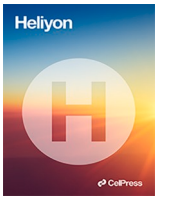
Heliyon 10 (2024) e28049

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Anaphylactic deaths: A retrospective study of forensic autopsy cases from 2009 to 2019 in Shanghai, China

Wen-xin Li [a,1], Cheng-hui Sun [b,1], Zheng-dong Li [c], Jun-yi Lin [a], Yu Shao [a], Long Chen [a], Li-liang Li [a], Xing Ye [a,*], Yi-wen Shen [a,**]

[a] Department of Forensic Medicine, School of Basic Medical Sciences, Fudan University, Shanghai, 200032, PR China
[b] Criminal Science and Technology Research Institute, Fengxian Branch of Shanghai Municipal Public Security Bureau, Shanghai, 201499, PR China
[c] Shanghai Key laboratory of Forensic Medicine, Academy of Forensic Science, Ministry of Justice, Shanghai, 200063, PR China

ARTICLE INFO

Keywords:
Anaphylaxis
Anaphylactic death
Forensic medicine
Allergens
Retrospective study

ABSTRACT

Anaphylaxis is a rare but well-known cause of sudden unexpected death, although data from forensic autopsies in anaphylactic deaths are limited. Herein, a retrospective study of a series of allergic deaths from 2009 through 2019 in Shanghai, China, was conducted to investigate the demographic, medical, and forensic pathological characteristics of fatal anaphylaxis to improve medicolegal understanding on anaphylactic death. Sixty-two autopsy cases of anaphylactic death were registered in this study. Males dominated the cases (74.2%) against females (25.8%), with an average age of 38.8 years. Medications (98.4%), particularly antibiotics (72.6%), were the most frequent cause of anaphylaxis, and 44 cases (71.0%) occurred in clinics administered illegally by unlicensed clinicians. The anaphylactic symptoms began within a few minutes to less than 1 h in 53 cases, with dyspnea (56.5%) and sudden shock (46.8%) being the most common clinical signs. Thirty cases (48.4%) of anaphylaxis resulted in death within 1 h. Laryngeal edema and multiple tissue eosinophil infiltration (85.5%) were the most prevalent autopsy findings, followed by pulmonary edema and congestion (24.2%), which were considered to be non-specific but suggestive. The comorbidities were mainly cardiovascular disease (33.9%), pneumonia (8.1%) and asthma (8.1%). Serum IgE were measured in 11 of 62 cases, ranging from 43.3 to 591 IU/ml, severed as a helpful marker. Therefore, we suggested a thorough analysis of allergen exposure, clinical history and autopsy findings is required for the diagnosis of anaphylactic death currently.

1. Introduction

Anaphylaxis is characterized as a severe, generalized or systemic hypersensitivity reaction that manifests rapidly and can even be life-threatening or lethal [1]. Anaphylactic reactions are caused by the release of mediators by activated mast cells and basophils in

* Corresponding author. Department of Forensic Medicine, School of Basic Medical Sciences, Fudan University, 131 Dong'an Road, Xuhui District, Shanghai, 200032, PR China.
** Corresponding author. Department of Forensic Medicine, School of Basic Medical Sciences, Fudan University, 131 Dong'an Road, Xuhui District, Shanghai, 200032, PR China.
E-mail addresses: 21111010103@m.fudan.edu.cn (X. Ye), shenyiwen@fudan.edu.cn (Y.-w. Shen).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e28049
Received 19 April 2023; Received in revised form 10 March 2024; Accepted 11 March 2024
Available online 12 March 2024

response to allergic (IgE-mediated) or nonallergic (non-IgE-mediated) activation, which can result in deadly airway blockage and cardiorespiratory arrest, leading in hypoxemia and/or shock [2,3]. The most prevalent causes of anaphylaxis include drugs [4,5], food [6] and insect stings [7], other allergens such as hair dye [8], ecstasy [9] and dust mites [10] have also been reported. The mechanism of anaphylaxis is usually attributed to the impact of inflammatory mediators on multiple organs, culminating in upper airway mucosal edema, hypotensive shock and bronchospasm due to peripheral vasodilation or massive fluid shifts [11,12].

Several studies have shown that anaphylaxis has become more common in many countries, although its true incidence is difficult to establish [13,14]. Published data suggests that the estimated prevalence of anaphylaxis is 0.3–5.1%, whereas the estimated incidence is 50–112 events per 100,000 person-years [13]. Between 2004 and 2016, the prevalence of anaphylaxis in the United States was 2.1 per 1000 person-years, and most allergic reactions occurred outside the hospital setting [15,16].

In forensic practice, forensic pathologists occasionally encounter cases of anaphylactic death, which is well-known as a cause of sudden death. Postmortem diagnosis of deadly anaphylaxis is frequently hampered by relatively poor or non-specific pathological findings. Currently, in routine cases, anaphylaxis is mostly diagnosed based on the medical history, clinical symptoms, and non-specific morphological manifestations [8], including airway and lungs edema, lung congestion, etc., while other causes of death must be excluded.

Currently, detailed analyses of the medical, demographic, and postmortem characteristics of anaphylaxis in China remain scarce. We have previously discussed the etiology and forensic examination of anaphylactic deaths that occurred in Shanghai, China, between 2004 and 2006 [8]. Nevertheless, it was far from sufficient to satisfy our understanding of fatal anaphylaxis as epidemiology and new technologies advance. Therefore, a retrospective study based on forensic cases of deadly anaphylaxis has become more pressing, promoting us to obtain more about the medical, demographic, and histopathologic findings of patients who died of anaphylaxis, and provided us with more valuable knowledge of etiology, medicolegal, and clinical facts. Our primary goal was to explore the medical and demographic characteristics, circumstances and postmortem examination findings of lethal anaphylaxis in shanghai between 2009 and 2019 to enrich forensic knowledge of this aspect.

2. Materials and methods

This study performed a retrospective analysis of anaphylaxis deaths in Shanghai, China, form January 2009 to December 2019. We collected a total of 62 cases of anaphylactic death from the Department of Forensic Medicine at Shanghai Medical College (FM-SHMC, n = 26), Academy of Forensic Science (AFS, n = 32), Department of Pathology at Shanghai Medical College (P-SHMC, n = 2), Department of Pathology at Shanghai Changhai Hospital (P–SCH, n = 1) and the Department of Pathology at Shanghai JiaoTong University School of Medicine (P-SJTSM, n = 1), of which FM-SHMC and AFS are mainly accountable for forensic investigation into sudden unexpected deaths, accidental deaths and unexplained deaths, particularly complicated cases in Shanghai, China. All cases for research purposes were approved by the five institutions in this study.

Cases of anaphylactic deaths were attributed to severe allergic reaction that develop quickly (minutes to several hours) following

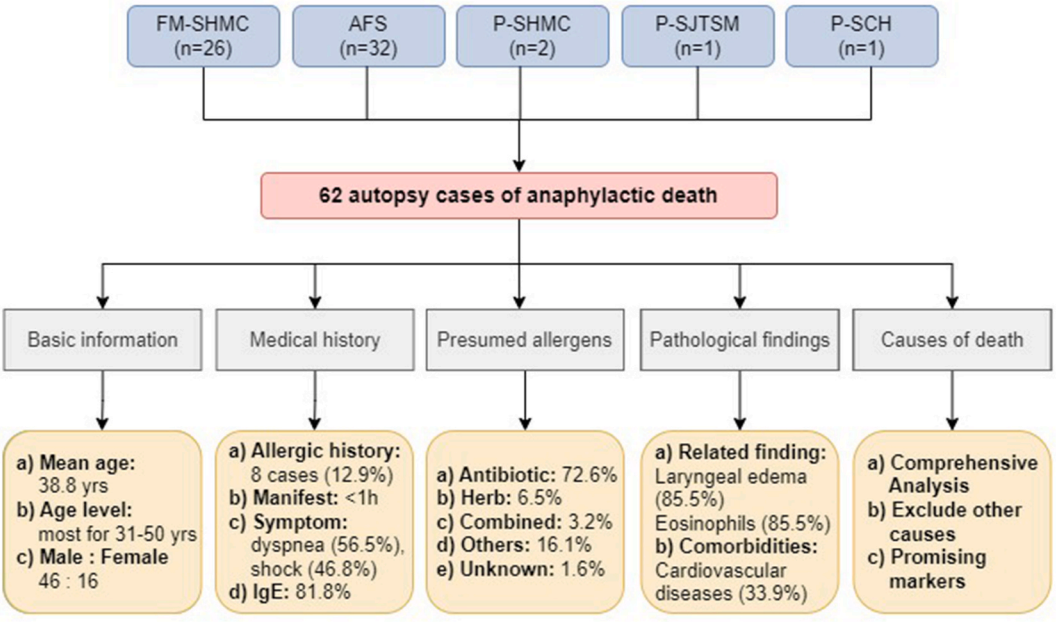


Fig. 1. Main results in this retrospective analysis of 62 autopsy cases of anaphylactic death from January 2009 to December 2019 in Shanghai. FM-SHMC, Department of Forensic Medicine at Shanghai Medical College; AFS, Academy of Forensic Science; P-SHMC, Department of Pathology at Shanghai Medical College; P-SJTSM, Department of Pathology at Shanghai JiaoTong University School of Medicine; yrs, years.

exposure to a plausible allergen, the postmortem diagnostic and inclusion criteria of anaphylaxis cases for this study are based on our previously published paper [8]. In some cases, blood samples were immediately collected after notification of death, sealed and sent to a laboratory for testing. Total serum immunoglobulin E (IgE) concentration was measured and its normal upper limit was set at 87 IU/ml in this research.

Data were extracted from all cases' autopsy archives, which were reviewed and analyzed as to (1) victim basic demographic data, such as gender and age; (2) medical history, history of allergies; (3) presumed allergens (where identified) and allergic symptoms prior to death; (4) pathological findings at autopsy; (5) causes of death. The autopsy and pathological examination of the decedents were performed by two or more qualified forensic pathologists. Comprehensive study of all relevant evidence resulted in a final determination on the cause of death. All cases were reviewed and re-identified prior to analysis by the authors together.

3. Results

From January 2009 to December 2019, a total of 62 autopsy cases were due to anaphylactic reactions (Fig. 1). The general characteristics of these cases were shown in Table 1. Of the 62 decedents, 46 were male (74.2%) and 16 were female (25.8%), a male-to-female ratio of 2.88:1. There are 27 victims at 31–50 years (43.6%), followed by those at ≤30 years (n = 16, 25.8%), at 51–60 years (n = 10, 16.1%) and at ≥61 years (n = 8, 12.9%), the mean age of these subjects was 38.8 years, excluding 1 (1.6%) decedent whose age was unknown or unrecorded.

3.1. Medical characteristics

There were 7 cases with a history of asthma and 1 suspected drug allergy, leaving 54 cases without recorded history of allergy in the archives. Symptoms that began within 1 min accounted for 30 cases (48.4%), followed by those within 1 h (n = 23, 37.1%), 1–4 h (n = 4, 6.5%), 4–8 h (n = 1, 1.6%), >8 h (n = 2, 3.2%) and unknown (n = 2, 3.2%) (Table 2). Table 3 reveals the symptoms recorded in the document. The symptoms and signs of anaphylactic reactions mainly involved dyspnea (n = 35, 56.5%), sudden shock (n = 29, 46.8%) and cyanosis (n = 24, 38.7%), vomiting (n = 14, 22.6%), convulsion (n = 9, 14.5%), cold moist limbs (n = 7, 11.3%), foaming at the mouth (n = 5, 8.1%), skin rash (n = 4, 6.5%) and stomach pain (n = 3, 4.8%). Any clinical findings of anaphylactic reactions were not reported in three individuals (4.8%).

The highest percentage of deaths occurred within 1 h of onset of symptoms (n = 30, 48.4%), followed by within 1–4 h (n = 14, 22.6%), >8 h (n = 14, 22.6%) and 4–8 h (n = 2, 3.2%), while 2 decedents (3.2%) were without a relative record of the interval between the onset of symptoms and death (Table 2).

In this study, total serum IgE levels were measured in 11 cases, which ranged from 43.3 to 591.0 IU/ml (Table 4). Nine cases (81.8%) displayed the elevated serum IgE concentration (>87 IU/ml), with 63.6% (7/11) exceeding two folds of the reference value.

3.2. Allergens

In regards to the allergens (Table 5), the majority (n = 61, 98.4%) were allergic to medications: 45 cases (72.6%) were due to antibiotics, 4 cases (6.5%) presented with the reactions to Chinese herbs, 2 cases (3.2%) involved a combination of antibiotics and Chinese herbs, and 10 cases (16.1%) were considered to have others allergens (1 to contrast media, 1 to anesthetic agent, 1 to vaccine, 1 to Docetaxel, 1 to Ribavirin, 1 to bone peptide, 1 to bone melon extract, 1 to Tetanus antitoxin, 1 to Ambroxol hydrochloride, and 1 to Mucosolvan). In these cases of drug allergy, both single and combined medications were involved. In the remaining 1 case (1.6%), the allergen was unknown. Of the 62 cases, 44 deaths (71.0%) from illegal medical practices were recorded, which mainly occurred in illegal clinics. Of note, there were 3 cases (4.8%) in which patients were given antibiotic skin tests or dexamethasone prophylaxis prior to the hospitalization.

3.3. Postmortem findings

The autopsy findings are shown in Table 6, including gross and histological examination. The most frequent findings in the autopsy involved laryngeal edema (n = 53, 85.5%), eosinophil in multiple tissues (n = 53, 85.5%), pulmonary edema and congestion (n = 15, 24.2%), mucus plugging in the airways (n = 8, 13.0%) and asthma findings (n = 5, 8.1%). Erythematous skin rash was presented in 2 cases (3.2%), while laryngeal mast cell infiltration (1.6%) and bronchiectasis (1.6%) were observed in 1 case respectively.

In our study examining 62 cases of fatalities related to allergic reactions, thorough postmortem examinations and histopathological

Table 1
General characteristics of anaphylaxis fatalities.

Age, years	Male, n = 46	Female, n = 16
≤30	11	5
31–50	19	8
51–60	9	1
≥61	6	2
Unknown	1	0

Table 2
The intervals from allergen exposure to the onset of symptoms and from symptoms onset to death.

Time interval	Time of onset of symptoms, n = 62	Time of death after onset of episode, n = 62
Within 1 min	30 (48.4%)	0 (0.0%)
Within 1 h	23 (37.1%)	30 (48.4%)
1–4h	4 (6.5%)	14 (22.6%)
4–8h	1 (1.6%)	2 (3.2%)
>8h	2 (3.2%)	14 (22.6%)
Unknown	2 (3.2%)	2 (3.2%)

Table 3
Symptoms and signs of the 62 cases of anaphylaxis.

Symptoms and signs	Number	%
Dyspnea	35	56.5
Sudden shock	29	46.8
Cyanosis	24	38.7
Vomiting	14	22.6
Convulsion	9	14.5
Cold moist limbs	7	11.3
Foaming at the mouth	5	8.1
Skin rash	4	6.5
Stomach pain	3	4.8
Unknown	3	4.8

Table 4
Total serum IgE measurements in 11 cases.

IgE levels (IU/ml)	Number	%
<87	2	18.2
87–174	2	18.2
174–261	3	27.3
262–348	3	27.3
>348	1	9.0

analyses were conducted. Among these cases, anaphylaxis was identified as the single cause of death in 24 cases, accounting for 38.7% of the total. Importantly, the remaining 38 cases (61.3%) exhibited not only anaphylaxis but also one or more comorbid conditions (Table 7). Of the 38 deaths, involvement of cardiovascular disease (n = 21, 33.9%) included 13 cases (21.0%) of atherosclerotic coronary artery disease, 3 cases (4.8%) of both hypertension and atherosclerotic coronary artery disease, and 5 cases (8.1%) of others. Five cases (8.1%) of pneumonia, four cases (6.5%) of asthma, three cases (4.8%) of tumors, and another 4 cases (1 asthma with hypertension, 1 DIC, 1 aspiration asphyxia, and 1 hysteromyoma in operation) (4.8%) were also recorded. The remaining one (1.6%) was positive for methamphetamine, which was screened out primarily through toxicology tests.

4. Discussion

Anaphylactic death is a medical emergency that necessitates a forensic examination due to uncertainty about the cause of death, which occurs at home, in public, or in hospital because of the failure of rescue before diagnosis [17]. There are few analyses of fatal anaphylaxis based on forensic cases, probably owing to the low frequency of lethal anaphylaxis [13,18,19], urging us to further focus on the general, medical, and forensic conditions of fatal anaphylaxis. Herein, we investigated the demographic, medical, and forensic pathological characteristics of fatal anaphylaxis in Shanghai from January 2009 to December 2019 to provide knowledge of anaphylactic death prevention for patients' families and clinicians, as well as diagnosis for forensic pathologists.

In this study, we collected 62 anaphylactic deaths in Shanghai over 11 years. Of the 62 cases, the majority (43.6%) of victims were between the ages of 31 and 50, and the mean age of all decedents was 38.8 years. Notably, our finding showed a discrepancy with some previous studies with the median or mean age higher than 50 [17,20,21], which may be caused by variations in the age distribution of the population in the nations where the research were conducted. In addition, nearly three-quarters of the 62 cases were males, which were consistent with many surveys [8,17,22] and suggested that males are more liable to allergic death. Only 7 cases had a history of asthma and 1 was suspected of being realted to drug allergy, leaving 54 cases without recorded history of allergy in the archives. The reasons for this phenomenon included the absence of detailed clinical history in most cases, and the possibility of concealment and unawareness by the victim's family members. Certainly, not a few patients have never been attacked by anaphylaxis before death, suggesting that anaphylactic reactions should not be ignored in allergic populations by both clinicians and forensic pathologists. Asthma has been shown to be a risk factor for severe anaphylaxis, and the majority of deaths due to anaphylactic reactions to food

Table 5
Allergens information of the 62 cases.

Allergens	Number	%
Antibiotics	**45**	**72.6**
Beta-lactams	25	40.3
Cephalosporin	23	37.1
Penicillins	2	3.2
Lincosamides	6	9.7
Clindamycin	4	6.5
Lincomycin	2	3.2
Quinolones	2	3.2
Levofloxacin	2	3.2
Two or more drugs involved	12	19.4
Cefuroxime/Levofloxacin	1	1.6
Cefradine/Levofloxacin	1	1.6
Cefaclor/Lincomycin	1	1.6
Ceftriaxone/Lincomycin/Ceftazidime/Amikacin	1	1.6
Ceftriaxone/Lincomycin/Ribavirin	1	1.6
Ceftriaxone/Ribavirin	3	4.8
Lincomycin/Levofloxacin	1	1.6
Lincomycin/Ribavirin	2	3.2
Sulfamethoxazole/Analginum	1	1.6
A combination of antibiotics and Chinese herb	**2**	**3.2**
Cefazolin/Qingkailing compound	1	1.6
Lincomycin/Levofloxacin/Qingkailing compound	1	1.6
Chinese herb	**4**	**6.5**
Qingkailing compound	2	3.2
Ginko biloba extract	1	1.6
Herba Houttuyniae/Andrographolide	1	1.6
Others	**10**	**16.1**
Contrast media	1	1.6
Anesthetic agent	1	1.6
Vaccine	1	1.6
Docetaxel	1	1.6
Ribavirin	1	1.6
Bone peptide	1	1.6
Bone melon extract	1	1.6
Tetanus antitoxin	1	1.6
Ambroxol hydrochloride	1	1.6
Mucosolvan	1	1.6
Unknown	**1**	**1.6**

Table 6
Autopsy findings for 62 cases of anaphylaxis.

Autopsy findings	Number	%
Laryngeal edema	53	85.5
Eosinophils infiltration	53	85.5
Eosinophils in multiple tissues (lung, spleen, heart, laryngeal etc.)	39	62.9
Eosinophils in laryngeal and gastrointestinal tract	8	13.0
Eosinophils in laryngeal	3	4.8
Eosinophils in laryngeal and bronchial	2	3.2
Eosinophils infiltration (unspecified position)	1	1.6
Pulmonary edema and congestion	15	24.2
Mucus plugging in the airways	8	13.0
Asthma	5	8.1
Erythematous skin rash	2	3.2
Mast cells in laryngeal	1	1.6
Bronchiectasis	1	1.6

suffer from asthma [23]. In contrast with our findings, the decedents of anaphylaxis with history of asthma in our study were mainly caused by medication. The relationship between asthma and fatal anaphylactic reaction have been well established in some reports [23,24]. Given their similar clinical manifestations, it needs to be highlighted that anaphylactic reactions in patients with asthma should not be considered severe asthma attacks [11]. Our study revealed that anaphylactic reactions can manifest within 1 min (48.4%) or 1 h (37.1%) after exposure to allergens, and the majority of fatal cases (48.4%) caused by anaphylaxis occurred within the first hour after the onset of symptoms. This finding revealed the golden hour for the treatment of anaphylaxis, also meaning the importance of prompt diagnosis.

Major allergens include drugs, food and inset venom [25]. Data from the European Anaphylaxis Registry, food anaphylaxis was

Table 7
Comorbidities among these deaths due to anaphylaxis.

Comorbid diseases	Number	%
One or more comorbid diseases	**38**	**61.3**
Cardiovascular disease	21	33.9
Atherosclerotic coronary artery disease	13	21.0
Hypertension/Atherosclerotic coronary artery	3	4.8
Others	5	8.1
Pneumonia	5	8.1
Asthma	4	6.5
Tumor	3	4.8
Asthma/Hypertension	1	1.6
DIC	1	1.6
Aspiration asphyxia	1	1.6
Methamphetamine poisoning	1	1.6
Hysteromyoma in operation	1	1.6
No comorbid diseases	**24**	**38.7**

Abbreviation: DIC, Disseminated intravascular coagulation.

reported to be more prevalent (66%), followed by inset venom (19%) in children and adolescents [26]. Research indicated that food is the main cause of anaphylaxis in children, whereas drug and venom-induced anaphylaxis are more frequent in adults [27]. Moreover, approximately in 20% cases no trigger is identified, which is known as idiopathic anaphylaxis. In this retrospective analysis, of the 62 cases, medications (98.4%) were identified as the primary cause of death resulting from anaphylaxis, and the remaining 1 (1.6%) was unknown, without records of allergies to food or inset stings. However, food was the most common allergen to result in anaphylaxis mortality (35.3%), followed by medicines (29.4%) and bee stings (11.8%) between 2004 and 2006 in Maryland, United States [8]. The differences in these results may be related to the demographics of each region and where allergic deaths occur. More people died of medication allergies in hospitals or healthcare settings than at home [17], fatal anaphylaxis due to food and stings occurred outside the home and in rural settings [28], respectively. In our study, we discovered that drugs (98.4%) were main contributors of fatal anaphylaxis, most commonly antibiotics (72.6%). Among them, beta-lactam antibiotics (40.3%) were the most frequent allergens, including cephalosporin (37.1%) and penicillins (3.2%), followed by lincosamides (9.7%) and levofloxacin (3.2%), and 12 cases (19.4%) involved 2 or more antibiotics. As traditional drugs, cephalosporin and penicillins were considered as major allergens in several reports. Delage et al. reported that 69% of deaths were caused by penicillins in drug-induced fatal anaphylaxis [29]. Meanwhile, other authors have shown that penicillins or cephalosporin in 5.9% and 4.8% of all cases of drugs induced-anaphylaxis [28]. According to a retrospective analysis of drug-related anaphylaxis deaths in the FDA Adverse Event Reporting System (FAERS) from 1999 to 2019 [30], it was found that ceftriaxone, cefoperazone and levofloxacin accounted for 28.57%, 27.66% and 4.72% of drug-specific anaphylactic reports, respectively. There were relatively few case reports of anaphylactic death associated with clindamycin and lincomycin and other antibiotics mentioned in our study. Chiuan et al. reported a case of clindamycin-induced anaphylactic shock during general anesthesia [31]. The discrepancy among them may be due to differences in the prevalence of allergens or in the methodologies used for data collection [17]. Besides antibiotics, 4 cases involved reactions to Chinese herbs in our study, which have complex ingredients, and it was difficult to identify the specific allergic substance. In addition, there was 1 case allergic to contrast media and 1 case allergic to anesthetic agents, which was not a rare finding and had been recorded in other studies [11]. We only found 1 victim who was allergic to the vaccine. Vaccines are a rare trigger of anaphylaxis, and allergic reactions to the vaccine have been reported in 5 cases after the administration of 7,644,049 vaccine doses [32]. The rest of the allergens, such as bone peptide, bone melon extract, etc., were rarely reported.

In this study, we recorded one or more comorbid diseases in 38 anaphylactic deaths by postmortem examination. Cardiovascular disease was the most frequent comorbidity (33.9%), including 13 cases of atherosclerotic coronary artery disease, 3 cases of both hypertension and atherosclerotic coronary artery disease, and 5 cases of others, followed by 5 cases of pneumonia, 4 cases of asthma, and 3 cases of tumor. According to research on concomitant conditions in fatal anaphylaxis, a study showed that ischemic heart disease and obesity or COPD were more frequent in drugs-related deaths [33]. Mosbech et al. reported that cardiovascular diseases accounted for 19.2%, arterial hypertension for 7.7% and asthma for 3.84% [34]. The report also indicated that ischemic heart disease was linked to an increased rate of comorbidities in anaphylaxis in 44% anaphylaxis patients and congestive heart failure in 16% [35]. Clearly, cardiovascular disease was more common in patients who died from fatal anaphylaxis, which was also consistent with our results, and probably due to high rates of comorbidities in older subjects with cardiovascular disease.

Admittedly, postmortem diagnosis of deadly anaphylaxis is still formidable for forensic pathologists, mainly due to poor or nonspecific gross and histological findings [36,37]. According to previous research, pulmonary edema and congestion were the most common histological characteristics (50–70%), while upper airway edema (30–70%) was secondary [17]. Mucus plugs and emphysema were also reported in anaphylaxis deaths, albeit the percentage (11.7–28.6%) was lower [8,20,22,29,35]. Laryngeal edema, petechial haemorrhages, and hyper-inflated lungs have been described, along with visceral congestion and pulmonary edema [21]. Anaphylactic mortality eosinophil and mast cell infiltration in the spleen, respiratory tract, and gastrointestinal tract were significant symbols for anaphylactic reactions [8,38,39], however, decomposition, a common occurrence in forensic practice, might impede our detection for it [5]. In our study, laryngeal edema (85.5%), eosinophil in multiple tissues (85.5%), pulmonary edema and congestion (24.2%), mucus plugging in the airways (13%) were the most frequent findings in the autopsy. The above nonspecific pathological

findings in our study were generally consistent with others, albeit there were differences in percentage among them. In routine cases, forensic pathologists currently rely on exclusion and circumstantial evidence to make a postmortem diagnosis of death due to anaphylaxis [8,40]. Given the dilemma, researchers are trying to explore postmortem diagnostic biomarkers for fatal anaphylaxis. From a forensic perspective, serum tryptase has been proven to be a promising diagnostic biomarker for deaths due to anaphylaxis [41, 42]. Chymase [43] histamine, diamine oxidase [44], and carboxypeptidase A [45] have also been reported as possible postmortem diagnostic markers in anaphylactic death. Nevertheless, the postmortem interval, sampling technique, and varied reference values may limit their usefulness, and non-specificity should be considered in some conditions. An increased specific IgE level in decedents who have been exposed to the allergen supports a diagnosis of fatal anaphylaxis [46]. Conversely, a lack of increased IgE does not rule out anaphylactic death [47]. So, elevated levels of IgE only support the diagnosis of anaphylactic death, but may not be a specific marker. In our study, serum IgE levels were measured in 11 cases, which ranged from 43.3 to 591 IU/ml, and 9 cases showed the serum IgE concentration was elevated. Our results further illustrated the role of IgE in anaphylactic death. The quantification of infiltration and activation of mast cells and eosinophils by immunohistological technique is a promising field and needs to be further studied in the postmortem diagnosis of fatal anaphylaxis [46]. We believe that it is urgent to further explore the diagnostic biomarkers of anaphylactic death, which should be specific, cost-effective and less affected by postmortem interval.

5. Conclusion

Males predominated in anaphylactic fatalities, and the average was 38.8 years in our study. Medications, particularly antibiotics, were the most prevalent causes of anaphylaxis, whereas illegal medical practice was the main characteristic of anaphylactic death in Shanghai between 2009 and 2019. The postmortem findings were not specific, but the most frequent comorbidity was cardiovascular disease. To diagnose anaphylactic death, detailed data on allergen exposure, clinical history and manifestations, autopsy findings of cases, as well as specific biomarkers or forensic workflow in cases of fatal anaphylaxis, are required. More importantly, understanding the demographics of individuals who experience fatal anaphylaxis can aid in identifying high-risk populations and informing targeted public health interventions. Analysis of medical histories in these cases plays a crucial role in identifying common triggers, which is instrumental in the development of preventive strategies and improved management guidelines. Additionally, by focusing on investigating fatal anaphylaxis cases resulting from antibiotic misuse, clinicians can enhance their understanding of the risks associated with inappropriate antibiotic use and implement measures to promote safer practices. The postmortem findings significantly contribute to identifying the organs involved in fatal anaphylaxis and discovering potential causative agents, which can greatly assist in improving the diagnosis, treatment, and overall management of patients in clinical practice.

Data availability statement

Data will be made available on request.

Funding

This work was supported by the Key Projects of National Natural Science Foundation of China (Grant Number 81430047), and National Key Research and Development Program (Grant Number 2018 YFC0807202).

Ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

CRediT authorship contribution statement

Wen-xin Li: Formal analysis, Methodology, Supervision, Writing – original draft. **Cheng-hui Sun:** Formal analysis, Methodology, Validation, Writing – original draft. **Zheng-dong Li:** Formal analysis, Methodology. **Jun-yi Lin:** Investigation, Resources. **Yu Shao:** Formal analysis. **Long Chen:** Formal analysis. **Li-liang Li:** Investigation, Methodology. **Xing Ye:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Yi-wen Shen:** Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to thank Ming-yao Zeng (Department of Pathology at Shanghai Medical College), Chen-guang Bai (Department of Pathology at Shanghai Changhai Hospital) and Lei Zhao (Department of Pathology at Shanghai JiaoTong University School of Medicine) for investigation of the anaphylaxis cases and submission of case materials.

References

[1] L.L. Reber, J.D. Hernandez, S.J. Galli, The pathophysiology of anaphylaxis, J. Allergy Clin. Immunol. 140 (2017) 335–348.
[2] F.E. Simons, L.R. Ardusso, M.B. Bilo, V. Cardona, M. Ebisawa, Y.M. El-Gamal, P. Lieberman, R.F. Lockey, A. Muraro, G. Roberts, M. Sanchez-Borges, A. Sheikh, L. P. Shek, D.V. Wallace, M. Worm, International consensus on (ICON) anaphylaxis, World Allergy Organ J 7 (2014) 9.
[3] D. LoVerde, O.I. Iweala, A. Eginli, G. Krishnaswamy, Anaphylaxis, Chest 153 (2018) 528–543.
[4] A. Nara, T. Aki, T. Funakoshi, K. Uchida, H. Nakayama, K. Uemura, Death due to blood transfusion-induced anaphylactic shock: a case report, Leg. Med. 12 (2010) 148–150.
[5] R. Erjon, R.B. Luca, C. Annalisa, S. Enrico, P. Cristian, Postmortem diagnosis of anaphylaxis in presence of decompositional changes, Journal of Forensic and Legal Medicine 38 (2016) 97–100.
[6] S. Unkrig, L. Hagemeier, B. Madea, Postmortem diagnostics of assumed food anaphylaxis in an unexpected death, Forensic Sci. Int. 198 (2010) e1–e4.
[7] J. Herbst, K. Heath, R. Heddle, J.D. Gilbert, R.W. Byard, Multiple bee stings, peritumoral mast cell degranulation and anaphylaxis–is there a relationship? J Forensic Leg Med 20 (2013) 591–594.
[8] Y. Shen, L. Li, J. Grant, A. Rubio, Z. Zhao, X. Zhang, L. Zhou, D. Fowler, Anaphylactic deaths in Maryland (United States) and Shanghai (China): a review of forensic autopsy cases from 2004 to 2006, Forensic Sci. Int. 186 (2009) 1–5.
[9] A. Sauvageau, Death from a possible anaphylactic reaction to ecstasy, Clin. Toxicol. 46 (2008) 156.
[10] E. Edston, M. van Hage-Hamsten, Death in anaphylaxis in a man with house dust mite allergy, Int. J. Leg. Med. 117 (2003) 299–301.
[11] L. Irene, S. Simon, Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985 to 2005, Pathology 38 (2006) 328–332.
[12] R.W. Byard, Anaphylaxis at autopsy, Forensic science, medicine, and pathology 13 (2017) 269–271.
[13] A.M.A. Tejedor, M.M. Moro, G.M.V. Múgica, Epidemiology of anaphylaxis, Clinical and experimental allergy, journal of the British Society for Allergy and Clinical Immunology 45 (2015) 1027–1039.
[14] S.M. Megan, M. F.B, K.V.H. Holly, D.S. Nilay, L.C. Ronna, Risk factors for severe anaphylaxis in the United States, Annals of Allergy, Asthma & Immunology 119 (2017) 356–361.
[15] M.R. Chaaban, Z. Warren, J.G. Baillargeon, G. Baillargeon, V. Resto, Y.-F. Kuo, Epidemiology and trends of anaphylaxis in the United States, 2004-2016, International forum of allergy & rhinology 9 (2019) 607–614.
[16] M.C. Pflipsen, K.M.V. Colon, Anaphylaxis: recognition and management, Am. Fam. Physician 102 (2020) 355–362.
[17] P. Martínez-Fernandez, G. Vallejo-de-Torres, M.S. Sánchez-de-León-Robles, E. Navarro-Escayola, M. Moro-Moro, N. Alberti-Masgrau, M.A. Tejedor-Alonso, Medical and pathologic characteristics of fatal anaphylaxis: a Spanish nationwide 17-year series, Forensic Sci. Med. Pathol. 15 (2019) 369–381.
[18] T. Umasunthar, J. Leonardi-Bee, M. Hodes, P.J. Turner, C. Gore, P. Habibi, J.O. Warner, R.J. Boyle, Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis, Clin. Exp. Allergy : journal of the British Society for Allergy and Clinical Immunology 43 (2013) 1333–1341.
[19] J. Elina, Y.L. Robert, M.S. Moira, P.M. Aileen, Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations, J. Allergy Clin. Immunol. 134 (2014) 1318–1328.e1317.
[20] B.U. Da, C. Moreschi, Post-mortem diagnosis of anaphylaxis: a difficult task in forensic medicine, Forensic Sci. Int. 204 (2011) 1–5.
[21] R.S. Pumphrey, I.S. Roberts, Postmortem findings after fatal anaphylactic reactions, J. Clin. Pathol. 53 (2000) 273–276.
[22] M. Larry, M.D. Theodore, B. Larry, Case fatality and population mortality associated with anaphylaxis in the United States, J. Allergy Clin. Immunol. 133 (2014) 1075–1083.
[23] S.A. Bock, A. Munoz-Furlong, H.A. Sampson, Fatalities due to anaphylactic reactions to foods, J. Allergy Clin. Immunol. 107 (2001) 191–193.
[24] H.A. Sampson, L. Mendelson, J.P. Rosen, Fatal and near-fatal anaphylactic reactions to food in children and adolescents, N. Engl. J. Med. 327 (1992) 380–384.
[25] A. Anagnostou, Anaphylaxis in children: epidemiology, risk factors and management, Curr. Pediatr. Rev. 14 (2018) 180–186.
[26] B.G. Linus, D. Sabine, M.-V. Anne, K. Alice, L. Lars, S. Thomas, R. Franziska, N. Katja, M. Ioana, R. Eirini, S. Kathrin, O. Hagen, R. Thomas, M. Tihomir, L. Roland, F.-R. Montserrat, L.K. Marek, B.B. Maria, O.B.H. Jonathan, G.P. Nikolaos, B. Kirsten, M. Antonella, W. Margitta, Anaphylaxis in children and adolescents: the European anaphylaxis Registry, J. Allergy Clin. Immunol. 137 (2016) 1128–1137.e1121.
[27] A. Muraro, G. Roberts, M. Worm, M.B. Bilò, K. Brockow, R.M. Fernández, A.F. Santos, Z.Q. Zolkipli, A. Bellou, K. Beyer, C. Bindslev-Jensen, V. Cardona, A. T. Clark, P. Demoly, A.E.J. Dubois, A. DunnGalvin, P. Eigenmann, S. Halken, L. Harada, G. Lack, M. Jutel, B. Niggemann, F. Ruëff, F. Timmermans, B.J. Vlieg-Boerstra, T. Werfel, S. Dhami, S. Panesar, C.A. Akdis, A. Sheikh, Anaphylaxis: guidelines from the European Academy of allergy and clinical immunology, Allergy 69 (2014) 1026–1045.
[28] R.J. Mullins, B.K. Wainstein, E.H. Barnes, W.K. Liew, D.E. Campbell, Increases in anaphylaxis fatalities in Australia from 1997 to 2013, Clinical and experimental allergy, journal of the British Society for Allergy and Clinical Immunology 46 (2016) 1099–1110.
[29] C. Delage, N.S. Irey, Anaphylactic deaths: a clinicopathologic study of 43 cases, J. Forensic Sci. 17 (1972) 525–540.
[30] R.J. Yu, M.S. Krantz, E.J. Phillips, C.A. Stone Jr., Emerging causes of drug-induced anaphylaxis: a review of anaphylaxis-associated reports in the FDA Adverse event reporting system (FAERS), J. Allergy Clin. Immunol. Pract. 9 (2021) 819–829 e812.
[31] C.S. Chiou, S.M. Lin, S.P. Lin, W.G. Chang, K.H. Chan, C.K. Ting, Clindamycin-induced anaphylactic shock during general anesthesia, J. Chin. Med. Assoc. 69 (2006) 549–551.
[32] K. Bohlke, R.L. Davis, S.M. Marcy, M.M. Braun, F. DeStefano, S.B. Black, J.P. Mullooly, R.S. Thompson, Risk of anaphylaxis after vaccination of children and adolescents, Pediatrics 112 (2003) 815–820.
[33] M.A. Tejedor-Alonso, P. Martínez-Fernandez, G. Vallejo-de-Torres, E. Navarro-Escayola, M. Moro-Moro, N. Alberti-Masgrau, Clinical and demographic characteristics of fatal anaphylaxis in Spain (1998-2011): a comparison between a series from the hospital system and a national forensic series, Clinical and experimental allergy, journal of the British Society for Allergy and Clinical Immunology 49 (2019) 82–91.
[34] H. Mosbech, Death caused by wasp and bee stings in Denmark 1960-1980, Allergy 38 (1983) 195–200.
[35] A.G. Paul, D.R. Brian, L. Barry, Fatal anaphylaxis: postmortem findings and associated comorbid diseases, Ann. Allergy Asthma Immunol. 98 (2007) 252–257.
[36] B. Kari, L.D. Robert, D. Frank, S. M.M, M. M.B, S.T. Robert, Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization, J. Allergy Clin. Immunol. 113 (2003) 536–542.
[37] R.J. Mullins, Anaphylaxis: risk factors for recurrence, Clinical and experimental allergy, journal of the British Society for Allergy and Clinical Immunology 33 (2003) 1033–1040.
[38] E. Edston, Accumulation of eosinophils, mast cells, and basophils in the spleen in anaphylactic deaths, Forensic Sci. Med. Pathol. 9 (2013) 496–500.
[39] T. Nicoletta, R.B. Luca, G. Giorgio, B. Giuseppe, Immediate anaphylactic death following antibiotics injection: splenic eosinophilia easily revealed by pagoda red stain, Forensic Sci. Int. 181 (2008) 21–25.
[40] C. Rossana, Diagnosis of anaphylactic death in forensics: review and future perspectives, Leg. Med. 22 (2016) 75–81.
[41] K.-J. Sun, J.-T. He, H.-Y. Huang, Y. Xue, X.-L. Xie, Q. Wang, Diagnostic role of serum tryptase in anaphylactic deaths in forensic medicine: a systematic review and meta-analysis, Forensic Sci. Med. Pathol. 14 (2018) 209–215.
[42] V. Payne, P.C. Kam, Mast cell tryptase: a review of its physiology and clinical significance, Anaesthesia 59 (2004) 695–703.
[43] H. Nishio, S. Takai, M. Miyazaki, H. Horiuchi, M. Osawa, K. Uemura, K. Yoshida, M. Mukaida, Y. Ueno, K. Suzuki, Usefulness of serum mast cell-specific chymase levels for postmortem diagnosis of anaphylaxis, Int. J. Leg. Med. 119 (2005) 331–334.
[44] D.E. Mayer, A. Krauskopf, W. Hemmer, K. Moritz, R. Jarisch, C. Reiter, Usefulness of post mortem determination of serum tryptase, histamine and diamine oxidase in the diagnosis of fatal anaphylaxis, Forensic Sci. Int. 212 (2011) 96–101.

[45] X.J. Guo, Y.Y. Wang, H.Y. Zhang, Q.Q. Jin, C.R. Gao, Mast cell tryptase and carboxypeptidase A expression in body fluid and gastrointestinal tract associated with drug-related fatal anaphylaxis, World J. Gastroenterol. 21 (2015) 13288–13293.
[46] N. Heldring, L. Kahn, B. Zilg, Fatal anaphylactic shock: a review of postmortem biomarkers and diagnostics, Forensic Sci. Int. 323 (2021) 110814.
[47] G. Jack, O. Benjamin, D.B. Ugo, P. Cristian, T. Rexson, Post mortem tryptase: a review of literature on its use, sampling and interpretation in the investigation of fatal anaphylaxis, Forensic Sci. Int. 314 (2020) 110415.