Revista Mexicana de
Cardiología
Vol. 27 No. 3
July-September 2016

ORIGINAL RESEARCH

# Acute pulmonary thromboembolism: risk stratification, treatment modalities, mortality and adherence to clinical guidelines

## *Tromboembolismo pulmonar agudo: estratificación del riesgo, modalidades de tratamiento, mortalidad y apego a guías clínicas*

Bertha Cadena Núñez,* Emilio Francisco Pelayo Treviño,* Ramón Treviño Frutos,**
Adrián Dávila Bortoni,*** Enrique Ponce de León,***
Ricardo García Sepúlveda,**** Manuel Nicolás Guerra Villa*****

**Key words:**
Acute pulmonary thromboembolism, venous embolism, guidelines of treatment, stratification.

***Palabras clave:***
*Tromboembolia pulmonar aguda, embolismo venoso, guías tratamiento, estratificación.*

**ABSTRACT**

**Introduction:** Pulmonary thromboembolism (PTE) is a cardiovascular emergency threatening life. It is classified at low, intermediate and high risk of mortality. By the above, it allows to establishing conservative treatment for low-intermediate risk PTE and more intense treatment for high risk PTE. **Objective:** To report the number of cases of acute PTE, risk stratification and prognosis in those treated with adherence to clinical guidelines. **Material and methods:** Review of clinical records with a diagnosis of acute PTE by confirmatory diagnostic test. The type of treatment was determined by: oral anticoagulation (OAC) or parenteral anticoagulation (PAC), percutaneous thrombectomy, supraselective thrombolysis, systemic thrombolysis, surgical thrombectomy or combinations. The type of initial anticoagulation and maintenance therapy. Hard results: TIMI major bleeding, re-thrombosis, death and brain stroke (BS). Normality was verified by Kolmogorov-Smirnov test. Then was compared with Student t or U Mann-Whitney. **Results:** A sample of 36 patients was obtained, the mean age was 67.24 ± 18.83 years, 62.2% were females. The 29.7% were low-risk PTE, 51.4% were intermediate risk and 18.9% were high risk. The 70.3% received OAC, 8.1% percutaneous trombectomy, 8.1% systemic thrombolysis, 10.8% systemic thrombolysis + percutaneous thrombolysis, 2.7% percutaneous trombectomy + supraselective thrombolysis. There is increased risk of death in this group OR = 2.63 (95% CI 0.45-16.08) but not significant (p = 0.255). **Conclusions:** Lack of adherence to clinical guidelines confers increased risk of death in patients with acute PTE, this difference is not statistically significant.

***RESUMEN***

***Introducción:*** *La tromboembolia pulmonar (TEP) es una urgencia cardiovascular que pone en riesgo la vida. Se cataloga en riesgo bajo de mortalidad, intermedio y alto. Lo anterior permite establecer estrategias terapéuticas conservadoras para la TEP de riesgo bajo-intermedio y más intensas para alto riesgo.* ***Objetivo:*** *Reportar el número de casos de TEP aguda, la estratificación de riesgo y el pronóstico en quienes recibieron tratamiento con apego a guías clínicas.* ***Material y métodos:*** *Revisión de expedientes clínicos con diagnóstico de TEP aguda, mediante prueba diagnóstica confirmatoria. Se determinó el tipo de tratamiento: anticoagulación (ACO), oral o parenteral (ACP), trombectomía percutánea(TBTP), trombolisis supraselectiva (TBLSU), trombolisis sistémica (TBLSIS), trombectomía quirúrgica (TBTQ) o sus combinaciones. El tipo de anticoagulación inicial y de mantenimiento. Los resultados duros: sangrado TIMI mayor, retrombosis, muerte y evento vascular cerebral (EVC). Se verificó la normalidad mediante prueba de Kolmogorov-Smirnov. Posteriormente se comparó con t Student o U de Mann-Whitney.* ***Resultados:*** *Se obtuvo una muestra de 36 pacientes, la edad media fue 67.24 ± 18.83 años, el 62.2% fueron del género femenino. El 29.7% correspondía a TEP de riesgo bajo, 51.4% riesgo intermedio y 18.9% a riesgo alto. El 70.3% se dio ACO y ACP, 8.1% TBTP, 8.1% TBLSIS, 10.8% TBLSIS + TBTP y 2.7% TBTP + TBLSU. Existe mayor riesgo de muerte en el grupo de falta de apego a guías OR = 2.63 (IC 95% 0.45-16.08), sin embargo, no es significativo (p= 0.255).* ***Conclusiones:*** *La falta de apego a guías clínicas confiere mayor riesgo de muerte en pacientes con TEP aguda, esta diferencia no es estadísticamente significativa.*

* Medicina Interna y Cardiología en Hospital Christus Muguerza Alta Especialidad.
** Departamento de Educación e Investigación en Salud del Grupo Christus Muguerza.
*** Cardiología en Hospital Christus Muguerza Alta Especialidad.

*Received:*
*28/04/2016*
*Accepted:*
*29/07/2016*

**** Dermatología en Unidad Médica de Altas Especialidades IMSS 25.
***** Medicina Interna en Hospital Christus Muguerza Alta Especialidad.

Hospital Christus Muguerza Alta Especialidad, Monterrey, Nuevo León, México.

## BACKGROUND

The PTE is a condition that confers risk of early death (hospital mortality and mortality at 30 days) depending on the presence of risk markers which are: clinical, biomarker of right ventricular dysfunction and myocardial damage.[1] To be rated low risk with < 1% mortality, intermediate risk (3-15%) and high risk (> 15%).[2] This allows establishing conservative therapeutic approaches for low-intermediate risk PTE and more intense (thrombolysis, thrombectomy, embolectomy and percutaneous fragmentation by catheter) for high risk PTE.[3]

Several scales have been used to determine the prognosis of patients with acute PTE. Of these the severity pulmonary embolism index is the best validated at the time to determine the 30 days prognosis. There is a simplified version that identifies patients at low risk. In the following table summarizes the risk stratification according to the Guidelines of the European Society of Cardiology 2014 *(Table I)*.[4]

In patients with acute pulmonary thromboembolism anticoagulation is recommended to prevent both premature death and recurrence. Treatment of acute phase consists of administering parenteral anticoagulation (unfractionated heparin [UFH], low molecular weight heparin [LMWH] or fondaparinux) during the first 5-10 days. In patients with high or intermediate clinical probability of pulmonary thromboembolism, it should initiate parenteral anticoagulation while the results of diagnostic tests are expected.[5] Thrombolytic therapy in the acute pulmonary thromboembolism restores perfusion faster than anticoagulation with UFH alone. The prompt resolution of pulmonary obstruction leads to a reduction in pressure and resistance of the pulmonary arteries with a concomitant improvement in the function of RV.[6] In the absence of hemodynamic deterioration at the time of the presentation, the clinical benefits of thrombolysis have been in controversy for many years.[7-10]

This study aims to make a report of cases of PTE presented over a period of time, perform risk stratification and show what the treatment that has been given. Besides analyzing the complications presented (increased bleeding risk, re-thrombosis and presence of CVA) according to provided treatment and short-term mortality.

## MATERIAL AND METHODS

It was sought through the clinical records from the period December first of 2012 to July 2015, the number of patients with a final diagnosis of acute PT were systematically reviewed in order to find if diagnostic confirmatory test such as pulmonary angiography (CT angiography lung), lower extremities ultrasound or ventilation-perfusion scintigraphy were performed as dictated by clinical guidelines of the (SEC) 2014. Those patients who did not meet the inclusion criteria and had incomplete records were excluded. As a final sample of 36 (n = 36). Risk stratification was performed according to clinical and labora-

**Table I. Adapted and modified table of the risk stratification according to the Guidelines of the European Society of Cardiology 2014.**

| | Risk parameters and scores | | | |
|---|---|---|---|---|
| Early mortality risk | Shock o hypotension | Pulmonary embolism severity index (PESI) III-V o > 1 simplified | Signs of right ventricular disfunction on an imaging test | Cardiac laboratory biomarkers (Troponin T/I o BNP/ pro BNP) |
| High | + | + | + | + |
| Intermediate-high | - | - | + | Both positive |
| Intermediate-low | - | - | + | Either one or none positive |
| Low | - | - | - | - |

tory criteria in: low, intermediate and high risk. Which are summarized in the *table I*.

Subsequently it sought the type of treatment given at the time of diagnosis, either oral or parenteral anticoagulation, percutaneous thrombectomy, supraselective thrombolysis, systemic thrombolysis, surgical thrombectomy or any combination thereof. The presence of risk factors associated were looked for: hypertension, diabetes mellitus, cancer, fractures or recent surgeries, presence of primary thrombophilia, chronic renal disease or connective tissue disease. Also the type of initial anticoagulation established and maintenance anticoagulation. And the days of hospital stay, and hard results as the presence of TIMI major bleeding, re-thrombosis (established in the record and defined by the clinical judgment of the treating physician), death, CVA for each patient.

### Statistical analysis

Traditional descriptive statistics, measures of central tendency and dispersion measurements were obtained. To evaluate the comparisons between groups were performed using Fisher and $\chi^2$ test for categorical data and quantitative data for normality was verified by the Kolmogorov-Smirnov test. Later as its result was compared with Student t or Mann-Whitney. The odds ratio was calculated, a p-value less than 0.05 was considered significant.

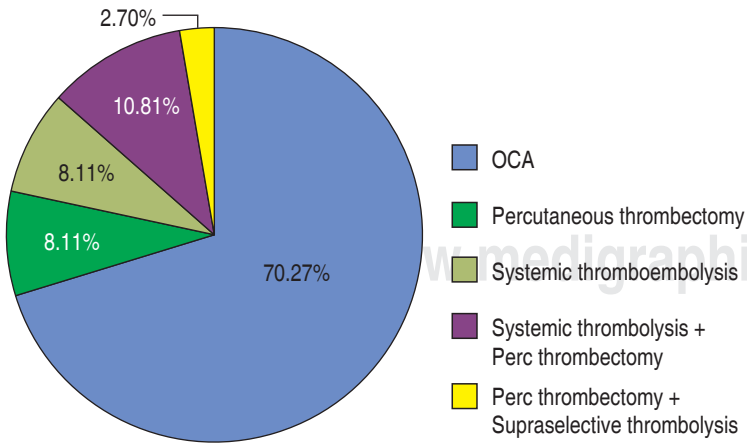


**Figure 1.** Initial treatment of PTE.

## RESULTS

A sample of 36 patients with confirmed diagnosis of PE was obtained, the average age was 67.24 ± 18.83 years of which 62.2% (n = 23) were females. Mean BMI was 26.84 kg/m$^2$. The average hospital stay was 9.16 ± 6.1 days. The prevalence of hypertension was 37.8%, 18.9% diabetes mellitus, cancer 2.7%, history of fracture, surgery or prostration 13.5%, primary thrombophilia 5.4%, 16.2% chronic kidney disease and connective tissue disease 16.2%.

It was found that 29.7% (n = 11) of patients corresponded to low-risk PTE, 51.4% (n = 19) at intermediate risk and 18.9% (n = 7) at high risk. As for treatment to 70.3% (n = 26) was given treatment with anticoagulation, 8.1% (n = 3) it was carried percutaneous thrombectomy, 8.1% (n = 3) systemic thromboembolism, 10.8% (n = 4) systemic thrombolysis + percutaneous thrombectomy and 2.7% percutaneous thrombectomy (n = 1) + supraselective thrombolysis *(Figure 1)*. As for the initial anticoagulant therapy, unfractionated heparin was used in 10.8%, low molecular weight heparin 81.1% and the oral anticoagulants 8.1%. Anticoagulant therapy support was with antagonists of vitamin K in 18.9%, rivaroxaban 54.1%, apixaban 2.7%, dabigatran 5.4%, low molecular weight heparin in 13.5% and none in 5.4% *(Figure 2)*.

The 100% of patients with low-risk PTE received anticoagulation treatment, which corresponds to the recommendation by the guidelines. In the intermediate-risk group 57.9% received anticoagulation, 10.5% percutaneous thrombectomy, 10.5% systemic thrombolysis and 21.1% systemic thrombolysis + percutaneous thrombectomy, with the recommendation for this group in the acute phase involves administering parenteral anticoagulation (unfractionated heparin [UFH], low molecular weight heparin [LMWH] or fondaparinux) during the first 5-10 days. In the high-risk group, the 57.1% received anticoagulation, 14.3% percutaneous thrombectomy, 14.3% systemic thrombolysis and the 14.3% percutaneous thrombectomy + supraselective thrombectomy. Thrombolysis is the treatment of choice in this group, the interventional treatment should be reserved for patients with absolute contraindications to thrombolysis. As

for the type of initial anticoagulant by group, in the high risk group 71.4% was treated with LMWH and 28.6% with oral anticoagulation. In the intermediate-risk group 5.3% received unfractionated heparin and 97.4% LMWH and at the low risk 27.3% unfractionated heparin, 63.6% LMWH and 9.1% oral anticoagulation therapy as initial treatment.

As for the analysis of outcome in the low-risk group not bleeding event was recorded, in the intermediate risk group 78.9% had no bleeding, 5.3% had TIMI minimal bleeding, 10.5% had TIMI minimal bleeding and 5.3% had TIMI major bleeding, in this group it was a increased bleeding tendency, without no significant differences (p = 0.568). In the high-risk group 85.7% had no bleeding, 14.3% had TIMI minimal bleeding and no other kind of bleeding was recorded. In the low-risk group not re-thrombosis event was recorded, in the intermediate-risk group was 15.8%, in the high risk group was 8.1%. Only the high-risk group presented CVA at 14.3%, which was a stroke, confirmed by magnetic resonance imaging. Mortality for the intermediate-risk group was 26.3% and for the high risk of 57.1%.

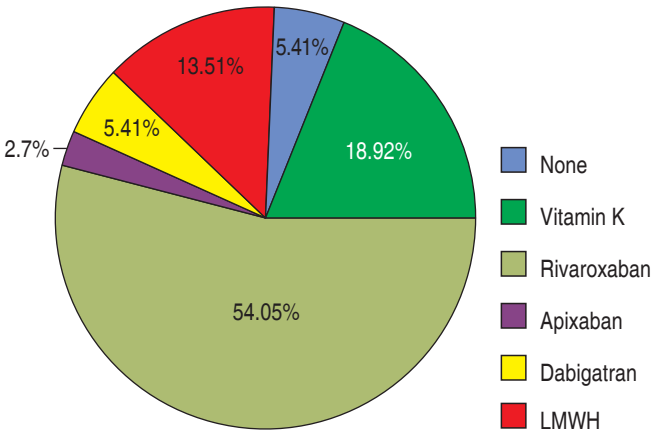


**Figure 2.** Maintenance anticoagulation.

The characteristics of the three groups were compared: low, intermediate and high risk, about the general characteristics age showed significant differences between groups (p = 0.047). For the characteristics of gender, body mass index, risk factors (surgical and prostration, cancer, hypertension, diabetes mellitus, connective tissue disease, chronic renal disease and primary thrombophilia), no significant differences were found. As for the type of initial anticoagulation significant differences were found in the high risk group, in which initially oral anticoagulation was used, which does not correspond to the recommendations of current guidelines, in the other groups the initial treatment was recommended (p = 0.038). As for Anticoagulation maintenance and hospital stay no significant differences were found *(Table II)*. It looked for if there was a relationship between

**Table II. Patient characteristics.**

| PTE-risk | Low n = 11 (29.7%) | Intermediate n = 19 (51.4%) | High n = 7 (18.9%) | p |
|---|---|---|---|---|
| AGE (mean, range) | 51 (14-91) | 77 (21-84) | 73 (17-71) | 0.047* |
| Sex | | | | |
| Male | 2 (36.3) | 9 (47.3) | 3 (42.8) | |
| Female | 9 (81.8) | 10 (52.6) | 4 (57.1) | 0.27+ |
| BWI | 24 (11-73) | 27.9 (23-08) | 26 (19-36) | 0.058* |
| Risk factors | | | | |
| Surgical/prostration | | | | |
| • Yes | 2 (36.3) | 2 (10.5) | 1 (14.2) | 0.838+ |
| • Not | 9 (81.8) | 17 (89.4) | 6 (85.7) | |
| Cancer | | | | |
| • Yes | 0 (0) | 1 (5.2) | 0 (0) | 0.615+ |
| • Not | 11 (100) | 18 (94.7) | 7 (100) | |

**Continuous Table II. Patient characteristics.**

| PTE-risk | Low n = 11 (29.7%) | Intermediate n = 19 (51.4%) | High n = 7 (18.9%) | p |
|---|---|---|---|---|
| Arterial hypertension | | | | |
| • Yes | 1 (9) | 10 (52.6) | 3 (42.8) | 0.058+ |
| • Not | 10 (91) | 9 (47.3) | 4 (57.1) | |
| Diabetes mellitus | | | | |
| • Yes | 2 (18.2) | 2 (10.5) | 3 (42.8) | 0.175+ |
| • Not | 9 (81.8) | 17 (89.4) | 4 (57.1) | |
| Connective tissue disease | | | | |
| • Yes | 1 (9) | 3 (15.7) | 2 (28.5) | 0.549+ |
| • Not | 10 (91) | 16 (84.2) | 5 (71.4) | |
| Chronic kidney disease | | | | |
| • Yes | 1 (9) | 4 (21) | 1 (14.2) | 0.685+ |
| • Not | 10 (91) | 15 (79) | 6 (85.7) | |
| Primary thrombophilia | | | | |
| • Yes | 1 (9) | 1 (5.2) | 0 (0) | 0.70+ |
| • Not | 10 (91) | 18 (94.7) | 7 (100) | |
| Type anticoagulation | | | | |
| • UFH | 3 (27.3) | 1 (5.3) | 0 (0) | 0.038+ |
| • LMWH | 7 (63.6) | 18 (94.7) | 5 (71.4) | |
| • Oral anticoagulation | 1 (9.1) | 0 (0) | 2 (28.6) | |
| Maintenance anticoagulation | | | | |
| • NONE | 0 (0) | 1 (5.3) | 1 (14.3) | 0.700+ |
| • Vitamin K | 3 (27.3) | 2 (10.5) | 2 (28.6) | |
| • Rivaroxaban | 6 (54.5) | 12 (63.2) | 2 (28.6) | |
| • Apixaban | 0 (0) | 1 (5.3) | 0 (0) | |
| • Dabigatran | 1 (9.1) | 1 (5.3) | 0 (0) | |
| • LMWH | 1 (9.1) | 2 (10.5) | 2 (28.6) | |
| Hospital stay | 7 (19-45) | 10 (20-74) | 5 (13-57) | 0.318* |
| History of stroke | | | | |
| • Yes | 0 (0) | 0 (0) | 1 (14.3) | |
| • Not | 11 (100) | 19 (100) | 6 (85.7) | 0.111+ |
| Dead | | | | |
| • Yes | 0 (0) | 5 (26.3) | 4 (57.1) | 0.016+ |
| • Not | 11 (100) | 14 (73.6) | 3 (42.9) | |
| Re-thrombosis | | | | |
| • Yes | 0 (0) | 3 (15.8) | 0 (0) | |
| • Not | 11 (100) | 16 (84.2) | 7 (100) | 0.213+ |
| Bleeding | | | | |
| • None | 11 (100) | 15 (78.9) | 6 (85.7) | 0.568+ |
| • Minimal | 0 (0) | 1 (5.3) | 1 (14.3) | |
| • Minor | 0 (0) | 2 (10.5) | 0 (0) | |
| • Major | 0 (0) | 1 (5.3) | 0 (0) | |

* = t de Student, + = $\chi^2$/Fisher.

**Table III. Presence of event and adherence to guidelines.**

| PTE-risk | Low n = 11 (29.7%) | Intermediate n = 19 (51.4%) | High n = 7 (18.9%) | Odds ratio (IC 95%) | p |
|---|---|---|---|---|---|
| Guidelenes adherence | | | | | |
| • Yes | 11 (100) | 11 (58) | 1 (14) | | 0.001+ |
| • Not | 0 (0) | 8 (42) | 6 (86) | | |
| Dead | | | | | |
| • Yes | 0 (0) | 4 (21.1) | 4 (57.1) | 2.63 | 0.255+ |
| • Not | 11 (100) | 15 (78.9) | 3 (42.9) | (0.45-16.08) | |

* = t de Student, + = $\chi^2$/Fisher.

the use of new oral anticoagulants and presence of bleeding, but no significant differences were found (p = 0.134).

In the evaluation of the presence of event, significant differences about the presence of death (p = 0.016) were found. No differences in relation to cerebral vascular event, re-thrombosis and bleeding *(Table II)*.

Adherence to guidelines regarding the established treatment was evaluated finding that the low-risk group had adherence to guidelines, in the intermediate risk only 58% and high risk only 14%, with statistically significant differences (p = 0.001). For this group of patients in the high risk group tend to be less intense about treatment. We determined the association between lack of adherence to clinical guidelines and the presence of death finding that there is increased risk of death in this group OR = 2.63 (95% CI 0.45-16.08) but not statistically significant (p = 0.255) *(Table III)*.

## CONCLUSIONS

The study found that patients with low-risk PE were treated with adherence to guidelines treatment but in the intermediate-risk group only 58% and in the high-risk 14%, with significant differences, and with a tendency to be not adhered fully to the guidelines in the latter group. There were significant differences about the presence of death (p = 0.016), without differences in relation to cerebral vascular event, re-thrombosis and bleeding for the three groups. According to these results it concludes that the lack of adherence to clinical guidelines confers increased risk of death in patients with acute PE but this difference is not statistically significant. However this is a small sample which shows the need for another design to determine the prognosis of patients.



## REFERENCES


1. White R. The epidemiology of venous thromboembolism. Circulation. 2003; 107: 4-8.
2. Kearon C. Natural history of venous thromboembolism. Circulation. 2003; 107: 22-30.
3. Konstantinides S, Agnelli G, Galie N et al. ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology 2008. Eur Heart J. 2008; 61: 1-52.
4. Konstantinides S, Torbicki A, Agnelli, G et al. ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology 2014. Eur Heart J. 2014; 68: 1-45.
5. Orde M, Puranik R, Morrow P et al. Myocardial pathology in pulmonary thromboembolism. Heart. 2001; 97: 1695-1699.
6. Konstantinides S, Meyer G, Lang I et al. Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the pulmonary embolism thrombolysis. Am Heart J. 2012; 163: 33-38.
7. Ferrari E, Moceri P, Crouzet C et al. Timing of troponin I measurement in pulmonary embolism. Heart. 2012; 98: 732-735.
8. Augustinos P, Ouriel K. Invasive approaches to treatment of venous thromboembolism. Circulation. 2004; 110: 127-134.

9. Iwase T, Nagaya N, Ando M et al. Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension. Heart. 2001; 97: 188-192.
10. Weitz J. New anticoagulants for treatment of venous thromboembolism. Circulation. 2004; 110: 19-26.

***Correspondence to:***

**Bertha Cadena Núñez**
Av. Hidalgo Núm. 2525 Pte., Col. Obispado,
64060, Monterrey, Nuevo León, México.
Cel.: +52 8116994787
**E-mail:** bertha.cadena.nu@gmail.com