Utility of D-Dimer in the Diagnosis of Patients with Chronic Thromboembolic Pulmonary Hypertension

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Abstract: Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is an important cause of severe pulmonary hypertension (PH). D-dimer, a degradation product of fibrin, has been used as a marker for various diseases. In patients with idiopathic pulmonary arterial hypertension there is evidence to suggest that D-dimer levels are associated with disease severity; however, data regarding D-dimer in patients with CTEPH are lacking.

Objective: To assess the significance of D-dimer in patients with CTEPH.

Patients and Methods: Retrospective chart review of 618 patients seen at our PH clinic from 1991 to June 2008. Data collection focused on patients diagnosed with CTEPH, D-dimer levels, demographics, clinical, and hemodynamics. We compared D-dimer levels in CTEPH patients or World Health Organization (WHO) diagnostic group 4 with PH patients in WHO group 1.

Results: Thirty-four patients with confirmed CTEPH were identified, of these 19 had D-dimer levels and 7 were positive. Of the 234 patients in WHO group 1 excluding patients with portopulmonary hypertension (n = 54) and pulmonary veno-occlusive disease (n = 2) 97 had D-dimer levels and 52 were positive. We found an estimated sensitivity of the D-dimer test in diagnosing CTEPH was 37% while the estimated specificity was 46%. The positive predictive value and negative predictive value were 12% and 79% respectively.

Conclusion: D-dimer is an insensitive and nonspecific test for the diagnosis of CTEPH. Despite a high negative predictive value D-dimer alone cannot be used to rule out CTEPH in patients with PH.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is an important cause of severe pulmonary hypertension associated with significant morbidity and mortality [1]. The exact incidence of CTEPH is not known with certainty but historically been estimated to occur in 0.1-0.5% of patients who survive an episode of pulmonary embolism [2, 3]. One recent study by Becattini reported an incidence of about 1% [4], while Pengo and colleagues found evidence of CTEPH in 3.8% of patients within two years after a first episode of symptomatic pulmonary embolism [5]. D-dimer, a degradation product of cross-linked fibrin, has been used as a marker for various diseases [6, 7]. In patients with idiopathic pulmonary arterial hypertension (IPAH) there is evidence to suggest that D-dimer levels are associated with disease severity. Shitrit et al. looked at 14 idiopathic patients with IPAH and found that D-dimer levels were positively correlated with New York Heart Association (NYHA) functional class, pulmonary artery pressure, and survival [8]. The same group separately reported that the mean ELISA D-dimer levels were significantly higher in the IPAH group compared with the matched control group [9]. The findings in IPAH have a sound basis as thrombosis-in-situ [10] may play a key role in the pathogenesis [11]. In contrast, CTEPH probably occurs as a result of incomplete resolution of pulmonary emboli [12]. Eventually, the clot becomes incorporated into the pulmonary arterial wall leading to increased pulmonary vascular resistance and hypertension. Furthermore, fibrin derived from patients with CTEPH seems resistant to lysis [13].

Data regarding D-dimer levels in patients with CTEPH are lacking. Given the chronic and fibrotic nature of vascular obstruction, we hypothesized that D-dimer levels would not correlate with CTEPH when compared with patients that have PH not due to chronic thromboembolism.

PATIENTS AND METHODS

After approval by our institutional review board a retrospective chart review of 618 patients seen at the pulmonary hypertension (PH) clinic at the Mayo Clinic, Jacksonville from 1991 to June 2008 was conducted.

Data collection focused on age on date of PH evaluation, gender, race, World Health Organization (WHO) functional classification and diagnostic group [14], and D-dimer level.

Pulmonary hypertension was defined as the presence of a mean pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg with exercise at catheterization [15] or an estimated right ventricular systolic pressure greater than 35 mmHg by echocardiogram [16].

D-dimer levels that were collected prior to February 2003 were performed using the latex agglutination test which is
semi-quantitative with a normal range of <250 μg/L. Thereafter, D-dimer was performed utilizing the turbidimetric titration assay with a normal range of ≤ 0.4 μg/ml. An elevated D-dimer level using the appropriate normal range for each test was considered to be positive.

Patients with CTEPH were diagnosed based on positive ventilation and perfusion (V/Q) lung scan [17], positive CT angiography, and/or by pulmonary arterial angiographic evidence of chronic thromboembolism. If V/Q scan was the primary mode of diagnosis, it was required to be high probability for thromboembolic disease in order to be considered a positive test for CTEPH. A negative CT angiogram was not considered sufficient to exclude CTEPH. For patients with WHO group 1 chronic thromboembolism was excluded via V/Q lung scan.

Numerical variables were summarized with the sample median, minimum, 25th percentile, 75th percentile, and maximum. Categorical variables were summarized with number and percentage. Patient characteristics were compared between CTEPH and WHO group 1 patients using Fisher’s exact test or a Wilcoxon rank sum test. Logistic regression was used to investigate the association between D-dimer test results (positive vs negative) and diagnosis group (WHO group 1 vs CTEPH WHO group 4); a single variable model was considered as well as a multivariate model adjusted for age and sex. Sensitivity, specificity, positive predictive value (PPV), and negative predicted value (NPV) were estimated along with exact binomial 95% confidence intervals (CIs). Statistical analyses were performed using SPLUS (version 8.0.1; Insightful Corporation, Seattle, Washington).

RESULTS

Thirty-four patients with confirmed CTEPH based on positive V/Q lung scan, CT angiography, and/or by pulmonary arterial angiogram were identified. Nine patients (26%) had a high probability V/Q scan alone, 5 (15%) had a positive CT angiogram alone, and 8 (24%) had a positive pulmonary arterial angiogram alone. There were 12 (35%) patients who had a combination of positive tests.

Nineteen of 34 (56%) CTEPH patients had D-dimer levels of which 7 were positive (37%). Table 1 compares the clinical and hemodynamic characteristics of the patients with available D-dimer levels in CTEPH and WHO group 1 or pulmonary arterial hypertension (PAH) excluding patients with portopulmonary hypertension (n = 54) and pulmonary veno-occlusive disease (n = 2). Ninety seven of 234 (41%) patients in WHO group 1 had D-dimer levels available.

The only statistically significant difference in demographics (age, race and sex) was that there were more men in the CTEPH group compared to WHO group 1 patients. Most patients were WHO functional class III or IV in both groups. The six-minute walk distance was also similar in both groups. Echocardiogram was performed on all patients and there was no difference between the two groups in the estimated pulmonary artery systolic pressure. Most patients in each group had right heart catheterization with similar hemodynamic results.

The patients who had D-dimer testing are compared in Table 2. In single variable analysis, there is no evidence of a difference in the proportion of positive D-dimer tests between CTEPH and WHO group 1 patients (37% vs 54%, p = 0.19). These findings remain consistent after adjusting for age and sex (p = 0.19). The estimated sensitivity of the D-dimer test in diagnosing CTEPH was 37% (95% CI: 16%-62%), while the estimated specificity was 46% (95% CI: 36-57%). The estimated PPV was 12% (95% CI: 5%-23%), while the NPV was 79% (95% CI: 66-89%).

The D-dimer test was performed in only 116 of the original 268 patients considered. When we compared patients with a D-dimer test to those patients without a D-dimer test for CTEPH and WHO group 1 patients separately, we noted no meaningful differences except that CTEPH patients with a D-dimer test were male more often than CTEPH patients without a D-dimer test (Table 3). Overall, patient characteristics appear similar between patients with and without a D-dimer test performed except for sex in CTEPH patients.

DISCUSSION

It has been suggested that CTEPH is an extension of the natural history of acute pulmonary embolic disease but it occurs only in a minority of patients after acute embolism [12, 18, 19]. However, CTEPH may occur in the absence of a clear history of acute pulmonary embolism [20]. Even in patients receiving appropriate treatment for an acute pulmonary embolism incomplete resolution occurs in a significant number of patients placing them at risk for developing CTEPH [21]. The occurrence of CTEPH portends a poor prognosis and if left untreated the probability of survival for 5 years is only 30% when the mean pulmonary artery pressure is >40 mmHg [22]. Because CTEPH is associated with significant morbidity and mortality, the recognition of patients who are at risk has been challenging. The prevalence of thrombophilic states in patients with established CTEPH has shown to be no different than in patients who have IPAH or control subjects [23, 24]. However some reports suggest that an underlying hypercoagulable state may be responsible for the development of CTEPH. One study by Bonderman and colleagues [25] showed increased levels of factor VIII in 41% of patients with CTEPH compared to 5% of normal controls. Antiphospholipid antibodies, another possible prothrombotic finding have been identified in up to 21% of patients who have CTEPH [22]. D-dimer assay, a specific marker for crossed linked fibrin is often used as a marker for thromboembolic disease. As mentioned previously in patients with IPAH there is evidence to suggest that D-dimer levels are associated with the status of disease severity [8, 9]. However, in 47 patients with PAH and systemic sclerosis according to a study by Kiatchoosakun and colleagues [26] showed no change in D-dimer levels.
Table 1. Patient Characteristics

| Variable       | CTEPH (N = 19) | WHO Group 1 (N = 97) | P-Value |
|----------------|----------------|----------------------|---------|
| Age            | 71 (31, 63, 74, 81) | 64 (21, 53, 73, 88) | 0.18    |
| Sex (Male)     | 10 (53%)        | 20 (21%)             | 0.008   |
| Race           |                |                      | 0.11    |
| Caucasian      | 15 (79%)        | 90 (93%)             |         |
| African American| 4 (21%)       | 6 (6%)               |         |
| Other          | 0 (0%)          | 1 (1%)               |         |
| WHO class      |                |                      | 0.75    |
| 1              | 1 (5%)          | 4 (4%)               |         |
| 2              | 3 (16%)         | 24 (25%)             |         |
| 3              | 13 (68%)        | 56 (58%)             |         |
| 4              | 2 (11%)         | 13 (13%)             |         |
| Six minute walk test (meters) | 319 (126, 266, 407, 460) | 293 (142, 235, 354, 432) | 0.27    |
| Echo RVSP (mmHg) | 81 (41, 73, 90, 132) | 74 (21, 51, 94, 145) | 0.23    |
| PAS (mmHg)     | 80 (50, 74, 86, 102) | 75 (32, 65, 89, 152) | 0.47    |
| mPAP (mmHg)    | 50 (26, 40, 52, 63) | 49 (19, 38, 54, 100) | 0.81    |
| Cardiac output (L/min) | 4.0 (1.9, 2.8, 5.5, 8.8) | 3.7 (1.3, 3.1, 4.6, 8.9) | 0.89    |
| Cardiac index (L/min/m²) | 2.0 (1.1, 1.6, 2.7, 3.5) | 2.2 (1.3, 1.8, 2.6, 4.7) | 0.59    |
| PVR (dyne*sec/cm²) | 515 (358, 478, 1153, 1501) | 610 (197, 476, 1005, 3692) | 0.81    |

*P-values result from Fisher’s exact test or a Wilcoxon rank sum test. The sample median (minimum, 25th percentile, 75th percentile, maximum) is given for numerical variables. Information was unavailable for the following variables: PAS (N = 34), MPAP (N = 32), Cardiac output (N = 42), Cardiac index (N = 49), PVR (N = 46), and six minute walk test (N = 24).

CTEPH = chronic thromboembolic pulmonary hypertension; WHO = World Health Organization; Echo = echocardiogram; RVSP = right ventricular systolic pressure; RCH = right heart catheterization; PAS = pulmonary artery systolic pressure; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance.

Table 2. D-Dimer Results According in CTEPH and WHO Group 1 Patients

| D-Dimer Test Result | CTEPH (N = 19) | WHO Group 1 (N = 97) |
|---------------------|----------------|----------------------|
| Positive            | 7 (37%)        | 52 (54%)             |
| Negative            | 12 (63%)       | 45 (46%)             |

CTEPH = chronic thromboembolic pulmonary hypertension; WHO = World Health Organization.

Our study shows that the ability of D-dimer to detect for CTEPH is insensitive even with a high negative predictive value which supports our hypothesis and the above postulated mechanism for CTEPH. We also could not find a statistical difference in the proportion of the positive D-dimer tests between CTEPH and WHO group 1 patients.

Conversely, the pathophysiology of PAH involves thrombosis in situ in a significant number of patients [12, 27, 28]. Indeed, a relationship between elevated D-dimer levels and the severity and prognosis of PAH has been demonstrated [8, 9]. In both studies [8, 9] by Shitrit et al. the majority of the PAH patients were women and most had class III or IV symptoms similar to our population. In our group of CTEPH patients there was slightly more males than females in the group with available D-dimer. However, in the CTEPH patients overall there was still a predominance of females (20 out of 34 or 59%). Other characteristics appeared similar in both groups with or without D-dimer testing including hemodynamic values.

D-dimer may not be an attractive test for screening for CTEPH but may have other implications including prognosis value which was not evaluated in our study.

This study has several limitations. It is retrospective and single-center in design. Due to the relatively small sample size, there is a lack of power to detect an association between D-dimer test result and diagnosis group (CTEPH WHO group 4 vs WHO group 1). Thus, there may be an association between these two variables that this study did not have enough power to detect. Secondly, the study was performed in a tertiary care center which could likely differ from other centers or in a primary care setting where D-Dimer is used as a screening test. Not all patients had D-dimer testing but the patients who did not seem similar in demographic and clinical characteristics which may lessen the likelihood of bias. Furthermore, there were two methods of testing for D-Dimer during the study period which could have different sensitivities or specificities in detecting CTEPH. Analyzing data from only one method of testing was felt that the power of the study would be insufficient due to the overall low number of patients having available D-Dimer values. However, we did interpret the tests results as positive and negative as opposed to using absolute values which cannot be compared head to head to reduce testing method bias. Another point worth mentioning is that the majority of
patients (17 out of 19) with CTEPH that had D-Dimer available were already on anticoagulation at the time of evaluation. Due to the study design which was a retrospective study we did not address or follow up D-Dimer levels after the diagnosis of CTEPH was made to allow for comparison. Further studies are required with larger number of participants utilizing one standard method for detecting CTEPH is needed. D-dimer itself though not appealing as a diagnostic test for CTEPH could have some light in following patients with already diagnosed CTEPH and suspecting of having an acute thromboembolic event thus this area would still need to be explored.

CONCLUSION

In summary the low sensitivity and specificity for D-dimer for the detection of CTEPH makes it an insensitive screening tool. Despite the high negative predictive value, D-dimer alone should not be used to rule out CTEPH. Conversely, the presence of an elevated D-dimer in PAH is quite common, the significance of which was not studied.

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Dr. Charles D. Burger contributed significantly towards intellectual manuscript preparation, data collection, and review of the literature.

CONFLICTS OF INTEREST

Dr. Vichaya Arunthari has no conflicts of interest to disclose.

Dr. Charles D. Burger has had limited consulting and/or advisory board relationships with the following companies: Actelion, Alkermes, United Therapeutics, Eli Lilly, and Gilead. In addition, has participated in the COPD task force sponsored by Boehringer-Ingelheim during which pulmonary hypertension was discussed.

ABBREVIATIONS

CI = Confidence interval
CTEPH = Chronic thromboembolic pulmonary hypertension
Echo = Echocardiogram
IPAH = Idiopathic pulmonary arterial hypertension
mPAP = Mean pulmonary artery pressure
NYHA = New York Heart Association
NPV = Negative predictive value

Table 3. Patient Characteristics According to D-Dimer Test Availability, Separately for CTEPH and WHO Group 1 Patients

| Variable                | CTEPH Patients | WHO Group 1 Patients |
|-------------------------|----------------|---------------------|
|                         | D-Dimer Available (N = 19) | D-Dimer Not Available (N = 15) | D-Dimer Available (N = 97) | D-Dimer Not Available (N = 137) |
| Age                     | 71 (31, 63, 74, 81) | 67 (28, 51, 70, 82) | 64 (21, 53, 73, 88) | 60 (15, 48, 71, 86) |
| Sex (Male)              | 10 (53%)        | 4 (27%)             | 20 (21%)           | 34 (25%)           |
| Race                    |                |                     |                   |                   |
| Caucasian               | 15 (79%)        | 13 (87%)            | 90 (93%)          | 119 (87%)          |
| African American        | 4 (21%)         | 2 (13%)             | 6 (6%)            | 15 (11%)           |
| Other                   | 0 (0%)          | 0 (0%)              | 1 (1%)            | 3 (2%)             |
| WHO class               |                |                     |                   |                   |
| 1                       | 1 (5%)          | 1 (7%)              | 4 (4%)            | 10 (7%)            |
| 2                       | 3 (16%)         | 3 (20%)             | 24 (25%)          | 29 (21%)           |
| 3                       | 13 (68%)        | 7 (47%)             | 56 (58%)          | 81 (59%)           |
| 4                       | 2 (11%)         | 4 (27%)             | 13 (13%)          | 17 (12%)           |
| Six minute walk test (meters) | 319 (126, 266, 407, 460) | 206 (206, 206, 206, 206) | 293 (14, 223, 354, 532) | 270 (51, 208, 348, 561) |
| Echo RVSP (mmHg)        | 81 (41, 73, 90, 132) | 79 (43, 60, 92, 125) | 74 (21, 51, 94, 145) | 77 (32, 55, 99, 140) |
| PAS (mmHg)              | 13 (68%)        | 8 (53%)             | 71 (73%)          | 92 (67%)           |
| mPAP (mmHg)             | 80 (50, 74, 86, 102) | 83 (47, 69, 92, 159) | 75 (32, 65, 89, 152) | 80 (32, 67, 96, 138) |
| Cardiac output (L/min)  | 4.0 (1.9, 2.8, 5.5, 8.8) | 4.5 (3.8, 4.0, 4.7, 5.9) | 3.7 (1.3, 3.1, 4.6, 8.9) | 3.9 (1.3, 3.3, 4.8, 9.3) |
| Cardiac index (L/min/m²) | 2.0 (1.1, 1.6, 2.7, 3.5) | 1.8 (1.7, 1.7, 1.8, 1.8) | 2.2 (1.3, 1.8, 2.6, 4.7) | 2.3 (0.8, 1.8, 2.9, 4.9) |
| PVR (dyne·sec/cm⁵)      | 515 (358, 478, 1153, 1501) | 620 (294, 531, 651, 813) | 610 (197, 476, 1005, 3692) | 726 (82, 429, 934, 2238) |

- The sample median (minimum, 25th percentile, 75th percentile, maximum) is given for numerical variables. Information was unavailable for the following variables: PAS (N = 88), MPAP (N = 84), Cardiac output (N = 118), Cardiac index (N = 132), PVR (N = 127), and six minute walk test (N = 142).
- CTEPH = chronic thromboembolic pulmonary hypertension; WHO = World Health Organization; Echo = echocardiogram; RVSP = right ventricular systolic pressure; RCH = right heart catheterization; PAS = pulmonary artery systolic pressure; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance.
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PAH = Pulmonary arterial hypertension
PAS = Pulmonary artery systolic pressure
PH = Pulmonary hypertension
PPV = Positive predictive value
PVR = Pulmonary vascular resistance
RCH = Right heart catheterization
RVSP = Right ventricular systolic pressure
V/Q = Ventilation and perfusion
WHO = World Health Organization

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