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ORIGINAL PAPERS

D-DIMER AS A SENSITIVE AND A VERY NONSPECIFIC PARAMETER FOR THE DIAGNOSIS OF PULMONARY EMBOLISM

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ABSTRACT

Background: Since the beginning of the Covid-19 pandemic there has been an immense increase of CT pulmonary angiogram (CTPA) requests at the Department of Radiology at our hospital. One of the most significant complications of Covid-19 is pulmonary embolism (PE). The gold standard for detecting pulmonary embolism is CTPA.
Aim: The aim of this study was to evaluate if an elevated value of D-dimer in both Covid-19 and non- Covid-19 patients, is reason enough for patients to undergo CTPA.
Methods: CTPA was used for PE evaluation. PCR testing was used in order to separate patients into positive and negative Covid-19 groups. Plasma D-dimer levels were measured using the BCS XP Siemens System.
Results: Covid-19 did not cause a significant difference in D-dimer values. Both Covid-19 and non-Covid-19 patients below the threshold of 0,5μg/mL, should not be considered for CTPA. Testing the sensitivity and specificity values at different cut-offs, provided us with an increase in specificity at higher cut-off values, but also a significant decrease in sensitivity.
Conclusions: D-dimer levels should be more often in correlation with clinical tests, since it has a low specificity for pulmonary embolism even at different cut-off values.

Keywords: D-dimer, CT pulmonary angiogram, Covid-19, pulmonary embolism

INTRODUCTION

On 31st of December 2019, World Health Organisation (WHO) was informed of cases of pneumonia of unknown cause in Wuhan City, China. Less than 3 months later, on March 11th 2020, WHO declared a state of pandemic of the now know "Covid-19 virus" [1]. On March 2nd 2020, the first two cases of Covid-19 were diagnosed in Bosnia and Herzegovina [2]. The highly contagious viral illness was a cause of more than 6 million deaths worldwide as of March 2022, mainly because of its many complications, making it the most consequential global health crisis since the influenza pandemic of 1918 [3,4]. One of the most significant complications of COVID-19 is a pro-coagulant state, which can biochemically be detected by increased D-dimer levels. Elevated D-dimer levels are associated with an increased mortality and morbidity, likely because of the activation of inflammatory and coagulation factors [5,6,7].
D-dimer is a fibrin split that is a result of fibrin degradation, which can be measured through a serum sample. It provides a global marker of activation of the coagulation and fibrinolytic systems, and serves as an indirect marker of thrombotic activity [8]. D dimer testing first began in the 1970s and at first the results were reported as either "positive" or "negative", which was completely dependent of the predesignated cut-off value. A threshold of 0,5μg/mL was suggested, which was used by many institutions since numerous studies confirmed that this value grants as a 100% sensitivity for venous thromboembolism [9]. However, numerous studies also suggested that levels above 0,5μg/mL are highly non-specific, because of which many other factors such as different comorbidities (malignancy, hemorrhage, trauma etc.) should be taken into consideration when interpreting these results [10,11,12].
In this study we have reflected on one of the most common and significant complications of the pro-coagulant state, which is pulmonary embolism (PE) [13]. This is probably the reason why D-dimer testing has dramatically increased during the Covid-19 pandemic [14,15]. At this time, it should be noted that there is no definitive laboratory workup for patients suspected of having pulmonary embolism [16]. However, a large group of patients is

being tested for D-dimer and consequently undergoes CT pulmonary angiography (CTPA). Diagnostic testing for PE is mainly done in order to identify patients who should be treated with anticoagulant therapy. It is of great importance to identify these patients, since failure to diagnose PE on time leads to as many as 30% of deaths with untreated patients, while only 8% of patients which are adequately managed die due to these complications [17].

Medical gold standard refers to a diagnostic test that is regarded as definitive detection or exclusion of disease, and CTPA is considered to be the gold standard for evaluating PE [18, 19, 20]. CTPA has become inevitable in diagnosing PE with certainty, however it does have certain disadvantages such as radiation exposure, possible contrast reactions, high costs, and can also be time consuming and an additional burden to the radiology department [21].

This retrospective study tries to provide the answer for the questions: Were we over-testing patients during the Covid-19 pandemic? Should we have relied more on clinical tests, rather than using elevated D-dimer as an indication for CTPA?

MATERIALS AND METHODS

In this retrospective study data from 987 patients which were admitted to our hospital during a one year period, from November 2020 to November 2021 was collected and further evaluated for possible PE via CTPA at the Department of Radiology. This study was approved by the ethics committee of our hospital.

The inclusion criteria were all patients that were admitted to the Department of Radiology with suspicion for PE, and who have had a PCR test for Covid-19 and a D-dimer test.

The exclusion criteria were past history of PE, known allergy to the contrast agent used for CTPA, anticoagulation therapy received before blood sampling, postoperative patients, and pregnancy.

PCR testing was used, as a determining factor in order to separate patients into positive and negative Covid-19 groups. Plasma D-dimer levels were measured using the BCS XP Siemens System. Blood sampling was done before the administration of anticoagulation therapy.

Patients were categorized by their D-dimer levels into groups by a 0,5μg/mL interval value. Also, indicators on PE and PCR test were scaled in binary (negative PE=0, positive PE=1) and (negative PCR test=0; positive PCR test=1).

In statistical analysis of the presented problem the JASP open-source project supported by
University of Amsterdam (JASP Team, Version 0.17.2, 2023) was used.

CT acquisitions were performed with two multidetector CT units, SOMATOM Definition Edge 128 (Siemens Healthineers, Erlangen, Germany) and Canon Aquilion Start 32 (Canon Medical, Tokyo, Japan), using a CTPA protocol at our hospital. The CTPA was performed during inspiration using bolus-tracking technique (60 mL of non-ionic contrast with a 100 mL saline chaser at 4.5 mL/s with a time delay of 6 s). Images of those records identified were reviewed by radiologists on a picture archiving and communications system (PACS) workstation for identification of patients with PE. Scans were analysed using 1mm slice thickness, and were further processed using MIP and MPR techniques. All images were reviewed by two experienced radiologists (with 5 and 10 years of experience in reading CTPA, respectively) for the presence or absence of intraluminal filling defects in the proximal or distal (segmental or sub-segmental) pulmonary arteries and signs of acute right ventricular dysfunction. Information regarding D-dimer level within 24h of the CT examination were obtained.

RESULTS

PE was diagnosed in 191 patients (19.3%) of the 987 patients who underwent CTPA suspected with diagnosis of PE. In comparison to the same period a year before Covid-19, at our Department of Radiology, we had a dramatically increase of about 3-fold in demand for CTPA. D-dimer levels were compared with CTPA results and PCR results. D-dimer levels were divided into categories, by a 0,5μg/mL interval, the last category being D-dimer levels over 5,0μg/mL.

The distribution of frequency of appearance of D-dimer values at positive pulmonary embolism (PE) is presented in Figure 1.

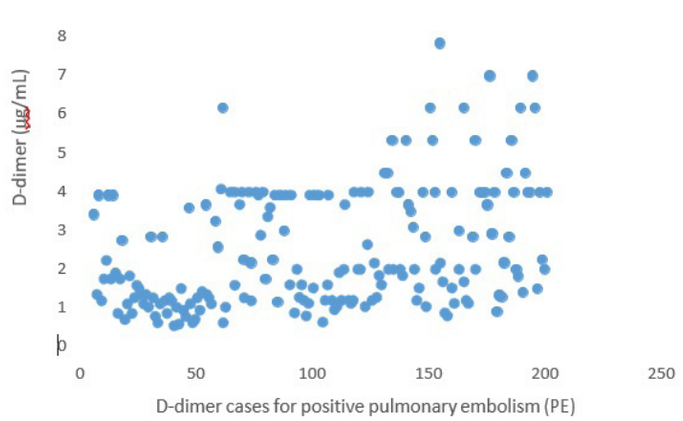

Figure 1. The distribution of frequency of appearance of D-dimer levels at positive PE

We further divided our patients in two different groups, PCR positive and PCR negative, and compared their D-dimer values. Covid-19 did not cause a significant difference in D-dimer values. Covid-19 positive patients had a D-dimer value of 2.9492±2.01923 (95% CI 1.64962-2.24868) compared to 2.7321±1.9087 (95% CI 2.5961-2.8680) for Covid-19 negative patients (p= 0.0870).

Comparing both Covid-19 positive and Covid-19 negative patients with the results of CTPA, we achieved mean D-dimer values for all four combinations. The mean D-dimer value for patients that were positive for PE and tested negative for Covid-19 was 3,16, while the mean D-dimer value for patients that were positive for PE but were tested positive for Covid-19 was 2,82. The mean value for patients that were negative for PE while tested negative for Covid-19 was 2,82, while the mean value for patients that were positive for PE and were also tested positive for Covid-19 was 2,62. In the PCR positive group there was a higher percentage of patients positive for pulmonary embolism (22,60%) compared to PCR negative group (15,60%). However, the obtained result is not significant (p=0.21).

Sensitivity and specificity of D-dimer in relation to the diagnosis of pulmonary embolism

D-dimer value of ≤0,5μg/mL was used as a cut-off value to determine if a patients is at risk of developing pulmonary embolism. At the value of ≤0,5μg/mL, we obtained a sensitivity level of 98%, but the specificity level was only 9,72%. At the cut-off value of ≤1,0μg/mL, we obtained a sensitivity level of 79,5%, and specificity level of 27,5%.

A recent study by The British Thoracic Society reported that the level of D-dimer of ≤1,3 μg /mL should be considered as a threshold to triage patients for CTPA [22]. At this threshold we achieved the sensitivity of 71%, and specificity of 36%. Tuck et al suggested that the D-dimer value of ≤1,5μg/mL should be taken as the best balance between sensitivity and specificity [15]. At this level we achieved the sensitivity of 64% and specificity of 39%. Also using the value of ≤1,9μg/mL as a threshold was suggested, at which we achieved sensitivity of 56%, and specificity of 45%. By raising the cut off value each time, we managed to improve the specificity of the test, but at a cost of reducing its sensitivity, as seen in Figure 2.

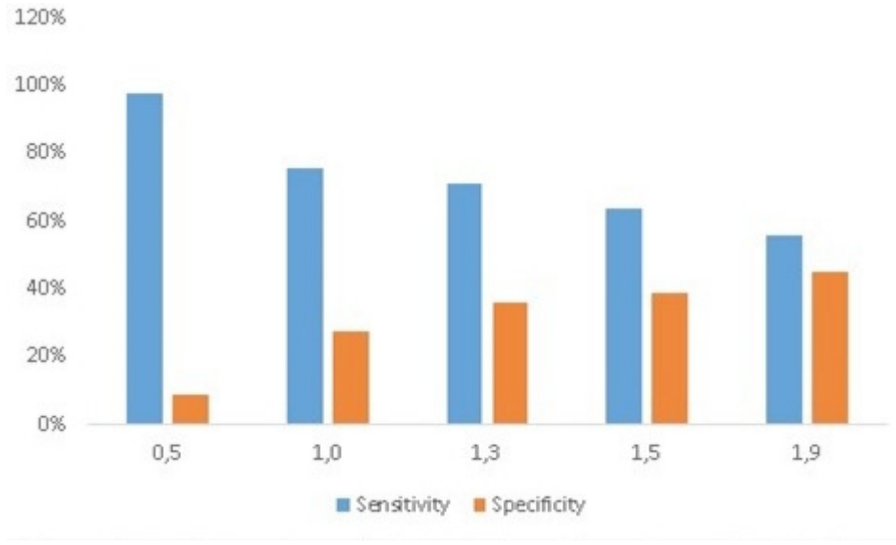

Figure 2. Sensitivity and specificity for both Covid-19 positive and negative patients

For the Covid-19 negative group at the D-dimer value of ≤0,5 μg/mL the sensitivity was 100% and the sensitivity of the test was 9,0%, compared to the sensitivity of 97,9% and specificity of 15% for the Covid-19 positive group. Tested at ≤1,3 μg/mL the sensitivity for the Covid-19 negative group was 76,4% and the sensitivity was 36,4%, compared to the Covid-19 positive group that had a sensitivity value of 71,7% and the specificity of 42,5%. By testing the sensitivity and specificity at the cut off value of ≤1,5 μg /mL we achieved the values of 73,5% and 37,8% for the Covid-19 negative group, and 63,6% and 37,3% for the Covid-19 positive group respectively. For the Covid-19 negative group at the cut off value of ≤1,9 μg /mL the sensitivity was 58,9% and specificity was 43,1%, while the Covid-19 positive group had values of 55,0% sensitivity and 46,5% specificity at the same cut off value.

DISCUSSION

Different studies used a similar approach to try and find a suitable cut-off value for D-dimer, one which would provide a good level of specificity, but not at the expense of losing too much sensitivity value of the test. At the value of ≤0,5μg/mL, we achieved a sensitivity

level of 98%, but the specificity level was rather low, only 9,72%. This is similar to other studies, where A. Tuck et al. obtained a sensitivity level of 98,5% and a specificity level of 12,0% [15], or another study by Vivan et al. that obtained the sensitivity of 98,2%, and specificity of 5,7% at the same cut-off value [12]. So far, we can say that the value of 0,5 μg /mL can be safely used to exclude pulmonary embolism, if the D-dimer values are below that threshold [24].

Optimal higher cut-off values of D-dimer were suggested for better prediction of PE [25,26,27]. Kearon et al. also suggested that pulmonary embolism can be ruled out if patients with a low to intermediate risk for PE have a D-dimer level of less than 0,5μg/mL [28]. Our study as well as many others suggest that setting higher D-dimer cutoffs improves specificity, but at the cost of reducing sensitivity, which can potentially be a fatal mistake in evaluating a condition such as PE [17].

Since the call for CTPA has significantly increased compared to the same period in the previous years, and it can safely be said due to the newfound disease-Covid-19, our main goal was to investigate if patients could be triaged only based on their D-dimer values, and if D-dimer can really be an independent risk factor as suggested in previous studies.

There were certain limitations to this study. The first one being that this is a retrospective study, so we could not test certain clinical parameters, such as the newly proposed modified Wells score or the revised Geneva score. This study did also not include patients that had elevated D-dimer levels, but did not undergo CTPA because of serious renal impairment, or other contraindications for CTPA. It is also a single center study, and patients were attended by many different physicians, and as such practice between them may vary.

It is understandable that clinicians may be over-investigating patients, as it is a novel pathogen that no one has had much experience with, and at the time there was not many scientific data about Covid-19 and its correlation to D-dimer.

Over-testing for PE has long been recognized as a significant problem in the process of patient management. In particular, the D-dimer test frequently results in a false positive test result that demands expensive and time-consuming radiological imaging [21].

A study by Ost et al. suggests that even though the spiral CT has led to an improvement in the diagnosis rate of PE, only one third of patients suspected of PE actually were diagnosed with PE [29].

Our yield of PE positive patients of 18,7% is comparable with other similar studies and within a Royal College of Radiologists guideline of 15,4-37,4% [22].

Similar to Chopra et al. [21], we can say that an elevated level of D-dimer should not be the only reason to undergo CTPA, as there are also certain risks that have to be considered. According to the American College of Radiologists, the average dose of radiation that a patient receives during a CTPA procedure is about 5,1mSv, which is about 2 years of natural background radiation exposure, and correlates to about 50 chest X-rays [30].

It should also be considered, that patients that are actually positive for PE, most commonly are called in after a certain period of time to undergo a control CTPA, which further increases the dosage of radiation that the patient receives.

Pre-testing the patient probability for the diagnosis of PE should be the very first step in determining weather there is indeed an indication for CTPA or other diagnostic tests. Other studies also agree that due to the poor specificity of D-dimer, further testing is often required [11,31,32].

Complimenting the clinical judgment could also be the PERC rule, as well as the revised Geneva score [10,21]. The test threshold defines the point of equipoise in pretest probability. When the pretest probability is lower than the test threshold, the probability that the patient will be harmed by further testing (including a screening test such as the D-dimer) exceeds the probability that the patient will benefit from further testing [21].

CONCLUSION

The diagnosis of any illness should always begin with acquiring the patient history and a detailed physical exam. It should not be otherwise even when we are dealing with Covid-19. D-dimer can be useful to some extent in excluding pulmonary embolism but with very great caution. However, due to its very low specificity even at higher cut-off values it should be always be in correlation with a thorough clinical exam before eventually confirming the diagnosis with CTPA. The results obtained in this study indicate that D-dimer levels should not be taken as the only factor to refer patients for CTPA. Adequate interpretation of D-dimer values, combined with a thorough clinical exam, as well as other valuable information on the condition of the patient can significantly reduce the pressure on radiology clinics regarding the requirements for CTPA.

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