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Original article

Unraveling determinants of severe anaphylaxis — A cluster analysis from a large national hospitalization database

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ABSTRACT

Background: Understanding potential risk factors and phenotypes at-risk of anaphylaxis can tailor public health actions to prevent avoidable deaths. Therefore, our aim was to explore patterns of hospital admissions diagnosed with anaphylaxis in France from 2012 to 2021, across different age groups, using the national French hospital database and to evaluate potential determinants to propose phenotypes at-risk, with a particular view to severe cases.**Methods:** This is a descriptive study, using data from the French Program for the Medicalization of Information Systems, from 2012 to 2021. We included all patients hospitalized for anaphylaxis using International Classification of Diseases (ICD)-10 codes listed as a primary diagnosis. Potential risk factors were selected according to corresponding ICD codes, available as secondary data of hospitalization. Severe anaphylaxis (SA) was defined based on the need of admissions in intensive care units. To explore the patterns and characteristics, we employed cluster analysis using the clustering large applications algorithm. Charlson comorbidity index (CCI) was used to evaluate comorbidities.**Results:** During the 9-year study period, 78,453 patients had 86,654 admissions due to anaphylaxis for all-causes. Most of the cases were non-severe anaphylaxis (93.7%), 5.9% were SA, and 0.4% evolved to fatal anaphylaxis (FA). Rate of admissions for SA was 0.08/100,000/year. Seasonal trend of cases of anaphylaxis due to Hymenoptera venoms were shown. Increased severity and risk of death were significantly higher in the elderly. Food-induced anaphylaxis is more frequent in childhood, but SA occurred at adolescence and early adulthood. The CCI was higher in SA and FA. By applying the clustering algorithm CLARA, we identified 3 clusters distributed according to the severity.**Conclusion:** More than providing a snap shot of potential risk factors for anaphylaxis in France, we were able to suggest phenotypes of anaphylaxis of different severities and to propose actions based on our findings. Although further research is needed in the field, we strongly believe that the data presented may contribute to public health advancements to ensure quality of care of patients suffering from anaphylaxis.

1. Background

Anaphylaxis is a non-communicable severe, life-threatening systemic hypersensitivity reaction, which requires prompt recognition and

treatment [1,2]. Understanding potential risk factors and phenotypes at-risk can tailor public health actions to prevent avoidable deaths.

Data suggests that although the number of hospital admissions for anaphylaxis via the emergency or intensive care units is increasing in

Abbreviations: AM, anaphylaxis mortality; CCI, Charlson comorbidity index; CLARA, clustering large applications; FA, fatal anaphylaxis; ICD, International Classification of Diseases; INSEE, French National Institute of Statistics and Economic Studies; NSA, non-severe anaphylaxis; SA, severe anaphylaxis; PMSI, Program for the Medicalization of Information Systems.

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many countries, anaphylaxis deaths remain rare [3]. However, descriptive data on anaphylaxis deaths are sparse and do not shed any light on the risk factors for severe allergic reactions. Anaphylaxis mortality (AM) has been estimated at less than 1 per million per year in the populations from the United States and the United Kingdom. [3–5]. In these countries, the AM remained stable during the last decade. In contrast, the incidence of AM increased in Australia from 1997 to 2013 [6].

While the frequency of hospital admissions for anaphylaxis appears to be increasing in many countries, these numbers can vary by geographical region due to differences in diagnostic criteria, classification methods, and the use of ICD codes for identifying anaphylaxis [7,8]. As a result, obtaining a comprehensive overview of anaphylaxis trends and potential risk factors is challenging. Utilizing national hospital admission data can help to ensure data consistency.

In France, all hospitalization data, in both public and private sectors, are systematically collected by the national program for the medicalization of information systems (PMSI) and codified with the International Classification of Diseases (ICD) [9–11]. But there is no study in France to explore hospital admissions related to anaphylaxis in the view of understanding its determinants. Therefore, our aim was to explore patterns of hospital admissions diagnosed with anaphylaxis in France from 2012 to 2021, across different age groups, using the PMSI database and to evaluate potential determinants to propose phenotypes at-risk, with a particular attention to severe anaphylaxis (SA).

2. Methods

2.1. Type of study, data source and collection

This is a descriptive study that used routinely reported data to the French PMSI during the period of 2012 to 2021. The PMSI system is electronic, stores information on hospital admissions that occur in the public and private health systems, is mandatory and thus accounts for 100% of hospitalizations in metropolitan France [10]. No personal identification is available in this database. Information available is coded based on the ICD-10 and covers main cause of hospitalization (primary cause).

From all 4,021,488 records collected during this period, we identified all consecutive patients hospitalized with anaphylaxis using the anaphylaxis-related ICD-10 codes listed as primary diagnosis (T78, T78.0, T78.2, T78-3, T80.5, T88.2, T88.6). Secondary data was used to evaluate comorbidities (Table S1).

The population of this study has been distributed in three groups: (i) non-severe anaphylaxis (NSA) for mild and moderate cases, (ii) SA for cases admitted critical care units, and (iii) fatal anaphylaxis (FA) for cases in which death was the outcome of the admission. In this last case, we did not consider cases of fatalities which occurred outside the health care settings and later addressed to emergency departments for death certification (Tables 1 and 2). SA cases were defined as cases needing admissions in intensive care units. Further analysis has been performed according to the main anaphylaxis triggers (Table 3).

2.2. Statistical analysis

All statistical analysis was performed using R version 4.3.0.

Descriptive analysis included annual anaphylaxis hospital admission and mortality rates per 100,000 population and 95% confidence intervals calculated for each year. Population estimates were obtained from the French national institute of statistics and economic studies (INSEE) [9]. Age-standardized rates for hospital admissions were calculated by standardizing to the age distribution of the population in mid-2010, the year of the last census. The relationship between categorical variables and severity was tested using Pearson's Chi squared tests and included data on gender, age, possible aetiology to both severe, non-severe cases and deaths due to anaphylaxis (Table 1). Poisson regressions were run to

model each type of anaphylaxis events according to the age tacking into account temporal tendency. Generalized additive model for Poisson-distributed data to predict the number of hospitalizations was applied to understand seasonal distribution, taking into account various predictor variables, including the monthly variation, etiology, age, sex and year. Charlson comorbidity index (CCI) was also used to evaluate comorbidities. The CCI was developed in 1987 by Charlson and colleagues to classify comorbid conditions which may influence mortality risk. The Charlson comorbidity index (CCI) is the most widely used comorbidity index used to determine survival rate (1 yr and 10 yr) in patient with multiple comorbidities [12].

The rate of hospitalization demonstrated in Figs. 2 and 3 is referred to the proportion of number of hospitalizations of each age group per severity and aetiology.

Data related to potential risk factors were evaluated according to the triggers (Table 2) and severity still using Poisson regression model. P-values of <0.05 were considered significant. Cluster analysis was conducted using the clustering large applications CLARA algorithm computed in R and to ensure compatibility with the Jaccard distance measure in the CLARA algorithm, all multinomial variables were transformed into a binary format. For the cluster analysis, single cases of anaphylaxis have been considered, regardless of recurrences. Pearson's Chi-squared test was employed to compare significant differences between variables within three clusters [13,14]. Chi square tests were performed for two qualitative variables. Kruskal–Wallis rank sum tests were utilized for quantitative variables and qualitative variables with more than two categories. The Wilson method was employed to calculate confidence interval. To assess the impact of year and month exposure on the number of global cases for each type of etiology and within each severity group, we employed different models bases on observed trends and seasonality in the data (Figs. 1–3): Generalized linear models (GLM) with Poisson distribution was used to evaluate the yearly trends. The incidence rate ratio (IRR) was calculated to determine the significance of year's effect on the total cases of anaphylaxis and specific triggers. The goodness of fit of these models was assessed using the Pseudo R-squared value, where a value greater than 75% indicates a strong fit. Generalized Additive Models (GAM) with a Poisson distribution were employed to assess the monthly trends. These models are adjusted for sex, age groups. Adjusted R-square were used to evaluate the goodness of fit. After analysing the trends and seasonality, we employed an unsupervised learning algorithm to unveil concealed patterns or groupings within the dataset. Given the substantial size our dataset, which comprised 86,654 rows, employing conventional clustering algorithms directly proved impractical. Consequently, we opted for the CLARA algorithm, introduced by Kaufman and Rousseeuw in 1990 [14–16], is an effective alternative. Our approach began by randomly selecting 50 samples, each containing 10,000 observations from the initial dataset of 86,654 observed events. The samples may contain repeated observations due to the random selection with replacement. For each sample, the CLARA algorithm was applied the Partitioning Around Medoids algorithm to determine the optimal medoids. We aimed to create three clusters within each sample corresponding to 3 severity levels (non-severe, severe, and death). To assess the similarity between observations, we employed the Jaccard similarity coefficient, a widely used metric for binary variables. To accommodate this metric, all multinomial variables including age group, aetiology, and severity were transformed into binary format. Subsequently, the best sample with the lowest dissimilarity cost was chosen. The medoids identified from the best sample, comprising 10,000 observations, were then used to create 3 clusters in the original dataset. To further analyse these clusters, we conducted Pearson's Chi-squared test to compare various attributes within each exposure category. These attributes encompassed sex, transformed age group, transformed aetiology, allergic comorbidities, non-allergic comorbidities, and transformed severity levels. Lastly, we employed a radar graph to visually represent the three clusters. This graph exclusively included variables

Table 1

Demographic data of cases of anaphylaxis, distribute as non-severe, severe and deaths, data from the French Program for the Medicalization of Information Systems (PMSI), 2012–2021.

Characteristic	Non-severe N = 81,191	95% CI	Severe N = 5076	95% CI	Death N = 387	95% CI	Overall N = 86,654	95% CI	P value
Sex									0.10
Male	41,394 (51%)	50.6%, 51.3%	2651 (52%)	50.8%, 53.6%	210 (54%)	49.2%, 59.3%	44,255 (51%)	50.7%, 51.4%	
Female	39,797 (49%)	48.7%, 49.4%	2425 (48%)	46.4%, 49.2%	177 (46%)	40.7%, 50.8%	42,399 (49%)	48.6%, 49.3%	
Mean age (years)	44	44.10, 44.43	53	52.01, 53.08	66	64.86, 68.07	45		<0.001
Age group									<0.001
0–4	5085 (6.3%)	6.10%, 6.43%	48 (0.9%)	0.71%, 1.26%	2 (0.5%)	0.09%, 2.06%	5135 (5.9%)	5.77%, 6.09%	
5–9	3716 (4.6%)	4.43%, 4.72%	29 (0.6%)	0.39%, 0.83%	0 (0%)	0%, 1.23%	3745 (4.3%)	4.19%, 4.46%	
10–14	5196 (6.4%)	6.23%, 6.57%	95 (1.9%)	1.52%, 2.29%	2 (0.5%)	0.09%, 2.06%	5293 (6.1%)	5.95%, 6.27%	
15–19	3533 (4.4%)	4.21%, 4.49%	157 (3.1%)	2.64%, 3.62%	1 (0.3%)	0.01%, 1.66%	3691 (4.3%)	4.13%, 4.40%	
20–29	6878 (8.5%)	8.28%, 8.67%	453 (8.9%)	8.16%, 9.75%	5 (1.3%)	0.48%, 3.17%	7336 (8.5%)	8.28%, 8.65%	
30–39	8082 (10.0%)	9.75%, 10.2%	488 (9.6%)	8.82%, 10.5%	6 (1.6%)	0.63%, 3.51%	8576 (9.9%)	9.70%, 10.1%	
40–49	10,494 (13%)	12.7%, 13.2%	706 (14%)	13.0%, 14.9%	30 (7.8%)	5.38%, 11.0%	11,230 (13.2%)	12.7%, 13.2%	
50–59	12,792 (16%)	15.5%, 16.0%	1039 (20%)	19.4%, 21.6%	72 (19%)	14.9%, 22.9%	13,903 (16%)	15.8%, 16.3%	
60–69	12,670 (16%)	15.4%, 15.9%	1061 (21%)	19.8%, 22.1%	105 (27%)	22.8%, 31.9%	13,836 (16%)	15.7%, 16.2%	
70–79	7858 (9.7%)	9.48%, 9.88%	675 (13%)	12.4%, 14.3%	77 (20%)	16.1%, 24.3%	8610 (9.9%)	9.74%, 10.1%	
>80	4887 (6.0%)	5.86%, 6.19%	325 (6.4%)	5.75%, 7.12%	87 (22%)	18.5%, 27.0%	5299 (6.1%)	5.96%, 6.28%	
Etiology									<0.001
Drug	18,969 (23%)	23.1%, 23.7%	2,276 (45%)	43.5%, 46.2%	218 (56%)	51.2%, 61.3%	21,463 (25%)	24.5%, 25.1%	
Food	8548 (11%)	10.3%, 10.7%	504 (9.9%)	9.13%, 10.8%	5 (1.3%)	0.48%, 3.17%	9057 (10%)	10.2%, 10.7%	
Insect	4659 (5.7%)	5.58%, 5.90%	368 (7.2%)	6.56%, 8.01%	30 (7.8%)	5.38%, 11.0%	5057 (5.8%)	5.68%, 5.99%	
Unspecified	49,015 (60%)	60.0%, 60.7%	1,928 (38%)	36.6%, 39.3%	134 (35%)	29.9%, 39.6%	51,077 (59%)	58.6%, 59.3%	
Number of hospitalization (recurrences)									<0.001
1	73,528 (91%)	90.4%, 90.8%	4549 (90%)	88.7%, 90.4%	376 (97%)	94.8%, 98.5%	78,453 (91%)	90.3%, 90.7%	
2	5237 (6.5%)	6.28%, 6.62%	377 (7.4%)	6.73%, 8.19%	11 (2.8%)	1.5%, 5.18%	5625 (6.5%)	6.33%, 6.66%	
>2	2426 (3%)	2.87%, 3.11%	150 (3%)	2.51%, 3.47%	0 (0%)	0%, 1.23%	2576 (3%)	2.86%, 3.09%	
Mean duration of hospitalization (day)	1.21	1.19, 1.23	3.25	3.06, 3.45	7.54	5.91, 9.16	1.36		<0.001
Mean cost of hospitalization (Euro)	840	830.23, 849.08	2,772	2638.02, 2906.53	8308	6949.93, 9666.49	986		<0.001

CI: confidence interval (Wilson method).

Pearson's Chi-squared test; Kruskal–Wallis rank sum test.

that exhibited statistically significant differences between the three clusters (Table 2, Fig. 4).

3. Results

3.1. Anaphylaxis admissions rates and trends

During a 9-year study period, 78,453 patients who had 86,654 admissions due to anaphylaxis for all-causes, with a mean number of 1.09 hospitalization per patient ($P < 0.002$ 95%CI [1.08, 1.1]). Triggers were split into iatrogenic/drugs, food, insect and unspecified anaphylaxis. The average hospitalization rate related to anaphylaxis for 9 years was 0.31 per 100,000 population per year, and the rate of admissions for severe

anaphylaxis during the same period was 0.08 per 100,000 population per year.

From overall cases, 81,191 were NSA (93.7%), 5,076 were SA (5.9%), and 387 FA (0.4%). The mean period of hospitalization to NSA cases was 1.2 days ($P < 0.001$, 95%CI [1.19, 1.23]). SA (3.25) counted with 3 folds days of hospitalization higher than NSA (1.21) ($P < 0.001$, 95%CI [3.0–3.45]), and FA (7.54) 7 folds higher than NSA (1.21) ($P < 0.001$, 95%CI [5.9–9.1]), impacting the costs of care of SA (mean cost: 2772 euros/patient) and FA cases (mean cost 8308 euros/patient) (Table 1). SA cases had 1.1 fold higher chance of new hospitalization when compared to NSA, 7.4% and 6.5% respectively ($P < 0.001$), mostly related to unspecified anaphylaxis 1.39 fold ($P < 0.001$). Others were not significant. There was a significant proportion of recurrences for anaphylaxis for all causes.

Table 2
Demographic data, severity and comorbidities of drug, food, insect and unspecified-induced anaphylaxis, data from the French Program for the Medicalization of Information Systems (PMSI), 2012–2021.

Characteristic	Drug				Food				Insect				Unspecified				Total			
	N	Non severe (95% CI)	Severe (95% CI)	Death (95% CI)	P value	N	Non severe (95% CI)	Severe (95% CI)	Death (95% CI)	P value	N	Non severe (95% CI)	Severe (95% CI)	Death (95% CI)	P value	N		Non severe (95% CI)	Severe (95% CI)	Death (95% CI)
Sex	21,463				<0.001	9,057				<0.001	5,057				0.4	51,077				0.062
Male		8573 (45%)	1107 (49%)	115 (53%)			4902 (57%)	260 (52%)	0 (0%)			3287 (71%)	271 (74%)	20 (67%)			24,632 (50%)	1013 (50.3%)	75 (56%)	
		(44.5%, 45.9%)	(46.6%, 50.7%)	(45.9%, 59.5%)			(56.3%, 58.4%)	(47.1%, 56.0%)	(0%, 53.7%)			(60.2%, 71.9%)	(68.8%, 78.0%)	(47.1%, 82.1%)			(49.8%, 50.7%)	(50.3%, 54.8%)	(64.4%, 64.4%)	
Female		10,396 (55%)	1169 (47%)	103 (47%)			3646 (43%)	244 (48%)	5 (2%)			1372 (29%)	97 (26%)	10 (33%)			24,383 (50%)	915 (47%)	59 (44%)	
		(54.1%, 55.5%)	(49.3%, 53.4%)	(40.5%, 54.1%)			(41.6%, 43.7%)	(44.0%, 52.9%)	(46.3%, 100.0%)			(28.1%, 30.8%)	(22.0%, 31.2%)	(17.9%, 52.9%)			(45.2%, 49.7%)	(45.2%, 49.7%)	(35.6%, 52.9%)	
Age	21,463	54 (53.80, 54.37)	57 (55.86, 57.28)	67 (64.76, 68.84)	<0.001	9,057	21 (20.15, 21.04)	32 (35.00, 38.78)	47 (18.47, 74.73)	<0.001	5,057	51 (50.63, 51.72)	55 (53.30, 56.56)	63 (58.13, 68.74)	<0.001	51,077	44 (43.72, 44.15)	51 (50.56, 52.29)	67 (64.44, 70.23)	<0.001
Age group	21,463					9,057					5,057					51,077				
0–4		239 (1.3%)	2 (<0.1%)	2 (0.9%)			2169 (25%)	32 (6.3%)	0 (0%)			63 (1.4%)	0 (0%)	0 (0%)			2614 (5.3%)	14 (0.7%)	0 (0%)	
		(1.1%, 1.4%)	(0.02%, 0.35%)	(0.16%, 3.63%)			(24.5%, 26.3%)	(4.4%, 8.94%)	(0%, 53.7%)			(1.05%, 1.74%)	0 (0%), 1.29%	(0%, 14.1%)			(5.14%, 5.58%)	(0.41%, 1.25%)	(0%, 3.47%)	
5–9		230 (1.2%)	6 (0.3%)	0 (0%)			1244 (15%)	16 (3.2%)	0 (0%)			107 (2.3%)	0 (0%)	0 (0%)			2135 (4.4%)	7 (0.4%)	0 (0%)	
		(1.06%, 1.38%)	(0.11%, 0.60%)	(0%, 2.16%)			(13.8%, 15.3%)	(1.89%, 5.21%)	(0%, 53.7%)			(1.89%, 2.78%)	0 (0%), 1.29%	(0%, 14.1%)			(4.18%, 4.56%)	(0.16%, 0.78%)	(0%, 3.47%)	
10–14		425 (2.2%)	18 (0.8%)	0 (0%)			1537 (18%)	34 (6.7%)	0 (0%)			123 (2.6%)	1 (0.3%)	0 (0%)			3111 (6.3%)	42 (2.2%)	2 (1.5%)	
		(2.04%, 2.46%)	(0.48%, 1.27%)	(0%, 2.16%)			(17.2%, 18.8%)	(4.78%, 9.39%)	(0%, 53.7%)			(2.6%, 3.15%)	1 (0.3%), 1.75%	(0%, 14.1%)			(6.13%, 6.57%)	(1.59%, 2.96%)	(0.26%, 5.83%)	
15–19		454 (2.4%)	40 (1.8%)	0 (0%)			641 (7.5%)	44 (8.7%)	1 (20%)			84 (1.8%)	9 (2.4%)	0 (0%)			64 (3.3%)	64 (3.3%)	0 (0%)	
		(2.18%, 2.62%)	(1.27%, 2.41%)	(0%, 2.16%)			(7.5%, 8.08%)	(6.48%, 11.6%)	(1.05%, 70.1%)			(1.45%, 2.24%)	9 (2.4%), 4.76%	(0%, 14.1%)			(4.8%, 5.00%)	(2.59%, 4.25%)	(0%, 3.47%)	
20–29		1093 (5.8%)	127 (5.6%)	1 (0.5%)			758 (9.0%)	15 (3.0%)	0 (0%)			267 (5.7%)	21 (5.7%)	0 (0%)			209 (11%)	209 (11%)	4 (3.0%)	
		(5.44%, 6.11%)	(4.69%, 6.62%)	(2.92%, 4.30%)			(8.28%, 9.49%)	(1.58%, 22.8%)	(0%, 53.7%)			(5.09%, 6.45%)	3 (8.3%), 8.73%	(0%, 19.1%)			(9.7%, 9.98%)	(9.51%, 12.3%)	(0.96%, 7.93%)	
30–39		1726 (9.1%)	302 (13%)	3 (1.4%)			509 (6.0%)	61 (12%)	1 (20%)			483 (10%)	33 (9.0%)	1 (3.3%)			5364 (11%)	190 (9.9%)	1 (0.7%)	
		(8.70%, 9.52%)	(7.84%, 10.2%)	(4.30%, 10.2%)			(5.47%, 6.48%)	(5.32%, 6.32%)	(1.05%, 70.1%)			(9.51%, 11.3%)	3 (9.0%), 12.5%	(3.3%), 19.1%)			(10.7%, 11.2%)	(8.58%, 11.3%)	(0.04%, 4.70%)	
40–49		2703 (14%)	302 (13%)	15 (6.9%)			496 (5.8%)	61 (12%)	1 (20%)			750 (16%)	58 (16%)	5 (17%)			6545 (13%)	285 (15%)	9 (6.7%)	
		(13.2%, 14.8%)	(11.9%, 14.7%)	(4.04%, 11.3%)			(5.32%, 6.32%)	(5.32%, 15.3%)	(1.05%, 70.1%)			(15.1%, 17.2%)	5 (17%), 20.0%	(6.30%, 35.5%)			(13.1%, 13.7%)	(13.2%, 16.5%)	(3.31%, 12.7%)	
50–59		3845 (20%)	496 (22%)	48 (22%)			506 (6.0%)	73 (14%)	0 (0%)			1063 (23%)	87 (24%)	4 (13%)			7378 (15%)	383 (20%)	20 (15%)	
		(19.7%, 20.9%)	(20.1%, 23.6%)	(16.8%, 28.2%)			(5.9%, 6.45%)	(11.4%, 17.9%)	(0%, 53.7%)			(21.6%, 24.1%)	28 (4%), 28.4%	(4.36%, 31.6%)			(14.7%, 15.4%)	(18.1%, 21.7%)	(18.1%, 22.4%)	
60–69		3985 (21%)	531 (23%)	59 (27%)			396 (4.6%)	48 (9.5%)	1 (20%)			1008 (22%)	99 (27%)	10 (33%)			7281 (15%)	383 (20%)	35 (26%)	
		(20.4%, 21.6%)	(21.6%, 25.1%)	(21.4%, 33.6%)			(5.11%, 5.11%)	(7.17%, 12.5%)	(1.05%, 70.1%)			(22.5%, 31.8%)	31.8%, 52.9%	(17.9%, 52.9%)			(14.5%, 15.2%)	(18.1%, 21.7%)	(19.1%, 34.5%)	
70–79		2604 (14%)	364 (16%)	40 (18%)			195 (2.3%)	30 (6.0%)	1 (20%)			537 (12%)	38 (10%)	6 (20%)			4,522 (9%)	243 (13%)	30 (22%)	
		(13.2%, 14.2%)	(14.5%, 17.6%)	(13.6%, 24.3%)			(1.98%, 2.63%)	(4.12%, 8.48%)	(1.05%, 70.1%)			(10.6%, 12.5%)	3 (10%), 14.0%	(6.40%, 39.1%)			(8.97%, 9.49%)	(8.97%, 14.2%)	(15.8%, 30.6%)	
>80		1665 (8.8%)	186 (8.2%)	50 (23%)			97 (1.1%)	9 (1.8%)	0 (0%)			174 (3.7%)	22 (6.0%)	4 (13%)			2951 (6.0%)	108 (5.6%)	33 (25%)	
		(8.38%, 9.19%)	(7.10%, 9.39%)	(6.2%, 29.2%)			(0.93%, 1.39%)	(0.87%, 3.49%)	(0%, 53.7%)			(3.22%, 4.33%)	3 (8.7%), 9.04%	(3.7%, 31.6%)			(4.36%, 6.24%)	(4.64%, 6.75%)	(17.8%, 33.0%)	
Duration of hospitalization (day)	21,463	2.02 (1.96, 2.08)	3.91 (3.91, 4.63)	4.27 (4.27, 4.63)	<0.001	9,057	0.85 (0.82, 0.87)	1.71 (1.55, 1.84)	5.00 (0.41, 8.31)	<0.001	5,057	0.81 (0.78, 0.83)	2.05 (1.67, 2.44)	5.23 (2.16, 9.128)	<0.001	51,077	1.00 (0.98, 1.02)	2.69 (2.42, 2.95)	5.01 (3.68, 6.35)	<0.001
Cost of hospitalization (euro)	21,463	1299 (1,264,1,333)	3490 (3,248, 3,732)	9539 (7,338, 11,740)	<0.001	9,057	578 (571, 585)	1549 (1,430, 1,669)	8802 (6,222, 15,007)	<0.001	5,057	551 (542, 561)	1772 (1,555, 1,989)	9128 (6,222, 12,035)	<0.001	51,077	735 (728, 742)	2436 (2,241, 2,631)	6103 (4,665, 7,542)	<0.001
Recurrences (number of hospitalization)	21,463	17,523 (92%)	2104 (92%)	213 (98%)		9,057	7655 (90%)	435 (82.9%)	5 (100%)	0.11	5,057	4542 (96%)	355 (96%)	30 (100%)	0.4	51,077	43,808 (89%)	1655 (86%)	128 (90.5%)	<0.001
1		92.0%	91.3%	94.4%			88.9%	86.9%	(46.3%, 100.0%)			93.9%	97.0%	85.9%			(89.1%, 89.6%)	(84.2%, 87.3%)	(90.1%, 96.2%)	
2		1097 (5.8%)	140 (5.46%)	14 (6.2%)			656 (7.7%)	46 (6.83%)	0 (0%)			104 (2.2%)	13 (3.5%)	0 (0%)			3380 (6.9%)	178 (8.0%)	178 (8.0%)	
		(5.46%, 6.13%)	(5.22%, 7.24%)	(5.57%, 7.24%)			(7.12%, 8.26%)	(6.83%, 12.1%)	(0%, 53.7%)			(1.84%, 2.71%)	(1.98%, 6.12%)	(0%, 14.1%)			(6.67%, 7.12%)	(8.00%, 10.6%)	(6.51%, 6.66%)	

Table 2 (continued)

Characteristic	Drug					Food					Insect					Unspecified					Total					
	N	Non severe	Severe	Death	P value	N	Non severe	Severe	Death	P value	N	Non severe	Severe	Death	P value	N	Non severe	Severe	Death	P value						
		(95% CI)	(95% CI)	(95% CI)			(95% CI)	(95% CI)	(95% CI)			(95% CI)	(95% CI)	(95% CI)			(95% CI)	(95% CI)	(95% CI)							
>2	349 (1.8%)	32 (1.4%)	0 (0%)	0 (0%)		237	23 (4.6%)	0 (0%)	0 (0%)		5057	13 (0.3%)	0 (0%)	0 (0%)		1,827	95 (4.3%)	0 (0%)	0 (0%)		2576	95 (4.3%)	0 (0%)	0 (0%)		
	(1.66%, 2.04%)	(0.98%, 2.00%)	(2.16%)			(2.44%, 3.15%)	(2.48%, 6.87%)	(53.7%)				(0.16%, 0.49%)	(1.29%)	(1.1%)		(3.7%), (3.90%)	(4.02%, 6.01%)	(3.47%)				(3%), (3.09%)	(4.02%, 6.01%)	(3.47%)		
Asthma	21,463	2160 (9.9%)	211 (9.7%)	211 (9.7%)	<0.001	9057	7799 (86.4%)	425 (4.7%)	4 (80%)		5057	4606 (91.6%)	360 (7.1%)	29 (97%)		51,077	47,712 (93.4%)	1836 (3.6%)	132 (0.3%)		<0.001	83,706	1836 (3.6%)	132 (0.3%)		
	(9.6%, 10.2%)	(9.3%, 10.0%)	(9.8%, 10.5%)			(8.1%, 9.3%)	(8.0%, 9.8%)	(80.8%)	(29.9%, 98.9%)			(91%, 93.2%)	(93.9%, 95.8%)	(90.9%, 99.7%)			(97%, 99.2%)	(94.2%, 96.6%)	(94.2%, 99.2%)			(96.6%), (96.6%)	(94.2%, 99.2%)	(94.2%, 99.2%)		
Yes	537 (2.5%)	116 (5.1%)	7 (3.2%)	7 (3.2%)		749 (8.1%)	87 (3.2%)	79 (3.2%)	1 (20%)		53 (1.1%)	8 (2.2%)	8 (2.2%)	1 (3.3%)		1,303 (2.6%)	92 (4.3%)	96 (4.3%)	2 (1.5%)			2,948	92 (4.3%)	96 (4.3%)	2 (1.5%)	
	(2.0%, 3.0%)	(4.2%, 6.1%)	(1.4%, 6.7%)			(8.1%, 9.3%)	(12.7%, 19.2%)	(1.05%, 70.1%)			(0.86%, 1.50%)	(1.01%, 4.41%)	(1.7%, 5.7%)	(0.17%, 19.1%)		(2.52%, 2.81%)	(3.88%, 5.83%)	(3.4%, 5.83%)	(0.26%, 5.83%)			(3.4%), (3.28%), (3.52%)	(3.4%), (3.28%), (3.52%)	(0.26%, 5.83%)		
Atopic dermatitis	21,463	18,951 (88.3%)	218 (1.1%)	218 (1.1%)	>0.9	9057	8399 (92.7%)	498 (5.5%)	5 (0.05%)		5057	4659 (92.3%)	368 (7.3%)	30 (0.6%)		51,077	48,909 (95.8%)	1,927 (3.8%)	134 (0.3%)		0.4	86,372	1,927 (3.8%)	134 (0.3%)		
	(87.8%, 88.8%)	(90.6%, 91.6%)	(97.8%, 98.8%)			(92.7%, 93.7%)	(98.0%, 99.5%)	(46.3%, 100.0%)			(90.0%, 95.9%)	(98.7%, 99.9%)	(98.7%, 100.0%)	(100%, 100%)			(96.7%, 99.7%)	(99.7%, 100.0%)	(100%, 100%)			(99.6%), (99.6%)	(99.7%, 99.7%)	(99.6%, 99.6%)		
Yes	18 (<0.1%)	2 (<0.1%)	0 (0%)	0 (0%)		149 (1.6%)	6 (1.2%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)		106 (0.2%)	1 (<0.1%)	1 (<0.1%)	0 (0%)			282	1 (<0.1%)	1 (<0.1%)	0 (0%)	
	(0.06%, 0.15%)	(0.02%, 0.35%)	(2.16%)			(1.7%, 2.05%)	(0.48%, 2.71%)	(0%, 53.7%)			(0%, 0.03%)	(0%, 1.29%)	(0%, 14.1%)	(0%, 14.1%)		(0.18%, 0.26%)	(0.34%, 0.34%)	(0.34%, 0.34%)	(0%, 3.47%)			(0.33%), (0.29%), (0.37%)	(0.33%), (0.29%), (0.37%)	(0%, 3.47%)		
Allergic contact dermatitis	21,463	18,944 (88.3%)	2274 (12.0%)	218 (1.1%)	0.7	9057	8544 (94.3%)	503 (5.5%)	5 (0.05%)		5057	4655 (92.1%)	368 (7.3%)	30 (0.6%)		51,077	48,937 (95.8%)	1,927 (3.8%)	134 (0.3%)		0.5	86,537	1,927 (3.8%)	134 (0.3%)		
	(87.8%, 88.8%)	(90.6%, 91.6%)	(97.8%, 98.8%)			(92.7%, 93.7%)	(98.0%, 99.5%)	(46.3%, 100.0%)			(90.0%, 95.9%)	(98.7%, 99.9%)	(98.7%, 100.0%)	(100%, 100%)			(96.7%, 99.7%)	(99.7%, 100.0%)	(100%, 100%)			(99.6%), (99.6%)	(99.7%, 99.7%)	(99.6%, 99.6%)		
Yes	25 (0.1%)	4 (0.2%)	0 (0%)	0 (0%)		4 (<0.1%)	1 (0.2%)	0 (0%)	4 (<0.1%)		4 (<0.1%)	0 (0%)	0 (0%)	0 (0%)		78 (0.2%)	1 (<0.1%)	1 (<0.1%)	0 (0%)			117	1 (<0.1%)	1 (<0.1%)	0 (0%)	
	(0.09%, 0.20%)	(0.02%, 0.48%)	(2.16%)			(0.01%, 0.13%)	(1.28%, 1.28%)	(0%, 53.7%)			(0.03%, 0.24%)	(0%, 1.29%)	(0%, 14.1%)	(0%, 14.1%)		(0.13%, 0.20%)	(0.34%, 0.34%)	(0.34%, 0.34%)	(0%, 3.47%)			(0.11%), (0.16%)	(0.11%), (0.16%)	(0%, 3.47%)		
Allergic rhinitis	21,463	18,956 (88.3%)	2274 (12.0%)	218 (1.1%)	0.7	9057	8510 (94.0%)	503 (5.5%)	5 (0.05%)		5057	4659 (92.3%)	368 (7.3%)	30 (0.6%)		51,077	48,971 (95.9%)	1,926 (3.8%)	134 (0.3%)		0.7	86,554	1,926 (3.8%)	134 (0.3%)		
	(87.8%, 88.8%)	(90.6%, 91.6%)	(97.8%, 98.8%)			(92.7%, 93.7%)	(98.0%, 99.5%)	(46.3%, 100.0%)			(90.0%, 95.9%)	(98.7%, 99.9%)	(98.7%, 100.0%)	(100%, 100%)			(96.7%, 99.7%)	(99.7%, 100.0%)	(100%, 100%)			(99.6%), (99.6%)	(99.7%, 99.7%)	(99.6%, 99.6%)		
Yes	13 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)		38 (0.4%)	1 (0.2%)	0 (0%)	4 (<0.1%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)		44 (<0.1%)	2 (0.1%)	2 (0.1%)	0 (0%)			100	2 (0.1%)	2 (0.1%)	0 (0%)	
	(0.04%, 0.12%)	(0.02%, 0.35%)	(2.16%)			(0.32%, 0.62%)	(1.28%, 1.28%)	(0%, 53.7%)			(0%, 0.01%)	(0%, 1.29%)	(0%, 14.1%)	(0%, 14.1%)		(0.07%, 0.12%)	(0.02%, 0.42%)	(0.02%, 0.42%)	(0%, 3.47%)			(0.12%), (0.09%), (0.14%)	(0.12%), (0.09%), (0.14%)	(0%, 3.47%)		
Allergic urticaria	21,463	18,041 (84.1%)	2172 (10.1%)	217 (1.0%)	0.008	9057	7621 (84.1%)	438 (4.8%)	5 (0.05%)		5057	4318 (85.4%)	317 (6.3%)	30 (0.6%)		51,077	46,730 (91.5%)	1,823 (3.6%)	131 (0.3%)		0.11	81,843	1,823 (3.6%)	131 (0.3%)		
	(84.1%, 85.1%)	(94.5%, 96.2%)	(97.1%, 100.0%)			(84.1%, 85.4%)	(83.6%, 89.7%)	(46.3%, 100.0%)			(85.4%, 89.8%)	(86%, 94.4%)	(86%, 94.4%)	(100%, 100%)			(95%, 99.4%)	(93.4%, 95.4%)	(93.1%, 99.4%)			(94.4%), (94.4%)	(94.4%, 94.4%)	(94.4%, 94.4%)		
Yes	928 (4.3%)	104 (4.6%)	1 (0.5%)	1 (0.5%)		927 (10.1%)	66 (13%)	0 (0%)	0 (0%)		341 (6.7%)	51 (10.1%)	7 (3%)	0 (0%)		2,285 (4.7%)	105 (2.1%)	105 (2.1%)	3 (2.2%)			4811	105 (2.1%)	105 (2.1%)	3 (2.2%)	
	(4.5%, 5.2%)	(4.5%, 5.2%)	(2.92%)			(11.5%, 11.5%)	(10.3%, 16.4%)	(0%, 53.7%)			(7.3%, 8.1%)	(10.6%, 17.9%)	(10.6%, 14.1%)	(0%, 14.1%)		(4.48%, 4.85%)	(5.4%, 6.90%)	(5.4%, 6.90%)	(0.58%, 6.90%)			(6.55%), (6.55%)	(5.4%, 6.90%), (5.71%)	(5.4%, 6.90%), (5.71%)		
Chronic urticaria	21,463	18,909 (88.1%)	2268 (10.8%)	218 (1.0%)	0.8	9057	8512 (94.0%)	502 (5.5%)	5 (0.05%)		5057	4645 (91.9%)	366 (7.2%)	30 (0.6%)		51,077	48,723 (95.4%)	1,911 (3.8%)	134 (0.3%)		0.2	86,223	1,911 (3.8%)	134 (0.3%)		
	(87.6%, 88.6%)	(90.3%, 92.0%)	(97.8%, 98.8%)			(94.0%, 95.9%)	(94.4%, 99.4%)	(46.3%, 100.0%)			(91.9%, 95.5%)	(97.8%, 99.7%)	(97.8%, 100.0%)	(100%, 100%)			(95.4%, 99.3%)	(98.6%, 99.5%)	(96.5%, 99.5%)			(99.5%), (99.5%)	(99.5%, 99.5%)	(99.5%, 99.5%)		
Yes	60 (0.3%)	8 (0.4%)	0 (0%)	0 (0%)		36 (0.4%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)		292 (0.6%)	17 (0.3%)	17 (0.3%)	0 (0%)			431 (0.5%)	17 (0.3%)	17 (0.3%)	0 (0%)	
	(0.24%, 0.41%)	(0.16%, 0.72%)	(2.16%)			(0.30%, 0.59%)	(1.59%, 1.59%)	(0%, 53.7%)			(0.17%, 0.52%)	(0.09%, 2.17%)	(0%, 14.1%)	(0%, 14.1%)		(0.53%, 0.67%)	(0.53%, 1.44%)	(0.53%, 1.44%)	(0%, 3.47%)			(0.45%), (0.55%), (0.55%)	(0.45%), (0.55%), (0.55%)	(0%, 3.47%)		
Mastocytosis	21,463	18,961 (88.4%)	2276 (10.6%)	218 (1.0%)	<0.001	9057	8546 (94.3%)	501 (5.5%)	5 (0.05%)		5057	4659 (92.3%)	368 (7.3%)	30 (0.6%)		51,077	49,011 (96.0%)	1,917 (3.8%)	134 (0.3%)		<0.001	86,626	1,917 (3.8%)	134 (0.3%)		
	(87.9%, 88.9%)	(90.7%, 92.4%)	(97.8%, 98.8%)			(94.3%, 95.8%)	(94.1%, 99.8%)	(46.3%, 100.0%)			(92.3%, 96.9%)	(98.7%, 99.9%)	(98.7%, 100.0%)	(100%, 100%)			(96.0%, 99.9%)	(99.9%, 100.0%)	(100%, 100%)			(99.9%), (99.9%)	(99.9%, 99.9%)	(99.9%, 99.9%)		
Yes	8 (<0.1%)	0 (0%)	0 (0%)	0 (0%)		2 (<0.1%)	3 (0.6%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)		4 (<0.1%)	11 (0.2%)	11 (0.2%)	0 (0%)			28 (0.03%)	11 (0.2%)	11 (0.2%)	0 (0%)	
	(0.02%, 0.09%)	(0.02%, 0.21%)	(2.16%)			(<0.01%, 0.09%)	(1.88%, 1.88%)	(0%, 53.7%)			(0%, 0.00%)	(0%, 1.29%)	(0%, 14.1%)	(0%, 14.1%)		(0.02%, 0.02%)	(0.30%, 1.05%)	(0.30%, 1.05%)	(0%, 3.47%)			(0.02%), (0.05%)	(0.02%), (0.05%)	(0%, 3.47%)		
Angioedema	21,463	12,637 (58.9%)	1815 (8.5%)	194 (0.9%)	<0.001	9057	7996 (88.3%)	433 (4.8%)	5 (0.05%)		5057	3108 (61.5%)	316 (6.2%)	26 (67%)		51,077	15,527 (30.4%)	1,042 (2.0%)	1042 (2.0%)		<0.001	43,181	1,042 (2.0%)	1042 (2.0%)		
	(58.9%, 67.3%)	(78.0%, 81.4%)	(83.9%, 92.7%)			(88.3%, 94.0%)	(82.5%, 88.8%)	(46.3%, 100.0%)			(67%, 81.1%)	(67%, 81.1%)	(81.8%, 89.2%)	(68.4%, 95.6%)			(32%, 32.1%)	(52.4%, 56.3%)	(52.4%, 56.3%)			(52.4%), (54%), (54%)	(52.4%), (54%), (54%)	(52.4%), (54%), (54%)		
Yes	78 (0.4%)	81 (0.4%)	92 (0.4%)			94 (0.4%)	88.8%)	(46.3%, 100.0%)			68.1%)	89.2%)	(81.8%, 89.2%)	(95.6%, 95.6%)			32.1%)	56.3%)	56.3%)				(49.5%), (50.16%)	(49.5%), (50.16%)	(49.5%), (50.16%)	

(continued on next page)

Table 2 (continued)

Characteristic	Drug				Food				Insect				Unspecified				Total				
	N	Non severe (95% CI)	Severe (95% CI)	Death N = 218 (95% CI)	P value	N	Non severe (95% CI)	Severe (95% CI)	Death N = 5 (95% CI)	P value	N	Non severe (95% CI)	Severe (95% CI)	Death N = 368 (95% CI)	P value	N		Non severe (95% CI)	Severe (95% CI)	Death N = 1928 (95% CI)	P value
History of medication allergy	21,463																				
No	6332 (33%) (32.7%, 34.1%)	461 (20%) (18.6%, 22.0%)	24 (11%) (7.32%, 16.1%)	0.4	9057	552 (6.5%, 7.00%)	71 (14%) (11.2%, 17.5%)	0 (0%) (0%, 53.7%)	0.082	5057	1551 (33%, 34.7%)	52 (14%) (10.8%, 18.2%)	4 (13%) (4.36%, 31.6%)	>0.9	51,077	33,488 (68%, 67.9%, 68.7%)	886 (46%) (43.7%, 48.2%)	52 (39%) (30.6%, 47.6%)	0.063	43,473 (50.17%, 49.84%, 50.5%)	
Yes	17,507 (92%) (91.9%, 92.7%)	2106 (93%) (91.4%, 93.6%)	206 (94%) (90.3%, 97.0%)	0.001	9057	8478 (99%) (99.0%, 99.4%)	495 (98%) (99.1%, 99.1%)	5 (100%) (46.3%, 100.0%)	0.005	5057	4656 (100%) (99.8%, 100.0%)	368 (98.7%) (98.7%, 99.7%)	30 (100%) (100.0%, 100.0%)	0.2	51,077	48,740 (99%) (99.4%, 99.9%)	1909 (99%) (98.4%, 99.8%)	134 (100%) (96.5%, 97.7%)	0.2	84,634 (97.67%, 97.57%, 2020)	
History of allergy to others	21,463																				
No	18,873 (99%) (99.4%, 99.6%)	2246 (99%) (98.1%, 99.1%)	218 (100%) (97.8%, 100.0%)	<0.001	9057	8305 (97%) (96.8%, 97.5%)	476 (94%) (92.0%, 96.2%)	5 (100%) (46.3%, 100.0%)	0.005	5057	4641 (100%) (99.4%, 99.8%)	364 (99%) (97.0%, 99.7%)	30 (100%) (100.0%, 100.0%)	0.2	51,077	48,640 (99%) (99.2%, 99.3%)	1906 (99%) (98.2%, 99.3%)	133 (99%) (95.3%, 100.0%)	0.2	85,837 (99.06%, 98.99%, 817)	
Yes	96 (0.5%) (0.41%, 0.62%)	30 (1.3%) (0.91%, 1.90%)	0 (0%) (0, 2.16%)	<0.001	9057	243 (2.8%) (2.51%, 3.22%)	28 (5.6%) (3.79%, 8.03%)	0 (0%) (0%, 53.7%)	0.005	5057	18 (0.4%) (0.24%, 0.62%)	4 (1.1%) (0.35%, 2.95%)	0 (0%) (0, 14.1%)	0.2	51,077	375 (0.8%) (0.69%, 0.85%)	22 (1.1%) (0.73%, 1.75%)	1 (0.4%) (0.04%, 4.70%)	0.2	817 (0.94%, 0.88%, 1.01%)	

CI: confidence interval (Wilson method).
 Pearson's Chi-squared test; Kruskal–Wallis rank sum test; Fisher's exact test.
 Fisher's exact test; Kruskal–Wallis rank sum test.

We observed possible seasonal trend of cases of anaphylaxis by trigger over the months per each year of the study. All the etiology-driven anaphylaxis had very significant p-values, indicating that the cases presented considerable relationship between ‘month’ and ‘etiology’. We confirmed a higher number of hospitalizations during the months of June, July, August, and September related to insect ($P < 0.001$) and unspecified anaphylaxis ($P < 0.001$) (Fig. 1). The adjusted R-squared indicates that the model explains 79% of the variation in the data.

Using GLM with Poisson regression, we found a significant effect of year on the total cases of anaphylaxis (mean trend = +2.2%/year [1.97%–2.45%], $P < 0.0001$) and on each specific anaphylaxis trigger, including iatrogenic/drugs (mean trend = +4.6%/year [4.1%–5.1%], $P < 0.0001$), insect (mean trend = +7.6%/year [6.6%, 8.7%], $P < 0.001$), food (mean trend = +13.9%/year [+13.1%, 14.8%], $P < 0.0001$) and unspecified (mean trend = -1.1%/year [0.8%, 1.4%], $P < 0.0001$). There was a significant increase of severe cases ratio admissions over the years for all causes of anaphylaxis (mean trend = +6.4%/year [5.4%, 7.4%], $P < 0.0001$) and on specific causes, including drugs (mean trend = +6.4%/year [4.9%, 7.9%], $P < 0.001$), insect (mean trend = +10.7%/year [6.7%, 14.9%], $P < 0.001$), food (mean trend = +10.3%/year [+6.9%, 13.8%], $P < 0.0001$) and unspecified (mean trend = +3.5%/year [1.9%, 5.1%], $P < 0.0001$). Pseudo R squared values exceeding 75% indicated a strong association most models, except for the models predicting the number of hospitalizations due to SA related to insect and food, in which Pseudo R-squared values ranged from 25% to 75%, signifying a moderate fit. (Table 1).

Fig. 2 demonstrates that drug-induced anaphylaxis is the main cause of SA and FA. There was a significant increase of severe cases ratio admissions over the years for all causes of anaphylaxis (mean trend = +6.4%/year [5.4%, 7.4%], $P < 0.0001$) and on specific causes, including drugs (mean trend = +6.6%/year [5%, 8.1.0%], $P < 0.001$), insect (mean trend = +12.4%/year [8.4%, 16.6%], $P < 0.001$), food (mean trend = +13.1%/year [+9.6%, 16.7%], $P < 0.0001$) and unspecified (mean trend = +3.5%/year [+1.9%, 5.1%], $P < 0.0001$).

3.2. Characteristics of the population

From the overall perspective of anaphylaxis, there was an increase in the rate of severity in males compared to a decrease in females for drug-induced anaphylaxis and unspecified anaphylaxis. There was a significant increase in SA ranging from 1.5% to 20% ($P < 0.001$) and a corresponding elevated risk of death ranging from 2.1% to 33% ($P < 0.001$) compared to NSA in the elderly. (Table 1). From all admissions for anaphylaxis, most were classified as unspecified (59%, 95CI [58.6%, 59.3%]), followed by triggered by drugs (25%, 95%CI [24.5%, 25.1%]), food (10%, 95%CI [10.2%, 10.7%]) and insect sting (5.8% 95%CI [5.68%, 5.99%]) (Table 1). Food-induced anaphylaxis was most common in children, while anaphylaxis due to drugs, insect, or unspecified had a higher frequency in adults. Drugs and insect venom were significantly associated to all ages (Table 1), but the rates of hospitalizations and deaths due to these triggers increased with age (Fig. 3). Fig. 3 displayed a significant increase in June, July and August for insect-induced hospitalized cases, in May, June, and July for unspecified-induced hospitalized cases. GAM with a Poisson distribution, adjusted for sex and age groups, confirmed these findings and demonstrated a strong fit to the data with an adjusted R-squared value of 86%.

Table 2 shows that among 21,463 cases of drug-induced anaphylaxis, 18,969 were NSA (88.4%), 2276 were SA (10.6%) and 218 (1%) evolved to death. The percentage of males increased according to the level of severity of drug-induced anaphylaxis, passing from 45% (NSA) to 53% (FA). Overall, males had a significant association with severe drug-induced anaphylaxis and deaths (49% vs. 45%, $P < 0.001$), and mean age above 50 years-old was associated with severe drug-induced anaphylaxis and deaths (59 vs. 51, $P < 0.001$) (Table 2 and Fig. 1).

Table 3

Comorbidities of non-severe, severe and deaths for anaphylaxis, data from the French Program for the Medicalization of Information Systems (PMSI), 2012–2021.

Characteristic	Non-severe N = 81,191	95% CI	Severe N = 5076	95% CI	Death N = 387	95% CI	Overall N = 86,654 [1]	95% CI	P value
Asthma									<0.001
No	78,549 (97%)	96.6%, (97%)	4781 (94%)	93.5%, (94.8%)	376 (97%)	94.8%, (98.5%)	83,706 (97%)	96.5%, (96.7%)	
Yes	2642 (3.3%)	3.13%, 3.38%	295 (5.8%)	5.19%, 6.50%	11 (2.8%)	1.50%, 5.18%	2,948 (3.4%)	3.28%, 3.53%	
Atopic dermatitis									
No	80,918 (100%)	99.6%, 99.7%	5067 (100%)	99.7%, 99.9%	387 (100%)	98.8%, 100.0%	86,372 (100%)	99.6%, 99.7%	
Yes	273 (0.3%)	0.30%, 0.38%	9 (0.2%)	0.09%, 0.35%	0 (0%)	0%, 1.23%	282 (0.3%)	0.29%, 0.37%	
Allergic contact dermatitis									>0.9
No	81,080 (100%)	99.8%, 99.9%	5070 (100%)	99.7%, 100.0%	387 (100%)	98.8%, 100.0%	86,537 (100%)	99.8%, 99.9%	
Yes	111 (0.1%)	0.11%, 0.17%	6 (0.1%)	0.05%, 0.27%	0 (0%)	0%, 1.23%	117 (0.1%)	0.11%, 0.16%	
Allergic rhinitis									>0.9
No	81,096 (100%)	99.9%, 99.9%	5071 (100%)	99.8%, 100.0%	387 (100%)	98.8%, 100.0%	86,554 (100%)	99.9%, 99.9%	
Yes	95 (0.1%)	0.10%, 0.14%	5 (<0.1%)	0.04%, 0.24%	0 (0%)	0%, 1.23%	100 (0.1%)	0.09%, 0.14%	
Allergic urticaria									<0.001
No	76,710 (94%)	94.3%, 94.6%	4750 (94%)	92.9%, 94.2%	383 (99%)	97.2%, 99.7%	81,843 (94%)	94.3%, 94.6%	
Yes	4481 (5.5%)	5.36%, 5.68%	326 (6.4%)	5.77%, 7.14%	4 (1.0%)	0.33%, 2.81%	4811 (5.6%)	5.40%, 5.71%	
Chronic urticaria									
No	80,789 (100%)	99.5%, 99.6%	5047 (99%)	99.2%, 99.6%	387 (100%)	98.8%, 100.0%	86,223 (100%)	99.5%, 99.5%	
Yes	402 (0.5%)	0.45%, 0.55%	29 (0.6%)	0.39%, 0.83%	0 (0%)	0%, 1.23%	431 (0.5%)	0.45%, 0.55%	
Mastocytosis									<0.001
No	81,177 (100%)	100.0%, 100.0%	5062 (100%)	99.5%, 99.8%	387 (100%)	98.8%, 100.0%	86,626 (100%)	100.0%, 100.0%	
Yes	14 (<0.1%)	<0.01%, 0.03%	14 (0.3%)	0.16%, 0.47%	0 (0%)	0%, 1.23%	28 (<0.1%)	0.02%, 0.05%	
Angioedema									<0.001
No	39,268 (48%)	48.0%, 48.7%	3606 (71%)	69.8%, 72.3%	307 (79%)	74.9%, 83.2%	43,181 (50%)	49.5%, 50.2%	
Yes	41,923 (52%)	51.3%, 52.0%	1470 (29%)	27.7%, 30.2%	80 (21%)	16.8%, 25.1%	43,473 (50%)	49.8%, 50.5%	
History of medication allergy									<0.001
No	79,381 (98%)	97.7%, 97.9%	4878 (96%)	95.5%, 96.6%	375 (97%)	94.5%, 98.3%	84,634 (98%)	97.6%, 97.8%	
Yes	1810 (2.2%)	2.13%, 2.33%	198 (3.9%)	3.39%, 4.48%	12 (3.1%)	1.69%, 5.50%	2020 (2.3%)	2.23%, 2.43%	
History of allergy to other substances (non-medicinal)									
No	80,459 (99%)	99.0%, 99.2%	4992 (98%)	97.9%, 98.7%	386 (100%)	98.3%, 100.0%	85,837 (99%)	99.0%, 99.1%	
Yes	732 (0.9%)	0.84%, 0.97%	84 (1.7%)	1.33%, 2.05%	1 (0.3%)	0.01%, 1.66%	817 (0.9%)	0.88%, 1.01%	
Acute myocardial infarction									
No	80,728 (99%)	99.4%, 99.5%	4979 (98%)	97.7%, 98.4%	380 (98%)	96.1%, 99.2%	86,087 (99%)	99.3%, 99.4%	
Yes	463 (0.6%)	0.52%, 0.63%	97 (1.9%)	1.56%, 2.34%	7 (1.8%)	0.79%, 3.86%	567 (0.7%)	0.60%, 0.71%	
Congestive heart failure									
No	80,693 (99%)	99.3%, 99.4%	4947 (97%)	97.0%, 97.9%	352 (91%)	87.5%, 93.5%	85,992 (99%)	99.2%, 99.3%	
Yes	498 (0.6%)	0.56%, 0.67%	129 (2.5%)	2.13%, 3.02%	35 (9.0%)	6.46%, 12.5%	662 (0.8%)	0.71%, 0.82%	
Peripheral vascular disease									
No	80,899 (100%)	99.6%, 99.7%	5010 (99%)	98.3%, 99.0%	378 (98%)	95.5%, 98.9%	86,287 (100%)	99.5%, 99.6%	
Yes	292 (0.4%)	0.32%, 0.40%	66 (1.3%)	1.01%, 1.66%	9 (2.3%)	1.14%, 4.53%	367 (0.4%)	0.38%, 0.47%	
Cerebral vascular accident									
No	80,774 (99%)	99.4%, 99.5%	4994 (98%)	98.0%, 98.7%	369 (95%)	92.6%, 97.1%	86,137 (99%)	99.3%, 99.5%	
Yes	417 (0.5%)	0.47%, 0.57%	82 (1.6%)	1.29%, 2.01%	18 (4.7%)	2.86%, 7.39%	517 (0.6%)	0.55%, 0.65%	

(continued on next page)

Table 3 (continued)

Characteristic	Non-severe N = 81,191	95% CI	Severe N = 5076	95% CI	Death N = 387	95% CI	Overall N = 86,654 [1]	95% CI	P value
Dementia									
No	80,992 (100%)	99.7%, 99.8%	5069 (100%)	99.7%, 99.9%	380 (98%)	96.1%, 99.2%	86,441 (100%)	99.7%, 99.8%	
Yes	199 (0.2%)	0.21%, 0.28%	7 (0.1%)	0.06%, 0.30%	7 (1.8%)	0.79%, 3.86%	213 (0.2%)	0.21%, 0.28%	
Pulmonary disease									<0.001
No	77,239 (95%)	95.0%, 95.3%	4535 (89%)	88.5%, 90.2%	340 (88%)	84.1%, 90.9%	82,114 (95%)	94.6%, 94.9%	
Yes	3952 (4.9%)	4.72%, 5.02%	541 (11%)	9.83%, 11.5%	47 (12%)	9.14%, 15.9%	4540 (5.2%)	5.09%, 5.39%	
Connective tissue disorders									
No	80,856 (100%)	99.5%, 99.6%	5041 (99%)	99.0%, 99.5%	385 (99%)	97.9%, 99.9%	86,282 (100%)	99.5%, 99.6%	
Yes	335 (0.4%)	0.37%, 0.46%	35 (0.7%)	0.49%, 0.97%	2 (0.5%)	0.09%, 2.06%	372 (0.4%)	0.39%, 0.48%	
Peptic ulcer									<0.001
No	81,143 (100%)	99.9%, 100.0%	5066 (100%)	99.6%, 99.9%	382 (99%)	96.8%, 99.5%	86,591 (100%)	99.9%, 99.9%	
Yes	48 (<0.1%)	0.04%, 0.08%	10 (0.2%)	0.10%, 0.38%	5 (1.3%)	0.48%, 3.17%	63 (<0.1%)	0.06%, 0.09%	
Liver disease									<0.001
No	81,109 (100%)	99.9%, 99.9%	5053 (100%)	99.3%, 99.7%	374 (97%)	94.2%, 98.1%	86,536 (100%)	99.8%, 99.9%	
Yes	82 (0.1%)	0.08%, 0.13%	23 (0.5%)	0.29%, 0.69%	13 (3.4%)	1.88%, 5.82%	118 (0.1%)	0.11%, 0.16%	
Diabetes									
No	81,075 (100%)	99.8%, 99.9%	5042 (99%)	99.1%, 99.5%	383 (99%)	97.2%, 99.7%	86,500 (100%)	99.8%, 99.8%	
Yes	116 (0.1%)	0.12%, 0.17%	34 (0.7%)	0.47%, 0.95%	4 (1.0%)	0.33%, 2.81%	154 (0.2%)	0.15%, 0.21%	
Diabetes complications									
No	81,191 (100%)		5076 (100%)		387 (100%)		86,654 (100%)		
Paraplegia									
No	81,191 (100%)		5076 (100%)		387 (100%)		86,654 (100%)		
Renal disease									>0.9
No	81,190 (100%)	100.0%, 100.0%	5076 (100%)	99.9%, 100.0%	387 (100%)	98.8%, 100.0%	86,653 (100%)	100.0%, 100.0%	
Yes	1 (<0.1%)	<0.01%, <0.01%	0 (0%)	0%, 0.09%	0 (0%)	0%, 1.23%	1 (<0.1%)	<0.01%, <0.01%	
Cancer									
No	80,489 (99%)	99.1%, 99.2%	4972 (98%)	97.5%, 98.3%	378 (98%)	95.5%, 98.9%	85,839 (99%)	99.0%, 99.1%	
Yes	702 (0.9%)	0.80%, 0.93%	104 (2.0%)	1.68%, 2.49%	9 (2.3%)	1.14%, 4.53%	815 (0.9%)	0.88%, 1.01%	
Metastatic cancer									<0.001
No	80,079 (99%)	98.5%, 98.7%	4949 (97%)	97.0%, 97.9%	367 (95%)	92.0%, 96.7%	85,395 (99%)	98.5%, 98.6%	
Yes	1112 (1.4%)	1.29%, 1.45%	127 (2.5%)	2.10%, 2.98%	20 (5.2%)	3.27%, 8.00%	1,259 (1.5%)	1.37%, 1.54%	
Severe liver disease									>0.9
No	81,187 (100%)	100.0%, 100.0%	5076 (100%)	99.9%, 100.0%	387 (100%)	98.8%, 100.0%	86,650 (100%)	100.0%, 100.0%	
Yes	4 (<0.1%)	<0.01%, 0.01%	0 (0%)	0%, 0.09%	0 (0%)	0%, 1.23%	4 (<0.1%)	<0.01%, 0.01%	
HIV									0.080
No	81,125 (100%)	99.9%, 99.9%	5068 (100%)	99.7%, 99.9%	386 (100%)	98.3%, 100.0%	86,579 (100%)	99.9%, 99.9%	
Yes	66 (<0.1%)	0.06%, 0.10%	8 (0.2%)	0.07%, 0.32%	1 (0.3%)	0.01%, 1.66%	75 (<0.1%)	0.07%, 0.11%	
Charlson comorbidity index	0.14	0.14,0.15	0.33	0.31, 0.35	0.60	0.49, 0.71	0.16		<0.001

CI: confidence interval (Wilson method).

From all 9057 cases of food-induced anaphylaxis, 8548 were NSA (94.4%), 504 were SA (5.5%) and 5 FA (0.1%). Although food-induced anaphylaxis is more frequent in childhood 0–14 years-old, the most severe cases and deaths occurred at adolescence and early adulthood (30–49 years-old and 60–79 years-old) ($P < 0.001$) (Table 2 and Fig. 1).

Among 5057 cases of insect-induced anaphylaxis, 4,659 were NSA (92.1%), 368 were SA (7.2%) and 30 FA (0.8%). Insect-induced

anaphylaxis was higher for males (71% vs. 29%). Age was associated with severe insect-induced anaphylaxis and deaths (55 vs. 63, $P < 0.001$) (Table 2 and Fig. 1).

From overall 51,077 cases of unspecified anaphylaxis, 49,015 were NSA (96%), 1,928 were SA (3.7%) and 134 evolved to death (0.3%). Male gender (53% vs. 56%, $P = 0.026$) and older ages, above 40 years-old (55

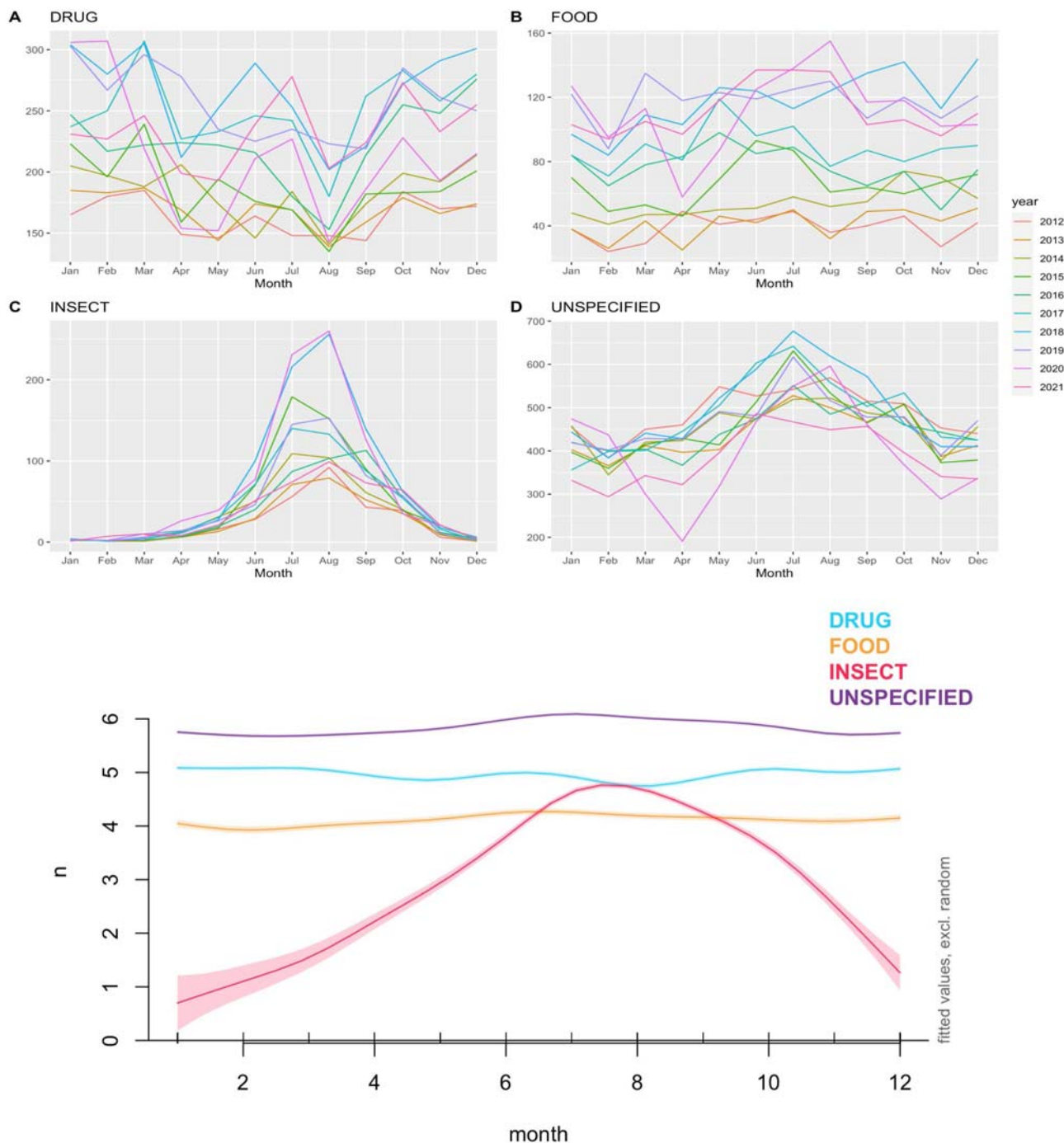


Fig. 1. Seasonal distribution of anaphylaxis by trigger. Data from the French Program for the Medicalization of Information Systems (PMSI), 2012–2021. Top panel: by study year; bottom panel: modelled seasonal distribution over 2012–2021.

vs. 46, $P < 0.001$) were associated with severe unspecified-induced anaphylaxis and deaths (Table 2 and Fig. 1).

3.3. Comorbidities, potential risk factors and phenotypes at-risk

Presence of pulmonary disease, including asthma, urticaria, mastocytosis, angioedema, personal history of drug allergy, peptic ulcer, liver injury and metastatic cancer were significantly associated with anaphylaxis of any severity, but their CCI was 0.14 for NSA ($P < 0.001$, 95%CI [0.13–0.15]), 0.33 to SA ($P < 0.001$, 95%CI [0.31–0.35]) and 0.6

to FA ($P < 0.001$, 95%CI [0.49–0.71]), meaning that the association was higher with SA and FA (Table 3).

By applying the clustering algorithm CLARA, 86,654 hospital admissions have been distributed in 3 clusters (Table 3 and Fig. 4):

Cluster 1 represents mild cases of anaphylaxis in which the lowest cases of FA were observed. This cluster is exclusively represented by women of all ages, but with higher proportion between 40-49 years. Patients of this cluster presented with predominancy unspecified anaphylaxis, and angioedema, allergic contact dermatitis, and chronic urticaria as comorbidities.

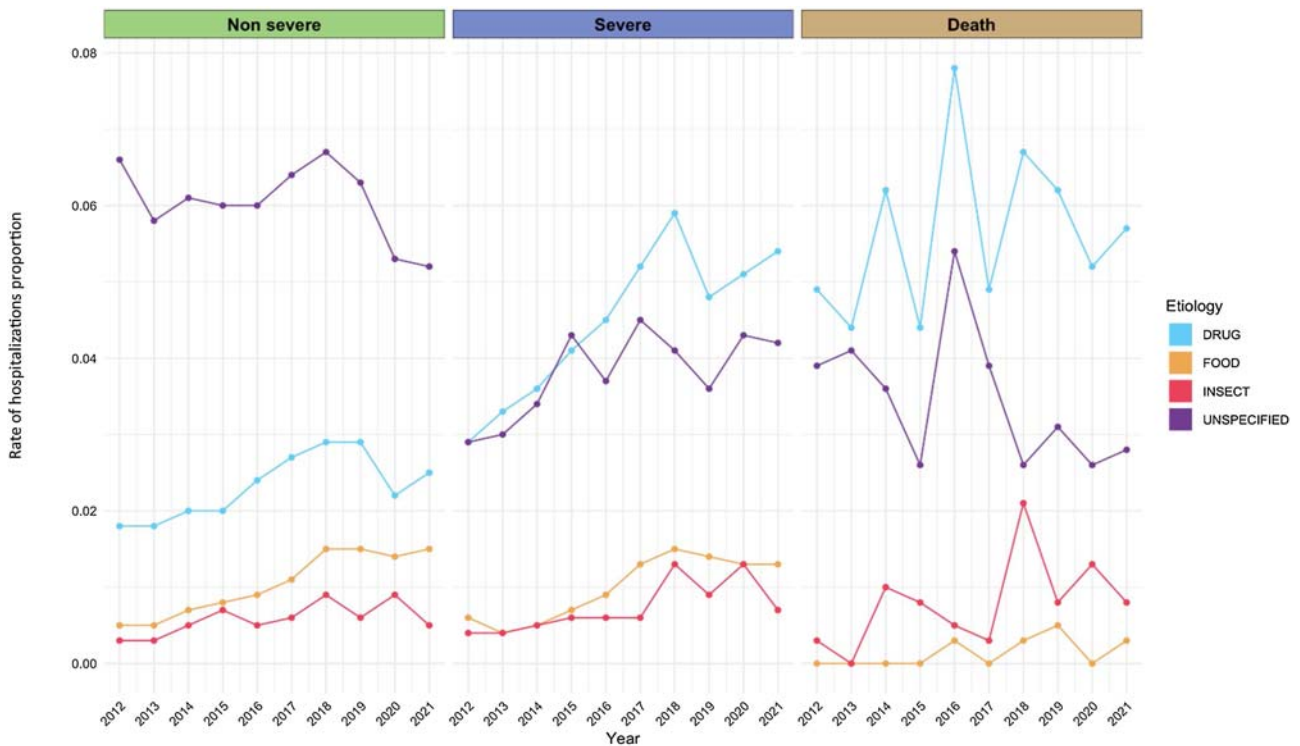


Fig. 2. Proportion of rates of hospitalization for each trigger of anaphylaxis over the years of the study by outcome, data from the French Program for the Medicalization of Information Systems (PMSI), 2012–2021.

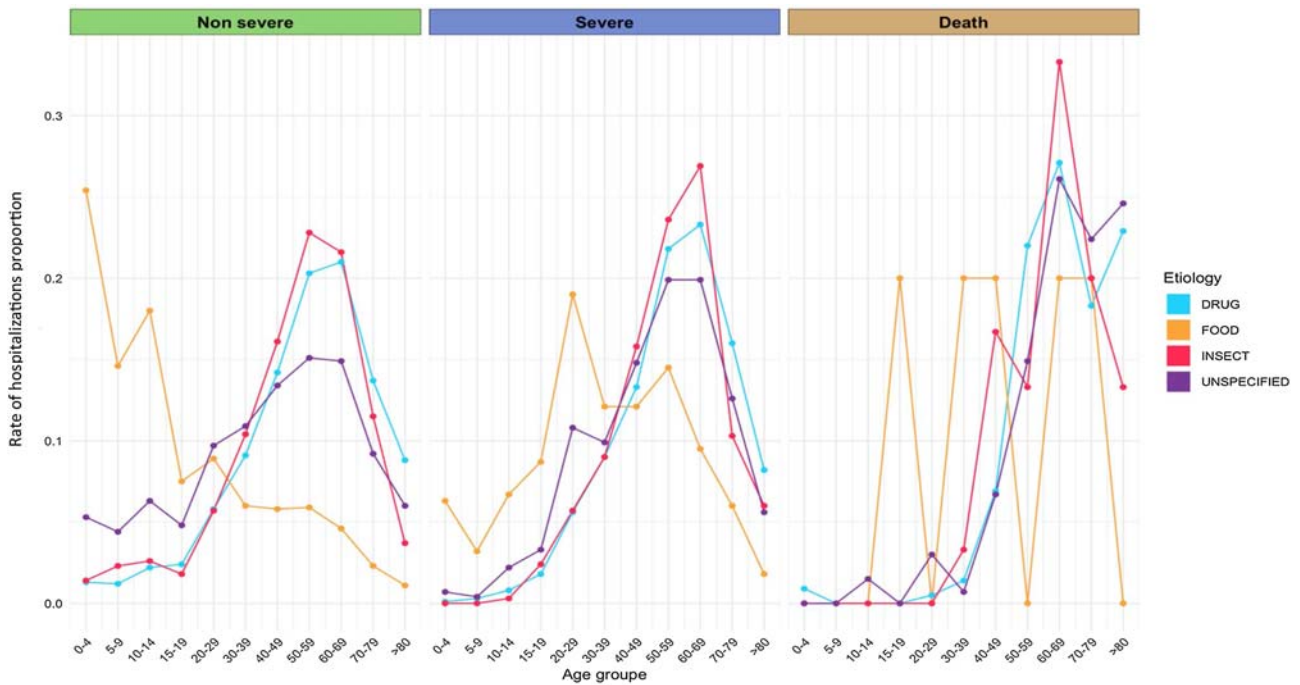


Fig. 3. Proportion of rates of hospitalizations for anaphylaxis per severity and trigger distributed by age groups, data from the French Program for the Medicalization of Information Systems (PMSI), 2012–2021.

Cluster 2: comprises moderate cases of anaphylaxis, represented mostly by men, aged 60–69 years or more, with personal history of allergy and/or angioedema, and who developed unspecified anaphylaxis or, less frequently, food-induced anaphylaxis.

Cluster 3: includes severe cases of anaphylaxis, mostly in females, aged 50–59 years or more, who developed drug-induced anaphylaxis.

Patients representing this cluster present with high number of comorbidities: acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, cancer, metastatic cancer, HIV, asthma, atopic dermatitis, allergic urticaria, personal history of drug allergy.

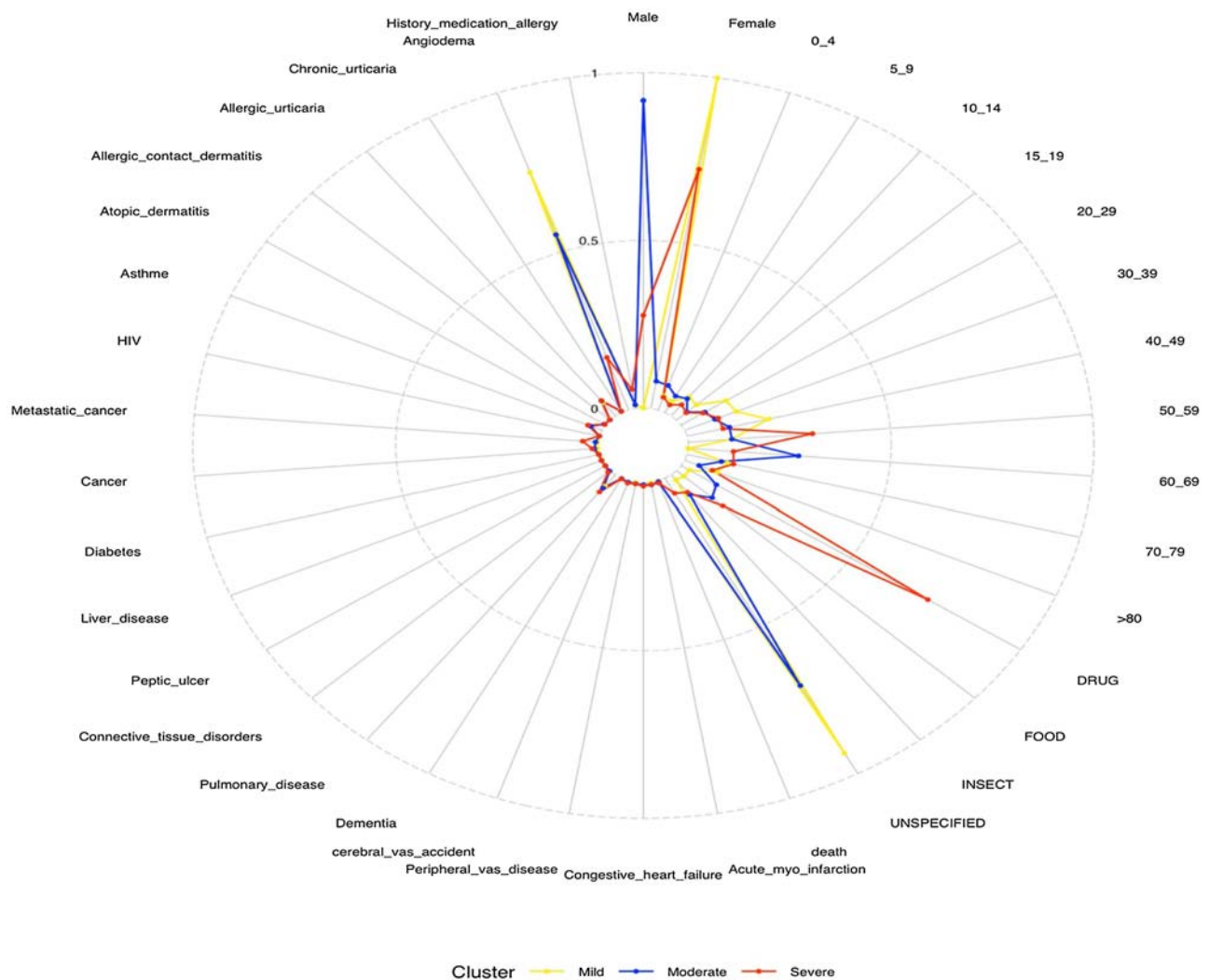


Fig. 4. Radar illustrating the cluster analysis of cases of hospitalization due to anaphylaxis, data from the French Program for the Medicalization of Information Systems (PMSI), 2012–2021.

4. Discussion

Aligning with the current core priorities of the World Health Organization of moving towards universal health coverage, protecting people better against health emergencies and ensuring health lives and well-being for all at all ages [17], our study succeeded in providing details regarding possible determinants of anaphylaxis and define possible phenotypes at-risk.

Anaphylaxis is a public health issue, which deserves a holistic approach to ensure better care and reduced burden. Besides the higher risk of death, we confirmed that SA increases the days of hospitalizations and costs for individuals and society. The mean cost for anaphylaxis admissions in France is estimated at 9 493 427,11 euros per year.

The rate of admissions due to SA for all causes was estimated by 0.08 per 100,000 population per year in France, with increasing trends overtime. Data about the characteristics of the French population were collected from the databases of the French national institute for economical and statistical studies [9]. Drug-induced anaphylaxis is the main cause of SA admissions and deaths in adults and elderly populations. Severe food-induced anaphylaxis and related deaths occurred mostly at adolescence and early adulthood. Severe insect-induced anaphylaxis and deaths are more prevalent in elderly males. Unspecified anaphylaxis is overall most prevalent, less severe, but relapse more.

Our data demonstrated an unexpected significant association of anaphylaxis with comorbidities infrequently reported, such as peripheral vascular disease, cerebral vascular accident, peptic ulcer, liver disease, diabetes, cancer, metastatic cancer and HIV. It flags the need of further research in the field to confirm the associations and understand underlying potential common mechanisms and interactions.

The data presented can tailor the implementation of public health interventions to prevent deaths and the burden of this condition. Although some associated factors of anaphylaxis are not modifiable, we believe that some actions in the individual and population levels are required [18]:

- (I) Optimization of healthcare pathways and referral: Strengthening the collaboration between all professions responsible for the management of anaphylaxis [19], such as firemen [20], health professionals of ambulances, emergency doctors [21], primary care physicians and allergists [22], is key to reduce risk for patients. As we observed in clusters 1 and 2, most of cases are unspecified anaphylaxis. Anaphylaxis cases labelled as unspecified may be, in part, due to the lack of recognition of a potential trigger, misdiagnosis or miscoding. In fact, we observed that most of cases of unspecified anaphylaxis are less severe but relapse more. All patients presenting with anaphylaxis should be early referred to allergists for risk stratification in order to decrease further

avoidable reactions [18]. Even ruled out as mild, the clusters counted with patients requiring hospitalization and some evolved to death. It means that the severity attributed to the clusters are not corresponding to the known severity scores of anaphylaxis [1,23].

- (II) Notification: Accurate data is key to support surveillance, in particular of SA cases. Presently, most robust data are derived from hospitalization datasets and national mortality databases [24–26]. They probably do not reflect the true rate of anaphylaxis since most of the cases occur in the community and not all cases are brought to hospital settings [2,7]. In France, there are other documented data from the allergy vigilance network [27,28], but they are less comprehensive and depend on voluntary notification. For this reason, the French Allergy Society is currently working together with national bodies, patients' associations and stakeholders to implement a national registry for the notification of SA.
- (III) Standardization of the anaphylaxis care centers: As for the neuro-vascular units for the management of stroke, we are advocating the creation of anaphylaxis care units in all major hospitals with specialized staff and routine individualized procedures to cases of SA [18,29,30].
- (IV) Prevention and control of comorbidities: Cluster 3 represented by the most severe cases manifested by drug-induced anaphylaxis in patients who have many comorbidities, both communicable and non-communicable. It is probable that the number of comorbidities is the reason for polypharmacy, which is a well-known risk factor for drug-induced anaphylaxis [30]. It is obviously unwise to recommend that older patients do not take medications, as they are necessary for more frequent comorbidities than anaphylaxis. However, the primary prevention strategies should be foreseen in a prospective and long-term way by promoting exercise and behaviour change in older adults, including measures to reduce the comorbidities such as increasing quality of life, reducing tobacco, salt and alcohol consumption [17].
- (V) Education and training: Anaphylaxis can virtually happen in every setting and prompt recognition and treatment of anaphylaxis are key to prevent deaths [1,26]. Training modules should be proposed for patients who experienced a reaction, medical students and general practitioners to advice the recognition of anaphylaxis and proper referral to specialists [14]. Training modules for better classifying and coding allergic and hypersensitivity conditions are also in preparation nationally and internationally [30].
- (VI) Adrenaline auto-injectors (AAI) in public settings: Adrenaline is the first-line treatment of anaphylaxis [1,26]. Its auto-injector form is recommended to virtually all cases of anaphylaxis, who should care them and use when needed. AAI are commercially available in many devices in doses suitable for most, but not all, adults and children. In France three commercial forms are available, but not available in public settings. All clustered patients would benefit from this public availability in the first episode or in cases of refractory anaphylaxis for instance. Recently, due to the efforts of the French Allergy Society's Allergy at School Working Group in collaboration with the Ministries of National Education and Health, non-identified AAI are available at primary schools [18,30].
- (VII) Anaphylaxis in the ICD-11: Anaphylaxis mortality and morbidity statistics will gain more accuracy thanks to the improvements of the classification and coding in the ICD-11, under implementation worldwide [31–38].

We were equally able to confirm seasonal patterns of anaphylaxis, which can differ according to the study performed. It is expected that countries from South hemisphere would present the opposite pattern [39]. Although we still do not have objective data, it is possible that our finding may be impacted by climate changes. Therefore, prospective studies may be required to follow the trends.

This study presents some limitations. As with any study reliant on government derived data, there is a number of caveats including accuracy

of coding, clinical diagnosis of anaphylaxis, and the proportion of cases either treated in the community without hospital admission or treated in outpatient accident and emergency departments without admission. However, these caveats should be stable over the 9 years of our study analysis. As expected in all population-based studies, it was not possible to identify detailed clinical data, biphasic or refractory cases of anaphylaxis. Subclusters would be probably helpful to implement details of the data, but the number of recurrences is not enough to perform the cluster analysis. The generalizability of French data to other countries is questionable, although triggers are the same worldwide. Mild reactions are usually not captured in these studies, mostly because the ICD-10 is not able to capture mild degrees of anaphylaxis [40,41]. The severity classification used in the cluster methodology is not equivalent to the usual classifications since it took into account the data from hospitalized patients, who would have presented reactions with enough severity to require hospital admissions. Many versions of the ICD-10 were used over the period of analysis, but anaphylaxis related codes have always been stable (although badly classified) in all versions of ICD-10 [34,37,41]. However, the ICD-11 may provide new perspective by allowing to add the severity of the reactions [35,38]. Findings should be validated in other countries and nationally prospectively.

5. Conclusion

Our findings significantly contributed to the better understanding of the determinants of anaphylaxis taking French data as a model. More than providing a snap shot of potential risk factors for anaphylaxis in France, we were able to suggest phenotypes of anaphylaxis of different severity and proposed actions based in our findings. Although further research is needed in the field, we strongly believe that the data presented contributed as a starting point of public health advancements to ensure quality of care of patients suffering from anaphylaxis.

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Authors' consent for publication

All the authors consent for publication.

Availability of data and materials

Raw data may be available after acceptance of the article and per request.

Conflict of interests

The authors declare that they do not have any conflict of interests related to the contents of this article.

Author contributions

Luciana Kase Tanno: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Pham Thao Van Luong:** Formal analysis, Data curation. **Megane Dieval:** Formal analysis, Data curation. **Caroline Dunoyer:** Formal analysis, Data curation. **Nicolas Molinari:** Methodology, Data curation. **Isabella Annesi-Maesano:** Validation, Data curation. **Pascal Demoly:** Validation, Supervision.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jahd.2024.100004>.

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