Clinical, imaging and hemodynamic correlates and prognostic impact of syncope in acute pulmonary embolism: A single-center study

Akut pulmoner embolide senkopun klinik, görüntüleme ve hemodinamik korelasyonları ve prognostik etkisi: Tek merkezi bir çalışma

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Abstract

Background: We aimed to determine the clinical, echocardiographic and hemodynamic correlates of syncope as a presenting symptom in pulmonary embolism and its impact on in-hospital and long-term outcomes.

Methods: Between July 2012 and October 2019, a total of 641 patients with PE (277 males, 364 females; median age: 65 years; range, 51 to 74 years) in whom the diagnostic work-up and risk-based management were performed according to the current pulmonary embolism guidelines were retrospectively analyzed. Clinical, laboratory and imaging data of the patients were obtained from hospital database system.

Results: Syncope was noted in 193 (30.2%) of patients on admission, and was associated with a significantly higher-risk status manifested by elevated troponin and D-dimer levels, a higher Pulmonary Embolism Severity Index score, deterioration of right-to-left ventricular diameter ratio, right ventricular longitudinal contraction measures, the higher Qanadli score, and higher rates of thrombolytic therapies (p<0.001) and rheolytic–thrombectomy (p=0.037) therapies. In-hospital mortality (p=0.007) and was associated with a significantly higher-risk status manifested by elevated troponin and D-dimer levels, a higher Pulmonary Embolism Severity Index score, deterioration of right-to-left ventricular diameter ratio, right ventricular longitudinal contraction measures, the higher Qanadli score, and higher rates of thrombolytic therapies (p<0.001) and rheolytic–thrombectomy (p=0.037) therapies.

Conclusion: Syncope as the presenting symptom is associated with a higher risk due to more severe obstructive pressure load and right ventricular dysfunction requiring more proactive strategies in patients with pulmonary embolism. However, with appropriate risk-based therapies, neither in-hospital mortality nor long-term mortality can be predicted by syncope.

Keywords: Acute pulmonary embolism, mortality, risk prediction, syncope.

ÖZ

Amaç: Bu çalışmada pulmoner embolide başvuru anında senkopun klinik, ekokardiyografik ve hemodinamik korelasyonları ve hastane içi ve uzun dönem sonuçları üzerindeki etkisini incelendi.

Çalışma planı: Temmuz 2012-Ekim 2019 tarihleri arasında tanı testleri ve risk esaslı tedaviye mevcut pulmoner emboli kılavuzlarına göre yapılan toplam 641 pulmoner emboli hastası (277 erkek, 364 kadın; ort. yaş: 65 yıl; dağılım, 51-74 yıl) retrospektif olarak incelendi. Hastaların klinik, laboratuar ve görüntüleme verileri hastane veri taban sisteminde edile edildi.

Bulgular: başvuru anında hastaların 193’ünde (%30.2) senkop belirlendi ve artmış troponin ve D-dimer düzeyleri, yüksek Pulmoner Emboli Şiddet İndeks skorları, sağ-sol ventrikül çapı oranı ve sağ ventrikülün uzunlamasına kontraksyon ölçümünün kötüleşmesi, yüksek Qanadli skoru ve yüksek trombolitik tedavi (p<0.001) ve reolitik-trombektomi tedavi (p=0.037) oranları ile belirlendiği üzere anlamlı düzeyde daha yüksek risk durumunu ile ilişkilidir. Hastane içi mortalitesi (p=0.007) ve minor kanama (p<0.001) senkop alt grubunda anlamlı düzeyde daha yüksek idi. Çok değişkenli lojistik regresyon analizi içinde, yüksek Pulmoner Emboli Şiddet İndeks skorları ve sağ-sol ventrikül çapı oranı senkop ile bağımsız düzeyde ilişkilidir. Çalışma, garden senkopun klinik, görüntüleme ve hemodinamik korelasyonları ve hastane içi ve uzun dönem sonuçları üzerindeki etkisinin önemini ortaya koydu.

Anahat sözcükler: Akut pulmoner emboli, mortalite, risk tahmini, senkop.
Acute pulmonary embolism (PE) has been considered among the most important world-wide cardiovascular diseases, resulting in morbidity and mortality. Risk stratification algorithm recommended by the currently available European Society of Cardiology (ESC) PE Guidelines is based on hemodynamic status and clinical characteristics at initial assessment, right ventricular (RV) dysfunction presence as assessed by echocardiography or computed tomographic pulmonary angiography (CTPA), and elevated cardiac biomarkers indicating RV strain and myocardial injury.[1,2]

Syncope has been documented as a presenting manifestation in approximately 25% of patients with PE.[3-6] Although current guidelines emphasize the importance of this presentation in risk-based in-hospital management algorithms of PE, as a result of the uncertainties regarding the prognostic impact of syncope on the early clinical course in this setting, only two out of currently available 20 risk prediction models have included the presence of syncope.[7,8] A systematic review and meta-analysis on PE series revealed that syncope was associated with a higher risk for hemodynamic deterioration and RV dysfunction on admission, and early PE-related adverse events. However, this increased risk of early mortality seemed to be more pronounced in studies consisting of unselected patients, but not in those comprising normotensive subjects only.[8] Therefore, the mechanisms of the syncope in hemodynamically stable and unstable patients may be different, and these results raise the question whether syncope itself may represent the independent prediction for in-hospital outcome.[8]

In the present study, we aimed to evaluate clinical, echocardiographic, and hemodynamic correlates of syncope presence in patients with PE and to assess whether it had a prognostic impact on the in-hospital and long-term outcomes.

**PATIENTS AND METHODS**

This single-center, retrospective study was conducted at the Department of Cardiology, Kartal Koşuyolu Heart and Research Hospital between July 2012 and October 2019. A total of 641 patients with PE (277 males, 364 females; median age: 65 years; range, 51 to 74 years) in whom the diagnosis was confirmed and risk-based management strategies were decided following the admission to emergency department of our center were included. All consecutive patients with PE who were diagnosed based on CTPA and hospitalized were included. In accordance with the 2014 and 2019 ESC PE Guidelines, a systematic work-up with CTPA, echocardiography, biomarkers, and PE severity indexes was routinely performed for risk-based management strategies.

The CTPA images were acquired at the time of admission and discharge using a 64-slice-helical computed tomography (CT) scanner (Toshiba Aquilion 64™, Toshiba Medical Systems Corp., Tokyo, Japan) and the images recorded at the time of diagnosis and discharge. A validated CT score for pulmonary artery (PA) occlusion suggested by Qanadli et al.[9] (Qanadli score, QS), RV to left-ventricle ratio (RV/LVr), right-atrial to left-atrial diameter ratio (RA/LAr) and main, left and right PA diameters were measured from CTPA images.

We retrospectively analyzed the prospectively collected pre-existing data set of PE patients who were admitted to the emergency service. The data set consists of prospectively obtained data of patients presented to emergency service with PE, including baseline characteristics, laboratory parameters, CTPA, and echocardiographic measurements were obtained from hospital database system. Patients without imaging evidence of PE were excluded.

According to the 2009 and 2018 ESC guidelines, syncope is defined as transient loss of consciousness due to brief global cerebral hypoperfusion.[10,11] We defined PE-related syncope, if syncope occurred during PE-related symptoms are present. Patients with a suspicion of traumatic syncope underwent to cranial CT to exclude intracranial events.

Troponin-T levels were measured to diagnose myocardial injury. According to the ESC guidelines, systolic blood pressure (SBP) less than 90 mmHg at initial presentation or a decline in SBP more than 40 mmHg and lasting longer than 15 min, were the parameters to define the high-risk status.[1,2] Laboratory results, imaging data and in-hospital outcome status were retrieved from the hospital database.

Data about long-term mortality were obtained from the national healthcare database and telephone visits in January 2020 and the accessible data referred to all-cause mortality. Therapies implemented to patients were documented, including intravenous fibrinolytics, catheter-directed treatments and anticoagulants. Major or minor bleeding events during hospitalization were also recorded.

**Statistical analysis**

Statistical analysis was performed using the R version 4.01 software (R Foundation for Statistical Computing, Vienna, Austria) with “rms” “survival”, “survminer”,
“ggdag” and “ggplot2” packages. Continuous data were presented in median and 25th-75th interquartile range (IQR), while categorical data were presented in number and frequency. The Mann-Whitney U test was used for the continuous data comparisons and Pearson chi-square or Fisher exact tests were used for categorical data comparison. A two-tailed \( p \) value of <0.05 was considered statistically significant.

Table 1. Clinical characteristics of patients with pulmonary embolism on admission according to the presence or absence of syncope as presenting finding

| Variables                              | Syncope absent (n=448) | Syncope present (n=193) | p     |
|----------------------------------------|------------------------|-------------------------|-------|
|                                        | n          | %       | Median | IQR  | n          | %       | Median | IQR  |       |
| Age (year)                             | 64         | 51-75   |        |      | 66         | 51-74   |        |      | 0.787 |
| Sex                                    |            |         |        |      |            |         |        |      |       |
| Female                                 | 251        | 56.02   | 113    | 58.54| 0.373      |         |        |      |       |
| Hypertension                           | 158        | 35.26   | 71     | 36.78| 0.835      |         |        |      |       |
| Coronary artery disease                | 49         | 10.9    | 17     | 8.8  | 0.285      |         |        |      |       |
| Hyperlipidemia                         | 32         | 7.14    | 9      | 4.66 | 0.169      |         |        |      |       |
| Diabetes mellitus                      | 66         | 14.73   | 40     | 20.72| 0.123      |         |        |      |       |
| Congestive heart failure               | 11         | 2.45    | 2      | 1.03 | 0.206      |         |        |      |       |
| Smoking history                        | 39         | 8.7     | 26     | 13.47| 0.115      |         |        |      |       |
| Chronic obstructive pulmonary disease  | 29         | 6.47    | 12     | 6.21 | 0.750      |         |        |      |       |
| Stroke history                         | 21         | 4.68    | 18     | 9.32 | 0.041      |         |        |      |       |
| Oral contraceptive use                 | 10         | 2.23    | 3      | 1.55 | 0.509      |         |        |      |       |
| Atrial fibrillation                    | 25         | 5.58    | 16     | 8.29 | 0.280      |         |        |      |       |
| Long-haul travel history               | 24         | 5.35    | 11     | 5.69 | 0.993      |         |        |      |       |
| Acute deep vein thrombosis             | 254        | 56.69   | 94     | 48.70| 0.086      |         |        |      |       |
| Prior venous thromboembolism           | 50         | 11.16   | 11     | 5.69 | 0.032      |         |        |      |       |
| Malignancy                             | 65         | 14.50   | 33     | 17.09| 0.342      |         |        |      |       |
| Postoperative status                   | 148        | 33.03   | 65     | 33.67| 0.732      |         |        |      |       |
| Symptom duration                       | 4          | 3-7     | 2      | 1-5  | <0.001     |         |        |      |       |
| SPO₂ (%)*                              | 90         | 87-93   | 88     | 85-92| <0.001     |         |        |      |       |
| SBP (mmHg)*                            | 122        | 110-138 | 113    | 93-130| <0.001     |         |        |      |       |
| Heart rate (bpm)*                      | 104        | 91-115  | 114    | 100-122| <0.001     |         |        |      |       |
| PESI Class                             |            |         |        |      |            |         |        |      | <0.001|
| 3                                      | 109        | 24.60   | 41     | 21.24|           |         |        |      |       |
| 4                                      | 80         | 17.85   | 39     | 20.20|           |         |        |      |       |
| 5                                      | 92         | 20.53   | 79     | 20.20|           |         |        |      |       |
| PESI score                             | 95         | 73-119  | 118    | 93-147| <0.001     |         |        |      |       |
| sPESI Class                            |            |         |        |      |            |         |        |      | <0.001|
| 0                                      | 124        | 27.67   | 24     | 12.43|           |         |        |      |       |
| 1                                      | 157        | 27.67   | 24     | 12.43|           |         |        |      |       |
| 2                                      | 104        | 23.1    | 52     | 26.94|           |         |        |      |       |
| 3                                      | 51         | 11.38   | 54     | 27.27|           |         |        |      |       |
| 4                                      | 11         | 2.45    | 13     | 6.73 |           |         |        |      |       |
| 5                                      | 1          | 0.22    | 2      | 1.03 |           |         |        |      |       |
| Shock index*                           | 0.83       | 0.68-1  | 0.96   | 0.79-1.3| <0.001     |         |        |      |       |
| Risk status (according to ESC algorithm)|            |         |        |      |            |         |        |      | <0.001|
| Low-risk                               | 78         | 17.41   | 13     | 6.73 |           |         |        |      |       |
| Intermediate-low risk                  | 86         | 19.19   | 14     | 7.25 |           |         |        |      |       |
| Intermediate-high risk                 | 257        | 57.36   | 117    | 60.62|           |         |        |      |       |
| High risk                              | 27         | 6.02    | 49     | 25.38|           |         |        |      |       |

IQR: Interquartile range; * At admission; SpO₂: Blood oxygen saturation; SBP: Systolic blood pressure; bpm: Beats per min; PESI: Pulmonary Embolism Severity Index; sPESI: Simplified Pulmonary Embolism Severity Index; ESC: European Society of Cardiology.
The primary outcome was in-hospital mortality. Secondary outcome was long-term mortality. Syncope before admission was used for primary and secondary outcome. We included following parameters for in-hospital all-cause mortality: age, SBP, heart rate, blood oxygen saturation (SpO2), echocardiographic PA systolic pressure (PASP), QS, presence of syncope and RV/LVr (at the time of admission). We included following parameters for long-term all-cause mortality: Age, sex, RV/LVr at discharge, syncope, SBP (at the time of admission), heart rate (at the time of admission), SpO2 (at the time of admission) and QS (at the time of admission), and malignancy. We included SBP Pulmonary Embolism Severity Index (PESI) score, QS, PASP, and RV/LVr at the time of admission for predictors of syncope. Adjustment variables were selected according to the subject matter knowledge and finally we drew a directed acyclic graph to inform regression models.

The in-hospital risk of mortality was assessed using the multivariate logistic regression models. Effects of individual exposure were reported using the odds ratio (OR) and 95% confidence interval (CI). Predictors of syncope were assessed with the multivariate logistic regression models. Effect of individual exposure was reported using OR and 95% CI. All-cause long-term mortality was displayed by using the Kaplan-Meier plot to examine the relationship between syncope groups. The multivariate Cox proportional hazard models were used to assess effect of exposure and confounders on long-term mortality. Effect of individual exposure was reported using the hazard ratio (HR) and 95% CI.

RESULTS

The 193 (30.2%) of 641 PE patients had a history of syncope on admission. Baseline demographic and clinical characteristics are presented in Table 1.
Although age, sex, and other demographic characteristics were not associated with syncope, patients presented with syncope demonstrated a higher heart rate, a lower SpO2 and SBP, a higher risk status (according to PESI score, shock index, ESC risk algorithm) and a shorter symptom duration before admission (p<0.001 for all).

Laboratory measurements, CT angiographic, and echocardiographic parameters on admission are summarized in Table 2. Patients presented with syncope had higher troponin-T and D-dimer levels on admission (p<0.001 for both of them), a lower tricuspid annular plane systolic excursion (TAPSE) (p<0.001) and tricuspid annulus systolic velocity (St) (p=0.01), and a higher PASP (p=0.01) on echocardiography, a higher thrombotic burden as assessed by QS (p<0.001), and a higher RV/LVr (p=0.001) and RA/LAr (p=0.004) on CTPA (Table 2). Furthermore, proactive therapies including intravenous tissue lasminogen activator (tPA) and rheolytic thrombectomy were more often utilized in patients presented with syncope (p<0.001 and p=0.037, respectively).

Post-treatment differences regarding clinical, echocardiographic, and CTPA findings were also evaluated (Table 3). There were no significant differences at discharge between syncope groups in all terms including hemodynamic variables such as SBP, heart rate, SpO2 (p=0.470, p=0.514, respectively), TAPSE, St, PASP (p=0.587, and p=0.460, respectively) and CTPA measures of QS, RV/LVr and RA/LAr (p=0.865, and p=0.025, respectively). In-hospital mortality and minor bleeding was more observed in patients presenting with syncope (p=0.007 and p<0.001, respectively), while major bleeding events and long-term mortality were comparable between patients with or without syncope at the time of admission (p=0.06).
| Variables                                               | Odds ratio | 95% CI   | p     |
|--------------------------------------------------------|------------|----------|-------|
| Systolic blood pressure at admission (mmHg)            | 0.991      | 0.981-1.002 | 0.115 |
| PESI score                                             | 1.015      | 1.008-1.022 | <0.001|
| Qanadli score                                          | 1.025      | 0.989-1.063 | 0.167 |
| Pulmonary artery systolic pressure at admission (mmHg) | 1.004      | 0.987-1.022 | 0.578 |
| Right ventricle/left ventricle ratio at CT at admission| 7.508      | 2.401-23.475| <0.001|

PE: Pulmonary embolism; CI: Confidence interval; PESI: Pulmonary Embolism Severity Index; CT: Computed tomography; Multivariate logistic regression analysis

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**Table 4. Predictors of syncope in patients with PE on admission**

**Figure 1.** Directed acyclic graph to inform about multivariate logistic regression model (syncope was the main exposure, in-hospital mortality was the primary outcome). RV: Right ventricle; LV: Left ventricle; PASP: Pulmonary artery systolic pressure.
In multivariate logistic regression analysis, higher PESI score and higher RV/LVr independently predicted syncope in PE patients (OR: 1.015, 95% CI: 1.008-1.022, p<0.001 and OR: 7.508, 95% CI: 2.401-23.475, p<0.001, respectively). The PAPS, QS and SBP at the time of admission were also included in the model; however, there was not statistically significant association (Table 4).

Age and heart rate (OR: 1.035, 95% CI: 1.011-1.060, p=0.004, and OR: 1.041, 95% CI: 1.018-1.070, p<0.001, respectively), but not syncope (OR: 0.655, 95% CI: 0.284-1.520, p=0.323), were found to be independent predictors for in-hospital mortality (Table 5, Figure 1).

Multivariate Cox proportional regression analysis was used to examine the association between the long-term mortality and mentioned nine candidate predictors (Table 6). Among variables, RV/LVr at discharge and malignancy were independently associated with long-term mortality (HR: 1.414, 95% CI: 1.02-1.946, p=0.033 and HR: 5.261, 95% CI: 2.702-10.242, p<0.001, respectively) (Figure 2). Kaplan-Meier curve showed no differences in terms of long-term survival probability between the groups (Figure 3).

**DISCUSSION**

Our single-center data suggest that presence of syncope in PE relates to a higher risk, a more severe PA obstructive burden, a more deteriorated hemodynamic status and RV dysfunction which required more proactive reperfusion strategies.[11] Mohebali et al.[12] also demonstrated that syncope was associated with increased RV strain and needed to advanced treatments in PE patients. However, possibly as a result of the appropriate risk-based PE management.

| Variables                        | Odds ratio | 95% CI   | p    |
|----------------------------------|------------|----------|------|
| Age (year)                       | 1.309      | 0.753-2.274 | 0.338 |
| Sex (female reference)           | 0.569      | 0.296-1.094 | 0.091 |
| RV/LV ratio at CT at discharge   | 1.414      | 1.028-1.946 | 0.033 |
| Syncope presence at admission    | 0.885      | 0.426-1.837 | 0.744 |
| SBP at admission (mmHg)          | 1.039      | 0.660-1.638 | 0.863 |
| Heart rate at admission (bpm)    | 0.984      | 0.550-1.761 | 0.958 |
| Blood oxygen saturation (at admission) (%) | 0.676    | 0.434-1.052 | 0.083 |
| Malignancy presence              | 5.261      | 2.702-10.242 | <0.001 |
| Qanadli score at admission       | 1.006      | 0.597-1.695 | 0.980 |

PE: Pulmonary embolism; CI: Confidence interval; RV: Right ventricle; LV: Left ventricle; CT: Computed tomography; SBP: Systolic blood pressure; bpm: Beats per min; Multivariate logistic regression analysis

![Figure 2. Hazard-ratio plot for long-term mortality.]
strategies, this relationship could not be translated to in-hospital (when adjusted with multivariate analysis) and long-term mortality.

The mechanisms and clinical impact of syncope as an early risk assessment parameter remain to be established. Although PE has been reported in up to 17% of patients with a first episode of syncope not due to other causes, one-fourth of these patients had no clinical signs or symptoms consistent with PE.[6] A systematic review and meta-analysis based on data from 29 PE studies showed that syncope related to a higher frequency of hemodynamic deterioration and RV dysfunction at presentation, a higher risk of 30-day all-cause cumulative mortality and PE-related adverse outcomes.[8,13-16] The absolute risk difference (95% CI) for all-cause death was reported to be 6% (1 to 10%) in studies consisting of unselected population, while it had no impact in PE studies restricted to normotensive patients.[8,17-22] Moreover, the association between syncope and all-cause mortality seems to be stronger than for PE-related mortality. The sensitivity analyses of this meta-analysis showed that the impact of syncope was mostly supported by studies with a lower score at formal quality assessment and by retrospective studies.[8]

In our univariate analysis, syncope was associated with a shorter symptom-diagnosis interval, a higher risk status manifested by significantly elevated biomarker levels, the higher PE severity indexes, a more severe obstructive burden and RV dysfunction, and the higher utilization rates of thrombolytics and rheolytic thrombectomy as proactive reperfusion therapies.

Surgical outcomes have improved substantially in the past decades and now offer a safe and appropriate treatment option that can reduce the mortality and morbidity associated with acute PE.[23,24] Surgical pulmonary embolectomy is another alternative in selected patients, with non-surgical approaches remaining the first-line treatment in most cases.[1,23,24] The presence of thrombolytic and catheter-directed treatment options in our center has led to the primary use of non-surgical treatments. There are no patients undergoing surgical treatment in this study population.

Although, syncope was independently associated with PESI score and RV/LVr, older age and increased heart rates, but not syncope itself, predicted in-hospital mortality. In line with the findings of meta-analysis by Barco et al.,[8] our results suggest that syncope may be only a surrogate for severity of RV dysfunction and pre-existing comorbidity, rather than an independent prognostic factor.

The present study also demonstrated the independent prognostic impact of RV/LVr at discharge and malignancy for long-term mortality. These results seem to explain the importance of the persistence of asymptomatic RV dysfunction even in the normotensive patients.

This study has some limitations. The retrospective design of this study may be considered as the main limitation. Adequately sized prospective cohort studies may clarify the question whether syncope has an independent prognostic impact beyond the currently available risk criteria. Moreover, a comparison among normotensive, hypotensive and unselected PE populations might provide a comprehensive assessment for prognostic impact of syncope in this setting.

In conclusion, syncope as presenting symptom relates to a higher risk status due to a more severe obstructive burden, pressure load and right ventricular strain requiring more proactive reperfusion strategies in pulmonary embolism patients. However, with appropriate management, syncope predicts neither in-hospital, nor long-term cumulative mortality.

**Ethics Committee Approval:** The study protocol was approved by the Kartal Koşuyolu Heart and Research Hospital Instutional Ethics Committee (date/no: 20.10.2020/372). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.
Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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