Original Article

Factors associated with mortality in patients hospitalized in Spain and Latin America for acute severe asthma in 1994, 1999, and 2004*,**

Fatores associados à mortalidade em pacientes hospitalizados por asma aguda grave em 1994, 1999 e 2004 na Espanha e América Latina

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Abstract

Objective: To evaluate, for the first time, the characteristics of patients with acute asthma who died during hospitalization in Spain and Latin America, as well as to evaluate factors associated with asthma mortality. **Methods:** A retrospective review of hospital records of 3,038 patients with asthma (aged 15-69 years) admitted to nineteen tertiary care hospitals in Spain and in eight Latin-American countries in 1994, 1999, and 2004. **Results:** There were 25 deaths (0.8% of all hospitalized patients) during the three years studied. Although there was a tendency towards a reduction in in-hospital mortality (from 0.97% in 1994 to 0.69% in 2004), there were no significant differences in terms of year or geographic area. Intensive care unit admissions and cases of out of hospital cardiopulmonary arrest increased the mortality rates to 8.3% and 24.7%, respectively. The multivariate analysis showed that gender (female; OR = 25.5; 95% CI: 2.6-246.8), out of hospital cardiopulmonary arrest (OR = 22.5; 95% CI: 4.4-114.7), and arterial pH < 7.3 during hospitalization (OR = 1.0; 95% CI: 1.1-3.4) were strongly associated with asthma mortality. **Conclusions:** Our study on mortality in patients hospitalized for acute severe asthma showed that deaths occurred almost exclusively in female patients and in patients who suffered out of hospital cardiopulmonary arrest, confirming previous findings from studies conducted in developed countries.

Keywords: Asthma/mortality; Asthma/epidemiology; Hospitalization; Hospital mortality.

Resumo

Objetivo: Avaliar, pela primeira vez, as características de pacientes com asma aguda que morreram durante a hospitalização na Espanha e na América Latina, bem como avaliar fatores associados à mortalidade por asma. **Métodos:** Revisão retrospectiva dos registros hospitalares de 3.038 pacientes com asma (com idade entre 15 e 69 anos) internados em dezenove hospitais de atendimento terciário na Espanha e em oito países da América Latina em 1994, 1999 e 2004. **Resultados:** Houve 25 mortes (0,8% de todos os pacientes hospitalizados) durante os três anos estudados. Embora tenha havido uma tendência de redução da mortalidade hospitalar (de 0,97% em 1994 para 0,69% em 2004), não houve diferenças significativas quanto ao ano ou à área geográfica. Internações em unidade de terapia intensiva e casos de parada pulmonar pré-hospitalar aumentaram as taxas de mortalidade para 8,3% e 24,7%, respectivamente. A análise multivariada mostrou que sexo (feminino; OR = 25,5; IC95%: 2,6-246,8), parada cardiopulmonar pré-hospitalar (OR = 22,5; IC95%: 4,4-114,7) e pH arterial < 7,3 durante a hospitalização (OR = 1,0; IC95%: 1,1-3,4) estavam fortemente associados à mortalidade por asma. **Conclusões:** Nosso estudo sobre mortalidade em pacientes hospitalizados por asma aguda grave mostrou que as mortes ocorreram quase que exclusivamente entre pacientes do sexo feminino e entre pacientes que sofreram parada cardiopulmonar pré-hospitalar, confirmando achados anteriores de estudos realizados em países desenvolvidos.

Descritores: Asma/mortalidade; Asma/epidemiologia; Hospitalização; Mortalidade Hospitalar.

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* Multicenter study carried out in Spain and Latin America.

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Introduction

Asthma is one of the most common chronic diseases worldwide.[1] In the United States, it is responsible for more than 1.5 million emergency room visits, approximately 500,000 hospitalizations, and almost 5,000 deaths each year.[2-4] In the last decade, epidemiological studies have shown that mortality rates have stabilized or gradually decreased in different countries.[5-11] Although most deaths occur out of the hospital, a significant number still occur in the emergency room or, more often, during hospitalization. However, there have been few studies assessing the characteristics of patients with acute asthma who died during hospitalization, and most have been conducted in countries such as the United States or those in the United Kingdom.[12-13] Very few studies have reported data from Latin America or Spain.[14]

In order to address this lack of information, we conducted a multinational, multicenter retrospective study to evaluate, for the first time, the characteristics of patients with acute asthma who died during hospitalization in Spain and Latin America, as well as to evaluate factors associated with asthma mortality.

Methods

In order to perform this study, we used the database of the project designated *Estudio del Asma Grave en Latinoamérica y España* (EAGLE, Study of Severe Asthma in Latin America and Spain), created by the respective asthma sections of the Spanish Society of Pulmonology and Thoracic Surgery and the Latin-American Thoracic Society.[15]

The study population included all inpatient hospital admissions (>48 h) for acute severe asthma in major urban areas of Spain (nine health facilities) and Latin America (ten health facilities in eight countries: Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay, and Venezuela) occurring in the years 1994, 1999, and 2004. Each hospital evaluated had, in the selected years, more than 200 beds, an active emergency room, and an intensive care unit (ICU). In each health facility, we reviewed and identified all hospital records of patients (aged 15-69 years) admitted with a primary diagnosis of acute asthma—International Classification of Diseases, ninth (493.01) and tenth (J45, J46) revisions. Since some patients were admitted more than once in each selected year, the analysis was restricted to the last admission of each patient in each year.

The detailed review of the records included demographic data, year/month of admission, previous hospitalization data—use of inhaled corticosteroids, long-acting beta-agonists, or theophylline as controller medications; asthma severity according to the Global Initiative for Asthma criteria[16]; and previous hospitalizations for asthma—and data obtained during hospitalization: lowest arterial pH at admission; forced expiratory volume in one second/peak expiratory flow ratio (FEV_1/PEF) in the emergency room; length of hospitalization; admission to the ICU and length of stay; cardiopulmonary arrest; intubation or mechanical ventilation during hospitalization; length of intubation or mechanical ventilation; and in-hospital mortality. As for seasonal variations in hospital admissions, summer was defined as July-September in the northern hemisphere, and as January-March in the southern hemisphere; fall was defined as October-December in the northern hemisphere, and as April-June in the southern hemisphere; winter was defined as January-March in the northern hemisphere, and as July-September in the southern hemisphere; and spring was defined as April-June in the northern hemisphere, and as October-December in the southern hemisphere.

All data were analyzed using the Statistical Package for the Social Sciences, version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation for continuous variables. The primary outcome measure was asthma mortality. The subjects were divided into two groups: those who died during hospitalization and those who were discharged (controls).

Table 1 - Mortality rates stratified by year and geographic area.

	1994	1999	2004	p
All nine countries[a]	7/718 (0.97%)	10/1166 (0.85%)	8/1154 (0.69%)	0.7
Spain	4/393 (1.01%)	4/643 (0.62%)	6/673 (0.89%)	0.6
Latin America	3/325 (0.92%)	6/519 (1.10%)	2/481 (0.41%)	0.2

[a]Argentina, Brazil, Chile, Colombia, Mexico, Peru, Spain, Uruguay, and Venezuela.

Continuous variables with normal distribution were compared using the t-test for independent samples, and continuous variables with non-normal distribution were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test with Yates' correction or Fisher's exact test. Factors associated with asthma mortality at a significance level of p = 0.05 in the univariate analysis were selected for inclusion in a multivariate analysis (multiple logistic regression). Values of p < 0.05, using a two-tailed test, were considered to be significant for all statistical tests. Ninety-five percent confidence intervals (95% CIs) were calculated using standard formulas.[17]

The study was approved by the local ethics committees.

Results

A total of 3,038 patients with asthma (37.5% aged 15-34 years, 32.5% aged 35-55 years, and 30% aged 56 years or older) were audited. Spain accounted for 56.4% of the total sample (nine large urban hospitals), and Latin America accounted for 43.6% (ten health facilities in eight countries).[15] At emergency room admission, 49.2% of the patients with asthma had severe exacerbations (baseline FEV_1/PEF < 50% of predicted), 27.2% had life-threatening exacerbations (FEV_1/PEF < 30% of predicted), and only 23.6% presented mild to moderate attacks (FEV_1/PEF > 50% of predicted). However, this variable was recorded in only 806 cases (26.5% of all patients admitted). Overall, there were 25 deaths (0.8% of all hospitalized patients) during the three years studied. There were no significant differences in terms of year or geographic area (Table 1), although there was a tendency towards a reduction in in-hospital mortality (from 0.97% in 1994 to 0.69% in 2004). The occurrence of events such as ICU admission or cardiopulmonary arrest increased the mortality rates to 8.3% and 24.7%, respectively. In the univariate analysis (Table 2), we found pronounced differences between surviving and nonsurviving asthma patients. There was a relationship between mortality and age,

Table 2 - Univariate analysis comparing survivors and nonsurvivors.

Variable	Survivors (n = 3,013)	Nonsurvivors (n = 25)	p
Age (years), mean ± SD	42.2 ± 19.1	58.6 ± 18.8	0.0001
Gender (female), n (%)	2080 (69.0)	23 (92.0)	0.002
Asthma severity and type			
Intermittent, n (%)	570 (18.9)	0 (0)	0.0001
Mild persistent, n (%)	557 (18.5)	2 (8.0)	
Moderate persistent, n (%)	1051 (34.8)	7 (28.0)	
Severe persistent, n (%)	835 (27.8)	16 (64.0)	
Previous admissions, n (%)	1771 (58.8)	17 (68.0)	0.4
Season			
Summer, n (%)	631 (20.9)	2 (8.0)	0.02
Fall, n (%)	881 (29.2)	8 (32.0)	
Winter, n (%)	879 (29.2)	13 (52.0)	
Spring, n (%)	712 (23.7)	2 (8.0)	
Previous use of ICS, n (%)	982 (32.6)	10 (40.0)	0.2
Previous use of LABA, n (%)	449 (14.9)	4 (16.0)	0.6
Previous use of theophylline, n (%)	512 (17.1)	10 (40.0)	0.004
FEV_1/PEF (% predicted) in the ER (n = 806), mean ± SD	42.1 ± 16.1	27.0 ± 12.5	0.02
Lowest in-hospital arterial pH (n = 2,229), mean ± SD	7.4 ± 0.08	7.2 ± 0.17	0.0001
Length of hospitalization (days), mean ± SD	7.5 ± 6.58	11.9 ± 12.2	0.0001
Intubation/mechanical ventilation, n (%)	159 (5.3)	4 (16.0)	0.04
ICU admissions, n (%)	189 (6.3)	17 (68.0)	0.0001
Cardiopulmonary arrest, n (%)	55 (1.8)	18 (72.0)	0.0001

SD: standard deviation; ICS: inhaled corticosteroids; LABA: long-acting beta-agonists; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; ER: emergency room; and ICU: intensive care unit.

since most asthma deaths occurred in patients over the age of 50 (68% *vs.* 12% in patients younger than 35 and 20% in patients aged 35-50). In addition, almost all deaths occurred in female patients. Nonsurviving asthma patients presented greater asthma severity, and there was a seasonal variation in the mortality rate among such patients (an excess of in-hospital deaths during winter months). Finally, the use of theophylline was significantly greater among nonsurviving asthma patients. It is of note that there was no difference between the groups in terms of the use of long-acting beta-agonists. Asthma attacks during hospitalization were more severe among nonsurviving asthma patients than among surviving asthma patients in terms of FEV_1/PEF and arterial pH. In addition, nonsurviving asthma patients were hospitalized for longer periods, were more often submitted to intubation/mechanical ventilation, were more often admitted to the ICU, and more often suffered cardiopulmonary arrest.

The variables significantly associated with asthma mortality during hospitalization were included in a multivariate analysis (Table 3). After adjusting for the other predictors in the model, we found three variables to be associated with asthma mortality. Two of those variables presented a particularly strong association with asthma mortality, independently increasing the probability of death during hospitalization: gender (female; OR = 25.5; 95% CI: 2.6-246.8) and cardiopulmonary arrest (OR = 22.5; 95% CI: 4.4-114.7). A third variable, arterial pH < 7.3 during hospitalization (OR = 1.9; 95% CI: 1.1-3.4), was also associated with a significant increase in asthma mortality.

Discussion

We found that the overall mortality rate during the three years studied was less than 1% of all patients admitted, and that there was a tendency towards a reduction in in-hospital mortality (from 0.97% in 1994 to 0.69% in 2004). Since this tendency cannot be explained by a decline in asthma prevalence, it could be argued that it was produced by an improvement in the management of patients with asthma in the periods between severe attacks and during hospitalizations.[15]

Among the patients who died during hospitalization, the mean interval between hospital admission and death was approximately 12 days. Deaths occurred more frequently among certain classes of patients: those > 50 years of age; those with severe persistent asthma; those hospitalized during the winter; those having previously used theophylline; those presenting more severe airway obstruction in the emergency room; those hospitalized for longer periods; those admitted to the ICU; and those submitted to intubation, mechanical ventilation, or both. However, the multivariate analysis showed that female gender and cardiopulmonary arrest were the only variables that were independently associated with a significantly increased mortality risk. Deaths occurred almost exclusively in female patients (92%

Table 3 - Univariate and multivariate analyses of factors potentially associated with mortality.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age > 50 years	3.9	1.6-9.3	0.002	3.0	0.8-11.7	0.1
Female gender	5.2	1.2-21.9	0.02	25.5	2.6-246.8	0.005
Severe persistent asthma	4.9	2.0-11.5	0.0001	1.5	0.4-5.0	0.4
Hospital admission during winter	2.1	1.1 -4.3	0.04	1.1	0.3-3.8	0.8
Use of theophylline	3.5	1.5-7.8	0.003	2.1	0.6-7.5	0.2
FEV_1/PEF < 35% of predicted	3.2	1.0-5.3	0.05	2.9	0.5-16.3	9.2
Arterial pH < 7.3	5.5	2.1-13.9	0.0001	1.9	1.1-3.4	0.02
Hospitalization for more than 12 days	12.8	2.8-58.3	0.001	1.9	0.1-22.3	0.5
Intubation/mechanical ventilation	3.4	1.1-10.0	0.02	1.4	0.3-6.3	0.6
ICU admission	31.7	13.5-74.9	0.0001	3.3	0.6-16.7	0.1
Cardiopulmonary arrest	138.2	55.5-344.5	0.0001	22.5	4.4-114.7	0.0001

FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; and ICU: intensive care unit.

of all deaths), and the mortality rate was quite high (24.7%) among patients suffering cardiopulmonary arrest. Arterial pH < 7.3 during hospitalization was also associated with an increased mortality risk.

Our data are in agreement with those of previous studies. The mortality rate among patients hospitalized in Spain and Latin America was similar to that found in previous studies conducted in the United States and the United Kingdom (less than 1% of all admissions).[12-13] Most of the patients who died were over 34 years of age. In addition, recent studies have reported that the incidence of asthma-related in-hospital mortality is higher among women than among men.[13-14,18] Although it is difficult to understand why the mortality risk is greater for female patients hospitalized for asthma, it might be due to the gender bias (predominance of females) among adults with asthma. Among patients with severe asthma, the female/male ratio can be as high as 4:1.[13-14,19] In addition, biological differences and other factors, including environmental concerns, poverty, and quality of care, might play a role.[20] Finally, 72% of the deaths appeared to be attributable to out of hospital cardiopulmonary arrest and the resulting anoxic encephalopathy.

This study had several limitations. Despite being a multinational and multicenter study, it was retrospective and focused on three discrete time periods. Therefore, there is a possibility that not all records in the years studied were located, and that continuous data might not show the same tendencies in patients hospitalized for acute severe asthma. Since there were no standardized admission criteria, some of the patients (such as those with chronic obstructive pulmonary disease and, in particular, those over the age of 50) might have been misdiagnosed. Although we selected a large sample of hospitalized patients with asthma from nineteen health facilities in major urban areas in Spain and in eight Latin American countries, the results are not necessarily representative of all patients hospitalized for acute severe asthma.

In conclusion, our study on mortality in patients hospitalized for acute severe asthma in Spain and Latin America showed that deaths occurred almost exclusively in female patients and in patients who suffered out of hospital cardiopulmonary arrest. These data confirm those of previous studies conducted in developed countries.

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