

Clinical Profile of Patients With Severe Anaphylaxis Hospitalized in the Spanish Hospital System: 1997-2011

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■ Abstract

Background: Studies assessing the severity of anaphylaxis lack a comprehensive approach to collecting data on comorbidities that may worsen prognosis.

Objective: Using the Elixhauser score (a systematic index associated with longer stay, hospital charges, and mortality), we determined which comorbidities were associated with more severe anaphylaxis.

Methods: We based our study on the Spanish Ministry of Health database of hospital discharges in Spain between 1997 and 2011. We constructed logistic regression models in which the dependent variables were outcomes related to greater severity (death, cardiac arrest, need for invasive mechanical ventilation or vasopressor drugs, admission to the intensive care unit, and length of stay) and the independent variables were the 30 comorbidities that comprise the Elixhauser score, age, sex, and main causes of anaphylaxis.

Results: We found that a higher risk of severe anaphylaxis was associated (3 or more logistic regressions) with age >50 years or having experienced cardiac arrhythmia, coagulation disorder, associated fluid-electrolyte imbalance, chronic pulmonary disease, or *Echinococcus* anaphylaxis. Likewise, in the adjusted analysis, a higher Elixhauser score was associated with most of the outcomes analyzed for severity of anaphylaxis.

Conclusions: Cardiovascular and respiratory diseases increase the severity of anaphylaxis, and the resulting poor health status (represented as a higher Elixhauser score) is associated with more severe anaphylaxis.

Key words: Severity. Anaphylaxis. Comorbidities. Elixhauser score. Cardiovascular. Respiratory. Diseases.

■ Resumen

Antecedentes: Los estudios que recogen datos sobre comorbilidades que empeoran la gravedad de la anafilaxia, carecen de un acercamiento exhaustivo.

Objetivo: Usando la puntuación de Elixhauser (un sistema de puntuación asociado con mayor estancia hospitalaria, mayor gasto hospitalario y muerte), establecimos que comorbilidades fueron asociadas con anafilaxia grave.

Métodos: Usamos para el estudio la base de datos de altas hospitalarias del Ministerio Español de Sanidad, entre 1997 a 2011. Se obtuvo varios modelos de regresión logística, en las cuales las variables dependientes fueron desenlaces relacionados con eventos asociados habitualmente a una gran gravedad de los episodios (muerte, parada cardio-respiratoria, necesidad de uso de ventilación mecánica invasiva o medicamentos vaso-pressores, ingreso en la Unidad de Cuidados Intensivos y duración de la estancia) y las variables independientes fueron las 30 comorbilidades que comprenden la puntuación Elixhauser, junto con edad, sexo y las grandes causas de anafilaxia.

Resultados: Encontramos que un mayor riesgo para anafilaxia grave estuvo asociado (3 o más regresiones logísticas con significación estadística) con una edad de más de 50 años, o haber experimentado arritmias cardíacas, alteraciones de la coagulación, desbalance hidro-electrolítico, enfermedad pulmonar crónica o anafilaxia por *Echinococcus*. Así mismo, en un análisis ajustado, una puntuación mayor del sistema Elixhauser se asoció con la mayoría de las variables de desenlace usadas para analizar la gravedad de la anafilaxia.

Conclusiones: Enfermedades cardio-vasculares y respiratorias incrementan la gravedad de la anafilaxia y un mal estado de salud (representado por mayores puntuaciones del Sistema de puntuación de Elixhauser) se asocian con mayor gravedad de la anafilaxia.

Palabras clave: Gravedad. Anafilaxia. Comorbilidades. Puntuación Elixhauser. Cardio-vascular. Respiratorias. Enfermedades.

Introduction

The severity of anaphylaxis can be classed as moderate (dyspnea, stridor, wheeze, vomiting, dizziness, chest or throat tightness, and abdominal pain), very severe (hypoxia, hypotension, and neurologic involvement) [1], and fatal [2-4]. The classic risk factors for more severe anaphylaxis are older age, cardiovascular and respiratory disease, antihypertensive drugs (principally β -blockers and ACE inhibitors), drugs, venom, and uncontrolled asthma [4-10].

Publications on the risk factors associated with the most severe presentations of anaphylaxis focus only partially on specific factors (eg, the importance of respiratory disease) [9], results are inconsistent (eg, aggravation of anaphylaxis by β -blockers, differences with respect to the most severe type of anaphylaxis) [5-8], or the principal outcome measures are different (eg, admissions for anaphylaxis, need for mechanical ventilation) [4-10].

We studied a cohort of patients with anaphylaxis admitted to hospitals of the Spanish National Health System from 1997 to 2011 to evaluate the risk factors associated with poor outcome. Our comprehensive approach was based on the severe chronic comorbidities in the Elixhauser score [11]. The score uses 30 different comorbidities from different groups of diseases, as follows: cardiovascular system (6), neurologic diseases (2), pulmonary diseases (1), endocrine and nutritional diseases (5), kidney failure (1), digestive diseases (2), HIV infection (1), cancer (3), connective tissue diseases (1), hematologic diseases (3), fluid-electrolyte imbalance (1), substance abuse (2), and psychiatric diseases (2). In addition, comorbidities associated with the principal diagnosis of an admission and acute comorbidities (pneumonia, pleural effusion, urinary tract infection, cardiac arrest, cardiogenic shock, and respiratory failure) are excluded. The Elixhauser score has been found to be significantly associated with substantial increases in length of stay, hospital charges, and mortality both for heterogeneous and for homogeneous disease groups [11].

Methods

Design and Selection of Cases

The study was carried out using the Spanish Minimum Basic Data Set (MBDS), which is a database created by the Spanish Ministry of Health to collect standardized information on hospital discharges in Spain. The database uses the codes of the Spanish version of the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* [12] and covers 98% of public hospitals in Spain and many private hospitals [12]. The study was performed using data from the MBDS between 1997 and 2011.

We chose a retrospective observational cohort design. Possible cases of anaphylaxis were based only on the principal diagnosis: thus, the most probable cause of admission was an anaphylaxis episode, and the remaining diagnoses were the comorbidities, which could worsen the anaphylaxis episode. Using all discharge diagnoses to identify anaphylaxis meant that comorbidities could have been associated with

an admission diagnosis other than anaphylaxis. We used 2 strategies to select cases of anaphylaxis, as described elsewhere (Table 1). First, we chose *ICD-9-CM* codes that were specifically associated with anaphylaxis and causes of anaphylaxis. In addition, following a strategy adapted from Harduar-Murano et al [13], we used codes related to the causes of anaphylaxis and symptoms or signs of organs or systems whose combination led us to select episodes that fulfilled the criteria for the definition of anaphylaxis of the NIAID-FAAN Symposium (National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network) [14] (Table 1).

We assessed the severity of anaphylaxis episodes using *ICD-9-CM* codes related to infusion of vasopressor drugs (00.17), invasive mechanical ventilation (96.70 to 96.72), and cardiorespiratory arrest (427.5). We also considered death, admission to the intensive care unit, and length of stay. Likewise, the comorbidities studied were chosen from the list of comorbidities used to calculate the Elixhauser score [11,15], and the *ICD-9-CM* codes that represent them were those proposed by the Agency for Healthcare Research and Quality (version 3.5) [16].

This study was approved by the Ethics Committee for Medical Research of Hospital Universitario Fundación Alcorcón (number 16/05).

Statistical Analysis

Given the nonparametric distribution of the variables, values are expressed as the mean, median, and interquartile range.

We constructed several logistic regression models (binomial and ordered according to the type of variable), where the dependent variable was the indicator of severity and the covariates the comorbidities comprising the Elixhauser score [11], major causes of anaphylaxis, sex, and age group. We used a modified version of the Elixhauser score [15] and not its individual diseases as the covariate in another cluster of logistic regression models adjusted for cardiac and respiratory diseases, cause of anaphylaxis, sex, and age in order to ascertain whether comorbidities other than cardiac and respiratory diseases increase the severity of anaphylaxis.

We calculated C statistics to assess the discriminatory power of each model [17] and measured the calibration of the models using the Hosmer-Lemeshow goodness-of-fit test [15,18].

The Elixhauser score was originally designed for discharged patients ≥ 18 years. However, given that our study population comprised patients of all ages, we assessed the discriminatory power of this score in patients older and younger than 18 years for the various outcomes of the study. We also carried out a factor analysis to assess the homogeneity of variables associated with severity and the underlying structure of the data.

The power of the study varied with the number of positive results for each independent variable studied: for variables with only 100 cases or similar, with a type I α error of 0.05, the study had a power close to or higher than 80% if the odds ratios were at least 1.75 and the risk factor studied appeared in at least in 20% of the controls. Such was the

Table 1. ICD-9-CM Codes Used to Select Admissions for Anaphylaxis

ICD-9-CM Code	Description of ICD-9-CM Code
SPECIFIC CODES FOR ANAPHYLAXIS AND FOR CAUSES OF ANAPHYLAXIS	
122	Echinococcosis
127.1	Anisakiasis
989.5	Venom
989.82	Toxic effect of latex
478.6 or 478.25	Laryngeal or naso-pharyngeal edema
995.6	Anaphylactic shock due to adverse food reaction
995.7	Other adverse food reactions, not otherwise classified
995.0	Unspecified anaphylactic shock
995.1	Angioneurotic edema
995.2	An unspecified adverse effect caused by the correct administration of a drug or medicinal or biologic substance
995.3	Unspecified allergic reactions
999.4	Anaphylactic shock due to serum
995.4	Shock due to anesthetic drugs
E905	Venomous animals and plants as the cause of poisoning and toxic reactions
E930 to E949	Drugs and biologic substances which cause adverse effects when used as therapy
SIGNS AND SYMPTOMS INCLUDED IN THE DEFINITION OF ANAPHYLAXIS OF THE NIAID-FAAN CONSENSUS	
Respiratory Involvement	
518.81	Acute respiratory episode
518.82	Other respiratory insufficiency, not otherwise classified concepts
786.00 to 786.09	Dyspnea and respiratory alterations
786.1	Stridor
493.0	Extrinsic asthma
493.9	Unspecified asthma
493.8	Other types of asthma
477.0 to 477.9	Allergic rhinitis
Decreased Arterial Tension	
458, 458.0, 458.2, 458.8, 458.9	Hypotension
Gastrointestinal Involvement	
558.3	Allergic gastroenteritis or colitis
787.0*	Nausea or vomiting
787.4	Visible peristalsis
787.5	Abnormal bowel sounds
787.6	Fecal incontinence
789.0	Abdominal pain
Mucosa and Skin Involvement	
2.73	Conjunctival edema
374.82	Eyelid edema
478.6	Laryngeal edema
478.25	Nasopharyngeal or pharyngeal edema
782.62	Flush
708	Urticaria
698.1, 698.8, 698.9	Pruritus

Abbreviations: ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; NIAID-FAAN, National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network.

case for cardiac arrest, discharge from the intensive care unit, and administration of vasopressor drugs. In the case of independent variables, again with a type I α error of 0.05, a population of 300-400 cases (for example, patients undergoing

invasive mechanical ventilation and patients with the longest stays in the hospital) gave a power of 80% or nearly 80% when the odds ratios were 1.5 and the risk factor studied appeared in at least 20% of the controls.

Table 2. Crude and Adjusted Analysis of Comorbidities (Logistic Regression) Associated With Invasive Mechanical Ventilation (IMV) in Patients Admitted to Spanish Hospitals With Anaphylaxis

Covariates	Cases		Not Cases		Crude Analysis			Adjusted Analysis				
	IMV Yes	IMV No	IMV Yes	IMV No	Crude Odds Ratio	95%CI, Lower Limit	95%CI, Upper Limit	P	Adjusted Odds Ratio	95%CI, Lower Limit	95%CI, Upper Limit	
Food anaphylaxis	66	1462	252	3481	0.62	0.46	0.83	<.001	3.67	.18	0.54	25.01
Drug anaphylaxis	161	1890	157	3053	1.66	1.31	2.09	<.001	3.94	.16	0.59	26.11
<i>Echinococcus</i> anaphylaxis	3	16	315	4927	2.93	0.54	10.32	.07	6.70	.04	1.12	40.11
Congestive heart failure	14	304	91	4852	2.46	1.28	4.40	.02	1.67	.11	0.89	3.16
Cardiac arrhythmias	53	265	416	4527	2.18	1.56	2.99	<.001	1.60	.007	1.14	2.26
Pulmonary circulation disorders	5	37	313	4906	2.12	0.65	5.45	.11	1.16	.76	0.43	3.12
Other neurologic diseases	11	89	307	4854	1.95	0.93	3.72	.04	1.56	.2	0.80	3.04
Chronic pulmonary disease	112	818	206	4125	2.74	2.13	3.51	<.001	2.57	<.001	2.00	3.32
Obesity	25	247	293	4696	1.62	1.01	2.50	.03	1.24	.36	0.79	1.96
Coagulation disorders	14	38	304	4905	5.94	2.94	11.36	<.001	5.27	<.001	2.69	10.34
Weight loss	2	6	316	4937	5.21	0.51	29.26	.02	7.17	.03	1.29	40.03
Fluid-electrolyte imbalance	24	128	294	4815	3.07	1.87	4.86	<.001	2.25	.001	1.38	3.67
Alcohol abuse	21	129	297	4814	2.64	1.56	4.28	<.001	1.91	.02	1.13	3.23
Drug abuse	8	25	310	4918	5.08	1.96	11.72	<.001	3.48	.005	1.45	8.38
Psychosis	4	22	314	4921	2.85	0.71	8.46	.05	2.27	.15	0.74	6.96
0 to 4 y	3	573										
5 to 9 y	6	281			4	1.01	16.50	.0326	3.34	.09	0.82	13.58
10 to 14 y	3	228			3	0.50	12.57	.2452	2.03	.39	0.40	10.22
15 to 49 y	108	1439			14	4.49	45.78	<.001	10.89	<.001	3.39	35.00
50 to 74 y	152	1836			16	4.98	50.23	<.001	11.42	<.001	3.52	37.00
≥75 y	46	586			15	4.55	49.36	<.001	8.87	<.001	2.63	29.99

Table 3. Crude and Adjusted Analysis of Comorbidities (Logistic Regression) Associated With Vasopressor Drugs in Patients Admitted to Spanish Hospitals With Anaphylaxis

Covariates	Cases		Not Cases		Crude Analysis			Adjusted Analysis			
	Vasopressor Use Yes	Vasopressor Use No	Vasopressor Use Yes	Vasopressor Use No	Crude Odds Ratio	95%CI, Lower Limit	95%CI, Upper Limit	Adjusted Odds Ratio	P	95%CI, Lower Limit	95%CI, Upper Limit
Drug anaphylaxis	33	2018	33	3177	1.57	0.94	2.64	7244.90	.99	0.00	
<i>Echinococcus</i> anaphylaxis	0	19	66	5176	0.00	0.00	15.98	1.00	.63		
Congestive heart failure	3	102	63	5093	2.38	0.47	7.47	1.33	.68	0.35	5.04
Cardiac arrhythmias	9	460	57	4735	1.63	0.70	3.33	1.43	.39	0.64	3.19
Valvular cardiac disease	4	103	62	5092	3.19	0.83	8.83	2.82	.08	0.88	9.02
Chronic pulmonary disease	8	922	58	4273	0.64	0.26	1.35	0.69	.33	0.32	1.47
Rheumatic arthritis/collagen vascular diseases	3	32	63	5163	7.68	1.47	2.55	9.82	.001	2.63	36.72
Fluid-electrolyte imbalance	3	149	63	5046	1.61	0.32	5.02	1.21	.77	0.35	4.14
0 to 4 y	11	565									
5 to 9 y	4	283			0.73	0.23	2.30	0.73	.59	0.23	2.33
10 to 14 y	4	227			0.91	0.29	2.87	0.89	.84	0.27	2.89
15 to 49 y	15	1532			0.50	0.23	1.10	0.40	.04	0.17	0.97
50 to 74 y	19	1969			0.50	0.23	1.05	0.27	.007	0.10	0.70
≥75 years	13	619			1.08	0.48	2.43	0.47	.18	0.16	1.43

Table 4. Crude and Adjusted Analyses of Comorbidities (Logistic Regression) Associated With Admission to the Intensive Care Unit (ICU)

Covariates	Cases		Not Cases		Crude Odds Ratio	Crude Analysis			Adjusted analysis			
	Admitted to ICU	Non Cases Not Admitted to ICU	Cases ICU	Not Admitted to ICU		95%CI, Lower Limit	95%CI, Upper Limit	P	Adjusted Odds Ratio	P	95%CI, Lower Limit	95%CI, Upper Limit
Food anaphylaxis	23	1505	84	3649	0.66	0.40	1.07	.08	0.25	.64	0.00	88.57
Drug anaphylaxis	55	1996	52	3158	1.67	1.12	2.50	.01	0.30	.69	0.00	106.79
<i>Echinococcus</i> anaphylaxis	0	19	107	5135	0.00	0.00	9.75	.53	1.00			
Congestive heart failure	4	101	103	5053	1.94	0.51	5.28	.19	0.86	.8	0.28	2.67
Cardiac arrhythmias	20	449	87	4705	2.41	1.39	4.00	.0003	1.80	.04	1.04	3.12
Pulmonary circulation disorders	4	38	103	5116	5.23	1.33	14.91	.0006	4.85	.008	1.51	1.56
Arterial hypertension	39	1140	68	4014	2.02	1.32	3.06	.0004	2.14	.002	1.32	3.49
Chronic pulmonary disease	25	905	82	4249	1.43	0.87	2.28	.12	1.31	.27	0.81	2.10
Rheumatic arthritis/collagen vascular diseases	3	22	104	5122	4.62	0.89	15.12	.006	3.74	.046	1.02	13.69
Coagulation disorders	6	46	101	5108	6.60	2.25	15.95	<.0001	4.24	.004	1.59	11.32
Fluid-electrolyte imbalance	15	137	92	5017	5.97	3.13	10.70	<.0001	4.39	<.001	2.34	8.24
0 to 4 y	1	575										
5 to 9 y	7	280			14.38	1.73	119.11	.001	13.31	.02	1.61	109.73
10 to 14 y	2	229			5.02	0.45	55.91	.14	4.41	.23	0.39	49.57
15 to 49 y	32	1515			12.11	1.65	89.54	.002	9.91	.03	1.32	74.62
50 to 74 y	49	1939			14.53	1.99	106.00	<.001	8.14	.04	1.06	62.48
≥75 y	16	616			14.94	1.95	114.23	.005	6.43	.08	0.79	52.65

Table 5. Crude and Adjusted Analysis of Comorbidities (Logistic Regression) in Patients With Cardiac Arrest

Covariates	Cases		Not Cases		Cases		Not Cases		Crude Analysis			Adjusted Analysis		
	Cardiac Arrest Yes	Cardiac Arrest No	Cardiac Arrest Yes	Cardiac Arrest No	Cardiac Arrest Yes	Cardiac Arrest No	Crude Odds Ratio	95%CI, Lower Limit	95%CI, Upper Limit	P	Adjusted Odds Ratio	P>z	95%CI, Lower Limit	95%CI, Upper Limit
Food anaphylaxis	19	1509	117	3616	0.39	0.23	0.64	<.001	0.29	.76	0.00	708.74		
Drug anaphylaxis	71	1980	65	1345	0.42	0.18	0.60	.001	0.39	.81	0.00	920.52		
<i>Echinococcus</i> anaphylaxis	0	19	136	5106	0.00	0.00	7.62	.48	1.00					
Congestive heart failure	2	103	134	5022	0.73	0.09	2.75	.66	0.39	.21	0.09	1.68		
Cardiac arrhythmias	28	441	108	4684	2.75	1.73	4.26	<.001	2.35	<.001	1.47	3.75		
Pulmonary circulation disorders	2	40	134	5085	1.90	0.22	7.45	.374	1.24	.78	0.28	5.54		
Other neurologic diseases	6	94	130	5031	2.47	0.87	5.72	.030	2.19	.08	0.90	5.34		
Chronic pulmonary disease	49	881	87	4244	2.71	1.86	3.93	<.001	2.45	<.001	1.68	3.57		
Solid tumor without metastasis	20	220	116	4905	3.84	2.22	6.35	<.001	2.85	.001	1.54	5.28		
Coagulation disorder	3	49	133	5076	2.34	0.46	7.39	.15	1.77	.37	0.51	6.17		
Fluid-electrolyte imbalance	9	143	127	4982	2.47	1.08	4.97	.009	2.07	.06	0.98	4.34		
5 to 9 y	3	284			3.15	0.63	58.97	.08	4.86	.17	0.50	47.13		
10 to 14 y	0	231			0.40			.53	1.00					
15 to 49 y	30	1517			9.09	1.54	83.97	.0023	7.45	.051	0.99	55.97		
50 to 74 y	83	1905			22.56	3.45	18.20	<.001	14.89	.009	1.99	111.37		
≥75 y	19	613			14.84	2.35	13.54	<.001	9.71	.03	1.23	76.85		

Table 6. Crude and Adjusted Analysis of Comorbidities (Logistic Regression) Involved in Deaths

Covariates	Cases		Not Cases		Cases		Not Cases		Crude Analysis				Adjusted Analysis			
	Deaths Yes	Deaths No	Deaths Yes	Deaths No	Deaths Yes	Deaths No	Crude Odds Ratio	95%CI, Lower Limit	95%CI, Upper Limit	P	Adjusted Odds Ratio	P>z	95%CI, Lower Limit	95%CI, Upper Limit		
Food anaphylaxis	13	1515	103	3630			0.30	0.16	0.54	<.001	2.44	.54	0.14	43.59		
Drug anaphylaxis	55	1996	3149	314			1.42	0.97	2.09	.06	3.39	.39	0.21	55.76		
<i>Echinococcus</i> anaphylaxis	2	17	114	5128			5.29	0.59	22.70	.01	12.72	.03	1.22	132.30		
Unknown cause of anaphylaxis	46	1565	70	3580			1.50	1.01	2.22	.03	5.41	.24	0.32	92.53		
Congestive heart failure	6	99	110	5046			2.78	0.97	6.46	.01	1.00	.99	0.38	2.61		
Cardiac arrhythmias	28	441	88	4704			3.39	2.11	5.31	<.001	2.20	.002	1.34	3.61		
Pulmonary circulation disorders	4	38	112	5107			4.80	1.22	13.66	.01	3.29	.048	1.01	10.70		
Other neurologic diseases	12	88	104	5057			6.63	3.20	1.26	<.001	6.01	<.001	2.99	12.06		
Chronic pulmonary disease	26	904	90	4241			1.36	0.84	2.13	.18	1.13	.62	0.70	1.82		
Obesity	1	271	115	4874			0.16	0.00	0.90	.03	0.15	.06	0.02	1.11		
Coagulation disorder	11	41	105	5104			13.04	5.87	2.67	<.001	7.21	<.001	3.22	16.11		
Fluid-electrolyte imbalance	20	132	96	5013			7.91	4.48	13.37	<.001	5.75	<.001	3.21	10.29		
0 to 4 y	1	575														
5 to 9 y	2	285					4.04	0.36	44.84	.22	3.39	.33	0.30	38.64		
10 to 14 y	2	229					5.02	0.45	55.91	.14	3.29	.34	0.28	38.69		
15 to 49 y	21	1526					7.91	1.06	59.15	.02	5.42	.11	0.70	42.01		
50 to 74 y	58	1930					17.28	2.37	125.80	<.001	12.52	.02	1.63	95.88		
≥75 y	32	600					30.67	4.08	230.54	<.001	17.45	.007	2.20	138.54		

Table 7. Crude and Adjusted Analysis of Length of Stay in Patients Admitted Owing to Anaphylaxis^a

Covariate	Length of Stay (Not Adjusted)					Length of Stay (Not Adjusted)							
	Frequency	Mean	Median	IQR	P	Absence of Characteristic Frequency	Mean	Median	IQR	Odds Ratio	P>z	95%CI, Lower Limit	95%CI, Upper Limit
Food anaphylaxis	1528	2.96	2	2	<.001	3733	5.12	3	5	0.71	.43	0.22	2.30
Drug anaphylaxis	2051	5.38	3	5	<.001	3210	3.93	2	3	1.05	.93	0.33	3.35
<i>Echinococcus</i> anaphylaxis	19	13.68	11	17	<.001	5.242	4.46	2	4	11.56	<.001	3.17	4.21
Congestive heart failure	105	8.75	7	9	<.001	5156	4.41	2	4	1.95	.001	1.33	2.85
Cardiac arrhythmias	469	7.26	5	7	<.001	4792	4.22	2	4	1.81	<.001	1.50	2.18
Valvular cardiac disease	107	7.60	6	8	<.001	5154	4.43	2	4	1.49	.04	1.02	2.18
Pulmonary circulation disorders	42	11.07	7.5	8	<.001	5219	4.44	2	4	1.73	.06	0.96	3.10
Peripheral vascular disorders	89	6.56	5	6	<.001	5172	4.46	2	4	1.43	.08	0.96	2.11
Paralysis	45	7.80	4	6	<.001	5216	4.46	2	4	2.15	.004	1.27	3.64
Other neurologic diseases	100	7.59	5	5	<.001	5161	4.43	2	4	2.20	<.001	1.53	3.17
Chronic pulmonary disease	930	5.27	3	4	<.001	4331	4.33	2	4	1.47	<.001	1.28	1.68
Uncomplicated diabetes	453	6.57	4	5	<.001	4808	4.30	2	4	1.19	.07	0.99	1.44
Complicated diabetes	103	8.60	5	7	<.001	5158	4.41	2	4	1.56	.02	1.08	2.26
Renal failure	139	10.71	5	9	<.001	5122	4.32	2	4	1.47	.02	1.06	2.06
Liver disease	103	5.59	4	5	<.001	5158	4.47	2	4	1.43	.053	1.00	2.06
Lymphoma	30	8.87	7	9	<.001	5.231	4.47	2.00	4	3.94	<.001	1.98	7.84
Obesity	272	5.73	4	6	<.001	4989	4.43	2	4	1.76	<.001	1.40	2.21
Coagulation disorder	52	8.44	5.5	10.5	<.001	5209	4.45	2	4	2.09	.01	1.19	3.67
Weight loss	8	10.13	8	12.5	.03	5253	4.48	2	4	5.47	.01	1.43	20.91
Fluid-electrolyte imbalance	152	7.92	4	8	<.001	5109	4.39	2	4	1.70	.0010	1.24	2.32
Blood loss anemia	17	10.06	8	10	<.001	5244	4.47	2	4	3.97	.003	1.60	9.87
Iron deficiency anemia	107	8.29	5	8	<.001	5154	4.41	2	4	2.69	<.001	1.86	3.88
0 to 4 y	576	2.23	1	1	<.001								
5 to 9 y	287	1.86	1	1						0.66	.0140	0.47	0.92
10 to 14 y	231	2.10	1	1						0.67	.0270	0.47	0.96
15 to 49 y	2	3.77	2	3						1.50	.0000	1.20	1.87
50 to 74 y	2	5.68	3	5						2.33	.0000	1.85	29.32
≥75 y	632	6.68	5	7						3.06	.0000	2.33	4.02

^aUnivariate analysis for all items made with a 2-sample Wilcoxon rank-sum (Mann-Whitney) test, except for age, which was analyzed using the Kruskal-Wallis equality-of-populations rank test. The multivariate analysis was performed using ordered logistic regression in which the dependent variable was length of stay quintiles.

Table 8. Summary of the Study Findings^a

Adjusted Covariates	Invasive Mechanical Ventilation			Cardiac Arrest			Death					
	Odds Ratio	95%CI, Lower Limit Upper Limit	Odds Ratio	95%CI, Lower Limit Upper Limit	Odds Ratio	95%CI, Lower Limit Upper Limit	Odds Ratio	95%CI, Lower Limit Upper Limit	Number of Significant OR			
<i>Echinococcus</i> anaphylaxis	6.70	1.12 40.11	1.00			12.72	1.22 132.30		4			
Cardiac arrhythmias	1.60	1.14 2.26	2.35	1.47	3.75	2.20	1.34 3.61		5			
Pulmonary circulation disorders	1.16	0.43 3.12	1.24	0.28	5.54	3.29	1.01 10.70		3.2			
Chronic pulmonary disease	2.57	2.00 3.32	2.45	1.68	3.57	1.13	0.70 1.82		3			
Coagulation disorder	5.27	2.69 10.34	1.77	0.51	6.17	7.21	3.22 16.11		4			
Fluid-electrolyte imbalance	2.25	1.38 3.67	2.07	0.98	4.34	5.75	3.21 10.29		5			
50 to 74 y	11.42	3.52 37.00	14.89	1.99	111.37	12.52	1.63 95.88		5			
>75 y	8.87	2.63 29.99	9.71	1.23	76.85	17.45	2.20 138.54		4			
				Critical Care Area			Vasopressor Drugs			Length of Stay		
	Odds Ratio	95%CI, Lower Limit Upper Limit	Odds Ratio	95%CI, Lower Limit Upper Limit	Odds Ratio	95%CI, Lower Limit Upper Limit	Odds Ratio	95%CI, Lower Limit Upper Limit	Odds Ratio	95%CI, Lower Limit Upper Limit	Number of Significant OR	
<i>Echinococcus</i> anaphylaxis	1.00		1.00		11.56		3.17 4.21		5			
Cardiac arrhythmias	1.80	1.04 3.12	1.43	0.64	1.81	3.19	1.50 2.18		3.2			
Pulmonary circulation disorders	4.85	1.51 15.6	1.00		1.73		0.96 3.10		3			
Chronic pulmonary disease	1.31	0.81 2.10	0.69	0.32	1.47	1.47	1.28 1.68		4			
Coagulation disorder	4.24	1.59 11.32	2.25	0.48	2.09	10.51	1.19 3.67		5			
Fluid-electrolyte imbalance	4.39	2.34 8.24	1.21	0.35	1.70	4.14	1.24 2.32		5			
50 to 74 y	8.14	1.06 62.48	0.27	0.10	2.33	0.70	1.85 29.32		4			
>75 y	6.43	0.79 52.65	0.47	0.16	3.06	1.43	2.33 4.02		4			

^aThe table shows the most frequent risk factors for severity of anaphylaxis crossed with the outcomes of the study.

Table 9. Percentage of Different Illnesses Included in the Most Relevant Groups of Diseases of the Elixhauser Score in Our Study. Only Individual Illnesses With Higher Percentages Are Shown

Arrhythmias	No.	%	Chronic Cardiac Failure	No.	%	Chronic Pulmonary Diseases	No.	%	Pulmonary Circulation Disorders	No.	%	Coagulation Disorders	No.	%	Fluid-Electrolyte Imbalance	No.	%
Chronic cardiac failure	45	9.59%	Arrhythmias	45	42.86%	Asthma	396	42.58%	Unspecified Other chronic cardiopulmonary disease	9	21.43%	Other congenital coagulation disorders	2	3.85%	Hyperosmolality and hyponatremia	4	2.63%
Left bundle branch hemiblock	13	2.77%	Chronic cardio-pulmonary disease with pulmonary hypertension	6	5.71%	Chronic obstructive pulmonary disease	211	22.69%	Other cardiopulmonary disease	9	21.43%	Defibrination syndrome	9	17.31%	Hypo-osmolality and hyponatremia	13	8.55%
Other left bundle branch block	21	4.48%	Cardio-myopathy	8	7.62%	Chronic respiratory failure	17	1.83%	Chronic cardio-pulmonary disease with hypertension	33	78.57%	Acquired deficit of coagulation factors	3	5.77%	Acidosis	88	57.89%
Right bundle branch block	43	9.17%	Ischemic heart disease	22	20.95%	Chronic and acute respiratory failure	12	1.29%	Other unspecified	13	25.00%	Mixed acid-based disorder	5	3.29%			
Other heart block	87	18.55%	Atrial fibrillation	36	14.29%							Other qualitative platelet disorders	2	3.85%	Hyperkalemia	9	5.92%
Ventricular fibrillation	12	2.56%	Any cardiac block	3	14.29%							Allergic purpura	5	9.62%	Hypokalemia	36	23.68%
Atrial flutter	16	3.41%										Unspecified thrombocytopenia	4	7.69%	Other hyper or hypo-osmolar disorders	5	3.29%
Atrial fibrillation	252	53.73%															
Rhythm disorder (coronary sinus ectopic nodal), or wandering pacemaker	68	14.50%															
Placement of pacemaker	40	8.53%															

Results

Based on the aforementioned criteria for the study period (1997 to 2011), we identified 5261 admissions in which the principal diagnosis was anaphylaxis. Of these, 53.75% involved males, with a median (IQR) age of 49 years (43 years).

Tables 2 to 7 show the crude and adjusted analyses. In general, patients with a specific characteristic (eg, use of invasive mechanical ventilation, vasopressor drugs) tended to have more comorbidities (cardiovascular, respiratory, and other diseases) in the corresponding crude analysis.

In the analysis of therapeutic management as proxies of a severe episode of anaphylaxis, admission to the intensive care unit and need for invasive mechanical ventilation (Tables 2 and 4) were more frequent in patients aged >15 years. Vasopressor drugs (Table 3) were used less frequently by patients aged 15 to 74 years. However, higher comorbidity was observed mainly in patients who needed mechanical ventilation. These patients more frequently had arrhythmias, chronic respiratory disease, coagulation disorders, weight loss and fluid-electrolyte imbalance. Invasive mechanical ventilation was more likely in *Echinococcus* anaphylaxis (Table 2). In patients admitted to the intensive care unit (Table 4), the most likely conditions were arrhythmias, arterial hypertension, pulmonary circulation disorders, coagulation disorders, and fluid-electrolyte imbalance. The C-statistic for the 3 items was 0.70 to 0.73, with good calibration for the 3 items ($P=.59$ for mechanical ventilation, $P=.45$ for admission to the intensive care unit, and $P=.34$ for use of vasopressor drugs).

Associated conditions were less common in the case of cardiac arrest and death due to anaphylaxis (Tables 5 and 6). Arrhythmias and age older than 50 years were common risk factors for cardiac arrest or death. In the case of cardiac arrest, other associated risk factors included chronic pulmonary diseases and age 15 to 49 years (Table 5). On the other hand, pulmonary circulatory disorders, coagulation disorders, and fluid-electrolyte imbalance were associated with a higher risk of death from anaphylaxis (Table 6). Likewise, the risk of death from *Echinococcus* anaphylaxis was higher than the risk of death from the remaining causes of anaphylaxis. For both outcomes, the C-statistic was higher than the remaining outcomes in this study (cardiac arrest, 0.77 [95% CI, 0.75-0.77]; death, 0.82 [95% CI, 0.80-0.83]). Good calibration was noted for cardiac arrest ($P=.59$), but not for death ($P=.03$).

Finally, we found that many comorbidities were associated with longer stay, namely, heart diseases (including congestive heart failure) and pulmonary disorders (chronic pulmonary diseases, pulmonary circulation disorders [in this case the difference was almost significant]) (Table 7). Finally, patients with anaphylaxis due to *Echinococcus* had longer stays than all other patients admitted with anaphylaxis.

Table 8 summarizes the odds ratios of the main risk factors for severity of anaphylaxis crossed with the outcomes of the study.

Sensitivity Study

We found that discrimination was almost always better in patients aged <18 years than in older patients and in the total

group, except for length of stay, where the discrimination of the model was better for the whole group (data not shown).

Study of Comorbidities Other Than Respiratory and Cardiovascular Diseases

In the adjusted logistic regression models, the Elixhauser score modified by van Walraven [15] increased severity of anaphylaxis, as ascertained using the outcomes investigated in this study (mechanical ventilation, OR, 1.02 [95%CI, 0.99-1.05]; cardiac arrest, OR, 1.07 [95%CI, 1.03-1.15]; death, OR, 1.10 [95%CI, 1.06-1.14]; admission to the intensive care unit, OR, 1.06 [95%CI, 1.02-1.10]; vasopressor drugs, OR, 1.06 [95%CI, 1.00-1.03]; and length of stay [quintiles] OR, 1.02 [95%CI, 1.00-1.05]).

Frequency of Illnesses From the Code Groups That Are Commonly Considered Risk Factors for Severe Anaphylaxis

Finally, in the group of comorbidities with a ≥ 3 -fold greater statistical significance in the logistic regression models (arrhythmias, fluid-electrolyte imbalance, coagulation disorders, chronic pulmonary diseases, and pulmonary circulation disorders [in which the difference in length of stay was almost statistically significant]), we assessed the frequency of the various diseases belonging to each of the groups. The results are shown in Table 9.

In the case of arrhythmias, 9.6% of patients had chronic heart failure. In the case of chronic heart failure, 42.8% of patients had arrhythmias. Arrhythmias and congestive heart failure had different distributions ($P<.001$).

When we analyzed asthma and chronic obstructive pulmonary disease (COPD) after adjustment for age, gender, and the remaining diseases in the Elixhauser score, we found that both were associated with invasive mechanical ventilation (asthma, OR, 2.23; 95%CI, 1.55-3.22; COPD, OR, 1.58; 95%CI, 1.13-2.19), whereas only COPD was associated with cardiac arrest (OR, 2.00; 95%CI, 1.26-3.19), and longer stay (quintiles) (OR, 1.33; 95%CI, 1.11-1.59).

Correlation Between Outcomes

We analyzed correlations between the dependent variables. Factor analysis revealed 3 components that accounted for 20% of variance. Almost all variables were involved in the first component, except the use of vasopressor drugs. This component can be interpreted as the component related to severity of anaphylaxis. The second component was length of stay, and the third component use of vasopressor drugs by patients with less severe conditions.

Discussion

Based on the registry of patients admitted to the Spanish Hospital System between 1997 and 2011 and various indicators of severe anaphylaxis, we found that a higher risk of severe anaphylaxis was associated (≥ 3 logistic regressions) with age >50 years, history of cardiac arrhythmia, coagulation disorders, fluid-electrolyte imbalance, chronic pulmonary

disease, anaphylaxis caused by *Echinococcus*, and pulmonary circulation disorders (in this case the difference in length of stay was almost statistically significant).

We chose the illnesses listed in the Elixhauser score [11] to create a comprehensive list of diseases that would enable us to assess whether comorbidities other than cardiac and respiratory diseases increased the severity of anaphylaxis. In our study, comorbidity was defined according to Elixhauser et al [11] "as a clinical condition that exists before a patient's admission to the hospital and is not related to the main reason for the hospitalization". For these authors, the first part of this definition is very difficult to confirm using clinical-administrative data, although the second part can be readily confirmed using administrative data.

The Elixhauser Score was validated in patients aged >18 years. However, in our study, almost 21% of admissions due to anaphylaxis involved patients aged <14 years. Although the Elixhauser score has also been used in the pediatric population [19,20], we performed a sensitivity analysis to ascertain the behavior of the logistic regression models of the different outcomes analyzed in patients older and younger than 18 years. Using the C statistic, we found that discrimination was better in patients aged <18 years than in patients aged >18 years and in the total group, except for length of stay.

For each group of diseases, when the probability of a specific outcome was high, the individual diseases were analyzed with the objective of determining whether the patient was more likely to have the comorbid condition before the episode of anaphylaxis or whether the comorbid condition developed during admission.

Cardiovascular diseases have traditionally been associated with a poorer clinical course of anaphylaxis. The presence of mast cells in the heart and the release of cardiotoxic mediators such as histamine, LTC₄, and platelet-activating factor [21], as well as the increase in mast cell counts in the coronary vessels of patients with ischemic heart disease, can render the heart incapable of overcoming the systemic and cardiac effects of anaphylaxis. In addition, the widespread concomitant use of β -blockers and ACE inhibitors in cardiovascular diseases [22,23] has been considered to cause more severe anaphylaxis in patients with heart disease [24]. Our literature review [5,6,24,25] revealed that several markers can be used to assess the severity of anaphylaxis and that not all markers of cardiovascular disease are associated with all severity markers.

The relationship between anaphylaxis and ischemic heart disease has been studied in depth [27]. However, based on our data, a logistic regression model adjusted for other cardiac comorbidities (cardiovascular diseases, diabetes, and respiratory, liver, and kidney diseases) showed that ischemic heart disease did not increase the probability of more severe anaphylaxis, using all the outcomes of our study as proxies of severity (data not shown). In addition, we found 12 cases of Prinzmetal angina or coronary vasospasm among all cases of anaphylaxis. These cases can be considered possible cases of Kounis syndrome. All cases had an associated diagnosis of ischemic heart disease, chronic heart failure, or arrhythmias. No patients died. One patient experienced cardiac arrest, and two-thirds were in the fourth and fifth quintiles for length of stay.

Arrhythmias were a significant variable in all of the severity outcomes analyzed, except for use of vasopressor drugs. Arrhythmias are associated with a worse course of anaphylaxis owing to mechanisms other than those involved in congestive heart failure, since the distribution of both variables differed. The appearance of heart block and arrhythmias may be related to myocardial hypoxia during anaphylaxis [24,26] or local secretion of noradrenaline from sympathetic nerve endings resulting from secretion of renin from mast cells and activation of the renin-angiotensin system [21]. The evidence presented above suggests that arrhythmias follow the onset of anaphylaxis.

We also found that chronic cardiopulmonary disorders with pulmonary hypertension were present in most of the 90% of cases of pulmonary circulation disorder, which in the adjusted multivariate analysis generated higher percentages of deaths, admissions to the intensive care unit, and longer hospital stays (in this case almost significant). The long progress of chronic pulmonary disease to pulmonary hypertension enables us to state that chronic cardiopulmonary disorders are previous to anaphylaxis episodes.

In our adjusted analysis, presence of asthma was associated with mechanical ventilation. COPD and all chronic pulmonary diseases were associated with invasive mechanical ventilation and an increased risk of cardiac arrest. Brown [5] observed that pre-existing lung disease was associated with an increased risk of hypoxia. In the study of Mulla and Simons [9], which was based on coded records of anaphylaxis admissions, an association was found between COPD and invasive mechanical ventilation and long hospital stay, between interstitial respiratory illnesses and invasive mechanical ventilation and death during admission, and between asthma and invasive mechanical ventilation.

Coagulation disorders and fluid-electrolyte imbalance also increased the severity of anaphylaxis episodes and were likely triggered by anaphylaxis episodes. The association between fluid-electrolyte imbalance and poorer prognosis is probably due to the severity of the anaphylaxis episode, since acidosis accounts for almost 60% of this item in the *ICD-9-CM*.

Individual coagulation disorders were very heterogeneous, and the only conditions with a notable percentage of cases were defibrination syndrome (17%), which includes disseminated intravascular coagulation, and other unspecific coagulation disorders (25%). Several studies have shown activation of clotting and clot lysis during severe anaphylaxis. The results of a murine study strongly suggest that disseminated intravascular coagulation occurs in systemic anaphylaxis and that platelet-activating factor is the main mediator responsible for the phenomenon [27]. Histamine induces tissue factor expression in human endothelial cells and vascular smooth muscle cells [28], leading to formation of thrombin. In 1980, Smith et al [29] reported that, of 3 patients experiencing anaphylactic shock during controlled hymenoptera challenges, 2 had decreased levels of factors V and VIII, fibrinogen, and high-molecular-weight kininogen [29].

In their study based on 2 databases covering a population with employer-sponsored health insurance and individuals aged ≥ 65 years, Clark et al [6] found that patients with more severe anaphylaxis (leading to admission) had a higher

Charlson-Deyo score (modified Charlson comorbidity index) [30,31], a higher number of laboratory/radiology tests performed during the year before admission, or a visit to the emergency department or admission (any cause) during the previous year. Both these findings and ours suggest that more severe anaphylaxis episodes were associated with more severe previous comorbidity.

Markers of severity of anaphylaxis tended to be more frequent in older patients (≥ 50 years). Consequently, the severity of anaphylaxis in older and elderly patients is due not only to the more marked presence of cardiorespiratory diseases or more frequent comorbidity, but also to other age-related factors. Several authors have also reported that older age is an independent risk factor that increases severity of anaphylaxis in their adjusted models [4-7]. One possible explanation for age as an independent risk factor is that the effects of comorbid conditions are more marked in older patients. However, in our study, the interaction between age and respiratory and cardiovascular diseases was not statistically significant (data not shown).

Except for *Echinococcus* anaphylaxis, our adjusted multivariate analysis did not reveal a major cause of anaphylaxis (eg, food, drugs) that had a higher risk of being associated with a worse course of anaphylaxis. Severe or recurrent anaphylaxis due to *Echinococcus* can occur if fluid from a cyst is released into a host who has developed IgE from a previous leakage [32,33]. Anaphylaxis complicates 10% of all intraperitoneal ruptures of cysts [34] and is responsible for 20% of sudden deaths occurring in echinococcosis [32,33]. In our literature review, we were unable to find an explanation for the severity of anaphylaxis in these patients. We can speculate that the sudden and marked presence of *Echinococcus* antigens in the body increases the severity of anaphylaxis, in much the same way as an intravenous medication does in drug anaphylaxis [35]. It is also possible that other mechanisms of death, such as shock secondary to a severe inflammatory response on peritoneal surfaces, can also play a role in increased severity of anaphylaxis.

It is important to ask whether our findings among hospitalized patients can be extrapolated to the general population. In the strictest sense, we can only state that among patients admitted to hospital, older patients seem to experience more severe anaphylaxis, a finding that has been reported in other studies of mortality and severity of anaphylaxis in various clinical settings (not only in patients admitted to hospital).

In extremely severe cases (fatal cases), the risk factors associated with fatal anaphylaxis include upright posture, uncontrolled asthma, tree nuts, male sex, drug anaphylaxis, African-American ethnicity, and, mainly, older age likely combined with multiple comorbidities [36,37]. In older patients, this risk has traditionally been explained as a reduced capacity to tolerate the effects of hypoxia, hypotension, and arrhythmia. In our study, age older than 50 years, *Echinococcus* anaphylaxis, and pulmonary circulatory disorders may have contributed to fatal anaphylaxis, whereas arrhythmias, coagulation disorders, and fluid-electrolyte imbalance were probably complications of anaphylaxis that led to death.

In addition to the limitations of secondary clinical-administrative data based on the *ICD-9-CM* coding used in

epidemiologic studies of anaphylaxis (intermediate positive predictive value and low internal validity) [38] and the limitations of the Elixhauser score (underrecording of relevant items, accuracy of secondary diagnosis, coding errors, and potential financial pressure to capture better remunerated comorbidities) [11], the large number of outcomes used to identify the most severe episodes reported makes it difficult to compare our findings with those from other studies. On the other hand, patients with anaphylaxis managed in the intensive care unit in the database used in this study did not represent all the patients who were attended in this setting during the study period, but only the patients who were discharged from the intensive care unit. Significant results from the smallest age groups related to some of the outcomes (length of stay, use of vasopressor drugs) may be inconsistent given the lower number of patients who had or experienced these outcomes in these age groups.

We provide a comprehensive assessment of the main chronic diseases that can aggravate an anaphylaxis episode. Our findings suggest that respiratory and cardiovascular diseases, other comorbidities, and older age can increase the severity of anaphylaxis episodes. Finally, the severity of anaphylaxis may be associated with the severity of a previous illness.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentations

Risk factors associated with cardiac arrest and death in hospitalized patients due to anaphylaxis during the period 1998-2011. EAACI Congress 2016, Vienna, Austria, June 11-15, 2016.

Severity of anaphylaxis is associated to higher comorbidity. Analysis of hospitalized patients in Spain during 1998-2011. EAACI Congress 2016, Vienna, Austria, June 11-15, 2016.

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