibrin degradation by plasmin. The DD concentration rises in various conditions in which coagulation and fibrinolysis are activated, e.g. in patients with VTE, but also in patients with cancer, myocardial infarction, infectious or inflammatory diseases, pregnancy and in the postoperative period. Practically, patients with acute VTE are very likely to present with an elevated DD level, corresponding to a very high sensitivity to VTE, which in turn results in a high negative predictive value. On the other hand, as DD rise in various pathologic conditions [1], the proportion of patients with increased DD may be substantial in patients without VTE: the specificity (proportion of patients with negative D-dimer test among those without VTE) of DD testing is low, resulting in a poor positive predictive value (PPV, proportion of patients with VTE among those with positive D-dimer tests).

Although available DD assays are heterogeneous, a negative result usually allows the exclusion of acute VTE: in low clinical probability patients only for whole blood agglutination assays [2] or even in all non-high clinical probability patients for the most sensitive tests (ELISA or immunoturbidimetric assays) [3, 4]. Hence, DD testing is widely used as a first-line test, at least in outpatients with suspected VTE, as VTE can be ruled out in about 30% of such patients without further invasive and/or expensive testing.

In this issue, Crowther et al. [5] report on a study using six different commercial DD assays in a prospective cohort of 197 critically ill medical-surgical patients. The test was performed upon admission to the ICU, and twice weekly during the ICU stay. Bilateral compression ultrasonography of the lower limbs was performed at the same time points, as well as at the time of any suspicion of VTE. All patients had some kind of thrombo-prophylaxis during their ICU stays. The results confirm the fact that DD testing is not useful for ruling out VTE in this setting. Indeed, the proportion of patients with low DD concentration decreases—and so does the clinical utility of this test—in cancer patients, older subjects [6], inpatients [7] or pregnant women [8]. Among the medical-surgical critically ill patients included in the study by Crowther et al., only 3.6% had negative bedside D-dimer tests (thereby ruling out VTE), which definitely precludes the use of these tests in ICU patients. This proportion was higher (15.9%) in a previous study in ICU, but that study included younger (62 vs 67 years) and less severely ill patients (APACHE II 20.2 vs 25.7) [9].

The results also indicate that DD testing is not able to identify correctly the ICU patients who have VTE. Admittedly, the areas under the ROC curve differ significantly from 0.5 (which indicates that these tests have a significant capacity to discriminate patients with and without the disease), but these curves show that DD testing reaches sufficient specificity to identify patients with VTE only for very high DD levels, that very few patients have. This observation is not surprising since the specificity of DD is known to be not high enough—about 40% at a 500 μg/l threshold and above 93% only for values above 4,000 μg/l when assayed by ELISA [10]—to

ensure a clinically interesting PPV. This is even more true when the prevalence of the disease is low. The prevalence was only 5/197 (2.5%) upon ICU admission in the present study. Consequently, specificity should have been particularly high to allow correct identification of the cases by a positive test.

The authors have also evaluated the capacity of four hypercoagulability tests (protein C, protein S, activated protein C resistance ratio and antithrombin) and of D-dimer to predict the occurrence of VTE during a mean ICU stay of 12 days, as recently suggested by two groups [11, 12]. Eventually, they found that none of these tests was able to predict VTE occurrence, as demonstrated by areas under the ROC curves that were not significantly different from 0.5.

Although this is an original result, it could have been anticipated, especially for DD testing [13]. Indeed, if DD levels are highly sensitive to the presence of a clot and even of a hypercoagulable state, as already said, their specificity for the diagnosis of VTE in patients suspected of having this is poor. Moreover, because of the low incidence—here 11.6% over 12 days, mostly asymptomatic—a high PPV was not to be expected.

In conclusion, thanks to its high sensitivity for the presence of VTE, DD testing allows, with some certainty, the exclusion of the disease when negative (i.e. when the concentration is below a validated diagnostic threshold) in patients who are suspected of having it, if those patients have (1) a low clinical probability when whole blood agglutination assays are used or (2) a low or intermediate clinical probability when highly sensitive tests such as ELISA or some immunoturbidimetric assays are used. Due to its poor specificity and to the relatively low prevalence of the disease in patients suspected of having it, DD testing can not be used to establish the diagnosis in these patients nor to predict VTE occurrence in at-risk patients. Moreover, because they have only little chance of being negative in critically ill patients, the use of these tests should be discouraged in such patients. New biologic tests must be applied for validated indications in appropriate patient populations. All divergent uses are likely to result in financial losses and, more importantly, in clinically useless or even misleading information.

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