REVIEW ARTICLE

# How to predict short- and long-term mortality in patients with pulmonary embolism?

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**KEY WORDS**

long-term prognosis, pulmonary embolism, shot-term prognosis

**ABSTRACT**

Pulmonary embolism (PE) is a common disease with a considerable short- and long-term risk of death. An adequate evaluation of the prognosis in patients with PE may guide decision making in terms of the intensity of the initial treatment during the acute phase, duration of treatment, and intensity of follow-up control visits in the long term. Patients with shock or persistent hypotension are at high risk of early mortality and may benefit from immediate reperfusion. Several tools are available to define the short-term prognosis of hemodynamically stable patients. The Pulmonary Embolism Severity Index (PESI) score, simplified PESI score, and N-terminal pro-B-type natriuretic peptide levels are particularly useful for identifying patients at low risk of early complications who might be safely treated at home. However, the identification of patients who are hemodynamically stable at diagnosis but are at a high risk of early complications is more challenging. The current guidelines recommended a multiparametric prognostic algorithm based on the clinical status and comorbidities. Unfortunately, only a few studies have evaluated the role of risk factors potentially affecting the long-term prognosis of these patients. The available studies suggest a potential role of the PESI score and troponin levels evaluated at the time of an index event. However, further studies are warranted to confirm these preliminary findings and to identify other long-term prognostic factors in this setting.

**Introduction** Venous thromboembolism (VTE) is the third most common cardiovascular disorder after myocardial infarction and brain ischemic stroke with an overall annual incidence of 100 to 200 cases per 100 000 inhabitants.[1,2] VTE encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). Due to population aging and improvement in diagnostic techniques, PE has been diagnosed increasingly more often in the last few years.[3] PE is the major cause of mortality, morbidity, and hospitalization with 350 000 VTE-related deaths estimated each year in 6 major European countries.[2]

Thus, despite progress in the diagnosis and acute and postacute management of PE, it may still have high short- and long-term mortality rates.[2,4,5] In the acute phase, mortality seems to be directly related to the characteristics of the thromboembolic event and to the rate of its short-term recurrence. On the other hand, the long-term prognosis of PE may be more influenced by the presence of underlying comorbidities. However, the short- and long-term prognosis varies widely among these patients, and strategies to predict the short- and long-term risk of death in PE patients would be extremely useful for clinicians. Risk stratification in the acute phase of PE is of paramount importance because it may help guide decision making in terms of the intensity of the initial treatment during an acute phase, duration of treatment, and intensity of follow-up control visits in the long term. Thus, the aim of this review was to provide clinicians with adequate background information to accurately assess the short- and long-term mortality risk of patients with PE.

**Short-term clinical outcomes and predicting factors for mortality** Short-term mortality varies widely among patients with PE, ranging from less than 2% to more than 95% in patients who experience cardiac arrest.[6,7] It is universally known that shock or persistent hypotension define a subgroup of PE patients that are at an exceptionally high risk

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Received: January 5, 2015.
Revision accepted: January 6, 2015.
Published online: January 12, 2015.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2015; 125 (1-2): 82-88

of early mortality and for whom a more aggressive therapeutic approach seems justified.[8,9] Nevertheless, this subgroup accounts only for 5% of the whole population of patients presenting with acute PE.[9] The absence of hemodynamic collapse or persistent hypotension at presentation is generally thought to predict a favorable outcome.[9,10] However, some of those patients may still have an elevated risk of clinical deterioration and in-hospital death; therefore, they may become candidates for rescue thrombolysis or embolectomy. On the other hand, a consistent group of patients may have a very low risk of early recurrence and/or major complications and may be discharged from the hospital after a very brief stay or even directly from the emergency department, just after the first assessment. Thus, a careful stratification of patients with acute PE seems to be particularly important for clinicians to guide the initial management and to protect patients against the hazard to be treated at home with an unacceptable level of risk, or to undergo unnecessary and potentially dangerous treatments.

In the last few years, several studies have assessed the role of potential risk factors for early complications or early death, and a number of different tools are currently available to better define the prognosis of PE patients, including clinical prediction rules (CPRs), biomarkers, and imaging tests.

**Clinical prediction rules** A number of CPRs have been proposed for stratifying the short-term mortality risk in patients with acute PE.[11] The Pulmonary Embolism Severity Index (PESI) was developed in 2005, and its accuracy has been repeatedly confirmed in several large prospective studies.[12-14] The original PESI includes 11 items: demographic (age and sex), anamnestic (history of cancer, heart failure, or chronic pulmonary disease), and objective (heart and respiratory rate, systolic blood pressure, body temperature, altered mental status, and oxygen saturation). The original PESI score has been shown to be superior to the Geneva score,[15] the other popular risk assessment model (area under the receiver operating characteristic curve [AUROC], 0.76; 95% confidence interval [CI], 0.69–0.83 vs 0.61; 95% CI, 0.51–0.71).[16]

A recent large meta-analysis confirmed the role of the PESI score in the identification of PE patients at a low risk of mortality,[11] and patients with a PESI score of I–II were included in a randomized controlled trial that confirmed the safety and efficacy of home treatment of acute PE.[17]

Unfortunately, the PESI score categorizes patients into 5 risk classes and it is not easy to compute. Thus, in an effort to overcome these limitations, Jiménez et al.[18] has developed and validated a simplified score (sPESI) that has only 6 items (age >80 years, history of cancer or chronic cardiopulmonary disease, heart rate, systolic blood pressure and oxygen saturation) and divided patients with acute PE into 2 categories (low risk, sPESI = 0; high risk, sPESI ≥1). In a large population of the RIETE study, the accuracy of the sPESI score was similar to the original PESI score (AUROC, 0.75; 95% CI, 0.69–0.80).

**Biomarkers** Serum biomarkers are used as a surrogate for myocardial injury, right ventricular (RV) dysfunction, and impending hemodynamic instability, and are therefore best used as markers of severity, but may serve also for triage of more stable patients when they are within normal limits.

Two large meta-analyses evaluating the role of cardiac troponins in this setting have been published.[19,20] Becattini et al.[19] summarized data from 20 studies for a total of 1985 patients. In this pooled analysis, 122 of 618 patients (19.7%) with elevated troponin levels and 51 of 1367 patients (3.7%) with normal troponin levels died, and elevated troponin levels showed to be significantly associated with short-term mortality (odds ratio [OR], 5.24; 95% CI, 3.28–8.38) and with PE-related death (OR, 9.44; 95% CI, 4.14–21.49). Interestingly, elevated troponin levels were associated with high mortality even in the subgroup of hemodynamically stable patients (OR, 5.90; 95% CI, 2.68–12.95). In a subsequent publication, focused on hemodynamically stable patients, Jimenez et al.[20] confirmed the association between elevated troponin levels and short-term mortality. However, the results of this meta-analysis suggested that elevated troponin levels did not adequately discern normotensive patients who are at a high risk of death from those who are at a low risk of death (positive likelihood ratio, 2.26; 95% CI, 1.66–3.07; negative likelihood ratio, 0.59; 95% CI, 0.39–0.88).

In a meta-analysis that included 13 studies for a total of 1132 patients with acute PE, Klok et al.[21] showed that elevated levels of brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide (NT-proBNP) were significantly associated with 30-day mortality (OR, 7.6; 95% CI, 3.4–17) and that patients with high NT-proBNP levels had a 10% risk of death (95% CI, 8.0%–13%).[21] Subsequently Agterof et al.[22] demonstrated that patients with acute PE and with NT-proBNP levels lower than 500 pg/ml (43% of the whole population) can be safely treated at home. More recently, a number of prospective studies have evaluated the role of heart-type fatty acid binding protein (H-FABP), a small (15 kDa) marker of myocardial ischemia with favorable release kinetics, in predicting short-term mortality in patients with acute PE.[23,24] In a meta-analysis that pooled the results of 6 studies for a total of 618 patients, elevated H-FABP levels were strongly associated with short-term death (OR, 40.78; 95% CI, 11.87–140.09) and 31% (95% CI, 24%–39%) of patients with elevated H-FABP levels died within 30 days after the acute event.[25]

There is a more limited evidence for D-dimer and for markers of kidney dysfunction (creatinine, estimated glomerular filtration rate,

cystatin-C, and neutrophil gelatinase-associated lipocalin).[26-28]

**Imaging tests** Both echocardiography and computed tomography are currently used in the management of patients with a suspicion of PE, but they are potentially useful for predicting the short-term prognosis of patients with established PE directly showing signs of RV impairment. Echocardiography may show RV dilatation and hypokinesis, an abnormal motion of interventricular septum, or tricuspid regurgitation, with or without elevated systolic pulmonary artery pressure (>30 mmHg).[29] The ratio of the right to left ventricular end-diastolic diameter is the most common parameter and, in patients with acute PE, a ratio of more than 0.9 is associated with worse prognosis.[30] However, corresponding pooled negative and positive likelihood ratios were unsatisfactory for risk stratification of these patients.[31] Thus, echocardiographic criteria should not be used alone to predict adverse outcomes in stable patients with PE.

RV dysfunction on multidetector contrast-enhanced computed tomography (MDCT) is currently defined as the right-to-left ventricular dimensional ratio, and this parameter appeared promising in some studies in patients with acute PE.[32] However, evidence on its prognostic role is conflicting, and MDCT alone appeared inadequate to predict the short-term prognosis in these patients.[32]

**Combining risk factors** According to the evidence presented above, many of the discussed parameters may be useful for identifying the subgroup of patients at a low risk of early complications. On the other hand, each parameter alone appeared insufficient to identify the subgroup of patients with acute PE hemodynamically stable at diagnosis who may benefit from primary reperfusion. Thus, a number of recent studies have tested various combinations of clinical findings with laboratory and imaging tests.[33-35]

The current European Society of Cardiology guidelines proposed a multiparametric prognostic algorithm based on the clinical status and comorbidities to select the appropriate management and treatment of these patients.[9] The PESI score or sPESI should be used to distinguish between intermediate (PESI class III–V and simplified PESI ≥0) and low-risk patients (PESI class I or II, or a simplified PESI of 0). A further risk assessment should be considered only in normotensive patients at intermediate risk evaluating cardiac biomarker levels in the circulation and signs of RV dysfunction (by echocardiography or MDCT), focusing on the status of the RV in response to PE-induced acute pressure overload. Patients with both elevated cardiac biomarker levels in the circulation and RV dysfunction on imaging tests should be classified into an intermediate-high risk category. Conversely, patients with normal cardiac biomarker levels and/or without signs of RV dysfunction should be classified into an intermediate-low risk category. Whether this strategy results in better patient outcomes remains to be shown.

**Long-term clinical outcomes and predicting factors for mortality** The long-term clinical course of acute PE may be complicated by high rates of serious adverse events, both before and after cessation of anticoagulant therapy. Patients with PE have an increased risk of venous and arterial thromboembolic events and may have a higher risk of all-cause and PE-related death compared with patients without thromboembolic disease. Besides, mortality due to direct hemodynamic effects of acute PE, other thrombosis-related conditions, and comorbidities may affect survival of these patients.

However, data on long-term mortality risk of patients with previous PE are conflicting. In 2 recent studies, the overall survival of PE patients was shown to be similar to that of the general population.[36,37] In a population-based study, Naess et al.[36] followed 258 Norwegian patients with PE for a maximum period of 6.5 years. In this population, the overall mortality risk was particularly high during the first month after an index event but later it gradually reached that of the general population. In another study including 1075 patients with noncancer-related PE, followed for a median time of 6.6 years, the survival rate was comparable to that of the general population.[36]

Conversely, in several other studies, the long-term survival of patients with a previous PE appeared lower in comparison with controls.[38-40] In 1998, Heit et al.[38] reported data from a cohort study including 2218 patients with VTE (1277 patients with PE) followed for a total of 14 629 person-years (median follow-up for PE patients: 6.1 years excluding cases diagnosed on autopsy) in Olmsted County.[38] At 8 years, the survival rate was significantly lower than the expected rate in PE patients who survived the first year (69.7% vs 78.5%, respectively, $P$ <0.001). More recently, Schulman et al.[39] reported long-term results (10 years) of the DURAC I study including 897 patients with noncancer-related VTE (107 with PE).[39] Death occurred in 28.5% of the patients, which constituted a higher mortality rate than expected with a standardized incidence ratio (SIR) of 1.43 (95% CI, 1.28–1.58), mainly because of a higher mortality from cancer than expected (SIR, 1.83; 95% CI, 1.44–2.23). Finally, Flinterman et al.[40] compared long-term survival (8 years) of 4947 patients with a first episode of DVT and PE and of 6154 control individuals using the database of the MEGA study.[40] The overall mortality rate was 22.7 per 1000 person-years (95% CI, 21.0–24.6) in patients and 4.7 per 1000 person-years (95% CI, 4.0–5.6) in controls for the whole population's standardized mortality ratio of 4.0 (95% CI, 3.7–4.3).

Different results available in the literature may be explained by the differences in study design

and patient selection. However, taking together all these studies, patients with acute PE appear to have a lower long-term survival compared with control individuals.

Thus, defining the prognosis of patients with an acute PE may have important clinical implications and may help clinicians allocate adequate resources for the management of these patients. Unfortunately, the existing guidelines generally recommend at least 3 months of therapeutic anticoagulation for patients with acute PE[8,9] but do not provide clear recommendations on the frequency and duration of medical follow-up after cessation of anticoagulant treatment. Furthermore, only a few studies have investigated possible predictors of long-term prognosis in these patients. PE-related factors on admission and patient-related factors have been correlated with adverse outcomes in different studies. In 1992, Carson et al.[41] published a secondary analysis of the PIOPED study where they prospectively followed 399 patients with PE for 1 year. The presence of cancer (relative risk [RR], 3.8; 95% CI, 2.3–6.4), left--sided congestive heart failure (RR, 2.7; 95% CI, 1.5–4.6), and chronic lung disease (RR, 2.2; 95% CI, 1.2–4.0) was significantly associated with a higher long-term mortality rate. Subsequently, Ribeiro et al.[42] showed that PE patients with systolic pulmonary arterial pressure of more than 50 mmHg on admission had a higher risk of persistent pulmonary hypertension at 1 year, as well as higher mortality at 5 years. Meneveau et al.[43] analyzed a registry of 249 patients with PE treated with thrombolytic drugs who were followed for a mean follow-up of 5.3 years.[43] In a multivariate analysis, the following variables were associated with long-term mortality: age >75 years (RR, 2.73; 95% CI, 2.18–3.21), persistence of vascular pulmonary obstruction exceeding 30% after thrombolytic treatment (RR, 2.22; 95% CI, 1.69–2.74), and cancer (RR, 2.03; 95% CI,1.40–2.65).

The prognostic impact of the Charlson Comorbidity Index (CCI), a measure of the burden of disease arising from multiple comorbidities, was evaluated in a retrospective cohort of 1023 consecutive patients with a median follow-up of 3.7 years.[44] About one-third of these patients had a CCI score of 0. Long-term mortality of these patients was similar to the population-derived age- and sex- matched mortality rate, and was significantly better than for those with a CCI score ≥1 (12.5 vs 47.5%; $P$ <0.001). Furthermore, in a multivariate analysis, CCI was significantly associated with death after discharge (HR 1.35, 95% CI, 1.29–1.42 per 1-score increase).

Two studies evaluated the role of troponin T in predicting the long-term mortality rate after an episode of acute PE.[45,46] In the first study, troponin T was determined in 563 patients with objectively diagnosed PE presenting at the emergency department of a tertiary care center.[45] Troponin T was positive in 27% of this population. One-year survival was significantly lower in patients with positive troponin T (71% vs 90%; $P$ <0.001). Elevated troponin levels were associated with a higher risk of mortality (HR, 2.76, 95% CI, 1.78–4.28) along with cancer (HR, 3.11, 95% CI, 2.00–4.82) and immobility at the time of the index event (HR, 2.41, 95% CI, 1.52–3.82) at 1 year in a multivariate analysis. Interestingly, this association was confirmed after exclusion of patients who were hemodynamically unstable at presentation but lost its statistically significance after the exclusion of in-hospital deaths. Ng et al.[46] assessed the prognostic role of troponin T in a retrospective cohort of 577 patients (selected from the previously described cohort of 1023 patients) with confirmed PE.[46] In this population, troponin T was significantly associated with an increased mortality at 1 year, and patients with troponin T levels of 0.1 μg/l or higher had a double risk of mortality (HR, 2.3; 95% CI, 1.4–3.8). Of note, in a multivariate analysis, a number of other variables including age, the presence of cardiovascular disease or neurodegenerative disease, cancer, and serum hemoglobin showed to be significant predictors of mortality at 1 year. In a subsequent analysis of the same population,[47] the authors assessed, in 773 patients, the prognostic role of serum sodium levels and its fluctuation. A total of 605 patients (78.3% of the whole population) maintained their serum sodium levels over 135 mmol/l during the whole period of hospitalization, whereas the other 168 patients had at least 1 episode of hyponatremia during hospitalization. Patients with either persisting or acquired hyponatremia had worse long-term survival than those who had corrected hyponatremia or had been normonatremic throughout (adjusted HR, 1.47; 95% CI, 1.06–2.03).

Finally, only 3 studies have investigated prognostic clinical variables formally combined in a CPR to predict long-term prognosis in PE patients.[48-50] Subramanian et al.[48] prospectively assessed the performance of the Geneva prognostic CPR in 105 PE patients at 3 and 12 months. At 12-month follow-up, death occurred in 5 of 88 patients (5.7%) with a score of 2 or lower and in 8 of 17 patients (47.1%) with a score of 3 or higher ($P$ <0.0001).

Yamaki et al.[49] evaluated the overall mortality and recurrent VTE at 12 months in 203 patients with PE. A CPR was derived using variables significantly associated with an adverse outcome in a multivariate analysis: active cancer, inadequate anticoagulation, leg symptoms, male sex, presence of DVT, presence of proximal DVT, and previous DVT.

Using this CPR, 166 patients (81.8%) were classified as being at low risk of an adverse outcome, and 37 patients (18.2%), at high risk. The adverse event rates were 6.0% for the low-risk group and 59.5% for the high-risk group. More recently, Dentali et al.[50] assessed the prognostic performance of the PESI and sPESI in 538 patients with PE followed for 1 year after the index event. Both the PESI and sPESI scores showed to be highly accurate in predicting the risk of mortality at 6

months (AUROC, 0.77; 95% CI, 0.73–0.81 vs 0.76; 95% CI, 0.72–0.80) at 6 months, whereas the accuracy of the sPESI was slightly but significantly lower at 12 months (0.79, 95% CI, 0.75–0.82 vs 0.75; 95% CI, 0.71–0.79).

**Conclusions** Patients suffering from an episode of acute PE varied widely in terms of short- and long-term prognosis. Several tools are available to define the short-term prognosis and they seem to be particularly useful in the identification of patients at a low risk of death. On the other hand, only a few studies have evaluated the role of risk factors potentially affecting the long-term prognosis of these patients. Therefore, other high-quality studies are warranted to better explore this issue.

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ARTYKUŁ ORYGINALNY

# Jak prognozować wczesne i odległe ryzyko zgonu u chorych z zatorowością płucną?

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**SŁOWA KLUCZOWE**

rokowanie krótkoterminowe, rokowanie długoterminowe, zatorowość płucna

**STRESZCZENIE**

Zatorowość płucna (ZP) jest często rozpoznawaną chorobą obciążoną niemałym wczesnym i odległym ryzykiem zgonu. Właściwa ocena rokowania u chorych z ZP może pomóc w wyborze intensywności wstępnego leczenia w ostrej fazie choroby, wpłynąć na czas trwania leczenia oraz na intensywność wizyt kontrolnych w długim okresie. Chorzy we wstrząsie lub z utrzymującą się hipotensją są obciążeni dużym ryzykiem wczesnego zgonu i mogą odnieść korzyści z natychmiastowej reperfuzji. Istnieje kilka narzędzi do oceny krótkoterminowego rokowania u chorych stabilnych hemodynamicznie. Jak się wydaje, skala PESI (Pulmonary Embolism Severity Index), uproszczona skala PESI oraz prawidłowe stężenie NT-pro-BNP są szczególnie użyteczne w identyfikacji chorych obciążonych małym ryzykiem wczesnych powikłań, których można bezpiecznie leczyć w domu. Niemniej jednak identyfikacja chorych stabilnych hemodynamicznie w chwili rozpoznania, ale obciążonych dużym ryzykiem wczesnych powikłań, nastręcza więcej problemów. W aktualnych wytycznych zaproponowano wieloparametryczny algorytm oparty na stanie klinicznym i chorobach współistniejących. Niestety, tylko w kilku badaniach oceniano rolę czynników ryzyka potencjalnie wpływających na długoterminowe rokowanie u tych chorych. Dostępne badania sugerują potencjalną rolę skali PESI i stężeń troponin ocenianych podczas epizodu zatorowości płucnej. Jednak uzasadnione są dalsze badania, aby potwierdzić te wstępne wyniki oraz zidentyfikować inne czynniki wpływające na długoterminowe rokowanie w tych przypadkach.

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**Praca wpłynęła:** 05.01.2015.
**Przyjęta do druku:** 06.01.2015.
**Publikacja *online*:** 12.01.2015.
**Nie zgłoszono sprzeczności interesów.**
Pol Arch Med Wewn. 2015; 125 (1-2): 82-88
Tłumaczył lek. Łukasz Strzeszyński