Pulmonary Embolism is Enigmatic Problem in Emergency Service: Performance of Wells Score, Geneva Score and Other Test

Pulmoner Emboli Acil Servisin Bilmece Gibi Sorunu: Wells Skoru, Geneva Skoru ve Diğer Testlerin Performansı

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ÖZET

Pulmoner emboli; teşhisini koymak için gizemli ve zor olup, kardiyovasküler hastalığa bağlı ölümlerin üçüncü nedenidir. Son yıllardaki klinik araştırmalara ve teknolojik gelişmelere rağmen, pulmoner emboli teşhisi zor ve karmaşıktır. Pulmoner emboli tanısı hekimin şüphesiyle başlar. Öncelikle, klinik ön test, olasılığının değerlendirilmesi için önemlidir. Klinik ön testler, semptomların ve işaretlerin pulmoner emboli için tipik olup olmadığının değerlendirilmesine dayanır. Geneva skoru ve Wells skoru en iyi bilinen ön testlerdir. Revize edilmiş Geneva skoru, pulmoner emboli (PE) tanısında standartlaştırılmış bir klinik karar verme kuralıdır. Wells skoru, PE ön test olasılığının değerlendirilmesi için yaygın olarak kullanılmaktadır. Gözden geçirilmiş Geneva skoru tamamen standart bir klinik karar kuralıdır. Çalışmamızda ön testlerin olasılıklarının doğruluklarını karşılaştırdık.

Yöntem:

Çalışmamızda retrospektif olarak 119 hastada PE'nin klinik olasılığı, Wells kuralı ile prospektif olarak gözden geçirilmiş ve Geneva skoru kullanılarak karşılaştırıldı. Hastalar, tek bir merkezden rasgele bir örnek oluşturularak çok merkezli geniş bir tanı çalışması olarak yapıldı.

Bulgular:

PE'nin genel prevalansı % 31'di. Düşük ihtimal, orta olasılık ve yüksek olasılık kategorilerinde PE prevalansı yeniden gözden geçirilmiş Geneva puanı ile gruplandırılmıştır. Üç aylık takipten sonra, herhangi bir hasta gözden geçirilmiş Geneva skoru ile düşük ya da orta düzeyde klinik olasılık kategorisine girdiği bulunmuştur. Akut venöz tromboemboli tanısı olanlarda D-dimer düzeyleri normaldi. Geneva ve Wells skorlarını karşılaştırdığımızda, prediktif değerleri PE grubunda benzerdi. PE ve non-PE için Cenevre puanlarının öngörü değerleri önemli farklılık göstermedi ($p = 0.169$). Wells skorları PE grubunda önemli derecede yüksekti ($p = 0.006$).

Sonuç:

Bu çalışma gözden geçirilmiş Geneva skorunun performansının Wells skoru ile aynı olduğunu gösnermektedir. Ek olarak, gözden geçirilmiş Cenevre skoru ile normal D-dimerin düşük ya da orta derecedeki klinik olasılığının kombinasyonu olan hastalarda PE'yi dışlamak için güvenli olduğu

görülmektedir. Klinik olasılığın belirlenmesi tanı için ana adımdır. Yüksek D-dimer değeri, klinik şüphe için önemli olup, ancak düşük değerler tanıyı ortadan kaldırmamaktadır. Ayrıca, Wells skorunun prediktif değerinin Genova skoruna göre daha yüksek olduğunu ancak mortalite tahminlerinde benzer olduğunu tespit edilmiştir. Şüpheli PE olgularında hem klinik risk sınıflaması hem de laboratuvar bulguları Genova skoruyla birlikte değerlendirilmelidir. Çalışmamızda, Wells skoru, basitleştirilmiş gözden geçirilmiş Geneva skorundan daha doğru olduğu bulundu. Prospektif olarak yapılacak çalışmalarla değerlendirilmesi önerilir.

Anahtar kelimeler: Pulmoner emboli, Geneva skoru, Wells skoru

SUMMARY

Background

Pulmonary embolism which is a mysterious and difficult disease to diagnose is the third most common cause of death from cardiovascular disease. Despite recent clinical studies and technological development, pulmonary embolism diagnosing is hard and complicated. Diagnosis of pulmonary embolism starts with physicians suspicion. Firstly, assessment of clinical pre-test probability is important. Clinical pre-test probability is based on an assessment of whether symptoms and signs are typical for pulmonary embolism. Geneva score and Wells score are most known pre-tests. The revised Geneva score, a standardised clinical decision rule in the diagnosis of pulmonary embolism (PE). The Wells score is widely used for the assessment of pretest probability of pulmonary embolism (PE). The revised Geneva score is a fully standardised clinical decision rule. We compared the predictive accuracy of these two pre-test probabilities.

Methods:

In 119 consecutive patients, the clinical probability of PE was assessed prospectively by the Wells rule and retrospectively using the revised Geneva score. Patients comprised a random sample from a single centre, participating in a large prospective multicenter diagnostic study.

Results:

The overall prevalence of PE was 31%. The prevalence of PE in the low-probability, intermediate-probability and high-probability categories are grouped by the revised Geneva score. After three months of follow-up, any patient categorised into the low or intermediate clinical probability category by the revised Geneva score. Normal D-dimer result was diagnosed with acute venous thromboembolism. When we compare Geneva and Wells scores, their predictive values were similar for PE group. Predictive values of Geneva scores for PE and non-PE were not importantly different (p=0.169), but Wells scores were importantly higher for PE group (p=0.006).

Conclusions:

This study recommends that the performance of the revised Geneva score is equal to that of the Wells score. In addition, it appears safe to exclude PE in patients by the combination of a low or intermediate clinical probability of the revised Geneva score and a normal D-dimer. Determining clinical probability is the main step for diagnosis. High D-dimer value is important for clinical suspicion, but low values can't eliminate the diagnosis. Also, we showed that Wells score's predictive value was higher than Genova score but predictions of mortality were similar. Both clinical risk

classification and laboratory results must be evaluated together with Genova score in suspected PE cases. In our population, the Wells score appeared to be more accurate than the simplified revised Geneva score. Patient outcomes should be examined in a prospective study.

Keywords: Pulmonary Embolism, Geneva Score, Wells Score

INTRODUCTION

Pulmonary embolism comprises the 3rd most common cause of death from cardiovascular disease after a heart attack and stroke (1,2). Venous thromboembolism and atherothrombosis contribute to familiar risk factors and general pathophysiological characteristics of inflammation, hypercoagulability, and endothelial injury(3). Clinical probability evaluation helps to identify patients with low clinical probability for whom the diagnosis of venous thromboembolism can be excluded solely with a negative result from a plasma D-dimer test(3). The diagnosis is generally confirmed with compression ultrasound showing deep vein thrombosis or with chest CT showing pulmonary embolism(1, 3). Clinical evaluation of pretest probability has become a key tool in the diagnostic approach of patients. Categorization of patients into pretest probability groups directs the diagnostic strategy by selecting patients in whom extra tests should be performed. The novel Wells score that categorises patients into low, moderate and high probability groups is probably the most extensively validated predictive model(4,5). This model is not fully systematised and has been analysed due to the presence of a subjective criterion, the physician's judgement of whether an alternative diagnosis is less likely than PE. The Geneva group developed and validated a fully standardised clinical decision rule exclusively based on objective clinical items to overcome this limitation of the Wells model. The so-called Geneva score was revised and more recently extra simplified into the simplified revised Geneva score. The fully standardised Geneva model appears attractive and its simplification may participate to increase its use in daily routine(4,5). We also investigated the reasons for differences in clinical evaluation.

Assessment of the Wells score

DVT signs and symptoms are frequently nonspecific, there is a low threshold to order a lower-extremity ultrasonography study (LEUS) to eliminate DVT. To cut down needless imaging, the Wells score was understood to ascertain a patient's pretest probability of DVT. Afterwards, the Wells score has comprised validated in outpatient and emergency section(Table 1). However, patients could bear different DVT risk profiles owing to use of thromboprophylaxis and enhanced prevalence of risk factors such as heart failure, chronic obstructive pulmonary disease, acute infection, coronary artery disease, malignant neoplastic disease, immobilisation, and new surgical operations.

Assessment of the revised Geneva score

The revised Geneva score comprises four variables not included in the Wells rule: age over 65 years, unilateral lower-limb pain, heart rate 75–94 beats per minute or more than 94 beats per minute, and pain on lower-limb deep venous palpation and unilateral oedema (Table 1). These items were abstracted from the patient charts after masking the final diagnosis. Values for each item were scored on the day of inclusion. Heart rate was obtained by using electrocardiograms obtained on the day of inclusion. Patients were excluded in cases of inaccessibility of patient's files or absence of relevant data.

MATERIALS AND METHODS

Patients

We applied the dichotomised Wells score. In all patients with a Wells score of four or less, a quantitative D-dimer assay (VIDAS, Biomerieux, Marcy L'Etoile, France) was performed. If the diagnosis of PE was less unlikely (Wells score, 4 or less) in combining with a normal quantitative D-dimer test result, PE was regarded to be excluded. Spiral CT-scanning was performed if PE was considered likely (Wells score greater than 4 points) or cases of an abnormal quantitative D-dimer test resultant. All patients were observed up for 3 months to evaluate the recurrence of PE.

Patient selection

After the local ethical committee of hospital gave approval for this prospective, cross-sectional study, we evaluated initially PE diagnosed patients and performed computed tomography (CT) thorax angiography in the emergency department of Diskapi Yildirim Beyazit Traning and Research Hospital from January 2013 to January 2014. 123 patients who accepted to sign voluntary consent form have incorporated the study. Patients were excluded if the diagnosis of the thromboembolic disease was documented. Pulmonary embolism was suspected among inpatients a hospital stay of more than two days. Diagnostic testing was cancelled for ethical reasons in patients who decided to leave the hospital against medical advice, pregnancy, postpartum patients and chronical drug users and patients died rapidly after admission.

Data Collection

With face to face interview symptoms of patients, risk factors, comorbidities, physical examinations were enlisted. Wells score and revised Geneva score were recorded in clinical form, but the physicians were not forced to calculate these scores. They were independent to handle patients as common, concording to legal practice. Arterial blood gases, electrocardiograms, laboratory results and imaging findings were examined. Frequencies of PE obtained with the revised Geneva score and trichotomized Wells rule were compared with those of the novel Geneva score dataset by comparing the related confidential intervals. D-dimer values were detected in twenty-four hours. CT thorax pulmonary angiographies of all patients were studied by Philips MX 8000 four Slice CT with pulmonary thromboembolism protocol in our hospital. Thrombus images and their localisations were detected and accepted as a gold standard for our study. Localisations of thromboses were listed as a main pulmonary artery, lobar and subsegmental arteries. Also, lower extremity venous doppler ultrasonography (USG) and concomitant DVT were detected performed by radiologists. Combined clinical rule and D-dimer results were associated the clinical issue. We examined the clinical course of patients with a normal D-dimer result and a low clinical probability as estimated by applying the revised Geneva score.

Statistical Analysis

Statistical analysis was performed by using SPSS software (SPSS for windows 22.0.1, Inc. 1989–2016, Chicago, IL, USA) and MEDCALC software (Medcalc Software version 9.2.1.0, Mariakerke, Belgium). Continuous variables determined as the mean ± standard deviation (SD) for normal distribution if they were in the normal range, and determined as median (min-max) if variables weren't in a normal range. Categorical parameters described as numbers and percents. Normal range evaluated by histogram analysis and 'One-Sample Kolmogorov-Smirnov Test' $p>0.05$ accepted as a normal distribution. Parameters are in normal range examined by 'Student's t-Test' and parameters which

are not in normal range examined by 'Mann-Whitney U Test'. For multivariate group analyses, 'Kruskal-Wallis Test' is used in all these methods differences were considered significant when the p-value was less than 0.05. For detecting and comparing the diagnostic value of Wells and Geneva methods, patients with low, middle, high scores determined for each method, and finally diagnosed the number of PE patients in each group established. The significances of difference in categoric variables are evaluated by 'x 2 Test'.

Results

The study consists of 119 patients (58 males and 61 females) with a mean age of 69.3±16.0 years.

37 patients (20 males and 17 females) were diagnosed as PE and 82 patients (38 males and 44 females) were not diagnosed as PE.

Mean ages were 65.6±16.9 and 70.9±15.4 for PE and non-PE groups, respectively (p=0.069).

Twenty patients in PE group were male (54%) and 38 patients in the nonPE group were male (46.3). There was no significant difference (p=0,281) as gender between two groups.

The most frequent symptoms were dyspnea (60.5%), chest pain 16(%), cough 8.4(%) for both groups. There was no statistically significant difference (Table 5) as differential symptoms between two groups.

Hypertension was the most frequent (72 patients, 60.5%) illness for all patients according to the questionnaire. Other diseases were chronic obstructive pulmonary disease (COPD) (32 patients, 26.8%), coronary artery disease (24 patients, 20.2%), osteoporosis (23 patients, 19.3%) and hyperlipidemia (22 patients, 18.4%). In non-PE group congestive heart failure rate was significantly higher (p=0.02), other chronic disease rates were similar for both groups (Table 6). There were no chronical diseases for only two cases in PE group. There was at least one chronic disease (94.6%) in PE group. All patients in the non-PE group had at least one chronic disease.

Thirty-seven patients (31%) certainly diagnosed as PE by CT thorax pulmonary angiography. Mean values of D-dimer were 4408 µg/mL and 3451 µg/mL for PE group and non-PE group, respectively. The difference was not significant (p=0.726).

The arterial blood gases of patients were analysed. Hypocapnia was detected in 20 cases (54.1%) and hypoxemia in 29 cases (78.4%) in PE group. These values were 37 cases (45.1%) and 76 cases (92.7%) for the non-PE group, respectively. Being hypocapnia was similar (p=0.367) in both groups, but hypoxemia was significantly higher in a non-PE group (p=0.025).

Previous surgical operations and malignancy are accepted as risk factors. There were 1 bronchogenic carcinoma, 1 brain tumour, 1 gastrointestinal and 2 breast malignancy in the history of the patients. 13 of the cases had previous surgical operation history. In both groups, history of previous surgical operation and malignancy rates were similar (p=0.543 ve p=0.560).

Bronchiectasis was the most common pathologies in PE patients, and pleural thickening was more common in a non-PE group in an evaluation of chest x-ray. (Table 7).

Deep venous thrombosis was detected in 20 cases (54.1%) for PE group, and in five cases (6.1%) for a non-PE group by venous doppler ultrasonography (Table 8). The most frequent localisation of thrombosis was in a left subsegmental artery (Table 9) in CT thorax pulmonary angiography.

When we compare Geneva and Wells scores, their predictive values were similar for PE group (Table 10). Predictive values of Geneva scores for PE and non-PE were not significantly different (p=0.169), but Wells scores were significantly higher for PE group (p=0.006).

Four patients were dead in this study, two of this patient had PE. There was no significant relation in mortalities with Geneva and Wells scores. (respectively p=0.527, p=0.454).

Discussion

PE is one of the common diseases in ED, which is a hardly diagnosing pulmonary disease. It is the third most frequent reason of death in ED almost 1/3 of the mortality occurs in first hours(6). The mortal rate decreases which patient has been diagnosed and treated. More than 50%of massive PE cases diagnosed in autopsies(6). The cause of the most PE patients is thromboembolism and 80-90% of theme originates from lower extremity deep venous system(7). Non speciCausesymptoms are the most important cause of hard diagnosis. There originated standard non-invasive diagnosing technique yet (7). In ED misleading diagnosis of PE is increasing the mortality rate five times. The incidence of PE is higher in old age technique ally it peaks in the seventh decade and often in this ages of male patients (8).

In PE related vs female/male rate was 1,24; especially in males older than 40 years old mortality rate was higher than females with no risk factors like pregnancy, oral contraceptive use(9). In this study, there were 4 deaths and mean age was higher than 65 years old and no difference in gender.

The most frequent symptom of acute PE is acute dyspnea. Also typically unidentified chest pain, arrhythmia and high fever can be seen in these cases(10). In four different studies that achieved by two different groups between 1981-1995, showed that 90% of patients have dyspnea and tachypnea, but 3% of them had no symptoms as dyspnea, tachypnea or pleuritic pain. In many studies showed that dyspnea, tachypnea, cough, hemoptysis symptoms in acute PE patients were 10% to 70% (11). In “prospective Investigation of Pulmonary Embolism Diagnosisé (PIOPED) study the symptoms in cases in without cardiac or pulmonary comorbidity were established as dyspnea (73%), pleuritic pain (66%), cough (37%), lower extremity deep venous failure (26%), hemoptysis (13%), tachycardia (10%), wheezing (9%) (12). In PIOPED study dyspnea and chest pain were the main symptoms and tachycardia was the most frequent findings(12). In a study dyspnea, chest pain, rale, tachypnea and tachycardia symptoms are common in Hatipoğlu et al. study in our country. In our study, the most frequently symptoms were dyspnea, chest pain and coughing similar to other studies. However, there were no significantly indifferences in symptoms between patients with PE and non-PE.

The risk factors of PE are determined as previous surgery (in last three months) 1-2 days of immobilisation, previous deep venous thromboembolism, cardiac diseases like acute myocardial infarction, congestive heart failure, malignancy, trauma, etc. (3,7). There was at least one risk factor in patients with PE (81%) and patient with non-PE (69%) in Miniati et al. study. The most frequently risk factors were congestive heart failure (26%) and DVT (13,4%) in our study. The others were a malignancy and previous surgery. Also after cardiac disease, COPD was the second comorbid disease. And there was at least one comorbid disease in patients non-PE and PE, except two patients.

Sensitivity of fibrin degradation products (D-dimer) testing with ELISA method is satisfied enough. But specificity is not good because surgery, renal pathologies, trauma could affect this parameter. Nevertheless, negative results can help to eliminate (95%) venous thromboembolism (5). In the PE

group mean D-dimer was 4408 µg/mL and in the non-PE group, this value was 3451,06 µg/mL. Furthermore, we could diagnose as PE in three cases that D-dimer was under 500. By this way, a D-dimer value was 91.9% negative in PE group. And this result is coherent with the other series.

Just as in PE cases arterial blood gases parameters can be in normal range (10-15%), also hypoxemia, hypocapnia, respiratory alkalosis and increasing p(A-a)O 2 can be seen frequently (13). Arterial blood gas parameters are not effective for diagnosis of PE because of these parameters could be different in a lot of diseases(20). In our study, rates for hypocapnia and hypoxemia for PE group were 54.1% and 78.4%, respectively. These rates were 45.1% and 92.7% for the non-PE group, respectively. We showed that arterial blood gases results alone have no significant role in diagnosing PE, on the contrary, in non-PE group hypoxemia rate was higher.

Chest x-rays are inadequate for diagnosing the PE. Approximately 40% of cases, imagings were normal and nonspecific(11,14). The main pathological images were atelectasis, Fleischer's lines (linear atelectasis areas), increases in density in the parenchyma, Westermark sign (oligemia in parenchyma), Hampton sign, pleural effusion and elevation of the diaphragm(6,11,14).Even the patient's pathology rate in chest x-ray was 84% Stein et al.'s study, we found this rate as 78%. Pleural effusion, linear shadows as atelectasis, hemidiaphragm elevation relation to this atelectasis are the most frequent radiological signs(4,15). In our study, 30.2% of cases had no pathology in chest x-rays. In PE group bronchiectasis (15.1%) and in non-PE group pleural thickening (28.5%) was more frequent that near significant statically (Table 5).

There is no finding of DVT on physical examination in 50% of cases with PE, which is frequently related to lower leg deep venous thrombosis, and 10-20% of these DVT can be detected with doppler USG. Even cases with negative USG, PE could not be eliminated; positive USG might cause false positivity(16). In our series, venous doppler USG findings' positivity for DVT were 75.6% and 9.7% for PE and non-PE groups, respectively.

Spiral CT has hopeful results in non-invasive PE diagnosis, but it's not effective enough for evaluating central pulmonary vessels(17). Prospective studies show that by the appropriate sensitivity and specificity values of CT were above 90% for central PE. However, when we include subsegmental arteries, embolism technics and true evaluations these rates decrease to 60% (17). In our study, the most frequent thrombus localisations were segmented and subsegmental arteries.

The gold standard method of PE diagnosis is accepted as CT thorax pulmonary angiography (17). Clinical suspicion is the first step to correctly diagnosis for every disease. Then some methods can be used for elimination of the other diagnosis. Diagnostic strategies must be reliable otherwise PE's mortality risk is higher without treatment. Diagnosis method must have high sensitivity and specificity. When ranges are determined for probability scales that give points to grade symptoms as Wells and Geneva, it's shown that these can provide high sensitivity and specificity rates(18). Two prospective studies about diagnosing of PE, PIOPED and PISA-PED emphasised the importance of clinical findings on diagnosis and necessary of advanced methods(19). A multicenter study PIOPED classified patients into high, middle, low-risk groups(3,14). Then in high-risk group 68%, in middle group 30%, in low-risk group 9% of patients diagnosed as PE. Geneva et al. formed a new classification by analysing age, risk factors, radiological images, arterial blood gases of 1090 cases that initial diagnosis PE in an emergency department. By this classification high-risk group 81%, in middle group 38%, in the low-risk group, 10% of patients diagnosed as PE (20). Ergun et al. achieved a retrospective study by categorised clinical probabilities experimental in Turkey and demonstrated

by CT thorax pulmonary angiography that 89.9% of patients were in the high-risk group. 11 . 7% of patients were in a middle-risk group and 2.8% of patients were in a low-risk group and explained that clinical assessment was a guide with non-invasive methods. Another study from our country compared Wells, Geneva, Ministry scores to diagnose PE and showed that the diagnostic value of Wells score was significantly higher statistical. Unlike this results in our study, we showed Geneva score was similar in PE and non-PE groups (p=0.169) but Wells score was significantly high in cases with PE (p=0.006). However, there was no correlation between mortality in both two scores.

Conclusion

Determining clinical probability is the main step for diagnosis. High D-dimer value is important for clinical suspicion, but low values can't eliminate the diagnosis. Furthermore, we showed that Wells score's predictive value was higher than revised Genova score but predictions of mortality were similar. With Genova score in suspected PE cases, both clinical risk classification and laboratory results must evaluate together.

Limitations of the study

The fact that our work has a low number of patients is the main limiting factor. The lack of a multicenter study is the limitations of this study.The study will be important for multi-center and diagnostic biochemical marker studies.

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