Allergic emergencies in the prehospital setting: a 5 year retrospective study

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ABSTRACT

BACKGROUND:
Patients with severe allergic conditions often request support from the prehospital emergency services given the rapid, unexpected and potentially life-threatening nature of the reactions, such as anaphylaxis. Studies regarding prehospital incidents for allergic conditions are scarce. This study aimed to characterize prehospitalar medical requesting assistance due to suspected hypersensitivity reactions (HSR).
METHODS:
Retrospective study of allergic-related requesting assistances between 2017-2022 of a Portuguese emergency dispatch centre - Emergency and Resuscitation Medical Vehicle (VMER), in Coimbra University Hospital. Demographic and clinical variables were analysed, including clinical manifestations, anaphylaxis severity grading, therapeutic interventions, and post-incident allergic work-up. Regarding anaphylactic events, three diagnosis timings were compared: on-site, hospital emergency department and Investigator-diagnosis based on data reviewed.
RESULTS:
Out of 12689 VMER requesting assistances, 210 (1.7%) were classified as suspected HSR reactions. After on-site medical evaluation, 127 (60.5%) cases maintained the HSR classification (median age 53 years; 56% males) and the main diagnoses included HSR to hymenoptera venom (29.9%), food allergy (29.1%), and pharmaceutical drugs (25.5%).

Anaphylaxis was assumed on-site in 44 (34.7%) cases, in the hospital emergency department in 53 cases (41.7%) and by investigators in 76 (59.8%) cases. Regarding management, epinephrine was administered on-site in 50 cases (39.4%).

CONCLUSIONS:

The main reason for prehospital requesting assistance was HSR to hymenoptera venom. A high proportion of incidents met the criteria for anaphylaxis and despite the inherent difficulties of the prehospital setting, many of the on-site diagnoses agreed with the criteria. Regarding management, epinephrine was underused in this setting.

After pre-hospital events, a proper referral to a specialized consultation is crucial for a full diagnostic work-up and disease management.

KEY WORDS: emergency; prehospital care; anaphylaxis; epinephrine; allergy

IMPACT STATEMENT: This pioneer study of allergic emergencies in the prehospital context highlights the main features of hypersensitivity reactions in this setting, particularly of anaphylaxis, which appears to be underdiagnosed on-site.

LIST OF ABBREVIATIONS

CODU: Urgent Patient Orientation Centres
EAACI: European Academy of Allergy & Clinical Immunology
ED: Emergency Department
EEN: European Emergency Number (112)
HCA: Hospital-classified anaphylaxis
HSR: hypersensitivity reactions
ICA: Investigator-classified anaphylaxis
IQR: interquartile range
INEM: National Institute of Medical Emergency
VCA: VMER-classified anaphylaxis
VMER: Emergency and Resuscitation Medical Vehicle
WAO: World Allergy Organization

Introduction

The National Institute of Medical Emergency (INEM) is responsible, in Portugal, for ensuring the proper functioning of an Integrated System of Medical Emergency and guaranteeing, whenever justified, immediate and appropriate healthcare assistance. Through on-site medical care, assisted victim transport and articulation between the various elements involved in the System, INEM asserts itself as a regulatory entity in medical emergency situations (1).

The Urgent Patient Orientation Centres (CODU), an integral part of the INEM, through the European Emergency Number (EEN) (112), analyse the multiple requests for emergency assistance aiming towards the optimal triage by applying medical algorithms, and if justified, the selection and activation of the proper means of medical emergency, including the Emergency and Resuscitation Medical Vehicle (VMER). By using these fluxograms, a priority grade is assigned according to the severity of the episode and its potential evolution.

CODU functioning is ensured continuously 24 hours a day by a team of qualified professionals (doctors, prehospital emergency technicians and psychologists), trained to provide care, triage, counselling, proper selection, activation, and management of the necessary emergency resources. In addition, they are also responsible for contacting the respective healthcare units, preparing hospital reception, and promoting an integrated approach to the urgent/emergent patient situations (1).

Hypersensitivity reactions (HSR) are characterized by an excessive or inappropriate immune response to a particular stimulus, with variable clinical presentation and severity. The World Allergy Organization (WAO) estimates that hypersensitivity reactions (HSR) affect about 30 to 40% of the world's population, emphasizing that both the severity and complexity of these reactions are increasing exponentially (2). In Portugal, it is estimated that more than 2 million people (~20%) will experience at least one HSR during their lifetime (3).

Anaphylactic reactions, globally considered the most severe, sudden, and potentially fatal form of HSR manifestation, are a rising concern worldwide (4-6). Mortality can occur within minutes, without being possible to predict the rate of progression or its ultimate severity. Thus, the proper diagnosis of an anaphylactic reaction is essential to determine the most suitable treatment, namely the early administration of epinephrine, associated with improved prognosis and reduced mortality (7,8). Despite clinical consensus establishing diagnostic criteria and guidelines for therapeutic approaches, national and international data consistently demonstrate that anaphylaxis remains underdiagnosed, underreported and undertreated (9,10).

The estimated incidence of anaphylaxis in Europe is 1.5-7.9 per 100,000 person per year (4). However, it is considered to be underestimated, given the high rate of underdiagnosis and underreported situations. Factors such as demographic heterogeneity, usage of different diagnostic and classification criteria, varying degrees of differentiation of the health care services where patients with anaphylaxis are assessed and the lack of a national mandatory notification registry contribute to the heterogeneous nature of the published data.

In Portugal, during a 10-year period, a national anaphylaxis reporting system was implemented depending on voluntary reporting by Clinical Allergists. Based on analysis of the collected data, it was observed that food allergens were the most frequent cause of anaphylaxis (48%) in paediatric age, while drugs were the main triggers in adulthood (37%) (3).

Allergic reactions, and anaphylaxis (given its sudden onset and unpredictability) are a frequent motive for the EEN requesting assistances, with an increase in referrals in recent years. According to the Portuguese CODU annual report for the year 2021, 7303 of the overall occurrences were encoded as "Allergy-ALR", representing a 21% increase from the 2020 report (1).

Even though emergency departments (ED) often encounter severe allergic reactions, there is a lack of national studies exploring the management of allergic emergencies in the prehospital setting (11-13).

The present study aims to characterize the VMER requesting assistances of a tertiary hospital for suspected HSR, describing their frequency, severity and outcomes, as well as their on-site therapeutic approach.

Material and methods

Study design and patient recruitment

A descriptive retrospective study was conducted, analysing data from all VMER requesting assistances that were referred to a tertiary hospital centre in the Central Region of Portugal, during a 5-year period, from June 2017 to June 2022.

Records (both digital and on paper) that lacked patient identification or clinical data, or that had imperceptible handwriting, were immediately excluded. Of the remaining requesting assistances, those coded by the CODU as "Allergy-ALR" (suspected HSR) were selected. Patients that, despite being initially coded as "Allergy-ALR", were given an alternative diagnosis by the physician on-site, and thus not suspected of having an allergic reaction, were subsequently excluded from this study.

Each requesting assistance episode corresponded to a single patient.

Data collection

Data regarding demographic characteristics, clinical manifestations described on-site, atopic and cardiovascular background, therapeutic approach (i.e. use of anti-histamines, corticosteroids, epinephrine, bronchodilators, supplementary oxygen) on-site and in the ED, suspected culprit allergens, referral to an Allergy Clinic and prescription of epinephrine auto-injector was collected through the analysis of the VMER episode files (both in physical and digital format using iTeams® software), as well as the hospital system database (SClinico®). Severity of reactions described on-site was graded using the adapted WAO severity reaction classification published in 2017 (14).

In order to assess potential differences in the interpretation of anaphylactic events, three diagnosis timings were used:

1) VMER-classified anaphylaxis (VCA): VMER episodes were classified by the on-site physician as “anaphylactic events”;
2) Hospital-classified anaphylaxis (HCA): VMER episodes were assessed in the ED by an observing physician and/or subsequently in an Allergy Clinic by an Allergist and registered as “anaphylactic events” after additional investigation or assumed in the absence of a more probable alternative.
3) Investigator-classified anaphylaxis (ICA): on-site clinical data was reviewed by the authors and classified according to the 2021 EAACI anaphylaxis guidelines (9).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics® 27. Frequencies were calculated for nominal variables; medians and interquartile ranges for continuous variables. The normality of the distribution of continuous variables was analysed using the Kolmogorov-Smirnov test. Chi-square ($\chi 2$) and Mann-Whitney U tests were used for determining differences in the distribution of nominal and continuous variables, respectively, between events with and without anaphylaxis criteria and events with and without epinephrine administration.
Statistical significance was considered for $p<0.05$.

Results

An overview of suspected HSR events

Out of a total 12689 VMER requesting assistances, 210 (1.7%) were coded by the CODU as "Allergy-ALR". After medical assessment on-site (mainly through anamnesis and objective examination plus information from relatives or individuals present at the scene), 83 episodes were excluded. In the remaining 127 occurrences, clinical suspicion of HSR was maintained, corresponding to 1.0% of the overall requesting assistances and to 60.5% of the episodes initially coded as "Allergy-ALR" (**figure 1**).

In our cohort of 127 episodes, affected patients were mainly adults (n=111, 87.4%), males (n=71, 56.0%), and with a median age of 54 (IQR 33-71) years.

Regarding clinical presentation of HSR, mucocutaneous symptoms were the most prevalent (88.2%) (mainly episodes of urticaria with or without angioedema), followed by respiratory symptoms (46.5%). By classifying the suspect HSR and the ICA through the modified WAO Severity Grading System, grade 3 was the most prevalent in our sample (mainly lower airway symptoms, such as dyspnea, associated with mucocutaneous symptoms such as urticaria and/or non-laryngeal angioedema). 18 patients had grade 5 reactions, the most severe, which progressed to respiratory failure and/or cardiovascular collapse and/or non-vasovagal loss of consciousness. (**table I**)

The pattern of clinical manifestations in both anaphylactic events defined by EAACI criteria and episodes with epinephrine administration appeared to follow a similar trend.

The suspected allergic culprits are represented in **table II**. The main suspected diagnosis was HSR due to hymenoptera venom, which corresponded to 29.9% of the episodes, mostly triggered by bee and wasp stings. Food allergy was the second most common suspicion, representing 29.1% of the cases, followed by drug allergy (25.2%). In the suspected food

allergy cases, the most commonly identified triggers were seafood/fish, fresh fruits and peanut/tree nuts.

Regarding suspected episodes of drug-induced HSR, beta-lactam antibiotics and nonsteroidal anti-inflammatory drugs, particularly metamizole, were the main implicated pharmaceuticals. In 15.8% (n=21) of the occurrences, the etiology of the reaction could not be determined. In 9.4% (n=12) of patients, diagnosis had already been confirmed at a Clinical Allergy consultation. After the presenting event, 47.2% (n=60) of the patients were referred to a consultation, while 10.2% (n=13) were already enrolled in an Allergist consultation.

Suspected anaphylactic events

From the 127 included reactions, anaphylaxis was diagnosed by the VMER medical team (VCA) in 44 (34.7%). In the hospital setting (in the ED and/or in an Allergy Clinic follow-up), however, anaphylaxis (HCA) was diagnosed in 53 cases (41.7%). The proportions of VCA and HCA were much lower than the investigators' anaphylaxis classification using the EAACI guidelines (ICA), which identified 76 (59.8%) events. Despite identifying fewer severe HSR, the VCA classification appeared to accurately interpret a high proportion of episodes – 40 (90.9%) VCA events were also classified as ICA, whereas 33 (75.0%) were defined as HCA episodes – **table III.** In the ICA group, the most frequent etiologic factors included food (31.6%) – mostly shellfish and peanut/tree nuts –, hymenoptera venom (28.9%), particularly bee stings, and drugs (27.6%), with special relevance for beta-lactam antibiotics and metamizole. In 11.9% of ICA cases, it was not possible to determine an etiologic factor (**table II**). At the ED, only 9 events had a measurement of acute-phase serum tryptase.

Management of episodes

Regarding HSR management, epinephrine was administered by VMER professionals in 50 cases (39.4%) and, particularly, in 39 of all VCA episodes (88.6%). Using both HCA and ICA classifications, however, epinephrine appeared to be underused, with roughly half of these patients receiving this medication on-site.

In addition, systemic corticosteroids were administered on-site in 82.9% of all patients, while antihistamine therapy was given in 75.0%. Supplementary oxygen associated with bronchodilator therapy was required by 18.4% of patients. At the emergency department, 56.6% received corticotherapy, 40.8% antihistamine therapy and 25.0% supplementary oxygen associated with bronchodilators. Seventeen percent (n=21) of patients carried an epinephrine

auto-injector pen. However, even though most of them (n=17, 81.0%) met criteria for anaphylaxis, only 23.8% (n=5) performed epinephrine self-administration.

Regarding whether or not epinephrine was administered on-site during the acute episodes, a comparison was made between the ICA group (n=76) and all other suspected HSR events that did not meet EAACI anaphylaxis criteria (n=51). It was found that in 46.1% (n=35) of the occurrences that met criteria for anaphylaxis, epinephrine was not administered. Conversely, epinephrine was administered in 17.6% (n=9) of patients who did not meet anaphylaxis criteria (**table IV**).Demographic characteristics, atopic and cardiovascular background, clinical manifestations, suspected etiology and Allergy Clinic referral of suspected HSR occurrences, ICA criteria *vs* no criteria and epinephrine administration *vs* no administration are displayed in **table V**.

A predominance of the male gender was observed (55.9%), with no statistically significant difference between those with ICA criteria or no criteria (p=0.364), nor between those treated with or without epinephrine (p = 0.065).

No statistically significant difference in age was found between occurrences with ICA criteria and no criteria (p=0.678) neither between occurrences with epinephrine administration and no administration (p=0.686).

Forty-four events (34.6%) occurred in patients with a personal history of atopy. The prevalence of atopy was significantly higher among those with ICA criteria (42.1% vs. 23.5%, p=0.031).

Regarding clinical manifestations, respiratory, cardiovascular and gastrointestinal symptoms was significantly higher among those with ICA criteria, while only cardiovascular symptoms was significantly higher between patients treated with epinephrine.

There was no difference in suspected etiology between patients with ICA criteria or no criteria and between those treated with epinephrine or not.

There was a statistically significant difference in the epinephrine prescription at discharge between the proportion of patients that received epinephrine and those that did not (26.0 vs 10.4; p=0.018). A similar trend was found between those with ICA criteria and those without criteria (22.4 vs 7.8, p=0.028). Regarding subsequent orientation of ICA occurrences, the majority of patients (n=41, 53.9%) were referred to external consultation for etiologic investigation and further guidance.

Discussion

The present study characterized the HSR events that triggered requests for assistance to the EEN (112) in a 5-year period, based on the consultation of physical and electronic hospital records.

The incidence of HSR in our sample was 1.7% of the total number of VMER requesting assistances. When compared with single centre studies of Australian and United Kingdom emergency departments, where the incidence was 1 in 439 episodes and 1 in 277 episodes, respectively (15, 16), our incidence was relatively higher and more in agreement with the values reported in a US study of emergency episodes for acute allergic reactions, where HSR accounted for 1% of all ED visits (17).

About 60% of the HSR observed (1% of all requesting assistances) by emergency medical teams met criteria for anaphylaxis, predominantly in suspected reactions to hymenoptera stings and food allergy.

The etiology of the HSR was previously known in only 9% of patients, thus hinting that unexpected and sudden events of HSR in patients without previous episodes or etiological suspicions seems to predispose to the request assistance of the VMER.

Of the 17% of patients that carried an epinephrine auto-injector, only about a quarter who met EAACI anaphylaxis criteria self-administered the device. These findings alert the authors to an underuse of epinephrine, even in cases where patients are equipped with the necessary tools. Strategies need to be created in specialized Allergy consultations to optimize the use of this treatment, namely through education and proper instruction for action in an anaphylactic event.

Anaphylaxis may present important quality of life and social repercussions, and inappropriate contact with the potential allergen may put the allergic patient's life at risk. After the occurrence, only 47% of patients were referred to a Clinical Allergy consultation, while just 10% were already undergoing follow-up. This insufficiency is even more apparent in severe situations, where only two-thirds of the occurrences that met the EAACI criteria for anaphylaxis (ICA) were referred to an external consultation. This highlights a need for referral increase.

Although intramuscular (IM) epinephrine is the first-line drug treatment in cases of anaphylaxis (18), it is still underused, particularly when compared to corticosteroids and antihistamines, which continue to be the most commonly used group of drugs in these situations, as is widely described in scientific literature (7,8,19).

On the other hand, it should be noted that only in 9 cases was IM epinephrine used inappropriately, particularly in patients who did not meet criteria for anaphylaxis, with no

reported severe adverse events. This highlights the need to implement and disseminate protocols that aim for a more accurate anaphylaxis diagnosis and a correct use of epinephrine. The collected data should be analysed taking into account the specificities of medical practice in the prehospital setting, since these may hinder the diagnosis and, consequently, the correct therapeutic approach. An accurate diagnosis of anaphylaxis can be difficult to assess, due to the wide spectrum of clinical presentations and the lack of laboratory markers to support the diagnosis, such as serum tryptase (20).

Although the applied clinical diagnostic criteria have demonstrated high sensitivity (21), the signs and symptoms of anaphylactic reactions may vary widely and mimic other urgent/emergent pathologies.

Differential diagnoses to consider in this context range from acute generalized urticaria with or without angioedema, acute asthma exacerbation, vasovagal syncope, panic attacks or foreign body aspiration, to cardiovascular events (acute myocardial infarction, pulmonary thromboembolism), among others (22).

Regarding the etiology of HSR in VMER requesting assistances, they appeared to be similar to those described in the few studies published on this topic, but with differences regarding the prevalence of each suspected culprit (13, 23).

In our study, the main suspected causes of HSR were hymenoptera stings (29.9%), followed by food (29.1%) and drugs (25.2%). This is in agreement with a previously published Australian cohort by L. Blackhall et al., which yielded a similar order of anaphylaxis diagnoses – hymenoptera stings (42.4%), food (36.6%), and lastly drugs (16.8%) (23). It should be noted that in approximately 1/3 of our sample, according to the registered data, it was not possible to identify a suspected triggering factor.

Other published cohorts depict important differences in etiological distribution. For example, in a study conducted by Capps et al. on British patients who activated medical services through emergency calls, 28% of events were food-HSR, 52% drug-HSR (mainly antibiotics), and only 7% were secondary to hymenoptera venom (13).

According to the Portuguese National Apiculture Program 2020-2022, the central region of Portugal, along with the northern region, is the area that gathers the largest number of beekeepers in the country (66% of the total), being the region with the largest number of collective apiculture associations, which may explain the high number of requesting assistances secondary to this etiologic factor in our study (24).

This is the first nationally-known case series to date, which aimed to characterize allergic emergencies in a prehospital setting, allowing for an understanding of the clinical characteristics and the management of these patients in such a particular setting.

There seem to be considerable differences in the approach to patients in the pre-hospital setting compared to the approach to patients in the emergency department (25).

The retrospective nature of our study, with data collection from medical records both in physical and digital files (computer system used by the VMER [iTeams®]), restricted the gathered data to the information recorded, thus making it susceptible to bias.

The relative rarity and unpredictability of HSR hinders prospective data collection. Inadvertently, HSR that were not coded as "Allergy-ALR" may have been excluded. Since CODU coding is operator-dependent and the information is provided by other elements, via telephone, this may not allow for a correct classification ad initium.

Additionally, due to the small number of paediatric patients in our sample, we were not able to draw conclusions regarding this particular age group.

Therefore, we believe that further studies would be beneficial to improve knowledge and outline better strategies to address HSR in pre-hospital settings, including multicenter and/or national studies.

In conclusion, these are the key messages to take into account:

This study provided a characterization of the VMER requesting assistances due to suspected HSR in a cohort of a tertiary hospital in the central region of Portugal.

HSR to hymenoptera venom was the most commonly identified trigger; nevertheless, food and drugs were also frequently implicated. In one-third of cases, the trigger was not identified.

A high percentage of confirmed on-site HSR met EAACI criteria for anaphylaxis (ICA). However, although epinephrine is the first-line drug in these cases, underutilization was noted.

The different forms of clinical presentation of HSR render them an entity of growing importance, both due to the increasing number of cases and the demand for an adequate etiologic study; however, referral to specialized consultation has proven to be insufficient in this cohort, and needs to be optimized.

The true epidemiological impact of HSR on national VMER requesting assistances still needs to be unveiled.

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JCL: conceptualization, data curation, investigation, methodology, Writing - original draft, Writing - review & editing

JCC: conceptualization, methodology, Writing - review & editing

HPP: Writing - original draft, Writing - review & editing

ICF: Software, formal analysis, Writing - review & editing

PBA: formal analysis, writing – review & editing

FCP: Project administration, Resources

CR: Supervision, Validation

ATB: Supervision and Validation

Conflict of interest:

The authors have no conflicts of interest.

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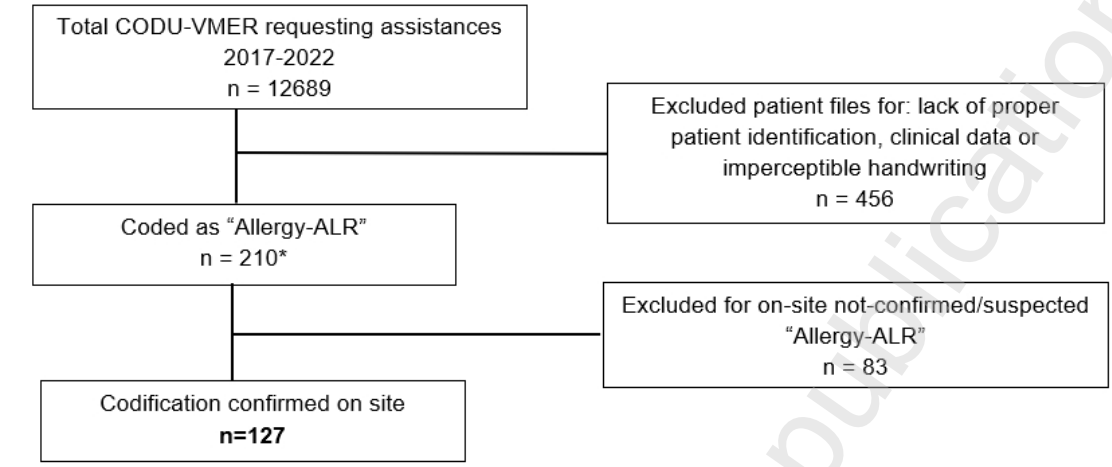
Figures legends:

Figure 1 - Study population selection



* excluded all occurrences not coded as "Allergy-ALR"

Clinical Manifestations	Suspected HSR (n=127)	ICA (n=76)	Epinephrine administration (n=50)
Mucocutaneous	112 | 88.2	70 | 92.1	46 | 92.0
Respiratory	59 | 46.5	48 | 63.1	29 | 58.0
Cardiovascular	34 | 26.8	27 | 35.5	19 | 38.0
Neurological	19 | 15.0	12 | 15.8	8 | 16.0
Gastrointestinal	11 | 8.7	9 | 11.8	7 | 14.0
Modified WAO Systemic Allergic Reaction Grading System			
1	16 | 12.6	0 | 0.0	2 | 4.0
2	34 | 26.7	14 | 18.4	8 | 16.0
3	46 | 36.2	36 | 47.4	20 | 40.0
4	13 | 10.2	9 | 11.8	8 | 16.0
5	18 | 14.2	17 | 22.4	12 | 24.0

Table I: Characterization of the clinical presentation of events (n|%)

Legend:
HSR - Hypersensitivity Reactions
ICA - Investigator-classified anaphylaxis
WAO - World Allergy Organization

Suspected HSR Etiology	Total Occurrences (n=127)	Anaphylaxis Criteria (ICA) (n=76)
Hymenoptera venom HSR	38 | 29.9	22 | 28.9
Bee	14 | 11.0	10 | 13.1
Velutine Wasp	11 | 8.7	5 | 6.6
Common Wasp	9 | 7.1	4 | 5.3
Unknown	4 | 3.1	3 | 3.9
Food HSR	37 | 29.1	24 | 31.6
Seafood/Fish	10 | 7.9	6 | 7.9
Fresh Fruits	7 | 5.5	3 | 3.9
Peanut/Tree Nuts	6 | 4.7	5 | 6.6
Unknown	14 | 11.0	10 | 13.2
Drugs HSR	31 | 25.2	21 | 27.6
Beta-Lactams	6 | 4.7	6 | 7.9
NSAIDs (including metamizole)	6 | 4.7	5 | 6.6
COVID-19 Vaccine	4 | 3.1	0 | 0.0
Others	15 | 11.8	10 | 13.2
Unidentifiable agent	21 | 15.8	9 | 11.9

Table II: Characterization of suspected hypersensitivity reaction (HSR) agents (n|%)

Legend:
COVID-19 - Coronavirus 19 disease;
ICA - Investigator-classified anaphylaxis;
NSAIDs - Nonsteroidal anti-inflammatory drugs.

Occurrences	Total (n=127)	ICA (n=76)	HCA (n=53)	VCA (n=44)
ICA	76 | 59.8	-	48 | 90.6	40 | 90.9
HCA	53 | 41.7	48 | 63.2	-	33 | 75
VCA	44 | 34.7	40 | 52.6	33 | 62.3	-
Epinephrine administration (on-site)	50 | 39.4	41 | 53.9	31 | 58.5	39 | 88.6

Table III: Characterization of occurrences, anaphylaxis and diagnoses by the VMER (n|%).

Legend:
ICA - Investigator-classified Anaphylaxis
HCA - Hospital-classified Anaphylaxis
VCA - VMER-classified Anaphylaxis
VMER - Emergency and Resuscitation Medical Vehicle

EAACI anaphylaxis criteria (ICA)	Epinephrine administration		Total
	Yes	No	
Yes	41 | 53.9	35 | 46.1	76
No	9 | 17.6	42 | 82.4	51

Table IV: Characterization of epinephrine administration in the groups that either fulfilled or not anaphylaxis criteria (n|%).

Legend:
ICA – Investigator-classified anaphylaxis

Variable	Total (n=127)	ICA (n=76)	*p value* (anaphylaxis criteria vs no criteria)	Epinephrine administration (n=50)	*p value* (Epinephrine vs no epinephrine)
Median Age (IQR)	54 (33-71)	53 (32-71)	0.678	56 (36-70)	0.686
Male	71 | 55.9	40 | 52.6	0.364	33 | 66.0	0.065
Female	56 | 44.1	36 | 47.4		17 | 34.0	
Patient Background					
Cardiovascular disease	55 | 43.3	32 | 42.1	0.739	21 | 42.0	0.811
Atopy	44 | 34.6	32 | 42.1	**0.031**	20 | 40.0	0.307
Clinical Manifestation					
Mucocutaneous	112 | 88.2	70 | 92.1	0.095	46 | 92.0	0.284
Respiratory	58 | 45.7	48 | 63.2	**<0.001**	28 | 56.0	0.060
Cardiovascular	33 | 26.0	27 | 35.5	**0.003**	18 | 36.0	**0.038**
Gastrointestinal	10 | 7.9	9 | 11.8	**0.049**	6 | 12.0	0.190
Neurological	19 | 15.0	12 | 15.8	0.749	8 | 16.0	0.791
Etiologic Suspected Factor					
Hymenoptera Venom	38 | 29.9	22 | 28.9	0.770	15 | 30.0	0.998
Food	37 | 29.1	24 | 31.6	0.459	12 | 24.0	0.305
Drugs	32 | 25.2	21 | 27.6	0.440	14 | 28.0	0.558
Adrenaline auto-injector Prescription	21 | 16.5	17 | 22.4	**0.028**	13 | 26.0	**0.018**
Allergy Clinic referral	60 | 47.2	41 | 53.9	0.065	27 | 54.0	0.219

Table V: Demographic and clinical characteristics of suspected hypersensitivity reactions (HSR), Investigator-classified anaphylaxis (ICA) and of those treated with epinephrine (n|%).

Legend:
ICA - investigator-classified anaphylaxis
IQR - interquartile range