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Original article

Diagnostic significance of combining D-dimer with high-sensitivity cardiac troponin I for improving the diagnosis of venous thromboembolism in the emergency department

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Abstract. *Background:* Although cardiac troponins are valuable tools for risk stratification in patients with venous thromboembolism (VTE), their significance remains elusive in diagnosing venous thrombosis. *Methods:* D-dimer (age-adjusted cut-off) and high-sensitivity cardiac troponin I (HS-cTnI; reference limit, <10.5 ng/L in women and <17.8 ng/L in men) were measured in 2199 consecutive patients (1106 women and 1093 men; mean age, 63±20 years), admitted to the Emergency Department of the University Hospital of Parma during a 3-month period. Overall, 53 patients were finally diagnosed with VTE (12 with deep vein thrombosis and 41 with pulmonary embolism). *Results:* The diagnostic performance (area under the curve; AUC) of D-dimer and HS-cTnI was 0.70 and 0.71 for all VTE episodes, 0.70 and 0.63 for deep vein thrombosis (DVT), 0.70 and 0.74 for pulmonary embolism (PE), respectively. The combination of positive values of both biomarkers yielded better diagnostic performance than D-dimer values alone for diagnosing PE (AUC, 0.80; p<0.001 vs. D-dimer alone), but not for diagnosing DVT (AUC, 0.73; p=0.458 vs. D-dimer alone). In patients with PE, positive HS-cTnI values in patients with concomitantly positive D-dimer values yielded identical diagnostic sensitivity compared to D-dimer positivity alone (i.e., 1.00), but nearly double diagnostic specificity (i.e., 0.71 vs. 0.40). Positive HS-cTnI values (AUC, 0.68), but not D-dimer positivity (AUC, 0.51), were associated with 30-day hospital readmission of VTE patients. *Conclusions:* The results of this study open intriguing opportunities for combining HS-cTnI and D-dimer in the diagnostic approach of patients with PE. (www.actabiomedica.it)

Key words: venous thromboembolism, pulmonary embolism, deep vein thrombosis; cardiac troponins, d-dimer

Introduction

Venous thromboembolism (VTE), a life-threatening disease which typically encompasses deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (1), has an estimated incidence of 3.2 cases per 1000 in the general US population (2.1 cases per 1000 of DVT and 1.1 cases per 1000 of PE, respectively) (2). The clinical severity of this pathology is clearly reflected by the remarkably high 30-days and 1-year death rates, which approximate 11% and 23%, respectively. It has been now clearly established that the prognosis of VTE depends largely on accurate and rapid diagnosis (3). Notably, both these aspects may be actually jeopardized in overcrowded and distressed environments, such as the Emergency Department (ED) (4), where a diagnostic delay may lead to an over twofold enhanced 30-day mortality for PE (odds ratio, 2.61; 95% CI, 1.05-6.51; p=0.039) (5).

Among the various strategies for diagnosing VTE, the most recent guidelines are aligned to suggest that an efficient combination of pre-test (clinical) probability, laboratory biomarkers and radiological investigations shall drive the diagnostic reasoning (6-8), whereby D-dimer is now universally considered the biochemical gold standard for diagnosing venous thrombosis (9). Briefly, patients with medium-to-high pre-test probability shall be subjected to diagnostic imaging (e.g., with ultrasonography for DVT and computed tomography pulmonary angiography, or, in selected cases, ventilation-perfusion scanning, for PE), whilst a negative D-dimer test result combined with low pre-test probability could be used to efficiently and safely discharge the patients and no need of performing additional and potentially invasive testing. Interestingly, the results of a recent study including 940 patients admitted to the ED with clinically suspected VTE revealed that this approach has a cumulative diagnostic efficiency comprised between 64-75% (10). Although the diagnostic sensitivity was found to be excellent, consistently higher than 0.94, the diagnostic specificity remained substantially low, even using age-adjusted cut-offs, and globally comprised between 0.58 and 0.72. This evidence leads the way to additional research aimed at identifying additional diagnostic tools for enhancing the diagnostic specificity of D-dimer testing. Among some promising laboratory tests, the measurement of cardiac troponins, especially using high-sensitivity (HS) immunoassays, has recently emerged as a potentially valuable tool for improving risk stratification in patients with VTE (11,12), so that we thought it would be reasonable to assess also its clinical significance for diagnosing VTE in the ED.

Methods

The study population consisted on all patients admitted to the Emergency Department (ED) of the University Hospital of Parma during a 3-month period (i.e., between October 1, 2018 to December 31, 2018), in whom both D-dimer and high-sensitive cardiac troponin I (HS-cTnI) tests were ordered. Both biomarkers were measured at patient admission, before a final diagnosis was made. The diagnosis of VTE (either of DVT or PE) was made according to the validated criteria of the European Society of Cardiology (ESC), as described elsewhere (7). D-dimer test (Hemosil D-Dimer HS 500 on ACL TOP analyzer; Instrumentation Laboratory) is a latex-enhanced turbidimetric immunoassay, characterized by a limit of blank of 146 ng/mL, a limit of detection of 203 ng/mL, functional sensitivity of 215 ng/mL and total imprecision comprised between 2.3-6.6% (13). Cut-offs have been adjusted for age, i.e., <245 in people aged ≤50 years and using the validate formula [D-dimer] = (age, years)×10 for patients aged >50 years, as endorsed by the ESC and other medical societies (7,8). The analytical characteristics of the HS-cTnI chemiluminescent immunoassay used in this study (Access hsTnI, Beckman Coulter) have been comprehensively described elsewhere (14). Briefly, the limit of blank, limit of detection and functional sensitivity were found to be 0.14, 0.34 and 1.35 ng/L, respectively, whilst the total imprecision was comprised between 5.4-6.1%. The diagnostic threshold was identified with the 99th percentile of the upper reference limit (URL) (i.e., <10.5 ng/L in women and <17.8 ng/L in men, respectively).

Results were finally expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), when appropriate. Difference between groups were analyzed with Mann-Whitney U test. The diagnostic performance was calculated as area under the curve (AUC) in receiver operating characteristic (ROC) curve analysis. The statistical analysis was carried out using Analyse-it (Analyse-it Software Ltd, Leeds, UK) and the statistical significance was set at $p<0.05$. The investigation was carried out in accordance with the Declaration of Helsinki, under the terms of relevant local legislation. This retrospective observational study was based on anonymized patients' data, so that the need for patient's informed consent and ethical committee approval was waived.

Results

The final study population consisted of 2199 consecutive patients (1106 women and 1093 men; mean age, 63±20 years), who presented to the emergency

department of the University Hospital of Parma throughout the study period. Overall, 53/2199 (2.4%) of such patients were finally diagnosed with VTE (12 with deep vein thrombosis and 41 with pulmonary embolism). The mean age of these patients was 76±13 years (p<0.001 vs. no-VTE patients), 25 were women and 28 were men. The other more frequent diagnoses encompassed cardiac arrhythmias (6%), myocardial infarction (5%), pneumonia (4%), trauma (3%) and sepsis (3%), along with 73% other different conditions less frequently represented in this population. In all VTE patients the median values of D-dimer (2980 ng/mL and IQR, 1335-6471 ng/mL vs. 350 ng/mL and IQR, 139-670 ng/mL; p<0.001) and HS-cTnI (31.9 ng/L and IQR 7.2-69.5 ng/L vs. 4.1 ng/L and IQR 1.2-12.8 ng/L; p<0.001) were significantly higher than in the remaining cohort of no-VTE patients. As regards patients diagnosed with PE, the median values of D-dimer (3371 ng/mL and IQR, 2384-6471; p<0.001 vs. no-VTE patients) and HS-cTnI (37.9 ng/L and IQR 10.9-106.3 ng/L; p<0.001 vs. no-VTE patients) were also found to be significantly higher than in the remaining cohort of no-VTE patients, as were the median values of D-dimer (1609 ng/mL and IQR 1202-4397; p<0.001 vs. no-VTE patients) but not those of HS-cTnI (19.3 ng/L and IQR 5.6-48.5; p=0.404 vs. no-VTE patients) in DVT patients.

The diagnostic performance of D-dimer and HS-cTnI was 0.70 (95% CI, 0.69-0.71) and 0.71 (95% CI, 0.65-0.78) for all VTE episodes, 0.70 (95% CI, 0.69-0.71) and 0.63 (95% CI, 0.48-0.78) for deep vein thrombosis, 0.70 (95% CI, 0.69-0.71) and 0.74 (95% CI, 0.67-0.81) for pulmonary embolism, respectively (Figure 1).

The combination of positive values of both D-dimer and HS-cTnI yielded a better diagnostic performance than D-dimer values alone for diagnosing pulmonary embolism (AUC, 0.80; 95% CI, 0.76-0.85; *P*<0.001 vs. D-dimer alone), but not for diagnosing deep vein thrombosis (AUC, 0.73; 95% CI, 0.64-0.83; *P*=0.458 vs. D-dimer alone). In patients with pulmonary embolism, positive HS-cTnI values in patients with concomitantly positive values of D-dimer yielded identical diagnostic sensitivity compared to D-dimer positivity alone (i.e., 1.00), but allowed to reach a nearly double diagnostic specificity (i.e., 0.71 vs. 0.40)

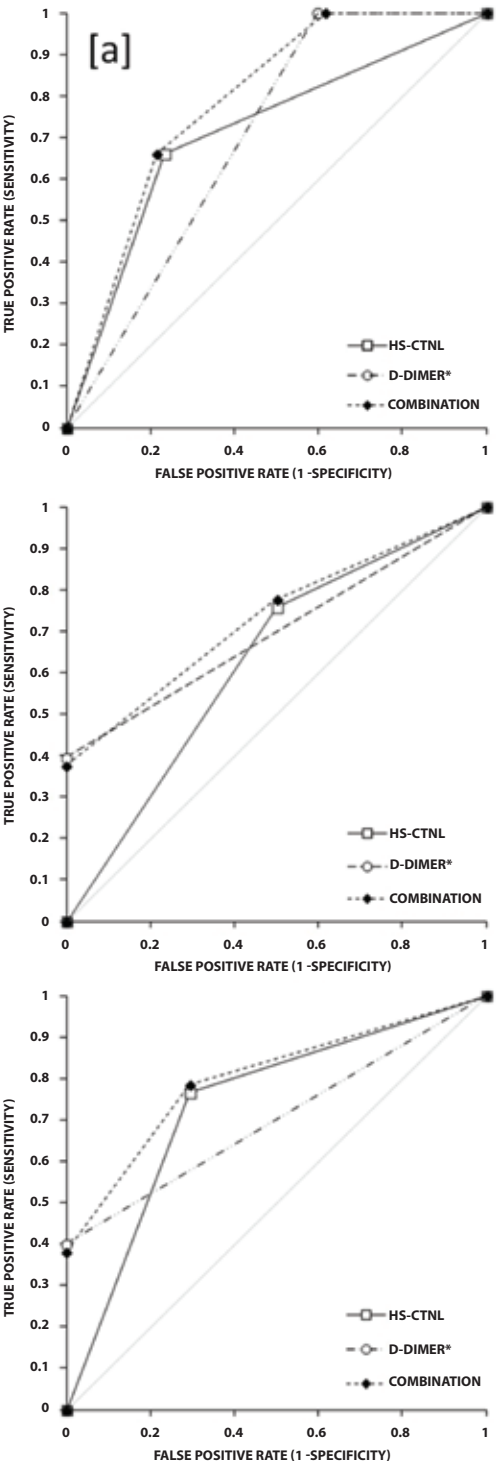

Figure 1. Receiver Operating Characteristics (ROC) curve analysis for diagnosing (a) venous thromboembolism (VTE), (b) deep vein thrombosis (DVT) and (c) pulmonary embolism (PE), by measuring D-dimer*, high-sensitivity cardiac troponin I (HS-cTnI) or their combination of positive values. ** D-dimer cut-off values have been adjusted for the age.*

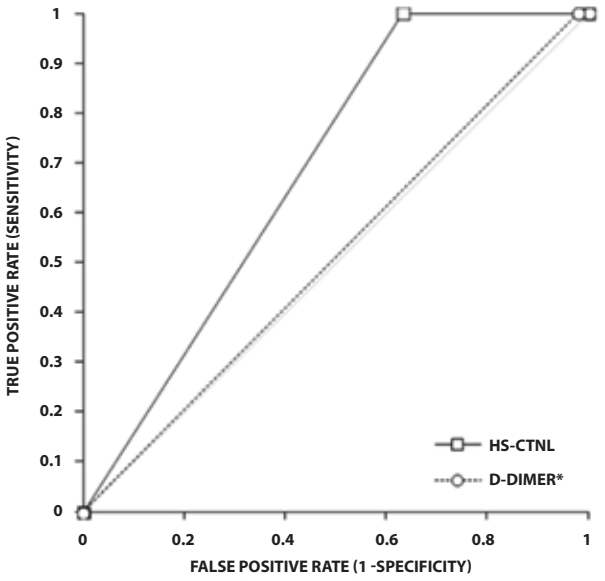

Figure 2. Receiver Operating Characteristics (ROC) curve analysis for predicting 30-day hospital readmission in patients with venous thromboembolism (VTE), by measuring D-dimer*, high-sensitivity cardiac troponin I (HS-cTnI) or their combination of positive values. **D-dimer cut-off values have been adjusted for the age.*

(Figure 1). Importantly, positive HS-cTnI values (AUC, 0.68; 95% CI, 0.62-0.75), but not D-dimer positivity (AUC, 0.51; 95% CI, 0.49-0.53), were associated with 30-days hospital readmission (n=4/53; 7.5%, all with PE) in patients with VTE (Figure 2).

Discussion

The measurement of cardiac troponins is not new in the setting of venous thrombosis, whereby reliable evidence has now been garnered in support of their valuable prognostic role in patients with VTE episodes (12,15), especially when assayed using the newer and more efficient HS immunoassays (11). Some scanty evidence has also been published on the possible contribution of cardiac troponins for diagnosis of VTE, with variably favourable results. Kilinc et al measured D-dimer and cTnI (with a contemporary-sensitive immunoassay) in 106 patients with suspected PE, 63 of whom were finally diagnosed with PE (16). The sensitivity and specificity of cTnI for diagnosing PE were 0.51 and 0.88, respectively, which then become 0.93 and 0.54 when positive D-dimer and cTnI values were combined. Demir et al also measured cTnI (with a contemporary sensitive method) in 117 patients urgently admitted with VTE symptoms, 59 of whom were finally diagnosed with PE (17). The overall diagnostic sensitivity and specificity of cTnI for diagnosing PE were 0.66 and 0.61, respectively. D-dimer values were unavailable in this study. In another very recent study, Kim et al measured D-dimer and cTnI (using a contemporary-sensitive immunoassay) in 861 consecutive patients with myocardial infarction (n=771) or PE (n=90) (18). ROC curve analysis for differentiating PE from myocardial infarction revealed an AUC of 0.86 for D-dimer (0.81 sensitivity and 0.70 specificity) and 0.87 for cTnI (0.81 sensitivity and 0.79 specificity), whilst the combination of both biomarkers increased the overall diagnostic performance to 0.95 (AUC), with 0.93 sensitivity and 0.87 specificity. Notably, unlike D-dimer values, which were not predictive of in-hospital mortality of VTE patients (P=0.237), cTnI concentration (p=0.001) and its combination with D-dimer values (P<0.001) help predicting the short-term risk of death.

Therefore, results of our investigation with an innovative HS-cTnI method reinforce previous evidence accumulated using contemporary-sensitive immunoassays, disclosing intriguing avenues for combining Hs-cTnI and D-dimer in the diagnostic approach of patients with VTE, particularly in those with PE. Notably, although we have found that the performance for diagnosing DVT remained virtually unchanged by combining positive values of HS-cTnI with D-dimer positivity (P=0.458), this strategy significantly increased the efficiency of D-dimer alone by nearly 10% for diagnosing PE (AUC variation, 0.10; 95% CI, 0.06-0.15; P<0.001). This improvement was mostly attributable to the enhanced diagnostic specificity, which increased from 0.40 to 0.71 by combining the two biomarkers. This would actually translate into a more efficient patient management in the ED, whereby pathologies other than VTE could be more efficiently and rapidly ruled out. The predictive value of HS-cTnI in VTE patients is another important - though not really

innovative - finding emerged from our study, whereby patients with increased HS-cTnI concentration were found to be at higher risk of rehospitalisation within 30 days after discharge. This evidence would contribute to confirm the hypothesis that PE patients with increased values of cardiac troponins are at increased risk of and complications, chronic disability and death than those with normal plasma levels (11).

There is a rather reasonable explanation for our findings, strictly connected with cardiac troponin biology in patients with different forms of cardiac injury (19,20). Previous studies in patients who have been diagnosed with EP in the ED show that cTnI elevations in these subjects are directly dependent on the level of involvement of main pulmonary arteries (21), on the presence of right ventricular dysfunction (22), as well as on the presence of subendocardial (or even transmural) ischemia evolving towards overt cardiomyocyte necrosis (11). Therefore, elevated cTnI value not only would reflect the frequent presence of cardiac injury in patients with PE, but may also help identifying a subset of patients with a higher risk of developing complications needing, for example, early rehospitalisation.

In conclusion, the results of our study show that the combination of HS-cTnI and D-dimer testing may increase the efficiency of D-dimer alone for diagnosing PE in the ED, thus deserving further assessment by means of larger and prospective investigations.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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