Epidemiology of suspected life-threatening perioperative anaphylaxis: a cross-sectional multicentre study in China

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Abstract

Background: Perioperative anaphylaxis is relatively rare but can be life-threatening. The incidence in China is unknown and may differ from other global geographic regions. This study was therefore designed to understand the incidence of perioperative anaphylaxis in China.

Methods: We enrolled 112 tertiary care hospitals from seven distinct geographic areas in mainland China. We collected information about Ring and Messmer III and IV reactions from September 2018 to August 2019. A collaborative educational learning network was used to reduce diagnostic errors. Information about patient characteristics, clinical features, treatment, and clinical outcomes were recorded and analysed.

Results: A total of 447 cases of 5 078 118 surgical procedures met inclusion criteria. The incidence of suspected perioperative anaphylaxis throughout China was one in 11 360 anaesthetics (95% confidence interval [CI], with a range of 1:12 521 to 1:10 397). The incidence in South China was higher (one in 6050; 95% CI, from 1:8013 to 1:4859) than in Northeast China (one in 19 262; 95% CI, from 1:33 088 to 1:13 585) (P<0.01) with an increasing trend from the north to the south. The most common clinical manifestations were hypotension (91.1%) and tachycardia (65.3%). The majority of patients (83.4%) were given epinephrine. A total of 27 patients (6.0%) required cardiopulmonary resuscitation. Ultimately, nine patients died (2.0%).

Conclusions: This nationwide survey showed an incidence of perioperative anaphylaxis of one in 11 360, but this varied significantly by region. The underlying reason for this pattern remains unknown and could be attributable to environmental or genetic influences, which requires further investigation.

Clinical registry number: ChiCTR1900025956.

Keywords: anaesthesia; allergy; China; epidemiology; perioperative anaphylaxis
Perioperative anaphylaxis can be life-threatening, leading to prolonged hospitalisation and death. Effective intervention requires a timely clinical diagnosis based on one or more signs of hypotension, arrhythmia, increased airway resistance, and cutaneous flushing or rash. Immune and non-immune drug reactions in addition to physiological responses to anaesthesia and surgery can be involved. Some investigators have grouped all potential causes of perioperative anaphylaxis into a category of ‘all cause’ as immediate triggers can be difficult to identify, respond to similar treatment, and have similar patient outcomes regardless of the offending trigger.

The recent publication by Harper and colleagues of 266 life-threatening, all-cause cases of perioperative anaphylaxis from the 6th National Audit Project (NAP6) in the UK reported differences between the estimated 1:10 000 incidence compared with other geographic locations such as the 1:11 000 in Australia, and 1:5500 in Thailand. The reasons for these differences were unclear but choice of medications, diagnostic accuracy, environmental factors, and fidelity of reporting have been proposed as contributing causes to the variance in incidence.

Previous investigators reported similar geographic differences in the frequency of perioperative anaphylaxis and questioned if characteristics of distinct populations could contribute to the variation in incidence. To confirm geographic variation as a descriptor of perioperative anaphylaxis, investigators called for repeated cross-sectional epidemiological surveys in different countries. These findings underlie the first purpose of our study, to describe the incidence of all-cause life-threatening suspected perioperative anaphylaxis in China.

The reasons for geographic variation in incidence of anaphylactic symptoms during anaesthesia are not fully understood. However, investigators have questioned if inherited differences between study populations could play a role. Although a genetic basis for allergy and anaphylaxis requires further study, new findings suggest a genetic component of anaphylaxis. For example, immune-driven immunoglobulin E (IgE) reactions to beta-lactam drugs can be affected by two unrelated loci on chromosome 6. Yet, proteins coded by chromosome 11 also cause direct mast cell degranulation, producing an end result that is identical to IgE degranulation.

The latter is one mechanism investigators are evaluating as a potential cause of anaphylactic symptoms after exposure to neuromuscular blocking drugs and opioids.

Data derived from the Human Genome Diversity and Genome Asia 100K Projects showed that inherited traits cluster in populations with a greater degree of overall genomic relatedness. Investigators have been able to trace populations with high gene frequencies to a common ancestry that is often identified through migration patterns. Genomic analysis has shown significant differences between the north and south of China that were traced to migration routes created by the Yangtze River. Information about genome associated migration ancestry within China helps us accomplish our second aim: to identify a population with a concentration of suspected perioperative anaphylaxis that overlapped with established genome-related ancestry. We suggest that genome-wide testing in related populations with higher and lower frequencies of suspected perioperative anaphylaxis will help determine what role if any genetics plays in the geographic variations between studies.

To accomplish these aims, our study was designed to sample all geographic regions of China for descriptive purposes. We developed a collaborative network of 112 study sites that used a common educational and quality review framework; this model has been shown to improve adherence to protocols.

**Methods**

**Study approval and funding**

The study was approved by the Institutional Review Board of China—Japan Friendship Hospital, on August 30, 2019 and registered at the Chinese Clinical Trials Registry on September 15, 2019 (ChiCTR1900025956). The study was conducted in compliance with the Declaration of Helsinki. All study subjects were de-identified, and therefore informed consent was waived by the Institutional Review Board. The study was funded by National Centre for Medical Service Administration, National Health and Family Planning Commission, China (Bureau of Medical Administration [2019] No. 049). The STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) checklist for cross-sectional studies was followed for the conduct and writing of this study.

**Organisation and process for multicentre data collection**

The 112 tertiary hospitals were enrolled from seven macro-geographic regions of China defined by the Ministry of Commerce of the People’s Republic of China. These regions include South and Southwest China, East China, Central China, and the regions of Northwest, North, and Northeast China. All participating hospitals had minimal case volumes of 6000 per year.

Principle investigators used a single set of educational modules and delivery methods (learning framework) at all 112 study centres in the collaborative network to minimise knowledge deficits among participants that could cause variations in reported cases (Supplementary Fig. S1). A central team of anaesthetists worked with representatives of the collaborative network to develop concise teaching modules for the diagnosis, reporting, and recording of data. All protocols were tested for ease of use at participating centres. The core
team instituted a ‘participant comment period’ to elicit input from staff at all participating sites each time procedural steps were built, or changes were made to the protocol. The first round of educational modules was completed at the 112 centres within 6 months before the data collection period. Each educational module/protocol was distributed on paper and electronically to the 112 centres in the network. One anaesthetist from each of the participating sites was trained by the central team to lead the teaching module at each centre. The lead anaesthetist at each centre was responsible for reporting, recording of data, reviewing cases, and consulting the central team. Allergy cases were collected from medical records, quality measures, adverse event reports, and death records, of which mandatory reporting are required in China. The same research toolbox was available at each site and included immediate online access to the learning module and a hotline service staffed by the central team of investigators who received additional training in allergy and anaphylaxis. Although the initial diagnosis was made in the operating room by the attending anaesthetist, all case entries were later reviewed by the team leader and used for teaching in regular educational reviews at each study site.

Quality assurance of data and collection process
All cases forwarded from study sites for submission into the databank were first reviewed by the lead investigator at each site. Cases that met diagnostic criteria were submitted to the core team of investigators for a second tier of quality analysis. The process used to identify and submit cases was reviewed at each study site. Lead investigators from the study sites met virtually with members of the central investigative team twice during the data collection period to address questions and review study protocols. If there was remaining uncertainty, an individual from the field of allergy medicine with prior experience in anaesthesia drug-induced reactions was consulted. If the evidence for perioperative anaphylaxis was not explicit, further evidence including medical history (especially cardiovascular, pulmonary, and neurological), medication history, blood loss, sepsis, physical examination, and laboratory results were collected and analysed.

Definition of terms
We collected information from cases of life-threatening clinical reactions corresponding to Ring and Messmer grade III and IV. This classification system allowed us to compare our findings with similar reactions in other studies. These reactions are generally associated with a mortality rate of 3–9%, in addition to the 2% of patients experiencing neurological injury.

Anaphylaxis was defined using published guidelines. A diagnosis was made when there was at least one of the following clinical signs: (1) life-threatening cardiovascular changes, defined as severe hypotension, tachycardia, or cardiac arrest; (2) respiratory symptoms including bronchospasm and airway obstruction in awake patients or increased airway pressures in ventilated patients; and (3) integument symptoms of erythema, urticaria, mucosal changes of angioedema, or oedema (Supplementary Table S1).

All study sites used the same standardised approach to differentiate possible causes of intraoperative haemodynamic instability and bronchospasm. All patients were evaluated for haemorrhagic shock, deep anaesthesia, and myocardial events. Conduction abnormalities suggestive of infarction or pulmonary embolus were examined by point of care ultrasound. Bronchospasm was evaluated by careful search for mechanical (tracheal tube, anaesthesia machine) or pulmonary causes. The presence of bilateral wheezing suggested a systemic process, whereas localised findings warranted an immediate chest radiograph. The strength of diagnosis was based upon a systematic evaluation of a standard differential diagnosis and a post hoc quality review.

Data collection
Written and electronic templated Case Report Forms were used to collect information about patient characteristics, signs of anaphylaxis, medications given, allergy histories, and comorbidities. The primary investigator at each hospital reviewed the templated checklist of all suspected perioperative anaphylaxis. If any data were missing, we asked the primary investigator to collect the data again. Cases were included when symptoms compatible with Ring and Messmer III and IV anaphylactic reactions occurred after patients entered the operating room. Patients with reactions that began in the preoperative and postoperative areas or those with suspected Ring and Messmer scores of I and II were excluded from study.

Statistical analysis
The EpiData 3.1 (Odense, Denmark) statistical software package was used for database design and data entry. Two data entry clerks who were blinded to the study objective input patient data. Accuracy was checked via visual inspection of the database and examination of data for unexplained outliers. Descriptive continuous variables were given as the mean or median (inter-quartile range [IQR], range) and dichotomous variables were described as frequency (percentage). Differences in categorical variables were determined using the Fisher’s exact or Pearson χ² test. A P value of <0.05 was considered statistically significant. All analyses were performed in SPSS Statistics 26.0 (IBM SPSS, Armonk, NY, USA).

Results
Patient populations with anaphylactic reaction
During the study period, 5 078 118 surgical procedures were performed with general or local anaesthesia with sedation at the 112 Chinese hospitals. A total of 551 life-threatening cases of suspected perioperative anaphylaxis were reported, and 97 cases were subsequently excluded. Seven cases were excluded by the central quality team because the event was not within the study period. The remaining 90 excluded cases had insufficient diagnostic criteria. The two-step quality review process accepted 447 cases of suspected perioperative anaphylaxis into the database (Fig. 1). The incidence of suspected life-threatening perioperative anaphylaxis at all study
The incidence of perioperative anaphylaxis was greater in South China compared with northern regions (Northeast, Northwest, and North China) at one in 6050 (95% CI, from 1.8013 to 1.4859; P<0.01) patients. Southwest China had the next highest incidence at one in 8280 (95% CI, from 1.11698 to 1.6408; P<0.05) patients affected. The lowest incidences were from the northern regions of China. The Northeast, North China and Northwest regions had rates of one in 19262 (95% CI, from 1.33088 to 1.13585), one in 18765 (95% CI, from 1.20232 to 1.11703), and one in 13319 (95% CI, from 1.20381 to 1.9892), respectively. Central China and East China had intermediate rates of one in 13265 (95% CI, from 1.17810 to 1.10568) and one in 11059 (95% CI, from 1.13001 to 1.9621), respectively (Fig. 2).

**Clinical features associated with perioperative anaphylaxis**

Most patients presented with more than one clinical sign. Hypotension and tachycardia were the most common presenting signs (n=424; 94.9%). Rash, erythema, hives, or mucosal swelling were part of the presenting signs in 306 cases (68.4%). In contrast, respiratory abnormalities including bronchospasm, increased airway pressures, or airway swelling were part of the initial presentation in only 155 patients (34.7%).

Hypotension was most common, affecting 407 (91.1%) patients whereas new onset tachycardia occurred in 292 patients (65.3%). Other signs were less common and included rash and hives (n=221; 49.4%), skin erythema (n=214; 47.9%), and airway obstruction/high airway pressure (n=82; 18.3%). The latter signs led to cyanosis/oxygen desaturation in all 82 patients (Fig. 3).

In 407 patients who developed hypotension, only 27 patients (6.6%) had hypotension without other signs. Hypotension caused cardiovascular collapse with systolic blood pressures that were unrecordable in 19 of 407 patients (4.7%), and <50 mm Hg in 76 patients (18.7%). All 292 patients with tachycardia exhibited another symptom, and the majority (n=276; 94.5%) had concomitant severe hypotension.

Most patients exhibited only two of the potential three types of signs. The combination of cutaneous and haemodynamic or haemodynamic and respiratory signs were the most common clusters. This is likely related to the preponderance of both signs. As anticipated, the combination of respiratory and cutaneous signs was rare (n=5). The minority of 447 patients exhibited all three typical signs (n=94; 21.0%) or a single sign (n=103; 23.0%). No patient with isolated cutaneous changes was diagnosed with perioperative anaphylaxis as this was not considered life-threatening.

**Choice of medical treatment**

Epinephrine was administered to 373 of all 447 affected patients (83.4%) for resuscitation, and 232 of these (62.2%) received epinephrine as the initial treatment. A total of 241 patients received repeated epinephrine. The total dose of epinephrine before continuous infusion was 60 μg (IQR, 20–265 μg). Far fewer of the 447 patients (n=151; 33.8%) received norepinephrine, and it was the first choice of treatment in only 36.4% (n=5) of 151 patients treated.

Continuous i.v. epinephrine infusions were used more often in patients who received less than the recommended initial dose of epinephrine (n=81/232; 35%) compared with patients who were given recommended doses (n=31/232; 13.4%) for treatment.

A total of 27 of the 447 patients (6.0%) required cardiopulmonary resuscitation. Most of these patients (n=20; 74%) had a diagnosis of pulseless electrical activity. The remaining seven patients had a palpable blood pressure <50 mm Hg. The median rescue time of all patients who received cardiac compressions was 7.5 min (IQR, 2–38.5 min).

**Patient outcomes**

Nine of the 447 patients (2.0%) died. Of these, seven patients had cardiopulmonary resuscitation. Two patients who did not
receive chest compressions died after high-dose vasopressors within 8 days of admission to the ICU. Although no patient characteristics distinguished survivors from non-survivors, the prevalence of coronary artery disease was greater in the patients who died; two of nine (22%) deaths compared with the remaining 438 patients (3.2%; \( P = 0.03 \)) had a history of coronary artery disease (Table 2).

**Discussion**

Using a study design to improve diagnostic and reporting accuracy across 112 participating study centres in China, we found that one in 11 360 patients had life-threatening reactions during anaesthesia care where hypotension was the most common sign and initial presentation. The geographic analysis confirmed a statistically significant higher incidence in southern provinces, a population with a high degree of shared genomic signatures compared with other regions of China. Future genomic testing is necessary to identify why the cause of incidence variations in suspected and even immune-tryptase-positive perioperative anaphylaxis is poorly understood. Contributing causes include differences in anaesthesia drugs and techniques, reporting fidelity, and diagnostic errors. The latter is of importance in the operating room as typical symptoms such as visceral cramping and altered sensorium are masked by sedation or general anaesthesia. A diagnosis may be overlooked in patients with milder symptoms, whereas the use of drugs with direct effects such as flushing and hypotension can lead to diagnostic errors. A lack of international standards defining clinical terms used in diagnosis adds to reporting variation.

Our study was designed to reduce sources of variation and error that influence estimates of incidence. We therefore used protocols that provided clear parameters of life-threatening reactions that were consistent with medical decisions to initiate treatment. These parameters corresponded most closely to Ring and Messmer III and IV reactions. Further, anaesthesia drugs and techniques did not vary significantly between regions of China (Supplementary Table S2 and S3).

We used the NAP6 as a measure of external validity because it collected information about similar severity of all-cause reactions. The signs of suspected perioperative anaphylaxis reported in our study and NAP6 were similar in frequency and groupings. In both studies, hypotension occurred in highest frequency whereas respiratory symptoms were least common, and cutaneous manifestations were always grouped with other signs. In our study, problems in diagnostic accuracy and reporting were targeted as sources of resolvable error and addressed using a learning framework where healthcare providers engaged in collaborative education using a single set of core competencies and a consensus-based process to build uniform knowledge at each study site. This approach has been shown to be effective and is used in diverse organisational conditions to improve adherence to protocols.

The incidence of suspected perioperative anaphylaxis from 112 sites in China of one in 11 360 was in the lower range of the one in 1250 to one in 18 600 cited for other countries. The estimate in this study was similar to that in NAP6 and may be related to the fact that both studies analysed similar clinical events. Although our numbers are similar to NAP6, we agree that use of life-threatening signs for diagnosis leads to an underestimation of incidence.

The rates of one in 6050 in south China were significantly higher than the rates of one in 19 262 from the northern provinces. The use of our single study design in all 112 sites suggests this magnitude of difference is unlikely because of overlooked diagnostic or reporting errors. Furthermore, the difference in incidence was observed for all northern compared with southern regions, and this strongly suggests a systematic difference that is population based. These findings are consistent with evidence from the Chinese Human Genome Diversity Project and the larger Human Genome Project showing differences in genetic ancestry and genomic-derived relatedness between inhabitants of the south and north of China.
This study did not examine genetic data, and future investigations are needed to test our hypothesis that population differences in the genome could cause some of the geographic variation in suspected cases of perioperative anaphylaxis. Testing is now possible with the catalogue of more than 3 billion genes for reference from the Human Genome Project.

![Incidence of suspected life-threatening perioperative anaphylaxis in seven geographical regions of mainland China.](image)

Fig 2. Incidence of suspected life-threatening perioperative anaphylaxis in seven geographical regions of mainland China.

![Common presenting features during anaphylactic reactions.](image)

Fig 3. Common presenting features during anaphylactic reactions.
We suggest the next step is testing for genes linked to anaphylactic symptoms in addition to genome-wide arrays for novel variants.

Genetic variants that can be examined include polymorphisms within major histocompatibility antigen loci HLA B and D on the short arm of chromosome 6, which are involved in the activation of IgE reactions during anaphylaxis. An example is beta-lactam antibiotic anaphylaxis recently mapped to a single nucleotide polymorphism, of which the HLA-DQA1*01:05 locus is an example. Other variants at the DBR1 site can be examined for their known role in perioperative radio-iodine contrast and latex anaphylaxis. The depth of testing needed for resolution is shown by the presence of more than a single loci with polymorphisms that are involved in penicillin anaphylaxis with a common variant on HLA-B*55:01.

We propose protein testing to identify changes in Mas-related G protein-coupled receptor X2 (MRGPRX2) on mast cells, coded by chromosome 11. This is one of the mechanisms where rocuronium, cis-atracurium, remifentanil, and morphine directly activate a variant receptor causing mast cell degranulation. Amino acid substitutions leading to faulty receptor function have been traced to single nucleotide polymorphisms. Other pathways associated with anaphylactic symptoms that require evaluation include IgG activation of the contact system (FXII) resulting in cytokine release. An examination of the distribution of polymorphisms or gene products in northern compared with southern populations would be a well-founded starting point for exploring these inherited differences.

There were limitations that arise from our aim to measure all-cause perioperative anaphylaxis cases. Tryptase and thorough allergy testing may have shown that some of the reactions in our study were not related to mast cell degranulation. Allergy testing would have helped us to understand the molecular pathways involved in the reactions we observed and facilitated our strategic plan to identify polymorphisms using genome-wide arrays that may be responsible for these reactions. It is also possible that our collaborative network learning did not eliminate all errors in diagnosis and recording. Poor compliance with evidence-based protocols is a recurring problem in all medical practices whether related to the management of anaphylaxis or other conditions. However, systematic interventions such as collaborative networking have improved adherence to protocols. The latter was chosen for this study as it was the most practical approach for the large number of study sites. This approach has been tested for effectiveness in a number of educational scenarios including the pharmaceutical industry. We did not measure effectiveness in our design as this would prevent us from performing a cross-sectional study of incidence. We are therefore unable to guarantee if all cases of suspected perioperative anaphylaxis were identified. However, to the best of our knowledge, no observational study designs can guarantee 100% diagnostic and reporting fidelity.

In summary, averaged reactions that met clinical diagnostic criteria for all-cause anaphylaxis in this study occurred in one in 11,360 surgical cases in China, which is similar to that calculated for all-cause cases from NAP6. We observed a significant demarcation by geographic location with a higher frequency in the southern (one in 6050) compared with the northern (one in 19,262) regions. These findings overlap with ancestral migration patterns. We suggest that a genomic study of southern compared with northern populations of China may help address contributing causes of geographic variation in incidence of all-cause perioperative anaphylaxis.

### Authors’ contributions

Study conception and design: PZ, XL, WL, RG, JZ, RS
Data collection: PZ, XL, WL, RG, JZ, RS
Data analysis: PZ, XL, WL, RG, JZ, RS, MSM
Scientific writing: PZ, JZ, MSM
Study supervision: JZ, MSM

All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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### Table 2: Comparison of patients who survived or died after perioperative anaphylaxis. *P<0.05. Fisher’s exact test.

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The other authors have no conflicts of interest to declare.

Declarations of interest

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.09.020.

References
35. Guéant JL, Romano A, Cornejo-Garcia JA, et al. HLA-DRA variants predict penicillin allergy in genome-wide fine-

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