

## Predictors of Hospital Mortality in Hemodynamically Stable Patients with Pulmonary Embolism

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### Summary

**Background:** Pulmonary embolism is associated with high mortality in patients with hypotension or circulatory shock. However, the association between some clinical variables and mortality is still unclear in hemodynamically stable patients.

**Objective:** To derive an in-hospital mortality risk stratification model in hemodynamically stable patients with pulmonary embolism.

**Methods:** This is a prospective multicenter cohort study of 582 consecutive patients admitted in emergency units or intensive care units with clinically suspected pulmonary embolism and whose diagnosis was confirmed by one or more of the following tests: pulmonary arteriography, spiral CT angiography, magnetic resonance angiography, Doppler echocardiography, pulmonary scintigraphy, or venous duplex scan. Data on demographics, comorbidities and clinical manifestations were collected and included in a logistic regression analysis so as to build the prediction model.

**Results:** Overall mortality was 14.1%. The following parameters were identified as independent death risk variables: age > 65 years, bed rest > 72h, chronic cor pulmonale, sinus tachycardia, and tachypnea. After risk stratification, mortalities of 5.4%, 17.8%, and 31.3% were found in the low, moderate and high-risk subgroups, respectively. The model showed 65.5% sensitivity and 80% specificity, with a 0.77 area under the curve.

**Conclusion:** In hemodynamically stable patients with pulmonary embolism, age > 65 years, bed rest > 72h, chronic cor pulmonale, sinus tachycardia and tachypnea were independent predictors of in-hospital mortality. However, further validation of the prediction model in other populations is required so that it can be incorporated into the clinical practice. (Arq Bras Cardiol 2009; 93(2):128-132)

**Key Words:** Hospital mortality; pulmonary embolism; pulmonary heart disease; tachycardia, sinus.

### Introduction

Pulmonary embolism (PE) is the third cardiovascular cause of hospital admission<sup>1</sup>, following acute coronary syndrome and stroke. It has a broad spectrum of clinical manifestations, especially when associated with decompensated heart failure<sup>2</sup> and chronic obstructive pulmonary disease. Massive PE characterized by hemodynamic instability defines the subgroup of more severely ill patients among whom high mortality rates are observed<sup>3,4</sup>, and who can benefit from a more aggressive therapeutic approach. On the other hand, clinically stable patients considered at low risk require a shorter

length of hospital stay and, in some cases, can be treated as outpatients with low-molecular-weight heparin<sup>5,6</sup>. Thus, prognostic assessment becomes useful to guide the therapeutic strategy and other care.

If, on one hand, hypotension characterizes patients with PE at a higher risk of death, on the other hand echocardiogram, troponin, and brain natriuretic peptide levels help identify cases with a worse prognosis in hemodynamically stable patients. Since the early 1990's, the presence of right ventricular dysfunction as detected in the echocardiogram of normotensive patients classified as having submassive PE has been related to higher mortality<sup>7,8</sup>. Despite its ability to stratify patients at a higher risk, echocardiography is not always available 24 hours a day, and this limits its use.

Troponin and brain natriuretic peptide are parameters that indirectly express ventricular involvement<sup>9,10</sup> and help select patients at a higher risk<sup>11,12</sup>. Although the use of these tests has

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progressively increased, they are still uncommonly used in less complex health centers that also admit patients with PE.

Prognostic clinical markers in stable patients that may contribute to death risk stratification in patients with PE have not been frequently studied<sup>13-15</sup>. Demographic data, risk factors, signs and symptoms comprise a group of low-complexity variables that can be assessed at any hospital environment, regardless of ancillary tests, and this makes this strategy universally usable.

## Objective

The objective of this study was to elaborate a model based on clinical stratification markers of in-hospital mortality risk in hemodynamically stable patients with PE.

## Methods

This is a prospective multicenter cohort study conducted in 24 investigation centers of 20 Brazilian tertiary-care hospitals from January 1988 to May 2003. From an initial group of 727 consecutive patients with suspected PE, those presenting hemodynamic instability were excluded; thus a sample of 582 consecutive patients (42.1% males, median age of 73 years, ranging from 18 to 102) admitted in emergency or intensive care units was analyzed. PE was clinically suspected by the physician who evaluated the patient, based on risk factors, signs and symptoms of the disease. Systolic blood pressure  $\geq$  90 mmHg was considered a criterion of hemodynamic stability. In addition to clinical suspicion, PE had to be documented using one of the following ancillary methods:

1. Pulmonary arteriography with visualization of the thrombus in pulmonary artery.
2. Spiral CT angiography with visualization of the thrombus in pulmonary artery.
3. Magnetic resonance angiography with visualization of the thrombus in pulmonary artery.
4. Echocardiography with visualization of the thrombus in pulmonary artery.
5. Ventilation/perfusion pulmonary scintigraphy with a high probability of PE.
6. Duplex scan with visualization of the thrombus and reduced compressibility in the deep venous system.

The following variables were considered for the univariate analysis: age, gender, previous history of venous thromboembolism, hip or lower limb fracture in the past 90 days, abdominal or pelvic surgery in the past 30 days, neoplasia, bed rest  $>$  72h, chronic cor pulmonale, cigarette smoking, heart failure, stroke, chest pain, sinus tachycardia (heart rate  $>$  100 bpm), syncope, dyspnea, tachypnea (respiratory rate  $>$  20 bpm), fever (axillary temperature  $>$  37 °C), cough, cyanosis and hemoptysis or bloody sputum.

The information collected was included in a standardized form by investigators of each study center and later sent to the chief investigator, to be stored in a CSV-format database and exported to the R statistical package version 2.6.0, where the analyses were carried out<sup>16</sup>.

## Statistical analysis

The model used demographic variables, comorbidities and clinical manifestations that could be easily collected during the baseline visit of patients with PE.

Data were described as percentages, means and standard deviation or median and interquartile deviation, according to the type of variable (categorical, normal, and nonparametric). Dichotomization of continuous variables was performed using the ROC (Receiver Operating Characteristic) curve. Student's t, Mann-Whitney, chi square or Fisher's exact tests were used to measure the association between clinical variables and the endpoint. P values  $<$  0.20 or the existence of a strong clinical association with mortality were used as selection criteria for inclusion in the multivariate model<sup>17</sup>.

The multivariate model was adjusted using logistic regression with the selection of variables guided by the likelihood ratio, using the least possible number of variables without loss of the predictive ability; its accuracy was assessed by the C statistics. After the model was created, a score was elaborated based on the odds ratio value approximate to the unit of each variable. The risk score was analyzed using the chi square test of linear trend, and the death risk was further evaluated in each stratum.

Survival analysis was carried out in the three subgroups using the Kaplan-Meyer estimator.

## Results

The overall mortality of this study was 14.1%; demographic and clinical characteristics are described in Table 1.

The median age was 73 years, ranging from 18 to 102 years, and the best cut-off point was the age of 65 years, as determined using the ROC curve<sup>16</sup>, with an area under the curve of 0.60 (Figure 1), sensitivity of 81.8%, specificity of 88.3%, and positive and negative likelihood ratios of 6.99 and 0.21, respectively. In addition to age  $>$  65 years, the model identified bed rest, chronic cor pulmonale, sinus tachycardia, and tachypnea as variables able to independently predict death risk, using logistic regression (Table 2).

From the prediction model, the expected death risk was calculated for each patient, and an ROC curve was constructed<sup>18</sup> (Figure 2). The area under the curve – also known as C statistics – was 0.77, which corresponds to the model accuracy, and operating characteristics with 65.5% sensitivity, 80.0% specificity, positive likelihood ratio of 3.3, and negative likelihood ratio of 0.4. Figure 3 shows the relationship between pre-test probability (14.1%), which corresponds to the overall mortality in the study, and the post-test probability of death in the case of a positive test (35.1%) and of a negative test (6.2%). Comparison of mortality curves (Figure 4) showed a significant difference between the risk groups, with p value = 0.000004.

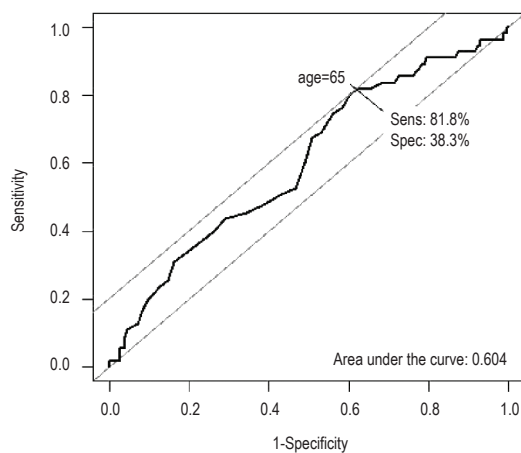
Based on the predictive power of each variable, as guided by the respective odds ratio, the model showed a linear association for prediction of death (p $>$ 0.001).

For the calculation of the score points of each patient, values described in Table 3 were used; the risk stratification showed a death risk of 5.4% among patients considered at low risk, and of 17.8% and 33.1% in the moderate and high risk groups, respectively, as shown in Table 4.

**Table 1 - Demographic and clinical characteristics.**

Variable	n	Percentage
Age > 65 years	391	67.2%
Male gender	245	42.1%
Previous history of DVT/PE*	102	17.5%
Abdominal/pelvic surgery	59	10.1%
Hip/LL fracture†	39	6.7%
Neoplasia	127	21.8%
Bed rest > 72h	194	33.3%
Chronic cor pulmonale	40	6.9%
Cigarette smoking	97	16.7%
Heart failure	88	15.1%
Stroke	33	5.7%
Chest pain	272	46.7%
Sinus tachycardia	232	39.9%
Syncope	32	5.5%
Dyspnea	455	78.2%
Tachypnea	365	62.7%
Fever	61	10.5%
Cough	133	22.9%
Cyanosis	71	12.2%
Hemoptysis	36	6.2%

DVT/OE - deep-vein thrombosis/pulmonary embolism, †LL - lower limbs

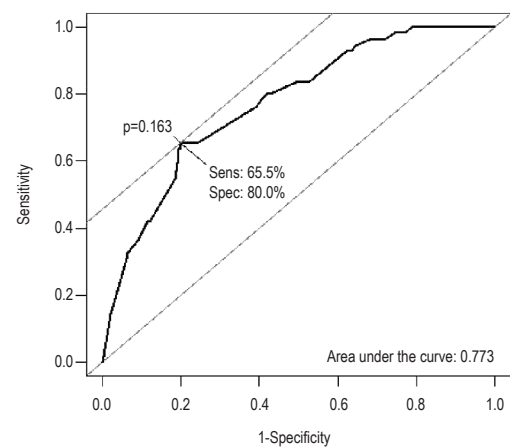


**Figure 1 - ROC curve for age cut-off point**

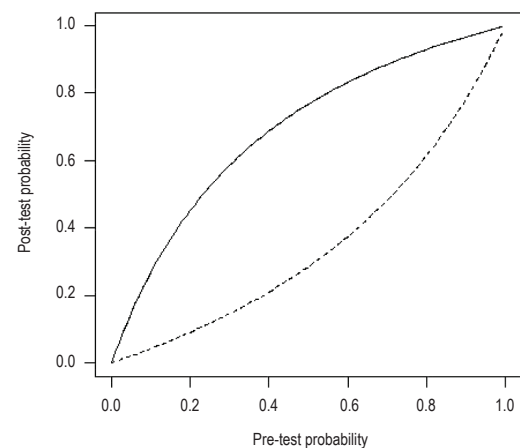
**Table 2 - Multivariate logistic regression analysis.**

Variable	OR	p
Age > 65 years	1.9 (1.6 a 2.4)	0.0061
Bed rest	2.1 (1.8 a 2.3)	0.0002
CCP*	2.5 (1.8 a 2.7)	0.0080
Tachycardia	1.7 (1.2 a 2.1)	0.0099
Tachypnea	1.8 (1.1 a 2.1)	0.0135

\* CCP – Chronic cor pulmonale



**Figure 2 - Operating characteristics of the model.**



**Figure 3 - Relationship between pre and post-test probability**

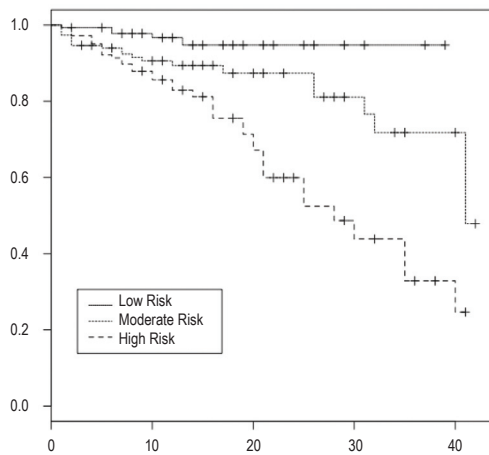


Figure 4 - Mortality curves (Kaplan-Meier)

Table 3 - Prediction score.

Variable	Points
Age > 65 years	3
Bed rest > 72h	2
Chronic cor pulmonale	4
Sinus tachycardia	2
Tachypnea	2

Table 4 - Death risk stratification.

Death risk stratification	Points	Mortality
Low Risk	0 to 3	5.4%
Moderate Risk	4 to 6	17.8%
High Risk	7 or higher	31.3%

## Discussion

Most of the studies on the prognosis of PE use echocardiographic data of right ventricular dysfunction<sup>19,20</sup> or laboratory data such as troponin<sup>21,22</sup> and brain natriuretic peptide<sup>23-25</sup> elevation to quantify the risk of a worse outcome for the patients. Despite their good prognostic accuracy, these tests are not broadly available.

In this first analysis of our study, we chose to use a model comprised of clinical variables only, based on the recommendations that by using a simpler prediction rule its application becomes more encompassing<sup>26</sup>. Hemodynamically unstable patients were excluded so that we could evaluate a more homogeneous subgroup at a lower death risk. Despite the fact that this population was less severely ill in comparison

to patients with hypotension, the overall mortality of 14.1% was higher than those found in related publications.

Wicki et al<sup>27</sup> studied 296 consecutive patients and constructed a prediction model, the Geneva prognostic score, and observed 10.1% of adverse events, with an overall mortality of 8.4%. The predictors of adverse events used in this model were cancer, hypotension, hypoxemia, heart failure, history of previous deep-vein thrombosis, and documented deep-vein thrombosis on duplex scan.

In the PESI study<sup>28</sup>, Aujesky et al derived a risk stratification model in a total of 10,534 patients distributed into five subgroups using 11 clinical variables, and observed an overall mortality of 9.2%, ranging from 1.1% (Class I, very low risk) to 24.5% (Class V, very high risk).

These two models were later compared as to their ability to select patients for treatment as outpatients, and demonstrated a significant difference for the prediction of 30-day mortality (PESI 0.9%; 95% CI, 0.3 to 2.2; vs Geneva, 5.6%; 95% CI, 3.6 to 7.6 -  $p < 0.0001$ )<sup>5</sup>.

The higher mortality in our case series suggests that, despite hemodynamic stability, the population studied, which was comprised of patients admitted in intensive care units, could be at a higher risk of complications. For the same reason, it is possible to understand the higher death risk in each stratum assessed in comparison with those of other studies mentioned<sup>27,28</sup>.

The identification of a subgroup that could be treated on an outpatient basis was not possible in this analysis, since the 5.4% mortality risk attributed to the low-risk stratum is too high to permit the choice of this treatment modality. On the other hand, the 31.3% mortality in the high-risk subgroup indicates the need for more complex interventions and surveillance of these patients.

Derivation of a prediction model is the starting point of a strategy to obtain a rule for clinical decision making. Thus, internal and external validation phases are fundamental for the model to be universally applied<sup>26</sup>. Similar databases are being collected in other investigation centers, so that we can validate the model in other populations.

## Conclusions

In hemodynamically stable patients with PE, age > 65 years, bed rest, chronic cor pulmonale, sinus tachycardia, and tachypnea were able to independently predict death risk using the logistic regression model.

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### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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