DIAGNOSTIC ACCURACY OF D-DIMER ASSAY IN PULMONARY EMBOLISM USING CTPA AS GOLD STANDARD

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ABSTRACT

Objective: To determine the sensitivity and specificity of D-dimer assay for the diagnosis of PE in resource limited settings using CTPA as a gold standard for comparison.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Radiology, Combined Military Hospital, Peshawar, from Feb 2019 to Jul 2020.

Methodology: A sample of 114 cases of clinically suspected PE presenting in ED were collected by non-probability sampling as per QUADAS 2 domains. D-dimer and CTPA reporting done by separate teams, compilation of data by third team. Using SPSS 23.0, 2×2 contingency table was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of D-dimer in diagnosing PE.

Results: Age range 20-50 years (mean: 40.54 ± 5.02 years). Sixty patients were female (52.3%). D- Dimer levels for the diagnosis of PE: Sensitivity: 92.86%, specificity 89.66%, positive predictive value (PPV): 89.66% and negative predictive value (NPV): 92.86%.

Conclusion: The D-Dimer levels are significantly sensitive and specific in the diagnosis of PE: however keeping in view the high mortality of PE, diagnostic accuracy may be further improved by using D-Dimer levels in conjunction with pretest clinical probability rules.

Keywords: CT pulmonary Angiography, D-Dimer, Pulmonary embolism, Sensitivity.

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INTRODUCTION

Cardiovascular diseases are the number one cause of death globally accounting for 17.9 million deaths per year, 85% of which are due to ischemic heart disease and strokes. The third leading cause of cardiovascular death worldwide is pulmonary embolism (PE).[1] The epidemiology of PE is difficult to determine because in addition to the burden of symptomatic disease; it may also be asymptomatic, may present as an incidental finding or as sudden death.[2] Pulmonary embolism is also one of the most important causes of sudden death which occurs in 10% of hospitalized patients, of which only 29% are correctly diagnosed before death. It is a common life-threatening complication in patients with long-term hospitalization, especially in intensive care units (ICUs).[3] Local data show a mortality of 12.6% with male preponderance in patients presenting in Emergency Department with clinical suspicion of PE.[4] The diagnostic tools for diagnosis of PE have evolved from pulmonary angiography to ventilation perfusion scanning and now CT pulmonary angiography (CTPA).[5] The gold standard for the diagnosis of pulmonary embolism is CTPA which has high specificity and sensitivity but also has high cost, risk of contrast reactions and radiation exposure.[6] The diagnosis of pulmonary embolism in resource limited settings may be challenging as evidenced by the search for clinical decision rules by various set ups.[7] The D-dimer is a breakdown product of the cross linked fibrin mesh and can be used to rule out pulmonary embolism in patients with low pretest clinical probability based on specified cut off levels e.g 1000ng/ml.[6] This finding has also been found to be true in children.[8] In the case of moderate clinical pretest probability the standard accepted approach is to perform chest imaging directly.[9] However it has also been shown that a combination of moderate pretest probability with D-dimer testing has resulted in reduced need for chest imaging associated with a negligible incidence of venous thromboembolism.[6] The wide variation in the different types of commercially available D-dimer assays may make extrapolation of study results difficult.[9] The rationale of our study was to determine the sensitivity and specificity of D- dimer assay for the diagnosis of

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PE in resource limited settings using CTPA as a gold standard for comparison.

METHODOLOGY

This was a descriptive, cross-sectional, diagnostic test accuracy study done at Department of Radiology, Combined Military Hospital, Peshawar from February 2019 to July 2020 after approval of institutional review board (IERB approval letter no 64-21). A sample size of 114 cases was calculated with 95% confidence level, 12% desired precision, keeping prevalence of pulmonary embolism as 50.61% with 70.3% sensitivity and 70.1% specificity of D-dimer in diagnosing pulmonary embolism.[10] Sample was collected using non-probability, consecutive sampling technique. The four domains of QUADAS 2 (Quality Assessment of Diagnostic Accuracy Studies-2) were kept in mind and applied (as feasible) during the planning stage of the study.

Inclusion criteria: All patients presenting in emergency department (ED) with clinical suspicion of pulmonary embolism of ≤24 hours i.e. sudden dyspnea, sudden, sharp chest pain aggravated by deep breathing or coughing, heart rate (>100/min), respiratory rate >30/min, sweating, hemoptysis.

Exclusion criteria: Patients with hypersensitivity to intravenous contrast agent, renal insufficiency and heart failure were excluded. Informed written consent was taken from each patient or next of kin where appropriate.

Data collection was done by 2 separate teams and compiled by a third team. The d-dimer team was responsible for collection of the d-dimer report only and then submitted the report to the compilation team and were not exposed to the result of the CTPA report. Venous sampling of 3 ml blood was withdrawn from all patients. The sample was then sent to the laboratory in a cold box. Within 48 hours of d-dimer testing CTPA was done for each patient by the CTPA team.

All images were obtained using a 128-slice multidetector CT scanner (Toshiba Aquilion Prime) by using a standard CTPA protocol for PE using Sure Start software (Toshiba medical systems). This technique uses the bolus-tracking method.[11]

It was reported upon by a consultant radiologist who was not aware of the d-dimer assay result at any time before, during or after the reporting process.

Only direct findings of acute PE in CTPA were used to diagnose pulmonary embolism including a "polo mint" appearance when a central filling defect was seen along short axis of the vessel or a "railway sign" when seen along long axis, an eccentric or luminal filling defect making an acute angle with a vessel wall, complete occlusion of a dilated vessel by a filling defect and a large defect sitting over the pulmonary trunk bifurcation also called a "saddle embolus".[11]

The reported CTPA diagnosis was submitted to the compilation team who then recorded both d-dimer result and CTPA report on a customized data collection proforma. A pre-specified cut off level of 500ng/ml was considered positive i.e. significant for PE. Collected data was analyzed Data was analyzed by using Statistical Package for the social sciences (SPSS) version 23.0. Age and duration of symptoms were presented as mean and standard deviation. Gender, hypertension (yes/no) and pulmonary embolism on d-dimer levels and CTPA were presented as frequency and percentage. 2×2 contingency table was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of D-dimer in diagnosing pulmonary embolism. Stratification was done for age, gender, duration of symptoms and BMI. Post-stratification chi square test was applied and the *p*-value ≤0.05 was taken as significant.

RESULTS

Fifty eight patients (50,9%) had a D-dimer value above the cut off value of 500ng/ml whereas 52 (45.6%) showed PE on CTPA as shown in Table-I. Age range in this study was from 20-50 years with mean age of 40.54 ± 5.02 years. Majority of the patients 92 (80.70%) were between 36-50 years of age. Out of these 114 patients, 60 (52.63%) were female. Mean duration of symptoms was 7.22 ± 2.60 hours.

Table-I: Frequency Table for positive and negative values of D-dimers and CTPA.

Variable	Above cut off value/ positive n (%)	Below cut off value/negative n (%)
D-Dimer levels	58 (50.9%)	56 (49.1%)
CTPA	52 (45.6%)	62 (54.4%)

In the 58 patients with D-dimer above the cut off range, CTPA also reported pulmonary embolism in 52 (true positive) cases whereas 6 (false positive) had no pulmonary embolism. In D dimer negative patients, 52 were true negative while 04 were false negative. Diagnostic accuracy calculated via 2x2 table (Table-II) is shown in Table-III.

Table-II: 2 x 2 Table showing comparison of D-dimer vs CTPA accuracy.

	Positive result on CTPA	Negative result on CTPA
Positive result on d-dimer	52 (TP)*	06 (FP)***
Negative result on d-dimer	04 (FN)**	52 (TN)****

-TP=True positive **-FP=False positive *-FN=False negative ****-TN=True negative*

Table-III: Validity of D-dimer test for pulmonary embolism.

Diagnostic Test Validity Parameter	Value (%)
Sensitivity	92.86%
Specificity	89.66%
Positive Predictive Value (PPV)	89.66%
Negative Predictive Value (NPV)	92.86%
Diagnostic Accuracy	91.23%

DISCUSSION

The role of the d-dimer in the diagnosis of PE has been shown in a 2016 Cochrane review which concludes that a negative D-dimer test is valuable in ruling out PE in patients who present to the A&E setting with a low clinical probability.[12] Clinical prediction rules such as Well's and Geneva criteria to determine pretest probability for PE are validated in well-resourced countries but seem to fall short in terms of applicability in low resource settings.[7,13] Clinical prediction rules have also been shown to be unreliable in pregnancy where D-dimer had a sensitivity of 88.4% and low specificity of 8% using a standard cut off.[14] Multiple studies have been conducted to determine the diagnostic accuracy of the d-dimer assay in diagnosis of PE. Gao *et al* did a retrospective analysis of 32 patients undergoing both d-dimer and CTPA and found a sensitivity of 96.2%, specificity of 50%, positive predictive value of 89.3%, negative predictive value of 75.0% and accuracy of 87.5% using a D-dimer cut off level of 1.9 µg/ml equivalent to 1900ng/ml. This was a far higher cut off than used in our study despite which it had a higher sensitivity.[15] Most studies have used a cut off of 500 ng/ml which is useful for ruling out PE and avoiding further testing when the pretest probability is low.[6] However, a higher sensitivity and positive predictive value (PPV) would be desirable and may be achieved by using higher cut off value as done by Gao *et al* and others. In one study a cut off of 2152 ng/ml was used with improved PPV (53%) and sensitivity of 82%.[16] A higher cut off level is also required in COVID-19.[17] Our study also showed a very high sensitivity comparable to that by Hui Gao et al with a remarkably high specificity despite a low cut off level of 500 ng/ml. Despite this the use of D-dimer as a diagnostic tool needs to be balanced against the fact that if a CTPA is still required after doing a D-dimer then it only increases care time without adding any benefit.[18] This is more relevant in scenarios with moderate to high clinical probability where CTPA is advised directly. The D-dimer test is thus most useful in low clinical probability by ruling out PE but its significant sensitivity is not supported by a high enough specificity. Therefore, given the high mortality and morbidity of the disease, D-dimer has to be considered after weighing risks of the tests vs benefit or lack thereof in high clinical probability cases.

The question of whether to test or treat at the bedside is not often guided by statistics and results of meta-analyses alone but by intangibles embedded within the experience of the clinician or diagnostician. The high mortality of PE lends to a lurking fear of losing a patient that may lead to unnecessary testing, the word unnecessary often being a retrospective conclusion. The risks of various tests and treatments need to be taken into account while ordering them such as the risk of carcinogenesis secondary to the exposure to the radiation inherent in a CTPA scan (1 in every 2000 exposures) and the risk of renal failure secondary to exposure to contrast agents (1 in every 200 exposures).[18] The lack of the use of tests such as clinical pretest probability and perhaps the D dimer may lead to an over prescription of the CTPA leading to unnecessary exposures to radiation and cost effects/wastage of resources.[19] It is therefore necessary to minimize the risk of such exposures by strengthening the ability to screen for PE effectively. D- dimer is one such promising test and carries sufficient sensitivity and specificity to act as an appropriate screening test especially if done alongside clinical rules for pretest probability testing. Further improvement in reducing care time and efficiency of diagnostic process to initiate timely definitive care can be achieved by point of care D-dimer testing which has comparable results and low costs. This may be useful in low resource settings where rapid screening prior to referral is required.[20] The high mortality of PE and the seriousness of the clinical scenario dictate the clinicians' actions and decisions at the bedside. The search for a less invasive and highly sensitive and specific test to rule in or rule out PE has been on for a considerable time. Is the sensitivity and specificity of the D-dimer test in our study significantly high to qualify as a stand-alone test in the diagnosis of PE and thus negate the need for a CTPA or further intervention when D-dimer is negative? Perhaps not, given the high risk of mortality of PE. However, adding the clinical pretest rules to this

scenario may successfully improve the predictive value of the D-dimer in the diagnosis of PE and guide further management.

What this study adds: The diagnostic accuracy of the D-dimer for PE in the local population has been ascertained and a high sensitivity /specificity suggests that it may be used as a screening test for PE prior decision for CTPA. The strengths of this study were the attention to the quality domains of QUADAS 2, blinding of CTPA reporter to D-dimer result and good sample size. The weakness of this study was the lack of use of clinical pre-test probability alongside d-dimer testing as per guidelines noted previously.

CONCLUSION

The D-Dimer levels are significantly sensitive and specific in the diagnosis of PE: however, keeping in view the high mortality of PE, diagnostic accuracy may be further improved by using D-Dimer levels in conjunction with pretest clinical probability rules.

LIMITATION OF STUDY

The weakness of this study was the lack of use of clinical pre-test probability alongside d-dimer testing as per guidelines noted previously.

Conflict of Interest: None.

Author's Contribution

SA: Performed computations, significant share in writing the manuscript and approval, MJ: Conceived and presented the idea, manuscript writing, NI: verified and analytical methods and helped shape the research, SS, AI, LA: Critical review and helped shape the research.

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