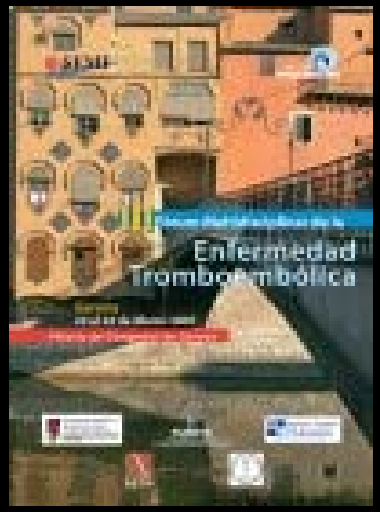
LOS MARCADORES BIOLÓGICOS NO SON ÚTILES EN LA ESTRATIFICACIÓN PRONÓSTICA DE LA EMBOLIA DE PULMÓN



Dr. D. Jiménez
Servicio de Neumología
Unidad de Enfermedad Tromboembólica
Hospital Ramón y Cajal

Gerona, Marzo 2007

D-DIMER LEVELS CORRELATE WITH MORTALITY IN PATIENTS WITH ACUTE PULMONARY EMBOLISM FINDINGS FROM THE RIETE REGISTRY

Enric Grau, MD, PhD; José María Tenías MD; María José Soto MD; María Reyes Gutierrez MD; **Ramón Lecumberri MD**; José Luís Pérez MD; Gregorio Tiberio MD; for the RIETE Investigators[1].

Índice

Marcadores biológicos

- Consideraciones generales
- Revisión sistemática
- Método óptimo de estratificación

Consideraciones generales

Estudios pronósticos

- Mejorar el conocimiento de la enfermedad
- Mejorar el diseño y análisis de los ensayos clínicos
- Definir poblaciones de riesgo
- Predecir la evolución de la enfermedad
- Guiar las decisiones clínicas, incluidos el tratamiento y el consejo a los pacientes

Altman DG. BMJ 2001

Consideraciones generales

Marcadores biológicos

- Población objeto de estudio
- Tratamiento ambulatorio
- Tratamiento fibrinolítico

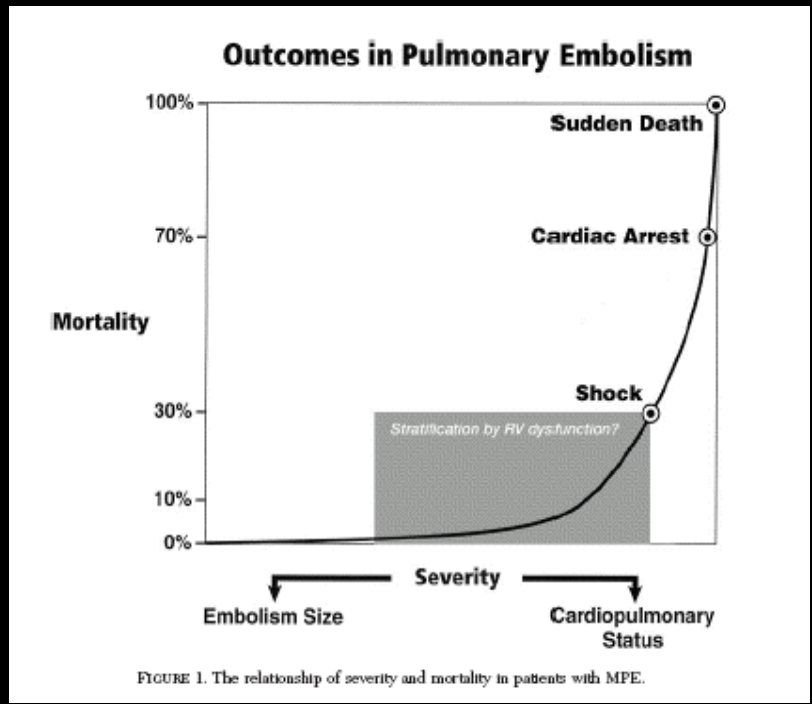


FIGURE 1. The relationship of severity and mortality in patients with MPE.

Kreit JW. Chest 2004

Marcadores utilizados

Marcadores biológicos

- Troponina I / Troponina T
- BNP / Pro-BNP
- Dímero D
- Proteínas de unión

Konstantinides S. Circulation 2002
Binder L. Circulation 2005
Aujesky D. Thromb Haemost 2006

Marcadores utilizados

Marcadores biológicos

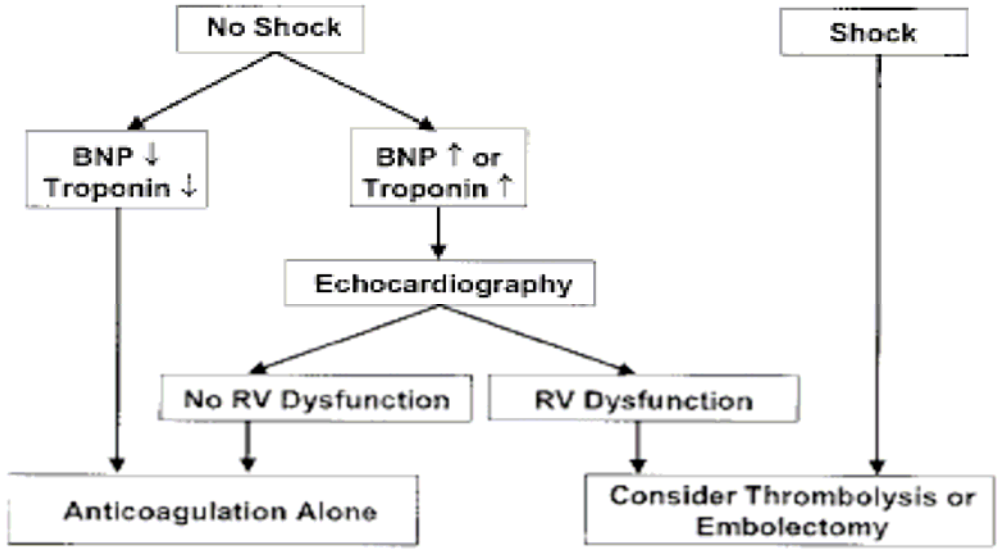


Figure 2. Pulmonary embolism management strategy. RV indicates right ventricular.

Kucher N. Circulation 2003

Marcadores utilizados

Marcadores biológicos

Accuracy of Cardiac Biomarkers for the Prediction of In-Hospital Death in Pulmonary Embolism

Reference	n	Biomarker	Assay	Cut-Off Level	Test +, %	NPV, %	PPV, %
Konstantinides et al[11]	106	cTnI	Centaur (Bayer)	0.07 ng/mL	41	98	14
Konstantinides et al[11]	106	cTnT	Elecsys (Roche Pharmaceuticals)	0.04 ng/mL	37	97	12
Giannitsis et al[12]	56	cTnT	TropT (Roche Pharmaceuticals)	0.10 ng/mL	32	97	44
Janata et al[24]	106	cTnT	Elecsys (Roche Pharmaceuticals)	0.09 ng/mL	11	99	34
Pruszczyk et al[13]	64	cTnT	Elecsys (Roche Pharmaceuticals)	0.01 ng/mL	50	100	25
ten Wolde et al[25]	110	BNP	Shionoria (CIS Bio International)	21.7 pmol/L	33	99	17
Kucher et al[16]	73	NT-proBNP	Elecsys (Roche Pharmaceuticals)	500 pg/mL	58	100	12
Kucher et al[17]	73	BNP	Triage (Biosite Technologies)	50 pg/mL	58	100	12
Pruszczyk et al[26]	79	NT-proBNP	Elecsys (Roche Pharmaceuticals)	153 to 334* pg/mL	66	100	23

NPV indicates negative predictive value; PPV, positive predictive value.
*Age and gender adjusted cut-off levels according to the manufacturer.

Kucher N. Circulation 2003

Revisión sistemática

¿Cúal es la capacidad pronóstica de la troponina en pacientes estables hemodinámicamente con TEP aguda sintomática?

- ¿Tiene capacidad pronóstica?
- ¿Pronostica la mortalidad por TEP?
- ¿Valores predictivos?

Revisión sistemática

Jiménez D, Uresandi F, Otero R, Lobo JL, et al. Troponin for risk stratification of patients with hemodynamically stable pulmonary embolism: systematic review

- Estrate
- Artícul
- Artícul

Pulmonary embolism
Thromboembolism
Troponin
Biomarkers
Biological markers
Prognostic studies

Revisión sistemáti

¿Cúal es la capacidad pronós

estables hemodinámicamer

No TEP: 260
Revisiones: 44
No pronóstico troponina: 233
No inglés: 11
Casos clínicos: 7
Otros: 12

No outcome: 3
Caso clínico: 1

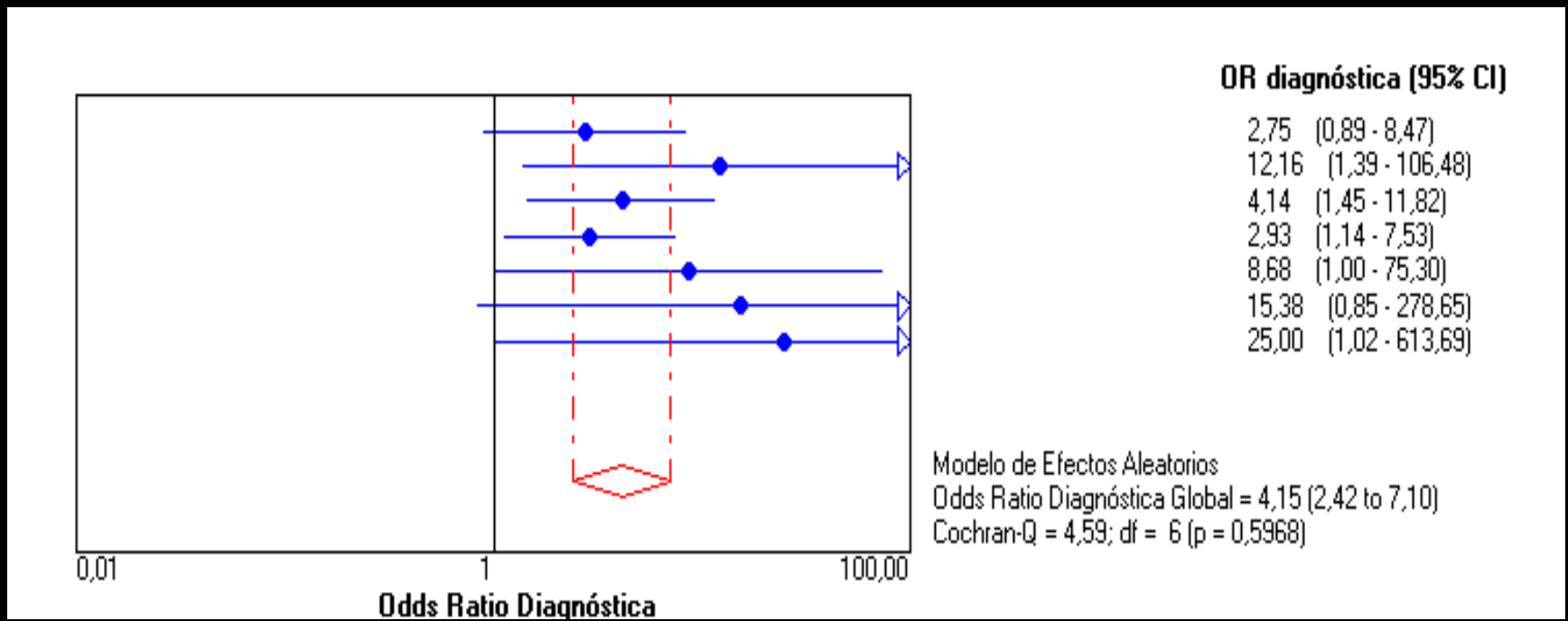
Revisión sistemática: artículos seleccionados

¿Cúal es la capacidad pronóstica de la troponina en pacientes estables hemodinámicamente con TEP aguda sintomática?

- Logeart D. Intensive Care Med 2007; DOI10.1007/s00134-006-0482-I
- Tulevski II. Int J Cardiol 2006; DOI10.1016/j.ijcard.2006.03.030
- Kline JA. Crit Care Med 2006; 34: 2773-2780
- Bova C. Haematologica 2005; 90: 423-424
- Douketis JD. J Thromb Haemost 2005; 3: 508-513
- Kostrubiec M. Eur Heart J 2005; 26: 2166-2172
- Pruszczyk P. Chest 2003; 123: 1947-1952

Revisión sistemática

Pooled odds ratio
4.14 (IC 95%, 2.42 to 7.10)



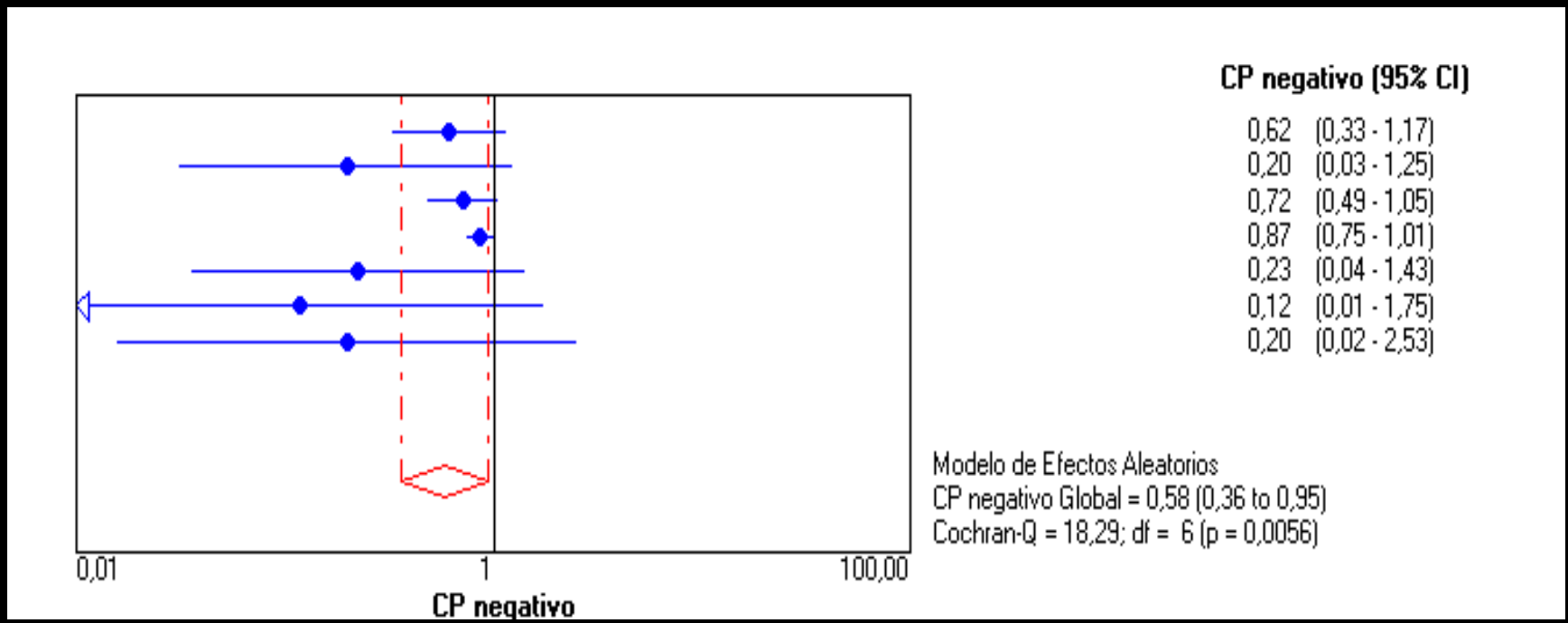
Revisión sistemática

Pitfalls

- Sesgo de publicación
- Diferentes endpoints:
  - Muerte total 40 días
  - Muerte total intrahospitalaria (x 3)
  - Muerte total 3 meses
  - Muerte total/escalada tratamiento intrahospitalaria (x 2)

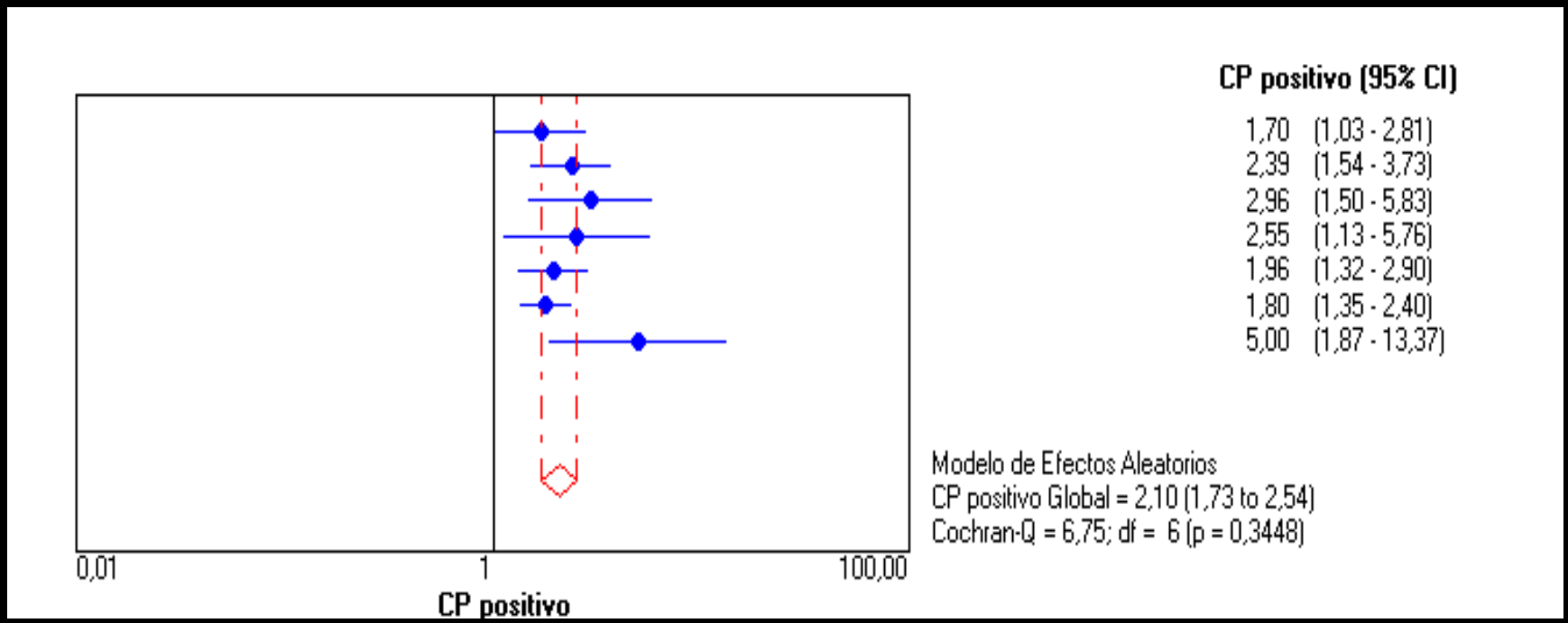
Revisión sistemática

Global negative likelihood ratio
0.58 (IC 95%, 0.36 to 0.95)



Revisión sistemática

Global positive likelihood ratio
2.09 (IC 95%, 1.73 to 2.54)



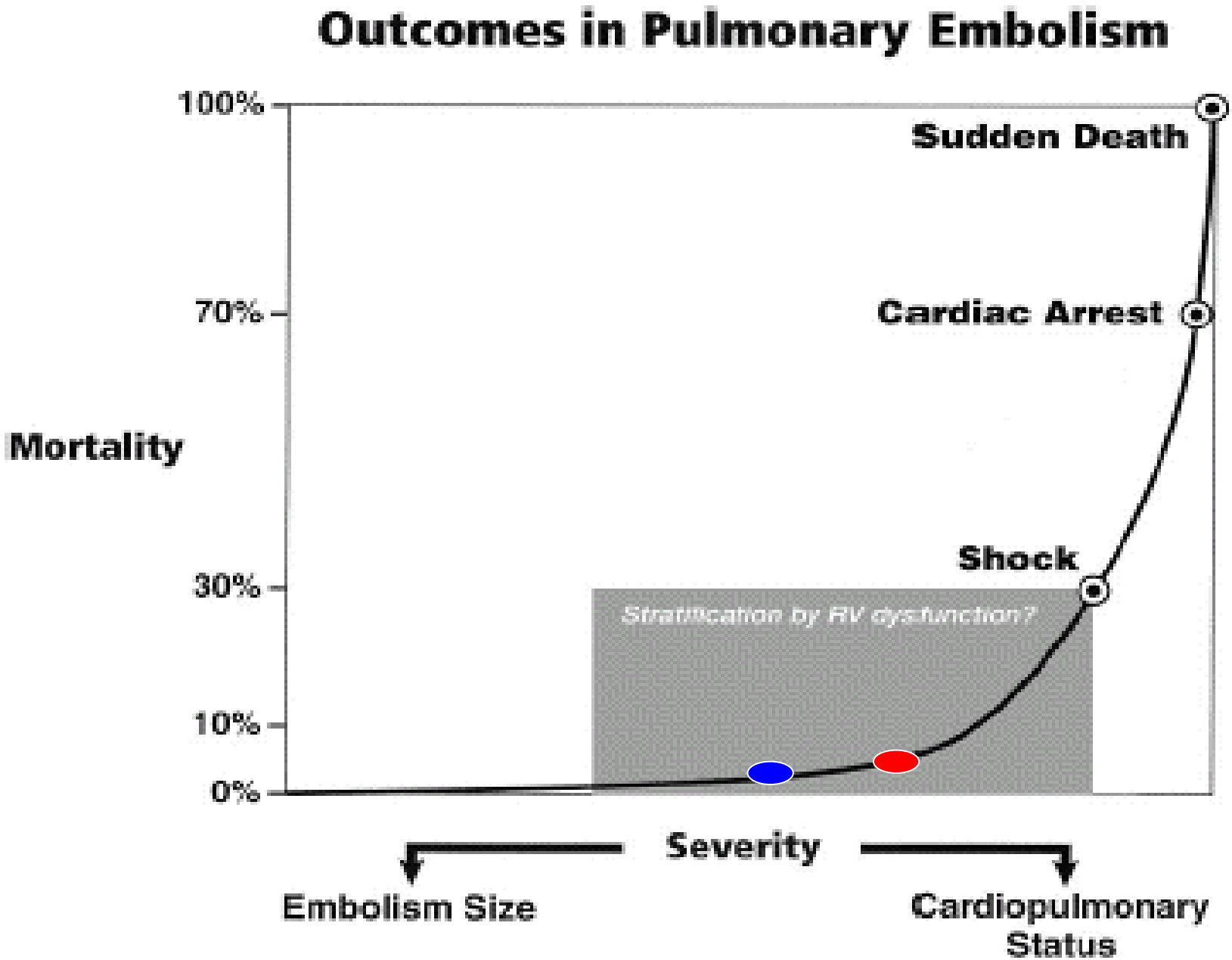
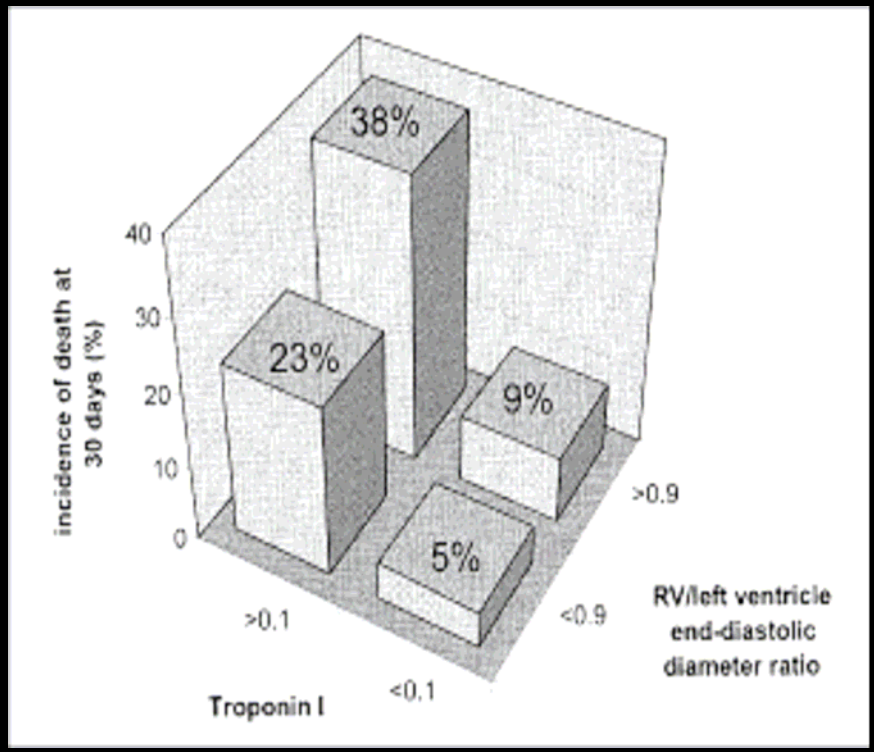


FIGURE 1. The relationship of severity and mortality in patients with MPE.

Tratamiento fibrinolítico

¿El valor predictivo positivo de la troponina para muerte por TEP/escalada tratamiento indica el tratamiento fibrinolítico?



Scridon T. Am J Cardiol 2005

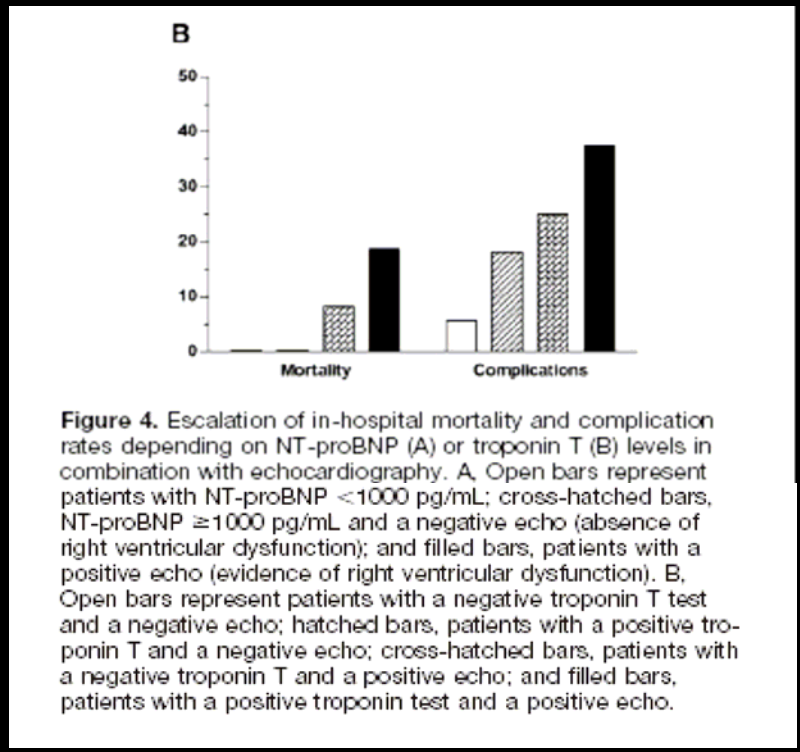


Figure 4. Escalation of in-hospital mortality and complication rates depending on NT-proBNP (A) or troponin T (B) levels in combination with echocardiography. A, Open bars represent patients with NT-proBNP <1000 pg/mL; cross-hatched bars, NT-proBNP ≥1000 pg/mL and a negative echo (absence of right ventricular dysfunction); and filled bars, patients with a positive echo (evidence of right ventricular dysfunction). B, Open bars represent patients with a negative troponin T test and a negative echo; hatched bars, patients with a positive troponin T and a negative echo; cross-hatched bars, patients with a negative troponin T and a positive echo; and filled bars, patients with a positive troponin test and a positive echo.

Binder L. Circulation 2005

Thrombolysis in Submassive PE

Primary Combined Endpoint

1. **Death from any cause**
2. **Cardiogenic shock** (BP <90 mm Hg, or drop in BP by at least 40 mm Hg over 15 minutes or longer)
3. **Endotracheal intubation**
4. **Cardiopulmonary resuscitation**

Courtesy: Dr. Konstantinides

Thrombolysis in Submassive PE

Expected Reduction of Primary Endpoint

	Heparin	Thrombolysis
All thrombolysis trials, n	358	359
Mortality, n	20 (5.6%)	15 (4.2%)
MAPPET-3, n	138	118
CPR / catecholamines / intubation, n	10 (7.3%)	4 (3.4%)
Combined endpoint	**12.9%**	**7.6%**

Courtesy: Dr. Konstantinides

Thrombolysis in Submassive PE

Inclusion Criteria

1. PE confirmed by lung scan, **Spiral CT**, or pulmonary angiography
2. Systolic blood pressure on admission ≥ **90 mm Hg**
3. RV dysfunction on **echocardiography**
4. Positive **Troponin I or TroponinT** test

Courtesy: Dr. Konstantinides

Prognostic Models for Selecting Patients With Acute Pulmonary Embolism for Initial Outpatient Therapy*

AQ: A

David Jiménez, MD; R. D. Yusen, FCCP; R. Otero; F. Uresandi; D. Nauffal; E. Laserna; F. Conget; M. Oribe; M. A. Cabezudo; and G. Díaz

Objective: To assess the performance of two prognostic models in predicting short-term mortality in patients with pulmonary embolism (PE).

Subjects and methods: We compared the test characteristics of two prognostic models for predicting 30-day outcomes (mortality, thromboembolic recurrences, and major bleeding) in a cohort of 599 patients with objectively confirmed PE. Patients were stratified into the PE severity index (PESI) risk classes I-V and the Geneva low-risk and high-risk strata. We compared the discriminatory power of both prognostic models.

Results: The PESI classified fewer patients as low risk (strata I and II) (36%; 216 of 599 patients; 95% confidence interval [CI], 32 to 40%) compared to the Geneva prediction rule (84%; 502 of 599 patients; 95% CI, 81 to 87%) [$p < 0.0001$]. Using either prediction rule, the low-risk groups showed statistically relevant 30-day mortality difference (PESI, 0.9%; 95% CI, 0.3 to 2.2; vs Geneva, 5.6%; 95% CI, 3.6 to 7.6) [$p < 0.0001$], although nonfatal recurrent venous thromboembolism or major bleeding rates were statistically similar (PESI, 2.8%; 95% CI, 0.6 to 5.0%; vs Geneva, 4.2%; 95% CI, 2.4 to 5.9%). The area under the receiver operating characteristic curve was higher for the PESI (0.76; 95% CI, 0.69 to 0.83) than for the Geneva score (0.61; 95% CI, 0.51 to 0.71) [$p = 0.002$].

Conclusions: The PESI quantified the prognosis of patients with PE better than the Geneva score. This study demonstrated that PESI can select patients with very low adverse event rates during the initial days of acute PE therapy and assist in selecting patients for treatment in the outpatient setting.

Tratamiento ambulatorio

Marcadores biológicos

RISK STRATIFICATION OF PATIENTS WITH ACUTE NON MASSIVE PULMONARY EMBOLISM

Authors:

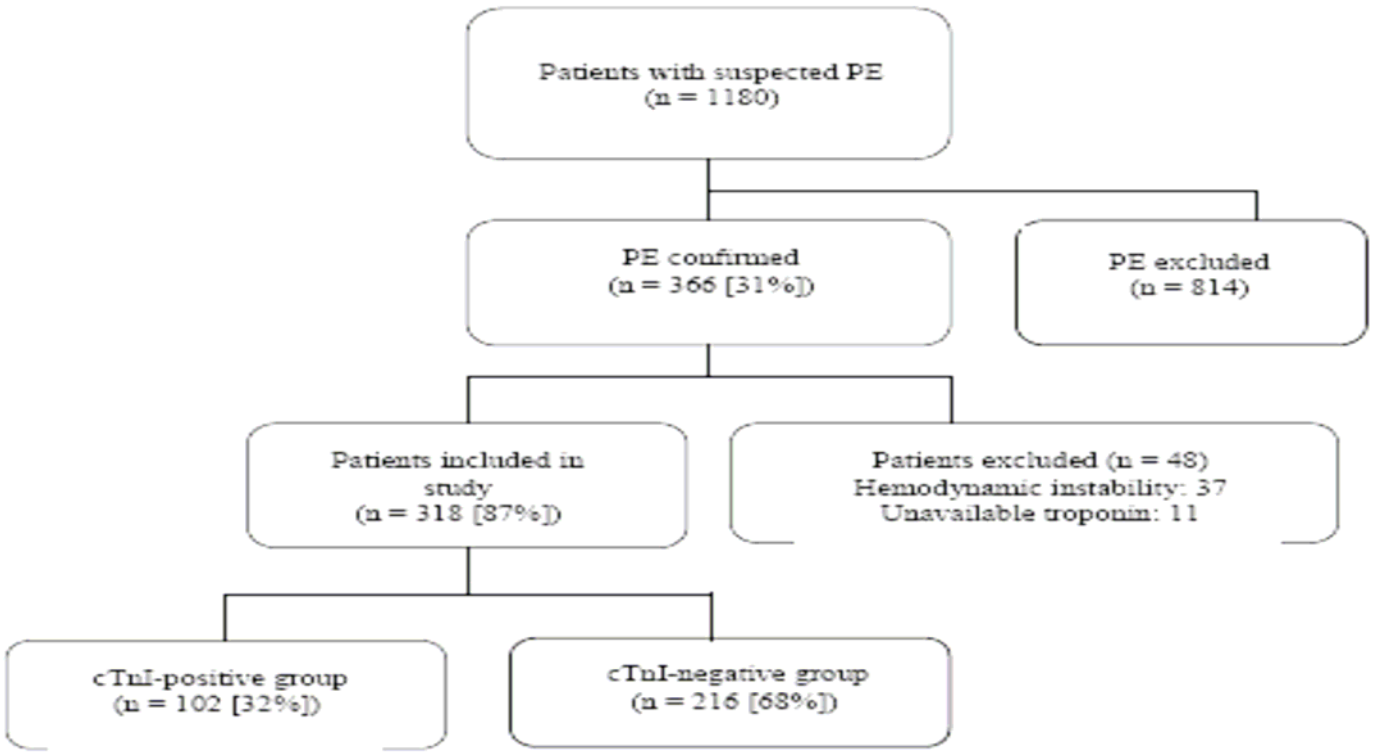
D. Jiménez[1], R. D. Yusen[2], Gema Díaz[3], D. Martí[4], J. Del Rey[5], Joaquín Picher[1], Sergio García-Rull[1], Carlos Escobar[4], Rafael Vidal[1], and Antonio Sueiro[1]

American Journal of Respiratory and Critical Care Medicine 2007 (press)

Tratamiento ambulatorio

Marcadores biológicos

Figure 1. Flow diagram of patients assessed for study eligibility



Tratamiento ambulatorio

Table 2. Risk factors for all-cause death (univariable analysis)

	Nonsurvivors, N = 23	*Survivors, N = 295*	*Odds ratio (95% CI)*	*P value*
Clinical characteristics,				
Age > 65 years	22 (96%)	218 (74%)	7.8 (1.0-58.6)	0.03
Male gender	10 (43%)	128 (43%)	1.0 (0.4-2.4)	0.83
Risk factors for VTE,				
Cancer	6 (26%)	42 (14%)	2.1 (0.8-5.7)	0.21
Surgery	1 (4%)	28 (9%)	0.5 (0.1-3.6)	0.66
Immobility for ≥ 4 days	7 (30%)	44 (15%)	2.5 (1.0-6.4)	0.11
Previous VTE	2 (9%)	35 (12%)	0.7 (0.2-3.1)	0.92
Underlying disease,				
Chronic lung disease	4 (17%)	49 (17%)	1.1 (0.3-3.2)	0.77
Congestive heart failure	3 (13%)	42 (14%)	0.9 (0.3-3.2)	0.86
Clinical presentation,				
Syncope	2 (9%)	57 (19%)	0.4 (0.1-1.7)	0.36
Chest pain	9 (39%)	161 (55%)	0.5(0.2-1.3)	0.20
Dyspnea	17 (74%)	215 (73%)	1.0 (0.4-2.8)	0.89
Heart rate ≥ 100 bpm	9 (39%)	120 (41%)	0.9 (0.4-2.2)	0.97
PO_2 < 60 mm Hg	14 (61%)	159 (54%)	1.3 (0.6-3.2)	0.66
SBP < 120 mm Hg	14 (61%)	94 (32%)	3.3 (1.4-8.0)	0.009
PESI high-risk strata (14)	22 (96%)	196 (66%)	11.1 (1.5-83.6)	0.006
ECG,				
SI-QIII pattern	0 (0%)	35 (12%)	-	0.16
Complete/incomplete RBBB	1 (4%)	46 (16%)	0.2 (0-1.9)	0.21
Inverted T waves in V_1 through V_3	3 (13%)	40 (14%)	1.0 (0.3-3.4)	0.86
Laboratory findings,				
cTnI > 0.1ng mL^{-1}	9 (39%)	93 (32%)	1.4 (0.6-3.3)	0.65

Abbreviations: VTE, venous thromboembolism; SBP, systolic blood pressure; RBBB, right bundle branch block; CI, confidence intervals.

Tratamiento ambulatorio

Table 3. Risk factors for fatal PE (univariable analysis)

	Fatal PE, N = 12	*Non fatal PE, N = 306*	*Odds ratio (95% CI)*	*P value*
Clinical characteristics,				
Age > 65 years	12 (100%)	228 (74%)	-	0.09
Male	5 (42%)	131 (43%)	0.9 (0.3-3.1)	0.82
Risk factors for VTE,				
Cancer	4 (33%)	44 (14%)	3.0 (0.9-10.3)	0.16
Surgery	1 (8%)	26 (8%)	1.0 (0.1-7.9)	0.58
Immobility for ≥ 4 days	3 (25%)	48 (16%)	1.8 (0.5-6.9)	0.67
Previous VTE	2 (17%)	35 (11%)	1.5 (0.3-7.4)	0.86
Underlying disease,				
Chronic lung disease	4 (33%)	49 (16%)	2.6 (0.8-9.0)	0.25
Congestive heart failure	3 (25%)	42 (14%)	2.1 (0.5-8.0)	0.52
Clinical presentation,				
Syncope	2 (17%)	57 (19%)	0.9 (0.2-4.1)	0.84
Chest pain	6 (50%)	164 (54%)	0.9 (0.3-2.7)	0.98
Dyspnea	8 (67%)	224 (73%)	0.7 (0.2-2.5)	0.89
Heart rate ≥ 100 bpm	5 (42%)	124 (40%)	1.0 (0.3-3.4)	0.87
PO_2 < 60 mm Hg	7 (58%)	165 (54%)	1.2 (0.4-3.8)	0.98
SBP < 120 mm Hg	6 (50%)	102 (33%)	2.0 (0.6-6.4)	0.36
PESI high-risk strata (14)	12 (100%)	206 (67%)	-	0.03
ECG,				
SI-QIII pattern	0 (0%)	35 (11%)	-	0.46
Complete/incomplete RBBB	1 (8%)	46 (15%)	0.5 (0.1-4.1)	0.79
Inverted T waves in V_1 through V_3	1 (8%)	42 (14%)	0.6 (0.1-4.5)	0.87
Laboratory findings,				
cTnI > 0.1ng mL^{-1}	8 (67%)	94 (31%)	4.5 (1.3-15.3)	0.02

Abbreviations: VTE, venous thromboembolism; SBP, systolic blood pressure; RBBB, right bundle branch block; CI, confidence intervals.

Tratamiento ambulatorio

Table 4. Prediction rule and troponin test characteristics for 30-day all-cause mortality in 318 patients with PE

	Percents (95% CI)				Value (95% CI)	
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
PESI (14)						
≥ II	100				.1 (0.9-1.1)	0
≥ III	95.6 (87.3-100)				.4 (1.3-1.6	0.1 (0-0.9)
≥ IV	78.3 (61.4-95.1)				.1 (1.6-2.7)	0.3 (0.2-0.7)
V	43.5 (23.2-63.7)				.9 (1.7-5.0)	0.7 (0.5-0.9)
Troponin levels						
≥ 0.1 ng mL^{-1}	39.1 (19.2-59.1)				.4 (04-2.2)	1.0 (0.9-1.1)

Probabilidad postprueba PESI bajo riesgo

0.44%

Abbreviations: CI, confidence intervals.

CONCLUSIONES

- La troponina se asocia a un peor pronóstico en pacientes estables hemodinámicamente con TEP aguda sintomática
- Su valor predictivo positivo es insuficiente para seleccionar pacientes subsidiarios de tratamiento trombolítico
- Se dispone de herramientas clínicas más sencillas (PESI) para seleccionar pacientes de bajo riesgo subsidiarios de tratamiento ambulatorio