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Original Article

Impact of syncope and pre-syncope on short-term mortality in patients with acute pulmonary embolism

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ABSTRACT

Background: Syncope and pre-syncope are well-known symptoms of acute pulmonary embolism (PE). However, data about their impact on short-term mortality are scant. We assess the short-term mortality (30-day) for all-causes in PE patients admitted with syncope or with pre-syncope, according their hemodynamic status at admission.

Methods: Patients from the prospective Italian Pulmonary Embolism Registry (IPER) were included in the study. At admission, subjects were stratified according to 2008 ESC guidelines (as high- and non-high-risk patients).

Results: Among the 1716 patients with confirmed acute PE, syncope or pre-syncope was the initial manifestation of the disease in 458 (26.6%) patients. Short-term mortality (30-day) for all causes were significantly higher in patients with syncope/presyncope (42.5% vs 6.2%, $p < 0.0001$) while PE patients with presyncope demonstrated a worst short-term outcome, in terms of mortality for all-causes, when compared to those subjects with syncope at admission (47.2% vs 37.4%, $p = 0.03$). A statistically significant difference in survival between pre-syncope and syncope was observed only in hemodynamically unstable patients [log rank $p = 0.036$]. Cox regression analysis confirmed that pre-syncope resulted an independent predictor of 30-day mortality in hemodynamically unstable patients at admission (HR 2.13, 95% CI 1.08–4.22, $p = 0.029$), independently from right ventricular dysfunction (RVD) (HR 6.23, 95% CI 3.05–12.71, $p < 0.0001$), age (HR 1.03, 95% CI 1.00–1.06, $p = 0.023$) and thrombolysis (HR 2.27, 95% CI 1.11–4.66, $p = 0.025$).

Conclusions: PE patients with syncope/presyncope had a higher 30-day mortality for all-causes as well as patients with presyncope had a worst short-term outcome when compared to PE patients with syncope. Moreover, hemodynamically unstable patients with presyncope had a worst prognosis independently from the presence of RVD, age, positive cTn and thrombolytic treatment.

1. Introduction

Syncope and collapse commonly occur in general population [1]. The overall prognosis of syncope is favourable but the prompt identification of patients with an underling potentially life-threatening disease, such as acute pulmonary embolism (PE), is of paramount importance in clinical practice [2–4]. However, nowadays, the real prevalence of syncope among patients with acute PE has not been completely established. Indeed, over the years, several studies have reported conflicting results [5,6]. The link between syncope and PE have been studied in terms of prognosis of PE patients and analysing the number of PE patients present in subjects hospitalized for syncope. This latter aspect has been analysed by Prandoni et al. which estimated that about one out of six patients hospitalized because of the first episode of syncope had acute PE [7,8]. Conversely, the short-term prognosis of PE patients with syncope or presyncope has been poorly investigated. Moreover, these previous studies have never considered a careful distinction between PE patients with syncope and pre-syncope (or collapse). As result, no large clinical trials and/or multicentre epidemiological studies, looking at the prognosis of PE patients with syncope or

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pre-syncope and stratified according their hemodynamic profile at admission, are currently available. However, it has been already established in the cardiovascular literature that patients with cardiac syncope have a higher risk of death in the short-term period [9]. The aim of this study is to elucidate the prevalence of both syncope and pre-syncope in PE patients and to evaluate in these subjects the short-term (30-day) mortality for all-causes according to their hemodynamic status at admission. For this purpose, subjects from the prospective Italian Pulmonary Embolism Registry (IPER) were included in the present study.

2. Material and methods

2.1. Study design

Patients enrolled in the Italian Pulmonary Embolism Registry (IPER) were considered eligible for the analysis. The protocol and the aim of this registry have been described elsewhere [10]. Briefly, IPER was designed as a prospective, multicentre and web-based registry. Specifically, 1716 patients (739 males and 977 females, mean age 69.96 ± 15.30 years), with confirmed diagnosis of acute PE were enrolled between September 2006 and August 2010 in 49 departments (cardiology, emergency and internal medicine departments) of 47 Italian hospitals. All patients aged > 18 years old, with confirmed PE and able to give informed consent were eligible for the inclusion in the registry. The protocol of the study was approved by the institutional review boards both at the coordinating center (San Carlo Borromeo Hospital, Milan, Italy) and in every recruiting hospital. All the procedures were performed in accordance with the Guidelines for Good Clinical Practice and the national regulations on observational studies. The registry was endorsed by the Italian Association of Hospital Cardiologists (ANMCO) and was designed by the Working Group on Pulmonary Circulation of the ANMCO. A list of participating institutions is given in the supplementary Appendix 1.

2.2. Syncope and collapse: definitions

According to the European Society of Cardiology (ESC) guidelines, syncope was defined as a transient loss of consciousness due to transient global cerebral hypoperfusion and characterized by rapid onset, short duration, and spontaneous complete recovery [1]. Conversely, pre-syncope (or collapse) was defined as a transient alteration of consciousness, without complete loss of consciousness [11]. Since the distinction between syncope and pre-syncope is often difficult, IPER investigators used different strategies to correctly assess the presenting symptoms at admission. Specifically, the definition of syncope or pre-syncope were obtained by the testimony of both medical or paramedical staff, even in the pre-hospital or hospital setting, if they were present during the event. Conversely, if this strategy was not feasible, the distinction between syncope and pre-syncope was obtained through a careful anamnesis, interviewing both the patient and/or family members who were present during the event. As per registry protocol, the definition of both syncope and pre-syncope were present from the beginning of the registry and subsequently applied during the enrolment phase. As results, all recruiter centres and local investigators used the cited definition of syncope and pre-syncope to stratify the patient at admission. All cases were reviewed by two independent physicians of the enrolling centre. All conflictual cases were collegially reviewed by local investigators and a third physician was consulted.

2.3. Patients assessment

Since the enrolment of patients taken place between the 2006 and 2010, after the diagnosis of acute PE, all patients were stratified according the ESC recommendations of that time [12]. Specifically, hemodynamically unstable patients, with a persistent systolic blood pressure (SBP) ≤ 90 mmHg or a pressure drop of ≥ 40 mmHg for > 15 min, not caused by new-onset arrhythmia, were categorized to be at high-risk. Conversely, hemodynamically stable PE patients were classified as non-high-risk patients. Heart rate (HR) was also evaluated at admission. Shock index (SI) was calculated as the ratio of HR and systolic blood pressure (SBP). Right ventricular dysfunction (RVD) was diagnosed by transthoracic echocardiography (TTE) in the presence of at least one of the following: 1) right to left ventricle end-diastolic diameter ratio > 1 in apical 4-chamber view; 2) right to left ventricle end-diastolic diameter ratio > 0.6 in parasternal long-axis or subcostal 4-chamber views and 3) right ventricular-to-right atrial pressure gradient > 30 mmHg [10,13]. RVD was not considered of acute onset in the presence of right ventricle wall thickness > 7 mm or documentation of right ventricle overload at previous examinations [13,14]. Assessment of deep vein thrombosis (DVT) was performed using B-mode and colour Doppler imaging. Cardiac injury was evaluated by measuring cardiac troponin (cTn) levels at admission, according to local standards. Specifically, cTn was evaluated in 1266 patients (73.7%), while in 450 (35.7%) cases the recruiting centers not reported the values into the web registry. Standard 12-lead electrocardiogram (ECG) (25 mm/s and 1 mV/cm) was always evaluated within 24 h from admission. In this analysis we considered the following ECG features: sinus rhythm, complete or incomplete right bundle branch block (RBBB), S1QT3 pattern, negative T waves from V1 to V4 (NTWs), ST segment elevation in inferior leads (DII.DII. aVf), Q waves in inferior leads, ST segment depression in at least two contiguous leads. Clinical deterioration was defined as a clinical worsening condition that required one of the followings: (1) IV catecholamine infusion, (2) endotracheal intubation or (3) CPR.

2.4. Treatments

No specific strategies regarding the treatment of the acute event were a priori planned by the registry protocol. Previous observations from IPER revealed that high-risk patients without absolute or relative contraindications to thrombolysis, were perfused as soon as possible after the diagnosis [10]. Moreover, some centres applied percutaneous pulmonary thrombectomy and surgery for the treatment of these patients. On the other hand, non-high-risk patients received heparin (either unfractionated or low-molecular weight or fondaparinux) [10].

2.5. Study end-points

The end-points of the study were the prevalence of both syncope and pre-syncope in PE patients and their prognostic role on 30-day mortality according to the patients' hemodynamic profile at admission.

2.6. Statistical analysis

First, PE patients with syncope/pre-syncope related to acute PE were compared to those without these symptoms at admission. Subsequently, we compared patients with syncope versus those with pre-syncope, stratifying the cohort by the hemodynamic status at admission. Continues variables were expressed as mean ± standard deviation (SD) and were compared by Student' *t*-test if the data had normal distribution, otherwise by Wilcoxon-Mann-Whitney *U* test. Categorical variables, presented as proportions and 95% confidence intervals (CIs), were compared by the Pearson's $\chi 2$ test. To estimate 30-day survival, the Kaplan–Meier method was applied, and the log-rank test was used to evaluate the differences between the two groups. Cox regression models for association between pre-syncope and short-term mortality were computed. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS package version 20.0 (SPSS, Chicago, IL, USA).