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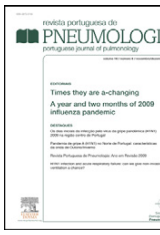

ORIGINAL

Dyslipidemia as a long-term marker for survival in pulmonary embolism

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KEYWORDS
Dyslipidemia;
Lipid metabolic disorders;
Pulmonary embolism;
Survival analysis;
Venous thromboembolism

Abstract
Objectives: To analyse survival rate after 24 months in consecutive patients with a diagnosis PE as well as associated factors.
Methods: Prospective cohort study during a follow-up period of two years in a series of cons cutive patients with PE.
Results: During the follow-up period, 34 out of 148 patients died (23%). Factors independent associated with reduced survival rate were: creatinine levels > 2 (OR, 8.8; 95% CI, 1.1 - 70.87 previous neoplasm (OR, 8.8; 95% CI, 3.69 - 20.98), dementia (OR, 6.85; 95% CI, 2.1 - 22.3 and dyslipidemia (OR, 5.07; 95% CI, 1.92 - 13.44). Forty four percent of the patients wi dyslipidemia died vs. 20.8% of patients without this condition.
Conclusions: In our study dyslipidemia shows as a long-term negative prognostic marker f survival in patients with EP.

PALAVRAS-CHAVE
Dislipidemia;
Doenças metabólicas lipídicas;

Dislipidemia como um marcador de longo prazo para a sobrevivência na embolia pulmonar

Resumo
Objetivos: Analisar a taxa de sobrevivência após 24 meses, em pacientes consecutivos co diagnóstico de PE, bem como fatores associados.

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Embolia pulmonar;
Análise de sobrevivência;
Tromboembolismo venoso

Métodos: Estudo prospectivo durante um período de seguimento de dois anos em uma s
consecutiva de pacientes com PE.
Resultados: Durante o período de acompanhamento, 34 dos 148 pacientes morreram (2
Fatores independentemente associados à reduzida taxa de sobrevivência foram: os nívei
creatinina> 2 (OR, 8,8; 95% CI, 1,1-70,87), neoplasia anterior (OR, 8,8; IC 95%, 3,69-20,
demência (OR, 6,85; 95% CI, 2,1-22,33) e dislipidemia (OR, 5,07; IC 95%, 1,92-13,44). Quar
e quatro por cento dos pacientes com dislipidemia morreram contra 20,8% dos pacientes
essa condição.
Conclusões: No nosso estudo, a dislipidemia mostra-se um marcador prognóstico negativ
longo prazo na sobrevida de pacientes com EP.

Introduction

Venous thromboembolic disease (VTE) is a complex condition with a multifactor aetiology in which both the clinical history of the patient and the genetic and environmental factors play a role.

Survival rate after VTE is worse than expected and it is even worse after pulmonary embolism (PE) than after deep venous thrombosis (DVT) alone[1]. Mortality during follow-up of patients with VTE has been the topic of several research studies and it ranges from 12.5%[2] to 37%[3]. VTE recurrence is so often that, about 30% of patients, present recurrences in the following 10 years[4].

Patients with VTE show several variables associated to a decreased survival rate. From a clinical point of view, it is interesting to which those aspects can be treated.

Patients with non treated dyslipidemia have a global mortality rate a year of 9.7%[5]. As shown by several double-blind placebo-controlled studies, the use of statins to reduce cholesterol levels significantly decrease cardiovascular risk[6]. Lower levels of cholesterol achieved by the administration of statins may reduce the incidence of ictus in high risk populations and in patients with ictus or transient ischemic attack[7].

Although we have found some studies which associate dyslipidemia with a higher risk of VTE[8–12], none of these works has documented the prognostic role dyslipidemia may play in this type of patients.

In this paper, we present a long-term study of a series of consecutive patients diagnosed with PE aiming to analyse the main complications of such condition and their distribution in time and to establish the factors associated with a lower survival rate.

Material and methods

Study design

Prospective cohort study with a follow-up period of two years.

Patients

We analysed a cohort of consecutive patients diagnosed with PE from February 2003 through September 2004 at the University Hospital Virgen del Rocío in Seville.

Methods

We considered as diagnostic criteria for PE: 1) high
bability ventilation/perfusion lung scan, 2) intermediat
low probability ventilation/perfusion lung scan with s
suggestive of arterial thrombosis as revealed by pulmo
angiography with or without signs of venous thrombos
lower limbs through ultrasound scan or venography. 3) In
luminal filling defect observed in pulmonary angiograph
consecutive sections of the vessels or more than 2.5 m
diameter as revealed by pulmonary angiography. 4) In
luminal filling defect in segmentary branches or in m
proximal branches as observed in helical CT scan.

Data collection strategy during the initial PE episode
Patients were enrolled in the study through periodical v
to the Emergency Unit, Internal Medicine Unit, Pneumol
Nuclear Medicine and Radiology Units. A series of varia
were noted down in a form designed for the purpose
were subsequently converted into computer format. F
odical visit were made to the units where the patients w
admitted in order to confirm the correct completion of
form. We also revised in the Computer System for the M
agement of Clinical and Analytical Documentation (SID
(Sistema Informático de Documentación Clínica y Analít
the list of patients with the EP code (CIE9) throughout
study period. This work has been approved for Ethical C
mittee in our hospital.

The variables collected during the acute episode w
divided into: epidemiological data (gender and age),
factors (family history of VTE, hormone therapy, prev
trauma, previous surgery, previous neoplasm (except
non-melanoma skin cancer), baseline disease (previous
tory of VTE, arterial hypertension, congestive heart fail
acute coronary syndrome, respiratory insufficiency, chr
airway obstruction, acute cerebrovascular accident, dem
tia, dyslipidemia and varicose syndrome) and prognostic
clinical characteristics (shock rate, partial oxygen press
heart rate, systolic arterial tension, creatinine). Dys
demia was defined as: hypertriglyceremia > 150 mg/dL (
mmol/L) or HDL cholesterol (high-density lipoprotein
40 mg/dL, (1.04 mmol/L) in males and < 50 mg/dL (
mmol/L) in females. Congestive heart insufficiency
defined taking into account the NYHA functional class
classification. Dementia was defined according to DSM-IV
teria (memory impairment and at least one of the follow

Table 1 Variables associated to less survival rate

Variable	Survive	Die	Relative Risk	CI 95%	p
Demographic characteristics					
Males	55 (74.3%)	19 (25.7%)	1.30	0.66-2.57	0.44 (NS
Age >70 yrs	52 (78.8%)	14 (21.2%)	0.85	0.43-1.69	0.65 (NS
Risk factors					
Hormonal therapy	16 (72.7%)	6 (27.3%)	1.20	0.50-2.90	0.68 (NS
Trauma	13 (92.9%)	1 (7.1%)	2.52	0.03-1.84	0.17 (NS
Surgery	31 (83.8%)	6 (16.2%)	0.61	0.25-1.48	0.27 (NS
Previous neoplasm	14 (45.2%)	17 (54.8%)	5.07	2.58-9.96	0.000[a]
Baseline disease					
Previous history of VTE	19 (86.4%)	3 (13.6%)	0.54	0.17-1.77	0.31 (NS
Hypertension	49 (73.1%)	18 (26.9%)	1.38	0.70-2.70	0.35 (NS
CHF	19 (73.1%)	7 (26.9%)	1.16	0.51-2.67	0.72 (NS
ACS	10 (58.8%)	7 (41.2%)	2.16	0.94-4.97	0.07 (NS
Chronic air-flow obstruction	13 (65%)	7 (35%)	1.74	0.76-4.00	0.19(NS)
Asthma	10 (90.9%)	1 (9.1%)	0.36	0.05-2.62	0.31 (NS
ACVA	15 (75%)	5 (25%)	1.10	0.43-2.85	0.84 (NS
Dementia	4 (50%)	4 (50%)	3.15	1.11-8.97	0.03[a]
Dislypidemia	10 (55.6%)	8 (44.4%)	2.64	1.19-5.3	0.02[a]
Varicose syndrome	23 (88.5%)	3 (11.5%)	0.42	0.13-1.38	0.15 (NS
Prognostic and evolutive characteristics					
Shock rate ≥1	21 (72.4%)		1.29	0.58-2.85	0.53 (NS
pO2 < 60 mmHg	25 (73.5%)	9 (26.5%)	1.01	0.50-2.43	0.82 (NS
HR > 90 spm	74 (77.9%)	21 (22.1%)	0.87	0.44-1.74	0.70 (NS
Systolic arterial pressure <100 mmHg	17 (77.3%)	5 (22.7%)	1.00	0.39-2.57	0.99 (NS
Creatinine >2 mg/dL	1 (33.3%)	2 (66.7%)	6.59	1.57-27.70	0.01[a]

CI: Confidence interval; VTE: Venous thromboembolic disease; CHF: Congestive heart failure; ACS: Acute coronary syndrome; ACVA Acute cerebrovascular accident; pO2: Partial oxygen pressure; HR: Heart rate; p: $p < 0.05$ is considered as statistically significant.
[a] Variables associated to lower survival at two years according to multivariate analysis.

cognitive alterations: aphasia, apraxia, agnosia, alteration of cognitive functions. Also, these factors must be intense enough to interfere with the occupational or social activities of the patients. The alterations indicate a deterioration of such functions in comparison to the previous situation of the patient. These symptoms are not exclusive of an embarrassment state.

Follow up of patients: In order to analyse survival rates and long term complications we followed up all patients who did not die during admission.

All patients were followed up in a monographic visit of thromboembolic disease at months 1, 3, 6, 12, 18 and 24. We noted down the date and cause of death of all the patients who died during the follow-up period.

Strategy to capture losses was divided into: 1) telephone contact with the patients who did not attend the follow-up visits, 2) Computer System for the Management of Clinical and Analytical Documentation (SIDCA) of the University Hospital Virgen del Rocío to identify episodes requiring admission or referral to other units, 3) Review of clinical histories.

Statistical analysis

In the statistical analysis of the results obtained we indicate both absolute and relative frequency for qualitative variables, and mean and standard deviation for quantitative variables. In case of asymmetrical distribution of the vari bles, we analysed median values and interquartile range. W compared the groups (deceased and non deceased) usi the chi-square test (qualitative variables) considering a value < 0.05 as statistically significant. The comparison time free from episodes has been performed by means the Kaplan-Meier test together with the log rank test a multivariate analysis in order to control possible confusi variables, according to the Cox regression model.

Results

The sample obtained in our cohort was 148 patients. Ha of the patients (n = 74) were male. Mean age of patien was 64.2 ± 17.2 yrs. During the two-year follow-up perio 34 patients died (23%). The causes of death were: ca cer (n = 20), acute coronary syndrome (n = 6), sudden dea with dyspnoea (n = 4), major bleeding in the digesti tract (n = 1), non hemorrhagic acute cerebrovascular strol (n = 1) and unknown causes (n = 2). Accumulated mortali rate reached 19.2% after one year and 29.6% after tw years.

Patients (272 patients/year) were followed up for period of 24 ± 23.8 (median ± range). 73.6% of the samp (23% dead and 3.4% lost) was followed up for 24 months.

Table (table 1) shows those variables whose possib association with less survival rate at two years has be

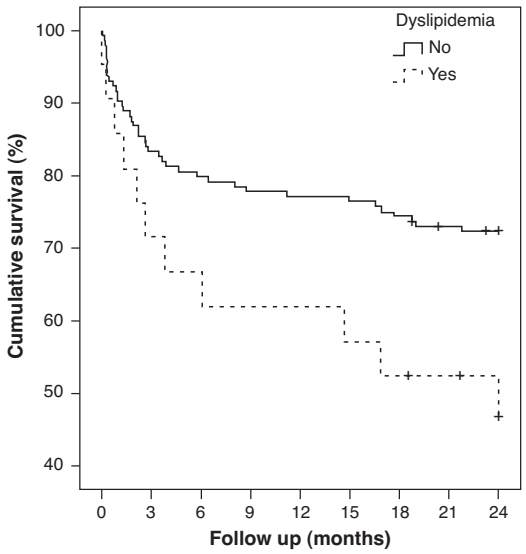

Figure 1 Cumulative survival in patients with and without dyslipidemia.

analysed. Independent variables associated to less survival rate were: creatinine levels > 2 (OR, 8.8; 95% CI, 1.1 — 70.87), previous neoplasm (OR, 8.8; 95% CI, 3.69 — 20.98), dementia (OR, 6.85; 95% CI, 2.1 — 22.33) and dyslipidemia (OR, 5.07; 95% CI, 1.92 — 13.44).

The 44.45% of patients with dyslipidemia died vs. 20.8% of patients who did not show such condition (Figure 1). No significant differences were observed in relation to mean age (63.8 vs. 68.7) or gender between patients with and without dyslipidemia.

Discussion

One of the most relevant data obtained in the present study, and which contributes to its seriousness and external accuracy, is the appropriate two-year follow-up of 97% of the sample made up only of patients with PE who were consecutively and prospectively enrolled in the study.

The sample of patients was homogeneous and its distribution between genders was similar to that observed in other studies[13,14]. Patient age was similar to that reported by different series in the United States[13], Spain[2] and other European studies[15—17].

Reported survival rate after VTE varies widely[17,18]. Such variability is probably the result of the shortcomings observed in study design: patients with negative clinical evolution[19—21], patients diagnosed in residences[15—22], age > 65 years[15,22], patients admitted to tertiary level hospitals[23,24] or patients from clinical trials[25,26]. As a result, an accurate estimate of global survival rate associated to VTE cannot be obtained. Anyway mortality observed in our study is similar to other series[2,3].

The factors associated to a lower survival rate mentioned in our study had already been analysed in previous studies, as in the case of neoplasm, dementia and renal insufficiency[27—29]. Dementia is considered a negative prognostic factor in new prognostic scales[29,30], but at present dyslipidemia is not included in any scale.

High serum cholesterol and LDL cholesterol levels, low HDL cholesterol levels are considered risk factors atherothrombosis[31]. Despite their potent effect on ath genesis, lipids and lipoproteins could affect haemost by modulating the procoagulant and fibrinolytic expres and function[32]. Doggen et al.[9] have shown that eleva triglycerides levels pose a higher risk (twofold) for ve thrombosis. A case-control study[10] also reported the that hypercholesterolemia is associated with a higher ris DVT. As regards hypertriglyceridemia, results are contro sial: some studies associate it with venous thrombosis but others do not report such interplay[33]. It is importan carry out the measurements prior to the onset of ther because it is known that lipid levels diminish in the e of an acute vascular episode[34]. Finally, Tsai et al.[8], in t analysis of cardiovascular risk factors and incidence of a episode of VTE, concluded that some arterial risk fact including dyslipidemia, were not associated with VTE.

All the above mentioned studies establish the associa of dyslipidemia with a first episode of VTE, but we report association of dyslipidemia, as an independent risk fa with lower long-term survival rate in patients with PE.

The interplay between dylipidemia and PE in this s has not been thoroughly analysed yet. In our series, l term mortality rate due to vascular reasons in patients dyslipidemia who have suffered PE is sevenfold greater t mortality in untreated dyslipidemic patients[5]. Moreover, mortality rate observed in our patients with PE is more t twofold greater in patients with dylipidemia than in th without this condition. We do not know for sure whe the fact of having suffered an episode of PE boosts effect of dyslipidemia as a prognostic factor for lower vival. Nor do we know whether patients with dyslipide who suffer PE are those with a more advanced or diffi to manage metabolic disease. Other questions we sh answer would be: which parameters defined as dyslipide are considered more determinant and whether the pro sis of these patients may improve with statin therapy. last question would have significant practical implicatio we already know that statin therapy in dyslipidemic pati reduces mortality in 12.37% a year, disregard of the caus death[5].This work has several limitations. Firstly, the sa of patients included in our study is not large but the re get at hypothetical new factor related to a poor surv Further studies with larger samples and primarily focu on this issue could answer many of the above mentio questions. Secondly, other data not available and woul interesting to contrast with the results obtained are q titative results of total cholesterol, LDL-cholesterol, cholesterol, triglycerides, duplication of tests and if analytical was fasting or not, and whether the patient taking statins. Individuals treated with lipid-lowering d should be excluded or taking into account, because t ment could affect lipid levels. Several studies, inclu ours, did not make such exclusion[10,35]. These data were considered when designing the study. The developmen prospective studies should collect these data.

We think that this finding also becomes more impor due mainly to two recently published papers. Khemasu et al. suggest that the use of statins is associated wi significant reduction in the occurrence of venous th boembolism in patients with cancer[36]. Glynn et al.

randomized trial of apparently healthy persons found that rosuvastatin significantly reduced the occurrence of symptomatic venous thromboembolism[37]. These previous results in addition to our work open a field of research on whether this type of Venous Thromboembolism patients may benefit from treatment with statins.

Conclusion

We could summarize that in our study, patients with dyslipidemia who suffered PE showed worse survival rate. The role dyslipidemia may have as a vascular risk factor especially in patients with PE and the possibility to improve survival rates warrants further investigation.

Conflict of interests

Authors declare that they don't have any conflict of interests.

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