International Journal of Clinical Trials
Ilkhan GD et al. Int J Clin Trials. 2020 Nov;7(4):229-234
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: https://dx.doi.org/10.18203/2349-3259.ijct20204479

Original Research Article

The effect of troponin values on prognosis in acute pulmonary embolism

Gulay Dasdemir Ilkhan[1]*, Hakan Celikhisar[2]

[1]Department of Chest Diseases, Tire Public Hospital, Izmir, Turkey
[2]Esrefpasa Metropolitan Municipality Hospital, Izmir, Turkey

Received: 19 July 2020
Revised: 10 September 2020
Accepted: 11 September 2020

***Correspondence:**
Dr. Gulay Dasdemir Ilkhan,
E-mail: gdasdemir1111@gmail.com

ABSTRACT

Background: The objective of this study is to evaluate the clinical usefulness of cardiac troponin levels in acute pulmonary thromboembolism (PTE) prognosis.
Methods: Thorax computed tomography (CT) angiography was performed and reported by the radiologist as pulmonary embolism and 193 patients older than 18 years of age who were considered PTE by the physician of chest diseases were included in the study. Patients diagnosed with PTE were divided into two groups as those who died within 30 days and did not die within 30 days. As a result of the statistically significant relationship between troponin and mortality, receiver operating characteristic (ROC) analysis was performed to determine the prognosis level of troponin and appropriate sensitivity and specificity cut-off values were determined.
Results: We determined that troponin levels of patients diagnosed with PTE in the emergency department were statistically significantly higher in the group with mortality (p=0.031). Since the area under the curve (AUC) value was calculated as 0.636, troponin value was found to have a weak-medium significance in terms of predicting 30-day mortality.
Conclusions: Troponin values are statistically significantly higher in patients with a one-month period than the survivor group in this period. However, we concluded that troponin values are not clinically usable as mortality markers due to their low sensitivity and specificity rates. However, due to its significant relationship with increased mortality, patients with PTE with high troponin values should be hospitalized and monitored closely.

Keywords: Pulmonary embolism, Prognosis, Troponin

INTRODUCTION

The most common cause of pulmonary thromboembolism (PTE) is that the thrombus formed in the veins breaks and clogs the pulmonary artery branches.[1] Pulmonary embolism (PE) is a disease with high mortality and morbidity, can be recurrent, difficult to diagnose but can be prevented and treated.[2] Right ventricular dilatation due to acute right heart failure due to PTE increases the oxygen requirement of the right ventricle. Right coronary artery circulation decreases, and as a result, micro infarctions may occur in the right ventricular muscles. Increased serum troponin level indicates right ventricular dysfunction.[2,3]

The aim of this study is to investigate the effect of troponin values on prognosis in patients diagnosed with PTE.

METHODS

The study was performed by retrospectively scanning the information of patients who applied to the emergency room of Okmeydanı training and research hospital and Esrefpasa metropolitan municipality hospital between

August 2015 and September 2019 through the hospital information processing system. Thorax computed tomography (CT) angiography was performed and reported by the radiologist as PE and patients older than 18 years of age who were considered PTE by the physician of chest diseases were included in the study. Patients under 18 years of age, patients with a lack of physical examination, history and laboratory data, patients with a history of acute coronary syndrome, patients with chronic renal failure (creatine clearance <60), patients with acute cerebrovascular accident and patients with suspected diagnosis of pulmonary embolism were excluded from the study. Patients' age, gender, vital signs, troponin, d-dimer, hemoglobin, leukocyte, platelet values, arrival complaints, resume information and treatment outcomes (discharge, service admission, referral to another hospital, referral to intensive care unit, death, voluntarily hospitalization) was recorded. Mortality information of the patients in a one-month period was also recorded using the death report system of the Ministry of health.

The study has been reviewed and approved by a certified ethical committee, including the number of the approval document and the date of the approval. The registration number (local ethics committee): 2011- KAEK-25 2019/22-09.

Statistical analysis

The data were entered into the statistical package for social sciences (SPSS) for Windows® 20 program and statistical analyzes were performed using the same program. The suitability of the data to normal distribution was measured by the Kolmogorov-Smirnov test. Values that conform to the normal distribution are expressed in mean and standard deviation, while those that do not fit are expressed in median and percentiles. Patients diagnosed with PTE were divided into two groups: group 1 included patients who died during the 30-day period after PTE, and group 2 included those who did not died in the 30-day period after PTE. When comparing groups, student-t test was used for the data that fit the normal distribution and Mann Whitney U test was used for the data that did not fit the normal distribution. Frequency data were compared with chi-square test. As a result of the statistically significant relationship between troponin and mortality, ROC analysis was performed to determine the prognosis level of troponin and appropriate sensitivity and specificity cut-off values were determined. In addition, troponin test results were categorized as positive (>0.03 ng/ml) and negative (<0.03 ng/ml) based on the value of 0.03 ng/ml, and the specificity, sensitivity, positive likelihood, negative likelihood, positive predictive value, negative predictive value and accuracy rate were calculated. P<0.05 value was considered significant.

RESULTS

Patient information with a total of 230 PTE diagnoses was scanned. 25 of these patients were excluded from the study because they were not the result of troponin. In addition, 4 patients were excluded from the study because of their hemogram results, vital signs of 4 patients and missing outcome data of another 4 patients. As a result, 193 patients in total were included in the study. 68 of the patients were male (35.23%) and 125 were female (64.76%). The average age was calculated as 69.25±16.10. The demographic and clinical features of the patients are given in Table 1.

Table 1: Demographic features of patients.

Variables	N	%
Gender		
Male	68	35.23
Female	125	64.77
Risk factors for PTE*		
History of DVT**	12	6.21
PTE history	6	3.10
Immobilization history	46	23.83
A history of malignancy	28	14.50
Tachycardia	87	45.07
The presence of DVT findings	13	6.73
Application complaint		
Syncope	34	17.61
Dyspnea	105	54.40
Chest pain	40	20.72
Arrest	5	2.59
Hypotension	23	11.91
Palpitation	87	45.07
Chronic disease		
Coronary artery disease	30	15.54
Congestive heart failure	27	13.98
Cerebrovascular accident	19	9.84
Chronic obstructive pulmonary disease	16	8.29
Asthma	10	5.18
Chronic renal failure	3	1.55
Hypertension	73	37.82
Diabetes mellitus	43	22.27
Anemia	9	4.66
Vital signs	**Median (interquartile range)**	
Pulse (beats/min)	98	83-115
Systolic blood pressure (mm Hg)	134	110-150
Diastolic blood pressure (mm Hg)	76	65-87
Oxygen saturation (%)	92	86-97

*PTE: Pulmonary thromboembolism, **DVT: Deep vein thrombosis

When the Wells scores of the patients included in the study were analyzed, 67.8% of the patients were found as low-risk, 30.4% as medium-risk and 1.8% as high-risk. Considering the outcomes of the patients, 36 (18.65%) patients were discharged, 40 (20.72%) were hospitalized,

70 (36.26%) were referred to the outer center, 26 (20.20%) were intense. It was observed that 3 (1.55%) died and 4 (2.07%) left the hospital at their own request.

Table 2: Clinical features of patients.

Variable	Group I*	Group II**	P value
Age	72 (64-77)	69 (65-71)	0.3
Gender (male)	14	55	0.7
Pulse (beats/min)	104 (68-138)	94 (62-128)	0.1
Systolic blood pressure (mm Hg)	108 (59-161)	132 (95-165)	0.007
Diastolic blood pressure (mm Hg)	60 (27-103)	75 (58-94)	0.005
Oxygen saturation (%)	88 (70-104)	94 (85-101)	0.018
Wells score	1.5 (0-4.5)	1.5 (0-4.0)	0.4
Malignancy (none)	25	139	0.003
Syncope (none)	36	123	0.1
D-dimer	7436±6845	5456±5531	0.3

*Group 1: died within 1 month, **Group 2: without extus within 1 month

When the relationship of troponin values of the patients diagnosed with PTE in the emergency department with the prognosis in the 30-day period was examined, it was found that troponin values were statistically significantly higher in the group with a mortal course (p=0.031). ROC analysis was performed to evaluate the usability of troponin values in predicting prognosis for 30-day mortality. Since the AUC value was calculated as 0.636, troponin value was found to have a weak-medium significance in terms of predicting 30-day mortality. The specificity and sensitivity values that can be used and which show the value of troponin values in terms of predicting mortality are shown in Tables 3 and 4.

Table 3: Sensitivity and specificity values of troponin values.

Statistics	Result	% 95 confidence interval
Sensitivity	70.14	47.87-86.76
Specificity	58.11	46.92-67.14
Positive likelihood rate	1.58	1.14-2.31
Negative likelihood rate	0.52	0.28-0.97
Prevalence	19.89	14.59-27.84
Positive predictive value	28.86	23.14-36.8
Negative predictive value	87.08	79.96-92.88
Accuracy	59.74	49.9-69.19

Table 4: Sensitivity and specificity values of troponin values at different troponin levels after ROC analysis.

Troponin level (ng/ml)	Sensitivity (%)	Specificity (%)
0.000	93.1	17.6
0.011	85.4	42.1
0.019	77.1	47.8
0.030	70.1	58.3
0.036	49.0	63.987.08

DISCUSSION

PTE is an important cause of morbidity and mortality in the United States and Europe, resulting in deaths of 100,000 in the United States and 300,000 in Europe annually.[4,5] It is responsible for 5-15% of all hospital deaths. In contrast, the annual incidence is considered to be higher than current data, given deaths that do not present clinical symptoms or undiagnosed deaths. The risk of PTE increases with age.[6,7] When the patients who died in 30 days and those who did not died were observed, mortality increased with age, but no statistically significant difference was found (p=0.374). Similar results have been reported in literature studies.[8,9]

When we look at the vital signs of the patients in our study, referee and friends - mean pulse value 99±20 beats/min, Systolic blood pressure (SBP) 129±23 mm Hg, Diastolic blood pressure (DBP) 78±15 mm Hg, oxygen saturation (SPO_2) 95±4%); and in the study of Dahhan et al - pulse median value 94 beats/min (similar results were found with his studies (84-111.5), Systolic blood pressure (SBP) 118 mm Hg (107-137), and Diastolic blood pressure (DBP) 73 mm Hg (61.5-81.5).[8] In the study of Dahhan et al it was reported that although the values of and implantable cardioverter-defibrillator (ICD) were not significantly related to mortality, lower values were found in the group of patients who died. When evaluated in terms of SPO_2 and pulse values, a statistically significant difference was found between patients with and without died within 30 days.[9,10] In our study, although the pulse values were higher in the group with mortality, the mortality relationship was not statistically significant. The other vital signs, SCB, ICD and SPO_2 values had lower values in the group with mortality, and there was a significant difference between the two groups in accordance with the literature (values p=0.006, p=0.005, p=0.019, Mann-Whitney U test, respectively).

The presence of hypotension and cardiogenic shock is directly related to the risk of premature death. In hypotensive PTE cases, early hospital mortality is at least 15%. Patients who are not hemodynamically stable due to shock or hypotension directly fall into the high-risk group.[11-13] When the mortality relationship of vital signs is examined, in the ınternational cooperative pulmonary embolism registry (ICOPER) study, the mortality in hemodynamically stable cases was found to be 15.1%, and 58.3% in unstable cases (hypotension and shock findings).

In the same study, hemodynamic status was shown as the most important prognostic factor for mortality.[14-16]

In some studies, it has been reported that there is a relationship between high D-dimer level and PTE severity.[17-19] In the study of Agarwal et al, it was found that in the group with similar massive PTE, the mean values of D-dimer level were statistically significantly higher than the non-massive group (p=0.02).[20] In the study of Bajaj et al, D-dimer values were found high in all groups according to the severity of PTE, but their relationship with 30-day mortality was not significant.[21-22] Similarly, in our study, although the D-dimer values were high in the group with mortality, no statistically significant difference was found between the surviving group at the end of one month. This may be due to the exclusion of patients without troponin testing.

In our study, troponin I (Tn I) value was found to be lower than 0.021 (0-0.130) ng/ml compared to other studies in the literature. However, in a study conducted by Keller et al in patients with and without normotensive right venicular dysfunction, the median values of troponin were 0.01 (0-0.03) ng/ml, 0.06 (0.02-0.23) ng/ml, similar to our study.[23-24] Considering the troponin values of patients diagnosed with PTE in the emergency department, in the study of Kalkan et al, it was found that troponin I was an average of 1.4±1.9 ng/ml. Similarly, in a study by Assab et al average Tn I value was 1.6±0.7 ng/ml, and in a study by Mehta et al average value found was 0.36±0.48 ng/ml.[21-23] In a study conducted by Martinez et al, troponin I value of 255 central PE patients was found to be 0.07 ng/ml (interquartile range i.e. IQR 0.14) and 272 peripheral PE patients as 0.02 (IQR 0.05).[24] In the study conducted by Konstam et al, patients were divided into three groups as massive, submassive and non-massive. The troponin T values examined were found to be 0.10±0.8 ng/ml, 0.05±0.03 ng/ml, 0.03±0.02 ng/ml, respectively.25 Campbell et al also found troponin T value as 0.017 ng/ml (0.008-0.034) in their studies.[26]

Considering the relationship between cardiac troponins (cTn) and mortality, our study found similar results with the literature. Troponin values of the patients who died during the 30-day period were higher than the other group and the difference was statistically significant (p=0.031). In the study of Jimenez et al no significant relation was found between logon regression analysis between Tn I and 30-day mortality in 318 hemodynamically stable cases. In fatal cases, a significant relation was found between multivariate logistic regression analysis (determined using pulmonary embolism severity ındex - PESI) and Tn I levels.27 In the study of 91 stable and unstable acute PTE cases performed by Kucher et al, it was shown that the combination of Tn I and ECO was more valuable than the use of any alone in evaluating the prognosis.[28]

In the study of Giannitsis et al consisting of 56 patients with PTE, the development of death, cardiogenic shock, inotropic agent and mechanical ventilation was higher in patients with high cTn levels. The mortality rate was found to be as high as 44% in the cTn positive group compared to 3% in the cTn negative group.[29] In the study of Dahhan et al it was observed that troponin values were lower in patients who experienced troponin values compared to the patients who died and the difference between the two groups was significant.[8] In the meta-analysis of Becattini et al which included 20 studies and evaluated the role of cardiac troponin values in prognosis in patients with PTE, troponin values were significantly higher in the patient group who died within 30 days. Similarly, studies in this meta-analysis showed that those with high troponin cut off values had higher mortality, but no significant difference was shown.[30] In the study of Tanabe et al, 30-day mortality was higher in patients with high troponin values and the difference was found statistically significant.[31]

In the study conducted by Jimenez et al, the limit value for Tn I level was found to be >0.1 ng/ml and its sensitivity alone was 54%, specificity 69.3%, positive predictive value 10.5%, negative predictive value in determining the 30-day mortality. It was found to be 95.8%.[32] In our study, AUC was found to be 0.636 as a result of ROC analysis conducted to evaluate the usability of troponin values in predicting prognosis for 30-day mortality, and in this respect, the test expresses a weak-medium significance in terms of predicting mortality. In our study, although the correlation between increased troponin level and poor prognosis was shown, the appropriate troponin level, which could show a clinically usable sensitivity and specificity value, was not given a cut-off value. Despite the low sensitivity in predicting 30-day mortality even when the troponin level is 0.5, however, there is a value of 64% specificity, which we think is not a viable clinical cut-off value according to the results of the study.

The biggest limitation of our study is that it is designed retrospectively. Patients with insufficient file information were not included in the study, which we think may have negatively affected the homogeneity of the patient pool. We think that if a similar study is designed prospectively, the results may be more generalizable to the universe.

CONCLUSION

Patients with low blood pressure and saturation values and inotropic need during application are those with statistically poor prognosis. In the studies on prognosis in the literature, similar results were reported with our study that the troponin values were statistically significantly higher in patients who died in a one-month period compared to the surviving group in this period. However, we think that troponin values are not clinically usable as mortality markers due to their low specificity and sensitivity rates. However, due to its significant relationship with increased mortality, patients with PTE with high troponin values should be hospitalized and followed closely.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Bennett A, Chunilal S. Diagnosis and Management of Deep Vein Thrombosis and Pulmonary Embolism in Pregnancy. Semin Thromb Hemost. 2016;42(7):760-73.
2. Widimský J. Diagnosis and treatment of acute pulmonary embolism in 2010. Vnitr Lek. 2011;57(1):5-21.
3. Bolt L, Lauber S, Limacher A, Samim D, Lowe A, Tritschler T, et al. Prognostic Value of Electrocardiography in Elderly Patients with Acute Pulmonary Embolism. Am J Med. 2019;132(12):835-43.
4. Carpenter SL, Richardson T, Hall M. Increasing rate of pulmonary embolism diagnosed in hospitalized children in the United States from 2001 to 2014. Blood Adv. 2018;2(12):1403-8.
5. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033-69.
6. Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients. A systematic review. Thromb Haemost. 2017;117(4):801-8.
7. Lee CH, Cheng CL, Lin LJ, Tsai LM, Yang YH. Epidemiology and predictors of short-term mortality in sympromatic venous thromboembolism-A nationwide population based study. Circ J. 2011;75:1998-2004.
8. Dahhan T, Siddiqui I, Tapson VF, Velazquez EJ, Sun S, Davenport CA, Samad Z, Rajagopal S. Clinical and echocardiographic predictors of mortality in acute pulmonary embolism. Cardiovasc Ultrasound. 2016;14(1):44.
9. Bajaj A, Rathor P, Sehgal V, Kabak B, Shetty A, Al Masalmeh O, Hosur S. Prognostic Value of Biomarkers in Acute Non-massive Pulmonary Embolism: A Systematic Review and Meta-analysis. Lung. 2015;193(5):639-51.
10. Xiao W, Cao R, Liu Y, Wang F, Bai Y, Wu H, et al. Association of high-sensitivity cardiac troponin T with mortality and cardiovascular events in a community-based prospective study in Beijing. BMJ Open. 2017;7(6):013431.
11. Secemsky E, Chang Y, Jain CC, Beckman JA, Giri J, Jaff MR, et al. Contemporary Management and Outcomes of Patients with Massive and Submassive Pulmonary Embolism. Am J Med. 2018;131(12):1506-14.
12. Hepburn-Brown M, Darvall J, Hammerschlag G. Acute pulmonary embolism: a concise review of diagnosis and management. Intern Med J. 2019;49(1):15-27.
13. Chaudhury P, Gadre SK, Schneider E, Renapurkar RD, Gomes M, Haddadin I, et al. Impact of Multidisciplinary Pulmonary Embolism Response Team Availability on Management and Outcomes. Am J Cardiol. 2019;124(9):1465-9.
14. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353:1386-9.
15. Wang H, Xu X, Pu C, Li L. Clinical characteristics and prognosis of cancer patients with venous thromboembolism. J Cancer Res Ther. 2019;15(2):344-9.
16. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet. 2016;388(10063):3060-73.
17. The PIOPED investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. JAMA. 1990;263:2753-9.
18. Alcaraz AC, Martínez AL, Solano FJS. Diagnosing pulmonary embolisms: the clinician's point of view. Diagnóstico de la embolia pulmonar. El punto de vista del médico clínico. Radiologia. 2017;59(2):166-76.
19. Ghanima W, Abdelnoor M, Mowinckel MC, Sandset PM. The performance of STA-Lia test D-Dimer assay in out-patients with suspected pulmonary embolism. Br J Haematol. 2006;132:210-5.
20. Agarwal A, Persaud J, Grabinski R, Rabinowitz D, Bremner A, Mendelson R. Pulmonary embolism: are we there yet? J Med Imaging Radiat Oncol. 2012;56(3):270-81.
21. Kalkan AK, Ozturk D, Erturk M, Kalkan ME, Cakmak HA, Oner E, et al. The diagnostic value of serum copeptin levels in an acute pulmonary embolism. Cardiol J. 2016;23(1):42-50.
22. Abu Assab T, Raveh-Brawer D, Abramowitz J, Naamad M, Ganzel C. The Predictive Value of Thromboelastogram in the Evaluation of Patients with Suspected Acute Venous Thromboembolism. Acta Haematol. 2020;143(3):272-8.
23. Mehta NJ, Jani K, Khan IA. Clinical usefulness and prognostic value of elevated cardiac Troponin I levels in acute pulmonary embolism. Am Heart J. 2003;145:821-5.
24. Martinez JLA, Sánchez FJA, Echezarreta MAU, García IV, Álvaro JR. Central Versus Peripheral Pulmonary Embolism: Analysis of the Impact on the Physiological Parameters and Long-term Survival. N Am J Med Sci. 2016;8(3):134-42.
25. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, et al. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2018;137(20):578-622.
26. Campbell AR, Rodriguez AJ, Larson DM, Strauss CE, Garberich RF, Partridge MF, Henry TD, Sharkey SW. Resource utilization and outcome among

patients with selective versus nonselective troponin testing. Am Heart J. 2018;199:68-74.
27. Keller K, Geyer M, Beule J, Coldewey M, Balzer JO, Dippold W. Impact of cancer on the effectiveness of cardiac Troponin I to predict right ventricular dysfunction in acute pulmonary embolism. Thorac Cancer. 2015;6(5):584-8.
28. Jiménez D, Díaz G, Molina J, Martí D, Del Rey J, García-Rull S, et al. Troponin I and risk stratification of patients with acute non massive pulmonary embolism. Eur Respir J. 2008;31:847-53.
29. Kucher N, Wallmann D, Carone A, Windecker S, Meier B, Hess OM. Incremental prognostic value of troponin I and echocardiography in patients with acute pulmonary embolism. Eur Heart J. 2003;24:1651-6.
30. Giannitsis E, Müller-Bardorff M, Kurowski V, Weidtmann B, Wiegand U, Kampmann M, et al. Independent prognostic value of cardiac troponin T in patientwitk confirmed pulmonary embolism. Circulation. 2000;102:211-7.
31. Tanabe Y, Obayashi T, Yamamoto T, Takayama M, Nagao K. Predictive value of biomarkers for the prognosis of acute pulmonary embolism in Japanese patients: Results of the Tokyo CCU Network registry. J Cardiol. 2015;66(6):460-5.
32. Jiménez D, Aujesky D, Moores L, Gómez V, Martí D, Briongos S, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax. 2011;66:75-81.

Cite this article as: Ilkhan GD, Celikhisar H. The effect of troponin values on prognosis in acute pulmonary embolism. Int J Clin Trials 2020;7(4):229-34.